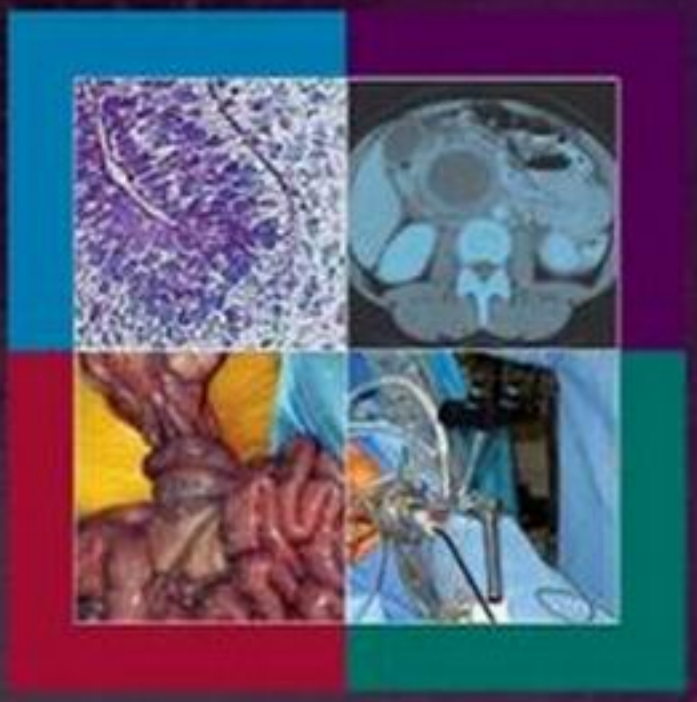
Shackelford's

Surgery of the Alimentary Tract

VOLUME I



SIXTH EDITION

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ANDREW S. KLEIN

JOHN H. PEMBERTON

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SAUNDERS

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Shackelford's Surgery of the Alimentary Tract

6th Edition

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To my wife, Theresa, and my children, William and Katerina;
to my many mentors (alive and deceased) who contributed to the science of surgery;
and to the many colleagues and friends whose work made this sixth edition possible.

CHARLES J. YEO

To my wife, Barbara, and my son, Patrick.

DANIEL T. DEMPSEY

To my wife, Julia, and my sons, Jeffrey, David, and Alexander
for their support, their understanding, and their willingness to savor life's adventures.

ANDREW S. KLEIN

To my mentors, Ollie Beahrs, Bob Beart, Keith Kelly, Roger Dozois, and Sid Phillips,
who each challenged me from the start to aim high;
to my colleagues who supported wordlessly (usually!) these desires,
and to my family, who put up with all of this for so long—my deepest respect, profound thanks, and love.

JOHN H. PEMBERTON

To the hard work and dedication of surgeons
struggling with esophageal disease throughout the world
and to those few who have generously shared their wisdom and experience
in my personal education toward the successful management
of diseases of the esophagus.

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Operations for Morbid Obesity

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New Developments in Chronic Pancreatitis: Before Head Resection, Try Endoscopic Treatment First

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Esophageal Cancer: Current Staging Classifications and Techniques, Endoscopic Ultrasound, and Laparoscopic and Thoracoscopic Staging

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Pseudocysts and Other Complications of Pancreatitis; Operative Management of Strictures and Benign Obstructive Disorders of the Bile Duct

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Appendix

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New Developments in Chronic Pancreatitis: Before Head Resection, Try Endoscopic Treatment First

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Epidemiology, Risk Factors, and Clinical Manifestations of Esophageal Carcinoma

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Lumbar and Pelvic Hernias

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Endoscopic Retrograde Cholangiopancreatography in the Evaluation and Management of Hepatobiliary and Pancreatic Disease

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Esophageal Replacement for End-Stage Benign Esophageal Disease

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Adenocarcinoma of the Colon and Rectum

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Endoscopic Esophageal Ultrasonography

Preface

It is with great delight that the section editors and I present the sixth edition of *Shackelford's Surgery of the Alimentary Tract*. This encyclopedic set has served as an invaluable resource for surgeons, internists, gastroenterologists, residents, medical students, and other medical professionals over the past 50 years. I know that you will find this sixth edition educationally fulfilling, nicely illustrated, and up-to-date.

The first edition of *Surgery of the Alimentary Tract* was written by Dr. Richard T. Shackelford and published in 1955. Following the success of that first edition, the W. B. Saunders Company urged Dr. Shackelford to produce a second edition. Between 1978 and 1986 consecutive volumes were released, culminating in a five-volume set that had been expanded substantially from the first edition. Dr. George D. Zuidema was added as a co-editor. It was this second edition that served as my "bible" for alimentary tract diseases during my surgical residency and early faculty appointment.

The third edition, edited by Dr. Zuidema, was published in 1991 and proved to be an important step forward. The field of alimentary tract surgery had advanced, and many emerging techniques and new research findings were included in that edition. For that third edition, Dr. Zuidema enlisted the help of a guest editor for each of the five volumes.

The fourth edition, which was published in 1996, was encyclopedic in scope, breadth, and depth of coverage. This led it to be consulted as the classic reference source for surgeons, internists, gastroenterologists, and others involved in the care of patients with alimentary tract diseases.

In 2002, the fifth edition was published. I was delighted that Dr. Zuidema asked me to join him as a co-editor for that edition. Its publication nicely presented numerous changes in surgical practice, operative techniques, molecular biology, and noninvasive therapies. The world of alimentary tract surgery had continued to change, and the textbook reflected these changes.

This current sixth edition represents even more change, both for the field of alimentary tract surgery and for the textbook itself. All involved listened to the book's many users and have made substantial changes in the look and content of the text. The book has gone from five volumes to two volumes, while adding material and including a four-color production scheme. The authors have emphasized new procedures, including endoscopic and minimally invasive ones, and advances in technology. Dr. Zuidema, who was involved with the second through the fifth editions, has passed the baton, but he remains an inspiration to all those in the field of alimentary tract surgery. I am delighted to keep this project moving forward and have done so with his blessings and oversight from afar.

This sixth edition has been completed with an enormous amount of help from four colleagues, who have served as section editors for the four major sections of the book. These section editors have worked tirelessly planning, organizing, and developing this massive textbook. They have incorporated numerous changes in surgical practice, operative approaches, and noninvasive therapies within the text. Each area retains extensive sections on anatomy and physiology but then directs attention to both standard and cutting edge innovations. This sixth edition includes the contributions of two new and two retained section editors, in order to provide both innovation and stability.

Section I, "Esophagus and Hernia," is now edited by Dr. Jeffrey H. Peters, the Seymour I. Schwartz Professor and Chairman of the Department of Surgery at the University of Rochester School of Medicine and Dentistry in Rochester, New York. Dr. Peters is a world-renowned expert who brings his detailed knowledge of the esophagus and esophageal diseases to the textbook. He has put together a spectacular section on esophageal diseases, focusing on esophageal pathology and ambulatory diagnostics, gastroesophageal reflux disease, esophageal motility disorders, and esophageal neoplasia. This represents an entirely new presentation of esophageal diseases in *Shackelford's Surgery of the Alimentary Tract,* sixth edition.

For Section II, "Stomach and Small Intestine," Dr. Daniel T. Dempsey has expanded his previous contribution by taking on the jejunoileum as part of his section. Dr. Dempsey is Professor and Chairman of the Department of Surgery at Temple University School of Medicine in Philadelphia, Pennsylvania. He has done a superb job of merging both standard and innovative areas in this field. New to the section are discussions of upper gastrointestinal foreign bodies and bezoars, as well as entirely redone sections dealing with neoplasia, gastrointestinal stromal tumors, and vascular diseases. Dr. Dempsey's section is an outstanding contribution to this area, advancing the field to new heights.

For Section III, "Pancreas, Biliary Tract, Liver, and Spleen," we have a new section editor, Dr. Andrew S. Klein. Dr. Klein is the Esther and Mark Schulman Chair in Surgery and Transplant Medicine and Director of the Cedars-Sinai Comprehensive Transplant Center in Los Angeles. Dr. Klein has put together a tremendous hepatopancreaticobiliary (plus spleen) section, including new contributions about acute pancreatitis, chronic

pancreatitis, cystic neoplasia of the pancreas, and laparoscopic approaches to biliary and liver diseases. Also included are top level discussions of fulminant hepatic failure and the bio-artificial liver, drug-induced liver damage, and extensive operative sections dealing with liver resection and liver transplantation. Dr. Klein has taken a previously very well done section and made it even better.

The last section, Section IV, "Colon, Rectum, and Anus," has again been supervised by Dr. John H. Pemberton, Professor of Surgery at the Mayo Clinic College of Medicine in Rochester, Minnesota. Dr. Pemberton is a world-renowned figure in his field, and his section has been nicely reworked. Included are new developments in the field, a better understanding of pelvic floor anatomy and physiology, updates regarding diagnosis and interventions for inflammatory bowel disease, as well as the addition of more extensive laparoscopic interventions and their outcomes.

This sixth edition would have been impossible without the hard work of each of these section editors. They have been helped immensely by their colleagues, staff, and all of the chapter contributors. I would like to thank each of these section editors for their hard work, vision, and skill in bringing this project to its fruition.

Very importantly, I would like to express my appreciation to the more than 300 individuals who have contributed chapters to this new, sixth edition. I understand how difficult it is to produce superb chapters, and I wish to recognize these individuals and thank them for their dedication and commitment. Many of the contributors here are topnotch, world class leaders in their fields, and I am deeply indebted to them for sharing their knowledge and enthusiasm, culminating in an outstanding product.

I would also like to thank the production team at Elsevier/W.B. Saunders, who have been instrumental in making this edition a reality. My thanks go out to Judith Fletcher, Kim Davis, Amy Cannon, and many others, who have been instrumental in overseeing this project. This edition represents an immense amount of new work, redesign, and illustration. These professionals have made it a labor of love to work on this project.

Finally, I must thank individuals who helped me during this process over the past 3 years. The majority of the early correspondence, mailings, and editorial oversight originated in the Department of Surgery at the Johns Hopkins University School of Medicine in Baltimore. My thanks go out to Janet Romanelli and Irma Silkworth for providing me with this support. Additionally, within the past year, Mary Toelke in my office here at the Thomas Jefferson University Hospital and the Jefferson Medical College has been an outstanding assistant and editor, providing me with tremendous support here in Philadelphia.

Charles J. Yeo, MD
Philadelphia, Pennsylvania

Part

1

The Normal Esophagus

Chapter

1

Perspectives on Esophageal Surgery

Tom R. DeMeester

To write a perspective on a subject is to clearly view a subject through a medium, usually an optical glass such as spectacles or some form of scope. In this instance the scope is history or, if you prefer, the retrospective scope. The accumulation of human experience makes up history and, according to C. S. Lewis, "authority, reason and experience; on these three, mixed in varying proportions all our knowledge depends."[1] If today's esophageal surgeon desires to stand on the shoulders of those who went before us and not repeat their mistakes, the knowledge and appreciation of important milestones in esophageal surgery must be appreciated and embraced.

To understand a surgical disease requires the capacity to see and touch the affected tissue. Until the science of surgery was translated to human patients, autopsy reports provided most of our understanding of esophageal disease. They consisted largely of spontaneous perforations (Boerhaave's syndrome)[2] and tumors of the esophagus and provided little to the understanding of benign inflammatory disease, such as esophagitis. This is because autolysis of the distal esophageal mucosa by digestive enzymes occurred during the interval between death and autopsy. Any tissue injury around the gastroesophageal junction was assumed to be a postmortem change, much like the organism *Helicobacter pylori* was assumed to not be a pathogen in the stomach. Consequently, the existence and pathologic description of esophagitis and inflammatory strictures were not appreciated until Heinrich Quincke, a German internist, brought attention to them through his publication on esophageal ulcers in 1879.[3]

Further, the remote inaccessibility of the esophagus in the posterior mediastinum surrounded by the lungs and heart deterred understanding of diseases that affect the organ until the introduction of rigid esophagoscopy 130 years ago by Bevan in 1868,[4] Kussmaul in 1868,[5] and Mikulicz in 1881.[6] Subsequently, several breakthroughs in technology permitted complete and safe endoscopic examination of the entire esophagus, stomach, and duodenum. First was the invention of the incandescent light bulb by Thomas Edison in the 1870s. Second was the introduction of the rod-lens system by Hopkins in the 1950s. Third was the development of fiberoptic cold-light transmission in the 1960s. Last was the evolution of the computer chip video camera in the 1980s.[7] Combined, these technologic advancements provided reliable clinical esophagoscopy with the ability to directly examine and biopsy the esophageal mucosa. This ability opened the door to understanding the pathophysiology of esophagitis, stricture, and Barrett's esophagus with its inherent cancer risk.

ESOPHAGEAL CANCER

Cancer of the esophagus was a unique challenge for the surgeon. For decades, surgical pioneers have struggled with safe removal of the diseased organ. Emslie in

his "Perspectives in the Development of Esophageal Surgery" states, "the history of esophageal surgery is the tale of men repeatedly losing to a stronger adversary yet persisting in this unequal struggle until the nature of the problems became apparent and the war was won."[8] The major obstacles were the continuation of respiration with an open thorax and the restoration of alimentary tract continuity after esophageal resection.

The first successful esophagectomy for squamous cell carcinoma was performed by Franz Torek.[9] General anesthesia was administered by a new technique called insufflation, in which ether was delivered through a woven silk tube used to intubate the patient. The existing technique of a differential pressure chamber was not considered because the rubber cuff around the patient's neck, used to create subatmospheric pressure about the body, prevented construction of a cervical esophagostomy. The esophagus with a cancer abutting the left main bronchus was removed by a transthoracic transpleural exposure. Dr. Torek avoided injury to the vagi and the possibility of "sudden death due to vagal collapse" by carefully dissecting them off the esophagus. His fear of vagal circulatory collapse is reflected in his statement: "At the site of the tumor the dissection of the vagi was more difficult, and some of the branches crossing over in front of it had to be cut in order to permit liberating the tumor without undue roughness in handling the vagi. To my great satisfaction the pulse never wavered during the procedure, remaining between 93 and 96. The dreaded vagus collapse had, therefore, been safely avoided."[9] A pleural infection from an esophageal leak was circumvented by carefully closing the cardia and performing a cervical esophagostomy. The reported existence of extensive adhesions between the left lung and the parietal pleura in all probability prevented collapse of the left lung and contributed as much to the success of the procedure as Torek's surgery. The patient recovered and survived for another 13 years, with continuity between the cervical esophagostomy and gastrostomy established by an external "rubber tube."

The fact that 20 barren years intervened between the first and second successful procedure testifies to the challenge that removal of the esophagus posed to surgeons. Wolfgang Denk took up the challenge and developed a totally different approach to resection of the thoracic esophagus.[10] He showed in cadavers that the esophagus could be removed by blunt dissection through the combination of an abdominal transhiatal and a cervical transthoracic inlet approach. This technique, knowingly or unknowingly, was used in the second successful esophagectomy reported by Grey Turner in 1933.[11] As suggested by Denk, the procedure was performed without opening the chest by blunt burrowing from the abdomen and neck. The esophagus with a midconstricting neoplasm was successfully removed. Alimentary tract continuity was re-established 7 months after the esophagectomy by a second procedure connecting the cervical esophageal and abdominal gastric stomas by a subcutaneous skin tube.

While surgeons struggled with esophagectomy, advances in anesthesia continued. The description of an intratracheal tube with an inflatable cuff by Theodore Tuffeir in 1896[12] and its introduction into clinical practice in 1928 by Magill[13] allowed the development of positive pressure anesthesia and the direct transthoracic approach to the esophagus. Similarly, experimental work on restoration of the alimentary tract after esophageal resection continued. Claude Beck in 1905 showed in animals that a tube constructed along the greater curvature of the stomach could be used to replace a portion of the esophagus.[14] Cesar Roux in 1907 developed the technique of using the jejunum to replace the distal end of the esophagus.[15] G. Kelling devised a method of using an isoperistaltic segment of transverse colon to completely replace the thoracic esophagus.[16]

In the wake of these accomplishments, it is not surprising that the final successful step of performing an esophagectomy with an intrathoracic esophagogastric anastomosis was reported by Tatsuo Ohsawa from Japan in 1933.[17] He successfully performed a simultaneous esophagogastrectomy and esophagogastrostomy in eight patients with carcinoma of the lower esophagus and cardia. No follow-up is available on Ohsawa's patients, and unfortunately his paper did not reach the attention of the Western world for 5 years. Samuel Marshall from the United States reported a similar procedure in one patient in 1938. However, this patient was plagued by persistent esophageal obstruction and esophagitis that required repetitive dilation.[18]

With initial success, surgeons realized that performing a dependable intrathoracic esophagogastric anastomosis was a major part of the challenge. Infection of the mediastinum and pleural cavities because of disruption of the anastomosis was the most frequent cause of failure of the operation. Adams and Phemister took the problem to the laboratory, and only when a high degree of success was attained in dogs was a similar anastomotic procedure applied to humans with carcinoma of the thoracic esophagus. Their report in 1938 popularized the one-stage resection for esophageal cancer with an intrathoracic esophagogastrostomy.[19]

Today, challenges still remain in the surgical treatment of esophageal cancer. Questions of temporal interest include the following: Does en bloc esophagogastrectomy reduce the incidence of local recurrence of cancer that occurs after more limited resections? Are limited resections for early cancer sufficient to eradicate the disease and are they superior to endoscopic methods of resection? Is a vagal-sparing esophagectomy without lymphadenectomy a less morbid and safer procedure, and is it adequate therapy for early disease?

In the history of surgical practice, therapy for carcinoma of the esophagus carries an aura of pessimism with an attitude that cure is a chance phenomenon. This setting has given rise to two current treatment philosophies. First is that surgical removal of the primary tumor is the goal of therapy and the need for lymph node dissection is of limited benefit. Second, is that surgery alone is insufficient therapy and neoadjuvant or adjuvant radiation therapy or chemotherapy (or both) is necessary to achieve cure. This philosophy persists even though contemporary surgical experience has validated that complete surgical resection of an early tumor and limited nodal disease can cure a patient of esophageal

cancer with an effectiveness better than that achieved by any other single or combined therapy.

ESOPHAGEAL MOTILITY DISORDERS

Surgical therapy for esophageal motility disorders started with the treatment of achalasia. *Megaesophagus*, or *achalasia* as it later came to be known, was first described by Willis in 1674. He advocated the use of a small sponge attached to a long strip of whalebone to force impacted food through the narrow distal esophagus.[20] Arthur Hurst showed that an abnormality of the intermuscular nerve plexus was responsible for the disease. He named the disease achalasia of the cardia because the continued tonic contraction of the cardiac sphincter prevented esophageal emptying. Hurst devised rubber tubes of various size with blunt tips filled with mercury to dilate the tonic sphincter. They are now referred to as Hurst dilators and were subsequently modified with tapered tips and called Maloney dilators.[21]

The initial surgical procedures used to relieve a spastic cardia were designed to enlarge the narrowed gastroesophageal junction with various cardioplasties of the Heineke-Mikulicz or Finney pyloroplasty type or to bypass the junction with an esophagogastrostomy. Ernst Heller in 1914 described a simple myotomy for the treatment of achalasia with the suggestion that it replace the more dramatic operation being performed.[22] The operation was based on Ramstedt's pyloromyotomy developed in 1912. Ramstedt's operation was immediately accepted by other surgeons for the treatment of congenital pyloric stenosis.[23] In contrast, despite knowledge of Heller's myotomy for achalasia, the procedure was seldom used and largely ignored in Germany, England, and the United States. Part of the problem of acceptance was the unknown etiology of achalasia, the absence of a histologic lesion, and disagreement over the nature of the physiologic abnormality and hence the purpose of the operation. According to Ravitch[24] this situation was changed dramatically by a paper from Norman Barrett in 1949 in which he described dismal results after esophagogastrostomy or cardioplasty operations.[25] Phillip Allison,[26] Barrett, and others were studying reflux esophagitis at the time and pointed out that destroying or bypassing the gastroesophageal junction encouraged esophagitis of such severity that patients suffered heartburn, would not eat, and bled seriously. Barrett proposed Heller's operation as an alterative and reported success with it. Barrett encouraged the use of Groeneveldt's modification of Heller's operation, specifically, performing only one myotomy instead of two. Barrett's paper and the increased awareness and interest in esophagitis led to widespread acceptance of the Heller procedure as the primary mode of operative therapy for achalasia. Dor in 1962[27] and Toupet in 1963[28] developed antireflux repairs to be used in conjunction with Heller myotomy to provide further protection against the sequelae of esophagitis. Eventually, gastroenterologists were able to rupture the muscle of the cardia with pneumatic dilators and obtain results close to those of surgery. This, along with the fear of surgery and the custom of patients first contacting the gastroenterologist, led to a decrease in referral of patients for surgical myotomy. The recent introduction of laparoscopic myotomy with its greater safety and minimal morbidity has reversed this trend.

Franz Ingelfinger[29] in 1959 and Charles Code[30] in 1958 introduced esophageal manometry to clarify the diagnosis of achalasia and identify other esophageal motility disorders such as diffuse spasm and hypertensive lower esophageal sphincter. These latter conditions very rarely require myotomy of the esophageal body or lower esophageal sphincter.

Today, laparoscopic myotomy is the accepted therapy for achalasia. The procedure has been standardized in that most esophageal surgeons perform a myotomy that extends at least 3 cm onto the stomach and add a partial fundoplication to reduce the reflux of gastric juice into the esophagus. The location of the myotomy, either in the anterior quadrant between the "clasps" and "oblique" fibers or in the left lateral quadrant in line with the greater curvature and cutting only the "oblique" fibers, is still debated. The performance of a surgical myotomy is the creation of a defect to correct a defect and, consequently, can never restore the function of the cardia to normal. Therefore, a modified Heller myotomy is a palliative procedure.

ESOPHAGEAL DIVERTICULUM

The first description of a pharyngoesophageal diverticulum is attributed to Abraham Ludlow. He observed the abnormality at an autopsy he performed and reported the finding to William Hunter, John's brother, in 1764. Ludlow eventually published the observation in 1767.[31] Today, Ludlow's autopsy specimen is registered in the Hunterian Museum. Sir Charles Bell, a surgeon who described Bell's palsy, was the first to define the abnormalities necessary for the development of a pharyngoesophageal diverticulum.[32] Before Bell's publication in 1816, the diverticulum was thought to be congenital or traumatic in origin. The two components that Bell identified as necessary for a diverticulum to form were discoordination of the inferior pharyngeal constrictors and the cricopharyngeus muscle and a preexisting anatomic defect between these muscles. These observations predated our modern acceptance of them by 100 years.

The first successful resection of a pharyngoesophageal diverticulum was performed in 1886 by a surgeon with the last name of Wheeler on a patient named Captain E.[33] Diverticulectomy became the standard form of treatment, but the incidence of salivary fistulas and late recurrence was high. This prompted Girard from France in 1896 to treat two patients by invagination of the diverticulum into the lumen of the esophagus and oversewing the resultant dimple.[34] This approach was apparently successful, but in subsequent follow-up of the patients, at least one had a complete recurrence. Diverticulopexy was also described during this early period as a means of avoiding contamination of the wound and fistula formation.

The dangers of surgical therapy for pharyngoesophageal diverticula were reported in 1906 by Zesas,[35]

who collected 42 patients from published reports and noted that primary healing occurred in only 6, fistulization in 26, and death in 8, for a mortality rate of 19%. To avoid the devastating results, Goldmann in 1909[36] devised a two-stage method of repair that was later modified by Lahey and Warren in 1954.[37] The modified procedure consisted of diverticulopexy and mediastinal packing in the first stage and resection of the diverticulum in the second. In 1945 the one-stage operation was readvocated by Harrington.[38] The battle between the protagonists of one-stage and two-stage resection continued for years and diverted attention from identifying the etiology of the diverticulum. Aubin, in 1936, was the first to propose, based on Bell's observations, a rational treatment of a pharyngoesophageal diverticulum that consisted of cricopharyngeal myotomy combined with diverticulectomy.[39] His publication refocused attention on the underlying pathology in the skeletal muscle of the cricopharyngeal sphincter and cervical esophagus. His report lead to the gradual abandonment of the two-stage operation. In 1966 Ronald Belsey,[40] in keeping with the desire to avoid contamination of the wound and fistula formation, advocated cricopharyngeal and cervical esophageal myotomy with diverticulopexy for all but very large diverticula.

The story of the pharyngoesophageal diverticulum is an object lesson from the history of surgery. It illustrates that medicine is a science often forced to be practiced before it is understood. It is not uncommon for observations, which form the bases for successful therapy, to be initially ignored or overlooked, rediscovered, and then adopted years later, in this example 2 centuries later!

In 1840 Rokitansky[41] described traction diverticula of the thoracic esophagus but was uncertain about their etiology. He thought that they were due to pressure from ingested food or obstruction of the distal esophagus by a stricture or extrinsic compression. Excision of an intrathoracic diverticulum was rarely reported, probably because of the disastrous results from leakage and fatal mediastinal and pleural sepsis. Moreover, considerable confusion existed during the middle of the 19th century regarding the etiology of the different diverticula affecting the esophagus. The confusion was resolved largely by the pathologist Albert Zenker, who with von Zeimssen in 1877 published "Krankheiten des Oesophagus," the best compendium of information on the esophagus in the latter part of the 19th century.[42] They introduced for the first time the separation of diverticula into two etiologic categories: traction and pulsion. The former is caused by inflammatory adhesions and the latter by forces within the esophageal muscular tube. The concept was quickly accepted, but confusion persisted with regard to terminology. The concept was further supported when esophageal manometry confirmed that development of a pulsion diverticulum was a complication of a motility disorder rather than a primary anatomic abnormality.[43] The major obstacle to accepting the concept was the inconsistency in identifying a motility disorder in all patients with a pulsion diverticulum. This inconsistency led to controversy over the necessity for primary correction of the motility abnormality before any direct attack was made on the diverticulum. With technical improvements in esophageal manometry, 24-hour ambulatory motility studies became possible and showed, in all patients who had a pulsion diverticulum, a disordered motility pattern distal to the diverticulum. Today, the combination of myotomy of the esophagus distal to the diverticulum, including the lower esophageal sphincter, resection of the diverticulum, and a Dor partial fundoplication has become the standard procedure.[27]

HIATAL HERNIA AND GASTROESOPHAGEAL REFLUX DISEASE

In 1853 Henry Ingersoll Bowditch commented on hiatal hernia in his published monograph titled *A Treatise on Diaphragmatic Hernia:* "Owing to the ignorance of most of the observers in regard to the true nature of the affection, their modes of treatment have been entirely empirical and generally very absurd, and not a few times absolutely hurtful to the patient."[44] Even though Heinrick Quinche described esophagitis in 1879,[3] symptoms of the abnormality were poorly understood and no consideration was given to reflux of gastric contents up into the esophagus as its cause. In 1928 Harrington reported on 51 patients with a diaphragmatic hernia and concentrated only on describing the anatomic defect and closure of the hiatus for therapy without discussing symptomatology.[38] It was not until Philip Allison's publication in 1951[26] that the symptoms associated with a hiatal hernia were linked to the reflux of gastric contents into the esophagus. Allison used the term reflux esophagitis to describe the cause of the symptoms and emphasized correction of the defect at the cardia as the proper therapy. The term reflux esophagitis was confusing to gastroenterologists, who emphasized increased gastric acidity as the major problem and advocated reduction of gastric acid and peptic secretion as a means of treating the esophagitis rather than stopping the reflux. This started a lasting controversy between gastroenterologists and surgeons. Gastroenterologists emphasized the use of bougies, antacids, and advice on posture, and surgeons devised operations to restore sphincter competence and sought methods to objectively select patients for the procedure.

Allison described the first logical hiatal hernia repair by emphasizing repositioning of the gastroesophageal junction into its normal intra-abdominal location in the hope of improving its function.[26] Recognition of the high incidence of symptomatic and anatomic recurrence after the Allison repair led to the development of procedures designed to place and anchor the lower esophagus in the intra-abdominal position in a more effective manner. A posterior gastropexy in which the phrenoesophageal membrane and the cardioesophageal junction are anchored to the median arcuate ligament of the aortic hiatus was devised, used, and reported by Lucious Hill in 1967.[45] Two additional operations, the Nissen fundoplication introduced in 1956[46] and the Belsey Mark IV introduced in 1967,[47] were designed to augment the lower esophageal sphincter with a cuff of stomach, as well as re-establish an intra-abdominal segment of esophagus.

An important contribution was made in 1957 by Lee Collis in the management of advanced gastroesophageal reflux disease when reflux-induced intramural fibrosis causes esophageal shortening. He worked out a technique to add 4 cm to the length of the esophagus by the creation of a proximal gastroplasty tube, around which later surgeons applied a partial or full fundoplication.[48]

Norman Barrett in 1950[49] opened a whole new era in esophageal disease that ultimately connected benign gastroesophageal reflux disease with esophageal adenocarcinoma, one of the most devastating cancers known to affect humans. He reported his experience on columnar-lined esophagus with accompanying esophagitis and ulceration. He thought that the condition was due to congenital shortening of the esophagus but was subsequently proved wrong by Allison and Johnstone in 1953, who noted normal esophageal musculature and esophageal submucosal glands underneath the columnar epithelium. They reported that the change in epithelium was acquired as a result of erosive injury of the squamous mucosa.[50] In 1975 Naef and Ozzello[51] cautioned that the acquired columnar epithelium had a predisposition to malignant change. In 1978 Haggitt[52] suggested and subsequently Skinner[53] and Reid[54] confirmed that only intestinalized columnar mucosa was associated with malignant degeneration.

The Nissen fundoplication, because of its simplicity and effectiveness, was rapidly adopted worldwide as the procedure of choice for gastroesophageal reflux disease. Dorothea Liebermann-Meffert, a personal friend of Nissen, archived the historical development of the Nissen fundoplication.[55] The first step toward the operation occurred in 1937 when Rudolf Nissen, then in Istanbul, Turkey, operated on a 28-year old man with a chronic bleeding ulcer in the distal esophagus. He resected the cardia and anastomosed the esophageal stump into the gastric fundus. To protect the anastomosis he covered the esophagogastrostomy with a cuff of stomach. Sixteen years latter Nissen had the opportunity to re-examine the patient, and in contrast to the usual experience after resection of the cardia and esophagogastrostomy, the patient was free of symptoms and signs of gastroesophageal reflux. The second step toward fundoplication occurred in 1946 when Nissen, then in New York, performed a transabdominal reduction of a paraesophageal hernia in a patient who refused a thoracotomy. He was surprised by the ease with which the hernia could be reduced and the degree of exposure of the esophageal hiatus through a transabdominal incision. The third and final step occurred in 1954 when Nissen, then in Basel, Switzerland, combined the two previous observations into a planned antireflux procedure in a patient suffering from severe gastroesophageal reflux disease. He formed a fold from the anterior and posterior gastric fundic walls and attached both to each other on the lesser curvature side of the stomach above the gastroesophageal junction. The clinical outcome, a complete success, could be reproduced in a subsequent patient. In the publication of the procedure in *Schweizer Medizinische Wochenschrift* in 1956 he termed the operation "gastroplication" and described it as a "simple and effective operation for reflux esophagitis."

During the 1960s and 1970s gastroesophageal reflux disease was accepted as a distinct disease entity independent of hiatal hernia. With the introduction of water perfusion esophageal manometry in 1956, the lower esophageal sphincter was identified as the major barrier against the reflux of gastric contents, and the physiology of barrier augmentation by a surgical antireflux procedure was clarified. The availability of 24-hour pH monitoring in 1974 allowed gastroesophageal reflux disease to be defined quantitatively and improved the selection of patients for antireflux surgery.[56] In 1991 Bernard Dallemagne of Liege, Belgium, performed the first known human laparoscopic Nissen fundoplication.[57] Successful laparoscopic ligation of the short gastric vessels and safe posterior dissection of the abdominal portion of the esophagus were the significant accomplishments at the time. Today, laparoscopic Nissen fundoplication has become commonplace. Its safe, effective, and user-friendly characteristics have positioned surgical therapy for earlier application in the treatment of gastroesophageal reflux disease.

THE ESOPHAGEAL SURGEON

The esophagus has never had a sizable patronage. This is well illustrated in a vignette recorded by Earle Wilkins about Dr. Willy Meyers, who reported successful esophageal resection at the annual meeting of the American Medical Association in 1903. The report was met with indifference and no discussion. The obvious lack of interest among physicians for problems concerning the esophagus was the direct impetus for Dr. Meyer to take the lead, with a small group of "interested" surgeons, and form the American Association for Thoracic Surgery, the founding organization in the clinical specialty of thoracic surgery.[58] Esophageal surgery, despite being the spark that ignited the first society for thoracic surgery, was soon crowded out by the burgeoning business of coronary bypass surgery. Consequently, over the years the esophagus has been used, sometimes ill-used and sometimes ignorantly used, by gastroenterologists, otolaryngologists, thoracic surgeons, general surgeons, and oncologic surgeons. There have been no specialty hospitals erected to care exclusively for esophageal illnesses. There have been no departments or clinics devoted exclusively to the diagnosis and treatment of esophageal diseases. Many hospitals did not have staff familiar with the postoperative care of esophageal patients. Surprisingly, such clinics are developing today, probably aided by the necessity for an esophageal laboratory to unsnarl complex esophageal disease, an awareness of the relationship of esophageal to pulmonary disease, and the metaplasia-dysplasia-carcinoma sequence in Barrett's esophagus. Virtual esophageal motility, wireless esophageal pH monitoring, esophageal impedance measurements, endoscopic ultrasound, and a variety of endoscopic diagnostic and therapeutic procedures are now commonplace and have accelerated the status of individual esophageal units. If the anatomic demarcation of the gastrointestinal and cardiothoracic surgeons could give way and the pharynx, esophagus, lungs, and stomach be coalesced, there could

be the advent of a new therapist—a foregut or esophageal surgeon who is competent at endoscopy, as skilled in transthoracic as in transabdominal operations, at home in the esophageal laboratory, and an expert at unsnarling complex foregut problems.

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Chapter

2

Human Foregut Anatomy, Prenatal Development and Abnormalities, and Their Relation to Surgical Approaches

Dorothea Liebermann-Meffert · Hubert J. Stein

Anatomy of the Esophagus

MACROSCOPIC FEATURES

General Aspects

The esophagus is a midline structure lying on the anterior surface of the spine. It descends through three compartments: the neck, the chest, and the abdomen. This progression has led to its classic anatomic division into cervical, thoracic, and abdominal segments (Fig. 2–1). Two new subdivisions more useful for clinicians have recently been proposed (see Fig. 2–1). One refers to functional aspects and makes a distinction between the esophageal body and the upper and lower sphincters.[1] The other refers to oncosurgery and distinguishes between the proximal and the distal esophagus, with the tracheal bifurcation used as a partition.[2] This concept integrates the features of embryologic development, in particular, the differently oriented pathways of lymphatic drainage (see the section "Lymphatic Drainage" later in this chapter).

The topographic relationships of the esophagus to its neighboring structures have been studied extensively by the authors and other experts using different technical approaches. The conclusions are as follows:

Joining the pharynx, the esophagus begins at the cricoid cartilage in front of the sixth cervical vertebra. It passes into the chest at the level of the sternal notch and travels within the chest cavity on the anterior limit of the posterior mediastinum. Between the thoracic inlet and the diaphragm, the esophagus remains in close relationship with the spine (Fig. 2–2). It ends at the inlet of the stomach, in front of the 12th thoracic vertebra. On radiologic evaluation, the esophageal axis is virtually straight. Unaffected by scoliotic curves of the vertebral column, the esophagus maintains a straight course; in contrast, the large neurovascular structures, because of their origin at the posterior body wall, follow the deformity of the skeleton.[3] Vascular anomalies or mediastinal masses, on the other hand, may displace, bow, or indent the esophagus. However, any distortion of its axis strongly suggests mediastinal invasion and retraction, usually by a malignancy.[4]

A healthy esophagus has three minor deviations along its trajectory (see Fig. 2–1). The first is toward the left at the base of the neck (see Fig. 2–2); hence surgical approaches to the esophagus are easier from the left than from the right when performing intestinocervical esophageal anastomoses after esophagectomy. The second deviation is at the level of the seventh thoracic vertebra, where the esophagus turns slightly to the right of the spine (see Fig. 2–1). Because of the third deviation, the terminal esophagus and the esophagogastric junction are positioned slightly lateral to the xiphoid process of the sternum and to the left of the spine. At this point, the fundus and proximal part of the stomach extend anterolateral to the body of the vertebra (see Fig.

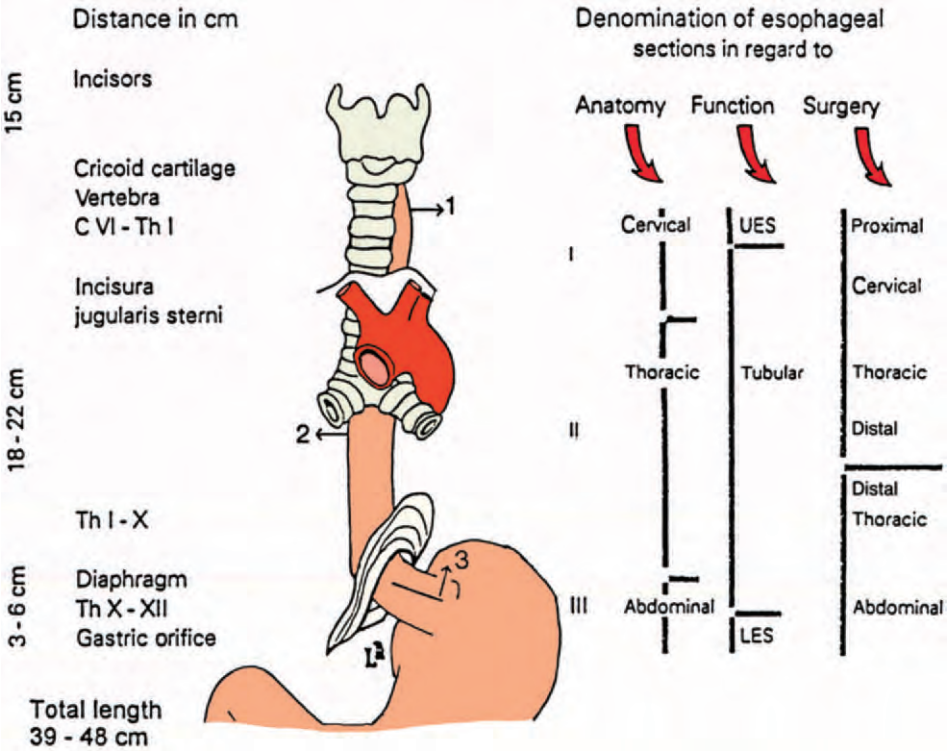


Figure 2–1. Classic anatomic division of the esophagus and its topographic relationship to the cervical (C) and thoracic (Th) vertebrae. The approximate length of each segment is given, and the three narrowings of the esophagus are shown. More recently, the esophagus has been subdivided according to its different functions by Diamant.[1] Based on the embryology and main direction of lymphatic flow, Siewert (1990) proposed a subdivision of the thoracic esophagus at the level of the tracheal bifurcation for determining treatment strategies in patients with esophageal cancer. LES, lower esophageal sphincter; UES, upper esophageal sphincter.

2–2); as a result, the greater curvature faces the posterior subdiaphragmatic space, and the anterior gastric wall faces laterally. This topographic feature is not well displayed in standard anatomy textbooks but is definitely clarified by computed tomographic studies (see Fig. 2–2). A better understanding of the function of the cardia and interpretation of pressure measurement data of the lower esophageal sphincter (LES) are based on this topography.

Measured Dimensions

Length of the Esophagus

The length of the esophagus is defined anatomically as the distance between the cricoid cartilage and the gastric orifice. In adults, it ranges from 22 to 28 cm (24 ± 5 SD), 3 to 6 cm of which is located in the abdomen (see "Suggested Readings").[5,6] In contrast to the previous assumption about the incidence of sex differences (see Lerche in "Suggested Readings"), Liebermann-Meffert et al.[6] found the length of the esophagus to be related to the subject's height rather than sex.

Identification and marking of the cricoid cartilage are rather difficult in a living individual. For practical reasons, therefore, clinicians measure the length of the esophagus by including the oropharynx and the pharynx and using the incisors as a direct macroscopic landmark during endoscopic procedures (see Savary and Miller in "Suggested Readings"). The distances are shown in Figure 2–1.

Length of the Orthotopic Bypass

Esophagectomy for cancer requires transfer of the substitute to the position formerly occupied by the esophagus. To measure the length required for esophageal replacement, the shortest distance between the cricoid cartilage and the celiac axis was found to be the orthotopic route in the posterior mediastinum (30 cm). The retrosternal location (32 cm) and the subcutaneous route (34 cm) proved to be longer.[7] There were no differences between men and women.

Diameter of the Esophagus

The esophagus is the narrowest tube in the intestinal tract. It ends by widening into its most voluminous part, the stomach. At rest, the esophagus is collapsed; it forms a soft muscular tube that is flat in its upper and middle parts, with a diameter of 2.5 × 1.6 cm. The lower esophagus is rounded, and its diameter is 2.5 × 2.4 cm.[6,8]

Compression or constriction by adjacent organs, vessels, or muscles may cause narrowing, which can be visualized by means of fluoroscopy and endoscopy (see "Suggested Readings"). The aortic compression, which is left sided and anterolateral, is caused by crossing of the aortic arch, the left atrium, and the left main bronchus at a location 22 cm from the incisors. Occasionally, a mechanical imprint of the diaphragm exists, but more apparent are two functional muscular constrictions: the upper and the lower esophageal sphincters. They are found manometrically at the esophageal opening, 14 to 16 cm distant from the incisors, and at the entrance into

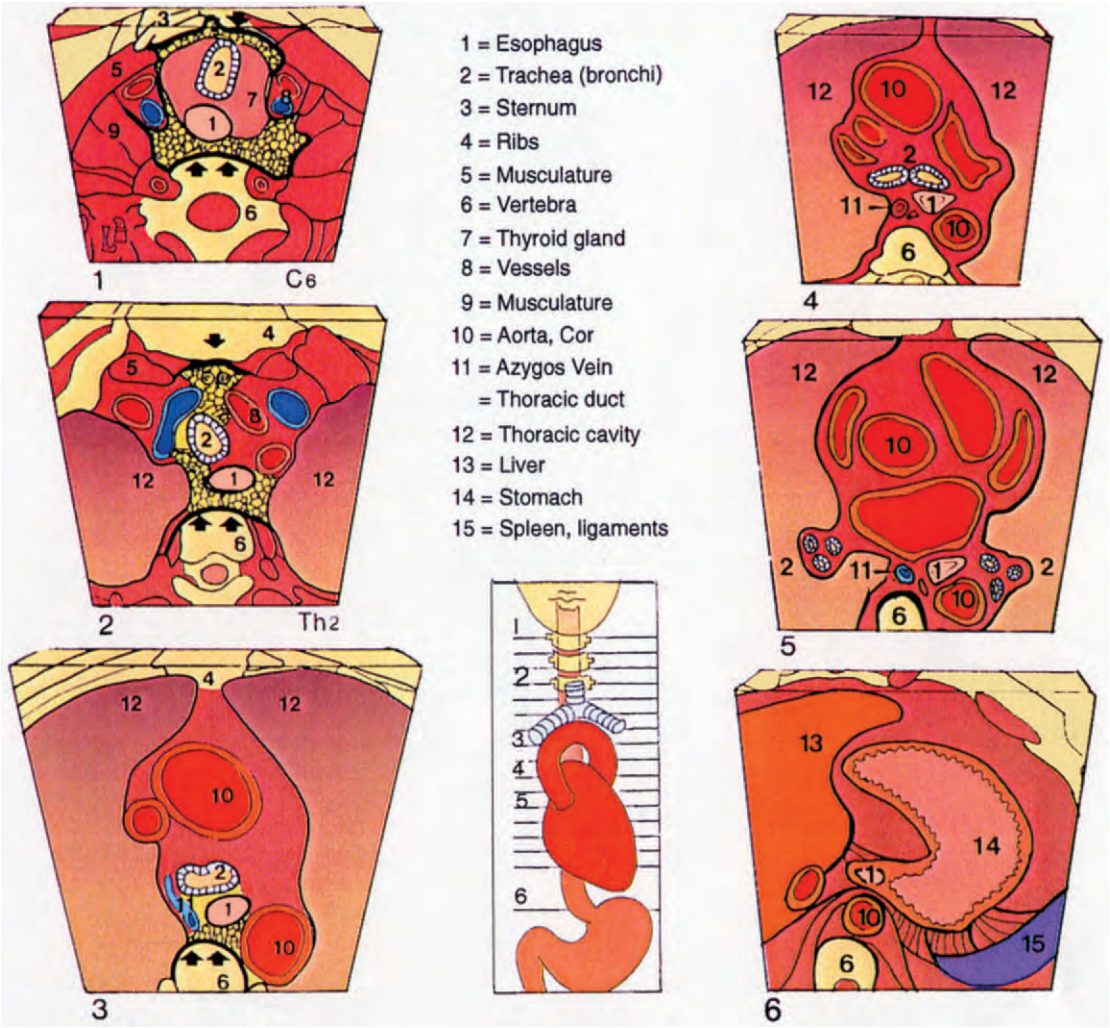


Figure 2–2. Topographic anatomy of the esophagus shown from the cervical level (1) to the esophagogastric junction (6). A transverse section through the mediastinum shows the esophagus and its surrounding structures in a computed tomographic aspect. The close positional relationship among the esophagus, trachea, and vertebrae and the fascial planes is displayed. The *thick dark lines* are the prevertebral and previsceral fascia (*arrows*); the net-like pattern represents the respective areolar connective tissue. (Modified after Wegener OH: Neuromuscular organization of esophageal and pharyngeal motility. Arch Intern Med 136:524, 1976, with permission.)

the stomach, between 40 and 45 cm from the incisors (see Fig. 2–1) (see the section "Esophageal Sphincters" later in this chapter).

Periesophageal Tissue, Compartments, and Fascial Planes

Unlike the general structure of the digestive tract, the esophageal tube has neither mesentery nor serosal coating. Its position within the mediastinum and a complete envelope of loose connective tissue allow the esophagus extensive transverse and longitudinal mobility.[9,10] Respiration may induce craniocaudal movement over a few millimeters, and swallows may result in excursion over as much as the height of one vertebral body. This mobility is also the reason why the esophagus may be subjected to easy blunt stripping from the mediastinum. Invasion by malignant tumor and fixation to the surroundings, however, strictly contraindicate the use of this technique.[4,6,11]

Another anatomic peculiarity is of clinical relevance: the connective tissues in which the esophagus and trachea are embedded are bounded by fascial planes, the pretracheal fascia anteriorly and the prevertebral fascia posteriorly. In the upper part of the chest, both fascias unite to form the carotid sheath, and the anterior and posterior spaces between these fascias form a communicating compartment between the neck and the chest that provides a plane for rapid spread of infection through the mediastinum (see Fig. 2–2).

The anterior space coincides with the previsceral (i.e., pretracheal) space. Infections spreading from anterior lesions of the esophagus may follow this route, but they

are limited distally by the strong fibrous tissue of the pericardium. The posterior space, which is the retrovisceral (i.e., prevertebral) space, extends from the base of the skull to the diaphragm. It is formed by the buccopharyngeal fascia spreading downward via a sheath that separates the esophageal tissue bed from the prevertebral fascia. This space is clinically of greater importance than the previsceral space. The reason is that most instrument perforations with subsequent outflow of esophageal contents occur above the narrowing of the cricopharyngeal sphincter in the posterior hypopharynx (see Savary and Miller in "Suggested Readings"). At this level, as in the chest, there is no barrier to the spread of infection into the mediastinum. Rupture of the esophagus or leakage of an esophageal anastomosis may result in descending mediastinitis along these planes as well. Prompt diagnosis is vital for the patient because the prognosis for esophageal perforation depends on the rapidity with which treatment is initiated!

Stabilizing and Anchoring Structures

The esophagus is stabilized by bony, cartilaginous, and membranous structures (Fig. 2–3).

Anchorage in the Neck

Through the exterior longitudinal layer of its muscle coat the cranial end of the esophagus fastens at the posterior ridge of the cricoid cartilage via the cricoesophageal tendon (Fig. 2–4).

Anchorage of the Body of the Esophagus

The tubular esophagus lies in the loose areolar tissue bed of the mediastinum (see Fig. 2–2). The claim that broad fibrous tissue or muscle strings connect the trachea and esophagus, as depicted by Laimer[10] and later adopted in Netter's atlas,[13] could not be substantiated by the authors' studies.[8,10] Instead, there were numerous delicate, slightly undulated membranes mostly 170 µm in thickness and approximately 3 to 5 mm in length (Fig. 2–5A and B). They connected the esophagus with the trachea (see Fig. 2–5A) and the surrounding tissue (see Fig. 2–5B). Consisting of collagen and elastic fiber elements and occasional interpositioned sparse muscle fibers, the membranes are stretchable to some extent and accumulate around the tracheal bifurcation.[10] A few individuals possess membranes up to 700 µm in thickness, together with firm intramural insertion (see Fig. 2–5A).

Anchorage of the Cardia

When the distal end of the esophagus traverses the diaphragm through the esophageal hiatus, it is bounded by the two diaphragmatic crura and the phrenoesophageal membrane (Figs. 2–6 and 2–7; see also Fig. 2–3).

The muscular portion of the diaphragm is inserted on the lumbar vertebrae, the ribs, and the sternum. The central membranous portion is frequently larger than that described in the literature, and the left crus of the diaphragm may consist of membranous tissue rather than a significant muscular mass (see Fig. 2–6) (see also Williams and Warwick in "Suggested Readings"). The subdiaphragmatic and endothoracic aponeuroses blend at the central margin of the diaphragm to constitute the phrenoesophageal membrane (PEM), also known as Laimer's ligament or Allison's membrane. Intraoperatively, the PEM can be recognized by its well-defined lower edge (Fig. 2–7) and its slightly yellow color, even in the presence of severe periesophagitis. The PEM is composed of elastic and collagenous fiber elements, which guarantee sufficient pliability. Because of its origin

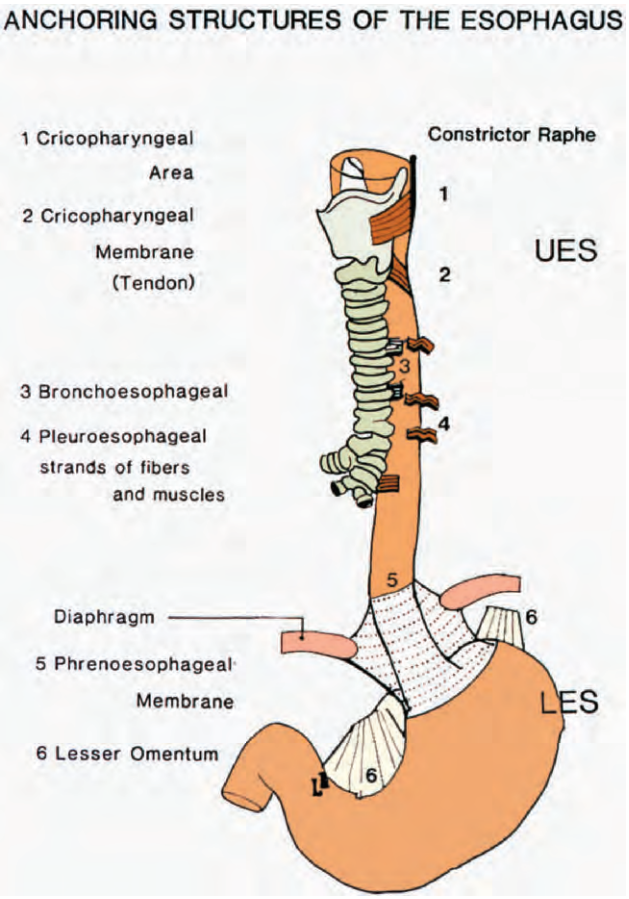
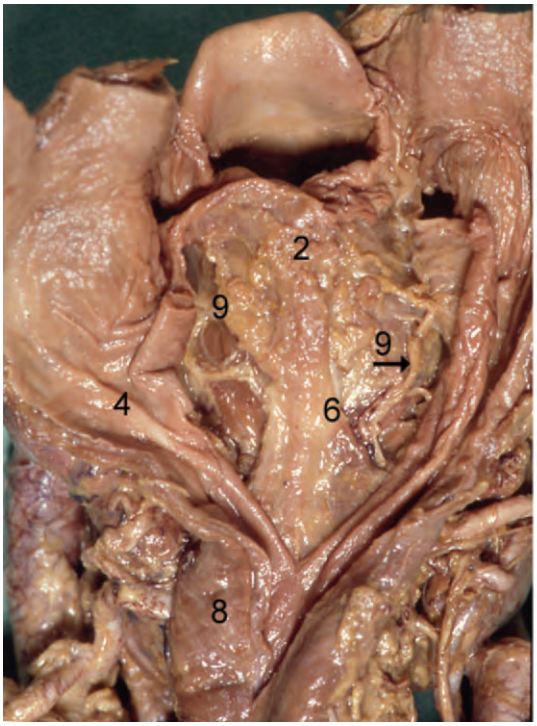


Figure 2–3. Attachments of the esophagus. The upper end of the esophagus obtains firm anchorage by the insertion of its longitudinal muscle into the cartilaginous structures of the hypopharynx (1) via the cricoesophageal tendon (2). The circular muscle is stabilized by its continuity with the inferior laryngeal constrictor muscles (1), which insert via the raphe to the sphenoid bone. Tiny membranes connect the esophagus with the trachea, bronchi, pleura, and prevertebral fascia (3 and 4). The attachment at the lower end by the phrenoesophageal membrane (5) is rather mobile, whereas the posterior gastric ligaments, such as the gastrosplenic, phrenicolienal, and phrenicogastric ligaments (6), and the lesser omentum (6) yield a tight adherence. LES, lower esophageal sphincter; UES, upper esophageal sphincter.



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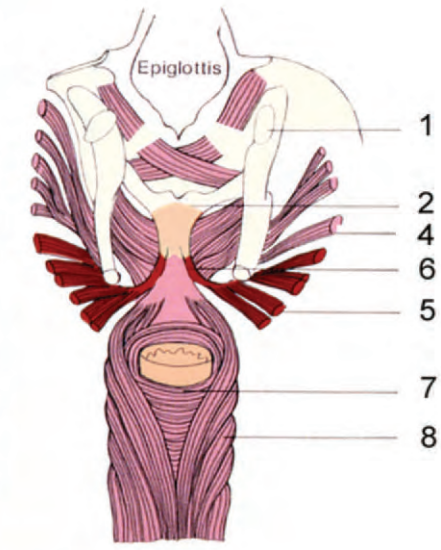
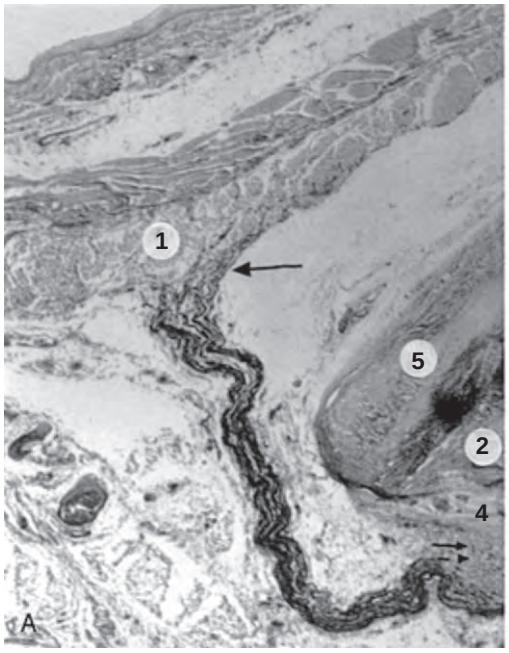


B

Figure 2–4. The posterior walls of the pharynx (4) and the esophagus (7 and 8) have been cut open in the midline, as shown in a specimen (**A**) and half-schematically (**B**). The structures of the hypopharynx are exposed by retracting the overlying incised tissue and removing the mucosa. In the center lies the cricoesophageal tendon (6), which attaches the longitudinal muscle layer of the esophagus (8) to the cricoid cartilage (2). The terminal branches of the left laryngeal recurrent nerve (9) are dissected and are seen lateral to the cricoesophageal tendon. 1, Thyroid cartilage. (Specimen and photo courtesy of Liebermann-Meffert, Munich.)



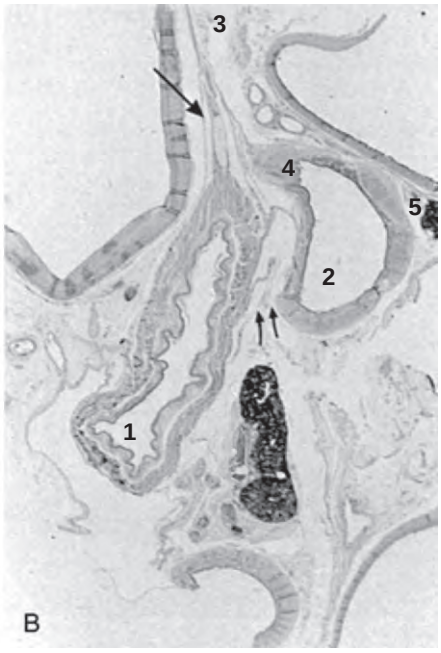


Figure 2–5. **A** and **B**, Example of the tiny fiber membranes that connect the esophagus (1), trachea (2), pleura (3), tracheal membrane (4), and cartilaginous structures (5). At their insertions, the fiber elements fan out to deep finger-shaped extensions between the muscular bundles of the esophagus (*arrow*) and into the membranous part of the trachea (*double arrows*). This texture, in conjunction with the elasticity of the membranes, certainly provides adequate adjustment during movement of the esophagus. In case of rapid pull, the fibers eventually tear off the tissues in which they are anchored (human esophagus, transverse section, hematoxylin and eosin stain). (Courtesy of Huber, Haeberle, and Liebermann-Meffert, Munich.)

from a fascia, the PEM in general is relatively strong. It splits into two sheets (Fig. 2–8). One sheet extends 2 to 4 cm upward through the hiatus, where its fibers traverse the esophageal musculature to insert on the submucosa.[10,14] The other sheet passes down across the cardia up to the level of the gastric fundus, where it blends into the gastric serosa, the gastrohepatic ligament, and the dorsal gastric mesentery (see Figs. 2–3 and 2–7). Although there are sparse attachments via elastic cords in the pattern shown in Figure 2–8, the PEM is clearly some distance away and separated by loose connective tissue and fat accumulation from the musculature of the gastroesophageal junction (see Fig. 2–7). This structural arrangement allows the terminal esophagus and the junction to move in relation to the diaphragm and to "slip through the hiatus like in a tendon sheath."[15] With

advancing age, the elastic fibers are replaced by inelastic collagenous tissue, and the adhesion of the PEM to the lower portion of the esophagus loosens,[14] which leads to loss of pliability. Disruption of the anchoring structures of the cardia and the proximal part of the stomach in conjunction with a wide hiatus may result in herniation of the gastroesophageal junction and the cardia, or even parts of the stomach, into the mediastinum. Abnormal anchoring of the PEM in youth and pathologic accumulation of adipose tissue in the separating connective tissue space between the PEM and the cardia musculature are thought to contribute to the development of a hiatal hernia.[14]

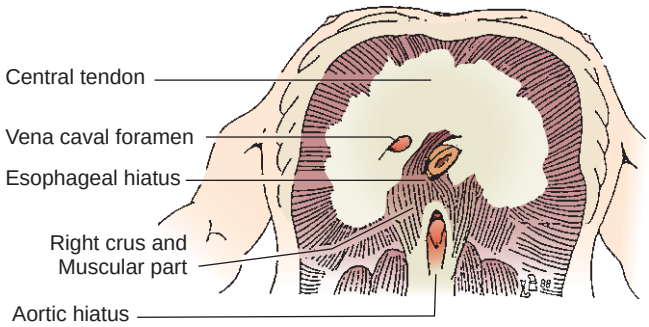


Figure 2–6. Diaphragm and esophageal hiatus viewed from the abdominal aspect.

Selected Topographic Relationships and Surgical Risk Areas

Neck

Ventral to the cervical esophagus lie the fibrous membranes that unite the adjacent hoops of the tracheal cartilage (Fig. 2–9). Note that only an inconspicuous amount of areolar connective tissue—if any—separates the two structures (see Figs. 2–5 and 2–9). Malignant

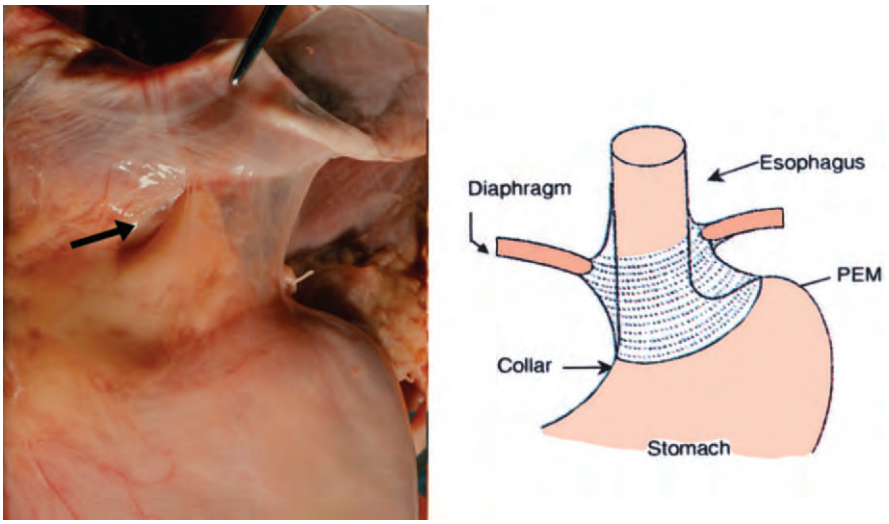


Figure 2–7. The phrenoesophageal membrane (PEM). The lower component of the membrane inserts on the gastric fundus. On the *left*, the diaphragm is held up with forceps. Diaphragmatic decussating fibers (*long arrow*) and a submembranous inlay of adipose tissue (*short arrow*) are seen. The PEM wraps the esophagogastric junction with a wide membranous collar. (Specimen and photo courtesy of Liebermann-Meffert, Munich.)

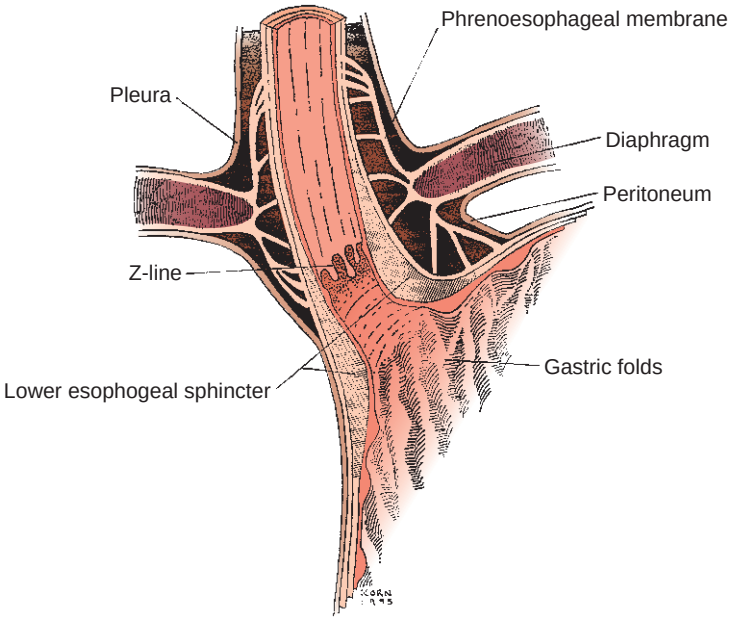


Figure 2–8. Diagram of the tissue organization and supporting structures at the esophagogastric junction. The esophagus is opened alongside the greater and lesser curvatures. The luminal aspect is displayed from the left side. The fiber elements that attach the phrenoesophageal membrane to the muscle wall of the terminal esophagus are shown. The fibers equal those shown in Figure 2–5. (Courtesy of Dr. Owen Korn, Munich and Santiago di Chile.)

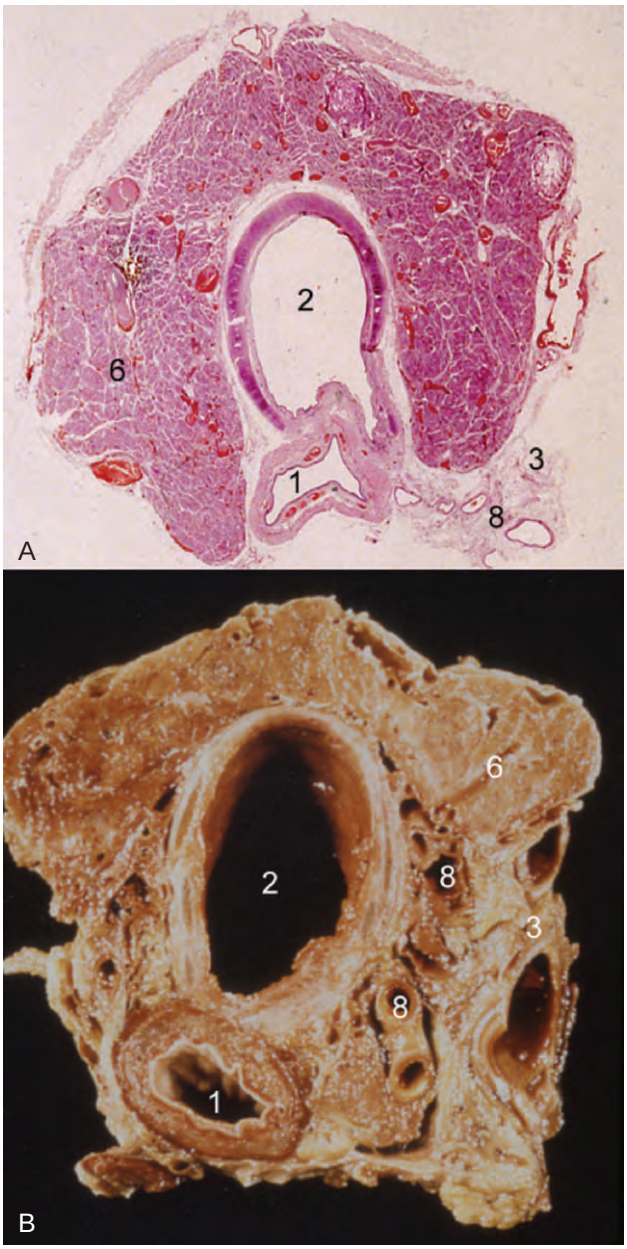


Figure 2–9. Transverse section through the neck and upper part of the chest of a human autopsy specimen viewed from a cranial aspect. 1, Esophagus; 2, trachea; 3, pleura; 6, thyroid gland; and 8, vessels. The histologic section shows the esophagus still in the midline posterior position (**A**), whereas on the more distal level of the macroscopic cut surface (**B**), the esophagus has shifted toward the left. Note the intimate local relationship between the esophagus and the trachea. (From Liebermann-Meffert D: Funktionsstörungen des pharyngo-ösophagealen Übergangs: Funktionelle und chirurgisch orientierte Anatomie. In Fuchs KH, Stein HJ, Thiede A [eds]: Gastrointestinale Funktionsstörungen. Berlin, Springer, 1997, with permission.)

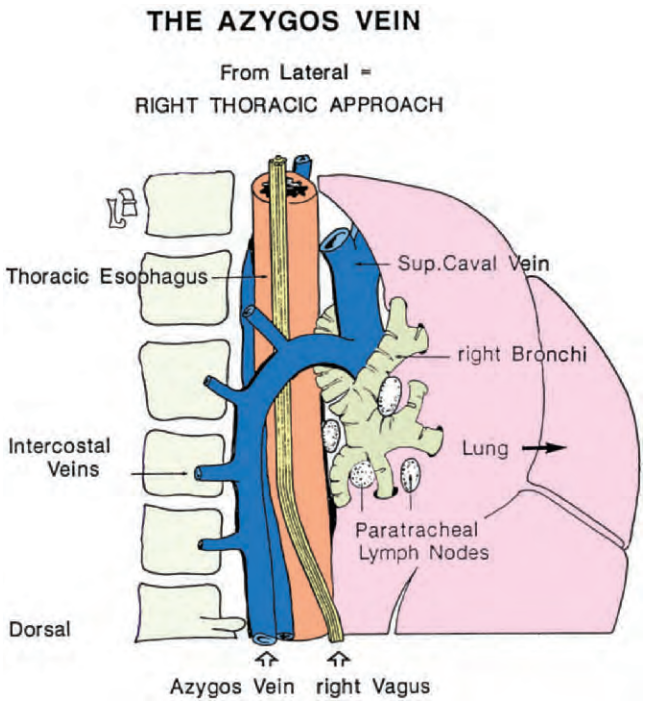


Figure 2–10. The position and relationships of the azygos vein, the thoracic duct, and the vagus nerve are shown from a right lateral aspect.

tumors are known to spread from the trachea to the esophagus and vice versa. Clinically, such spread results in an "acquired fistula."[16-18] Unfortunately, it appears that the lack of interposed connective tissue between the two organs predisposes to this unlucky event. Remember that a tracheoesophageal fistula after either an instrumental perforation, esophagectomy, or chemotherapy and irradiation in this inherently weak area is a catastrophic problem for both the patient and physician.[16-19]

Chest

Between the thoracic inlet and the tracheal bifurcation (which lies at the level of the fifth thoracic vertebra), the esophagus retains its intimate relationship to the trachea ventrally and to the prevertebral fascia posteriorly (see Fig. 2–2). The mediastinal pleura, the lungs, and their hila are positioned on both sides. On the right lies the subclavian artery and the azygos vein, which arches over the right main bronchus to end in the superior vena cava (Fig. 2–10). When performing transthoracic esophagectomy, surgical access for safe removal of the esophagus is preferably through the right side of the chest, and the azygos vein must usually be divided before the esophagus can be dissected free (see "Suggested Readings"). The primarily right side–positioned thoracic duct crosses behind the esophagus just above the arch of the azygos vein at the level of T4 to T5. Structures on the left of the esophagus are the aortic arch and the aorta, which subsequently turns to the midline and travels in a posterior course behind the esophagus (see Fig. 2–2). In front of

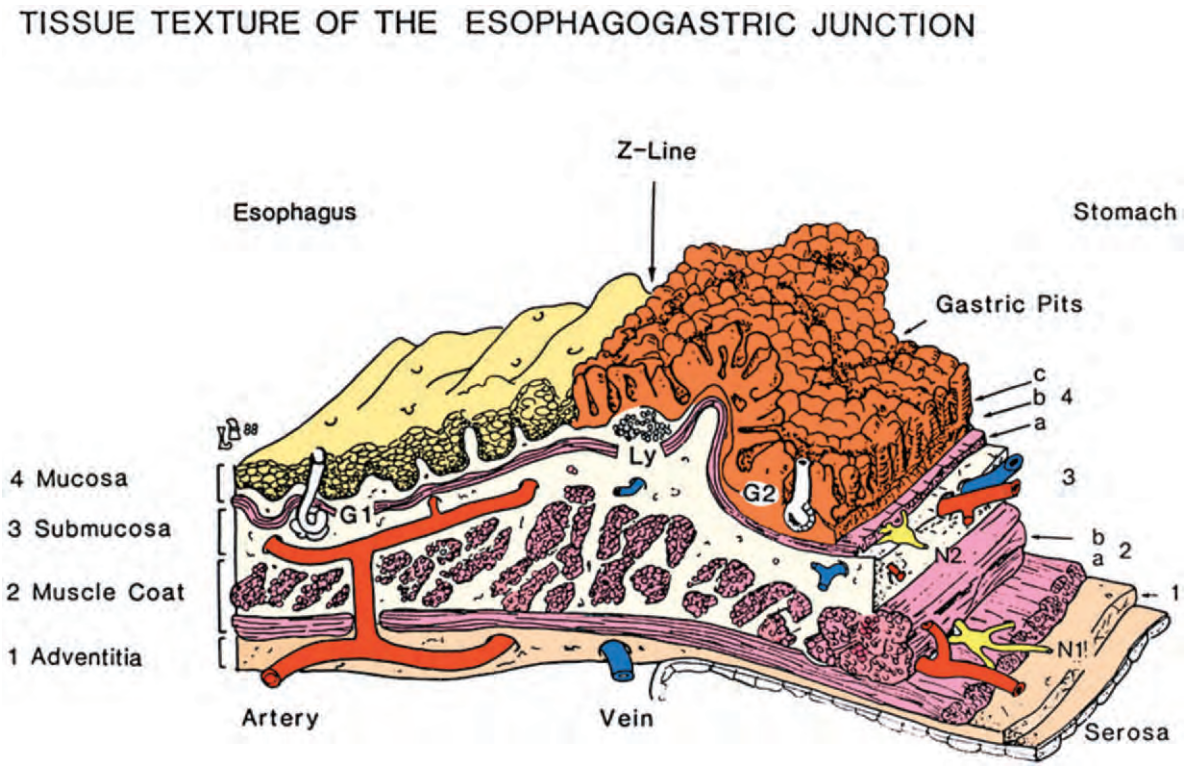


Figure 2–11. Wall structure at the esophagogastric junction. The tunica muscularis is composed of both a longitudinal (2a) and a circular layer (2b). a, muscularis mucosae; b, lamina propria; c, epithelium; G1, esophageal glands; G2, gastric glands; Ly, lymph vessels; N1, myenteric plexus; N2, submucous nerve plexus.

the esophagus are the lung hilum and the heart. The pleura on the left side of the mediastinum may occasionally extend behind the esophagus. Both vagi accompany the esophagus as it passes through the hiatus at the level of the 10th thoracic vertebra.

Abdomen

In the abdomen, part of the left lobe of the liver lies ventral to the esophagus. The two diaphragmatic crura are lateral and posterior. The inferior vena cava is lateral to the right crus, whereas the aorta is posterior to the left crus. The cranial pole of the spleen is in close relationship to the terminal esophagus (see Fig. 2–2). Other vessels and nerves that supply the esophagus and the adjacent organs are discussed later in this chapter.

Constituents and Tissue Organization of the Foregut

The basic tissue organization of the esophagus and cardia is shown in Figure 2–11.

TISSUES

Tunica Adventitia

This thin coat of loose connective tissue envelops the esophagus, connects it to adjacent structures, and contains small vessels, lymphatic channels, and nerves (see Fig. 2–11).

Tunica Muscularis

Esophageal Body

Muscular Arrangement The tunica muscularis coats the lumen of the esophagus in two layers, the fibers of which follow a diametric course: the external muscle layer parallels the longitudinal axis of the tube, whereas the muscle fibers of the inner layer are arranged in the horizontal axis (Fig. 2–12). For this reason, these muscle layers are classically called longitudinal and circular, respectively.

The *longitudinal layer* originates from the dorsal plane of the cricoid cartilage as shown earlier in Figure 2–4. Its muscular bundles fan out in a posterior direction, with an area of circular muscle left vacant—Laimer's triangle—before they wrap the esophagus entirely (Figs. 2–13 and 2–14; see also Fig. 2–11).[8,20] As long bundles, they run in a straight course down the esophageal tube and cross the gastric inlet (see Fig. 2–12).

The *circular layer* begins at the level of the cricoid cartilage. In their descent, the short fibers of the inner muscular layer form imperfect circles with overlapping ends, as illustrated in Figures 2–12 and 2–13.[8,20]

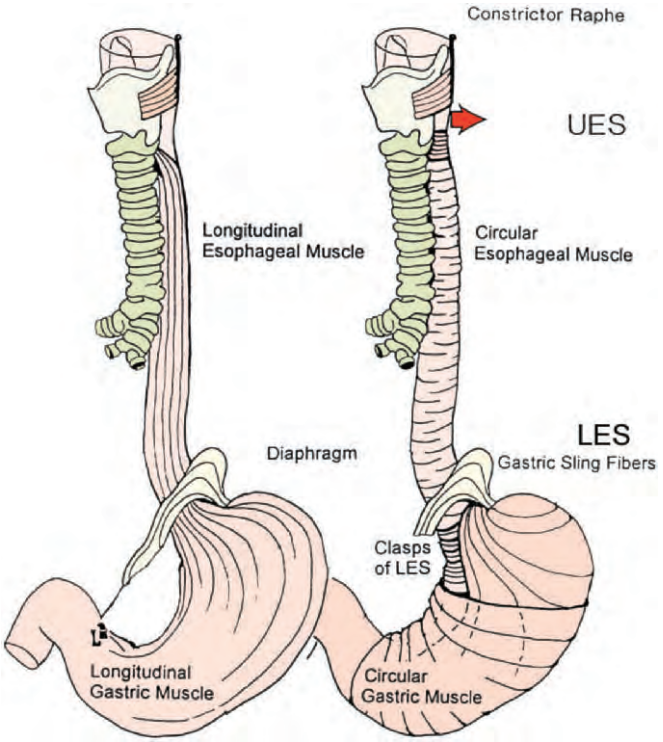


Figure 2–12. Architecture of the longitudinal and circular muscle layers across the esophagus, stomach, and respective junctions. LES, lower esophageal sphincter; UES, upper esophageal sphincter.

Muscle Types: Striated Versus Smooth It is generally accepted that the striated musculature behaves different from smooth muscle. Both types of muscle are present in the esophagus. The question has been raised of how the striated and smooth muscle is distributed in the wall of the esophagus. When systematically examining serial histologic sections of the esophagus from 15 individuals,[21] the authors found exclusively striated musculature in the pharynx and particularly in the cricopharyngeal muscle, which of course is the upper esophageal sphincter muscle (UES). The first sparse smooth muscle fascicles appear 2 to 3 mm caudal to the UES. Farther caudally, progressively more and more smooth muscle bundles replace the striated muscle in both the external and internal layers. The transition between both types is neither abrupt nor confined to individual muscle bundles and lacks any distinct anatomic border (Fig. 2–16).[10,21] Caudal to the tracheal bifurcation, no striated muscle elements are seen any more. With regard to sphincter function, it might be of interest to be aware that the muscle type of the UES differs completely from that of the LES!

The muscularis mucosa is composed uniquely of smooth muscle fibers throughout the entire esophagus.

Esophageal Sphincters

Zones of increased pressure in the esophagus have been verified, one at the upper and the other at the lower end. Diverse factors and mechanisms are suggested as the cause of the sphincter pressure, but ultimately, all remain disputable. This has prompted us to reinvestigate the human muscle morphology of the esophagus and both sphincters with special techniques. The results have been published previously in detail,[8,9,20,22] and the findings are presented in abridged version in the following two sections.

Structural Counterpart of the High-Pressure Zone: The Upper Esophageal Sphincter The UES is manometrically a 2- to 4-cm-long zone of elevated pressure[23] and marks the entrance into the esophagus. The high pressure results from contraction of the cricopharyngeus muscle. This semicircular muscle originates from the lateral cricoid processes (see Figs. 2–13 and 2–14) and closes the esophageal opening by exerting pressure toward the posterior plane of the cricoid cartilage. This arrangement accounts for the asymmetric pressure profile in manometric measurements.[23-25] The position of the cricopharyngeal muscle at the end of the pharynx implies that the structure is a "lower pharyngeal" rather than an "upper esophageal" sphincter.

Muscular Counterpart of the High-Pressure Zone: The Lower Esophageal Sphincter The LES is manometrically a 3- to 5-cm-long zone of elevated pressure and marks the end of the esophagus and the entry into the stomach.[26] Biochemically, the muscle of this area behaves differently from the muscle above and below it.[2,24,27] Markers applied surgically to these muscles in a simultaneous radiomorphologic study have shown that this high-pressure zone correlates with the thickened musculature at this site.[20,22] The high pressure results from contraction of the special muscle organization at this location.

It is unfortunate that fresh muscle tissue inevitably retracts when cut through, in particular, hollow organs such as the intestinal tube. Distorted muscle architecture escapes critical examination; sphincters can neither be palpated nor compared with the neighboring muscle wall. To circumvent this dilemma, the authors used en bloc fixation of the chest and upper abdominal organs to study this anatomic situation in autopsy specimens.[20,22] Such study allowed macroscopic measurement of the muscle thickness of the LES in order to compare it with that of the esophageal body and stomach. Another group of specimens was used to study the respective muscle arrangement.[20,22] The results indicated that the muscular sphincter was the equivalent of the physiologic high-pressure zone (Fig. 2–15).

We described in this paper and depicted in detail[20] that approximately 3 cm cranial to the junction with the stomach, the imperfect muscle circles of the circular layer (see Fig. 2–12) increase in number and result in a stepwise, significant thickening ($P < .001$) of the terminal esophageal musculature.[10,20] This transition is consistent with conspicuous remodeling of the muscle architecture, specifically, asymmetric rearrangement of the muscle fibers of the inner layer (see Figs. 2–12 and 2–15). The bundles on the side of the lesser curvature retain their orientation and form short muscle clasps, whereas those on the greater curvature change to

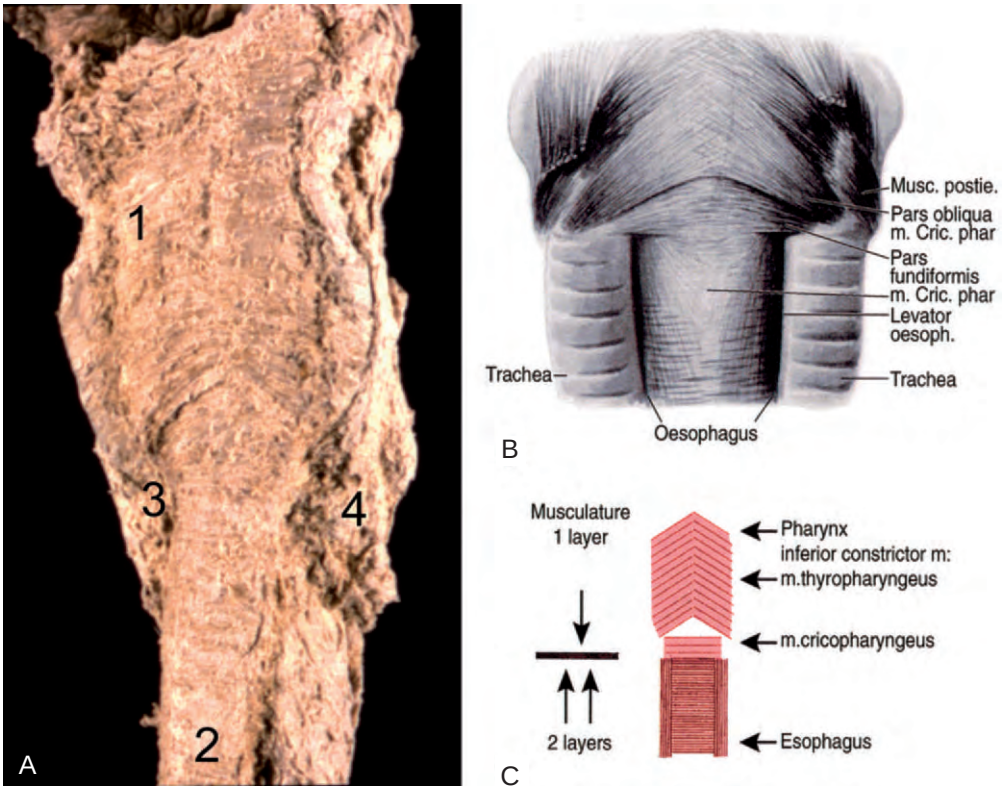


Figure 2–13. Structures at the pharyngoesophageal junction viewed from a posterior aspect. They are shown in a human dried-fiber specimen (**A**) (by Liebermann-Meffert), of a schematic drawing of an anteriorly opened and unfolded specimen (**B**) (by Killian), and in a simplified diagram of the muscle organization (**C**). The muscular arrangement of the inferior constrictor of the pharynx (1) confirms Killian's observation of the tile-shaped arrangement of the bundles of the inferior constrictor muscle (Killian G: Z Ohrenheilk 55:1, 1908). With respect to the junction, two features should be emphasized: (a) the change of one muscle layer at the pharynx (1) into two at the esophagus (2) just caudal to the cricopharyngeal muscle (3) (upper esophageal sphincter); (b) the cricopharyngeal muscle is part of the pharynx by position and anatomic characteristics. 4, Residual tissue from the removed thyroid gland. (From Liebermann-Meffert D: Funktionsstörungen des pharyngo-ösophagealen Übergangs: Funktionelle und chirurgisch orientierte Anatomie. In Fuchs KH, Stein HJ, Thiede A [eds]: Gastrointestinale Funktionsstörungen, Berlin, Springer, 1997, with permission.)

become the oblique gastric sling fibers. It has been suggested that myotomy for achalasia should preferably be performed between the muscle clasps and gastric sling fibers to preserve the complete strength of the sling (i.e., maintain sphincter competence).[28]

The specific arrangement of the musculature, which we have shown in Figures 2–12 and 2–15, also accounts for sphincter asymmetry.[9,20,22,29] Asymmetry of the high-pressure zone at this position has likewise been proved manometrically.[26] The manometric pressure image of the lower esophageal high-pressure zone, obtained by a three-dimensional computerized vector diagram, matches the muscular asymmetry at the human cardia perfectly (see Fig. 2–15).[30-32] Surgical removal of these structures by partial or total myectomy was shown to significantly reduce the specific sphincter pressure values of this muscle arrangement as recorded on manometry.[2,28,33] Displacement of the LES into the chest through the diaphragm or dissection of the PEM produced no effect on the pressure values of the sphincter in long-lasting animal experiments.[22]

Tela Submucosa

The submucosa is the connective tissue layer that lies between the muscular coat and the mucosa. It contains a meshwork of small blood and lymph vessels, nerves, and mucous glands. The deep esophageal glands are small branching glands of a mixed type, and their ducts pierce the muscularis mucosae (see Fig. 2–11).

Tunica Mucosa

The mucous layer is composed of three components: the muscularis mucosae, the tunica propria, and the inner lining of nonkeratinizing stratified squamous epithelium (see Fig. 2–11). The muscularis mucosae forms the long mucosal folds that run in the longitudinal axis of the tube and shapes the small transverse ripple folds at the cardia.[20,34] All these folds disappear on distention of the esophageal lumen. The tunica propria contains areolar connective tissue, blood vessels, and lymph channels derived from the lower level of the mucosa. At

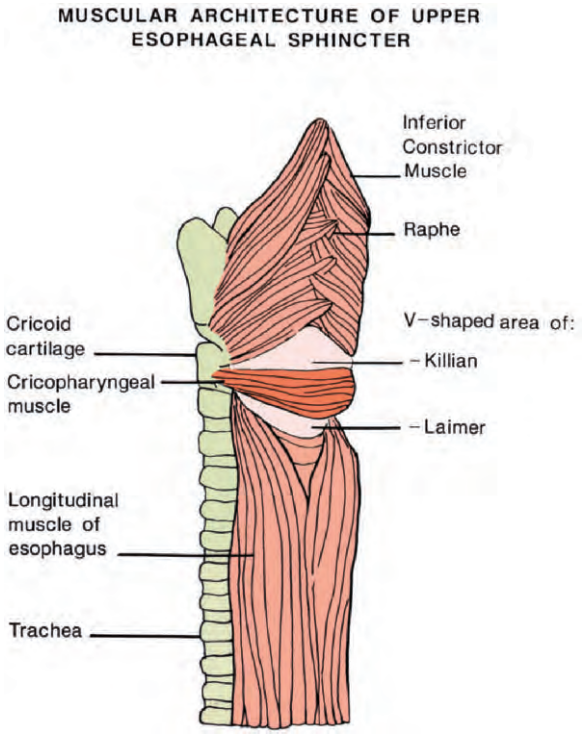


Figure 2–14. Schematic drawing of the structures at the pharyngoesophageal junction seen from the posterior aspect. The location of Killian's and Laimer's triangles is indicated; Zenker's diverticula develop cranial to the cricopharyngeal muscle, and the upper esophageal sphincter is located caudal to the V-shaped area of Killian.

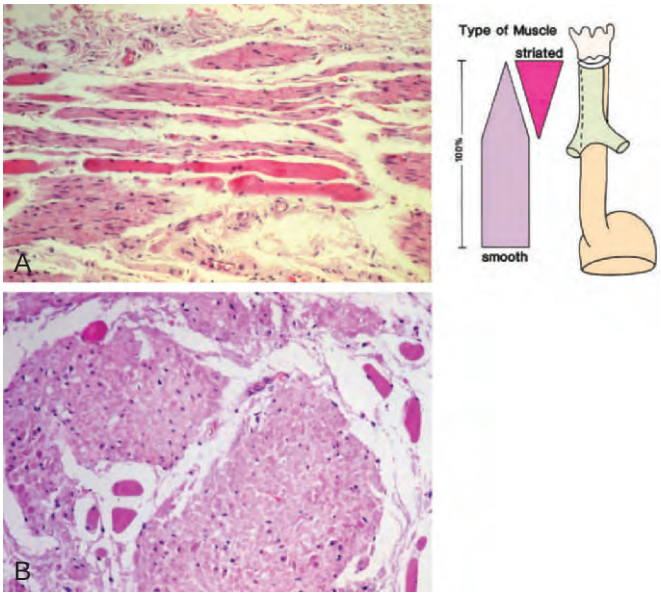


Figure 2–16. Histologic specimens of the human esophagus taken in transverse (**A**) and longitudinal (**B**) sections 4 cm above the tracheal bifurcation cranial to the transition between striated and smooth muscle. Individual striated muscle fibers are interspersed among smooth muscle strands. The diagram shows the distribution of striated and smooth muscle in adult esophagus as evaluated from consecutive serial histologic sections of 13 esophagi. (Specimen and photo courtesy of Liebermann-Meffert, Geissdörfer, and Winter, Munich.)

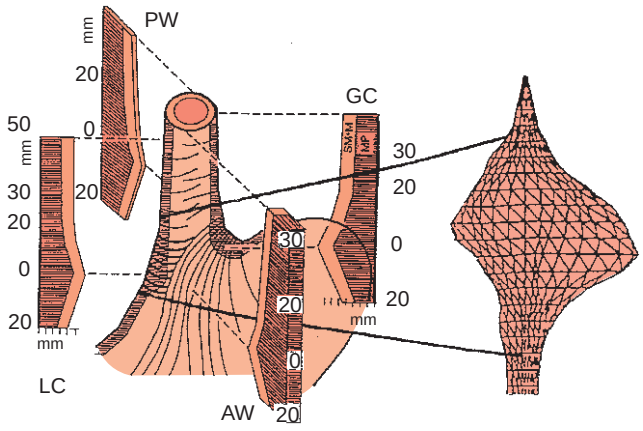


Figure 2–15. Schematic drawing showing the correlation between radial muscle thickness (*left*) and a three-dimensional manometric pressure image (*right*) at the gastroesophageal junction. Muscle thickness across the gastroesophageal junction at the posterior gastric wall (PW), greater curvature (GC), anterior gastric wall (AW), and lesser curvature (LC) is shown in millimeters. Radial pressure at the gastroesophageal junction (in mm Hg) is plotted around an axis representing atmospheric pressure. Note the marked radial and axial asymmetry of both the muscular thickness coinciding with the manometric pressure profile.

the esophagogastric junction, a short 0.5- to 1.0-cm area of superficial (mucous) glands that resemble cardiac glands is a consistent finding.[35,36] Heterotopic gastric mucosa may occasionally also be found at the upper end of the esophagus.[37]

Clinically, the surface of the esophageal mucosa is reddish but becomes paler toward the lower third of the esophagus. The smooth esophageal mucosa can easily be distinguished from the dark mammillated gastric mucosa. The mucosal transition at the squamocolumnar junction is an objectively recognizable reference point for the endoscopist (see Savary and Miller in "Suggested Readings"). On fresh anatomic specimens, the transition is characterized by a serrated, but abrupt demarcation line. The so-called Z-line is located at or immediately above the gastric orifice. Any proximal extension of gastric- or intestinal-type columnar epithelium is considered pathologic and attributed to long-standing reflux of gastric contents causing chronic, severe esophageal mucosal damage.[38] The transition between the two types of mucosa is a "mucosal junction" wherever it is positioned. By no means should it be considered a "sphincter" (as the mucosal transition at the cardia is occasionally termed by gastroenterologists). The term *sphincter* by traditional anatomic definition is restricted to the presence of muscular constrictor structures.

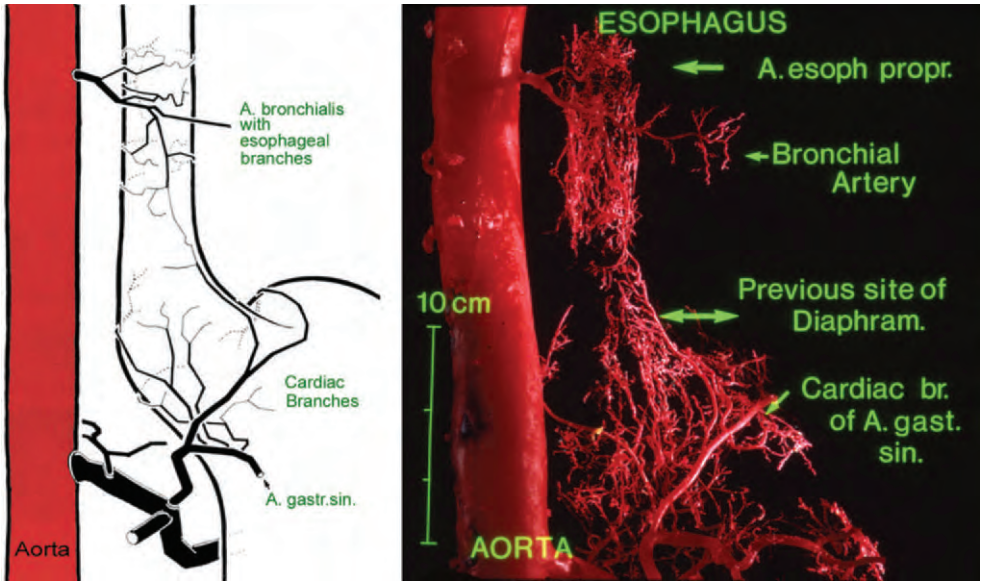


Figure 2–17. Arterial cast showing the vascular supply to the middle and lower portions of the esophagus. Note that the esophageal branch derives from the bronchial artery. During esophageal resection, it should be ligated close to the esophageal wall so that the blood supply of the left main bronchus is not jeopardized. In this context, it should be mentioned that the esophagus shares its blood supply with other organs: the thyroid gland, the trachea, the stomach, and the spleen.

STRUCTURES SUPPLYING THE ESOPHAGUS

Arterial Supply

Extraparietal Sources

Knowledge of the blood supply of the foregut assumes increasing importance. Adequate display of the esophageal vessels is technical difficult, and inadequate technique has caused errors in evaluation and description. Angiograms do not outline the arterial pattern well because of the overlying arteries associated with other structures. Large en bloc corrosion casts, however, produce realistic three-dimensional replicas of the macrovascular and microvascular systems, as seen in Figures 2–17 and 2–18. Such casts establish that the esophagus is an organ of "shared vasculature" because it receives its blood through vessels feeding mainly other organs such as the thyroid gland, trachea, and stomach.[6] There are three principal extraparietal arterial sources for the esophagus (Fig. 2–19). In the neck, the upper superior and inferior thyroid arteries send small descending arteries to the cervical esophagus. At the level of the aortic arch, a group of three to five tracheobronchial arteries arise from the concavity of the arch and give rise to several tracheoesophageal tributaries. Small proper esophageal arteries most often arise from the anterior wall of the thoracic aorta via a larger bronchial artery (see Fig. 2–17). At the cardia, the left gastric artery gives off up to 11 branches that ascend and supply the anterior and right aspects of the lower part of the esophagus (see Fig. 2–17).[6,39] Vessels arising from the splenic artery supply the esophageal wall and parts of the greater curvature from the posterior aspect as seen in Figures 2–17 and 2–19. Two facts became obvious through Liebermann-Meffert and colleagues' studies[6] that had not been appreciated before: all the major arterial vessels divide into minute branches at some distance from the esophageal wall (see Fig. 2–17), and it appears that such small esophageal tributaries, when torn from the esophagus, have the benefit of contractile periesophageal hemostasis.

Intraparietal Vascularity

Previous claims that essential nutritional vessels arise from the intercostal or phrenic arteries or directly from the aorta could not be confirmed.[6] The minute extraesophageal branches enter the esophageal wall, pass through the tunica muscularis, and give off branches to the muscle before they form the wide vascular plexus within the submucosa and mucosa as seen in Figure 2–18. The clear continuity of the vessels and the rich anastomosing intramural vascularity[6,40,41] explain why a mobilized esophagus retains an excellent blood supply over a long distance[42]; on the other hand, the extremely small caliber of the nutritional vessels also explains leaks after esophagointestinal anastomosis in the event of mechanical damage to the microvascular circulation.

Blunt pull-through stripping of the esophagus without thoracotomy for cancer of the cardia has found an increasing number of advocates.[4,6,11,41] It is described as a relatively safe procedure[6,11,41] that involves minor blood loss, provided that dissection is undertaken close to the esophagus. When hemorrhage has occurred after stripping of the esophagus, it was most often from the site of malignant tumor fixation and, in particular, from injury to the azygos vein.

Venous Drainage

Intraparietal Veins and Plexuses

The most comprehensive macroscopic description of esophageal venous drainage was presumably presented by Butler[43] in 1951. He classified the esophageal veins

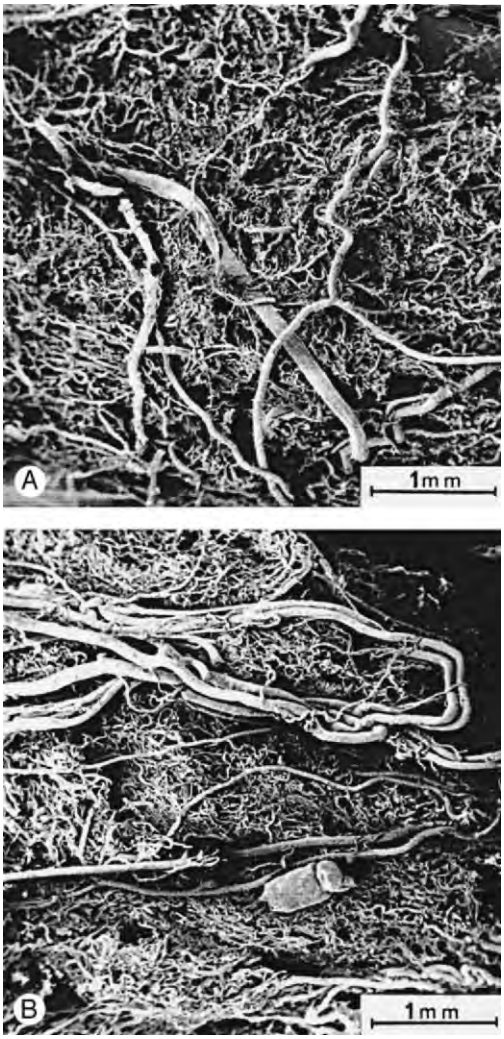


Figure 2–18. Scanning electron micrographs of complete vascular casts using a specially created resin without particles. The microvascular supply in the esophageal submucosa in the midesophagus (**A**) and in the cardia (**B**) is displayed. The vessels form a polygonal meshwork overlying the mucosa. (Courtesy of Duggelin and Liebermann-Meffert, Basel.)

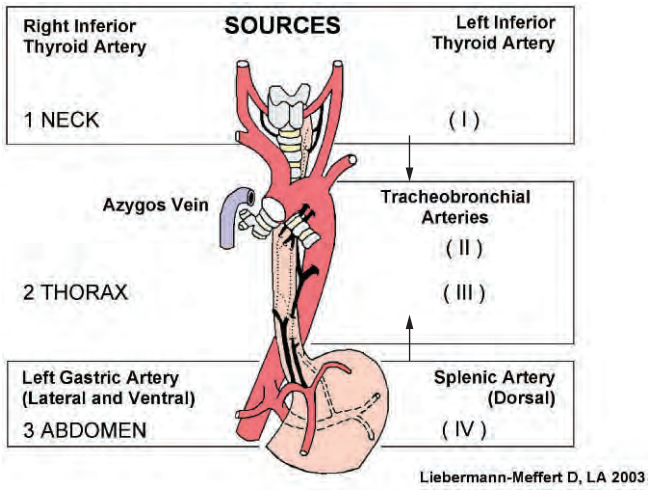


Figure 2–19. Extravisceral sources of arterial blood supply to the esophagus, intramural anastomoses (*dotted line*), and topographic relationship of the azygos vein to the esophagus and tracheal bifurcation. The *arrows* indicate the direction of flow.

into *intrinsic* and *extrinsic* veins, referring to intraesophageal and extraesophageal wall veins. The intraesophageal veins include a subepithelial plexus in the lamina propria mucosa that receives blood from the adjacent capillaries. Aharinejad et al.[40] described two small veins that usually accompany the arteries in the lamina submucosa, pierce the muscular wall of the esophagus together with the perforating arteries, and then form the extramural veins at the surface of the esophagus.[40] No valves were found within the esophageal venous circulatory system.[40,43]

It is clinically noteworthy that two clearly delineated venous plexuses are present beneath the mucosa of the hypopharynx. These plexuses had been described in 1918 by Elze and Beck,[8] but their report had not hitherto been well appreciated (Fig. 2–20). One plexus lies on the dorsal aspect of the inferior constrictor muscle, and the other is in the midline posterior to the cricoid cartilage. This is exactly at the level of the pharyngoesophageal junction. In the 10 specimens restudied by Liebermann-Meffert,[8] the plexuses were located within an extremely thin submucosa; both were 2 to 3 cm broad and 4 cm long. The veins were up to 4 mm thick and of mostly longitudinal orientation, similar to Figure 2–20. The plexuses receive blood from the mucosa of the laryngopharynx and esophagus and drain into the thyroid and jugular veins. Considered to account for the postcricoid impression on the esophagus (for reference, see legend for Fig. 2–20), they may be involved in the "globus sensation" in patients with venous stasis and tissue swelling. It is tempting to postulate that the plexuses also contribute to some extent to the competence and action of the UES.

It may be of further clinical interest that a specialized venous arrangement, clearly documented by Vianna et al., is present at the terminal esophagus (Fig. 2–21). It has been suggested that these venous anastomoses possibly constitute a communication between the azygos and the portal systems. The intermediate "palisade zone" (see Fig. 2–21) is thought to act as a high-resistance watershed between both systems that provides bidirectional flow. Anastomoses between the systemic and the portal systems are found in the submucosa and lamina propria of the lower end of the esophagus and may enlarge in patients with portal venous obstruction to form varices.

Extraparietal Veins

The extrinsic veins drain into the locally corresponding large vessels: the inferior and superior thyroid veins, the azygos and hemiazygos veins, and the gastric and splenic veins. One point of surgical interest is that because of the

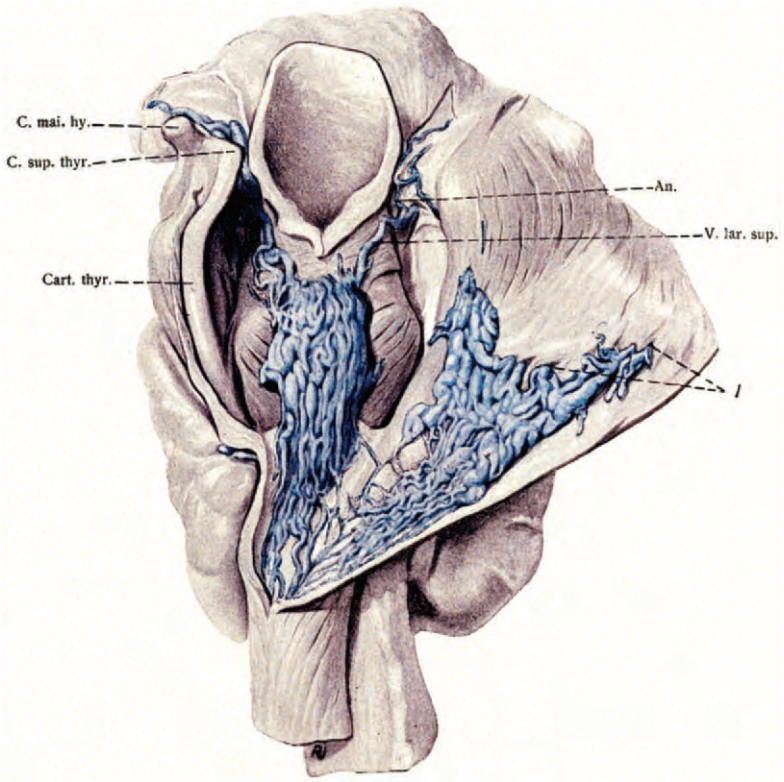


Figure 2–20. The hypopharyngeal-endoesophageal venous plexuses, which are located just underneath the mucosa. Original drawing. (From Elze C, Beck K: Die venösen Wundernetze des Hypopharynx. Z Ohrenheilk 77:185, 1918.)

proximity to the hilum of the lung and its lymph nodes, the azygos vein is one of the initial structures to become involved by extramural spread of tumors of the midesophagus (see Fig. 2–10). In this situation, the azygos vein may easily be injured during esophageal resection. In particular, during blunt pull-through stripping, injury to this vein is a high-risk factor for fatal hemorrhage. Collateral circulation between the azygos vein and the hemiazygos vein is well known. However, the hemiazygos, the accessory hemiazygos, and the superior intercostal trunks may also form a vessel that does not connect with the azygos vein. The hemiazygos vein, if not ligated out, can be a source of severe bleeding when the esophagus is resected through a right thoracotomy.

Lymphatic Drainage

Initial Lymphatic Pathways

The lymphatic drainage in healthy individuals has been sparsely investigated. At present, the authors are conducting a study to demonstrate the pathways of the lymphatic drainage of the esophagus. The histologic picture of the initial lymphatics (as demonstrated by electron microscopy) resembles that elegantly shown by Lehnert in Figure 2–22 concerning the stomach.

Lymph capillaries may commence in the tissue spaces of the mucosa and then unite to form blind endothelial sacculations or channels (see Fig. 2–22). These initial lymphatics appear to originate exclusively in the region between the mucosa and the submucosa and form a network of collecting channels within the submucosa that run parallel to the organ axis (Fig. 2–23). Eventually, the plexuses give off branches that pass the muscle layers and empty into the collecting subadventitial and surface trunks. In contrast to the esophageal veins, all these channels possess valves (see Fig. 2–23).

Clinical Implication The concept that lymph flows in the submucosal channels more readily longitudinally than through the few transverse connections in the muscle (see Fig. 2–23) and that only finally does lymph flow through the subadventitial lymphatics and small ducts into the mediastinal lymph nodes is supported by the clinical observation that initial tumor spread follows the longitudinal axis of the esophagus within the submucosa rather than extending in a circular manner. A paucity of lymphatics within the lamina mucosa and the abundance of submucosal lymphatic channels[10] may explain why intramural cancer spreads predominantly within this layer. Unappreciated malignant mucosal lesions may be accompanied by extensive tumor spread underneath an intact mucosa, and tumor cells may follow the lymphatic channels for a considerable distance before they pass the muscular coat to empty into the lymph nodes. A tumor-free margin at the resection line, as confirmed from the anatomic point of view, does not guarantee radical tumor removal. This may be consistent with the relatively high postoperative recurrence rate at the resection line, including satellite tumors and metastases in the submucosa far distant from the primary tumor,[4] even if the margins at the resection line were previously tumor-free.

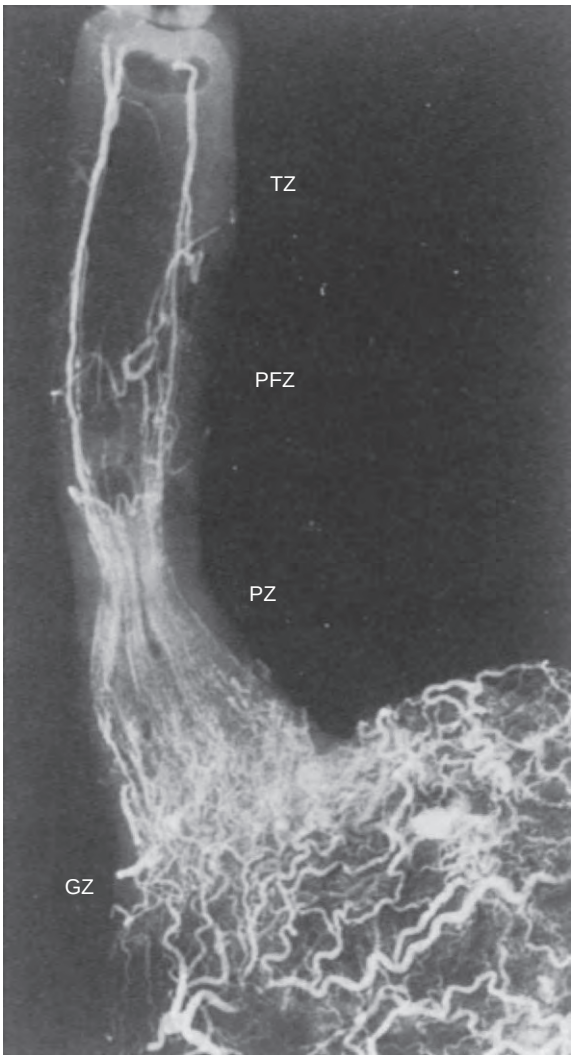


Figure 2–21. Radiograph of the venous circulation at the esophagogastric junction and the esophagus after injection with barium gelatin. This example shows the various zones of different venous architecture, such as the gastric zone (GZ), the palisade zone (PZ), the perforating zone (PFZ), and the truncal zone (TZ), as well as the irregular polygonal network of the proper gastric veins. (From Vianna A, Hayes PC, Moscoso G, et al: Normal venous circulation of the gastroesophageal junction: A route of understanding varices. Gastroenterology 93:876, 1987, with permission.)

From clinical observations in cancer patients,[4] one may deduct (see Fig. 2–24) that lymph from above the carina flows in a cranial direction into the thoracic duct or subclavian lymph trunks whereas lymph from below the carina flows mainly toward the cisterna chyli via the lower mediastinal, left gastric, and celiac lymph nodes. Flow may, however, change under pathologic conditions. When lymph vessels become blocked and dilated because of tumor invasion, the valves become incompetent and the flow reverses (see Figs. 2–22 and 2–23). This explains the retrograde and unexpected spread of some malignant tumors but limits the value of establishing pathways of normal flow.

Lymphatic Ducts and Lymph Nodes

The lymphatic ducts at the surface of a healthy esophagus are thought to empty into the regional lymph nodes. As has been postulated,[13] the thoracic esophagus drains into the paratracheal, tracheobronchial, carinal, juxtaesophageal, and intra-aorticoesophageal lymph nodes, and the abdominal esophagus empties into the superior gastric, pericardiac, and inferior diaphragmatic lymph nodes. Large, often dark lymph nodes normally accumulate around the tracheal bifurcation (Fig. 2–24). However, the author's study failed to display the classic chain of lymph nodes surrounding the esophagus as described in textbooks and illustrated by Netter.[13] Instead, 17 noncancerous autopsy specimens revealed only a small number of lymph nodes being prominent in the periesophageal tissue. This observation coincides with the report of Wirth and Frommhold,[44] who found mediastinal lymph nodes in only 5% of 500 normal lymphograms. Moreover, the authors microscopically identified multiple tiny lymph nodes with a diameter less than 1 mm located in the entire tracheoesophageal sulcus. It is conceivable that such small lymph nodes could increase in size when involved in inflammatory processes or tumor disease, thus augmenting the number of visible nodes. Furthermore, regional differences may potentially prevail.

Thoracic Duct

The thoracic duct begins at the proximal end of the cisterna chyli, at the level of the 12th thoracic vertebra, and passes up through the diaphragm via the aortic foramen. It then ascends through the posterior mediastinum, between the aorta on its left and the azygos vein on its right aspect, and continues left dorsal to the esophagus (Fig. 2–25; see also Fig. 2–10). At the level of the fifth thoracic vertebra and just above the arch of the azygos vein, the thoracic duct inclines to the left to become left side positioned with regard to the esophagus and spine.[44] Then it ascends lateroposteriorly parallel to the trachea and esophagus to convey the lymph into the bloodstream and terminates at the confluence between the left subclavian and jugular veins. There are, however, numerous anatomic variations.[13,44] The close local relationship of the delicate thoracic duct to the esophagus and trachea accounts for the occasional injury causing chylothorax during esophagectomy and cervical anastomosis.[11]

Innervation

Innervation of the esophagus is through the visceral (splanchnic) component of the autonomic nervous system. It consists of two parts, the sympathetic and the parasympathetic systems, that exert antagonistic influences on the viscera. The various pathways have been described in detail elsewhere.[24] The nerve trunks and the

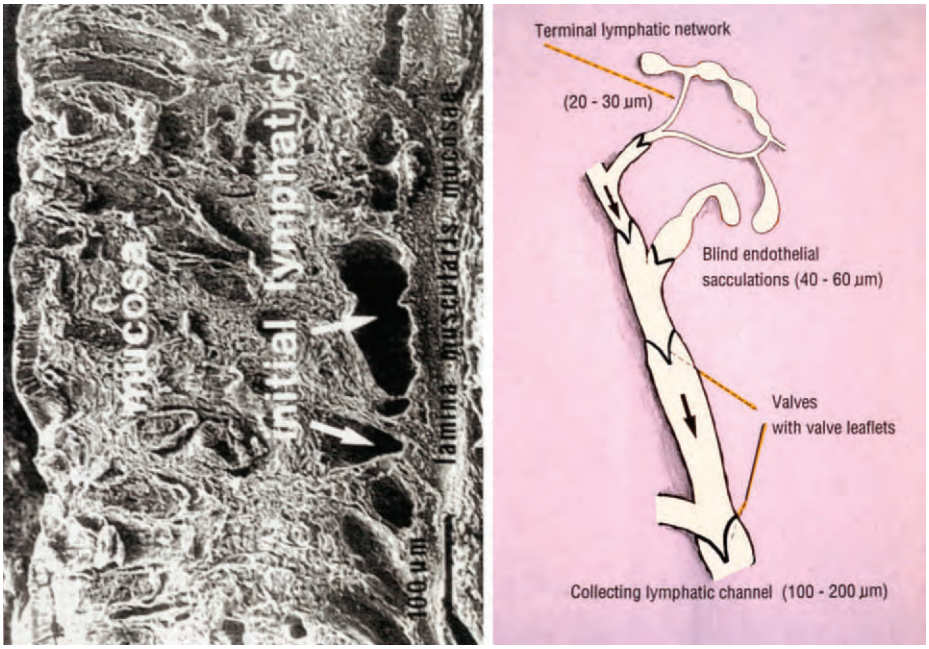


Figure 2–22. Initial lymphatics (*arrows*) between the lower border of the tunica mucosa and the tela submucosa seen on a histologic photomicrograph and in a schematic drawing. This view is taken from the gastric wall, but it also seems to be of relevance for the esophagus. (*Left*, from Lehnert T, Erlandson RA, Decosse JJ, et al: Lymph and blood capillaries of the human gastric mucosa. Gastroenterology 89:939, 1985.)

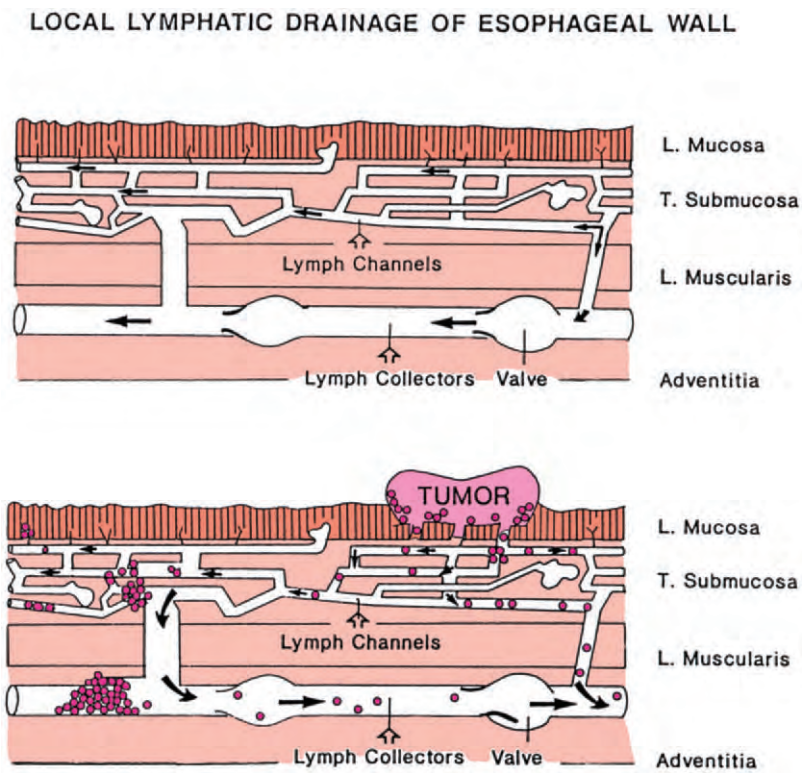


Figure 2–23. Lymphatic pathways in the esophageal wall. The suggested pattern of lymph flow is shown to explain the possible local and distal spread of tumor cells, including the block of distal lymphatics. The embryologic development and the presence and alignment of valves suggest this pattern of lymph flow, although it has never been substantiated experimentally up to now.

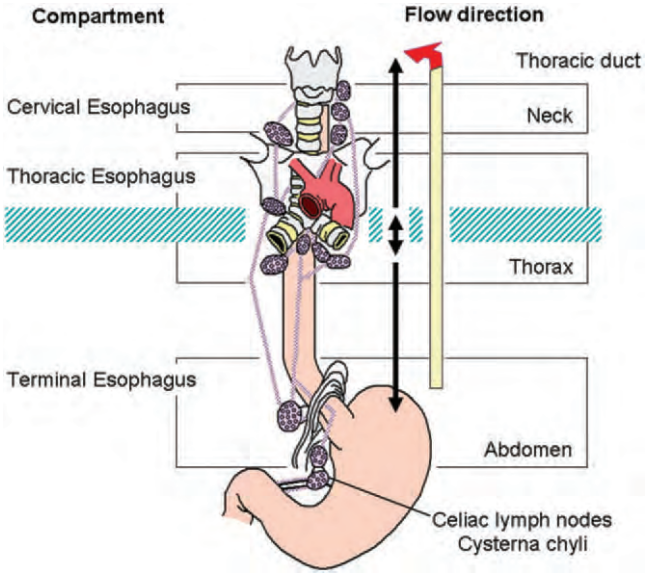


Figure 2–24. Knowledge of the direction of lymph flow and the position of major lymph nodes is essential for understanding the potential spread of an esophageal malignancy. Lymph from areas above the tracheal bifurcation drains mostly toward the neck, and that below the tracheal bifurcation flows preferentially toward the celiac axis. Lymph flow at the bifurcation appears to be bidirectional. The dimensions of the lymph nodes are out of scale. In the normal, nonmalignant condition, esophageal and mediastinal lymph nodes are difficult to discern because of their small diameter of only 3 to 7 mm. Lymph nodes that drain the lung are usually bigger and can be easily visualized by their carbon particle content.

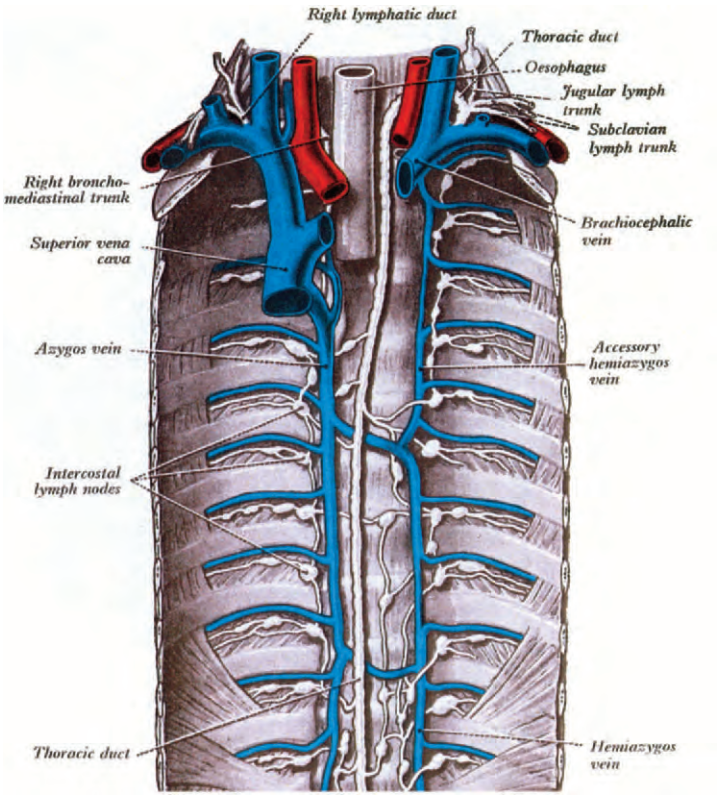


Figure 2–25. The upper thoracic and right lymphatic ducts. (From Warwick R, Williams RL [eds]: Gray's Anatomy, 35th ed. Edinburgh, Longman, 1973, p 727.)

principal branches are composed of parallel nerve bundles that contain efferent or afferent axons. The epineurium, a dense connective tissue sheath, surrounds the nerve trunk.

Extramural Innervation

The *sympathetic nerve* supply, according to the classic description, is via the cervical and thoracic sympathetic chain, which runs downward lateral to the spine (Fig. 2–26). The other sources of sympathetic supply to the middle and lower portions of the esophagus are the cardiobronchial and periesophageal splanchnic nerves, which derive from the celiac plexus.[13] Interconnecting with fibers of the parasympathetic cervical and thoracic plexus, the sympathetic nervous system also uses the vagus nerve as a carrier for some of its fibers.[13,24]

The *vagus nerve* is the 10th cranial nerve and is derived from the dorsal vagal nucleus. The fibers that supply the striated musculature in the pharynx and esophagus, however, derive from the nucleus ambiguus. The vagus is a mixed nerve that also carries sensory fibers from the superior ganglion and inferior ganglion (nodose ganglion). As thick trunks, the right and left vagus nerves descend bilaterally (see Fig. 2–26); they reduce their diameters by giving off fibers in the neck to the superior laryngeal nerves (SLNs), which innervate the pharynx and larynx musculature. The inferior (recurrent) laryngeal nerves (RLNs) originate within the chest. The right RLN leaves the vagus and turns dorsally around the subclavian artery (see Fig. 2–26). The left RLN leaves the vagus and circles around the aortic arch. On both sides, the RLNs ascend as slack cords that sinuously pass upward within the lateral peritracheal loose connective tissue, the left being closer to the tracheal groove than the right (Figs. 2–27 and 2–28).[12] The left RLN lies closer to the esophagus than the right does. Both RLNs give off 8 to 14 branches to the esophagus and trachea in equal distribution.[12] When stretched, they are 2.5 mm to 1 cm long. Toward the cranial aspect, the RLNs "disappear" beneath the thyroid glands, where the thyroid vessels, in an unpredictable manner, encircle the RLNs in the fashion displayed in Figure 2–29. They enter the larynx laterocaudad to the cricopharyngeal muscle (see Figs. 2–28 and 2–29; see also Fig. 2–4A). Except for the cricothyroids, they innervate all the muscles of the larynx via small branches.[12,45] Injury to the RLN is an unwelcome and not infrequent complication of operations on or near the upper thoracic and cervical esophagus. Because the RLN and SLN supply the same laryngeal

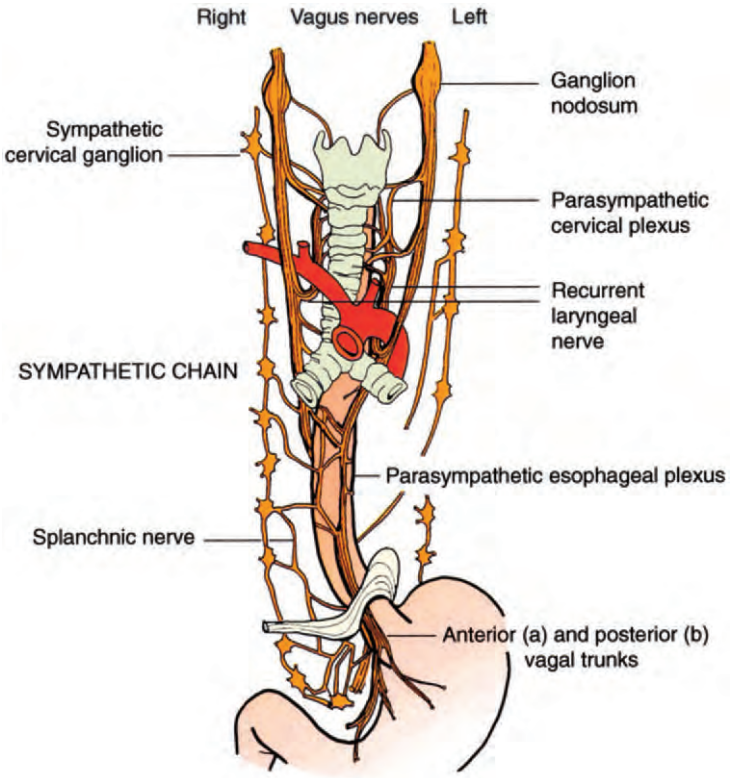


Figure 2–26. Sympathetic and parasympathetic nerve systems. The sympathetic system forms a chain of ganglia from the base of the skull to the coccyx. In the neck, the sympathetic chain is posterior to the carotid sheath. In the chest, it is found anterolateral to the bodies of the vertebrae. Both vagus nerves carry the parasympathetic innervation and travel along the esophagus. The locations of the right and left superior and inferior recurrent laryngeal nerves are shown.

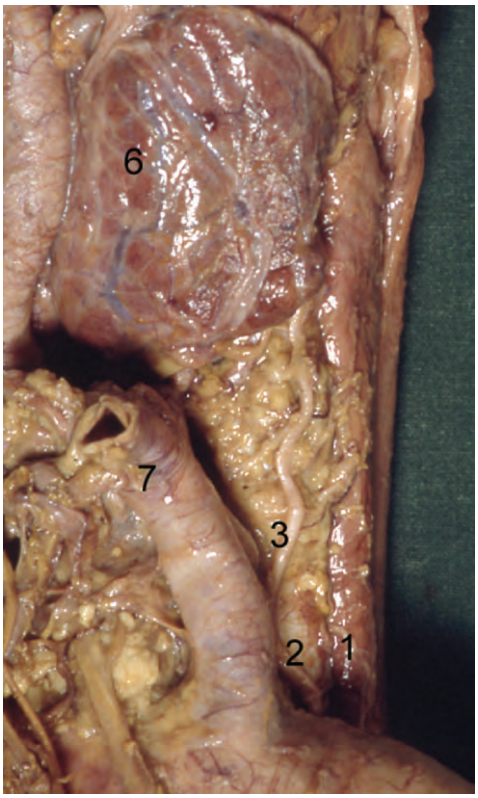


Figure 2–27. Meandering course of the left recurrent laryngeal nerve (3) shown before its dissection from the underlying peritracheal tissues (2). The thyroid gland (6) is still in place. 1, Esophagus; 7, left common carotid artery.

muscles, this twofold innervation may compensate for some sequelae of RLN injury. Displaying the RLNs (an important step in a number of neck operations[12,18,45]), dissecting the RLN branches close to the esophagus, and placing intestinocervical anastomoses as low as possible will certainly reduce RLN injury.[45]

The vagal trunks, at the level of the tracheal bifurcation and posterior to the lung hilum, give off numerous branches to form pulmonary plexuses. More distally, the vagal trunks separate into the coarse network of the anterior and posterior esophageal plexuses (see Fig. 2–26). Before they cross the diaphragm through the esophageal hiatus, these plexuses join again to form the anterior and posterior vagus nerves. The anterior branch has a number of anatomic variants and is usually found on the anterior esophageal wall, where it is visible underneath the PEM. The posterior vagus nerve is usually at some distance from the esophagus and to its right.

Intramural Innervation

The fine structure of the esophageal innervation is composed of a dense network of nerve fibers containing numerous groups of ganglia. The ganglia are located either between the longitudinal and circular muscle layers (Auerbach's plexus) or in the submucosa (Meissner's plexus). The ganglia of Auerbach's plexus are scattered throughout the entire esophagus and have a variable number of cells. However, the concentration of ganglion cells is greatest in the terminal esophagus and at the gastroesophageal junction.[13,24,34]

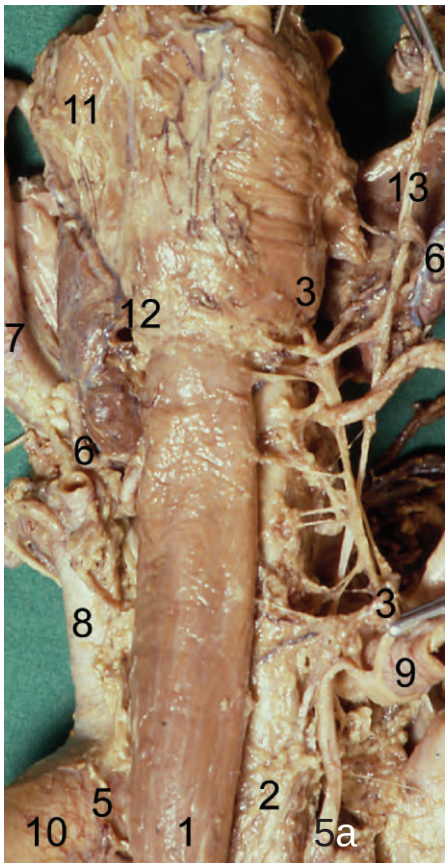


Figure 2–28. Posterior aspect of the muscular wall of the esophagus (1) and pharynx (11). The right recurrent laryngeal nerve (3), largely removed from its peritracheal tissue bed, is pulled down toward the lateral aspect behind its turning point (forceps) around the subclavian artery (9). The rami of the recurrent laryngeal nerve enter the lateral wall of the esophagus (1) and trachea (2). The left thyroid gland (6) is in its natural position, with the right gland displaced posteriorly. Underneath the lower lobe, the thyroid artery and its branches encircle the recurrent laryngeal nerves. The turning point of the left recurrent laryngeal nerve (5) is seen under the aortic arch (10). 7, Common carotid artery; 8, brachiocephalic trunk. Note the venous network on top of the pharyngeal muscle (11), the upper esophageal sphincter (12), the right vagus nerve (5a), and the phrenic nerve (13).

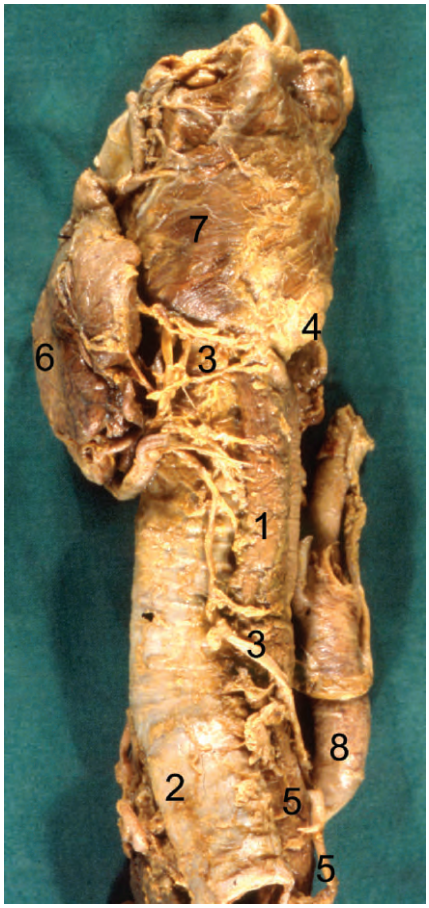


Figure 2–29. The course of the left recurrent laryngeal nerve (3) between the turning point from the vagus nerve (5) and its entry into the larynx is photographed from the left lateral aspect after removal from the peritracheal tissues. The attachments of the thyroid gland (6) are removed, and the gland is shifted posteriorly to display the left recurrent laryngeal nerve (3) and the vascular arrangement underneath. 1, Esophagus; 2, trachea; 8, subclavian artery; 11, inferior constrictor muscle of the pharynx wall. Note the Zenker diverticulum on the right (4).

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Clinically Related Prenatal Development

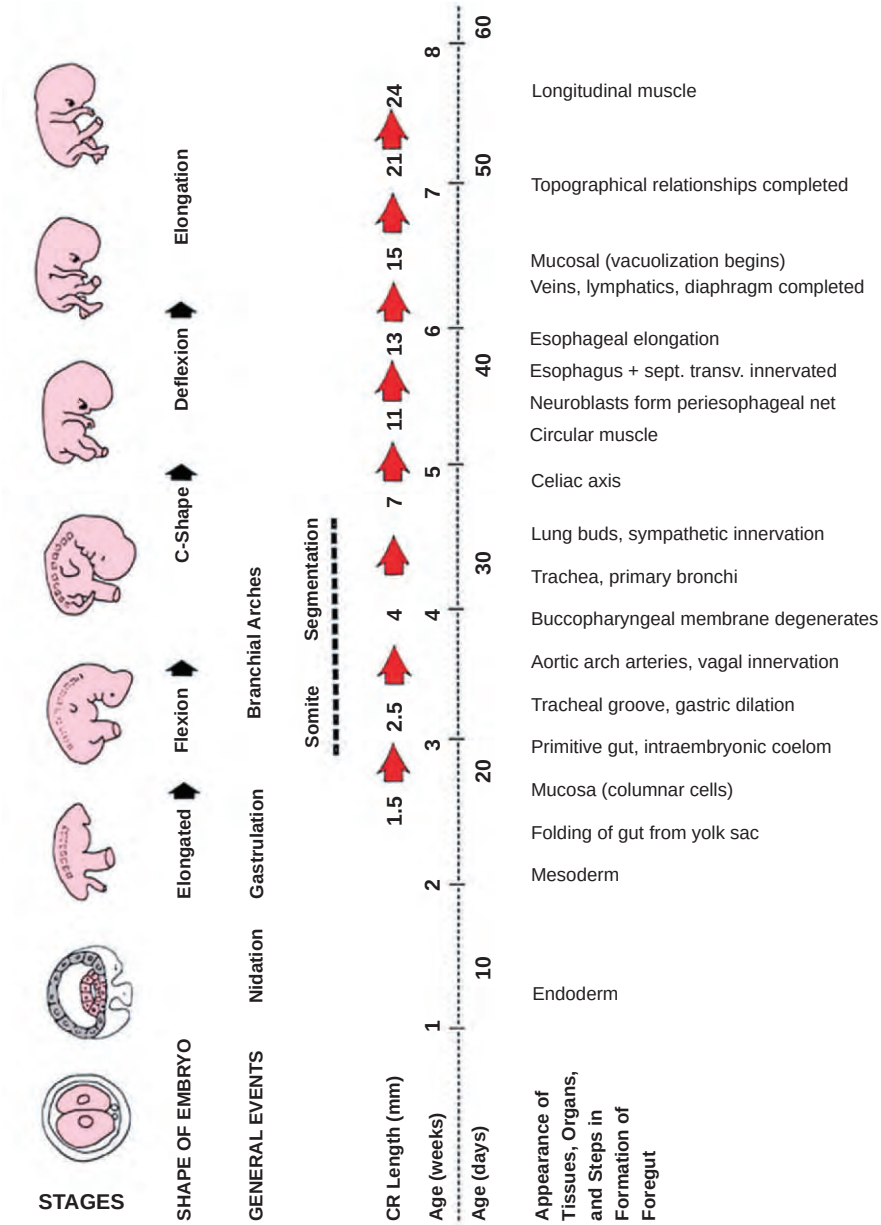
PRENATAL FOREGUT DEVELOPMENT AND ABNORMALITIES

The first stages of life take place in the embryonic period, which extends from fertilization to the fetal period. The fetal period starts at the ninth week of gestation and ends at birth. The age of the embryo is estimated by the number of somites and by the crown-rump length (CRL) when this measure becomes adequate at the end of the fifth week.[1] The events that take place during the various stages of development are shown in Table 2–1.

Because species differences have caused erroneous conclusions in the past, we omit accounts of development obtained from animals as much as possible. The

Table 2–1 Progression of Various Stages of Esophageal Development

DEVELOPMENT OF THE HUMAN EMBRYONIC ESOPHAGUS



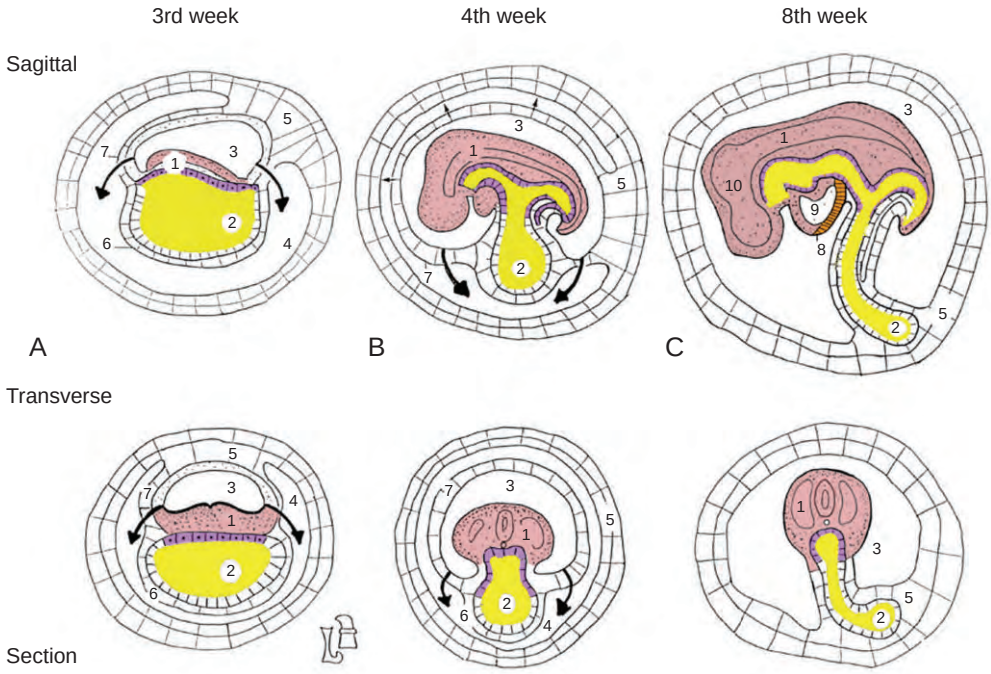


Figure 2–30. The primitive intestinal tube is shown at three stages of its development (**A** to **C**) during the third, fourth, and eighth weeks of gestation. Before formation of the head fold, during the third week the yolk sac is an ovoid cavity. Its roof is the endoderm, which is the underlayer of the embryonic disk. With formation of the head fold during the fourth week, a portion of the yolk sac becomes included within the embryo. This process results in an endodermal tube dorsal to the pericardial cavity and the septum transversum; it adopts a medial position. The tissues of the cranial foregut form the buccopharyngeal membrane, which separates the future digestive tube from the primitive mouth, the stomodeum. Laterally, the foregut is bounded by the bronchial mesoderm. Rapid growth of the brain with transverse and sagittal folding during the fifth week results in apparent flexion of the embryo. Simultaneous constriction at the junction between the embryo and the yolk sac separates the primitive midgut from the yolk sac remnant. The amniotic cavity expands and obliterates the extraembryonic coelom. 1, Embryo; 2, yolk sac cavity; 3, amniotic cavity; 4, extraembryonic coelom; 5, cytotrophoblast and extraembryonic mesenchyme; 6, somatopleure; 7, splanchnopleure; 8, septum transversum; 9, cardiac tube; 10, developing brain.

information presented in the following pages is based on original research, includes personal studies,[2-4] and uses the teaching of established embryology textbooks (see "Suggested Readings").

Basic Tissue and Organ Development

During the first to second week, the embryo develops in its blastocyst cavity from the inner cell mass. It forms a flattened plate of cells, the embryonic disk, that initially consists of two layers, the ectoderm (which gives rise to the nervous system and the epidermis) and the endoderm (which gives rise to the epithelial lining of the respiratory tract and the gut and its derivatives). The precursor tissue of the mucosa, the endoderm, is recognizable by the eighth day of the embryonic period, when its cells rapidly form the lining of the yolk sac (Fig. 2–30A). A third embryonic layer, which appears to develop between the two initial layers on the 15th day, is the mesoderm. According to its position it is classified into paraxial, intermediate, and lateral intraembryonic mesoderm. Mesodermal cells give rise to the mesenchyme, the loosely organized embryonic connective tissue. The pluripotential mesenchymal cells have the ability to differentiate into the material necessary for connective tissues, muscles, blood and lymph cells, and the serous coverings. By the 21st day, the mesenchyme has thickened on both sides lateral to the neurotube and the notochord. It forms longitudinal masses called paraxial mesoderm, which segments progressively in a cranial/caudal direction into cubes of tissue called somites (Fig. 2–31; see also Table 2–1). This process ends by the 31st embryonic day (≈5-mm CRL).

Congenital Malformations and Anomalies

Arrest in development of the foregut may be caused by defective embryogenesis as a result of

- Environmental factors (viruses, drugs, alcohol, etc.)
- Genetic factors (chromosomal abnormalities)
- Multifactorial inheritance
- Unknown etiology

For more information, see Moore and Skandalakis in "Suggested Readings."

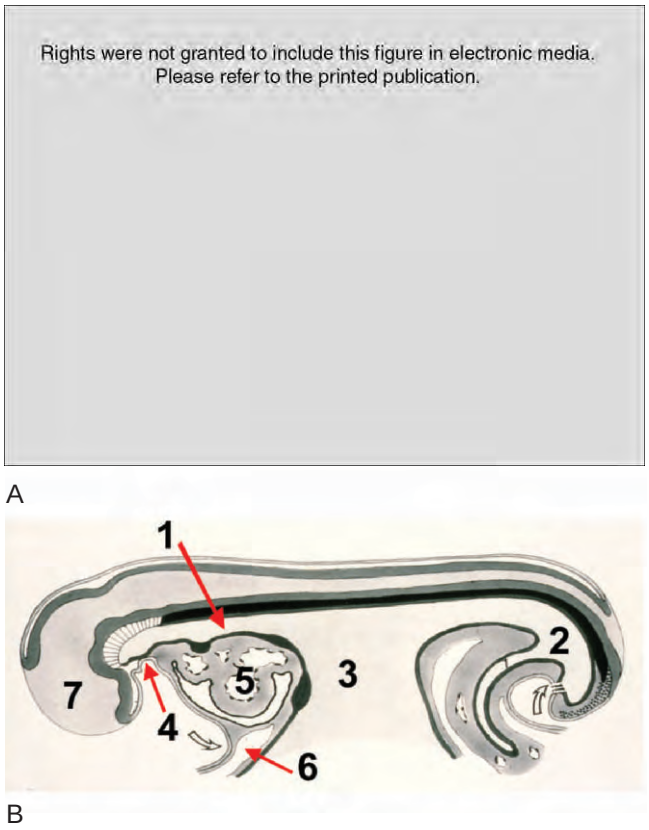


Figure 2–31. Formation of the gut in the human embryo, 3-mm crown-rump length, at the end of the first month of gestation. **A**, Scanning electron micrograph showing an embryo with paired somites (S) that develop from the mesenchymal plate (P). **B**, Schematic counterpart in the sagittal plane showing the developing structures: 1, foregut; 2, hindgut; 3, yolk sac cavity; 4, stomodeum and buccopharyngeal membrane; 5, developing heart; 6, septum transversum; and 7, brain. (**A** From Jirásek JE: Atlas of Human Prenatal Morphogenesis. Boston, Nijhoff, 1983, with permission; **B** from Hinrichsen KV: Human Embryologie. Heidelberg, Springer-Verlag, 1990, with permission. Modified from Liebermann-Meffert D: Anatomy, embryology, and histology. In Pearson FG, Delauriers J, Ginsberg RJ, et al [eds]: Esophageal Surgery. New York, Churchill Livingstone, 1995, with permission.)

Mesenchymal Clefts and Development of the Intraembryonic Body Cavity (Coelom)

Isolated small spaces appear in the lateral and cardiogenic mesenchyme in the 21-day-old embryo and subsequently form the intraembryonic coelom. Partial degeneration of the mesenchyme results in fusion of the paired cavities and the development of clefts that will allow growth of the foregut derivatives. The coelom enlarges to extend from the thorax to the pelvis. The common body cavity can now be subdivided into three parts: (1) the pericardial cavity, (2) the channel-like pericardioperitoneal cavity, and (3) the peritoneal cavity. The mesothelium derived from the somatic mesoderm lines the parietal wall, and the mesothelium from the splanchnic mesoderm lines the visceral wall.

FORMATION OF THE PRIMITIVE DIGESTIVE SYSTEM

The digestive tube is derived from the endoderm and the mesoderm. The appearance of mesoderm allows the endoderm to undergo the extensive changes needed for establishment of the primitive gut during the fourth week (see "Suggested Readings").

Formation of the somites curves the embryonic disk ventrad into a C shape (see Fig. 2–31). Excessive growth of the brain, heart, tail, and lateral folds and expansion of the amniotic cavity simultaneously narrow the dorsal portion of the yolk sac so that it becomes incorporated stepwise and channel-like into the embryo (see Fig. 2–31A and B). The resulting compression of the yolk stalk divides the yolk sac successively into (1) an extraembryonic portion, which regresses and disappears at about the 12th week, and (2) an intraembryonic portion, which represents the developing digestive tract and its accessory glands (Figs. 2–32 and 2–33, see also Fig. 2–30C). The early digestive system at this point is divided into the foregut, the midgut, and the hindgut (see Fig. 2–33). The tubular structures are attached to the posterior body wall by a relatively broad and strong mass of mesenchyme.

SHAPING THE FOREGUT AND ITS DERIVATIVES

As part of the intraembryonic portion of the yolk sac, the primitive foregut tube is initially nearly uniform in shape (see Fig. 2–32A). It then gives rise to pouches or buds (diverticula) through which develop the paired pharyngeal pouches, the ventral laryngotracheal tube and lungs, the stomach and duodenum, the liver bud, the biliary system, and the pancreatic buds (see Fig. 2–33).

Pharynx, Hypopharynx, Larynx, and Respiratory System: Cranial Foregut Segment

The pharynx, larynx, trachea, and lungs originate from the wide cranial portion of the foregut (i.e., from the branchial apparatus).[5] The primordium of the aditus into the larynx is bounded by the hypobranchial eminence, which becomes the epiglottis. Caudal to the primitive aditus, T-shaped arytenoid swellings develop from the anterior pharyngeal wall and constrict the lumen. The swellings fuse with the lateral margins of the epiglottis to form the aryepiglottic folds. Development of the lower respiratory system is marked by a ventral outgrowth in the wall of the pharyngoesophageal foregut (Figs. 2–34 and 2–35).[5-7] Called the tracheal bud, this protrusion gives rise to the trachea and the lungs and appears during the fourth week, as early as the 25-somite stage.[8]

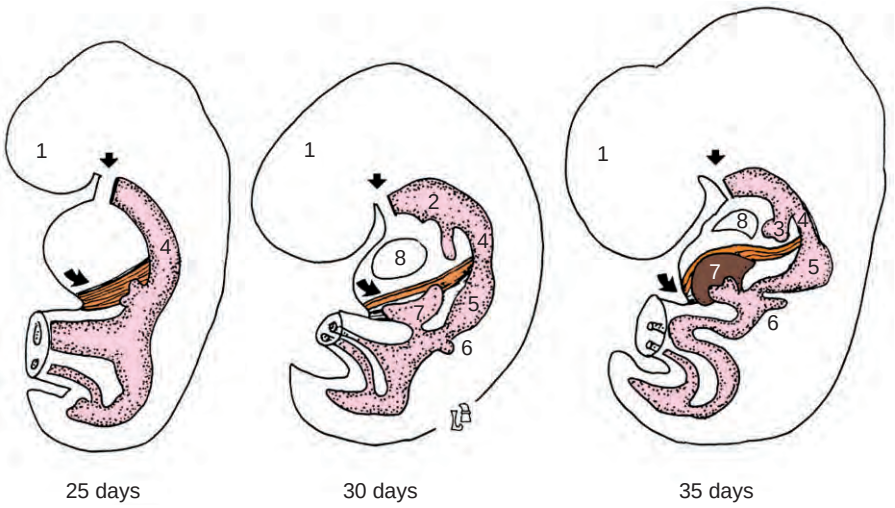


Figure 2–32. Diagrams of sagittal sections through human embryos of different stages. The digestive tract and its accessory glands undergo rapid development between the 25th and 35th days. 1, Head; 2, pharynx; 3, tracheal bud; 4, esophagus; 5, stomach; 6, pancreas; 7, liver; 8, heart. The septum transversum and the buccopharyngeal membrane are indicated by *short* and *curved arrows*, respectively. (Diagram by Liebermann-Meffert.)

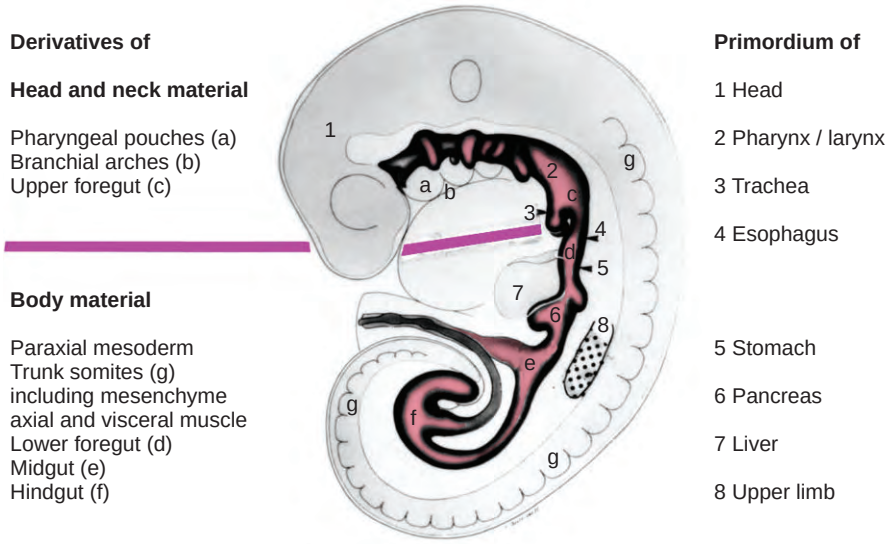


Figure 2–33. Schematic drawing of a sagittal section through the body of a 28-day-old human embryo. The foregut, midgut, and hindgut are differentiated. The stomach, however, is still an asymmetric tubal segment. The initially elongated body bends because of the increasing number of somites and the prominence of the head. This gives the embryo a C shape. The *horizontal line* at the left indicates the limits between the branchial derivatives and those of the somites. The *dotted area* in the gut marks the caudal border of the foregut, which is disproportionately large when compared with the midgut and hindgut. (After Hinrichsen KV: a. Intestinaltrakt, b. peripheres Nervensystem, c. Venen. In Hinrichsen KV [ed]: Human Embryologie: Lehrbuch und Atlas der vorgeburtlichen Entwicklung des Menschen. Berlin, Springer-Verlag, 1990, pp 105, 449, 516, with permission.)

It forms a tube, half the diameter of the pharynx, that rapidly elongates downward within the anterior mesenchyme of the foregut before it bifurcates into the lung buds in the 4-mm CRL embryo (see Fig. 2–35). The elongating tracheal tube immediately approaches the esophagus, but in my extensive embryologic material never was found to fuse with it. By the end of the seventh week, the lung tissue has developed and distinct rings of cartilage are seen within the tracheal wall (Fig. 2–36A and B).

Malformations: The Myth of Esophageal Atresia

Downward growth of the tracheal bud has been described in detail in newer anatomic and scanning electron microscopic studies (see Fig. 2–34).[6-9] These studies contradict the misleading concept initiated in 1887 by His,[10] who taught that the trachea "pinches off" the primitive foregut by means of wall folding.[7] Although this claim has not been substantiated, it is still wrongly regarded as one cause for the formation of esophageal atresia.[8]

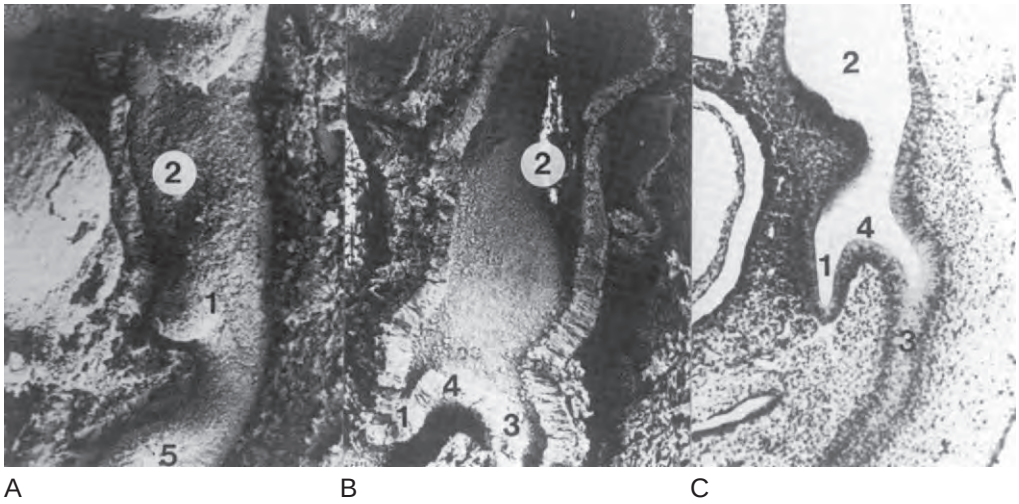


Figure 2–34. Sprouting of the tracheal bud (1) from the foregut. The primitive pharynx (2), esophagus (3), tracheoesophageal fold (4), and stomach (5) are shown. Although this is a photograph of a chick embryo, it strongly resembles the wax plate reconstructions of 3- to 5-mm crown-rump length human embryos studied by Zwa-Tun,[7] who used the material of the Carnegie collection. Sagittal sections; scanning electron micrographs from the external (**A**) and internal (**B**) aspects and histologic section (**C**). (Courtesy of D. Kluth, M.D., Hamburg, Germany.)

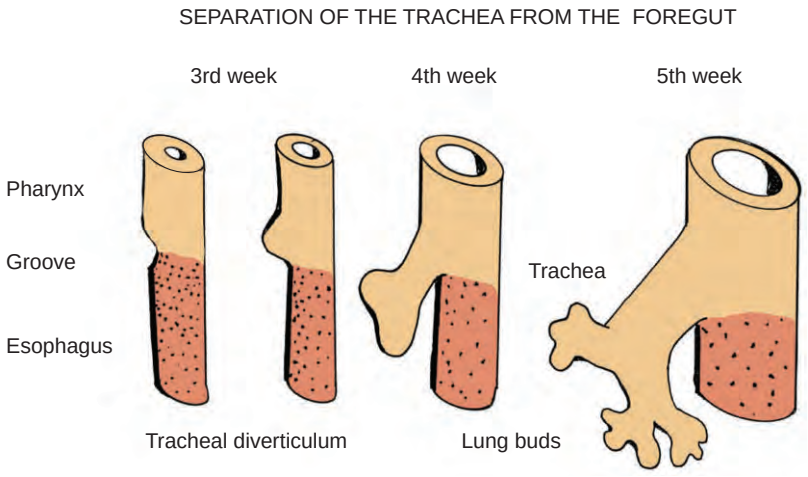


Figure 2–35. Diagram showing the event of separation of the trachea from the foregut. After formation of the primitive foregut, the appearance and downward elongation of the tracheal and lung bud make the trachea and esophagus two different entities. Both structures become intimately positioned but do not fuse. Sagittal sections. (Diagram by Liebermann-Meffert.)

Congenital anomalies of the esophagus are uncommon. The most frequently encountered are congenital atresia, usually combined with a fistula from the distal segment into the trachea, or a fistula without atresia.

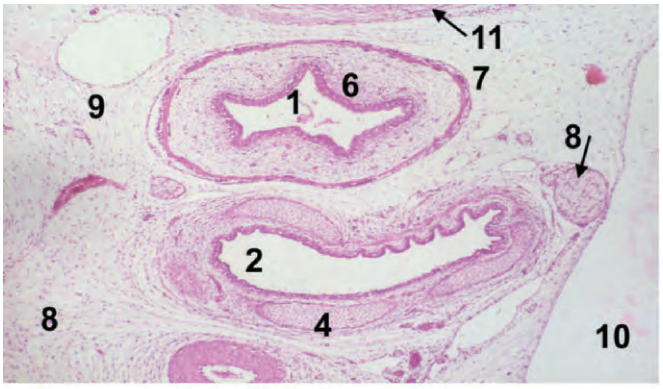
Recent Concepts of the Development of Atresia

Different factors are thought to cause esophageal atresia, such as failure in folding the trachea from the esophageal tube,[8,10] epithelial occlusion caused by the lack of recanalization,[11] a growth potential difference secondary to genetic defects,[12] and teratogenic agents[12] (see also Moore in "Suggested Readings").

Recent researchers suggest that tracheoesophageal anomalies are not a failure of organogenesis. They are believed to be due to secondary lesions of the already differentiated organs.[7,12] Local disorders of the microcirculation in utero can explain partial necrosis of the wall of the esophagus because interruption of the blood supply, as found in animal experiments, induces atresia of the intestines.[6,9] The same authors emphasize that fistula formation is due to mechanical injury caused by too close proximity of the epithelia of both organs. This event is known to occur in normal development during organ regression.

Esophagus: Intermediate Foregut Segment

During incorporation of the endodermal yolk sac material into the body, tubular structures—the primitive esophagus and hindgut—are formed in the head and tail area of the embryo[13] (see Patten in "Suggested Readings"). The esophagus is recognizable at the 2.5-mm stage.[14] It begins at the tracheal groove, lies between the heart and neural tube, follows the curvature of the



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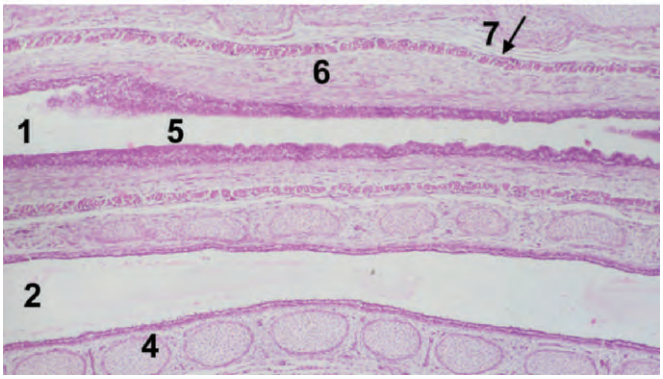


B

Figure 2–36. Histologic sections, hematoxylin and eosin staining, 5 µm, through two human embryos of similar age, 44-mm (**A**) and 46-mm (**B**) crown-rump length, and similar level, which is at the entry into the chest. **A** is in the transverse plane viewed from caudal aspect, and **B** is in the sagittal plane viewed from the left. The esophagus is in the posterior position. Both slices show developing tissues but definite adult organ relationships, such as the intimate location of the esophagus (1) relative to the trachea (2). 3, Tracheal membrane; 4, tracheal cartilages; 5, developing mucosa (note the difference of the cell layers between 1 and 2); 6, esophageal submucosa (note the dimension of the tissue portion when compared with 7); 7, muscle coat with large circular and small longitudinal layer; 8, future inferior laryngeal (recurrent) nerves; 9, primitive mediastinum with undifferentiated tissue of the previsceral and retrovisceral spaces; 10, pleural cavities (coelom); 11, primitive vertebral fascia. (From the collection of Liebermann-Meffert.)

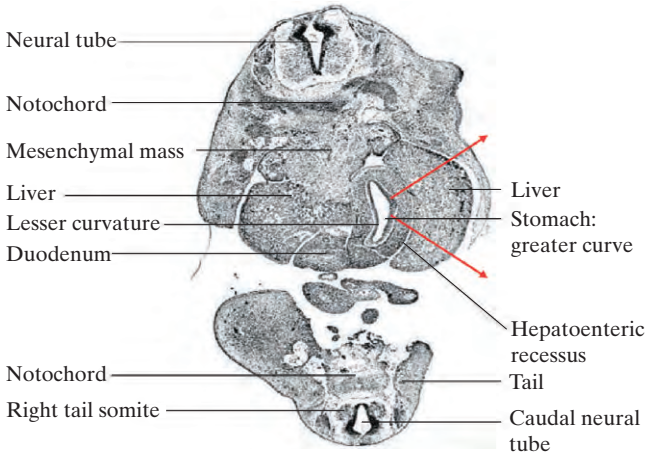


Figure 2–37. A histologic transverse section through an 8.5-mm crown-rump length embryo, 8 µm, hematoxylin and eosin staining, shows the attachment of the developing stomach. The stomach is attached to the posterior wall by the mesenchymal mass. *Arrows* indicate the asymmetric growth of the gastric wall toward the left lateral aspect. The neural tube is cut twice because of the C-shaped bending of the young embryo. (From the collection of Liebermann-Meffert.)

embryo, and extends down to the dilatation of the foregut, which is to become the stomach (see Fig. 2–32). By the end of the sixth week, the esophagus stretches and lengthens by two means: (1) extensive growth of the embryonic head and (2) deflection of the body backward away from the pericardium (see Table 2–1).[13] The shift of the head and vertebral column away from the heart at this stage of 6 to 8 weeks accounts for the classic misinterpretation that organs migrate upward or downward within the body. In reality, the esophagus elongates by extension in conjunction with prominent growth processes of its wall. The esophagus attains its definite topographic relationships to adjacent structures by the end of the seventh week (18- to 22-mm CRL stage).

Cardia, Stomach, and Duodenum: Lower Foregut Segment

Having passed the septum transversum at the level of the yolk stalk, the lower part of the foregut lies embedded in the ventral portion of the huge posterior mesenchymal mass (Fig. 2–37).[3,4] This part of the foregut represents the developing cardia, stomach, and duodenum with its derivatives. Even in the very early stages of development, the subdiaphragmatic foregut is locally fixed: (1) ventrally by the septum transversum, the yolk stalk tissue, the ducts of the growing liver, and the pancreas and (2) dorsally by the branches of the celiac vessels.

At the time when the tracheal bud pushes downward, a one-sided dilatation of the foregut, the primitive stomach, appears caudal to the septum transversum at the 6- to 7-mm CRL stage (see Fig. 2–32).[2-4] The protrusion extends in a laterodorsal direction and successively shapes the greater gastric curvature (Fig. 2–38).[4,5] The greater gastric curvature grows at a much faster rate with age than does the wall of the opposite right side, which is to become the lesser gastric curvature (see Fig. 2–37). The tissue dilatation coincides with extensive local mitotic activity.[15] This in particular concerns the area of the future gastric fundus. The growing fundus delineates the initially ill-defined gastroesophageal junction (Fig. 2–39; see also Fig. 2–38A through D).[3,4] Individual varia-

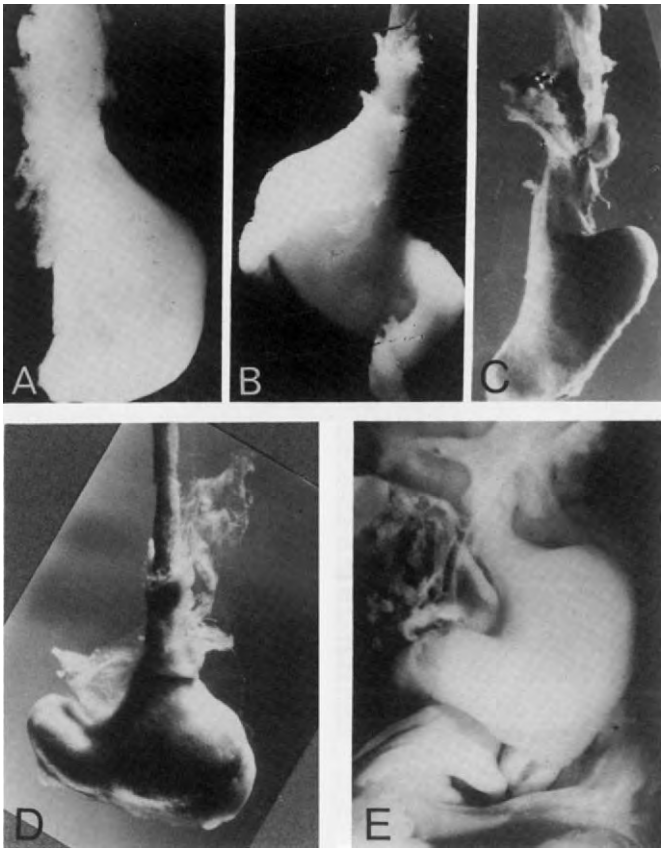


Figure 2–38. **A** to **E**, Macroscopic view of human stomachs of embryos between 8- and 22-mm crown-rump (CR) lengths. Because of localized cell proliferation, the greater curvature undergoes extensive growth toward the left during the 5- through 25-mm stages. This growth will also give rise to the gastric fundus, the cardiac angulation, and the esophagogastric junction. Both the cardia and pylorus are connected by the stalk of the celiac and superior mesenteric vessels. Thereafter, growth processes will occur mainly at the free margin of the stomach, at the greater curvature. The lesser curvature does not take part in this excessive growth stimulation, which causes the gastric asymmetry. This event is illustrated by the series of human embryos of different CR length: **A**, 8 mm; **B**, 14 mm (posterior view); **C**, 18 mm; **D**, 19 mm; **E**, 22 mm.

tions in the height of the fundus and the acuteness of the angle of His (cardiac angle) persist during the subsequent fetal period (see Fig. 2–38). Finally, the stomach, limited by the prospective cardia and pylorus, assumes its definite shape.

The Myth of Gastric Rotation

The asymmetric growth of the gastric wall[3,4,15] simulates positional changes of the stomach; in fact, there is no evidence at all of any esophageal[16] or gastric mechanical rotation.[2,3,15] Instead, the differences between the vertical and oblique axes show little change with age (Fig. 2–39), and their curves remain almost parallel. This means that the future cardia and pylorus are definitely fixed at the posterior wall.[3,15] However, despite the lack of evidence for the concept of gastric rotation, the embryologic enigma continues.

Congenital Malformation of the Stomach

With the exception of congenital pyloric stenosis (2.4 per 1000 live births), malformations of the stomach are rare. According to Skandalakis et al.[17] and Moore (see "Suggested Readings"), anomalies include microgastria and agastria, atresia and stenosis, duplication, defects of the gastric musculature, malposition (situs inversus), and other even less frequent abnormalities.

MEDIASTINUM AND DIAPHRAGM

The cranial foregut lies in the mesenchymal mass of embryonic connective tissue that extends from the heart to the primordium of the spine. This tissue forms the primitive ventral and dorsal mediastinum that holds the foregut in place. Caudally, the ventral portion is bounded by a transverse mesenchymal plate separating the primordium of the heart from the liver. This plate is the septum transversum (see Fig. 2–32). Within the umbilical cord and caudal to the septum transversum course the omphaloenteric and umbilical veins.

As mentioned earlier, the lung buds grow into the mesenchyme that surrounds the pericardioperitoneal spaces. Yet the developing trachea maintains close tissue contact with the esophagus (see Figs. 2–36 and 2–44). During the sixth week, bulges extend ventrally and medially. These bulges develop mesentery-type folds that later become membranes, the free ends of which fuse with the mesoderm located ventral and dorsal to the esophagus and with the septum transversum (see Fig. 2–32). Supported by the rapid growth of the liver, the partitions that will become the diaphragm isolate the caudal portion of the pericardioperitoneal channel, thus closing the pleural and peritoneal cavities (Fig. 2–40).

The diaphragm develops from four sources (Fig. 2–41).[18,19] The largest portion derives from the septum transversum, which has already fused with the ventral mesenchyme of the esophagus in the 7-mm embryo. It eventually forms the central tendon of the diaphragm. The median portion derives from the dorsal mesenchyme of the esophagus and gives rise to the crura of the diaphragm. The crura are formed at a point where the septum transversum and the pleuroperitoneal membrane fuse. The peripheral muscular diaphragm originates from the dorsolateral body wall tissue. What is initially the largest portion of the primitive diaphragm eventually forms the small intermediate muscular portion of the diaphragm. It is derived from the pleuroperitoneal membranes at the point where they have fused with the dorsal mesenchyme of the esophagus and the septum transversum (see Fig. 2–41). Rapid growth of the dorsal body of the embryo, as opposed to the more slowly growing pericardium, causes an apparent descent of the diaphragm.[19] By the end of the sixth week, the diaphragm is complete and is located at the level of the thoracic somites. By the end of the seventh week, it

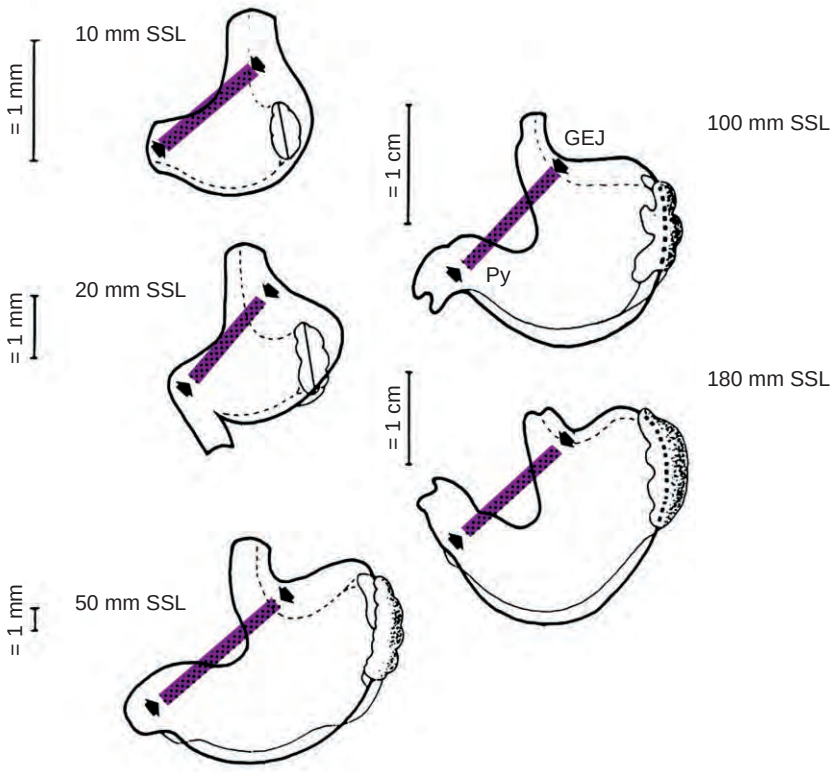


Figure 2–39. The asymmetric growth process involves the greater curvature and is caused by extensive mitotic activity within the wall.[2,3,15] The cardia and the pylorus remain in place anterior to the spine, where they are held because of their firm dorsal attachment (GEJ and Py) and their relationship to the vessel stalks. GEJ, Gastroesophageal junction; Py, = pylorus; SSL, crown-rump length of the embryo (i.e., fetus).

reaches its final position at the level of the first lumbar vertebra. The future diaphragm can already be easily identified by its distinctive musculature at the 12- to 15-mm CRL stage (see Fig. 2–40).

The phrenoesophageal membrane, which holds the esophagus in place within its diaphragmatic hiatus (see Fig. 2–40), differentiates when the muscle of the esophagus has specialized.

By the end of the embryonic period, in the early ninth week, the definite shape of all the main organ systems are established. The external appearance of the organs is now less affected by further development. During the fetal period, maturation and growth of the various tissues and organs take place.

Anomalies: Congenital Diaphragmatic Hernias and Deformations

An enlarged esophageal hiatus and a congenital defect of the phrenoesophageal membrane are considered predisposing factors for sliding and paraesophageal hernia in childhood.[17,20]

Occasionally, and mainly on the left, the pleuroperitoneal cavity remains open and a posterolateral defect is created. This is the congenital foramen of Bochdalek, which allows free communication between the chest and abdomen. The abdominal contents may then herniate into the thorax (mostly during return of the intestines from the umbilicus) and cause neonatal problems. The foramen of Morgagni, a rare parasternal defect, is the result of a persisting gap from the costosternal origin of the diaphragm; it permits herniation into the anterior

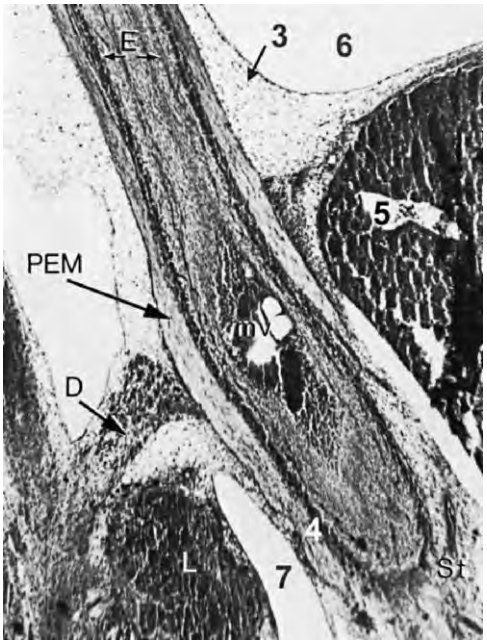


Figure 2–40. Anchoring structures above the esophagogastric junction (sagittal section through a 15-mm crown-rump length human embryo). The axial section parallels but does not cut the esophageal and gastric lumen. Developing structures: D, diaphragm; E, esophagus; 3, PEM, phrenoesophageal membrane; 4, stomach; 5, liver; 6, pleural cavity; 7, abdominal cavity; mv, vacuoles in the mucosa. The *small arrows* show the differentiated muscular wall. (Courtesy of Fernandez de Santos, MD, Madrid, with permission.)

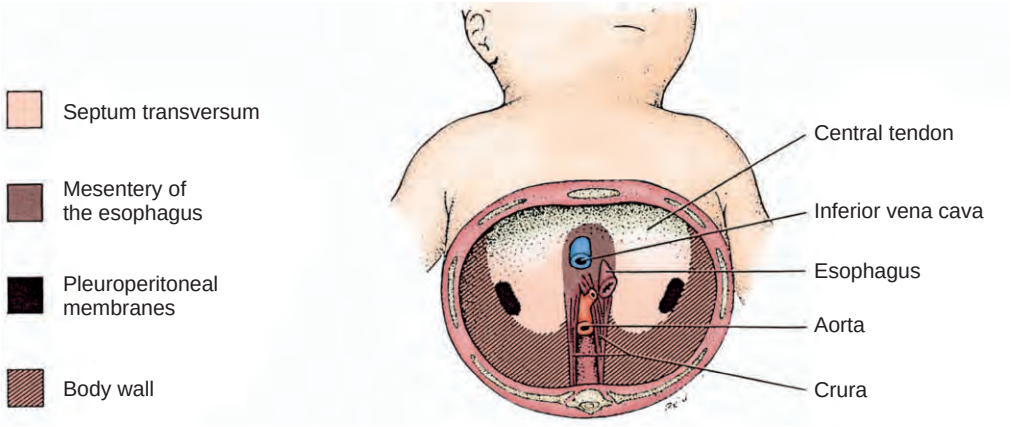


Figure 2–41. Tissue origin of the diaphragm and its four sources. (From Moore KL: The Developing Human. Philadelphia, WB Saunders, 1988.)

mediastinum. Incomplete development of the musculature deriving from the lateral body wall may lead to congenital eventration of the diaphragm. The rare diaphragmatic agenesis is due to failure of formation of the diaphragmatic components or failure to join properly.[18,21] For more information, see Skandalakis et al.[17]

TISSUE ORGANIZATION OF THE FOREGUT

Formation of the Foregut Muscular Systems

The esophageal musculature develops from myoblasts originating in the splanchnic mesenchyme that surrounds the endoderm of the early gut. The myoblasts give rise to the cells that constitute the muscular system of the esophagus. At first a ring-shaped condensation of elongated, fusiform nuclei can be distinguished around the external aspect of the entire esophageal tube in the 8- to 10-mm CRL embryo (Fig. 2–42A). Similar muscular precursor cells are present in the esophageal wall of the 12- to 14-mm CRL embryo (see Fig. 2–42B) and appear as a ring-shaped cellular condensation on the outer surface of the tube. The muscular nuclei, however, are arranged in the opposite (i.e., longitudinal) direction from the upper toward the terminal esophagus. Thereafter, the surface of each precursor nucleus acquires a lamellar tissue cover and develops into bundles and sheets of tissue that resemble smooth muscle. These cells constitute the circular and the longitudinal layers of the esophagus. They form complete sheets surrounding the epithelial lumen of the esophagus at the 20-mm CRL stage (see Fig. 2–42C). However, at this stage the musculature is very thin in comparison to the extent of the submucosa and mucosa. By the 24-mm CRL stage (see Fig. 2–42D), the muscularis mucosae becomes apparent, and it is well defined in the 65-mm CRL stage.

Striated musculature can be distinguished only much later in the fetal stage (about 40-mm CRL) and is found in the pharynx, larynx, and upper half of the esophagus. The striated muscle derives from the caudal branchial arches and is innervated by the branchiomotor branches of the vagus nerves. The smooth foregut muscle rises from the visceral splanchnopleural mesoderm and is innervated by the sympathetic nervous system.

The muscle bundles of the esophagus can be distinguished and the fibers seen macroscopically in the 76- to 90-mm fetus. The fiber arrangement of the muscle layers in the esophagus and at the esophagogastric junction[2,3] is comparable at that point to the arrangement seen in the adult.[2,22,29] This is also the case for the sphincter at the cardia, the structures of which have been discussed previously[22] (see Liebermann-Meffert in Pearson et al. in "Suggested Readings").

Formation of the Lamina Mucosa, Submucosa, and Esophageal Lumen

Discussion about the developmental changes of the mucosa of the human esophagus dates back to the turn of the 19th to the 20th century.[11,23-25] Up to the present, however, these changes have been a matter of debate (Table 2–2).[26-28] New attention arose because of the diversity of opinion about the histopathologic background in the development of gastric metaplasia of the esophageal mucosa in connection with Barrett's esophagus.

Differentiation from Endoderm to Mature Foregut Mucosa: Sequence of Events

Proliferation of the Precursor Mucosa Differentiation of the intraembryonic epithelium from the endoderm has been identified at about the third week of gestation (see Patten in "Suggested Readings" and Table 2–1). By the fifth week, when the embryo is 6- to 8-mm in CRL, the internal coat of the foregut is lined with two or three layers of pseudostratified columnar epithelium; this layer is uniformly thick, spreads along the entire esophageal tube, and is surrounded by undifferentiated mesenchymal cells (Figs. 2–43 and 2–44; see also Fig. 2–42). This aspect of the developing mucosa lasts until the 10- to 12-mm CRL stage.[13,27] At that time, the embryonic mucosa becomes multilayered and thickens as a result of excessive cell proliferation (see Fig. 2–43 and Table 2–2). This thickening of the mucosa narrows the esophageal lumen considerably.

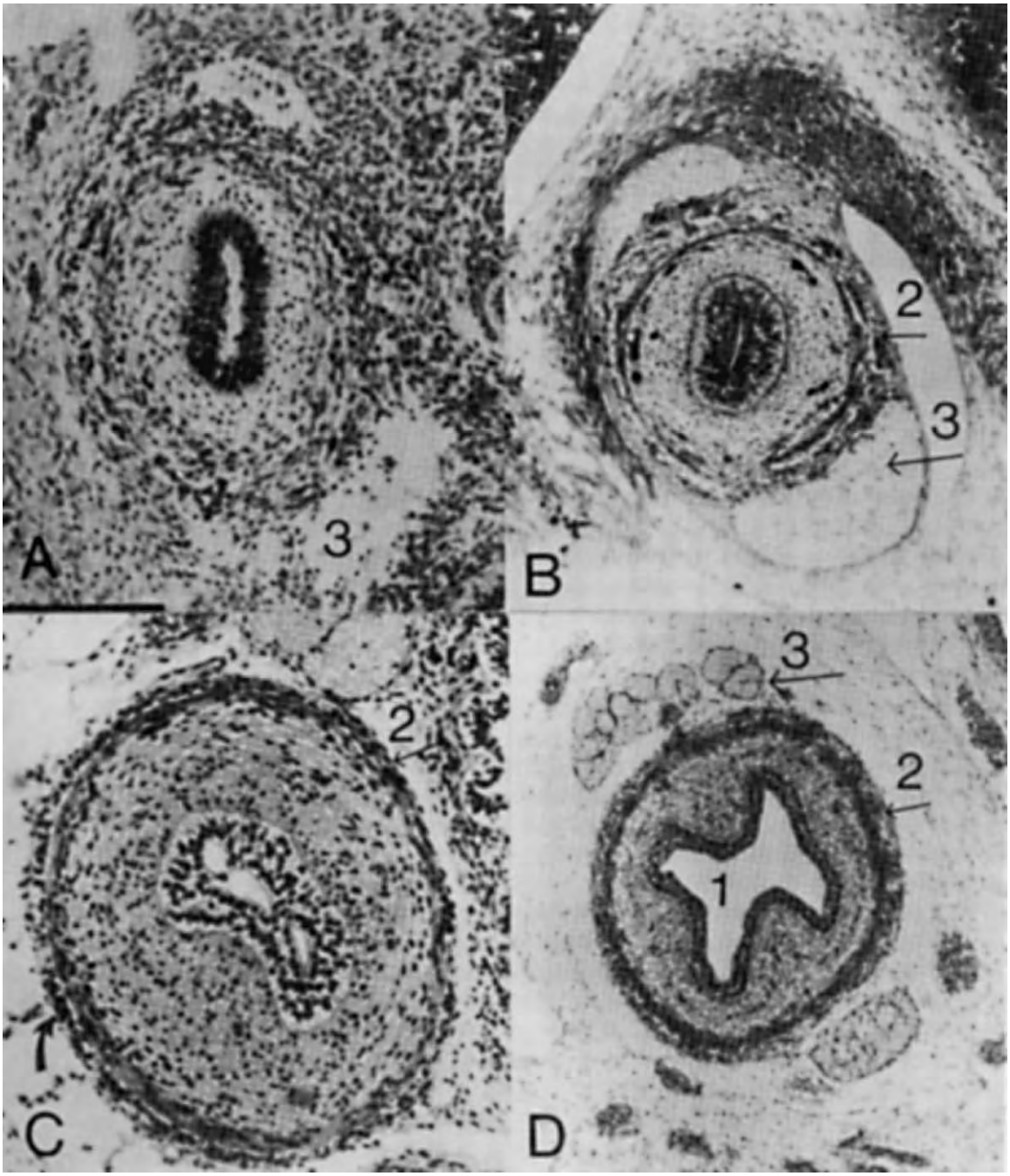
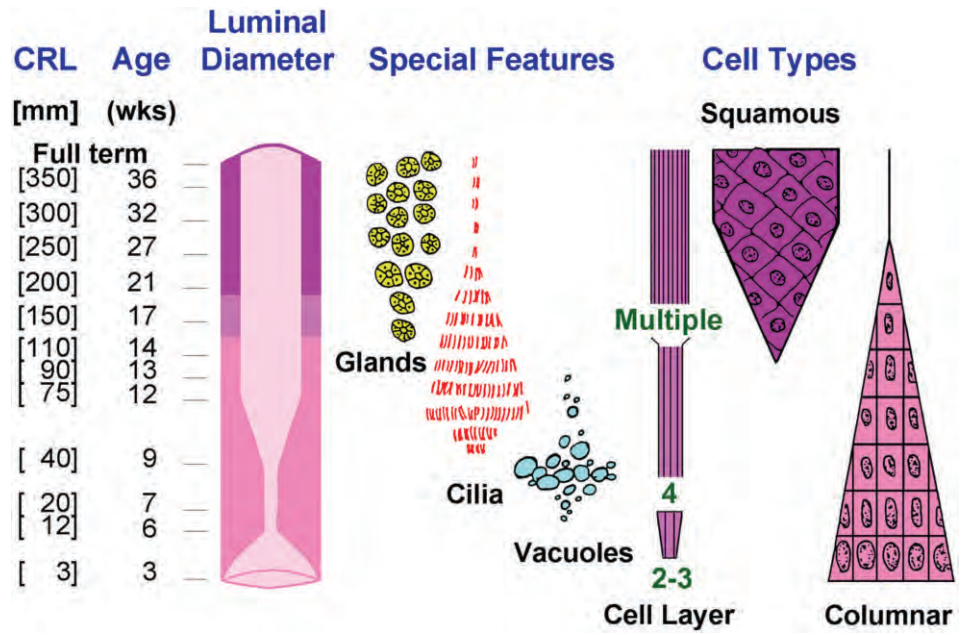


Figure 2–42. Transverse section through the upper chest level of the esophagus in embryos of 8.5-mm (**A**), 12.5-mm (**B**), 20-mm (**C**), and 23-mm (**D**) crown-rump length (CRL). The mucosal epithelium lining the lumen (1) is stratified columnar in the 8.5-mm CRL embryo and will become vacuolized between 12.5- and 20-mm CRL and multilayered columnar in the 25- to 40-mm CRL stage. The tissue that surrounds the mucosal epithelium consists mainly of undifferentiated mesenchyme in the 8.5-mm CRL embryo. Differentiation of the inner muscle coat is identified in the 8.5-mm CRL embryo but more prominent by the cell condensation around the mucosal ring seen in the 12.5-mm CRL embryo in **A** (2). Pale areas of neural cells that are precursors to the vagal nerves are seen exterior to the foregut tube (3). In the 12.5- and 20-mm CRL stages, the inner and outer muscular layer is further advanced. The muscularis mucosae, however, can be identified only at the 23-mm CRL stage. During this development, the extrinsic innervation, in particular, the recurrent laryngeal nerve, has become conspicuous in size (3). The developmental changes in luminal diameter and the shape of the esophagus are caused by submucosal protrusions toward the lumen (mesenchymal proliferation). (**A**, **B**, and **D** From the collection of Liebermann-Meffert; **C** from Enterline H, Thompson J: Pathology of the Esophagus. Heidelberg, Germany, Springer, 1984, with permission.)

Table 2–2 Prenatal Development of the Mucosa in the Human Esophagus



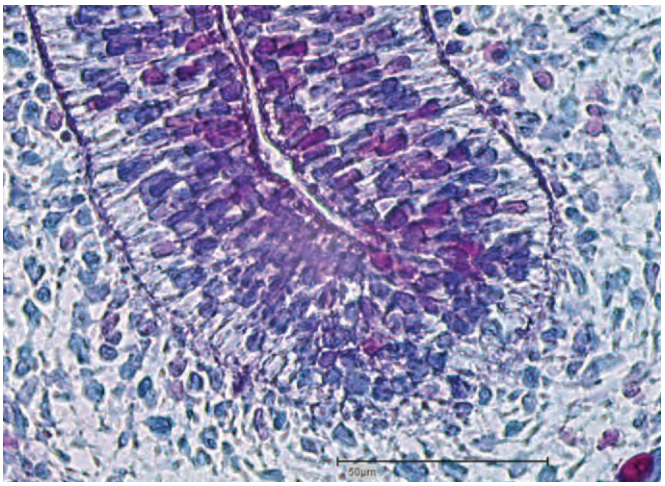


Figure 2–43. Transverse section through the esophagus in a 12.5-mm crown-rump length embryo. Consisting of three layers, the esophageal epithelium is stratified and columnar; it shows a layer of proliferating cells with large oval nuclei. The basement membrane seen here is now distinct in all embryos at this stage of development. (From the collection of Liebermann-Meffert.)

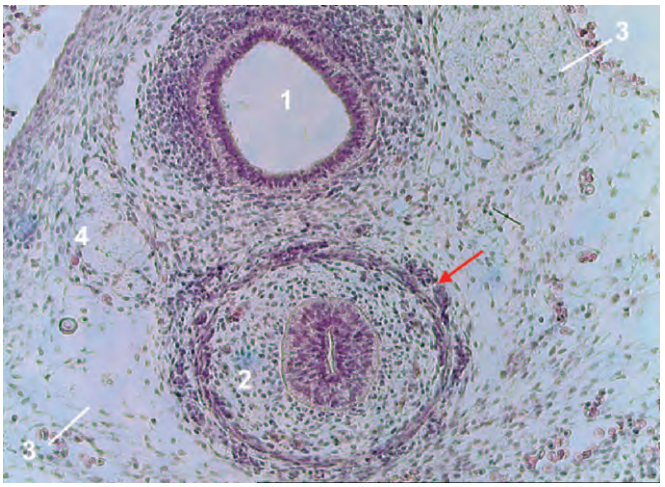
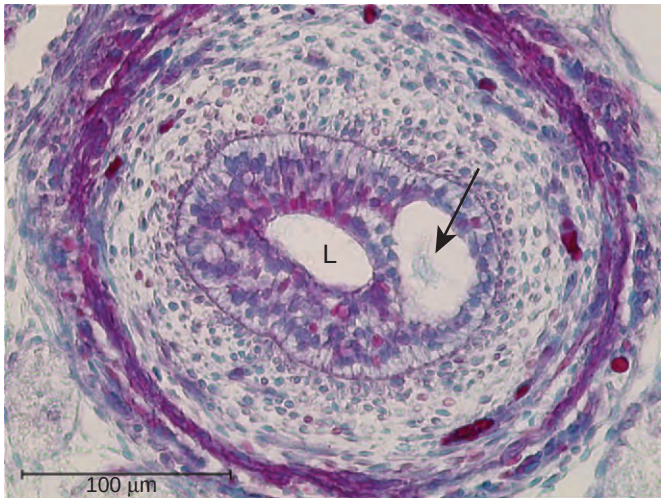


Figure 2–44. Transverse section through the upper part of the esophagus of a 12.5-mm crown-rump length embryo above the level of the developing tracheal bifurcation with narrowing of the lumen because of extreme cell proliferation. The *arrow* shows the differentiating circular muscle layer of the esophagus. 1, Primordium of the trachea; 2, esophagus; 3, vagus; 4, recurrent laryngeal nerve). (From the collection of Liebermann-Meffert.)

Vacuolization of the Epithelium When the embryo is at the 12-mm CRL stage, thin-walled hollow spaces appear in the proliferating epithelium (Fig. 2–45A; see also Table 2–2); subsequently, when the embryo is about 6 weeks old and has attained 13- to 14-mm CRL, the spaces form differently sized cellular vacuoles. The vacuoles increase to a huge number. They may also become much larger than the esophageal lumen itself (see Fig. 2–45B) because the vacuoles fuse through rupture of their thin membranes. In the embryologic material examined by the authors, vacuoles are most conspicuous in the 14- to 22-mm CRL stage. This feature occurs in our own serial sectioned specimens earlier than claimed previously by others.[13] Condensation and size of the vacuoles vary individually. They are smaller and less frequent in the upper portion of the esophagus, but largest and most numerous at levels close to the tracheal bifurcation, followed by those at the junction into the stomach. Small circular vacuoles are found in a far smaller amount in the mucosa of the trachea, but never in the stomach. Vacuolization



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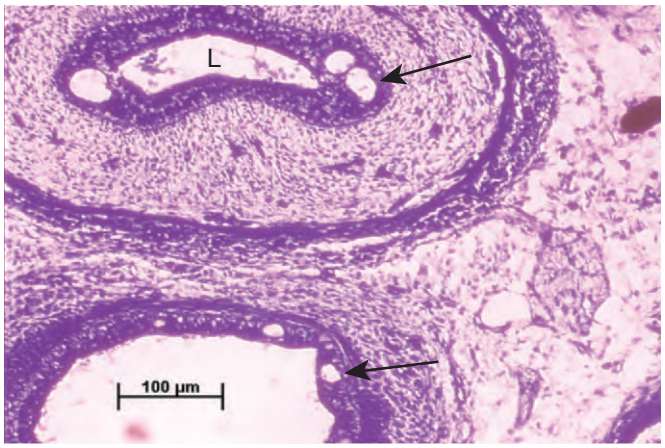
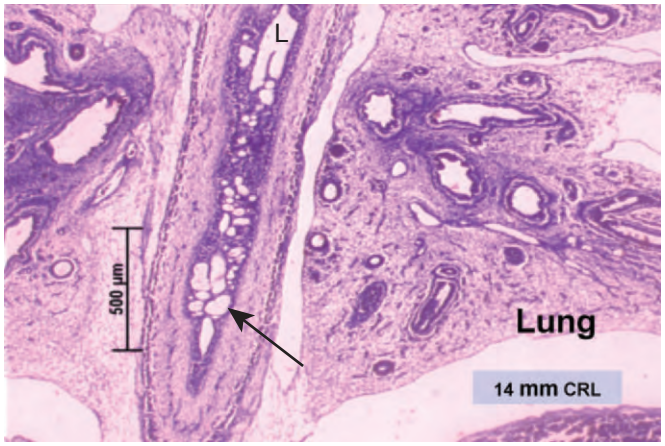


B1



B2

Figure 2–45. Transverse section of the middle portion of the esophagus at the vacuolated stages of the mucosa in 12.5-mm crown-rump length (CRL) (**A**) and 14.5-mm CRL (**B**) embryos. The vacuoles are located within the epithelial cells. Some are multichambered and large because of fusion and occasionally have a diameter greater than that of the esophageal lumen. Some of the vacuoles contain aggregated fiber material (*arrows* in **A** and **B**). L, esophageal lumen. (From the collection of Liebermann-Meffert.)

is an indicator of cell death. At first, the vacuoles seem to be empty; at second look, however, it becomes evident that many of the larger vacuoles contain lysate (cytolytic content) (see Fig. 2–45A). Finally, the vacuoles rupture and discharge their contents into the esophageal lumen. At a stage of 32-mm CRL (month 3), the vacuoles have disappeared, except that very occasionally small ones have been observed by us until the 75-mm CRL embryo (late 12th week).[13,29]

Lumen Occlusion Secondary to Vacuoles: Fact or Myth? Histologic sections made in the sagittal plane of the embryo during the period of vacuolization eventually cut parts of the muscular layers of the wall instead of the lumen; an image of "occlusion" may result as shown in Figures 2–40, 2–45, and 2–49. This picture is probably what led Kreuter[11] in 1905 to suggest, erroneously, that a physiologic solid occlusion of the esophageal lumen takes place during this stage of development. He concluded that esophageal atresia results if "recanalization" of the lumen does not occur. Although no subsequent investigator has ever reconfirmed Kreuter's claim,[5,13,20] his opinion[11] is still a dogma presented in a number of current surgery and anatomic textbooks. It is better to remember that vacuolization in the esophageal mucosa occurs long before the trachea and lungs are already fully developed. From this observation and the normally patent lumen, recent researchers have emphasized that atresia of the esophagus, as well as esophagotracheal fistula formation, is mostly due to a congenital growth defect of the esophagus or trachea (or both).[6,9,12]

Ciliated Columnar Epithelium and Goblet Cells Large, darker-stained cells appear in the basal epithelial cell layer of the 30- to 40-mm CRL embryo. The stratified columnar epithelium is generally four to six cells deep. The surface epithelial cells show a clear affinity to eosin and project toward the lumen to increasingly become ciliated columnar cells (Fig. 2–46; see also Table 2–2). These cells progress from the middle third of the esophagus in a cranial and caudal direction and are usually interspersed among nonciliated cuboidal surface cells. Ciliated cells line the entire mucosa of the esophagus of the 60 mm CRL fetus.[13,27] Successively, the epithelium now consists of a single layer of large columnar cells containing mucin-bearing cells (goblet cells).[27] In the 70- to 90-mm CRL fetus, the cells below the surface layer become squamous and some in the proliferative zones are vacuolated. In 100- to 150-mm CRL fetuses, alternating patches of ciliated cells and nonciliated cells are seen in the squamous epithelium. In the 200-mm CRL fetus, the area of these cells is reduced by cell degeneration[27,28] (Fig. 2–47B and C), and in large areas they are lost at about the 240-mm CRL stage. Stratified columnar epithelium persists in the upper part of the esophagus only, which is consistent with our own results.[27]

An interesting aspect of the mechanisms of the developing esophageal mucosa was studied by Menard and Arsenault.[30] These investigators were able to study explants of the esophagus from early-stage human fetuses maintained in organ culture. Using this fresh material, they charted the ultrastructural changes that

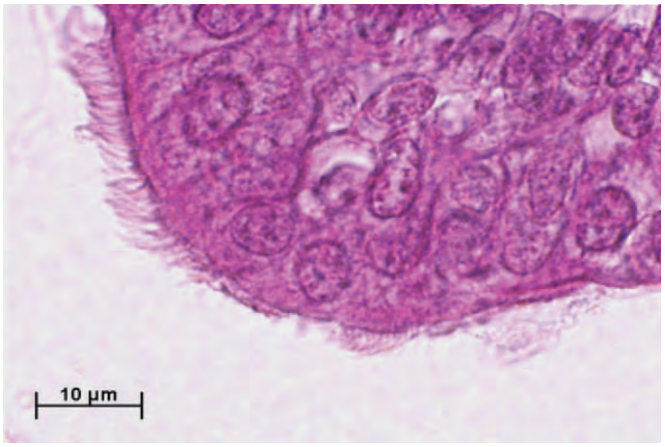


Figure 2–46. Transverse section through the surface mucosa of a 25-mm crown-rump length embryo showing a border of ciliated and nonciliated columnar epithelial cells. (From the collection of Liebermann-Meffert.)

occurred in esophageal epithelialization during maturation of the tissue. They observed that during replacement of the epithelium, islets of ciliated cells actually developed into squamous epithelium.

Stratified Squamous Epithelium Squamous cells are markedly flattened. Stratified epithelium can be seen in patches in the 60-mm CRL fetus and progressively increases in the 90- to 130-mm CRL fetus[13,27] (see Fig. 2–47C). Replacing the ciliated cells, this epithelium spreads from the middle third of the esophagus craniad and caudad until squamous epithelium has progressively and almost completely replaced the ciliated columnar epithelium in the 250-mm CRL fetus.[13] Some patches of ciliated columnar cells, however, occasionally remain until birth. They are usually also found in the proximal part of the esophagus in the newborn.

Glands

The first superficial glands have been observed to develop during the 160-mm CRL stage (see Table 2–2). They contain acini. These glands are superficial to the muscularis mucosa and are numerous in the esophagus of 210-mm CRL fetuses; they are located mostly at the level of the cricoid cartilage and at the lower end of the esophagus.[27,31] Not before the last 3 months of gestation does the downward growth of the surface epithelium begin to generate deep submucosal glands (Fig. 2–48).

The Specialized Cardia Mucosa: Acquired or Congenital?

The presence of a small area of specialized so-called cardiac mucosa has been identified at the junction between the squamous mucosa of the esophagus and the pure oxyntic cells of the stomach. In full-term specimens the zone of superficial glands was limited to a 5-mm distance.[27,31] Some authors regard this cardiac mucosa as a

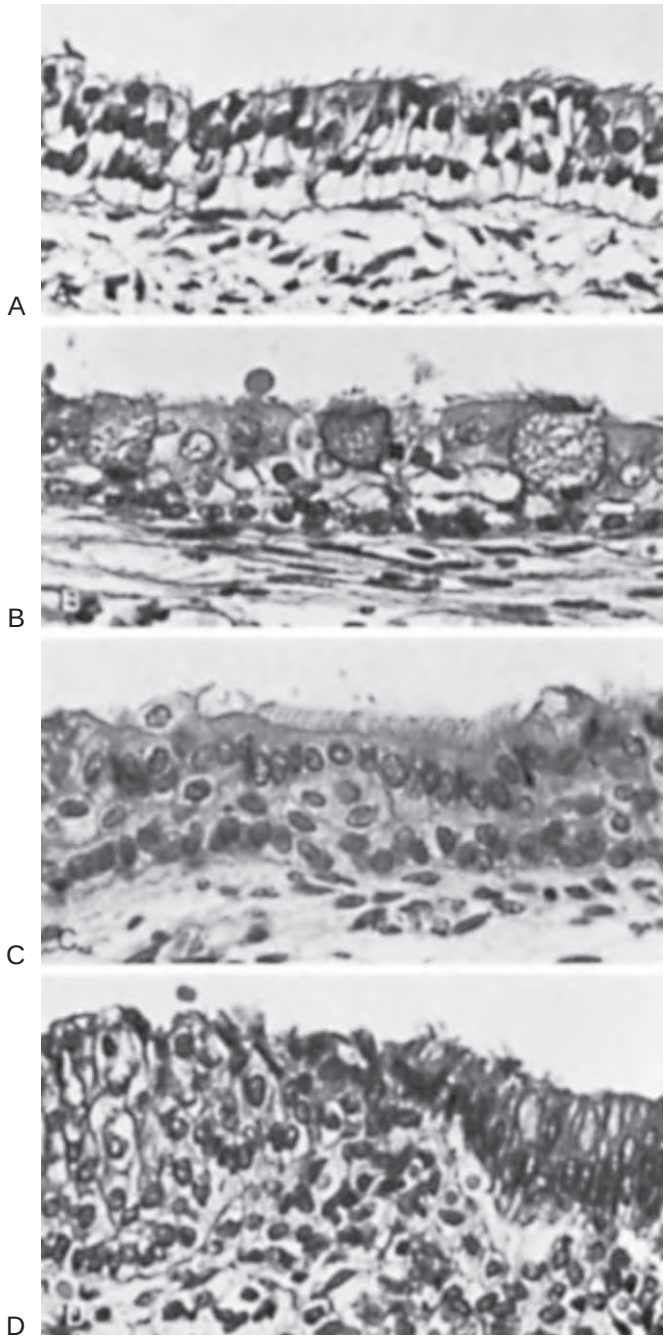


Figure 2–47. Transverse sections through the esophagus at different stages of mucosal development. **A**, Ciliated pseudostratified columnar epithelium at the 28-mm crown-rump length (CRL) stage. **B**, Ciliated columnar cells. Goblet cells are present on top of several layers of polygonal cells and represent the early squamous replacement found in the 190- to 230-mm CRL fetus. **C**, A later stage in the process of squamous replacement in which patchy remnants of ciliated epithelium may remain until birth. **D**, A residual island of mucin-secreting cells in the esophagus of a newborn. (From Enterline H, Thompson J: Diseases of the Esophagus. Heidelberg, Germany, Springer-Verlag, 1984, with permission.)

pathologic condition acquired by acid and bile gastroesophageal reflux,[32-34] whereas others deny such an etiology and consider the cardiac mucosa to be a normal development.[31,35-37]

Shaping the Esophageal Lumen

The shape of the esophageal lumen is greatly influenced by the development of the mucosa. Because of cell proliferation and the appearance of vacuoles between the 10- and 21-mm CRL stages, the initially oblong (Fig. 2–49; see also Figs. 2–42 and 2–44) or elliptical lumen of the embryonic esophagus narrows and then assumes a bizarre configuration (see Figs. 2–36, 2–42C, and 2-49). This phenomenon is more pronounced at levels between the tracheal bifurcation and the cardia than in the upper part of the esophagus (see Fig. 2–49). As the process of vacuolization continues and larger vacuoles appear, the deformation of the entire esophageal lumen becomes apparent. During the next stages when the vacuoles rupture, this space is incorporated into the widening lumen. Formation of the longitudinal folds appears as an outgrowth of the surrounding mesenchyme toward the lumen. This coincides with local condensation of the mesenchyme at the 23-mm CRL stage (see Fig. 2–42D). These events lead to the bizarre form of the upper esophagus and the star-like shape present in the cross-sectional view of the lower esophagus (Fig. 2–50). These folds parallel the longitudinal axis of the esophagus and constitute the definite configuration of the esophageal lumen. The muscularis mucosa follows the protrusions of the mesenchyme, but the main external muscular layer of the esophagus never follows these folds at any time.

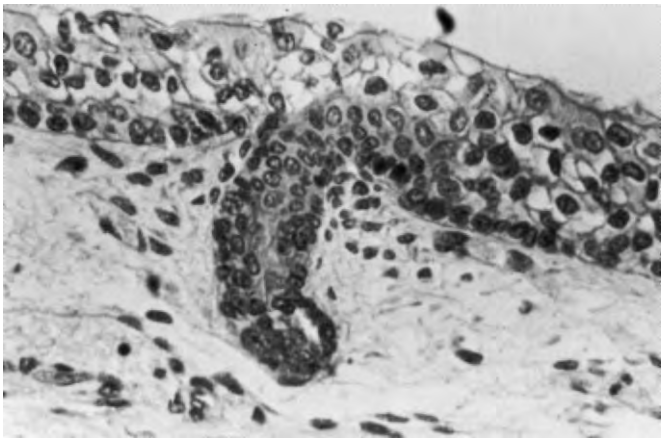


Figure 2–48. During the last trimester of fetal development, downward growth of the surface epithelium begins to generate submucosal glands. A few short ciliated cells are present on the surface above the squamous epithelium. (From Enterline H, Thompson J: Diseases of the Esophagus. Heidelberg, Germany, Springer-Verlag, 1984, with permission.)

Formation of the Foregut Vascular System

The vasculature is formed in the early somite stage in the somatopleural mesenchyme of the body wall. Two major arterial sources supply the foregut. One is located in the

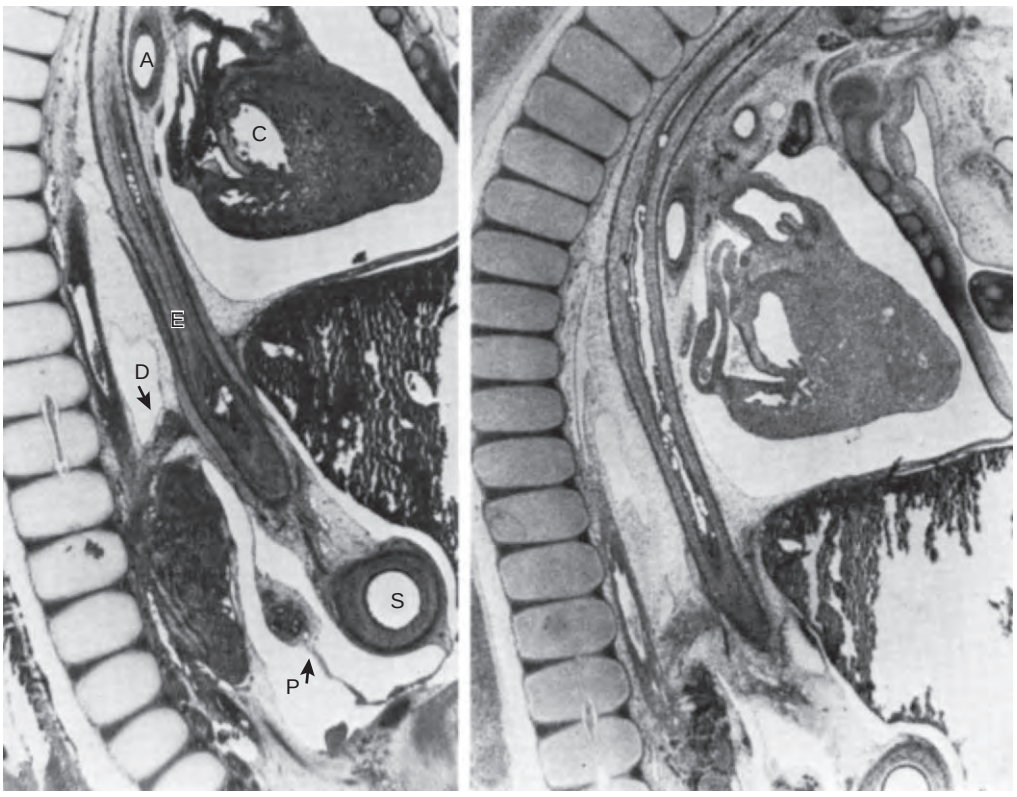


Figure 2–49. Sagittal sections through the curved esophagus of a 15-mm crown-rump length embryo seen here at two consecutive levels. **A**, The muscular wall of the esophagus is cut partially at its peripheral limits; the lumen therefore appears to be obliterated and the musculature mimics a solid structure. **B**, A deeper slice through the esophageal wall displays the vacuolated, but patent esophageal lumen. A, aorta; C, heart; D, diaphragm; E, esophagus; P, pancreas; S, stomach. (Courtesy of Fernandez de Santos, M.D., and Tello Lopez, M.D., Madrid, with permission.)

mesenchyme of the fourth to the sixth pharyngeal arches and represents the arterial system of the aortic arches that partly encircle the pharynx (Fig. 2–51). These vessels supply the thyroid diverticula (the future thyroid glands) and the tissues of the upper half of the esophagus. At the end of the somite period (5-mm CRL), a pair of pharyngeal arch arteries develop in the mesenchyme of the sixth branchial arch and give rise to vascular branches that descend to supply the primordium of the trachea and the lung buds. The second major source develops at the level where the initially paired dorsal aortas fused caudally to form a single midline vessel, the infradiaphragmatic aorta. The second visceral blood vessel forms the celiac axis, which gives off tributaries to the lower portion of the foregut. These vessels supply the developing stomach, duodenum, liver, pancreas, and greater omentum (see Fig. 2–51).

During this period a number of changes alter the primitive original vascular pattern to result in establishment of the final arterial pattern of the fetus. As shown in Figure 2–52, vessels deriving from the branchial pharyngeal region maintain blood and lymph flow in a caudal direction, whereas vessels deriving from the celiac axis contribute the arterial vascular supply to the esophagus in a cranial direction of flow. Venous and lymphatic drainage follows the same bidirectional pattern of flow, but in a reverse orientation (Fig. 2–52). This orientation never changes from the fetal pattern throughout adult life. In light of this, one must keep in mind that the esophagus originates from two different tissue sources: (1) one from the branchial apparatus (head and neck material) and (2) the other from body tissues. The two sources maintain a delimitation at the level of the tracheal bifurcation (see Fig. 2–52) throughout life.

The lymphatic system itself appears concurrently with the venous system 2 weeks after the cardiovascular system. Lymph sacculations develop in the jugular region (Fig. 2–53), and definitive lymph vessels are identified in the 11-mm CRL embryo during the sixth week and supply the foregut and trachea.[6,14]

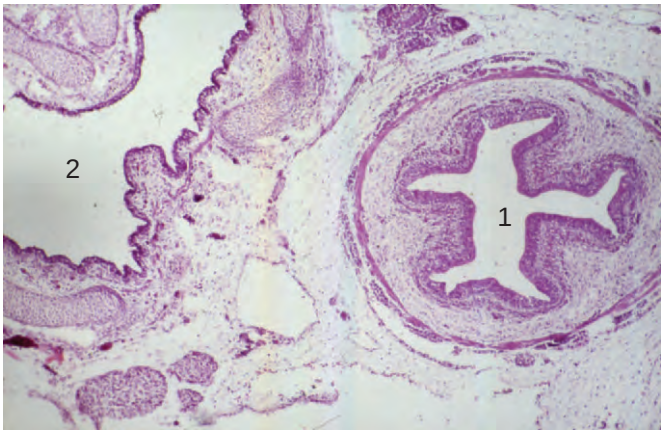


Figure 2–50. Transverse section through the esophagus of a 25-mm crown-rump length embryo showing the bizarre shape of the lumen caused by fold formation of the submucosal mesenchyme 1, esophagus; 2, trachea.

Formation of the Foregut Nervous System

The nervous system develops during the third week from the neural plate. This is an area where the dorsal embryonic ectoderm thickens by cell proliferation and, during the fourth week, folds into the neural tube. The tissue of the neural tube then gives rise to the brain cranially and the spinal cord caudally.

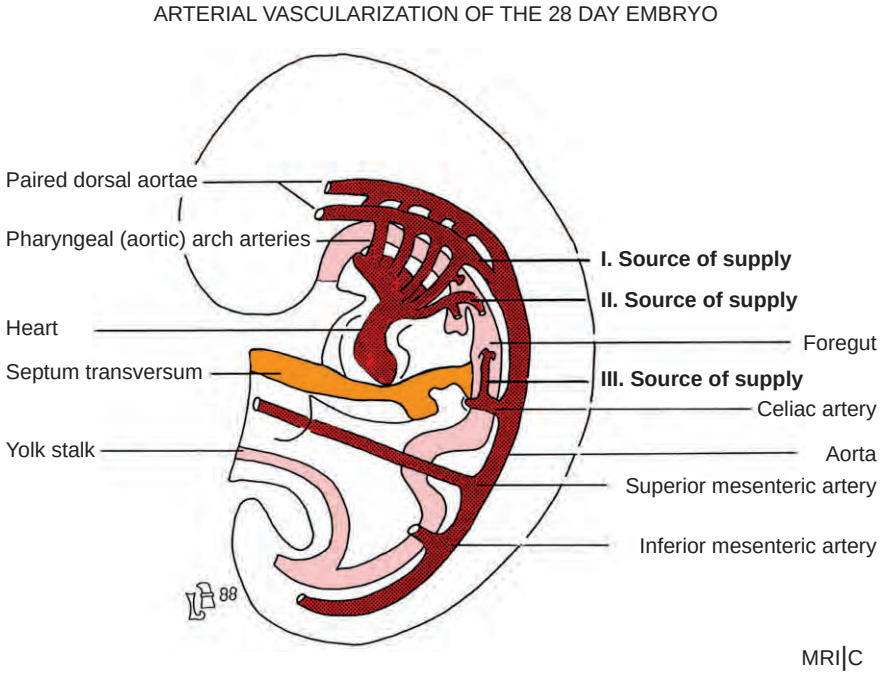


Figure 2–51. Schematic drawing of a sagittal section through an embryo of month 2. The foregut and its blood vessels are displayed. Two of the three main sources of the adult blood supply of the foregut are derived from branchial arch arteries. These are the esophageal branches from source I, the later thyroid arteries, and from source II, the tracheobronchial arteries. The third source (III) derives from the gastric and splenic branches of the celiac artery. The septum transversum is related to the position of the celiac vessels. (Modified from Moore KL: The Developing Human. Philadelphia, WB Saunders, 1988.)

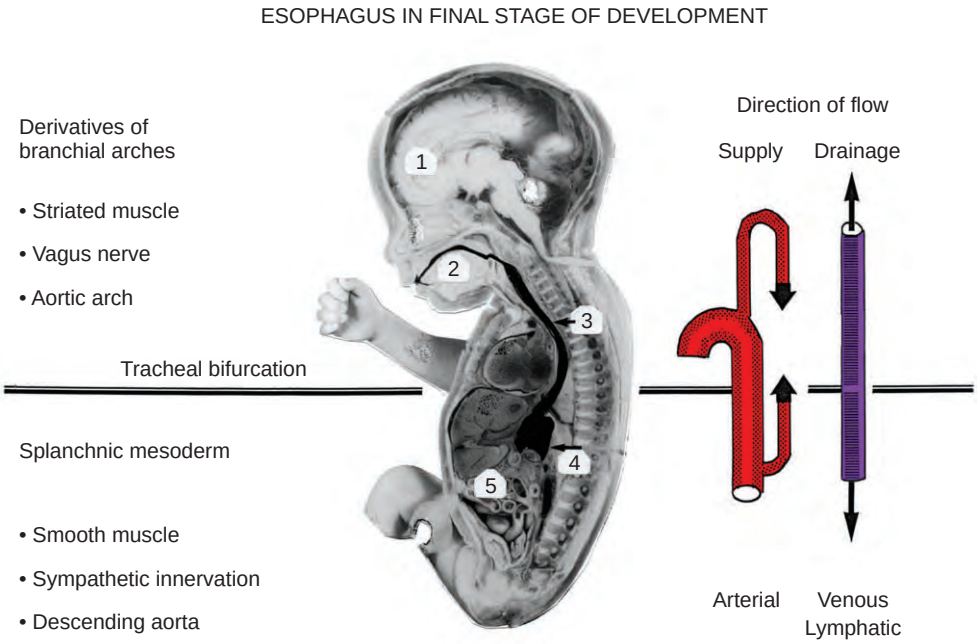


Figure 2–52. The esophagus in the fetus and its topographic development. Structures above the line of the tracheal bifurcation (vessels, nerves, and lymphatics) originate from the tissue of the branchial arches and pharyngeal pouches (branchial apparatus). Below this line, the structures derive from the lateral plate of the body mesenchyme. This border, located at the level of the tracheal bifurcation, permanently defines the direction of vascular flow (see *arrows*). 1, Head; 2, oral cavity and pharynx; 3, esophagus; 4, stomach; 5, bowel.

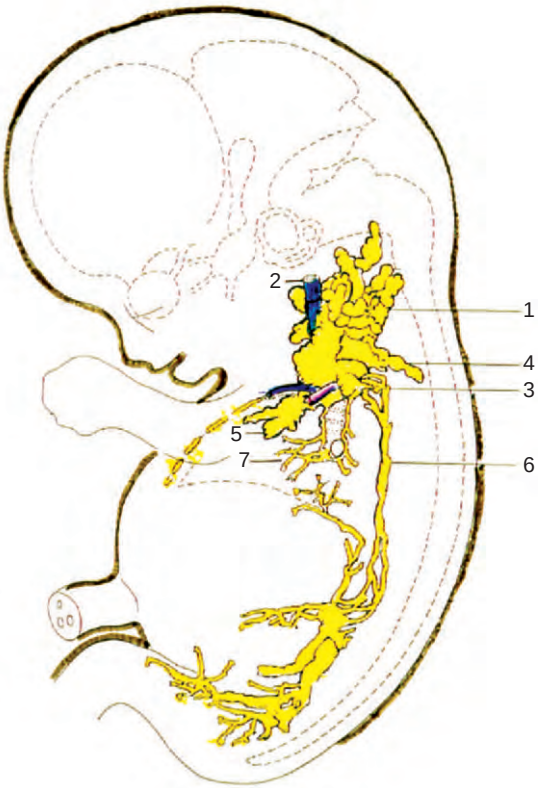


Figure 2–53. Schematic illustration of the saccular lymphatic system at the 30-mm crown-rump length stage, eighth week of gestation. The branchiogenic part into which the upper foregut drains is far more voluminous than that of the lower foregut, midgut, and hindgut. The saccus jugularis (1); the jugular vein (2); the suprascapular (3), supraclavicular (4), and axillary lymphatic protrusions (5); the thoracic duct (6); and the bronchoesophagomediastinal lymphatics (7) are seen. (Modified after von Gaudecker B: Lymphatische Organe. In Hinrichsen KV [ed]: Human Embryologie: Lehrbuch und Atlas der vorgeburtlichen Entwicklung des Menschen. Berlin, Springer-Verlag, 1990, p 340, with permission.)

The Cranial Nerves: Their Origin and Distribution

The cranial nerves develop during weeks 5 and 6. According to their embryologic origin they are classified into "somatic efferent cranial nerves" and "nerves of the branchial arches." The structures that derive from the branchial arches maintain their respective innervation throughout life. One of the branchial arch nerves (i.e., the cranial nerve) is the vagus nerve.

The Vagus Nerve: The Major Foregut Nerve

The vagus nerve is the 10th cranial nerve and is formed by the early fusion of nerves from the last three branchial arches (Fig. 2–54). Large efferent and afferent compo-

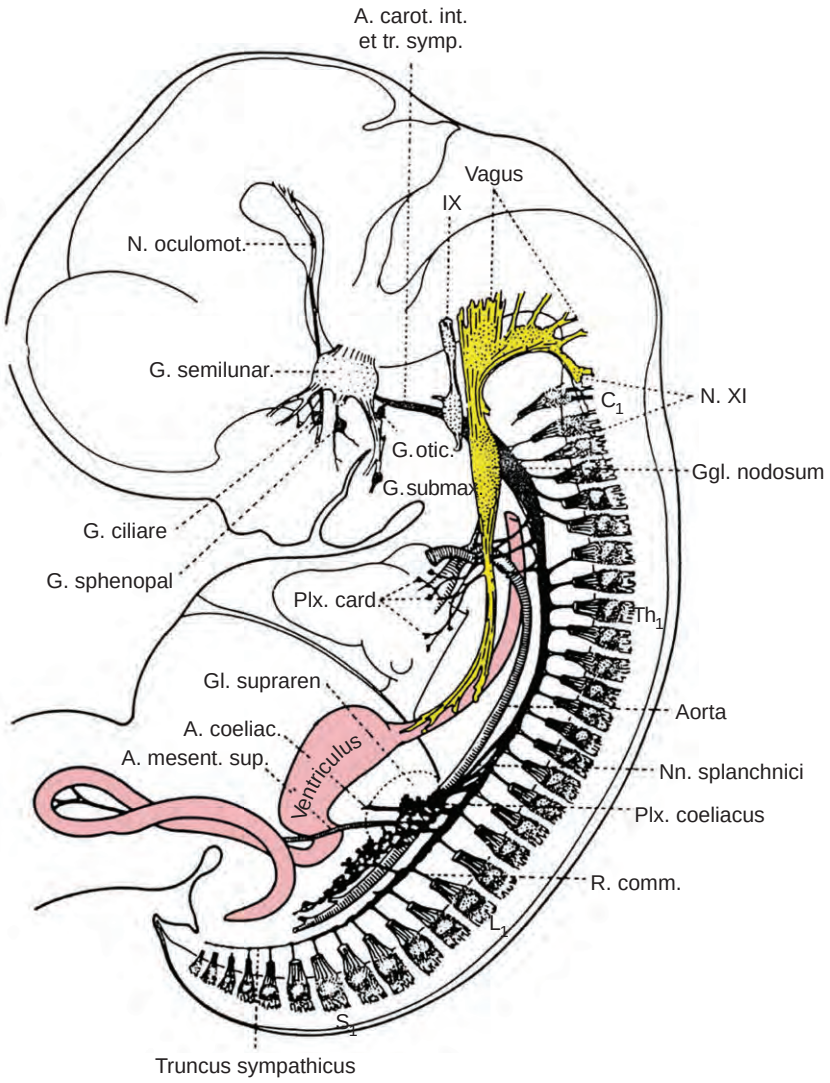


Figure 2–54. The parasympathetic and sympathetic nervous systems in relation to the foregut in a human embryo of 18-mm crown-rump length. (From Hinrichsen KV: a. Intestinaltrakt, b. peripheres Nervensystem, c. Venen. In Hinrichsen KV [ed]: Human Embryologie: Lehrbuch und Atlas der vorgeburtlichen Entwicklung des Menschen. Berlin, Springer-Verlag, 1990, pp 305, 449, 516, with permission.)

nents of the vagus nerve are distributed to the heart, the foregut and its derivatives, as well as part of the midgut.[14,17,38,39] The efferent fibers arise from the specialized dorsal motor nucleus, whereas the afferent fibers derive from neuroblasts of the neural crest. Removal of the neural crest at an early stage of development has been shown to result in an absence of ganglia in the esophagus.[14,40]

Smith and Taylor[41] reviewed the subject of vagal system development and emphasized the diverse opinions that exist on the issue. Liebermann-Meffert has clearly identified the two precursor vagal trunks in the 8.5-mm CRL embryo[3] (see Fig. 2–42). The superior laryngeal nerves can be distinguished at 7- to 9-mm CRL; the inferior laryngeal (recurrent) nerves can be seen at almost the same stage (see Fig. 2–42A). The vagus nerves are extremely large at the 12- to 20-mm CRL stage (see Figs. 2–42 and 2–44). Both vagal nerves (see Fig. 2–54) and the recurrent laryngeal nerves keep their definite position alongside and attached to the esophagus at an early stage of development when the embryonal body straightens by the end of the sixth week (14-mm CRL).[29]

The fibers of the superior laryngeal nerves derive from the mesenchyme of the fourth branchial arches, whereas the nerves of the sixth branchial arches become the inferior (laryngeal) recurrent nerves (see Moore in "Suggested Readings").

Congenital Malformation: The Nonrecurrent Inferior Laryngeal Nerve

This anomaly occurs as a result of the embryologic interrelationships of development of the inferior RLN and the subclavian artery. In the presence of an aberrant retroesophageal right subclavian artery, the nerve passes to the larynx without recurring. This is related to abnormal degeneration of the sixth and fifth aortic arteries (see Skandalakis and Moore in "Suggested Readings").

Origin of the Sympathetic (Thoracolumbar) Nervous System, the Phrenic Nerve

Neural crest cells of the sympathetic nervous system migrate along the rami of the thoracic spinal nerves in the late somite stage (week 5) (see Hamilton and Mossman and Moore in "Suggested Readings"). The

nerve fibers then leave their medial position and form segmentally arranged paired cell masses behind the aorta. They constitute the primordium of the sympathetic nervous system (see Fig. 2–54). The precise origin of these cells has not yet been clarified.

The phrenic nerve, which is responsible for innervation of the developing diaphragmatic muscle, is formed from the anterior primary rami of the third to the fifth cervical nerves.[41]

Distribution of the Developing Periesophageal Nerves

van Campenhout[38] observed that neuroblasts from the periesophageal plexus enter the esophageal wall very early in development, before the embryo has reached 10-mm CRL. The neuroblasts form a complete periesophageal network at the outer limits of the circular muscle layer of the esophagus before the longitudinal muscle differentiates. In the 40-mm CRL embryo, 8 to 12 nerve bundles cover the mid and terminal portions of the esophagus. By the time that the embryo reaches 65-mm CRL, the periesophageal plexus of the lower esophagus consists of large, interlacing vagal bundles that contain ganglia.

The Myenteric Plexus

The myenteric plexus is identifiable in the 10-week-old fetus.[14,41,42] At this stage, ganglion cells are not positively identifiable but are represented by numerous pale areas in the myenteric plexus. The number of cells, cell size, and nerve density peak at the 16th to 20th week of gestation.[39] Sparse submucosal nerve fibers can be discerned in the 35-mm CRL embryo. These fibers become the submucosal plexus. According to Hewer,[42] this plexus is not well developed until the 67-mm CRL stage, but it is complete in the 80-mm CRL fetus.[41] In the 90-mm CRL fetus, the submucosal plexus is extensive and consists of fine nerve fibers and ganglia. The innervation of the muscularis mucosae is particularly rich in the fetus at the 140-mm CRL stage.

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Chapter

3

Physiology of the Esophagus and Its Sphincters

Radu Tutuian · Donald O. Castell

The esophagus is a muscular tube whose major role is transporting nutrients from the mouth to the stomach. It also allows evacuation of gas (belching) or gastric content (vomiting) from the stomach. In humans, the musculature of the esophagus transitions from (1) predominantly striated at the level of the upper esophageal sphincter (UES) and proximal 1 to 2 cm of the esophagus through (2) a mixed striated–smooth muscle transition zone spanning 4 to 5 cm to (3) an entirely smooth muscle structure in the distal 50% to 60% of the esophagus, including the lower esophageal sphincter (LES) (Fig. 3–1).[1] Recognizing this difference in the muscular sequence of the esophagus is important to understanding swallowing and the pathophysiology of diseases affecting the esophagus.

SWALLOWING PROCESS

Normal human subjects swallow on average 500 times a day.[2] The act of swallowing can be divided into three stages: the oral (voluntary) stage, the pharyngeal (involuntary) stage, and the esophageal stage. These stages are a continuous process closely coordinated through the medullary swallowing centers.[3]

Oral Stage

The oral stage of the swallowing process involves the tongue and the extrinsic oropharyngeal muscles and is the phase during which the swallowing mechanism is primed. During the oral phase, the tongue changes its three-dimensional configuration to allow contraction of the tongue to push the bolus backward and upward toward the hard palate. The configuration of the tongue is changed so that it forms an "expulsion chamber" in which the bolus is contained by the base of the tongue (anterior and inferior), the peripheral edges of the tongue (lateral), the hard palate (superior), and the closed glossopalatal gate (posterior). The size of the bolus-loading chamber varies with the size of the bolus. The loading time of the expulsion chamber also varies with the size of the bolus. However, expulsion time is independent of the size of the bolus and lasts around 0.5 second. Volume-independent oral expulsion and clearance are achieved by increases in glossopalatal gate opening, lingual propulsion velocity, and contraction amplitude with increasing bolus volumes. Once the bolus passes through the glossopalatal opening, swallowing enters the pharyngeal phase and the process becomes involuntary.

Pharyngeal Stage

In the pharyngeal stage of swallowing, food passes from the oral cavity into the pharynx, across the UES, and into the proximal end of the esophagus. This involuntary phase consists of a series of rapid, carefully coordinated striated muscular contractions (Fig. 3–2). Aside from propelling the food bolus from the mouth into the esophagus, the muscular activity in the pharyngeal phase of deglutition has to prevent food from entering the airways (i.e., a "safe" swallow). Once the food is inserted into the mouth and masticated, the swallowing reflex is initiated by stimulating receptors at the base of the tongue, tonsils, anterior and posterior pillars, soft palate, posterior pharyngeal wall, epiglottis, and larynx.[4] The afferent information from these receptors is carried through the maxillary branch of the trigeminal nerve (cranial nerve V), the glossopharyngeal nerve (cranial nerve IX), and the superior laryngeal branch of the vagus nerve (cranial nerve X).[5] Swallowing can also be initiated voluntarily from the cerebral cortex, but some additional sensory input is required because voluntary deglutition is difficult when the pharynx is anesthetized or no bolus is present in the pharynx.[6] Sensory and cortical input is integrated in the swallowing center located in the brainstem. The swallowing center includes neurons in the

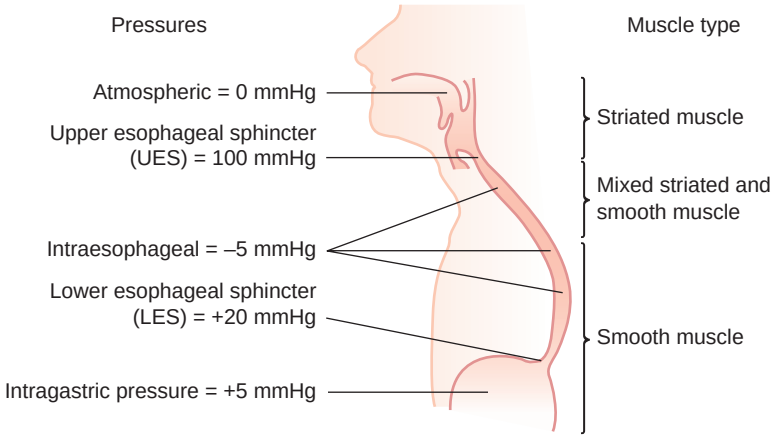

Figure 3–1. Pressures recorded in the upper esophageal sphincter, esophagus, lower esophageal sphincter, and stomach in reference to atmospheric pressure. The type of musculature varies from striated in the pharynx and proximal part of the esophagus, through a transition zone of mixed striated and smooth muscle, to only smooth muscle in the distal part of the esophagus.

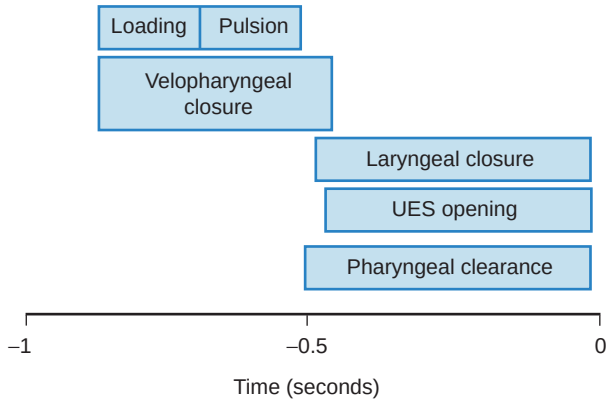

Figure 3–2. Time course of events during swallowing of liquid boluses. The timing of events is presented in reference to closure of the upper esophageal sphincter (UES) (time zero).

nucleus tractus solitarius, the nucleus ambiguus, and the adjacent reticular formation. These centers send efferent information to the oropharyngeal musculature via the trigeminal nerve (cranial nerve V), facial nerve (cranial nerve VII), glossopharyngeal nerve (cranial nerve IX), vagus nerve (cranial nerve X), and hypoglossal nerve (cranial nerve XII).

Just before the beginning of the pharyngeal stage, in anticipation of the arrival of a food bolus, respiration is temporarily suppressed and the pharynx is converted from a respiratory to a swallowing pathway.[7] Conversion of the pharynx into a swallowing pathway requires (1) closure of the openings of the pharynx to the nasal passages, oral cavity, and laryngeal vestibule; (2) opening of the UES; and (3) shortening and widening of the pharyngeal chamber. The following steps are involved in these processes:

1. Pulling up the soft palate and closing the posterior nares
2. Medial pulling of the palatopharyngeal folds, leading to closure of the velopharyngeal junction (this process limits the opening through the pharynx, which can impair the passage of larger boluses)
3. Closing the vocal cords and a backward and downward swing of the epiglottis to close the larynx
4. Upward and forward movement of the larynx, leading to stretching of the esophageal and UES opening
5. Active relaxation of the UES from the usually tonic cricopharyngeus
6. Passive opening of the UES created by the laryngeal movement
7. Contraction of the superior constrictor muscle of the pharynx, which represents the beginning of pharyngeal peristalsis to clear the food into the esophagus

Combined videofluoroscopic and manometric studies indicate that the pharyngeal peristaltic contraction begins by apposition of the soft palate and contraction of the posterior pharyngeal wall. During the progression of peristalsis toward the esophagus, the posterior pharyngeal wall sequentially comes in contact with the posterior surface of the tongue; the epiglottis; the laryngeal, arytenoid, and interarytenoid muscles; and the cricoid cartilage.[8] Before complete occlusion occurs, the anatomic structure of the pharynx, epiglottis, and cricoid cartilage occludes the medial part of the swallowing chamber and thereby splits the bolus into two lateral halves. Pharyngeal clearance has very rigorous timing and does not vary much with the size of the bolus. The propagation velocity of the tail end of the bolus overlaps the propagation velocity of the pharyngeal contraction and does not vary with the volume of the bolus. This constancy is achieved by earlier opening of the UES and higher bolus-head velocity as the size of the bolus increases.

Anatomically, the UES is composed of the cricoid cartilage ventrally and the cricopharyngeal muscle laterally and dorsally. The insertion of the cricopharyngeal muscle on the cricoid cartilage results in an asymmetric pressure profile of the UES. Normal UES pressure is approximately 100 mm Hg in the anterior-posterior direction and approximately 50 mm Hg laterally.

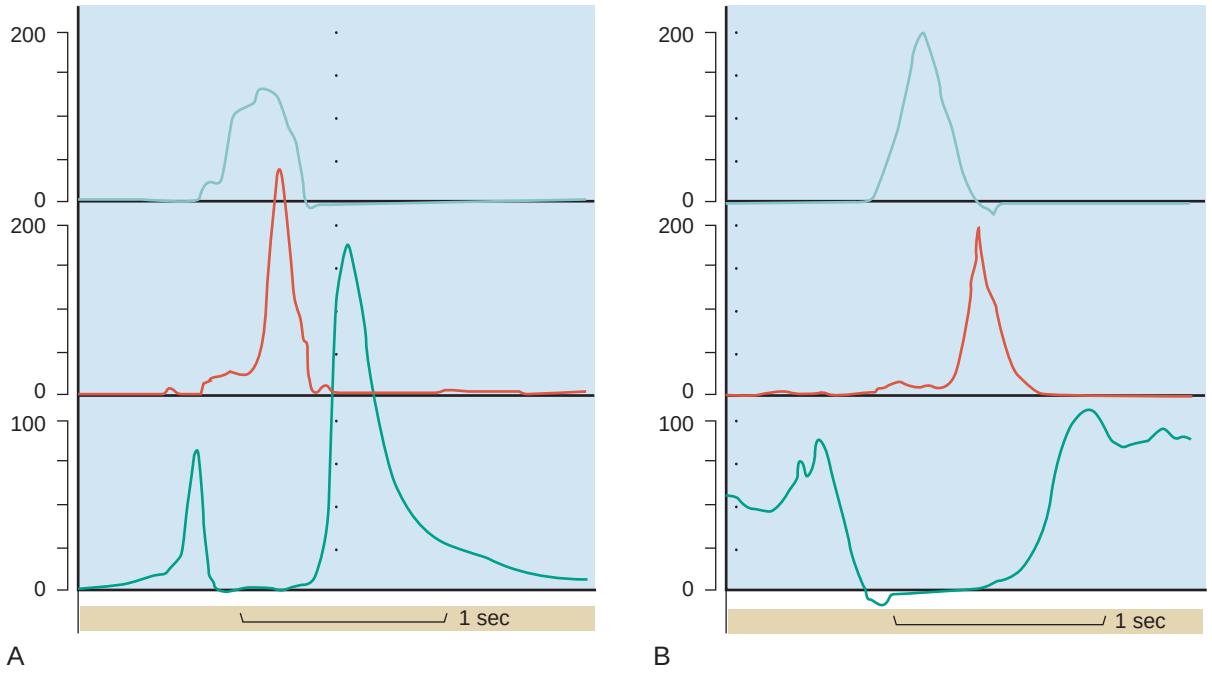

Figure 3–3. Oropharyngeal manometry tracings recorded with the distal transducer above the upper esophageal sphincter (UES) (**A**) and in the UES (**B**). When the distal sensor is placed above the UES, a typical "M" pattern is identified in the distal channel. Initially, the pressure rises as the UES ascends on the transducer, followed by relaxation of the UES. The pressure will then rise again once the UES closes and will return to the pharyngeal baseline when the UES descends back into the initial position. If the distal pressure transducer is placed in the UES, during deglutition it will "drop" into the esophagus and thereby actually lead to overestimation of UES relaxation duration (because it also includes ascent and descent of the UES) and misinterpretation of UES residual pressure (because esophageal baseline pressure is actually being measured).

In view of the asymmetric pressure profile, timing of the pharyngeal-UES transfer and vertical movement of the UES during deglutition are important details when performing UES manometry studies. To obtain accurate information on UES dynamics, circumferential solid-state pressure transducers are preferred because of the rapid response time of the transducers and the capability of evaluating radial forces over the entire 360 degrees.[9] Because the UES ascends approximately 1 cm during deglutition, we prefer placing the UES pressure transducer about 1 cm above the sphincter. During deglutition, the sphincter will initially rise onto the transducer, then open, let the bolus move through, close, and then descend into the initial position. It is our opinion that this approach allows more accurate determination of UES dynamics. When the distal sensor is placed above the UES, a typical "M" pattern is identified in the distal channel. Initially, the pressure rises as the UES ascends onto the transducer, followed by UES relaxation (Fig. 3–3). The pressure will then rise again once the UES closes and will return to the pharyngeal baseline when the UES descends back into the initial position. If the distal pressure transducer is placed in the UES, it will "drop" into the esophagus during deglutition and therefore lead to an overestimation of the duration of UES relaxation (because it also includes ascent and descent of the UES) and misinterpretation of UES residual pressure (because the transducer is actually measuring esophageal baseline pressure).

Esophageal Stage

The esophageal stage of swallowing starts once the food is transferred from the oral cavity through the UES into the esophagus. The main function of the esophagus is to transport the ingested bolus from the pharynx into the stomach. This active process is achieved by contractions of the circular and longitudinal muscles of the tubular esophagus and coordinated relaxation of the LES. Sequential contraction of the esophageal circular muscle in a proximal-to-distal direction generates a peristaltic clearing wave (Fig. 3–4). Esophageal peristalsis is controlled by afferent and efferent connections of the medullary swallowing center via the vagus nerve (cranial nerve X). The proximal striated esophageal musculature is directly innervated by the nucleus ambiguus, whereas innervation of the distal, smooth musculature of the esophagus and LES comes from the dorsal motor nucleus of the vagus. The vagus nerve carries both stimulating (cholinergic) and inhibitory (noncholinergic, nonadrenergic) information to the esophageal muscula-

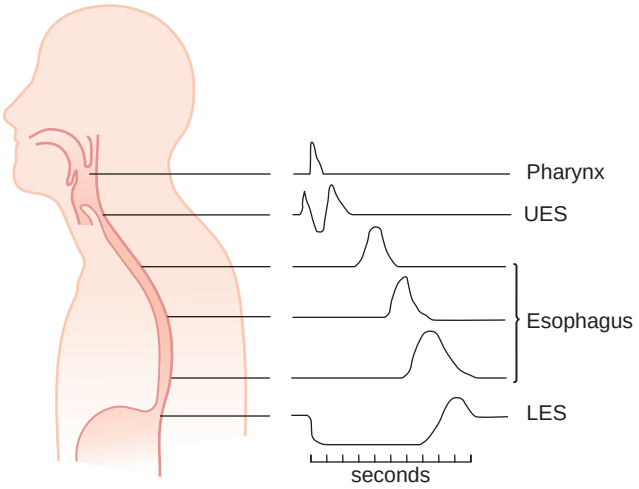

Figure 3–4. Schematic representation of pressure changes recorded in the pharynx, upper esophageal sphincter (UES), esophagus, and lower esophageal sphincter (LES) during esophageal peristalsis.

ture. In addition to the central nervous system control, the myenteric (Auerbach) plexus located between the circular and longitudinal muscle layers plays a major role in coordinating peristalsis in the smooth muscle portion of the distal esophagus. The importance of the myenteric plexus in controlling distal, smooth muscle peristalsis is shown by observations that bilateral cervical vagotomy in animals does not abolish peristalsis in this portion of the gastrointestinal tract.

Esophageal Peristalsis

Esophageal peristalsis is the result of sequential contraction of the circular esophageal muscle. Three distinct patters of esophageal contractions have been described: primary and secondary peristalsis and tertiary contractions.

Primary peristaltic contractions are the usual form of the contraction waves of circular muscles that progress down the esophagus; they are initiated by the central mechanisms that follow the voluntary act of swallowing. The contraction wave begins in the pharynx and requires approximately 8 to 10 seconds to reach the distal part of the esophagus. During primary peristalsis, the LES is relaxed, starting at the initiation of swallowing and lasting until the peristalsis reaches the LES.

Secondary peristaltic contractions are the contraction waves of the circular esophageal muscle occurring in response to esophageal distention. They are not a result of central mechanisms and can be experimentally demonstrated by distending a balloon in the proximal section to midsection of the esophagus. The role of secondary peristaltic contractions is to clear the esophageal lumen of ingested material not cleared by primary peristalsis or material that is refluxed from the stomach. Secondary peristaltic contractions are not accompanied by pharyngeal peristalsis or UES relaxation. However, in the distal part of the esophagus, secondary peristaltic contractions resemble those of primary peristalsis.

Tertiary contractions are primarily identified during barium x-ray studies and represent nonperistaltic contraction waves that leave segmental indentations on the barium column. The physiologic role of these contractions is unknown, and obliteration of the lumen is their only potential pathologic consequence.

The amplitudes of contractions vary throughout the esophagus. Contraction amplitudes are higher in the proximal and distal parts of the esophagus, with a midesophageal low-pressure zone located at the junction of the striated and smooth muscle portion of the esophagus (Fig. 3–5). High-resolution manometry studies using catheters with pressure sensors at each centimeter in the esophagus suggest the existence of two distinct pressure waves, proximally and distally, in the midesophageal low-pressure zone (Fig. 3–6). In healthy individuals, primary esophageal peristalsis during wet swallows of the same volumes is very reproducible. There is little swallow-by-swallow variation in amplitude and velocity when swallows are spaced at least 20 to 30 seconds apart (see later). There is no "fatigue" of the esophageal musculature inasmuch as similar amplitudes have been recorded during as many as 50 consecutive swallows. Esophageal contraction amplitudes are lower in the upright position,[10] and the velocity is higher in the proximal than in the distal esophagus.[11] The amplitude and duration of contraction are increased and the velocity decreased when fluid swallows are given as opposed to dry swallows.[12] Larger bolus volumes elicit stronger peristaltic contractions,[13] warm boluses augment[14] and cold boluses inhibit peristaltic contractions,[15] and the osmolality of the bolus has no influence on esophageal peristalsis.[16] Contrary to popular belief regarding "presbyesophagus," esophageal peristalsis is not affected by age in healthy volunteers.[17]

In vitro studies on sections of esophageal smooth muscle from the opossum have increased our understanding of the activities of circular and longitudinal esophageal muscle during peristalsis.[18] Circular and longitudinal muscles differ not only in the orientation of their fibers but also in their response to electrical stimuli (Fig. 3–7). A stimulus applied to an isolated section of longitudinal esophageal muscle will lead to a sustained contraction of the muscle ("duration response") lasting as long as the stimulus is applied. This response is mediated by acetylcholine because it can be blocked with both atropine and tetrodotoxin. In contrast, circular muscle will show a brief contraction ("on response") at the onset of the electrical stimulus, followed by a period of relaxation lasting as long as the stimulus is applied. Once the stimulus is discontinued, a much larger contraction occurs ("off response"). Furthermore, smooth muscle strips taken from different segments of the esophagus show progressively longer time intervals (latency) from the termination of the stimulus to the onset of the "off response" as one progresses more distally in the esophagus (Fig. 3–8).

Based on these observations, the following model of esophageal peristalsis has been proposed. When a swallow is initiated, the longitudinal muscle contracts

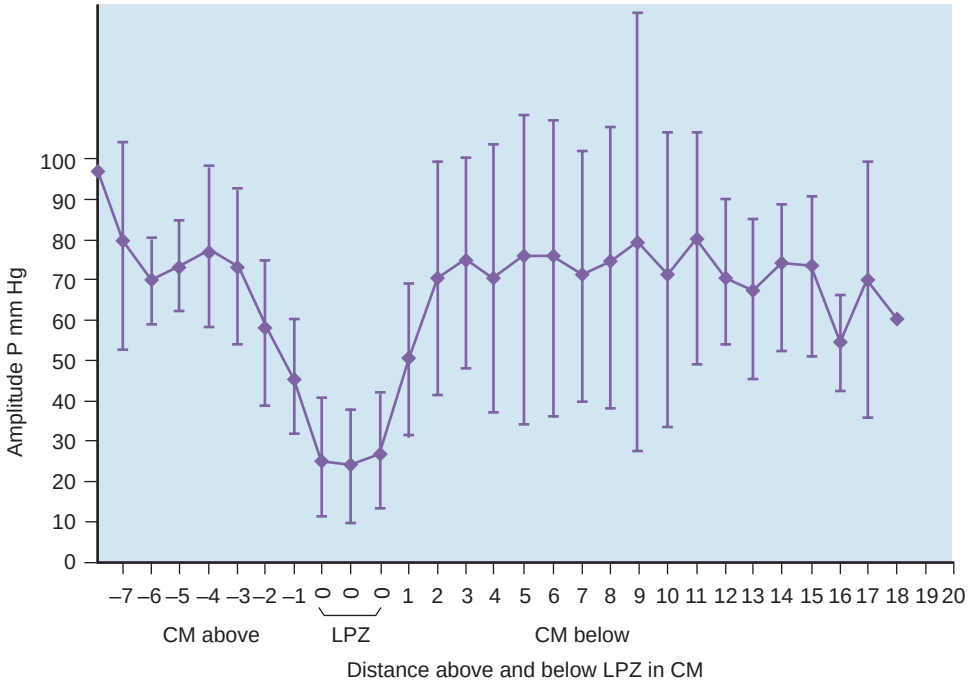

Figure 3–5. Esophageal pressure profile in the esophagus during contractions.

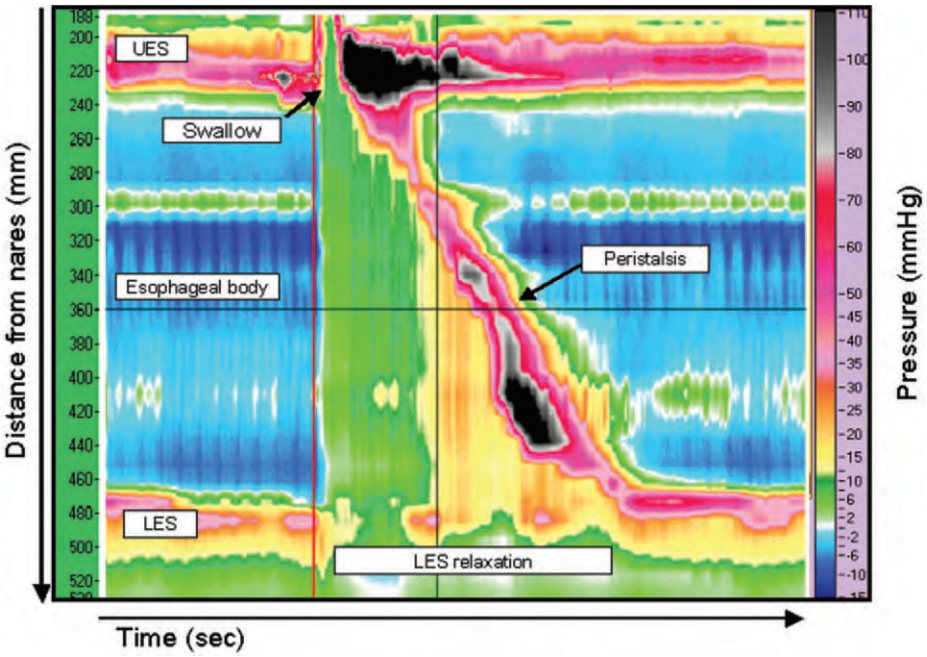

Figure 3–6. Spatial-temporal plots of esophageal peristalsis recorded by high-resolution manometry. The 32 pressure channels located every 1 cm span the entire esophagus, including the pharynx, upper esophageal sphincter (UES), lower esophageal sphincter (LES), and proximal part of the stomach. Intraesophageal pressures of the same amplitude are coded with the same color, starting at –10 mm Hg (blue) and ranging through 110 mm Hg (black).

and "stiffens" the walls of the esophagus to provide support for the circular muscle contractions. The circular muscle responds by a short contraction ("on response"), followed by relaxation of the entire esophagus, including the LES. The increase in the latency gradient, as one progress more distally in the esophagus, is responsible for the delay in esophageal contractions that generates the peristaltic wave. This model does not entirely explain all the phenomena that have been observed in human esophageal peristalsis, but the aforementioned in vitro observations are consistent with many aspects of normal human physiology.

One example is deglutitive inhibition. Although pharynx and UES dynamics last less than 1 second, which allows them to respond with a 1:1 ratio to closely spaced swallows, it takes 8 to 10 seconds for a single food bolus to pass through the esophagus into the stomach. When swallows are very closely spaced (i.e., between 2 and 5

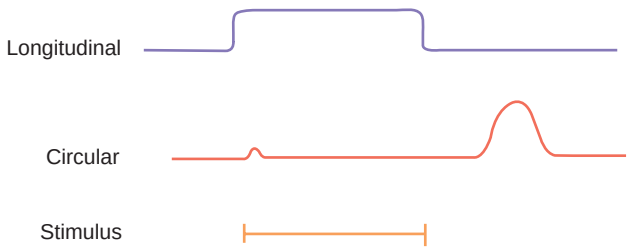

Figure 3–7. Differences in response of longitudinal and circular esophageal musculature to electrical stimuli. Longitudinal muscle exhibits sustained contractions ("duration contraction") lasting as long as the stimulus is present. Circular muscle has a brief contraction ("on response") at the onset of the stimulus, followed by a period of relaxation lasting as long as the stimulus is present. A second, stronger response ("off response") is noted after a lag period once the stimulus is discontinued.

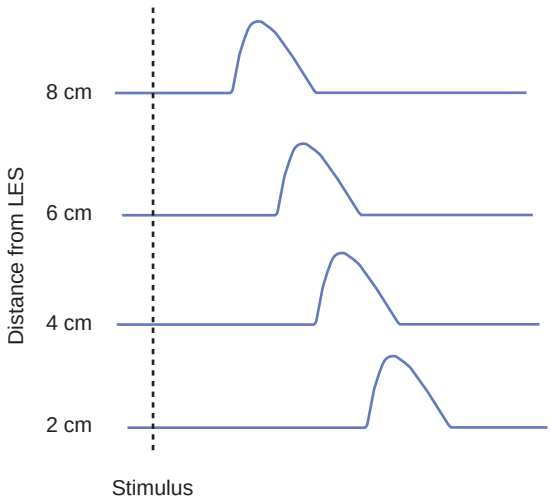

Figure 3–8. Increase in the lag period between the end of the stimulus to the onset of the "off response" in circular muscle fibers harvested at different levels above the lower esophageal sphincter (LES).

seconds), contraction of the distal part of the esophagus is inhibited by the inhibitory neural impulses sent by the subsequent swallow. This phenomenon of "deglutitive inhibition" is physiologically beneficial in that an improperly timed contraction that impairs bolus transit is avoided during subsequent swallows (Fig. 3–9). The off-response and latency period will then produce one peristaltic contraction at the end of a series of closely spaced swallows to allow proper clearance of the esophagus.[19]

The presence of the inhibitory relaxation wave can be demonstrated by measuring the pressure in an inflated balloon in the distal esophagus.[20] Positioning an inflated balloon at either 3 or 8 cm above the LES, Sifrim et al. have documented a decrease in pressure in the artificially balloon-created high-pressure zone starting at the time of swallowing and lasting until the peristaltic contraction reaches the segment. The same investigators found this phenomenon to be absent in patients with achalasia and distal esophageal spasm.[21]

Nonadrenergic, noncholinergic mediators are thought to control in part the latency phase responsible for esophageal peristalsis. From this group of substances, vasointestinal peptide (VIP) and nitric oxide (NO) appear to play an important role in the human esophagus. With the use of NO scavengers (recombinant human hemoglobin) during esophageal contractions, Murray et al.[22] evaluated the role of NO in human esophageal peristalsis. Studying healthy volunteers, they documented altered esophageal peristalsis and simultaneous contractions (resembling esophageal spasm) during the administration of recombinant human hemoglobin.

In addition to peristaltic contractions, clinical studies support the existence of an esophageal propulsive force. This was first reported by Winship et al.[23] during swallowing studies in healthy volunteers when they noticed a steady, aborally directed force of up to 200 g exerted on a balloon that was inflated in the esophagus and prevented from moving distally. The esophageal propulsive force increases with an increase in the diameter of the bolus and is greatest in the distal end of the esophagus. The propulsive force is produced by tonic and phasic contractions of the longitudinal and circular muscle just above the balloon.[24] Once the balloon is released, the propulsive force is converted into a peristaltic sequence that progresses distally and pushes the balloon ahead of it.

Lower Esophageal Sphincter

The LES can be located during manometric stationary pull-through as a tonically contracted region at the esophagogastric junction. Normal LES resting pressure ranges from 10 to 45 mm Hg above the gastric baseline level and results from the tonic (intrinsic) LES component augmented by the phasic (extrinsic) diaphragmatic pressure, which varies with respirations. The function of the LES is to prevent gastroesophageal reflux and to relax with swallowing to allow movement of ingested food into the stomach.

The mechanism by which the circular musculature in the LES maintains tonic closure has been investigated considerably. At present, it is believed to be predominantly due to intrinsic muscle activity because the resting LES tone persists even after surgical or pharmacologic destruction of all neural input.[25] Calcium channel blockers that exert their effect directly on circular muscle can reduce resting LES pressure,[26] and there appears to be some cholinergic tone because resting LES pressure can be reduced with anticholinergic agents.[27] In addition, LES tone can be influenced by a series of hormones and pharmacologic agents (Table 3–1).

The LES relaxes to allow passage of food from the esophagus into the stomach or to allow material from the stomach to come back into the esophagus. Even though

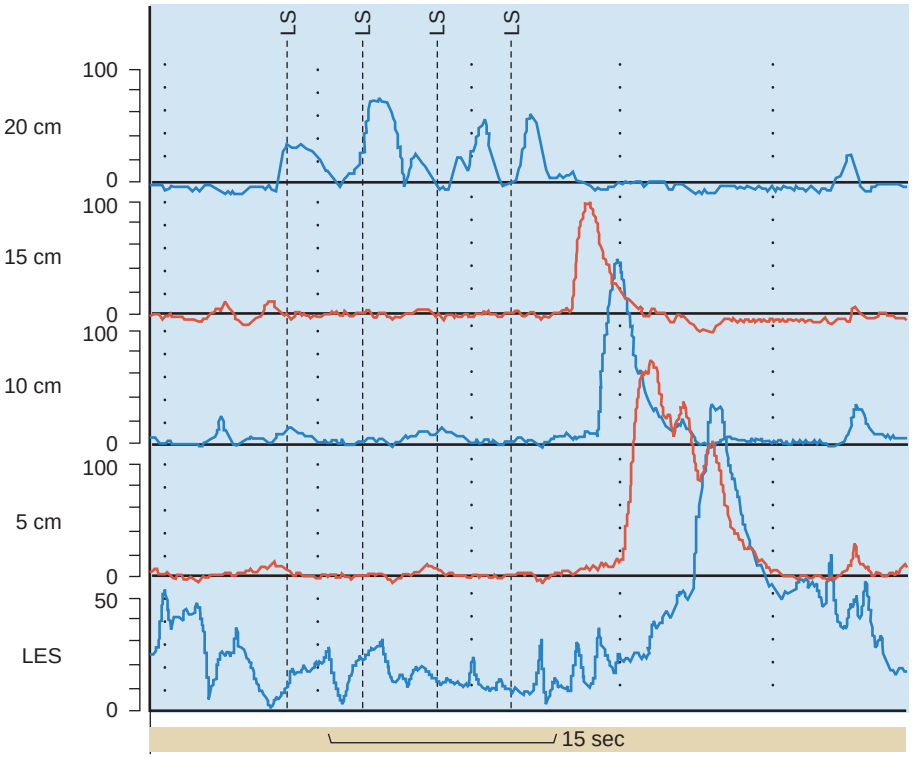

Figure 3–9. Manometric example of deglutitive inhibition. Distal esophageal body contractions of the first three swallows are inhibited when swallows are given 5 seconds apart. The last (fourth) swallow produces a peristaltic contraction that will clear the esophageal lumen. The lower esophageal sphincter is relaxed the entire time during closely spaced swallows.

Table 3–1 Hormonal and Pharmacologic Agents Influencing Lower Esophageal Sphincter Resting Pressure

Increase LES Pressure	Decrease LES Pressure
Gastrin	Secretin
Motilin	Cholecystokinin (CCK)
Substance P	Glucagon
Pancreatic polypeptide	Gastric inhibitory peptide (GIP)
Bombesin	Vasointestinal peptide (VIP)
Angiotensin II	Progesterone
Cholinergic agents (e.g., bethanechol)	Atropine
Metoclopramide	Nitrates
Dopamine	Calcium channel blockers
Cisapride	Morphine

the relaxations are transient in both instances, many clinicians and investigators attribute the term *transient lower esophageal sphincter relaxation* (tLESR) to the inappropriate LES relaxations resulting in belching or gastroesophageal reflux. Therefore, the term *deglutitive lower esophageal sphincter relaxation* (dLESR) has been used to describe the relaxations that allow material to pass from the esophagus into the stomach.

dLESRs are reflex relaxations starting less than 2 seconds after the initiation of a swallow. Liquid boluses, especially when assisted by gravity in the upright position, may reach the LES before it relaxes and may therefore be slightly delayed in their passage into the stomach. The relaxation usually lasts 8 to 10 seconds and is followed by an after-contraction in the proximal part of the LES. The after-contraction is a continuation of esophageal peristalsis and lasts 7 to 10 seconds. Therefore, after a swallow at least 15 to 20 seconds elapse before the LES reaches the preswallow steady state.

Relaxation of the LES is the most sensitive component of the swallowing reflex. Isolated dLESRs can be provoked by pharyngeal tactile stimulation that is at a subthreshold for producing a full swallowing response. LES relaxations induced by primary peristalsis or pharyngeal tactile stimuli are mediated via the vagus nerve and can be abolished by bilateral vagal nerve section or cooling.[28,29] LES relaxations can also be produced by esophageal distention. Distention of the striated portion of the esophagus leads to a centrally mediated LES relaxation that can be abolished by vagal nerve section. In contrast, vagal nerve sectioning does not abolish LES relaxations triggered by distention of the smooth muscle portion of the esophagus, which suggests that this reflex is mediated via the intramural nerves.[30]

tLESRs occur in response to proximal gastric fundus distention and permit gastroesophageal reflux, belching, retching, and vomiting. Not all tLESRs are accompanied by gastroesophageal reflux, and the proportion of tLESRs associated with reflux varies from 10% to 93%.[31,32] tLESRs are vagally mediated and controlled by the same

central structures that control swallow-induced LES relaxations. Pharmacologic interventions that affect the vagal pathways of the medullary center can influence the frequency of tLESRs, and vagotomy or vagal cooling can block tLESRs.[33] Noncholinergic, nonadrenergic mediators such as NO and VIP can facilitate tLESRs.

LES relaxation is different from LES opening. LES relaxation is required for the LES to open, but there is a slight delay in opening of the LES during both dLESRs and tLESRs. Most recently, combined multichannel intraluminal impedance and manometry have been adapted to evaluate the relationship between these two phenomena without the use of radiation.[34]

SUMMARY

During food ingestion, the primary function of the esophagus is to facilitate the passage of boluses from the oral cavity into the stomach. This process can be separated into transfer of food from the oral cavity through the pharynx into the proximal part of the esophagus, where it is transported distally into the stomach. The initial part of the swallowing reflex is voluntary, after which carefully coordinated contractions transform swallowing into an involuntary series of events. Functional changes of the pharynx during deglutition transiently transform this airway conduit into a digestive conduit to ensure that food is not aspirated into the lungs. Once food passes into the esophagus, peristaltic contractions transport the bolus into the stomach while the LES is temporary relaxed and opened. In between swallowing, the esophagus and its sphincters prevent food from coming back from the stomach into the pharynx and oral cavity.

Recognizing the functional organization of each stage of swallowing and reflux prevention is important for understanding the pathophysiology of esophageal and esophagus-related diseases.

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Part

2

Evaluation of Esophageal Pathology and Ambulatory Diagnostics

Chapter

4

Assessment of Symptoms and Approach to the Patient with Esophageal Disease

Jeffrey H. Peters

A careful, detailed, and structured assessment of the patient's symptoms is critical to any medical treatment, even more so in the decision to perform esophageal surgery. Accordingly, such evaluation should not be left to the referring physician or gastroenterologist. Experienced clinicians soon realize that many symptoms of esophageal disease can be confused or accompanied by non–esophageal-related gastrointestinal and respiratory symptoms that will not improve or may be worsened by specific therapy. This is particularly true of functional disorders, including gastroesophageal reflux disease (GERD) and esophageal motility abnormalities. Symptoms consistent with irritable bowel syndrome, such as alternating diarrhea and constipation, bloating, and crampy abdominal pain, should be sought and detailed separately from GERD symptoms. Likewise, symptoms suggestive of gastric disorders, including nausea, early satiety, epigastric abdominal pain, anorexia, and weight loss, are important to note and discuss with the patient.

SYMPTOMS OF FOREGUT DISEASE

Heartburn, regurgitation, dysphagia, and chest pain are the most prevalent symptoms of esophageal disease. A myriad of other foregut symptoms may or may not be present, including dyspepsia, anorexia, epigastric pain, nausea, vomiting, and early satiety. These symptoms are considerably more nonspecific and may indicate concomitant gastric or intestinal disease.

Heartburn is generally defined as a substernal burning-type discomfort beginning in the epigastrium and radiating upward. It is often aggravated by meals, spicy or fatty foods, chocolate, alcohol, and coffee and can be worse in the supine position. It is commonly, though not universally, relieved by antacid or antisecretory medications. Epidemiologic studies have shown that heartburn occurs monthly in as many as 40% to 50% of the Western population. The occurrence of heartburn at night and its effect on quality of life have recently been highlighted by a Gallup poll conducted by the American Gastroenterologic Society (Box 4–1).[1]

Regurgitation, the effortless return of acid or bitter gastric contents into the chest, pharynx, or mouth, is highly suggestive of foregut disease. It is often particularly severe at night when supine or when bending over and can be secondary to either an incompetent or an obstructed gastroesophageal junction. With the latter, as in achalasia, the regurgitant is often bland, as though the food were put into a blender. When questioned, most patients can distinguish the two. It is the regurgitation of gastric contents that may result in associated pulmonary

Box 4–1 Nighttime Heartburn Is an Underappreciated Clinical Problem

50 million Americans have nighttime heartburn at least once per week

80% of heartburn sufferers had nocturnal symptoms—65% both day and night

63% report that it affects their ability to sleep and has an impact on their work the next day

72% are taking prescription medications

Nearly half (45%) report that current remedies do not relieve all the symptoms

symptoms, including cough, hoarseness, asthma, and recurrent pneumonia. Bronchospasm can be precipitated by esophageal acidification and cough by either acid stimulation or distention of the esophagus.

Dysphagia, or difficulty swallowing, is a relatively nonspecific term but arguably the most specific symptom of foregut disease. It is often a sign of underlying malignancy and should be aggressively investigated until a diagnosis is established. Dysphagia refers to the sensation of difficulty in passage of food from the mouth to the stomach and can be divided into oropharyngeal and esophageal causes. Oropharyngeal dysphagia is characterized by difficulty transferring food out of the mouth into the esophagus, nasal regurgitation, aspiration, or any combination of these symptoms. Esophageal dysphagia refers to the sensation of food sticking in the lower part of the chest or epigastrium. It may or may not be accompanied by pain (odynophagia), which will be relieved by passage of the bolus.

Chest pain, though commonly and appropriately attributed to cardiac disease, is frequently secondary to esophageal disease as well. As early as 1982, DeMeester et al. showed that nearly 50% of patients with severe chest pain, normal cardiac function, and normal coronary arteriograms had 24-hour pH studies with positive results, implicating gastroesophageal reflux as the underlying cause.[2] Exercise-induced gastroesophageal reflux is a well-known occurrence and may result in exertional chest pain similar to angina.[3] It can be quite difficult if not impossible to distinguish the two causes, particularly on clinical grounds alone.[4,5] Nevens et al. evaluated the ability of experienced cardiologists to differentiate pain of cardiac versus esophageal origin.[6] Of 248 patients initially seen by cardiologists, 185 were thought to have typical angina and 63 to have atypical pain. Forty-eight (26%) of those thought to have classic angina had normal coronary angiograms, and 16 of the 63 with atypical pain had abnormal angiograms. Thus, the cardiologists' clinical impression was wrong 25% of the time. Finally, Pope et al. investigated the ultimate diagnosis in 10,689 patients going to an emergency department with acute chest pain.[7] Seventeen percent were found to have acute ischemia; 6%, stable angina; 21%, other cardiac causes; and 55%, noncardiac causes. They concluded that the majority of people going to the emergency department with chest pain do not have an underlying cardiac cause for their symptoms. Chest pain that is precipitated by meals, occurring at night while supine, nonradiating, responsive to antacid medication, or accompanied by other symptoms suggesting esophageal disease, such as dysphagia or regurgitation, should trigger the thought of possible esophageal origin. Furthermore, the distinction between heartburn and chest pain is also difficult and largely dependent on the individual patient. One person's heartburn is another's chest pain.

MECHANISMS OF ESOPHAGEAL SYMPTOMS

The precise mechanisms accounting for the generation of symptoms secondary to esophageal disease remain unclear. Considerable insight has been acquired, however. Investigations into the effect of luminal content,[8,9] esophageal distention[9-11] and muscular function,[12] neural pathways, and brain localization[13,14] have provided a basic understanding of the stimuli responsible for the generation of symptoms. It is also clear that the visceroneural pathways of the foregut are complexly intertwined with those of the tracheobronchial tree and heart. This fact accounts for the common overlap of clinical symptoms with diverse disease processes in the upper gastrointestinal, cardiac, and pulmonary systems.

Early investigations of the pathogenesis of esophageal symptomatology studied the effects of balloon distention or esophageal acid infusion (or both) on symptom generation. Classic studies, reported as early as the 1930s, investigated the type and location of symptom perception in patients after balloon distention at 5-cm increments in the esophagus.[15] These data revealed highly variable patient responses (Fig. 4–1). Patients rarely localized the origin of the stimulus accurately, often perceiving the symptom in areas above, below, or quite distant from the location of the distending balloon. Some patients perceived chest pain, some heartburn, and others nausea. Symptoms between the shoulder blades and at the base of the neck, as well as retrobulbar eye pain, were also observed. These findings underscore the highly variable nature of symptom generation secondary to foregut epithelial stimuli. More recent studies have confirmed these findings. Taken together, they suggest considerable variability in individual sensory sensitivity or cerebral cortical processing, or both.

Esophageal perfusion with either acid or bile salts can elicit various degrees of symptoms ranging from mild heartburn to severe angina-like chest pain. Symptom perception is dependent on both the concentration and contact time of the offending agent and is highly variable from individual to individual. In general, discomfort becomes reproducible below pH 4, a fact demonstrated in the early years of esophageal pH testing. This was, in part, responsible for the selection of pH 4 as the threshold pH below which acid reflux was considered present on ambulatory esophageal pH testing. Acid perfusion was the basis for the Bernstein test used historically as a

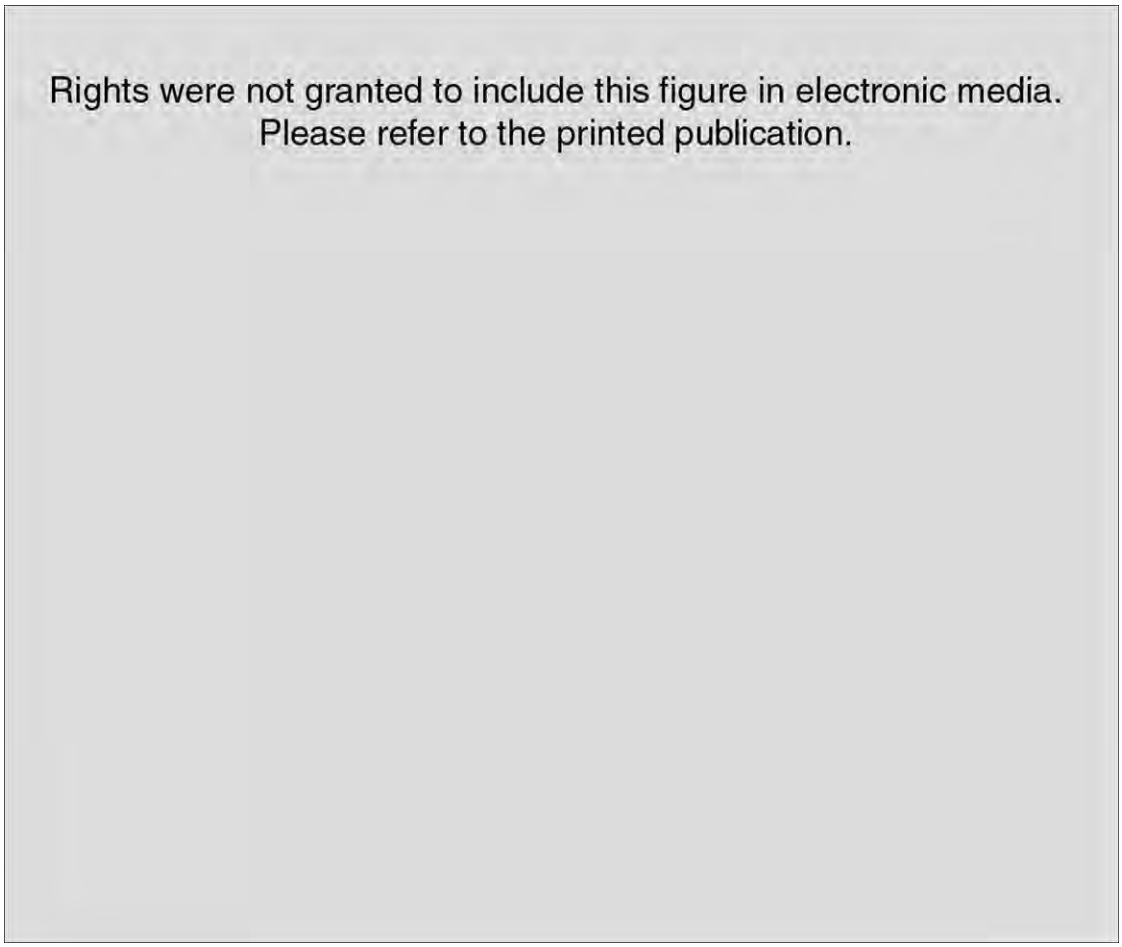

Figure 4–1. Location of symptoms with esophageal balloon distention in six patients. The *legend* indicates the level (20 to 40 cm) of balloon distention within the esophagus and the *circles* denote the location of the referred symptom. (From Polland WS, Bloomfield AL: Experimental referred pain from the gastrointestinal tract. Part I; the esophagus. J Clin Invest 10:435-452, 1931.)

means to diagnose GERD. The test has largely fallen by the wayside, in part because of its poor sensitivity and specificity. Similarly, studies of the effects of bile salt perfusion of the esophagus have shown nociception with perfusion. Simultaneous measurement of pH and motility and ultrasound have shown that sustained contraction of the esophageal longitudinal muscle correlated with the onset of chest pain.[13]

A number of studies have investigated the cortical response to esophageal balloon distention and acid perfusion. Responses have been detected via cortical evoked potential, positron emission tomography, and magnetic resonance imaging (MRI). Kern et al. recently reported the cerebral cortical MRI response to esophageal acid exposure and balloon distention in 10 healthy volunteers.[13] Intraesophageal perfusion of 0.1 N HCl for 10 minutes increased functional MRI signal intensity in all subjects, with an average 6.7% increase in signal occurring approximately 5 minutes after perfusion without inducing heartburn or chest pain. Saline perfusion elicited no detectable change. Similar changes were seen with balloon distention, although the response times were significantly longer for acid perfusion. Responses were seen in the posterior cingulate, parietal, and anterior frontal lobes. The authors concluded that esophageal mucosal acid contact produces a cerebral cortical response detectable by functional MRI and that the temporal characteristics of the acid response are different from those of balloon distention.

APPROACH TO A PATIENT WITH SUSPECTED GASTROESOPHAGEAL REFLUX DISEASE

GERD-related symptoms can be divided into "typical" symptoms, consisting of heartburn, regurgitation, and dysphagia, and "atypical" symptoms, consisting of cough, hoarseness, asthma, aspiration, and chest pain. Because there are fewer mechanisms for their generation, typical symptoms are more likely to be secondary to increased esophageal acid exposure than atypical symptoms are. The patient's perception of what each symptom means

should be explored in an effort to avoid their misinterpretation.[16] Of equal importance is to classify them as primary or secondary for prioritization of therapy and to allow an estimate of the probability of relief of each of the particular symptoms. The response to acid-suppressing medications predicts success and symptom relief after surgery.[17] In contrast to the widely held belief that failure of medical therapy is an indication for surgery, a good response to proton pump inhibitors is desirable because it predicts that the symptoms are actually due to reflux of gastric contents.

The relationship of atypical symptoms such as cough, hoarseness, wheezing, or sore throat to heartburn or regurgitation, or both, should be established. Other more common factors that may contribute to respiratory symptoms should also be investigated. The patient must be made aware of the relatively diminished probably of success of surgery when atypical symptoms are the primary symptoms.[18] Of note is the comparatively longer duration needed for improvement of respiratory symptoms after surgery.[19] It has become increasingly recognized that oral symptoms such as mouth and tongue burning and sore throat rarely improve with antireflux surgery.

The initial diagnostic evaluation should include videoesophagography, upper gastrointestinal endoscopy, stationery esophageal manometry, and 24-hour esophageal pH monitoring (distal ± proximal). These four tests allow the surgeon to determine the presence of gastroesophageal reflux in an objective fashion; the underlying reasons for its presence, such as hiatal hernia or a deficient lower esophageal sphincter; and its severity, including the presence or absence of complications. Although it has been argued that one or more of these studies are superfluous, experience constantly reminds us that they are complementary and that all add useful information before antireflux surgery. Further investigations, in particular, gastric emptying studies or pancreaticobiliary testing or both, are added depending on the findings of the other tests.

Radiographic assessment of the anatomy and function of the esophagus and stomach is one of the most important elements of the preoperative evaluation. A carefully performed videoesophagogram not only provides information about the underlying anatomic defects, such as the presence or absence of a stricture and the size and reducibility of a hiatal hernia, but is also one of the few ways to assess actual bolus transport. A standardized protocol is advised to ascertain different aspects of esophagogastric function during different phases of the study. Given routine review before antireflux surgery, its value becomes increasingly clear. A hiatal hernia is present in more than 80% of patients with gastroesophageal reflux. It is best demonstrated with the patient in the prone position, which causes increased abdominal pressure and promotes distention of the hernia above the diaphragm. The presence of a hiatal hernia is an important component of the underlying pathophysiology of gastroesophageal reflux. Other relevant findings include a large (>5 cm) or irreducible hernia, which suggests the presence of a shortened esophagus[20]; a tight crural "collar" that inhibits barium transit into the stomach, which suggests a possible cause of dysphagia; and the presence of a paraesophageal hernia, which is likely to influence the surgeon's decision on the operative approach.

One of the key goals before taking a patient to the operating room is to connect the patient's complaints to gastroesophageal reflux. Antireflux surgery will reliably and reproducibly prevent the return of gastric contents into the esophagus, but it does little else. If the symptoms that drove the patient to seek surgical treatment are not secondary to reflux, there will be no benefit. Indeed, one will have a patient who is not only no better but often also unusually focused on normally trivial side effects such as bloating and flatulence. The single best way to prevent this scenario is to use 24-hour pH monitoring to prove the presence of pathologic esophageal acid exposure before surgery. The study not only provides for an objective diagnosis but also contributes other useful information. A multivariate analysis of the factors that predict a successful outcome after laparoscopic Nissen fundoplication was recently published.[17] One hundred ninety-nine consecutive patients undergoing laparoscopic Nissen fundoplication were studied, and a variety of demographic, anatomic, clinical, and physiologic factors were analyzed. The three most important predictors of a successful clinical outcome, in order of importance, were an abnormal pH score, a typical primary symptom, and a complete or partial (>50%) response to medical therapy. When all three were present, the patient was 90 times more likely to have relief of symptoms than when they were not!

The choice of treatment of GERD in present-day practice ideally should take into account the underlying severity of the disease and the patient's risk for complications of end-stage reflux disease. This is particularly true given the rising incidence of Barrett's esophagus and adenocarcinoma of the gastric cardia. Studies of the natural history of GERD have shown that although the vast majority of the patients have limited disease and respond well to lifestyle modifications and medical therapy, a substantial proportion (22% to 50%) progress to complications of GERD.[21] This group should be identified early and offered antireflux surgery. The following factors, when identified during the work-up of patients, will help in detecting those at risk: (1) anatomic and physiologic markers of severe disease, such as a defective lower esophageal sphincter, poor contractility of the esophageal body, large hiatal hernias, or bile reflux; (2) severe erosive esophagitis on initial evaluation or the development of esophagitis or peptic strictures during the course of medical therapy; (3) Barrett's esophagus; (4) young age, particularly in patients with the aforementioned characteristics; and (5) progressive respiratory symptoms, aspiration, or pneumonia.

Patients seen for the first time with symptoms suggestive of gastroesophageal reflux may be given initial therapy with H_2 blockers. In view of the availability of over-the-counter medications, many patients will have already self-medicated their symptoms. Failure of H_2 blockers to control the symptoms or immediate return of symptoms after stopping treatment suggests that either the diagnosis is incorrect or the patient has relatively severe disease. Endoscopic examination at this stage of

the patient's evaluation provides the opportunity for assessment of the severity of mucosal damage and the presence of Barrett's esophagus. Finding both of these factors on initial endoscopy predicts a high risk for medical failure. The degree and pattern of esophageal exposure to gastric and duodenal juice should be determined at this point via 24-hour pH and bilirubin monitoring. The status of the lower esophageal sphincter and the function of the esophageal body should also be evaluated. These studies identify features that predict a poor response to medical therapy, frequent relapses, and the development of complications; risk factors include supine reflux, poor esophageal contractility, erosive esophagitis or a columnar-lined esophagus at initial evaluation, bile in the refluxate, and a structurally defective sphincter. Patients who have these risk factors should be given the option of surgery as a primary therapy with the expectation of long-term control of symptoms and complications.

APPROACH TO A PATIENT WITH BARRETT'S ESOPHAGUS

Management of Barrett's esophagus is becoming an increasingly common health problem. Long-segment Barrett's esophagus has been estimated to be present in 4% to 6% of patients with reflux symptoms, 1% of all patients who undergo upper endoscopy, and 0.3% of the U.S. population. Short-segment Barrett's esophagus (<3 cm) is probably even more prevalent and has accounted for half to two thirds of all patients with Barrett's esophagus identified in most recent studies. It is commonly argued that most patients with Barrett's esophagus are asymptomatic and therefore need no treatment at all. Although epidemiologic studies suggest that a large reservoir of undiagnosed asymptomatic or minimally symptomatic patients with Barrett's esophagus does exist, there are hundreds of thousands if not millions of symptomatic patients undergoing treatment.

Barrett's esophagus represents severe end-stage GERD, which without surgical prevention of reflux will almost certainly require high-dose, lifetime drug therapy. The severity of the disease has been shown in numerous epidemiologic, clinical, and physiologic studies. Case-controlled epidemiologic studies have shown that patients with Barrett's esophagus have reflux symptoms at an earlier age and have more severe symptoms and that severe complications of reflux, including esophagitis, stricture, and ulceration, occur more frequently in patients with Barrett's esophagus than in age- and gender-matched GERD or upper endoscopy control patients.[22] Physiologic studies reveal markedly abnormal esophageal acid exposure,[23,24] an incompetent lower esophageal sphincter,[25,26] and impaired esophageal body motility in a large majority of patients.[27] The pattern, frequency, and duration of reflux episodes are increased in comparison to patients with no intestinal metaplasia.[28] Contractility of the esophageal body may be profoundly reduced in patients with Barrett's esophagus, and this decreased contractility results in prolonged contact times. The clinical and physiologic severity in patients with short-segment Barrett's esophagus is generally intermediate between that of patients with long-segment Barrett's esophagus and those with erosive esophagitis.[29,30] Most patients with Barrett's esophagus have a hiatal hernia that is often larger than in patients with reflux esophagitis without Barrett's esophagus.[31]

Studies of the constituents of the refluxate provide further indications that patients with Barrett's esophagus differ significantly from those with GERD without Barrett's esophagus; in addition, such studies have a bearing on the decision regarding medical versus surgical treatment. Patients with Barrett's esophagus are more likely to have mixed reflux of both gastric and duodenal contents into the esophagus.[32] Direct measurement of aspirated bile or measurement of esophageal bilirubin in the distal esophagus as a marker for duodenal juice has shown that duodenoesophageal reflux is significantly more frequent in those with Barrett's esophagus than in those with GERD without Barrett's esophagus.[33] A study of 100 patients with GERD found a significant association between the degree of mucosal injury and the presence of duodenogastroesophageal reflux rather than gastroesophageal reflux only.[34] Some animal model studies indicated that duodenal reflux plays a significant role in esophageal tumor promotion.[35]

Second, there is a growing consensus that the ideal end point of treatment has shifted away from simple symptomatic relief toward the elimination of pathologic esophageal acid exposure. This shift has been stimulated by the desire to prevent neoplastic development, together with the results of basic studies on the biology of Barrett's epithelium. These studies have shown disconcerting reflux-induced cellular changes in a Barrett's mucosa organ culture system. Fitzgerald et al., for example, found that a dramatic increase in cellular proliferation resulted after Barrett's tissues were exposed to short pulses of acid at pH 3.5.[36,37] Interestingly, continuous acid exposure had minimal effect. Cellular differentiation was also assessed by quantifying expression of the apical membrane cytoskeletal protein villin, which is important for brush border microvillus assembly. Increased villin expression was found with exposure to acid in a pH range of 3 of 5. Although these in vitro findings may not reflect the situation in vivo, the finding that short pulses of acid induce proliferation suggests that complete and continuous acid suppression is necessary to prevent these abnormal cellular biologic changes. Though theoretically possible with both medical and surgical treatments, complete esophageal acid control is more reliably provided by antireflux surgery.

Finally, it is increasingly being recognized that using medication to normalize esophageal acid exposure is difficult in patients with Barrett's esophagus, even with proton pump inhibitors. Sampliner et al. reported that a mean dose of 56 mg of omeprazole was necessary to normalize 24-hour esophageal pH studies after multipolar electrocoagulation.[38] Several studies have shown that nocturnal acid breakthrough resulting in supine GERD is common, even with 20 mg of proton pump inhibitor therapy twice daily.[39,40] Although this nocturnal acid breakthrough period can be reduced by adding a histamine H_2 receptor antagonist before sleep, short

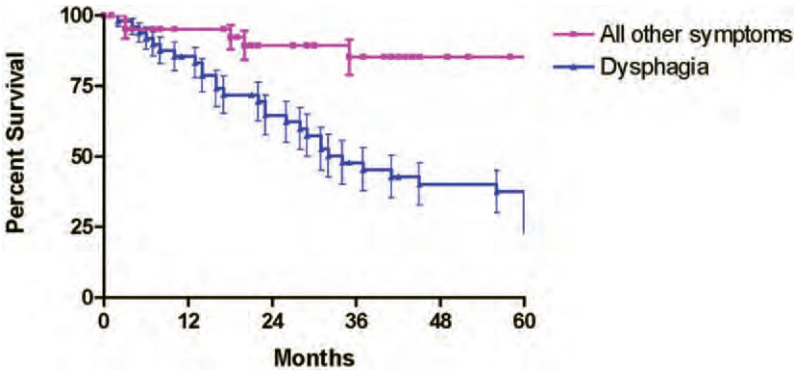

Figure 4–2. Kaplan-Meier actuarial survival curve for patients with esophageal adenocarcinoma with and without dysphagia.

pulses of esophageal acid exposure still occur in some patients.[41]

APPROACH TO A PATIENT WITH A MOTOR DISORDER

Dysphagia, or difficulty swallowing, is the primary symptom of esophageal motor disorders. Its perception by the patient is a balance between the severity of the underlying abnormality causing the dysphagia and the adjustment made by the patient in altering eating habits. Consequently, any complaint of dysphagia must include an assessment of the patient's dietary history. It must be known whether the patient experiences pain, choking, or vomiting with eating; whether the patient requires liquids with the meal, is the last to finish, or has interrupted a social meal; or whether the patient has been admitted to the hospital for food impaction. These assessments, in addition to the ability to maintain nutrition, help quantify the dysphagia and are important in determining the indications for surgical therapy.

Depending on the underlying cause of the nonobstructive dysphagia, the surgeon has a number of options designed to improve the patient's swallowing ability. The results can profoundly improve the patient's ability to ingest food but rarely return the function of the foregut to normal. In most situations, the principle of the operation is to make a defect in order to correct a defect to improve the patient's ability to swallow.

To apply surgical therapy to the problem of dysphagia, the surgeon needs to know the precise functional abnormality causing the symptom. Such knowledge usually entails a complete esophageal motility evaluation. A clear understanding of the physiologic mechanism of swallowing and determination of the abnormality in motility giving rise to the dysphagia are essential for deciding on the choice of surgery. Endoscopy is necessary only to exclude the presence of tumor or inflammatory changes as the cause of dysphagia.

APPROACH TO A PATIENT WITH ESOPHAGEAL CANCER

Dysphagia and weight loss are, by far, the most common symptoms at the time of diagnosis of esophageal cancer. A complaint of dysphagia in patients of any age should be investigated thoroughly because carcinoma is the most common cause of dysphagia. Occasionally, symptoms may arise from invasion of the primary tumor into adjacent structures or from metastasis. Extension of the primary tumor into the tracheobronchial tree can cause stridor, and if a tracheoesophageal fistula develops, coughing, choking, and aspiration pneumonia result. Severe bleeding from erosion into the aorta or pulmonary vessels occurs on rare occasion. Vocal cord paralysis may result from invasion of either recurrent laryngeal nerve. Metastases are usually manifested as jaundice or bone pain.

A surprisingly high proportion of patients with resectable esophageal adenocarcinoma are now identified before the development of dysphagia. In fact, survival in this group of patients is significantly better than if dysphagia heralds the diagnosis (Fig. 4–2). Twenty-five percent of the patients in our recent study were enrolled in a surveillance program for Barrett's esophagus or had a long history of GERD symptoms, and in another 30% of these patients, occult bleeding, anemia, or abdominal symptoms such as pain or discomfort prompted the physician visit leading to a diagnosis of cancer.[42]

Unfortunately, dysphagia usually occurs late in the natural history of the disease because the lack of a serosal layer in the esophagus allows the smooth muscle to dilate with ease. As a result, the dysphagia becomes severe enough to motivate the patient to seek medical advice only when more than 60% of the esophageal circumference is infiltrated with cancer and the lumen is reduced to less than 12 mm in diameter. Because of this insidious onset, the disease is usually advanced at the time of diagnosis. Tracheoesophageal fistula occurs in up to 10% of patients on their first visit to the hospital, and greater than 40% will have evidence of distant metastases or recurrent nerve paralysis. With tumors of the cardia, anorexia and weight loss usually precede the onset of dysphagia.

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Chapter

5

Imaging in Esophageal Disease

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NORMAL ANATOMY, FUNCTION, AND RADIOGRAPHIC TECHNIQUES OF EXAMINATION

Although endoscopy has largely replaced contrast studies of the stomach and colon, barium examination is still considered a valuable diagnostic tool for evaluation of the esophagus. Indeed, as we have seen a precipitous drop in the number of upper gastrointestinal (UGI) studies and barium enemas in our practice, the number of barium swallows has remained virtually constant over the past 30 to 40 years. The ability of the barium examination to demonstrate the structure and function of the esophagus has stood the test of time. Its relatively low cost and universal availability add to its value in the management of patients with esophageal disease. Although the introduction of newer imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) has proved valuable in special circumstances, barium examination remains the mainstay of esophageal imaging.

PET has largely replaced CT in initial cancer staging and evaluation of recurrent tumor, but CT remains a useful tool for evaluating early complications after esophageal surgery. MRI is of limited usefulness in the management of esophageal disease, but it is likely to become more important in the future. These specialized imaging techniques are discussed in appropriate sections of this chapter.

Normal Anatomy and Function

The esophagus is a muscular tube, 20 to 24 cm in length, that is bounded by a sphincter at both ends. The upper esophageal sphincter (UES), made up of striated muscle and known anatomically as the cricopharyngeus, consists of the thickened horizontal portion of the inferior pharyngeal constrictor. The lower esophageal sphincter (LES) consists of an ill-defined high-pressure zone at the esophagogastric junction (EGJ). The proximal third of the esophagus is made up of striated muscle with a gradual transition to smooth muscle in the middle third. The distal third is composed exclusively of smooth muscle. Because of these anatomic differences, diseases affecting striated and smooth muscle have different regional distributions.

The function of the esophagus is to transport material from the mouth to the stomach and to prevent entry of swallowed material into the airway. The UES and LES act as valves and remain closed at each end of the esophagus until a swallow is initiated. This process prevents inspired air from entering the gastrointestinal (GI) tract from above and gastric contents from entering the esophagus from below. When swallowing is initiated, both sphincters relax to allow passage of the bolus into the stomach. Beginning at the pharyngoesophageal junction, peristaltic contractions traverse the entire esophagus and push the swallowed bolus into the stomach. As the bolus passes into the stomach, the sphincters close again.

The swallowed bolus must be of sufficient volume to consistently sustain peristalsis. If the bolus is too small, the peristalsis may die away and result in stasis in the esophageal body. Secondary peristalsis occurs below the pharyngoesophageal junction as a response to esophageal distention.

In the upright position, a liquid bolus is propelled primarily by gravity, and peristalsis plays almost no role, which explains why motility testing needs to be performed with the subject in the recumbent position. Solid boluses require peristaltic contractions (usually multiple swallows) to be transported effectively in the upright position.

Examination Techniques and Normal Radiographic Appearance

The equipment necessary to perform barium esophageal studies can be found in virtually all radiology departments. Digital spot devices are now in common use and facilitate rapid acquisition of high-quality static images. The addition of a large image intensifier (12 inches and larger) allows the fluoroscopist to see and record events though the entire length of the esophagus. This is especially important when evaluating esophageal function because clinically important motor activity may occur outside the field of view if a small image intensifier is used. A motion-recording device, such as a VCR or digital recorder, is desirable so that rapidly occurring swallowing events are more easily observed when viewed at a slower rate. Motion recording captures the dynamic nature of events far better than rapid sequential spot films do. The tape recording also provides a valuable educational tool during discussions with the patient.

Proper barium swallow technique includes a multiphasic examination, including air-contrast, full-column, and mucosal relief techniques.[1] Each technique has unique advantages and disadvantages.

The air-contrast technique allows detailed evaluation of the esophageal mucosa. Maximum distention of the esophageal body is achieved by the administration of an effervescent solution that produces CO_2. With the esophagus distended with gas, high-density barium is quickly administered to coat the mucosal surfaces. When performed in the upright position, the distended esophageal wall, with its thin coating of barium, is displayed in exquisite detail. The normal esophageal mucosa appears featureless on air-contrast views. Occasionally, tiny filling defects, representing undissolved effervescent crystals, are seen (Fig. 5–1). In patients with normal motility, the esophagus may remain distended only for a short time. Incomplete distention of the esophagus, especially the distal portion, may mask the presence of segmental narrowing and prevent visualization of mucosal detail.

As the esophagus empties of gas, the lumen collapses. Barium is caught in the redundant longitudinal folds, and this constitutes the mucosal relief examination. Mucosal folds should appear as continuous linear structures less than 3 mm thick (Fig. 5–2). Mild thickening and irregularity of the folds in the distal end of the esophagus may be the only sign of reflux esophagitis.

The full-column technique is performed in the prone oblique position and requires rapid swallowing of barium. Patients are encouraged to drink as much and as rapidly as possible to produce maximal distention. By maximally distending the esophagus, areas of fixed narrowing become visible. Should the patient not be able to drink rapidly enough to sufficiently distend the lumen, areas of segmental narrowing may go undetected.[2]

On full-column films, the margins of the esophagus should appear smooth with no areas of fixed irregularity (Fig. 5–3). Normal extrinsic impressions occur at the level of the transverse aorta, the left main stem bronchus, and the esophageal hiatus (Fig. 5–4). Extrinsic impressions occurring elsewhere and areas of fixed irregularity should be viewed with suspicion.

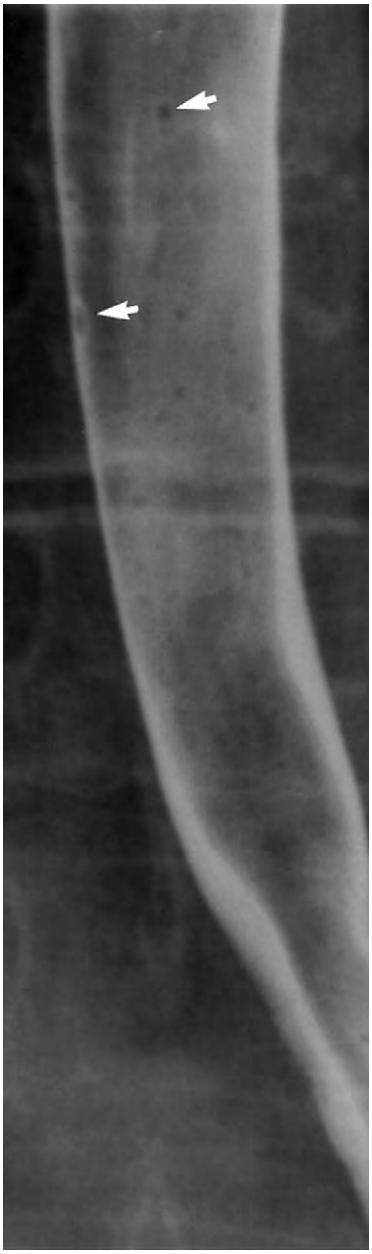


Figure 5–1. Normal air-contrast esophagogram. The mucosa is featureless except for the occasional tiny filling defect caused by undissolved effervescent crystals (*arrows*).

Esophageal motility should be tested with single swallows of barium while the patient is in the prone oblique position. Patients should be instructed to swallow up to five single swallows of barium. During each swallow, the tail of the bolus is observed as the bolus is carried from the cervical esophagus to the stomach. The peristaltic contraction should traverse the entire esophagus from the cervical portion to the stomach. To avoid the effect of deglutitive inhibition, subjects are asked to not swallow between boluses. The temperature and viscosity should

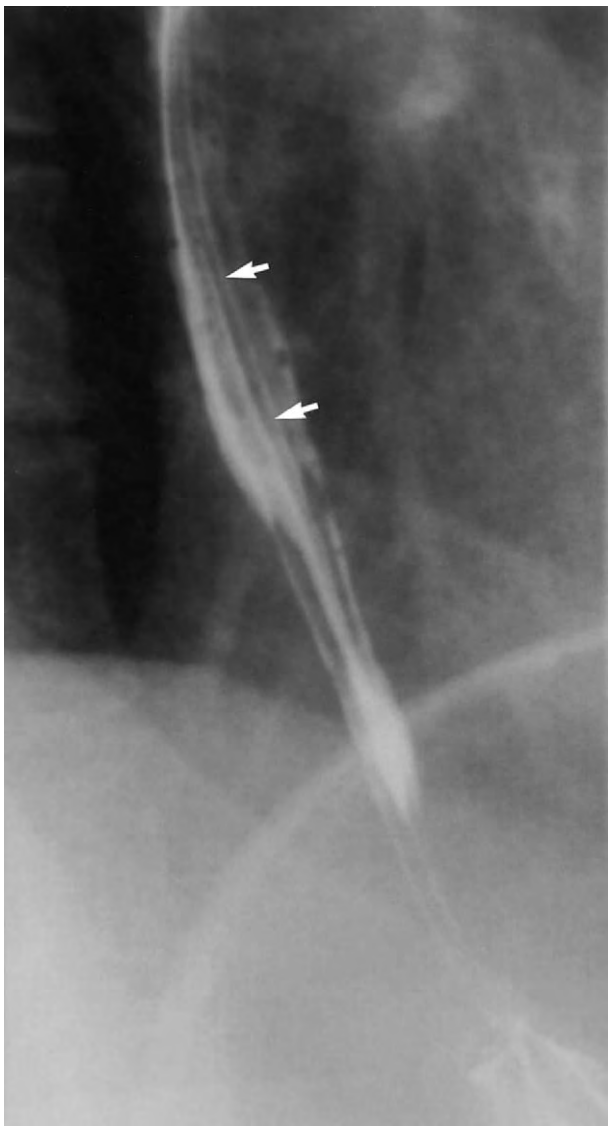


Figure 5–2. Normal mucosal relief esophagogram. The mucosal folds (*arrows*) appear smooth, continuous, and less than 3 mm in thickness.

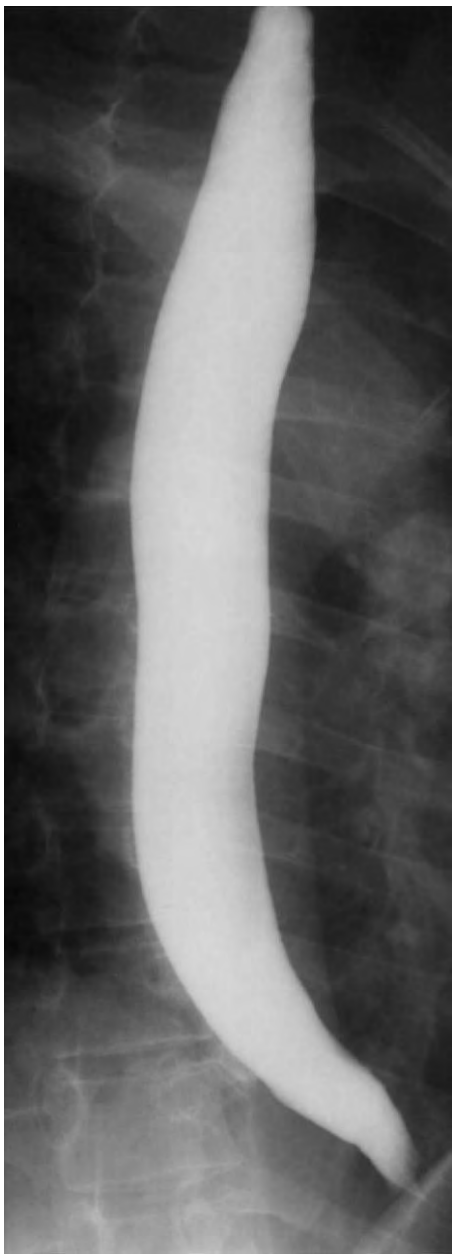


Figure 5–3. Normal full-column esophagogram. The margins of barium are smooth without any fixed irregularities.

be controlled to avoid inducing abnormal motility. A normal swallow should be accompanied by an effective peristaltic wave that strips the esophagus of all barium. The leading edge of the wave resembles an inverted V, with the apposing walls of the esophagus obliterating the lumen and pushing the bolus ahead. Frequently, a small amount of stasis is seen in the middle third of the esophagus as a result of nonocclusive peristalsis and should not be interpreted as abnormal motility. This is the area of transition from striated to smooth muscle and is normally the zone of lowest normal contraction amplitude. Frequent nonocclusive peristalsis in the distal third or failure of peristalsis to traverse the entire length of the esophagus may indicate a motility disorder. Completion of the peristaltic contraction is accompanied by relaxation of the LES as the bolus is emptied into the stomach. Three out of five swallows should result in complete clearance of barium. Three or more swallows out of five that result in stasis in the esophageal body may reflect abnormal motility.[3] Abnormal contractions include incomplete or ineffective peristalsis that causes incomplete clearance of the barium bolus, tertiary contractions, simultaneous contractions, and failure of the LES to relax.

In normal young patients, 95% of swallows are accompanied by normal peristalsis.[4] Though not universally accepted, the incidence of failed and low-amplitude peristaltic contractions probably increases with age.[5] Whether this is a normal aging process or represents subclinical disease is not known. Therefore, abnormal

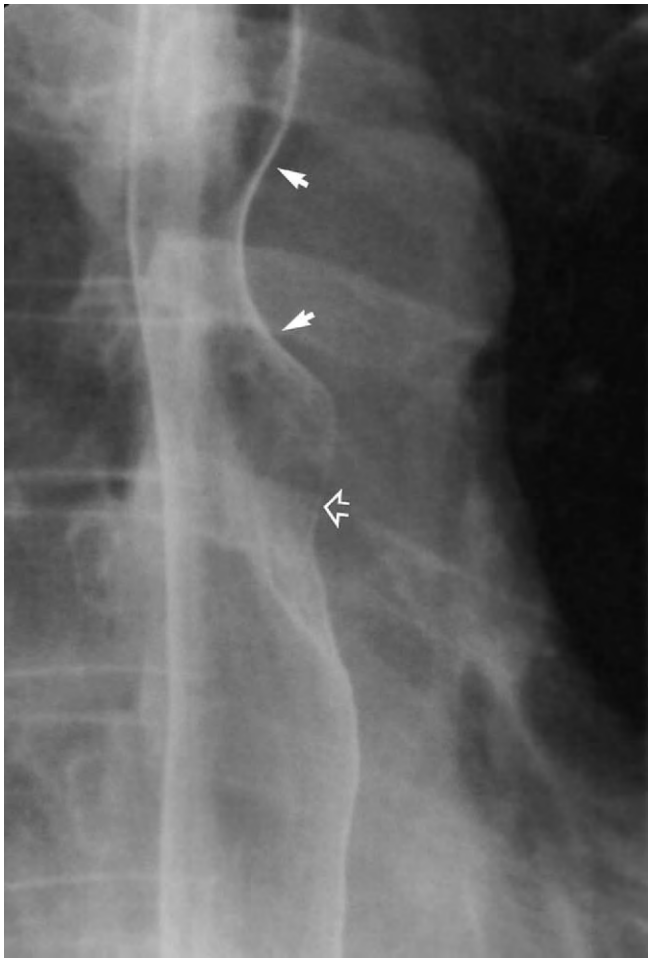


Figure 5–4. Left posterior oblique air-contrast view demonstrating normal extrinsic impressions on the esophagus from the aorta (*closed arrows*) and left main bronchus (*open arrow*).

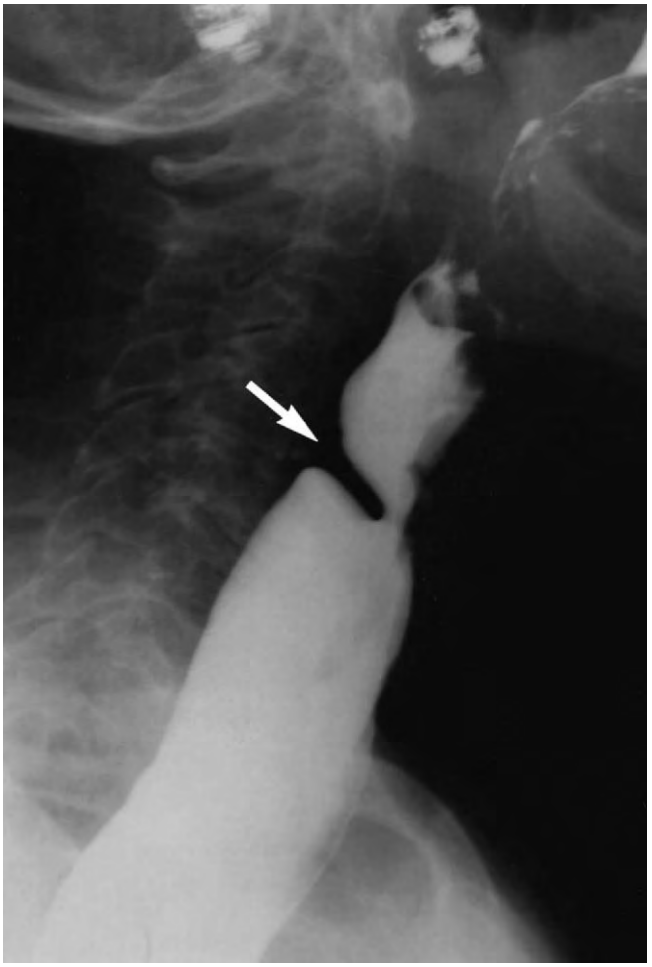


Figure 5–5. Cricopharyngeal bar—a smooth posterior defect (*arrow*) at the level of the cricopharyngeus muscle (usually C5-C6).

peristaltic function, especially tertiary contractions, should be interpreted with caution in older individuals.

Patients with dysphagia and a normal barium examination should be challenged with a solid bolus. Those complaining of difficulty swallowing pills should be challenged to swallow a 12.5-mm barium tablet with 60 ml of water in the 45-degree upright position. In normal subjects, the tablet should pass into the stomach within 60 seconds.[6] A marshmallow cut in half or thirds, swallowed with thin barium, may hang up at areas of narrowing not otherwise visible on the routine examination.[7,8] Single bites of cooked hamburger may be used to assess the functional severity of dysphagia. With severe dysphagia caused by structural narrowing, the patient may chew excessively to pulverize the bolus before swallowing. In these patients, the bolus may be swallowed piecemeal to avoid symptomatic holdup at an area of stenosis. Most patients with motility disorders chew and initiate swallowing normally.

All examinations should include at least a brief look at the oropharyngeal phase of swallowing. Symptoms in patients with dysphagia are frequently difficult to localize; therefore, all areas, from the oropharynx to the stomach, should be examined. In addition, structural abnormalities at the pharyngoesophageal junction occasionally accompany more distal disease and may contribute to the dysphagia (Fig. 5–5).[9] The radiographic findings may provide clues to which abnormalities may account for the symptoms.

Examination of the stomach should be included in patients complaining of dysphagia or gastroesophageal reflux disease (GERD). Neoplasms of the gastric cardia can cause dysphagia and would otherwise be overlooked if the stomach were not evaluated.[10] In patients with GERD, gastric dysfunction may be an important contributory factor, so evidence of delayed gastric emptying (e.g., retained secretions, dilated stomach, previous surgery) and hypersecretion (retained secretions, abnormal gastric folds, gastritis) should be noted.

Common Normal Variants

The esophageal ampulla appears as a smoothly marginated short segmental dilatation of the esophagus just above the hiatus (Fig. 5–6). It is sometimes confused with

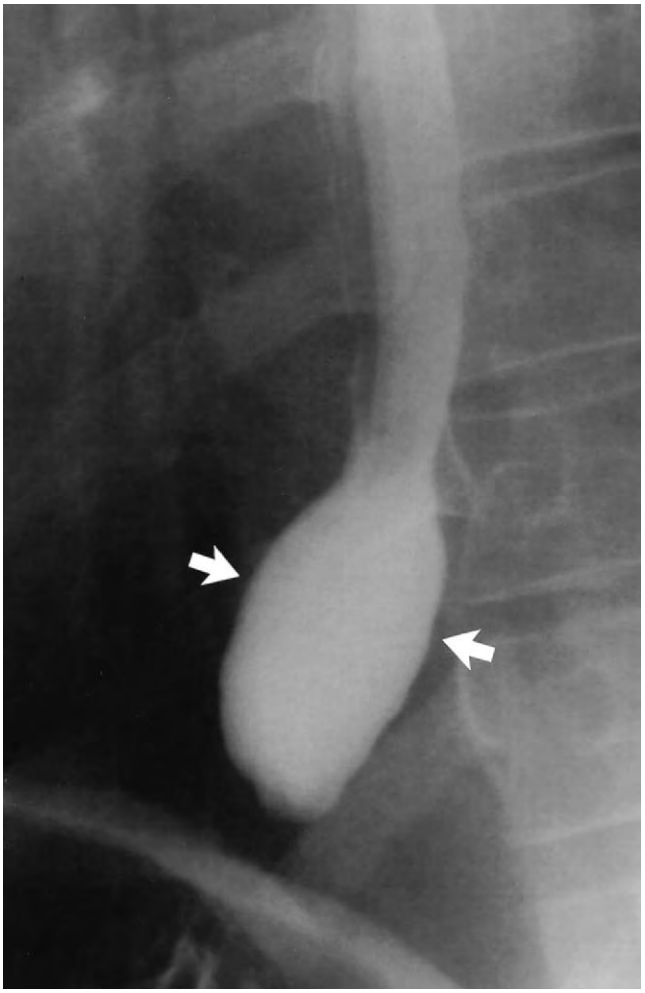


Figure 5–6. Esophageal ampulla—normal slight widening of the distal end of the esophagus (*arrows*).

a small hiatal hernia; however, the absence of gastric folds and the presence of typical esophageal peristalsis within the ampulla distinguish it from a herniated stomach.

The occasional appearance of fine, evenly spaced transverse folds that occur transiently in normal patients is called *feline esophagus* (Fig. 5–7). This condition has reported to be more frequent in patients with GERD but is more commonly seen in asymptomatic patients. It is thought to be due to contraction of the longitudinal muscle layer.

GASTROESOPHAGEAL REFLUX DISEASE

One of the earliest reports of abnormal reflux of gastric contents into the esophagus was based on observations made during GI contrast studies.[11] Barium studies were considered so important that the diagnosis of GERD was synonymous with the presence of reflux on barium studies. Until the introduction of endoscopy and ambulatory pH monitoring, the barium UGI study remained a cornerstone in the evaluation of GERD patients. Today,

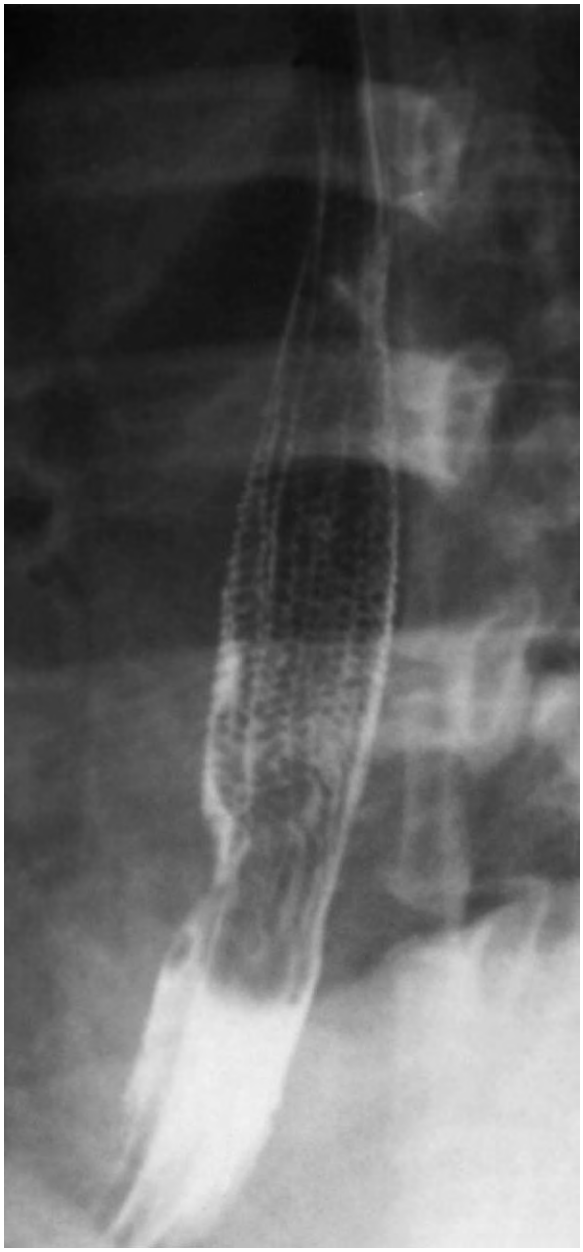


Figure 5–7. Feline esophagus. Regular, closely spaced transverse ridges occurring transiently in the esophageal body are thought to be related to longitudinal muscle contractions.

the importance of the barium examination has diminished, but it remains useful in evaluating GERD patients, especially those considering surgical intervention.

GERD is extremely common, especially in Western cultures, and it occurs in approximately 15% to 20% of the U.S. population. The popularity of over-the-counter acid-suppression medications testifies to the widespread nature of the condition. In mild, uncomplicated cases, the annoying symptoms of heartburn and regurgitation may not cause permanent changes but may have a significant impact on quality of life. More severe cases may be complicated by permanent esophageal injury and even malignancy.

GERD consists of a constellation of signs and symptoms produced by abnormal exposure of the esophageal lining to gastric contents. The cause of GERD is multifactorial. The most common etiologic factor is abnormality of the LES leading to loss of the normal antireflux barrier. Contributory factors include the volume and composition of the gastric refluxate, altered esophageal mucosal resistance, the effectiveness of esophageal clearance, and abnormal gastric emptying. Although other tests are more accurate in quantifying these etiologic factors, barium studies may provide clues that point to the need for further studies. For example, the demonstration of a hiatal hernia on a barium study suggests alteration of the normal antireflux barrier, which can be confirmed with LES manometry. Radiographic signs of abnormal esophageal motility point to poor esophageal clearance of refluxed material, which can be evaluated with esophageal body manometry. Radionuclide studies may be useful to confirm delayed gastric emptying in patients with a dilated atonic stomach seen during a UGI study.

Role of Barium Examination in Gastroesophageal Reflux Disease

Exclude Motility Disorder The classic symptoms of GERD, namely, heartburn and regurgitation, are nonspecific and may be seen with a variety of esophageal diseases, including motility disorders. A small group of patients (less than 10%) with motility disorders may have symptoms suggestive of GERD, namely, heartburn and regurgitation. Dysphagia and chest pain, typical symptoms in patients with motility disorders, may be absent. Symptoms of heartburn are, in fact, common and occur in 40% of achalasia patients. In the majority of patients with classic achalasia, the barium examination is characteristic. In these patients, the correct diagnosis is easily made and a potential catastrophe resulting from inappropriate antireflux surgery can be avoided.

Detection of Gastroesophageal Reflux The role of barium studies in detecting abnormal gastroesophageal reflux (GER) is controversial. The sensitivity of barium examination in the diagnosis of GERD ranges from 20% to 74% (average, 39%). Many early studies reported favorable results in correlating the presence of radiographically demonstrated GER with symptoms of heartburn or the presence of esophagitis. However, as mentioned earlier, heartburn is a nonspecific symptom seen with many other esophageal disorders, and endoscopic esophagitis occurs in only half the patients with positive pH monitoring. Therefore, one cannot rely on the accuracy of early studies published before the introduction of ambulatory pH testing. We also know that spontaneous GER occurs normally as a result of transient lower esophageal sphincter relaxation (tLESR), which if interpreted as pathologic GER will lead to a false-positive diagnosis. Furthermore, the absence of GER episodes during the short observation period of a barium examination may be erroneously interpreted as evidence against the diagnosis of GERD.

Ambulatory pH monitoring is the gold standard for the diagnosis of GER. A pH of 4 or less for greater than 5% of the 24-hour monitoring period is considered a positive test.[12] A few studies have correlated pH results with radiographic detection of GER. One study[13] demonstrated favorable results and showed a radiographic sensitivity of 70% and specificity of 74% with both spontaneous reflux and the water siphon test. A subsequent study[14] failed to confirm the earlier findings and concluded that barium radiography lacks sufficient sensitivity and specificity to be used as a screening procedure for GERD. In general, the response to trials of proton pump inhibitors in patients with typical symptoms of heartburn and regurgitation and the presence of a hiatal hernia are more predictive of pH test results than the presence of radiologically detectable GER.

GER is diagnosed radiographically when barium is seen to reflux into the distal part of the esophagus from the stomach. A small amount of refluxed barium that occurs infrequently is probably not significant and may reflect normal tLESR. However, frequent episodes of reflux that reach high into the esophagus, particularly in the presence of a large hiatal hernia, are often predictive of a high pH score.

Provocative tests, such as the water siphon test, increase the sensitivity of radiologic detection of reflux disease but result in lower specificity. The water siphon test is performed by having the recumbent subject take a single swallow of water while the gastric fundus is filled with barium.[15,16] A positive test result consists of reflux of barium into the distal esophagus just after the water bolus traverses the gastroesophageal junction (GEJ). Additional provocative testing to increase intra-abdominal pressure and thus promote GER includes the Valsalva maneuver and having the patient ingest a bolus while supine.

Evaluation of Esophageal Clearance Abnormal motility causing poor clearance of refluxed material may promote esophageal damage by prolonging exposure of the esophageal lining to the noxious effects of the refluxate. Before the advent of esophageal motility testing, barium swallows were used to evaluate esophageal motor function. Studies have shown relatively good correlation between the results of stationary manometry and barium swallows and suggest that barium examination may provide accurate estimates of esophageal function.[17] Radiographic evidence of poor esophageal body function may help identify patients who will be resistant to conventional-dose antisecretory therapy. This information is also helpful in selection of the appropriate surgical approach and type of antireflux repair.

Motility disturbances associated with GERD usually involve the distal half of the esophagus. Failed propagation of peristalsis and ineffective contractions resulting in significant stasis of barium in the esophageal body are commonly associated with GERD. In the most severe cases, the pattern of disease is similar to that of scleroderma (discussed later).

Detect Evidence of Esophageal Injury Esophageal injury is manifested by esophagitis, scarring, stricture, Barrett's changes, and alterations in esophageal motility.

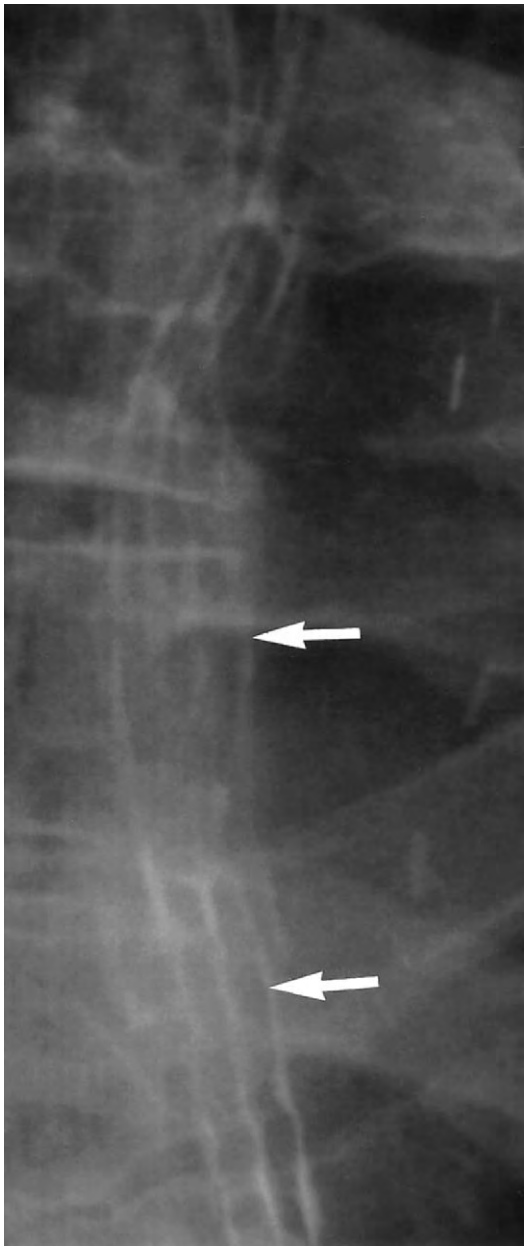


Figure 5–8. Acute reflux esophagitis. Mucosal relief views demonstrate thickened, slightly irregular folds (*arrows*) in the distal end of the esophagus.

Radiographic detection of esophagitis depends on the severity of changes. Mild to moderate degrees of inflammation are frequently not obvious radiographically.[18] Severe esophagitis is more readily diagnosed, but such cases have become less prevalent as a result of the widespread use of acid-suppression therapy.

Signs of acute esophagitis include thickening and irregularity of the distal esophageal folds, best seen on mucosal relief images (Fig. 5–8). Less frequently, nodularity and erosions are visible on air-contrast films. Occasionally, edema or spasm may produce areas of segmental narrowing that improve after successful treatment.

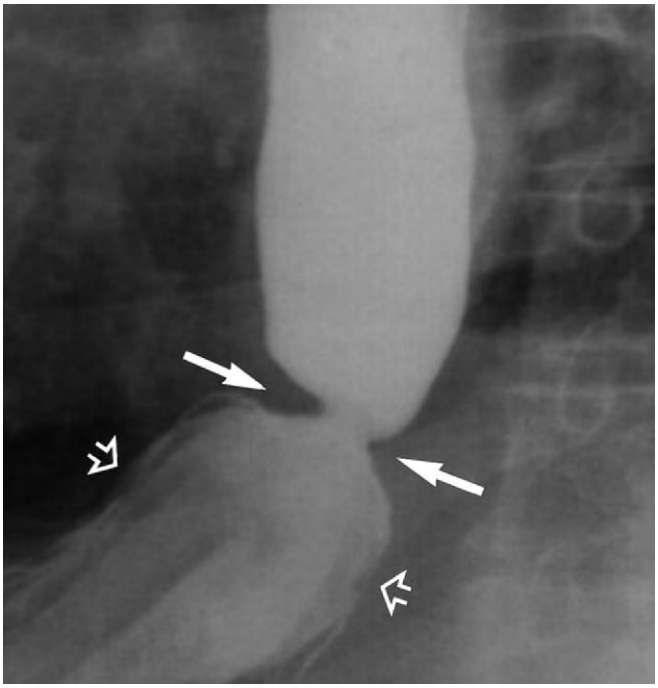


Figure 5–9. Esophageal stricture secondary to gastroesophageal reflux disease. Asymmetric narrowing (*closed arrows*) is evident at the gastroesophageal junction above a hiatal hernia (*open arrows*).

Scarring and stricture represent more severe and permanent changes of injury from GERD and are generally visible radiographically. Their appearance is typical enough to exclude malignancy.[19] Strictures usually occur at the GEJ and may be smoothly tapered or irregular (Fig. 5–9). When compared with mucosal rings, strictures are generally eccentric and involve a longer segment of the esophagus. Scarring can occur without esophageal narrowing and may be seen as areas of fixed irregularity of the esophageal contour. Air-contrast views may show them as transverse linear defects (Fig. 5–10).

Barium studies are superior to endoscopy in detecting areas of segmental narrowing,[2,20] especially for larger-diameter strictures and those that taper gradually. The latter type may not be appreciated endoscopically, particularly with small-diameter endoscopes.

Radiographic technique is important in detecting areas of segmental narrowing. The examination must be performed with the patient in the recumbent position. Up to half of strictures and rings may be missed if patients are examined only in the upright position.

Initial reports suggested high sensitivity of air-contrast esophagograms for the detection of columnar epithelium in Barrett's esophagus.[21] The changes are described as a reticular mucosal pattern best appreciated on air-contrast views (Fig. 5–11). Others found this radiographic feature to be present in only 23% of cases.[22] Barrett's changes are seen in a large percentage of patients with hiatal hernia, esophageal stricture, and thickened, irregular folds.[23,24] Midesophageal strictures are a relatively specific sign of Barrett's esophagus.

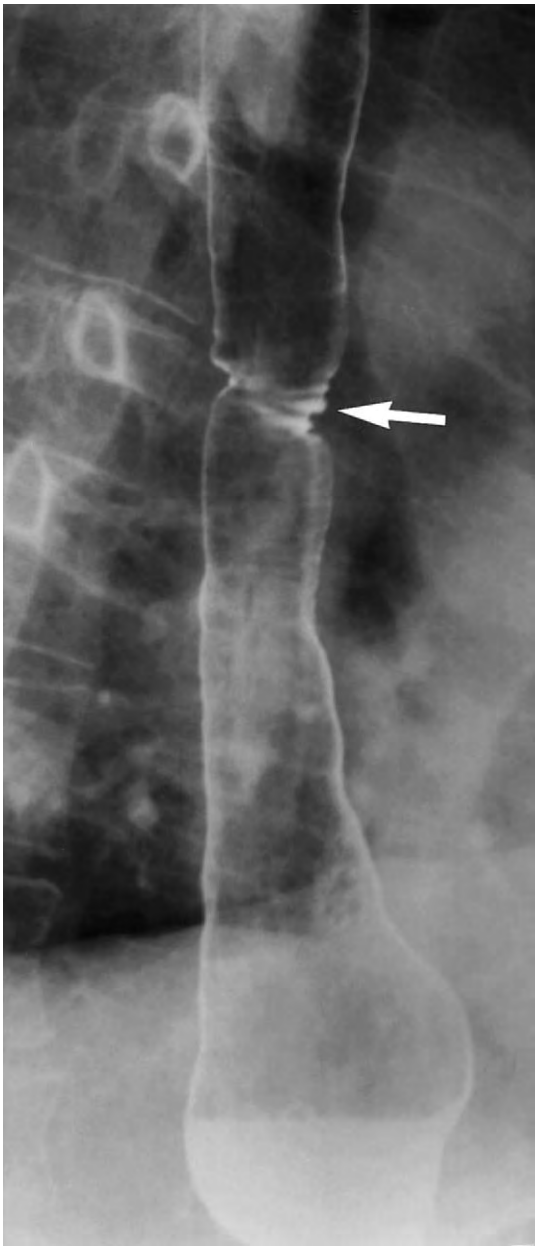


Figure 5–10. Scarring secondary to gastroesophageal reflux disease (GERD). Transverse scars (*arrow*) are typical for a benign stricture caused by GERD.

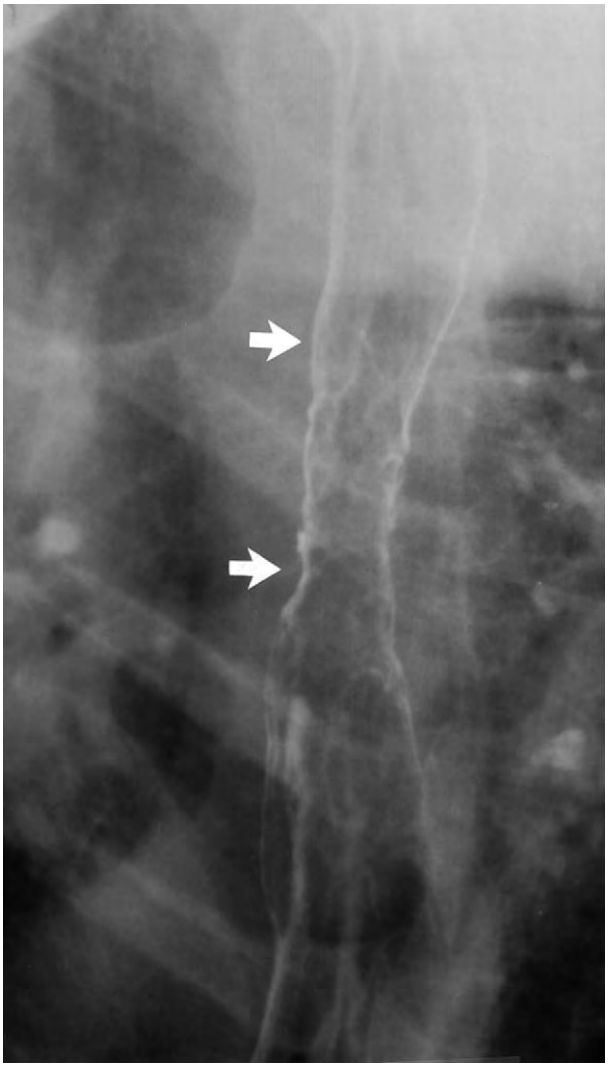


Figure 5–11. Barrett's esophagus. Mild narrowing and a reticular mucosal pattern are apparent in a segment of the midesophagus (between *arrows*)

Preoperative Planning The presence of a large hiatal hernia (>5 cm) or evidence of a shortened esophagus may influence the type of surgical repair and operative approach. Failure to recognize these conditions may lead to surgical failure as a result of an inappropriate surgical approach or type of repair.

The size of a hiatal hernia is best estimated during a barium study. Hernia size is determined by measuring the distance from the GEJ to the esophageal hiatus during maximum filling of the hernia. Our experience suggests that hernia size is underestimated with endoscopy, probably because of partial reduction of the hernia by passage of the endoscope.

Esophageal shortening is the result of injury, usually from severe reflux disease, producing fibrosis in the periesophageal tissue. In such cases, inadequate surgical dissection during laparoscopic fundoplication may leave the repair under tension and lead to early surgical failure. Clues to the diagnosis of esophageal shortening include esophageal scarring, stricture, and the size and shape of the hiatal hernia. A hiatal hernia with tapered shoulders, especially in the presence of scarring or stricture, suggests shortening (Fig. 5–12).

Postoperative Complications Anatomic failure of an antireflux repair occurs in 5% to 15% of cases. Barium examination along with endoscopy and pH monitoring is used to evaluate this group of patients. Findings related to failure of fundoplication are discussed in another section.

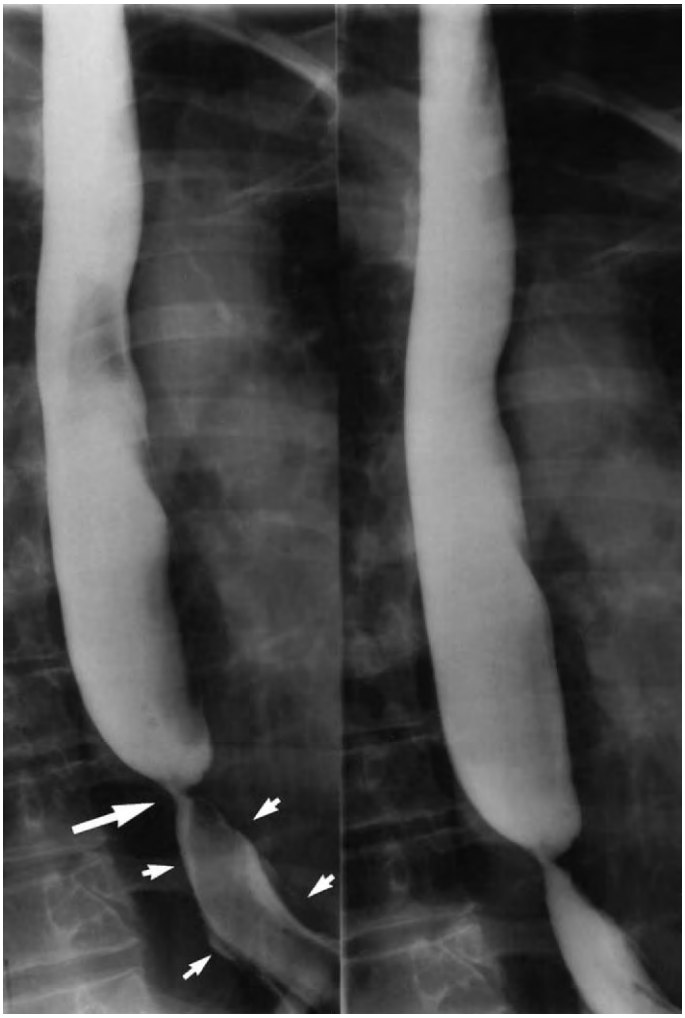


Figure 5–12. Scleroderma with esophageal shortening. A tight stricture at the gastroesophageal junction (*large arrow*) with proximal dilatation is indicative of poor motility. The hiatal hernia demonstrates tapered shoulders with an elongated body (*small arrows*). Compare the appearance with the hiatal hernia in a normal-length esophagus in Figure 5–35.

ESOPHAGEAL MOTILITY DISORDERS

Conditions associated with abnormal esophageal motor function are classified as motility disorders. Common to all these disorders are definable abnormalities demonstrated on manometric examination. Established manometric criteria exist for all of the motility disorders,[25] and the diagnosis is based on a combination of manometric and clinical findings. Barium swallows may suggest the diagnosis and help select patients who would benefit from further functional evaluation.

Simultaneous manofluorography has confirmed the accuracy of barium studies for the evaluation of esophageal function. Agreement between the two studies, when performed simultaneously, is as high as 96%.[17] Agreement is somewhat less (approximately 80%) in studies correlating manometry and barium swallows when they are performed separately.[17]

The efficacy of the barium swallow is dependent on the type of motility disorder. Although the examination is very sensitive for the detection of achalasia (95%), it is less sensitive for diffuse esophageal spasm (71%) and nonspecific esophageal motility disorder (NEMD) (46%).[26] In a group of patients with dysphagia, the overall sensitivity of barium swallow for the detection of a motility disorder was 56%. The sensitivity increased to 89% when patients with nutcracker esophagus and NEMD were excluded.[27]

Symptoms in motility disorders are nonspecific and include dysphagia, regurgitation, chest pain, and heartburn. Dysphagia to both liquids and solids is more common in motility disorders, and this symptom is sometimes helpful in distinguishing motility disorders from conditions that cause esophageal narrowing. When present, regurgitation is usually described as bland rather than acidic as a result of its origin from the esophagus rather than the stomach. Chest pain may vary from intermittent and sharp to constant and pressure-like. It may mimic pain of cardiac origin and trigger a work-up for coronary artery disease. When dysphagia accompanies chest pain, an esophageal origin is more likely. Heartburn is a common complaint, especially in patients with achalasia. The heartburn may be due to esophageal distention or fermentative esophagitis, commonly seen with a massively dilated atonic esophagus. The nonspecific nature of the symptoms in motility disorder makes additional diagnostic studies necessary to clarify the nature of the disease.

Primary Motility Disorders

Motility disorders are classified as either primary or secondary. This distinction is based on whether the esophagus is primarily involved or whether the esophageal involvement is part of a systemic process.

The nature of the motility disorder in an individual patient may not fit into one of the defined classifications. Indeed, this group of diseases represents a continuous spectrum of motor abnormalities. Patients may have characteristics of more than one motility disorder. Furthermore, over time, the character of the motor disturbance may change from one disease to another. It is probably better to describe the nature of the motor abnormalities rather than force a patient into a defined disease category.

Achalasia is a disease of unknown cause characterized manometrically by absent esophageal body peristalsis and abnormally high LES resting pressure or incomplete relaxation of the LES. Histologic findings in the dorsal motor nucleus, vagus nerve, and myenteric plexus suggest a process causing smooth muscle denervation.

In classic achalasia, the esophageal body is markedly dilated. Little or no motor activity is visible except in the proximal third. Sometimes, weak tertiary contractions are visible as minute undulations along the barium column margins. As the patient drinks, barium produces an irregular pattern as it falls through a column of retained food material within the lumen. This produces incomplete opacification of the lumen and mimics the

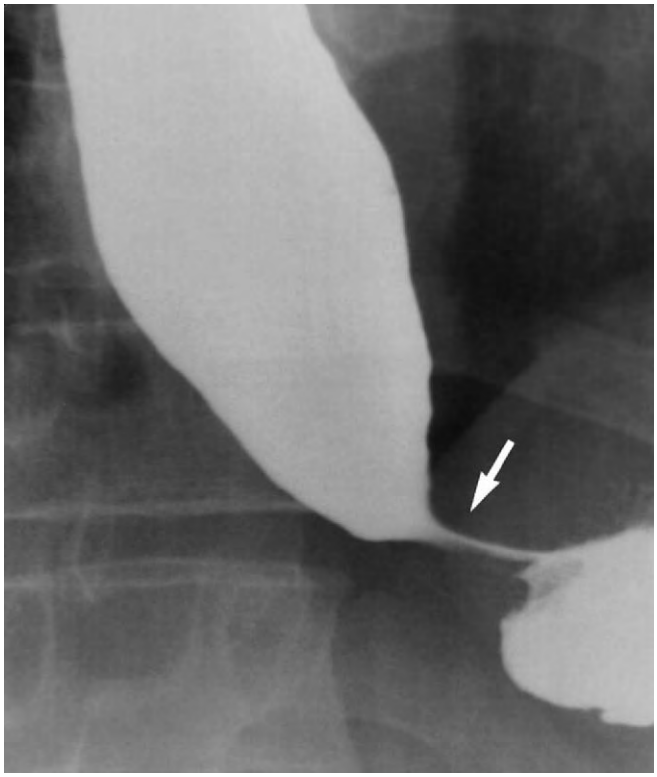


Figure 5–13. Classic achalasia—a markedly dilated atonic esophageal body with tapered narrowing (i.e., "bird's beak" deformity) (*arrow*) at the gastroesophageal junction.

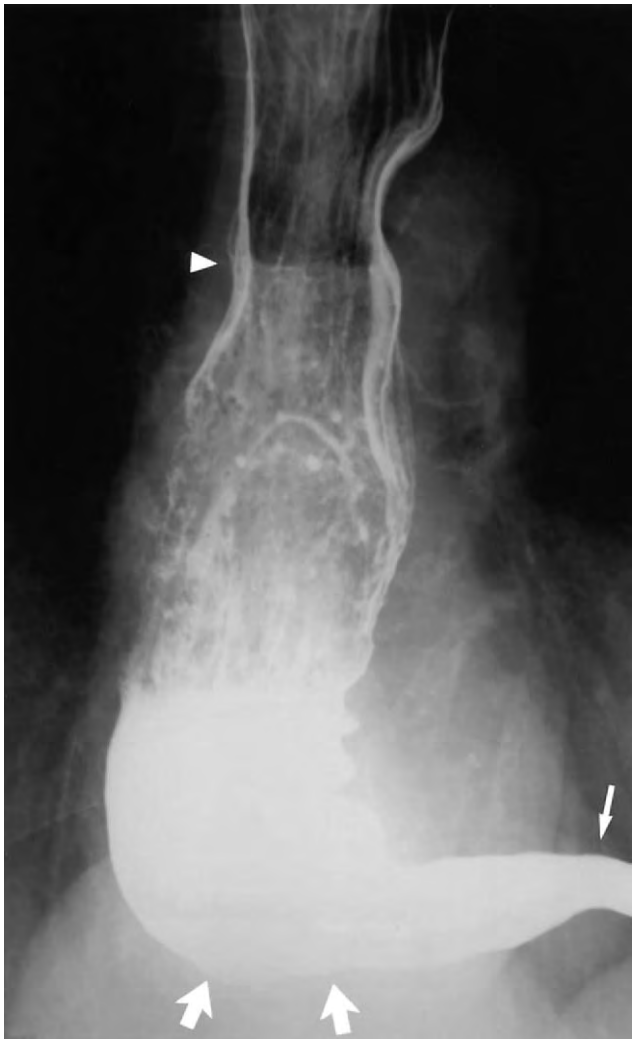


Figure 5–14. "Sigmoid" esophagus. Long-standing achalasia has resulted in an elongated, tortuous esophagus with a dependent segment (*large arrows*) with respect to the esophageal outlet (*small arrow*) that is the cause of poor drainage into stomach. Note the retained debris and air-fluid level (*arrowhead*) near the aortic arch.

appearance of extraluminal contrast. Initially, little if any barium exits the esophagus into the stomach. The lower end of the obstructed contrast column is tapered to a point and resembles a "bird's beak" (Fig. 5–13). The barium-fluid level within the esophagus rises with the addition of more barium from above. Intermittent opening of the lower part of the esophagus causes small amounts of barium to squirt into the stomach, thereby maintaining a relatively constant barium-fluid level. The height of the barium-fluid level is usually characteristic for each patient—the more severe the obstruction, the higher the level. With extreme degrees of dilatation, the esophagus becomes tortuous and nondependent segments are visible (i.e., the so-called sigmoid esophagus) (Fig. 5–14). In the erect position, fluid within these nondependent areas is unable to drain into the stomach, and the constant weight of the fluid within the nondraining segment may accelerate the process of dilatation.

In early or mild achalasia, esophageal body abnormalities may predominate. The esophagus may drain well in the erect position, but poor bolus transport is seen in the recumbent position as a result of ineffective peristalsis. Mild dilatation of the esophageal body and increased tertiary contraction may also be seen. These changes are nonspecific and may occur with other motility disorders. However, in the appropriate clinical setting, these findings should lead to manometric examination to identify LES abnormalities consistent with achalasia.

A less common variant, vigorous achalasia, is characterized by strong tertiary contractions of the esophageal body instead of the atonic esophageal body seen with classic achalasia (Fig. 5–15). Like the classic type, LES abnormalities are seen. The appearance of the esophageal body contractions resembles the findings seen in diffuse esophageal spasm. However, unlike diffuse esophageal spasm, the esophageal body is slightly dilated and the esophagus drains poorly.

Pseudoachalasia may result from malignancies at the GEJ that infiltrate the submucosa. Associated aperistalsis of the esophageal body and narrowing of the GEJ simulate the findings of classic achalasia. In many cases, no mucosal lesion is visible endoscopically, and the diagnosis is suspected only because of the older age of the patient and the recent onset of dysphagia. One paper suggests that the length of the "bird's beak" is greater in

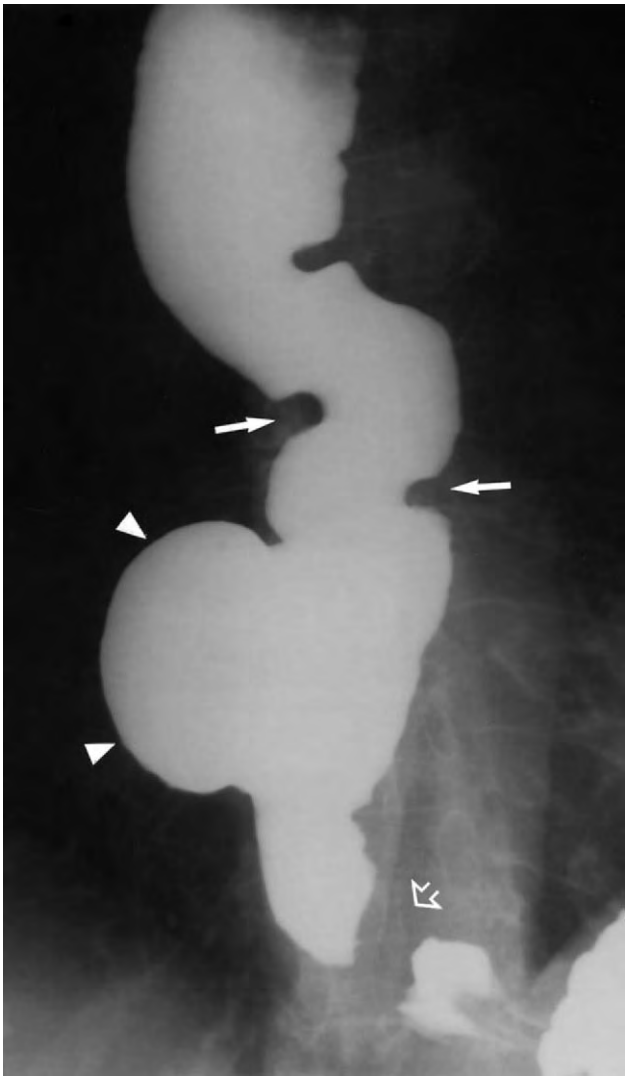


Figure 5–15. Vigorous achalasia identified by a dilated esophageal body with prominent tertiary contractions (*arrows*) and a narrowed gastroesophageal junction (*open arrow*) above a small hiatal hernia. A large pulsion diverticulum (*arrowheads*) arises from the distal esophageal body.

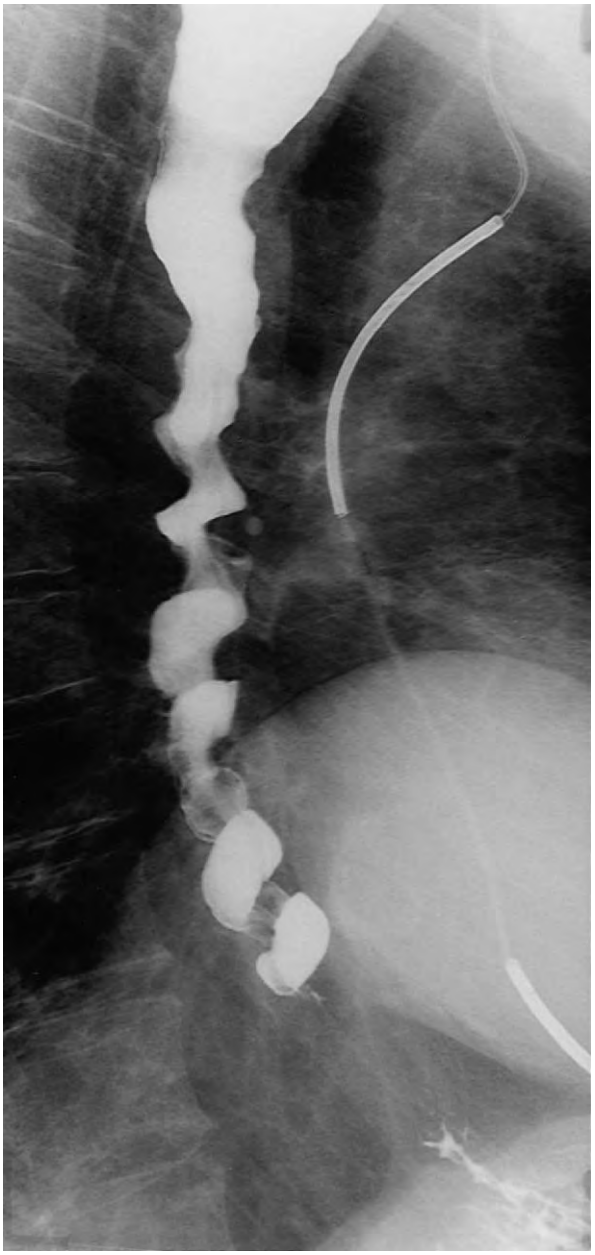


Figure 5–16. Diffuse esophageal spasm. Multiple tertiary contractions are producing a "corkscrew" appearance of the esophageal body.

patients with pseudoachalasia associated with malignancy than in those with classic achalasia.[28]

Diffuse esophageal spasm is a disorder of unknown cause characterized by intermittently abnormal motility associated with symptoms of chest pain and dysphagia. Dysphagia is variably present and does not necessarily accompany the chest pain. Chest pain and dysphagia may be exacerbated by the ingestion of cold liquids.

Manometrically, simultaneous contractions are seen in greater than 10% of wet swallows. Radiographic features reflect the manometric findings—peristalsis is intermittently replaced by tertiary contractions, and a "corkscrew" or "rosary-bead" appearance is produced (Fig. 5–16). Normal peristalsis is usually present in the proximal end of the esophagus. A recent report has suggested that abnormalities of the LES producing delayed esophageal emptying may be more common than a "corkscrew" appearance of the esophageal body.[29]

Radiographic sensitivity in the diagnosis of diffuse esophageal spasm is low in comparison to its sensitivity in the diagnosis of achalasia, probably because of the intermittent nature of the motility disturbance and the nonspecific nature of the radiographic findings. Tertiary contractions are common in both normal patients and those with motility disorders and should not be interpreted as indicative of diffuse esophageal spasm unless accompanied by appropriate symptoms and confirmed with manometry.

Nutcracker esophagus is a term coined for a condition characterized by chest pain in patients with high-amplitude peristaltic contractions in the distal part of the esophagus. The existence of the condition is disputed. Peristaltic wave propagation is otherwise normal and is not accompanied by simultaneous or multipeaked contractions. Precise manometric criteria for diagnosis are not universally agreed on, and overlap between normal and abnormal manometric findings exists.

Radiographically, patients with nutcracker esophagus have normal findings on barium swallow. Because the peristaltic wave is normal except for amplitude, barium peristalsis appears to be normal.

NEMD is a "waste basket" category used to describe motility disorders that do not meet established manometric criteria. Manometric abnormalities include failed peristalsis, low-amplitude contractions, prolonged duration of peristalsis, simultaneous contractions, tertiary contractions, and incomplete relaxation of the LES. Symptoms are nonspecific and include chest pain and dysphagia. Radiographic findings are frequently normal. When present, abnormalities are nonspecific and include ineffective peristalsis causing stasis and tertiary contractions.

Recently, a subgroup of patients with NEMD has been classified as having ineffective esophageal motility. These patients have defined manometric criteria demonstrating hypocontraction of the distal end of the esophagus. GERD is a common accompaniment in these patients. Radiographic findings are nonspecific and are similar to those of NEMD.[30]

Secondary Motility Disorders

Secondary motility disorders include systemic disorders that secondarily affect the esophagus. The list of diseases is diverse and includes collagen vascular disease, diabetes, alcoholism, hypothyroidism, amyloidosis, Chagas' disease, and chronic intestinal pseudo-obstruction. With a few exceptions, the radiographic appearance is nonspecific.

Of the collagen vascular diseases, scleroderma most often involves the esophagus and occurs in 80% of cases. Mixed connective tissue disease, dermatomyositis, polymyositis, systemic lupus, and Behçet's disease have similar findings but involve the esophagus less often. Abnormal motility is due to smooth muscle atrophy and fibrosis. These pathologic changes result in hypomotility in the distal esophageal body and a hypotensive LES. The combined disorders set the stage for severe reflux disease because of profound loss of the antireflux barrier and poor acid clearance.

The radiographic changes reflect a combination of poor esophageal peristalsis and esophageal injury caused by severe reflux disease. Ineffective peristalsis in the distal third of the esophageal body is indicated by nonocclusive peristalsis and stasis. Hiatal hernias with scarring and stricture are common (see Fig. 5–12). In severe cases, signs of esophageal shortening may be seen. Similar but less severe changes may be seen with other collagen vascular disorders.

Chagas' disease is caused by the tropical protozoan *Trypanosoma cruzi*. It is endemic to South and Central America and is rarely seen in the United States. Cardiac muscle and smooth muscle of the GI tract are commonly involved. The radiographic appearance of the esophagus is identical to that of classic achalasia.

Changes in the esophagus as a result of diabetes, hypothyroidism, alcoholism, amyloidosis, and intestinal pseudo-obstruction are similar and usually mild. Increased tertiary contractions and nonocclusive peristalsis resulting in bolus stasis are common but nonspecific findings.

ESOPHAGEAL NEOPLASMS

Esophageal neoplasms are generally found by means of barium esophagography or upper endoscopy. Most malignancies are discovered in symptomatic patients and are high stage with a poor prognosis. The majority of benign tumors are incidental findings, but when they are symptomatic, excision is usually curative. CT can occasionally suggest the diagnosis of esophageal neoplasm, but it is more useful in staging esophageal malignancies, along with newer, more specific modalities such PET imaging and endoscopic ultrasound (EUS).

Carcinoma

Esophageal carcinoma accounts for about 1% of all malignancies and 5.6% of GI malignancies. In 2004, the American Cancer Society estimated that esophageal cancer would be diagnosed in 14,250 people in the United States and that 13,300 would die of this malignancy.[31] The symptoms causing patients with esophageal malignancy to seek medical care are typically significant dysphagia of recent onset (1 to 4 months) and weight loss. The prognosis for symptomatic patients is dismal. Historically, more than 95% of esophageal cancers have been due to squamous cell carcinoma, with adenocarcinoma accounting for most of the rest. In recent decades, the incidence of adenocarcinoma arising in the columnar-lined epithelium of Barrett's esophagus has risen dramatically, with estimates of up to 34% of all esophageal cancers in some series[32] and more than 70% in others. This increase in prevalence is widespread regardless of race and gender, but its relative increase is greatest in white men. The radiographic appearance and clinical features of these two main esophageal cancers are similar regardless of the pathologic subtype. However, the preponderance of adenocarcinomas occurs in the distal esophagus within regions of Barrett's esophagus. Squamous cell carcinoma, by comparison, tends to occur in the upper two thirds of the esophagus. Other primary malignancies of the esophagus, such as sarcomas, melanoma, and lymphoma, are rare.

Radiologic Appearance

Barium studies of the esophagus are useful in the initial diagnosis of esophageal cancer. They can aid in characterizing the size, location, and morphology of the

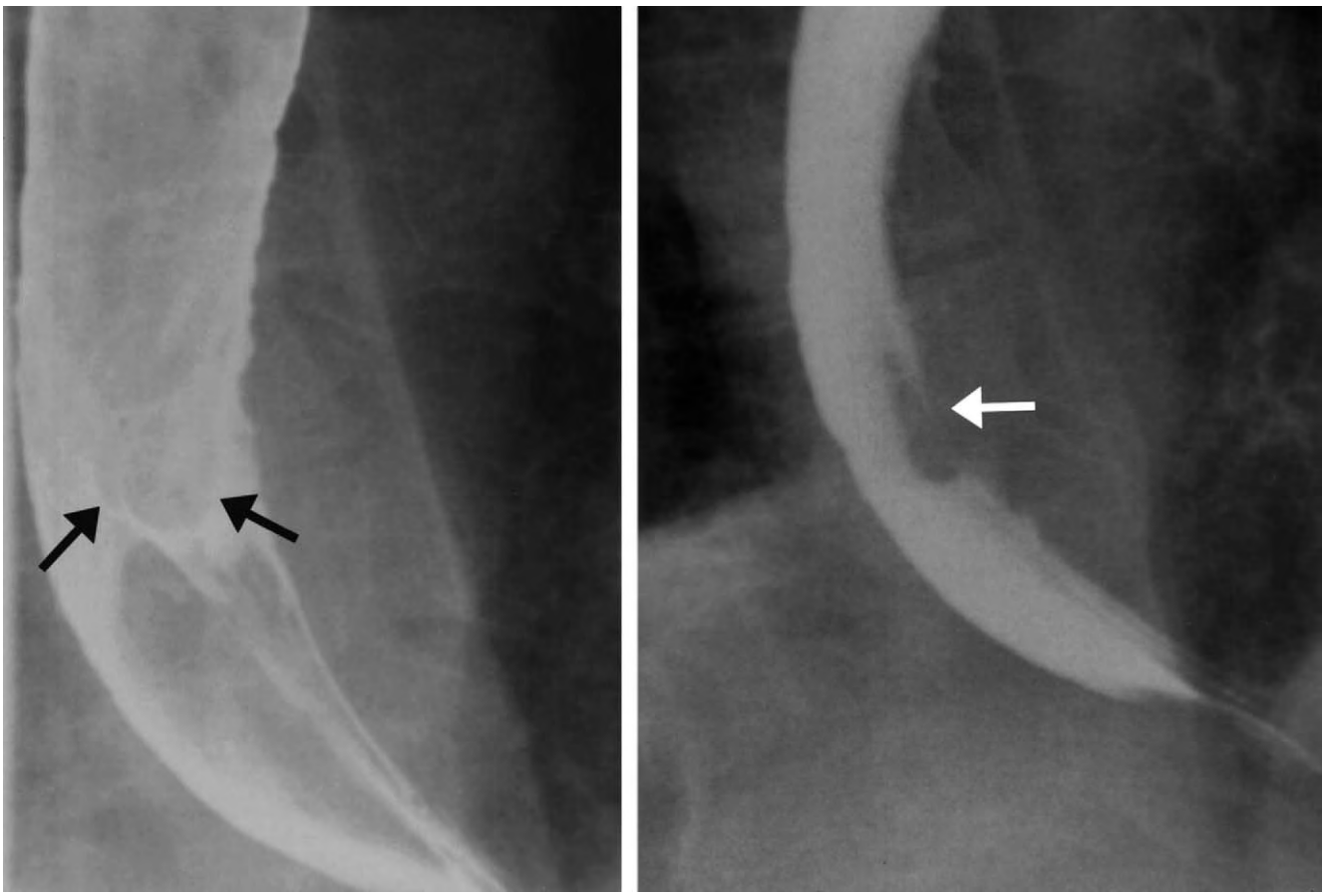


Figure 5–17. T2 adenocarcinoma within a region of Barrett's esophagus in a 71-year-old man. **A,** An air-contrast image in the left posterior oblique projection shows barium outlining subtle areas of mucosal irregularity (*arrows*) in this sessile 1-cm cancer seen en face. **B,** A single-contrast image in the anteroposterior projection shows a plaque-like lesion (*arrow*) in profile along the left side of the lower part of the esophagus.

disease, both before and after radiation or chemotherapeutic treatment. They can demonstrate complications of unresectable cancer, such as a fistula to the tracheobronchial tree, either primarily or after treatment. Coexistent disorders can be identified, such as benign strictures, hiatal hernias, motility disorders, and rare synchronous second tumors. They are also useful in postoperative evaluation, as discussed later.

Early resectable esophageal carcinomas can be detected or suggested on double-contrast barium esophagograms performed with careful radiographic technique. Single-contrast barium evaluation is not as sensitive but may be complementary to the air-contrast technique. Early disease has a variety of subtle radiographic appearances, including fixed mucosal irregularity, irregular strictures, polypoid filling defects, or plaque-like filling defects (Fig. 5–17). When radiographic findings of a smooth benign-appearing stricture are seen, they can reliably be considered benign.[19] Endoscopy may still be useful to search for signs of esophagitis or Barrett's disease. When radiographically equivocal or malignant-appearing strictures are seen, endoscopy is required for definitive diagnosis of possible malignancy. It has been said that barium studies of the esophagus are highly accurate for the detection of esophageal neoplasm, but this has been found to be true only in symptomatic (therefore high-risk) patients.[33] Furthermore, detection of esophageal malignancy in symptomatic patients is usually associated with high-stage malignancy and its associated poor prognosis. Early, curable esophageal malignancy is best found by endoscopy in high-risk patients (such as those with known Barrett's esophagus).

More advanced esophageal cancer can readily be detected with a single- or double-contrast barium technique, although the double-contrast technique is nearly always more revealing of mucosal abnormalities. Advanced esophageal cancer is usually manifested as a focal ulcerated or fungating mass extending into the lumen with irregular, eccentric luminal narrowing (Fig. 5–18). The luminal caliber is often narrowed by 50% to 75%, frequently with at least two thirds of the circumference involved.[34] The transition from normal esophagus to carcinoma is usually abrupt, as

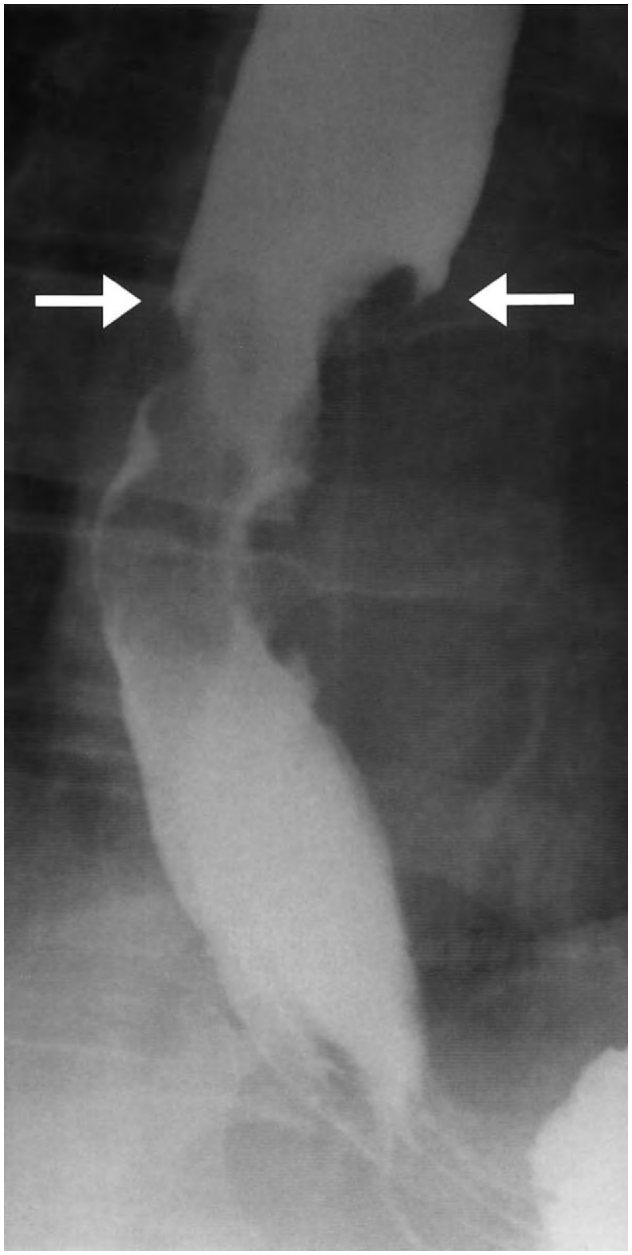


Figure 5–18. Adenocarcinoma in the lower part of the esophagus in a 54-year-old man. An esophagogram shows asymmetric circumferential luminal narrowing, mucosal ulceration, and an abrupt transition (*arrows*) from normal to abnormal mucosal contours.

demonstrated on barium esophagograms. Aspiration can be seen as a result of partial esophageal obstruction, particularly in high esophageal lesions (Fig. 5–19). A carcinoma near the EGJ can cause high-grade obstruction with dilatation of the proximal esophagus, retention of barium, and significant fixed narrowing of the lumen at the EGJ. This appearance is called *secondary achalasia* because of an appearance and functional behavior similar to that of true achalasia (Fig. 5–20).

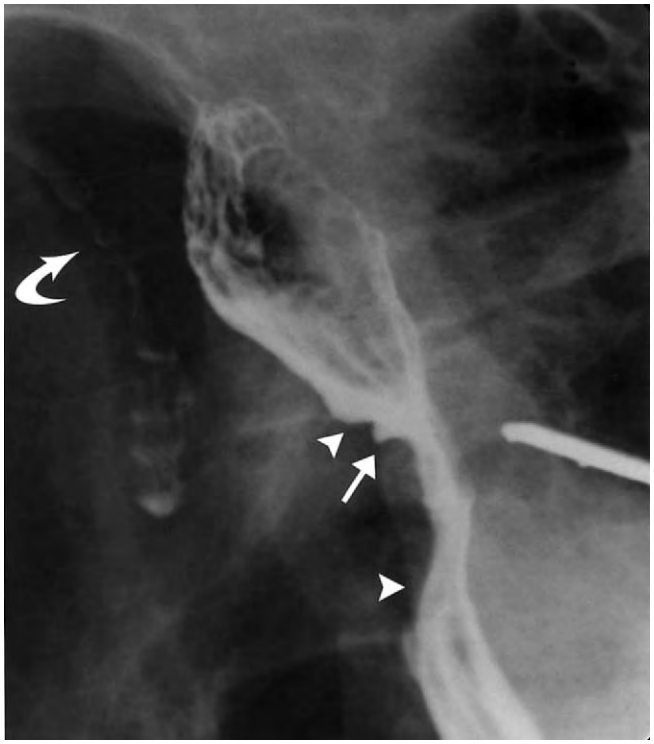


Figure 5–19. Adenocarcinoma in the upper thoracic esophagus arising from the right anterior surface in an 83-year-old man. This is a broad-based eccentric mucosal mass (*arrowheads*) with ulceration (*arrow*). Note the aspirated barium in the trachea (*curved arrow*) related to the dysphagia caused by this tight malignant stricture.

Barium studies can detect some complications of high-stage disease, such as the formation of a fistula to the tracheobronchial tree (Fig. 5–21). The ability of barium studies to give a "global" view of the esophagus, even in the presence of tight strictures, makes it useful in detecting coexistent disorders, including benign strictures, hiatal hernia, motility disorders, and synchronous neoplasms (Fig. 5–22).

Staging

The depth of invasion of esophageal cancer within the wall of the esophagus determines whether a tumor is T1 (limited to the lamina propria or submucosa), T2 (invading the muscularis propria), or T3 (invading the adventitia). Whereas lesions that are T2 or lower have a 5-year survival rate of 40%, T3 (or higher) lesions have a 5-year survival rate of 4%.[35] Additionally, involvement beyond the mucosa is associated with nodal disease in 50% of patients,[35] which also reduces survival. Obviously, the presence of direct invasion of adjacent structures (T4) or the presence of distant metastases (M1) portends a poor prognosis. Unfortunately, many esophageal cancers are unresectable at the time of initial evaluation, thus precluding curative therapy.

A multimodality imaging approach, often including barium studies, CT, endoscopy, EUS, and PET imaging,

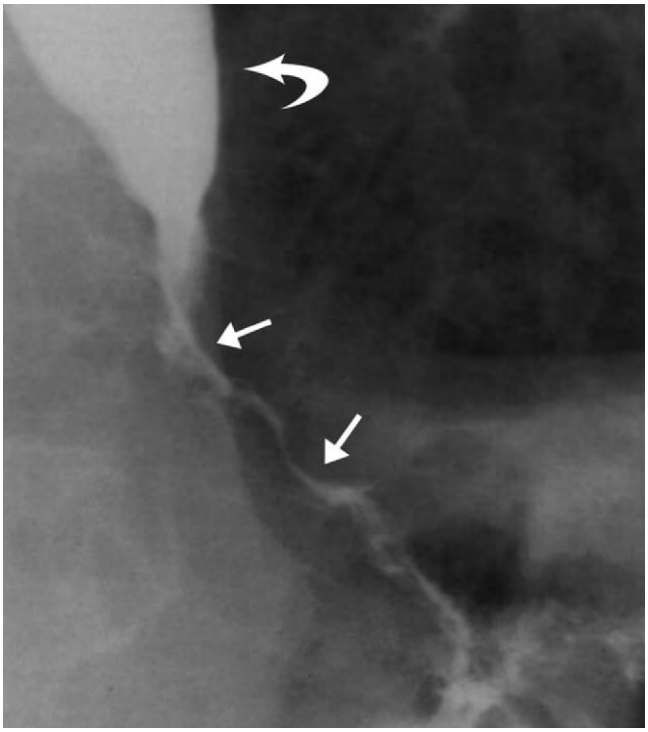


Figure 5–20. Seventy-seven-year-old man with grade 4 adenocarcinoma within Barrett's esophagus located at the esophagogastric junction causing the appearance of secondary achalasia. Note the retained barium in the dilated esophagus (*curved arrow*) above the fixed, narrowed esophagogastric junction from this nearly obstructive carcinoma (*arrows*).

is usually necessary to demonstrate that an esophageal cancer is resectable. CT and PET/CT cannot determine the depth of invasion and are not useful in confirming low-stage disease. However, they are useful in demonstrating the presence of metastatic disease, which confirms high-stage disease, or suggesting the absence of high-stage disease. PET/CT fusion scans are the more useful of these two modalities, but PET is not nearly as available as CT in many regions at this time.

Barium Studies Barium examination has little role in the staging of recently diagnosed esophageal cancer, unless it happens to show the unusual finding of direct invasion of the tracheobronchial tree (see Fig. 5–21), thereby demonstrating a T4 lesion. If a newly diagnosed esophageal cancer is thought to possibly be early stage (see Fig. 5–17), EUS is useful to determine the depth of invasion within the esophageal wall.

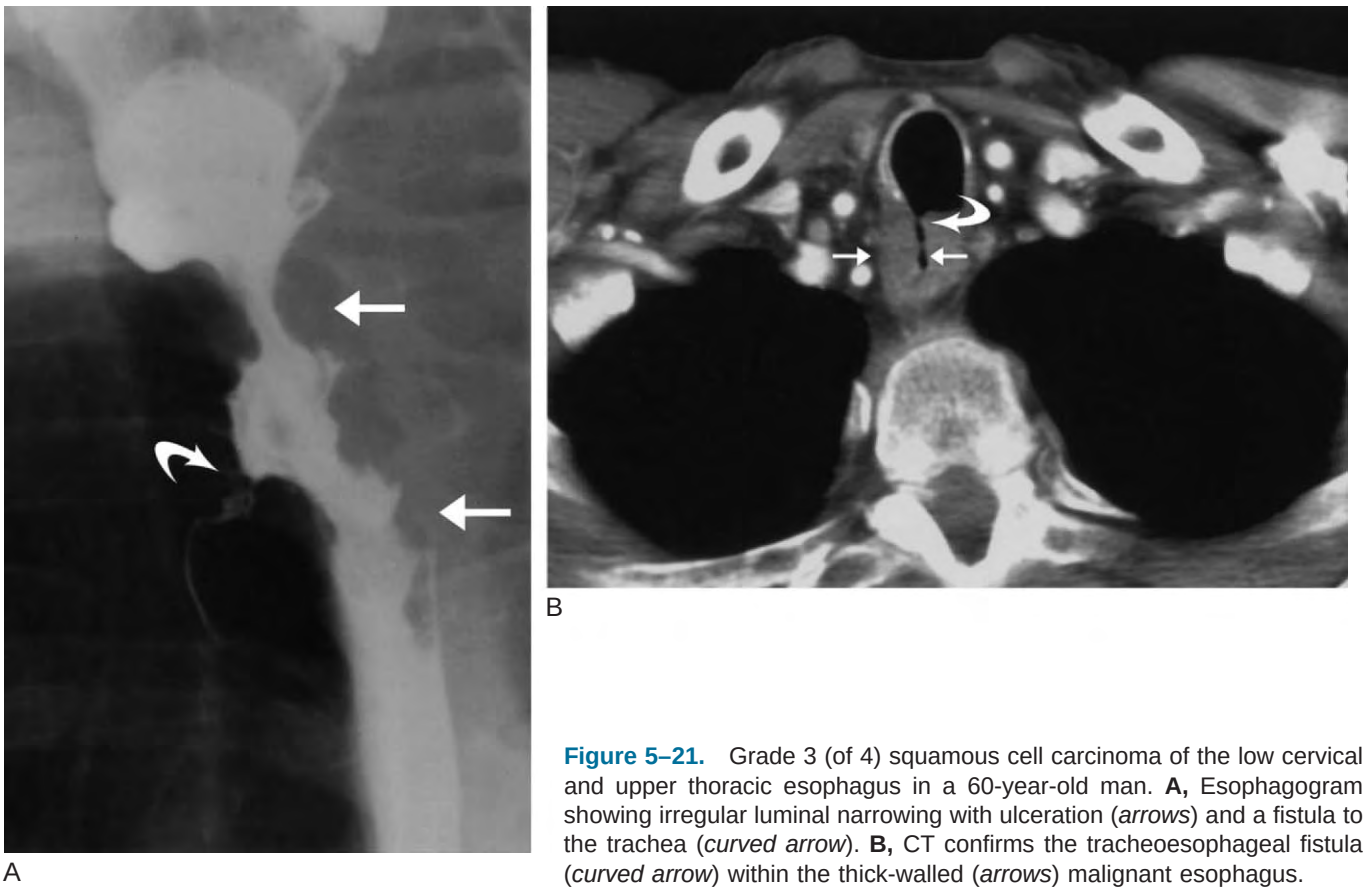
Computed Tomography CT can often detect primary changes of esophageal cancer and suggest its diagnosis, but it is inferior to barium studies and endoscopy in this role. CT can sometimes detect esophageal wall thickening, particularly when it is large enough or when esophageal contrast has been used and wall thickening is seen to be asymmetric about the lumen (Fig. 5–23). However, this is particularly difficult near the EGJ (where many adenocarcinomas develop in the setting of Barrett's esophagus) because of the oblique course that the esophagus takes as it passes through the diaphragmatic hiatus toward the stomach; in such cases, a normal esophagus often appears abnormal on standard axial images. CT is also poor in demonstrating the length of involvement by esophageal cancer, which is quite obvious on barium studies and endoscopy.

CT's greatest contribution is its ability to demonstrate high-stage, often unresectable disease. CT can demonstrate stranding into adjacent fat (confirming invasion beyond the adventitia), direct invasion of adjacent structures (see Fig. 5–21), and worrisome adenopathy (greater than 1 cm in diameter) in adjacent and subdiaphragmatic locations (see Fig. 5–23). Most lymph nodes detected by CT with a minimum diameter greater than 1 cm will represent metastatic adenopathy (in the setting of known esophageal cancer). Unfortunately, lymph nodes that are less than a centimeter in size are frequently metastatic in this setting as well yet could represent benign reactive lymph nodes. These subcentimeter lymph nodes can sometimes be confirmed as metastatic when PET/CT fusion scans show activity in these smaller nodes. When PET/CT is not available, these small nodes may remain indeterminate in the staging process. EUS biopsy techniques can be used to prove metastatic involvement in localized adenopathy. These and other areas of adenopathy can be treated with neoadjuvant chemotherapy or surgical excision (or both), if palliative or definitive surgery is undertaken.

Distant metastases, such as liver, omental, or adrenal involvement, are often well demonstrated by CT. CT is also an appropriate modality to use to guide percutaneous biopsy of suspected metastatic disease. Lymph nodes can be sampled by percutaneous biopsy, which can be useful if it confirms metastatic involvement. However, understaging of lymph nodes because of the limited sampling process can be a problem for accurate staging, particularly with micrometastases in small lymph nodes. MRI has most of the same advantages and disadvantages as CT but often suffers from problems with motion artifact (especially respiratory and cardiac motion), is more expensive than CT, and is an impractical modality to use to provide image-guided percutaneous biopsy. MRI has no routine role in esophageal cancer staging.

Positron Emission Tomography The usefulness of PET is in evaluating documented high-grade malignancies of the esophagus. There is no documented role for PET in differentiating benign tumors or inflammatory conditions such as Barrett's esophagus from malignancy. Generally, some mild inflammation in such cases can result in PET uptake that is indistinguishable from that seen in early malignancy.

PET staging of documented esophageal cancer can provide additive information in several respects. One potential PET contribution is detection of metastatic disease in lymph nodes smaller than the standard CT criteria for nodal enlargement. Additionally, in enlarged lymph nodes without metastasis, PET can improve specificity by excluding some nodes that may be enlarged because of inflammation or reactivity alone. PET



A

B

Figure 5–21. Grade 3 (of 4) squamous cell carcinoma of the low cervical and upper thoracic esophagus in a 60-year-old man. **A,** Esophagogram showing irregular luminal narrowing with ulceration (*arrows*) and a fistula to the trachea (*curved arrow*). **B,** CT confirms the tracheoesophageal fistula (*curved arrow*) within the thick-walled (*arrows*) malignant esophagus.

findings can be falsely negative when the burden of nodal disease is below the detection ability of PET, such as in micrometastases. Certainly, some highly active inflammatory lymph nodes that do not harbor malignancy can have elevated uptake on a PET scan as well. The current data have demonstrated such to be the case, but, even so, some variation in the accuracy of assessing nodal disease has been noted in publications. Variation in the ability of PET to detect lymph node metastasis depends a great deal on how close the nodal regions are to the primary tumor—with those adjacent to a metabolically active tumor being more difficult to detect—and what patient groups are included in the analysis. In one study, PET demonstrated a sensitivity for predicting local nodal disease of 76% (22/29) versus 45% (13/29) for CT in patients who all underwent curative surgery.[36] The sensitivity for detection of nodal metastasis by PET has also been reported to be as low as 33% for local nodal disease elsewhere, however.[37-39] These studies have often been performed in different patient groups. Some authors looked only at patients who were determined to be clinically resectable (i.e., negative on CT for metastasis) before performing PET. This subset selection of patients and the use of some variable PET imaging methods could explain the differences. In our experience, local nodal staging has been roughly equivalent between EUS, CT, and PET when all of the referred patients are included. In about 10% of cases, one imaging method does identify disease not seen by the other, however.

Identifying distant metastatic disease has some important caveats for PET. Relative to distant nodal disease, identification of M1a disease can be difficult without the use of CT fusion imaging to provide anatomic guidance on location of the celiac axis. For M1b disease, having CT fusion with PET may not be as uniformly important but can help in locating metastases in bone versus soft tissue, for example. These issues make the use of PET with CT fusion of significant importance when performing PET imaging for esophageal cancer.

For distant disease staging, PET can be quite enlightening. It can improve distant disease staging, and, in addition, identification by PET of other sites of metastatic disease not previously noted may help facilitate confirmation of disease. In one study, of seven patients who did not undergo surgery, PET detected distant metastases that were not identified on CT in five. Another patient had an unsuspected concomitant primary lung tumor discovered by PET alone. In another study of 35 patients with potentially resectable esophageal cancer as determined by CT, PET identified distant metastatic disease in 20%. The accuracy of PET in determining distant metastatic disease in this group was 91%.[40] Others have reported similar findings. Figure 5–24 illustrates a patient with esophageal cancer in whom widespread distant disease was identified by PET that was underestimated on other imaging modalities.

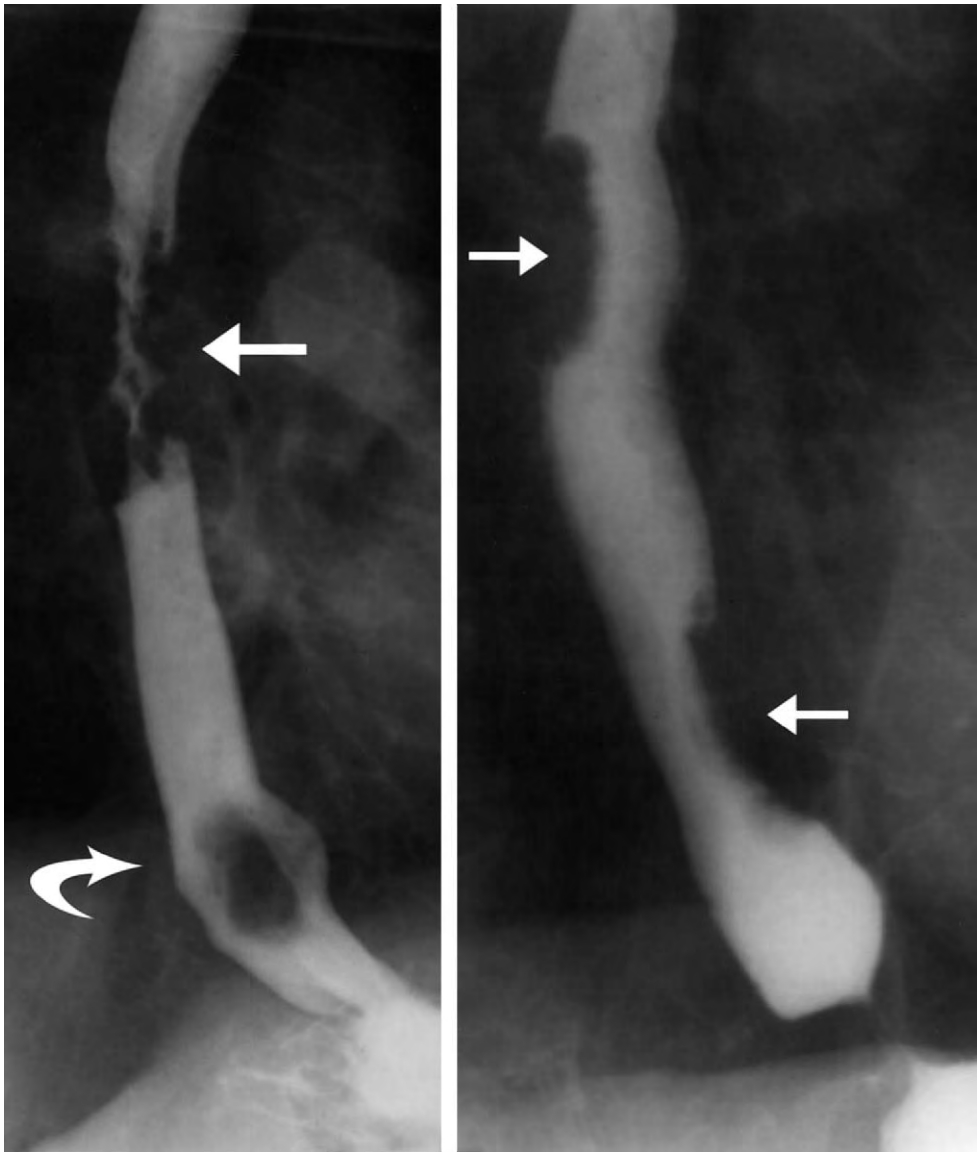


Figure 5–22. Two synchronous squamous cell carcinomas in two separate patients. **A,** Ulcerated infiltrating mass (*arrow*) in the midesophagus with a rare polypoid intraluminal mass (*curved arrow*) in the lower esophagus. **B,** Broad-based sessile polypoid masses (*arrows*) arising eccentrically from opposite sides of the mid and lower portions of the esophagus.

Evaluation of Therapy for Esophageal Cancer

Attempts to improve the survival of patients with esophageal cancer are leading to multimodality treatment regimens. Time will tell whether survival will be extended, but the use of PET in selecting successful treatment paradigms early in the course of therapy holds the promise of more rapid discovery of a treatment combination that may improve survival. Recent work has shown that PET is able to detect which tumors are responding as early as 14 days into therapy. In a group of 40 patients with locally advanced adenocarcinoma of the EGJ, Weber et al. showed that reduction of tumor fluorodeoxyglucose (FDG) uptake after 14 days of therapy was significantly different between responding and nonresponding tumors. Optimal differentiation was achieved by a cutoff value of 35% reduction of initial FDG uptake. Applying this cutoff value as a criterion for a metabolic response predicted clinical response with a sensitivity and specificity of 93% (14 of 15 patients) and 95% (21 of 22), respectively. Patients without a metabolic response were also characterized by significantly shorter time to progression/recurrence ($P = .01$) and shorter overall survival ($P = .04$).[41]

Assessment of Recurrent Esophageal Cancer

At the present time, there is little benefit to additional therapy after esophageal cancer recurs following curative resection or multimodality therapy. In patients with a suspicion of recurrence from radiographic or other clinical indicators, PET imaging is able to detect more sites of recurrence than conventional tests can. Whether this is important is still a reasonable question. Flamen et al. showed that PET detected 100% of the documented recurrences in a group of 40 patients who were suspected of having disease recurrence.[42] No data are yet available on the potential role that PET could play in disease surveillance. Hopefully, early detection of recurrence could

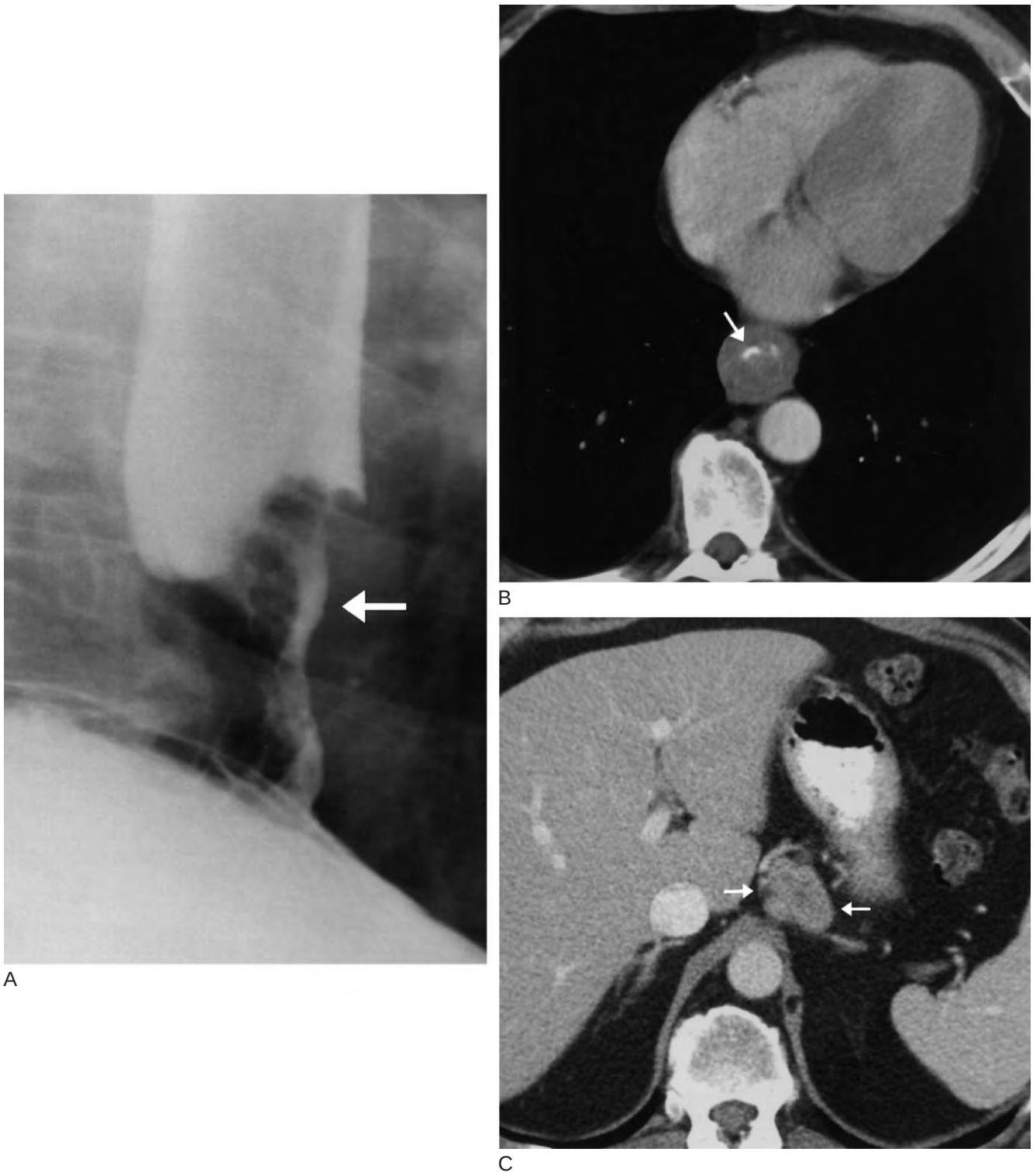


Figure 5–23. Grade 4 adenocarcinoma of the lower part of the esophagus within an area of Barrett's esophagus in a 65-year-old man. **A,** An esophagogram shows an abrupt fungating mass with ulceration and asymmetric luminal narrowing (*arrow*). **B,** An axial CT image shows asymmetric esophageal wall thickening, confirmed by the presence of esophageal luminal contrast (*arrow*) within the eccentrically narrowed lumen. **C,** Enlarged (2.7 × 4 cm) celiac lymphadenopathy (*arrows*) is seen on this axial CT image. Fine-needle aspiration of these nodes by endoscopic ultrasound confirmed adenocarcinoma metastases, thus making this lesion M1a.

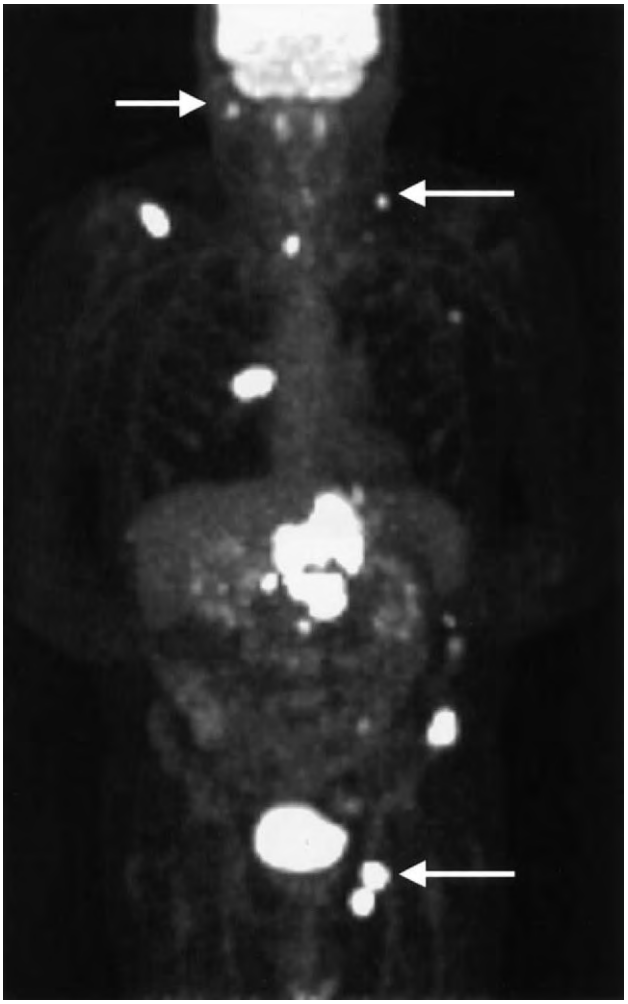


Figure 5–24. Coronal PET in a patient with esophageal cancer. Endoscopic ultrasound had revealed the tumor and suspicious peritumoral nodes, but no biopsy of the nodes could be performed. CT also demonstrated the tumor and suspicious gastrohepatic nodes. PET showed multiple distant metastasis not otherwise described, some of which, right neck, left supraclavicular, and left groin areas (*arrows*), would be easily accessible for biopsy.

play some role in improving survival from recurrent esophageal cancer, and PET could make a contribution in this respect based on its ability to detect recurrence with high sensitivity.

Other Esophageal Malignancies

Other primary malignancies of the esophagus are rare and generally have a poor prognosis. Lymphoma is exceedingly rare as a primary esophageal lesion. Esophageal lymphoma represents less than 1% of lymphoma cases. When it involves the esophagus, it is more likely an extension of gastric lymphoma (causing abnormal thickened longitudinal folds) or due to direct compression from mediastinal lymphoma (with associated luminal narrowing as a result of a mass effect of the tumor arising outside the esophagus). The most common nonepithelial neoplasm of the esophagus is leiomyosarcoma. Like other sarcomas of the GI tract, it usually has a bulky exophytic component, so much so that it may show up on a chest radiograph. The intraluminal component is often a polypoid mass expanding the lumen, frequently ulcerated but sometimes smooth and relatively benign in appearance. Melanoma accounts for 0.1% to 0.2% of all primary esophageal malignancies. It is usually polypoid but can be plaque-like. These and other unusual primary esophageal malignancies are usually definitively diagnosed in symptomatic patients after endoscopic biopsy. Their imaging characteristics are generally nonspecific.

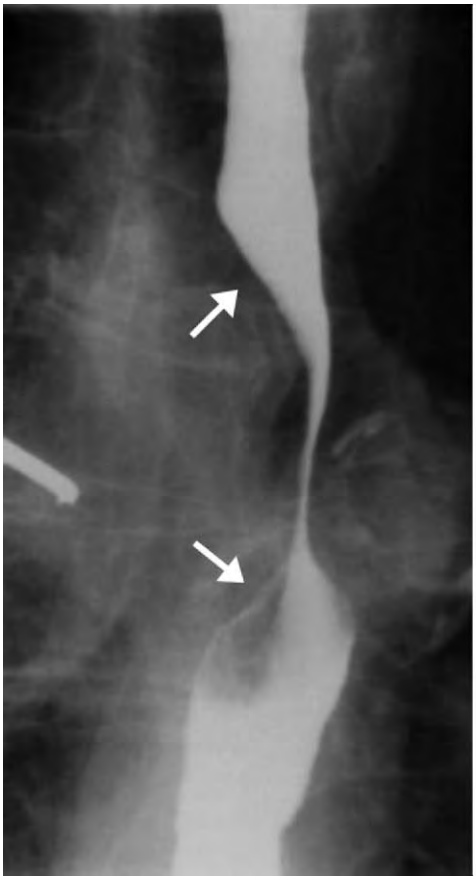
Metastatic disease to the esophagus is most commonly from stomach, lung, or breast cancer. The method of spread to the esophagus can be by way of direct invasion, lymphatic spread, or hematogenous spread. For example, malignancy from the gastric cardia can spread across the GEJ to directly involve the lower part of the esophagus. Lymphatic spread to the mediastinal lymph nodes can be seen with lung, breast, head/neck, and pancreas cancer. This is seen on barium esophagograms as an extrinsic mass compressing, narrowing, and displacing the esophageal lumen and is readily apparent on CT (Fig. 5–25). Hematogenous spread of metastatic disease to the esophagus is very rare; the appearance can be variable.

Benign Esophageal Neoplasms

Benign neoplasms of the esophagus are rare, with the exception of leiomyoma, which is the most common esophageal neoplasm. Most benign esophageal tumors are asymptomatic and found incidentally. Symptoms, when they occur, are usually those of obstruction, often partial or intermittent. Some of these lesions can be confidently diagnosed on the basis of their CT characteristics. The remainder can be diagnosed by EUS or endoscopy with biopsy. Treatment of these rare benign lesions is based on the severity of symptoms, if present.

The presence and type of symptoms are related to the size and location of these benign tumors. Intraluminal masses usually arise from the esophageal mucosa or protrude through the mucosa to reside within the esophageal lumen. On barium studies, a well-circumscribed intraluminal mass is seen (Fig. 5–26) that often expands the lumen and causes a filling defect in the surrounding barium. These lesions need to be differentiated from an impacted foreign body, such as retained food above a stricture. This is usually easily accomplished fluoroscopically or endoscopically.

Intramural lesions occur within the wall of the esophagus and generally have normal, intact overlying mucosa. An intramural lesion appears as a smooth convex impression on the esophagus that causes focal narrowing of the lumen. These lesions form a right angle or slightly obtuse angle with the normal esophageal wall as they protrude into the lumen. EUS with biopsy capability is useful for diagnosing these lesions because a simple "pinch" biopsy of the overlying mucosa will show only normal esophageal mucosa.



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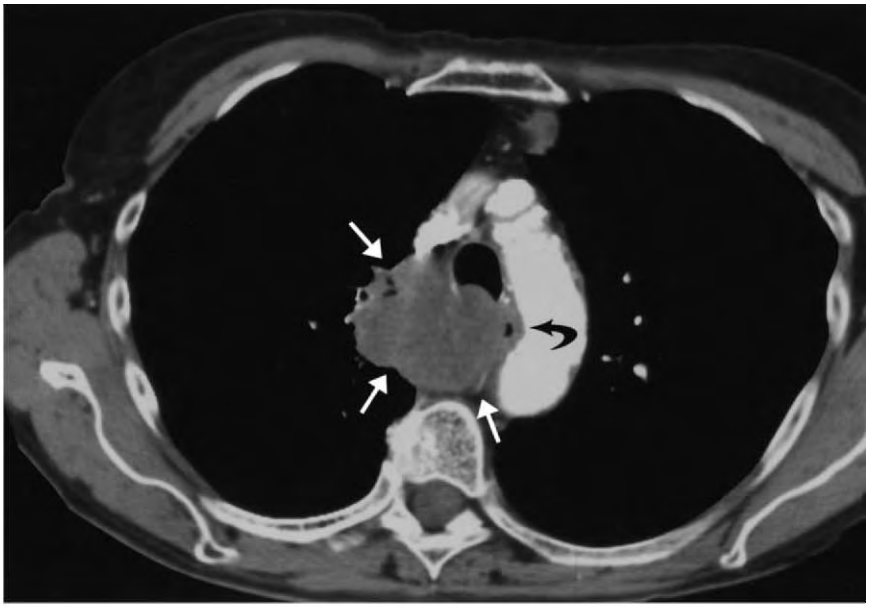


B

Figure 5–25. Grade 4 adenocarcinoma of the right lung in a 78-year-old woman. **A,** An esophagogram shows a long extrinsic impression on the right side of the midesophagus (*arrows*) with intact esophageal mucosa. **B,** CT shows bulky metastatic mediastinal adenopathy (*arrows*) compressing and displacing the esophagus (*curved arrow*) to the left.

Extrinsic lesions arise outside the normal confines of the wall of the esophagus. On barium studies (or endoscopically), an extrinsic mass appears as a smooth convex impression narrowing the esophageal lumen. The main distinction from intrinsic masses is that extrinsic masses cause a more shallow, longer, obtuse impression on the lumen, whereas intrinsic masses are more focal with an abrupt onset of luminal narrowing.

Specific benign lesions deserve some discussion. Fibrovascular polyps (see Fig. 5–26) arise from the submucosa yet are manifested as an intraluminal mass. Typically they arise from the upper part of the esophagus but can occur anywhere. They are frequently quite mobile within the esophagus and are tethered to the esophageal wall by a relatively long, narrow pedicle or point of attachment. Papillomas are smooth-walled polyps, sometimes multiple, arising from the mucosa. They protrude into the lumen, often with a wide base of attachment. Hemangiomas, though rare, may result in esophageal hemorrhage. Inflammatory esophagogastric polyps are actually clubbed, bulbous gastric folds that arise from the gastric cardia and protrude into the lower part of the esophagus at the EGJ. They usually represent inflamed mucosal hypertrophy secondary to GERD.

Leiomyomas (Fig. 5–27) are the most common benign esophageal neoplasm. They are often asymptomatic and discovered incidentally and can be multiple. Leiomyoma is the classic intramural lesion and appears as a focal narrowing with a smooth contour arising from one side of the esophageal wall. They are most commonly seen in the mid and lower portions of the esophagus, particularly near the EGJ. Despite being the most common esophageal neoplasm, leiomyomas often go undetected on most imaging studies because of their frequent lack of symptoms, intact overlying mucosa, and often-subtle impression on the esophageal lumen. Occasionally, they can be quite large and have their epicenter located outside the esophageal wall. In such cases, sarcoma needs to be excluded. EUS can demonstrate a benign-appearing mass, usually arising from the muscularis mucosa, and biopsy is not generally necessary for small, asymptomatic incidental lesions. Other benign lesions, such as lipoma, fibroma, neurofibroma, hamartoma, and hemangioma, have a similar radiographic appearance but are far less common.

The main extrinsic mass arising from the esophagus is an esophageal duplication cyst. Technically, it is a congenital lesion and not a true neoplasm. On CT, an esophageal duplication cyst appears as a well-circumscribed, benign-appearing, thin-walled cystic structure with a CT density value (Hounsfield units) slightly higher than that of water. Other structures that frequently cause an extrinsic impression on the esophagus and potentially narrow the lumen include normal anatomic structures such as the left atrium (particularly if enlarged) on the lower part of the esophagus and the aortic arch (particularly if tortuous and ectatic) on the midportion of the esophagus. They have a

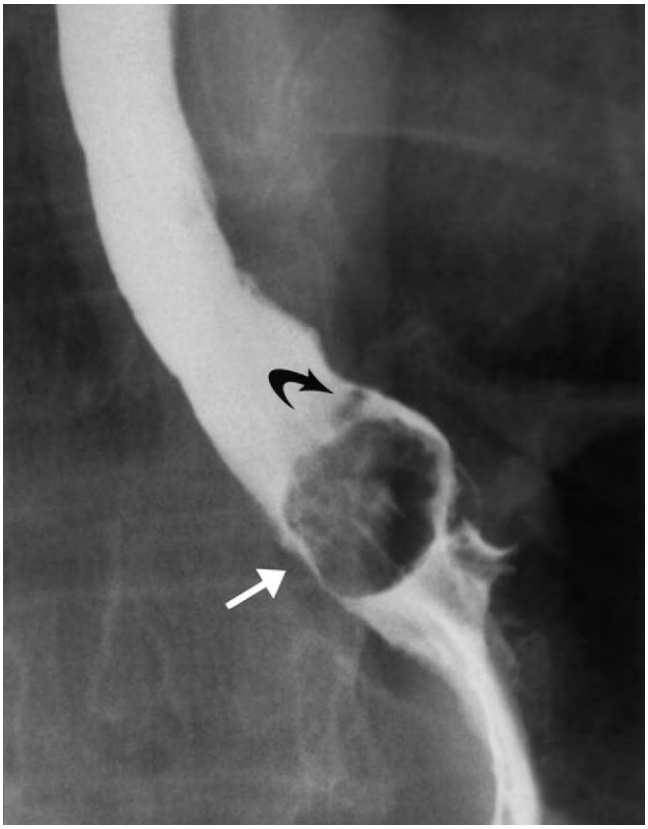


Figure 5–26. Forty-five-year-old woman with a pedunculated fibrovascular polyp seen as an intraluminal filling defect (*arrow*) expanding the lower part of the esophagus. At fluoroscopy, it was noted to move several centimeters within the lower esophagus, tethered by a thin stalk (*curved arrow*).

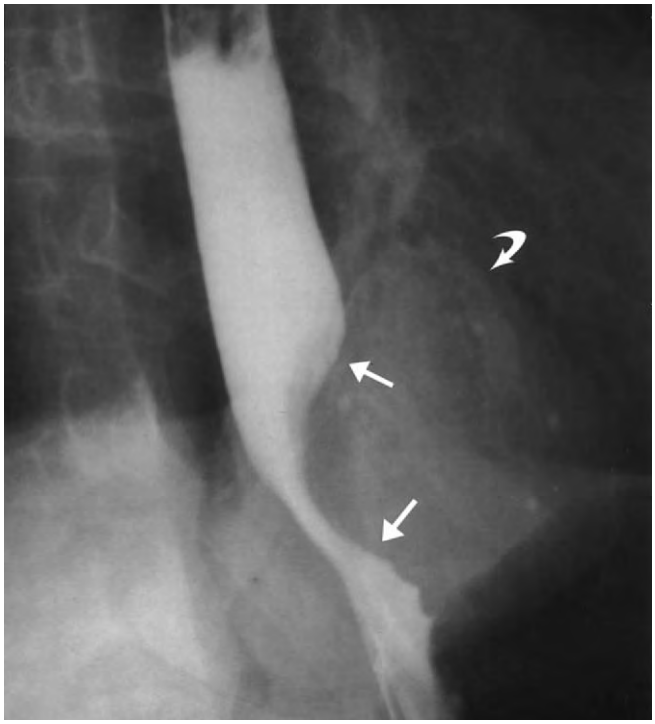


Figure 5–27. Asymptomatic 52-year-old woman with an abnormal chest radiograph. A barium esophagogram shows a mass effect in the lower esophagus on the left that is causing a smooth, sharply obtuse impression on the esophageal lumen (*arrows*). This was shown by biopsy to be a large benign leiomyoma with a prominent exophytic component (*curved arrow*).

characteristic appearance on barium studies and can be confirmed with CT if necessary. Mediastinal neoplasms or adenopathy (see Fig. 5–25), if in direct contact with the esophagus, can also cause extrinsic narrowing of the esophageal lumen, and CT of the chest can identify these mediastinal abnormalities.

POSTOPERATIVE ESOPHAGUS

Goals and Techniques of Postoperative Esophageal Imaging

Radiologic evaluation of a postoperative esophagus is performed to demonstrate the postoperative anatomy, judge the effectiveness of the surgery, and detect postoperative complications.[43] Postoperative images also establish a baseline for comparison of future radiographic studies. The effectiveness of the surgery may not be fully revealed by a radiographic examination performed in the early postoperative period because of transient changes of edema and hematoma. During the early postoperative period (less than 4 weeks), the most common complications after esophageal surgery include leakage, obstruction, and stasis. During the late postoperative period (longer than 4 weeks), the most common complications include GER, stricture, and recurrent carcinoma.[43]

Techniques: Imaging Modalities

Chest radiography plays an important role in the early postoperative period, especially after esophagectomy, because of the high incidence of respiratory complications in these patients, particularly those who have undergone thoracotomy.[44] Complications such as pneumothorax, pleural effusion, and pneumonia are the most frequent cause of morbidity after esophagectomy.[45] Additionally, chest radiographs can provide indirect evidence of esophageal leakage. Findings such as pneumomediastinum, mediastinal widening, or a rapidly growing pleural effusion suggest esophageal leaks. However, chest radiographic findings are relatively insensitive in the diagnosis of leaks. A normal chest radiograph in the appropriate clinical setting should not discourage further investigation.[43]

Esophagography is the major imaging modality for evaluation of a postoperative esophagus. This fluoroscopic esophagogram is performed as the patient drinks contrast material to opacify the esophageal lumen. Radiographs obtained during (spot films) and after (overhead films) fluoroscopy tell only part of the story. The

Table 5–1 Barium Versus Water-Soluble Contrast Material for Postoperative Esophagograms

	Barium	Water-soluble Contrast Material
Advantages	Increased density shows leaks missed by water-soluble contrast material	Leakage into the mediastinum does not cause mediastinitis
	Aspiration does not cause pulmonary edema	Reabsorption from the mediastinum makes future esophagograms easier to interpret
Disadvantages	There is a risk of mediastinitis with leakage into the mediastinum	Aspiration can cause pulmonary edema
	Barium remaining in the mediastinum may suggest persistent leakage on future esophagograms	Leaks can be missed because of decreased density in comparison to barium

radiologist who observed the dynamic fluoroscopic images may report findings that are not included or poorly demonstrated on the radiographic films.

In the early postoperative period, esophagograms are often limited to examination in the recumbent position. Decreased ability to swallow and poor patient mobility add to the difficulty of performing the examination. These early postoperative esophagograms are carried out, at least initially, with water-soluble contrast material in case of leaks. Later in the postoperative period, esophagograms are typically performed as upright, air-contrast images obtained with high-density barium and recumbent, single-contrast images with low-density barium.[43]

CT is not a primary imaging modality in the early postoperative period after esophageal surgery. However, as a secondary modality, CT provides important additional information after the discovery of a postoperative esophageal leak by esophagography. Chest CT demonstrates the severity and extent of mediastinal inflammation associated with such a leak. It also demonstrates the size and location of any mediastinal fluid collection or abscess. This information is especially helpful in planning further treatment. CT images can guide the placement of drains into these collections by surgeons or interventional radiologists.[46] In the later postoperative period, CT or MRI can detect mediastinal cancer recurrence and metastases.

Techniques: Contrast Materials

Two types of contrast material are used during esophagography: barium and water soluble. Each of these contrast materials has advantages and disadvantages (Table 5–1). The type of contrast material used is at least partially dependent on the time since surgery. Water-soluble contrast material is used, at least initially, for early postoperative esophagograms (less than 4 weeks). Barium is used later in the postoperative period (longer than 4 weeks).

Leaks can occur after any esophageal surgery, but they are most common after esophagectomy. The appearance of pain and fever after esophagectomy warrants emergency esophagography.[44] The examination should be performed initially with water-soluble contrast material. If this initial esophagogram is negative, the examination should be immediately repeated with barium. As a result of the superior opacity of barium, small leaks may be diagnosed only with barium. Because many postoperative esophageal leaks are asymptomatic, many institutions perform routine esophagography between 7 and 10 days after surgery.

In a recent retrospective study of 24 esophagectomy patients with postoperative leaks, 16 (67%) of these leaks were demonstrated only with use of high-density (250% weight per volume [w/v]) barium.[47] This percentage of esophageal leaks demonstrated only with barium is higher than in previous studies performed with 60% w/v and 100% w/v barium solutions. The authors speculate that the higher rate of leak detection resulted from the use of higher-density barium. The benefit of demonstrating a leak usually outweighs the risk for mediastinitis secondary to barium leakage.[48]

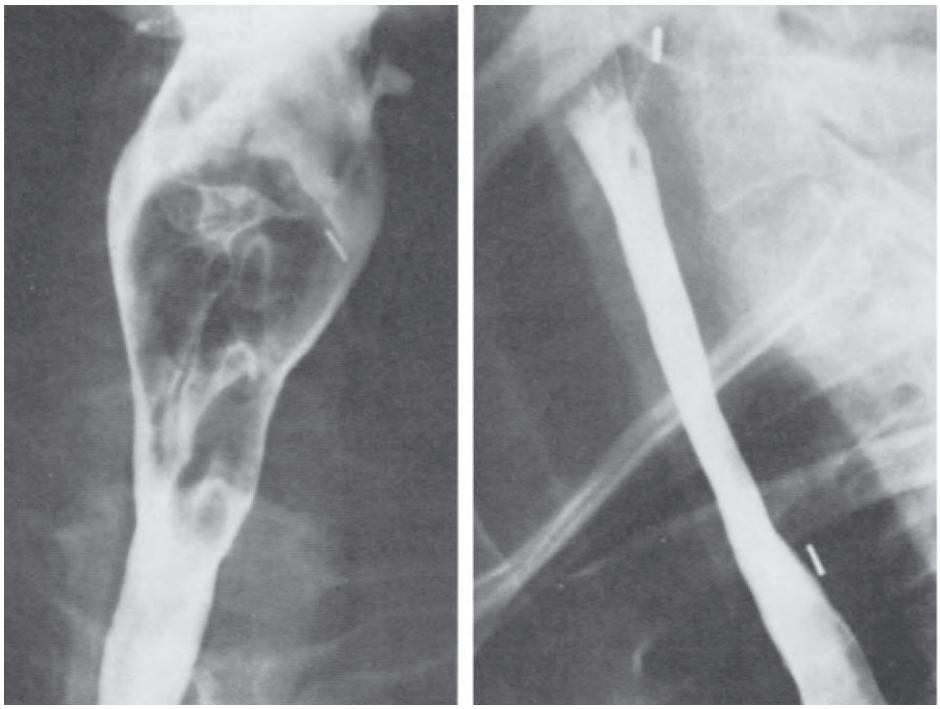
The risk for pulmonary edema after the aspiration of water-soluble contrast material depends on the volume and osmolarity of the material aspirated. Aspiration of high-osmolar water-soluble contrast material, such as diatrizoate meglumine (Gastrografin) or diatrizoate sodium (Gastroview), is more likely to cause pulmonary edema than is aspiration of a similar amount of low-osmolar water-soluble contrast material, such as iohexol (Omnipaque) or metrizamide (Amipaque). Therefore, the use of low-osmolar water-soluble contrast material should be considered in postoperative patients to reduce the risk for pulmonary edema after aspiration.[48]

Specific Findings

Cricopharyngeal Myotomy

Cricopharyngeal myotomy for Zenker's diverticulum is typically combined with diverticulectomy or diverticulopexy. Postoperative esophagography in successfully treated patients shows resolution of the prominent cricopharyngeus muscle and nonfilling of the diverticulum (Fig. 5–28). Mild irregularity with outpouching of the pharyngoesophageal segment posteriorly, superior to the level of the cricopharyngeus muscle—referred to as "mucosal beaking"—is not a worrisome finding.[49]

Because the major complication of cricopharyngeal myotomy is leakage, the postoperative esophagogram should be performed initially with water-soluble contrast material. This contrast material needs to be administered



A B

Figure 5–28. Cricopharyngeal myotomy. Frontal and lateral views from a postoperative barium esophagogram demonstrate extended cervical esophagomyotomy. The surgical clips mark the superior and inferior limits of the myotomy. An obstructing posterior cricopharyngeal muscle is not evident.

cautiously because transient postoperative pharyngeal dysfunction predisposes these patients to aspiration (low-osmolar water-soluble contrast material can be considered for these examinations). If the water-soluble contrast study is negative, re-examination with high-density barium should be performed. Leaks often appear as blind-ending tracts extending from the esophagus posteriorly into the prevertebral space.[49]

Cardiomyotomy

Normally, a postcardiomyotomy esophagogram demonstrates good esophageal emptying and no widely patent GEJ.[43] Eccentric ballooning of the esophageal mucosa through the myotomy defect is a common finding postoperatively (Fig. 5–29) and occurs in 50% of patients after cardiomyotomy.[50] Frequently, an antireflux procedure is performed in conjunction with cardiomyotomy, and radiographic evidence of this procedure may be seen on the postoperative esophagogram.

An early complication of cardiomyotomy is leakage secondary to perforation. Evaluation for this complication should begin with water-soluble esophagography followed by barium to more confidently evaluate for a perforation. Late complications include dysphagia secondary to inadequate myotomy or tight fundoplication. Demonstration of reflux esophagitis suggests the need for an antireflux procedure.[43]

Antireflux Procedures

The appearance of a normal esophagogram after antireflux procedures reflect the goals of these procedures: reduction of esophageal hiatal hernia, diaphragm repair, restoration of an intra-abdominal esophageal segment, and gastric fundal wrap around the proximal part of the stomach. Common antireflux surgeries include the Nissen, Belsey Mark IV, and Hill procedures.[43] The Nissen procedure results in a 360-degree wrap of the gastric fundus around the esophagus. Radiographic findings include a wrap creating a smooth, symmetrical mass within the fundus. With a Nissen procedure, the esophagus passes through the center of the mass (Fig. 5–30). The Belsey Mark IV procedure uses a 240-degree fundal wrap with suturing of the esophagus to the gastric fundus to recreate an acute angle at the GEJ (angle of His). On barium swallow, this procedure results in a smaller soft tissue mass in the fundus and angulation of the intra-abdominal esophagus. During the Hill procedure, the GEJ is sutured to the median arcuate ligament posteriorly. No fundoplication is performed. By means of esophagography, one sees lengthening of the intra-abdominal esophagus and exaggeration of the angle of His. Regardless of the specific antireflux procedure, one should not see a hiatal hernia or evidence of reflux esophagitis.[43]

The most common early complication of fundoplication demonstrated by esophagography is obstruction of the distal end of the esophagus secondary to self-limited edema of the fundal wrap. This process usually resolves in a matter of weeks, and the esophagus will then drain well. Late complications include (1) esophageal obstruction caused by a tight fundal wrap or tight esophageal hiatus, (2) recurrent hiatal hernia and GER caused by disruption of fundoplication sutures (fundal soft tissue density not visible), and (3) recurrent hiatal hernia (fundal soft tissue density visible) caused by dehiscence of diaphragmatic sutures.[43]

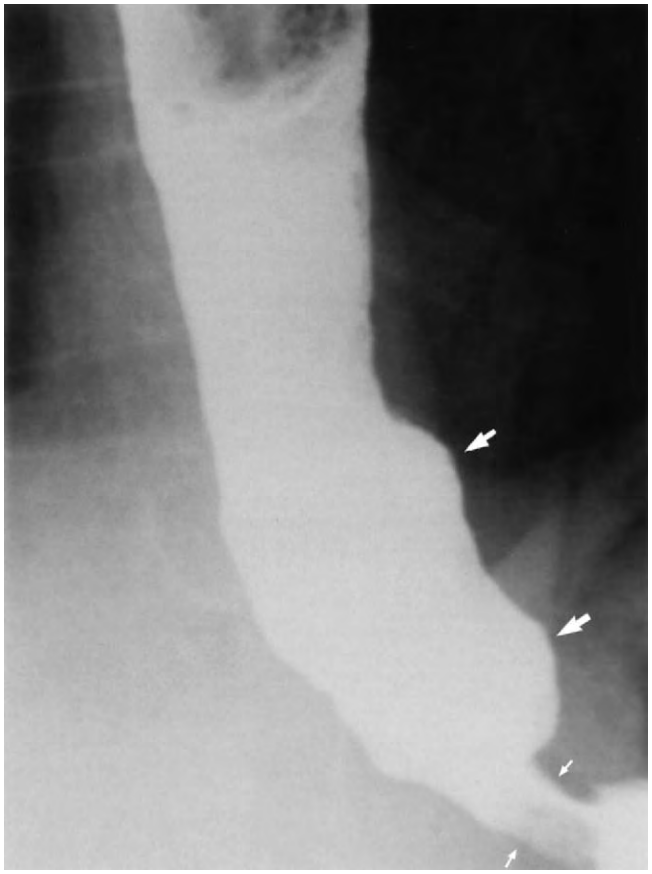


Figure 5–29. Cardiomyotomy (Heller myotomy). An upright, frontal view from a postoperative barium esophagogram demonstrates a common distal esophageal deformity after cardiomyotomy. The distal esophageal mucosa "ballooned" through the myotomy defect and has created a wide-mouthed, false diverticulum (*arrows*). Decreased caliber of the esophagus distal to the myotomy deformity (*small arrows*) should result from partial anterior fundoplication (Dor procedure).

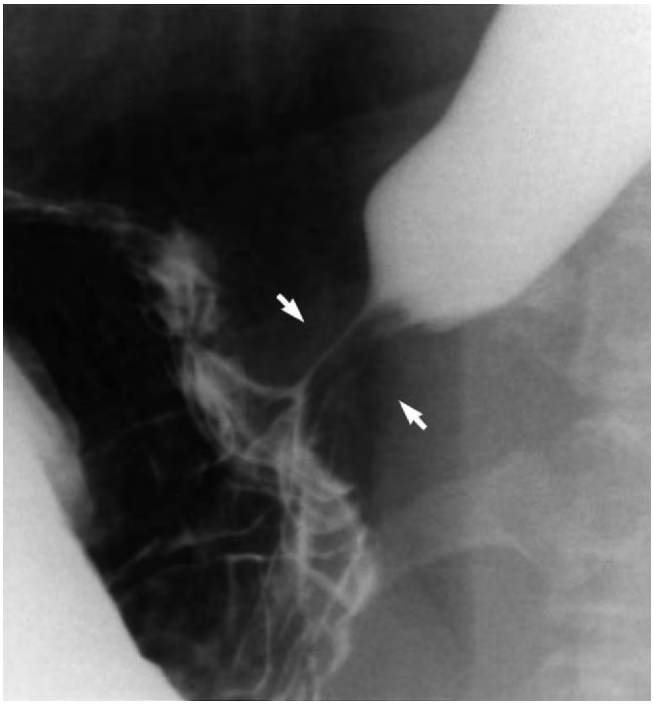


Figure 5–30. Nissen fundoplication—prone, oblique, single-contrast view of the gastroesophageal junction from a barium esophagogram performed 6 weeks after laparoscopic Nissen fundoplication. A smooth, symmetrical, and extrinsic fundal mass resulted from the 360-degree fundal wrap around the intra-abdominal esophagus (*arrows*). The esophagus passes through the center of this mass.

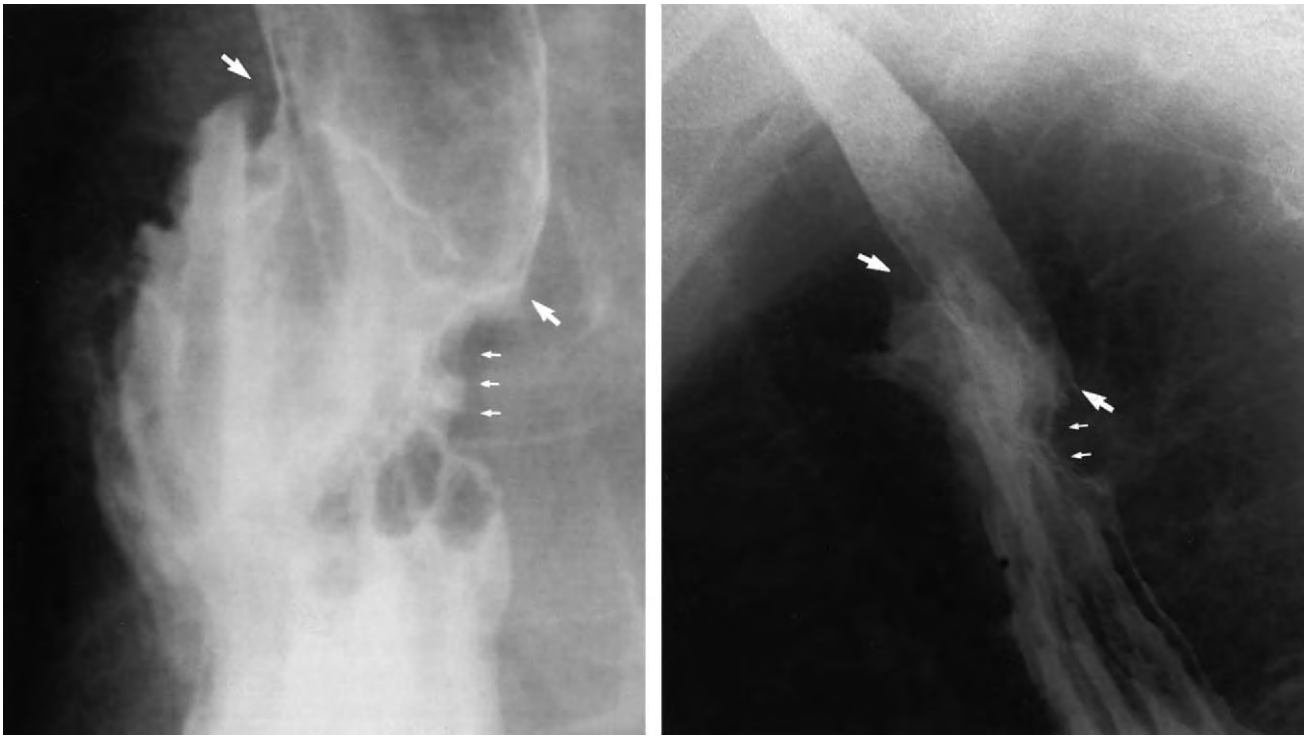
Esophageal Resection

The radiographic appearance after esophagectomy depends on the bowel segment used as an esophageal substitute. Stomach, colon, and jejunum are used as esophageal substitutes, with gastric substitution being most common. Gastric substitution requires resection of the esophagus and cardia, mobilization of the stomach, and anastomosis of the esophagus to the stomach. Pyloromyotomy, or pyloroplasty, and partial resection of the gastric fundus may also be performed to facilitate drainage of the denervated stomach.[43] (Vagotomy is unavoidable during this surgery.) Therefore, a normal postoperative esophagogram should demonstrate patency of the esophagogastrostomy (Fig. 5–31), patency of the stomach as it passes through the esophageal hiatus, and patency of the pylorus.

Leakage is the most feared early postoperative complication of esophagectomy and esophagogastrostomy. The leak may occur at the esophagogastric anastomosis, at the pyloroplasty or pyloromyotomy, or along the gastric staple line resulting from partial gastric resection.[43] Pain and fever after esophagectomy warrant emergency esophagography[44] with water-soluble contrast material and barium. High-density barium has been reported to be more effective in demonstrating leaks.[47]

Early postoperative obstruction may result from edema at the esophagogastrostomy or pyloroplasty/pyloromyotomy sites. Obstruction may also be seen as a result of diaphragmatic compression of the distal part of the stomach or may be due to gastric volvulus.[43] Gastric atony can cause similar obstructive symptoms.

Late complications after esophagectomy and esophagogastrostomy include GER, stricture, and tumor recurrence. GER can cause reflux esophagitis, stricture (above the esophagogastric anastomosis), Barrett's esophagus, and adenocarcinoma.[43] Postesophagectomy patients with dysphagia should be initially evaluated with a barium swallow. Anastomotic strictures are usually well demonstrated (Fig. 5–32). Reflux esophagitis and Barrett's esophagus are best evaluated with endoscopy. CT and PET are best for detection of recurrent tumor and are discussed in another section of this chapter.



A B

Figure 5–31. Esophagogastrostomy. Upright, frontal (magnified) **(A)** and lateral air-contrast images **(B)** from a barium esophagogram performed 1 month after esophagectomy for T1N0 adenocarcinoma of the lower esophagus demonstrate a side-to-side esophagogastric anastomosis along the greater curve (*arrows*). The mass along the left posterior margin of the gastrostomy, just distal to the anastomosis (*small arrows*), should represent a benign postoperative finding (the patient had no evidence of recurrent or metastatic disease 10 months after this esophagogram).

MISCELLANEOUS CONDITIONS

Hiatal Hernias

Hiatal hernias can be classified into several types depending on their appearance. By far, the most common type is a sliding hiatal hernia (type I) (Fig. 5–33). Strictly speaking, a sliding hiatal hernia should be transient and is diagnosed when a portion of the stomach is fluoroscopically seen to enter the thorax through the esophageal hiatus of the diaphragm and later to return to the abdomen. Not uncommonly, however, large sliding hernias remain in the chest during the entire fluoroscopic examination. Such hernias should still be considered the sliding type, as long as there is no evidence of esophageal shortening. The observation that sufficient esophageal redundancy exists to allow reduction of the hernia is important to the surgeon in planning hiatal hernia repair. Although the correlation between GER and sliding hiatal hernias is far from perfect, such hernias are thought to predispose to reflux.[51]

The second major type of hiatal hernia (type II) (Fig. 5–34) is a paraesophageal hernia, in which the EGJ remains within (or very near) the esophageal hiatus and a portion or all of the stomach herniates superiorly through the esophageal hiatus and comes to lie adjacent to the esophagus. Such hernias are important to recognize because although they are not strongly associated with GER, they are more likely than sliding hernias to be associated with symptomatic gas entrapment, incarceration, obstruction, and strangulation. These important symptoms are more common with large paraesophageal hernias, in which the greater curvature of the stomach rotates superiorly 180 degrees to lie above the lesser curvature ("upside-down, intrathoracic stomach"). At this point, elective surgical repair should be considered to prevent severe complications, especially those resulting from obstructive gastric volvulus.[52,53]

When the EGJ is located above the esophageal hiatus and a portion of the stomach is located adjacent to the esophagus, the term combined (or "mixed") sliding and paraesophageal hernia is sometimes used. These hernias can be considered to essentially be sliding hiatal hernias until the paraesophageal component becomes dominant. When superior rotation of the greater curvature is observed, they should be treated as paraesophageal hernias.

A third type of hernia is a short esophagus hiatal hernia (Fig. 5–35). Sometimes considered to be congenital in origin, most are now believed to be acquired secondary to chronic reflux esophagitis. Although GER is often difficult to elicit in patients with sliding hiatal hernias, it is usually readily apparent in those with a short esophagus hiatal hernia.

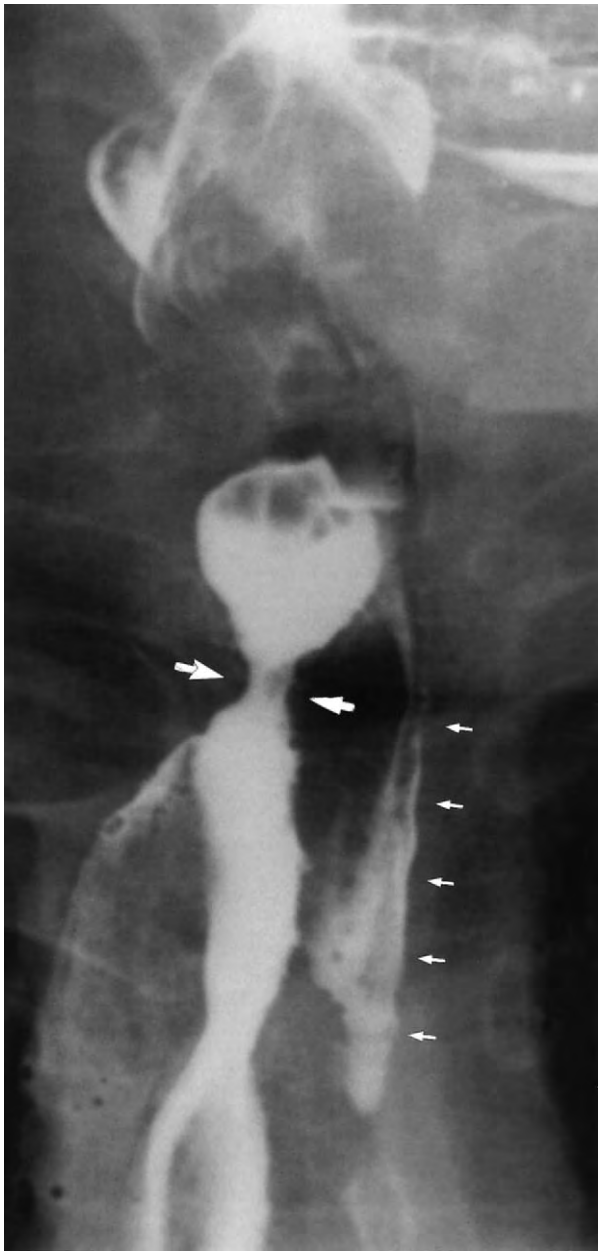


Figure 5–32. Stricture of esophagogastrostomy. An upright, frontal air-contrast view from a barium esophagogram was performed 6 weeks after esophagectomy for T2N0 adenocarcinoma of the proximal third of the esophagus associated with Barrett's mucosa of the distal esophagus. An anastomotic stricture (*arrows*) is causing aspiration of barium into the trachea (*small arrows*) secondary to obstruction of barium and overflow into the trachea.

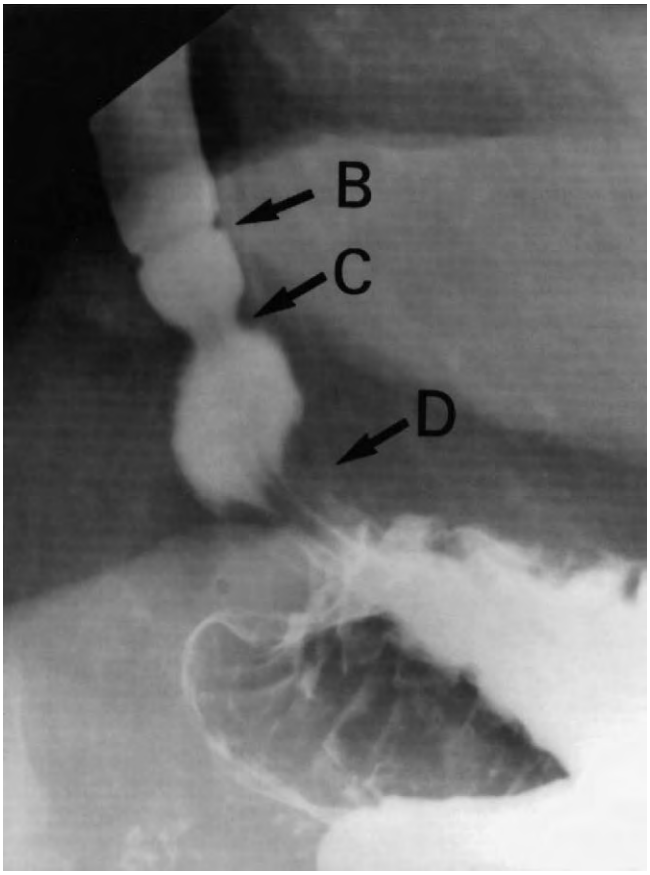


Figure 5–33. Single-contrast barium esophagogram demonstrating a small sliding hiatal hernia. B, mucosal ring; C, muscular ring; D, diaphragmatic impression.

Esophageal Rings and Web

Mucosal rings are short (2 to 3 mm), diaphragm-like, circumferential indentations commonly observed in the lower part of the esophagus. They are visible only when they are located above the esophageal hiatus and when the esophagus is well distended (see Figs. 5–33 and 5–35). As a marker of the transition between esophageal squamous epithelium above and columnar gastric epithelium below, they are a useful sign that a hiatal hernia is present. Most have a luminal diameter of at least 2 cm and are asymptomatic. When the diameter is less than 2 cm, patients may have dysphagia. In Schatzki's original article,[54] all patients with ring diameters less than 14 mm were symptomatic. Although some investigations have used the term "Schatzki ring" and "mucosal ring" interchangeably, the term Schatzki ring should be reserved for stenotic rings (<14 mm in diameter) (Fig. 5–36) that are associated with dysphagia and the risk of food impaction to avoid inappropriate interventions in patients with nonobstructive mucosal rings.

Schatzki's rings are idiopathic and not thought to be causally related to reflux esophagitis. Occasionally, however, a peptic stricture from reflux esophagitis may resemble a Schatzki ring. Such rings can usually be distinguished from Schatzki's rings by their more superior location relative to the EGJ and the associated changes of reflux esophagitis (Fig. 5–37). Congenital or idiopathic esophageal webs may also occasionally occur in the lower part of the esophagus (Fig. 5–37), but again are located more superiorly than Schatzki's rings.

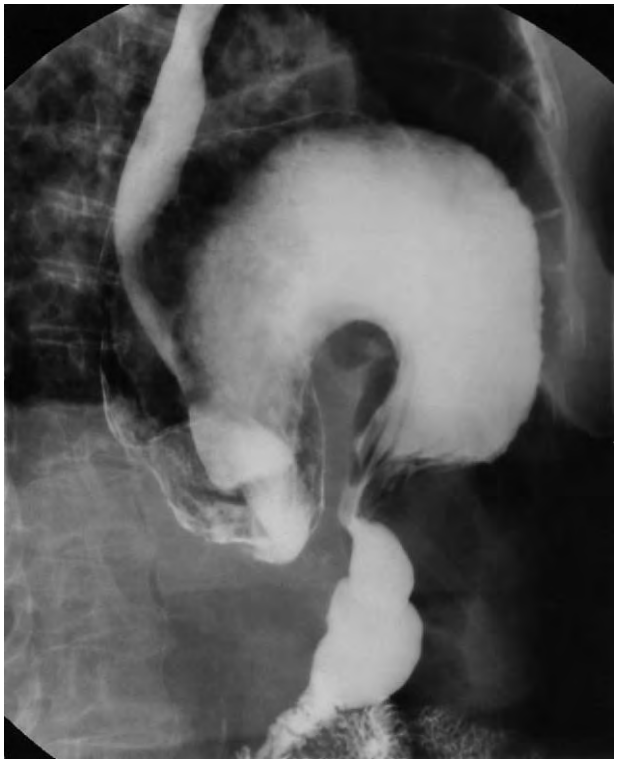


Figure 5–34. Double-contrast upper gastrointestinal examination showing a large paraesophageal hiatal hernia. The greater curvature of the stomach has rotated 180 degrees superiorly ("upside-down, intrathoracic stomach"). The esophagogastric junction has remained within the esophageal hiatus of the diaphragm.

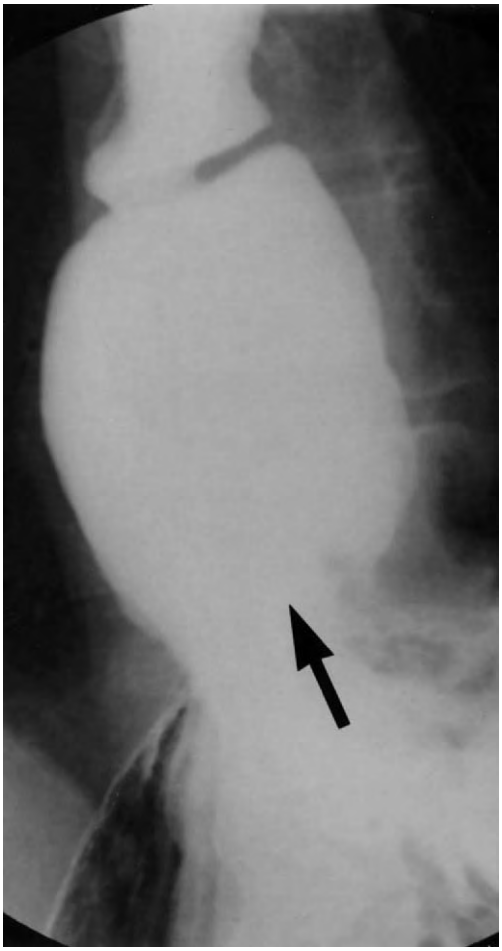


Figure 5–35. Double-contrast upper gastrointestinal examination demonstrating a moderate-sized short esophagus hiatal hernia. Barium is refluxing freely (*arrow*) into the lower part of the esophagus above a mucosal ring.

The classic esophageal web occurs in the cervical esophagus, just below the cricopharyngeal muscle (Fig. 5–38). In contradistinction to Schatzki's rings and lower esophageal mucosal rings, cervical esophageal webs are not usually circumferential; rather, they are U shaped and indenting the anterior and lateral walls but sparing the posterior wall. Most cervical esophageal webs measure 1 to 2 mm in thickness, do not narrow the esophageal lumen significantly, and are asymptomatic. They are easily overlooked at fluoroscopy and require maximum luminal distention with large boluses of barium to be detected reliably. Some do narrow the lumen, however, may become circumferential, and may be associated with obstructive symptoms. The common observation of cervical esophageal webs as incidental findings in asymptomatic, otherwise healthy individuals calls into question the classic association of cervical esophageal webs with iron deficiency, splenomegaly, and an underlying predisposition to hypopharyngeal and esophageal cancer (Plummer-Vinson or Paterson-Kelly syndrome).[55,56] Cervical esophageal webs should be differentiated from ectopic gastric mucosa (Fig. 5–39), which produces indentations that may be confused with laterally positioned, incomplete webs. Ectopic gastric mucosa has a classic appearance and location and is asymptomatic.

Muscular rings may be observed in the lower esophagus as transient ring-like narrowings that are longer than mucosal rings and are not normally associated with obstruction (see Fig. 5–33). They occur within the LES mechanism and are considered to be physiologic, unless associated with symptomatic esophageal motility disorders, including achalasia, in which case failure of relaxation of the LES effectively results in a fixed obstructive muscular ring.

Miscellaneous Strictures

The blistering skin diseases cicatricial pemphigoid and epidermolysis bullosa occasionally involve the esophagus.[57,58] Webs and strictures of various length are typical findings (Fig. 5–40), usually more common in the upper part of the esophagus. The skin lesions are the key to diagnosis of the esophageal lesions. The rare skin disorder lichen planus may also involve the esophagus. Strictures may be seen in any portion of the esophagus

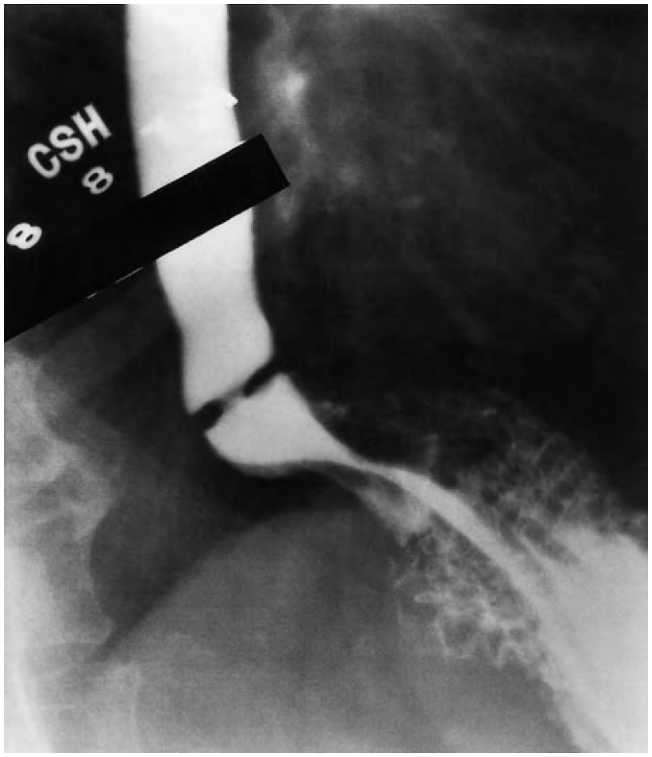


Figure 5–36. Single-contrast barium esophagogram in a patient with dysphagia. A Schatzki ring and a short, stenotic diaphragm-like indentation can be seen in the lower part of the esophagus. The diameter of the ring is less than 1 cm.

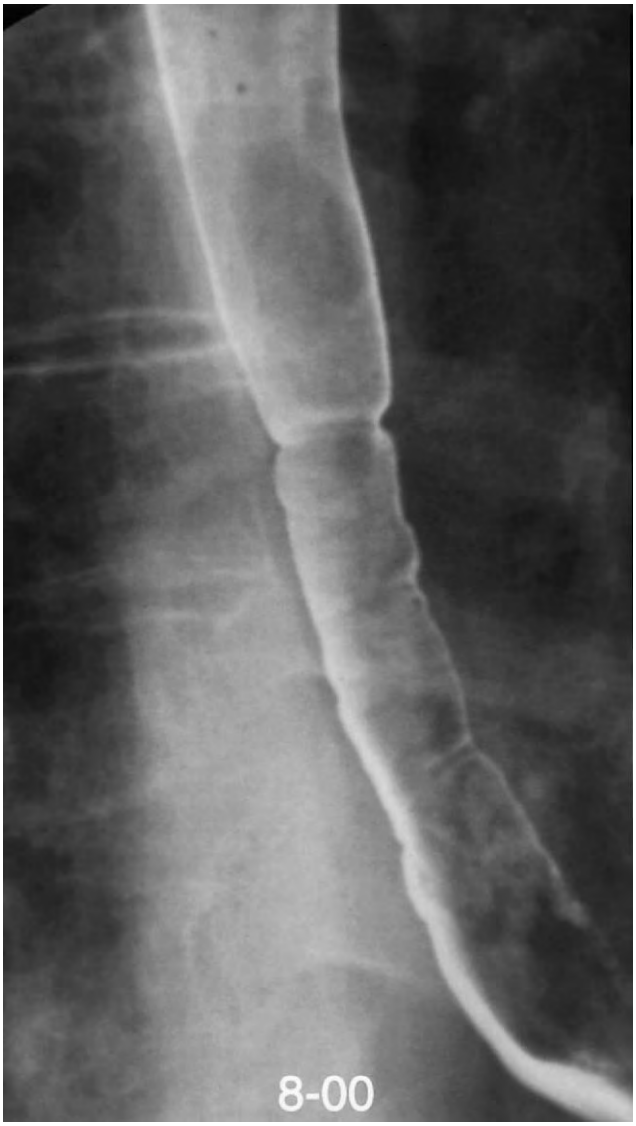


Figure 5–37. Double-contrast barium esophagogram in a 45-year-old woman who had surgery at birth for congenital diaphragmatic hernia. She had medically refractory gastroesophageal reflux disease, mild diffuse narrowing of the lower 3 to 4 cm of the esophagus, and several web-like indentations, findings thought to be due to congenital stenosis of the esophagus with a possible gastroesophageal reflux–related structure.

and are typically long and smoothly tapered; they may be difficult to detect without adequate luminal distention (Fig. 5–41).

Prolonged nasogastric intubation may result in esophageal strictures. These are, classically, long, smoothly tapered strictures in the mid and lower portions of the esophagus. Reflux esophagitis is thought to be the underlying mechanism of stricture formation, but the nasogastric tube is potentiating and results in a more aggressive, rapidly progressive stricture. In the differential diagnosis of long strictures in the lower part of the esophagus are other conditions that predispose to severe reflux esophagitis, such as severe mental handicap and neglected Zollinger-Ellison syndrome. Ingestion of caustic substances is another important cause of long smooth strictures in the mid and lower esophagus. In patients with lifelong dysphagia and a long smooth stricture of the esophagus, the rare condition of congenital esophageal stenosis should be considered (see Fig. 5–37).[59,60]

Smooth strictures of the midesophagus are often the result of radiation therapy in patients with central lung carcinoma or lymphoma when the midesophagus must be included in the radiation field. Similar strictures may also be the result of extrinsic involvement by adjacent mediastinal lymph nodes in malignant neoplasm or granulomatous infection (Fig. 5–42).

Eosinophilic esophagitis is a rare cause of esophageal stricture that may be a component of the more generalized condition eosinophilic gastroenteritis, but it is increasingly being recognized as a disorder confined to the esophagus.[61] Strictures usually involve the upper portion or midportion of the esophagus and often have a "corrugated or multiring" appearance, sometimes referred to as "trachealization" of the esophagus (Fig. 5–43). A history of allergy and peripheral eosinophilia is an important clue to the diagnosis.

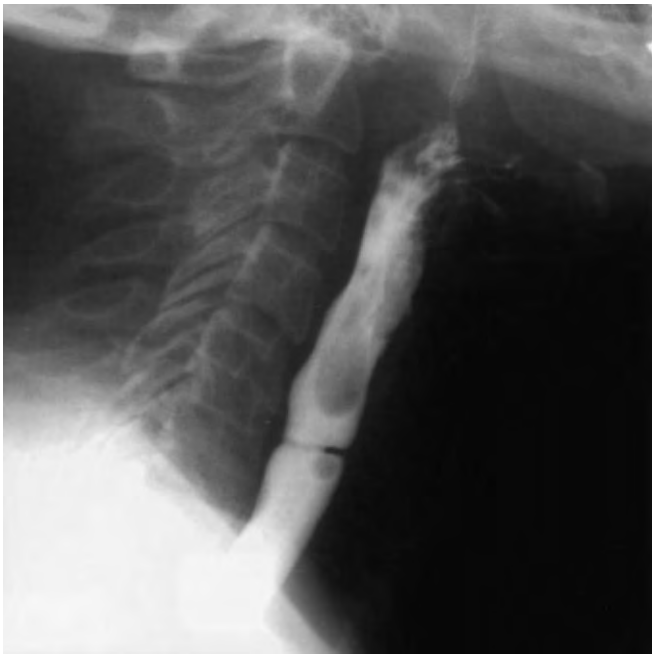


Figure 5–38. Single-contrast barium swallow, lateral view, demonstrating a cervical esophageal web, nonobstructive, and a 1-mm-long indentation in the upper cervical esophagus, most prominent anteriorly.

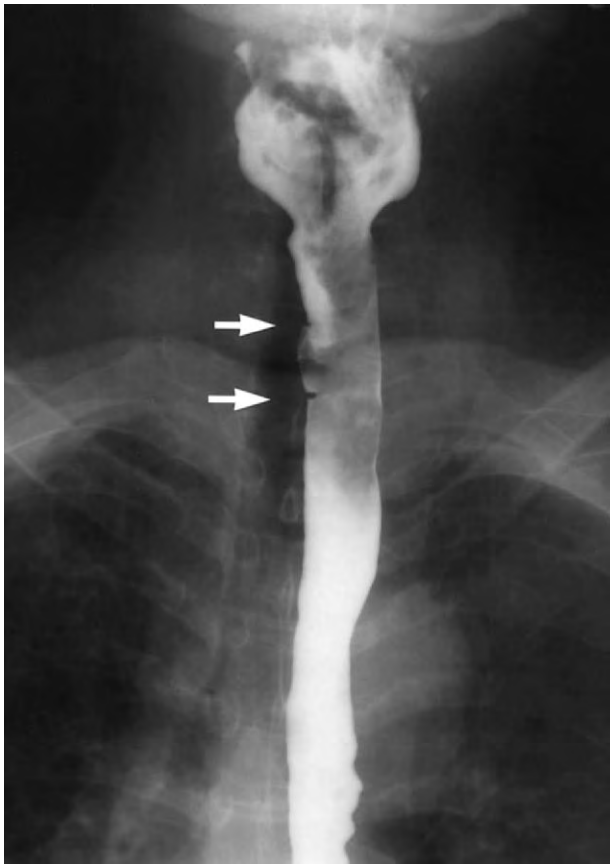


Figure 5–39. Single-contrast barium esophagogram showing ectopic gastric mucosa. Two indentations are evident along the right lateral aspect of the cervical esophagus (*arrows*). Endoscopic biopsy between the indentations confirmed ectopic gastric mucosa.

Patients with Crohn's disease may rarely have esophageal involvement. Manifestations of esophageal Crohn's disease are highly variable, as is true elsewhere in the GI tract, and include ulceration, fold thickening, and stricture (Figs. 5–44 and 5–45). Involvement elsewhere in the colon or small intestine is almost always present, so the diagnosis is usually established when esophageal lesions are discovered.

Caustic Injury

Caustic esophagitis has been a significant medical problem in the United States since the mid-1960s, when liquid solutions of concentrated lye became available as drain cleaners. In children, caustic esophageal injuries result from accidental ingestion, whereas in adults, they usually result from attempted suicide.

The degree of injury varies with the volume and concentration of the caustic agent and the duration of tissue contact.[62] Mild injuries may be confined to the mucosa and heal with little or no sequelae. Severe injuries may result in esophageal perforation, mediastinitis, and death. Patients who survive severe injury are typically left with long, irregular strictures beginning in the mid to upper part of the esophagus. The entire esophagus may be affected, with marked narrowing of the lumen producing a threadlike appearance.[63]

Less severe injury to the esophagus may result from the ingestion of other household products, including ammonium chloride, as well as a variety of medications,[64] such as tetracycline, doxycycline, potassium chloride, quinidine, nonsteroidal anti-inflammatory drugs, and alendronate sodium (Fosamax). Medication-induced esophagitis is a contact esophagitis. Patients at increased risk include those with esophageal motility disorders and those who ingest medications in the recumbent position with insufficient water to propel the medication into the stomach. The diagnosis should be considered in the appropriate clinical context when superficial ulcers are encountered in the midesophagus. In rare instances, deep ulcers and strictures may be seen.

Esophageal Perforation

In addition to caustic ingestion, esophageal perforation may follow blunt or penetrating chest trauma, foreign body ingestion, instrumentation, or breakdown of a surgical anastomosis. Spontaneous perforation (Boerhaave's syndrome) is the result of a sudden, violent increase in intraluminal pressure, usually from extreme

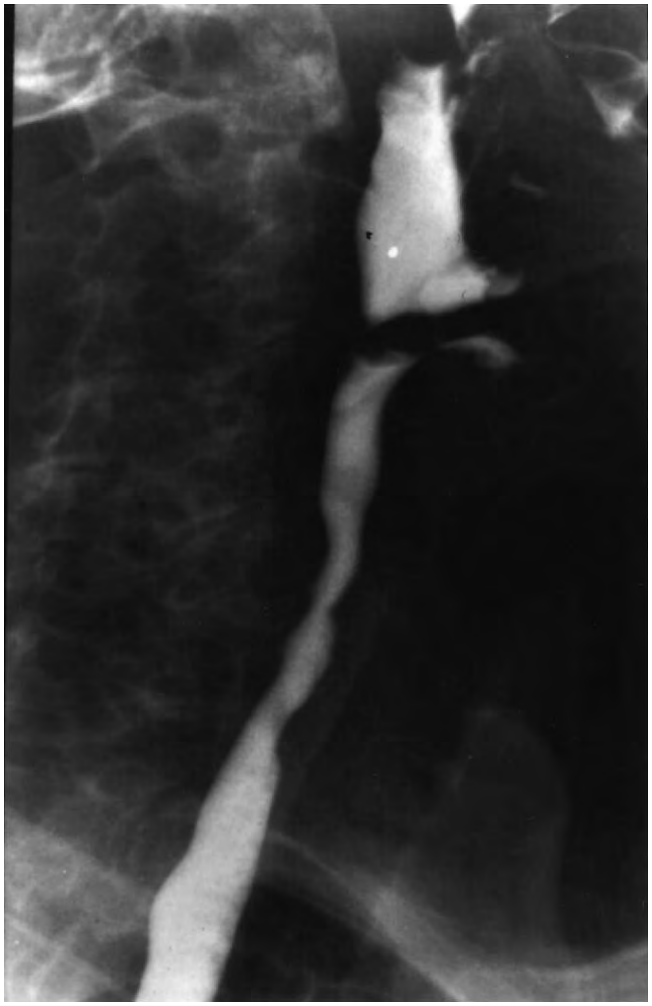


Figure 5–40. Single-contrast barium swallow, left oblique view, from an 86-year-old man with cicatricial pemphigoid and a moderate stricture involving the hypopharynx and upper cervical esophagus. (Note the laryngeal penetration of barium.)

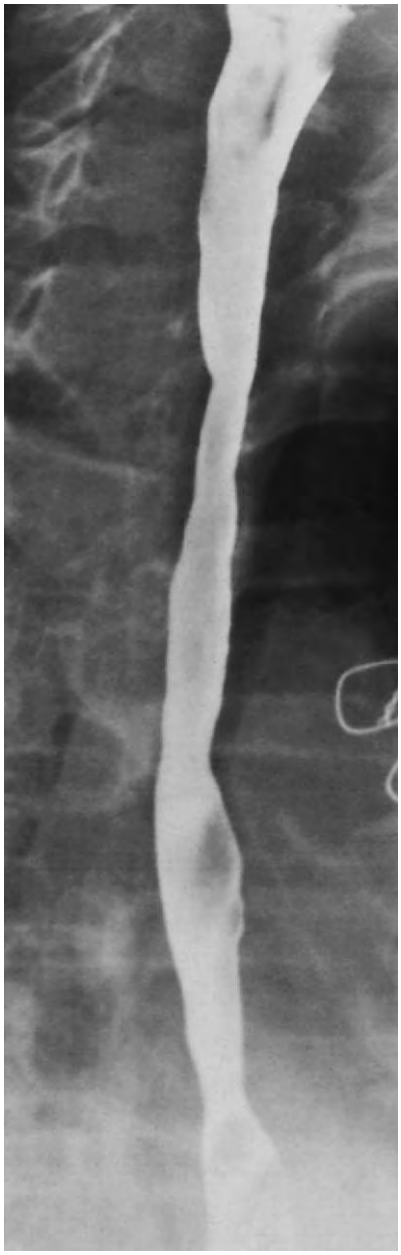


Figure 5–41. Single-contrast barium esophagogram in a 73-year-old woman with oral lichen planus and a moderate, smooth stricture in the mid to upper part of the esophagus, approximately 10 cm in length. Endoscopic biopsies were consistent with lichen planus involving the esophagus.

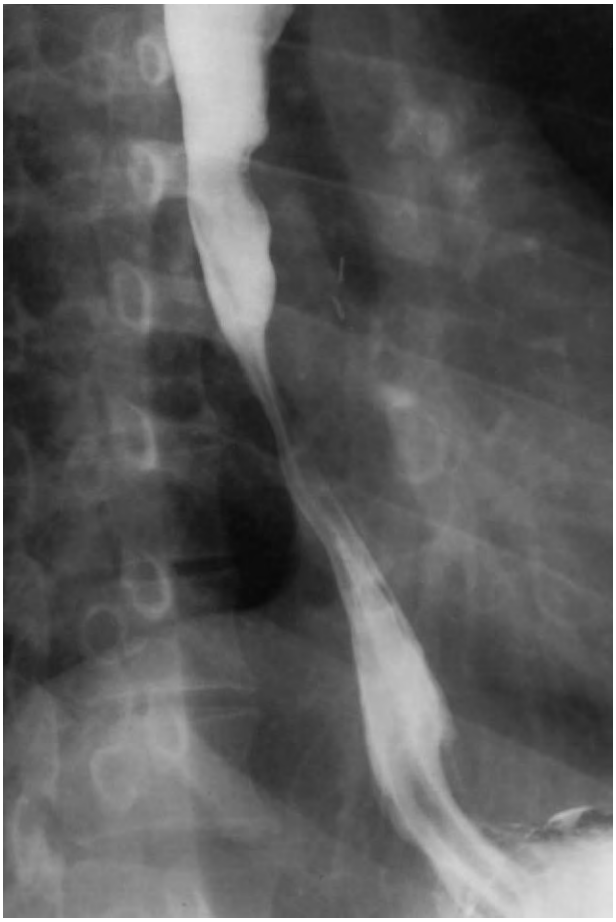


Figure 5–42. Single-contrast barium esophagogram in a 26-year-old man with mediastinal histoplasmosis. Extrinsic narrowing of the midesophagus is due to mediastinal lymphadenopathy.

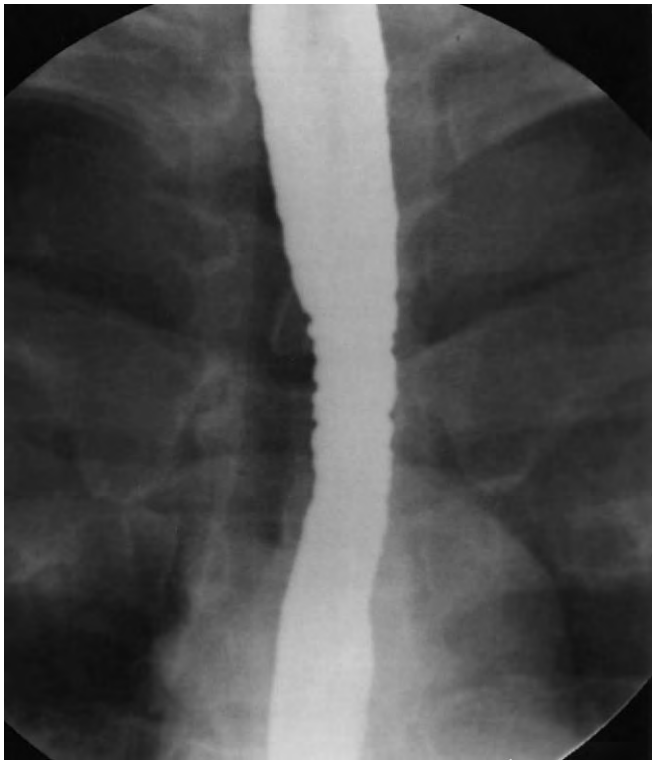


Figure 5–43. Single-contrast barium esophagogram in a 38-year-old man with a long history of dysphagia and food impaction. A midesophageal stricture with a corrugated appearance ("trachealization" of the esophagus) is apparent. Biopsies demonstrated eosinophilic esophagitis.

retching or vomiting, classically after alcoholic binge drinking.

Regardless of cause, esophageal perforations are potentially life threatening and require immediate attention. Localized perforations, especially of the cervical esophagus, may be managed nonoperatively, but perforations of the thoracic esophagus almost always require surgical intervention.[65]

Plain film findings of esophageal rupture include retropharyngeal gas, cervical subcutaneous emphysema, widening of the mediastinum, pneumomediastinum, pleural effusion, and hydropneumothorax (more commonly on the left) (Fig. 5–46A). Rarely, lower esophageal perforations may occur below the diaphragm and produce pneumoperitoneum or retroperitoneal gas collections.

Because plain films are relatively insensitive and often nonspecific, contrast esophagograms should be used early in the investigation of clinically suspected esophageal perforations (Fig. 5–46B). Water-soluble contrast agents, either high or low in osmolarity, taken by mouth or injected into a nasogastric tube are the agents of first choice. For patients who are at risk for aspiration (or airway fistula), low-osmolar agents should be used to avoid pulmonary edema, which may result when high-osmolar agents enter the lung.

When water-soluble agents are extravasated into the mediastinum, they are rapidly absorbed and do not incite an inflammatory response. This confers a margin of safety over barium contrast agents, which are nonabsorbable and may incite foreign body granuloma formation.[66,67] Whenever an initial study with water-soluble contrast material is negative, however, it should be immediately followed by a barium esophagogram, which because of its higher density has been reported to increase the sensitivity for detecting esophageal leaks by 15% to 25%.[68,69] The low risk for mediastinal complications from barium extravasation is more than offset by the benefits of earlier diagnosis.

Chest CT is more sensitive in detecting pneumomediastinum than plain films are and is useful after a negative contrast esophagogram in high-risk patients or when contrast esophagograms are difficult to perform in seriously ill patients. With modern, fast scanners, chest

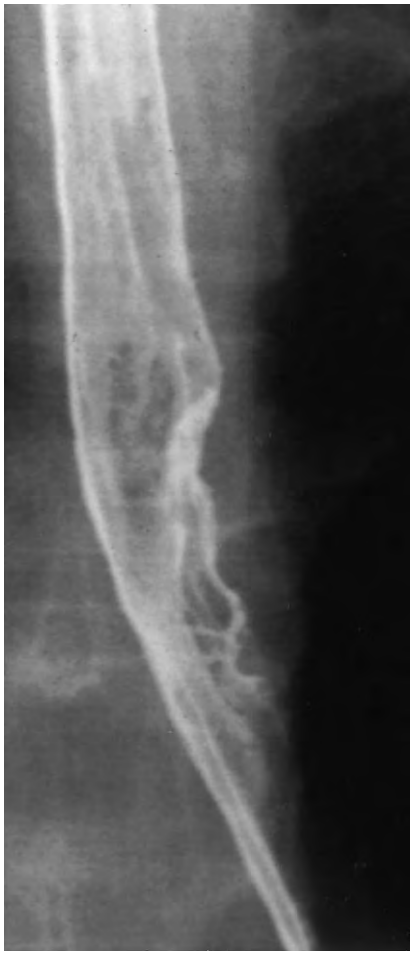


Figure 5–44. Double-contrast barium esophagogram showing Crohn's disease of the esophagus in a 25-year-old man with Crohn's colitis. Thickened, irregular folds can be seen in the lower part of the esophagus. Biopsies demonstrated granulomatous inflammation.

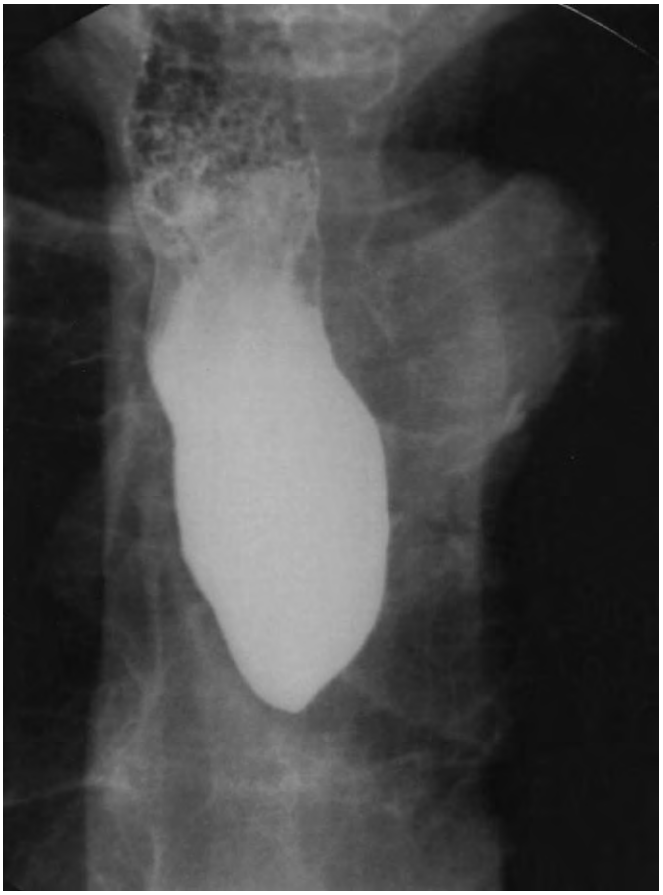


Figure 5–45. Water-soluble contrast esophagogram in a 78-year-old woman with Crohn's disease and an esophageal stricture causing complete obstruction.

CT can be combined with contrast esophagography to expedite the diagnosis of esophageal rupture.[70]

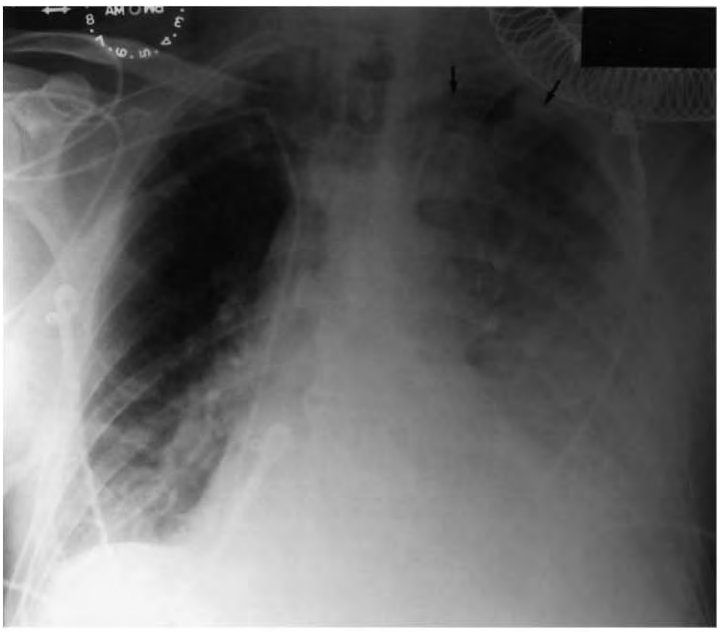
Diverticula

Esophageal diverticula vary greatly in size, shape, location, cause, and significance. Even incidentally discovered diverticula are important to document because they may predispose the patient to injury during instrumentation.[71]

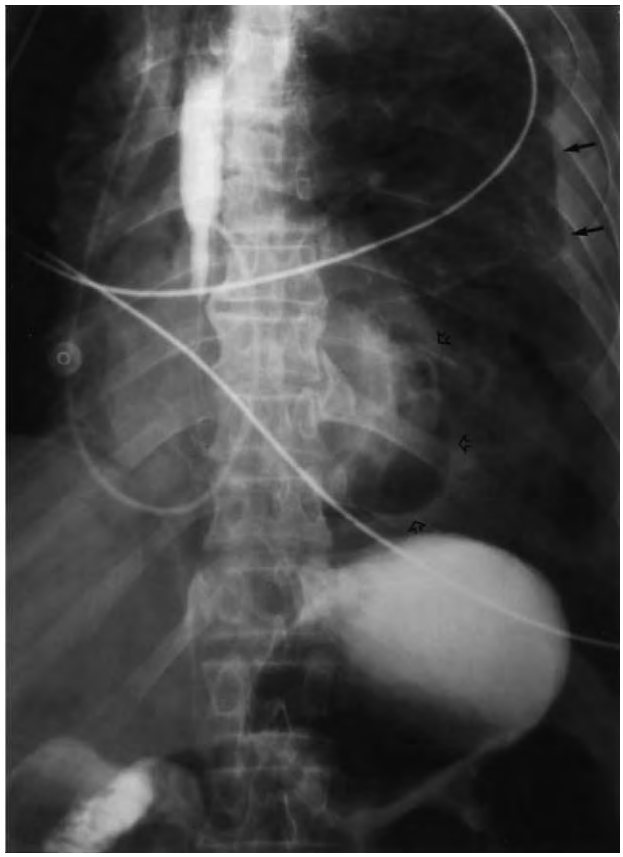
Traditionally, esophageal diverticula are classified as either traction diverticula, which occur primarily in the midesophagus, or pulsion diverticula, which typically occur in the upper or lower esophagus. In practice, many midesophageal diverticula are pulsion type[72] and are due to increased intraluminal pressure causing "ballooning" of localized weak areas of the esophageal wall around the aortic arch and left main stem bronchus. True traction diverticula are recognized by elongation, or "tenting," of the diverticulum (Fig. 5–47), typically the result of fibrosis in adjacent lymph nodes involved by granulomatous inflammation.

Pulsion diverticula of the mid and lower part of the esophagus are often associated with an underlying esophageal motor disorder, especially those that are characterized by strong, nonperistaltic tertiary contractions of the muscularis propria, and they are often multiple. In this clinical setting, the motor disorder is more likely to be the cause of symptoms than the diverticula. When large, especially when located near the diaphragm (epiphrenic), pulsion diverticula may empty poorly, thereby serving as a reservoir of ingested food, and become symptomatic (Fig. 5–48).[73]

Zenker's diverticula are pulsion diverticula occurring at the junction of the hypopharynx and cervical esophagus.[74] They are the result of posterior outpouching of the hypopharynx through a weak area near the superior aspect of the cricopharyngeus muscle (Killian's dehiscence) (see Fig. 5–17). Large Zenker's diverticula may retain food and put patients at risk for regurgitation, aspiration, hoarseness, and halitosis. Dysphagia is a common symptom and is usually attributed to a promi-



A



B

Figure 5–46. **A,** Anteroposterior portable chest radiograph in a patient with Boerhaave's syndrome and left apical pneumothorax (*arrows*). Increased density was noted over the left hemothorax as a result of a left pleural effusion. **B,** Water-soluble contrast upper gastrointestinal examination showing a left pleural effusion (*closed arrows*). A retrocardiac mediastinal collection of gas and contrast medium (*open arrows*) is indicative of esophageal rupture.

nent cricopharyngeus muscle that compromises the hypopharyngeal lumen (Fig. 5–49). Treatment planning should take into account the contribution of a prominent, poorly relaxing (or prematurely closing) cricopharyngeus muscle to the patient's symptoms and formation of the diverticulum.

Just inferior to the cricopharyngeus muscle, in the lateral aspect of the cervical esophagus, is a second area of anatomic weakness. Pulsion diverticula occurring in this region are referred to as lateral cervical esophageal diverticula, or Killian-Jamison diverticula. They can be distinguished from Zenker's diverticula by their location below the cricopharyngeus muscle and their lateral orientation. Most are asymptomatic.

Varices

Though less sensitive than endoscopy, barium esophagography, carefully performed, may demonstrate esophageal varices as undulating, sometimes nodular defects, often easily effaced and transient. They are more commonly seen in the lower part of the esophagus as the result of portal hypertension, usually secondary to cirrhosis ("uphill varices") (Fig. 5–50). Rarely, they may be seen in the upper part of the esophagus secondary to obstruction of the superior vena cava ("downhill varices") (Fig. 5–51).

Esophageal varices are identifiable on contrast-enhanced CT scans as enhancing structures in the esophageal wall supplied by collateral veins. Large varices in and around the lower part of the esophagus may simulate a mediastinal mass or adenopathy on chest films or unenhanced CT scans. CT is well suited to displaying the venous anatomy (in two- or three-dimensional rendering) in addition to providing important related information concerning its cause and associated conditions—such as cirrhosis, splenomegaly, ascites, and hepatocellular carcinoma—as well as superior vena cava obstruction, a mediastinal mass, or adenopathy in patients with "downhill" varices.

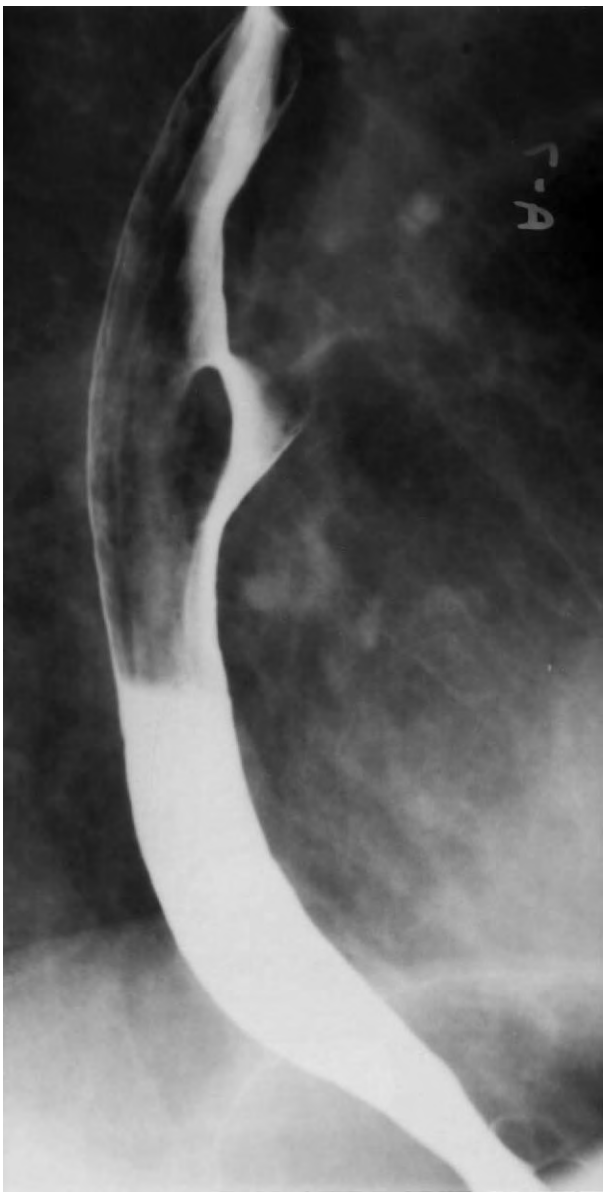


Figure 5–47. Double-contrast barium esophagogram demonstrating a midesophageal traction diverticulum. Note the elongated, "tented" appearance of the diverticulum.

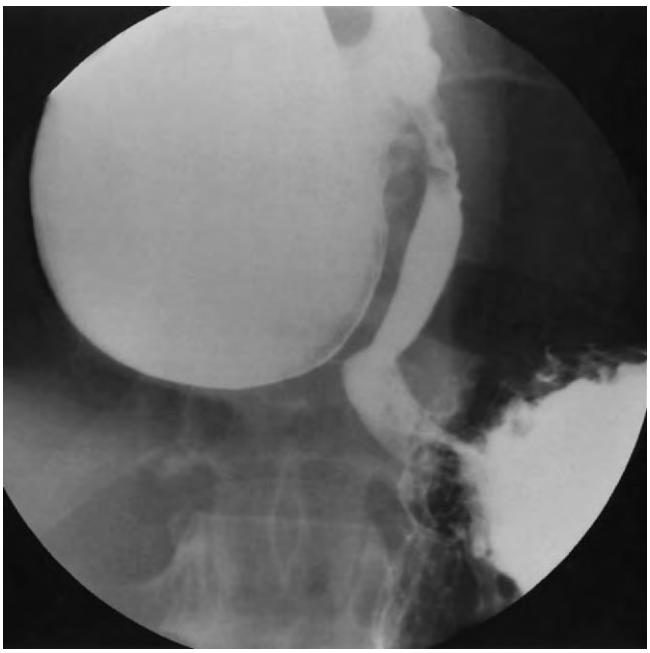


Figure 5–48. Double-contrast barium esophagogram in a 62-year-old man with dysphagia and regurgitation. A large epiphrenic diverticulum is projecting to the right. Barium preferentially filled the diverticulum, with reflux from the diverticulum into the proximal part of the esophagus.

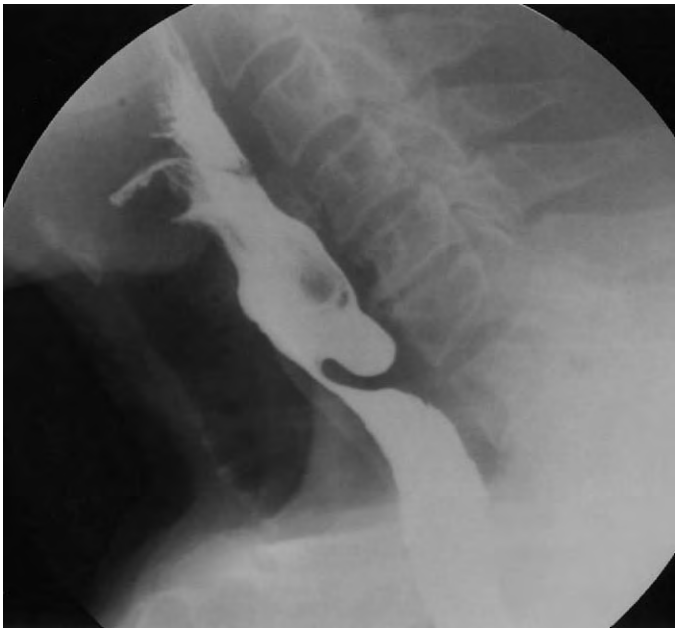


Figure 5–49. Single-contrast barium swallow, lateral view, showing Zenker's diverticulum and a prominent cricopharyngeus muscle encroaching on the lumen. (Note the laryngeal penetration of barium.)

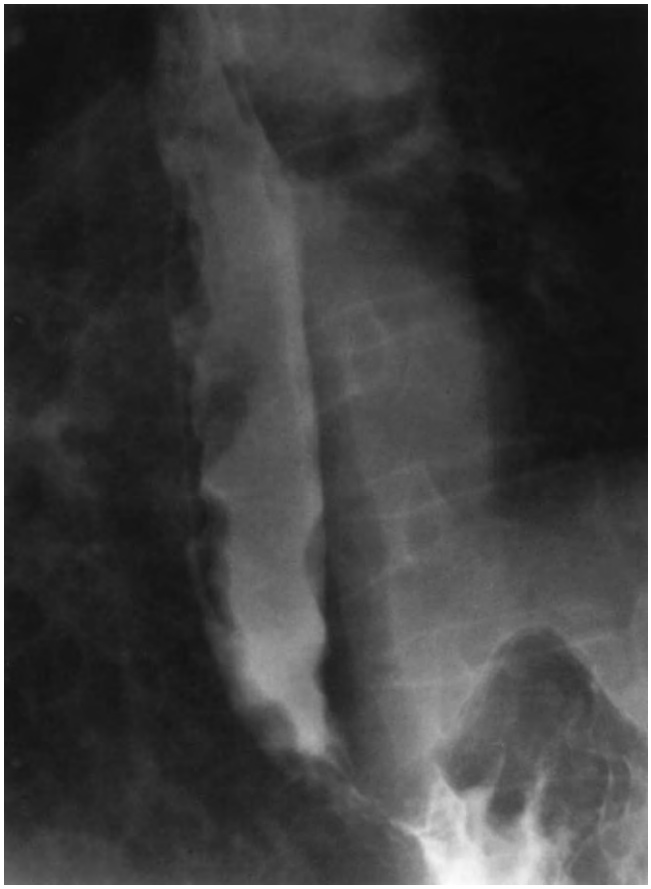


Figure 5–50. Single-contrast barium esophagogram revealing "uphill" varices. Nodular serpentine filling defects are present in the lower part of the esophagus.

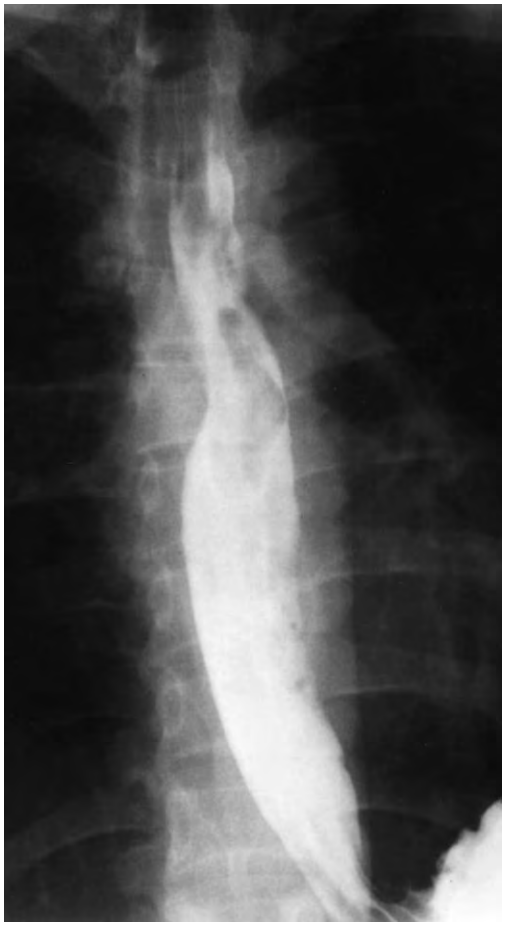


Figure 5–51. Single-contrast barium esophagogram demonstrating "downhill" varices in a 26-year-old man with mediastinal histoplasmosis and superior vena caval obstruction. Smooth, wavy filling defects are present in the upper part of the esophagus.

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Chapter

6

Endoscopic Evaluation of the Esophagus

Stuart Jon Spechler · Jacques J. G. H. M. Bergman

The endoscopist who examines the esophagus evaluates a muscular tube whose primary function is to convey swallowed material from the mouth to the stomach. The esophagus is approximately 25 cm in length measured from its origin in the neck just below the cricoid cartilage (C6 level, approximately 15 cm from the incisor teeth as measured by the endoscopist) to its termination in the abdomen at the gastric cardia (T10-T11 level, approximately 40 cm from the incisor teeth).[1] Proximally, the upper esophageal sphincter (UES) separates the pharynx from the esophagus. The UES extends approximately 3 cm in length and comprises three skeletal muscle groups, including the distal portion of the inferior pharyngeal constrictor, the cricopharyngeus, and the circular muscle of the proximal esophagus.[2] Introduction of the endoscope into the UES often causes gagging, and the muscles relax only briefly during a swallow. Consequently, the endoscope is typically passed quickly through the UES, and endoscopic visualization of its mucosal lining is frequently limited.

The esophagus passes from the chest into the abdomen through the diaphragmatic hiatus, a canal-shaped opening in the right crus of the diaphragm. Approximately 2 cm of the distal end of the esophagus normally lies within the abdomen.[3] The lower esophageal sphincter (LES) comprises both the skeletal muscle of the crural diaphragm (external LES muscle) and the circular smooth muscle of the distal esophagus itself (internal LES muscle), although endoscopists often refer only to the latter when describing the LES. Unlike the UES, endoscopic examination of the LES region is not generally limited either by sustained sphincter muscle contraction or by patient discomfort.

The esophageal lumen is collapsed at rest and must be distended with air during endoscopy so that the stratified squamous epithelial lining can be visualized well. When so distended, the squamous epithelium appears pale, glossy, and relatively featureless. Within the chest at about the T4 level, the esophagus is indented on its left side by the aortic arch. This pulsating indentation can be noted during endoscopic examination at a distance of approximately 23 cm from the incisor teeth (Fig. 6–1).[4] Just below the arch at approximately 25 cm, the left main bronchus causes a subtle indentation on the left anterior aspect of the esophagus (see Fig. 6–1). Below the bronchus, the esophagus abuts the left atrium. The heart normally causes no prominent indentation of the esophageal lumen, but atrial pulsations can often be visualized at a level approximately 30 cm from the incisor teeth.

ENDOSCOPIC EVALUATION OF THE GASTROESOPHAGEAL JUNCTION

The gastroesophageal junction (GEJ) is the level at which the esophagus ends and the stomach begins. Unfortunately, there are no universally accepted landmarks that clearly delimit the distal end of the esophagus and the proximal part of the stomach, and the GEJ has been defined differently by anatomists, radiologists, physiologists, and endoscopists.[5] Landmarks suggested by anatomists, such as the peritoneal reflection or the character of the muscle bundles in the esophageal wall, are not useful for endoscopists. Radiologists refer to the region of the GEJ as the vestibule, and they seldom attempt to localize the precise point at which the esophagus joins the stomach.[6] Physiologists have used the distal border of the LES (determined manometrically) to define the GEJ,[7] but it is difficult to identify this border precisely by endoscopic techniques. Indeed, one study has shown that manometric and endoscopic localization of the LES often differs by several centimeters.[8]

When considering any proposed landmark for the GEJ, it is important to appreciate that there is no clear-cut "gold standard" for the structure and, consequently, all of the suggested landmarks can be considered arbitrary. Furthermore, for most disorders of the esophagus and stomach that are diagnosed endoscopically, it is not

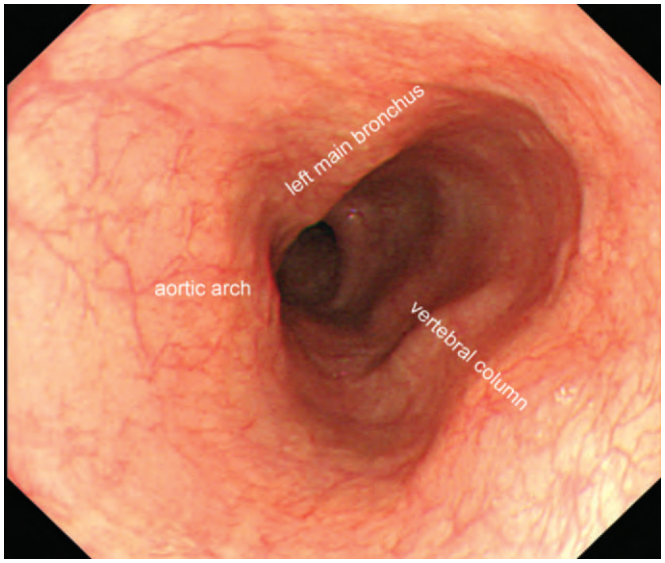


Figure 6–1. Endoscopic photograph of the proximal end of the esophagus showing the normal indentations caused by the aortic arch, the left main bronchus, and the vertebral column.

important that the GEJ be identified with great precision. For some disorders, most notably Barrett's esophagus, for which the endoscopist must determine the extent of esophageal columnar lining, precise localization of the GEJ can be critical for establishing the diagnosis.

Suggested endoscopic criteria for the GEJ include the level at which the tubular esophagus flares to become the sack-like stomach,[9] the proximal margin of the gastric folds when the esophagus and stomach are partially distended,[10] and the distal end of the esophageal palisade vessels.[11,12] Although these landmarks may be readily recognized in still photographs of the junction region, the distal esophagus in vivo is a dynamic structure whose appearance changes from moment to moment. The location of the point of flare changes with respiratory and peristaltic activity. The proximal gastric folds can prolapse transiently up into the esophagus. The appearance of the junction region also varies with the degree of distention of the esophagus and stomach, and the palisade vessels can be difficult to identify with conventional endoscopes.

The proximal extent of the gastric folds is the landmark for the GEJ used frequently by Western endoscopists (Figs. 6–2 to 6–4).[13] This landmark was proposed by McClave et al. in 1987 based on their endoscopic observations in only four subjects who were identified as normal controls because they had "no clinical evidence of esophageal disease."[10] The junction between squamous and columnar epithelia (the SCJ) was located within 2 cm of the gastric folds in all of these four subjects, and thus the authors concluded that the diagnosis of columnar-lined esophagus should be considered only when the SCJ is located more than 2 cm above the GEJ (i.e., the proximal level of the gastric folds). This study can be criticized both for the small number of control subjects and for the lack of documentation that the four

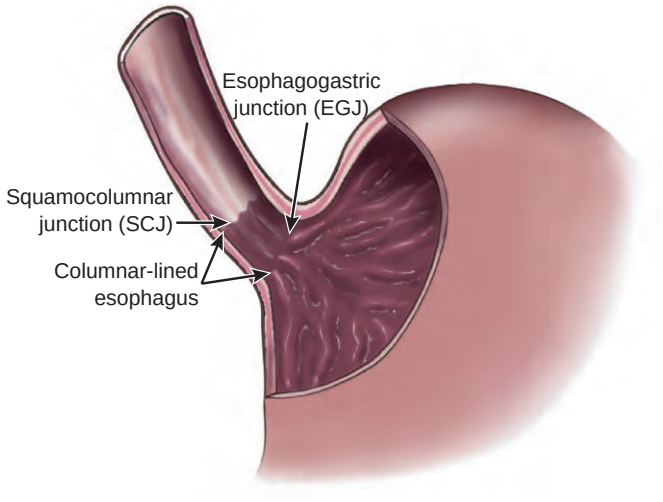


Figure 6–2. Endoscopic landmarks. The squamocolumnar junction (SCJ or Z-line) is the visible line formed by the juxtaposition of squamous and columnar epithelia. The esophagogastric junction (EGJ) is the imaginary line at which the esophagus ends and the stomach begins. The most proximal extent of the gastric folds has been proposed as a marker for the EGJ. When the SCJ is located proximal to the EGJ, there is a columnar-lined segment of esophagus. (From Spechler SJ: The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. Gastroenterology 117:218-228, 1999.)

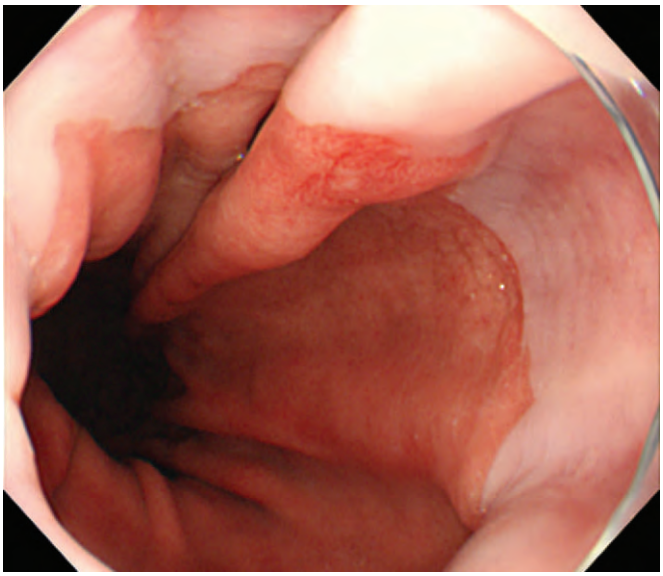


Figure 6–3. Endoscopic photograph of the gastroesophageal junction region in a patient who has a hiatal hernia. The squamocolumnar junction (SCJ) is located above some of the gastric folds (i.e., there is a columnar-lined segment of esophagus), whereas for others the SCJ seems to coincide with the proximal extent of the folds.

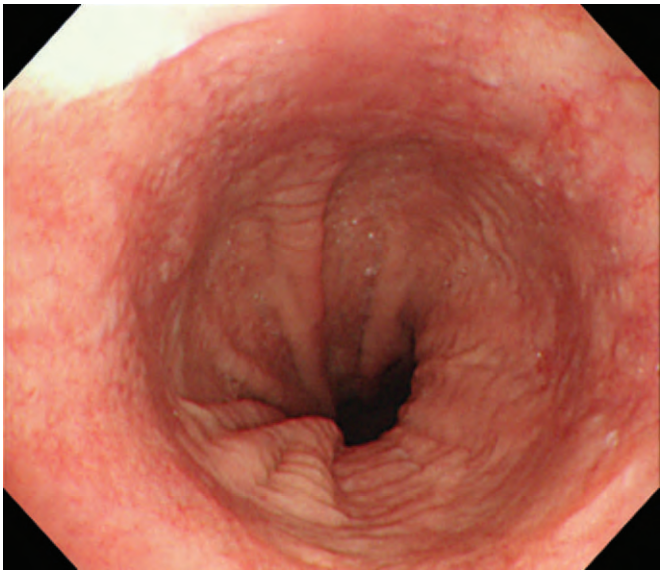


Figure 6–4. Endoscopic photograph of the gastroesophageal junction region in a patient with long-segment Barrett's esophagus. Columnar epithelium extends above the tops of the gastric folds to involve the distal end of the esophagus in a circumferential fashion.

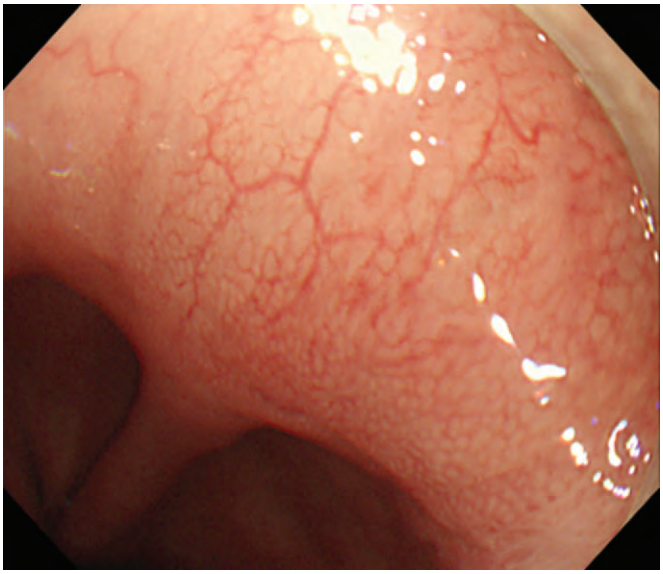


Figure 6–5. The palisade vessels in the distal part of the esophagus are fine, longitudinal veins in the lamina propria. The distal end of the palisade vessels has been proposed as an endoscopic landmark for the gastroesophageal junction.

controls were indeed normal. Esophageal pH monitoring studies were not performed, and therefore it is not clear that the control subjects had normal esophageal acid exposure. Biopsy specimens of the columnar-lined esophagus were not taken, and thus short-segment Barrett's esophagus was not excluded (see later). Furthermore, three of the four control subjects had hiatal hernias and one had reflux esophagitis. It seems surprising that a proposed landmark based on such questionable data has been so widely accepted by endoscopists.

A number of Asian investigators use the end of the esophageal palisade vessels as their landmark for the GEJ (Fig. 6–5).[12] Elegant anatomic studies of the GEJ have revealed four distinct zones of venous drainage, including a gastric zone, a palisade zone, a perforating zone, and a truncal zone.[14] The palisade zone comprises a group of fine, longitudinal veins located largely within the lamina propria of the distal esophagus. The palisade vessels pierce the muscularis mucosae distally to join the submucosal vessels of the gastric zone and proximally to join the submucosal vessels of the perforating zone. The palisade vessels can be difficult to visualize by conventional endoscopy, especially if there is distal esophageal inflammation. The appearance of these vessels can be enhanced by narrow-band imaging endoscopy, which uses primarily blue light that penetrates only the superficial layers of the mucosa (where the palisade vessels are found) and is absorbed by the hemoglobin within the vessels. Presently, narrow-band imaging is not widely available. Furthermore, even in autopsy studies in which blood vessels of the GEJ region are injected with resins that provide exquisite detail of the venous structures, it is difficult to precisely identify the termination of the palisade vessels.[14] Finally, it is not clear conceptually why the distal end of the palisade vessels should be considered the precise end of the esophagus.

Few studies have specifically addressed the problem of endoscopic localization of the GEJ, and even in those that have done so, the accuracy of the criteria used cannot be assessed meaningfully in the absence of a gold standard. It is not clear which is the best diagnostic criterion for the GEJ, and reproducibility of the various criteria has not been established. If one cannot determine with certainty where the esophagus ends and the stomach begins, any assessment of the extent of esophagus lined by columnar epithelium will be inherently imprecise. This unresolved problem continues to confound clinicians and investigators who deal with Barrett's esophagus.

CONVENTIONAL ENDOSCOPIC DIAGNOSIS OF BARRETT'S ESOPHAGUS

Endoscopic examination is required to establish a diagnosis of Barrett's esophagus, and the endoscopic impression must be confirmed by histologic evaluation of biopsy specimens from the columnar-lined esophagus. Specifically, the endoscopist must ensure that the following two criteria are fulfilled[13]: (1) columnar epithelium lines the distal esophagus, and (2) biopsy specimens of the columnar-lined esophagus show specialized intestinal metaplasia. To document that columnar epithelium lines the esophagus, the endoscopist must identify both the SCJ and GEJ (see Fig. 6–2). Columnar epithelium has

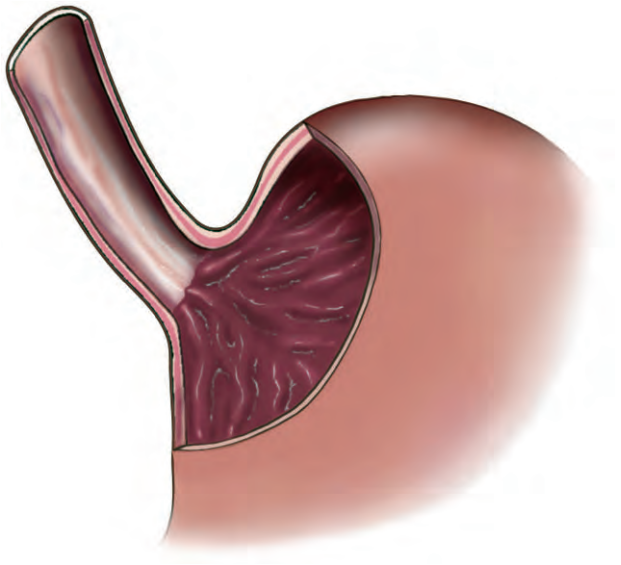


Figure 6–6. In this drawing, the gastroesophageal junction and the Z-line coincide, and there is no columnar-lined segment of esophagus.

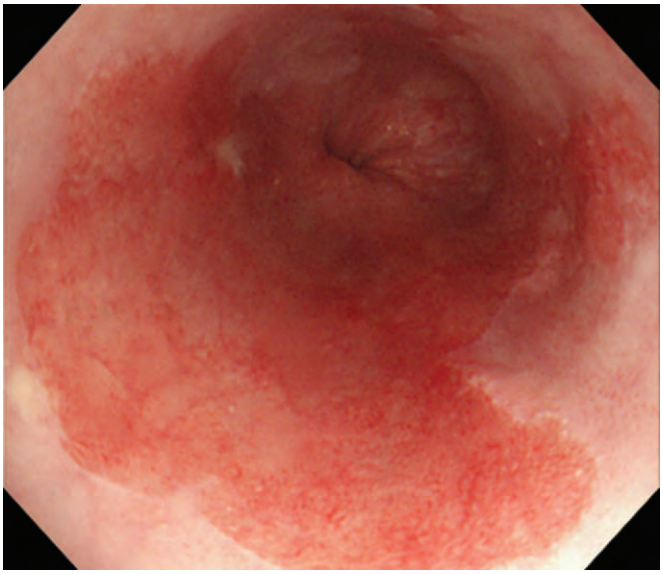


Figure 6–7. In this patient with long-segment Barrett's esophagus, the Z-line is relatively smooth.

a reddish color and coarse texture on endoscopic examination, whereas squamous epithelium has a pale, glossy appearance. The juxtaposition of these epithelia at the SCJ forms a visible line called the Z-line. As discussed, Western endoscopists generally identify the GEJ as the level of the most proximal extent of the gastric folds. The distal extent of the palisade vessels can also be used as a marker for the GEJ, but this level may differ from that of the proximal extent of the gastric folds. When the SCJ and GEJ coincide (Fig. 6–6), the entire esophagus is lined by squamous epithelium. When the SCJ is located proximal to the GEJ (see Fig. 6–2), there is a columnar-lined segment of esophagus. If the endoscopist takes biopsy specimens from that columnar-lined segment and histologic evaluation shows specialized intestinal metaplasia, the patient has Barrett's esophagus.

Several classification systems for Barrett's esophagus have been proposed on the basis of the extent of columnar-lined esophagus and the appearance of the Z-line. Perhaps the most widely used system classifies patients as having either "long-segment" or "short-segment" Barrett's esophagus.[15] Patients have long-segment Barrett's esophagus when the distance between the GEJ and the most proximal extent of the Z-line is 3 cm or more, and they have short-segment Barrett's esophagus when that distance is less than 3 cm. The cutoff value of 3 cm is arbitrary, and this classification has no clear implications regarding the pathogenesis of the condition or the clinical management of affected patients. Furthermore, there can be substantial variation in the appearance of the Z-line in patients with Barrett's esophagus (Figs. 6–7 to 6–9), and the short-long classification provides no specific information about that appearance.

In 2000, Wallner et al. proposed the ZAP (*Z*-line *AP*pearance) classification for evaluating the SCJ. The ZAP classification has four categories[16]: grade 0—the Z-line is sharp and circular; grade I—the Z-line is irregular and there are tongue-like protrusions or islands of columnar epithelium (or both); grade II—there is a distinct, obvious tongue of columnar epithelium less than 3 cm in length; and grade III—there are distinct tongues of columnar epithelium greater than 3 cm in length, or the Z-line is displaced cephalad more than 3 cm. The likelihood of finding intestinal metaplasia (and hence having Barrett's esophagus) was shown to increase sig-

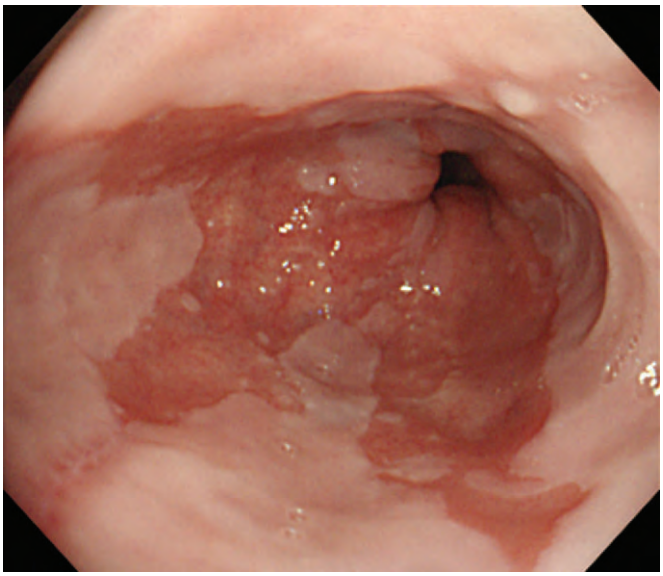


Figure 6–8. In this patient with short-segment Barrett's esophagus, the Z-line is jagged and eccentric.

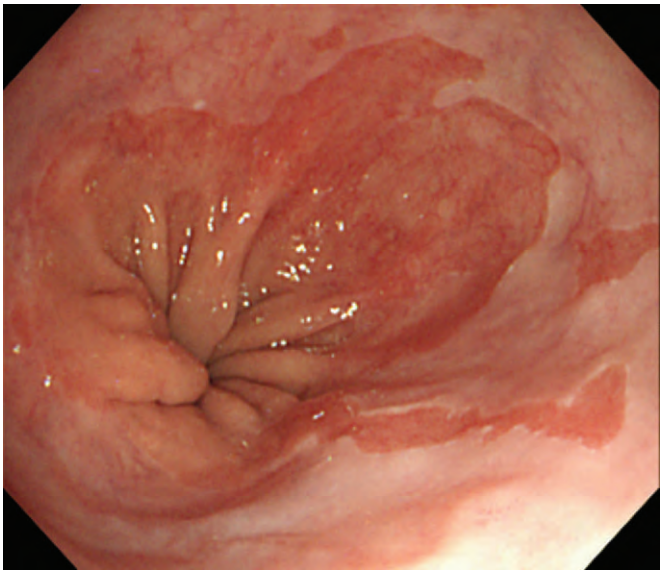


Figure 6–9. In this patient with short-segment Barrett's esophagus, the Z-line extends approximately 2 cm above the gastroesophageal junction (the tops of the gastric folds) on the right, but there is virtually no columnar-lined esophagus on the left.

nificantly with increasing ZAP grades, and the classification was found to have excellent reproducibility among endoscopists.[17] However, the clinical utility of the ZAP classification has not been established.

The International Working Group on the Classification of Oesophagitis is developing a "C and M" classification system for Barrett's esophagus that describes both the extent of circumferential metaplasia (C, measured from the GEJ to the most proximal extent of circumferential esophageal metaplasia) and the extent of the longest tongue of esophageal metaplasia (M, measured from the GEJ to the most proximal extent of esophageal metaplasia).[18] For example, a patient classified as C2M5 has columnar metaplasia involving the distal 2 cm of the esophagus in a circumferential fashion with a tongue of metaplasia that extends 5 cm above the GEJ. Presently, the advantages (if any) of this system over the others have not been established.

Some have argued that the term "Barrett's esophagus" itself is artificial and that the condition has been defined variably by investigators who have imposed arbitrary criteria that fit their personal perspectives.[19] In 1996, Spechler and Goyal proposed a simple classification system as follows: whenever columnar epithelium is seen in the esophagus, regardless of extent, the condition is called "columnar-lined esophagus." In these cases, biopsy specimens can be obtained from the esophageal columnar lining to seek specialized intestinal metaplasia. The condition can then be classified as either "columnar-lined esophagus with specialized intestinal metaplasia" or "columnar-lined esophagus without specialized intestinal metaplasia." Despite the simplicity and conceptual appeal of this system, the term Barrett's esophagus has become so firmly entrenched among clinicians that it is unlikely to be abandoned.

SPECIALIZED ENDOSCOPIC TECHNIQUES FOR BARRETT'S ESOPHAGUS

A variety of specialized endoscopic techniques are available for the evaluation of Barrett's esophagus, including chromoendoscopy, magnification endoscopy, narrow-band imaging, endosonography, optical coherence tomography, and spectroscopy using reflectance, absorption, light-scattering, fluorescence, and Raman detection methods.[20-25] These techniques have been used to enhance the identification of both intestinal metaplasia in the esophagus and neoplasia in Barrett's esophagus. Only chromoendoscopy, magnification endoscopy, and narrow-band imaging will be discussed in this chapter.

In chromoendoscopy, the esophageal mucosa is painted either with dyes that stain the cells that absorb them or with dyes that accumulate in mucosal crevices to enhance the architectural features of the epithelium. When potassium iodide is absorbed by squamous epithelial cells, it binds to their glycogen and stains them brown. Application of this dye can help delineate the SCJ. For individuals who are at high risk for squamous cell cancer of the esophagus (e.g., patients who have had cancer of the head and neck, individuals living in high-incidence areas for squamous cell carcinoma such as northern China), potassium iodide staining has also been used to identify areas of early neoplasia in the squamous epithelium. Methylene blue dye is absorbed by intestinal-type cells, and this dye can be applied to identify areas of intestinal metaplasia in Barrett's esophagus. In addition, areas of dysplasia and early cancer in the specialized intestinal metaplasia of Barrett's esophagus can be identified by their failure to absorb methylene blue. One recent report has shown that application of methylene blue may cause DNA damage in Barrett's esophagus, and thus the use of this dye could conceivably be dangerous.[26] Indigo carmine is a chromoendoscopy dye that is not absorbed and is used to enhance architectural features. Cresyl violet dye stains the columnar cells that absorb it purple, and the dye also accumulates in crevices to enhance architectural features. Acetic acid, though not a dye, is often sprayed on the mucosa before chromoendoscopy as a mucolytic agent. Application of acetic acid also causes the columnar epithelium to swell, and this effect may enhance the evaluation of architectural features.

In magnification endoscopy, an optical zoom device is used to magnify the mucosa up to 150-fold. Magnification endoscopy is often combined with chromoendoscopy as just described. Investigators using this technique have identified a variety of "pit patterns" that might be typical of the intestinal metaplasia of Barrett's esophagus (Figs. 6–10 and 6–11).[27-29] Magnification endoscopy can also be combined with narrow-band imaging, which uses primarily blue light that penetrates

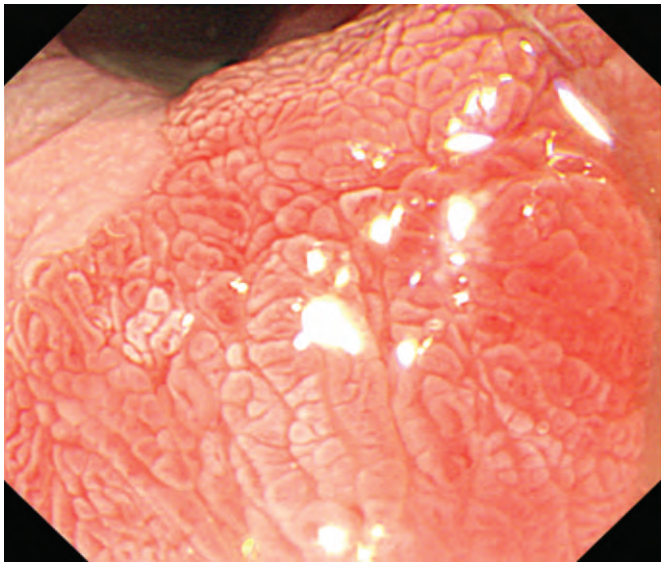


Figure 6–10. Magnification endoscopy of mucosa sprayed with acetic acid showing the pit pattern of columnar epithelium at the squamocolumnar junction. The relatively featureless squamous epithelium is seen adjacent to the columnar epithelium in the upper left corner of the slide.

only the superficial layers of the mucosa and is absorbed by hemoglobin (Fig. 6–12).

ENDOSCOPIC DIAGNOSIS OF REFLUX ESOPHAGITIS

Gastroesophageal reflux disease (GERD) is a condition in which gastric juice that refluxes into the esophagus causes symptoms, tissue injury, or both.[30] Heartburn is the most common symptom of GERD, and tissue injury results when esophageal epithelial cells succumb to the caustic effects of the refluxed acid and pepsin. When these caustic agents cause macroscopic injury to the esophageal epithelium, the endoscopist can make a diagnosis of reflux esophagitis. However, more than 50% of patients who have typical GERD symptoms have normal endoscopic examinations.[31,32] Thus, it appears that GERD does not usually cause visible damage to the esophageal mucosa in most patients.

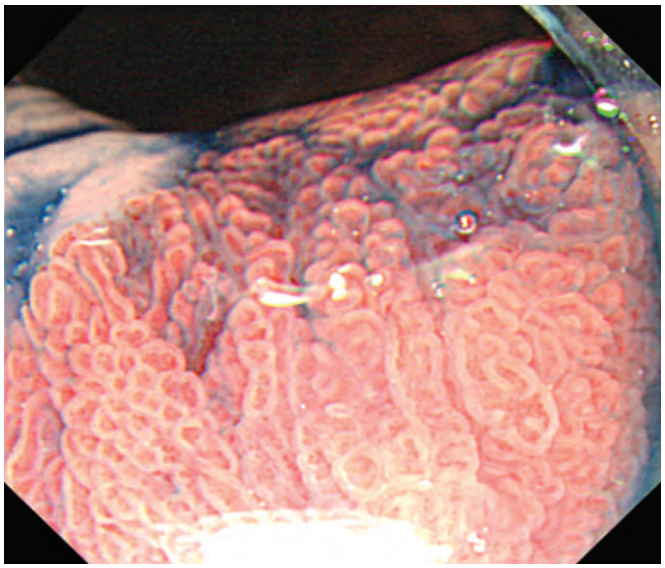


Figure 6–11. Magnification endoscopy of the region shown in Figure 6–10 after the application of indigo carmine dye.

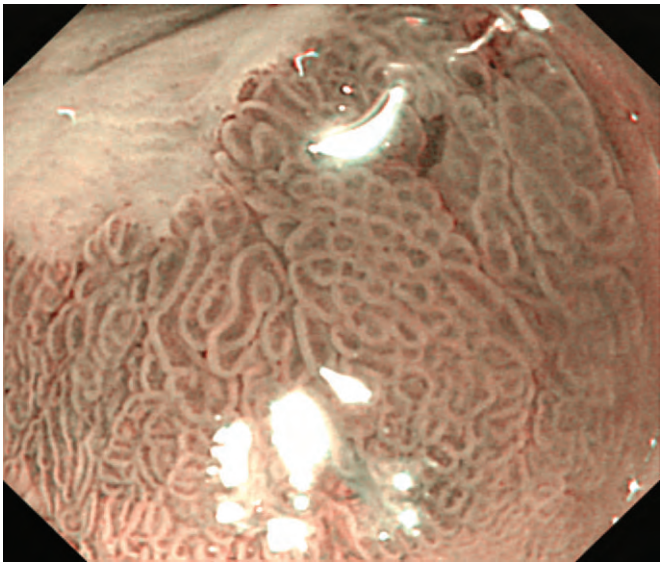


Figure 6–12. Magnification endoscopy of the region shown in Figure 6–10 combined with narrow-band imaging.

Mild changes of GERD that may be visible to the endoscopist include mucosal erythema, edema, hypervascularity, friability, and blurring of the SCJ. Identification of these changes is a subjective skill, however, and agreement among endoscopists regarding the presence of such minimal signs of reflux esophagitis can be very poor.[33,34] More severe GERD can result in esophageal erosions and ulcerations. Histologically, erosions are defined as superficial necrotic defects that do not penetrate the muscularis mucosae, whereas ulcerations are deeper defects that extend through the muscularis mucosae into the submucosa.[35] Endoscopically, these peptic esophageal lesions are identified on the basis of their gross features, and clinicians seldom have histologic confirmation that the lesions they call "esophageal ulcers" have in fact breached the muscularis mucosae. Thus, the distinction between esophageal ulceration and erosion is usually based on a subjective assessment of the depth of the necrotic lesion. One modern system for grading the severity of reflux esophagitis, the Los Angeles classification, avoids the problem of distinguishing erosions from ulcerations by referring to both as "mucosal breaks."[36]

More than 30 systems for the classification of reflux esophagitis have been proposed over the past few decades.[36] The endoscopic criteria for three of the most widely used systems are listed in Table 6–1.[34,36-38] All of the

Table 6–1 Classification Systems for Reflux Esophagitis

The Savary Miller Classification

Grade 0	Normal mucosa
Grade I	Discrete areas of erythema
Grade II	Noncircumferential erosions
Grade III	Circumferential erosions
Grade IV	GERD complications (ulcers, strictures, Barrett's esophagus)

The MUSE (*M*etaplasia, *U*lceration, *S*tricture, *E*rosion) Classification

	Metaplasia	*Ulceration*	*Stricture*	*Erosion*
Grade 0	M0 absent	U0 absent	S0 absent	E0 absent
Grade 1	M1 one	U1 one	S1 > 9 mm	E1 one
Grade 2	M2 circumferential	U2 ≥ 2	S2 ≤ 9	E2 circumferential

The Los Angeles Classification

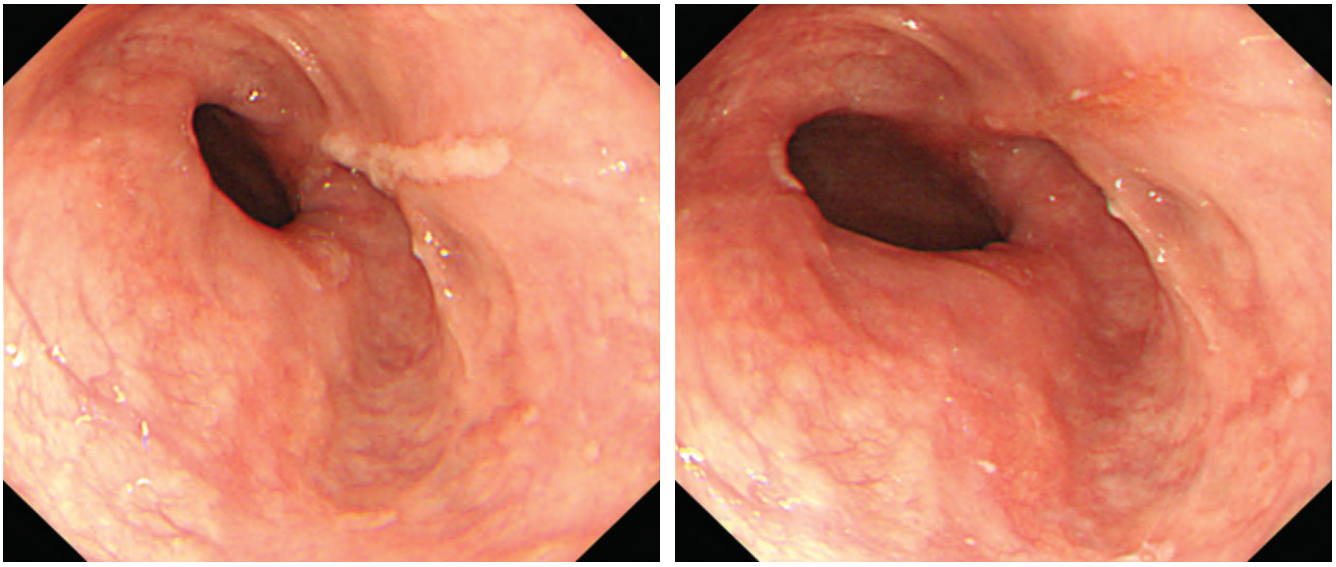
Grade A	≥1 Mucosal break <5 mm long that does not extend between the tops of 2 mucosal folds
Grade B	≥1 Mucosal break >5 mm long that does not extend between the tops of 2 mucosal folds
Grade C	≥1 Mucosal break that extends between tops of ≥2 mucosal folds involving <75% of the esophageal circumference
Grade D	≥1 Mucosal break that involves ≥75% of the esophageal circumference

proposed systems have limitations, and no individual system has been shown to be clearly superior to another for establishing the diagnosis of GERD or for predicting the response to treatment. Arguably, the best validated and most widely used system is now the Los Angeles classification, which was proposed at the meeting of the World Congress of Gastroenterology in Los Angeles in 1994.[36] In this system, a mucosal break is defined as "an area of slough or erythema with a discrete line of demarcation from the adjacent, more normal-looking mucosa" (Fig. 6–13A and B). Esophagitis is graded on a scale of A to D, depending on the length and circumferential extent of the mucosal breaks (Fig. 6–14A and B; see also Fig. 6–13). Los Angeles grades C and D represent severe reflux esophagitis. Originally, grade D esophagitis was defined as a mucosal break that involved the entire circumference of the esophagus, but this was modified in 1999 to the criterion shown in Table 6–1 because it can be difficult to ascertain that a mucosal break is completely circumferential.[34]

ENDOSCOPIC EVALUATION OF PATIENTS WHO HAVE UNDERGONE ANTIREFLUX SURGERY

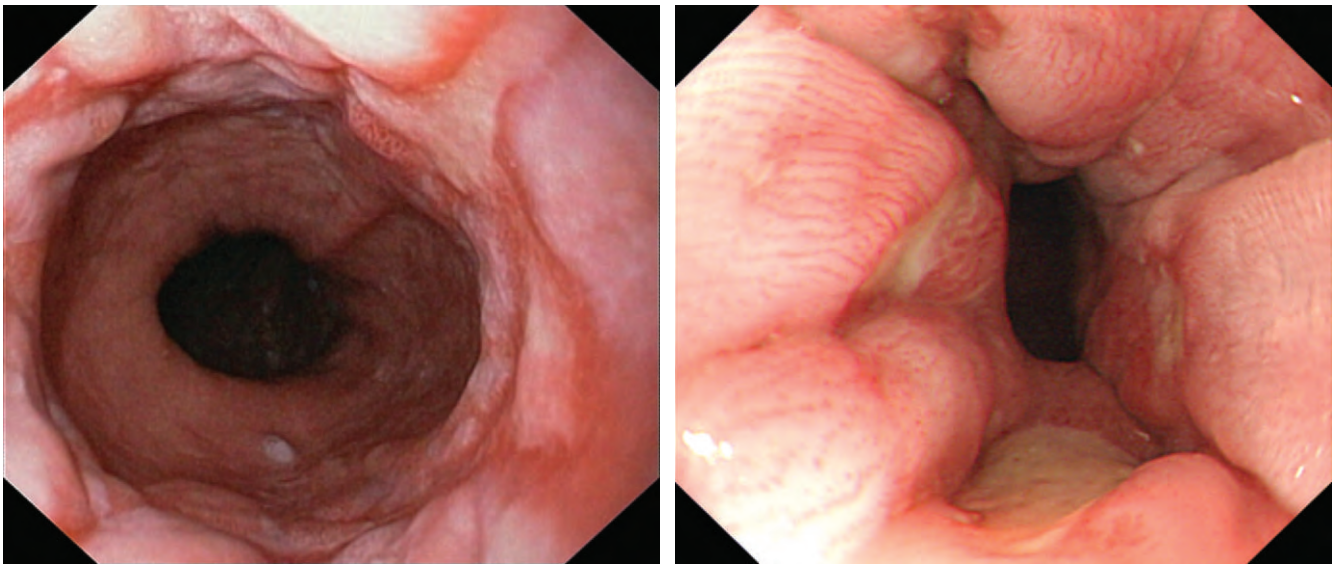
The two most commonly used fundoplication procedures (Nissen and Toupet) create characteristic folds in the proximal part of the stomach that are best appreciated with the endoscope in the retroflexed position.[39] The folds of the fundoplication should be located just below the diaphragm (Fig. 6–15). If the folds are seen above the diaphragm, it is an indication that the fundoplication has herniated into the chest, which usually results from disruption of the crural repair. If there is a pouch of stomach proximal to the folds of the fundoplication, the condition is called a "slipped" fundoplication (e.g., a "slipped Nissen"). A slipped fundoplication can occur in two ways: (1) the fundoplication is fashioned in the correct location, but a portion of the stomach later herniates ("slips") through the fundoplication, or (2) the surgeon mistakes the proximal part of the stomach for the distal end of the esophagus and inadvertently fashions the fundoplication around the stomach. Although the latter situation represents an initial surgical error rather than later slippage (herniation), the condition is called a slipped fundoplication despite the misnomer. Finally, the absence of fundoplication folds suggests total disruption of the antireflux procedure (the "missin' Nissen"). Any of these abnormalities can render the antireflux surgery ineffective.

The folds of a properly constructed fundoplication should be oriented parallel to the diaphragm. An oblique orientation of the folds suggests twisting of the fundoplication or improper construction of the wrap involving the body rather than the fundus of the stomach (Fig. 6–16).[34] Either of these conditions can cause postoperative gastroesophageal reflux, dysphagia, or both. The folds should measure approximately 1 to 2 cm in



A B

Figure 6–13. **A,** Endoscopic photograph of Los Angeles grade B esophagitis. There is a mucosal break defined as "an area of slough or erythema with a discrete line of demarcation from the adjacent, more normal-looking mucosa." Notice the whitish exudates covering the mucosal break, which is greater than 5 mm in length. In addition, scarring of the distal end of the esophagus is indicated by the fibrous strands that run perpendicular to the mucosal break at the 12- and 5-o'clock positions. **B,** Same area shown in **A** after the whitish exudates have been washed off. The mucosal break is still visible, but less prominent.



A B

Figure 6–14. **A** and **B,** Two examples of Los Angeles grade C esophagitis.

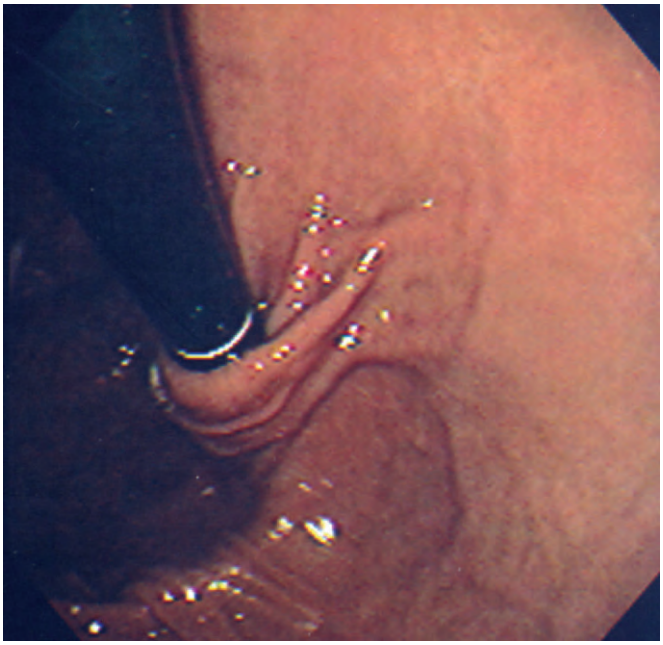


Figure 6–15. Endoscopic photograph of an anatomically correct Nissen fundoplication, retroflexed view. The fundoplication folds are located below the diaphragm and run parallel to the white distance line on the endoscope. (From Spechler SJ: The management of patients who have "failed" antireflux surgery. Am J Gastroenterol 99:552-561, 2004.)

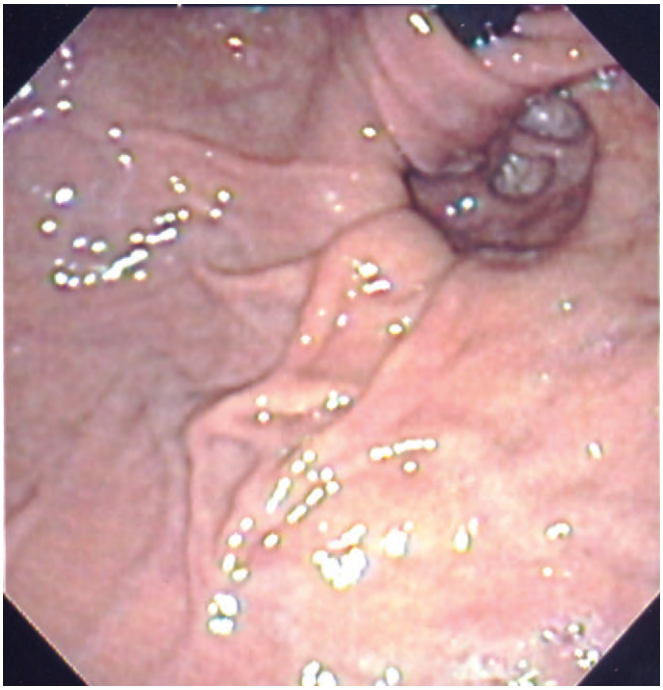


Figure 6–17. Endoscopic photograph of a paraesophageal hernia, retroflexed view. The herniated pouch of stomach is located next to the fundoplication folds. (From Spechler SJ: The management of patients who have "failed" antireflux surgery. Am J Gastroenterol 99:552-561, 2004.)

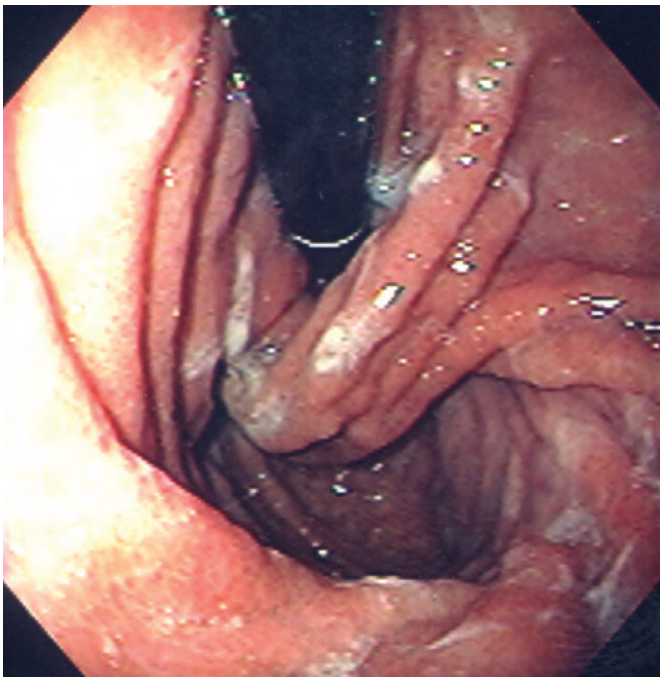


Figure 6–16. Endoscopic photograph of a slipped Nissen fundoplication, retroflexed view. The fundoplication folds are oriented obliquely to the white distance line on the endoscope, and there is a pouch of stomach proximal to the folds. (From Spechler SJ: The management of patients who have "failed" antireflux surgery. Am J Gastroenterol 99:552-561, 2004.)

span. A wider span indicates a too-generous fundoplication, which can cause dysphagia. A paraesophageal hernia can also cause dysphagia by pressing on the distal part of the esophagus (Fig. 6–17). The herniated portion of the stomach in these cases often originates from the fundoplication itself and may result from attempts to construct a "floppy" wrap.

ESOPHAGEAL CANCER

Esophageal cancers that are recognizable by conventional endoscopy appear as masses that protrude into the lumen of the esophagus. The masses are often nodular, irregular, and ulcerated, and the tumors may have a different color and texture than the surrounding normal mucosa. Squamous cell carcinoma and adenocarcinoma of the esophagus cannot be differentiated on the basis of endoscopic appearance, but the location of the tumor and its associated features may provide important clues regarding its histology. Tumors that involve the proximal and middle portions of the esophagus and that are separated from the stomach by a segment of squamous epithelium are very likely to be squamous cell carcinomas. Distal esophageal tumors can be either squamous cell carcinomas or adenocarcinomas. If there is associated Barrett's esophagus, the tumor is likely to be an adenocarcinoma (Figs. 6–18 and 6–19). However,

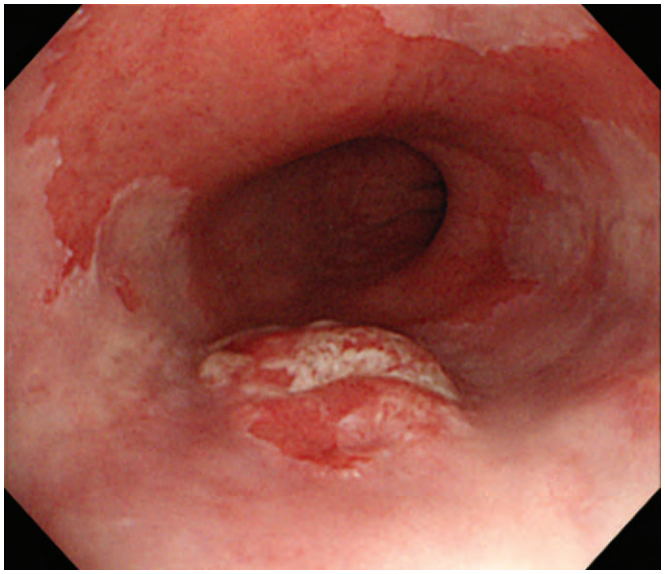


Figure 6–18. Early cancer in Barrett's esophagus. Note the background of flat Barrett's epithelium with the nodular mass in the foreground.

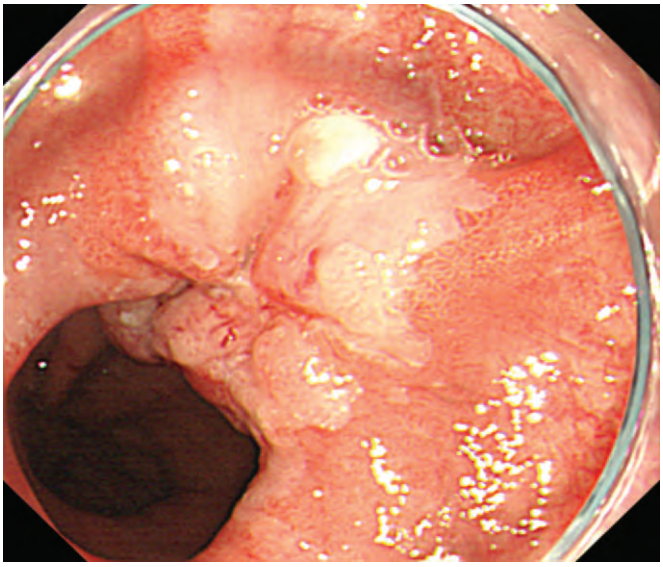
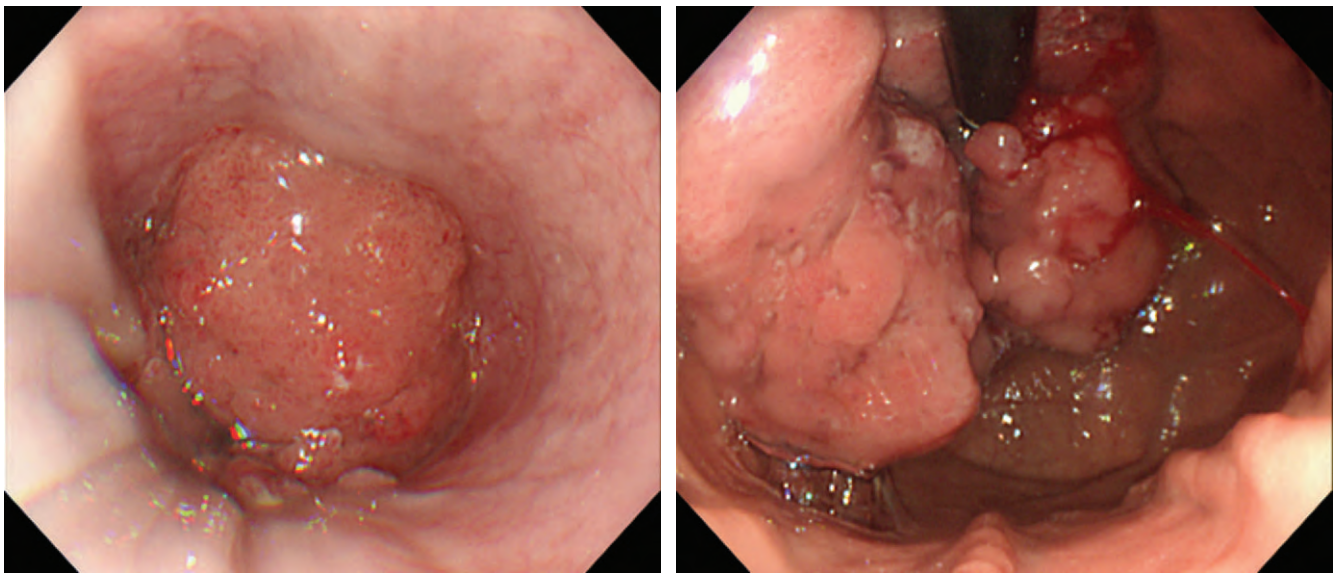


Figure 6–19. Ulcerated cancer of the distal end of the esophagus.



A B

Figure 6–20. Adenocarcinoma of the gastroesophageal junction photographed from the esophageal side **(A)** and from the gastric side **(B).** If there is no Barrett's epithelium seen in the esophagus, it is not possible to determine whether such a tumor originated from the distal esophagus or from the gastric cardia.

adenocarcinomas that cause symptoms have often grown so large that they have obliterated any evidence of the Barrett's esophagus that spawned them. It can be especially difficult to determine the origin of an adenocarcinoma that straddles the GEJ (Fig. 6–20A and B). Such tumors can arise either from Barrett's esophagus or from the proximal part of the stomach. If no Barrett's esophagus is apparent, investigators have relied on the location of the tumor epicenter to classify the tumor as esophageal or "cardiac."

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Chapter

7

Endoscopic Esophageal Ultrasonography

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Endoscopic esophageal ultrasonography (EUS) extended endoscopic examination of the esophagus beyond the mucosa into the esophageal wall and paraesophageal tissues. The diagnostic capabilities of surface ultrasound have been expanded by endoscopic placement of ultrasound transducers adjacent to the gastrointestinal mucosa. These transducers, operating at relatively high frequencies, provide detailed examination of the esophageal wall and surrounding tissues. EUS is the most significant advance in the diagnosis of esophageal disease since the introduction of flexible fiberoptic endoscopy. These intracorporeal examinations have proved beneficial in the diagnosis and treatment of both benign and malignant diseases of the esophagus and adjacent structures.

FUNDAMENTALS OF ULTRASONOGRAPHY

Sound is produced by vibration of a source within a medium. Vibration produces waves, cyclic compression, and rarefaction (expansion) of molecules in the medium, thus transmitting the sound wave through the medium. The number of cycles (compression and rarefaction) of a sound wave occurring in 1 second is the frequency and is measured in hertz. The frequency of sound waves audible to the human ear is between 20 and 20,000 Hz. Sound waves with frequencies higher than 20,000 Hz are ultrasound waves. Frequencies used in medical ultrasound imaging range from 1 to 20 million Hz (1 MHz to 20 MHz).

Ultrasound waves may be produced by electrical excitation of a piezoelectric crystal. The application of voltage across a crystal causes it to deform. Alternating electrical energy vibrates the crystal and produces sound waves. Conversely, if a sound wave deforms a crystal, electrical energy is produced. It is this ability to convert electrical energy into sound energy and, conversely, to convert sound energy into electrical energy that allows these crystals to function as both transmitters and receivers (i.e., as *transducers*). These transducers are responsive to a limited range of frequencies; hence, more than one transducer may be required for an ultrasound examination.

The speed of a sound wave within a medium (tissue) is defined by the following relationship: $V = (K/p)^{½}$. V is the velocity of the sound wave, K is the bulk modulus of the tissue (a measure of stiffness), and p is the density of the tissue.

The resistance to passage of a sound wave through tissue is called acoustic impedance (Z), which is defined by the following relationship: $Z = pV = (pK)^{½}$.

Sound waves travel best through dense or elastic tissue. Absorption of some of the energy of an ultrasound wave occurs as the wave passes through tissue. The amount of absorption is determined by tissue characteristics and the frequency of the sound wave. Higher-frequency waves have greater absorption.

Interactions occurring as a sound wave encounters different tissues are critical to the diagnostic capabilities of ultrasound. As a sound wave passes from one tissue to the next, a portion of the wave is transmitted and a portion is reflected. The reflected wave is received by the transducer, thereby providing the diagnostic information of ultrasound. The difference in acoustic impedance between the two tissues and the angle at which the sound wave enters the new medium (angle of incidence) determine the portion of the wave that is reflected and the portion that is transmitted. In tissue with similar acoustic impedance, most of the wave is transmitted. Soft tissue has excellent transmission qualities; the density and velocity vary only by 12% to 14% among different soft tissues. Because acoustic impedance is the product of velocity and density, the product of these small changes results in a 22% difference in acoustic impedance between fat and muscle.[1] Useless, bright echo images are obtained when an ultrasound wave encounters air or

bone. Air is very compressible and of low density, whereas bone, although dense, has low compressibility and high reflectivity. These properties account for the poor transmission of ultrasound waves from tissue to air or tissue to bone. The amount of reflected sound is also related to the angle of incidence: as the angle of incidence increases, less sound is reflected. In addition, sound waves are bent as they travel from one tissue to the next. This process is termed *refraction*.

Absorption, reflection, and refraction are major sources of energy loss. Some ultrasound wave energy is also lost by scattering (diffusion), which occurs when a sound wave encounters heterogeneous tissue. Tiny particles within tissue (such as fat in muscle), smaller than the ultrasound wavelength, scatter the ultrasound wave. As a sound wave passes through tissue, a portion of its energy is lost; this is called *attenuation*. Attenuation increases as more tissues are encountered and as the wave travels farther from the source. If the returning ultrasound wave is not processed, the same tissue would be imaged differently, depending on its distance from the transducer. The intensity of the returning waves must be amplified (gain) to ensure that distant waves are correctly represented. Attenuation increases as ultrasound frequency increases.

Resolution is the ability to discriminate among different tissues with ultrasound waves. Depth or axial resolution is the ability to differentiate between two tissues along the path of the ultrasound wave. Lateral resolution is the ability to distinguish between adjacent tissues. Transducer characteristics and focus determine resolution. Higher frequencies allow better resolution but decreased tissue penetration.

Pulse-echo technique is used in EUS. Ultrasound waves are emitted for a brief period, followed by a subsequent listening period during which the reflected waves are received. The returning ultrasound waves are displayed such that the brightness is proportional to the amplitude of the returning ultrasound waves. This is known as *B-mode ultrasonography*. Because the amplitude is presented in a range from white to gray to black, the display is also termed *gray-scale ultrasound*. Individual scans are shown at a rate at which the eye cannot detect single images (12/sec). This fast-frame display is called *real-time ultrasound* and allows the ultrasonographer to study tissue temporally as well as spatially.

INSTRUMENTS AND TECHNIQUES

Because EUS does not provide adequate endoscopic inspection of the upper gastrointestinal tract, every ultrasound study should be preceded by a standard flexible endoscopic upper gastrointestinal examination. This provides precise location and mucosal definition (including biopsy) of the esophageal lesion and guides the ultrasound examiner. Intravenous administration of a narcotic, such as meperidine, and a benzodiazepine, such as midazolam, usually provides adequate sedation. The ultrasound endoscope is generally passed blindly through the oropharynx and hypopharynx. Care must be taken because the distal tip containing the transducer is rigid. For complete examination, the endoscope must be passed beyond the esophagus into the stomach.

Figure 7–1. The Olympus GF-UM130 ultrasound endoscope. *Upper right inset*, The control section contains the deflection controls and air/water and suction valves similar to those on a standard endoscope. *Upper left inset*, The ultrasound transducer is housed in the tip of the endoscope. The forward oblique viewing endoscope and suction channel are proximal to the ultrasound transducer. *Lower left inset*, The distal tip of the ultrasound endoscope with the water-inflated contact balloon, which covers the ultrasound transducer.

The radial mechanical ultrasound endoscope (Fig. 7–1) is the principal instrument used for EUS. The ultrasound transducer is housed in the tip of the endoscope. It produces up to a 360-degree sector scan perpendicular to the transducer tip. Because the transducer is adjacent to tissues to be examined, higher frequencies than those used in extracorporeal ultrasound can be used. In the newest models a range of transducer frequencies from 5 to 20 MHz are available. These transducers allow adequate visualization of anatomic structures to a depth of 3 to 12 cm. An acceptable acoustic interface between the transducer and the tissue being examined must be obtained to ensure good-quality ultrasound images. This is most commonly accomplished by covering the tip of the endoscope with a latex balloon, which can be filled with water to provide an excellent acoustic interface (see Fig. 7–1). A less commonly used technique is rapid insufflation of the esophageal lumen with water. This provides an excellent, but transient acoustic interface without the tissue compression that may occur with the latex balloon. Current echoendoscopes also provide a video endoscopic image, albeit with a somewhat limited view in a forward oblique direction.

The control section contains the deflection controls and air/water and suction valves, similar to those on a standard endoscope (see Fig. 7–1). A water inflation/deflation system for the balloon is incorporated into the air/water and suction valve mechanisms. A direct-current

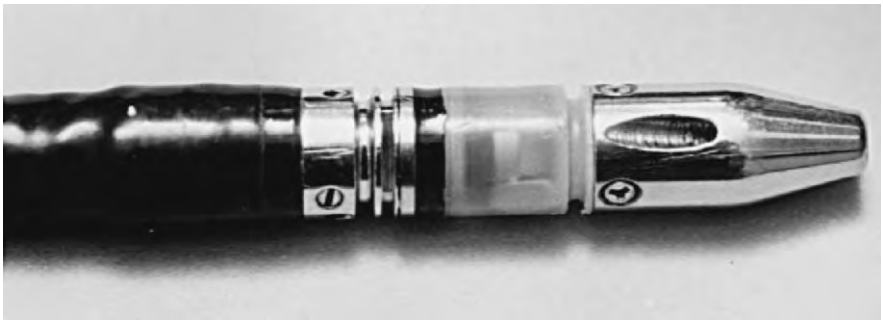
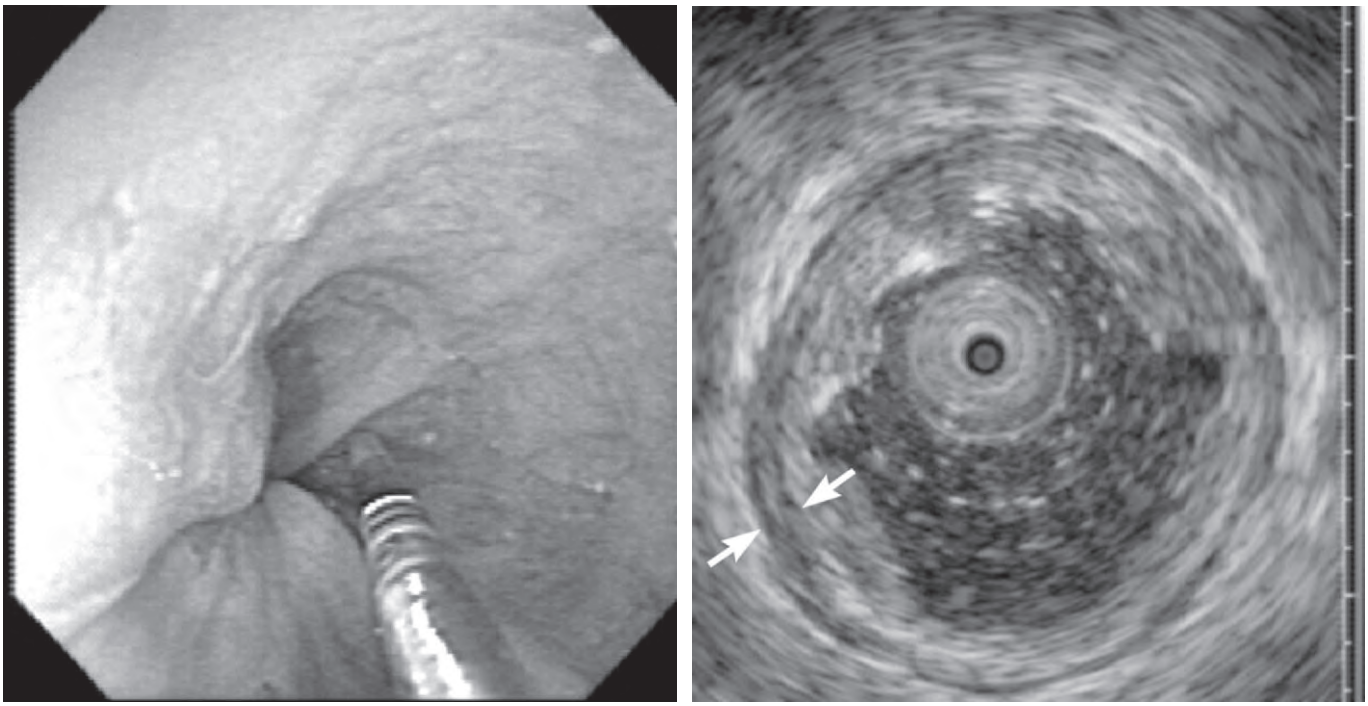


Figure 7–2. Radial mechanical blind probe. The tip is tapered to allow passage through tight strictures. The radial ultrasound transducer is positioned behind the tapered tip.



A B

Figure 7–3. **A,** High-frequency (12 to 30 MHz) miniprobe passed through the operating channel of a standard endoscope. **B,** Miniprobe ultrasound image of a normal esophagus. The probe is not centered in the undistended esophageal lumen. The mucosa and submucosa are the inner hyperechoic layer. The muscularis propria (*arrows*) is the inner hypoechoic layer.

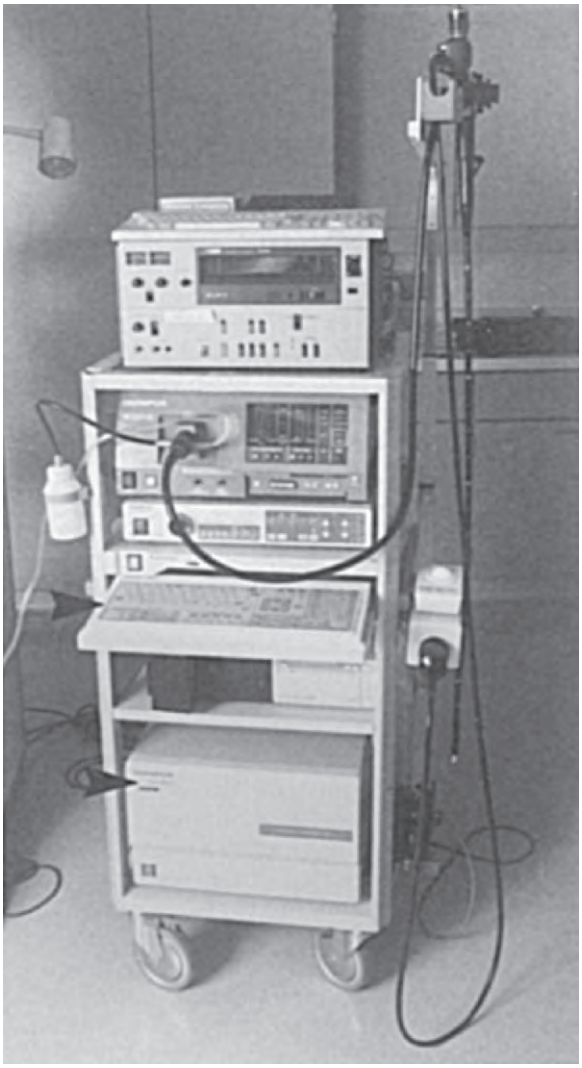
motor and drive mechanism that rotates the ultrasound transducer are housed in the control section. Current ultrasound endoscopes are totally immersible.

A radial mechanical blind probe (Fig. 7–2) is available for the evaluation of esophageal strictures. This echoendoscope provides images similar to those of larger-diameter radial mechanical echoendoscopes, but it has no endoscopic optical capabilities and is less than 8 mm in diameter. More commonly used in current practice are higher-frequency miniprobes passed through the operating channel of standard endoscopes (Fig. 7–3); these miniprobes provide radial images from 12 to 30 MHz.

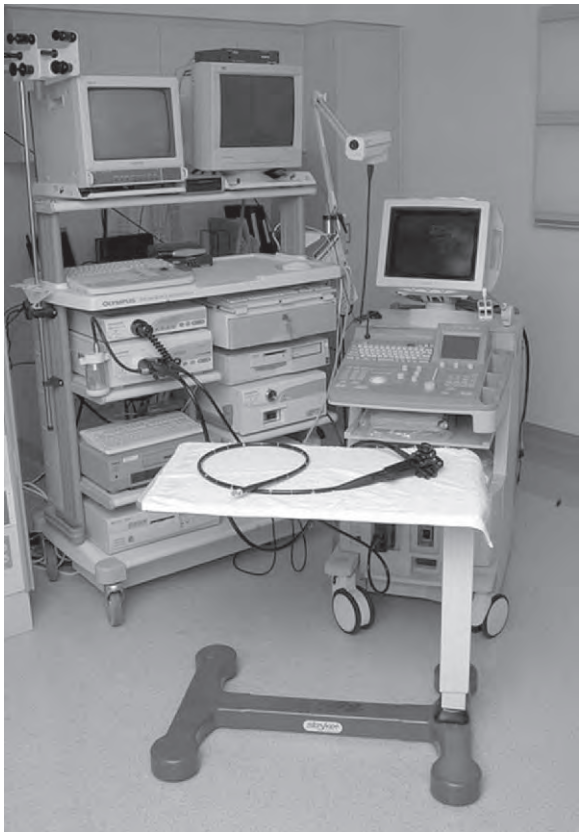
These three instruments are used in conjunction with an image processor (Fig. 7–4). The image processor allows for adjustment of gain, contrast, and sensitivity time control in order to regulate the strength of the returning echo at different depths. On-screen calibration and labeling can be done with the image processor. The image may be displayed on a video monitor or stored digitally or on videotape. The image processor has been refined and miniaturized with successive generations of endoscopic ultrasound equipment.

Newer electronic endoscopes are also available that have the advantage of providing color Doppler. They may be less susceptible to breakdown because moving parts are eliminated. In some cases, both radial and linear echoendoscopic examination may be possible with one power source and image processor system.

The curvilinear electronic echoendoscope (Fig. 7–5) also has also has video endoscopic capability and can produce up to a 180-degree oblique forward field. It



A



B

Figure 7–4. **A,** The Olympus EU-M20 image processor (*lower arrow*) is rack-mounted in a standard cart, which includes the other essential endoscopic equipment. The keyboard (*upper arrow*) can be used to measure and mark ultrasound findings. **B,** The complete system includes the light source rack, image processor, and ultrasound endoscope.

allows a range of scanning frequencies from 5 to 10 MHz with a depth of penetration of 4 cm or greater. This system can provide color Doppler examination and direct visualization of cytology needles passed into and beyond the esophageal wall.

Radial mechanical and electronic curvilinear scanners have increased the accuracy of EUS. However, the availability and use of two systems necessarily increase both the complexity and the cost of EUS examinations. For diagnostic purposes, the radial mechanical scanner is preferable because it allows a 360-degree view and is known as the "workhorse" of EUS. Because the radial mechanical scanner does not allow safe directed passage of a needle into the esophageal wall or adjacent tissue if a tissue sample is required for cytologic evaluation, the electronic curvilinear echoendoscope, powered by a separate system, is used. It is possible to perform both diagnosis and fine-needle aspiration (FNA) with the electronic linear echoendoscope alone, but the limitation in viewing field requires significant torque on the insertion tube to image the esophageal wall and adjacent tissues for a 360-degree view. Comparable results, however, for staging examinations have been reported with the electronic curvilinear echoendoscope.[2] Both systems must be available for adequate EUS evaluation.

THE ESOPHAGEAL WALL AND ULTRASOUND ANATOMY

The esophageal wall is composed of three distinct layers: mucosa, submucosa, and muscularis propria (Fig. 7–6). The mucosa has three elements: epithelium, lamina propria, and muscularis mucosae. The innermost layer is stratified, nonkeratinizing squamous epithelium. It is separated and isolated from the remainder of the esophageal wall by a basement membrane. Immediately beneath is the lamina propria. This loose matrix of collagen and elastic fibers forms a superficial undulating layer; invaginations into the epithelium produce epithelial papillae. Lymphatic channels in the lamina propria are an anatomic feature unique to the esophagus. The

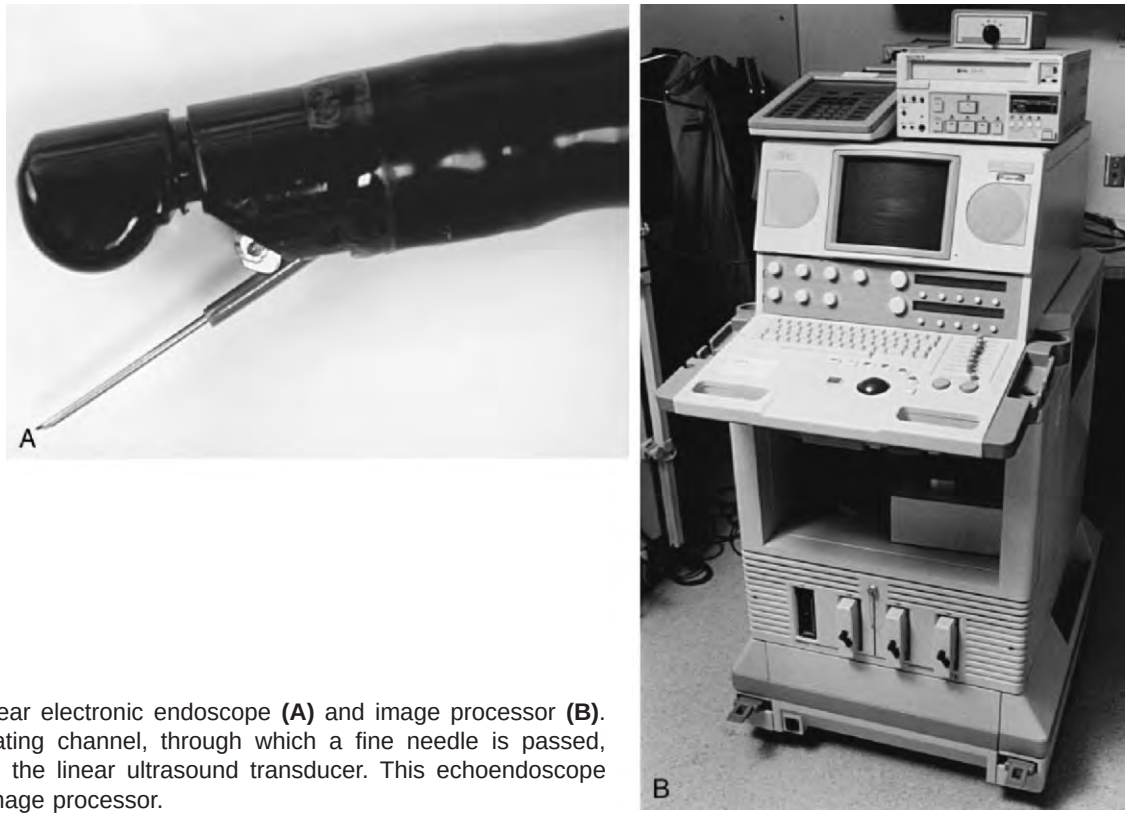


Figure 7–5. Curvilinear electronic endoscope **(A)** and image processor **(B)**. The optics and operating channel, through which a fine needle is passed, are positioned behind the linear ultrasound transducer. This echoendoscope requires a separate image processor.

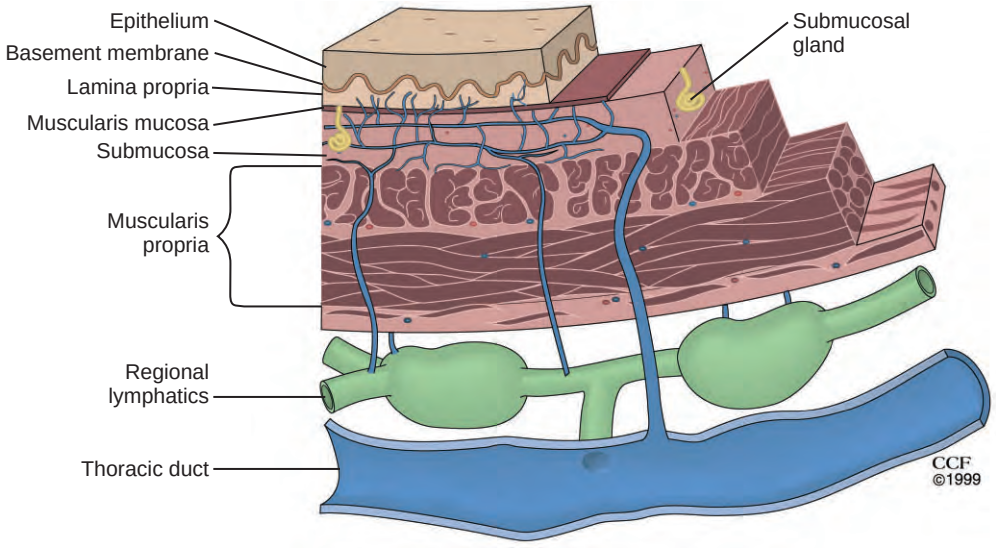


Figure 7–6. The esophageal wall is composed of mucosa, submucosa, and muscularis propria. The mucosa is composed of epithelium, lamina propria, and muscularis mucosae.

muscularis mucosae surrounds the lamina propria. This smooth muscle layer pleats the two inner layers of the mucosa into folds that disappear with distention of the lumen.

The submucosa is composed of connective tissues that contain a rich network of blood vessels and lymphatics. The dense submucosal lymphatic plexus facilitates early dissemination of esophageal malignancies. Elastic fibers and collagen combine to make this the strongest esophageal layer. Submucosal glands of mixed type are characteristic of the esophagus.

The muscularis propria is the muscular sleeve that provides the propulsive force necessary for swallowing. There are two layers of muscle: an inner circular layer

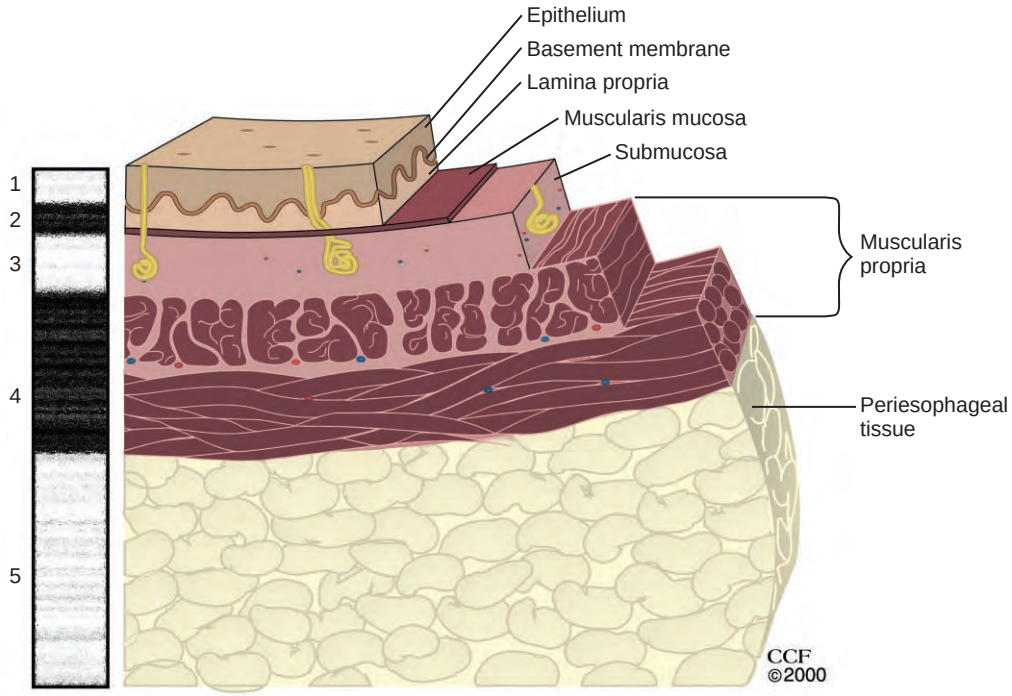


Figure 7–7. The esophageal wall is visualized as five alternating layers of differing echogenicity by esophageal ultrasound. The first layer, which is hyperechoic (white), represents the superficial mucosa (epithelium and lamina propria). The second layer, which is hypoechoic (black), represents the deep mucosa (muscularis mucosa). The third layer, which is hyperechoic (white), represents the submucosa. The fourth layer, which is hypoechoic (black), represents the muscularis propria. The fifth layer, which is hyperechoic (white) is the periesophageal tissue.

and an outer longitudinal layer. The upper cervical esophagus is composed entirely of striated muscle. There is a gradual transition from striated to smooth muscle within muscle bundles until the esophagus is entirely smooth muscle at the upper and midthird junction. Lymphatic channels pierce the muscularis propria and drain into regional lymphatics or directly into the thoracic duct.

The esophagus has no investing adventitia. The paraesophageal tissue is composed of fibrofatty tissue that lies directly against the outer fibers of the muscularis propria.

The normal esophagus is usually viewed as five discrete layers by EUS (Fig. 7–7). These layers are seen as alternating hyperechoic (white) and hypoechoic (black) rings. Studies have demonstrated that the five layers seen by EUS correspond to the balloon-mucosa interface, the mucosa deep to this interface, the submucosa and the acoustic interface between the submucosa and muscularis propria, the muscularis propria minus the acoustic interface between the submucosa and the muscularis propria, and the periesophageal tissue.[3,4] For clinical purposes, these layers represent the superficial mucosa, deep mucosa, submucosa, muscularis propria, and periesophageal tissue. In the upper part of the esophagus, with overdistention of the examining balloon or if the transducer is too close to the esophageal wall, only three layers of the esophageal wall may be apparent because the superficial mucosa, deep mucosa, and submucosa compose one hyperechoic layer. The thickness of each ultrasound layer is about equal and does not represent the thickness of the tissue layer but, instead, the time that it takes the ultrasound wave to traverse this layer.

ESOPHAGEAL CARCINOMA

The stage of an esophageal carcinoma, as defined by its anatomic extent, is the best predictor of outcome for patients with esophageal carcinoma. Recent refinements in the staging of esophageal carcinoma have resulted in the present staging system, which is based on the TNM classification (Box 7–1).[5] The primary tumor (T) is defined only by the depth of invasion; EUS is ideally suited for this determination. T1 tumors are confined to the submucosa or more superficial esophageal layers. T2 tumors invade into, but do not breach the muscularis propria. T3 tumors invade beyond the esophageal wall and into periesophageal tissue but do not invade adjacent structures. T4 tumors directly invade structures in the vicinity of the esophagus.

Lymph nodes in the area of the primary tumor, or regional lymph nodes (N), are characterized only by the presence (N1) or absence (N0) of metastases. Similarly, distant sites (M) are characterized by the presence (M1) or absence (M0) of metastases. The recent revision of the staging system for esophageal carcinoma subdivides distant metastatic carcinomas (M1) into M1a (distant,

Box 7–1 TNM Classifications and Stage Groupings of Esophageal Carcinoma

Classification

T: Primary Tumor

TX	Tumor cannot be assessed
T0	No evidence of tumor
Tis	High-grade dysplasia
T1	Tumor invades the lamina propria, muscularis mucosa, or submucosa. It does not breach the submucosa. Tumors may be subdivided into T1a (intramucosal) and T1b (submucosal)
T2	Tumor invades into and not beyond the muscularis propria
T3	Tumor invades the periesophageal tissue, but does not invade adjacent structures
T4	Tumor invades adjacent structures

N: Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases

M: Distant Metastasis

MX	Distant metastases cannot be assessed
M1a	Upper thoracic esophagus metastatic to cervical lymph nodes Lower thoracic esophagus metastatic to celiac lymph nodes
M1b	Upper thoracic esophagus metastatic to other nonregional lymph nodes or other distant sites Midthoracic esophagus metastatic to either nonregional lymph nodes or other distant sites Lower thoracic esophagus metastatic to other nonregional lymph nodes or other distant sites

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

nonregional lymph node metastases) and M1b (other distant metastases).[5] M1a disease is further classified by tumor location: M1a tumors of the upper thoracic esophagus have metastasized to cervical nodes, and M1a tumors of the lower thoracic esophagus have metastasized to celiac lymph nodes. These TNM descriptors are grouped into stages with similar behavior and prognoses (see Box 7–1).

EUS may be used at two different periods in the course of esophageal carcinoma. The staging examination may be done before (clinical stage) or after (re-treatment stage) treatment.

Clinical Stage (cTNM)

Determination of cT Classification

Detailed images of the esophageal wall by EUS make it the most accurate modality available for determination of the depth of tumor invasion (T) before treatment (Figs. 7–8 to 7–11).[6-11] The same definition of the esophageal wall is not offered by computed tomography (CT). A thickened esophageal wall, the principal CT finding in esophageal carcinoma, is not specific for esophageal carcinoma and lacks the definition required to distinguish T1, T2, and T3 tumors.[12] In differentiation of T3 from T4 tumors, EUS is superior to CT. Evaluation of the fat planes is used to define local invasion at CT examination. The obliteration or lack of fat planes is not sensitive in predicting local invasion, but preservation of these planes is specific for the absence of T4 disease.[13-20] When compared with CT, EUS provides a more sensitive and reliable determination of vascular involvement.[21]

Experience with both examination technique and ultrasound interpretation is critical to accurately determine the clinical depth of tumor invasion. Seventy-five to 100 examinations are required before competence is obtained.[22,23] A review of 21 series reported an 84% accuracy of EUS for T classification.[24] Accuracy is not constant and varies with the T classification. In this meta-analysis, accuracy for T1 carcinomas was 83.5%, with 16.5% of tumors over-staged; accuracy for T2 was 73%, with 10% under-staged and 17% over-staged; accuracy for T3 was 89%, with 5% under-staged and 6% over-staged; and accuracy for T4 was 89%, with 11% under-staged.[24] A review of the literature shows variation in accuracy with T classification: 75% to 82% for T1, 64% to 85% for T2, 89% to 94% for T3, and 88% to 100% for T4.[24]

The greatest inaccuracy is reported for T2 tumors. EUS anatomy, in part, accounts for this problem. The muscularis propria is vital in defining T1, T2, and T3 tumors. For clinical assessment the fourth ultrasound layer is interpreted as the muscularis propria. This layer, however, does not include the interface between the submucosa and muscularis propria; it is contained in the third ultrasound layer. Thus, the border necessary to completely differentiate T1 from T2 tumors is contained in the third ultrasound layer. Since two boundaries must be assessed for determination of T2 and errors might occur at each, the inaccuracy is potentially twice that of T1 and T4 tumors.

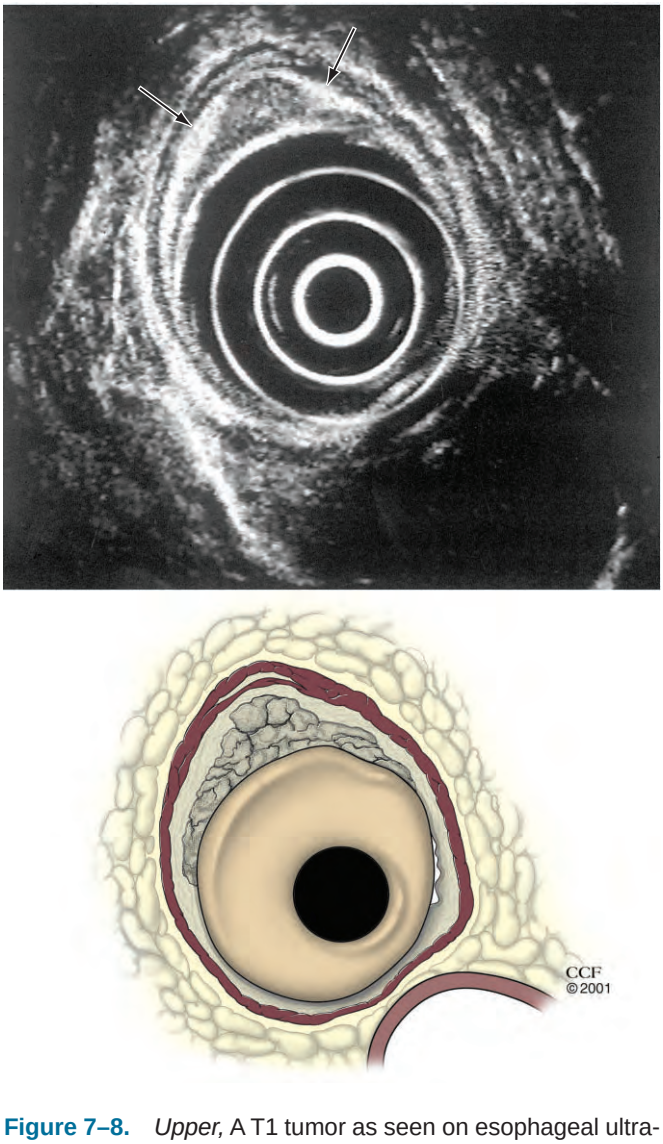


Figure 7–8. *Upper,* A T1 tumor as seen on esophageal ultrasound. The hypoechoic (black) tumor invades the hyperechoic (white) third ultrasound layer (submucosa) but does not breach the boundary between the third and fourth layers (*arrows*). *Lower,* A T1 tumor invades, but does not breach the submucosa.

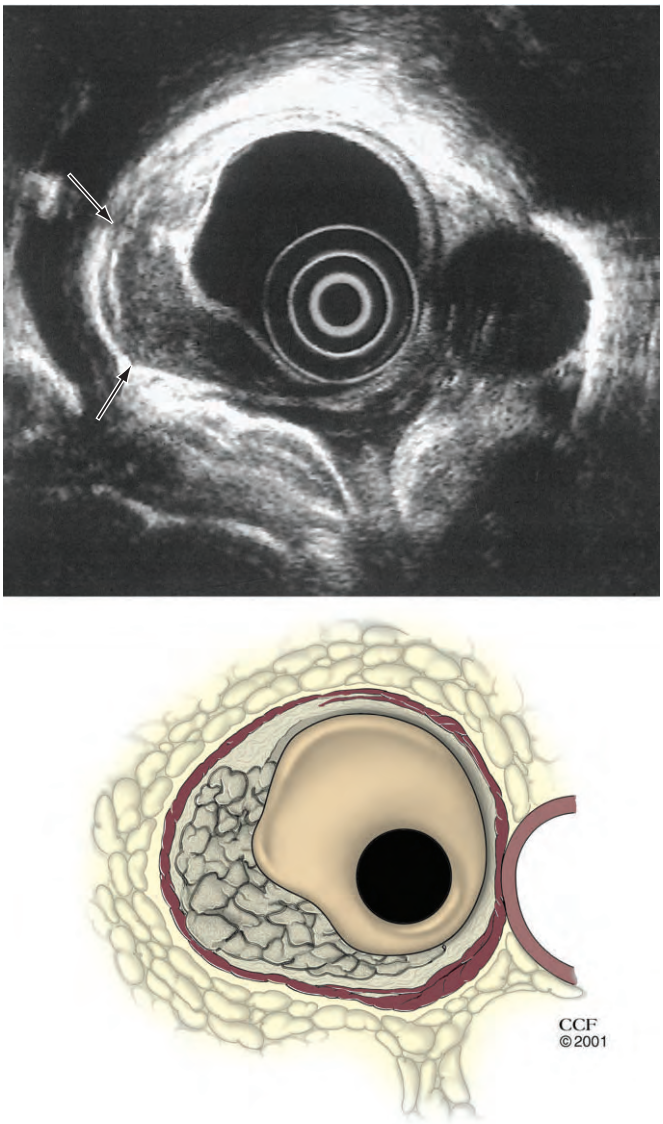


Figure 7–9. *Upper,* A T2 tumor as seen on esophageal ultrasound. The hypoechoic (black) tumor invades the hypoechoic (black) fourth ultrasound layer but does not breach the boundary between the forth and fifth layers (*arrows*). *Lower,* A T2 tumor invades, but does not breach the muscularis propria.

Because invasion beyond the esophageal wall is important in determining therapy, some investigators have examined the accuracy of EUS in determining T classification dichotomously. When compared with T classification determined pathologically, EUS was 87% accurate, 82% sensitive, 91% specific, 89% positively predictive, and 86% negatively predictive of tumors confined to the esophageal wall (≤T2) or invading beyond the esophageal wall (>T2).[25] A systematic review of 13 studies also confirmed that EUS was highly effective in differentiating T1/T2 from T3/T4 tumors.[26]

EUS interpretation is not done in the absence of clinical information; patient history and preceding esophagoscopy and imaging are usually available. This fact was illustrated by Meining and colleagues, who reported that a blinded review of EUS studies was significantly less accurate than a retrospective review of EUS reports, 53% versus 73%, respectively.[27] When interpreters were unblinded and given endoscopy tapes, accuracy improved to 62%. Tumor length and luminal obstruction are known at the time of EUS and are predictive of the T classification.[28] In this report, tumor length greater than 5 cm had a sensitivity of 89% and specificity of 92% for diagnosing T3 tumors. Thirteen patients with luminal obstruction had at least T3 tumors. Clinically, EUS examinations are never interpreted in the absence of history and esophagoscopy.

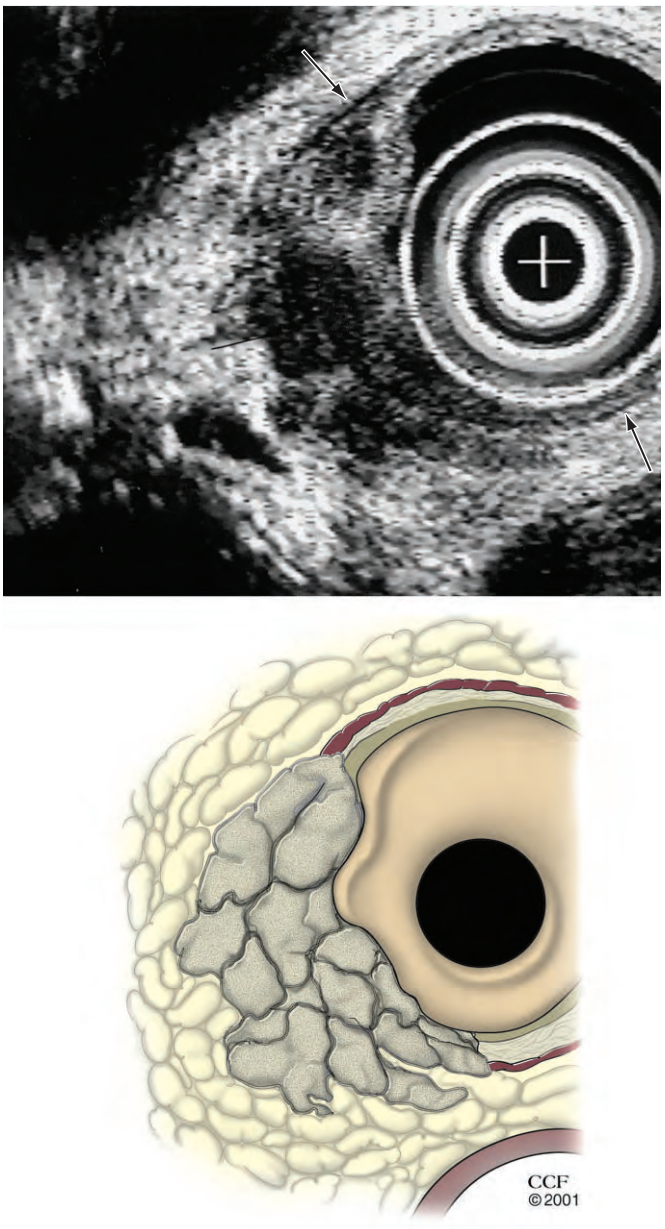


Figure 7–10. *Upper,* A T3 tumor as seen on esophageal ultrasound. The hypoechoic (black) tumor breaches the boundary between the fourth and fifth ultrasound layers (*arrows*) and invades the hyperechoic (white) fifth ultrasound layer (periesophageal tissue). *Lower,* A T3 tumor invades the periesophageal tissue but does not involve adjacent structures.

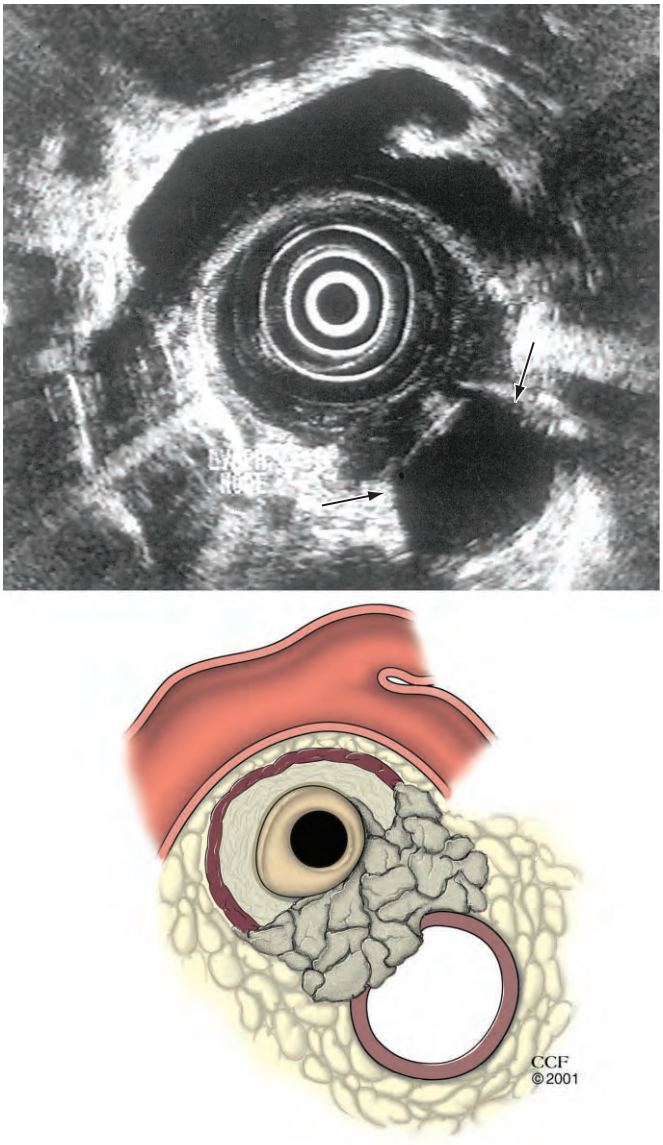


Figure 7–11. *Upper,* A T4 tumor as seen on esophageal ultrasound. The hypoechoic (black) tumor invades the aorta. The tumor breaches the boundary between periesophageal tissue and the aorta (*arrows*). *Lower,* A T4 tumor invades the aorta.

Esophageal obstruction caused by a malignant high-grade stricture prohibits staging in 19% to 63% of examinations.[11,29,30] Two studies have reported that EUS may be less reliable in nontraversable esophageal cancers.[10,31] Failure to pass an ultrasound probe beyond a malignant stricture has been found to be an accurate predictor of advanced stage. More than 90% of these patients have stage III or IV disease.[32] These discordant findings may be reconciled when viewed in the context of a study by Hordijk and colleagues[30] that assessed the severity of malignant strictures. In this study, the accuracy of T classification was 87% for nontraversable strictures, 46% for tight strictures that were difficult to pass, and 92% for easily traversable strictures. Options in the case of nontraversable strictures include limited examination of the proximal tumor margin, dilation and subsequent EUS examination, and the use of miniprobes. Limited examination of the tumor above the stricture has variable accuracy, but may be useful in staging if T3 or N1 disease is seen. Dilation of malignant strictures followed by EUS examination may be associated with an increased incidence of perforation.[32] However, it allows a complete examination in 42% to 95% of patients with high-grade strictures[33-35] and is not associated with perforation if

careful stepwise dilation is performed. Careful dilation followed by EUS allowed Wallace and colleagues[35] to detect advanced disease in 19% of patients, mostly because of the detection of celiac lymph node metastases. This problem may be overcome by the use of miniature ultrasound catheter probes (see Fig. 7–4). Passed through the biopsy channel of the endoscope and advanced through the stricture, these probes accurately determined T classification in 85% to 90% of patients.[36-39] Because most of these data are uncontrolled, it is not clear whether the additional effort and cost provide staging benefits. These 20-MHz probes have limited depth of penetration, which may prevent full ultrasound assessment. Since most nontraversable tumors are at least T3, it is crucial to evaluate the outer boundary of the tumor and adjacent structures and regional lymph nodes, which may be outside the range of the miniprobe.

Conventional EUS does not image the mucosa well; however, EUS is useful in staging patients suspected of having high-grade dysplasia or intramucosal cancer by detecting unexpected submucosal invasion or regional lymph node metastases, or both.[40,41] High-resolution EUS has the ability to assess the mucosa and shows promise in staging superficial esophageal cancer.[42,43]

Determination of N and M (Nonregional Lymph Node) Classifications

In addition to size, EUS evaluates nodal shape, border, and internal echo characteristics in lymph node assessment (Fig. 7–12). Large (>1 cm in long axis), round, hypoechoic, nonhomogeneous, sharply bordered lymph nodes are more likely to be malignant; small, oval or angular, hyperechoic, homogeneous lymph nodes with indistinct borders are more likely to be benign.[44] In a retrospective review of 100 EUS examinations, EUS determination of N classification was 89% sensitive, 75% specific, and 84% accurate.[44] The positive predictive value of EUS for N1 cancer was 86%; the negative predictive value was 79%. A patient was 24 times more likely to have N1 cancer if EUS detected regional lymph nodes. The single most sensitive predictor in detecting N1 cancer was a hypoechoic internal echo pattern, followed by a sharp border, a round shape, and size greater than 1 cm. When all four factors are present, the accuracy of N1 detection is 80% to 100%.[44,45] Unfortunately, all four features are present in only 25% of N1 lymph nodes.[45] In a meta-analysis of 21 series, the overall accuracy of EUS determination of N status was 77%: 69% for N0 and 89% for N1.[24] The ability to use EUS to diagnose nodal metastases varies with the location. It is better in the assessment of celiac lymph nodes (accuracy, 95%; sensitivity, 83%; specificity, 98%; positive predictive value, 91%; negative predictive value, 97%) than in mediastinal lymph nodes (accuracy, 73%; sensitivity, 79%; specificity, 63%; positive predictive value, 79%; and negative predictive value, 63%).[46]

There are associations between the primary tumor and N classification. Close proximity of the regional node to the primary tumor is a predictor of N1 cancer.

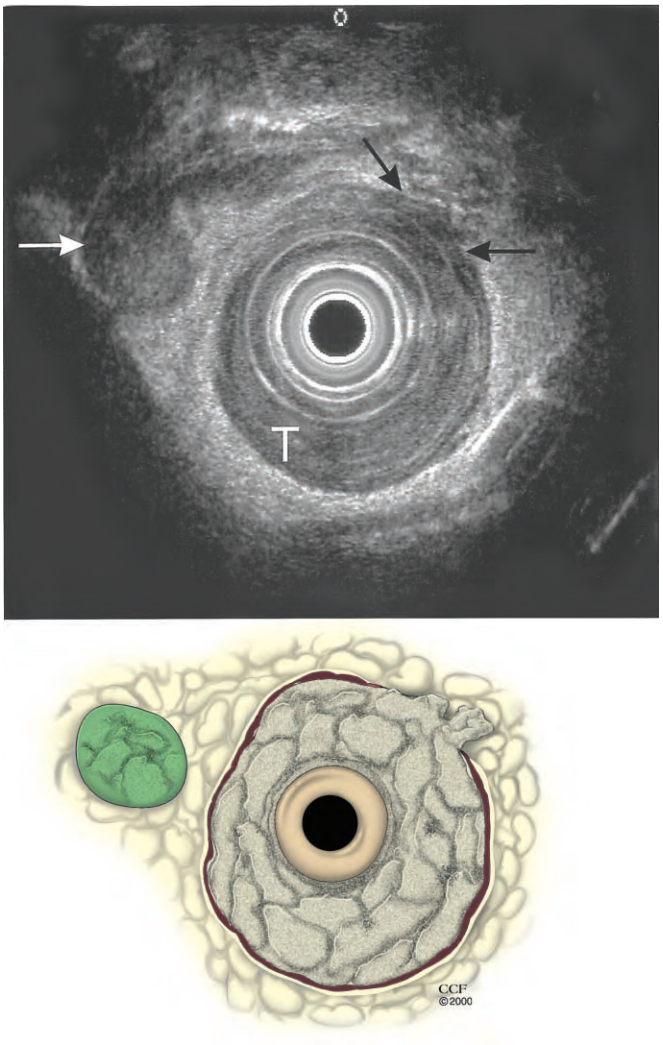


Figure 7–12. T3 N1 esophageal carcinoma. *Upper,* A T3 tumor (T) obliterates the ultrasound anatomy at this level. At 1 o'clock (*black arrows*), the tumor breaks through the fourth ultrasound layer and invades the fifth. An N1 regional lymph node (*white arrow*), close to the primary tumor, is large (2.2 cm in diameter), round, hypoechoic, and sharply demarcated. *Lower,* A T3 N1 tumor breaches the muscularis propria to invade periesophageal tissue and metastasizes to a regional lymph node.

Comparison of the echo characteristic of the tumor and regional lymph nodes is useful for EUS lymph node evaluation. The relationship of T classification to N1 must be considered during EUS examinations. The incidence of N1 cancer increases with deeper tumor invasion: for a patient with poorly differentiated adenocarcinoma, the probability of N1 is 17% for T1 tumors, 55% for T2, 83% for T3, and 88% for T4.[47] For T3 and T4 cancers, an EUS assessment of N0 does not ensure absence of N1 disease.

N classification accuracy and overall survival correlate with the number of lymph node metastases detected by EUS. Natsugoe and colleagues reported an accuracy of

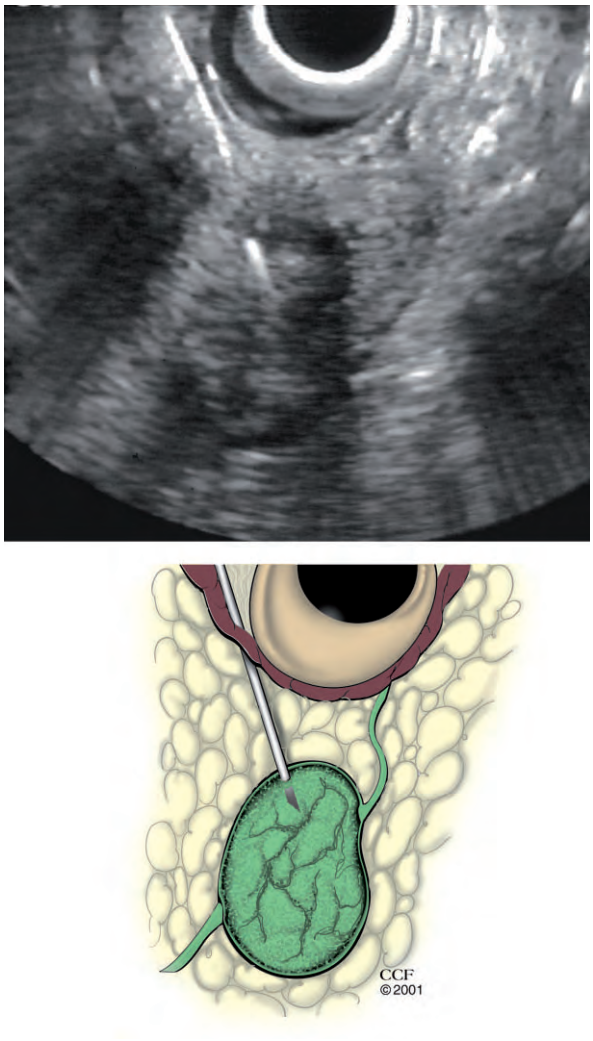


Figure 7–13. Esophageal ultrasound fine-needle aspiration (FNA) of an N1 regional lymph node. *Upper,* Ultrasound image with a needle passed through the esophageal wall and into the N1 node. *Lower,* An N1 regional lymph node undergoing FNA under curvilinear electronic endoscopic examination.

84% with no N1 nodes, 60% with one to three, 43% with four to seven, and 96% with eight or more.[48] Five-year survival rates were 53%, 34%, 17%, and 0% for none, one to three, four to seven, and eight or more N1 lymph nodes, respectively.

Endosonography-directed fine-needle aspiration (EUS FNA) further refines clinical staging by adding tissue sampling to endosonography findings (Fig. 7–13).[49-53] In a multicenter study, 171 patients underwent EUS FNA of 192 lymph nodes.[54] Referent values for EUS FNA in determination of N classification were as follows: sensitivity, 92%; specificity, 93%; positive predictive value, 100%; and negative predictive value, 86%. Accuracy of N classification increased from 69% for EUS alone to 92% for EUS FNA. Two to three passes of the needle were made through each node. There was one nonfatal complication: an esophageal perforation during dilation of an esophageal stricture before EUS FNA. Subsequent studies from Vazquez-Sequeiros and colleagues have confirmed and extended these findings.[52,53] In the most recent report, the first prospective, blinded study, EUS FNA was more accurate than EUS (87% versus 74%, respectively) as determined by histopathologic review of surgical specimens.[53] When compared with CT, EUS FNA changed the tumor stage in 38% of patients. Complications are extremely rare.[55] Unfortunately, some lymph nodes cannot be aspirated because of proximity to the primary tumor. Only nodes in which the needle path avoids the primary tumor are appropriate for EUS FNA because false-positive results might otherwise be obtained.

The combination of EUS and EUS FNA of celiac lymph nodes (M1a classification), deemed positive by EUS, had a sensitivity of 77%, specificity of 85%, positive predictive value of 89%, and negative predictive value of 71%.[56] EUS FNA confirmed a positive M1a classification in 94% of patients and was 98% accurate. EUS detection of M1a disease in the celiac axis and the avoidance of unnecessary surgery make EUS FNA the least costly staging strategy in patients with non-M1b esophageal cancer.[57]

For preoperative EUS examinations, N classification best predicts patient survival.[58] It is a superior predictor of patient survival than EUS determination of T and M1a classification. The use of EUS FNA is associated with improved recurrence-free and overall survival.[59] Therefore, careful EUS N classification with aggressive EUS FNA lymph node sampling is mandatory and critical to treatment planning and prognostication.

Determination of Non-nodal M1b Classification

EUS has limited value in screening for distant metastases (M1b). The distant organ must be in direct contact with the upper gastrointestinal tract for EUS to be useful. The left lateral segment of the liver and retroperitoneum are two such sites (Fig. 7–14).

Re-treatment Stage (yTNM)

After induction therapy, a subset of patients with esophageal cancer will be disease-free. Because significant morbidity and mortality are associated with surgery for esophageal cancer, the ability to detect patients who have no residual cancer (T0 N0) after induction therapy is theoretically desirable. Esophageal ultrasonography has been used in multiple clinical series for this purpose. Early series indicated that EUS was very accurate in determining T classification after chemotherapy. In these series, however, the presurgical therapy was largely ineffective in causing pathologic down-staging; therefore, EUS was accurate by merely indicating that no significant change had occurred.[60-62] In two series in which radiation therapy was provided along with chemotherapy, the accuracy of determination of T classification was again high (72% to 78%), but the prevalence of pathologic T0 disease was low or not

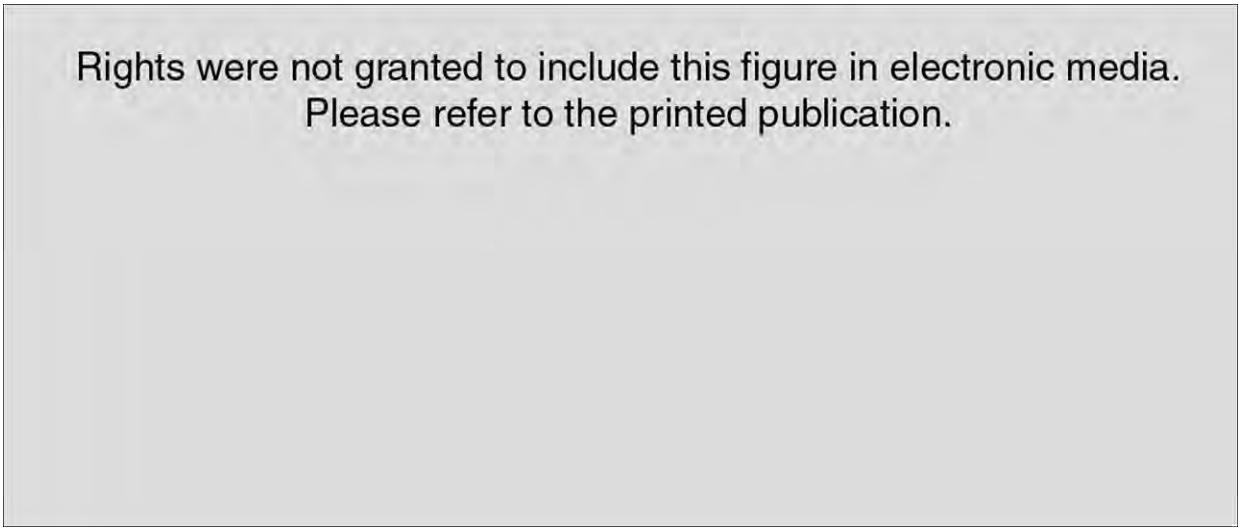


Figure 7–14. **A,** Hepatic metastasis (*upper arrow*) in the left lateral segment of the liver. A perigastric lymph node metastasis is shown (*lower arrow*). The esophageal ultrasound probe is seen in the gastric cardia. **B,** Hepatic metastasis (*upper arrow*) as seen from the gastric cardia by esophageal ultrasound. The metastasis was imaged only by esophageal ultrasound. A perigastric lymph node metastasis is shown (*lower arrow*). (From Rice TW, Boyce GA, Sivak MV, et al: Esophageal carcinoma: Esophageal ultrasound assessment of preoperative chemotherapy. Ann Thorac Surg 53:972, 1992.)

reported.[63,64] Accuracy of T classification can therefore be attributed primarily to a lack of tumor response to chemoradiotherapy.

Later series incorporate more aggressive regimens of chemoradiotherapy, with higher rates of significant down-staging of tumor and pathologic T0 N0 M0 cancer. In these series, up to 31% of patients had pathologic T0 N0 M0 stage grouping after chemoradiotherapy.[65] EUS was poor in accurately determining T classification, with reported rates of 27% to 47%.[65-69] The most common mistake made in determining T classification was overstaging because EUS is unable to distinguish tumor from inflammation and fibrosis produced by chemoradiotherapy. Similar difficulties in this differentiation have also been reported with EUS staging of rectal cancer.[70]

EUS accuracy for N classification after chemoradiotherapy has been reported in only four clinical series. The reported accuracy ranged from 49% to 71%.[65,67-69] The accuracy of N classification in patients who undergo chemoradiotherapy is lower than in patients not treated with chemoradiotherapy. Primary reasons for this inaccuracy are alterations in the ultrasound appearance of nodes after chemoradiotherapy such that established EUS criteria do not apply and residual foci of cancer within the nodes that are too small for detection by any modality other than pathologic analysis.

Change in maximal cross-sectional area before and after chemoradiotherapy appears to be a more useful means of assessing the response of esophageal cancer to preoperative therapy.[66,71] Chak and colleagues defined a response as a 50% or greater reduction in tumor area. Improved survival was reported in responders and responder subgroups who had surgery after chemoradiotherapy, adenocarcinoma, and T3 N1 M0 cancer before treatment.[71] Identification of persistent tumor in lymph nodes by EUS FNA has been used to modify the treatment of patients receiving preoperative chemoradiotherapy.[72]

EUS has been useful in the diagnosis and restaging of patients with anastomotic recurrence that is not endoscopically visible.[73,74]

BENIGN ESOPHAGEAL DISEASES

Benign Esophageal Tumors

Detailed EUS examination of the esophageal wall has improved the diagnosis of benign esophageal tumors. EUS identification of intramural masses relies on both the layer from which the tumor arises (Table 7–1) and the ultrasound characteristics of the tumor. Homogeneous lesions that are anechoic, of intermediate echogenicity, or hyperechoic are almost exclusively benign.[75] A heterogeneous echo pattern may be seen in benign tumors, but this endosonographic finding, particularly in lesions greater than 3 cm to 4 cm in largest diameter, may be indicative of malignancy.

Tumors of the Mucosa

Fibrovascular polyps are collections of fibrous, vascular, and adipose tissue lined by normal squamous epithelium. Microscopically, fibrovascular polyps are expansions of the lamina propria.[76] These polyps usually arise in the cervical esophagus, extend into the esophageal lumen, and may reach into the stomach. Most patients eventually complain of dysphagia or respiratory symptoms, or both. Spectacular manifestations include regurgitation into the hypopharynx and mouth with subsequent aspiration and, occasionally, sudden death by

Table 7–1 Endoscopic Ultrasonographic Classification of Benign Esophageal Tumors

EUS Layer	Esophageal Tumor
First/second (mucosa/deep mucosa)	Fibrovascular polyp
	Granular cell tumor
	Retention cyst
	Leiomyoma*
Third (submucosa)	Lipoma
	Fibroma
	Neurofibroma
	Granular cell tumor
Fourth (muscularis propria)	Leiomyoma*
	Cysts
Fifth	Cysts

*Leiomyomas may arise from the second or fourth ultrasound layer.

asphyxiation. Barium esophagography and CT best detect these lesions. Because fibrovascular polyps fill the esophageal lumen and have a composition similar to the mucosa, definition by esophagoscopy or EUS may be difficult or impossible.[77]

Granular cell tumors are the third most common benign esophageal tumor, and the esophagus is the most common gastrointestinal site of these tumors. Most are located in the distal end of the esophagus. Their origin is neural from the Schwann cell. Most patients with granular cell tumors are asymptomatic and rarely require surgery. At endoscopy, these lesions are yellow, firm nodules. Endoscopic biopsy is diagnostic in only 50% of patients.[78] EUS evaluation typically demonstrates a tumor less than 2 cm in diameter that has an intermediate or hypoechoic, mildly inhomogeneous solid pattern with smooth borders and rising from the inner two EUS layers.[78,79] Less than 5% originate from the submucosa. Malignant variants are rare and distinguished by size (>4 cm), nuclear pleomorphism, and mitotic activity.[80] Atypical EUS findings may predict the rare malignant granular cell tumors.

Tumors of the Submucosa

Esophageal stromal tumors are rare and include lipomas, fibromas, and hemangiomas. Lipomas are indirectly detected at esophagoscopy as a bulging of the overlying esophageal mucosa. They have a pale yellow appearance and soft texture when probed with an esophagoscope. Endoscopic biopsy usually produces normal overlying squamous epithelium because these samplings rarely penetrate the submucosa. EUS demonstrates a hyperechoic homogeneous lesion that originates in and is confined to the submucosal layer. Generally asymptomatic and most often found incidentally, lipomas require no EUS follow-up. Fibromas and neurofibromas are very uncommon. At endoscopy, they are firm "to the touch." These lesions are less hyperechoic than lipomas. Symptomatic submucosal tumors are uncommon and the symptoms may be unrelated. These tumors are typically incidental findings of a "shotgun" investigation of atypical symptoms such as chest pain and cough. EUS is critical in diagnosis and, thus, in avoiding excision.

Hemangiomas may present with dysphagia and bleeding. Most hemangiomas are in the lower part of the esophagus and may be mistaken for esophageal varices. EUS examination reveals a hypoechoic mass with sharp margins arising from the second or third EUS layer.[81,82]

Tumors of the Muscularis Propria

Leiomyomas are benign smooth muscle tumors of the muscularis propria. Symptomatic tumors arising from the muscularis mucosa are rare, with the majority arising from the inner circular muscle layer in the distal and midthoracic esophagus.[83] EUS examinations reveal that the majority of esophageal leiomyomas are greater than 1 cm in diameter and are most frequently found in the muscularis mucosae.[84] Leiomyomas are the most common benign esophageal tumors and account for more than 70% of all benign tumors. There is no gender preponderance, and they typically occur in patients 20- to 50- years old, significantly younger than patients with esophageal carcinoma. Though frequently asymptomatic and discovered incidentally, leiomyomas can cause dysphagia, pain, or bleeding. Distal esophageal leiomyomas are often associated with symptoms of gastroesophageal reflux disease. Barium esophagography demonstrates smooth filling defects; esophagoscopy reveals a normal overlying mucosa. EUS displays a hypoechoic, sharply bordered tumor arising in the fourth ultrasound layer (Fig. 7–15). The diagnosis of small leiomyomas (<1 cm in diameter) may be enhanced with the use of miniature ultrasound probes.[84] Atypical EUS findings are a tumor larger than 4 cm, irregular margins, mixed internal echo characteristics, and associated regional lymphadenopathy. Endoscopic biopsies do not reach the muscularis propria. EUS FNA is unlikely to provide the cellular architectural characteristics necessary to differentiate leiomyomas from leiomyosarcomas, which are exceedingly rare. Malignant transformation of benign leiomyomas has been infrequently reported. Surgical resection, by minimally invasive techniques if possible, is indicated for symptomatic leiomyomas. In asymptomatic tumors with typical EUS features, expectant therapy plus EUS observation is indicated.

Miscellaneous Esophageal Diseases

Esophageal Cysts

Esophageal cysts, the second most common benign esophageal tumor, account for 20% of these lesions. The minority are acquired epithelial cysts arising in the lamina propria. Submucosal glandular inflammation is the suspected cause. The majority of esophageal cysts are congenital foregut cysts. They are lined with squamous,

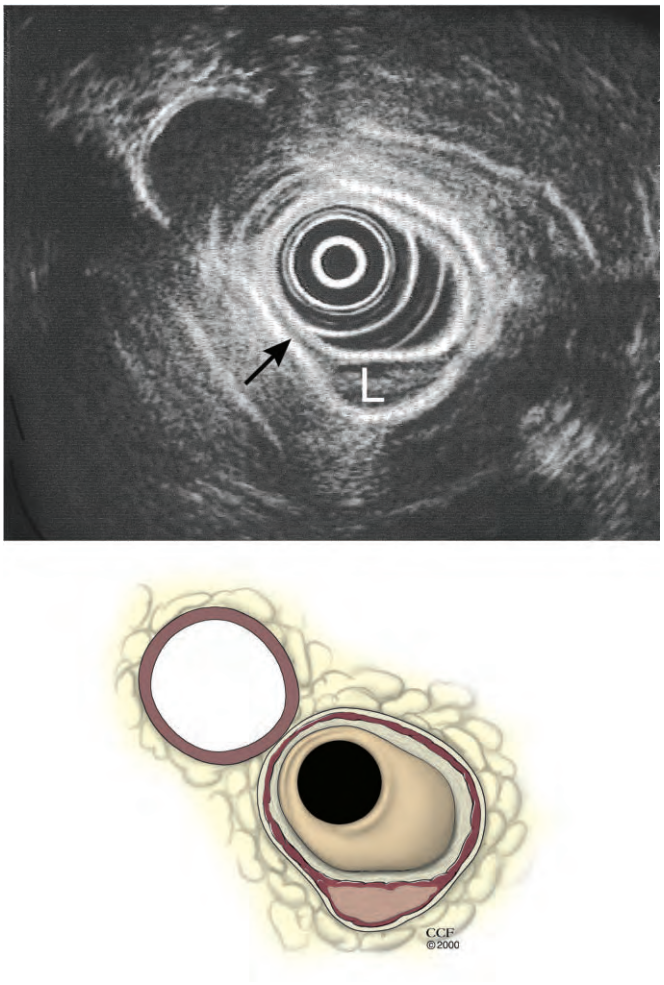


Figure 7–15. Esophageal leiomyoma. *Upper,* Endoscopic ultrasonography (EUS) of this most common benign tumor demonstrates a hypoechoic, homogeneous, well-demarcated tumor with no associated lymphadenopathy. EUS balloon overdistention blends the first three ultrasound layers into one hyperechoic layer. The tumor arises from and is confined to the fourth ultrasound layer (*arrow*). *Lower,* A benign leiomyoma arises from and is confined to the muscularis propria.

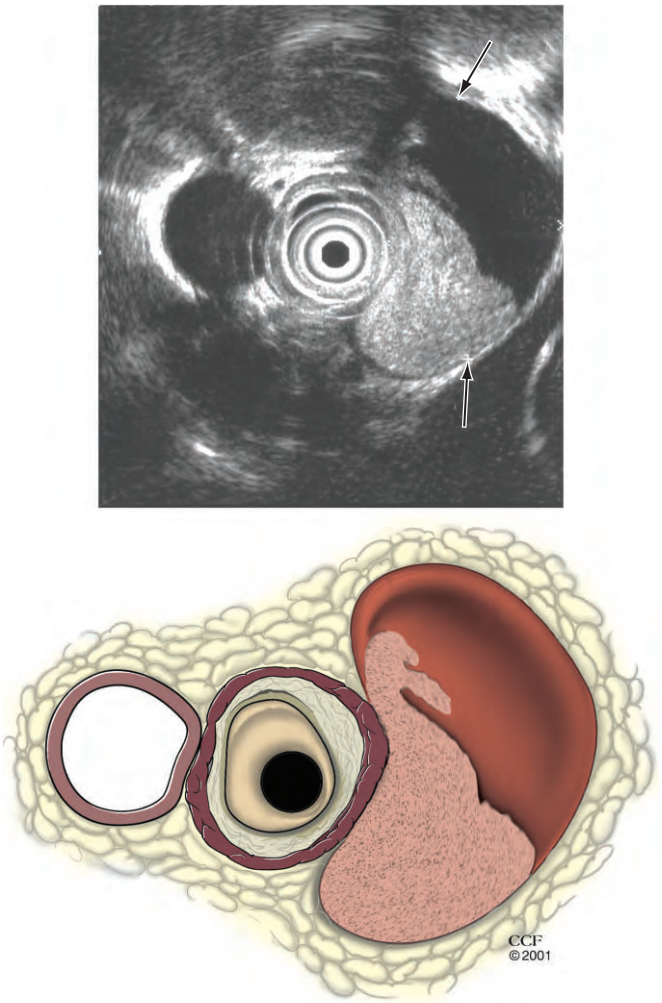


Figure 7–16. Foregut cyst. *Upper,* Endoscopic ultrasound demonstrates a mass (*arrows*) adjacent to the trachea and esophagus. The cyst has two components, one hyperechoic (white), representing proteinaceous material, and one hypoechoic (black), representing fluid. *Lower,* A foregut cyst in close proximity to the esophagus and trachea.

respiratory, or columnar epithelium and may contain smooth muscle, cartilage, or fat. Esophageal duplication is a subtype of foregut cyst; it is lined with squamous epithelium and its submucosal and muscularis elements interdigitate with the muscularis propria of the esophagus. EUS can clearly define the intramural or extraesophageal nature of these tumors and further determine their anechoic, cystic nature (Fig. 7–16).[85-88] Transesophageal EUS drainage of a foregut cyst has been reported, but drainage of the cyst without destruction of its lining may result in recurrence.[89]

Esophageal Varices

Esophageal varices have the typical appearance of blood vessels at EUS. Appearing as tubular, round, or serpiginous echo-free structures, they may be visualized within the submucosa or in tissues adjacent to the esophagus (Fig. 7–17). These EUS patterns change after sclerosis.[90] Intravariceal sclerosis fills the varix with echogenic material representing thrombus. Paravariceal injection leads to obliteration of the varix with hypoechoic extravariceal thickening.

Achalasia

EUS findings in achalasia are controversial. Some authors have reported thickened esophageal wall in most patients examined.[91,92] This excessive thickening, however, may be artifactual. In a dilated and convoluted esophagus, the ultrasound transducer may orient at an angle oblique to the esophageal wall and give a false

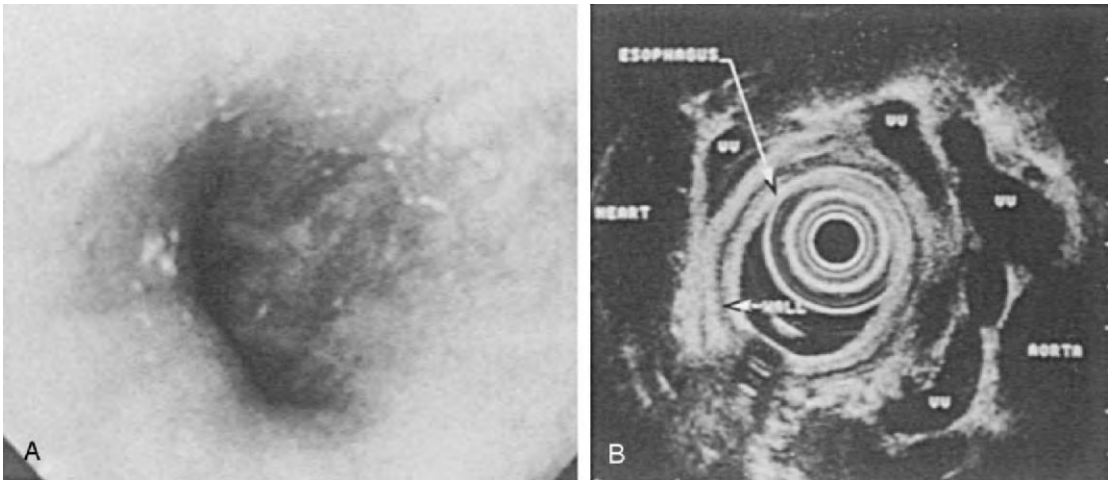


Figure 7–17. Paraesophageal varices. **A,** At endoscopy, small varices are not visible. **B,** On esophageal ultrasound, the varices (VV) are prominent anechoic, tubular, and rounded structures outside the esophageal wall.

appearance of wall thickening.[93] The main role of EUS in achalasia is to exclude other mural abnormalities.[94-96]

PARAESOPHAGEAL DISEASES

EUS has been used to examine the mediastinal lymph nodes in patients with bronchogenic carcinoma.[97-99] In this setting, EUS has a reported positive predictive value of 77%, a negative predictive value of 93%, and an overall accuracy of 92% when using criteria similar to regional lymph node evaluation in esophageal carcinoma.[98] Anatomic constraints limit its usefulness for evaluation of lymph nodes in proximity to the airway. EUS FNA provides cytologic differentiation between benign and malignant lymphadenopathy[100] and has successfully diagnosed solid lesions of the mediastinum and lung.[75,101-103]

CONCLUSIONS

EUS and EUS FNA are essential in determining the clinical stage and directing treatment of esophageal cancer. The diagnosis of benign esophageal tumors requires EUS examination, which determines both the layer of origin in the esophageal wall and the ultrasound characteristics of the tumor. Because many of these tumors are asymptomatic, EUS affords simple follow-up and avoids unnecessary excision. EUS is a useful adjuvant for the diagnosis and treatment of paraesophageal disease.

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Chapter

8

Esophageal Motility

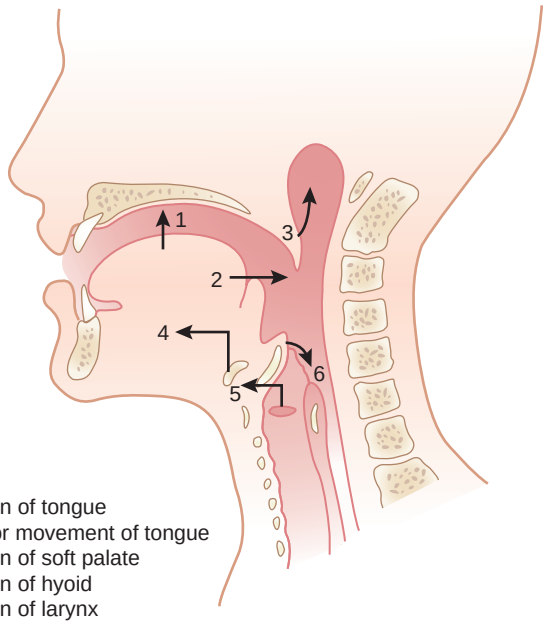
Rodney John Mason

The major function of the esophagus is to transport food from the mouth to the stomach. Secondary functions are to keep the esophagus empty, prevent regurgitation of gastric contents into the esophagus and trachea, and vent the stomach of excessive swallowed air. Functional disorders of the esophagus often give rise to symptoms before the development of injury recognizable by structural, histologic, or biochemical changes. They can exist for a period without causing morphologic changes while causing considerable symptoms. The symptoms typically associated with esophageal motility disorders are nonspecific and include dysphagia, regurgitation, and chest pain, which may be manifested as either a pressure-like sensation or retrosternal burning. Ascribing these symptoms to a specific esophageal abnormality in the absence of structural or histologic findings and without further investigation can lead to an error in diagnosis because a variety of gastric, duodenal, cardiac, and pulmonary disorders can cause symptomatology similar to esophageal abnormalities, thus making it difficult to differentiate and discriminate them from the latter. Furthermore, esophageal motility disorders can cause atypical symptoms, such as chest pain, chronic cough, or shortness of breath, that lead the investigator to suspect abnormalities of the heart or lung. Complicating matters even more, functional esophageal motility disorders can also occur concomitantly with gastroduodenal, cardiac, and pulmonary disease. Consequently, objective methods are required to confirm the presence of an esophageal motor abnormality and distinguish it from other conditions. Correct diagnosis of the abnormality and identification of the underlying cause are essential for the selection of appropriate therapy and to avoid failure or recurrence. This requires a sound understanding of normal esophageal physiology and the functional abnormalities that may result in tissue injury if allowed to persist.[1]

Esophageal motility disorders consist of a number of specifically identifiable disorders and a number of poorly characterized conditions that show a spectrum of esophageal motor abnormalities. The two best-characterized motility disorders, achalasia and diffuse esophageal spasm, represent only a small percentage of diagnosed motility disorders. The incidence of achalasia is 1 case per 100,000 population per year. As with any other chronic illness, prevalence exceeds incidence significantly. Familial clustering is observed, but a genetic relationship has not been established. Nutcracker esophagus is the most common motility disorder, but it is the most controversial in significance.

PHYSIOLOGIC ASPECTS OF ESOPHAGEAL MOTILITY

The esophagus is a muscular tube that traverses the neck and two body cavities—the chest and abdomen. The two body cavities have different pressure profiles, which is important for understanding esophageal motility. The intrapleural space that surrounds the esophagus in the chest cavity has a pressure that is essentially below atmospheric pressure during most of the respiratory cycle, whereas the distal esophagus in the abdominal cavity has a surrounding pressure that is always above atmospheric pressure. Striated muscle is found in the upper two thirds of the esophagus and nonstriated muscle is found in the lower third. In the upper quarter both layers are striated. In the second quarter of the esophagus, bundles of nonstriated muscle appear first on the internal aspect of the muscle and gradually replace the striated muscle more caudally. The act of alimentation requires the passage of food and drink from the mouth into the stomach. One third of this distance consists of the mouth and hypopharynx, and two thirds consist of the esophagus. To comprehend the mechanics of alimentation, it is useful to visualize the gullet as a mechanical model in which the tongue and pharynx function as a piston pump with three valves and the body of the esophagus and cardia function as a worm drive pump with a single valve. The three valves in the pharyngeal cylinder are the soft pallet, the epiglottis, and the cricopharyngeus. The valve of the esophageal pump is the lower esophageal sphincter (LES). Failure of the valves or the pumps leads to motility abnormalities manifested as difficulty in the



1. Elevation of tongue
2. Posterior movement of tongue
3. Elevation of soft palate
4. Elevation of hyoid
5. Elevation of larynx
6. Tilting of epiglottis

Figure 8–1. Sequence of events during the oropharyngeal phase of swallowing.

propulsion of food from the mouth to the stomach or regurgitation of gastric contents from the stomach into the pharynx.

Upper Esophageal Sphincter

The first phase of swallowing is the oral phase. Food is taken into the mouth in a variety of bite sizes, where it is broken up, mixed with saliva, and lubricated. When food is ready for swallowing, the tongue, acting like a piston, moves the bolus into the posterior oropharynx and forces it into the hypopharynx (Fig. 8–1). This marks the pharyngeal phase, and swallowing then passes out of conscious control and is entirely a reflex. Concomitant with posterior movement of the tongue, the soft palate is elevated, thereby closing the passage between the oropharynx and nasopharynx. This partitioning prevents pressure generated in the oropharynx from being dissipated through the nose. When the soft palate is paralyzed, as occurs after a cerebrovascular accident, food is commonly regurgitated into the nasopharynx. During swallowing, the hyoid bone moves upward and anteriorly to elevate the larynx and open the retrolaryngeal space. This action brings the epiglottis under the tongue (see Fig. 8–1). The backward tilt of the epiglottis covers the opening of the larynx to prevent aspiration. The entire pharyngeal portion of swallowing occurs within 1.5 seconds.

The pressure in the hypopharynx rises abruptly during swallowing to reach at least 60 mm Hg. A sizable pressure difference develops between the pharyngeal pressure and the less than atmospheric midesophageal or intrathoracic pressure (Fig. 8–2). This pressure gradient speeds the movement of food from the hypopharynx into the esophagus when the cricopharyngeus or upper esophageal sphincter (UES) relaxes and opens and the cervical esophagus is appropriately compliant. The bolus is propelled through the open sphincter by the piston-like action of the tongue and the peristaltic contractions of the posterior laryngeal constrictors and is sucked into the thoracic esophagus by the pressure differential. Compliance of the striated muscle of the cervical esophagus is crucial for this phase of swallowing, and loss of compliance results in severe dysphagia. The UES closes within an additional 0.5 second, with the immediate closing pressure reaching approximately twice the resting level of 30 mm Hg. This postrelaxation contraction continues down the esophagus as a peristaltic wave (Fig. 8–3). The high closing pressure and initiation of the peristaltic wave prevent regurgitation of the bolus from the esophagus back into the pharynx. After the peristaltic wave has passed farther down the esophagus, the pressure in the UES returns to its resting level (see Fig. 8–3).

Swallowing can be started at will, or it can be reflexively elicited by stimulation of areas in the mouth and pharynx, including the anterior and posterior tonsillar pillars and the posterior lateral walls of the hypopharynx. The afferent nerves of the pharynx are the glossopharyngeal nerve and the superior laryngeal branches of the vagus. Once aroused by stimuli entering via these nerves, the swallowing center in the medulla coordinates the complete act of swallowing by discharging impulses through the 5th, 7th, 10th, 11th, and 12th cranial nerves, as well as the motor neurons of C1 to C3. Discharges through these nerves occur in a rather specific pattern and last for approximately 0.5 second. Little is known about the organization of the swallowing center except that it can trigger swallowing after a variety of different inputs, but the response is always a rigidly ordered pattern of outflow. After a cerebrovascular accident, this coordinated outflow may be altered and result in mild abnormalities of swallowing. In more severe injury, swallowing can be grossly disrupted and lead to repetitive aspiration.

The striated muscles of the cricopharyngeus and the upper third of the esophagus are activated by efferent fibers distributed through the vagus nerve and its recurrent laryngeal branches. Integrity of innervation is required for the cricopharyngeus to relax in coordination with the laryngohyoid elevation and pharyngeal contraction and resume its resting tone once a bolus has entered the upper part of the esophagus. Concomitantly, the striated muscle of the cervical esophagus must have the compliance to dilate and accept the swallowed bolus. Central nervous system damage from a variety of causes can interfere with innervation of the larynx, cricopharyngeus, and upper esophagus. The resulting loss of muscle function and compliance can predispose the patient to aspiration or dysphagia.

Esophageal Body

The pharyngeal activity in swallowing initiates the esophageal phase. Because of the helical arrangement of its circular muscles, the body of the esophagus functions

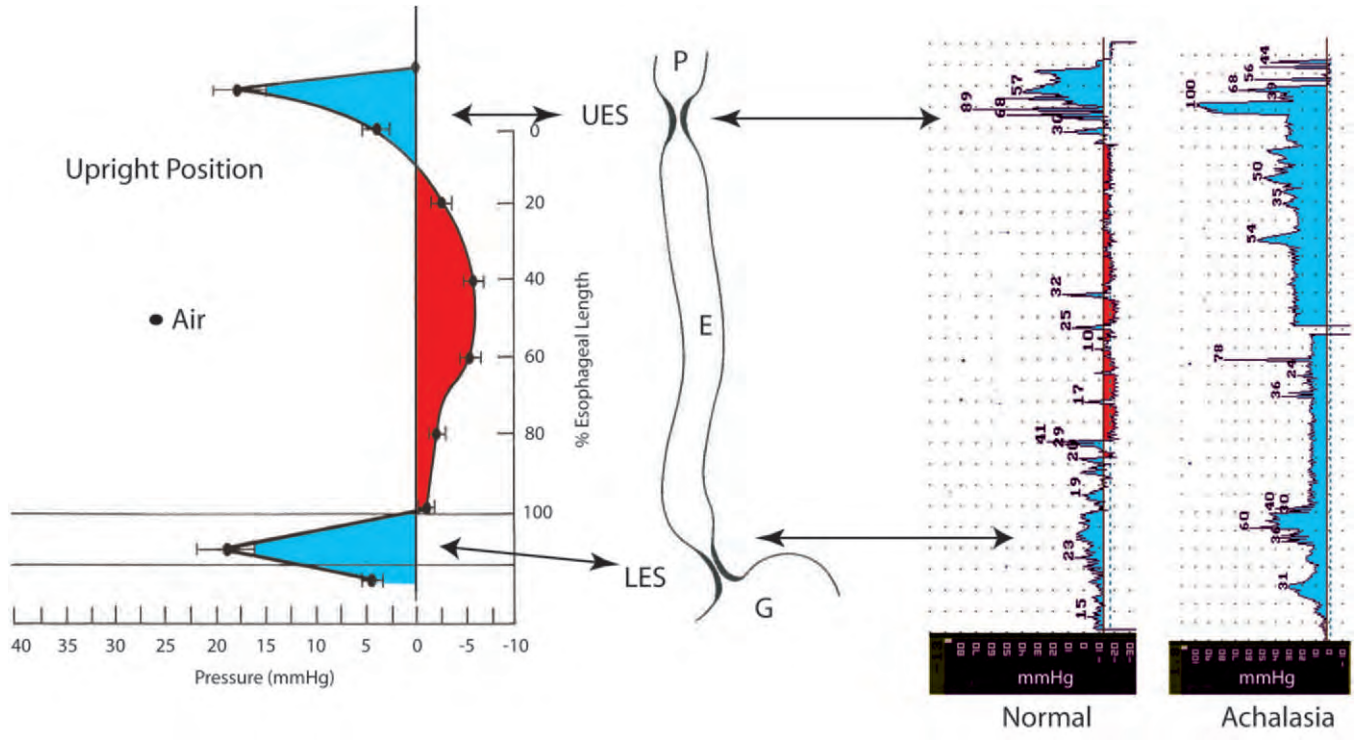


Figure 8–2. Resting pressure profile of the foregut showing the pressure differential between the atmospheric pharyngeal pressure (P), the less than atmospheric midesophageal pressure (E), and the greater than atmospheric intragastric pressure (G), with the interposed high-pressure zones of the upper esophageal sphincter (UES) and lower esophageal sphincter (LES). The necessity for coordinated relaxation of the UES and LES to move a bolus into the stomach is apparent. Esophageal work occurs when a bolus is pushed across the pressure gradient from the midesophageal area (E) into the stomach (G). A sample of a normal resting pressure profile is compared with the resting profile of a patient with achalasia. The patient with achalasia has a resting baseline pressure that is substantially above atmospheric pressure, a pattern of esophageal pressurization commonly seen in such patients.

as a worm drive propulsive pump and is responsible for transmitting a bolus of food from the distal end of the esophagus into the stomach. The esophageal phase of swallowing represents esophageal work performed during alimentation in that food is moved into the stomach from an intrathoracic pressure of −6 mm Hg to an average intra-abdominal pressure of +6 mm Hg, that is, a gradient of 12 mm Hg (see Fig. 8–2). Effective and coordinated smooth muscle function in the lower third of the esophagus is therefore important in pumping food into the stomach.

The act of pumping is termed peristalsis, which denotes a progressive sequential aboral contraction that traverses the entire esophagus. During this process the longitudinal muscle contracts and shortens, thereby providing a base for segmental contraction of the rings of the circular muscular fibers.[2] The circular muscle contractions can take the form of primary or secondary peristalsis or nonperistaltic tertiary contractions. Contraction of the striated esophageal muscle is dependent on sequential activation of neurons situated in the nucleus ambiguus. Peristalsis in the nonstriated muscle is mediated at the level of the dorsomotor nucleus of the vagus nerve at the level of the myenteric plexus.

Primary peristalsis is a biphasic response consisting of a wave of initial inhibition of the circular smooth muscle, followed by a wave of contraction.[3,4] Electrical stimulation, or the "on response," causes the circular muscle to relax. When the stimulus is removed (the off response), the muscle contracts. The latency of contraction is variable. The distal end of the esophagus shows greater inhibitory innervation than the proximal end does.[5] The shorter latency period in the proximal esophagus in conjunction with the longer latency in the distal esophagus results in the so-called latency gradient, which is thought to result in peristalsis down the esophagus (Fig. 8–4). The latency gradient appears to be mediated by nitric oxide. Blockage of nitric oxide reduces the latency between the onset of swallowing and esophageal contractions while increasing the velocity of the onset of propagation and thus converts a peristaltic contraction into a simultaneous contraction. The proximal esophagus is under greater cholinergic control than the distal esophagus, and an increase in cholinergic stimulation will delay the latency of contraction in the proximal esophagus and thereby result in the loss of peristalsis.[6] Longitudinal muscle contracts with stimulation and sustains contraction until the stimulus is removed.

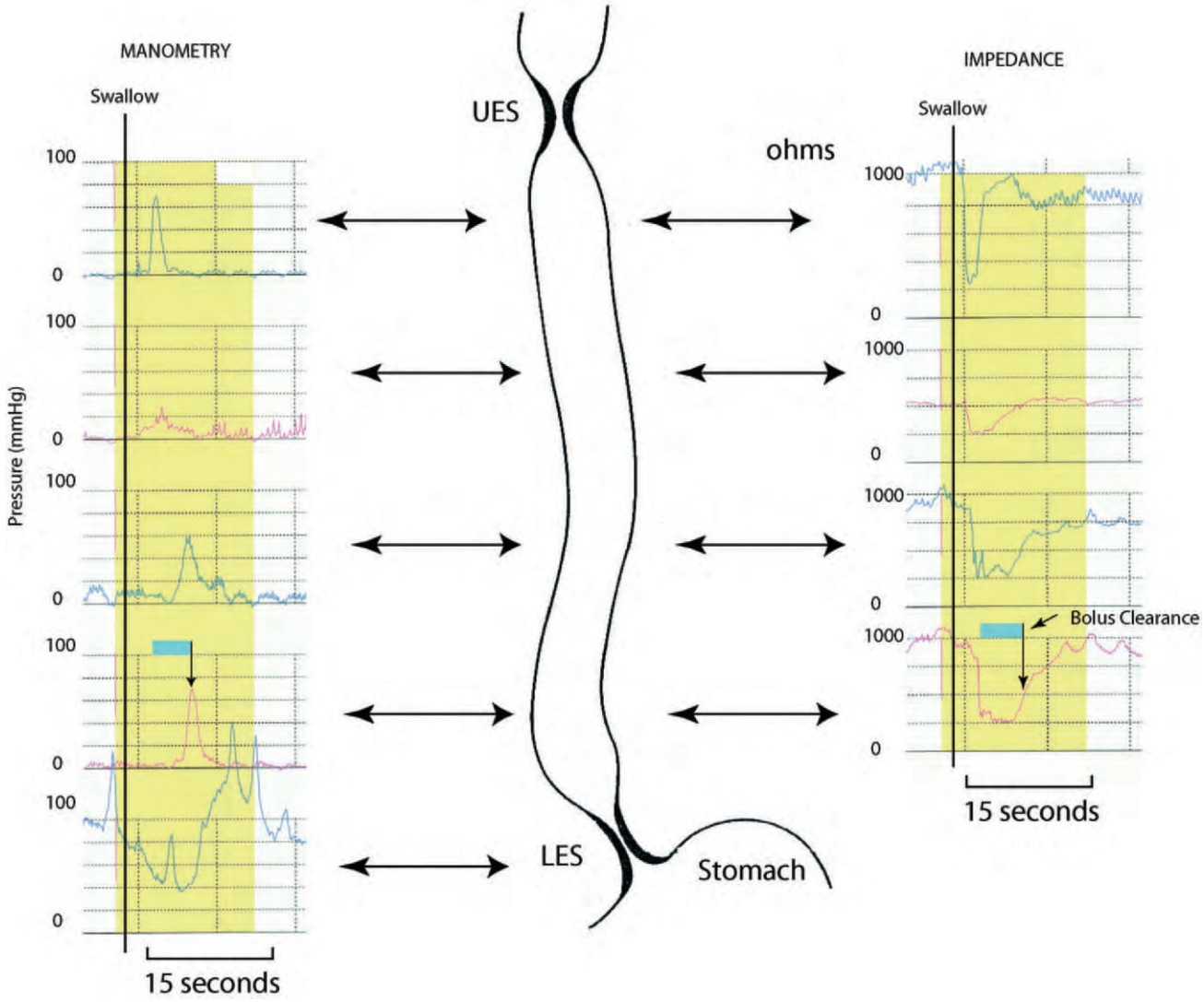


Figure 8–3. Combined intraluminal esophageal impedance and esophageal pressure in response to swallowing. An example of bolus transport is shown in channel 4. The duration of flow is depicted by the blue rectangle. The tail of the bolus corresponds to the maximum upstroke in the peristaltic contraction wave on the manometry tracing. The bolus clearance is antegrade and complete, and the manometry pressure wave is peristaltic. LES, lower esophageal sphincter; UES, upper esophageal sphincter.

The contraction wave appears manometrically as a bell-shaped curve and is seen to form when the circular muscle contracts around the pressure transducer on the manometry catheter. The peristaltic wave generates an occlusive pressure varying from 30 to 150 mm Hg (see Fig. 8–3). The wave rises to a peak in 1 second, lasts at the peak for about 0.5 second, and then subsides in about 1.5 seconds. The entire course of the rise and fall in occlusive pressure may occupy one point in the esophagus for 3 to 5 seconds. A small plateau is often seen before the sharp upstroke of the bell-shaped curve and represents the pressure within the swallowed bolus. The pressure is usually highest in the tail of the bolus. The peak of a primary peristaltic contraction initiated by a swallow moves down the esophagus at 2 to 4 cm/sec and reaches the distal esophagus about 9 seconds after swallowing has been initiated (see Fig. 8–3). Consecutive swallows produce similar primary peristaltic waves, but when the act of swallowing is repeated rapidly, the amplitudes of the second and subsequent swallow fall within the refractory period of the first swallow and result in an esophagus that remains relaxed and refractory. The peristaltic wave occurs only after the last movement of the pharynx and forms the basis for the practice of spacing swallows at least 30 seconds apart.[7] This phenomenon is referred to as postdeglutitive inhibition.

Progress of the wave down the esophagus is caused by sequential activation of its muscles initiated by efferent vagal nerve fibers that arise in the swallowing center. Continuity of the esophageal muscle is not necessary if the nerves remain intact. If the muscles but not the nerves are cut, the pressure wave begins distally below

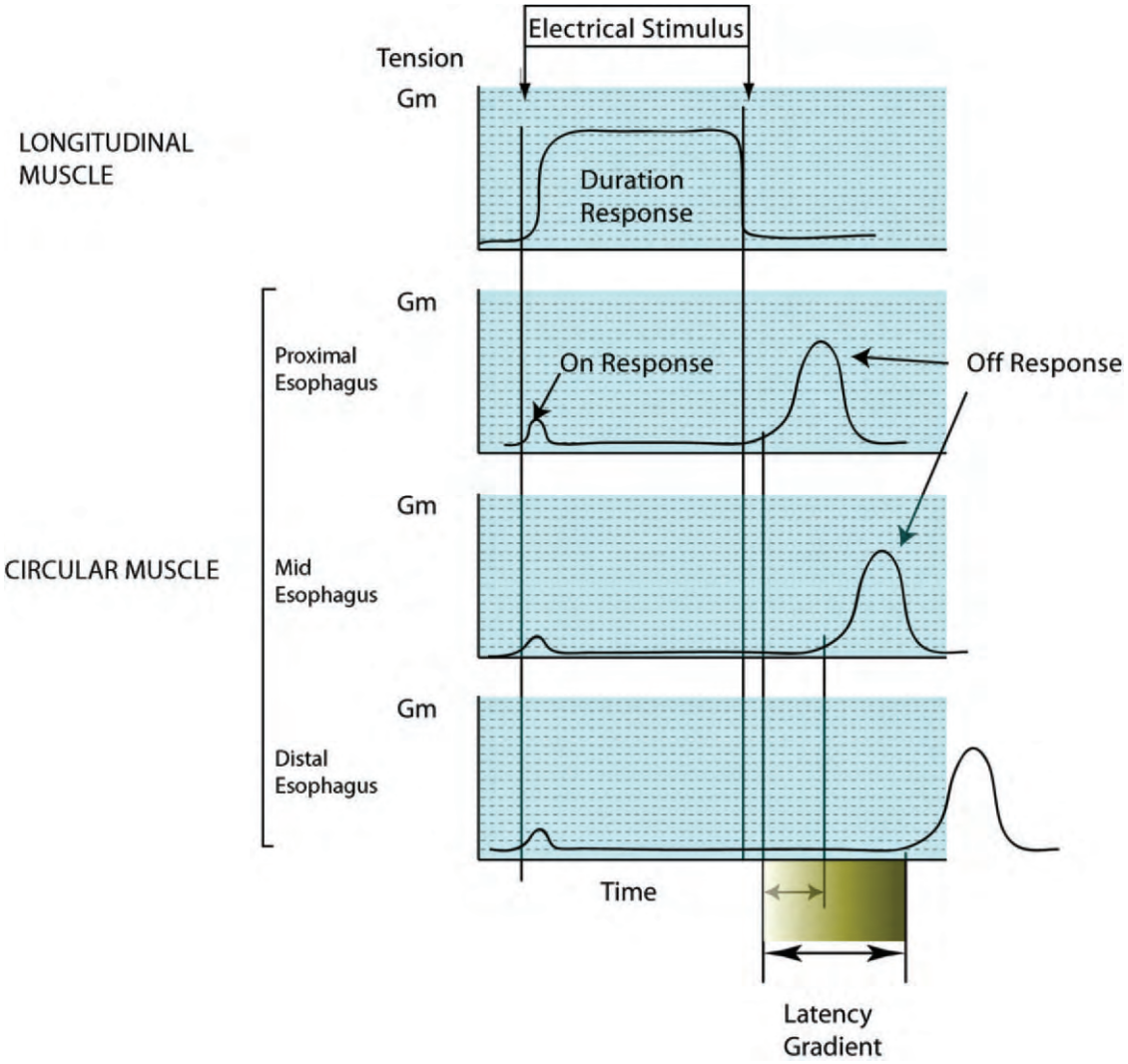


Figure 8–4. In vivo longitudinal and circular muscle contraction responses in the opossum after electrical stimulation. Longitudinal muscle shows a contraction response that is maintained throughout the duration of the stimulus (Duration Response). Circular muscle shows an initial brief contraction at the initiation of the stimulus (On Response), followed by a period of inhibition that is maintained throughout the duration of the stimulus. Once the stimulus is removed, there is a much greater contraction response (Off Response). The duration of inhibition increases while moving distally down the esophagus, the so-called latency gradient. This gradient results in propagation of a peristaltic contraction wave down the esophagus. Gm, contraction force in grams.

the cut because it dies out at the proximal end above the cut. This allows a sleeve resection of the esophagus to be performed without destroying its normal function. Afferent impulses from receptors within the esophageal wall are not essential for progress of the coordinated wave. However, afferent nerves do go to the swallowing center from the esophagus. If the esophagus is distended at any point, a contractual wave begins with forceful closure of the UES and sweeps down the esophagus. This secondary contraction occurs without any movement of the mouth or pharynx. Secondary contractions can occur as an independent local reflex to clear the esophagus of material left behind after passage of the primary wave, but they are less common than previously thought.

Despite the rather powerful occlusive pressure, the propulsive force of the esophagus is relatively feeble. If one attempts to swallow a bolus attached by a string to a counterweight, the maximum weight that one can overcome is 5 to 10 g. Orderly contractions of the muscular wall and anchoring of the esophagus at its inferior end are necessary for efficient and aboral propulsion to occur. Loss of the inferior anchor, as occurs with a large hiatal hernia, can lead to inefficient propulsion.

Lower Esophageal High-Pressure Zone

The esophagus passes through the right crus of the diaphragm at about the level of the 10th thoracic vertebra. The fascia on the inferior surface of the

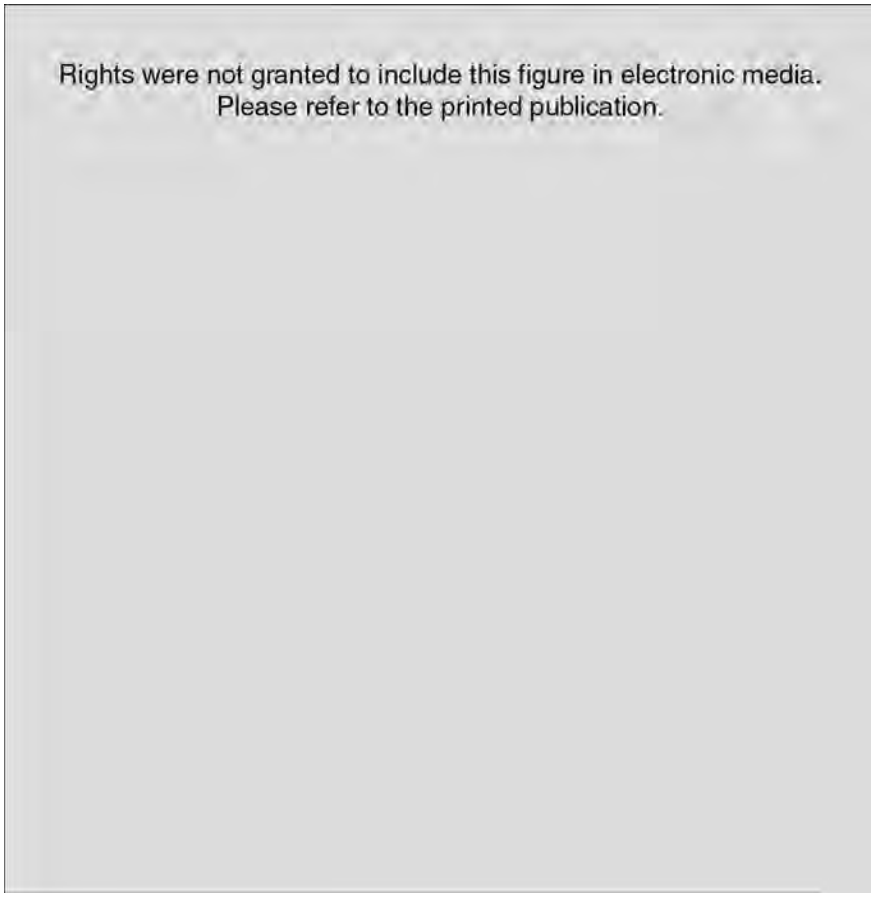


Figure 8–5. Schematic drawing showing wall thickness and orientation of fibers on microdissection of the cardia. At the junction of the esophageal tube and the gastric pouch, there is an oblique muscular ring composed of an increased muscle mass inside the inner muscular layer. On the lesser curve side of the cardia, the muscle fibers of the inner layer are oriented transversely and form semicircular muscle clasps that insert into the submucosal connective tissue. On the greater curve side of the cardia, these muscle fibers form long oblique loops that run parallel to the lesser curve of the stomach and encircle the distal end of the cardia and gastric fundus. (From DeMeester TR, Skinner DB: Evaluation of esophageal function and disease. In Glenn WWL [ed]: Thoracic and Cardiovascular Surgery, 4th ed. Norwalk, CT, Appleton-Century-Crofts, 1983, p 461, with permission.)

diaphragm is in continuity with the transversalis fascia, and fibroelastic fibers extend upward into the opening of the diaphragm in a cranial fashion to be attached to the wall of the esophagus about 2 cm above the gastroesophageal junction. Some of the elastic fibers penetrate to the mucosa of the esophagus and form the phrenoesophageal ligament. The esophagus below the phrenoesophageal ligament lies within the abdominal cavity and after a short distance of 2 to 3 cm enters into the stomach. A high-pressure zone can be identified in this area; it provides a pressure barrier between the esophagus and stomach and acts as the valve on the worm drive pump of the esophageal body. This barrier or high-pressure zone represents contributions made by the crus of the diaphragm,[8] the angle of His, and an intrinsic LES. Although an anatomically distinct LES has been difficult to identify, microdissection studies show that in humans, the sphincter-like function of this segment is related to the architecture of the muscle fibers at the junction of the esophageal tube and the gastric pouch[9] (Fig. 8–5). The lower esophageal muscle fibers are arranged as clasp and sling fibers. Clasp fibers have higher resting pressure and are less responsive to cholinergic stimulation.[10,11] This observation most probably accounts for the asymmetry of the sphincter, which shows more circularity on the left than on the right side and causes asymmetric LES pressure readings on manometric studies.[12] Nitric oxide causes LES relaxation, which is generated at the neuromuscular junction with some interaction by vasoactive intestinal polypeptide.[13] The sphincter actively remains closed to prevent reflux of gastric contents into the esophagus and opens via the relaxation that coincides with a pharyngeal swallow. LES pressure returns to its resting level after the peristaltic wave has passed through the esophagus (see Fig. 8–3). Consequently, any reflux of gastric juice that may occur through the open valve during a swallow is pumped back into the stomach. An important trigger for gastroesophageal reflux appears to be gastric distention, which results in shortening of the LES as it is taken up into the fundus of the expanding stomach. The progressive shortening of the sphincter reaches a point where the pressure in the remaining length gives way and the sphincter opens to allow reflux. Loss of sphincter barrier function also occurs if the pharyngeal swallow does not initiate a peristaltic contraction; in this case, coincident relaxation of the LES is unguarded, and reflux of gastric juice can occur. This appears to be the major cause of the so-called transient or spontaneous LES relaxations, thought by some to be a causative factor in gastroesophageal reflux disease (GERD).[14] In dogs, bilateral cervical parasympathetic blockade abolishes the LES relaxation that occurs with pharyngeal swallowing or distention of the esophagus.[15] This indicates that vagal function is important in maintaining LES barrier function and in coordinating LES relaxation with esophageal contraction. Rostral cells in

motor neurons of the dorsal motor nucleus are involved in excitatory control of the LES, and caudal cells of the dorsal motor nucleus are involved in inhibition of the LES.[16,17]

The ability of the LES to protect the esophageal mucosa from excessive exposure to gastric juice depends on the resistance that it imposes to the flow of gastric juice from an environment above atmospheric pressure, the stomach, into an environment below atmospheric pressure, the esophagus (see Fig. 8–2). Clinical and in vitro studies have shown that this resistance is due to the integrated mechanical effect of sphincter pressure, overall length, and length exposed to the positive environmental pressure of the abdomen.[18-20]

PATHOPHYSIOLOGIC ASPECTS OF ESOPHAGEAL MOTILITY

In the normal situation, there is a coordinated interplay between the esophagus and its adjacent valves and compartments to propel food from the mouth to the stomach. Failure of the propulsive ability of a compartment hampers the forward movement of food and enhances regurgitation. Failure of the valve between two adjoining compartments results in exposure of the proximal compartment to the luminal contents of the distal compartment (i.e., gastroesophageal and esophagopharyngeal reflux).

Pharyngoesophageal Swallowing Disorders

Disorders of the pharyngoesophageal phase of swallowing result from dyscoordination of the neuromuscular events involved in chewing, initiation of swallowing, and propulsion of material from the oropharynx to the cervical esophagus. This results in dysphagia, nasal regurgitation, aspiration, and repetitive respiratory infections. The disorders can be categorized into one or a combination of the following: (1) inadequate oropharyngeal bolus transport, (2) inability to pressurize the pharynx,[21] (3) inability to elevate the larynx and open the UES, (4) impaired cricopharyngeal muscle relaxation and pharyngeal contraction, and (5) decreased compliance of the pharyngoesophageal segment and cervical esophagus secondary to restrictive myopathy.

Pharyngoesophageal swallowing disorders are usually an acquired condition that involves the central and peripheral nervous systems. Swallowing abnormalities caused by cricopharyngeal dysfunction are of increasing importance. The problem is associated with increasing age and carries high morbidity, mortality, and cost. Possible diseases and conditions include cerebrovascular accidents, brainstem tumors, poliomyelitis, multiple sclerosis, Parkinson's disease, pseudobulbar palsy, peripheral neuropathy, and operative damage to the cranial nerves involved in swallowing. Muscular diseases, such as radiation-induced myopathy, dermatomyositis, myotonic dystrophy, and myasthenia gravis, are less common. Occasionally, extrinsic compression as a result of thyromegaly, cervical lymphadenopathy, or hyperostosis of the cervical spine can cause cervical dysphagia. It should be noted, however, that in our series, almost 40% of patients had no discernible underlying disease process that could be identified. The rapidity of the oropharyngeal phase of swallowing, movement of the gullet, and asymmetry of the cricopharyngeus account for the difficulty in assessing abnormalities of esophagopharyngeal swallowing disorders with manometry. Videocineroentgenography is the most objective test for evaluating oropharyngeal bolus movement, pharyngeal contraction, cricopharyngeal relaxation, and the dynamics of airway protection during swallowing.[22] Careful analysis of videocineroentgenographic studies and manometry with a specially designed catheter, ideally performed simultaneously (Fig. 8–6), can identify the cause of pharyngoesophageal dysfunction in most situations.[23] UES opening, UES relaxation, the concept of sphincter resistance, and compliance are key to understanding disorders related to the pharyngoesophageal segment. These factors are important for the clinician to keep in mind when distinguishing between frequently encountered radiologic abnormalities (e.g., cricopharyngeal bars) and clinically important disturbances in swallow function. A distinction must be made between two biomechanical events that are related but not synonymous, namely, UES relaxation and opening.

Characterization of pharyngoesophageal dysfunction and the associated mechanical abnormality of the swallow has potentially important clinical implications for the surgeon because the effect of a myotomy is mechanical. If a definite mechanical defect can be identified, myotomy may be of potential benefit to this subgroup of patients. The mechanical effects of a myotomy are to improve compliance, reduce resistance to transsphincteric flow, and improve the opening traction force on the UES. The efficacy of cricopharyngeal myotomy for some structural disorders of the UES (e.g., Zenker's diverticulum) is indisputable; however, the efficacy of procedures designed to reduce resistance to sphincteric flow in patients without Zenker's diverticulum is far less convincing and dependent on identification of some underlying mechanical abnormality of the UES. In patients with Zenker's diverticulum, it has been difficult to consistently demonstrate a motility abnormality of the pharyngeal phase of swallowing. The abnormality most apt to be present is loss of compliance in the pharyngoesophageal segment manifested by increased bolus pressure[24] (Fig. 8–7). Esophageal muscle biopsy results in patients with Zenker's diverticulum have shown histologic evidence of a restrictive myopathy correlating with decreased compliance of the upper esophagus on videocineradiographic and detailed manometric studies. These findings suggest that the diverticulum develops as a consequence of the repetitive stress of bolus transport through noncompliant muscle of the pharyngoesophageal segment. Other roentgenographic manifestations of a noncompliant segment in the proximal esophagus are a cricopharyngeal bar or more extended narrowing of the pharyngoesophageal segment. Dyscoordination of sphincter relaxation with pharyngeal contraction together with impaired sphincter opening is another cause of the development of Zenker's

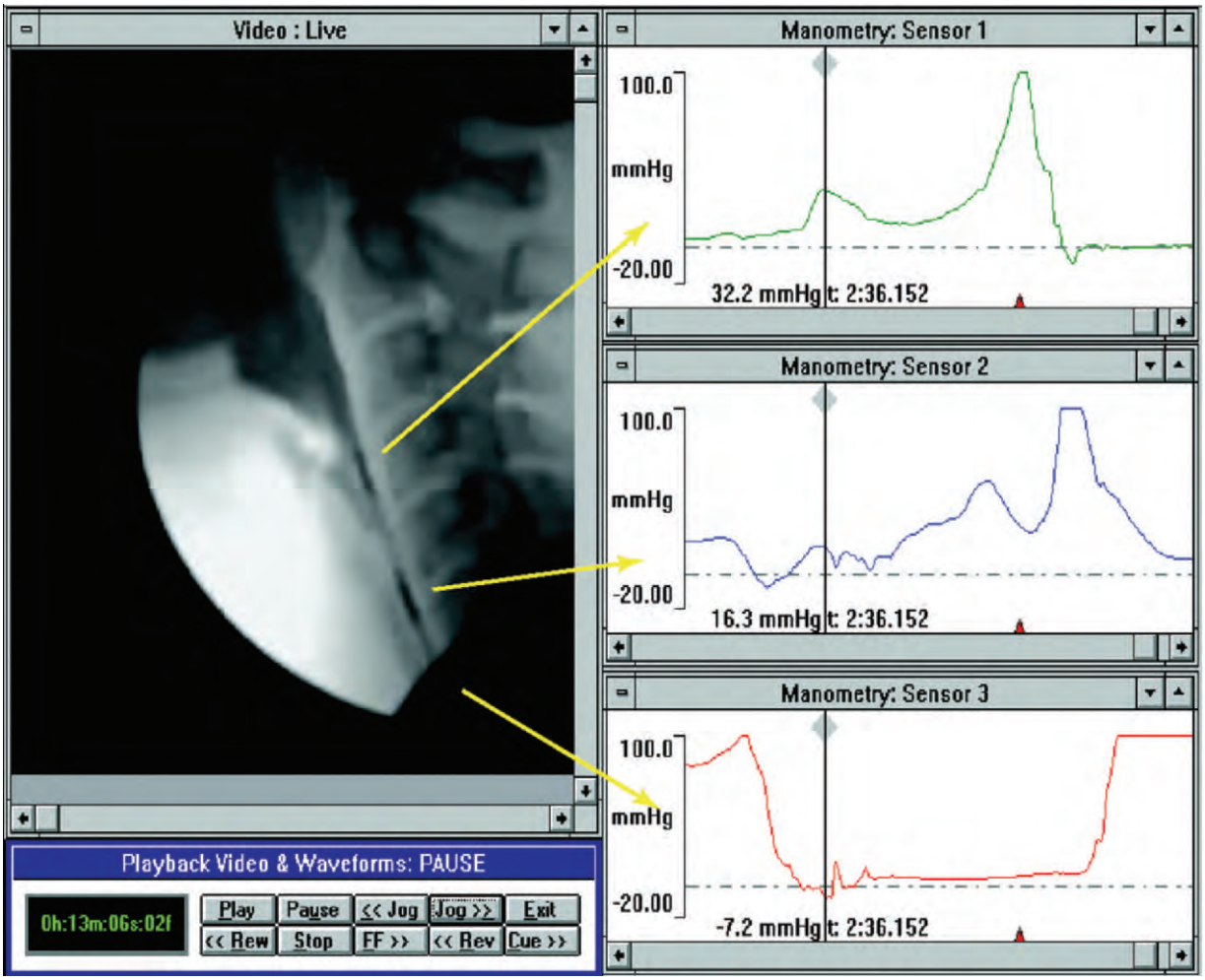


Figure 8–6. Combined manovideofluorography of the upper esophageal sphincter (UES) in a normal patient using a three-channel solid-state catheter with the distal transducer placed in the UES and the proximal two transducers in the pharynx. The UES is open and demonstrates a subatmospheric pressure drop before arrival of the bolus. The intrabolus pressure is depicted in the proximal channel of the manometry catheter. Manovideofluorography allows for optimal assessment of the dynamics involved in the pharyngeal swallow because manometric sphincter opening and bolus clearance can be accurately determined from the linked videoesophagogram and manometry tracing.

diverticulum. This may not occur throughout the full length of the sphincter and can easily be missed on manometric assessment because of movement of the cricopharyngeus on swallowing. Failure of the cricopharyngeal muscle to relax on swallowing, or so-called cervical achalasia, and failure of initiation of an esophageal contraction after a pharyngeal swallow have also been observed in patients with Zenker's diverticulum.[25]

Primary Motor Disorders of the Esophageal Body and Lower Esophageal Sphincter

Nonobstructive dysphagia (i.e., dysphagia in the absence of structural abnormalities) is the primary symptom of esophageal motor disorders. Its perception by the patient is a balance between the severity of the underlying cause that is producing the difficulty and the patient's adjustment to that difficulty through alteration in eating habits. Consequently, any complaint of dysphagia requires a detailed assessment of the patient's dietary history in addition to a clear understanding of the physiologic abnormalities that may cause the patient's symptoms.[1]

Abnormalities that occur in the worm drive pump of the esophageal body or the LES can give rise to a number of disorders in the esophageal phase of swallowing. These disorders are due to primary abnormalities in the esophagus or result from a more generalized neural, muscular, or systemic disease (Box 8–1). With the introduction of standard esophageal manometry, a number of primary esophageal motility disorders have been reclassified from nonspecific to separate disease entities, including achalasia, diffuse esophageal spasm, the so-called nutcracker esophagus, and the hypertensive LES.[26] Classification of these disorders is usually based on

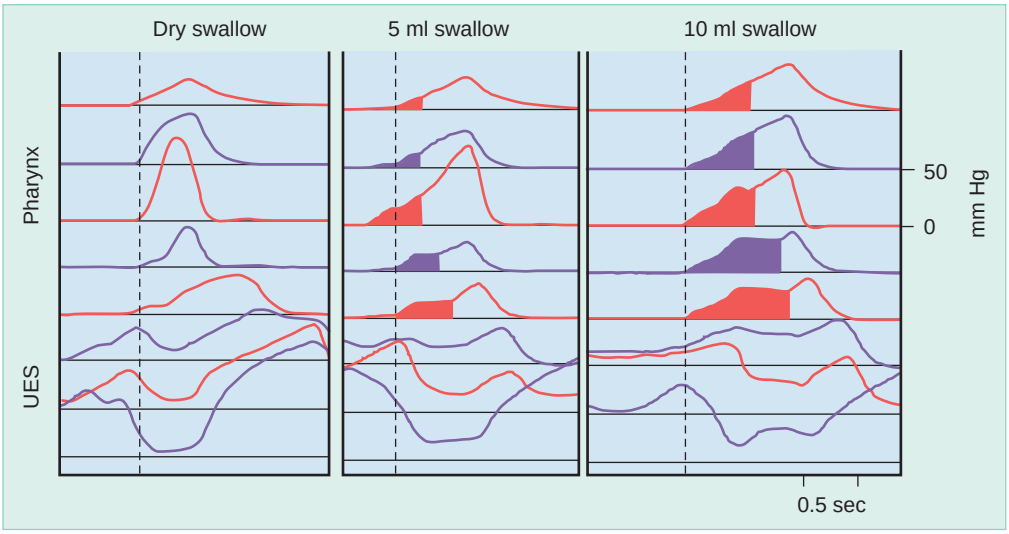


Figure 8–7. Manometric pharyngeal and upper esophageal sphincter (UES) tracings from a patient with a Zenker diverticulum. Tracings obtained during a dry, 5-ml, and 10-ml swallow are depicted. The intrabolus pressure wave (*shaded portion of tracing*) was above normal. With increasing bolus volumes there is a significant increase in intrabolus pressure, thus demonstrating loss of muscle compliance.

analysis of the manometric recordings of 10 wet swallows performed in a laboratory setting.[27] Recently, an updated classification of the primary esophageal motor disorders based on manometric abnormalities found in the LES and esophageal body has been proposed (Table 8–1).[28]

The pathogenesis of these primary abnormalities is either defective inhibition or defective excitatory innervation of the LES and esophagus. Achalasia is associated with loss of inhibitory innervation of the LES and loss of nitric oxide.[29,30] This unopposed excitatory innervation leads to high LES pressure and defective or absent LES relaxation in patients with achalasia.

The technique of ambulatory 24-hour monitoring of esophageal motor activity multiplies the number of esophageal contractions available for analysis and provides an opportunity to assess esophageal motor function in a variety of physiologic situations. This increases the accuracy and dependability of the measurement.[31] The application of ambulatory 24-hour esophageal motility monitoring has shown that there are marked differences in the classification of esophageal motor disorders between standard manometry and ambulatory motility monitoring.[32] The degree of reclassification that occurs when analysis of esophageal motor function is conducted on the basis of ambulatory manometry indicates that the classic categories of esophageal motor disorders are inappropriate. This appears to be due to the intermittent expression of esophageal motor abnormalities that can be missed or overdiagnosed during the unphysiologic setting of standard manometry but are detected with a higher degree of reliability when motor activity is monitored over a 24-hour period under a variety of physiologic conditions. Based on these observations, esophageal motility disorders should be looked at as a spectrum of abnormalities that reflect various stages of deterioration of esophageal motor function rather than as separate entities.[1] This view is supported by the observation that the severity of esophageal motor disorders can progress or regress during the natural course of the disease.

Recently, we have seen the introduction of combined multichannel intraluminal impedance and esophageal manometry (Fig. 8–8). This technique allows for the simultaneous assessment of esophageal bolus transport together with esophageal manometry. With this technique, Tutuian and Castell[33] have shown that when

Box 8–1 Esophageal Motility Disorders

Primary

- Achalasia, "vigorous" achalasia
- Diffuse and segmental esophageal spasm
- Nutcracker esophagus
- Hypertensive lower esophageal sphincter
- Nonspecific esophageal motility disorders

Secondary Esophageal Motility Disorders

- Collagen vascular diseases: progressive systemic sclerosis, polymyositis and dermatomyositis, mixed connective tissue disease, systemic lupus erythematosus
- Chronic idiopathic intestinal pseudo-obstruction
- Neuromuscular diseases
- Endocrine and metastatic disorders

Table 8–1 Manometric Classification of Primary Esophageal Motility Disorders

Manometric Classification	Motor Disorders	Manometric Findings
Inadequate LES relaxation	Achalasia	Elevated LES resting pressure Incomplete LES relaxation Elevated baseline esophageal pressure Absent distal esophageal peristalsis
	Atypical disorders of LES relaxation	
Uncoordinated motility	Diffuse esophageal spasm	Simultaneous esophageal contractions (>20%) Intermittent normal peristalsis Repetitive contractions (multipeaked waves >3) Prolonged contraction durations (>6 sec) Retrograde contractions Isolated incomplete LES relaxation
Hypercontracting esophagus	Nutcracker esophagus	Contraction amplitudes >180 mm Hg Increased contraction duration >6 sec Peristaltic contractions
	Hypertensive LES	Resting LES pressure >25 mm Hg May have partial LES relaxation
Hypocontracting esophagus	Ineffective esophageal motility	Increase nontransmitted peristalsis (>30%) Low distal peristaltic contraction amplitudes (<30 mm Hg)
	Hypotensive LES	Resting LES pressure <6 mm Hg

LES, lower esophageal sphincter.
Adapted from Spechler SJ, Castell DO: Classification of oesophageal motility abnormalities. Gut 49:145, 2001.

evaluating patients with motility disorders by combined multichannel intraluminal impedance and esophageal manometry, two distinct patterns emerge. Some patients have manometric pressure defects and associated defective bolus transit on impedance, whereas a second group of patients have pressure defects only (that is, normal bolus transit) (Table 8–2). Similar to the observations found when using ambulatory manometry, this study showed that manometry tends to overestimate the functional defect detected by impedance (Fig. 8–9). This most probably has important implications when assessing patients before antireflux surgery. Standard manometry appears to be too sensitive and should not be used alone to exclude or select patients for different surgical procedures. However, if normal esophageal function or isolated LES abnormalities are found on manometry, it is unlikely that impaired esophageal body peristalsis or clearance will be found with impedance. Isolated LES abnormalities impair bolus transit only when esophageal body contractions are defective. Of note is that there appears to be poor correlation between symptoms of dysphagia and abnormal bolus transport inasmuch as only

Table 8–2 Classification of the Primary Motor Disorders Based on Impedance Manometry

Impedance Classification	Manometric Findings	Prevalence of Normal Bolus Transport
Pressure defects *and* associated bolus transit abnormalities	Achalasia	0%
	Scleroderma	0%
	IEM	50%
	Diffuse esophageal spasm	5%
Pressure defects *only*	Nutcracker esophagus	97%
	Hypotensive LES	100%
	Hypertensive LES	96%
	Poor LES relaxation	100%

IEM, ineffective esophageal motility; LES, lower esophageal sphincter.
Adapted from Tutuian R, Castell DO: Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: Study in 350 patients. Am J Gastroenterol 99:1011, 2004.

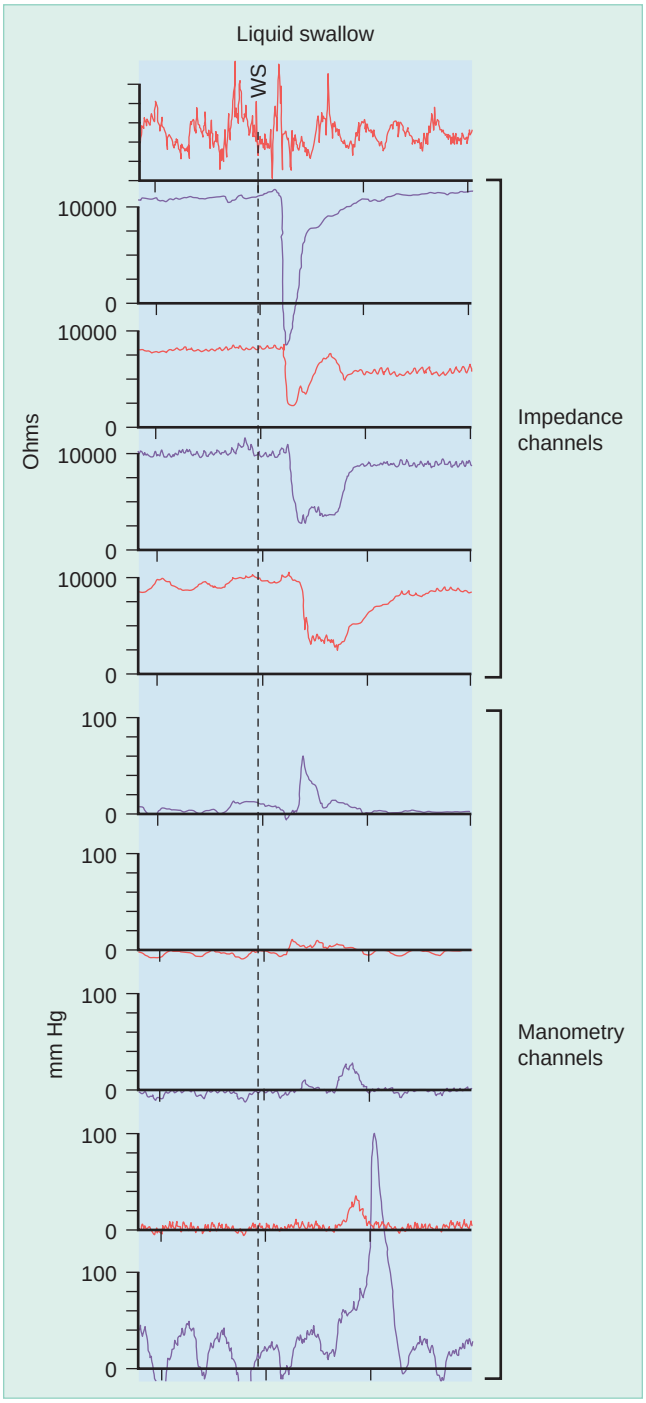


Figure 8–8 A sample tracing of a swallow using a combined multichannel impedance–manometry catheter. By linking the impedance tracing with the manometry tracing, the effectiveness of esophageal contraction pressure on bolus clearance can be evaluated.

50% of patients with dysphagia have abnormal bolus transit and about 30% of patients with no dysphagia have abnormal bolus transport (Fig. 8–10).

The symptom of dysphagia in patients without structural abnormalities of the esophagus can be caused by distal obstruction from a nonrelaxing LES or by disorganized contractions of the esophageal body. In patients with a nonrelaxing sphincter, the function of the esophageal body deteriorates secondary to the distal obstruction and may recover if the obstruction is relieved early during the disease process. In patients with a primary motor disorder of the esophageal body, dysphagia appears to be due to an inability of the esophageal body to organize its motor activity into peristaltic contractions during meals. Ambulatory 24-hour monitoring of esophageal body function has shown that in normal asymptomatic volunteers, the prevalence of "effective contractions" (i.e., peristaltic contractions with sufficient amplitude to propel a bolus) increases with increasing states of consciousness (i.e., from sleep, to the upright position, to meal periods), probably because of a modulatory effect of the central nervous system on esophageal motor activity. Patients with nonobstructive dysphagia lack this ability to increase the prevalence of effective contractions with increasing states of consciousness.[34,35] Clinical studies using ambulatory esophageal motility have shown that the frequency of effective contractions increases during meal periods. Monitoring can be used to express the severity of esophageal body dysfunction on a linear scale. This can be related to the presence of nonobstructive dysphagia (Fig. 8–11), and it obviates the need for the current categories of esophageal motor disorders and permits objective assessment of the effect of medical or surgical therapy on esophageal body function.[35]

Esophageal contractions of an abnormally high amplitude or long duration have been suggested to be responsible for chest pain in patients with esophageal motor disorders.[36] Ambulatory 24-hour motility monitoring in these patients has, however, shown that the amplitude and duration of esophageal contractions associated with chest pain episodes are similar to those of asymptomatic contractions during the upright or supine recording. Esophageal chest pain episodes were preceded immediately by a markedly increased frequency of simultaneous and repetitive contractions.[32] Using simultaneous manometry, pH, and ultrasound imaging, Balaban et al.[37] have shown that these sustained esophageal contractions are related to the symptoms of chest pain and that the sustained contractions actually involve the longitudinal muscle of the esophagus and not the circular. The contractions may be confused with heartburn; however, it seems that the chest pain is on average about 25 seconds longer than that associated with a reflux event.[38] As in the heart, the esophageal blood supply may be interrupted during bursts of disorganized muscular contractions. Such interruption may become crucial in situations in which resting blood flow to the esophagus is already compromised, as has been shown for the hypertrophic esophageal muscle in patients with esophageal motor disorders. A burst of disorganized motor activity in this situation may give rise to ischemic pain. Consequently, chest pain caused by a burst of uncoordinated esophageal motor activity under ischemic conditions has been called *esophageal claudication*.[32] Studies using simultaneous manometry and high-frequency intraluminal ultrasound probes have shown an increase in muscle

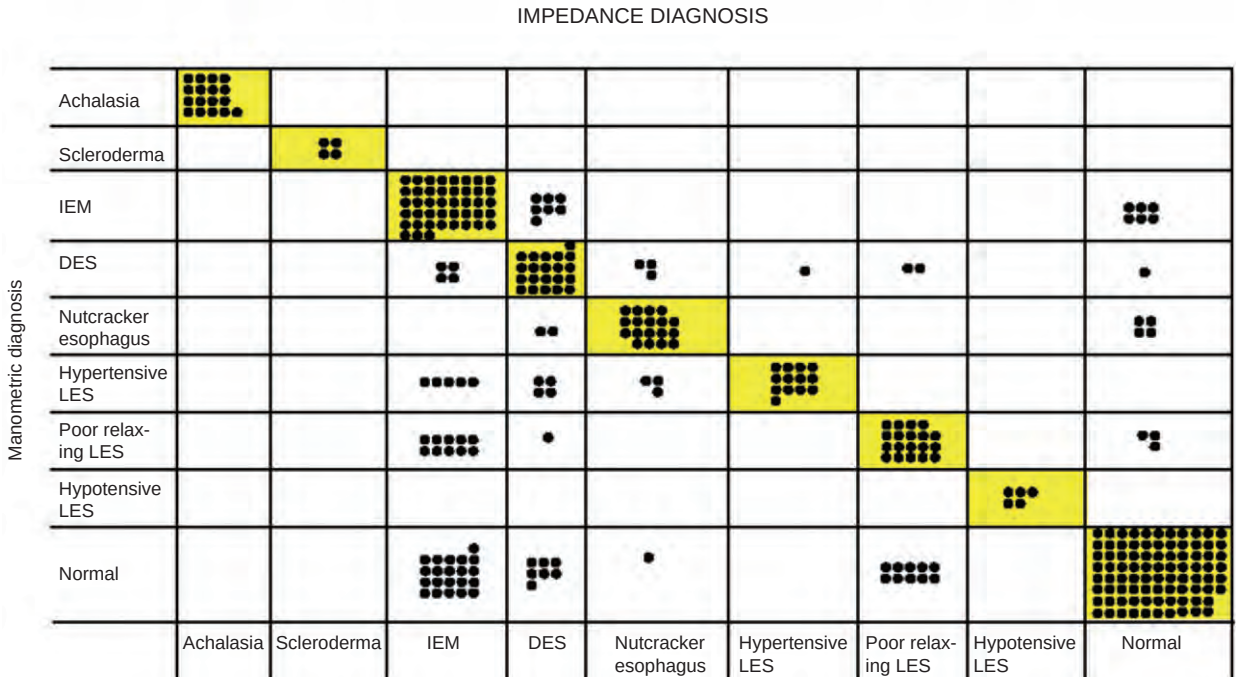


Figure 8–9. Classification of esophageal motor disorders in 350 patients with dysphagia or noncardiac chest pain according to findings on standard manometry or impedance. DES, diffuse esophageal spasm; IEM, ineffective esophageal motility; LES, lower esophageal sphincter. (Adapted from Tutuian R, Castell DO: Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: Study in 350 patients. Am J Gastroenterol 99:1011, 2004.)

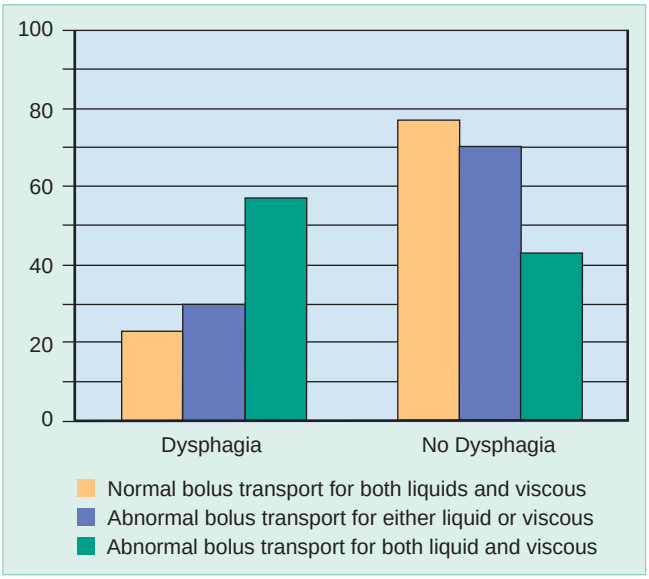


Figure 8–10. Prevalence of normal and abnormal bolus transport of liquids and viscous bolus material in patients with and without the symptom of dysphagia. Bolus transport was evaluated by combined multichannel intraluminal impedance and manometry. (Adapted from Tutuian R, Castell DO: Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: Study in 350 patients. Am J Gastroenterol 99:1011, 2004.)

thickness and mass. When compared with normal subjects, patients with achalasia have the greatest increase in muscle thickness, followed by patients with diffuse esophageal spasm and those with nutcracker esophagus. It appears that the primary disorder is loss of this LES opening and relaxation and that the esophageal muscle hypertrophy is a secondary response to outflow obstruction at the level of the LES.[39]

Roentgenographic abnormalities in motility disorders such as segmental spasms with compartmentalization of the esophagus or the formation of a diverticulum are the anatomic results of disordered esophageal motor function. Detailed analysis will reveal that a motility disorder was usually present for years before documentation of these roentgenographic findings. The development of a diverticulum may temporarily alleviate the symptom of initial dysphagia during eating and replace it with the symptom of postprandial regurgitation of undigested food. In the few patients with a diverticulum in whom an abnormality of esophageal body or LES function cannot be identified manometrically, a traction or congenital cause of the diverticulum should be sought.

Diffuse esophageal spasm is relatively rare. There is evidence to support the fact that the dyscoordination usually seen in these patients is due to a deficiency of nitric oxide. Patients with higher contraction amplitudes have primarily chest pain and those with lower contraction amplitudes have primarily dysphagia. Although the pathophysiology is understood, the underlying cause of the loss in inhibitory nerves and degeneration of the

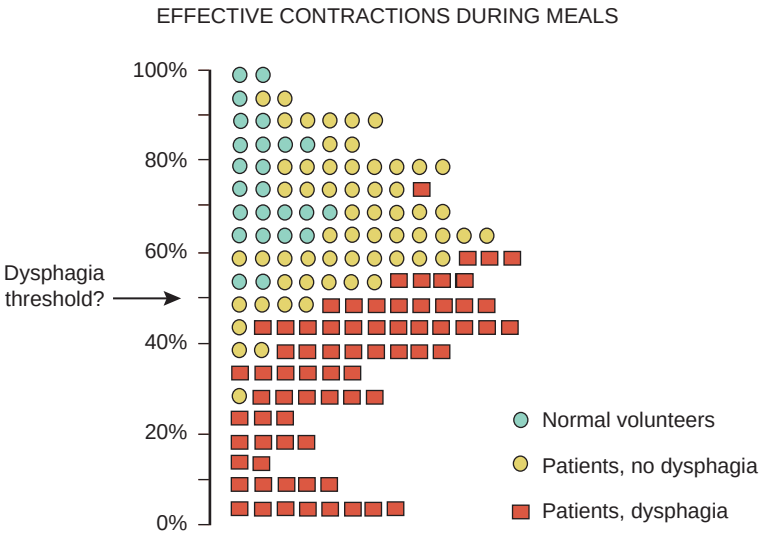


Figure 8–11. Prevalence of "effective contractions" during meal periods in normal volunteers, patients with nonobstructive dysphagia, and patients without dysphagia. Having less than 50% effective contractions during meals is associated with a high prevalence of nonobstructive dysphagia.

myenteric plexus is not known. GERD causes injury to the LES muscle. The inflammation somehow causes defective excitatory innervation that results in low contraction amplitudes or ineffective esophageal contractions. It is uncertain whether the monitor abnormality is primary or secondary to reflux damage.

Secondary Esophageal Motor Disorders

Esophageal motility disorders may also result from more generalized neural, muscular, or systemic metabolic abnormalities. The esophagus is particularly affected by almost any of the collagen vascular disorders; the most common are progressive systemic sclerosis, mixed connective tissue disease, polymyositis, and dermatomyositis (see Box 8–1).[40-42] Eighty percent of patients with progressive systemic sclerosis have an esophageal motor abnormality. In most cases, the disease follows a prolonged course and usually affects only the smooth muscle in the distal two thirds of the esophagus. In these patients the muscle fibers in the LES and esophagus are replaced by connective tissue.[43] Typical findings on esophageal manometry are normal peristalsis in the proximal striated esophagus and weak or absent peristalsis in the distal smooth muscle portion. LES pressure is progressively weakened as the disease advances, and this decline in pressure results in increased esophageal exposure to gastric juice because of a mechanically defective LES and poor clearance function of the esophageal body.[42]

In patients with polymyositis or dermatomyositis, the upper striated muscle portion is the major site of esophageal involvement, and such patients suffer from aspiration, nasopharyngeal regurgitation, and cervical dysphagia. Mixed connective tissue disease is associated with a mixture of the manometric findings of progressive systemic sclerosis and polymyositis. In patients with diabetes mellitus, an autonomic neuropathy is responsible for the findings of low contraction amplitude and double-peaked contraction waves. Infiltration of the myenteric plexus of the LES in neoplastic disease and Chagas' disease is the cause of secondary achalasia. Patients with amyloidosis, alcoholism, and multiple sclerosis exhibit low-amplitude contractions in the distal esophagus.

Gastroesophageal Reflux Disease and Esophageal Motility Disorders

GERD is the most common foregut disorder in the Western world and accounts for approximately 75% of esophageal disorders. In about 50% of affected patients, it can lead to complications such as esophagitis, stricture, ulceration, Barrett's esophagus, repetitive pulmonary aspiration, recurrent pneumonia, and progressive pulmonary fibrosis.[44] Despite its prevalence, GERD can be one of the most challenging diagnostic problems in benign esophageal disease because the occurrence of specific symptoms or detection of endoscopic or histologic esophageal mucosal injury is unreliable in indicating the presence of the disease. With the introduction of 24-hour esophageal pH monitoring, the basic pathophysiologic abnormality of GERD (i.e., increased esophageal exposure to gastric juice) has been quantified.[45,46] This has provided an opportunity to conceptualize the pathophysiology of a complicated disease process, stimulated a rational stepwise approach to determine the cause of increased esophageal exposure to gastric juice, and led to the design of specific therapy to correct the underlying abnormalities. The problem is that there is no correlation between the majority of esophageal chest pain events and abnormal esophageal motor events or acid reflux events. Impedance testing has shown that there can, however, be non-acid reflux episodes and that the frequency of these non-acid reflux events in certain patients is high. Some of these patients demonstrate mechanical hypersensitivity to esophageal distention. Sarkar and colleagues have shown that in normal subjects and patients with symptoms, acid in the

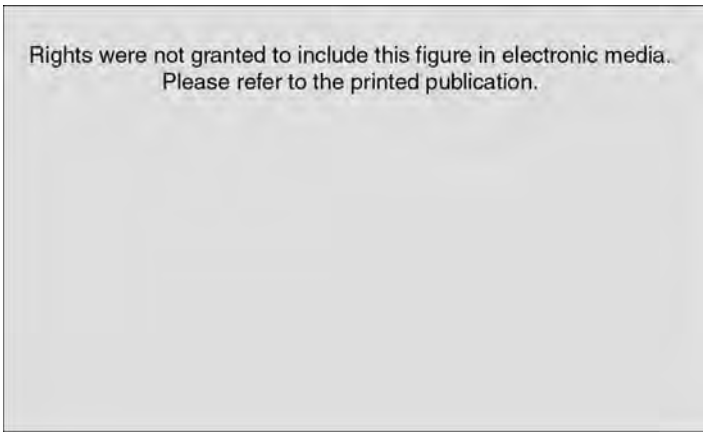


Figure 8–12. Mechanical model of the esophagus as a propulsive pump, the lower esophageal sphincter as a valve, and the stomach as a reservoir. Esophageal clearance of refluxed gastric juice is determined by esophageal motor activity, salivation, gravity, and the presence of an anatomic alteration such as a hiatal hernia. The competency of the lower esophageal sphincter depends on its pressure, overall length, and length exposed to abdominal pressure. Gastric function abnormalities causing gastroesophageal reflux include increased intragastric pressure, gastric dilatation, decreased emptying rate, and increased gastric acid secretion. (From DeMeester TR, Attwood SE: Gastroesophageal reflux disease, hiatus hernia, achalasia of the esophagus and spontaneous rupture. In Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations, 9th ed. Norwalk, CT, Appleton & Lange, 1989, with permission.)

esophagus induces a hypersensitivity that is mediated at the level of the spinal cord or higher.[47,48]

Three causes of increased esophageal exposure to gastric juice are known. The first is a mechanically defective LES, which accounts for about 60% to 70% of GERD and is due to inflammatory damage to the sphincter muscle.[20] Identification of this cause is important because antireflux surgery is the only therapy designed to correct the abnormality. The other two causes are inefficient esophageal clearance of refluxed gastric juice and abnormalities of the gastric reservoir that result in transient loss of the sphincter barrier because of progressive shortening of the sphincter with gastric distention. Conceptually, these three main causes of gastroesophageal reflux can be thought of as abnormalities of a pump, a valve, or a reservoir (Fig. 8–12). The relative contributions of each of these components of the antireflux mechanism to increased esophageal exposure to gastric juice should be determined before consideration of surgical therapy.

Failure of the LES can be caused by inadequate pressure, overall length, or intra-abdominal length (i.e., the portion of the sphincter exposed to the positive-pressure environment of the abdomen on manometry). Failure of one or two of the components of the sphincter may be compensated for by clearance of the esophageal body. Failure of all three sphincter components inevitably leads to increased esophageal exposure to gastric juice. The most common cause of a mechanically defective LES is inflammatory loss of myogenic function, which can result in loss of sphincter pressure, overall length, abdominal length, or a combination of these factors. Normal sphincter pressure can be nullified by an inadequate abdominal length or an abnormally short overall length of the sphincter.[20] Adequate abdominal length of the sphincter is important in preventing reflux caused by increases in intra-abdominal pressure. Adequate overall length is important in preventing reflux caused by gastric distention, such as may occur with a meal.

The combined effects of sphincter pressure, overall length, and abdominal length can be determined by integrating the radial pressure exerted over the entire length of the sphincter. This can be done by calculating the volume of the three-dimensional sphincter pressure profile (i.e., the sphincter pressure vector volume).[19,49]

A second cause of increased esophageal exposure to gastric juice is inefficient esophageal clearance of refluxed material.[50] Because of failure to clear physiologic reflux, abnormal esophageal exposure to gastric juice can occur even in individuals who have a mechanically intact LES and normal gastric function. This situation is relatively rare, however, and ineffective clearance is more apt to be seen in association with a mechanically defective sphincter, where it augments the esophageal exposure to gastric juice by prolonging the duration of each reflux episode. The four factors important in esophageal clearance are gravity, esophageal motor activity, salivation, and anchoring of the distal esophagus in the abdomen. The bulk of refluxed gastric juice is cleared from the esophagus by a primary peristaltic wave initiated by a pharyngeal swallow. Secondary peristalsis initiated by either distention of the lower esophagus or a drop in intraesophageal pH is less important. Combined videocineradiographic and manometric studies have shown that failure of esophageal clearance can be caused by a nonperistaltic esophageal contraction waveform or contractions of low amplitude.[51] Salivation contributes to esophageal clearance by neutralizing the minute amount of acid that is left after a peristaltic wave. The presence of a hiatal hernia can also

Table 8–3 Prevalence of Esophageal Motor Disorders in Obese Patients

	Hong et al.[52] *N* = 61	Jaffin et al.[53] *N* = 111	Percentage
Hypotensive LES	10	28	22
Hypertensive LES	11		6
Achalasia		1	0.5
Diffuse esophageal spasm	2	8	6
Nutcracker esophagus	3	16	11
Ineffective esophageal motility	1		0.5
Nonspecific dysmotility	11	15	15

LES, lower esophageal sphincter.

cause increased acid exposure by reducing the efficiency of esophageal contractions through loss of its distal anchor.

Gastric abnormalities that increase esophageal exposure to gastric juice include gastric dilatation, increased intragastric pressure, a persistent gastric reservoir, and increased gastric acid secretion.[44] The effect of gastric dilatation is to shorten the overall length of the LES, which results in a decrease in sphincter resistance to reflux. Increased intragastric pressure occurs in patients with outlet obstruction caused by a scarred pylorus or duodenum, after vagotomy, or as a result of diabetic neuropathy. Persistence of the gastric reservoir results from delayed gastric emptying secondary to myogenic abnormalities, as seen in patients with advanced diabetes and diffuse neuromuscular disorders and after viral infections. Gastric hypersecretion can increase esophageal exposure to gastric juice by the physiologic reflux of the excessive volume of gastric juice of low pH that occurs in this condition.

Obesity and Esophageal Motility Disorders

Over recent years there has been a dramatic increase in the number of obese patients coming to the surgeon for surgical procedures designed to restrict eating and cause weight loss. This trend has resulted in a new group of patients with esophageal motility disorders. It appears that some of these obese patients have a preexisting motility disorder and that in others the surgery itself may cause a secondary esophageal motility disorder. This is particularly seen with operations that inherently produce a relative outflow resistance just below the gastroesophageal junction, such as the gastric banding procedure and Roux-en-Y gastric bypass. Various observational studies have shown that there appears to be an increase preoperatively in the manometric findings of a motility disorder in the obese population (Table 8–3). Although two studies have shown the prevalence of motility disorders to be high, namely, 54%[52] and 61%,[53] one study showed no increase in any esophageal dysmotility.[54] The correlation with symptoms is, however, only about 50%. Esophageal bolus transit determined by radionuclide scintigraphy has also been shown to be significantly prolonged in patients with morbid obesity.[55,56] Part of the reason may be an increase in the esophageal-gastric pressure gradient. Body mass index has been shown to be positively related to intra-abdominal pressure,[57] and the increased pressure causes a relative outflow resistance and decreased flow from the esophagus to the stomach. The motility changes seen may also be related to altered gut neuropeptides inasmuch as it has been shown that neurotensin is significantly decreased and motilin is significantly increased in obese patients when compared with lean controls.[58] A small number of patients require reoperation and revision surgery after gastric banding because of esophageal dysmotility.[59-62] DeMaria et al.[59] reported that 71% of patients had a significant increase in esophageal diameter on barium studies that was associated with dysphagia, regurgitation, and vomiting. Weiss and associates[63] looked at esophageal manometry before and after gastric banding and showed significant deterioration in esophageal body function 6 months after surgery. This deterioration was mainly due to an increase in the number of simultaneous contractions and a significant decrease in contraction amplitude to less than 30 mm Hg. Some studies have, however, shown no deterioration in esophageal body function postoperatively. Theoretically, with weight loss there is normalization of gut hormones, a decrease in intra-abdominal pressure, and improvement in the esophageal-gastric pressure gradient. These factors would possibly be associated with an improvement in bolus transit and esophageal clearance of the esophagus, which has been demonstrated by Seymour et al.[56] Thus, the manometric findings may not be of clinical significance if there is no interference with bolus transit.

OBJECTIVE ASSESSMENT OF ESOPHAGEAL MOTILITY DISORDERS

A number of tests are available for the diagnosis and evaluation of esophageal motor disorders, but they vary greatly in reliability and appropriate application. When

assessing patients with a suspected pharyngeal swallowing disorder, the gastrointestinal surgeon should ask seven key questions:

1. Does the patient aspirate?
2. Does the patient have a Zenker diverticulum?
3. Does the patient have some underlying disorder known to be associated with dysphagia (e.g., stroke, parkinsonism)?
4. In what swallowing phase does the abnormality occur (i.e., oral, preparatory, pharyngeal, or esophageal)?
5. Is the patient able to maintain adequate nutrition orally?
6. Is there manometric evidence of any swallowing dysfunction? Specifically, is their any manometric evidence of impaired sphincter opening or impairment to trans-sphincteric flow across the UES, and what is the state of the pharyngeal stripping wave?
7. Finally, if considering an operative procedure, has the upper esophageal high-pressure zone been localized manometrically?

Similarly, when assessing a patient with a suspected esophageal body or LES motor abnormality, the gastrointestinal surgeon should ask nine key questions:

1. Does the patient have pathologic acid gastroesophageal reflux?
2. Does the patient have a structural abnormality of the esophagus such as a diverticulum or hiatal hernia?
3. Does the patient have some underlying disorder known to be associated with an esophageal motor disorder (e.g., diabetes, alcoholism)?
4. Does the patient have a manometrically identifiable motor disorder of the esophageal body, such as achalasia?
5. Does the patient have defective esophageal bolus clearance, such as stasis, retrograde transport, or incomplete bolus transit?
6. Is the patient able to maintain adequate nutrition orally?
7. Is there impaired LES sphincter opening and resistance to bolus transport across the LES?
8. Is the LES mechanically defective?
9. Finally, if considering an operative procedure, are the manometric length of the esophagus, the esophageal contraction amplitudes, and the percentage of wet swallows that are considered effective known?

The answer to these questions can be determined only by performing additional tests on patients suspected of having an esophageal motility disorder. The diagnostic tests necessary may be divided into five broad groups: (1) tests to detect structural abnormalities of the esophagus, (2) tests to detect esophageal body contraction abnormalities, (3) tests to evaluate esophageal bolus clearance, (4) tests to provoke esophageal symptoms, and (5) tests to detect increased esophageal exposure to gastric and duodenal juice.

Tests to Detect Structural Abnormalities of the Esophagus

The first diagnostic evaluation in patients with suspected esophageal disease should be a contrast roentgenographic examination of the esophagus with full assessment of the stomach and duodenum, followed by upper gastrointestinal endoscopy with biopsy. Effective roentgenographic evaluation of the esophagus is dependent on the use of a combination of different examining techniques.

In any patient with dysphagia, endoscopy is indicated even in the face of a normal roentgenographic study. Regardless of the radiologist's interpretation of an abnormal finding, each structural abnormality of the esophagus should be confirmed visually and through biopsy. Endoscopy and biopsy are also necessary to assess for the presence of complications of GERD (i.e., esophagitis, stricture, and Barrett's esophagus). Fiberoptic endoscopic examination of swallowing is another valuable technique to assess pharyngeal sensitivity and swallowing. It provides a clear and direct view of the hypopharynx and larynx. Aspiration or evidence of aspiration can be directly observed. It allows for rapid clinical evaluation of patients in nursing homes, outpatient clinics, or intensive care units when videofluoroscopic examination is unavailable or unsuitable. It can evaluate vocal cord movement and the physical appearance of the pharyngeal and laryngeal structures.[64] The success of fiberoptic endoscopic examination of swallowing has led to the development of transnasal and transoral diagnostic endoscopy with narrow-diameter endoscopes (5.3 mm) in unsedated patients.[65]

The advance of endoscopic ultrasonography allows improved assessment of the esophageal wall. It is performed with a side-view endoscope that has a radial scanning ultrasound probe mounted at its tip. Contact with the esophageal wall is accomplished with a water-filled balloon over the ultrasound probe. This provides a circular ultrasound cross section of the esophageal wall that can be visualized on an image processor. On the ultrasound image, the wall of the esophagus consists of five layers that correspond to the acoustic reflections and the interfaces between them. With this technique, thickening of the wall in the distal end of the esophagus can easily be demonstrated in patients with achalasia and diffuse esophageal spasm. Fibrosis of the wall can be recognized in patients with scleroderma. Intramural tumors not seen on computed tomography or endoscopy can be detected and, in some situations, may be responsible for an observed motor disorder.[1]

Tests to Detect Esophageal Contraction Abnormalities

Many patients with symptoms of an esophageal motor disorder do not show a structural abnormality on standard roentgenographic and endoscopic evaluation. In these situations, esophageal function tests are necessary to identify a functional disorder. Tests to evaluate esophageal contraction abnormalities include stationary

manometry of the pharyngoesophageal segment, esophageal body, and LES and ambulatory 24-hour esophageal motility monitoring.

Stationary Esophageal Manometry

Stationary esophageal manometry is a widely used technique to examine the motor function of the esophagus and its sphincters. It is indicated whenever a motor abnormality of the esophagus is suspected on the basis of complaints of dysphagia, odynophagia, or noncardiac chest pain and when the barium swallow or endoscopy does not show a clear structural abnormality.[1] Esophageal manometry is particularly necessary to confirm the diagnosis of specific primary esophageal motility disorders (i.e., achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive LES).[26] It also identifies nonspecific esophageal motility abnormalities and esophageal motor disorders secondary to systemic disease, such as scleroderma, dermatomyositis, polymyositis, and mixed connective tissue disease. Stationary manometry is the most accurate method for assessing LES function and has been the basis for identification and classification of the motor disorders of the esophageal body.[27] In patients with disorders of the pharyngoesophageal phase of swallowing, manometry is complementary to and should ideally be performed simultaneously with videocineroentgenography.[66,67] In patients with GERD, manometry of the esophageal body can identify a mechanically defective LES as the cause of increased esophageal acid exposure and evaluate the adequacy of esophageal clearance function.[44]

Esophageal manometry is performed with electronic pressure-sensitive transducers located within a catheter or water-perfused catheters with lateral side holes attached to transducers outside the body. The catheter usually consists of a train of five or more pressure transducers or water-perfused tubes bonded together with lateral openings placed at 5-cm intervals from the tip and oriented radially around the circumference. A special catheter assembly consisting of four or eight lateral openings at the same level, oriented radially at 90 or 45 degrees to each other, is useful when constructing a three-dimensional image of the LES. Other specially designed catheters are used to assess the UES. When water-filled catheters are used, the rate of water infusion must be adjusted to obtain reliable and reproducible pressure tracings. This is best achieved with a low-compliance pneumohydraulic capillary infusion system.[1]

The manometric catheter is passed through the nose and esophagus and into the stomach, and the gastric pressure pattern is confirmed. The catheter is withdrawn across the cardia to identify the high-pressure zone of the LES. Although some advocate steady, rapid withdrawal while patients hold their breath, we have found that stepwise withdrawal of the catheter at 0.5- or 1.0-cm intervals or slow motorized pullback at a speed of 1 mm/sec for 60 seconds provides reproducible and more quantitative information and allows patients to breathe normally during the procedure.[1,20] As the pressure-sensitive station is brought across the gastroesophageal junction, a rise in pressure off the gastric baseline identifies the beginning of the LES. The respiratory inversion point is identified when the positive excursions that occur with breathing in the abdominal cavity change to negative deflections in the thorax. The respiratory inversion point serves as the reference point at which the amplitude of LES pressure and the length of the sphincter exposed to abdominal pressure are measured. As the pressure-sensitive station is withdrawn into the body of the esophagus, the upper border of the LES is identified by the drop in pressure to the esophageal baseline. From these measurements, the resting pressure, abdominal length, and overall length of the sphincter are determined (Fig. 8–13). To account for the asymmetry of the sphincter, the pressure profile is repeated as each of the five radially oriented transducers is pulled through the sphincter, and sphincter pressure values above gastric baseline, overall sphincter length, and abdominal length of the sphincter are averaged. Alternatively, if the pressure-sensitive stations are radially oriented at the same level on the catheters, a single pull-through is all that is necessary.

Table 8–4 shows the values for these parameters in 50 normal volunteers without subjective or objective evidence of a foregut disorder. The level at which incompetence of the LES occurs was defined by comparing the frequency distribution of these values in the 50 healthy volunteers with the values for a population of similarly studied patients with symptoms of GERD.[20] The presence of increased esophageal exposure to gastric juice was documented by 24-hour esophageal pH monitoring. Based on these studies, a mechanically defective sphincter is identified by having one or more of the following characteristics: an average LES pressure of less than 6 mm Hg, an average length exposed to the positive-pressure environment in the abdomen of 1 cm or less, and an average overall sphincter length of 2 cm or less. When compared with the normal volunteers, these values are below the 2.5 percentile for sphincter pressure, overall length, and abdominal length.

If manometry of the LES is performed with four to eight radially oriented pressure transducers, a three-dimensional image of the sphincter can be constructed by plotting the pressure measured at each station of the pullback radially around an axis representing the gastric baseline.[19,49] For visual purposes, three-dimensional reconstruction of the sphincter pressure image can be enhanced by applying a cubic curve-smoothing interpolation that retains the original points while adding intermediate ones to give a smoother surface to the three-dimensional sphincter image and thus improve its readability. Commercially available computer programs enable the creation of three-dimensional sphincter images that can be rotated on a computer screen. This allows inspection of the sphincter image for asymmetry.

The volume circumscribed by the three-dimensional sphincter image integrates pressure exerted over the entire length and around the circumference of the sphincter into one value that represents sphincter resistance to reflux of gastric contents. This value has been termed the *sphincter pressure vector volume* and can be calculated with standard trigonometric formulas. Validation studies and application of this technique in a large

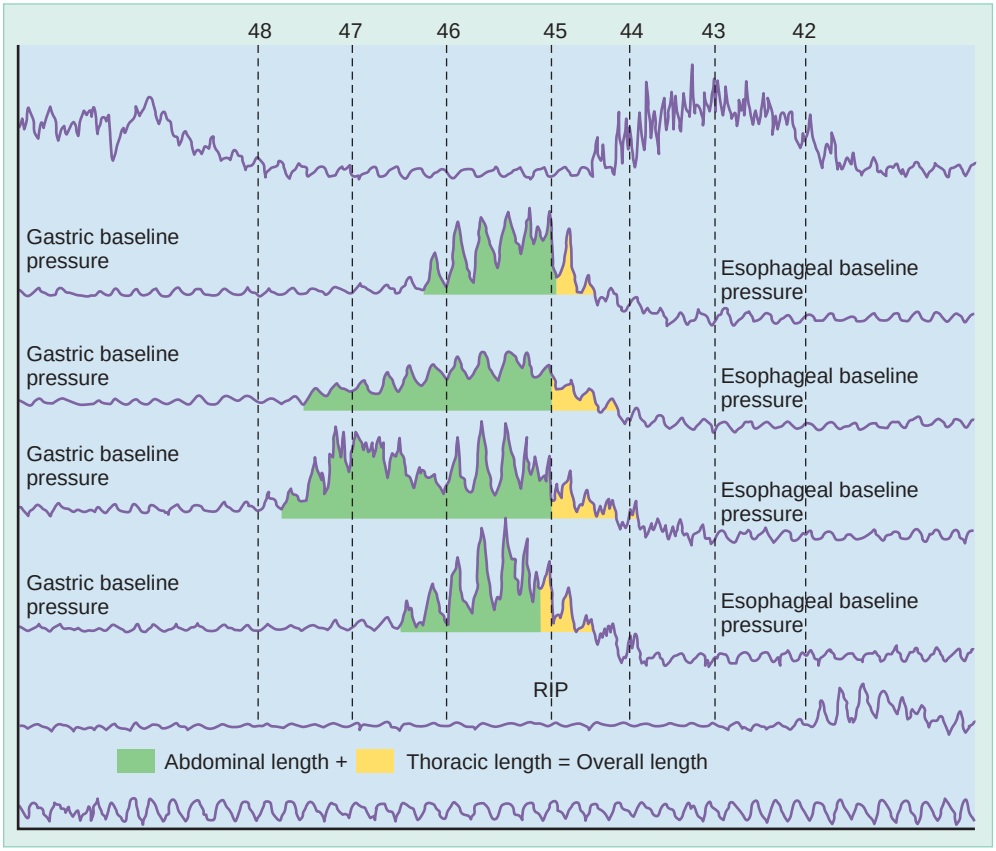


Figure 8–13. Sample manometric measurement of the lower esophageal sphincter using four radially orientated pressure transducers. The distances are measured from the nares. The asymmetry of the sphincter can be seen, as well as the portion of the sphincter exposed to abdominal pressure. RIP, respiratory inversion point.

number of patients with GERD have shown that calculation of the sphincter pressure vector volume is superior to standard techniques in assessing sphincter resistance to reflux of gastric juice,[19] particularly in patients with increased esophageal acid exposure but no mucosal injury and in those with borderline sphincter abnormalities.

To assess relaxation and postrelaxation contraction of the LES, a pressure transducer is positioned within the high-pressure zone, with a distal transducer located in

Table 8–4 Normal Manometric Values of the Lower Esophageal Sphincter ($N = 50$)

		Percentile	
	Median	**2.5**	**97.5**
Pressure (mm Hg)	13.0	5.8	27.7
Overall length (cm)	3.6	2.1	5.6
Abdominal length (cm)	2	.9	4.7
	Mean	**Mean – 2 SD**	**Mean + 2 SD**
Pressure (mm Hg)	13.8	4.6	23
Overall length (cm)	3.7	2.1	5.3
Abdominal length (cm)	2.2	.6	3.8

From DeMeester TR, Stein HJ: Gastroesophageal reflux disease. In Moody FG, Jones RS, Kelly KA, et al: Surgical Treatment of Digestive Disease, 2nd ed. Chicago, Year Book, 1989, p 65.

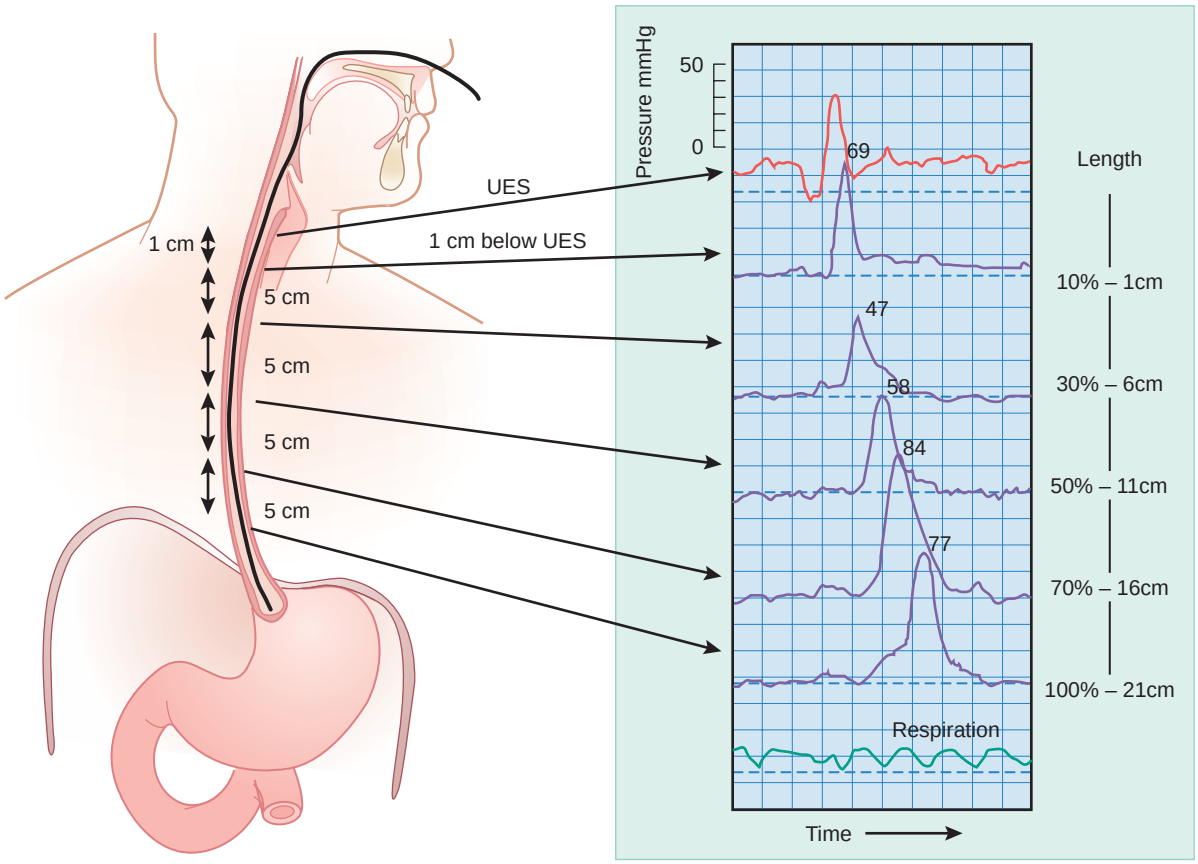


Figure 8–14. Schematic drawing combined with a sample manometric tracing showing placement of the transducers for standard manometry and the pressure response throughout the esophageal body during a swallow. UES, upper esophageal sphincter.

the stomach and the proximal transducer within the esophageal body. Ten wet swallows with 5 ml of water are performed. The pressure of the LES should drop to the level of gastric pressure during each wet swallow. The function of the esophageal body is assessed with three to five pressure transducers located at various levels in the esophagus. To standardize the procedure, the most proximal pressure transducer is placed 1 cm below the well-defined cricopharyngeal sphincter, with the distal orifices trailing at 5-cm intervals over the entire length of the esophagus. With this method, a pressure response throughout the whole esophagus can be obtained on swallowing (Fig. 8–14). The response to 10 wet swallows with 5 ml of room-temperature water is recorded. The amplitude, duration, and morphology of contractions (i.e., the number of peaks and repetitive activity) after each swallow are calculated at all recorded levels of the esophageal body. The delay between esophageal contractions at the various levels of the esophagus is used to calculate the speed of wave propagation and to classify contractions as peristaltic, simultaneous, or not transmitted. Based on this information, motor disorders of the esophagus are identified and classified (see Table 8–1). Typical manometric tracings of a patient with nutcracker esophagus, diffuse esophageal spasm, and achalasia are shown in Figures 8–15 through 8–17. Display of a patient's values at the various levels of the esophagus against a background of normal values can make abnormalities more apparent (Fig. 8–18).

Because of the rapidity of events during the pharyngeal phase of swallowing, manometry in patients with suspected cricopharyngeal dysfunction should be performed with specially designed catheters. Both water-perfused and electronic systems have been used. Some advocate that electronic pressure-sensitive transducers are superior because they have a much higher frequency response than water-perfused catheters do and avoid the pharyngeal irritation that occurs with a water-perfused system.[66] The position, length, and pressure of the cricopharyngeal sphincter are assessed with a stationary pull-through technique. The manometry catheter is withdrawn in 0.5-cm intervals from the upper esophagus through the UES region into the pharynx.

To account for the anatomic asymmetry of the UES (Fig. 8–19), five measurements with the pressure transducers oriented in various directions are made, and an average is calculated. Localization of the upper and lower border of the UES can be determined manometrically during the station pull-through of the sphincter. Such localization may be helpful if an operative procedure is planned because a nasogastric tube can be marked at a

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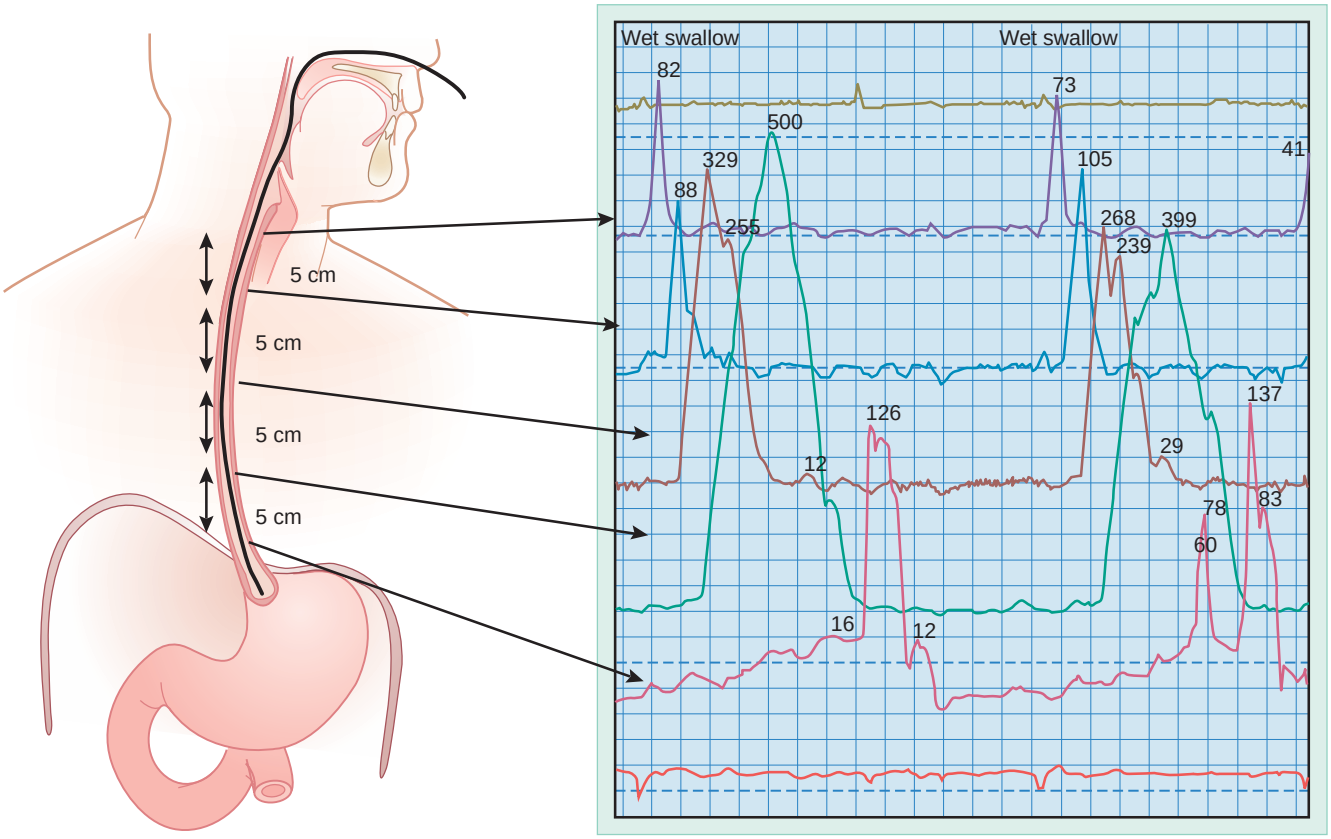


Figure 8–15. Manometric record from a patient with nutcracker esophagus showing distal esophageal peristaltic contractions of excessively high amplitude and long duration of contractions after wet swallows.

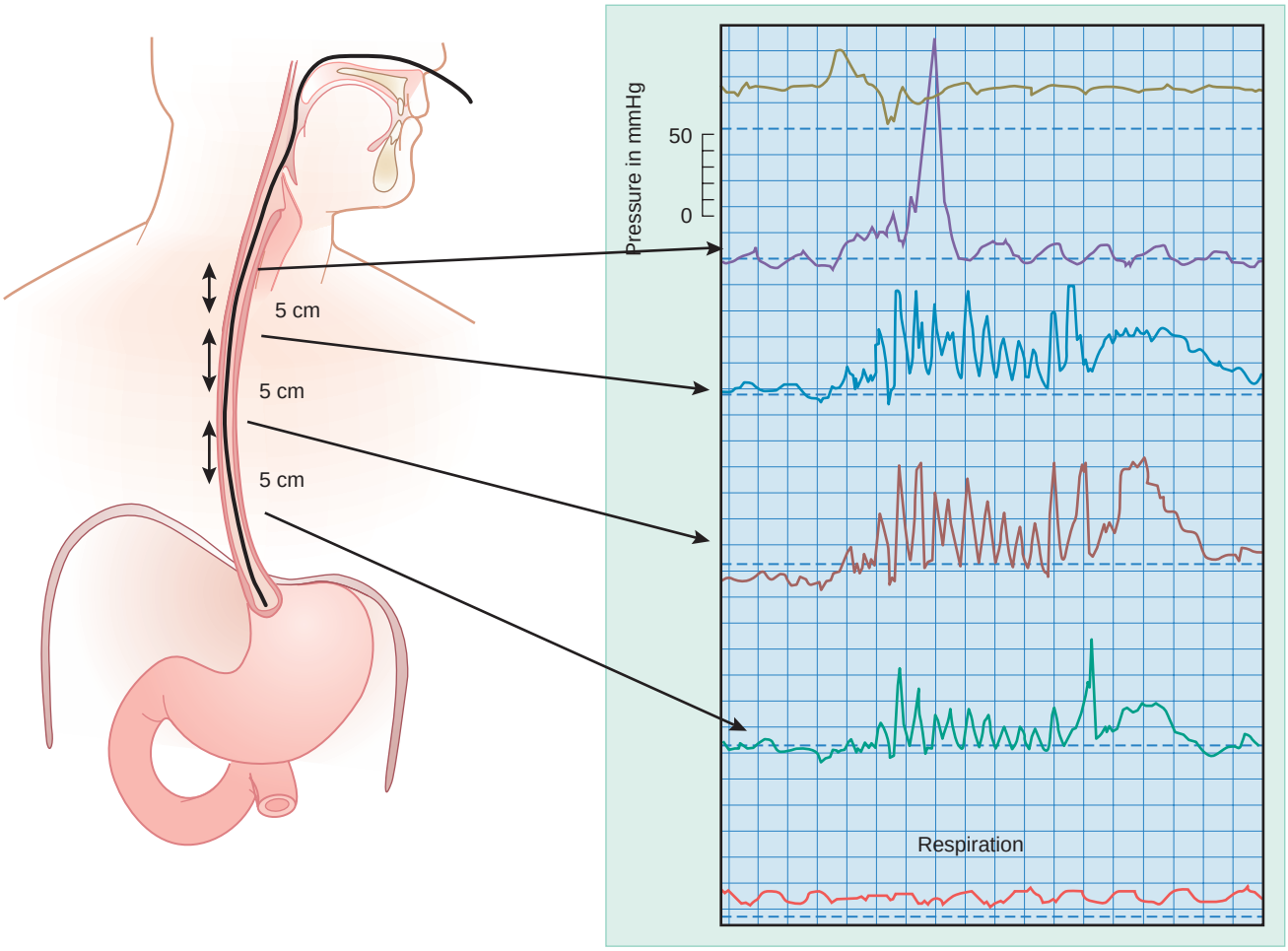


Figure 8–16. Manometric record from a patient with diffuse esophageal spasm showing repetitive, simultaneous contractions in the distal esophageal body.

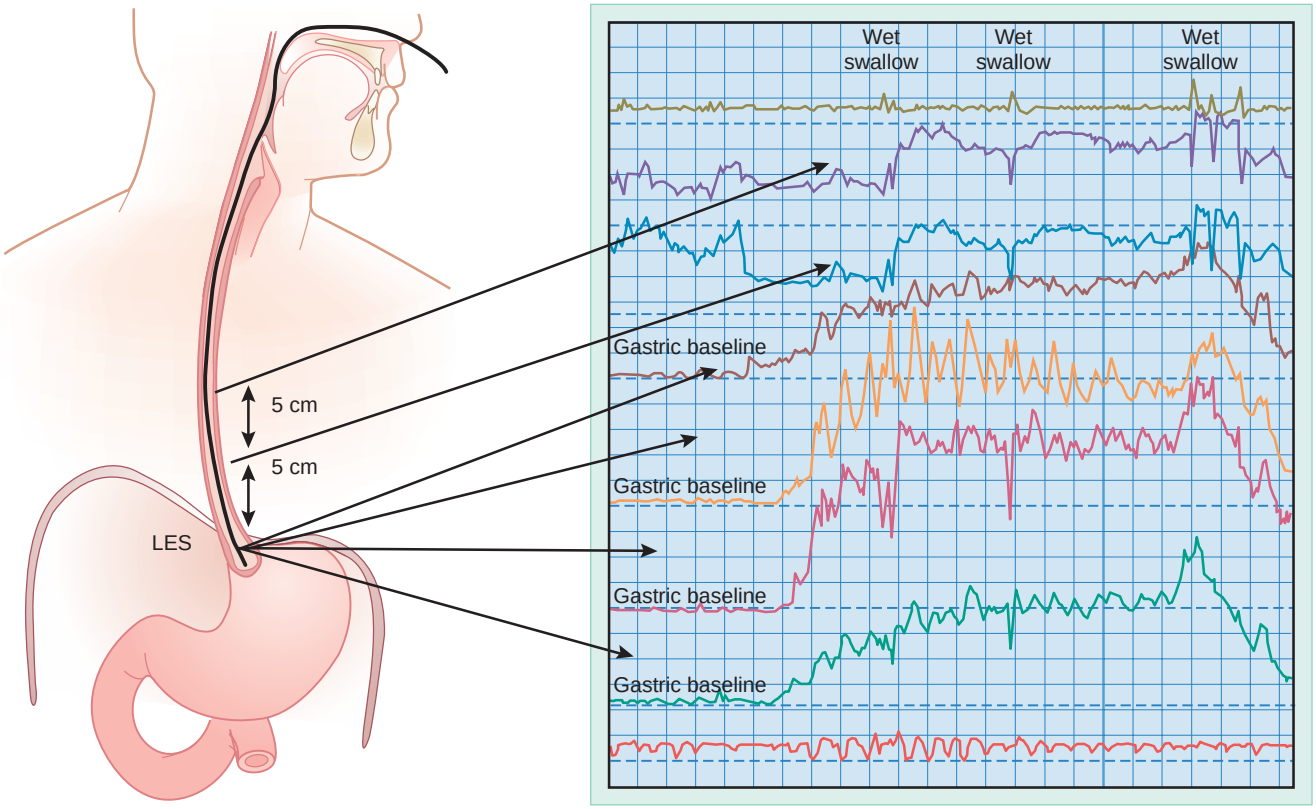


Figure 8–17. Manometric record from a patient with achalasia showing failure of the lower esophageal sphincter (LES) to relax on swallowing. The esophageal body shows aperistalsis.

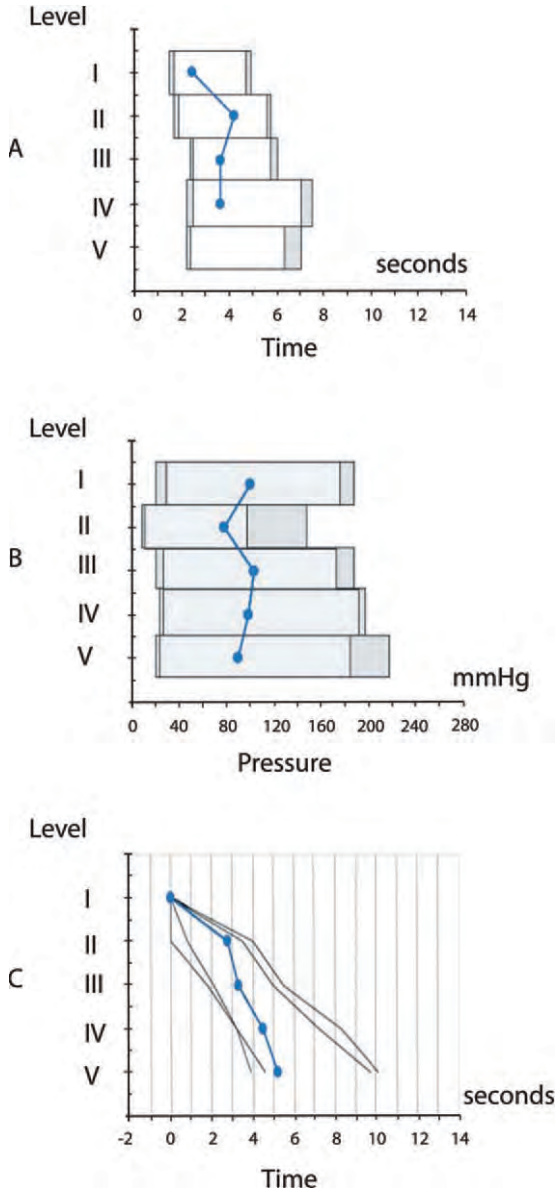


Figure 8–18. Graphic display of esophageal contraction characteristics at five levels of the esophagus (wet swallows). Patient values (*blue line*) are displayed against a background of normal values obtained in 60 asymptomatic volunteers (*solid lines*: 5th, 10th, 19th, and 95th percentiles). **A,** Duration of esophageal contractions. **B,** Amplitude of esophageal contractions. **C,** Wave progression.

site corresponding to the location of the patient's UES and placed in the patient's esophagus. During the operation the surgeon can then palpate the tip of the nasogastric tube, which will help guide the surgeon to the upper extent of the myotomy because failure to incorporate the proximal UES in the myotomy is one of the most frequent mistakes made. A dedicated water-perfused catheter consisting of eight lateral ports located at 0.5-cm intervals is of special use to evaluate abnormalities of sphincter opening and to detect evidence of increased outflow resistance through the pharyngoesophageal segment. The opening of the UES is studied by placing one of the middle eight lateral pressure ports at the upper border of the cricopharyngeal sphincter while the other ports straddle the hypopharynx and upper esophagus (Fig. 8–20).[66] High-speed graphic recordings (50 mm/sec) are necessary to obtain an assessment of the coordination of cricopharyngeal relaxation with hypopharyngeal contraction.

The UES is opened by a traction force acting on the relaxed cricopharyngeus. This force is the consequence of the significant laryngohyoid elevation that occurs during the swallow. Normal swallowing and normal UES relaxation are associated manometrically with a subatmospheric pressure drop. The pressure at sphincter opening is determined by using a series of dry swallows. Atmospheric pressure is used as a baseline to determine whether the patient's opening pressure is subatmospheric. The pressure drop usually occurs early in the manometric tracing before any pharyngeal events can be seen (Fig. 8–21). An inability to achieve a subatmospheric pressure drop may be associated with impaired sphincter opening and relaxation (Fig. 8–22).

Normally, the sphincter is open and fully relaxed before the bolus arrives at this segment, and thus flow through the sphincter usually occurs with very little resistance. A measure of the resistance to flow through the sphincter can be determined by measuring the intrabolus pressure on the manometric tracing. Resistance to trans-sphincteric flow will occur if there is impaired sphincter opening, impaired relaxation, or decreased compliance of the upper esophageal musculature. Manometrically, this will be manifested by raised intrabolus pressure. Resistance to trans-sphincteric flow is determined by giving the patient a 5-ml bolus of water to swallow. This requires detection of the pressure at the bolus tail, which is most consistently and reliably determined by measuring the pressure just before the major upstroke of the pharyngeal stripping peristaltic contraction wave in the pharynx or just before the major upstroke of the UES postcontraction wave. Accurate determination of intrabolus pressure requires manovideofluorography (see Fig. 8–6); however, it is possible to get some indication of intrabolus pressure by routine manometry testing. Compliance of the pharyngoesophageal segment can also be determined by measuring intrabolus pressure during a series of swallows with an incremental increase in the swallowed volume. Compliance of the pharyngoesophageal segment is assessed by determining the rise in intrabolus pressure during a combination of 5-, 10-, and 15-ml swallows of water. There is usually only a slight increase in intrabolus pressure when going from a 5-ml to a 10-ml to a 15-ml swallow of water. A more steeply rising intrabolus pressure associated with an increase in swallow volume is indicative of decreased compliance of the pharyngoesophageal segment (see Fig. 8–7). Contraction amplitudes and wave progression of the pharyngeal stripping wave are assessed during the water swallows.

Carefully performed motility studies may demonstrate impaired sphincter opening, insufficient relaxation (Fig. 8–23) or premature contractions of the cricopharyngeus,

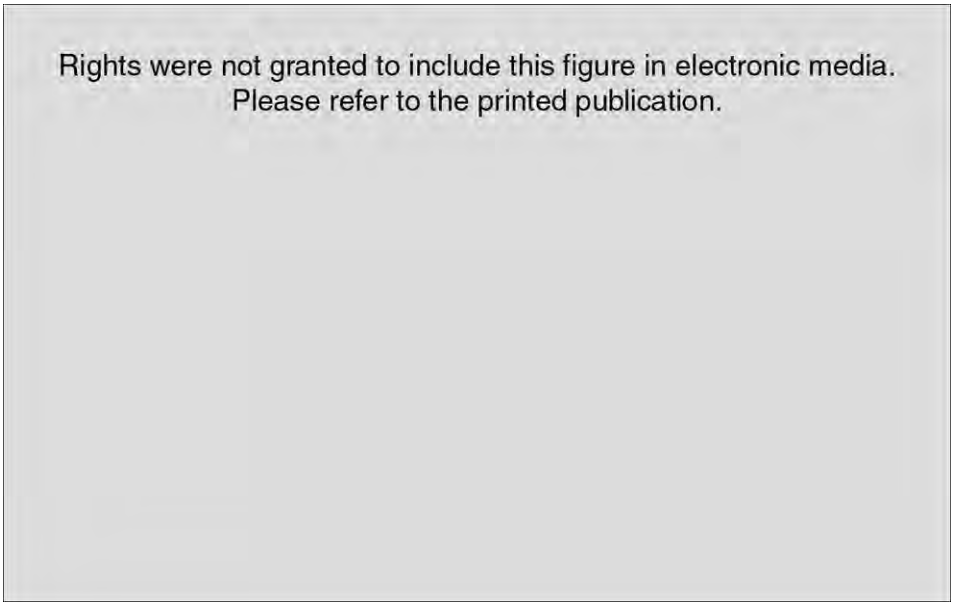


Figure 8–19. Three-dimensional pressure profile of the upper esophageal sphincter illustrating the short axial zone of maximal pressure and the marked radial asymmetry. UOSP, upper esophageal sphincter pressure. (From Welch RW, Luckmann K, Ricks PM, et al: Manometry of the normal upper esophageal sphincter and its alterations in laryngectomy. J Clin Invest 63:1039, 1979, with permission.)

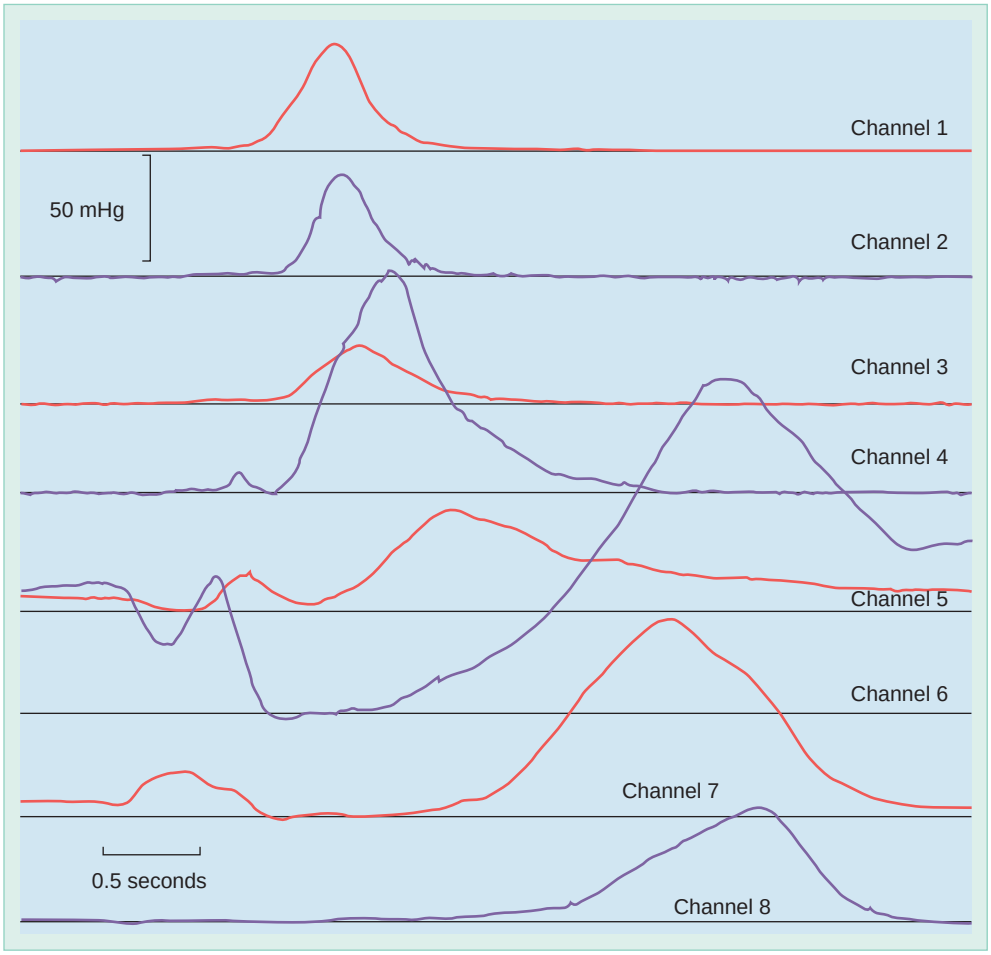


Figure 8–20. Record of a detailed manometric study of the pharyngoesophageal phase of swallowing showing the manometric correlates of pharyngeal peristalsis, elevation of the larynx, opening of the upper esophageal sphincter from proximal to distal, elevation of the cricoid, and the start of esophageal peristalsis.

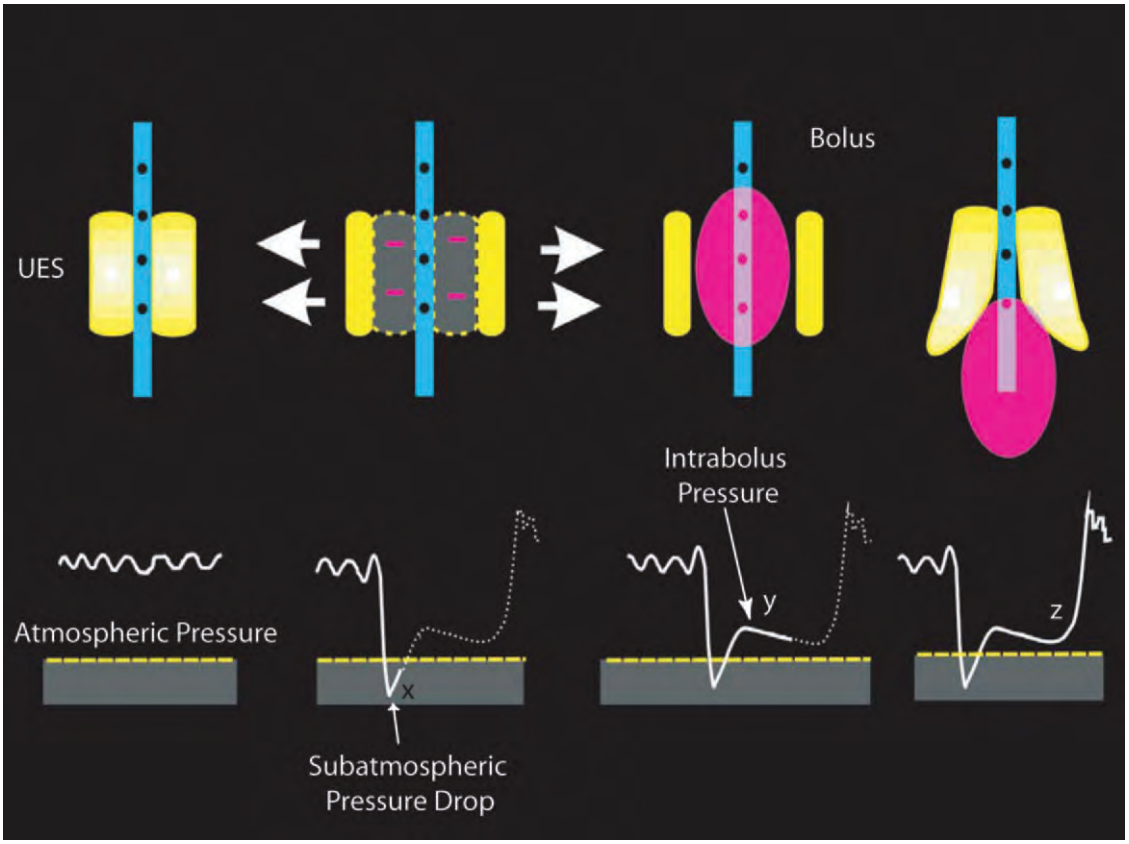


Figure 8–21. Schematic representation of upper esophageal sphincter (UES) dynamics and manometric correlates found in normal patients. At the initiation of the swallow, the cricopharyngeus relaxes and the UES is pulled open by the laryngohyoid elevation, which results in a subatmospheric pressure drop (x), followed by a rise in pressure as the bolus enters the UES (y). As the UES closes and the cricopharyngeus contracts, there is a sharp rise in the pressure tracing (z)

high sphincter pressure, or inadequate pharyngeal pressurization. Decreased compliance of the UES caused by restrictive myopathy can be recognized manometrically by the observation of a shoulder on the hypopharyngeal pressure wave (Fig. 8–24). The size of this shoulder correlates directly with the degree of outflow obstruction. The sensitivity of manometry to detect abnormalities in pharyngoesophageal function is further increased by simultaneous videocineradiography.[24,67] A patient should be considered for cricopharyngeal myotomy if the disorder occurs in the pharyngeal phase of the swallow and is associated with evidence of impaired sphincter opening or increased outflow resistance (or both).

It should be remembered that all recorded manometric pressures are affected by variables such as the age of the patient, posture, bolus characteristics, catheter diameter, swallowing frequency, and compliance of the perfusion system.[68] Because these parameters are not necessarily standardized, they must be controlled within an individual laboratory. Each laboratory should define normal values from volunteers who have no subjective or objective evidence of a foregut disorder; alternatively, one laboratory may adopt the normal values of another laboratory, provided that identical procedures and equipment are used.

Ambulatory 24-Hour Esophageal Manometry

The intermittent and unpredictable occurrence of motor abnormalities and symptoms in patients with esophageal motility disorders limits the diagnostic value of stationary motility performed in a laboratory setting and consisting of 10 swallows over a short period. The technique of ambulatory esophageal manometry was developed to overcome these shortcomings by monitoring esophageal motor activity over a prolonged period during a variety of physiologic activities and correlating esophageal motor abnormalities with spontaneously occurring symptoms.[31,69,70]

Because of the high sampling frequency required to evaluate esophageal motor activity, prolonged outpatient monitoring of esophageal motility became available only after the introduction of portable digital data recorders with large storage capacity. Today, ambulatory esophageal motility monitoring allows the evaluation of esophageal motor function based on more than 1000 contractions recorded over an entire circadian cycle under a variety of physiologic conditions (i.e., upright activity, eating, and sleeping). This technique provides a more than 100-fold larger database for the assessment of esophageal motor function than standard manometry does.[35]

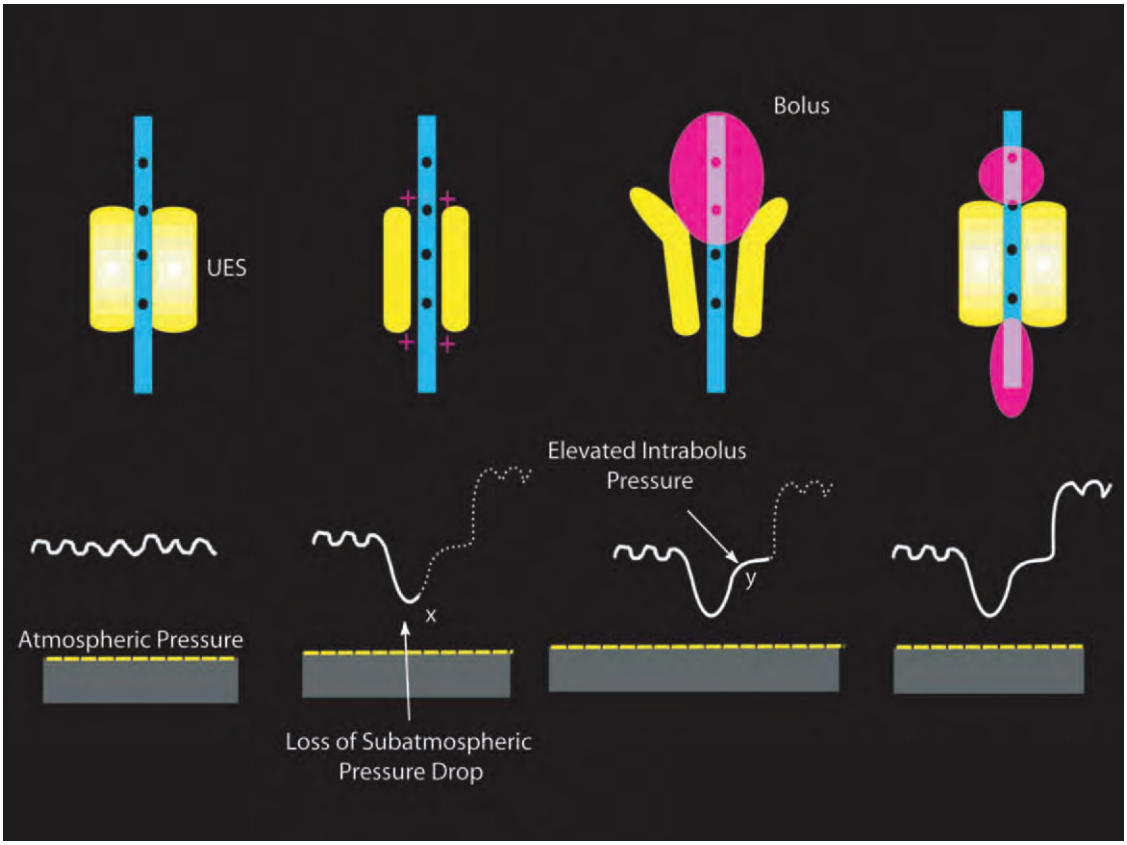


Figure 8–22. Schematic representation of upper esophageal sphincter (UES) dynamics and manometric correlates found in a patient with impaired sphincter opening and outflow resistance as a result of reduced compliance at the level of the UES. With impaired sphincter opening caused by either inadequate cricopharyngeus relaxation or impaired laryngohyoid elevation, there is loss of the normal subatmospheric pressure drop (x). With bolus entry into the UES, there is increased intrabolus pressure corresponding to the resistance to flow of the bolus through the UES (y).

Ambulatory esophageal motility monitoring is usually performed by placing a catheter with three or more electronic pressure transducers at 5-cm intervals above the upper border of the manometrically determined LES. The transducers are connected to a portable digital data recorder with sufficient memory to store pressure recordings from each channel over an entire circadian cycle. After placement of the transducers, the individuals are sent home and instructed to keep a diary for the next 24 hours in which they indicate when they retired for the night and awoke in the morning, when they ate their meals, and whenever a symptom occurred. The subjects are encouraged to perform normal daily activities during the study and to press an event marker when a spontaneous symptom occurs. After the 24-hour period, the subjects return to the laboratory, where the pressure transducers are removed and the data from the recorder are unloaded onto a personal computer. Data analysis is usually performed separately for the upright, supine, meal, and symptomatic periods with a computer program. This approach allows quantification of abnormal esophageal motor events and direct correlation of spontaneously occurring symptoms with motor abnormalities.

After its clinical introduction in 1985, ambulatory esophageal motility monitoring has been used primarily to identify esophageal motor abnormalities as the cause of noncardiac chest pain.[69,70] Recent studies in a larger number of unselected patients have found that many patients do not experience these typical symptoms during the 24-hour monitoring period.[32,71] Even when a spontaneous episode of chest pain occurred during the monitored period, motor abnormalities associated with the symptoms were rare and gastroesophageal reflux was found to be a far more frequent cause of noncardiac chest pain than esophageal motor disorders were. Consequently, ambulatory manometry in this situation should be performed simultaneously with esophageal pH monitoring and should be reserved for patients with daily symptoms.

Because of the enlarged database and the more physiologic conditions under which data are acquired, ambulatory manometry is superior to standard manometry for the evaluation of esophageal body function in patients with symptoms suggestive of a primary or secondary esophageal motor disorder.[35] The efficacy of esophageal motor activity can be determined by assessing the prevalence of peristaltic contractions with sufficient amplitude

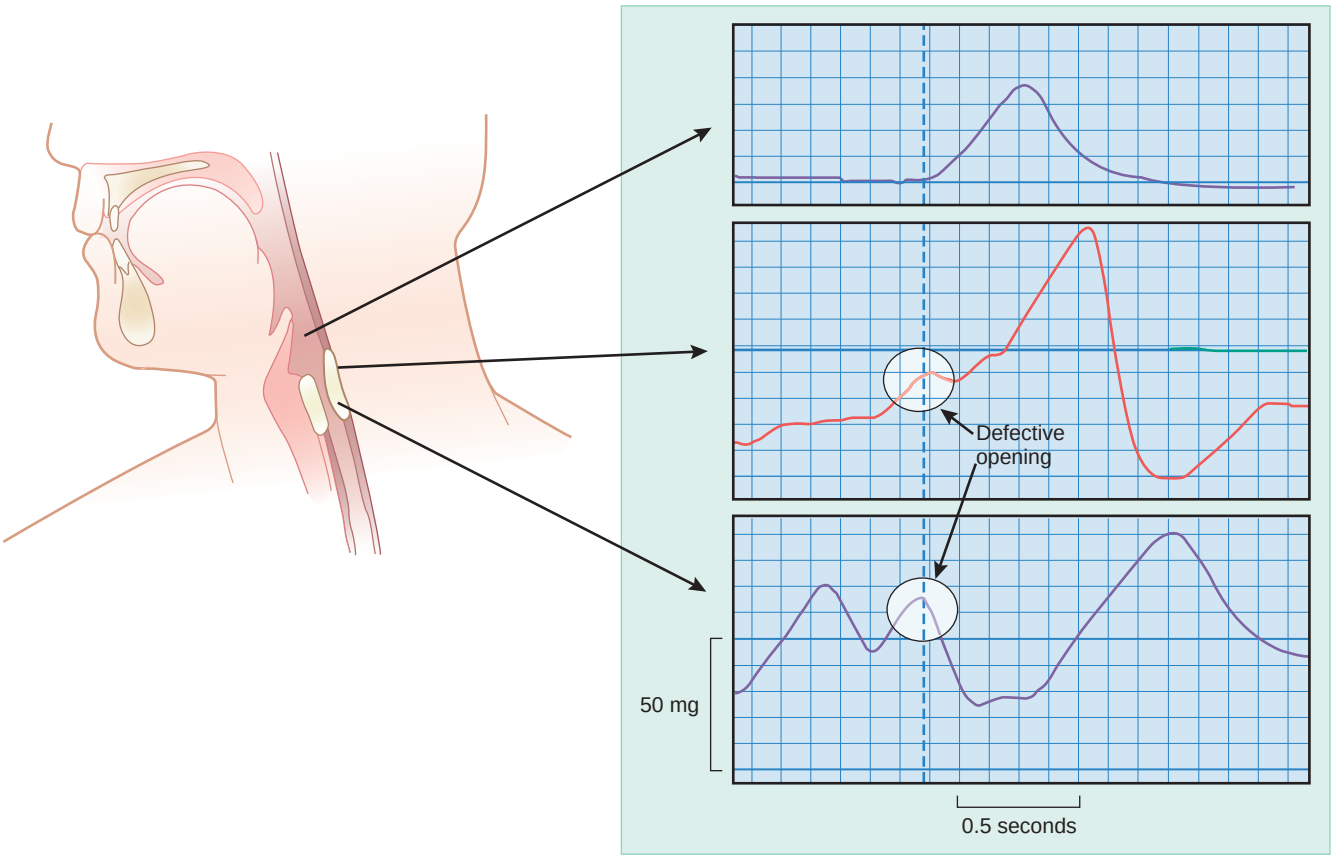


Figure 8–23. Manometric record showing defective and impaired upper esophageal sphincter (UES) opening. On initiation of the swallow, the UES should demonstrate a subatmospheric pressure drop. This record shows failure to achieve the drop.

to propel a bolus and clear refluxed gastric contents during the 24-hour monitoring period. Less than 50% of effective contractions during meals on ambulatory esophageal motility monitoring indicates the presence of a severe esophageal motor abnormality (see Fig. 8–11). Our experience with more than 300 ambulatory esophageal motility recordings in patients with esophageal motor disorders has shown that this approach allows quantification of the severity of a motor disorder and objective assessment of the effects of medical or surgical therapy.[35]

Tests to Evaluate Esophageal Bolus Clearance

Videocineroentgenography

High-speed cinerecording or videotaping of roentgenographic pharyngoesophageal contrast studies allows reevaluation of individual swallows through review of the study at various speeds. The study is very useful for evaluation of the pharyngeal phase of swallowing. Observations that suggest oropharyngeal or cricopharyngeal dysfunction include misdirection of barium into the trachea or nasopharynx, prominence of the cricopharyngeal muscle (i.e., cricopharyngeal bar (Fig. 8–25), Zenker's diverticulum (Fig. 8–26), a narrow pharyngoesophageal segment, and stasis of contrast medium in the valleculae or hypopharyngeal recesses (Fig. 8–27).[72] These findings are not usually specific but are common manifestations of neuromuscular disorders that affect the pharyngoesophageal area. Studies using liquid barium, barium-impregnated solids, or radiopaque pills greatly aid in the evaluation of normal and abnormal motility in the esophageal body. Loss of the normal stripping wave or segmentation of the barium column with the patient in the recumbent position can be correlated with reduced contraction amplitude or abnormal waveforms in the esophageal body on manometry.[51,73] In addition, subtle structural abnormalities such as small diverticula, webs, and extrinsic impressions of the esophagus may be recognized only with motion-recording techniques.

Esophageal Transit Scintigraphy

Esophageal transit scintigraphy is another technique for the evaluation of esophageal function.[74] The esophageal transit of a 10-ml water bolus containing sulfur colloid is recorded with a gamma camera. Transit time is measured separately in the proximal and distal esophagus. With this technique, delayed bolus transit can be shown in patients with a variety of esophageal motor disorders,

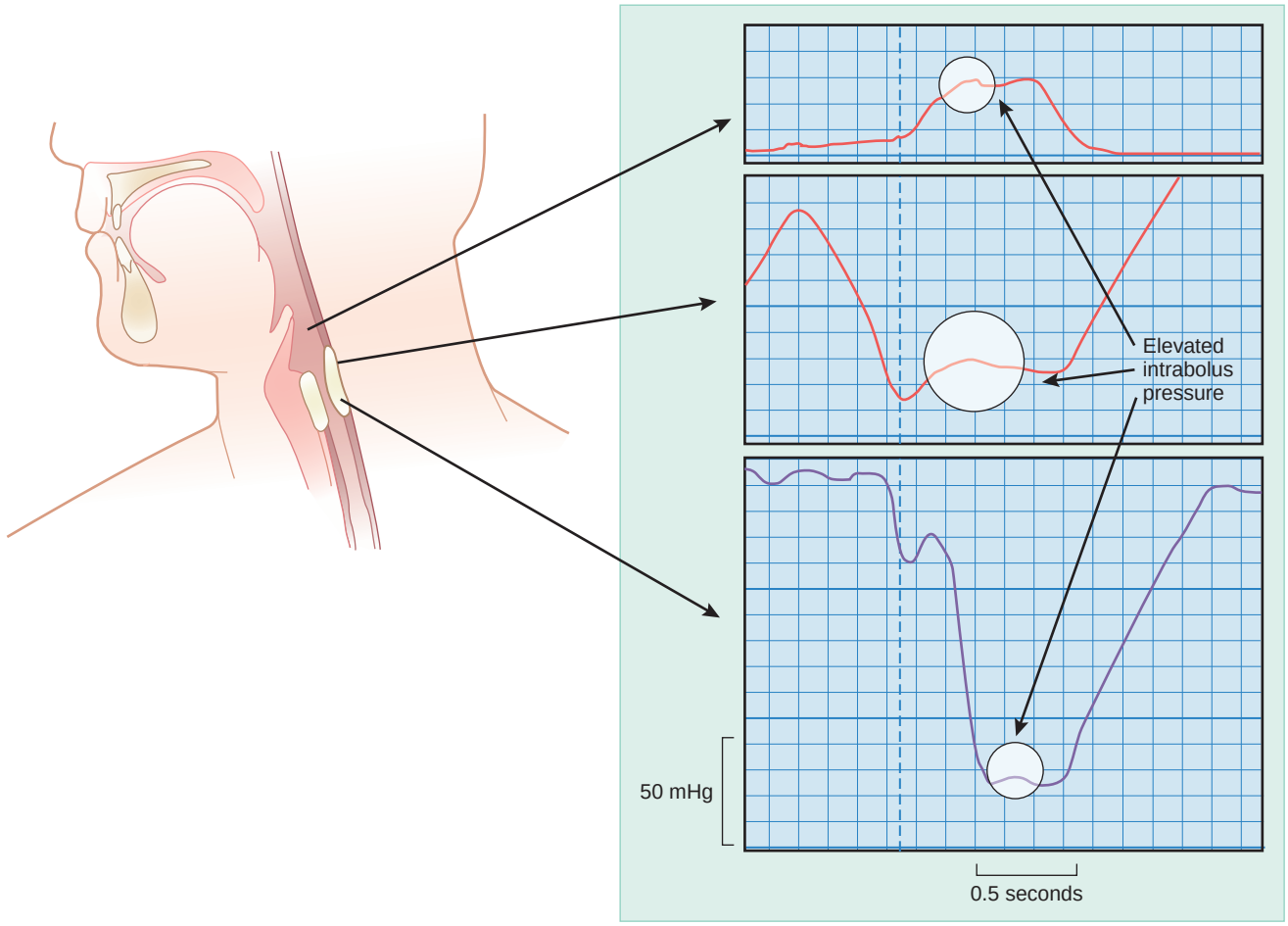


Figure 8–24. Manometric record showing impaired sphincter opening and decreased compliance of the upper esophageal sphincter (UES) resulting in elevated intrabolus pressure on both the pharyngeal and UES manometric pressure waves.

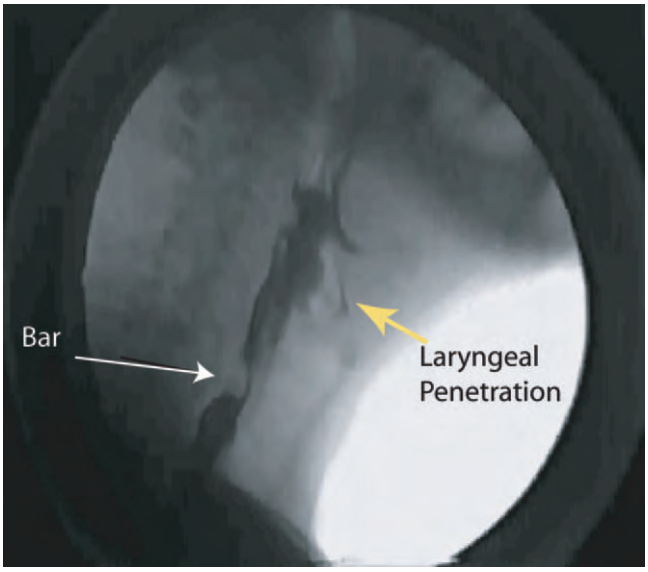
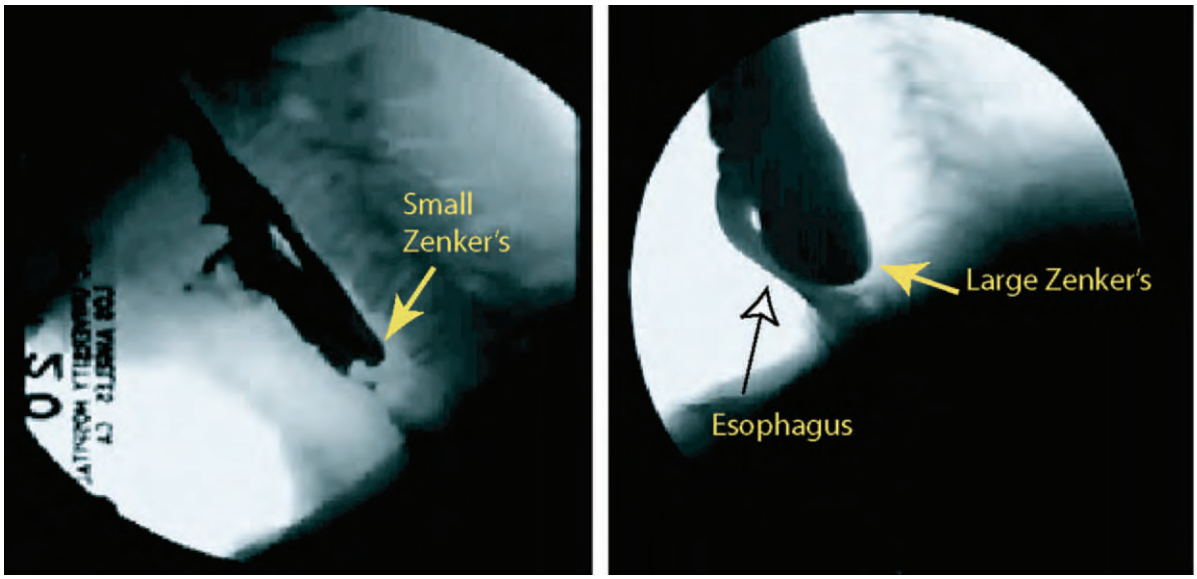


Figure 8–25. Barium contrast roentgenogram of pharyngeal swallowing activity showing a prominent cricopharyngeal indentation (*white arrow*) in a patient with dysphagia resulting from bulbar poliomyelitis. The patient also showed evidence of laryngeal penetration (*yellow arrow*).

including achalasia, scleroderma, diffuse esophageal spasm, nutcracker esophagus, and nonspecific motor disorders. It appears that transit scintigraphy is a reliable technique to quantify and document esophageal transit abnormalities.[21] However, the test lacks specificity because it cannot define the precise nature of a swallowing abnormality. Its best use is to quantify the effect of an esophageal motor abnormality by measuring esophageal emptying time.

Impedance

Impedance testing has recently been used to examine the clearance function of the esophagus and is indicated for all patients with suspected esophageal motility disorders. Impedance allows detection of all bolus movement in the esophagus without radiology. It is basically a measurement of opposition to electrical current flow. Esophageal impedance testing is performed with a specially designed catheter. The body of the catheter is electrically inert and has a series of ring electrodes spaced at various distances. The ring electrodes are essentially metallic conductors. An electrical current is sent to the individual electrodes with a current generator. The electrical conductivity between two ring electrodes



A B

Figure 8–26. **A,** Barium contrast roentgenogram of pharyngeal swallowing activity showing a small early Zenker diverticulum. **B,** If left untreated, a Zenker diverticulum will enlarge and the pouch itself may cause obstruction of the esophagus when filled with swallowed food.

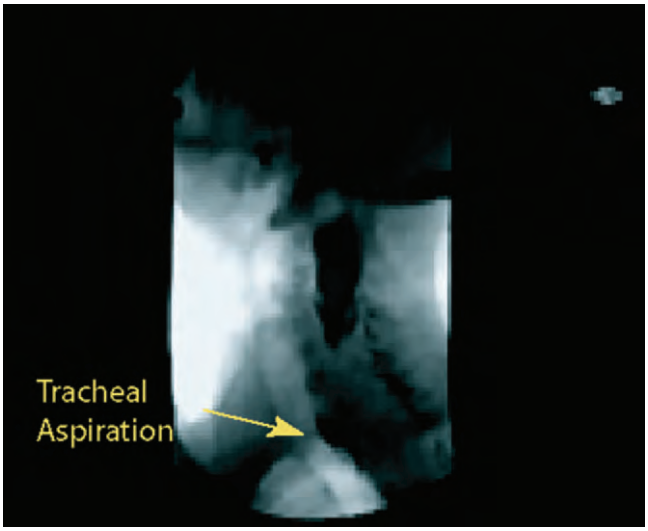


Figure 8–27. Barium contrast roentgenogram from a patient with cricopharyngeal achalasia and poor upper esophageal sphincter opening. There is significant retention of contrast medium at the level of the vallecula and piriform recesses, with no barium passing into the esophagus. The patient also shows significant aspiration of contrast into the trachea (*yellow arrow*).

can then be measured for this segment. A measure of the surrounding impedance can then be obtained and will reflect the background impedance of the esophageal wall. Any swallowed bolus, whether air, liquid, or solid, will have different impedance or conduct electricity differently. When a swallowed bolus spans two consecutive ring electrodes, electrical current flows between the two ring electrodes and the resistance can be measured. When no bolus is present, the impedance will be high. When the impedance falls, a bolus will be present between the two recording electrodes. A single impedance channel will detect bolus movement through the esophagus; however, if multiple impedance channels are used, it is possible to measure segmental changes and detect the direction of bolus movement and the propagation rate or clearance time (Figs. 8–28 and 8–29).

The impedance catheter is passed through the nose and esophagus into the stomach in much the same way as for esophageal manometry. The technique calls for obtaining baseline impedance for at least 5 seconds before a swallow. This baseline value represents the impedance of the surrounding esophageal mucosa and esophageal wall. Swallows consisting of normal saline and a viscous material that has a known standardized impedance value are then given. A liquid bolus is more electrically conductive than the esophageal lining. When a liquid bolus enters, impedance falls. Entry of the liquid bolus is depicted by a 50% drop in ohms from the preepisode baseline impedance.[75] Bolus exit is depicted when the impedance returns to the 50% point on the impedance recovery slope of the curve. The difference yields the bolus clearance time. A gas bolus is less electrically conductive than the esophageal lining. When a gas bolus enters, impedance rises. Gas entry is defined by a 50% rise in impedance with a mean impedance of 3000 ohms or greater (Fig. 8–30).

The multichannel intraluminal impedance catheter has now been combined with a standard manometry catheter to create a unique way to examine esophageal function. Currently, the standard combined

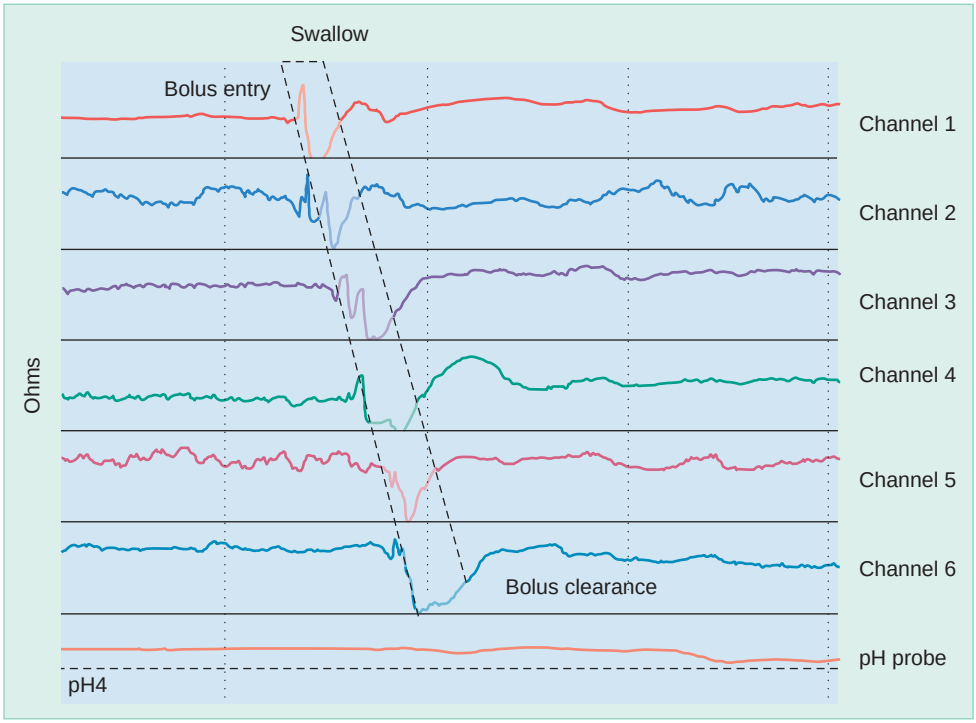


Figure 8–28. Impedance tracing depicting a normal liquid swallow. By using a multichannel catheter, the direction of bolus flow as well as the bolus clearance characteristics and propagation velocity can be calculated.

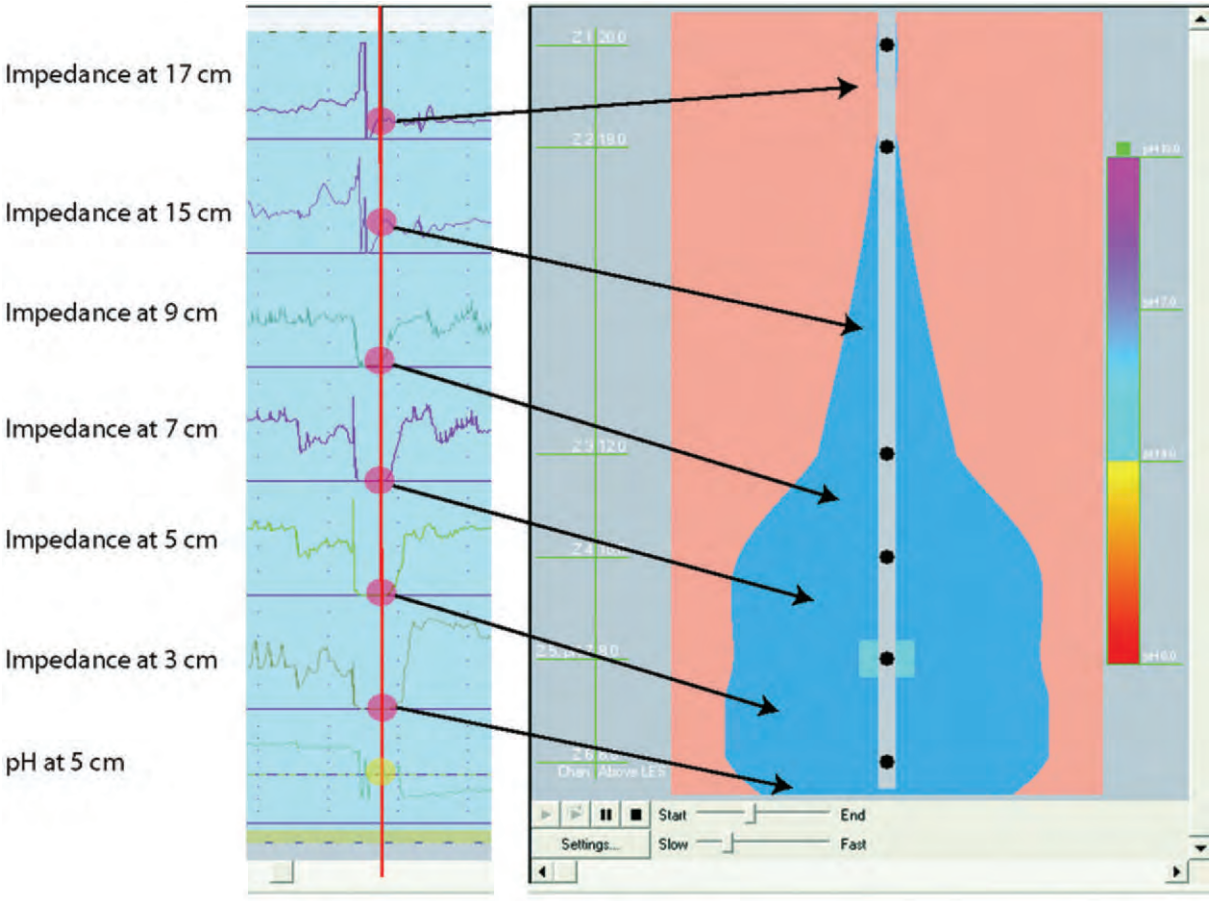


Figure 8–29. A sample tracing of an impedance record showing a software construct of a two-dimensional graphic of the bolus. A playback video of the bolus showing a two-dimensional moving waveform of the bolus as it traverses the esophagus can also be constructed. This can give further insight into bolus transit dynamics during a swallow.

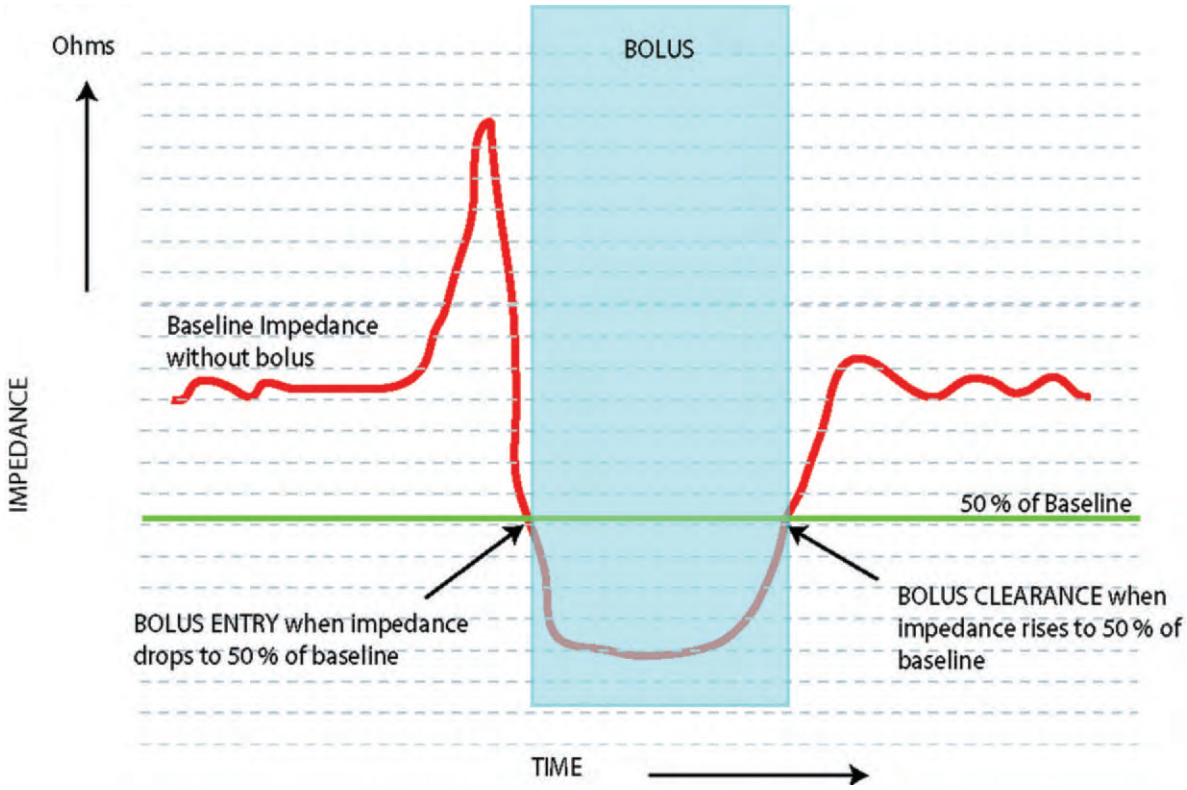


Figure 8–30. Diagrammatic representation of an impedance trace depicting the characteristics as the bolus enters the recording segment on the catheter. Before the swallow the impedance measured reflects the baseline conductivity of the segment and the impedance imparted by the esophageal wall and lumen. As air enters the segment, there is a sharp rise in impedance because air is a poor conductor of electricity. As the liquid bolus enters the segment, the impedance falls as a result of the increased electrical conductivity of the bolus. Bolus entry is defined by the point reflecting the 50% drop in impedance from preswallow baseline values. As the bolus passes, there is recovery of the impedance back to baseline values. The bolus exit position is defined on the impedance recovery curve at the point reflecting the 50% return to preswallow impedance.

impedance-manometry catheter consists of two circumferential solid-state pressure transducers located 5 and 10 cm from the tip and three unidirectional transducers spaced 15, 20, and 25 cm from the tip. By placing the impedance rings so that they straddle the pressure sensors, four impedance-measuring segments can be created at a distance of 10, 15, 20, and 25 cm from the tip of the catheter. This allows for quantization of esophageal squeeze pressure combined with an assessment of bolus velocity and clearance whether complete or incomplete (see Fig. 8–8).

Ambulatory Esophageal Impedance and pH Monitoring

Today, ambulatory esophageal impedance combined with esophageal pH monitoring allows for the evaluation of esophageal bolus clearance and esophageal pH over an entire 24-hour period. It is now possible to evaluate esophageal bolus clearance during eating, sleeping, and upright activity. The circadian motor pattern can be graphically displayed by showing the bolus clearance sequences (Fig. 8–31) during the monitored period.

Combined ambulatory pH and impedance monitoring is generally performed with a catheter that has six impedance channels and one to two pH electrodes. The impedance segments are usually positioned at 17, 15, 9, 7, 5, and 3 cm above the LES with the pH electrode 5 cm above the LES. If a second pH electrode is used, it is usually placed in the stomach to measure gastric pH (Fig. 8–32). This spacing allows for the optimum evaluation of retrograde and antegrade bolus movement.

It is possible to distinguish between primary and secondary peristaltic contractions. A determination of gastroesophageal reflux can be made, and it can further be categorized into either acid reflux or non-acid reflux. The advantage of 24-hour monitoring is that the patients can keep a diary of symptoms. Correlation can then be made between the symptoms and gastroesophageal reflux regardless of its pH. Noncardiac chest pain events related to esophageal distention and poor esophageal clearance can be evaluated with this new technique. Data analysis is usually performed with a computer program that specifically locates waveform areas with retrograde bolus movement. The program will also determine bolus entry and clearance points when reflux occurs and will

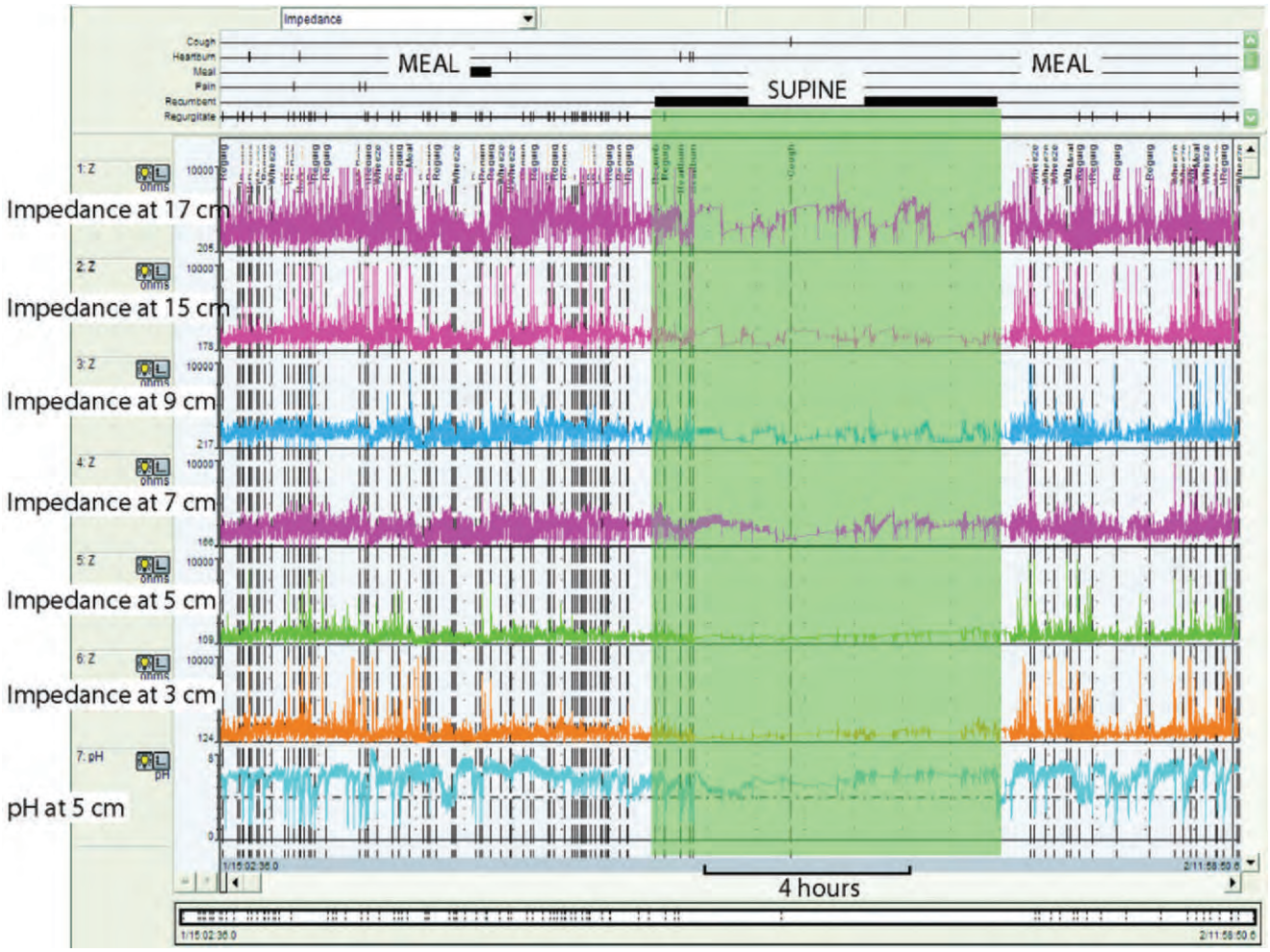


Figure 8–31. Condensed six-channel circadian esophageal combined impedance and pH motility tracing. Recording was started at 15:00 hours and terminated at 12:00 hours the next day. Time is shown on the x-axis. The six impedance segments were located 17 (*top tracing*), 15, 9, 7, 5, and 3 cm (*bottom tracing*) above the lower esophageal sphincter (LES). An electrode measuring pH was located 5 cm above the LES. Meal periods, the nighttime sleeping period, and reflux episodes are indicated at the bottom. The *dotted vertical lines* indicate the patient's symptoms during the recording period. Bolus movements and swallowing events in the esophagus are depicted by changes in impedance to give an indication of the motor activity occurring during the recording time. The circadian variability of esophageal motor activity can easily be recognized.

analyze the pH channel to determine drops below 4.0. In addition, the program will correlate the patient's specific symptoms with bolus movement and pH. In particular, the esophageal motor or clearance abnormalities associated with gastroesophageal reflux can be determined, and with a symptom index it is possible to ascertain whether the patient's symptoms are due to acid reflux or esophageal distention secondary to an esophageal clearance abnormality. The use of this tool in evaluating patients with esophageal motor disorders is still in its infancy, but it promises to yield further insight in these conditions. Currently, evaluation of antegrade swallows during a meal has to be reviewed manually. Although there are no reports on combined ambulatory multichannel intraluminal impedance and esophageal manometry, the technology exists to perform this acquisition.

Tests to Provoke Esophageal Symptoms

Acid Perfusion Test

Since its introduction in 1958 by Bernstein and Baker,[76] the esophageal acid perfusion test has been widely used to determine whether a patient's symptoms can be reproduced by infusion of acid into the esophagus. If positive, the test indicates that the esophagus is sensitive to acid and increased esophageal exposure to acid is assumed. In the original technique, the distal end of the esophagus was perfused with 0.1 N HCl at a rate of 6 to 8 ml/min with the patient sitting upright. Ideally, a placebo is also infused (i.e., acid is alternately perfused with physiologic saline without the patient knowing the identity of the perfusate). The patient is asked to report any symptom that develops during infusion. Consistent reproduction

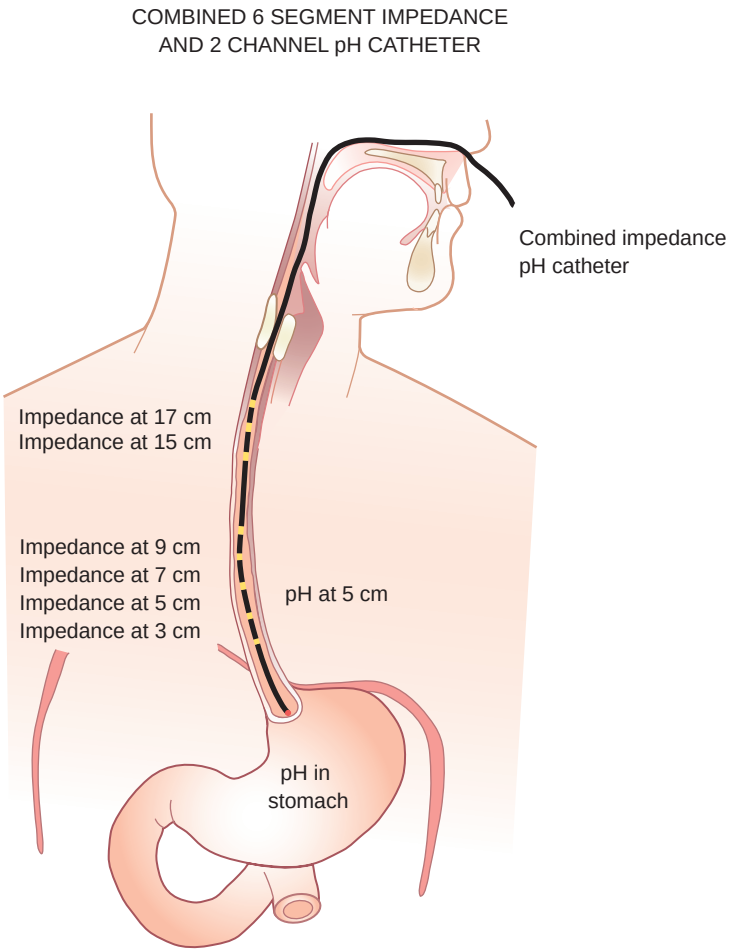


Figure 8–32. Placement of the catheter and location of the impedance segments and pH electrodes for combined ambulatory 24-hour esophageal impedance and pH monitoring.

of the patient's usual symptoms only during acid perfusion and rapid abatement during saline perfusion indicates a positive test. The development of symptoms during both the saline test and the acid perfusion test or the development of symptoms foreign to the patient's usual experience represents an equivocal test. Failure to develop any symptoms during a 30-minute acid perfusion indicates a normal test.

Various investigators have reported that 34% to 100% of patients with typical symptoms of GERD have a positive acid perfusion test. Failure to include certain components of gastric juice (e.g., pepsin, bile, pancreatic enzymes, food) in the perfusate may account for some of the normal results. A false-negative result can also occur in patients who have an insensitive esophagus. False-positive results are seen in 15% of symptomatic subjects. Of concern is that symptomatic subjects whose pain is not due to reflux may have a similar incidence of false-positive tests, thereby resulting in an erroneous diagnosis.

Edrophonium (Tensilon) Test

The edrophonium test has been introduced to identify chest pain of esophageal origin in patients in whom cardiac disease has been excluded.[77,78] The cholinesterase inhibitor edrophonium hydrochloride (Tensilon) is injected intravenously at a dose of 80 µg/kg. A syringe with 1 mg of the antidote atropine should always be at hand when performing the test. The test is ideally placebo controlled. A positive test is defined as replication of chest pain similar to the pain that the patient experiences spontaneously after edrophonium injection but not placebo injection. The test is positive in 20% to 30% of patients with noncardiac chest pain but not in asymptomatic volunteers.[78] In both normal volunteers and symptomatic patients, edrophonium causes a marked increase in the amplitude and duration of esophageal contractions. Because reproduction of the patient's typical symptoms rather than a specific change in esophageal motility is considered the end point of the test, manometry does not have be performed. Disadvantages of the test are that its helpfulness is limited to only a small proportion of patients with chest pain, there is a risk of side effects, and it reproduces symptoms with an unphysiologic stimulus. The test should not be performed in patients with asthma, chronic obstructive airway disease, or cardiac arrhythmias. This test is rarely performed.

Esophageal Balloon Distention

Balloon distention of the esophagus was described in 1955 as a diagnostic test to distinguish esophageal from cardiac chest pain.[79] An inflatable balloon is positioned

10 cm above the LES and gradually inflated with air in 1-ml increments. Esophageal motility is simultaneously monitored. The test is considered positive when typical symptoms are reproduced with gradual distention of the balloon. Studies indicate that the procedure induces spastic esophageal motor activity and reproduces chest pain episodes in up to 50% of patients with noncardiac chest pain, but not in volunteers.[80] Although the test has greater diagnostic yield than drug provocative studies do, it is relatively invasive and provides no information on spontaneously occurring symptoms.

Tests to Detect Increased Esophageal Exposure to Gastric and Duodenal Juice

24-Hour Esophageal pH Monitoring

The most direct method of measuring increased esophageal exposure to gastric juice is 24-hour monitoring of esophageal luminal pH with an indwelling pH probe placed 5 cm above the upper border of the LES. It quantifies the actual time that the esophageal mucosa is exposed to acid gastric juice, measures the ability of the esophagus to clear refluxed acid, and correlates esophageal acid exposure to the patient's symptoms. A 24-hour monitoring period is necessary so that measurements are made over one complete circadian cycle. This allows for assessment of the effect of physiologic activity such as eating or sleeping on reflux of gastric juice into the esophagus. If a combined impedance-pH catheter is used, an assessment of all gastroesophageal reflux events, both acidic and nonacidic, can be made. The frequency of reflux episodes, their nature and duration, and the clearance time associated with the reflux event can be determined. Many patients with esophageal motor disorders have increased esophageal acid exposure that may be an important trigger for their symptoms or a secondary effect caused by poor esophageal clearance.

SUMMARY

Primary motor disorders of the esophagus affect neural as well as muscular elements of the UES, body of the esophagus, and LES. The cause of disorders of upper esophageal function is known in about 60% of patients, and the dysfunction is secondary to a variety of neurologic and muscular conditions. The cause in the remainder is uncertain. The cause of esophageal body and LES disorders is unknown; however, the hypertrophic myopathic state of the esophagus may be a consequence of LES dysfunction and the neural dysfunction may be secondary.[81]

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Chapter

9

pH and Bilirubin Monitoring

Leah M. Backhus ▪ Ross M. Bremner

Gastroesophageal reflux (GER) is defined as excessive exposure of the esophageal lumen to refluxed gastric juice. Because gastric juice is characteristically acidic, recording intraluminal pH has become a convenient means of measuring this exposure. Similarly, knowing that gastric juice may contain duodenal contents refluxed from beyond the pylorus, measuring bilirubin in the refluxate has become a means by which duodenogastroesophageal reflux can be quantitated. This chapter discusses the relevance of pH and bilirubin monitoring as it pertains to foregut disorders, how these tests are accurately performed, and their applicability and limitations.

TESTS TO DETECT INCREASED ESOPHAGEAL EXPOSURE TO GASTRIC JUICE

To definitively make a diagnosis of gastroesophageal reflux disease (GERD), the presence of increased esophageal exposure to gastric juice has to be confirmed objectively. Historically, numerous methods have been used to characterize the extent of esophageal acid exposure, including symptom indices, esophagogastroduodenoscopy, videoesophagography, and scintigraphy. Each of these tests is limited in that they infer the presence of acid within the esophagus by indirect means and thus lack sensitivity. Consequently, a number of provocative tests have been designed to identify the esophagus as the cause of symptoms of GERD. Of these, the intraesophageal acid perfusion (Bernstein) test, the standard acid reflux test, and provocation maneuvers during barium esophagography are the most familiar. Common to all provocative tests is that they are dependent on the patient's perception and do not definitively prove an esophageal cause of a spontaneously occurring symptom. The sensitivity and specificity of various tests for GERD are listed in Table 9–1.

24-HOUR ESOPHAGEAL pH MONITORING

Extensive clinical experience has shown that 24-hour esophageal pH monitoring has the highest sensitivity and specificity for the detection of acid GERD. It is the most direct method of measuring increased esophageal exposure to gastric juice. It quantifies the actual time that the esophageal mucosa is exposed to acid gastric juice, measures the ability of the esophagus to clear refluxed acid, and correlates esophageal acid exposure to the patient's symptoms. It has been shown that a prolonged monitoring period is the most accurate means of detecting abnormal reflux because measurements are made over one complete circadian cycle.[1] The prolonged period allows for assessment of the effect of physiologic activity such as eating or sleeping on the reflux of gastric juice into the esophagus.

pH is a symbol for the logarithm of the reciprocal of the measure of hydrogen ion concentration and is mathematically described by the formula:

$$pH = -\log_{10}[H^+]$$

Because it is a logarithmic measurement, a solution with a pH of 1 contains 10 times the hydrogen ions of a solution with a pH of 2 and 1 million times (10^6) the activity of a solution with a pH of 7. A pH of 7 is considered neutral because at this pH the concentration of hydrogen ions equals the concentration of hydroxyl ions. The pH in the esophagus results from swallowed saliva and esophageal bicarbonate secretion and spans a range from 5 to 7. Because the esophagus normally has an intraluminal pH between 4 and 7 for 94% of the time, a pH of 4 has become the threshold that is used to detect increased esophageal acid exposure. Gastric acid secretion is responsible for a pH in the range of 1 to 2 and rarely more than 3, which is why a change in intraluminal esophageal pH to less than 4 quite reliably reflects reflux of gastric juice. The exception is patients taking antacids (especially proton pump inhibitors [PPIs]) or

Table 9–1 Sensitivity and Specificity of Tests for Gastroesophageal Reflux Disease

Test	Sensitivity (%)	Specificity (%)
LES manometry (<10 mm Hg)	58	84
Esophagogastroduodenoscopy (>grade 1 esophagitis)	68	96
Mucosal biopsy	77	91
Gastroesophageal scintiscanning	61	95
Barium esophagography	40	85
Acid perfusion test (Bernstein)	79	82
Standard acid reflux test	84	83
Ambulatory 24-hour pH esophageal monitoring	96	96

LES, lower esophageal sphincter.

patients with achlorhydria. Exposure of the esophagus to higher concentrations of H^+ ions (i.e., lower pH) has also been correlated with the degree of mucosal injury.[2] Duodenal contents account for a pH environment of 6 to 8, which has given some investigators reason to interpret an esophageal pH greater than 7 as a reflection of reflux of duodenal contents into the esophagus.

HOW TO PERFORM A pH TEST

Instrumentation

pH Catheters/Probes Currently, two means of detecting pH in the esophagus are available. One is by means of a catheter-based electrode that is placed through the nose and situated 5 cm above the manometrically determined upper border of the lower esophageal sphincter (LES). This is the gold standard technique, and protocols regarding performance of the study are detailed later. Nasal and nasopharyngeal local anesthesia is recommended and is induced by asking the patient to sniff after 2% lidocaine jelly is squirted into the nose. Alternatively, cotton-tipped applicators with a topical anesthetic such as cocaine can be applied directly to the nasopharynx, but this is often uncomfortable for the patient.

A newer catheter-less technique is now also available. This technique is accomplished with a radiotelemetry device (Bravo probe) that is placed either at the time of endoscopy or via a transnasal catheter placement system and secured to the mucosa of the esophagus 6 cm above the visualized gastroesophageal junction. This technique is described briefly later.

Both systems rely on a pH detection probe located either at the end of the catheter or in the Bravo capsule. Different types of pH probes are available, with no single electrode being optimal (Fig. 9–1). Glass electrodes measure the electrical potential across a thin glass membrane set up by a concentration gradient of hydrogen ions; these electrodes have good reliability and sensitivity. The probes need to be soaked continuously in a saturated solution of KCl and have a relatively large diameter, which can potentially lead to more difficult insertion.[1,3] They are also comparatively expensive ($400 to $600). Antimony probes measure pH by virtue of a corrosion potential at the hydrogen ion and antimony surface. They are smaller, better tolerated, and cheaper than glass electrodes ($40 to $75). Values recorded by antimony probes are 2.1 ± 0.8 units higher in the alkaline range than those of glass electrodes and are therefore not useful for measuring alkaline GER.[4] Multiprobe catheters with proximal and distal electrodes are available and can be useful in evaluating patients with atypical symptoms and cervical esophageal acid exposure.[5]

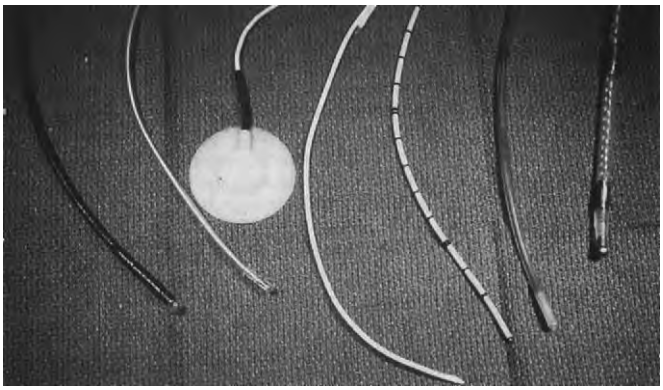


Figure 9–1. Types of pH probes.

Data-Recording Devices Solid-state data loggers are now lightweight, compact, and easily portable. They are usually worn on the patient's belt. The currently available data loggers record digital pH data every few seconds throughout the 24-hour period of study. These data loggers also have buttons (known as event markers) that allow the patient to record mealtimes, times of sleep, and any symptoms experienced during the study. The data recorded from the 24-hour study are uploaded to a personal computer at the end of the recording period for further analysis.

Software Analysis Various commercially available software programs are available to assist with the analysis. Once the data have been viewed in graphic format on

the computer screen and the study periods of upright, supine, and meals have been validated, the software can provide an automated analysis of the entire 24-hour period of study and generate parameters of exposure as detailed later.

Protocols for Performing the Test

Catheter Systems Probes are always first calibrated in pH solutions with pH values of 1, 4, and 7 to ensure integrity of the probe. After calibration, the catheter is passed transnasally so that the tip of the electrode lies 5 cm above the upper border of the LES as measured previously with manometry. Studies have demonstrated that the LES moves cephalad a distance of up to 5 cm with swallowing.[6] Precise positioning is important because normal values for esophageal acid exposure vary with location of the probe. A probe too high will potentially miss reflux episodes and decrease sensitivity, whereas a probe positioned too low may drift into the stomach with swallowing and yield false-positive readings. Probes are recalibrated when the patient returns at the end of the 24-hour study period to rule out electrode failure or pH drift.

Preparation of the Patient Patients are instructed to not eat after midnight before a morning test. PPI use is stopped 2 weeks before the test, and H_2 receptor antagonists are discontinued 48 hours before the study.[7] Antacids may be used up until the night before. The probes are placed either transnasally (catheter based) or at the time of endoscopy (Bravo probe). Patients are allowed to go home and are encouraged to perform normal activities of daily living. Previous protocols have outlined dietary instructions that avoid acidic foods to limit false-positive results. Carbonated beverages have typically been forbidden because they have an acidic pH and may cause belching of gastric juice into the esophagus. Recently, however, the goal has been to minimize restrictions and encourage patients to record the foods that they have eaten along with their symptoms, which are analyzed together at the end of the study. In this way, the study period mimics their normal day (Box 9–1).

The Diary Patients are asked to keep an accurate diary during the 24 hours of the study or signal significant events by using the event marker buttons on the digital recording device. In particular, they are asked to document the start and end times of meals, the time when going to sleep and waking up, and the occurrence and nature of any symptoms experienced during the recording period. The latter has led to development of the symptom index, which is used by some investigators to correlate patient symptoms with esophageal pH changes. This index has been useful in patients with noncardiac chest pain and in those with other atypical symptoms such as cough or wheeze.[8]

Data Analysis At the end of the study, the data are downloaded from the data logger to a computer, which generates a pH tracing and data summary (Fig. 9–2). It is important to emphasize that 24-hour esophageal pH monitoring is not a test for reflux but rather a measurement of esophageal exposure to gastric juice. The measurement is expressed as the time that esophageal pH is below a given threshold during the 24-hour period. This single assessment, though concise, does not characterize the exposure. Consequently, two other assessments are necessary: the frequency of reflux episodes and their duration.

The units used to express esophageal exposure to gastric juice are (1) cumulative time that esophageal pH is below a chosen threshold (expressed as a percentage of the total, upright, and supine monitored time), (2) frequency of reflux episodes below a chosen threshold (expressed as the number of episodes per 24 hours), and (3) duration of the episodes (expressed as the number of episodes longer than 5 minutes per 24 hours and the time [in minutes] of the longest recorded episode).[9] Most centers use pH 4 as the threshold. With this threshold, it has been shown that there is a remarkable degree of uniformity of normal values for the six components throughout the world,[10] thus indicating that normal individuals have similar values for esophageal acid exposure despite nationality or dietary habits. Normal values obtained from 50 healthy volunteers are shown Table 9–2.[11]

To combine the result of the six components into one expression of overall esophageal acid exposure below a pH threshold, a pH score has been developed by

Box 9–1 Dietary Restrictions and Patient Instructions for 24-Hour Ambulatory Esophageal pH Testing

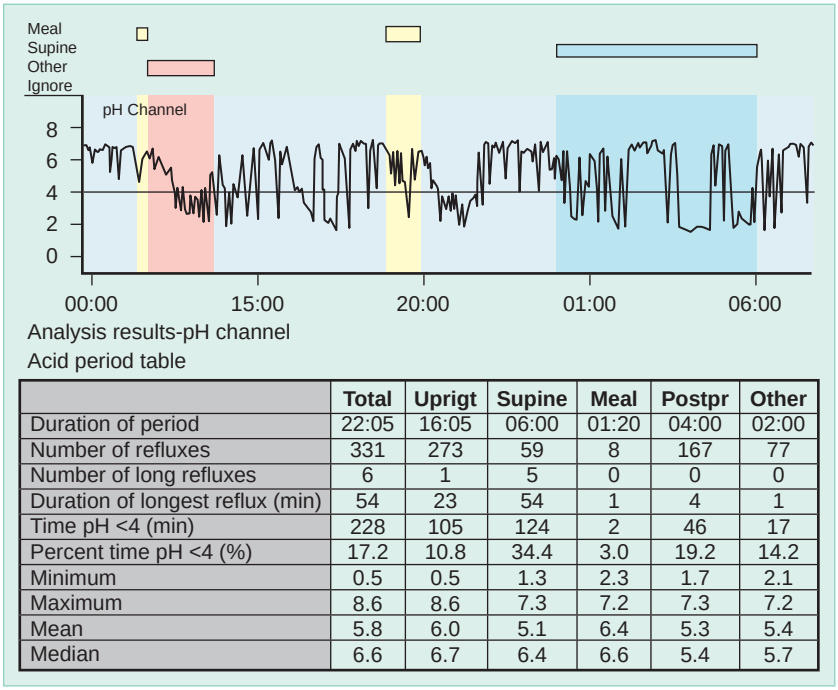
pH Test Diet*

- Meat, fish, cheese, eggs
- Vegetables
- Noncitrus fruit
- Butter, margarine
- Bread, cereal
- Vanilla ice cream, candy
- Milk, water, coffee, tea

Avoid the Following

- Citrus fruits
- Grapefruit or other fruit juices
- Lemonade
- Alcohol
- Carbonated beverages
- Hard candy, lozenges, or chewing gum

*Smoking is allowed; however, note any/all cigarettes, cigars, pipe use, or chewing tobacco.



	Total	Upright	Supine	Meal	Postpr	Other
Duration of period	22:05	16:05	06:00	01:20	04:00	02:00
Number of refluxes	331	273	59	8	167	77
Number of long refluxes	6	1	5	0	0	0
Duration of longest reflux (min)	54	23	54	1	4	1
Time pH <4 (min)	228	105	124	2	46	17
Percent time pH <4 (%)	17.2	10.8	34.4	3.0	19.2	14.2
Minimum	0.5	0.5	1.3	2.3	1.7	2.1
Maximum	8.6	8.6	7.3	7.2	7.3	7.2
Mean	5.8	6.0	5.1	6.4	5.3	5.4
Median	6.6	6.7	6.4	6.6	5.4	5.7

Figure 9–2. Display of a 24-hour esophageal pH monitoring study in a patient with increased esophageal acid exposure. DeMeester score (total): 92.5; DeMeester normal values: less than 14.72 (95th percentile).

Table 9–2 Normal Values of Six Components of the 24-Hour Record for 50 Healthy Volunteers

	Mean	95th Percentile
Total time pH <4 (%)	1.51	4.45
Upright time pH <4 (%)	2.34	8.42
Supine time pH <4 (%)	0.63	3.45
Number of episodes	19.00	46.9
Number of episodes ≥5 min	0.84	3.45
Longest episode	6.74	19.8

DeMeester et al. and is currently provided as an automatic option on most commercially available software products.[9] This score has been shown by receiver operating curves to be the most accurate means of assessing abnormal GER, although some centers still use the total time that the luminal esophagus has a pH below 4 as their predictor.[6,11] A composite score greater than 14.7 is considered pathologic.

The "Bravo" Probe

The Bravo (Medtronic, Shoreview, MN) pH system is a catheter-free esophageal pH monitoring system. It consists of an antimony pH electrode, a radio transmitter, and a battery contained in a capsule (Fig. 9–3). Capsule placement is accomplished with the aid of a delivery device and upper endoscopy or manometry. The delivery device is inserted through an anesthetized nostril and the probe positioned appropriately in the esophagus—5 cm above the manometrically determined proximal border of the LES. Alternatively, the probe can be positioned via the mouth, which is an easier procedure for the patient, but the accuracy of the method has not been defined. Those who are using the oral technique position the probe 6 cm above the endoscopically observed position of the squamocolumnar junction. A vacuum pump is attached to the port on the handle of the delivery device to draw a bleb of esophageal mucosa into the probe chamber. Once a steady vacuum has been achieved, the plunger on the handle of the delivery device is depressed to fire a locking pin through the bleb of mucosa, thus securing it to the esophagus. The vacuum is then released and the plunger rotated to detach the probe from the delivery device. The latter is subsequently removed from the patient. Proper capsule placement can be confirmed endoscopically while taking care to not dislodge the device. Esophageal pH is measured every 6 seconds, and two pH data points are transmitted every 12 seconds to the receiver unit over a 48-hour study period. The capsule is designed to dissolve in 3 to 7 days and pass through the gastrointestinal tract. There are reports of the probe remaining attached for longer periods, but without consequence.[12]

Studies using the Bravo catheter-free pH monitoring system are few; however, there are reports that claim the ability to obtain interpretable data 96% to 97% of the time.[12,13] The overall sensitivity and specificity in identifying patients with GERD vary with the length of the study period. Twenty-four-hour data yield a sensitivity and specificity of 67.5% and 89.7%. Using data from the worse of 2 days tested yields a sensitivity and specificity of 83.8% and 84.5%. Taking both days combined brings

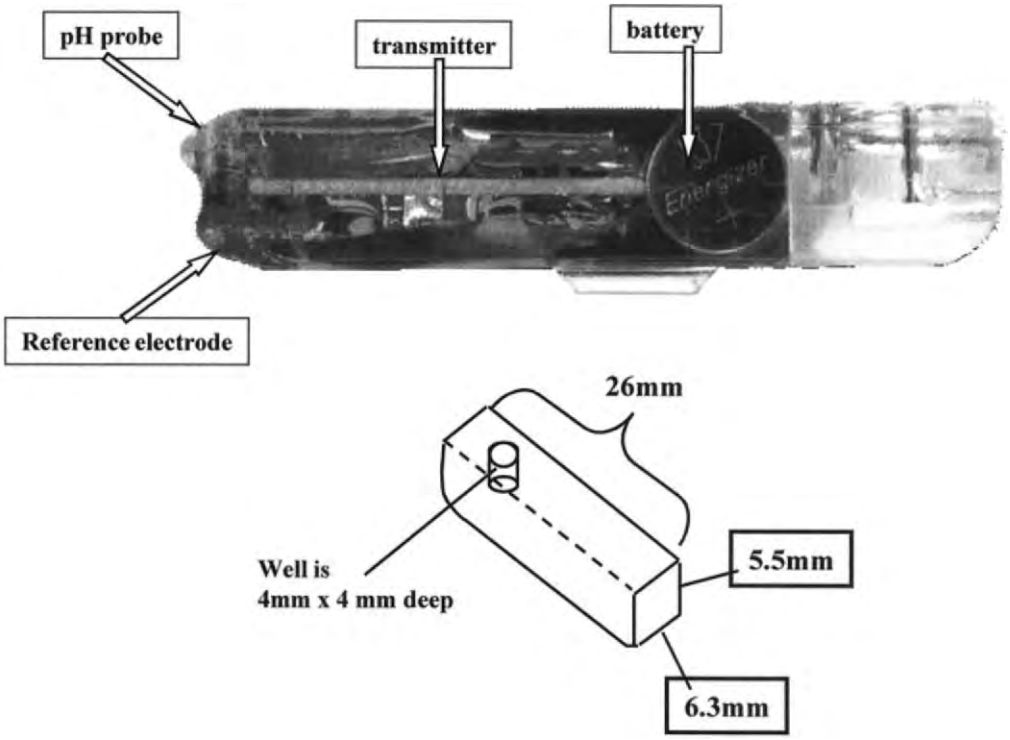


Figure 9–3. Dimensions and electronics of the Bravo pH capsule. The capsule is oblong (6.3 × 5.5 × 26 mm). A well (diameter, 4 mm; depth, 4 mm) is located on the superior-lateral aspect of the probe. The well is connected to a custom-made vacuum unit capable of generating 600 mm Hg vacuum pressure to the well via the delivery system. An antimony pH electrode and reference electrode are located on the distal tip of the capsule, and an internal battery and transmitter are contained within the capsule.

those numbers to 64.9% and 94.8%.[12] The data highlight one advantage of the wireless system: patients may have less discomfort, which allows for a longer evaluation period and thus increases the sensitivity of the test. One disadvantage, however, is the price, which is approximately $225 versus $62 for a traditional pH probe.

24-HOUR AMBULATORY DETECTION OF ESOPHAGEAL BILIRUBIN EXPOSURE

Duodenogastroesophageal reflux (DGER) is defined as the pathologic regurgitation of duodenal contents into the stomach with subsequent reflux into the esophagus. Previous terms have been used to describe this process, including bile reflux and alkaline reflux. Neither is appropriate in that duodenal fluid consists of many substances besides bile and an esophageal pH higher than 7 does not necessarily coincide with reflux of duodenal contents.

DGER has been associated with complications of GERD, including stricture formation, complicated Barrett's esophagus, and adenocarcinoma. The mechanisms involved in the esophageal mucosal damage seen in DGER are not fully understood. Activated pancreatic enzymes can cause mucosal damage from direct exposure; however, bile acids are the predominant constituent in DGER. Data from animal studies have shown that exposure of isolated esophageal mucosa to bile acids results in significant disruption of the mucosal barrier.[14,15] The extent of mucosal damage has been further linked to the conjugation state of the bile acids, as well as the pH of the refluxate. Conjugated bile acids and pepsin produce more injury at an acidic pH, whereas unconjugated bile acids and trypsin are more deleterious at a pH in the range of 5 to 8.[16] Twenty-four-hour gastric pH monitoring allows simultaneous evaluation of gastric acid secretion and an estimate of duodenogastric reflux and gastric emptying.

Bilitec Probe

Bechi et al. developed the apparatus known as the Bilitec probe (Medtronic), which indirectly measures bilirubin content in the stomach or esophagus, or in both.[17] In the absence of carotene and various lipids, the bilirubin concentration in a solution can be directly measured by spectrophotometry based on specific absorption at a wavelength of 453 nm. Surprisingly, reflux of alkaline components into the stomach is not completely neutralized by the gastric pH. Bile acids and lecithin are naturally present in the gastric environment, even at low pH values, and both taurine and glycine conjugated bile acids are present in the stomach at a pH of less than 2.

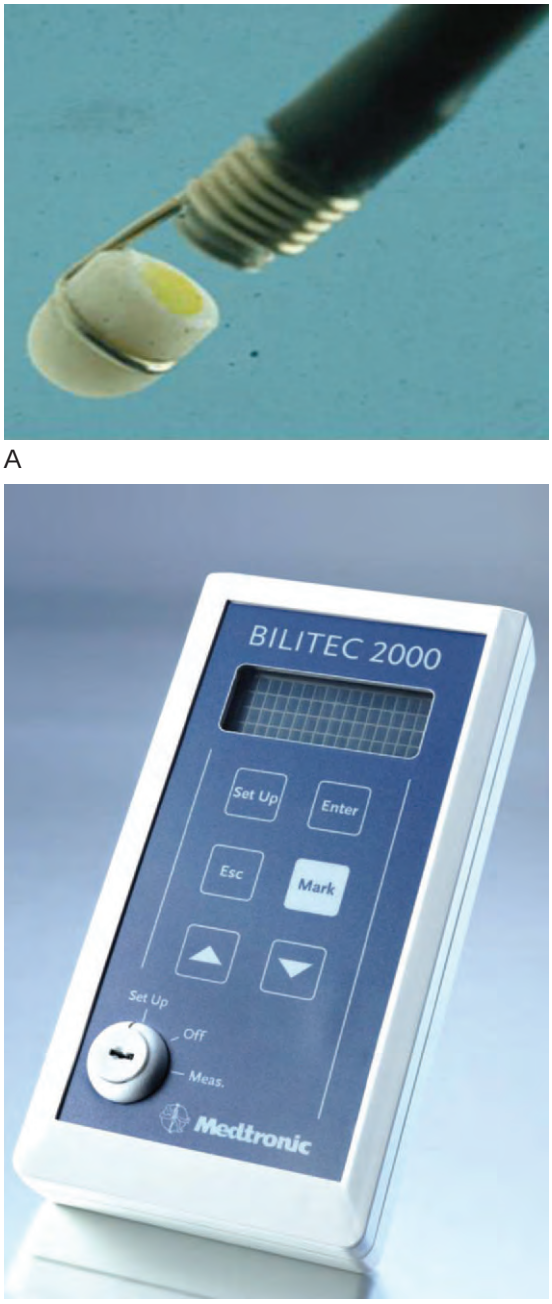
The apparatus used to measure the presence of bilirubin in the esophagus consists of a portable optoelectronic data logger weighing 1200 g that is strapped to the patient's side and a fiberoptic probe that is passed transnasally and positioned anywhere in the lumen of the foregut (Fig. 9–4). The spectrophotometric probes contain bonded optical fibers and are 3 mm in diameter and 140 cm in length. Two plugs connect 50% of the fibers to the light-emitting diodes and 50% to the receiving photodiode. The tip of the probe contains a 2-mm space for sampling. Fluids and blenderized solids can easily flow through the space and their bilirubin concentration measured. The probes are flexible, durable, easy to sterilize, and reusable.

The optoelectronic unit acts simultaneously as a light signal generator, a data processor, and a data storage device. The unit has two channels, thus allowing dual measurement with two probes if desired. The light source for each channel is provided by two light-emitting diodes that give off a 470-nm signal light (blue spectrum) and a 565-nm reference light (green spectrum). Optical signals reflected back from the probe are converted to electrical impulses by a photodiode. This electrical signal is then amplified and processed within the data logger (Minneapolis, Minnesota). Absorbance readings are averaged every two cycles. The system is capable of recording 225 individual absorbance values per hour and allows up to 30 hours of continuous monitoring. An in vivo validation study of the Bilitec fiberoptic system has shown that intraesophageal bilirubin absorbance correlates well with the presence of total bile acids and bilirubin.[18]

Performing the Test

For esophageal monitoring, the Bilitec probe is passed through an anesthetized nostril and positioned 5 cm above the upper border of the LES as previously determined by esophageal manometry. For intragastric monitoring, the probe is positioned 5 cm below the lower border of the LES. The test depends on patient avoidance of eating anything green or yellow or anything that may have green or yellow substances in it. As a result, patients are given a list of foods allowed during the study (Box 9–2). The probe is connected to a data logger and the patient allowed to go home and resume normal activities of daily living. As with pH monitoring, the patient returns at the end of the study period and data from the logger are uploaded to a computer and analyzed with commercially available software (Fig. 9–5).

Normal values for esophageal exposure to bilirubin from 35 healthy volunteers have shown a median percent time with absorbance greater than 0.2 of 0% and a 95th percentile of 1.7%. Consequently, abnormal esophageal exposure to bilirubin as measured by Bilitec monitoring is defined by absorbance above 0.2 greater than 1.7% of the total time of the study. In a study by Cuemo et al., the total bilirubin absorbance above 0.14 was 7.8 ± 2.2 (percentage of total study time) in patients without esophagitis, 11.7 ± 4.4 in patients with grade 1 to 2 esophagitis, and 17 ± 4.2 in those with grade 3 to 4 esophagitis.[19] Thus, esophageal bilirubin exposure correlates with the degree of esophageal mucosa damage.



A

B

Figure 9–4. Bilitec probe **(A)** and electronic data logger **(B)** for 24-hour esophageal bilirubin monitoring.

CLINICAL USE OF AMBULATORY ESOPHAGEAL pH AND BILIRUBIN MONITORING

In the clinical setting, there are three main circumstances in which pH and bilirubin monitoring are useful in the day-to-day management of patients.

Box 9–2 **Dietary Restrictions and Patient Instructions for 24-Hour Ambulatory Bilirubin Monitoring**

Bilitec Test Diet

- Bananas, apples
- Saltine crackers
- Cottage cheese
- Chicken breast—skinless
- Rice, pasta
- Bread
- Vanilla ice cream
- Low-fat milk
- Water

Avoid the Following

- Carbonated beverages
- Coffee
- Tea
- Alcohol
- Butter, Margarine
- Candy
- Anything green or yellow or that might have green or yellow substances in it

Diagnosis of "Typical" Gastroesophageal Reflux Disease

GERD is such a common disorder that the acronym in now a household term. Who needs to be studied with 24-hour pH monitoring? It is obviously not feasible, nor necessary, to perform 24-hour pH testing on all patients with suspected reflux disease. The *American Journal of Gastroenterology* recently published guidelines regarding the diagnosis and evaluation of patients with suspected GERD.[20] Although it is recognized that symptoms may be a poor guide to the underlying disease, it is considered cost-effective in patients with "typical" symptoms (heartburn and acid regurgitation) to attempt a trial of PPIs. This acts as both a diagnostic and therapeutic approach, with further work-up being indicated in patients who do not appropriately respond.[21] Of course, this approach should not obviate education in terms of lifestyle changes that may help alleviate the degree of reflux, such as smoking cessation, moderation in alcohol consumption, and weight loss for those who are obese. The knee-jerk approach to prescribing PPIs for all patients with reflux symptoms will unfortunately subject many patients to unnecessary medication or miss patients with complicated reflux disease such as Barrett's esophagus or dysplasia. Physicians should be alerted to symptoms of dysphagia, odynophagia, anemia, or weight loss because they may be indicators of stricture, ulceration, Barrett's esophagus, or malignancy.

In patients with typical reflux symptoms (heartburn, regurgitation) *and* endoscopic findings of esophagitis (mucosal erosions), pH monitoring is probably unnecessary because this combination is about 97% specific for GERD, with infective esophagitis and pill-induced injury being nonreflux causes of mucosal damage.[22] Most patients, however, will have GERD without endoscopic evidence of mucosal injury (so-called endoscopically

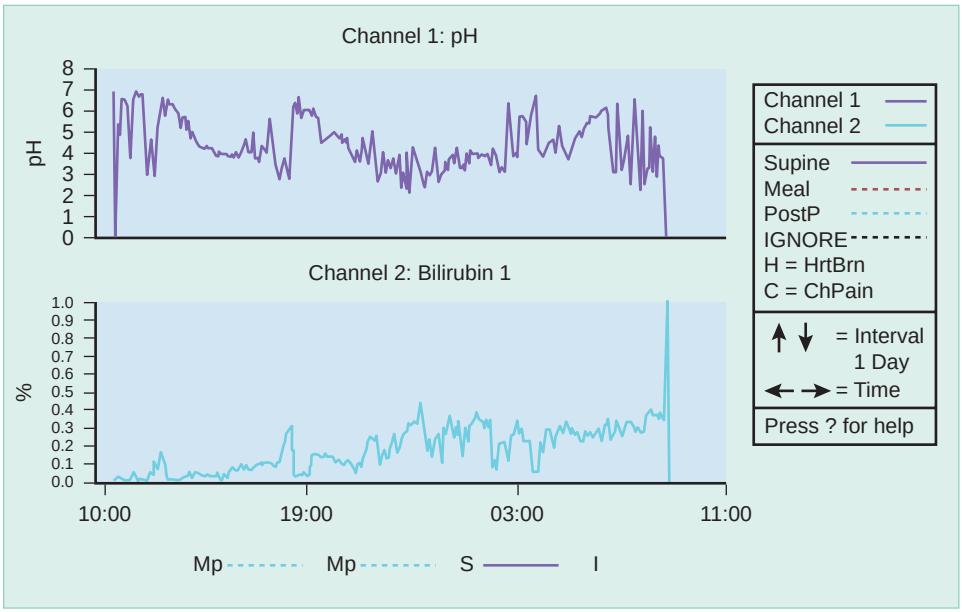


Figure 9–5. Display of a 24-hour esophageal pH and bilirubin monitoring system.

negative GERD), and to correctly document GERD as a source of the patients' symptoms, pH testing *is* necessary. Such an approach has also been shown to be cost-effective.[23] Certainly in endoscopically negative GERD, pH monitoring is considered essential before performing an antireflux operation so that a Nissen fundoplication is not performed on a patient without excessive esophageal exposure to gastric juice and an incompetent valve. It has been shown that the best surgical outcomes are achieved in patients with typical symptoms, abnormal pH scores, and a good response to acid-suppression therapy.[24] On the other hand, it is well documented that patients with achalasia may have symptoms suggestive of reflux disease, and performing an antireflux procedure in this situation has obvious consequences.

Some authors have also documented the value of increased exposure of the stomach and esophagus to bilirubin and have attempted to correlate such exposure with patient symptoms. There appears to be some valuable information regarding gastric symptoms; however, correlation with esophageal symptoms has been more difficult. Certainly, the most severe reflux patients have increased esophageal exposure to both acid and bile, as is the case in patients with Barrett's esophagus. Detection of increased bilirubin in the esophagus is a marker of more severe disease and possibly a marker of increased risk for complications of reflux, such as stricture, Barrett's esophagus, dysplasia, or adenocarcinoma.[25,26] Freedman et al. have noted that increased bilirubin exposure is also associated with less effective esophageal motility in patients with GERD.[27] Although useful in terms of understanding the pathophysiology of many of these diseases, bilirubin monitoring is not routinely carried out in the community during a work-up for GERD or esophageal symptoms, and usually these probes are found only in academic centers.

Diagnosis and Evaluation of Atypical Symptoms of Gastroesophageal Reflux Disease

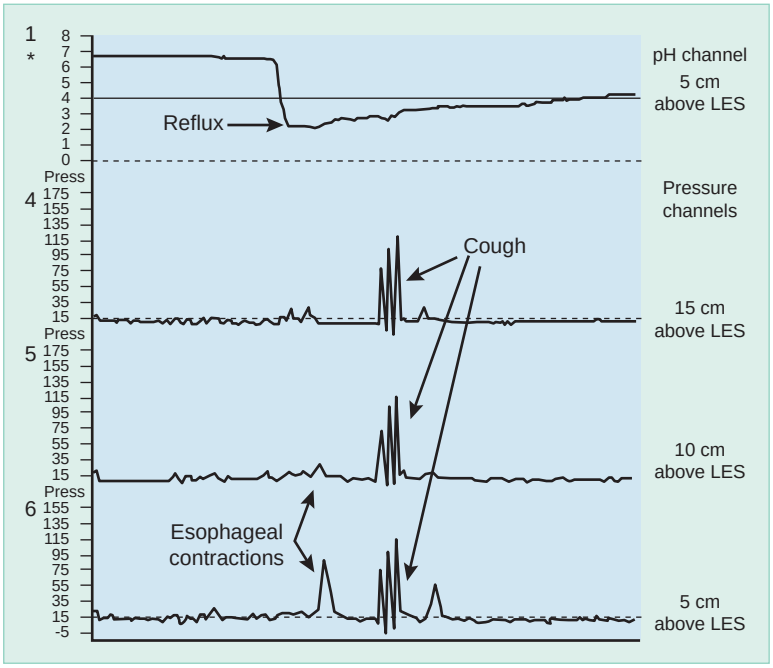
GERD has been associated with so-called atypical symptoms such as cough, asthma, hoarseness, dental caries, chest pain, dysphagia, and globus sensation. It is recommended that pH testing be available in the diagnostic armamentarium of the physician diagnosing these disorders.

Asthma and Cough Alexander and colleagues noted that asthmatic patients have an increased prevalence of GERD symptoms and increased esophageal exposure to acid.[28] Schnatz and Castell also noted a high proportion (78%) of positive pH tests in patients with chronic cough or asthma.[29] Increased esophageal exposure to gastric juice in these patients is probably both cause and effect. Severe coughing plus wheezing increases intra-abdominal pressure and drives gastric juice into the negative-pressure environment of the chest, and esophageal acidification has been shown to result in a reflex bronchospastic response (Fig. 9–6). Furthermore, as noted later, chronic aspiration contributes to continued cough as well as progressive parenchymal fibrosis. Evidence of pharyngeal reflux on pH testing has been shown to assist in the identification of patients with respiratory symptoms who will benefit from an antireflux operation.[30]

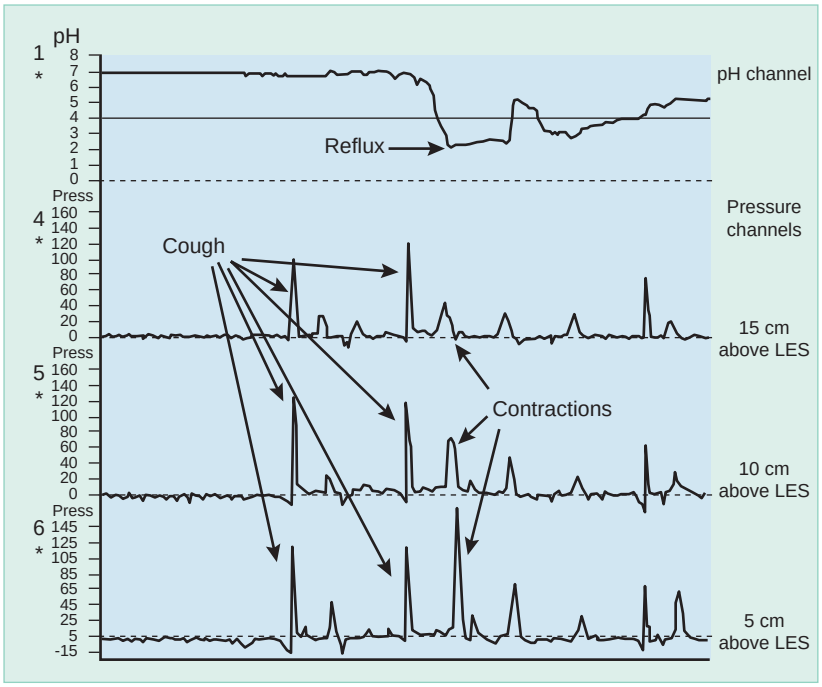
Hoarseness and Dental Caries Reflux of gastric juice up to the laryngeal aditus or into the mouth has been associated with laryngeal symptoms and dental caries. In the work-up of patients suspected of having "high" reflux, catheters containing two or more probes have been used to assess reflux into the more proximal esophagus or even the pharynx.[31,32] Furthermore, the addition of impedance catheter monitoring has shown that reflux into the pharynx is more frequent than previously thought, even with pH monitoring. Kawamura et al. have shown that gaseous reflux with weak acidity is more common in patients with reflux-related laryngeal lesions.[33]

Noncardiac Chest Pain The esophagus has frequently been implicated as the cause of noncardiac chest pain. Twenty-four-hour pH monitoring has enabled us to understand this phenomenon, especially when combined with 24-hour ambulatory manometry. Chest pain that coincides with esophageal acidification during the study is evidence that the two may be related. Ambulatory manometry has shown that occasionally, esophageal acid exposure is associated with marked motor disturbances of the esophagus, although it has been difficult to show an association with pain exactly at the time of these abnormalities.[8,34] However, pH testing has been found to be predictive of a therapeutic response to omeprazole in severe refluxers with noncardiac chest pain.[35]

End-Stage Lung Disease and Lung Transplantation The role of GERD in patients with end-stage lung disease and in patients after lung transplantation has been underestimated in the past. A high proportion of patients with end-stage lung disease will have pathologic GERD, and it has been suggested that "silent" aspiration contributes to pulmonary injury in many of these patients. Similarly, the chronic cough associated with many end-stage lung diseases is thought to promote reflux because of the increased intra-abdominal pressure and trans-sphincteric gradient associated with coughing. One group found 35% of patients before lung transplantation to have GERD.[36] Recently, GERD has also been implicated as a significant adverse contributor to the development of bronchiolitis obliterans syndrome after lung transplantation.[37,38] Davis and colleagues have shown that 73% of patients after lung transplantation had GERD by pH monitoring.[37] This may in part be due to the significant number of patients with unrecognized GERD before transplantation, to vagal damage at the time of surgery, or to reflux-promoting side effects of the postoperative immunosuppressive medications. Nonetheless, this group has shown that fundoplication in lung transplant recipients with GERD is associated with significant improvement in lung function, particularly if performed before the late stages of bronchiolitis obliterans syn-



A



B

Figure 9–6. Cause-and-effect relationship between cough and esophageal acid exposure. **A,** Coughing precipitated by a reflux episode may be the result of occult aspiration of refluxed gastric juice or a reflex brought on by esophageal acidification. **B,** Conversely, increased intra-abdominal pressure as occurs with coughing may overcome antireflux mechanisms and result in a gastroesophageal reflux episode.

drome.[37] Furthermore, they have noted that many patients with progressive deterioration in lung function referred for transplantation have had stabilization of their pulmonary disease after fundoplication, again emphasizing the effect that GERD and silent aspiration have on pulmonary function. It is now believed essential to have a good understanding of a patient's reflux history before consideration of lung transplantation, and in our center all patients being considered will be evaluated for GERD by manometry, videoesophagography, and 24-hour pH testing. Those with severe reflux and nonprohibitive risk for surgery will undergo fundoplication before transplantation. Consideration is given to early post-transplant antireflux surgery in those who cannot undergo surgery before transplantation or in those in whom GERD develops after transplantation. pH monitoring has helped us understand the significance of GERD in this complex group of patients and continues to provide important information to direct therapy.

Evaluation of Patients Receiving Medical Therapy or After Surgery

As noted earlier, it is strongly recommended that pH testing, endoscopy, manometry, and videoesophagography be performed before contemplating antireflux surgery.[39] pH testing is also of value in evaluating patients after antireflux surgery and after initiation of medical therapy. Leite and colleagues noted that a significant number of patients are resistant to standard doses of omeprazole when studied with pH monitoring.[40] Katzka and associates studied patients while receiving PPI therapy with 24-hour pH testing. They showed that tolerance to standard PPI doses develops in a significant number of patients and they require ever-increasing doses of medication to control the acid secreted by the stomach and subsequent acid GER.[41] To evaluate the effect of the dose of PPIs in patients with recurrent or persistent symptoms, it is necessary to quantitate the esophageal acid exposure with 24-hour pH monitoring. Similarly, the 24-hour test is useful in evaluating patients with recurrent symptoms after laparoscopic fundoplication inasmuch as it has been shown that only about half these patients will have increased esophageal acid exposure.[42] Attributing the symptoms to failure of surgery without studying the patient via 24-hour pH testing may condemn a patient to an unnecessary redo operation.

pH monitoring has also been used to assess proximal esophageal acid exposure after esophagectomy and has shown that the acid secretory status of the stomach returns with time and that reflux of gastric juice into the proximal remaining esophagus does occur. Johansson and colleagues used this technique to compare the exposure of the cervical esophagus to acid after either transhiatal or Ivor-Lewis–type esophagectomy and have found that a cervical anastomosis is associated with higher acid exposure.[43]

INTEGRATED AMBULATORY FOREGUT MONITORING

The availability of portable digital recorders with large storage capacity now allows outpatient 24-hour monitoring of pharyngeal and esophageal motility simultaneous with esophageal and gastric pH.[44,45] Integrated evaluation of foregut motor and secretory function over an entire circadian cycle has thus become possible and has been found to be useful in many patients. In one study, integrated foregut monitoring established one or more functional or secretory abnormalities as the underlying cause of symptoms in 84% of the patients studied.[45] Prolonged ambulatory monitoring is the most physiologic way to assess foregut function and has the potential to replace the series of individual laboratory tests that have been necessary to thoroughly evaluate patients with complex foregut disorders. Ambulatory integrated foregut monitoring and computerized evaluation of the recorded data put into the physician's hand the ability to evaluate foregut motor and secretory abnormalities within the office. This will enable easier and more scientific evaluation of patients with symptoms possibly attributable to esophageal or gastric dysfunction.

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Chapter

10

Multichannel Intraluminal Impedance

Radu Tutuian · Donald O. Castell

Multichannel intraluminal impedance (MII) is a relatively new technique for evaluating esophageal bolus transit during swallowing without the use of radiation and for monitoring gastroesophageal reflux (GER) independent of its pH. First described by Silny[1] in 1991, this technique has evolved over the years and is currently available for routine clinical use. The principles of MII are relatively simple, but important in understanding the advantages that MII has when combined with esophageal manometry (MII-EM) or pH (MII-pH).

PRINCIPLES OF MULTICHANNEL INTRALUMINAL IMPEDANCE

The principle for detecting the presence and movement of an intraesophageal bolus by MII is based on measuring differences in electrical conductivity determined by the presence of various materials within the esophagus. The basic components of the impedance circuit are two metal rings connected to an alternating current source. An isolator (i.e., body of the catheter) separates the rings so that the electrical circuit is closed by the electrical charges (i.e., ions) surrounding the catheter. Simply stated, impedance is a measure of electrical resistance in an alternating current circuit. While suspended in air, the impedance is very high. Once placed in the esophagus, the ions of the esophageal mucosa close the circuit and the system measures a relatively stable resistance of approximately 2000 to 3000 ohms. When a liquid bolus is present in the esophagus, the increased number of ions allows for better conductivity, thus decreasing the electrical impedance (Fig. 10–1). Based on differences in the electrical conductivity of air, esophageal mucosa, and liquids, intraluminal impedance can detect the entry and exit of boluses within the esophagus (Fig. 10–2).

The changes recorded by MII during bolus passage have been validated by simultaneous videofluoroscopy and impedance testing (Fig. 10–3).[2] Most recently, Simren et al.[3] reported a strong correlation between fluoroscopy and impedance when measuring esophageal filling ($r^2 = .89$; $P < .0001$) and esophageal emptying ($r^2 = .79$; $P < .0001$) in a group of healthy volunteers. Imam et al.[4] have also reported on the correlation between MII and barium swallows in 13 healthy volunteers and indicated that barium and impedance bolus transit or stasis correlated in 97% (72/74) of swallows.

Mounting multiple impedance-measuring segments on a catheter allows determination of the direction of bolus movement based on the timing of changes in impedance at individual levels. A decline in impedance progressing proximally to distally indicates aboral (antegrade) bolus movement as seen during swallowing, whereas a rapid decline in impedance progressing distally to proximally is indicative of oral (retrograde) bolus movement as seen during reflux episodes (Fig. 10–4).

The ability of MII to assess bolus transit without the use of radiation offers a great opportunity to evaluate the functional implications of pressure measurements when combined with manometry (i.e., MII-EM). When combined with pH, MII expands the ability of reflux testing to evaluate the presence of refluxate independent of its pH, thereby allowing the detection of acid and non-acid GER.

COMBINED MULTICHANNEL INTRALUMINAL IMPEDANCE AND MANOMETRY

Combined MII-EM was approved by the U.S. Food and Drug administration as a diagnostic test for esophageal function in July 2002. Adding MII capability to the manometry catheter does not change the dimensions of the catheter. Therefore, from a patient perspective, combined MII-EM testing is no different from conventional esophageal manometry. Although impedance-measuring

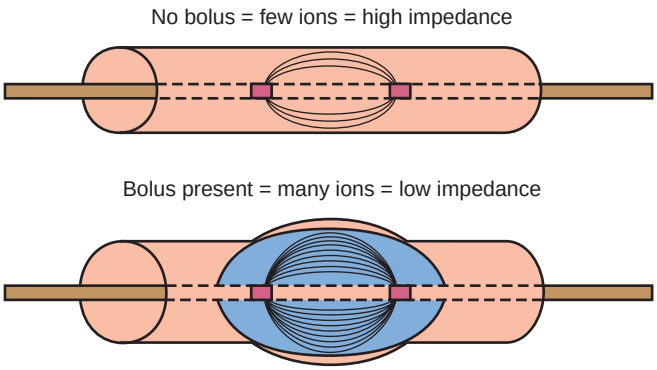


Figure 10–1. Changes in intraluminal impedance are determined by an increased number of ions during the presence of a bolus.

segments can be added anywhere on the catheter, currently available designs place impedance rings around the pressure transducers so that pressure and bolus presence can be measured at the same level (Fig. 10–5).

Studies in our laboratory using normal volunteers have confirmed the ability of MII to characterize the transit of liquid, semisolid, and solid boluses through the esophagus.[5] In this study we found that liquid boluses of 1 to 10 ml produced the same changes in intraluminal impedance, thus indicating the high degree of sensitivity in identifying the presence of a bolus but the limited ability to estimate the volume of an intraesophageal bolus.

Normal values for this technique have been established by a multicenter study involving 43 healthy volunteers.[6] When MII changes during 10 saline and 10 viscous swallows were studied, it was found that more than 90% of these healthy volunteers cleared at least 80% of liquid swallows and at least 70% of viscous swallows, thus allowing us to establish normal values for esophageal bolus transit.

After studying 350 consecutive patients with various manometric abnormalities via combined MII-EM, we subsequently evaluated the ability of MII to characterize bolus transit abnormalities in different groups of patients.[7] All patients with achalasia and scleroderma of the esophagus were found to have abnormal liquid bolus transit (i.e., incomplete bolus transit for at least 30% of liquid swallows) and viscous bolus transit (i.e., incomplete bolus transit for at least 40% of viscous swallows). Normal liquid bolus transit was identified in at least 95% of patients with normal manometry, nutcracker esophagus, and isolated lower esophageal sphincter (LES) abnormalities (i.e., poorly relaxing LES, hypertensive and hypotensive LES). Approximately half the patients with ineffective esophageal motility (IEM) and distal esophageal spasm had normal liquid bolus transit (Fig. 10–6).

A more detailed study in 70 patients with IEM identified that there is no perfect (i.e., highly sensitive and highly specific) manometric cutoff that would predict complete bolus transit and that the current manometric criterion for diagnosing IEM (i.e., 30% or more manometrically verified ineffective swallows) is too sensitive and lacks the specificity for identifying patients with abnormal bolus transit. Normal bolus transit in the group of patients with IEM appeared to be dependent on distal esophageal amplitude (i.e., average amplitude at two distal esophageal sites 5 and 10 cm above the LES), the number of sites with low contraction amplitude, and the overall number of manometrically determined ineffective swallows (Fig. 10–7). Another important finding of this study (Fig. 10–8) was that approximately a third of patients with IEM had normal transit of liquid and viscous boluses (suggesting a mild functional defect), approximately a third had abnormal transit of either liquid or viscous boluses (i.e., moderate functional defect), and the remaining third of IEM patients had abnormal transit of both liquid and viscous boluses (i.e., severe functional defect).[8] Outcomes studies are warranted to evaluate whether grading of esophageal function defects in patients with manometrically verified IEM has the potential to identify patients at risk for postoperative dysphagia (i.e., those with a severe functional defect).

Combined MII-EM provides better information about bolus transit in patients with dysphagia after fundoplication.[9] Combined impedance-manometry and

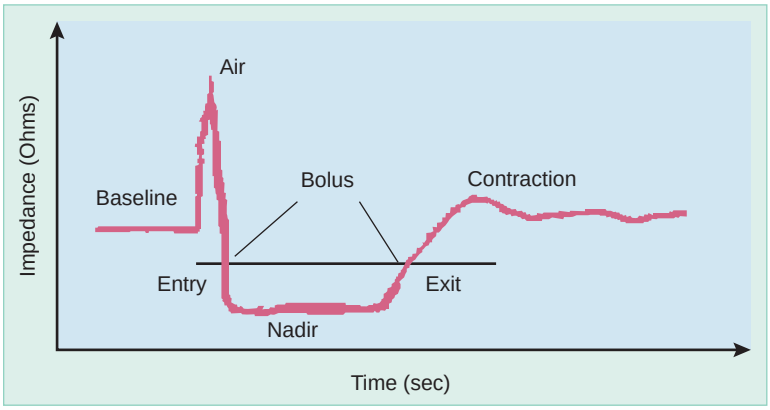


Figure 10–2. Impedance changes observed during bolus transit over a single pair of measurement rings separated by 2 cm. A rapid rise in resistance is noted when air traveling in front of the bolus head reaches the impedance-measuring segment, followed by a drop in impedance once the more conductive bolus material passes the measuring site. Bolus entry is considered to occur at the 50% drop in impedance from baseline relative to the nadir and bolus exit at the 50% recovery point from the nadir to the baseline. Lumen narrowing produced by the contraction transiently increases the impedance above baseline.

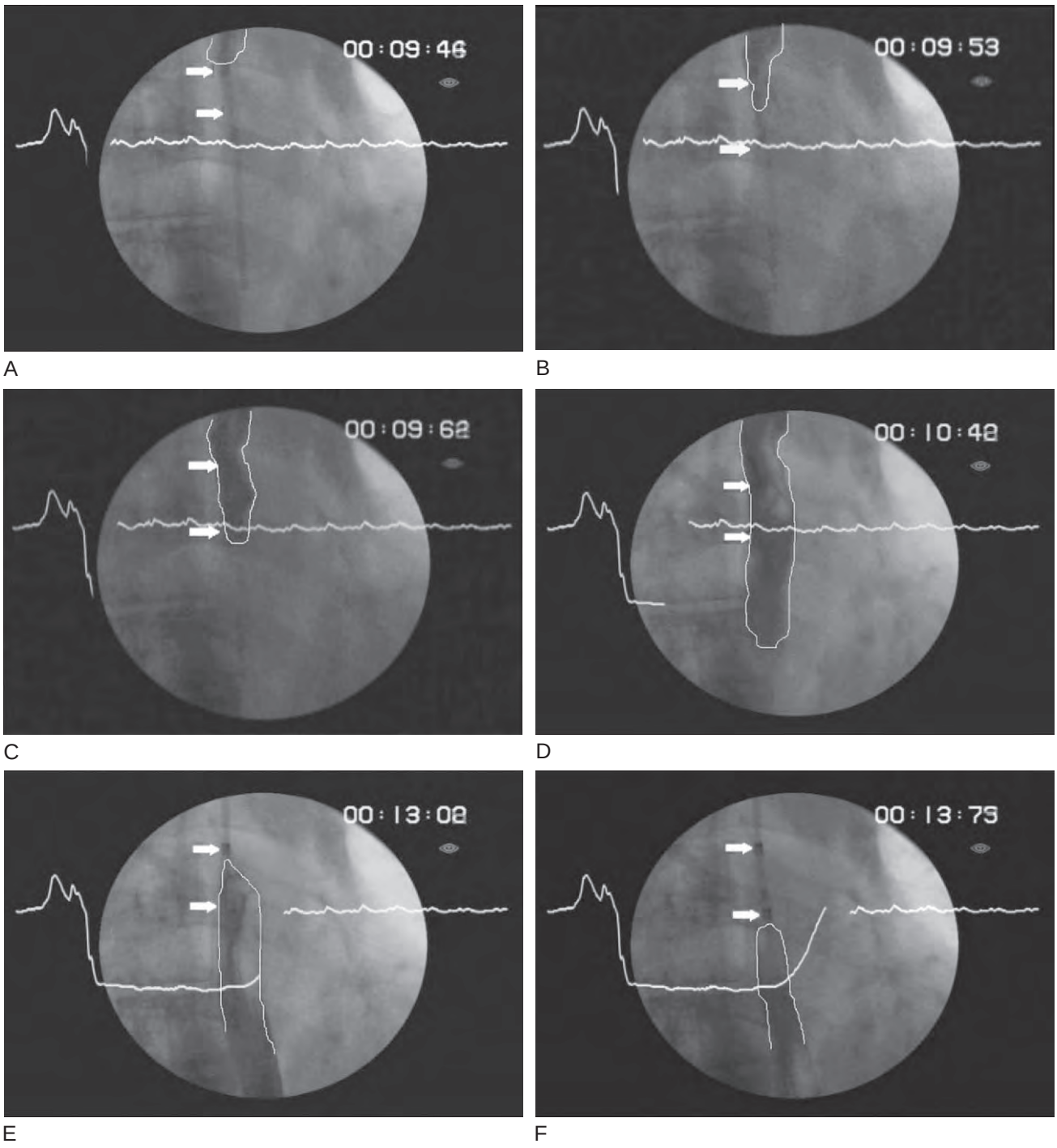


Figure 10–3. Validation of impedance changes during bolus transit by combined videofluoroscopy and impedance. The *arrows* indicate the position of the impedance-measuring segment. The contour of the bolus is highlighted by drawing a margin in *white*. Before the bolus arrives in the impedance-measuring segment, the impedance has a relatively stable baseline value **(A)**. A bolus entering the segment will produce a rapid drop in impedance **(B)**, with a relatively stable nadir value reached once the liquid component of the bolus covers both segments **(C)**. The impedance will stay at these low values as long as the bolus is present between the rings **(D)**. Impedance starts rising once the tail of the bolus passes the proximal ring **(E)** and recovers to baseline once the tail of the bolus passes the second ring **(F)**. (Courtesy of Dr. J.H. Peters, University of Rochester, Rochester, NY.)

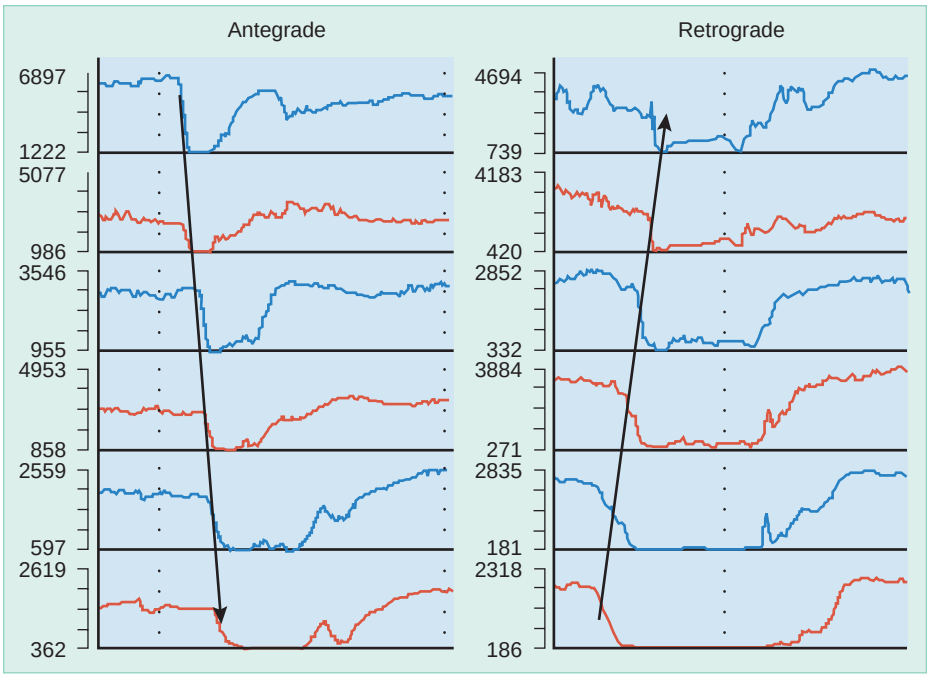


Figure 10–4. Bolus movement detected by multichannel intraluminal impedance. Swallowing is detected as antegrade bolus movement producing a decline in impedance starting proximally and progressing distally **(A)**, whereas reflux is detected as retrograde bolus movement producing a decline in impedance starting distally and progressing proximally **(B)**.

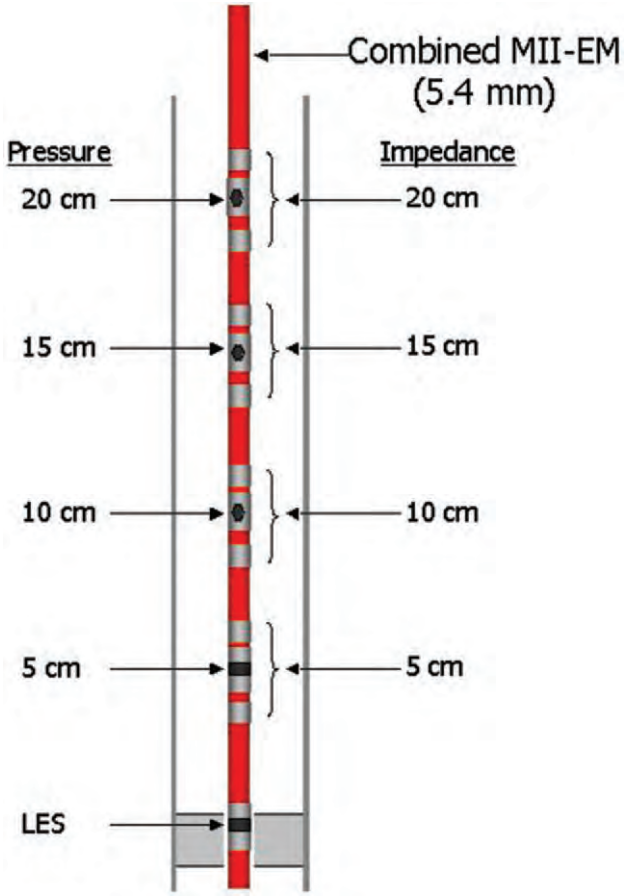


Figure 10–5. Nine-channel esophageal function catheter. Circumferential solid-state pressure sensors are located in the lower esophageal sphincter (LES) high-pressure zone (P5) and 5 cm above it (P4); unidirectional solid-state pressure sensors are located 10 cm (P3), 15 cm (P2), and 20 cm (P1) above the LES. Impedance-measuring segments are centered at 5 cm (Z4), 10 cm (Z3), 15 cm (Z2), and 20 cm (Z1) above the LES. MII-EM, multichannel intraluminal impedance with esophageal manometry.

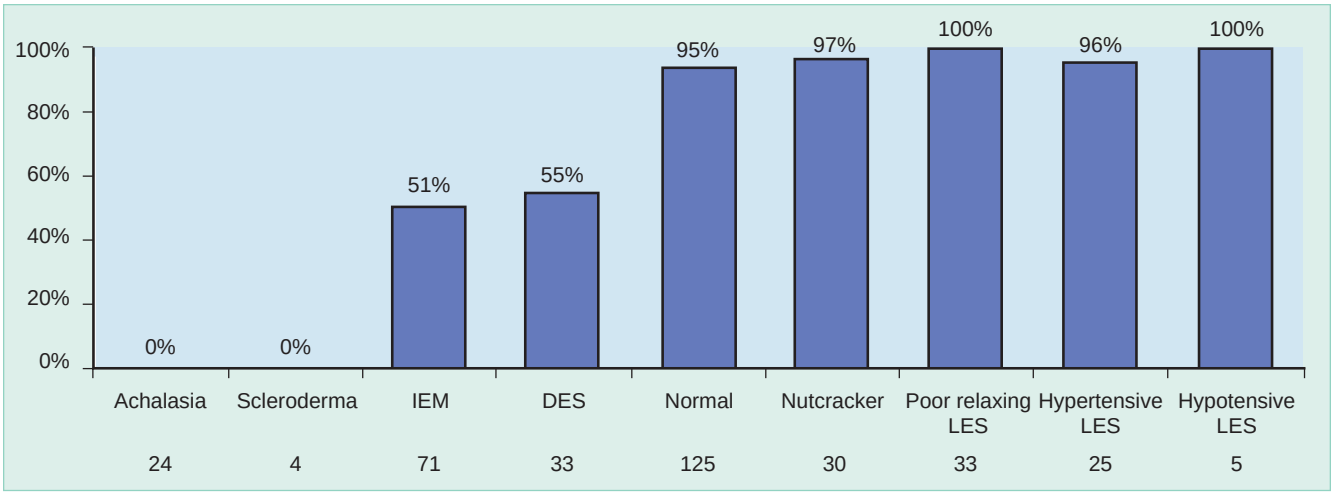
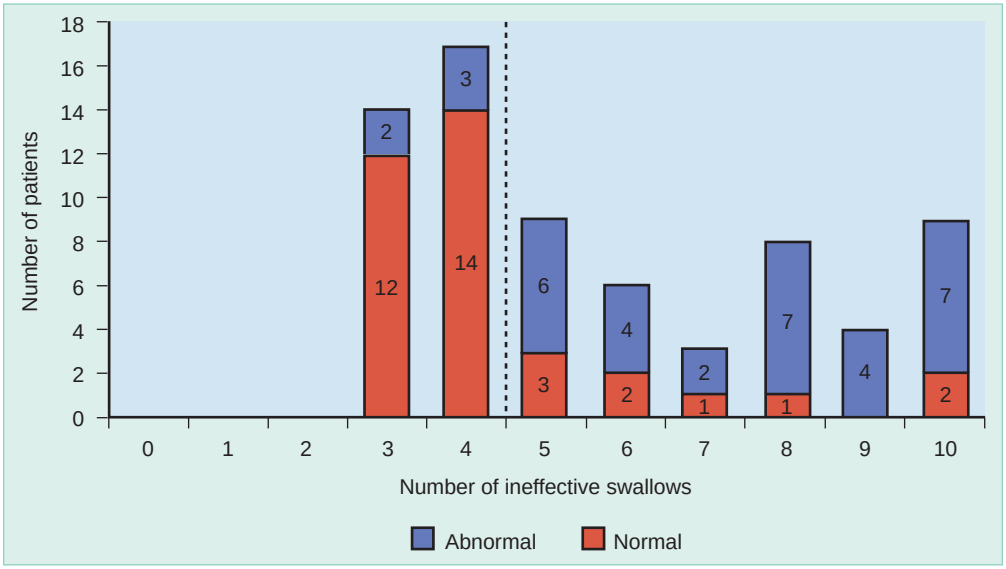


Figure 10–6. Percentage of 350 patients with normal liquid bolus transit based on manometric diagnoses. DES, distal esophageal spasm; IEM, ineffective esophageal motility; LES, lower esophageal sphincter.

Figure 10–7. Number of patients with normal/abnormal bolus transit depending on the number of manometrically verified ineffective swallows. A greater proportion of patients with less than five low-amplitude contractions had normal bolus transit as compared with those who had five or more low-amplitude contractions ($P < .05$).



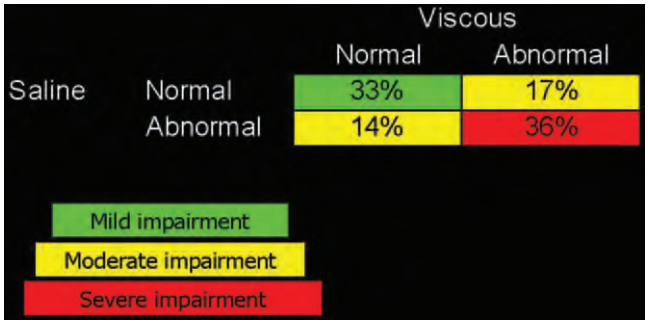


Figure 10–8. Degree of functional defect in patients with ineffective esophageal motility. Mild impairment, normal transit of both liquid and viscous boluses; moderate impairment, abnormal transit of liquid or viscous boluses; severe impairment, abnormal transit of both liquid and viscous boluses.

videofluoroscopy studies in patients with postfundoplication dysphagia indicate the ability of MII-EM to identify intraesophageal bolus pooling proximal to the fundoplication and retrograde escape of the bolus into the proximal esophagus after the completion of an otherwise normal peristaltic contraction. These studies underscore the potential of combined MII-EM to evaluate patients with esophageal symptoms after fundoplication.

Prospective studies evaluating the role of combined MII-EM in assisting in the selection of patients for antireflux surgery and in evaluating postoperative dysphagia are under way. The studies discussed earlier suggest that combined MII-EM, through its capability of assessing bolus transit during esophageal manometry without the use of radiation, has great potential to expand and refine the clinical diagnostic abilities of a modern esophageal testing laboratory.

COMBINED MULTICHANNEL INTRALUMINAL IMPEDANCE AND pH

For many years, the majority of clinicians and investigators considered esophageal pH monitoring the "gold standard" in diagnosing GERD, especially in the absence of endoscopically identified esophageal erosions. Esophageal pH monitoring quantifies the amount of distal esophageal acid exposure as the percentage of time when an intraesophageal pH less than 4 is recorded. This approach is very limited in detecting GER when the intraluminal pH does not go below 4.0. GER with a pH above 4.0 is difficult to detect by conventional pH monitoring, and different approaches (e.g., bilirubin monitoring, scintigraphy, manometry) have been proposed to overcome this limitation. Because impedance can detect the presence of refluxate in the esophagus independent of pH, bilirubin, and other factors and can be mounted on a regular pH catheter, MII has several advantages in monitoring GER. A recent consensus statement has identified combined MII-pH as the most sensitive test "to detect reflux of all types."[10]

For monitoring of GER via MII-pH, multiple impedance-measuring segments are mounted on a regular 2.1-mm pH probe (Fig. 10–9). Combined MII-pH represents a shift in the GERD testing paradigm. GER episodes are detected by retrograde (i.e., distal to proximal) declines in intraluminal impedance determined by increased conductivity of the liquid GER, whereas data from the esophageal pH sensor are simply used to categorize the GER into acid or non-acid (Fig. 10–10). Traditionally, GER with a pH above 4.0 is considered non-acid in order to underscore the difference in the acid reflux episodes detectable by conventional pH monitoring. In an attempt to comply with the chemical definition of acid and non-acid based on the chemical dissociation equation of water, a group of leading esophageal experts have proposed separating GER detected by MII into acid if the pH drops from above to below 4.0, weakly acidic if the pH is between 4.0 and 7.0, and non-acid if the intraesophageal pH during an MII-detected reflux episode remains above 7.0.[10]

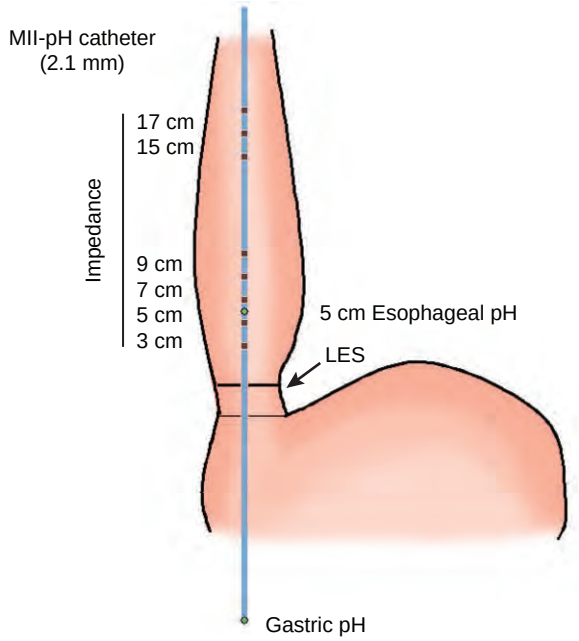


Figure 10–9. Combined multichannel intraluminal impedance (MII) and pH catheter. During reflux monitoring the esophageal sensor is located 5 cm above the proximal border of the lower esophageal sphincter (LES). Impedance-measuring segments are centered at 3, 5, 7, and 9 cm above the LES in the distal end of the esophagus and around 15 and 17 cm above the LES in the proximal end of the esophagus. This catheter also allows monitoring of gastric pH (10 cm below the LES).

In addition to the chemical properties of the gastroesophageal refluxate, MII has the ability to clarify some of its physical properties. MII can differentiate between liquid only, gas only, and mixed gas-liquid reflux episodes based on changes in intraluminal impedance. Gas or air has very poor electrical conductivity and, when present between impedance-measuring rings, will produce a rise in impedance; in contrast, liquid, which has better electrical conductivity, will produce a decline in impedance (Fig. 10–11).

The ability to detect GER episodes when the pH remains above 4.0 has important implications for both gastroenterologists and gastrointestinal surgeons. Non-acid reflux (i.e., GER episodes with a pH above 4.0) is relatively infrequent in subjects not taking acid-suppressive therapy; it occurs primarily in the postprandial periods[11] and rarely at night.[12] On the other hand, in subjects taking acid-suppressive therapy, the medications may change the composition of the gastroesophageal refluxate without affecting the total number of GER episodes.[13,14] Currently, normal values for acid and non-acid reflux in 60 healthy volunteers not receiving acid-suppressive therapy[12] and in a small ($N = 6$) number of volunteers receiving acid-suppressive therapy (omeprazole, 20 mg twice daily before meals) have been published.[14]

Non-acid reflux is not likely to cause esophageal lesions because esophageal mucosal healing rates of up to 90% have been documented in patients taking potent acid-suppressive therapy.[15] Quantifying non-acid reflux may be of interest in patients with supraesophageal (ear, nose, and throat and pulmonary) symptoms inasmuch as studies suggest that patients with pharyngeal lesions are more likely to have more gas-containing reflux episodes, a type of reflux episode detected primarily by impedance.[16] Although non-acid reflux may have a limited contribution to esophageal structural lesions, it appears to have a major role in causing persistent symptoms in patients taking acid-suppressive therapy. There is both direct evidence of postprandial symptoms being associated with non-acid reflux[13] and indirect data from a large PPI trial indicating that 35% to 40% of patients receiving acid-suppressive therapy continue to have symptoms.[15] Clarifying the relationship between reflux symptoms and ongoing GER (both acid and non-acid) is

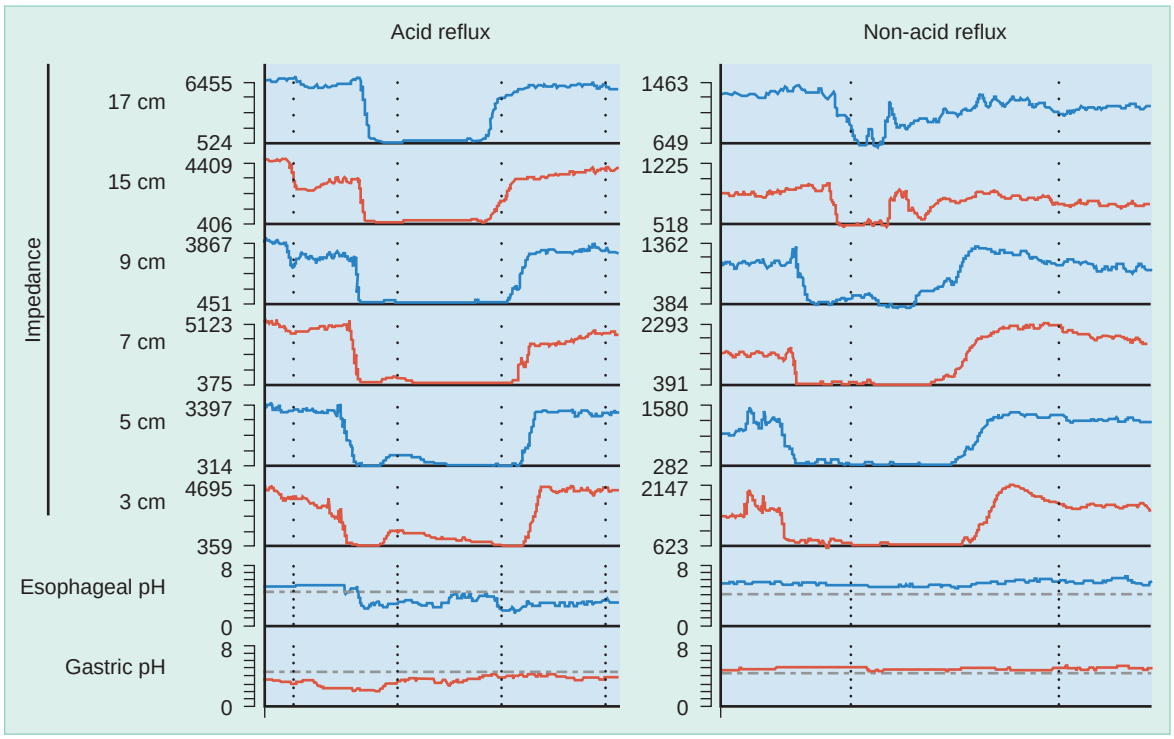


Figure 10–10. Acid and non-acid reflux episodes detected by using combined multichannel intraluminal impedance (MII) and pH monitoring. Reflux episodes are detected by MII as a retrograde drop in impedance starting distally and moving proximally. Traditionally, a reflux episode is classified as acid if the esophageal pH drops below 4.0 or as non-acid if the pH remains above 4.0.

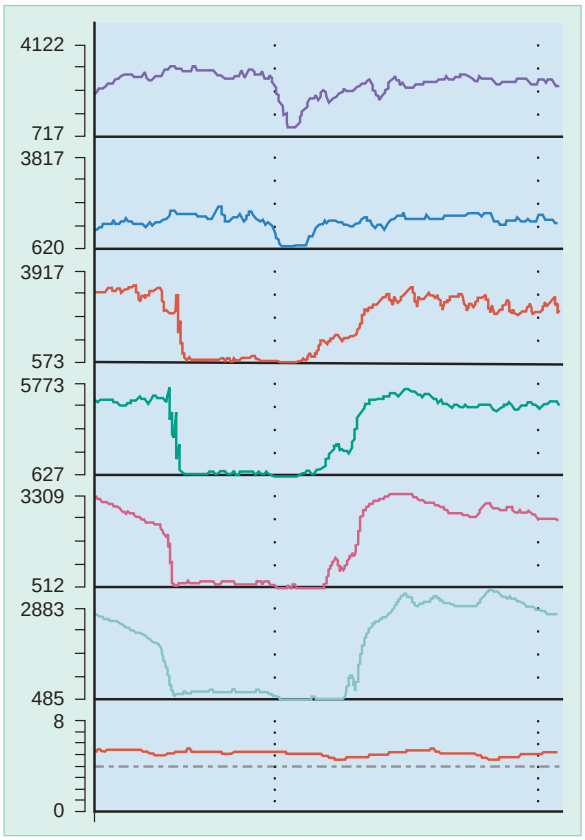
very important in clinical decision making because patients are more likely to be referred to gastroenterologists and gastrointestinal surgeons only after they have "failed" PPI trials.

Current clinical practice guidelines recommend empirical trials of PPIs instead of pH testing for patients complaining of reflux symptoms. The favorable side effect profile of PPIs has encouraged this initial step to be taken by primary care physicians, and patients are referred to specialists only if they have persistent symptoms with acid-suppressive therapy. In these circumstances esophageal pH testing is performed, but before testing, an important decision has to be made whether to test the patient while taking or while not taking PPIs. Esophageal pH testing without medication is more accurate, and a negative result (i.e., normal distal esophageal pH with negative symptom association) is very helpful in suggesting that the symptoms are not due to acid reflux. A positive esophageal pH test while not receiving therapy, on the other hand, does not necessarily explain why the patient is still having symptoms while taking PPIs. Esophageal pH testing during therapy is also helpful if the test result is abnormal (i.e., increased amount of distal esophageal acid exposure with therapy and a positive symptom association for acid reflux) because it suggests that the acid suppression may be insufficient. A negative esophageal pH test while receiving therapy cannot exclude non-acid reflux being associated with the residual symptoms. In our opinion, combined MII-pH has the potential to overcome this impasse. We propose the algorithm depicted in Figure 10–12 for evaluating patients with GERD symptoms.

In our experience[17] with MII-pH monitoring in more than 150 patients, less than 10% of patients with persistent symptoms during acid-suppressive therapy have symptoms associated with acid reflux (a group of patients who can potentially be detected by conventional pH alone). In the remaining 90% or more patients with symptoms while receiving twice-daily PPIs, combined MII-pH is of pivotal importance in separating those with persistent non-acid reflux associated with symptoms (about a third) from those with symptoms not associated with reflux (about two thirds). The type of reflux symptoms (typical versus atypical) plays a major role relative to whether they are associated with ongoing GER. In our experience, approximately half the patients with typical GERD symptoms had a positive symptom index for ongoing reflux, whereas more than 70% of patients with atypical symptoms had a negative symptom index with concurrent acid-suppressive therapy.

SUMMARY

MII is a valuable addition to both conventional manometry and pH testing. Combined MII-EM helps clarify the functional aspects of esophageal motility abnormalities



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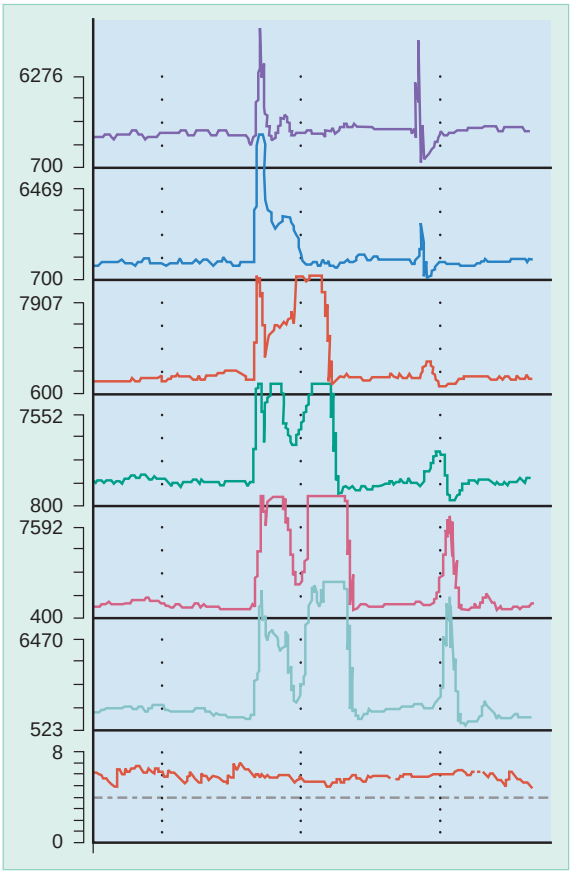

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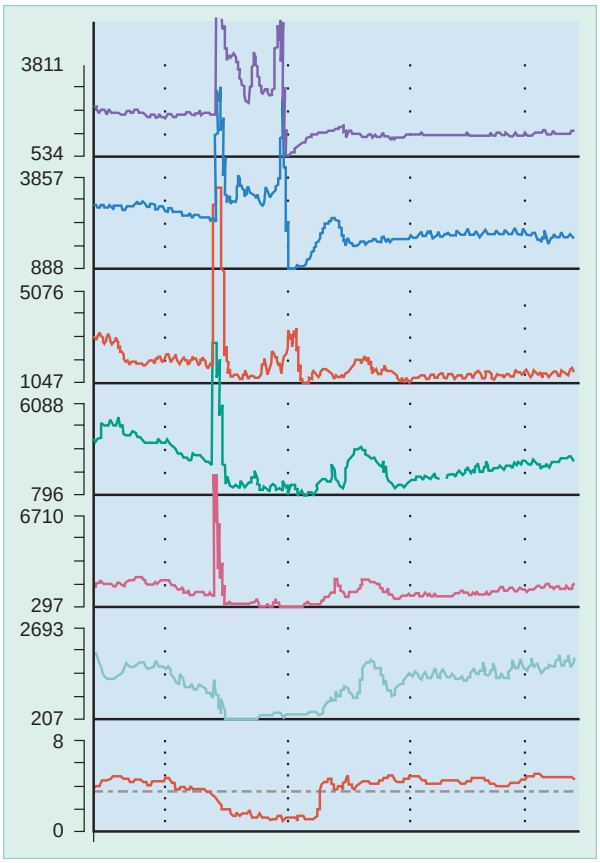

C

Figure 10–11. Different types of gastroesophageal reflux episodes based on liquid-gas content: liquid only **(A)**, gas only **(B)**, and mixed gas and liquid **(C)**.

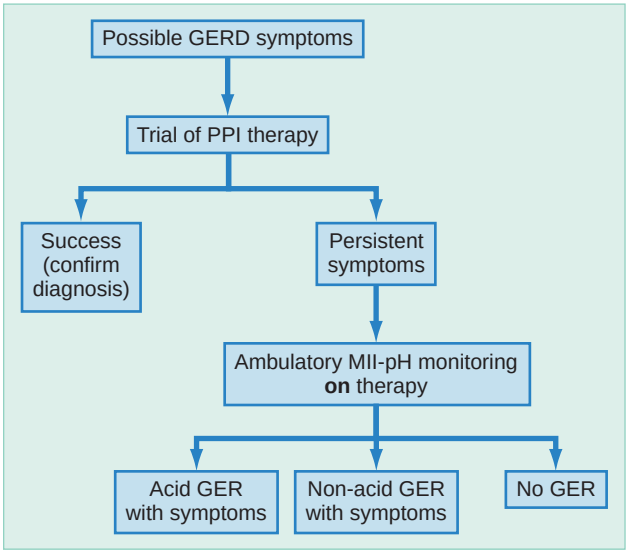

Figure 10–12. Suggested diagnostic gastroesophageal reflux disease (GERD) algorithm. GER, gastroesophageal reflux; MII-pH, combined multichannel intraluminal impedance and pH monitoring; PPI, proton pump inhibitor.

and has the potential to refine patient selection for antireflux procedures and to clarify the mechanisms of postfundoplication dysphagia. Combined MII-pH expands the ability to monitor for both acid and non-acid reflux and thus helps select patients who may benefit from antireflux procedures.

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Chapter

11

Tests of Gastric Function and Their Use in the Evaluation of Esophageal Disease

Karl-Hermann Fuchs

The pathophysiologic background of functional esophageal disorders is multifactorial.[1-3] The upper gastrointestinal tract is responsible for transport, reservoir function, and initiation of the digestion of food as an integrated system of different elements. Malfunction of only one of these constituents can have an impact on the whole process. The stomach and duodenum follow the esophagus and have special connections to the latter. The complex system of the antireflux barrier at the esophagogastric junction underlines the close relationship between the two organs. Malfunction or anatomic changes in the stomach and duodenum (or both) will have an influence on esophageal function and can be the background of esophageal disease.[1]

The clinical manifestation of esophageal functional disorders does not always allow for precise localization of the cause of the underlying problem.[4] Whereas heartburn and dysphagia are rather specific symptoms with a high probability of an esophageal origin, more nonspecific symptoms such as epigastric pain, nausea and vomiting, uncomfortable fullness and belching, hoarseness, and chronic cough lack this specificity. A number of other extraesophageal symptoms can occur in patients with gastroesophageal reflux disease (GERD), but they can also be present in other disorders or their presence can be a clue to concomitant disorders of the stomach, duodenum, or both.[1,3,5]

As a consequence, objective testing is needed to evaluate not only esophageal but also gastric and duodenal function, especially in patients in whom surgery is being considered. Even if classic esophageal functional testing such as 24-hour pH monitoring, as well as endoscopic or radiographic findings (or both), lead to a diagnosis, a work-up to evaluate function of the gastroduodenal segment should be completed before surgery because it can be involved in the process. It is important to evaluate all involved functional defects along the upper gastrointestinal tract before changing one component by surgery since the remaining problems can lead to failure or new symptoms. Even if newly detected disorders will not lead to an alteration in the initial therapeutic plan, the information about a concomitant disorder is important for both the surgeon and patient because it could be the basis of a clinical problem in the future. Therefore, understanding of gastrointestinal pathophysiology and objective testing of gastric and duodenal function, as well as a focused history of symptoms regarding extraesophageal signs, are important in the management of esophageal disease.

PHYSIOLOGIC AND PATHOPHYSIOLOGIC ASPECTS OF THE STOMACH AND DUODENUM IN ESOPHAGEAL DISEASE

The physiologic tasks of the esophagus and stomach are transport, reservoir function, initiation of digestion by the secretion of acid and enzymes, and grinding of food. A major impairment is dysmotility causing obstruction and reflux.

Food is passed in small portions through the pharynx and esophagus into the stomach. In physiologic conditions this transportation process is well coordinated and usually occurs without any special mental effort. Once this process is disturbed by mechanical obstruction or malfunction of the esophagus and transport of the bolus is impaired, the person becomes aware of the swallowing process and realizes that such transport is difficult. Because of the physiologic connection between the gastric reservoir and the duodenum and esophagus, this

phenomenon can also occur if gastric emptying is prohibited and the person feels that it is impossible to eat and swallow food. Any functional obstruction at the gastric level can cause or increase gastroesophageal reflux or inhibit transport.[1]

Duodenogastric reflux (DGR) has been known for years to influence esophageal exposure to gastric juice if duodenogastroesophageal reflux (DGER) occurs.[3,6,7] DGR is a physiologic phenomenon. If the amount of such reflux is excessive and exceeds a certain threshold, a mixture of duodenal juice and gastric acid can reach the esophageal lumen and cause damage.[6] Functional disorders of gastric acid secretion can have an impact on esophageal acid exposure.[8]

Two major functional disorders of the gastroduodenal segment are most relevant in esophageal disease: delayed gastric empting, and DGER. Both these disorders can occur as a primary dysfunction or be secondary to previous gastric surgery.

DELAYED GASTRIC EMPTYING

After the ingestion of fluids and solids, the gastric reservoir can be filled with several liters of volume. The stomach gradually dilates after a bolus enters as a result of relaxation, especially of the gastric fundus, where the storage of solids is accomplished. Dysfunction of accommodation of the gastric fundus can have an impact on functional disorders and the development of symptoms.[9,10] Motor activity is different in the fundic area, where relaxation, followed by low-amplitude tonic contractions, occurs to move solids more distal in the corpus. The gastric pacemaker is located in the upper part of the corpus and is responsible for orthograde motility from the corpus and antrum into the duodenum by creating a stimulus of approximately three contractions per minute. Fluids and small food particles leave the stomach earlier than solids do. When more than half the fluids are emptied, solids are moved by increasing fundic tonus toward the corpus in order to enter the antrum. The antral grinding mechanism will downsize the food particles for passage through the pylorus. If these particles are too large, they will be rejected back into the corpus via pyloric and antral motility to reenter the grinding process. Redistribution of food and fluids within the stomach can have a connection with the spectrum of symptoms.[11]

Gastric motor function includes, in addition to reception, storage, and grinding of food, mixing of food with acid and pepsin, discrimination between solids and fluids, recognition of the composition of food components such as fat and protein, and finally, advancement of chyme through the pylorus into the duodenum with the appropriate speed for further physiologic digestion. Duodenal motor activity is also involved in this process by varying duodenal resistance to the transpyloric flow of chyme.

Gastric and antroduodenal motility disorders may contribute to several foregut pathologies, such as gastroesophageal reflux, DGER, gastritis, and ulcerations, and are discussed as potential background for dyspepsia.[12-16] Delayed gastric emptying can be detected in patients with diabetes, neurologic disorders, and postoperative syndromes, as well as be a primary finding.[10] The classic clinical manifestation is early satiety, regurgitation and heartburn, uncomfortable fullness, nausea, vomiting, anorexia, and weight loss. The diagnostic workup consists of upper gastrointestinal endoscopy to verify mucosal damage, mechanical obstruction, or stenosis, as well as methods to evaluate gastric emptying, such as gastric emptying scintigraphy, the ^{13}C breathing test, antroduodenal manometry, gastric emptying ultrasound, barium sandwich emptying radiography, or any combination of these tests.

Gastric Emptying Scintigraphy

Scintigraphy, performed by ingesting a test meal with radioactive markers, is the most frequently used test for evaluation of gastric emptying.[17-19] It represents the optimal method, if performed by a validated protocol, because it allows for precise quantification. Solids as well as fluids can be marked with tracers, and emptying can be monitored with gamma cameras. It is important to use a posterior and anterior camera position in a sandwich technique to obtain representative data for calculation of geometric mean data.[19] Modern systems have dual-head gamma cameras. The most frequently used tracer is ^{99m}Tc, which has a short half-life of 6 hours. If fluid and solid emptying needs to be differentiated, ^{111}In is mixed, for example, with orange juice, and detected separately via the dual-isotope technique.

"Regions of interest" are marked in the upper abdominal quadrants such that the area of the stomach is covered, and initial and declining tracer activity is measured as food leaves the marked regions. Segments of the esophagus and stomach can also be differentiated to assess emptying of the proximal and distal parts of the stomach separately. Often, the time that it takes for 50% of the tracer to leave the "region of interest" is identified as the empting half-time. Alternatively, activity can be measured after 100 minutes or 2 hours (Figs. 11–1 and 11–2).

However, it must be emphasized that the results of gastric emptying scintigraphy have considerable interindividual and even intraindividual variability, which can be as high as 20% to 30%. This variability also depends on the food and tracer preparation. In clinical practice, it is convenient to mix the two components just before the test. However, fluids can wash the tracer off the solid food, which can lead to misinterpretation and therefore underestimation of the true emptying rate. More precise is a stronger bond between food and tracer, but tremendous logistic effort is required that cannot be realized in clinical practice.[18] It is important to follow a standardized protocol with a uniform meal and evaluation process.[17]

^{13}C Breathing Test

The advantage of this test is the absence of radiation problems because ^{13}C is a stabile isotope, and it is increasingly being used in clinical practice. The principle of this

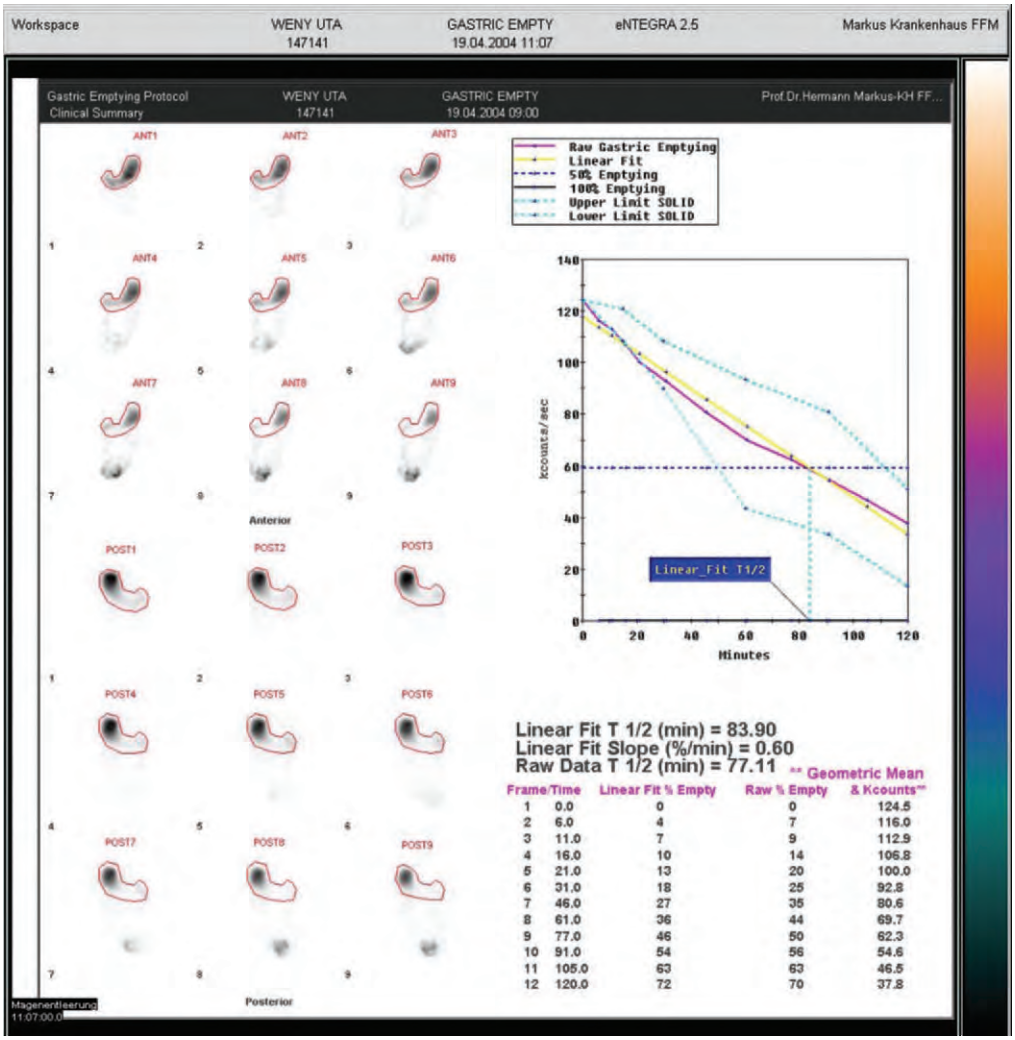

Figure 11–1. Gastric emptying scintigraphy with a dual-head gamma camera to evaluate emptying of solid food. The person investigated has normal emptying. (Investigation by M. Fobbe, Department of Radiology, Markus-Hospital, Frankfurt.)

method is based on emptying a combination of ^{13}C together with food (e.g., scrambled eggs) from the stomach to the duodenum. The tracer is mixed and fried together with the eggs to keep the marker on the semisolid food when emptying occurs. In the small bowel, ^{13}C is oxidized to $[^{13}C]CO_2$, which is exhaled and measured. Breath tests are performed before and after ingestion for 2 or 4 hours. Several studies have shown the validity of this test.[21-22]

Antroduodenal Manometry

Antroduodenal manometry assesses gastric and duodenal motor activity, which can be altered in foregut disorders such as gastric emptying problems, non–ulcer-related dyspepsia, and GERD, as well as panmotility disorders associated with achalasia.[13,14,16,23-25] Functional obstruction by antroduodenal motility disorders can lead to gastric dilatation, widening of the lower esophageal sphincter, and gastroesophageal reflux, as well as retention of ingested gastric contents with stimulation of acid secretion, thus increasing the potential for acid exposure in the esophagus.

Antroduodenal motility has been assessed by evaluating electrical activity or measuring the intraluminal mechanical activity of gastric and duodenal wall contractions by manometry. The latter is rather easy to manage in a clinical laboratory. Antroduodenal manometry can be performed with a perfusion manometry system in a gastrointestinal function laboratory or as a 24-hour monitoring test, depending on the equipment. Generally, a motility catheter is used with measuring points (openings on a perfusion catheter) or sensors (solid-state catheter) located a distance of 5 or 10 cm apart. Often, laboratories use catheters with a set of measuring points 1 cm apart at the pyloric region to record a representative image of this important segment. However, the choice of equipment depends on the particular patient, disorder, and questions that need to be answered with the test. Frequently, a six- or eight-channel system is used with 5-cm separation between the proximal three measuring points/sensors and 10-cm

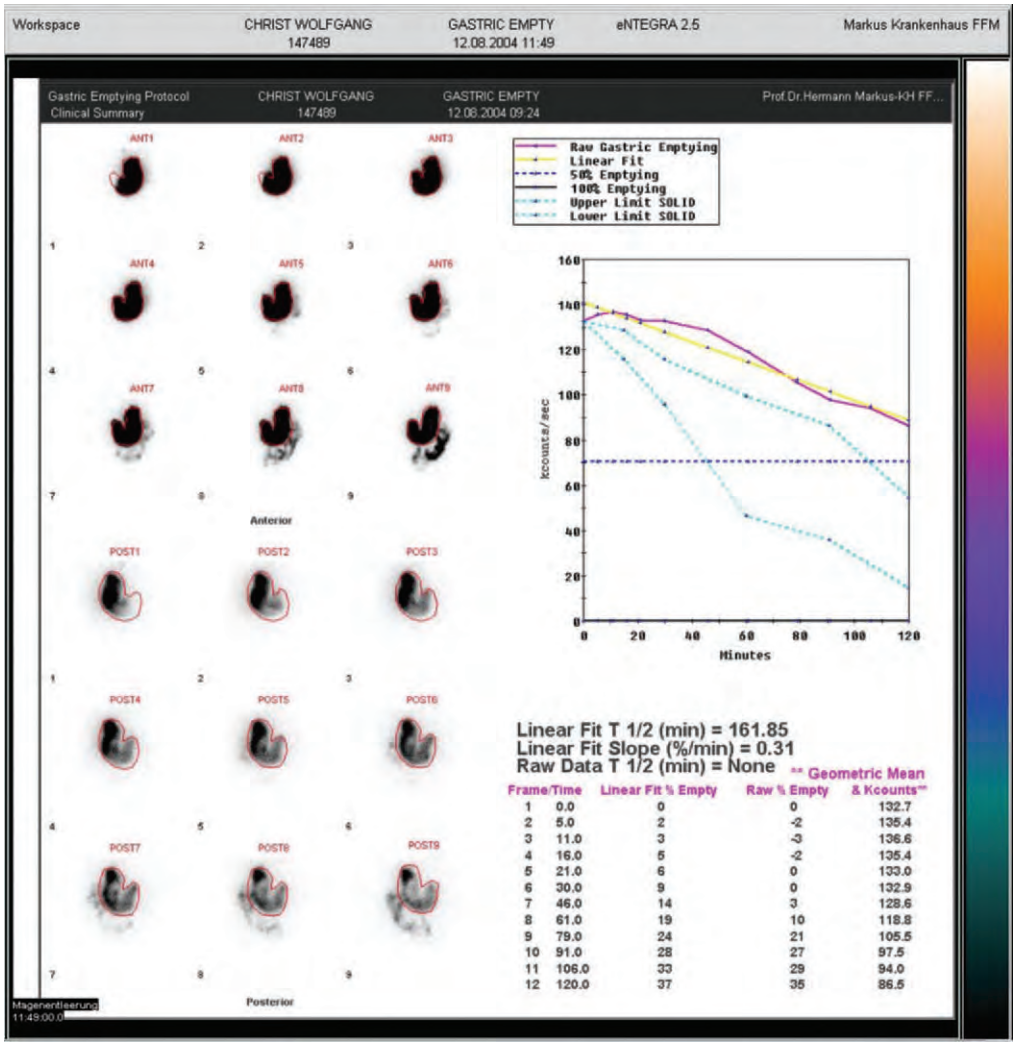

Figure 11–2. Gastric emptying scintigraphy in a patient with gastroparesis showing delayed gastric emptying. (Investigation by M. Fobbe, Department of Radiology, Markus-Hospital, Frankfurt.)

separation between the distal two or three points. This setup enables valid assessment of both antral and duodenal motility without a special focus on the pyloric region.

Before the test, the patient has to discontinue taking all potentially motility-interfering drugs for at least for 48 hours. After 6 hours of fasting, the catheter is passed transnasally into the duodenum. Under fluoroscopic guidance or by endoscopic means, the final position of the catheter is achieved in the duodenum (Fig. 11–3). It is important that the two or three oral pressure sensors be located in the antrum 5 and 10 cm above the pylorus and the most distal two sensors be located in the distal part of the descending duodenum or even around the bend in the ascending part. Depending on the number of available recording channels or sensors, reliable data require two full recordings in the prepyloric antrum and two in the descending duodenum. During antroduodenal motor activity, the catheter will move considerably, in addition to movement of the pylorus and duodenum around the catheter. As a consequence, the channels or sensors in the pyloric region will sometimes record antral and sometimes record duodenal motility, depending on the position. This lead can be neglected in the final analysis, but it is a valuable parameter to be able to identify the pyloric region. If the purpose of the investigation is assessment of the pylorus, a special catheter is necessary that has many sensors positioned 1 cm apart over a distance of 5 to 10 cm to precisely register any movement and all contractions of the pylorus.

The protocol for the test depends on the equipment used, such as a solid-state sensor system or perfusion manometry. With the latter, the patient is connected to the perfusion pump and has to stay in the laboratory for the duration of the investigation. With the solid-state system, the patient should perform normal daily activities as much as possible. The patient should eat and drink at set meal times only and document this in the diary in order to provide data on both fasting and fed-state motility patterns. All special events and symptoms should be documented in the diary during the investigation.

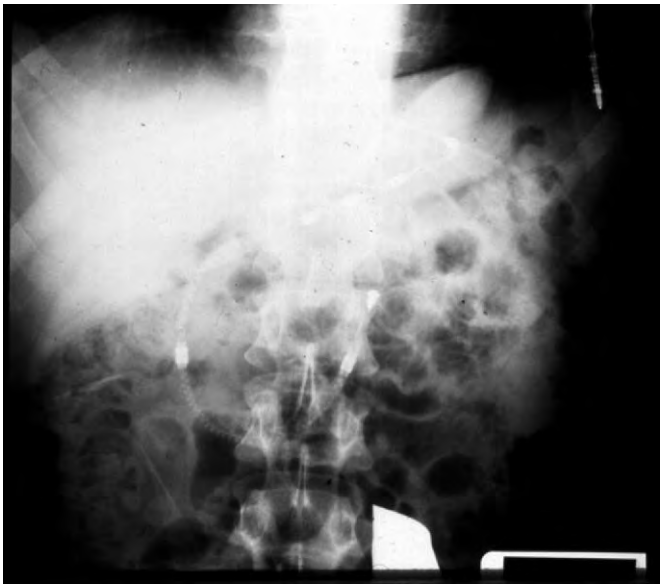

Figure 11–3. Fluoroscopic control after placement of an antroduodenal motility catheter for 24-hour antroduodenal manometry. It is important that the distal sensors be beyond the proximal duodenal bulb and be able to record duodenal motility in the descending and ascending portion of the duodenum.

Table 11–1 Normal Values of Antroduodenal Manometry in Healthy Volunteers

Motility Criteria	Antrum	Duodenum
IMMC—phase duration (%)		
Phase I	15-30	10-25
Phase II	20-50	40-60
Phase III	3-5	3-5
Fed pattern	5-20	5-20
Antroduodenal linkage—orthograde migration	>80%	>80%
Contractions—phase II		
Frequency per minute	1-1.5	1.5-4.5
Mean duration (sec)	1.7-3.5	1.5-3.0
Mean amplitude (mm Hg)	10-25	10-20
Contractions—phase III		
Frequency per minute	2.5-4	7-14
Mean duration (sec)	1.5-4	1.3-3
Mean amplitude (mm Hg)	40-100	10-40
Contractions—fed pattern		
Frequency per minute	0.5-3	0.5-2.7
Mean duration (sec)	2-3.6	2-3.8
Mean amplitude (mm Hg)	15-35	13-28

IMMC, interdigestive migrating motor complex.
From Heimbucher J, Fuchs KH, Freys SM, Thiede A: Antroduodenal motility in patients with gastroesophageal reflux disease. Langenbecks Arch Surg Forum (Suppl I):89-93, 1998.

Usually, commercially available software will provide an analysis of the data. Normal data, generated from 30 normal healthy volunteers tested with the same standardized protocol as used for patients, are demonstrated in Table 11–1.

The recording system will analyze the contractions for each lead. The investigator identifies and, from the diary documentation, marks positions and activity patterns of the patient, such as mealtimes and upright and supine body positions, from which the fed pattern and phases I, II, and III of the interdigestive migrating motor complex (IMMC) can be deducted and separately analyzed (Figs. 11–4 and 11–5). Contraction frequency and morphology for phases II and III, as well as for the fed pattern, representative characteristics of the IMMC, and antroduodenal coordination are expressed. Depending on the purpose of the investigation, more parameters can be analyzed, but clinical experience has shown that contraction frequency and IMMC phase coordination, together with fed-pattern morphology, are the most sensitive in comparing data from healthy volunteers with data from patients with esophageal disorders.

Three major dysfunctions can be identified by antroduodenal manometry:

1. Antral hypomotility. Hypomotility is usually seen in patients with a decreased contraction amplitude and a decreased frequency of contractions. In some patients, this phenomenon is seen in the fasting as well as the postprandial state. A shortening or even absence of phase II and III and absence of a physiologic fed pattern is possible. Hypomotility during the fed state is regarded as the most severe problem.
2. Disturbance of phasic IMMC activity. When this problem is present, the physiologic sequence of phases from I to III does not occur on a regular basis or is absent. Instead, the phases are irregular in occurrence and duration. Antroduodenal coordination and linkage of phases can be absent. The percentage of orthograde migration of contraction patterns is decreased, as well as the number of complete IMMCs. This problem often occurs after previous upper gastrointestinal surgery, especially gastric surgery.
3. Focal dysfunction. Episodes of simultaneous contractions are recorded, followed by hypomotility segments. In addition, bursts of high-amplitude contractions may occur at only one level, so interpretation is difficult. This phenomenon can also be seen more frequently toward the oral side of an obstruction.

In patients with esophageal disorders, most often GERD, antroduodenal motility disorders can be associated with extraesophageal symptoms such as nausea, early satiety, uncomfortable fullness, and vomiting. Antral or antroduodenal hypomotility can be detected most frequently in these patients. Table 11–2 presents the results of a comparative study.[13] In these patients, the

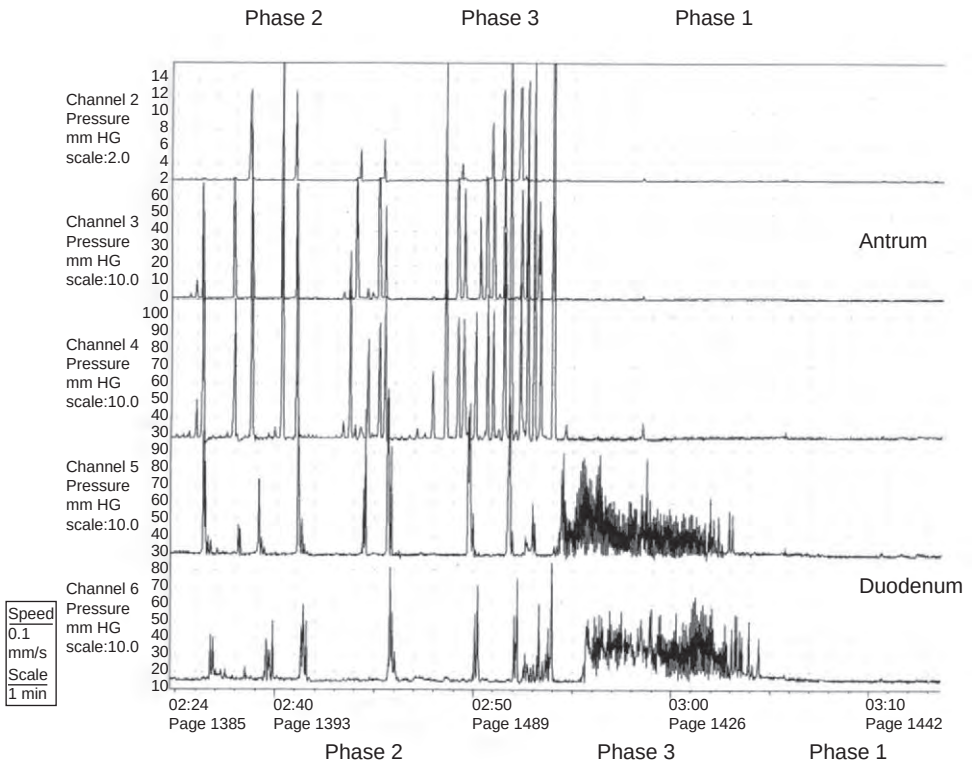

Figure 11–4. Example of a normal physiologic motility pattern of the interdigestive migrating motor complex as recorded by antroduodenal manometry.

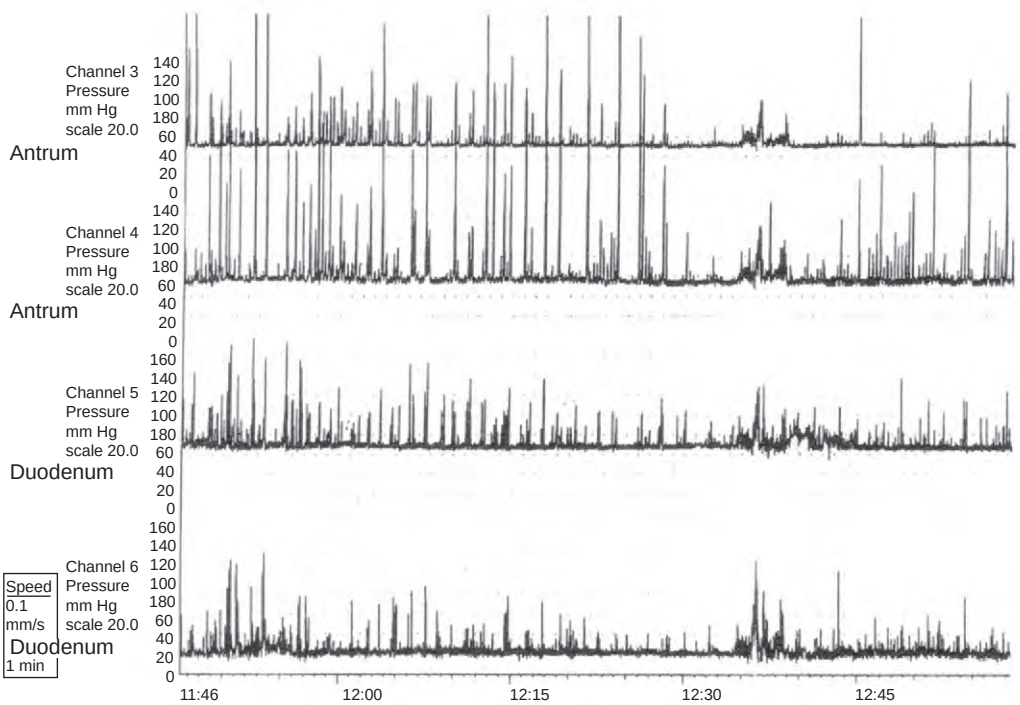

Figure 11–5. Example of normal physiologic antroduodenal motility of the fed pattern as recorded by antroduodenal manometry.

Table 11–2 Results of Antroduodenal Manometry in Patients with Gastroesophageal Reflux Disease Versus Healthy Volunteers

	Antrum			Duodenum		
	Control	GERD	*P*	Control	GERD	*P*
IMMC						
Number/24 hr	5	3	<.05	8	4	<.01
Duration (min)	120	122	NS	65	76	<.05
Frequency						
Total	1.1	0.8	<.01	1.8	1.9	NS
Upright	1.4	1.3	NS	2.1	1.9	NS
Supine	0.7	0.3	<.01	1.1	1.0	NS
Postprandial	1.7	1.0	<.05	4.7	3.2	<.01

IMMC, interdigestive migrating motor complex; NS, not significant.
From Heimbucher J, Fuchs KH, Freys SM, Thiede A: Antroduodenal motility in patients with gastroesophageal reflux disease. Langenbecks Arch Surg Forum (Suppl I):89-93, 1998.

number of IMMCs and hypomotility in both the antrum and duodenum can be the background for associated gastric symptoms. In patients with GERD, nonspecific symptoms such as nausea, epigastric pain, vomiting, and uncomfortable fullness are associated with the presence of antroduodenal dysmotility.

Additional Miscellaneous Gastric Emptying Tests

Assessment of the stomach and emptying of fluids or even standardized particles with real-time ultrasound has been shown to be helpful. Its high dependence on observer competence and its potential variability remain a problem. It is, however, a cheap and noninvasive procedure.

Radiographic barium burger studies to evaluate esophageal passage and gastric emptying can be performed in clinical practice in any radiology unit. Emptying is difficult to precisely quantify with this method, and radiation is invasive. Usually, the result is expressed as percent emptying after standardized time segments with respect to initial filling. It is helpful in clinical practice if no other more extensive evaluation is available.

Sophisticated technology such as the Barostat technique, single-photon emission computed tomography, and impedance epigastrography have been used, generally in research centers.[26,27] Further investigation will provide more insight into gastric physiology. There could be a simple alternative to assessment of gastric emptying in patients with gastroesophageal reflux, such as correlation of intraluminal pH values with gastric emptying data.[28-30]

DUODENOGASTROESOPHAGEAL REFLUX

DGR is a natural physiologic phenomenon.[30,31] It is part of the normal complex motility pattern of the upper gastrointestinal tract. The gastric mucosa is able to cope with a certain level of exposure to duodenal juice, including its various components, such as pancreatic enzymes and related agents, bile acids and bile salts, and varying amounts of bicarbonate. The constituents of duodenal juice have been demonstrated to have a tremendously damaging effect on gastric mucosa[32,33] and even more so on esophageal mucosa.[6,34] DGER is associated with two major clinical problems in gastrointestinal surgery: reflux problems after gastric surgery and Barrett's esophagus.[3,6,34,35]

In many patients with postgastrectomy syndromes and in some with postfundoplication problems, DGER is the major associated cause. As classic symptoms, Ritchie has defined epigastric pain, nausea, bile vomiting, and weight loss as indicating the possible presence of DGR.[33] In patients with mechanical and functional weakness of the lower esophageal sphincter, the combined problem will cause a mixed reflux. Accurate objective assessment of this pathologic process should include, in addition to endoscopic evaluation, 24-hour esophageal and gastric pH monitoring and 24-hour esophageal and gastric bilirubin monitoring.[31,34-38] Often, the problem can be corrected by surgical duodenal diversion procedures.

The association of Barrett's esophagus and its progression to cancer with DGER has been extensively investigated in the past. There is no doubt that DGER occurs significantly more frequently in GERD patients with Barrett's esophagus than in those without this condition.[6,34,35,39] Substantial experimental and clinical evidence is available to support the injurious effect of duodenal juice on esophageal mucosa.[39]

Evaluation of DGER has a long history and has involved several techniques, such as aspiration of intraesophageal fluid, scintigraphy, and pH monitoring in the esophagus and stomach. However, either the accuracy of the tests limited their diagnostic value or their invasive approach restricted their applicability in patients. Assessment by intraluminal probes connected to data loggers

is currently still the most frequently used procedure. Objective assessment of DGER and its relationship to acid reflux is best evaluated by esophageal and gastric 24-hour pH and bilirubin monitoring.[31,40]

24-Hour Gastric pH Monitoring

After an 8-hour fasting period, pH probes are placed in the esophagus and stomach.[30,41] The gastric probe is positioned 5 cm below the lower boarder of the lower esophageal sphincter (Fig. 11–6). The probe is connected to a data logger and the data recorded over one circadian cycle of at least 20 hours. Both the pH probe and the bilirubin probe can be taped together if monitoring is performed as a combined test. During the test period, the diet is restricted to food with a pH between 5 and 7. Individuals are allowed to continue their daily activities exclusive of hard work or sports. If the test is performed in the hospital setting, the patients should move about, go for long walks, or sit in chairs and restrict their supine position to night hours. Body position and meal activities, as well as symptoms, should be documented in a diary. More important than in esophageal pH monitoring, in gastric pH monitoring mealtimes are standardized to three periods per day, and drinking must also be restricted to these periods and carefully documented.

Recorded pH data can be analyzed by a commercially available computer program (Medtronic GmbH, Düsseldorf, Germany). The analysis separates the 24-hour period into four different phases: upright, supine, mealtime, and postprandial periods. This is important because of the great influence of the meal on gastric intraluminal food and fluid (Fig. 11–7). The program provides data on intraluminal gastric pH, separated into the four different phases, as a frequency distribution of pH values from 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 7, and 7 to 8. Table 11–3 lists normal values of healthy volunteers.

Pathologic changes in this physiologic gastric pH spectrum can be determined. These changes can be identified as persistent gastric acidity when the percentage of pH distribution above pH 3 is less than 1% (Fig. 11–8). In contrast, a less acidic gastric pH environment can be detected if the intragastric pH profile is more frequently above pH 3 than the physiologic values are.[30,41] Figure 11–9 shows an example of a less acidic pH distribution

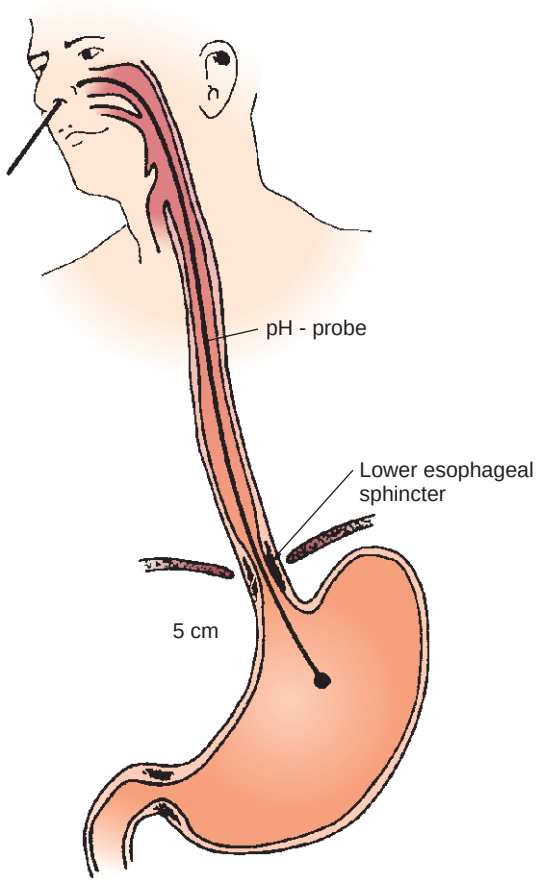

Figure 11–6. Positioning of the gastric pH probe and bilirubin monitoring probe in the proximal gastric lumen 5 cm below the lower border of the lower esophageal sphincter.

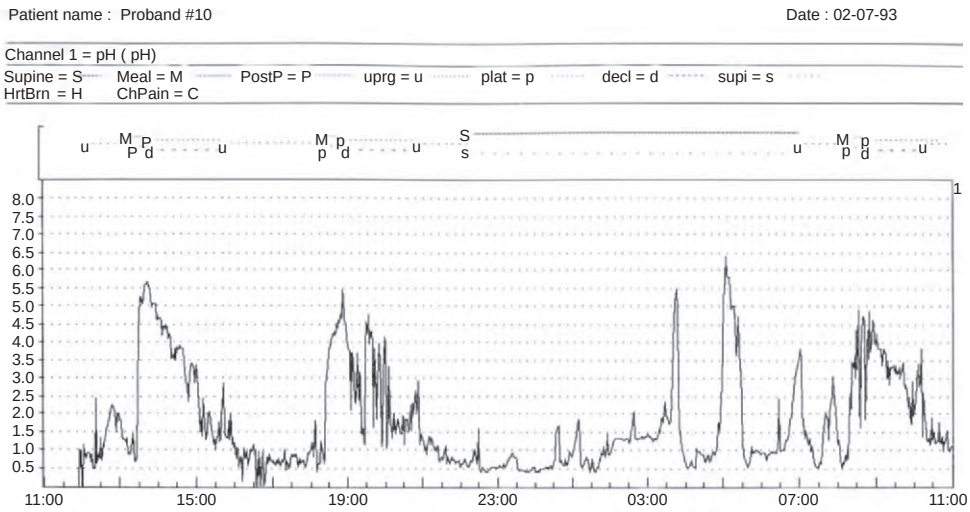

Figure 11–7. Physiologic 24-hour gastric pH monitoring record with a rather acidic gastric pH baseline interrupted by several rises in the pH value, mainly during meals consisting of food and drink with different pH values.

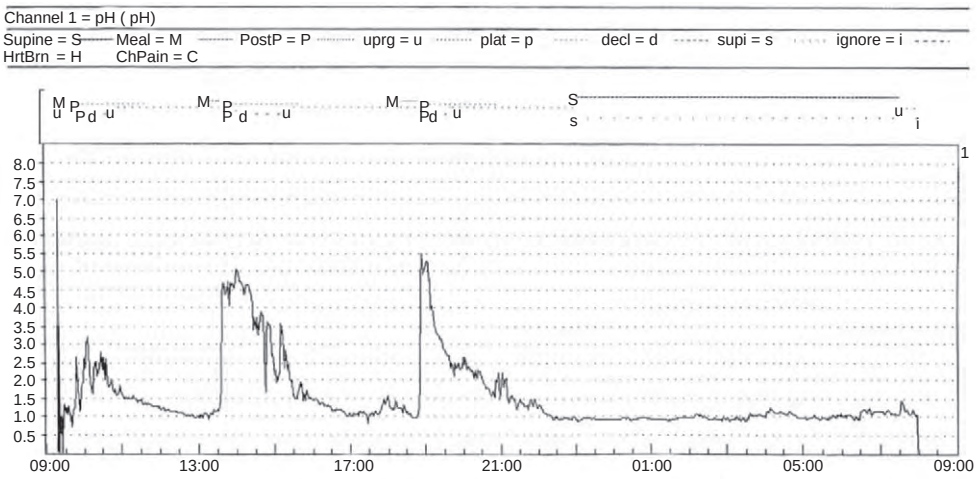

Figure 11–8. Persistent gastric acidity as measured by 24-hour gastric pH monitoring. The tracing shows hardly any changes in the very acidic gastric pH baseline.

Table 11–3 Normal Values for 24-Hour Gastric pH Monitoring in Healthy Volunteers: pH Value Distribution During a 24-Hour Circadian Cycle Exclusive of Mealtimes

Criteria	Body Position	5th Percentile	Median	95th Percentile
pH—mean	Upright	0.9	1.6	2.6
pH—mean	Supine	0.8	1.6	3.7
pH—intervals	Upright			
0-1		0	13.4	57.0
1-2		28	61.8	94.0
2-3		1.4	7.6	42.7
3-4		0	1.9	15.3
4-5		0	0.6	9.5
5-6		0	0.1	8.9
6-7		0	0	1.4
7-8		0	0	0.1
pH—intervals	Supine			
0-1		0	16.1	76.8
1-2		14	50.1	98.8
2-3		0	8.1	28.8
3-4		0	3.0	17.4
4-5		0	0.9	6.9
5-6		0	0	6.3
6-7		0	0	19.7
7-8		0	0	8.4

Data from Fuchs KH, DeMeester TR, Hinder RA, et al: Computerized identification of excessive duodenogastric reflux: Discriminant analysis of 24 hour gastric pH recording. Ann Surg 213:13-20, 1991; and Fuchs KH, Maroske J, Fein M, et al: Variability in the composition of duodenogastric reflux. J Gastrointest Surg 3:389-396, 1999.

in a patient with a high probability of reflux of duodenal juice with combined pH and bilirubin monitoring. It is clear that not all rises in pH in the recording are associated with reflux of bile and vice versa.[31]

An important application of 24-hour gastric pH monitoring in conjunction with esophageal pH monitoring is to verify negative esophageal pH testing (Fig. 11–10). If performed as a single procedure, esophageal pH monitoring in the event of a negative test does not tell the investigator whether acid in the gastric lumen influenced the refluxate. Combined esophageal and gastric pH monitoring will clarify the acidity in the stomach and the possible acid exposure in the esophagus, thereby shedding light on the competence of the antireflux barrier. The combined test can also be used to evaluate response in patients receiving proton pump inhibitor (PPI)

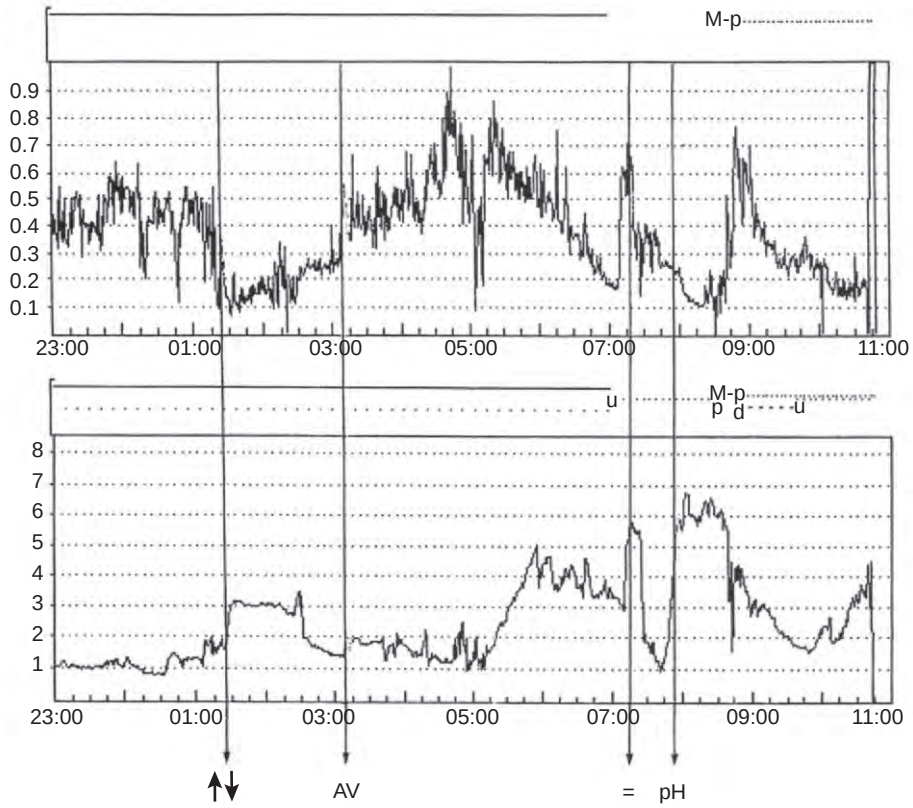

Figure 11–9. Example of a combined recording of 24-hour gastric pH monitoring and 24-hour gastric bilirubin monitoring showing changing acidity in the gastric lumen, as well as changing levels of absorption, indicating various levels of bile reflux. It is important to recognize that these changes do not occur simultaneously.

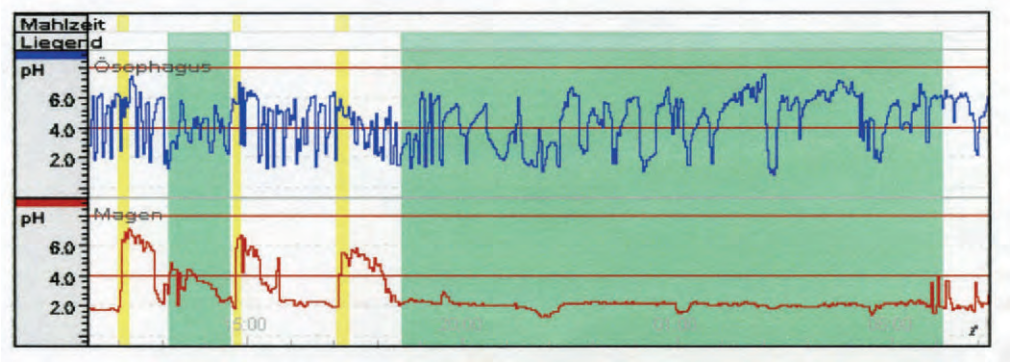

Figure 11–10. Example of combined esophageal and gastric pH monitoring to clarify gastric acidity during a gastroesophageal reflux episode.

therapy.[42-45] Persistent acidity of the gastric environment with PPI treatment enables the investigator to better interpret the therapeutic effect and allows for adjustment of dosage and timing.[46] Nightly acid breakthrough has been described as one of the causes of partial failure of PPI therapy in patients with GERD. In clinical practice, complex data analysis is often not even necessary. Visual control and evaluation of the 24-hour record will tell the investigator immediately the connection between the intraluminal gastric pH environment and esophageal acid exposure with regard to time during the circadian rhythm and duration of exposure. Accordingly, gastric pH testing is a valuable method in patients with esophageal disease that can help clarify pathophysiologic mechanisms, as well as control therapeutic activities.

24-Hour Bilirubin Monitoring

An indirect method to assess DGR or DGER is bilirubin monitoring by the Bilitec device. The system detects intraluminal bilirubin by spectrophotometric measurement. The spectophotometric probe contains optical fibers connected to light-emitting diodes and receiving photo diodes. This photoelectronic device can emit a 470-nm signal light and a 565-nm reference light. By reflection of signals from the probe, which is enveloped in esophageal and gastric fluids, the system can provide absorbance values that reflect intraluminal bilirubin concentrations. Several published validation studies have shown remarkable reliability of the system.[31,36-38,47] This test is valuable for the detection of bilirubin as an important marker of DGER.

The investigation is performed with a protocol similar to that for long-term pH monitoring. It is important to impose further dietary restrictions inasmuch as validation studies have shown that foods with a similar wavelength as bilirubin can cause severe artifacts.

Best is a diet consisting of food and drink with white or bright colors, such as chicken meat. Analysis of the recorded data provides absorption values distributed over the investigation period and subdivided into different phases, such as upright, supine, and meal periods. Table 11–4 presents normal data generated from healthy volunteers. Figure 11–11 illustrates pathologic bilirubin exposure in a patient with pathologic DGR and DGER.

Although DGR occurs physiologically, DGER has not been detected in normal healthy volunteers by bilirubin monitoring.[6,40] The role of DGER in Barrett's esophagus is well investigated and a documented fact.[35] Recent studies have shown that DGER and DGR can be associated with severe GERD.[40,48] The clinical application of such monitoring is limited to centers where the equipment is available. Because of the lack of a proven benefit or positive therapeutic effect in GERD patients with or without DGER, application of 24-hour bilirubin monitoring is limited. For precise determination of the severity of GERD, evaluation of DGER is necessary. Recently, a study in GERD patients has shown that the combination of esophageal pH and bilirubin monitoring is able to identify the reason for failure of PPI therapy.[48] Combined pH and Bilitec monitoring was superior to pH recording alone in detecting ongoing pathologic reflux in patients with poor clinical response to PPI treatment. In addition, gastric pH and bilirubin monitoring will provide the underlying basis for the intragastric acid and bile load. This information seems to also be helpful in surgical decision making. The documented presence of

Table 11–4 Normal Values of Esophageal and Gastric 24-Hour Bilirubin Monitoring in Healthy Volunteers

Percentage of Measured Time Above Threshold	25th Percentile	Median	95th Percentile
Esophagus—threshold absorption value >0.14			
Total time	0	0.5	11.8
Stomach—threshold absorption value >0.25			
Total time	0.35	1.45	28.2
Upright	0.08	0.85	15.4
Supine	0.07	0.75	37.7
Meal	0	0.1	14.5

Data from references 6, 31, 37.

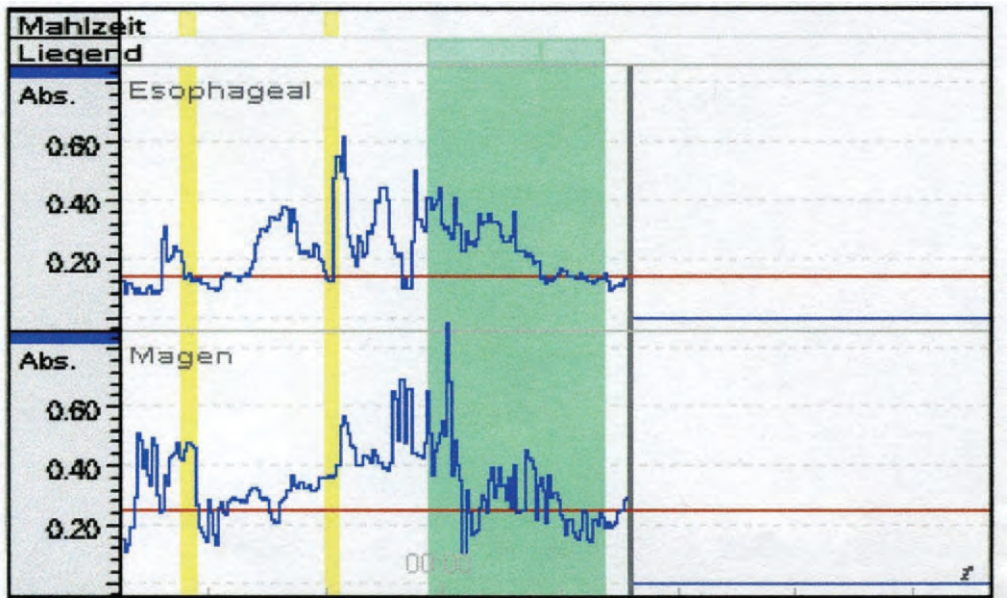

Figure 11–11. Example of combined esophageal and gastric bilirubin monitoring to clarify the level of gastric bile exposure during a gastroesophageal reflux episode.

pathologic esophageal and gastric acid and bilirubin exposure can make a stronger case for performing antireflux surgery, if all other indications are fulfilled.

Miscellaneous Gastric Functional Tests

Gastric acid secretion was studied for many years in clinical practice when gastroduodenal ulcer disease was still considered a problem of the secretory state.[8] This test was also used as a therapeutic control after surgery to reduce acid secretion, such as all forms of vagotomy. Because it is known that the majority of the ulcers develop from *Helicobacter pylori* infection or the use of nonsteroidal anti-inflammatory drugs, the clinical value of this test has diminished. Basal acid secretion was measured after overnight fasting by the instillation of a standardized saline solution and aspiration of the intragastric fluid with subsequent titration for determination of its hydrogen ion content. Basal acid secretion could vary between 0 and 5 mEq/hr. After stimulation with pentagastrin, the maximal secretory output of gastric acid can be determined and ranges between 10 and 15 mEq/hr. This test requires several hours of aspiration. Therefore, ambulatory 24-hour gastric pH monitoring is a better test for assessing intragastric acidity.

The Barostat test measures accommodation, gastric dilatation, and contractions, especially in the proximal part of the stomach.[26] Because it is a rather complex technology and requires testing in a laboratory, it is not used widely in clinical practice but remains a research tool in selected units. It can provide more insight into the relationship between esophageal function and gastric motility.[49]

Electrogastrography is technique that assesses gastric motility by monitoring electric activity. Initial experience with the cutaneous application of electrodes to record this activity has been achieved, but the clinical value of the recorded data is limited because of the need for investigation in a laboratory setting and a number of possible artifacts.

Measurement of impedance in the esophagus and gastroesophageal junction is increasingly gaining importance in assessing esophageal function.[50,51] Because the resistance of gastric mucosa is different from that of esophageal mucosa, however, application of impedance measurement to the gastric lumen is difficult.

ASSESSMENT OF GASTRIC FUNCTION IN ESOPHAGEAL DISEASE

The most important esophageal disorder that also involves the stomach is GERD. Gastric and duodenal dysfunction can have an influence on or even cause esophageal functional problems. As a consequence, assessment of gastric and duodenal function is important in both diagnosis and therapeutic decisions regarding esophageal disease. Such assessment is frequently necessary in patients with GERD, but it also relevant in patients with extensive gastrointestinal motility disorders such as achalasia associated with delayed gastric emptying or panmotility problems with slow transit constipation, small bowel hypomotility, and delayed gastric emptying.

Especially in surgical patients, detailed evaluation of esophageal and gastric function is of utmost importance before surgery because postoperative failure can be caused by an underlying and undetected problem in gastric function.

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Part

3

Gastroesophageal Reflux Disease

Chapter

12

Epidemiology and Natural History of Gastroesophageal Reflux Disease

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The prevalence of gastroesophageal reflux disease (GERD) in the United States is high, with approximately 20% of the population experiencing weekly symptoms. Despite the fact that GERD is common, understanding the epidemiology and natural history of GERD is hampered by several factors, including an evolving definition of GERD, lack of a diagnostic gold standard, and a paucity of population-based data. Furthermore, there is an unclear demarcation between physiologic reflux and gastroesophageal reflux as a disease. Consequently, our understanding of the true epidemiology and natural history of GERD is limited.

EPIDEMIOLOGY OF GERD

Prevalence estimates of GERD primarily depend on the definition used in a given study. In general, GERD has been defined as a disorder in which gastric contents recurrently reflux into the esophagus and cause heartburn and other symptoms. GERD is typically classified into erosive and nonerosive disease based on endoscopic findings. In the absence of a gold standard for diagnosing GERD, various investigators have applied symptoms, endoscopic findings, 24-hour esophageal pH monitoring, or even response to acid inhibitor therapy in an attempt to define GERD. The American College of Gastroenterology suggests the following definition of GERD: "chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus."[1] A group of experts at the Geneva Workshop on Reflux Management offered the following definition of patients with nonerosive reflux disease (NERD): "These are individuals who satisfy the definition of GERD but who do not have either Barrett's esophagus or definite endoscopic esophageal breaks."[2] A similar definition, proposed by Waring, cites "burning retrosternal discomfort for at least 3 months, but with normal esophageal mucosa on upper endoscopy."[3] Fass et al. proposed a different definition for NERD that underscores the close relationship between symptoms and reflux of gastric contents.[4] They defined NERD as the presence of typical symptoms of GERD caused by intraesophageal gastric contents in the absence of visible esophageal mucosal injury on endoscopy. However, there remains debate regarding when the frequency of symptoms denotes gastroesophageal reflux the disease versus occasional heartburn. The demarcation between "physiologic" and abnormal acid reflux remains undefined.

The prevalence of GERD differs, depending on the variable measured. Most studies have focused on symptoms (primarily heartburn) or endoscopic findings (i.e., esophagitis). Unfortunately, each approach has limitations. Questionnaire studies are limited by the poor correlation between symptoms and objective findings. In addition, questionnaires often do not recognize the myriad of extraesophageal symptoms associated with GERD. Alternatively, investigators have sought to define the prevalence of GERD in populations with the use of physiologic data, such as endoscopy and 24-hour pH monitoring. Although this approach has the strength of more objective criteria on which to base the diagnosis, it is invasive, time-consuming and expensive. Endoscopy misses the large group of GERD patients, approximately 50%, who suffer from nonerosive disease. Although 24-hour esophageal pH testing is useful in defining GERD, it is too resource intensive for assessing population-based prevalence.

Epidemiology of GERD Symptoms

When based on symptoms, GERD is common in Western countries (Table 12–1). In a nationwide population based study by the Gallup Organization in the United States, 44% of the population reported heartburn at least once a month.[6] Another survey of presumably healthy hospital employees demonstrated that 7% reported symptoms of heartburn daily and an additional 14% experienced it weekly.[5] More convincing data were obtained by Locke et al., who mailed out 2200 validated self-report questionnaires to a predominantly white population residing in Olmsted County Minnesota.[10] The prevalence of heartburn and acid regurgitation in the previous 12 months was noted to be 42% and 45%, respectively. Frequent symptoms occurring at least weekly were reported by 20% of respondents, with an equal gender distribution across all ages (Fig. 12–1). The majority reported that the heartburn was of moderate

Table 12–1 Studies Reporting GERD Symptoms by Questionnaire

Reference	Population	Symptoms Elicited	Frequency Reported	Percentage Affected
Nebel et al. (1976)[5]	U.S. hospital workers	Heartburn	Daily	7
Gallup Poll (1988)[6]	General U.S. sample	Heartburn	Monthly	44
			Weekly	14
			Yearly	42
		Acid regurgitation	Weekly	6
			Yearly	45
Jones et al. (1990)[7]	United Kingdom	Heartburn	Previous 6 months	18
Ruth et al. (1991)[8]	Sweden	Heartburn	Overall prevalence	21
		Regurgitation	Overall prevalence	20
Isolauri et al. (1995)[9]	Finland	Heartburn	That day	9
			Previous week	15
			Previous month	21
			Previous year	27
		Regurgitation	That day	5
			Previous week	15
			Previous month	29
			Previous year	45
Locke et al. (1997)[10]	Olmsted County, MN	Heartburn	Weekly	18
Norrelund and Pederson (1998)[11]	Norway	Heartburn	Previous 6 months	12
		Regurgitation	Previous 6 months	9
Valle et al. (1999)[12]	Italy	Heartburn	Daily	2.3
			Weekly	5.4
			Monthly	5.6
		Acid regurgitation	Daily	1.3
			Weekly	5.3
			Monthly	7
Frank et al. (2000)[13]	US and Canada	Heartburn	Weekly	6.2
			Previous 3 months	19.5
Louis et al. (2002)[14]	Belgium	Heartburn	Daily	6.3
			Weekly	11.3

Modified from Shaheen N, Provenzale D: The epidemiology of gastroesophageal reflux disease. Am J Med Sci 326:265, 2003.

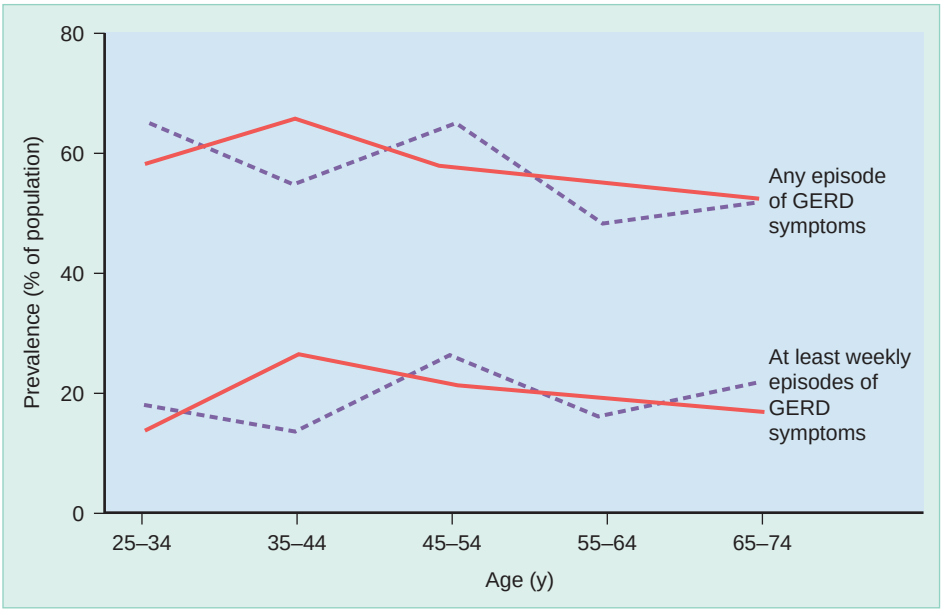

Figure 12–1. Prevalence of heartburn by age and sex in a random population sample. (Modified from Locke GR III, Talley NJ, Fett SL, et al: Prevalence and clinical spectrum of gastroesophageal reflux: A population-based study in Olmsted County, Minnesota. Gastroenterology 112:1448-1456, 1997.)

severity and had a duration of 5 years or longer, and only 5.4% reported a physician visit for reflux complaints within the previous year.

These data are similar to those of a recent Canadian study involving 1036 subjects in which the prevalence of heartburn in the previous 3 months was 43%; symptoms of moderate severity occurred at least once a week in 13%.[15] More variable prevalence rates for symptomatic GERD have been reported from Europe, with a range of 5% in Switzerland to 27% in Finland.[9] A Swedish study demonstrated a 21% cross-sectional prevalence of heartburn symptoms. Twenty percent also reported regurgitation and 12% reported noncardiac chest pain.[8] This population was evaluated 10 years later, and the prevalence of heartburn, acid regurgitation, and chest pain was essentially unchanged.[16] Louis et al. recently attempted to define the prevalence of heartburn in 2000 randomly selected Belgians.[14] They found that 6.3% of the population experienced daily substernal chest burning and 11.3% had weekly symptoms. Twenty-seven percent reported that they found their heartburn symptoms to interfere greatly with their daily activities. Similarly, Valle et al. recently reported on an Italian cohort of factory and hospital workers. They found that 21% described at least monthly symptoms of heartburn or regurgitation.[12]

As mentioned previously, prevalence estimates based on symptoms are limited by the poor correlation between symptoms and objective findings. This in part relates to the fact that GERD symptoms are not always caused by esophageal acid exposure. There are sufficient data to suggest that acid is not the only intraesophageal stimulus that can lead to a heartburn sensation. In fact, heartburn appears to be the "common pathway" of a variety of intraesophageal events, of which acid reflux is only one.

Epidemiology of GERD Based on Endoscopic Assessment

The prevalence of erosive esophagitis in the general population is difficult to ascertain in the absence of population-based studies. Estimates suggest that 7% of persons in the United States have erosive esophagitis.[17] Akdamar et al. reported that among 355 healthy volunteers undergoing upper endoscopy before inclusion in clinical trials, 13.8% had abnormal endoscopic findings and 8.5% had erosive esophagitis.[18] A study from China estimated a 5% rate of erosive esophagitis.[19] The prevalence of erosive esophagitis in those with reflux symptoms has also been extensively studied. There is a broad range in the reported prevalence of erosive esophagitis in those undergoing endoscopy in the literature, with rates ranging from 10% to 60% (Table 12–2). This range may represent underlying differences in the patients being studied, as well as differences in the availability of health services. In addition, many patients with GERD symptoms never seek medical attention. Voutilainen et al. performed upper endoscopy on 1128 Finnish patients with complaints of dyspepsia and reflux symptoms.[23] They found 25% of their population to have erosive esophagitis. In subjects complaining solely of reflux symptoms, 38% had esophagitis. Venables et al., in a multicenter study in the United Kingdom, studied the prevalence of esophagitis in patients in a general practice with heartburn as a predominant symptom.[24] Of the 944 patients studied, 32% were noted to have erosive esophagitis. One of the strengths of this study was the rapid access to endoscopy (within 14 days) from the time of the first evaluation in the primary care setting and the absence of antisecretory medications pending endoscopic evaluation. A considerable time lapse between clinical assessment and endoscopic evaluation may allow

Table 12–2 Prevalence of Erosive Esophagitis in Subjects Undergoing Endoscopy for Reflux Symptoms

Reference	Patient Population	Mean Age (yr)	Gender (% Female)	Erosive Esophagitis (%)
Behar et al. (1976)[20]	Sweden	52	64	35
Johansson et al. (1986)[21]	United Kingdom	NR	38	9.9
Howard and Heading (1992)[22]	Unites States	55.2	56	46
Chang et al. (1997)[19]	Japan	NR	38%	18.5
Voutilainen et al. (2000)[23]	Finnish population with dyspepsia or reflux symptoms	57	58	60

NR, not reported.
Modified from Shaheen N, Provenzale D: The epidemiology of gastroesophageal reflux disease. Am J Med Sci 326:269, 2003.

healing of esophagitis in a substantial number of patients and thereby lead to underestimation of erosive esophagitis. Achem et al. observed that the use of antisecretory medications may have accounted for the false-negative endoscopic results in up to 50% of patients with NERD.[25] Additionally, several groups have attempted to quantitate the amount of reflux in the normal population by 24-hour pH studies.[26,27] These studies have demonstrated considerable overlap between those with proven GERD and asymptomatic control subjects.[28,29] Thus, approximately a third to at most half of patients with GERD symptoms who seek medical help have erosive esophagitis. The amount of reflux experienced in the esophagus correlates only loosely with the signs and symptoms of reflux disease.

Population Risk Factors for GERD

Although GERD is ubiquitous, several risk factors have been suggested. The effect of age on the prevalence of reflux disease is inconsistent in the literature. Several groups have demonstrated that GERD symptoms are more common in older populations.[30,31] A Veterans Affairs study found evidence that more severe manifestations of reflux, such as strictures and ulcers, occur more commonly in elderly patients, probably as a result of cumulative acid injury to the esophagus over time. However, the finding of increasing prevalence of GERD symptoms with increasing age is not seen in all studies.[10] Some investigators have even found a negative association between GERD symptoms and age, with younger subjects suffering more severe symptoms than older persons.[7,32] Population-based studies also suggest a correlation between reflux symptoms and obesity. In morbidly obese patients, rates of both asymptomatic and symptomatic reflux have been reported to be high and directly correlate with weight.[33-36] The pathophysiology is most likely increased intra-abdominal pressure resulting in alterations in the gastroesophageal junction. Dietary factors, primarily high-fat diets, have been associated with a higher prevalence of GERD. The presence of a hiatal hernia has also been linked to more severe forms of reflux disease. Although the majority of subjects with hiatal hernias do not have esophagitis, it has been demonstrated that most subjects with esophagitis do have a hiatal hernia.[37,38] Among those with esophagitis, the size of the hiatal hernia is also correlated with the severity of esophagitis, with those possessing the largest hernias having the most severe mucosal disease.[38,39] Additionally, Barrett's esophagus seems to be more common in those with a hiatal hernia.[40] Analysis of the gender ratio of patients with symptomatic GERD shows nearly equal proportions of men and women affected, but a male preponderance occurs with esophagitis (2 : 1 to 3 : 1) and Barrett's esophagus (10 : 1).[41-43] Pregnancy is associated with the highest incidence of symptomatic GERD; 48% to 79% of pregnant women complain of heartburn.[44] All forms of GERD affect whites more frequently than members of other races. There have been several case reports in the literature describing families with multiple members who have documented GERD. Jochem et al. described a family spanning three generations in which six cases of Barrett's esophagus were detected.[45] The acquisition of Barrett's esophagus was compatible with an autosomal form of inheritance. However, family members usually share other environmental risk factors for reflux besides genetic make-up. More research is needed regarding the genetic contribution to GERD.

The role of *Helicobacter pylori* with regard to the epidemiology of GERD remains unanswered. el-Serag and Sonnenberg observed opposing time trends in the prevalence of peptic ulcer disease and GERD in the United States: rates of peptic ulcer and gastric cancer fell between 1970 and 1995, whereas the prevalence of GERD and esophageal adenocarcinoma rose significantly (Fig. 12–2).[46] The authors speculated that the decreasing prevalence of *H. pylori* might play a contributory role to the increased prevalence of GERD. Data suggest that *H. pylori*–induced gastritis involves both the antrum and corpus and affects the parietal cell, thus reducing acid secretion and elevating gastric pH. Such infection may have a protective influence on the esophageal mucosa in patients susceptible to GERD. Furthermore, reversal of gastritis-associated hypochlorhydria renders individuals more susceptible to reflux of acid

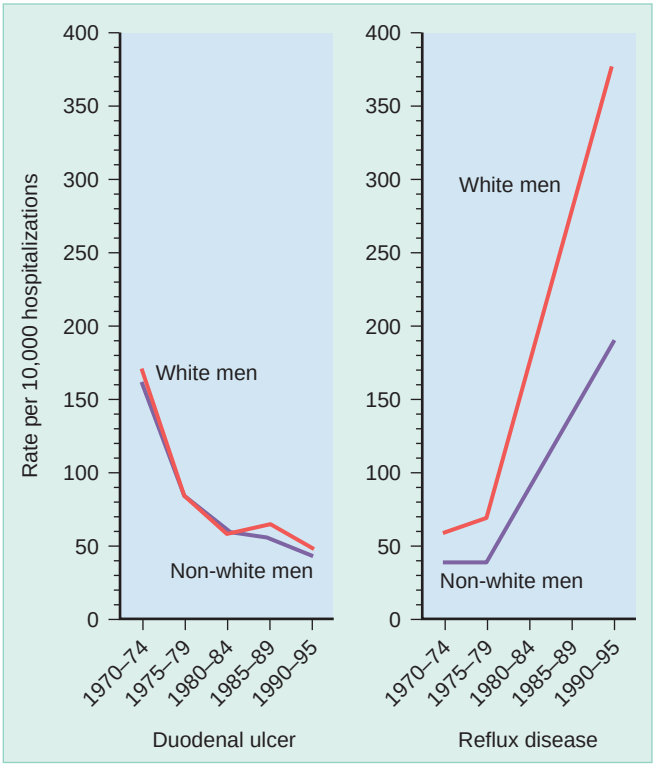

Figure 12–2. Opposing time trends in the rates of hospitalization for duodenal ulcer and gastroesophageal reflux disease. The computerized database of the U.S. Department of Veteran Affairs was used to analyze hospitalization rates. (Modified from El-Serag HB, Sonnenberg A: Opposing time trends of peptic ulcer and reflux disease. Gut 43:327-333, 1998.)

and the development of erosive esophagitis. Labenz et al. monitored patients with duodenal ulcer after antibiotic cure of *H. pylori* infection for 3 years.[47] The incidence of reflux esophagitis was 25.8% after eradication of *H. pylori* versus 12.9% in patients with persistent infection. Other groups have also observed higher rates of *H. pylori* infection in patients without than in those with severe forms of esophagitis characterized by erosions and Barrett's esophagus. Additional data suggest that *H. pylori* infection improves the efficacy of antisecretory therapy in healing esophagitis and maintaining remission.[48,49] These epidemiologic data have led some to believe that *H. pylori* should not be eradicated in patients with GERD. However, the fact that *H. pylori* is a risk factor for the development of peptic ulcer and gastric cancer has caused many practitioners to be uncomfortable with that recommendation. Long-term epidemiologic studies will be required to address this question more appropriately.

Finally, there is evidence that psychosocial factors promote health care seeking for GERD. Johnston et al. evaluated new patients with the primary complaint of heartburn and compared them with community controls with and without reflux symptoms.[50] They found that age and symptom severity were associated with seeking medical care. However, after controlling for these factors, they also found a higher incidence of phobia, obsessive disorder, and somatization in patients seeking medical care. Presumably, the interaction of heartburn with psychosocial factors is therefore relevant in promoting care seeking. Whether treatment of psychosocial distress assists in providing symptom relief has not been adequately explored.

Regional Variation in the Prevalence of GERD

Investigators internationally have attempted to describe the prevalence of reflux symptoms in their populations. The prevalence of GERD varies markedly between different populations. It seems that the prevalence of GERD symptoms and signs is greater in Western countries than in African or Asian cultures. Ho et al. recently described the prevalence of reflux symptoms in 696 randomly selected Chinese, Malays, and Indians living in Singapore.[51] They found that the prevalence of at least monthly heartburn among the Chinese, Malays, and Indians was 0.4%, 3.0%, and 5.3%, respectively. Corresponding percentages for at least monthly acid regurgitation among Chinese, Malays, and Indians were 0.4%, 2.1%, and 4.8%. These numbers are clearly lower than comparable percentages from Western populations. Chang et al. performed an endoscopic study of 2044 symptomatic Chinese patients.[19] They found that the incidence of erosive esophagitis in their cohort was 5%, much lower than that observed in Western cohorts. Of those who did have esophagitis, almost 90% had mild disease. Similarly, a recent publication reporting on the prevalence of GERD symptoms and complications in sub-Saharan Africa noted that "there are too few reports of GERD to allow analysis."[52] From these studies, it seems that the prevalence of GERD symptoms in non-Western cultures is significantly less than in the West. Possible reasons for the lower GERD prevalence include low dietary fat, lower body mass index, and lower maximal acid output related to infection with *H. pylori*.

Increasing Prevalence of GERD

One question of great importance, currently unanswered, is whether the prevalence of GERD is increasing. There is reason to believe that GERD may be becoming more common in the U.S. population. Hospitalization rates for erosive esophagitis, sometimes used as a surrogate for reflux disease, have increased severalfold over the past 3 decades.[53] Using the database of the Department of Veterans Affairs, el-Serag and Sonnenberg found that a discharge diagnosis of erosive esophagitis, esophageal ulcer, esophageal stricture, or hiatal hernia increased fourfold in nonwhites and sevenfold in whites between the periods 1970-1974 and 1990-1995.[46] Obesity, a putative risk factor for GERD, has been rising in epidemic proportions in the United States. In addition, esophageal adenocarcinoma, the cancer with which GERD is associated, has undergone a substantial increase in incidence over the last 30 years.[54] In the late 1970s, squamous cell carcinoma accounted for 70% of all esophageal tumors whereas

adenocarcinoma accounted for only 17%. However, since then the prevalence of adenocarcinoma of the esophagus has continued to increase alarmingly; it now accounts for more than 50% of all esophageal cancers. Lagergren et al. have recently shown that adenocarcinoma of the esophagus was strongly associated with the presence of reflux disease (odds ratio, 44).[55] This association was found to be independent of the presence of Barrett's esophagus.

NATURAL HISTORY OF GERD

GERD is a chronic medical disorder, similar to arthritis or hypertension. Although reflux symptoms may appear to wax and wane, they probably do not disappear permanently in the majority of patients who seek medical care. Antisecretory medications, especially proton pump inhibitors, have made a tremendous impact on GERD and have resulted in significantly improved healing rates of erosive lesions and better symptom control. Consequently, erosive disease–related complications, such as esophageal strictures, have decreased significantly. Thus, medication use has probably modified the natural history of GERD. As a result, conducting studies in patients not exposed to medical therapy is now rare; it is ethically difficult to justify withholding therapy from patients with erosive esophagitis.

Traditionally, patients with erosive esophagitis were thought to have a more severe form of GERD and thus were at greater risk for complications such as stricture, ulcer, Barrett's esophagus, and even adenocarcinoma of the esophagus. The focus of esophageal mucosal injury as a step in disease progression was further reinforced by the concept that GERD is a "spectrum" of disease: on one end are patients with classic symptoms of GERD (heartburn and acid regurgitation) but without any evidence of mucosal injury, and on the other end are patients with erosive esophagitis and GERD complications. The "spectrum" hypothesis assumes that patients with GERD symptoms but no esophageal inflammation (NERD) represent only a milder form of the disease, a concept that resulted in a decade of therapeutic studies focused exclusively on GERD patients with erosive esophagitis. However, recent studies have demonstrated that patients with NERD are less likely to achieve complete symptomatic relief and need a longer time for symptom resolution during proton pump inhibitor therapy. Additionally, Fenton et al. reported that patients with NERD undergoing laparoscopic Nissen fundoplication are less likely to achieve symptom improvement or resolution, are more likely to experience postoperative dysphagia, and more commonly report dissatisfaction with surgery.[56] This unpredictable response to antireflux treatment in GERD patients without esophageal injury has perplexed many investigators. Consequently, much of the research interest in GERD in the last few years has shifted to further understanding of this disorder. Fass and Ofman have recently suggested that instead of looking at reflux disease as a continuum from nonerosive to erosive to stricture to Barrett's esophagus, it may be more appropriate, with regard to the epidemiology and pathophysiology of these diseases, to consider them separate disease categories.[57] They propose a paradigm in which GERD is divided into three unique patient groups: NERD, erosive esophagitis, and Barrett's esophagus. They group extraesophageal manifestations of GERD in the NERD group and strictures and ulcers into the erosive esophagitis group. They suggest that this conceptual framework is more in line with what is known about NERD and will better serve as a conceptual platform to elucidate the causes and treatment of this disease.

Natural History of Nonerosive GERD

As mentioned earlier, NERD appears to be a discrete disease category, with an epidemiology and response to therapy different from that of erosive reflux disease. NERD should not be considered "less severe" GERD because subjects with NERD often display elevated acid exposure on 24-hour pH studies without progression to GERD.[58,59] The factors responsible for erosive disease are not well understood. This variability is multifactorial and most likely relates to factors of host resistance. Interestingly, transformation from nonerosive to erosive disease over time is seen in only a minority of cases, unlike what might be expected if GERD were a true disease spectrum. In a follow-up study of 17 patients with NERD over a 39-month period, McDougall et al. noted the development of new erosions in 24%.[53] At 6-month follow-up, Pace et al. observed new erosive changes in 15% of subjects with NERD treated with antacids or prokinetic drugs.[60] Unfortunately, both these studies are limited by small numbers, and further research is needed to truly understand the natural history of NERD. Currently, no data demonstrate an increased risk for Barrett's esophagus or esophageal adenocarcinoma in these patients over the long term.

Natural History of Erosive GERD

Although GERD symptoms may wax and wane over time, the data available suggest a more predictable course for those with erosive esophagitis. Since the early 1990s, proton pump inhibitors have been accepted as the mainstay of therapy for erosive GERD. Proton pump inhibitors not only have a greater success rate in healing than H_2 receptor antagonists do but also achieve healing faster. However, an important clinical question is whether ongoing medical therapy is required on a long-term basis after successful healing of esophageal erosions. Numerous studies have evaluated the course of erosive GERD patients with and without ongoing prophylactic therapy after the healing phase. Controlled studies have consistently showed that in the absence of ongoing maintenance therapy, a large number (up to 85%) of patients with erosive GERD will relapse within 6 months and the relapse rate is highest in those with the most severe grades of inflammation.

Most of the reported literature has focused on the short-term assessment of relapse, with only a few small case series reporting follow-up longer than 1 year. McDougall et al. conducted a postal questionnaire

follow-up of 101 patients with erosive GERD 11 years after their initial diagnosis.[61] Only 15% of the patients remained asymptomatic without the use of medications. A further 26% reported infrequent symptoms, provided that they took regular antisecretory medications. However, the majority (51%) continued to have at least weekly symptoms of heartburn; half this group was taking regular antisecretory medication. The prevalence of endoscopically confirmed esophagitis in this study was unknown because the repeat endoscopy rate was only 8%. Based on this study, it appears that most patients with erosive GERD at index endoscopy will require chronic medical therapy. The long-term natural history of GERD in the absence of antisecretory therapy was retrospectively studied by Isolauri et al. in Finland.[62] Patients with symptomatic GERD were treated with lifestyle modification, antacids, prokinetic therapy, or any combination of these measures between 1973 and 1976. At initial assessment, 20 patients had erosions, but Barrett's esophagus was not found in any patient. After a median follow-up of 19 years, 14 patients continued to have erosions, but 6 new cases of long-segment Barrett's esophagus were detected. All cases of Barrett's esophagus developed in patients with previously documented erosive esophagitis. This suggests that suboptimal treatment of erosive esophagitis may have the potential to lead to the development of Barrett's esophagus. Furthermore, it has been shown that the degree of abnormal esophageal acid exposure directly correlates with the severity of esophagitis and is predictive of the development of stricture. An estimated 10% of patients who seek medical attention have strictures. However, up to a quarter of those with strictures do not have significant heartburn or regurgitation. In patients with Barrett's esophagus, strictures develop in 19% to 81%. Conversely, up to 50% of stricture are associated with Barrett's esophagus.

It is accepted that Barrett's esophagus results from chronic GERD. The prevalence of long-segment Barrett's metaplasia in patients who undergo upper gastrointestinal endoscopy is approximately 1% and increases with increasing severity of GERD.[63-65] In patients with GERD symptoms, the prevalence of Barrett's mucosa is 4.5% to 20%. In the United States, the average age of affected patients is 55 to 65 years, with a male-to-female ratio of 10:1 and a white-to-African American ratio of 10:1.[17,66] Although the annual incidence of adenocarcinoma in patients with long-segment Barrett's metaplasia has been reported to be as high as 1.5%,[67] an analysis in 2000 suggested that this risk is overestimated because of publication bias and that the actual incidence is probably closer to 0.5% per year.[68] Short-segment Barrett's metaplasia is clearly more prevalent than long-segment Barrett's metaplasia, but the precise incidence is difficult to define because published reports do not distinguish it from gastric cardia intestinal metaplasia. Although dysplasia and adenocarcinoma have been reported in patients with short-segment Barrett's metaplasia, the magnitude of this risk is unknown; reports attempting to quantify it concluded that the malignant potential of short-segment Barrett's metaplasia was much lower than that of long-segment Barrett's metaplasia.[69-72]

GERD would appear to be associated with a very low mortality rate. However, if one accepts that the development of Barrett's esophagus is part of the natural history of chronic GERD, death from adenocarcinoma should also be considered in the overall mortality figures for GERD.

CONCLUSION

Although GERD is widely reported to be one of the most prevalent clinical conditions afflicting the gastrointestinal tract, incidence and prevalence figures are based more on estimates than on actual data. This difficulty occurs partly because GERD and esophagitis cannot be differentiated by clinical history and partly because there is no gold standard for the recognition or exclusion of GERD. NERD is a relatively newly appreciated entity and may be more difficult to treat than classic erosive disease. Evidence is accumulating that these patients should be viewed as having a separate disease entity, not just a mild form of classic GERD. Large-scale, prospective data collection with standardized terminology and longitudinal follow-up will allow a clearer picture of the incidence, prevalence, natural history, and complications of GERD.

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Chapter

13

The Pathology of Gastroesophageal Reflux Disease

Parakrama Chandrasoma

Gastroesophageal reflux, which is defined as the entry of gastric contents into the esophagus, is an extremely common event that occurs sporadically in most people. Reflux is caused by failure of the normal lower esophageal sphincter mechanism. As Allison, in the first accurate description of reflux esophagitis in 1948,[1] stated: "A failure of this mechanism will allow acid to reach the esophagus, and in time this leads inevitably to inflammation and ulceration." At that time, ulceration and strictures were the dominant problems in patients with reflux disease. Since that time, other consequences of esophageal epithelial damage have been recognized: columnar-lined esophagus, first described by Allison and Johnstone in 1953[2] and correctly named by Barrett in 1957,[3] and adenocarcinoma of the esophagus. The last 3 decades have seen an alarming increase in the incidence of adenocarcinoma of the esophagus, which is now the most rapidly increasing cancer type in Western Europe and North America.[4,5] There is also a parallel, but less dramatic increase in the incidence of adenocarcinoma of the cardia.[6,7] Symptomatic gastroesophageal reflux is a risk factor for both esophageal and cardia adenocarcinoma, with odds ratios of 7.7 (confidence interval [CI], 5.3 to 11.4) and 2.0 (CI, 1.4 to 2.9), respectively, for those with symptoms and those without.[8] The risk increased with reflux severity; patients with long-standing and severe reflux symptoms had odds ratios of 43.5 for the development of esophageal adenocarcinoma and 4.4 for the development of adenocarcinoma of the cardia. The same study showed no increase in the incidence of squamous carcinoma of the esophagus in patients with reflux. This establishes that gastroesophageal reflux is very likely the cause of adenocarcinoma of the esophagus and cardia as defined in this study.

The amount of reflux into the esophagus can be assessed by determining the presence of some measurable component of the gastric refluxate, such as acid (the ambulatory 24-hour pH test)[9] or bilirubin (Bilitec test),[10] and by performing impedance studies, which detect the retrograde entry of fluid into the esophagus.[11] Studies using 24-hour pH testing have documented that symptoms associated with reflux occur when the pH is less than 4 for a period exceeding 4.5% of the 24-hour period.[12] It should be recognized that 4.5% of a 24-hour period is 64.8 minutes, which means that esophageal epithelium exposed to a pH less than 4 for less than 1 hour per day is not usually associated with symptoms. There is a probability that exposure not sufficient to cause symptoms may produce significant cellular pathologic changes in the esophagus; it is only when we develop the ability to recognize subclinical early disease that we will be able to begin making an effective impact on it. There is strong indirect evidence for subclinical reflux disease in that a significant number of patients with reflux-induced adenocarcinoma of the lower part of the esophagus have never had any symptoms of reflux.

The gastroesophageal refluxate contains many chemicals, including endogenous secretory products of the stomach such as acid and pepsin; duodenal contents such as the secretory products of the intestine, bile, and pancreatic juice, which frequently enter the stomach via duodenogastric reflux; and exogenous chemicals ingested as food. Correlation of esophageal damage with acid exposure by a 24-hour pH study does not necessarily indicate that the damage is caused by acid. The 24-hour pH study simply quantitates the amount of reflux; any injury-causing molecule in the refluxate that accompanies the acid will show a correlation with the 24-hour pH study abnormality. The 24-hour pH study is better than Bilitec for quantitating reflux because of the more constant presence of acid in the refluxate. This is not true, however, in patients who have atrophic gastritis and

those taking acid-suppressive medications. Impedance studies have shown continuing reflux in patients taking acid-suppressive drugs, thus indicating that the esophageal epithelium continues to be subject to other molecules in the gastric refluxate after acid secretion has been suppressed.

Acid suppression has been the mainstay of treatment of reflux disease. In effect, this has been a human experiment over the past several decades that can be used to provide important conclusions. The manifestations of reflux disease that have declined in frequency, such as ulceration and stricture, are very likely directly caused by acid. Others such as Barrett's esophagus and adenocarcinoma, which have increased in prevalence, are very likely caused by unidentified molecules in the gastric refluxate other than acid.

There has been an unusual dichotomy in the minds of physicians treating patients with reflux, and this dichotomy persists to date. Reflux disease is seen as a squamous epithelial disease classified by symptoms as typical and atypical, classified by endoscopy as erosive and nonerosive, and graded by systems such as the Savary-Miller and Los Angeles systems by endoscopic changes in the squamous epithelium. Patients with reflux disease are treated by acid suppression, and the success of treatment is defined by relief of symptoms and healing of erosions.

Although everyone agrees that a columnar-lined esophagus is caused by reflux, physicians tend to regard it as a separate entity. When they see a columnar-lined esophagus, the intent is to make a diagnosis of Barrett's esophagus, which requires the presence of intestinal metaplasia in a biopsy specimen. This enters the patient into an endoscopic surveillance program to detect the occurrence of dysplasia and early adenocarcinoma. There is almost no recognition in practice that a columnar-lined esophagus is a manifestation of reflux disease and can be used to diagnose and classify reflux disease. The link that must exist between the pathology of reflux and Barrett's esophagus and adenocarcinoma is almost completely ignored.

DEFINITION OF NORMAL ENDOSCOPY AND HISTOLOGY

With most organs, normalcy is defined by autopsy examination of large numbers of patients of all ages who have never had symptoms related to that organ during life. When these are compared with the same organs that have had evidence of disease during life, differences between the normal and pathologic state can be determined. This usual method of establishing normalcy never occurred with regard to the epithelium of the esophagus. The new millennium dawned before the first autopsy study of the gastroesophageal junctional epithelium was published. The rapid postmortem autolysis that occurs in the columnar epithelium of the gastrointestinal tract after death is a serious deterrent to autopsy study. As a result, normalcy with regard to the esophagus was historically defined by the study of esophagectomy specimens and endoscopy, which are performed in patients with the highest likelihood of esophageal disease. We must recognize that defining normalcy by studying an abnormal population is a potential source of serious error.

In 1961, Hayward defined normalcy for the anatomy and histology of the lower part of the esophagus.[13] Hayward did not cite any data for his conclusions but obviously drew from his experience with surgical specimens and endoscopy. According to Hayward, the distal 1 to 2 cm of the tubular esophagus was lined by columnar epithelium of cardiac (or junctional) type. This led to the general belief that persisted well into the 1990s that columnar lining in the distal tubular esophagus should be regarded as abnormal only if it exceeds 3 cm in length.

The recognition of short-segment Barrett's esophagus in the 1990s resulted in a change in the definition of normalcy.[14] As endoscopy became a common procedure, it was seen that squamous epithelium frequently extended to the end of the tubular esophagus. Endoscopic normalcy was therefore defined as the absence of any visible columnar lining in the esophagus (Box 13–1). The normal squamocolumnar junction was coincident with the proximal limit of the gastric rugal folds, which had become recognized as the best endoscopic indicator of the true gastroesophageal junction. This led to the recommendation that patients with any endoscopically visualized columnar epithelium in the esophagus undergo biopsy. When intestinal metaplasia is present in this biopsy tissue, a diagnosis of Barrett's esophagus is made; long- and short-segment disease is defined according to whether the endoscopic segment is greater or less than 2 cm (Figs. 13–1 and 13–2). Incredibly, when the biopsy specimen does not reveal intestinal metaplasia, the patient reverts to being classified as "normal," and the fact that there was an endoscopically visualized columnar-lined esophagus is largely ignored in practice (see Box 13–1).

Hayward also presented contradictory opinions in his paper about the distal extent of cardiac mucosa.[13] On the one hand he says that cardiac mucosa "extends a little way into the stomach" and has an illustration that clearly shows cardiac mucosa lining the proximal part of the stomach. On the other hand, Hayward states: "I suggest that junctional (cardiac) epithelium should be regarded as esophageal" and "the stomach should be described as lined by two sorts of epithelium, fundal and pyloric, except for a small area around the esophageal opening where esophageal junctional epithelium protrudes into it." Despite his stated belief that cardiac mucosa was esophageal, the effect of Hayward's paper was to establish a dogma that cardiac mucosa normally lined the proximal part of the stomach. This has no basis in fact, but exists to the present time.

When we performed our first autopsy study in the mid-1990s,[15] it was generally accepted that the distal 2 to 3 cm of the esophagus and an undefined part of the proximal stomach were normally lined by cardiac mucosa. Our autopsy study included 18 subjects who were prospectively studied by removing the gastroesophageal region and sectioning it vertically to examine the entire circumference microscopically. Astonishingly, 10 (56%)

Box 13–1 Presently Accepted Endoscopic and Biopsy Definitions of Normal and Pathologic States

1. **Endoscopic normalcy**: Coincidence of the squamocolumnar junction (Z-line) and the gastroesophageal junction (proximal limit of the rugal folds). There is no visible columnar lining in the esophagus, either as tongues of mucosa extending into the squamous epithelium or as a circumferential columnar-lined region in the tubular esophagus that separates the squamocolumnar junction from the proximal limit of the rugal folds.
2. Columnar-lined esophagus >3 cm (2 cm in some studies) with biopsy specimens showing intestinal metaplasia: **long-segment Barrett's esophagus.**
3. Columnar-lined esophagus >3 cm (2 cm in some studies) with biopsy specimens showing no intestinal metaplasia: **no conclusion.**
4. Columnar-lined esophagus <3 cm (2 cm in some studies) with biopsy specimens showing intestinal metaplasia: **short-segment Barrett's esophagus.**
5. Columnar-lined esophagus <3 cm (2 cm in some studies) with biopsy specimens showing no intestinal metaplasia: **normal or no conclusion.**
6. The practice guidelines of the American Gastroenterology Association recommend that patients who are endoscopically normal should not undergo biopsy. This recommendation is a statement that **ignorance is bliss.**
7. When there is no endoscopic abnormality and biopsy specimens show intestinal metaplasia, confusion reigns; some call this "**ultrashort-segment Barrett's esophagus"** and others call it "**intestinal metaplasia of the gastric cardia."**
8. When there is no endoscopic abnormality and biopsies show no intestinal metaplasia: **normal.**

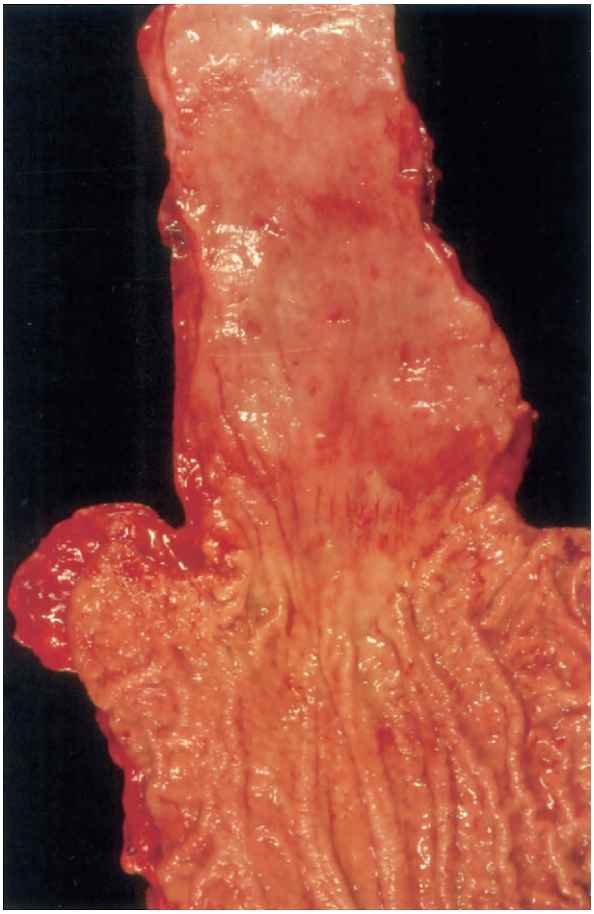

Figure 13–1. Long-segment columnar-lined esophagus characterized by flat columnar epithelium extending from the proximal limit of the rugal folds to the irregular squamocolumnar junction near the top of the picture. This is pathognomonic grossly and endoscopically for severe reflux disease. It is Barrett's esophagus only if intestinal metaplasia is demonstrated by biopsy.

subjects had no cardiac mucosa whatever, and those who did all had lengths of cardiac mucosa that were all less than 1 cm. The presence of cardiac mucosa in everyone was a myth when scientifically studied in an appropriate normal population for the first time (Figs. 13–3 and 13–4).

Jain et al.[16] confirmed the fact that cardiac mucosa is infrequently present at the junction in what is the only "normal" population studied. Many of these were patients who were undergoing upper endoscopic screening for nonesophageal diseases; many did not have clinical evidence of reflux, and the gastroesophageal region was endoscopically normal. Only 35% of these patients had cardiac mucosa in extensive sampling biopsies. Even studies in clinical endoscopy units with a bias toward patients with reflux show patients without cardiac mucosa, though much less frequently. Marsman et al.[17] found that pure cardiac mucosa was absent in 38% of patients in whom the actual squamocolumnar junction was present in the biopsy specimen. The data in these studies strongly suggest that cardiac mucosa is not universally present in the gastroesophageal junction and therefore highly unlikely to be normal epithelium.

If it is accepted that cardiac mucosa does not normally exist, the definition of histologic normalcy becomes feasible and in line with the endoscopic definition (Box 13–2). Normal histology can be defined as an esophagus that is completely lined by squamous epithelium (Fig. 13–5), ends normally at the squamocolumnar junction, and transitions at that point to gastric oxyntic mucosa (Fig. 13–6), which is characterized by rugal folds. Only two histologic zones exist normally: esophageal squamous epithelium and gastric oxyntic mucosa. The lower esophageal sphincter protects the

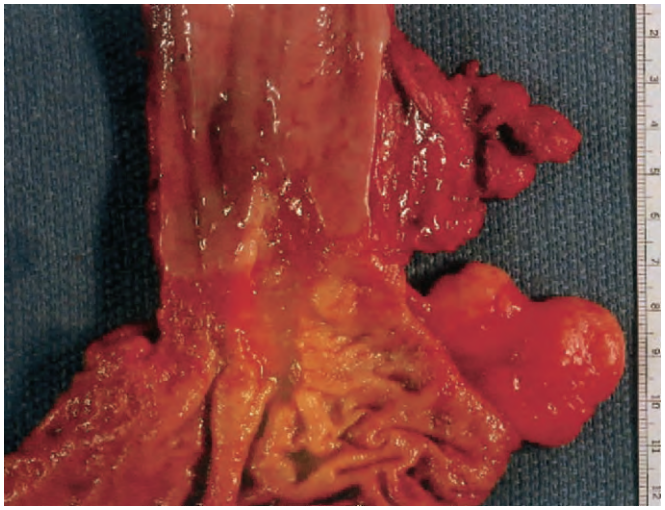

Figure 13–2. Short-segment columnar-lined esophagus characterized by flat columnar epithelium extending from the proximal limit of the rugal folds to the irregular squamocolumnar junction. This is pathognomonic of reflux disease of a lesser severity than in Figure 13–1. It is Barrett's esophagus only if intestinal metaplasia is demonstrated by biopsy.

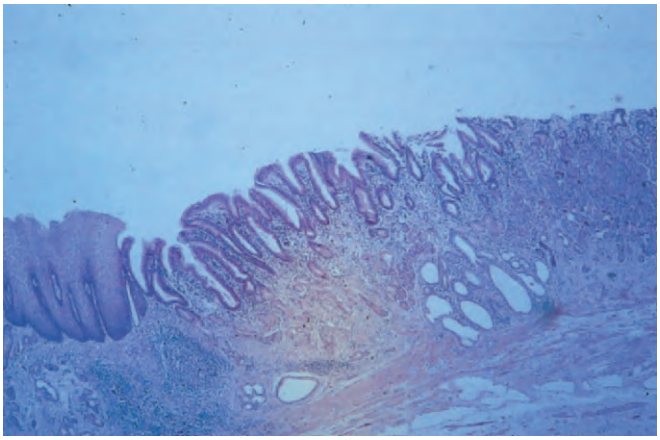

Figure 13–4. Squamocolumnar junction in a patient undergoing esophagectomy for squamous carcinoma of the midesophagus (hematoxylin-eosin stain). There is an approximately 0.6-cm length of cardiac mucosa interposed between the squamous epithelium (the Z-line) and gastric oxyntic mucosa (the gastroesophageal junction). This cardiac mucosa represents metaplastic columnar-lined esophagus, which is cellular evidence of reflux-induced damage.

squamous epithelium from gastric contents by normally preventing gastroesophageal reflux. A normal person has no acid-induced damage of the esophageal squamous epithelium. Endoscopy will be normal, the 24-hour pH study will be normal, and histology will reveal only squamous and gastric oxyntic mucosa.

We have proposed this concept of histologic normalcy for many years.[18] Although the trend is toward slow acceptance, most people still continue to believe that a third histologic zone characterized by cardiac mucosa normally exists between esophageal squamous epithelium and gastric oxyntic mucosa. Authorities holding this belief agree that this zone is as small as 1 mm in some patients and almost always less than 5 mm. Marsman et al. hold this belief despite the fact that their own excellent study showed an absence of cardiac mucosa in 38% of patients.[17] Old dogmas die painfully, and the dogma that cardiac mucosa is found normally in the gastroesophageal junctional region is close to its demise. The problem is that until this dogma dies, there can be no histologic definition of normal. A biopsy sample showing cardiac mucosa can be considered "normal gastric

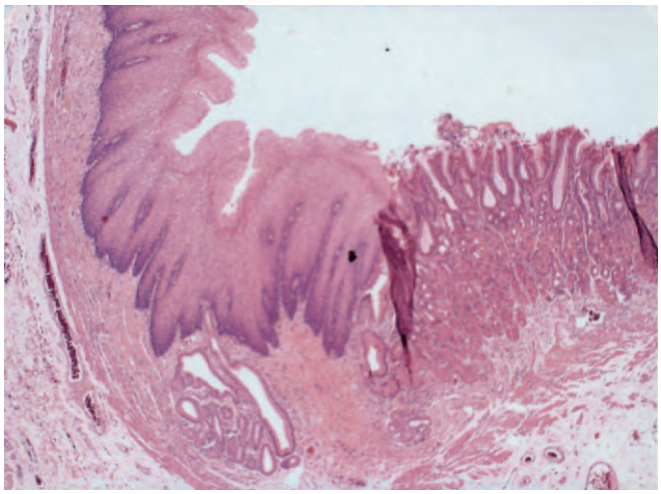

Figure 13–3. Squamocolumnar junction in a patient undergoing esophagectomy for squamous carcinoma of the midesophagus (hematoxylin-eosin stain). The squamous epithelium of the esophagus transitions directly to gastric oxyntic mucosa without intervening columnar-lined esophagus. This patient has no cellular evidence of reflux-induced damage.

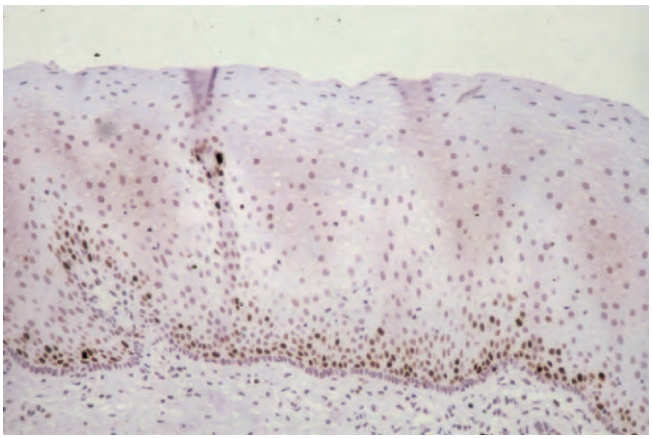

Figure 13–5. Normal squamous epithelium showing proliferative cells in the basal region (immunoperoxidase stain for Ki67).

Box 13–2 **Suggested Histologic and Endoscopic Definitions**

1. **Endoscopic normalcy:** coincidence of the squamocolumnar junction (Z-line) and the gastroesophageal junction (proximal limit of the rugal folds). There is no visible columnar lining in the esophagus.
2. **Histologic normalcy:** coincidence of the distal limit of the squamous epithelium and the proximal limit of gastric oxyntic mucosa. There is no microscopic esophageal metaplastic columnar epithelium between the two.
3. **Endoscopic columnar-lined esophagus:** the presence of any columnar epithelium between the squamocolumnar junction (Z-line) and the proximal limit of the gastric rugal folds, either as tongues of mucosa extending into the squamous epithelium or as a circumferential columnar-lined region that separates the squamocolumnar junction from the proximal limit of the rugal folds.
4. **Histologic columnar-lined esophagus:** the presence of any microscopic metaplastic esophageal columnar epithelium between the squamous epithelium and gastric oxyntic mucosa.
5. **Metaplastic esophageal columnar epithelium:** Cardiac mucosa with and without intestinal metaplasia and oxyntocardiac mucosa.

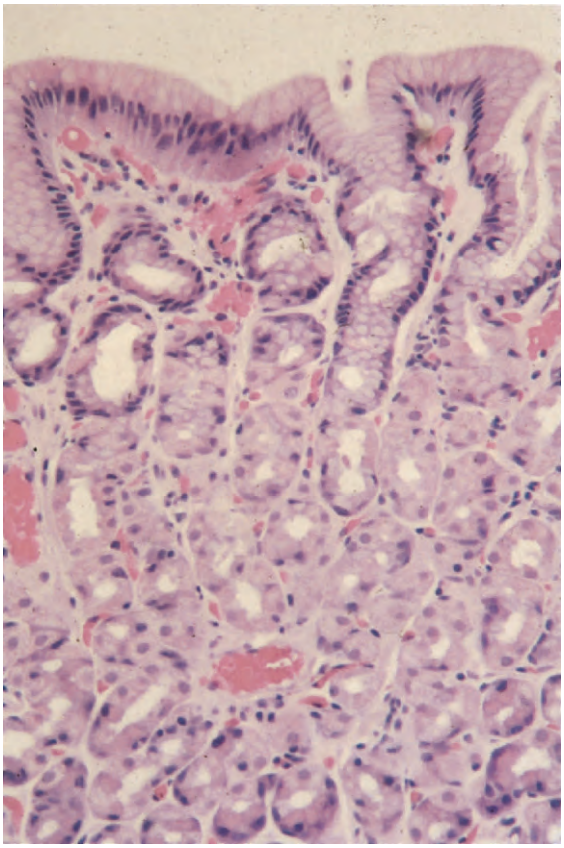

Figure 13–6. Normal oxyntic mucosa of the stomach characterized by straight tubular glands composed of parietal and chief cells below the short foveolar pit (hematoxylin-eosin stain).

mucosa" or "normal esophageal epithelium" by those holding the belief that such mucosa is normal.

PATHOLOGY OF GASTROESOPHAGEAL REFLUX

Acid-Induced Damage

The stratified squamous epithelium of the esophagus has an unknown, but definite amount of resistance to acid exposure. Although reflux is an almost universal phenomenon, a majority of the adult population do not have symptoms of reflux. The structure of stratified squamous epithelium is designed to withstand injury; squamous cells have tight cell junctions that form an effective barrier to resist penetration by luminal molecules (see Fig. 13–5).

As the amount of acid exposure increases, the ability of squamous epithelium to resist injury is overwhelmed. The first change is most likely an increased rate of loss of surface cells, which stimulates a compensatory increase in the rate of proliferation of basal esophageal stem cells. Increased proliferative activity is manifested histologically by basal cell hyperplasia and elongation of the papillae of the epithelium. Expression of proliferative markers such as Ki67 is increased. These are the first identifiable changes of reflux and are recognized as histologic criteria of reflux. Basal cell hyperplasia and papillary elongation are, however, relatively nonspecific changes that are seen with any cause of esophageal surface injury.

With increasing damage, the cell junctions between squamous cells separate, thereby resulting in dilated intercellular spaces. Tobey et al. showed by electron microscopic measurement that an increase in intercellular spaces results from exposure of esophageal squamous epithelium to acid.[19] Villanacci et al. have demonstrated that the severity of dilatation of intercellular spaces correlates with the severity of reflux.[20] This finding, which is equivalent to spongiosis of squamous epithelium, is a common finding in biopsy specimens from patients with reflux disease (Fig. 13–7).

Entry of acid into the epithelium produces direct cell damage that very likely results in the liberation of cytokines that stimulate sensory nerve endings in the epithelium, thereby causing heartburn. The fact that this symptom is effectively controlled by acid-suppressive drugs provides evidence that stimulation of nerve endings is an acid-dependent phenomenon.

The cell damage must also result in the release of cytokines that are chemotactic for eosinophil leukocytes.

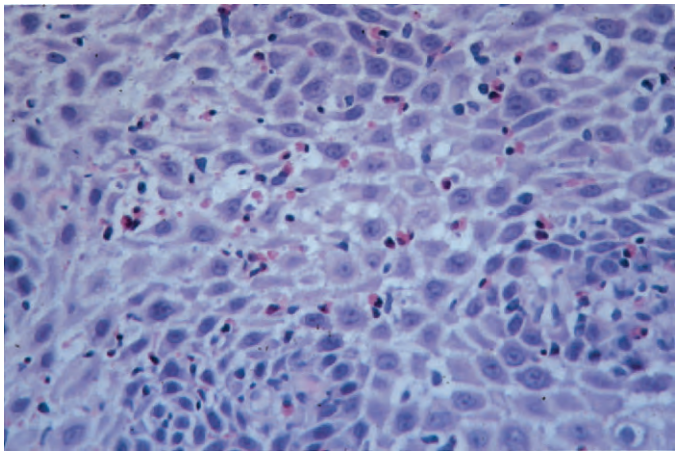

Figure 13–7. Reflux esophagitis showing squamous epithelium with intraepithelial eosinophils and separation of squamous cells (dilated intercellular spaces) (hematoxylin-eosin stain).

Intraepithelial eosinophils are a recognized criterion of reflux damage to squamous epithelium (see Fig. 13–7). The presence of intraepithelial eosinophils is nonspecific; eosinophils enter squamous epithelium in conditions other than reflux, such as eosinophilic esophagitis, which has an allergic basis.

With further cell damage, erosion and finally ulceration of the epithelium may occur. With ulceration, fibrosis of the submucosa and deeper layers may follow and lead to shortening of the esophagus and circumferential strictures. In the early days, the main clinical problem associated with reflux disease was the occurrence of ulcers and strictures. With the increasing efficacy and use of acid-suppressing agents in the treatment of reflux disease, complicated and nonhealing ulcers and complex strictures have become relatively uncommon. This suggests that acid is primarily responsible for the erosions and ulcerations that occur in squamous epithelium.

Separation of the tight junctions between squamous cells increases the permeability of squamous epithelium to luminal molecules. Tobey et al. have shown that in vitro exposure of squamous epithelium to acid permits the entry of small molecules up to 20 kD all the way down to the basal region of the epithelium.[21] Tobey and colleagues' studies are extremely valuable because the esophageal epithelium was exposed in vitro to acid alone and the damage described can therefore be directly attributed to acid. No other molecule in the refluxate has been shown to cause separation of squamous cells, and it is very likely that this is a unique injurious effect attributable to acid.

Acid is the key that opens the lock of the squamous epithelial barrier. Its action allows all the other molecular intruders in gastric refluxate to enter the squamous epithelium and interact with the proliferating stem cell population that is normally sequestered in the basal region.

Esophageal Squamous Epithelium Primed by Acid-Induced Damage

Whereas normal esophageal squamous epithelium has the capacity to resist the entry of luminal molecules, acid-damaged squamous epithelium permits the entry of such molecules. The degree of separation of squamous cells varies with the severity of acid-induced damage. With mild damage, only very small molecules enter the superficial region of the epithelium; as damage levels increase, the epithelium very likely becomes increasingly permeable to larger particles that penetrate a greater distance into the epithelium. With the maximum acid-induced damage, the squamous epithelium displays the characteristics of Tobey and colleagues' experimental model in which molecules up to a size of 20 kD penetrate the full thickness to reach the basal region of the squamous epithelium.[21]

Many patients with symptoms of reflux do not have erosive esophagitis. This condition has been termed nonerosive reflux disease (NERD). No histologic abnormality has been associated with NERD, largely because physicians perceive reflux disease as a purely squamous epithelial abnormality. These patients have intact and histologically normal esophageal squamous epithelium that, however, has been primed by acid-induced damage; light microscopy is not a sensitive method of detecting dilated intercellular spaces. Although it looks normal, the acid-primed squamous epithelium is like a sieve that permits the entry of small molecules.

Normal esophageal squamous epithelium is a dynamic structure that is multilayered and continually undergoing renewal. The renewal is directed by continuous proliferation of esophageal stem cells located in the basal layer of the epithelium (see Fig. 13–5). These stem cells are identical to the fetal foregut stem cells from which the esophagus developed. In the early fetal foregut, the esophageal stem cells were columnar in nature until the 20th week of gestation, when they acquired a genetic signal that directed squamous differentiation.[22,23] It should be recognized that the esophageal stem cell retains its multipotential capability to differentiate in any direction seen in the endoderm. The fact that it produces squamous epithelium means only that it expresses the genetic signal that directs squamous differentiation while genes that direct other types of differentiation are suppressed. The normal genetic signaling mechanism that directs squamous differentiation is yet unknown.

The esophageal stem cells proliferate during life to replace cells that are continuously lost at the surface. The first division of the stem cell in the basal zone produces a daughter cell that has been given the genetic signal to become squamous. This daughter cell divides a few times while differentiating into a keratinizing squamous cell and moves up the stratified epithelium to the surface. The average time for the daughter cell to be lost at the surface is 7.5 days.[24] By the time that it reaches the midregion of the stratified squamous epithelium, the cell has become terminally differentiated and incapable of mitotic division. This can be demonstrated by Ki67 staining. Ki67, which is an antigen expressed in cells that are

in the mitotic cycle,[25] shows positive staining restricted to the basal two to three cell layers.

Epithelium that is primed by acid damage is different. Luminal molecules permeate through the epithelium and can reach the normally sequestered stem cells at the base of the epithelium. Interactions between these luminal molecules and surface receptors on the actively proliferating multipotential stem cells now become possible. These interactions must form the basis for the genetic changes that occur in these cells to drive the further evolution of this pathologic process.

Columnar Transformation—The First Genetic Switch

Columnar transformation has long been recognized as a complication of gastroesophageal reflux. Hayward, in 1961,[13] describes the process well: "When the normal sphincteric and valvular mechanism in the lower oesophagus and oesophago-gastric junction . . . fails, . . . reflux from the stomach occurs and acid and pepsin reach the squamous epithelium and begin to digest it. . . . In quiet periods some healing occurs, and in these periods the destroyed squamous epithelium may re-form, often with . . . junctional epithelium, usually not very healthy-looking. . . . Further reflux therefore attacks principally the squamous epithelium higher up. In the next remission it may be replaced by more junctional epithelium. . . . With repetition over a long period the metaplastic junctional epithelium may creep higher and higher. . . ."

Hayward, as did Barrett before him, believed that this process required erosion of the squamous mucosa.[3,13] It is now apparent that columnar transformation occurs without ulceration. Nonerosive acid-primed squamous epithelium, which has increased permeability, permits small molecules in the refluxate to enter the epithelium and, when the damage is severe, reach the basal region. These luminal molecules can interact with receptors on the surface of the proliferating stem cells. Such interactions can have many potential effects, but the one that is significant is columnar transformation of the epithelium. The exact mechanism by which this transformation takes place is not known, but it must involve a change in the genetic signal in the stem cell from squamous to columnar differentiation. This change can be either suppression of the normal squamous genetic signal, thereby permitting the epithelium to revert to its original fetal columnar state, or activation of a new genetic signal that directs columnar differentiation. The genetic basis for columnar metaplasia is not yet known, but its existence can be assumed by recognizing the phenotypic expression of the change, which is columnar transformation of the squamous epithelium.

The daughter cell of stem cell division that is given the genetic signal to differentiate into a columnar cell develops features of columnar cells, not squamous cells. One inevitable effect is the loss of normal cellular attachments, which results in loss of adhesion between the new columnar cell and its squamous neighbors and ultimately converts the area of epithelium involved into columnar epithelium. The area involved is short, possibly one cell, but as described by Hayward, the change is cumulative and results in a progressive increase in the amount of squamous epithelium that undergoes columnar transformation.[13]

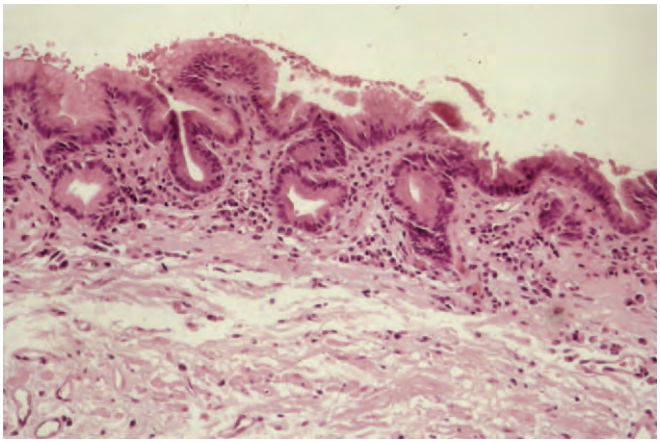

Figure 13–8. Newly formed metaplastic cardiac mucosa characterized by mucous cells lining the surface and a short foveolar pit (hematoxylin-eosin stain). Note the presence of chronic inflammatory cells in the lamina propria.

The histologic product of the initial columnar metaplasia of esophageal epithelium is columnar epithelium devoid of specialized cells; these cells are recognized histologically as mucous cells, and the mucosa falls within the definition of cardiac mucosa (Fig. 13–8). The newly formed cardiac mucosa is interposed between the squamocolumnar junction and gastric oxyntic mucosa. In the earliest stages, the cardiac mucosa is so short that it is detectable only by histology; these patients have a normal appearance at endoscopy. When the columnar transformation reaches sufficient length, it becomes visible endoscopically as flat columnar epithelium interposed between the tops of the rugal folds and the squamocolumnar junction (see Fig. 13–2). This columnar epithelium may be seen as irregular tongues extending up into the squamous epithelium or as a circumferential segment.

Columnar transformation of the esophageal squamous epithelium to form cardiac mucosa is a change that is highly specific for reflux. It requires acid damage of the squamous epithelium to cause increased permeability, followed by a genetic switch resulting from an interaction between an unknown molecule in the refluxate and the esophageal stem cell. Although there is strong evidence that acid acts as the key to permitting access to the squamous epithelium, it is very likely that a molecule other than acid is responsible for the actual genetic switch that leads to columnar transformation in the stem cell. This is strongly suggested by the fact that columnar-lined esophagus has increased in prevalence in the past 3 decades despite increasingly effective acid suppression.

Cardiac Mucosa Is Reflux Carditis

The presence of cardiac mucosa between the squamous epithelium and gastric oxyntic mucosa has been incorrectly interpreted as normal gastric mucosa for nearly a century. The reason for this is surprising. Because autopsy studies were never performed, the original histologic data came from the study of esophagectomy specimens. The first successful thoracic esophagectomy was reported in 1913.[26] Between that time and 1953, when Allison and Johnstone first introduced the concept of columnar-lined esophagus,[2] the esophagus was thought to end at the squamocolumnar junction. Early histologists, studying abnormal esophagectomy specimens in the elderly, found cardiac mucosa distal to the squamous epithelium. In line with the definition of the time, they concluded that cardiac mucosa normally lined the proximal part of the stomach. This simple error led to great confusion. When Allison and Johnstone described the columnar-lined esophagus in 1953, they called it "oesophagus lined by gastric mucous membrane."[2] In 1957, Barrett disagreed with Allison's term and coined the more accurate term columnar-lined esophagus[3]; Barrett was stating the obvious: the esophagus is lined by esophageal epithelium, not gastric epithelium.

There has never been any evidence that cardiac mucosa is present in the true stomach. Allison and Johnstone, in their 1953 description of the columnar-lined esophagus, clearly showed that cardiac mucosa is restricted to the esophagus.[2] In a beautiful description of one of their esophagectomy specimens, Allison and Johnstone showed that the mucosa distal to the peritoneal reflection, which is the most accurate external marker for the gastroesophageal junction, is gastric oxyntic mucosa. Hayward,[13] to whom the dogma that cardiac mucosa lines the proximal part of the stomach is often attributed, also placed cardiac mucosa in the esophagus and not in the stomach, although his illustration shows cardiac mucosa extending into the proximal portion of the stomach, thus contradicting the ideas expressed in his own paper.

There is a great deal of evidence supporting the concept that columnar metaplasia of squamous epithelium to produce cardiac mucosa is a reflux-induced event. Oberg et al. showed that the presence of cardiac mucosa in a biopsy sample taken at the junctional region is associated with abnormal reflux.[27] In a study of 334 patients, the 246 with cardiac mucosa had a significantly greater likelihood of abnormality in a 24-hour pH study, as well as lower esophageal sphincter abnormality, than did the 88 patients who did not have cardiac mucosa. Glickman et al.,[28] in a study of pediatric patients with reflux disease, showed that patients who had greater than 1 mm of cardiac mucosa distal to the squamocolumnar junction had a greater likelihood of reflux symptoms than did patients with less than 1 mm of cardiac mucosa. This finding indicates that even a minute amount of cardiac mucosa (1 mm is about 30 cells, assuming that a mucous cell is 30 µm in diameter) is predictive of reflux.

When found, cardiac mucosa is always inflamed and shows reactive villiform change in the epithelium (Fig. 13–9).[2] Der et al.[29] showed that the amount of chronic inflammation in cardiac mucosa correlates with 24-hour pH abnormality, thus making it likely that cardiac mucosa is damaged by the gastric refluxate. Because cardiac mucosa is always inflamed, its presence is equivalent to carditis. We believe there is adequate evidence that carditis is caused by reflux to use the term "reflux carditis." Because the generation of cardiac mucosa is a highly specific change that results from acid damage of esophageal squamous epithelium, followed by a genetic switch that causes the squamous stem cell to undergo cardiac metaplasia, we believe that reflux carditis is a highly specific histologic criterion of reflux disease. In fact, we use it to define reflux disease histologically.

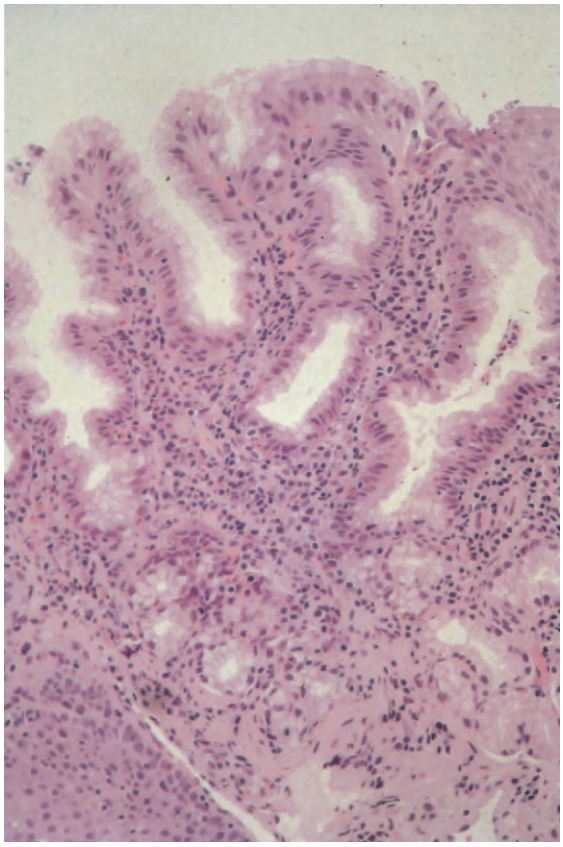

Figure 13–9. Well-formed cardiac mucosa showing only mucous cells (hematoxylin-eosin stain). There is evidence of damage indicated by severe chronic inflammation and by foveolar hyperplasia and serration, which has produced the villiform appearance typical of reflux carditis.

There is controversy in the literature regarding the etiology of carditis. According to some authorities, carditis is a disease that can be produced by *Helicobacter pylori* infection, as well as by reflux.[30] Reports that show an association of carditis with *H. pylori* do not depend on histologic criteria to define carditis. Rather, they define carditis as the presence of inflammation in a biopsy sample taken distal to the anatomically defined gastroesophageal junction,[30] usually in patients with a normal endoscopic appearance. This definition is meaningless. In patients without reflux damage to squamous epithe-

lium, a biopsy specimen immediately distal to the squamocolumnar junction will consist of gastric oxyntic mucosa, and inflammation therein is gastritis caused by *H. pylori* or autoimmunity. In patients who have microscopic reflux disease, a biopsy sample distal to the squamocolumnar junction contains reflux-induced cardiac mucosa; in these patients carditis will correlate with reflux. Cardiac mucosa is never generated from any change in gastric oxyntic mucosa; it is specific for acid-induced columnar metaplasia of the esophagus. Atrophy of gastric mucosa in chronic gastritis may result in loss of parietal cells in gastric mucosa and give rise to a flat mucosa composed of only mucous cells; this is atrophic gastritis, not carditis. No study in the literature that has defined carditis correctly by histologic criteria as inflamed cardiac mucosa has shown a relationship with anything other than reflux.[29,31,32]

Careful review of two papers shows that the lack of definition of terms plus failure to use histology is rife in the literature. A recent study in *Gastroenterology* by Rex et al.[33] in which screening biopsies of the region were evaluated for the prevalence of Barrett's esophagus shows the typical lack of histologic data. In 961 patients studied, visible columnar-lined esophagus was present in 176 patients, greater than 3 cm in 12 (all with intestinal metaplasia) and 0.5 to 3 cm in 164 (53 with intestinal metaplasia). There is no mention of histology apart from the presence or absence of intestinal metaplasia. A total of 940 patients in this study underwent biopsy of the cardia ("defined as the proximal edge of the gastric folds, just distal to the end of the tubular esophagus"); of these, "intestinal metaplasia (IM-cardia) was identified in 122 (12.9%)." There is no mention of any other histology except that seven of these patients had concomitant intestinal metaplasia in the tubular esophagus. Without knowledge of the histology in these cardiac specimens, it is impossible to know whether what the authors call IM-cardia is actually intestinal metaplasia in cardiac mucosa (which would be Barrett's esophagus because cardiac mucosa is esophageal metaplastic epithelium) or intestinal metaplasia in gastric oxyntic mucosa, which is atrophic gastritis. Lagergren and associates' highly influential report in the *New England Journal of Medicine* in 1999 uses the following definition in their methods section[8]:

> *The distances between the gastroesophageal junction (defined as the point where the proximal longitudinal mucosal folds begin in the stomach) and the upper and lower borders of the tumor were measured. . . . For a case to be classified as a cancer of the gastric cardia, the tumor had to have its center within 2 cm proximal, or 3 cm distal, to the gastroesophageal junction.*

According to these definitions, the *gastric cardia extends 2 cm proximal to the authors' own gastroesophageal junction!* Until reviewers of these most prestigious journals demand histologic data and standardize definitions, this subject will remain confused. The use of our suggested histologic definitions (see Box 13–2) is the only available answer to standardization because unlike clinical definitions, these histologic definitions are highly reproducible.[17,34,35]

We recommend using reflux carditis to define reflux disease at a cellular level. Its presence is a highly sensitive indicator of reflux. This definition converts reflux disease from a clinically defined entity to a histologically defined entity and forms a sound basis for scientific study. Patients with reflux carditis may or may not have symptoms; reflux carditis is the only method of identifying patients who have asymptomatic reflux. This is critical when one recognizes that the majority of patients with adenocarcinoma of the esophagus are asymptomatic. Patients with reflux carditis in a biopsy specimen may or may not have an abnormal 24-hour pH test. In our study, 39% of patients with reflux carditis had a pH test that was within the normal range.[29] It should not be surprising that levels of reflux insufficient to cause symptoms may cause cellular abnormalities. Reflux carditis is the histologic change seen in subclinical, asymptomatic reflux and in patients with symptoms who are presently classified as having NERD. Although the squamous epithelium is not eroded in these patients and although it may be histologically normal, it has undergone columnar transformation. Patients with NERD are histologically normal only because it is not recognized that their histologic abnormality is located in a place where it is not looked for; it is not in the squamous epithelium, but in the cardiac mucosa that is found immediately distal to the squamocolumnar junction.

The severity of reflux damage can be quantitated by the amount of squamous epithelium that has transformed into columnar epithelium. Csendes et al.[36] showed that the squamocolumnar junction moves proximally in a manner that correlated with the severity of reflux disease. We demonstrated that patients with greater than 2 cm of columnar transformation of the esophageal epithelium had highly significantly greater reflux by 24-hour pH study than did patients with less than 2-cm transformation.[37] Glickman et al.[28] showed that this correlation between reflux and the amount of cardiac mucosa present was significant at 1 mm, thus indicating that this is an exquisitely sensitive indicator of reflux disease.

The columnar transformation of squamous epithelium is a cumulative change. As Hayward described,[13] the amount of columnar metaplasia progressively increases with time. Because reflux is very common, the change is common. The number of people in the population who have cardiac mucosa is unknown but can be estimated as being between 35%, which was the number in Jain and colleagues' endoscopic study,[16] and 44%, which was the number in our autopsy study.[15] The prevalence is higher in clinical studies where there is an inevitable bias toward including patients with reflux. In our unit, 492 of 811 (60.5%) consecutive patients with less than 1 cm of columnar-lined esophagus had cardiac mucosa, with and without intestinal metaplasia.[38] In Marsman and associates' study, 62% of patients had cardiac mucosa.[17] Although the absence of cardiac mucosa is common in children, it becomes increasingly prevalent with increasing age.

We use these data to histologically grade reflux disease in a highly predictive manner as follows[27,37]: (1) *no evidence of reflux:* cardiac mucosa is absent in adequate

biopsy samples taken from the junctional region in patients who are endoscopically normal; (2) *mild reflux:* cardiac mucosa is present in biopsy samples from patients without an endoscopically visible columnar-lined esophagus; (3) *moderate reflux:* cardiac mucosa is present in biopsy specimens from an endoscopically visible columnar-lined esophagus measuring less than 2 cm; and (4) *severe reflux:* cardiac mucosa present in biopsy specimens from an endoscopically visible columnar-lined esophagus measuring greater than 2 cm. This grading can be applied only if specimens are taken in a systematic manner at upper endoscopy, including specimens from patients who have no endoscopically visible abnormality. This practice is not presently recommended by the American Gastroenterology Association.

Evolution of Reflux Carditis

Hayward, in 1961, described cardiac mucosa as being an epithelium that was resistant to reflux.[13] Cardiac mucosa does not have any intraepithelial nerve endings and is probably less pain sensitive than squamous epithelium. However, there is much evidence that reflux damages cardiac mucosa. Cardiac mucosa invariably shows inflammation, with the number of eosinophils and plasma cells correlating with the severity of reflux, and it almost invariably displays reactive hyperplasia of the foveolar region, with elongation, serration, mucin distention of the cells, and smooth muscle proliferation (see Fig. 13–9).[29,39] In some cases, this hyperplastic cardiac mucosa produces small polypoid excrescences near the squamocolumnar junction.

The exact agents responsible for the damage to cardiac mucosa are unknown. These agents produce two effects on epithelial cells: (1) direct cell damage, which causes reactive hyperplasia, increased Ki67 expression, and chronic inflammation, and (2) molecular interactions at the cell surface that result in genetic changes. These genetic switches alter the differentiation model of cardiac mucosa and result in the development of specialized cells within the mucous cell–only cardiac mucosa. Many different types of specialized cells appear in metaplastic esophageal cardiac mucosa, including parietal cells, goblet cells, Paneth cells, pancreatic cells, and neuroendocrine cells. The appearance in cardiac mucosa of glands containing parietal cells is recognized as one of three main types of metaplastic esophageal epithelium (Fig. 13–10). Paull et al. called this fundic epithelium[35]; we call it oxyntocardiac mucosa because this epithelium is nowhere near the fundus of the stomach.[37] The appearance of goblet cells in cardiac mucosa results in intestinal metaplasia or the specialized columnar epithelium of Paull et al. (Fig. 13–11).[35,37]

Paull et al.,[35] in their classic study of the histology of columnar-lined esophagus, recognized that these three main epithelial types are seen in a very regular manner, and we have confirmed this finding.[40] When present, intestinal metaplasia was usually seen in the most proximal region of the segment of columnar-lined esophagus. The amount of intestinal metaplasia in any columnar-lined segment of esophagus varied from very short (one-gland Barrett's esophagus) to several centimeters.

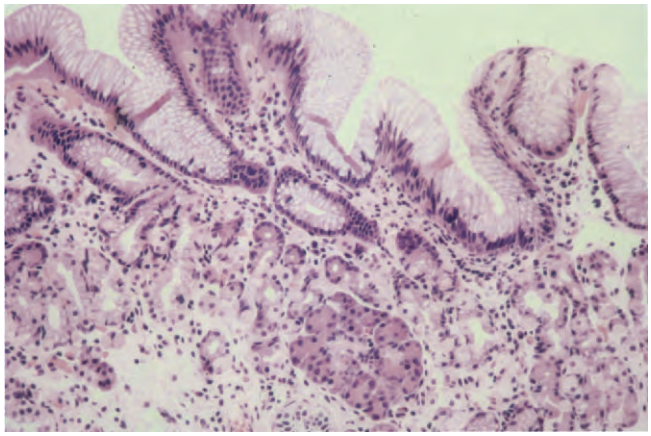

Figure 13–10. Oxyntocardiac mucosa showing lobulated glands containing parietal cells, mucous cells, and a focus of pancreatic metaplasia (hematoxylin-eosin stain). The chronic inflammation is mild.

In contrast, oxyntocardiac mucosa tends to be found in the more distal segment of the columnar-lined esophagus, a fact that was recognized even in Allison and Johnstone's original description of columnar-lined esophagus.[2] Cardiac mucosa was found proximal to oxyntocardiac mucosa and is frequently admixed with intestinal epithelium when the latter is present.

Intestinal Metaplasia—The Second Genetic Switch

Metaplastic cardiac mucosa in columnar-lined esophagus is an active epithelium. The proliferative stem cells are located in the basal region of the foveolar pit, where they multiply to renew the epithelium. The rate of proliferation depends on the rate of cell loss resulting from reflux-induced damage. Luminal molecules have access to the stem cells in cardiac mucosa and can interact with

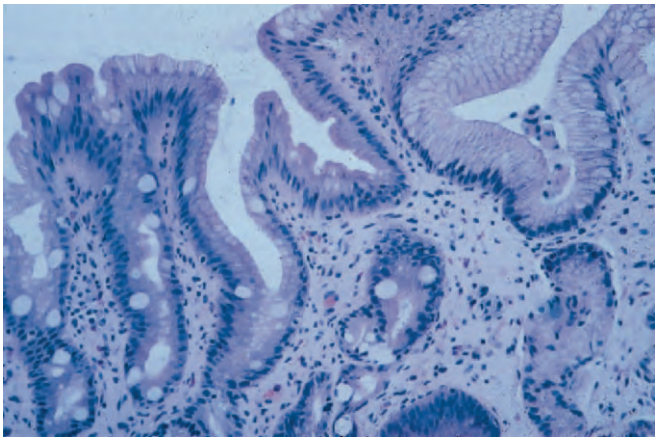

Figure 13–11. Intestinal metaplasia characterized by the presence of goblet cells (hematoxylin-eosin stain). Note the presence of residual nonintestinalized cardiac mucosa on the right side. Intestinal metaplasia defines Barrett's esophagus.

them to cause further genetic changes. Of these changes, intestinal metaplasia is the most important because it is necessary for carcinogenesis to progress.

There is good evidence that the genetic switch that causes intestinal differentiation in cardiac mucosa is activation of the *CDX* homeobox gene system, which includes CDX-1 and CDX-2.[41-43] These genes are suppressed in the normal esophagus and stomach. However, they are expressed in the normal small and large intestine and are believed to be the genes that drive differentiation in these sites.[41] CDX-2 is expressed in most cases of intestinal metaplasia of the esophagus.[42,43] In a quantitative study, we showed that CDX-2 expression was up-regulated in a stepwise manner from esophageal squamous epithelium (not expressed) to nonintestinalized cardiac mucosa (low level of expression) to intestinal metaplasia (highly significant expression). We interpreted these data to indicate that CDX-2 expression in the esophageal stem cell was the driving genetic signal causing intestinal metaplasia.

The pattern of CDX-2 expression in columnar epithelia of the esophagus also suggests that the metaplastic process is a multistep process: an intermediate columnar transformation to cardiac mucosa, followed by intestinal metaplasia in the cardiac mucosa. There is evidence from clinical observations to support such a two-step metaplastic process. Reflux-induced columnar-lined esophagus in children consists predominantly of cardiac mucosa without intestinal metaplasia.[44,45] After esophagectomy, cardiac mucosa develops in the esophagus above the anastomotic line in many patients. This progresses to intestinal metaplasia in some patients, often after many years.[46-48]

Recognition of this two-step process provides a potential method of preventing reflux-induced adenocarcinoma of the esophagus. Cardiac mucosa is easily identified by biopsy in the first phase of the metaplastic sequence, which can last many years before the development of intestinal metaplasia. Transformation of cardiac mucosa to intestinal metaplasia must occur as the result of an interaction of a luminal molecule and the stem cells in cardiac mucosa to cause CDX-2 activation. If this molecule can be identified and inactivated, CDX-2 activation and the resulting intestinal metaplasia in cardiac mucosa can be prevented. Because intestinal metaplasia is an essential precursor to reflux-induced carcinogenesis, prevention of CDX-2 activation will theoretically prevent the development of carcinoma.

Intestinal metaplasia does not occur randomly in the columnar-lined segment of the esophagus. Not only does intestinal metaplasia arise in the most proximal part of the columnar-lined segment, but there is also an increasing prevalence of intestinal metaplasia with increasing length of columnar-lined esophagus. In a study in which we mapped these epithelial types in columnar-lined esophagus,[38] almost 100% of patients with a columnar epithelium segment greater than 5 cm had intestinal metaplasia, as compared with 90% when the length was 3 to 4 cm, 70% when the length was 1 to 2 cm, and 15% when the length was less than 1 cm.

This distribution suggests that factors causing CDX-2 activation and intestinal metaplasia operate proximally in the esophagus much more than distally. Two reasons can be suggested for the proximal region of the esophagus providing a better milieu for intestinal metaplasia than the more distal region. First, it has been shown with the use of multiple-level pH electrodes that the pH tends to progressively increase more proximally in the esophagus. If the molecule that causes CDX-2 activation in cardiac mucosa is more active in an alkaline milieu, it could explain the distribution of intestinal metaplasia. Second, Fitzgerald et al.[49] have shown that pulse exposure to acid is associated with a greater proliferative rate in cells from columnar-lined esophagus than continuous exposure is. This suggests that pulse-type exposure is associated with a higher damage level than continuous exposure is. Pulse-type exposure is much more likely in the more proximal region of the esophagus, and the higher proliferative rate of the cells could also explain the higher likelihood of the genetic change required for intestinal metaplasia.

Oxyntocardiac Mucosa—The Benign Genetic Switch

Allison and Johnstone, in the original description of columnar-lined esophagus in 1953, recognized that the proximal region of the columnar-lined esophagus was lined by pure cardiac mucosa but that oxyntic (parietal) cells started appearing in the more distal region.[2] Paull et al., in their histologic classification of columnar-lined esophagus, recognized this mucosa, in which there are glands containing a mixture of parietal and mucous cells, as the third epithelial type; they called it "fundic" mucosa.[35] Because this has nothing to do with the gastric fundus, which is lined by pure gastric oxyntic mucosa, we prefer to use the term oxyntocardiac mucosa for this epithelium (see Fig. 13–10).[37]

Oxyntocardiac mucosa is an important epithelial type in the columnar-lined esophagus. As first reported by Paull et al. and confirmed by us, it is almost never associated with intestinal metaplasia.[35,38] As such, it is unlikely to progress to carcinogenesis; it is a benign epithelium.

Oxyntocardiac mucosa is formed when cardiac mucosa develops a genetic signal that causes its stem cells to differentiate into parietal cells and move downward into glands in the deeper part of the mucosa below the proliferative stem cell region in the base of the foveolar pit. Oxyntocardiac mucosa is very similar to gastric oxyntic mucosa, except for the presence of chronic inflammation, residual mucous cells in the glands, and frequent lobulation of the glands in contrast to the straight tubular glands of normal gastric mucosa (see Fig. 13–10). We postulate that oxyntocardiac mucosa develops when cardiac mucosa acquires a "gastric-type genetic signal" that results in the phenotypic expression of parietal cells that are highly specific for the stomach. The nature of this gastric-type genetic signal is unknown.

The distribution of oxyntocardiac mucosa in the columnar-lined esophagus is the exact opposite of intestinal metaplasia; it is present in the most distal segment.[2,35,40] It is the only epithelial type that is always present in the columnar-lined esophagus. In patients

with very short (<1 cm) lengths of columnar-lined mucosa, oxyntocardiac mucosa represents the only metaplastic epithelium in about 20% of patients.[38] In our autopsy study, microscopic lengths of oxyntocardiac mucosa were present in some part of the squamocolumnar junction in all patients.[15] In these patients, all the cardiac mucosa had been transformed into oxyntocardiac mucosa.

The proliferative characteristics of oxyntocardiac mucosa show that it is less proliferative than cardiac and intestinal epithelia, thus indicating that it is associated with a low damage environment. The milieu in which oxyntocardiac mucosa occurs has damage factors that are opposite that in the proximal part of the esophagus (lower pH and continuous rather than pulse exposure to refluxate). The "gastric-type genetic signal" appears to be generated only in the low damage environment of the distal end of the esophagus.

Reversibility of Genetic Switches

We have suggested three genetic switches being responsible for the array of metaplasia that converts squamous epithelium to columnar. The first causes squamous epithelium to transform into undifferentiated cardiac mucosa composed of only mucous cells. Evolution of the columnar mucosa proceeds in one of two directions from cardiac mucosa. The development of a "gastric-type genetic signal" occurs in the low damage environment of the distal region and results in oxyntocardiac mucosa, which is characterized by the development of parietal cells. This is the benign pathway that is no longer susceptible to reflux-induced genetic transformations because it does not progress to intestinal metaplasia or adenocarcinoma. The second direction is the premalignant pathway. The development of intestinal-type genetic signals, probably the homeobox *CDX* genes, occurs in the high damage environment of the proximal end of the esophagus and results in the development of goblet cells, which defines intestinal (or Barrett-type) metaplasia. This is the only epithelium in columnar-lined esophagus that is at risk for the development of adenocarcinoma.

Genetic switches result from expression and suppression of normal genetic pathways in the cell as a result of cell surface interactions. They are reversible; removing or altering the surface interactions can drive these differentiation pathways in different directions. If this is true, intestinal metaplasia can revert back to cardiac mucosa if the *CDX* gene activation is reversed; cardiac mucosa can revert to squamous epithelium if it loses the first columnar genetic switch or becomes oxyntocardiac mucosa if it can be made to acquire the "gastric-type genetic signal." The ability to manipulate the columnar epithelia in the esophagus to move it away from intestinal metaplasia and toward squamous and oxyntocardiac mucosa is equivalent to preventing adenocarcinoma. We believe that the most beneficial reversion is the generation of oxyntocardiac mucosa because it is a full-thickness mucosal change. Squamous re-epithelialization of the surface is frequently associated with the presence of residual glandular elements below the epithelium, and these have been known to progress to adenocarcinoma.

The best method of manipulating these genetic shifts in columnar-lined esophagus is to characterize the nature of the interactions that cause the genetic changes and neutralize them. Until these specific interactions are characterized, however, the only logical method of achieving reversal is to alter the damage environment or abolish reflux completely. Acid-suppressive therapy is unlikely to achieve either of these goals; the reflux persists and may actually become even more alkaline, and the pulse effect does not change.[50] The fact that the prevalence of intestinal metaplasia and adenocarcinoma has risen even as acid suppression has improved is evidence that acid is a relatively minor factor in these genetic switches. On the other hand, successful antireflux surgery abolishes all reflux into the esophagus by creating a new valve. We have observed the phenotypic expression of some of these reversals; intestinal metaplasia accompanying short-segment Barrett's esophagus frequently reverses,[51] and we have observed an increased amount of oxyntocardiac mucosa in postfundoplication biopsy specimens as compared with preoperative specimens. Both these changes are highly beneficial and occur at a histologic level without any change in the endoscopic length of the columnar-lined esophagus. However, it is unlikely that fundoplication will have an impact on the incidence of adenocarcinoma of the esophagus, even if it is effective in preventing cancer in the individual patient, because of the high frequency of intestinal metaplasia and low frequency of adenocarcinoma.

The most promising point of attack in the attempt to prevent cancer is the stage of reflux disease before the development of intestinal metaplasia. The patients at risk in the future are those who have cardiac mucosa that is detectable by screening and biopsy. There is a long lag phase before cardiac mucosa progresses to intestinal metaplasia in most patients. Recognition of the molecular component in the refluxate that drives *CDX* activation and the "gastric-type genetic signal" can lead to the production of drugs that have an effect on these molecules and drive differentiation of cardiac mucosa away from intestinal metaplasia toward oxyntocardiac mucosa. This will theoretically prevent progression to adenocarcinoma. Of course, mass population screening is not cost-effective at the present time, but it may become so in the future if the incidence of adenocarcinoma continues its upward trend. In an individual patient undergoing endoscopy for any reason, taking a biopsy sample from the squamocolumnar junction is a screening opportunity.

Irreversible Genetic Mutations—Carcinogenesis in Intestinal Metaplasia

Once intestinal metaplasia develops in columnar-lined esophagus, the carcinogenetic pathway can begin. It probably occurs through a series of irreversible genetic mutations that are expressed phenotypically as low-grade dysplasia, high-grade dysplasia, and invasive adenocarcinoma. The exact molecular changes associated with these changes are unknown as yet.[52]

The frequency with which adenocarcinoma develops in patients with intestinal metaplasia is low. An individual who has intestinal metaplasia has a low risk for cancer; most patients do not progress. However, every patient with adenocarcinoma of the esophagus comes from the pool of patients who have esophageal intestinal metaplasia. There is no other pathway for adenocarcinoma of the esophagus. This set of data makes this disease very difficult to treat from a practical standpoint. Although it is impossible to ignore an individual patient with intestinal metaplasia because of the proven cancer risk, it stretches resources to keep all patients with intestinal metaplasia under surveillance, and the cost-effectiveness of such surveillance is questionable.

The development of adenocarcinoma in esophageal intestinal metaplasia is probably not related to its length. Although it was initially believed that only patients with long-segment Barrett's esophagus were at risk, there is convincing evidence now that short-segment Barrett's esophagus carries a similar risk.[14] The exact risk associated with very short segments of Barrett's esophagus is unknown because these patients remain undetected as a result of the standard of practice in gastroenterology that recommends that no biopsy be performed in patients without endoscopically visible columnar-lined esophagus. However, it is very likely that the junctional region adenocarcinomas that occur in asymptomatic patients are caused by a similar process as adenocarcinomas of the tubular esophagus. We have encountered patients who have had adenocarcinoma in extremely short lengths of columnar-lined esophagus.

The carcinogenic mechanism in reflux-induced adenocarcinoma is unique. Let us postulate that patients have different carcinogenic potential for reflux-induced adenocarcinoma of the esophagus resident in their gastric contents. Patients who have a high potential for carcinogenesis will remain without progression to cancer until intestinal metaplasia develops in the esophagus; at that time cancer can develop rapidly because of the high carcinogenic milieu irrespective of the amount of intestinal metaplasia that is present. In contrast, reflux-induced columnar metaplasia and intestinal metaplasia can develop in patients with a low carcinogenic milieu but not progress to dysplasia for long periods. If the major factor for development of adenocarcinoma in reflux disease is the carcinogenic potential of the refluxate, it is unlikely that present methods of surveillance will have an impact on the incidence of adenocarcinoma. Clinical experience supports such a hypothesis. Most patients in whom cancer is diagnosed do not have a long premalignant course, and most patients with long-segment Barrett's esophagus remain stable without progressing to cancer.

BARRETT'S ESOPHAGUS—DIAGNOSIS

The diagnosis of Barrett's esophagus at the present time is based on identification of goblet cells in a biopsy sample taken from an endoscopically visualized columnar-lined segment of esophagus (see Fig. 13–11). Goblet cells define intestinal metaplasia. There is consensus that the goblet cells should be well defined and recognizable on routine hematoxylin-eosin–stained sections. Alcian blue staining at pH 2.5 is positive in goblet cells that contain acid mucin, in contrast to non-intestinalized columnar epithelium, which contains Alcian blue–negative neutral mucin. However, cardiac mucosa frequently shows Alcian blue positivity ("columnar blue cells") that is unrelated to intestinal metaplasia and probably represents a reactive phenomenon. As a result, if Alcian blue positivity is used to define intestinal metaplasia, there will be a significant overdiagnosis of Barrett's esophagus. Other types of mucin, sialomucin and sulfated mucin, can be demonstrated by high-iron diamine stain. This is not presently used in routine pathology practice or for defining intestinal metaplasia. The use of CDX-2 immunoperoxidase staining to define Barrett's intestinal metaplasia has been suggested but not accepted yet.[43]

Because most authorities follow the recommendations of the American Gastroenterology Association and avoid biopsy when endoscopic findings are normal, there is no attempt to diagnose the microscopic stage of Barrett's esophagus. It is obvious that a microscopic phase must precede the stage of the disease in which metaplastic epithelium is visible by endoscopy. If biopsies are performed in patients who are endoscopically normal, a significant percentage (probably 5% to 10%) of the population will have microscopic Barrett's intestinal metaplasia. This is easily recognized by histologic criteria as intestinal metaplasia occurring in cardiac (i.e., metaplastic esophageal) mucosa. It is distinguishable from chronic atrophic gastritis, which is the occurrence of gastric intestinal metaplasia in gastric oxyntic mucosa.

The most important practical function of the pathologist is to detect neoplastic change in Barrett's esophagus in patients undergoing either primary or surveillance biopsy. The neoplastic change progresses through low- and high-grade dysplasia to invasive adenocarcinoma (Figs. 13–12 to 13–14).

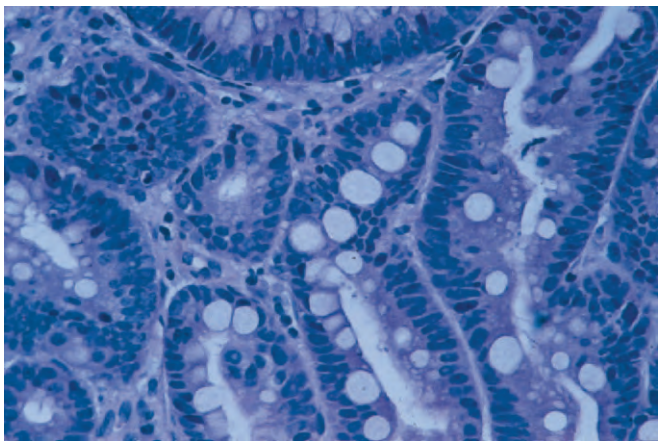

Figure 13–12. Intestinal metaplasia with low-grade dysplasia (hematoxylin-eosin stain). There is nuclear enlargement, stratification, and hyperchromasia. The glands are simple, and nuclear polarity is maintained. There is only minimal chronic inflammation.

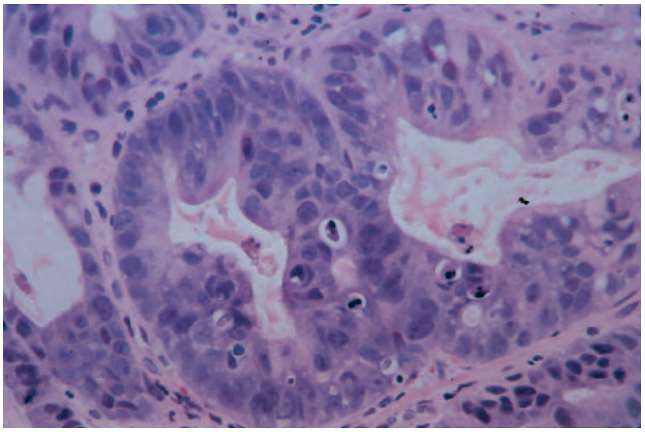

Figure 13–13. Intestinal metaplasia with high-grade dysplasia (hematoxylin-eosin stain). There is severe cytologic abnormality, complete loss of nuclear polarity, and early gland complexity.

The diagnosis of invasive adenocarcinoma and high-grade dysplasia is highly accurate and dependent on well-established criteria.[53] High-grade dysplasia (which includes the older terms severe dysplasia and carcinoma in situ) is characterized by a severe cytologic abnormality associated with complete loss of polarity of nuclei or the presence of gland complexity manifested by luminal bridging and cribriform architecture, or by both (see Fig. 13–13). Invasive carcinoma is characterized by the presence of irregularity of glands, often associated with microcystic change, and desmoplasia or the presence of single invasive cells in the lamina propria (see Fig. 13–14).

Differentiation of low-grade dysplasia from high-grade dysplasia is critical because high-grade dysplasia is an indication for esophagectomy in some centers. The fact that such differentiation is a problem should not be surprising; dysplasia is a continuous spectrum, and pathologists are drawing an artificial line separating low- from high-grade dysplasia. I tend to draw the line at a point where the specificity of the diagnosis of high-grade dysplasia is 100%; patients whom I consider to have high-grade dysplasia can proceed to esophagectomy. Increasing the specificity of the diagnosis of high-grade dysplasia necessarily decreases the sensitivity; I call borderline cases low-grade dysplasia, recommend a decreased surveillance interval, and defer the decision until future serial biopsies have been performed.

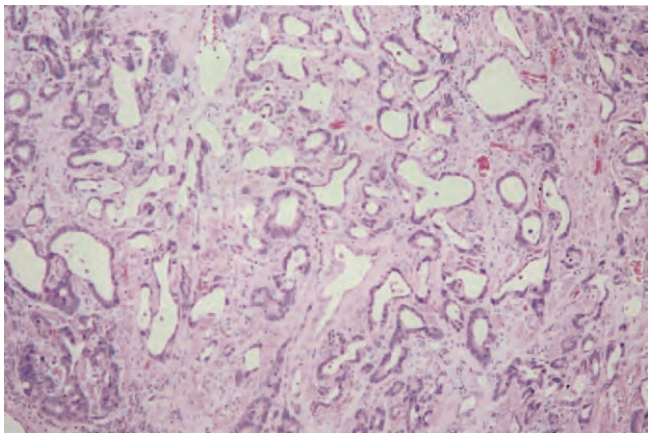

Figure 13–14. Invasive adenocarcinoma in Barrett's esophagus characterized by irregular malignant glands surrounded by desmoplasia (hematoxylin-eosin stain).

The diagnosis of low-grade dysplasia tends to have a greater degree of interobserver variation, even among experts.[53] Criteria for low-grade dysplasia are the presence of a cytologic abnormality that is significantly greater than normal with involvement of the surface epithelium to a similar extent as the foveolar region (see Fig. 13–12). When these strict criteria are used, low-grade dysplasia becomes an uncommon diagnosis in patients with Barrett's esophagus and justifies the decrease in surveillance interval that is recommended.

Most authorities recognize a category of "indefinite for dysplasia."[53] This category is used when cytologic changes are present but the criteria for low-grade dysplasia are not satisfied. I do not use the diagnosis "indefinite for dysplasia"; if there are no definite diagnostic criteria for low-grade dysplasia, it is negative for dysplasia. I use the term "reactive cytologic changes" for these cases. These patients simply stay at the regular surveillance interval for Barrett's esophagus that is recommended for nondysplastic Barrett's esophagus.

An important variable in the assessment of patients with columnar-lined esophagus is sampling. Harvesting biopsy specimens is a time-consuming activity for the endoscopist. It is not uncommon to see a sample with four to six biopsy specimens taken during surveillance endoscopy for long-segment Barrett esophagus. The chance of missing dysplasia in such a sample is significant. Patients under surveillance for Barrett's esophagus must undergo the four-quadrant biopsy per 2-cm segment protocol that is recommended. A correctly obtained surveillance biopsy sample from a 10-cm segment of Barrett's esophagus will have six separate levels with four specimens in each level.

HISTOLOGIC CLASSIFICATION OF REFLUX DISEASE

We recommend a histologic classification of reflux disease designed to predict cancer risk in patients, as well as histologically diagnose reflux disease and its severity (Box 13–3). This is highly controversial and not likely to be accepted, but we believe that there are more data to support it than any classification presently in use.

Any definition of reflux disease must recognize an end point. Present definitions use reversal of symptoms and healing of erosions and are helpful for the clinical management of patients with reflux. In the past 3 decades, however, the main life-threatening complication of reflux disease has become recognized as adenocarcinoma. Present definitions that use adenocarcinoma as an end point begin with Barrett's esophagus and not with

Box 13–3 Grading System for Reflux Disease

Grade 0: No Evidence of Reflux Disease (No Risk for Intestinal Metaplasia or Adenocarcinoma)

Definition: No cardiac mucosa or intestinal metaplasia at the junction

Features: These patients often have mild reflux by 24-hour pH test (within limits of normal or slightly abnormal) and are usually asymptomatic and endoscopically normal

- **Grade 0A: Normal:** Only squamous epithelium and gastric oxyntic mucosa present
- **Grade 0B: Compensated reflux:** Oxyntocardiac mucosa present in addition to squamous epithelium and gastric oxyntic mucosa

Grade 1: Reflux Disease (at Risk for Intestinal Metaplasia; No Risk for Adenocarcinoma)

Definition: Cardiac mucosa present at the junction; no intestinal metaplasia

Features: These patients often have an abnormal 24-hour pH test and may or may not be symptomatic and may or may not have endoscopically visible columnar-lined esophagus

- **Grade 1A: Mild reflux disease:** 24-hour pH study often mildly abnormal, endoscopy normal, cardiac mucosa seen at microscopy
- **Grade 1B: Moderate reflux disease:** Almost always have an abnormal 24-hour pH test; endoscopy shows a <2-cm short-segment columnar-lined esophagus
- **Grade 1C: Severe reflux disease:** Severely abnormal 24-hour pH test; endoscopy shows >2-cm long-segment columnar-lined esophagus

Grade 2: Barrett's Esophagus (at Risk for Adenocarcinoma)

Definition: Intestinal metaplasia present

Features: Similar to those of reflux disease without intestinal metaplasia

- **Grade 2A: Microscopic Barrett's esophagus:** Endoscopy normal; intestinal metaplasia in cardiac mucosa seen at microscopy
- **Grade 2B: Short-segment Barrett's esophagus:** Almost always have an abnormal 24-hour pH test; endoscopy shows <2-cm short-segment columnar-lined esophagus
- **Grade 2C: Long-segment Barrett's esophagus:** Severely abnormal 24-hour pH test; endoscopy shows >2-cm long-segment columnar-lined esophagus

Grade 3: Neoplastic Barrett's Esophagus

Definition: Histologic evidence of dysplasia/neoplasia present

Features: Similar to those of reflux disease and intestinal metaplasia

- **Grade 3A: Low-grade dysplasia**
- **Grade 3B: High-grade dysplasia**
- **Grade 3C: Invasive adenocarcinoma**

reflux disease. The present classifications and grading systems seem to treat reflux disease and Barrett's esophagus as separate entities rather than different stages of one disease. The classification suggested here represents a unified concept that recognizes the entire reflux-adenocarcinoma sequence. The major grades in this system are designed to predict the risk for future adenocarcinoma. Subdivisions within each grade are designed to assess the amount of reflux-induced damage and are predictive of the severity of reflux-induced damage. Reflux-induced columnar transformation of squamous epithelium provides a far more accurate assessment of the severity of reflux than do changes in intact squamous epithelium. The length of columnar-lined esophagus has the greatest correlation with reflux when assessed by the 24-hour pH test. In many patients with a long-segment columnar-lined esophagus, who almost invariably have severe reflux, changes in squamous epithelium are frequently minimal. This is easy to understand; as the squamous epithelium moves proximally as a result of columnar transformation, it becomes removed from the point of reflux and separated from it by a buffer zone of columnar-lined esophagus.

The grading system recommended here recognizes the significance of the different genetic changes that occur in patients with reflux disease. Patients without reflux-induced genetic changes will have only normal squamous epithelium lining the esophagus. Patients enter grade 1 when cardiac mucosa develops as a result of columnar transformation. Cardiac mucosa remains as such or evolves by the development of specialized cells. If all the cardiac mucosa changes to oxyntocardiac mucosa, the patient moves out of the reflux-adenocarcinoma sequence and reverts back to grade 0. This is a very

common circumstance in mild reflux disease; in patients with higher grades, conversion of columnar epithelium to oxyntocardiac mucosa essentially represents a histologic cure because oxyntocardiac mucosa does not progress to intestinal metaplasia and adenocarcinoma. When cardiac mucosa progresses in the direction of adenocarcinoma, intestinal metaplasia (grade 2) and increasing neoplastic change recognized morphologically as low-grade dysplasia, high-grade dysplasia, and adenocarcinoma (grade 3) develop. In the future, as molecular alterations specific for these changes are discovered, they can replace the morphologic criteria used at present to define these grades.

The most important element in this grading system is that it permits recognition of patients who are not at risk for adenocarcinoma or intestinal metaplasia. These patients are in grade 0 and probably represent about 50% to 60% of the general population and 35% to 40% of patients who undergo endoscopy for upper gastrointestinal symptoms and are endoscopically normal. If symptomatic, these patients can be confidently managed with acid suppression to heal and stabilize the squamous epithelium. Effective acid suppression in these patients is very likely to prevent the occurrence of columnar metaplasia because it reverses the squamous epithelial damage and removes exposure of the basally located stem cells to agents that cause genetic changes. Once cardiac metaplasia has occurred, however, the focus must shift to an attempt to convert it back to squamous epithelium or direct it to form oxyntocardiac mucosa. This grading system can form the basis for evaluating therapeutic measures that have an impact on esophageal columnar epithelium better than any other system in effect can.

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Chapter

14

The Gastroesophageal Barrier

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The gastrointestinal tract is a continuous hollow tube whose function is ingestion and digestion of food, absorption of chemical energy, and elimination of residue. These functions are performed separately in different compartments whose boundaries differ from our customary anatomic divisions of the gastrointestinal tract. Common to each compartment is a pumping mechanism to propel contents into the reservoir portion of the compartment, a sphincter to separate the pump from the reservoir, and the ability to maintain within the reservoir a distinct chemical, enzymatic, and pH environment appropriate to its function. In the most proximal compartment, the tongue and pharynx function as a pump; the upper esophageal sphincter, soft palate, and epiglottis function as valves; and the striated muscle portion of the upper esophagus functions as a receptacle. In the second compartment, the smooth muscle portion of the distal esophagus, characterized by peristaltic contractions of high amplitude, pumps food through a valve, the lower esophageal sphincter (LES), into the gastric fundus, which acts as a reservoir. In the third compartment, the antrum behaves as a pump to propel chyme through a valve, the pylorus, into a reservoir, the duodenum. Similarly, the small intestine pumps its contents through the ileocecal valve into a capacitance organ, the cecum. An important principle is that breakdown of function in one compartment of the gastrointestinal tract tends to produce secondary effects in the proximal compartments rather than in the distal compartments. Thus, problems originating in the stomach commonly cause symptoms in the esophagus or symptoms referable to the pharyngeal and laryngeal area. This concept of the gastrointestinal tract is important in understanding the pathophysiology of gastroesophageal reflux disease (GERD) and structuring a rational approach to its therapy.

The common denominator for virtually all episodes of gastroesophageal reflux, whether physiologic or pathologic, is loss of the normal gastroesophageal barrier and the resistance that it imposes to the flow of gastric juice from an environment of higher pressure, the stomach, to an environment of lower pressure, the esophagus. This barrier is composed of both anatomic (flap valve) and physiologic (sphincter) components that combined act to prevent reflux during stressed and unstressed conditions. Its key determinants include

1. The resting structural integrity of the LES
2. The frequency of swallow- and non–swallow-induced transient loss of sphincter competence
3. Anatomic configuration of the diaphragmatic crura and gastroesophageal flap valve represented by the angle of His

In severe GERD, reflux is usually due to a permanently nonexistent or reduced high-pressure zone. In early disease or normal subjects, it is usually due to a transient loss of the high-pressure zone.[1] The presence or absence of pathologic esophageal acid exposure (i.e., abnormal 24-hour pH studies) is influenced not only by the degree of barrier loss but also by the function of the esophagus and stomach, most importantly the effectiveness of esophageal peristalsis and clearance and any gastric motility abnormalities that affect gastric relaxation or distention (or both).

LOWER ESOPHAGEAL SPHINCTER

In humans, the primary physiologic barrier between the esophagus and stomach that confines the gastric fluid to the stomach is the lower esophageal "sphincter." The LES has few anatomic landmarks, but its presence can be identified by a rise in pressure over gastric baseline pressure as a pressure transducer is pulled from the stomach into the esophagus (Fig. 14–1). This high-pressure zone is normally present except in two situations: (1) after a swallow, when it is momentarily dissipated or relaxes to allow passage of food into the stomach (Fig. 14–2), and

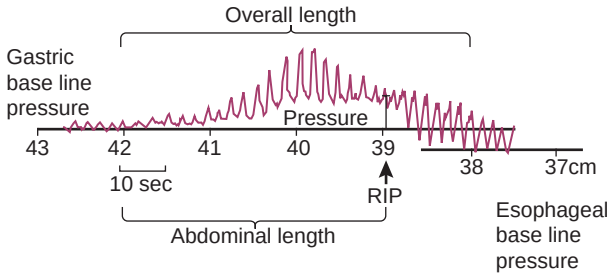

Figure 14–1. A pressure profile of the lower esophageal high-pressure zone or "sphincter" measured in a normal subject. The high-pressure zone has no anatomic landmarks, but is identified by a rise in pressure over the gastric baseline as the pressure transducer is pulled from the stomach into the esophagus. Note the long intra-abdominal portion identified by the positive respiratory excursions and the short intrathoracic portion identified by the negative respiratory excursions. The point where the respiratory excursions reverse is called the *respiratory inversion point*. The pressure scale is 3 mm Hg between *vertical dots.*

(2) during distention of the fundus with gas, when the high-pressure zone is eliminated to allow venting of the gas (a belch).

Three characteristics of the lower esophageal high-pressure zone, or "sphincter" as it is commonly referred to, maintain its resistance or "barrier" function to intragastric and intra-abdominal pressure challenges. Two of these characteristics work together and are dependent on each other for proper sphincter function. They are its pressure, measured at the respiratory inversion point, and its overall length. The tonic resistance of the LES is a function of both its pressure and the length over which the pressure is exerted.[2,3] The shorter the overall length of the high-pressure zone, the higher the pressure must be to maintain sufficient resistance to remain competent (Fig. 14–3). Consequently, normal sphincter pressure can be nullified by a short overall sphincter length. Furthermore, as the stomach fills, the length of the sphincter decreases, rather like the neck of a balloon shortening as the balloon is inflated. If the overall length of the sphincter is abnormally short when the stomach is empty, with minimal gastric distention there will be insufficient sphincter length for the existing pressure to maintain sphincter competency, and reflux will occur. The integrated effects of radial pressure exerted over the entire length of the high-pressure zone can be measured to form a three-dimensional computerized image of the sphincter.[4] The volume of this image is a reflection of the sphincter's resistance and is called the sphincter pressure vector volume (Fig. 14–4). A calculated volume less than the 5th percentile in normal subjects is an indication of a permanently defective sphincter.

The third characteristic of the lower esophageal high-pressure zone, or "sphincter," is its position, and a portion of the overall length of the high-pressure zone should be exposed to positive intra-abdominal pressure. This portion of the high-pressure zone is commonly referred to as the abdominal length of the sphincter.

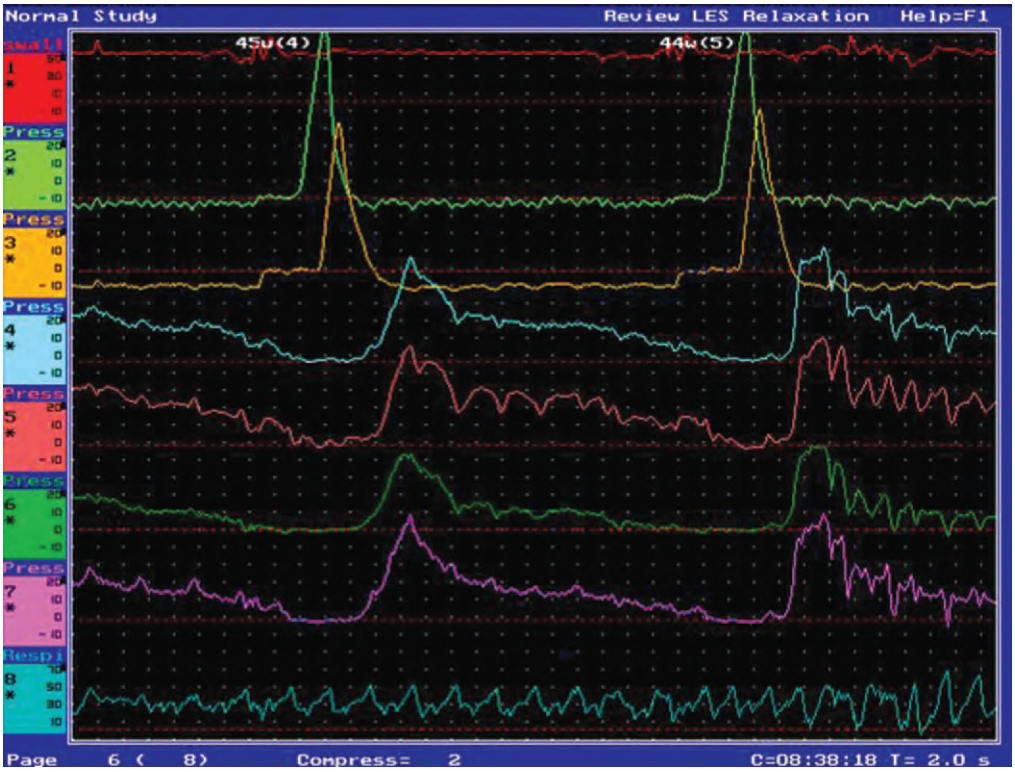

Figure 14–2. Manometric example of relaxation of the lower esophageal sphincter with swallowing.

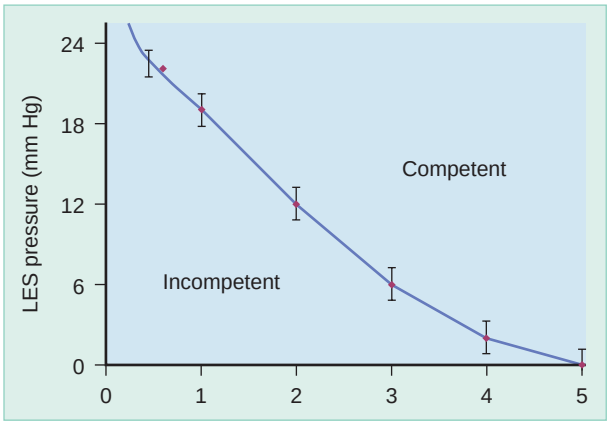

Figure 14–3. Relationship between the magnitude of pressure in the high-pressure zone measured at the respiratory inversion point and the overall length of the zone to the resistance to flow of fluid through the zone. Competent equals no flow. Incompetent equals flow of varied volume. Note that the shorter the overall length of the high-pressure zone, the higher the pressure must be to maintain sufficient resistance to remain competent. LES, lower esophageal sphincter.

During periods of increased intra-abdominal pressure, the resistance of the LES would be overcome if the abdominal pressure were not applied equally to the high-pressure zone and the stomach.[5-7] Think of sucking on a soft soda straw immersed in a bottle of Coke; the hydrostatic pressure of the fluid and the negative pressure inside the straw as a result of sucking cause the straw to collapse instead of allowing the liquid to flow up the straw in the direction of the negative pressure. If the abdominal length is inadequate, the sphincter cannot respond to an increase in applied intra-abdominal pressure by collapsing, and reflux is more liable to result.

If the high-pressure zone has an abnormally low pressure, a short overall length, or minimal exposure to the abdominal pressure environment in the fasting state, there is permanent loss of LES resistance and unhampered reflux of gastric contents into the esophagus throughout the circadian cycle. This is referred to as a permanently defective sphincter and is identified by one or more of the following characteristics: a high-pressure zone with an average pressure of less than 6 mm Hg, an average overall length of 2 cm or less, or an average length exposed to the positive-pressure environment of the abdomen of 1 cm or less.[8] When compared with normal subjects, these values are below the 2.5th percentile for each parameter (Table 14–1). The most common cause of a permanently defective sphincter is inadequate pressure, but the efficiency of a sphincter with normal pressure can be nullified by an inadequate abdominal length or an abnormally short overall length.

For the clinician, the finding of a permanently defective sphincter has several implications. Foremost, it is almost always associated with esophageal mucosal injury[9] and predicts that the patient's symptoms will be difficult to control with medical therapy.[10] It is a signal that surgical therapy is likely to be needed for consistent and long-term control of the patient's symptoms. It is now accepted that when the sphincter is permanently defective, it is irreversible, even when the associated esophagitis has healed.[11] The presence of a permanently defective sphincter is commonly associated with reduced esophageal body function, and if the disease is not brought under control, the progressive loss of effective esophageal clearance can lead to severe mucosal injury,

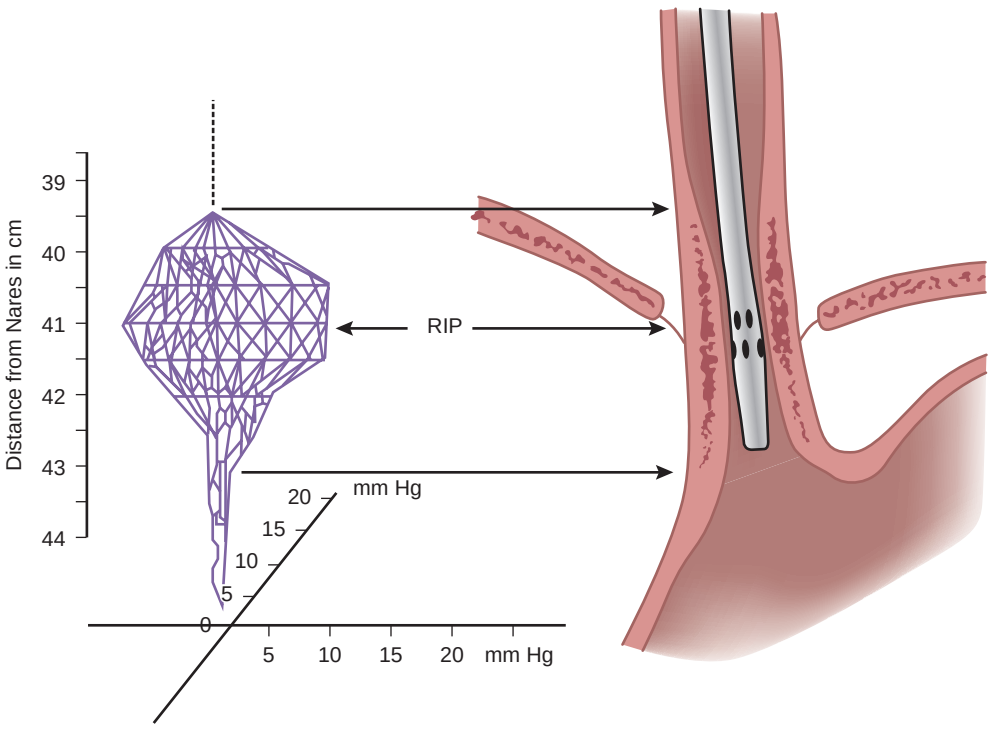

Figure 14–4. Computerized three-dimensional imaging of the lower esophageal sphincter. A catheter with four to eight radial side holes is withdrawn through the gastroesophageal junction. For each level of pullback, the radially measured pressure is plotted around an axis representing gastric baseline pressure. When a stepwise pullback technique is used, the respiratory inversion point (RIP) can be identified. (From Stein HJ, DeMeester TR, Naspetti R, et al: Three-dimensional imaging of the lower esophageal sphincter in gastroesophageal reflux disease. Ann Surg 214:374-384, 1991.)

Table 14–1 Normal Manometric Values of the Distal Esophageal Sphincter ($N = 50$)

Parameter	Median Value	2.5th Percentile	97.5th Percentile
Pressure (mm Hg)	13	5.8	27.7
Overall length (cm)	3.6	2.1	5.6
Abdominal length (cm)	2	0.9	4.7

repetitive regurgitation, aspiration, and pulmonary failure.[8,12,13]

TRANSIENT LOSS OF LOWER ESOPHAGEAL SPHINCTER COMPETENCE

Transient loss of the lower esophageal high-pressure zone occurs in association with swallowing and when the fundus is distended with gas, fluid, or food, which probably "unfolds" the sphincter. In 1980, Dent and Dodds reported that non-swallow–induced transient lower esophageal sphincter relaxation (tLESR) was a significant mechanism of gastroesophageal reflux in normal individuals and patients with GERD.[14] These spontaneous relaxations occurred without pharyngeal contraction, were prolonged (>10 seconds), and when reflux occurred, were associated with relaxation of the crural diaphragm. Indeed, Mittal et al. later showed that pharmacologic elimination of LES pressure to zero did not result in reflux unless crural diaphragmatic contraction was also absent.[15] Gastric distention, upright posture, and meals high in fat have all been shown to increase the frequency of tLESRs. These observations suggest that unfolding of the sphincter may be responsible for the loss of sphincter pressure.

As a result of these findings, tLESRs became commonly accepted as the major mechanism of gastroesophageal reflux regardless of the underlying severity of disease, despite evidence to the contrary. The fact that a hiatal hernia could be identified in more than 80% of patients with symptomatic gastroesophageal reflux and that most patients with erosive esophagitis and Barrett's esophagus had incompetent LES characteristics at rest were largely ignored. When these facts are taken into account, particularly in association with the known characteristics of tLESRs, it seems likely that they are (1) a physiologic response to gastric distention by food or gas, (2) the mechanism of belching, and (3) responsible for physiologic reflux episodes in individuals with normal LES and hiatal anatomy. Evidence supporting this conclusion was recently published by Van Herwaarden et al., who performed ambulatory esophageal manometry and pH studies on patients with and without hiatal hernia.[16] Although patients with hiatal hernia had greater esophageal acid exposure and more reflux episodes, the frequency of tLESRs and the proportion associated with reflux were similar in both groups. They concluded that excess reflux in patients with GERD and hiatal hernia is caused by low LES pressure, swallow-induced relaxation, and straining.

Transient loss of the high-pressure zone can also occur and is usually due to a functional problem of the gastric reservoir. Ingestion of excessive air or food can result in gastric dilatation and, if the active relaxation reflex has been lost, increased intragastric pressure. When the stomach is distended, the vectors produced by gastric wall tension pull on the gastroesophageal junction with a force that varies according to the geometry of the cardia; that is, the force is applied more directly when a hiatal hernia exists[5] than when a proper angle of His is present.[17,18] The force pulls on the terminal esophagus and causes it to be "taken up" into the stretched fundus, thereby reducing the length of the high-pressure zone, or "sphincter."[19] This process continues until a critical length is reached, usually about 1 to 2 cm, when the pressure drops precipitously and reflux occurs (Fig. 14–5). If

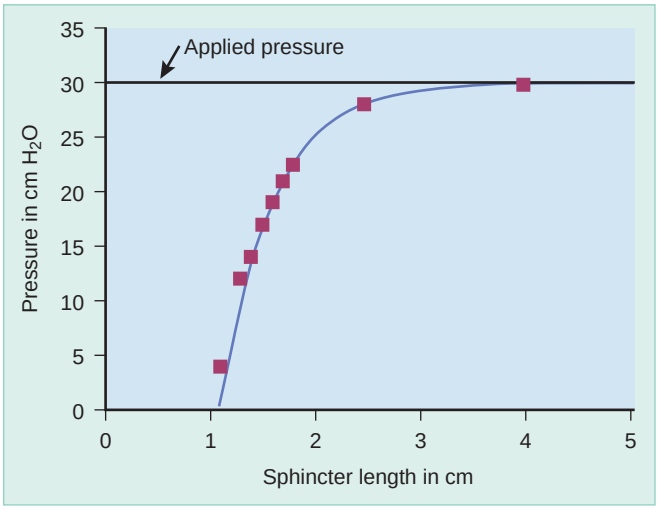

Figure 14–5. Relationship between resting sphincter pressure and sphincter length when applied pressure or "sphincter squeeze" is kept constant. Analysis was made with a model of the lower esophageal high-pressure zone. Note that as sphincter length decreased, the pressure recorded within the sphincter decreased only slightly until a length of 2 cm was reached, as which point sphincter pressure dropped precipitously and competency of the sphincter was lost. (From Pettersson GB, Bombeck CT, Nyhus LM: The lower esophageal sphincter: Mechanisms of opening and closure. Surgery 88:307-314, 1980.)

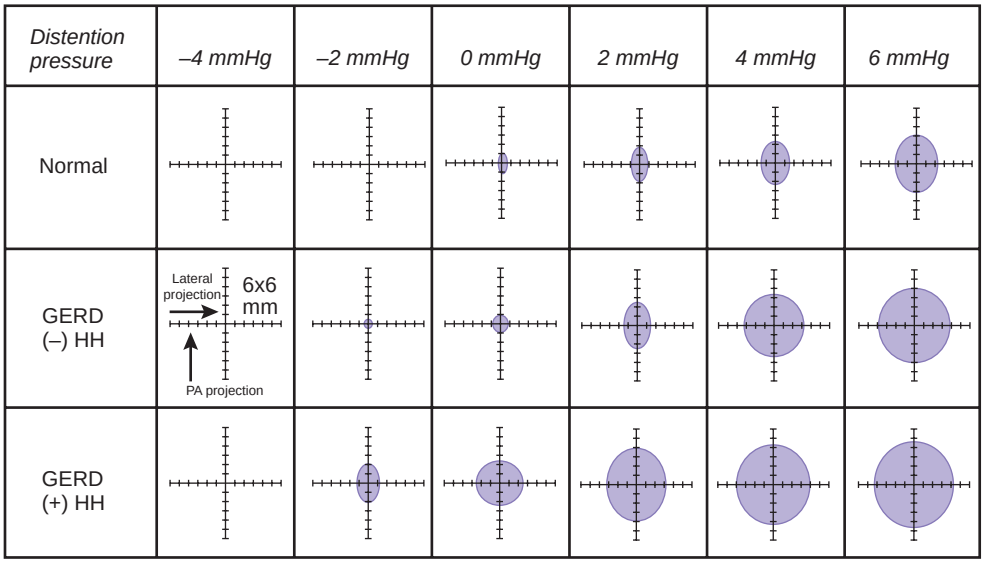

Figure 14–6. Radiographic measures of gastroesophageal junction opening size and shape under various clinical conditions for normal subjects, gastroesophageal reflux disease (GERD) patients without hiatal hernia (HH), and GERD patients with HH. Note the hiatal openings in patients with HH under conditions of minimal distention pressure. PA, posteroanterior. (Pandolfino JE, Shi G, Trueworthy B, Kahrilas PJ: Esophagogastric junction opening during relaxation distinguishes non-hernia reflux patients, hernia patients, and normal subjects. Gastroenterology 125:1018-1024, 2003.)

the pressure rather than the length of the high-pressure zone is measured, as with a Dent sleeve,[20] this event will appear as a spontaneous dissipation or "relaxation" of the high-pressure zone.

Gastric distention results in shortening of the length of the high-pressure zone along with a concomitant drop in LES pressure, which provides a mechanical explanation for "transient" relaxations of the LES without invoking a neuromuscular reflex. Rather than a "spontaneous" muscular relaxation, there is unfolding of the sphincter, secondary to progressive gastric distention, to the point at which it becomes incompetent. Consequently, non–swallow-induced relaxations of a normal high-pressure zone, or "sphincter," are inappropriately termed transient LES relaxations; rather, they should be called "transient sphincter shortenings." These "transient sphincter shortenings" occur in the initial stages of GERD and are the mechanisms for excessive postprandial reflux. After gastric venting, the length of the high-pressure zone is restored and competence returns, until distention again shortens it and encourages further venting and reflux. This sequence results in the common complaints of repetitive belching and bloating in patients with GERD. The increased swallowing frequency seen in patients with GERD aggravates gastric distention and is probably due to repetitive swallowing of saliva in an unconscious attempt to buffer acid refluxed into the esophagus.[21] Thus, the early pathogenesis of GERD may begin in the stomach, with gastric distention caused by overeating or the ingestion of fried foods, which delays gastric emptying, or subclinical gastric motility abnormalities.[22] Both characteristics are common in Western society and may explain the high prevalence of the disease in the Western world.

The mechanical forces set in play by gastric distention and their effect on sphincter unfolding are also influenced by the "geometry" of the gastroesophageal junction. The presence of a normal acute angle of His, in contrast to the abnormal dome architecture of a sliding hiatal hernia, markedly influences the ease with which the sphincter is pulled open (Fig. 14–6).[23] There is a close relationship between the degree of gastric distention necessary to overcome the high-pressure zone and the morphology of the cardia.[24] Greater gastric dilatation, as reflected by higher intragastric pressure, is necessary to "open" the sphincter in patients with an intact angle of His than in those with a hiatal hernia (Fig. 14–7). This is what would be expected if the high-pressure zone were shortened by mechanical forces and accounts for why a hiatal hernia is often associated with the presence of GERD.

In normal subjects, almost all reflux episodes are precipitated by belching. In patients with GERD, belching remains an important, but decreasing cause of reflux as the grade of esophagitis worsens.[25] Activities that produce a pressure gradient across the diaphragm, such as coughing, sniffing, or straining, become increasingly important in precipitating reflux as the degree of disease, graded according to the severity of esophagitis, becomes more severe. In patients with severe grades of esophagitis, episodes of acid reflux occur spontaneously, thus suggesting that the sphincter was permanently defective in its resting state and there is persistent loss of the barrier. Reflux episodes associated with belching are by inference due to gastric distention and are responsible for increased esophageal acid exposure in patients with early or less mucosal disease. In this situation there is a transient loss of the barrier. Mucosal damage caused

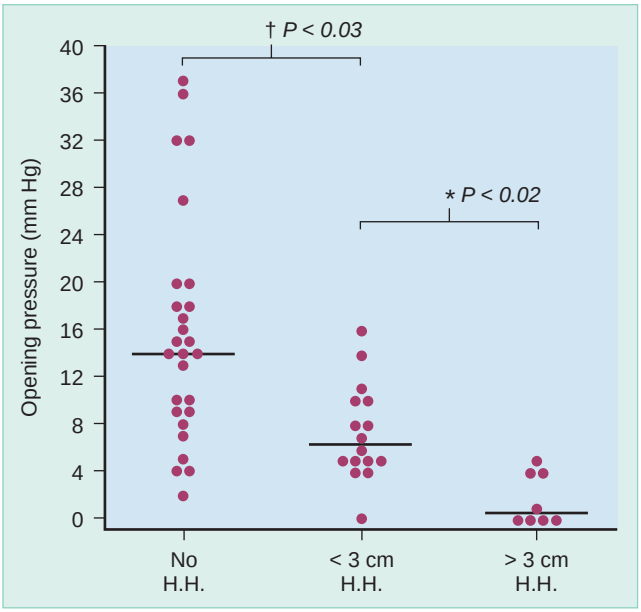

Figure 14–7. Intragastric pressure at which the lower esophagus endoscopically opened in response to gastric distention by air during endoscopy. Note that the dome architecture of a hiatal hernia (H.H.) influenced the ease with which the sphincter can be pulled open by gastric distention. (From Ismail T, Bancewicz J, Barlow J: Yield pressure, anatomy of the cardia and gastroesophageal reflux. Br J Surg 82:943-947, 1995.)

by repetitive exposure to gastric juice results in inflammatory injury to the underlying muscle.[26] Such injury leads to a permanently defective high-pressure zone, or "sphincter," that is initially due to the loss of abdominal length and eventually due to the loss of pressure and overall length. Subsequent inflammation in the esophagus results in the loss of its clearance ability and thereby leads to prolonged esophageal exposure to gastric juice.[27] This signals the presence of advanced disease and places the patient at risk for Barrett's metaplasia, stricture formation, and aspiration.

ANATOMIC ALTERATIONS

With the advent of clinical roentgenology, it became evident that a hiatal hernia was a relatively common abnormality, although not always accompanied by symptoms. Philip Allison in his classic treatise published in 1951 suggested that the manifestations of GERD were caused by the presence of a hiatal hernia.[28] For most of the next 2 decades, hiatal hernia was considered the primary pathophysiologic abnormality leading to GERD. Indeed, the Allison repair, among the first surgical attempts to treat GERD, was limited to reducing the hernia. Attention was slowly diverted away from hiatal hernia as the main pathophysiologic abnormality, however, as techniques of esophageal manometry developed in the late 1950s and 1960s allowed identification and study of the LES in subjects with and without reflux. In 1971, Cohen and Harris published a study of the contributions of hiatal hernia to LES competence in 75 patients and concluded that hiatal hernia had no effect on gastroesophageal junction competence.[29] This paper, published in the *New England Journal of Medicine,* and the growing use of esophageal manometry shifted the emphasis away from hiatal hernia almost exclusively toward features of the LES as the primary abnormality in symptomatic GERD.

Perhaps serendipitously, studies of the phenomenon of tLESR identified the diaphragmatic crura as an important factor in preventing reflux during periods of loss of LES pressure. In normal subjects, even with absent LES pressure, reflux does not occur without relaxation of the crural diaphragm.[30] Coincidentally, Hill et al. stressed the importance of the physiologic flap valve created by the angle of His as a barrier to gastroesophageal reflux.[31] The endoscopic appearance of the flap valve can be correlated with abnormal esophageal acid exposure, thus emphasizing that the geometry of the gastroesophageal region is also important in barrier competence. Further evidence was provided by Ismail et al., who showed that the geometry of the gastroesophageal junction was an important factor in competency of the cardia regardless of sphincter status.[24] They reported a close relationship between the size of the hiatal hernia and the intragastric pressure required to open the sphincter, or the yield pressure. No relationship between yield pressure and LES resting pressure and length was found. Higher intragastric pressure was needed to open the sphincter in patients with an intact angle of His than in patients with a hiatal hernia. The presence of a hiatal hernia also disturbs esophageal clearance mechanisms, probably because of loss of anchorage of the esophagus in the abdomen. Kahrilas et al. have shown that complete esophageal emptying was achieved in 86% of swallows in control subjects without a hiatal hernia, in 66% of swallows in patients with a reducing hiatal hernia, and in only 32% of swallows in patients with a nonreducing hiatal hernia.[32] The impaired clearance in patients with nonreducing hiatal hernias suggests that the presence of a hiatal hernia contributes to the pathogenesis of GERD. Thus, present evidence is overwhelming that hiatal hernia does indeed play a significant, if not primary role in the pathophysiology of GERD.

INTEGRATED HYPOTHESIS OF THE PATHOPHYSIOLOGY OF GASTROESOPHAGEAL REFLUX DISEASE

The data support the likelihood that GERD begins in the stomach. Fundic distention occurs because of overeating and delayed gastric emptying secondary to the high-fat Western diet. The distention causes the sphincter to be "taken up" by the expanding fundus, thereby exposing the squamous epithelium within the high-pressure zone, which is the distal 3 cm of the esophagus, to gastric juice. Repeated exposure causes inflammation of the squamous epithelium, columnarization, and carditis. This is the initial step and explains why in early disease the

esophagitis is mild and commonly limited to the very distal part of the esophagus. The patient compensates by increased swallowing, which allows saliva to bathe the injured mucosa and alleviate the discomfort induced by exposure to gastric acid. Increased swallowing results in aerophagia, bloating, and repetitive belching. The distention induced by aerophagia leads to further exposure and repetitive injury to the terminal squamous epithelium and the development of cardiac-type mucosa. This is an inflammatory process, commonly referred to as "carditis," and explains the complaint of epigastric pain so often registered by patients with early disease. The process can lead to a fibrotic mucosal ring at the squamocolumnar junction and explains the origin of a Schatzki ring. Extension of the inflammatory process into the muscularis propria causes progressive loss in length and pressure of the distal esophageal high-pressure zone, associated with increased esophageal exposure to gastric juice and the symptoms of heartburn and regurgitation. Loss of the barrier occurs in a distal-to-proximal direction and eventually results in permanent loss of LES resistance and explosion of the disease into the esophagus with all the clinical manifestations of severe esophagitis. This accounts for the observation that severe esophageal mucosal injury is almost always associated with a permanently defective sphincter. At any time during this process and under specific luminal conditions or stimuli, such as exposure time to a specific pH range, intestinalization of the cardiac-type mucosa can occur and set the stage for malignant degeneration.

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Chapter

15

Esophageal Mucosal Injury and Duodenal Reflux

Hubert J. Stein · Werner K. H. Kauer · Dorothea Liebermann-Meffert

The existence of primary duodenogastroesophageal reflux disease, or excessive reflux of bile and pancreatic enzymes into the esophagus in patients with an intact stomach, has been questioned for years. Today, it is well established that both gastric juice and duodenal contents can reflux into the esophagus and contribute to esophageal mucosal injury, namely, inflammation, ulcerative esophagitis, intestinal metaplasia (so-called Barrett's esophagus), and esophageal adenocarcinoma.[1-4] Discoordination of antropyloroduodenal motility, frequently found after cholecystectomy, and defective barrier function of the lower esophageal sphincter are the underlying conditions predisposing to excessive reflux of duodenal contents through the stomach into the esophagus.[5] The individual and combined contributions of gastric juice and duodenal components to the development of esophageal mucosal damage have been studied extensively in vitro and in vivo.

ESOPHAGEAL MUCOSAL INJURY AND DUODENAL REFLUX IN ANIMAL STUDIES

Using a dog model, Bremner at al.[6] were the first to demonstrate that columnar epithelial metaplasia in the distal end of the esophagus could result from prolonged gastroesophageal reflux. This finding was confirmed by Gillen et al.,[7] who studied canine esophageal mucosa under basal conditions and in the presence of gastroesophageal reflux. Under normal conditions, mucosal defects in the esophagus are regenerated by squamous epithelium. In the presence of gastroesophageal reflux of acid or a combination of acid and bile, the mucosa is frequently regenerated by columnar epithelium.[8]

Lillimoe et al.[9] have shown that the reflux of bile and pancreatic enzymes into the stomach can protect or augment esophageal mucosal injury. In a rabbit whose gastric acid secretion maintains an acid environment, the presence of bile salts would attenuate the injurious effect of pepsin, and the acid gastric environment would inactivate trypsin. Such a rabbit would have bile-containing acid gastric juice that when refluxed into the esophagus would injure the mucosal barrier and the epithelium but would be less caustic than the reflux of acid gastric juice alone. In contrast, in a rabbit with significant duodenogastric reflux, a more alkaline intragastric pH environment may be present and encourage the solubility of bile salts.

This finding was supported in a study by Ireland et al.,[10] who manipulated rats so that the esophagus was exposed to reflux of gastric juice, duodenal juice, or a combination of both. In this rat model, the presence of gastric juice protected against the development of esophageal adenocarcinoma. The absence of gastric juice resulted in a threefold increase in the prevalence of adenocarcinoma. The protective effect of the stomach seems to be related to the secretion of acid because there was a progressive increase in the prevalence of esophageal adenocarcinoma as the amount of gastric acid that was permitted to reflux with duodenal juice into the esophagus was reduced. A recent study by Theisen et al.[11] using a similar rat model provided preliminary evidence of the mutagenic potential of bile reflux on esophageal epithelium. In rats suffering from duodenogastroesophageal reflux, specific mutations (*lacI* mutations) were markedly more frequent than would be expected and were similar to those found in the p53 mutations of human esophageal adenocarcinoma, thus providing a link to human esophageal cancer.

ESOPHAGEAL MUCOSAL INJURY AND DUODENAL REFLUX IN HUMAN STUDIES

Ambulatory 24-hour esophageal pH monitoring has become the gold standard for the diagnosis of gastroesophageal reflux disease.[12] In addition to significantly

increased acid exposure, patients who suffer from gastroesophageal reflux disease can also have increased esophageal exposure to duodenal juice, especially when Barrett's esophagus is present on endoscopy and biopsy. On pH monitoring, this may be indicated by the time that the pH is greater than 7.[1,13] The alkaline component of the refluxed juice seems to result from contamination of the refluxed gastric contents with excessive duodenogastric refluxate.[14] Measurement of esophageal exposure to duodenal contents is, however, less dependable than measurement of esophageal acid exposure.[15]

A fiberoptic system (Bilitec) for circadian monitoring of duodenogastroesophageal reflux was proposed by Bechi et al.,[16] who used bilirubin as another indirect marker for reflux of duodenal juice. Major advantages of the system are that it allows prolonged simultaneous measurements at multiple sites in the foregut on an ambulatory basis and can be combined with pH monitoring. With the Bilitec system, it has been shown that patients who have reflux of acid gastric juice alone have less severe esophageal mucosal injury than do patients who have reflux of gastric juice contaminated with duodenal components.[17-19] Furthermore, reflux of duodenal juice into the esophagus is significantly more common in patients who have Barrett's esophagus than in patients who have erosive esophagitis or those with reflux who have no mucosal injury. In addition, the mean percentage of time that the esophagus is exposed to duodenal juice is markedly increased in patients who have Barrett's esophagus and is highest in the group of patients with high-grade dysplasia or early carcinoma in Barrett's esophagus.[17] Analysis of the circadian pattern of esophageal bilirubin exposure showed that bile reflux occurs primarily during the postprandial and supine periods.[17-19]

Simultaneous esophageal pH and bilirubin monitoring confirmed that esophageal exposure to duodenal juice occurs at all pH values.[20] In patients with gastroesophageal reflux, the presence of duodenal content within the esophagus could be demonstrated more than 15% of the time when the pH was less than 4, 19% of the time when the pH was between 4 and 7, and 6% of the time when the pH was higher than 7. Analysis of the cumulative period during which the esophagus was exposed to duodenal juice showed that the pH of the esophagus was between 4 and 7 more than 87% of the time. This pH is considered normal for the esophagus, and consequently such reflux goes undetected and unappreciated when analyzed by traditional pH criteria.

Only a few studies have measured reflux of duodenal juice into the esophagus directly. Via prolonged ambulatory aspiration in the distal end of the esophagus, it could be shown that patients who have reflux esophagitis and Barrett's esophagus have greater and more concentrated bile acid exposure to the esophageal mucosa than do normal subjects and reflux patients without mucosal injury.[13,18,20] This increased exposure occurs most commonly during the supine period while asleep and during the upright period after meals. Aspiration studies also delivered more details on the noxious effects of specific bile salts. Glycine conjugates of cholic, deoxycholic, and chenodeoxycholic acid have been identified as the predominant bile acids aspirated from the esophagus of patients with gastroesophageal reflux disease. This predominance is, as would be expected, due to the fact that glycine conjugates are three times more prevalent than taurine conjugates in normal human bile.

MECHANISM OF BILE ACID INJURY TO ESOPHAGEAL MUCOSA

In humans, a normal liver converts a daily average of 0.78 to 1.29 mmol of cholesterol into bile acids.[21-23] These primary bile acids, cholate and chenodeoxycholate, are synthesized from cholesterol by hepatocytes. Secondary bile acids, including deoxycholic and lithocholic acid, are formed as metabolic by-products of intestinal bacteria. Before secretion into the biliary tract, 98% of the bile acids are conjugated with taurine or glycine at a ratio of 3 : 1. Conjugation, especially with taurine, increases the solubility of bile acids by lowering their pK_a. Soluble bile acids can enter mucosal cells when they are in their nonionized lipophilic form, specifically, at a pH between 2 and 5 for the conjugated bile acids. Because intracellular ionization results in entrapment, bile acids accumulate within intestinal cells. In vivo studies have shown that accumulation of bile acid in mucosal cells is driven by the pH gradient between the acidic lumen and the neutral cytosol; that is, intracellular accumulation is higher and occurs faster at a more acidic pH. The intracellular bile acid concentration can reach levels as high as eight times the luminal concentration.[24,25] Such excessive intracellular concentrations of bile acids result in increased mucosal permeability by dissolution of cell membranes and tight junctions and, eventually, cell death. This effect is related not only to the concentration of luminal bile acids but also to the time that the mucosa is exposed to bile acids. Depending on their conjugation status, bile acids, however, also precipitate irreversibly at an acidic pH. Precipitation occurs at a pH below 3 to 4 for unconjugated bile acids, whereas conjugated bile acids precipitate only at a pH below 1.5.[24] Because precipitated bile acids are innocuous, bile reflux into the stomach with an intact acid secretory capacity (i.e., a pH of about 1.2) does not cause any mucosal injury. At a pH between 2 and 4, conjugated bile acids are, however, both soluble and in an ionized form; that is, they are able to enter and accumulate in intestinal cells. Thus, the potentially injurious effect of bile reflux is not only related to the concentration of bile acids but also dependent on the pH.[26]

Recent studies have confirmed significant effects of bile acids on cellular physiology. Bile salts have been shown to activate protein kinase C and nuclear transcription factors.[27,28] Nuclear receptors for bile acids have been identified.[29] Parks et al. have shown that physiologic concentrations of free and conjugated chenodeoxycholic acid, lithocholic acid, and deoxycholic acid activate the farnesoid X receptor, a heretofore orphan nuclear receptor.[29] This provides evidence that bile acids may modulate nuclear activity. These findings, in concert with the strong link between gastroesophageal reflux and

esophageal adenocarcinoma, suggest that bile salts may play a role in the pathogenesis of esophageal adenocarcinoma.[30]

Cyclooxygenase-2 (COX-2) has been shown to be involved in chronic inflammation and epithelial cell growth. The role of COX-2 in various stages of Barrett's esophageal metaplasia and in response to pulses of acid and bile salts in an ex vivo organ culture system was investigated by Shirvani and co-workers.[31] There was a progressive increase in expression of COX-2 with disease progression from Barrett's metaplasia to dysplasia and adenocarcinoma. This increase indicates that COX-2 overexpression is an early event in the neoplastic transformation process of Barrett's columnar metaplasia. Even more interesting, these studies showed that bile and acid could induce COX-2 expression in ex vivo human epithelial explants because COX-2 induction was increased significantly in the presence of acid and bile. The highest induction could be found when the explants were exposed to a 1-hour pulse of bile salts, which in part could be related to protein kinase C activation by bile salts.[32] Similar results were reported by Kawabe et al.,[33] who suggested that duodenogastroesophageal reflux may induce COX-2 expression and prostaglandin E_2 production in esophageal epithelial cells and that COX-2–specific inhibitors may have a chemopreventive effect on esophageal carcinoma.

Thus, bile reflux into the esophagus may be linked to the development of adenocarcinoma arising in Barrett's esophagus.[34] The exact mechanism by which reflux of duodenal juice induces foregut cancer is unclear at the present time. Bile salts alone do not seem to be mutagenic, but they promote the mutagenicity of aromatic amines. Alternatively, bile acids and pancreatic enzymes may also facilitate the action of other endoluminal carcinogenic agents by disruption of the mucosal barrier and exposure of the proliferative epithelial compartment.[18]

SUMMARY

Gastric and bile acids are a particularly noxious combination when they interact with the mucosa of the esophagus. There is a critical pH range between 3 and 6 in which bile acids exist in their soluble, unionized form and can penetrate cell membranes and accumulate within mucosal cells. At a lower pH, bile acids are precipitated, and, at a higher pH, bile acids exist in their noninjurious, ionized form. Experimental and clinical studies have shown that increased esophageal exposure to bile in conjunction with acid predisposes to severe esophageal mucosal injury and is the key factor in the pathogenesis and malignant degeneration of Barrett's esophagus.

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Chapter

16

Reflux Strictures and Short Esophagus

Allan Pickens · Mark B. Orringer

It has been estimated that 60% to 70% of all benign esophageal strictures in the United States are the consequence of reflux esophagitis.[1] Esophageal reflux strictures result from the inflammatory reaction that is induced in the esophagus by exposure to regurgitated gastric contents, both acid and alkaline.[2] It is unknown why strictures develop in certain patients with gastroesophageal reflux (GER). GER occurs independently of the presence or size of a hiatal hernia. Incompetence of the lower esophageal sphincter (LES) is the critical pathologic lesion. Reflux of gastric contents across the LES causes ulceration, submucosal edema, and inflammatory cell infiltration. Acute reflux esophagitis occurs in cycles and progresses to transmural fibrous infiltration. The inflammation may involve the muscular layers of the esophagus, as well as periesophageal soft tissues. Surrounding mediastinal edema and lymphadenopathy may be present. With healing, varying degrees of fibrosis occur. Contraction of collagen within the esophageal scar produces both circumferential narrowing and esophageal shortening.

Controversy regarding the concept of the "short esophagus" has existed for many years. Tileston reported patients with ulcerative reflux esophagitis and described associated esophageal stenosis.[3] As the term "reflux esophagitis" was popularized as a distinct clinical entity by Allison[4] and Barrett,[5] the occurrence of columnar epithelium distal to the stenosis in many of these patients began to be recognized. Although he was a pioneer in his efforts to define reflux esophagitis, Barrett unfortunately concluded that any portion of the swallowing passage that is lined by columnar epithelium is stomach.[5] Thus, the term "short esophagus" was coined because the columnar-lined esophagus distal to the stricture was regarded as stomach. With time, it became apparent that columnar lining of the lower part of the esophagus is an acquired lesion that results from reflux esophagitis.[6,7] Development of the techniques of esophageal manometry confirmed a definite, yet weak LES at the anatomic esophagogastric junction in patients with a columnar-lined lower esophagus. As a result, some investigators have disputed the very existence of a short esophagus and argue that the esophagogastric junction can always be reduced below the diaphragmatic hiatus for an antireflux operation.[8] Such thinking contradicts the preponderance of evidence from pathologic specimens, data from animal models, and the known response of tissue to burns. This is not the viewpoint of most esophageal surgeons, who recognize that fibrous contracture may occur in the esophagus just as it does at other sites in the body in response to a burn. Furthermore, it is apparent that acquired esophageal shortening in response to GER may occur even in patients who do not have esophageal fibrosis or stricture formation. Therefore, the term short esophagus can be applied appropriately to any patient who has an unacceptable degree of stretch of the distal esophagus once the esophagogastric junction is reduced below the diaphragm. This type of short esophagus may be found in association with hiatal hernia, Barrett's metaplasia, caustic ingestion, scleroderma, and Crohn's disease. It is reported that a shortened esophagus occurs in 10% to 15% of patients who undergo antireflux surgery.[9] Because the majority of antireflux operations are performed transabdominally, assessment of tension on the distal esophagus at completion of the repair is seldom possible. Furthermore, the elevation of the diaphragm caused by the pneumoperitoneum required for laparoscopy makes transabdominal assessment of esophageal tension less accurate. Consequently, esophageal shortening is grossly underestimated. Failure to recognize a short esophagus is thought to be responsible for 20% to 30% of surgical failures after open or laparoscopic fundoplication.[10] Reflux strictures and short esophagus have immediate and long-term implications for the success of antireflux operations.

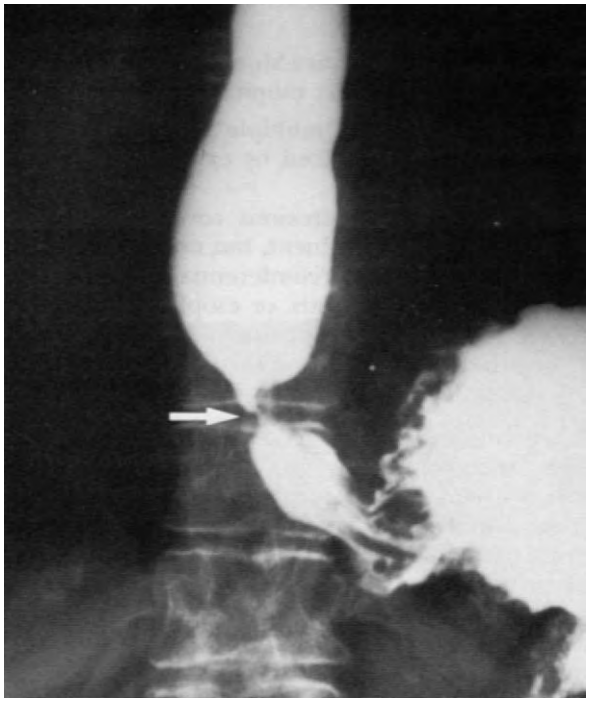

Figure 16–1. Barium esophagogram demonstrating the most frequent type of esophageal reflux stricture: a short stenosis *(arrow)* less than 2 cm occurring at the esophagogastric junction just proximal to a sliding hiatal hernia. (From Orringer MB: Short esophagus and peptic stricture. In Sabiston DC Jr, Spencer FC [eds]: Surgery of the Chest, 6th ed. Philadelphia, WB Saunders, 1995, p 1059.)

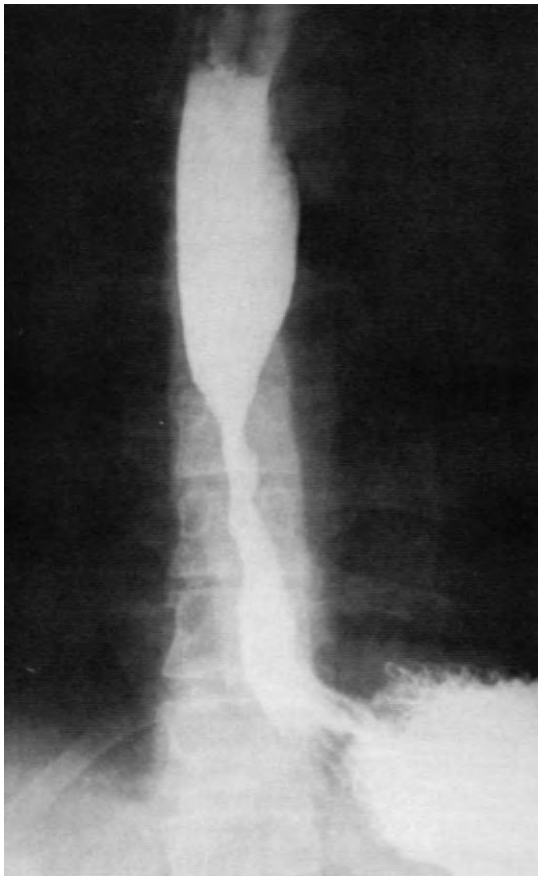

Figure 16–2. Barium esophagogram demonstrating an 8-cm-long esophageal reflux stricture that occurred after protracted vomiting. There is an associated sliding hiatal hernia. (From Orringer MB: Short esophagus and peptic stricture. In Sabiston DC Jr, Spencer FC [eds]: Surgery of the Chest, 6th ed. Philadelphia, WB Saunders, 1995, p 1060.)

ANATOMIC VARIATION AND EVALUATION

Esophageal reflux strictures occur in three general varieties. Most reflux strictures are 1 to 2 cm in length and are localized to the anatomic esophagogastric junction (Fig. 16–1). Less frequently, long strictures occur in the distal half or third of the esophagus in critically ill supine patients with nasogastric tubes (Fig. 16–2). Finally, short strictures form in the mid or upper thoracic esophagus at the squamocolumnar epithelial junction in patients with Barrett's esophagus (Fig. 16–3). The presence of a benign mid- or upper-esophageal stricture in a patient with GER should always alert the physician to the possibility of Barrett's esophagus. The stricture characteristically occurs at the squamocolumnar epithelial junction, and a sliding hiatal hernia is usually, but not always present.

The presence of an esophageal reflux stricture is typically diagnosed by means of a barium esophagogram obtained in a patient who has dysphagia or reflux symptoms. There is debate regarding whether barium esophagography should be performed early in the evaluation of such esophageal symptoms or whether one should proceed directly to endoscopic evaluation. Endoscopy may be both diagnostic and therapeutic, but the barium esophagogram provides valuable anatomic information about the esophagus that may help direct therapy and prevent endoscopic complications. The barium esophagogram provides information regarding the length, extent, and degree of narrowing of the stricture, which may be helpful in choosing the best method of dilatation. The barium esophagogram also appears to be more sensitive than endoscopy for the detection of subtle narrowing of the esophagus that is less than 10 mm in diameter.[11] Finally, the barium esophagogram provides an objective baseline record of the esophagus that can be used to assess the response to therapy or progression of disease.

Although it would obviously be desirable to treat GER before mural fibrosis occurs, early diagnosis of reflux esophagitis is hampered by the curious nature of this disease. A notoriously poor correlation between symptoms and the degree of esophagitis prevents physicians from relying on patient complaints as the primary indicator of the need for evaluation. The barium esophagogram provides no real information about the likelihood of successful stricture dilatation. The narrowing seen on a barium esophagogram in a patient with a

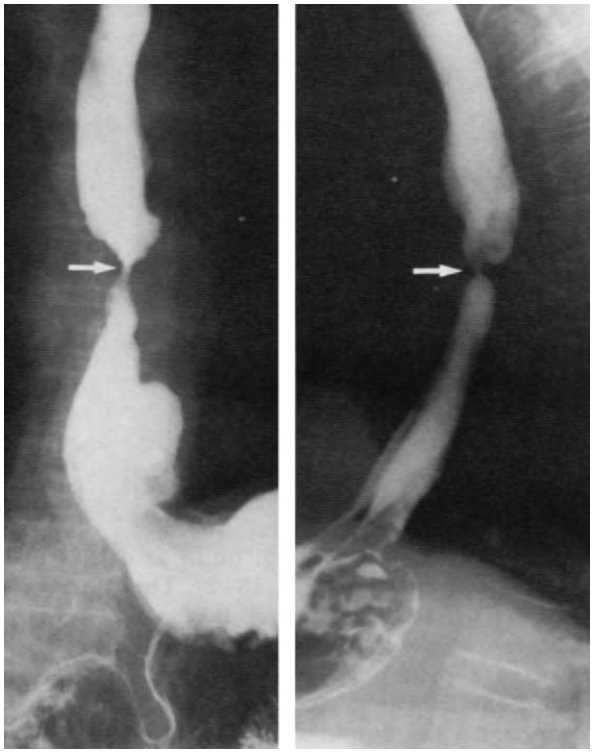

Figure 16–3. Posteroanterior *(left)* and lateral *(right)* views from an esophagogram demonstrating a short midesophageal stricture *(arrows)* in a patient with chronic reflux symptoms and dysphagia. This "high" stricture suggested Barrett's esophagus.

reflux stricture has two components: (1) edema and the cellular inflammatory reaction of acute reflux esophagitis and (2) varying degrees of fibrosis caused by previous reflux episodes. The ease with which progressively larger esophageal dilators can be passed through the radiographic narrowing (i.e., the "hardness" of the stricture) cannot be predicted from an esophagogram.

Endoscopic evaluation is recommended for most patients with dysphagia to establish a diagnosis, seek evidence of esophagitis, exclude malignancy, and implement appropriate therapy. Technologic advances in endoscopic optics and instruments have made the flexible esophagoscope the most common means of visualizing the esophageal lumen. Adequate esophageal biopsy and brushings for cytologic evaluation of the stricture should be performed at the initial endoscopic assessment of the stricture. The combination of esophageal biopsy and brushing establishes the diagnosis of carcinoma in more than 95% of patients with a malignant stricture. If there is no evidence of neoplasm with either of these studies, it is highly likely that the esophageal stenosis is benign.

A variety of classifications of esophageal inflammation have been proposed. Esophagitis is an endoscopic diagnosis, and several established classifications of reflux esophagitis may be applied to strictures. Skinner and Belsey[12] proposed four grades of esophagitis:

- Grade I: distal esophageal mucosal erythema (which may obscure the esophagogastric squamocolumnar epithelial junction)
- Grade II: mucosal erythema with superficial ulceration, typically linear and vertical and with an overlying fibrinous membranous exudate that is easily wiped away to leave a bleeding surface (which is often misinterpreted as "scope trauma" by an inexperienced endoscopist)
- Grade III: mucosal erythema with superficial ulceration and associated mural fibrosis—a dilatable "early" stricture
- Grade IV: extensive ulcerative and fibrous luminal stenosis, which may represent irreversible panmural fibrosis

In the Savary-Monnier classification,[13] there are five grades of reflux esophagitis:

- Grade 1: single or multiple erosions (may be erythematous or covered by exudates) on a single mucosal fold
- Grade 2: multiple erosions covering several mucosal folds (may be confluent, but not circumferential)
- Grade 3: multiple circumferential erosions
- Grade 4: ulcer, stenosis, or esophageal shortening
- Grade 5: Barrett's epithelium (columnar mucosa reepithelialization in the form of an island or strip or circumferential)

The Los Angeles classification of reflux esophagitis[14] similarly has five grades of esophagitis:

- Grade 0: normal mucosa
- Grade A: single erosion 5 mm or smaller on top of a fold
- Grade B: single erosion greater than 5 mm on top of a fold
- Grade C: confluent erosions 75% or less of the circumference
- Grade D: confluent erosions greater than 75% of the circumference

Regardless of which endoscopic grading system is used, such objectivity in describing the pathologic changes seen endoscopically is preferable to the traditional designations of "mild," "moderate," or "severe" esophagitis, which have inherent wide variation and observer variability.

In addition to endoscopic grading of esophagitis, there is a need to classify reflux strictures according to the degree of resistance encountered during attempts at dilatation. The "hardness" of a reflux stricture reflects the degree of fibrosis present and has direct implications for successful treatment with conservative measures. The severity of a stricture can be classified on the basis of the degree of resistance encountered during dilatation. A *mild* stricture is defined as one in which minimal resistance is encountered as progressively larger dilators are passed through the stenosis. A *moderate* stricture requires some, but not excessive forceful dilatation. A *severe* stricture requires forceful dilatation and is inevitably associated with marked periesophageal inflammation

and mural thickening of the esophagus. Determination of the severity of a reflux stricture may not be possible with the flexible esophagoscope. Rigid esophagoscopy still has its place in the esophageal surgeon's armamentarium because it allows larger biopsy specimens to be harvested and permits direct assessment of stricture length and the degree of stenosis by direct gentle probing with a bougie. With a more severe stricture, it is dangerous to advance either the flexible or rigid esophagoscope. After the initial assessment and biopsy to exclude carcinoma, treatment of the esophageal reflux stenosis is addressed.

Preoperative assessment of the presence of a short esophagus is notoriously difficult. In a retrospective analysis of the preoperative predictability of a short esophagus in patients with stricture and paraesophageal hernia, an esophagogram had a sensitivity of 66% and a positive predictive value of 37%, whereas manometric length had a sensitivity of 43% and a positive predictive value of 25%.[15] Neither esophagography nor manometry was a reliable predictor of a short esophagus. Esophageal length is best evaluated in the operating room. It is helpful to think of a short esophagus as falling into two categories: (1) a truly nonreducible short esophagus in which the esophagogastric junction fails to reduce beneath the diaphragm and (2) a relatively short esophagus in which the esophagogastric junction fails to reduce beneath the diaphragm without undue tension. Perioperative endoscopic and radiologic studies document that both groups have an esophagogastric junction located at or above the hiatus. Both the truly nonreducible esophagus and the relatively short esophagus have sustained enough chronic damage to lead to actual intrinsic shortening. Some patients may have an apparently short esophagus that has a normal length accordioned into the mediastinum. The only absolute way to document esophageal shortening is direct assessment of the degree of tension remaining on the distal end of the esophagus after positioning of the esophagogastric junction below the diaphragm at the time of surgery.

TREATMENT

Nonoperative Management

Adequate treatment of esophagitis is critical to the prevention and management of esophageal stricture. Preventive treatment of esophageal reflux strictures is hampered by the fact that many patients remain relatively asymptomatic as their esophageal inflammation progresses through the initial pathologic and endoscopic stages of reflux esophagitis. In the era before proton pump inhibitors (PPIs), peptic strictures were widely regarded as fixed, fibrotic lesions that would respond only to dilatation or resection. Antireflux therapy was used to control symptoms of esophagitis and prevent progression of the stricture, but there was little expectation that elimination of reflux esophagitis would widen the established stenosis. Clinical trials comparing treatment with histamine receptor antagonists and placebo in patients with peptic esophageal strictures supported this view.[16,17] These studies showed a significant decrease in reflux esophagitis in patients treated with histamine blockers, but no reduction in the need for stricture dilatation. It has been demonstrated that chronic, aggressive acid-suppression therapy with PPIs both improves dysphagia and decreases the need for subsequent esophageal dilatation.[18,19] In a study of 366 patients with peptic esophageal strictures who were randomly assigned to receive medical therapy with either omeprazole (20 mg daily) or ranitidine (150 mg twice daily) for 1 year after baseline stricture dilatation, repeat dilatation was required in 30% of patients in the omeprazole group versus 46% in the ranitidine group.[20]

The degree of esophagitis is believed to be as important as stricture diameter in causing dysphagia, and the esophagitis can be controlled with medical management. A good antireflux medical regimen includes compliant PPI use, true elevation of the head of the bed at night, regular use of antacids after meals, and refraining from eating for several hours before bedtime. Additional medications may be added as needed to help control reflux. Metoclopramide has been used because it enhances distal esophageal sphincter tone, increases gastric emptying, and relaxes the pyloric sphincter.[21] Sucralfate (aluminum sucrose sulfate) is used primarily in the intensive care setting to form a viscous fluid that binds protein exudates in areas of inflammation to function as a cytoprotective layer. For patients who remain symptomatic despite medical management, 24-hour esophageal pH monitoring can be used to document the adequacy of therapy in controlling acid reflux.

In addition to aggressive antireflux therapy, patients with benign esophageal strictures are usually treated with at least an initial dilatation. Up to 60% of patients require subsequent dilatation.[22] Many patients accept outpatient esophageal dilatation several times per year as a relatively minor price to pay for comfortable swallowing.

Some peptic strictures can be dilated initially with the flexible esophagoscope. The standard adult flexible esophagoscope is the size of a 32-French esophageal dilator, and a mild stricture can be dilated directly by advancing the instrument through the narrowing. Subsequently, blind passage of progressively larger tapered dilators is performed, beginning with a 32-French size and advancing to at least a 46-French size.

Four major types of esophageal dilating devices are commonly used: (1) mercury- or fiber-filled bougies that are passed blindly through the mouth (e.g., tapered Maloney dilators [Fig. 16–4] and blunt Hurst dilators); (2) gum-tipped dilators that are passed through the standard rigid esophagoscope (e.g., Jackson dilators [Fig. 16–5]); (3) polyvinyl bougies passed over a guidewire that is positioned within the stricture under endoscopic or fluoroscopic guidance (e.g., Savary dilators [Fig. 16–6]); and (4) balloon dilators that are passed over a guidewire or through the endoscope (e.g., TTS balloons). Esophageal dilators are sized by using the French gauge system, in which 1 French equals 3 mm (e.g., a 50-French dilator has a 1.5-cm diameter). Restoration of comfortable swallowing generally requires that at least a 46-French dilator be passed through the

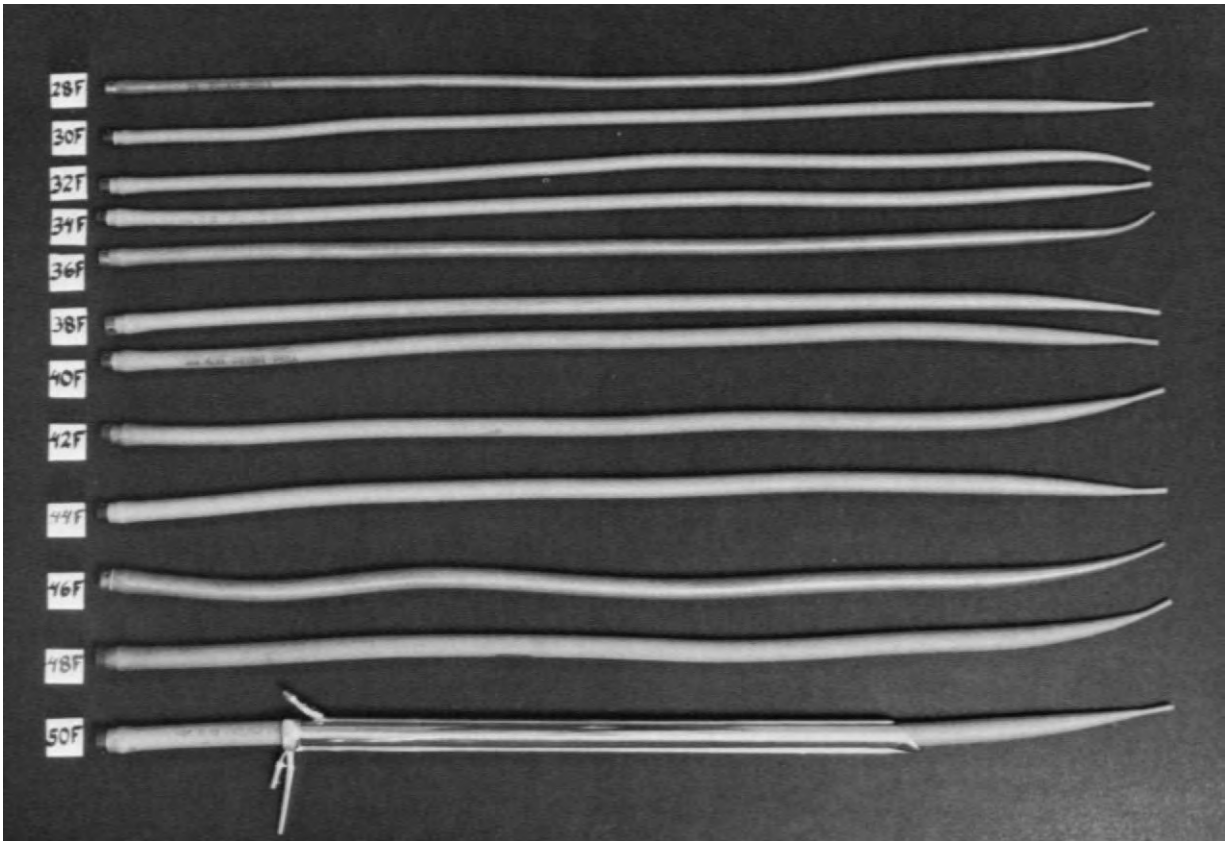

Figure 16–4. Tapered Maloney esophageal dilators and Pilling 45-cm esophagoscope used to dilate dense, severe reflux strictures under direct vision.

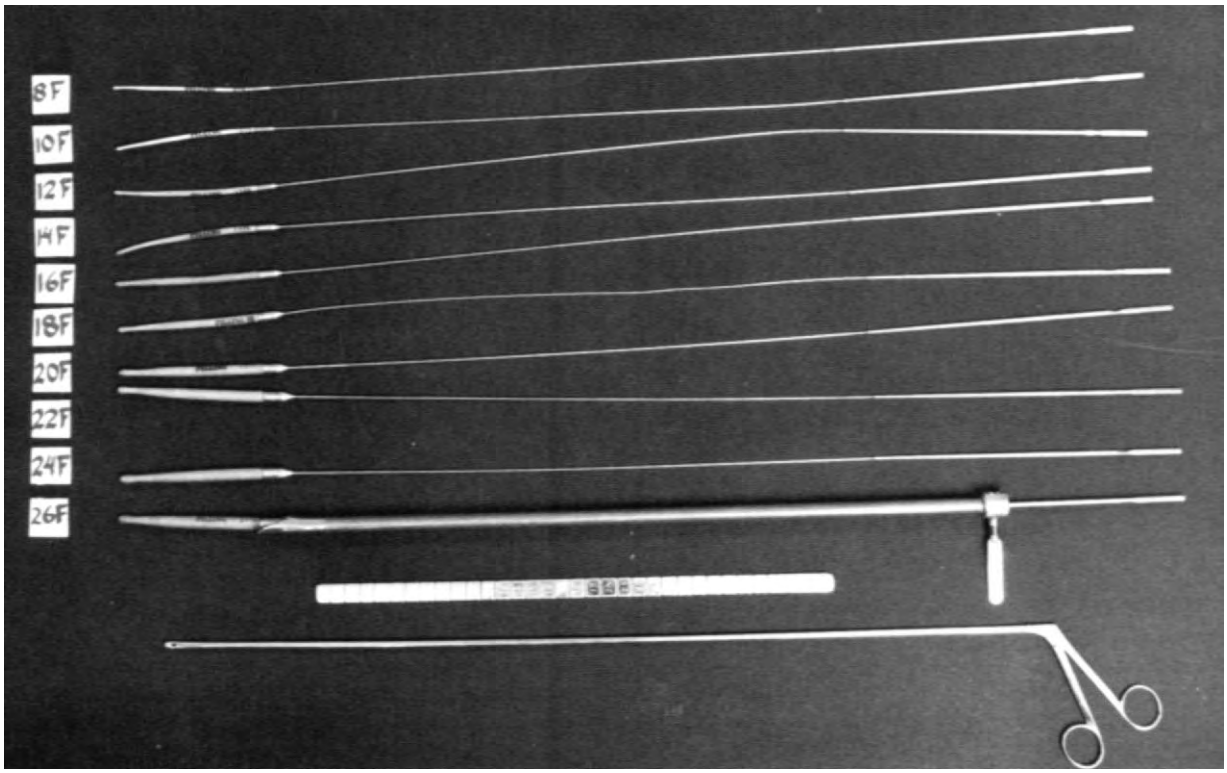

Figure 16–5. Gum-tipped Jackson dilators that can be gently manipulated through a stricture to assess length and pliability of the obstruction. The 26 French is the largest dilator that will pass through a standard 45-cm rigid esophagoscope.

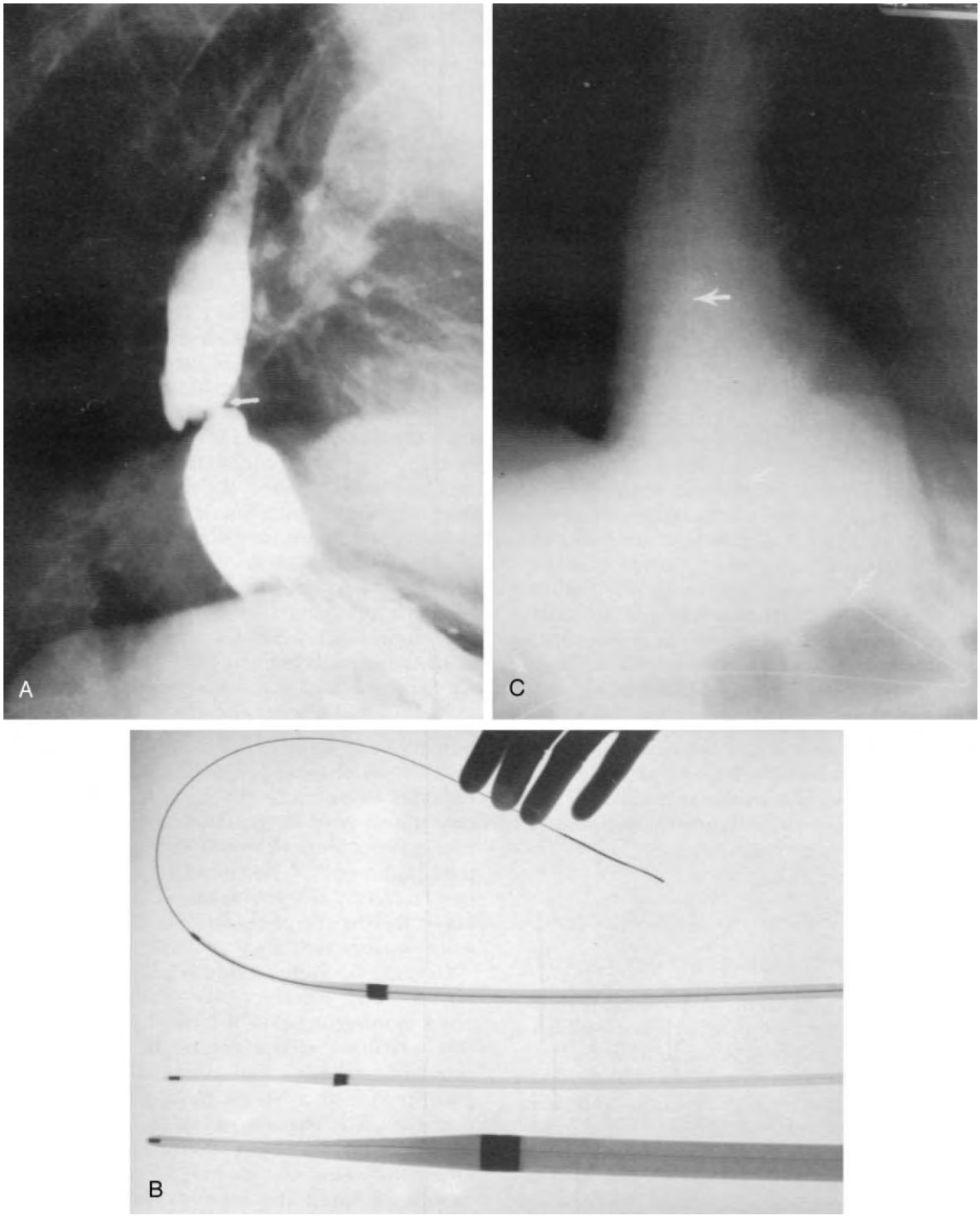

Figure 16–6. **A,** Esophagogram showing an eccentric complex reflux stricture *(arrow)* at the esophagogastric junction proximal to a large sliding hiatal hernia. Because of the diverticulum-like configuration of the lumen in the region of the stricture, blind passage of a Maloney bougie was thought to be unsafe. **B,** Several sizes of polyvinyl Savary-Gillard dilators with a guidewire passed through the upper dilator. **C,** Radiographic confirmation of the proper course of the endoscopically placed Savary guidewire *(arrow)* through the esophageal stenosis and into the stomach (same patient as shown in **A**). Progressively larger Savary dilators up to 54 French were passed over the wire and through the stricture. Blind passage of Maloney dilators on an outpatient basis was then achieved without difficulty. (From Orringer MB: Short esophagus and peptic stricture. In Sabiston DC Jr, Spencer FC [eds]: Surgery of the Chest, 6th ed. Philadelphia, WB Saunders, 1995, p 1060.)

esophageal stricture; a larger size is preferable if it can be passed safely.

When dilating a stricture with bougies, the initial choice of dilator size is based on estimates from a barium esophagogram or endoscopic examination. A more physiologic approach to estimation of stricture diameter involves having the patient swallow barium spheres of known diameter, but this is seldom used in clinical practice and has not been found to improve dilatation results. The historic "rule of threes" is a clinical maxim that states that no more than three bougies of progressively increasing size should be passed at any one dilatation session to minimize the risk for esophageal perforation and hemorrhage.[23] Although this rule seems reasonable as a clinical guideline, no studies have verified that adherence to the rule improves dilatation efficacy or safety.[22] Furthermore, balloon dilatation routinely dilates strictures in one session to a diameter far greater than that achieved with three sequential bougies. Balloons are designed to burst if a certain pressure is exceeded during dilatation, but it is not clear that the burst pressure is less than that required to rupture a diseased esophagus. If one elects to dilate a stricture with tapered mercury-filled dilators rather than balloons, it seems a reasonable concession to the unvalidated rule of threes to pass bougies of progressively increasing diameter until resistance is first encountered and to pass no more than two subsequent bougies in the same session.[22] This may not be a reasonable approach when using polyvinyl (e.g., Savary) dilators passed over a guidewire because these dilators may not provide the operator with a meaningful tactile impression of stricture resistance. With polyvinyl dilators, the resistance to passage perceived by the operator may be more a function of friction produced by the guidewire than resistance created by the esophageal stenosis. In reality, there is no perfect predictor of impending complication from esophageal dilatation.

Mercury-filled bougies, or the fiber-filled bougies that have replaced them, are the dilator of choice for esophageal strictures with diameters larger than 10 to 12 mm.[24,25] These dilators are passed without a guidewire and frequently without fluoroscopic assistance. In addition, they can often be passed with minimal or no sedation. In fact, some patients can perform self-dilatation after proper instruction. The flexibility of fiber-filled dilators that contributes to their safety becomes a disadvantage when dilating complicated strictures that are long, tight, or tortuous. Fiber-filled dilators with diameters smaller than 10 mm (30 French) are so floppy that they may curl in the esophagus proximal to a tight stricture, thereby increasing the risk for perforation (Fig. 16–7). Complex strictures can be dilated under general anesthesia through a rigid esophagoscope with gum-tipped bougies that are passed through the stenosis under direct vision. Most standard rigid esophagoscopes will accommodate up to a 26-French bougie in this manner. After reaching this size, the rigid esophagoscope is removed and the dilatation is often continued blindly by passing a mercury-filled tapered dilator. Alternatively, a special-order rigid esophagoscope that accommodates up to a 50-French dilator may be passed to allow progressive dilatation of the stricture under direct vision. With the decreasing popularity of rigid esophagoscopy, a Savary guidewire is passed through the flexible esophagoscope and across the stricture into the stomach. After removing the esophagoscope, progressively larger tapered Savary dilators are passed over the guidewire until there is an adequate lumen to permit endoscopic assessment along with biopsy and cytologic brushings. Alternatively, balloon dilatation over a guidewire or under endoscopic guidance has been shown to be effective.[26] Balloon dilators deliver only radial force, in contrast to pushed bougies, which deliver axial shear force as well as radial dilating force to the stricture. Despite the reported advantages of the isolated radial dilating force of the balloon, no studies have convincingly demonstrated that any dilator is superior.

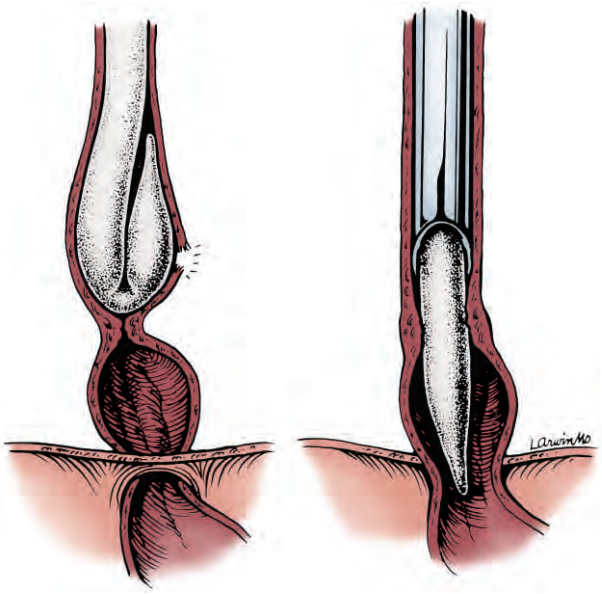

Figure 16–7. *Left,* Esophageal perforation caused by "curling" of an esophageal dilator passed blindly in an attempt to dilate a tight stricture. *Right,* A special-order, large rigid esophagoscope accommodates up to a 50-French dilator and permits dilatation of the stricture. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 310.)

The major complications of esophageal dilatation are perforation and bleeding. These two complications occur with approximately equal frequency. An American Society for Gastrointestinal Endoscopy survey found an average rate of perforation and bleeding of 0.2% with mercury-filled bougies and 2.5% with balloon dilatation.[27,28] The complication rate is highest with dilatation performed for strictures that are complex (i.e., long, tight, or tortuous). Endoscopic interventions such as a heater probe and injection can control most bleeding, but a contrast study is recommended if perforation is suspected. Although water-soluble contrast (e.g., diatrizoate

meglumine [Gastrografin]) is commonly recommended for this study, such hypertonic agents can cause chemical pneumonitis if they are aspirated into the lungs. Consequently, these agents should not be used in sedated patients who have recently undergone an endoscopic procedure. Most patients experience pain and possibly pneumomediastinum after perforation. Dilute barium is recommended as the contrast agent of choice because it does not cause chemical pneumonitis and identifies small perforations with greater sensitivity. Perforations after stricture dilatation can be observed if contained or primarily repaired if not contained.

Stricture recurrence is common after initial dilatation. Neither the severity of the initial stenosis, the dilatation method, nor dilator size appears to have a major influence on the likelihood of stricture recurrence. Before PPIs became available, approximately 60% of patients would require multiple dilatations.[29,30] With PPI therapy, as few as 30% of patients may require repeat dilatation within 1 year.[19] There are reports that intralesional corticosteroid injection decreases the recurrence of refractory benign strictures and the need for subsequent endoscopic dilatation, but the exact mechanism is unknown.[31] It has been suggested that intralesional corticosteroids inhibit collagen synthesis and fibrosis, thereby reducing stricture severity. Self-expanding metal stents have also been used as an alternative treatment of refractory strictures.[32] The long-term potential consequences of such a foreign body in the esophagus are worrisome. Laser therapy has also been used for the treatment of refractory benign strictures.[33] This approach has not received widespread acceptance because of inability to assess the depth of penetration of the laser beam. Despite advances in technology, there is no reliable method to predict or totally eliminate the need for future dilatation of benign strictures. Dysphagia serves as the primary indicator of the need for additional treatment.

A patient who has a reflux stricture associated with Barrett's mucosa without endoscopic ulceration or histologic atypia may be treated effectively with a complete antireflux medical regimen, intermittent dilatation, and endoscopic surveillance at 1- or 2-year intervals to exclude dysplastic or neoplastic changes.

Once the esophageal stricture is dilated, gastric contents can again reflux into the esophagus and produce symptomatic GER. With the availability of highly effective antisecretory medications such as PPIs, concern about exacerbation of reflux symptoms should not be a major factor limiting the extent of dilatation. In fact, it has been suggested that esophageal dilatation in combination with antireflux medical therapy is the treatment of choice for virtually all patients with peptic esophageal strictures.[19] The poor operative results with long-term reflux control in patients treated with standard hiatal hernia repairs (e.g., Belsey, Nissen, or Hill operations) or the technical difficulty of esophageal resection with reconstruction has been used as a strong argument against the operative treatment of reflux strictures. Without question, the availability of PPI therapy has drastically reduced the need for operative intervention in patients with reflux strictures.

Surgical Treatment

Modern surgical advances have altered the traditional operative approach to reflux strictures. There is still a small, but definite population of patients with reflux strictures who are candidates for surgical intervention. These patients are debilitated by intractable reflux symptoms or dysphagia despite aggressive medical therapy and dilatation. There are two general approaches to the surgical treatment of esophageal strictures: (1) antireflux surgery with intraoperative stricture dilatation and (2) esophageal resection and reconstruction. Antireflux surgery combined with intraoperative dilatation produces success rates similar to those reported for nonsurgical dilatation therapy.[34-36] The major advantage is that successful surgery obviates the need for lifelong medical therapy with its attendant expense and inconvenience. However, there is no clear difference in the relief of dysphagia achieved with such surgery versus dilatation and medical therapy. There is a small operative mortality of less than 1% associated with fundoplication. The incidence of repeated dilatation after antireflux surgery for stricture ranges between 1% and 31%, which is still less than that reported for medical therapy and dilatation.[37] A thorough understanding of the "short esophagus" concept and the methods for addressing it is fundamental to obtaining good outcomes and avoiding complications such as "slipped" wraps and gastric herniation into the mediastinum.

Hayward first suggested that most reflux strictures could be treated successfully with operative dilatation in conjunction with an antireflux operation.[38] Hill et al. were the first in the United States to advocate this approach.[8] However, the presence of a peptic stricture with its inevitable esophageal shortening adversely affects long-term reflux control after standard antireflux operations. In a large retrospective review of the Belsey Mark IV operation, there was a 45% incidence of recurrent reflux or hernia in patients with esophagitis and stricture versus an 11% incidence of recurrent reflux or hernia in patients without esophagitis and stricture.[39] Based on these data, Belsey advocated distal esophagectomy and reconstruction with colon rather than a standard hiatal hernia repair in patients with a stricture and shortening. Mural inflammation, esophagitis, and esophageal shortening are characteristic of peptic esophageal strictures and prevent tension-free reduction of the 3 to 5 cm of distal esophagus below the diaphragm, which is a prerequisite for successful fundoplication. In addition, the Belsey repair requires placement of fundoplication sutures between the diaphragm, fundus, and inflamed distal esophagus. Any antireflux operation performed in the presence of mural inflammation or esophageal shortening jeopardizes the long-term success of the repair.

The most popular antireflux operations—the Belsey fundoplication[12] and the Nissen fundoplication[40]—advocate an intra-abdominal location of the gastroesophageal junction and require sutures in the distal end of the esophagus as part of the procedure. Despite the obvious undesirability of attempting to "drag" the esophagogastric junction of a shortened esophagus below the diaphragm, treatment of reflux strictures with a combi-

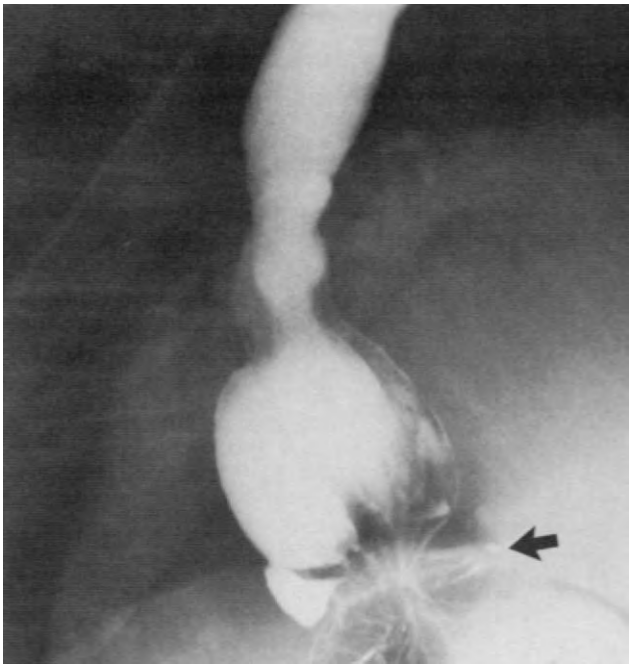

Figure 16–8. Esophagogram demonstrating a "slipped Nissen" fundoplication in an obese woman with esophageal shortening caused by reflux esophagitis. She had undergone an antireflux operation 9 months earlier. After initial control of reflux symptoms, regurgitation, pyrosis, and dysphagia developed. The stomach has "telescoped" through the fundoplication, the horizontal folds of which *(arrow)* can still be seen below the diaphragm. There is a recurrent hiatal hernia, and intermittent obstruction occurs.

nation of dilatation and a standard antireflux procedure has become common. The majority of standard antireflux operations are performed transabdominally, and the ability to assess the degree of esophageal shortening or tension on the distal esophagus after the completed fundoplication is limited. By elevating the diaphragm, the pneumoperitoneum required for laparoscopy further reduces the ability to assess distal esophageal tension. Attempting to pull down a shortened esophagus from an abdominal approach may produce elongation of the proximal part of the stomach, which is then inappropriately identified as the distal esophagus and wrapped by the fundoplication. The resultant "slipped Nissen" seen on subsequent barium esophagography is more a function of an improperly performed initial operation than disruption of the repair. A properly performed fundoplication that encircles the distal end of the esophagus but has been reduced beneath the diaphragm under tension is subject to dehiscence and slippage (Fig. 16–8). Any patient with a failed fundoplication should be evaluated with a barium swallow to delineate herniation and to define the anatomy, as well as upper endoscopy to assess the wrap and locate the esophagogastric junction. If symptoms indicate, an esophageal motility study should be performed to assess esophageal body function, and a 24-hour pH study should be performed to evaluate acid reflux.[10] Reoperative surgery to correct such failure is known to have a higher rate of complications and less favorable long-term results.[41-44]

To circumvent the problem of trying to maintain the fundoplication below the diaphragm in a patient with esophageal shortening, some have advocated leaving the fundoplication within the thorax.[45,46] This approach creates an iatrogenic paraesophageal hiatal hernia with its potential for mechanical complications, including strangulation, perforation, ulceration, and bleeding. Such complications have been reported after intrathoracic fundoplication.[47,48] Although effective reflux control can be achieved whether the fundoplication is intra-abdominal or intrathoracic, there are obvious advantages when the reconstructed esophagogastric junction is intra-abdominal.

Combined Collis-Belsey Procedure

In 1971, Pearson and associates reported excellent reflux control in patients with strictures treated with the combination of esophagus-lengthening Collis gastroplasty[49] and Belsey repair.[50] The rationale for this approach followed the conclusions of the long-term Belsey study[39]: in a patient with a reflux stricture undergoing fundoplication, it should be possible to minimize recurrent reflux if additional distal esophageal length is made available, thereby minimizing tension on the repair and avoiding the need to suture the diseased esophagus. The combined Collis-Belsey operation is a transthoracic procedure performed through the sixth intercostal space (Fig. 16–9). After mobilizing the distal esophagus, the gastric fundus is delivered into the chest through the diaphragmatic hiatus. This involves routine ligation and division of several short gastric vessels along the high greater curvature of the stomach. With the surgeon's hand supporting the esophagogastric junction to reduce the risk for disruption, the anesthetist passes progressively larger Maloney tapered dilators per os, up to the 54- to 56-French range. With the dilator displaced against the lesser curvature of the stomach and the fundus retracted upward, the GIA stapler is applied to the stomach adjacent to the dilator and parallel to the lesser curvature. Use of the GIA stapler for construction of the gastroplasty tube keeps the operation closed. Advancement of the knife assembly creates a 5-cm-long tube extension of the esophagus. On rare occasion it may be necessary to apply the stapler a second time to gain an additional 2 to 3 cm of esophageal length. The staple line is oversewn, the dilator is removed, and the standard crural sutures are placed but left untied. A standard Belsey repair around the new distal esophagus (i.e., the gastroplasty tube) was recommended by Pearson and associates[51] (Fig. 16–10). After placing and tying two rows of three horizontal mattress sutures to secure the stomach below the diaphragm, the posterior crural sutures are tied. This creates a tension-free segment of intra-abdominal "esophagus" compressed by the partial fundoplication. The fundoplication sutures are placed into the healthy gastroplasty tube instead of the inflamed distal esophagus.

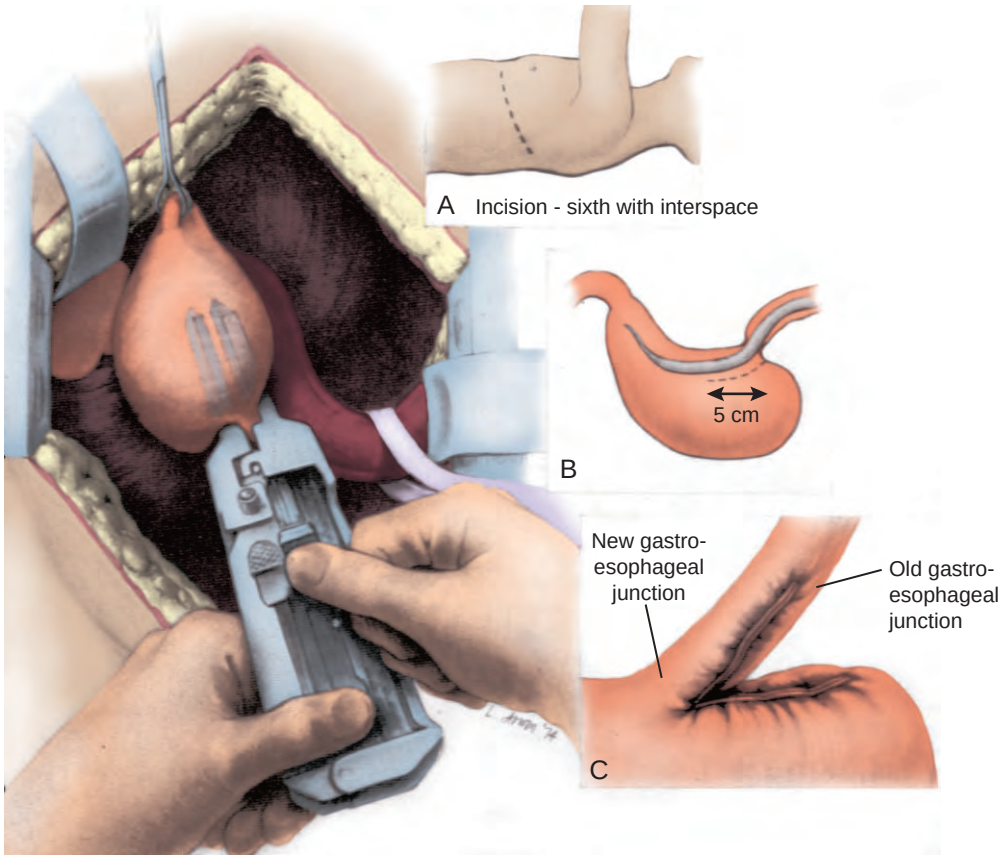

Figure 16–9. Construction of the Collis gastroplasty tube with the GIA surgical stapler. **A,** A sixth left interspace incision is used. **B,** The 54-French dilator inserted through the stricture is displaced against the lesser curvature of the stomach. The *dotted line* indicates the site of application of the stapler. The main illustration shows advancement of the knife assembly. **C,** The new functional distal esophagus is a 5-cm tube of healthy stomach. (From Orringer MB, Sloan H: An improved technique for the combined Collis-Belsey approach to dilatable esophageal strictures. J Thorac Cardiovasc Surg 68:298, 1974.)

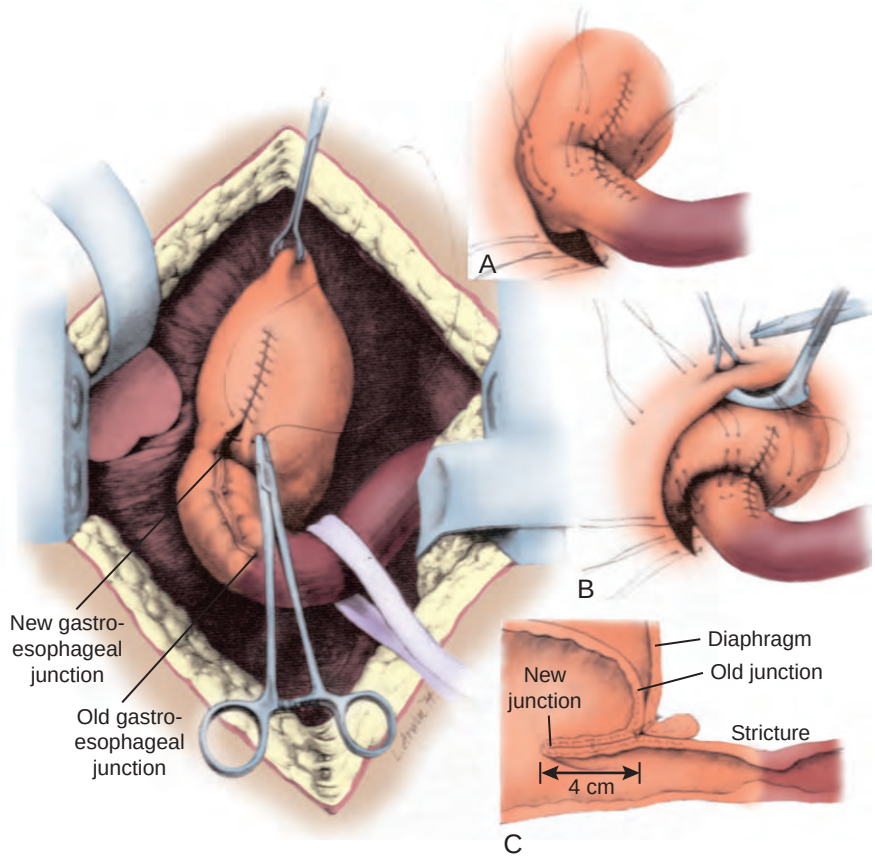

Figure 16–10. Belsey reconstruction of the esophagogastric junction after construction of the Collis gastroplasty tube. *Main illustration,* Oversewing the staple suture line. **A,** Placement of the first row of three mattress sutures between the new distal "esophagus" and the gastric fundus. The posterior crural sutures have been placed but are left untied at this point. **B,** Placement of the second row of mattress sutures through the diaphragm, gastric fundus, and distal esophagus 2 cm proximal to the first row. **C,** The completed repair reduced beneath the diaphragm shows a 4-cm intra-abdominal distal esophageal segment (the gastroplasty tube) partially compressed by the Belsey fundoplication. The posterior crural sutures have been tied. (From Orringer MB, Sloan H: An improved technique for the combined Collis-Belsey approach to dilatable esophageal strictures. J Thorac Cardiovasc Surg 68:298, 1974.)

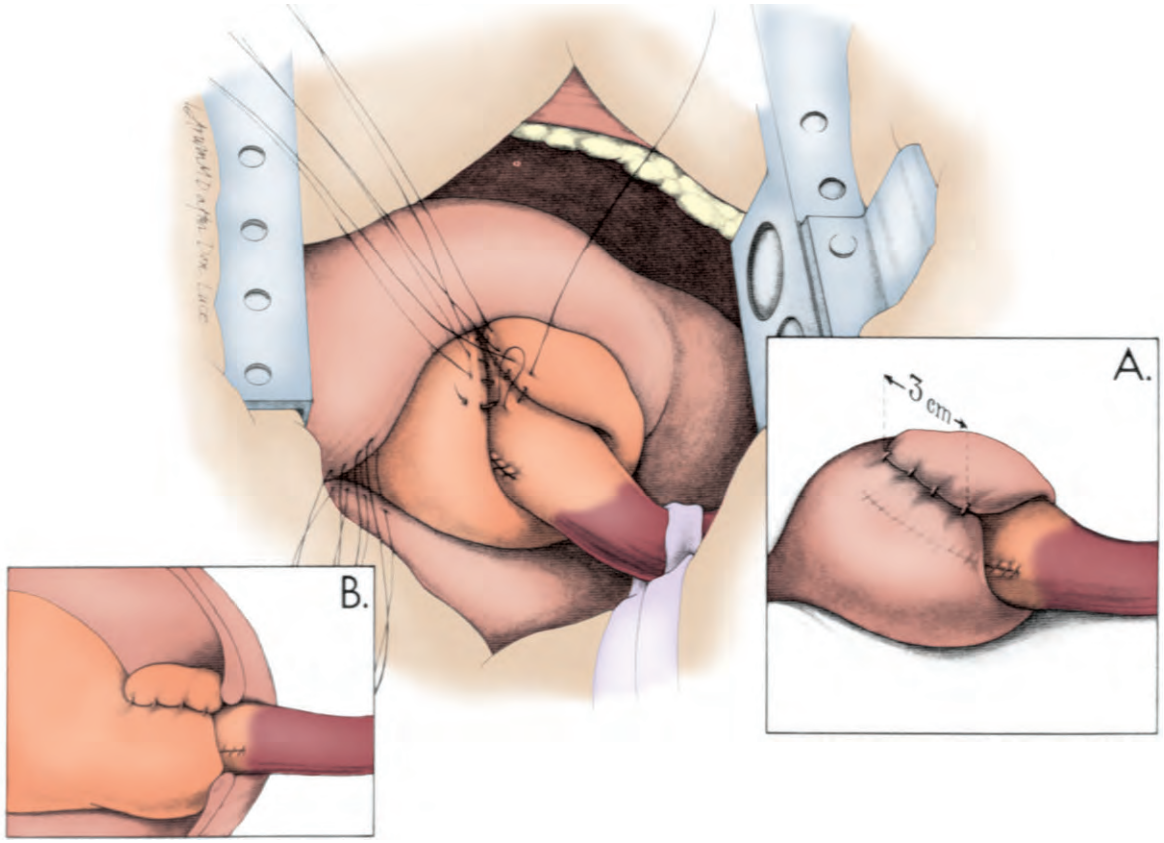

Figure 16–11. A 3-cm long fundoplication after Collis gastroplasty. Four seromuscular 2-0 silk sutures placed 1 cm apart *(main illustration)* result in a 3-cm-long fundoplication around the gastroplasty tube **(A),** not the proximal part of the stomach. **B,** The fundoplication reduced beneath the diaphragm. (From Stirling MC, Orringer MB: The combined Collis-Nissen operation for esophageal reflux strictures. Ann Thorac Surg 45:148, 1988.)

Collis-Nissen Procedure

With the use of postoperative intraesophageal pH monitoring, data emerged showing unsatisfactory long-term reflux control with the Collis-Belsey procedure. Orringer and Sloan[51] suggested that the amount of remaining gastric fundus was inadequate to perform a functioning 240-degree Belsey fundoplication after construction of the gastroplasty tube. To improve reflux control after performance of the Collis gastroplasty, Orringer and associates[52-54] described the use of a 360-degree Nissen-type fundoplication. The cut Collis gastroplasty combined with a 360-degree fundoplication has been successful in patients with dilatable reflux strictures that are amenable to an antireflux operation. Patients in whom initial endoscopic assessment has indicated that the stricture is benign and can be dilated with a 40-French bougie will most likely have a stenosis that can be dilated to the 56-French range at the time of a Collis-Nissen repair. In the combined Collis-Nissen operation, five or six short gastric vessels are routinely divided as the gastric fundus and greater curvature of the stomach are delivered into the chest through the diaphragmatic hiatus. Careful ligation of these vessels without undue tension is required to avoid injury to the spleen and unrecognized intra-abdominal hemorrhage. Adhesions from previous operations at the hiatus may necessitate a diaphragmatic counterincision for exposure. When necessary, a 5- to 10-cm peripheral diaphragmatic incision is made 5 cm from the diaphragmatic attachment to the costal arch. Division of the costal arch is avoided to minimize postoperative incisional pain and chest wall instability. The reflux stricture is supported by the surgeon as the dilator is passed per os. The gastroplasty tube is constructed with the GIA stapler (see Fig. 16–9). To avoid narrowing of the "neo-esophagus," the gastroplasty and fundoplication are performed with either a 54-French dilator (in women) or a 56-French dilator (in men) within the esophagus.[54] The fundoplication is limited to 3 cm in length and is performed only around the gastroplasty tube (neo-esophagus) (Fig. 16–11). The fundoplication is fashioned with four interrupted seromuscular 2-0 silk sutures placed 1 cm apart, with each suture passing through the gastric fundus, gastroplasty tube, and gastric fundus again. The suture line is oversewn with a 4-0 running polypropylene Lembert seromuscular stitch. This is done prophylactically to prevent a fundoplication suture leak. The dilator is removed, and the fundoplication is reduced beneath the diaphragm. The fundoplication is secured to the under-

surface of the diaphragm with three horizontal mattress sutures of 2-0 polypropylene suture placed between the fundoplication and the diaphragm around the circumference of the hiatus. The posterior crural sutures are tied to narrow the hiatus until it admits one finger comfortably alongside the esophagus. Silver clip markers are placed at the apex of the gastroplasty tube (the new gastroesophageal junction) before the fundoplication and at the edges of the diaphragmatic hiatus after the fundoplication has been reduced beneath the diaphragm. The distance between these two sets of silver clip markers on postoperative roentgenograms indicates the intra-abdominal segment of esophagus wrapped by the fundoplication (Fig. 16–12).

Although the severity of the stricture (i.e., the ease with which it can be dilated) cannot be predicted by its appearance radiographically or endoscopically, almost every reflux stricture can be dilated intraoperatively with the esophagus supported by the surgeon's hand as the dilator is passed. Stirling and Orringer found that 95% of esophageal reflux strictures could be dilated to a size compatible with comfortable swallowing (at least to 46 French but generally 54 or 56 French). Successful control of both reflux symptoms and dysphagia was accomplished in 77% of patients, but a 23% failure rate still leaves much to be desired. Occasionally, antegrade dilatation as described is not possible, and it may be necessary to pass a Hegar dilator retrograde through a high gastrotomy,[54] but this is rarely necessary.

When reflux disease has resulted in peptic stricture and shortening of the esophagus, long-term control of reflux with a standard antireflux operation is jeopardized.[39] The uncut Collis-Nissen gastroplasty is a technique designed to relieve distal esophageal obstruction and improve GER. Bingham[55] and Demos et al.[56] suggested retaining the benefits of a total fundoplication around a gastroplasty without transecting the gastric wall. Through a left thoracotomy, the anterior and posterior fundic walls are apposed over a bougie and stapled with a noncutting stapler. The remaining fundus is used to wrap the uncut gastroplasty. The fundoplication is secured with four sutures passed in front of the staple line. The fundoplication is reduced under the diaphragm and fixed in place by three sutures passing through the esophageal wall, apex of the fundoplication, and diaphragm. The procedure has the combined advantages of lengthening the distal esophagus while providing an "anchor" for the fundoplication to reduce the incidence of anatomic hernia recurrence or slipping of the esophagus out of the wrap.[57] Because mucosal apposition of the uncut gastroplasty tube may set the stage for recanalization, the uncut gastroplasty presents the potential for dehiscence of the gastroplasty. In a study of 80 patients who underwent this procedure, 1 patient required reoperation for a recurrent hernia.[58] In another review of 27 patients who underwent an uncut Collis-Nissen gastroplasty, 6 patients had slow esophageal emptying and 3 had occasional episodes of dysphagia. None required postoperative dilation. At least initially, ulcers and erosions healed in all 26 patients. It was concluded that the uncut Collis-Nissen procedure provides acceptable control of GER.[57]

More recently, several minimally invasive techniques have been developed to deal with an esophageal stricture in conjunction with a short esophagus. Decades of experience with the previously described open gastroplasty and fundoplications have established certain principles that are essential for successful outcomes in the treatment of this condition. These concepts include thorough preoperative testing, effective stricture dilatation, routine division of short gastric vessels, crural closure, and wraps performed without tension around 2.5 to 3 cm of tension-free intra-abdominal esophagus (the gastroplasty tube).[10] These principles are equally important in minimally invasive surgical treatment of esophageal strictures.

In the early years of laparoscopic fundoplication surgery, preoperative suspicion of a short esophagus was commonly listed as a contraindication to this approach, and the finding of esophageal shortening at surgery was an indication for conversion to an open procedure.[59] With rapidly evolving technology and increasing experience with minimally invasive approaches, an esophageal reflux stricture with an associated shortened esophagus can be treated while maintaining the benefits of a less invasive approach.

A standard setup for laparoscopic fundoplication is used despite the esophageal stricture or suspected shortened esophagus. Port placement is quite variable, but many surgeons use a midline port (camera), two subcostal retractor ports (liver retractor and assistant retractor), and two subcostal working ports (dissector, stapler, etc.). The phrenoesophageal ligament is dissected to access the distal 3 to 4 cm of esophagus. Care must be taken to preserve the vagi and avoid overly aggressive resection of the gastric fat pad, which can lead to perforation. Esophageal dilators are passed per os and their course in the stomach verified laparoscopically. Laparoscopic instruments are used to support the esophagus along its longitudinal axis during dilatation. Adequacy of the intra-abdominal length of the esophagus is assessed at this point. Assessment can be accomplished by holding the crura together with atraumatic graspers and releasing the stomach. There should be 2.5 to 3 cm of intra-abdominal esophagus without tension. If there is confusion about the location of the gastroesophageal junction, intraoperative endoscopy should be performed. Care must be taken to place the esophagus in position for measurement and avoid forcibly pulling it inferiorly (Fig. 16–13). Pulling the esophagus inferiorly, along with the diaphragmatic elevation created by the pneumoperitoneum, can cause misjudgment of adequate esophageal length. Excessive traction can elongate the proximal part of the stomach and cause it to resemble the esophagus. This can result in a misplaced wrap or a wrap under tension. If 2.5 cm of tension-free intra-abdominal esophagus cannot be obtained, the patient has a short esophagus and needs an esophageal lengthening procedure. Some suggest that extended transhiatal esophageal mobilization (>5 cm) will provide adequate esophageal length and reduce the incidence of fundoplication failure in patients with esophageal shortening.[60] Caution is advised when considering this extent of dissection from a transhiatal view because an esophageal

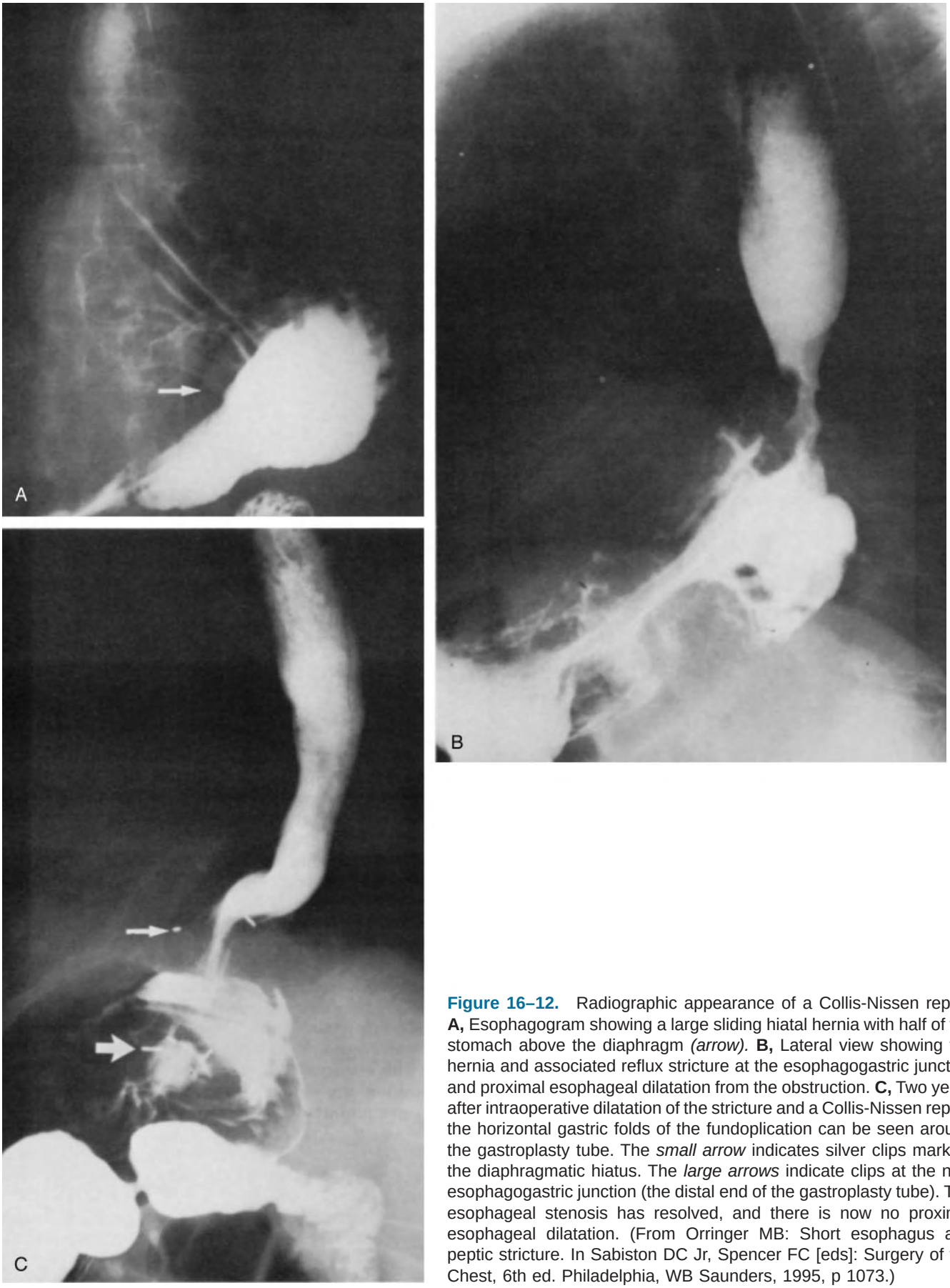

Figure 16–12. Radiographic appearance of a Collis-Nissen repair. **A,** Esophagogram showing a large sliding hiatal hernia with half of the stomach above the diaphragm *(arrow).* **B,** Lateral view showing the hernia and associated reflux stricture at the esophagogastric junction and proximal esophageal dilatation from the obstruction. **C,** Two years after intraoperative dilatation of the stricture and a Collis-Nissen repair, the horizontal gastric folds of the fundoplication can be seen around the gastroplasty tube. The *small arrow* indicates silver clips marking the diaphragmatic hiatus. The *large arrows* indicate clips at the new esophagogastric junction (the distal end of the gastroplasty tube). The esophageal stenosis has resolved, and there is now no proximal esophageal dilatation. (From Orringer MB: Short esophagus and peptic stricture. In Sabiston DC Jr, Spencer FC [eds]: Surgery of the Chest, 6th ed. Philadelphia, WB Saunders, 1995, p 1073.)

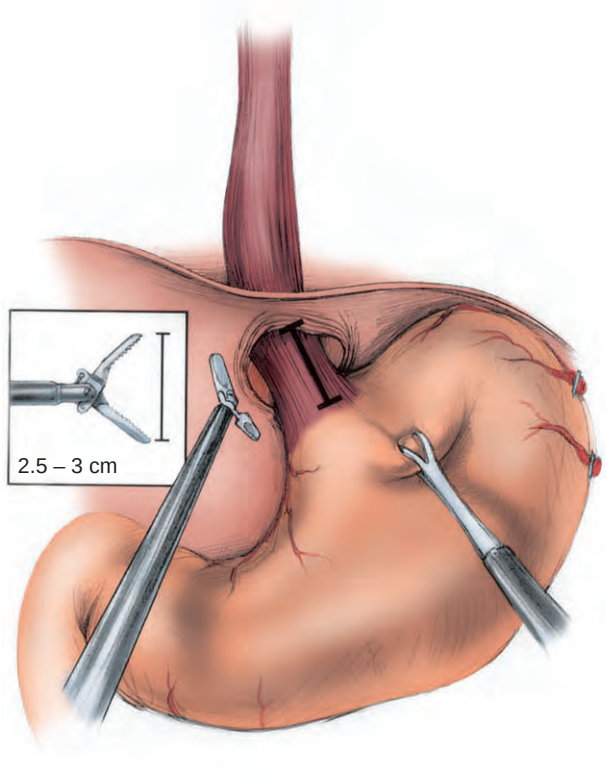

Figure 16–13. Intraoperative assessment of esophageal length. If there is confusion about the location of the gastroesophageal junction, intraoperative endoscopy should be performed. (From Horvath KD, Swanström LL, Jobe BA: The short esophagus: Pathophysiology, incidence, presentation, and treatment in the era of laparoscopic antireflux surgery. Ann Surg 232:630-640, 2000.)

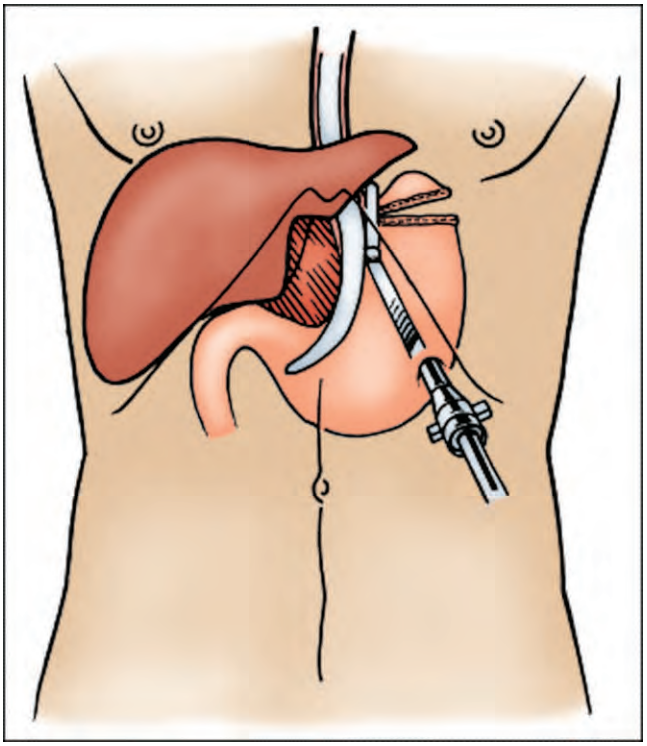

Figure 16–14. An endoscopic stapler is inserted and reticulated to make a horizontal staple line followed by a vertical staple line parallel to and abutting the dilator. A stapled wedge of stomach approximately 15 mL in volume is excised and removed. (From Terry ML, Vernon A, Hunter JG: Stapled-wedge Collis gastroplasty for the shortened esophagus. Am J Surg 188:258-294, 2004.)

lengthening procedure may be far wiser than risking severe hemorrhage, esophageal perforation, and vagus nerve injury.

Two laparoscopic Collis gastroplasty techniques have been described. They rely on laparoscopic esophageal and gastric mobilization, followed by creation of the gastroplasty tube and subsequent fundoplication. Swanström et al. described a totally laparoscopic version of the Collis gastroplasty with fundoplication.[37] With a standard setup for laparoscopic fundoplication, the initial description involved the use of an endoscopic circular stapler to create a window below the angle of His for the insertion of a linear stapler to create the neoesophagus. This technique caused relative ischemia of the apex of the fundus. The minimally invasive Collis gastroplasty was revised to a stapled wedge gastroplasty.[61] The esophagus is mobilized and assessed for length. If there is less than 2.5 cm of tension-free intra-abdominal esophagus, the orogastric tube is removed and a 48-French dilator is advanced under vision with the laparoscope. A point approximately 3 cm inferior to the angle of His is marked with electrocautery. A left subcostal port is used to insert a reticulating endoscopic 45-mm linear cutting stapler that is maximally flexed. The assistant retracts the gastric fundus inferiorly, and the surgeon maintains traction on the greater curve just below the angle of His as the stapler is advanced into position. The stapler is fired one to three times until the marked point inferior to the angle of His is reached. Once the transverse staple line is completed, a vertical staple line is created parallel to the esophagus and abutting the dilator (Fig. 16–14). The stapler is fired once or twice to produce a stapled wedge of stomach approximately 15 ml in volume, which is removed from the abdomen. This creates a tube, or neo-esophagus, that is 3 to 4 cm in length. The crura are closed, and a 360-degree tension-free fundoplication is performed around the neo-esophagus. The staple line is oriented so that it is apposed to the stomach wall. Swanström et al. described an alternative technique involving a combined laparoscopic and thoracoscopic Collis gastroplasty with fundoplication.[37] The essentials of this procedure involve placing an endoscopic stapler into the right chest (double-lumen intubation is not required), across the right mediastinal pleura, and transhiatally into the abdomen. This technique allows 3- to 4-cm stapling of the stomach parallel to the lesser curve. The resulting intra-abdominal neo-esophagus can subsequently be wrapped with the fundus (Fig. 16–15). After both minimally invasive Collis gastroplasty techniques, most patients undergo a contrast study

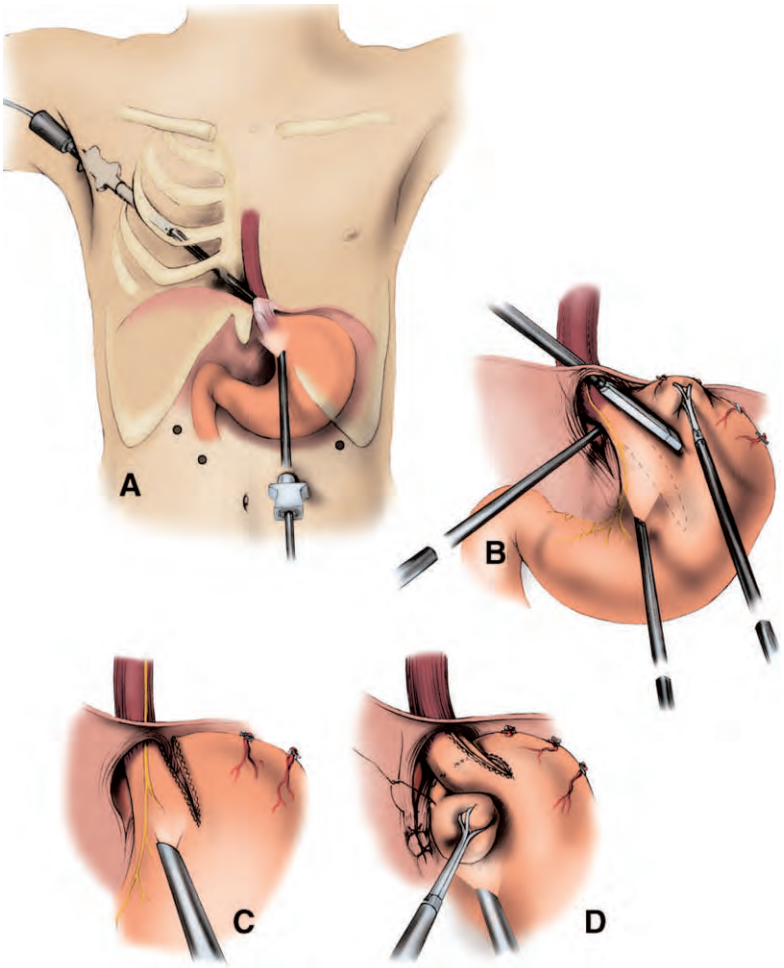

Figure 16–15. **A** to **D,** After the neoesophagus has been created, a standard fundoplication is performed around it. (From Horvath KD, Swanström LL, Jobe BA: The short esophagus: Pathophysiology, incidence, presentation, and treatment in the era of laparoscopic antireflux surgery. Ann Surg 232:630-640, 2000.)

before discharge. The reported average length of hospital stay is 3 days, and most patients experience good results. Both techniques are reproducible and safe, but long-term follow-up is needed.

The Collis neo-esophagus typically lacks normal motility. This aperistaltic segment may theoretically be at risk during eventual dilatation or become a source of postoperative dysphagia. In any patient who continues to experience significant dysphagia after a Collis procedure, outpatient esophageal dilatations are performed liberally. A Collis gastroplasty also results in a small segment of gastric mucosa proximal to the newly constructed distal high-pressure zone. This "ectopic" gastric mucosa has been reported to secrete acid and cause localized esophagitis.[42,62] It is advisable to have all Collis gastroplasty patients closely monitored with objective testing. If esophageal acid exposure is documented, long-term medical therapy is indicated. Other complications from the gastroplasty procedure include leaks from the gastroplasty line and fistulas. Complications are reported to occur in up to 10% of open gastroplasty cases[10] and up to 22% of laparoscopic gastroplasty cases.[63] In our review of 240 patients who underwent primary transthoracic repair of paraesophageal hiatal hernias, with a Collis gastroplasty performed in 96% of cases, there was a 0.8% incidence of esophageal leak.[64]

Resection

In some situations a patient with an esophageal reflux stricture is best treated by esophageal resection. Such situations include extremely long nondilatable strictures, strictures with associated Barrett's mucosa with high-grade dysplasia, and strictures after multiple failed antireflux operations. Esophagectomy for nondilatable strictures was necessary in 22% of the patients with benign strictures from reflux disease reported by Bonavina et al.[65] A "nondilatable" stricture is generally defined as (1) one through which a dilator cannot be passed because of luminal narrowing or tortuosity, (2) one that causes persistent dysphagia despite dilatation, and (3) one with a previous perforation during dilatation. Complications of Barrett's esophagus were reported to be the indication for esophagectomy in 20% of patients undergoing resection for benign disease by Salamao et al.[66] Previous unsuccessful antireflux procedures constitute a common indication for esophagectomy for benign disease. Orringer reported a series in

which 56% of resections for benign disease were performed for end-stage GER disease.[67] Repeated operations at the esophagogastric junction are associated with tissue damage, loss of function, and reduced blood supply leading to potential ischemic necrosis of either the distal esophagus or gastric fundus. Conserving a devitalized and dysfunctional esophagus invariably leads to poor outcomes. A number of reports have shown that after two previous antireflux procedures, the third antireflux operation is likely to fail in more than 50% of patients.[66,68]

The best conduit for esophageal reconstruction continues to be debated. Reconstruction for benign disease, such as a stricture, requires a substitute organ that is durable and associated with satisfactory long-term functional results. Important factors to consider when selecting the replacement conduit include absence of intrinsic disease, adequacy of blood supply, patient age, and the surgeon's own experience.[69] Proponents of gastric interposition emphasize the technical ease, single anastomosis, and faster return of normal alimentation.[66,70] Total thoracic esophagectomy with a cervical esophagogastric anastomosis is the authors' preferred approach in patients requiring esophageal resection for benign as well as malignant disease. Placing the esophageal anastomosis in the neck avoids the potential for mediastinitis associated with an intrathoracic anastomotic leak. The stomach is positioned in the posterior mediastinum in the original esophageal bed, and an end-to-side cervical esophagogastric anastomosis is constructed several centimeters from the apex of the gastric fundus. Clinically significant reflux is uncommon after a properly performed cervical esophagogastric anastomosis. In the largest series (>1500 patients) of transhiatal esophagectomy and cervical esophagogastric anastomosis, Orringer et al. reported anastomotic leak rates as low as 2.7%, clinically significant postoperative reflux in less than 10%, and good to excellent overall functional results in 70% of patients.[71,72] A cervical esophagogastric anastomotic leak after transhiatal esophagectomy is a predictor of subsequent unsatisfactory function; nearly half of such leaks result in an anastomotic stricture once healing of the fistula is complete. Dilatation of a cervical esophagogastric anastomosis is far safer than dilatation of an intrathoracic anastomosis. The stapled end-to-side cervical esophagogastric anastomotic technique described by Orringer and associates has been shown to decrease the incidence of anastomotic leaks and the need for anastomotic dilatation.[71]

An intrathoracic esophagogastric anastomosis is a poor choice for a patient who has reflux esophagitis with or without stricture. Resection of the lower esophageal sphincter and creation of an iatrogenic hiatal hernia with a portion of the stomach above and a portion below the diaphragm explain the reported 20% to 40% incidence of reflux esophagitis in the residual esophagus of patients undergoing an intrathoracic esophagogastric anastomosis.[73] The reflux that follows construction of an intrathoracic esophagogastric anastomosis may result in a recurrent peptic esophageal stenosis. Distal esophagectomy plus reconstruction with either a jejunal[45] or short-segment colonic interposition[74] is an excellent option in patients with reflux strictures requiring resection, and these procedures are associated with reasonable elimination of reflux symptoms. Both these reconstructions, however, are of considerable magnitude and are technically demanding. If an anastomotic stricture develops, dilatation of an intrathoracic esophagojejunal or esophagocolonic anastomosis is dangerous.

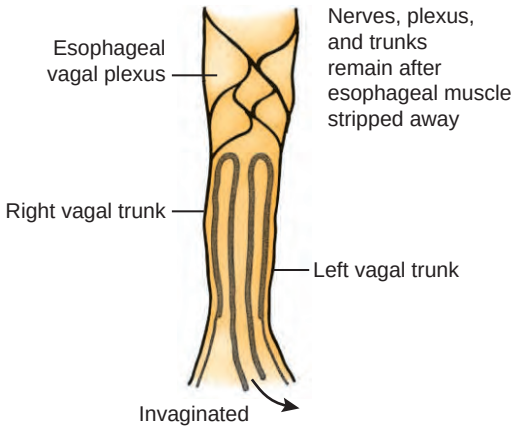

Figure 16–16. The esophagus is stripped out of the mediastinum with simultaneous mucosal inversion. The nerves are sheared off the muscularis propria with the esophageal plexus left intact (From Banki F, Mason RJ, DeMeester SR, et al: Vagal-sparing esophagectomy: A more physiologic alternative. Ann Surg 236:324-336, 2002.)

Vagal-sparing esophagectomy has been described as an ideal procedure for patients with end-stage benign esophageal disease.[75] This method of esophagectomy involves removal of the esophagus while preserving the vagal nerves and gastric reservoir. The esophagus is stripped out of the mediastinum and inverted in the process. This results in shearing the nerve fibers off the muscularis propria with the esophageal plexus left intact (Fig. 16–16). Colon is used as the replacement conduit. The preservation of gastric secretory, motor, and reservoir function reportedly allows normal alimentation, bowel regulation, and less weight loss. Vagal-sparing esophagectomy is reportedly associated with less postoperative dumping, diarrhea, and early satiety.[75]

One final method of indirect resectional therapy for esophagitis with stricture is partial gastrectomy and Roux-en-Y biliary diversion. Wangensteen and Levin were the first to report resolution of benign esophageal stenosis after partial gastrectomy for peptic ulcer disease.[76] The importance of bile in refluxed gastric contents in the development of severe esophagitis was then recognized both clinically and experimentally.[77,78] Consequently, some surgeons have treated reflux strictures with partial gastrectomy and Roux-loop gastrojejunostomy,[79] whereas others advocate antrectomy and Roux diversion in conjunction with resection.[80,81] In the opinion of the authors, it is difficult to rationalize leaving behind the inflamed, scarred, strictured esophagus, which may contain premalignant Barrett's epithelium, while sacrificing the healthy stomach, perhaps the best organ with which to replace the esophagus.

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Chapter

17

Medical Therapy for Gastroesophageal Reflux Disease

Eugene Y. Chang ▪ Blair A. Jobe

Although surgical antireflux procedures are indicated for complicated or medically refractory cases of gastroesophageal reflux disease (GERD), initial treatment relies primarily on medical therapy. Pharmacologic therapy for acid reflux has progressed from antacids to histamine H_2 receptor antagonists (H2RAs) and, most recently, to proton pump inhibitors (PPIs). An understanding of the proper use of these medications is important because a course of optimal medical management is generally warranted before considering surgery. Moreover, the limitations of therapy with H2RAs and PPIs should be recognized, particularly with regard to treatment and prevention of the complications of GERD. In this respect, it should be understood that GERD results from potentially three different pathophysiologic processes. First, the lower esophageal sphincter (LES) may be incompetent and allow the reflux of gastric contents into the esophagus. Second, the esophagus may have a motility disorder that results in impaired or delayed clearance of refluxate from the esophagus. Third, hypersecretion of acid in the stomach may contribute to increased esophageal exposure to acidity. In addition, delayed gastric emptying may impair the forward progression of stomach contents, thereby increasing the opportunity for reflux. It is important to distinguish among these processes when determining the most appropriate treatment for patients with GERD. Finally, a comprehensive understanding of the medical alternatives to surgery is necessary for proper counseling of a patient who wishes to make an informed decision regarding whether to undergo an antireflux operation.

LIFESTYLE MODIFICATIONS

Numerous studies have demonstrated physiologic factors that increase esophageal exposure to acid by decreasing LES pressure, prolonging acid clearance time, or both. These factors include various foods, body position, and lifestyle variables.[1-6]

Foods

Certain foods have been shown to decrease LES pressure in human studies, including chocolate, peppermint, and spearmint[7] and foods rich in fat.[3,8,9] Other foods have been postulated to cause heartburn by direct irritation of the esophagus or by inducing the reflux of gastric contents. Chocolate and peppermint, for example, have been shown to increase esophageal reflux,[10] and a survey of individuals with and without symptoms of GERD identified chocolate as a food that precipitates heartburn.[11] Patients with esophagitis had a significant rise in esophageal exposure time to acid within 1 hour after eating chocolate.[12] Ingestion of onions has also been reported to increase esophageal exposure to acid.[13]

Beverages

Alcohol consumption has been associated with decreased LES pressure[14] and prolonged esophageal exposure to acid.[15] Although drinking coffee does not affect LES pressure, it has been shown to induce GERD symptoms, possibly by direct mucosal irritation and effects on acid production.[16] Similarly, beer, wine, and, to a lesser extent, tea and soft drinks have been associated with heartburn. This observation has been attributed to the osmolarity or acidity of these beverages.[17]

Body Position

Because patients typically report that symptoms are precipitated by reclining, practitioners naturally recommend that recumbent positions be avoided for 3 to 4

hours after a meal. When sleeping, patients have traditionally been advised to elevate the head of the bed. This is accomplished by resting on foam wedges or placing books underneath the legs of the bed to raise the head by 4 to 8 inches. In one study, patients with GERD reported a reduction in symptoms when sitting up or lying with the head of the bed elevated as opposed to lying flat. The same study showed reduced esophageal exposure to acid when the head of the bed was elevated by 28 cm versus lying flat.[1] In patients with GERD, placing 6-inch blocks under the head of the bed significantly improved acid clearance times and reduced esophageal exposure to acid.[2] These sleep positions, however, may not be acceptable to many patients because they may be uncomfortable and cause the sheets, the patient, and bedmate to slide toward the foot of the bed. Alternatively, patients may observe some improvement in symptoms in the left lateral decubitus position. This position has been reported to improve esophageal acid clearance and reduce the time with a pH less than 4 when compared with other positions.[18]

Obesity

GERD is more prevalent among morbidly obese patients,[19] and it is thought that this finding may be related to the persistently increased pressure gradient between the abdomen and thorax.[20] Similarly, tight-fitting clothing around the waist has also been inculpated as a contributor to heartburn.[20] Although obese patients with GERD are often given the classic recommendation to lose weight, clinical studies have failed to show any efficacy in treating GERD with this strategy. In one study, placing obese patients with erosive esophagitis on a 6-month weight loss program failed to produce any objective or subjective improvement despite demonstrable weight loss.[21]

Smoking Cessation

Cigarette smoking has been demonstrated to decrease LES pressure and prolong esophageal acid clearance in healthy individuals.[22-25] Although smoking cessation in individuals with GERD has been shown to reduce the number of upright reflux episodes, it failed to have any impact on total esophageal acid exposure time.[4] Furthermore, smoking did not appear to affect rates of healing in patients with esophagitis who were undergoing treatment with ranitidine or omeprazole.[26,27]

Recommendations for Lifestyle Modifications

Although the impact of lifestyle factors may be demonstrated on the basis of symptoms and esophageal acid exposure, it should be kept in mind that few prospective studies have been conducted to determine whether these measures are sufficiently efficacious as a treatment of GERD. However, lifestyle modifications often bring about benefits outside the gastrointestinal system and may augment pharmacologic therapy for GERD.

MEDICAL TREATMENT OF GERD SYMPTOMS

Antacids

Commonly used antacids include aluminum hydroxide and magnesium hydroxide, which exert their effects by neutralizing gastric acid. Because they are over-the-counter medications, antacids and acid suppressants have frequently been used as first-line therapeutic agents. These medications may produce mild short-term symptomatic relief of postprandial heartburn but are of very limited efficacy. A comparison of magnesium hydroxide and placebo in patients with esophagitis demonstrated that the antacid had only minimal effect on the frequency and severity of heartburn.[28] Furthermore, their use is limited by side effects, including diarrhea in the case of magnesium hydroxide and hypophosphatemia in patients taking aluminum hydroxide. Antacid foam tablets also failed to reduce esophageal acid exposure.[2] Sucralfate, a drug that reacts with gastric acid to produce a barrier coating the mucosa of the upper gastrointestinal tract, has demonstrated limited or no clinical efficacy in patients with GERD.

Promotility Agents

Cisapride, an agent that stimulates upper gastrointestinal motility through the indirect stimulation of acetylcholine release from the postganglionic nerve endings in the myenteric plexus, has been of value in the treatment of symptoms, thus underscoring the role of esophageal dysmotility and delayed gastric emptying in the pathogenesis of GERD. It reduces esophageal exposure to acid by increasing lower esophageal motility, reducing gastric emptying time, and increasing salivation.[29] It has typically been prescribed in a regimen of 10 mg four times a day. A study by Castell et al. demonstrated that when given at a dosage of 20 mg twice a day, it maintained the ability to reduce heartburn, regurgitation, eructation, and the use of antacids in comparison to placebo.[30] In this study, 67 of 188 patients reported a response in daytime heartburn, and 73 of 188 reported a response in nighttime heartburn. The most commonly reported adverse event was diarrhea, seen in 10% of patients. Because of a low incidence of cardiac arrhythmias, however, cisapride has been removed from the U.S. market and is issued only on a named-patient basis.

Other prokinetic agents that have been studied for GERD include metoclopramide, bethanechol, and domperidone. Unlike cisapride, however, none of these agents has consistently demonstrated clinical efficacy.[2,31] Furthermore, the side effects of metoclopramide (fatigue, restlessness, tremor, extrapyramidal movement disorders) further limit its usefulness. Domperidone is not available on the U.S. market. Tegaserod, a histamine 5-HT_4 receptor partial agonist, has been shown to have prokinetic effects and has demonstrated reduced esophageal exposure to acid at its lowest dose.[32] Whether this observation translates into an effect of therapeutic value remains to be seen.

Bethanechol, a cholinergic agent, was shown to decrease esophageal exposure time to acid in recumbent but not upright patients.[2] However, its use is limited by cholinergic adverse effects, including increased gastric acid secretion, bronchoconstriction, and increased bladder contraction.

H_2 Receptor Antagonists

The commonly used H2RAs, which include ranitidine and famotidine, are more efficacious than antacids and were once considered revolutionary in the treatment of GERD. These agents block the histamine receptor of the parietal cell, thus eliminating one of the pathways by which gastric acid secretion is promoted. The standard dosage of ranitidine is 150 mg twice a day; that of famotidine is 20 mg twice a day. H2RAs produce at least partial relief of symptoms in 50% to 70% of patients with GERD[33] and may be the most cost-effective approach to treating uncomplicated GERD in patients in whom symptomatic relief can be achieved. However, tolerance to an H2RA can develop within several weeks of starting therapy. Furthermore, in patients who have persistent symptoms despite treatment with an H2RA, escalation to a higher dose (ranitidine, 300 mg twice daily) has not been shown to improve symptoms significantly.[34] With the advent of more potent antisecretory agents, the role of H2RAs as primary therapy for GERD has largely been supplanted.

Proton Pump Inhibitors

PPIs include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. They have become the mainstay of therapy and are often used as first-line treatment of GERD. Despite the widespread use of PPIs, an understanding of the optimal dosage schedule is lacking among nongastroenterologists.[35] This class of agents accumulates in the secretory canaliculi of active parietal cells and covalently binds to the proton-potassium ion exchange pump, irreversibly inhibiting it. Because the proton pump is maximally recruited to the secretory canaliculus after a period of fasting, the optimal time for once-daily dosing is 30 minutes before breakfast. For twice-daily dosing, a second dose is added before dinner.

In patients with GERD, omeprazole reduces heartburn, regurgitation, and the use of antacids.[36,37] In patients without esophagitis, omeprazole has been demonstrated to be superior to cisapride[38] and H2RAs in the short-term symptomatic control of GERD.[39] Maintenance of symptomatic remission generally requires continuous, lifelong therapy with PPIs. In patients with nonerosive GERD treated until symptomatic remission and then placed on a treatment strategy with a placebo, the majority taking the placebo become unwilling to continue the treatment strategy within 6 months.[40] In patients with esophagitis, symptomatic remission after 12 months of treatment with placebo fell to 34% versus 62% to 82% in patients who continued omeprazole therapy and 45% in patients treated with ranitidine.[41-43]

Alternatives to lifelong continuous therapy with PPIs have been studied and include strategies such as on-demand therapy. In contrast to scheduled dosing, on-demand therapy allows patients with infrequent symptoms to take the medication only when symptoms recur. Advantages of this regimen include the decreased use (and decreased cost) of medications. Proponents of this strategy also point out that patients told to take scheduled PPIs often take the medications on an on-demand basis despite the instructions given to them.[44] A major disadvantage, however, is that this strategy permits the recurrence of symptoms, which may take some time to resolve after resumption of the medication. When compared with placebo, on-demand therapy with omeprazole, 10 or 20 mg, or esomeprazole, 20 mg, in patients with nonerosive GERD was superior and well accepted by patients. In this study, 85% of patients taking the active medication were willing to continue the strategy at the end of 6 months of therapy.[40] Similar findings in studies using lansoprazole suggest that on-demand therapy with other PPIs may be feasible. Although on-demand therapy may be successful in patients with endoscopically negative GERD, its usefulness has not been demonstrated in those with GERD-related complications (such as erosive esophagitis)—these patients generally require lifelong continuous antisecretory agents. Another alternative to lifelong continuation of PPIs is a "step-down" strategy to less potent medications such as H2RAs or lower dosages of PPIs. In patients who have been rendered asymptomatic with PPIs or H2RAs, cisapride demonstrated no benefit over placebo in maintaining symptomatic remission, thus suggesting that it is not appropriate as a "step-down" agent.[45]

Response to a particular PPI varies among individuals, and this variation has been attributed to polymorphisms in the proton-potassium pump. Although numerous studies have been conducted to compare their efficacy in different situations,[46] there is generally little difference among PPIs with regard to their efficacy.[47]

Even though PPIs are generally well tolerated, they may be associated with side effects, with an overall incidence of 5%.[48] The most commonly reported side effects include headache, nausea, diarrhea, and abdominal pain.[49] In a study to assess the safety of omeprazole, 116 patients with Zollinger-Ellison syndrome were treated with dosages of omeprazole up to 60 mg twice daily for up to 114 months without any observed toxicity. In addition, no patients discontinued the medication secondary to drug-induced side effects.[50] Initial concerns that PPIs may lead to atrophic gastritis or gastric cancer have not been manifested.[48]

Acid suppression with antisecretory medications (including PPIs) has the major limitation that although these medications may eliminate the symptoms of esophageal reflux, they do not prevent the reflux of gastric contents into the esophagus. Simultaneous monitoring of intraesophageal impedance and pH (Fig. 17–1) can detect and discriminate between acid and non-acid reflux. Studies using impedance-pH monitors have demonstrated that PPIs shift the proportion of acid to non-acid reflux episodes, which dramatically reduces the number of acid reflux episodes but does not affect the

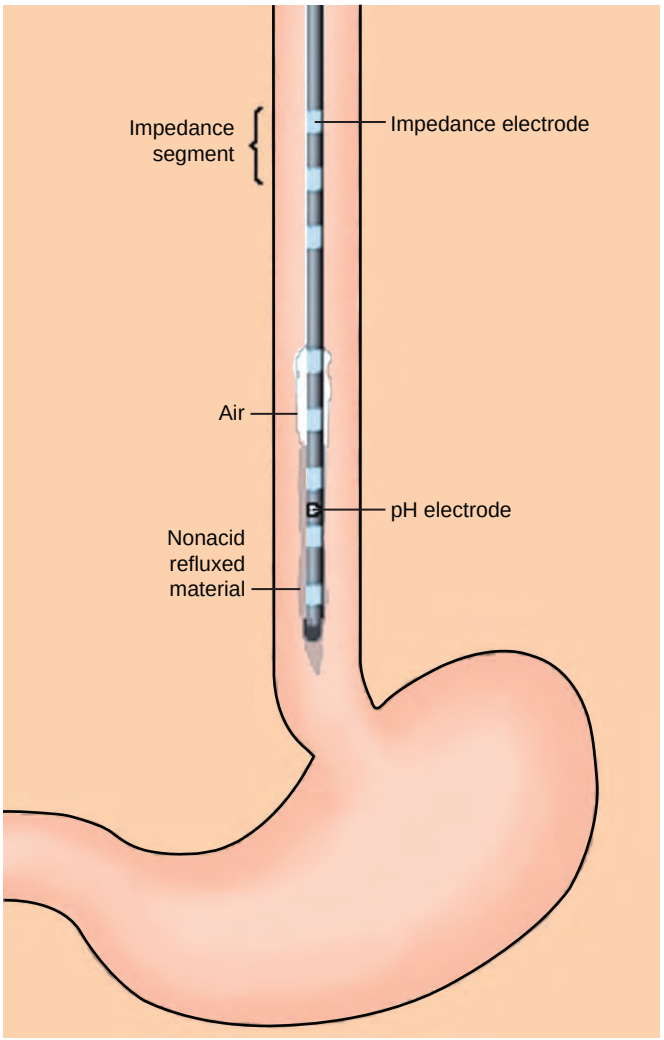


Figure 17–1. Simultaneous pH and impedance monitoring probe. Impedance is measured between electrodes along an intraesophageal catheter. One or more pH-sensing electrodes are also present. Whereas the pH probe detects esophageal acid exposure, impedance monitoring detects all forms of reflux irrespective of pH, including air (which raises the impedance between electrodes) and liquids (which decreases the impedance). Esophageal impedance also defines the proximity of the reflux episode in relation to the proximal end of the aerodigestive tract.

overall number of reflux episodes.[51] It has been suggested that persistence of non-acid reflux in the face of PPI therapy contributes to the pathogenesis of complications of Barrett's esophagus, such as stricture, ulceration, or carcinoma.[52] Furthermore, concern has been raised that acid-suppression therapy increases the risk for aspiration pneumonia because of loss of the antimicrobial effect of gastric acid. This possibility has been substantiated in a cohort study that demonstrated an increased risk for community-acquired pneumonia in patients taking PPIs and H2RAs.[53]

Nocturnal Acid Secretion

Despite therapy with PPIs, the stomach may not be rendered fully achlorhydric in some situations. Nocturnal gastric acid breakthrough is a phenomenon in which patients who are treated twice daily with PPIs have an intragastric pH less than 4 for at least 1 hour overnight. This has been reported in more than 70% of normal subjects and patients with GERD.[54,55] The mechanism by which it occurs is unclear, but explanations that have been put forth cite the limited duration of action of PPIs, the absence of food to buffer gastric acidity at night, and the possibility that the evening dose of PPI is less effective than the morning dose.[56] The addition of a nighttime H2RA has been shown to control nocturnal acid secretion.[56-58] However, recent studies suggest that nocturnal breakthrough returns after 1 week of therapy, which is probably due to the development of tolerance to the H2RA.[59] Nevertheless, the clinical significance of nocturnal acid breakthrough has not been well established, and it is recommended that in patients with difficult-to-manage GERD, the adequacy of acid suppression be determined by esophageal pH rather than intragastric pH.[59]

MEDICAL THERAPY FOR COMPLICATIONS OF GERD

Esophagitis

It is thought that esophagitis, a complication of GERD, requires more intensive therapy than nonerosive reflux does. Historically, H2RAs and promotility agents have been used to treat erosive esophagitis. Ranitidine,[60] cimetidine,[60] famotidine,[33] and nizatidine[61] have been shown to promote healing of esophagitis. After 12 weeks of therapy with standard doses, famotidine, ranitidine, and cimetidine produce healing in 68% to 74% of patients. Nizatidine, which has been given less attention, has demonstrated a 39% healing rate. Healing rates also vary with the grade of esophagitis; the probability of healing decreases with higher grades. Trials conducted with higher doses of H2RAs have demonstrated a slightly improved rate of endoscopically confirmed healing at approximately 77%.[60] Cisapride has also been shown to improve the healing of esophagitis, but it has very limited availability in the United States.[62]

PPIs are also effective in the treatment of esophagitis and have become the mainstay of therapy.[63] In a meta-analysis comparing H2RAs, PPIs, and placebo, esophagitis healed more quickly in patients treated with PPIs than in those treated with H2RAs.[64] This study demonstrated an overall 12-week healing rate of 79% to 88% with PPIs, 47% to 57% with H2RAs, and 19% to 37% with placebo.

Maintenance therapy for esophagitis requires lifelong continuation of PPI therapy. After successful treatment of esophagitis with omeprazole, only 14% of patients maintained on placebo remained in remission after 12 months as compared with 50% of patients who continued treatment with omeprazole, 10 mg, and 74% of

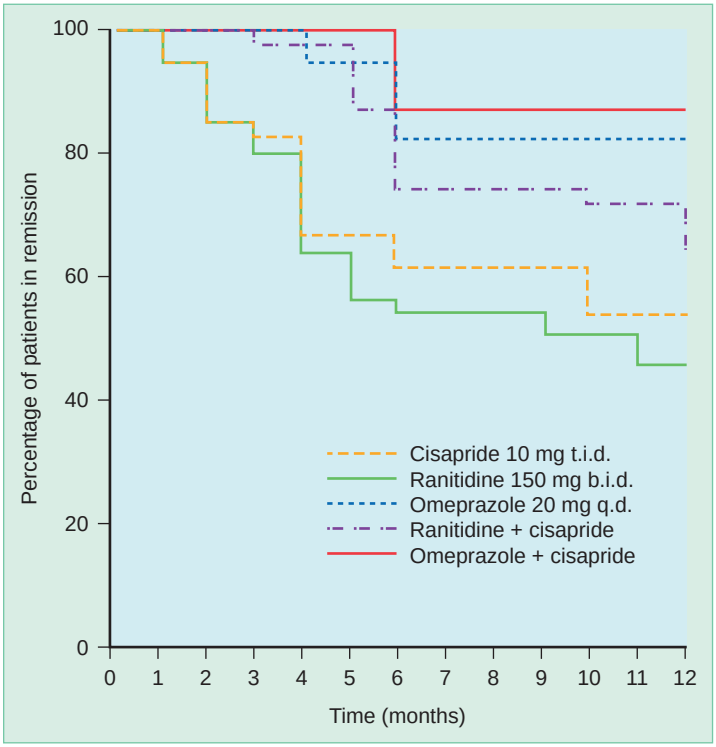


Figure 17–2. Percentage of patients remaining in remission from esophagitis while treated with various medications. (Adapted from Vigneri S, Termini R, Leandro G, et al: A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med 333:1106-1110, 1995.)

those treated with omeprazole, 20 mg (Fig. 17–2).[42] Similar results have been noted for other PPIs.[65-67] When relapses occur, the vast majority take place within 12 months of therapy. Maintenance therapy with omeprazole continues to be effective at least 5 years after initiation of therapy.[68] The use of H2RAs as a step-down agent has been evaluated, but with disappointing results. In a study of 159 patients in which ranitidine, 150 mg twice daily, was compared with omeprazole, 20 mg taken daily, for the prevention of relapse of erosive esophagitis, 89% of patients in the omeprazole arm were free of esophagitis at the end of 12 weeks as compared with 25% in the ranitidine arm.[69] Another study of 392 patients showed a 72% 12-month remission rate in patients treated with omeprazole, 20 mg daily, versus 62% in those treated with omeprazole, 10 mg daily, and 45% in those treated with ranitidine, 150 mg twice daily.[42] These data argue against the use of H2RA as a step-down agent in the maintenance of remission.

Since the advent of PPIs, improvements in the success rate of treating esophagitis have been modest. Esomeprazole, an S-isomer of omeprazole, has shown some potential for improved results. Because it is undergoes less first-pass hepatic metabolism and has decreased plasma clearance, esomeprazole has higher bioavailability. In a study of 1960 patients, the pharmacodynamic advantages of this drug appear to translate into a small but statistically significant improvement over omeprazole. This study demonstrated a 94% healing rate after 8 weeks of treatment with esomeprazole, 40 mg daily, as compared with 87% in those treated with omeprazole, 20 mg daily.[70] Another potential improvement on treatment with omeprazole is the addition of a promotility agent. In a comparison of omeprazole and ranitidine with and without cisapride, the combination of omeprazole and cisapride produced higher remission rates than omeprazole alone did, although the difference did not appear to be statistically significant.[71] Progress with this strategy has been limited because cisapride has been removed from the U.S. market and other promotility agents have not been adequately evaluated.

Strictures

Peptic strictures of the esophagus are estimated to occur in 7% to 23% of patients with untreated reflux esophagitis.[72] The mainstay of therapy for esophageal strictures is mechanical dilation, which must be repeated if the stricture recurs. To date, there is no direct evidence that aggressive medical treatment of reflux prevents the *development* of esophageal strictures. Nonetheless, antisecretory therapy plays an important role in the management of esophageal strictures. An epidemiologic study has demonstrated a decline in the number of dilations performed in community hospitals as the use of PPIs has increased.[73] Aggressive therapy with PPIs (e.g., omeprazole, 20 to 40 mg/day) has been demonstrated to reduce the probability of needing redilatation when compared with H2RA therapy.[73,74] Despite improved healing rates for erosive esophagitis, H2RAs do not appear to reduce the need for dilation.[75] One report showed that the extent of dysphagia in patients with esophageal strictures depends not only on stricture diameter but also on the presence of esophagitis, thus suggesting a possible mechanism by which PPIs reduce the need for redilation.[76] Despite the higher cost of PPIs, the use of PPIs to treat patients with esophageal strictures appears to be more

cost-effective than using H2RAs because of the decreased need for repeat endoscopy and dilation.[77]

Injection of triamcinolone into the stricture has also gained some interest. In a longitudinal study of 71 patients treated with four-quadrant injections of triamcinolone, it was found that the patients required dilation less frequently after starting treatment.[78] Potential adverse effects include esophageal candidiasis, although this was not observed in the study. No randomized, blinded studies to test the efficacy and safety of intralesional steroid injection have been performed.

Barrett's Esophagus

Evidence that adequate medical treatment of GERD prevents the development of Barrett's esophagus has largely been indirect.[79] Using a database of 2641 patients undergoing elective esophagogastroduodenoscopy, Lieberman et al. demonstrated that a longer duration of GERD symptoms was a significant risk factor for Barrett's disease, with an odds ratio rising steadily for patients with a longer history of symptoms. Patients who have had symptoms for longer than 10 years had an odds ratio of 6.4 for the development of Barrett's esophagus in comparison to those who have had symptoms for less than a year. In this study, Barrett's esophagus was 1.8 times more likely to develop in patients with a history of esophagitis, but this relationship did not reach statistical significance.[80]

It has long been thought that patients with GERD have a higher incidence of Barrett's disease, although evidence to support this notion is not entirely convincing, in part because of the unknown prevalence of GERD in the general population. Various studies have found that Barrett's disease has a prevalence of 3% to 15% in patients with GERD.[81,82] Most recently, a study of 378 consecutive veterans with a history of GERD who were undergoing a first upper endoscopy found that 13.2% of patients had biopsy-confirmed Barrett's disease.[83] Although the true prevalence of Barrett's disease in the general population is unknown, recent evidence suggests that it may be similar to the prevalence in patients with GERD. In a study enrolling 110 asymptomatic veterans undergoing screening colonoscopy, Barrett's disease was endoscopically visible in 25% of individuals, and an additional 16% with an endoscopically normal gastroesophageal junction had intestinal metaplasia on biopsy.[84] Such a high prevalence has not been confirmed in other studies, however. A larger study of 961 patients showed a 6.8% prevalence in all patients and a 5.6% prevalence in 556 patients who had never experienced heartburn.[85]

Controlled studies comparing the incidence of Barrett's esophagus in medically treated patients versus untreated patients are not available. In a cohort study comparing medical with surgical treatment of GERD, Barrett's esophagus developed in 12 of 83 patients treated with PPIs and cisapride over a follow-up period of 24 months, thus calling into question the ability of medical therapy to prevent Barrett's disease.[86] To date, no conclusive evidence has established that any therapy can prevent Barrett's disease.

Under the current recommendations of the American College of Gastroenterologists, Barrett's disease (intestinal metaplasia of the esophageal epithelium) should be treated to the end point of symptom control and maintenance of healed esophageal mucosa—the same treatment end points for GERD.[87] These recommendations are supported by a case-control study demonstrating that the risk for esophageal adenocarcinoma was strongly correlated with symptoms of heartburn or regurgitation. In this study, the strength of the association between symptoms and the development of adenocarcinoma was virtually identical in patients with Barrett's disease and those without, thus supporting the use of similar end points of treatment in both populations.[88]

Nonetheless, controversy exists over whether treatment should seek to accomplish more aggressive goals. In patients with Barrett's disease, treatment with PPIs to the point of eliminating the symptoms of reflux does not necessarily indicate that reflux into the esophagus has been eradicated. In one study of 30 patients with Barrett's esophagus whose symptoms had been completely eliminated with lansoprazole therapy, persistent pathologic acid reflux was demonstrated in 12 patients.[89] These findings have been confirmed in other studies[90] and are explained by the theory that patients with Barrett's disease may have a decreased visceral ability to sense acid reflux.[91] Furthermore, although the amount of bile reflux may be reduced by PPI therapy,[92] it persists in a substantial portion of Barrett's patients rendered asymptomatic with PPIs.[93] These findings raise the suggestion that PPI therapy in patients with Barrett's esophagus should be titrated according to pH monitoring rather than by symptomatic response, although no firm recommendation for pH monitoring is currently in place.

Because Barrett's disease is a significant risk factor for the development of esophageal adenocarcinoma, there has been considerable interest in the use of pharmacologic agents to prevent the progression to cancer. One form of chemoprevention is the use of acid-suppression mechanisms to normalize intraesophageal pH. Laboratory studies have offered theoretical evidence that effective control of intraesophageal pH may promote the regression of Barrett's esophagus or prevent progression to adenocarcinoma. In a prospective study of 42 patients, Ouatu-Lascar et al. demonstrated that patients with normalized intraesophageal pH have decreased proliferation cell nuclear antigen (PCNA) expression, which is a marker of cellular proliferation, and an increase in the expression of villin, a marker of differentiation.[94] It is unknown, however, whether these markers can reliably predict the likelihood of development of esophageal adenocarcinoma.

Clinical evidence to support this strategy has been inconsistent and suggests very modest benefits with medical therapy, at best. In one study, 68 patients with Barrett's esophagus were randomized to receive aggressive acid-suppression therapy (omeprazole, 40 mg twice a day) or standard therapy (ranitidine, 150 mg twice a day). Patients who received omeprazole showed significantly better normalization of intraesophageal pH and demonstrated a greater decrease in the area and length of Barrett's esophagus, with 8% demonstrating regression after 2 years.[95] An uncontrolled study of a cohort of 14 patients treated with omeprazole, 60 mg daily, showed a

mean reduction in the length of Barrett's esophagus. Twelve patients in that study had complete normalization of intraesophageal pH. Several other studies of cohorts treated with H2RAs or PPIs have not demonstrated significant regression, but they may have been limited by their small sample size, short length of follow-up, or failure to normalize intraesophageal pH.[96,97] A finding that has been observed in multiple studies is the appearance of squamous islands of tissue within the field of intestinal metaplasia. Although it was hoped that the squamous islands were indicative of some form of regression, biopsies of these islands have demonstrated the presence of underlying columnar epithelium, thus suggesting that the islands represent overgrowth of squamous epithelium rather than true regression.[98] The prognostic significance of regression of the length or area of Barrett's metaplasia is unclear. A nonrandomized study demonstrated that patients with Barrett's disease in whom dysplasia did not develop were more likely to have been treated with PPIs and were treated for a longer duration than those in whom dysplasia did develop.[99]

Another potential approach to chemoprevention uses nonsteroidal anti-inflammatory drugs (NSAIDs). A large-scale case-control study using a national research database of patient records throughout the United Kingdom identified a lower odds ratio for the development of esophageal cancer in patients who were prescribed NSAIDs.[100] Another case-control study of 293 patients with esophageal adenocarcinoma demonstrated an odds ratio of 0.37 for the development of cancer in patients taking aspirin.[101] These results are supported by data from laboratory experiments, in which it was found that cyclooxygenase-2 (COX-2) inhibition is associated with antiproliferative and proapoptotic effects in Barrett's-associated esophageal adenocarcinoma cells in culture.[102] In a rat model of Barrett's esophagus, treatment with an NSAID or COX-2 inhibitor yielded lower rates of esophageal adenocarcinoma than did treatment with a placebo. Although Barrett's esophagus is associated with a 50- to 100-fold increase in the risk for adenocarcinoma in comparison to the general population, the absolute incidence is still small, as shown in a Mayo Clinic retrospective review in which adenocarcinoma developed in 2 of 104 patients observed an average of 8.5 years.[103] Consequently, the number of patients treated with a chemopreventive strategy to prevent a single case of esophageal adenocarcinoma would be very high. Such a strategy would therefore need to be safe, inexpensive, and readily available, thus making NSAIDs an appropriate candidate as a chemopreventive agent. Large-scale prospective trials to test chemoprevention strategies are needed.

EXTRAESOPHAGEAL MANIFESTATIONS OF REFLUX

Asthma

Several mechanisms have been demonstrated by which reflux induces the symptoms of asthma, including the microaspiration of gastric contents,[104-107] vagally mediated bronchoconstriction,[108,109] chest pain, and increased airway reactivity.[110,111] The cause-and-effect relationship between the two entities is not entirely clear because it has been postulated that asthma may contribute to GERD. Inspiratory airway obstruction may accentuate the negative thoracic pressure and alter the abdominal-thoracic pressure gradient, thus overcoming the valve mechanism of the gastroesophageal junction. Forced expiration in the presence of airway obstruction may cause the diaphragm to flatten and thereby compromise the anatomic antireflux mechanism.[112] Specific modalities to diagnose GERD-related asthma include sputum inspection for lipid-laden alveolar macrophages and scintigraphic technetium monitoring, but these tests are poorly sensitive for the condition and are rarely used in clinical practice. Dual-probe pH monitoring of the pharynx and distal esophagus is considered the standard for the diagnosis of GERD-related asthma and may document reflux of acidic material into the pharynx and correlate reflux events with respiratory symptoms. The temporal relationship between reflux events and respiratory symptoms is not entirely consistent. In a study of wheezing episodes in 48 patients, 10% of the episodes were preceded by reflux, 20% were followed by reflux, and 15% occurred concurrently.[113] Another study found that only 48% of cough or wheezing events correlated with reflux events.[114]

In practice, the diagnosis of reflux-induced asthma is made empirically on the basis of an improvement in pulmonary symptoms after treatment with antisecretory medications.[115] Although studies have sought to determine whether treatment of reflux improves respiratory symptoms in patients with GERD-related asthma, most are flawed by small sample size, short duration of treatment, and failure to demonstrate normalization of intraesophageal pH.[116-118] In a study performed by Harding et al., which evaluated PPI therapy in patients with GERD-related asthma, 30 patients were treated with 3 months of omeprazole.[119] The medication dosage was started at 20 mg daily and titrated according to 24-hour pH testing results until adequate acid suppression was achieved. Asthma symptom scores were assessed on monthly follow-up and demonstrated that 22 of the 30 patients showed at least 20% improvement in asthma symptom scores or peak expiratory flow. Among responders, asthma symptom scores decreased steadily from 1 month to the next over the 3-month period (Fig. 17–3). These findings suggest that the majority of patients with GERD-related asthma stand to benefit from treatment with PPIs and support treatment with a regimen of omeprazole for at least 3 months with monitoring of asthma symptoms, medication use, and peak expiratory flow. Patients who fail to improve with treatment should undergo 24-hour pH testing to assess the adequacy of acid suppression. In patients who do not respond to PPI therapy after pH probe–guided optimization, medical therapy is not likely to improve the symptoms (Fig. 17–4).

Chronic Cough

Patients with symptoms of cough persisting for at least 3 weeks in the absence of any known cause (confirmed by a normal chest radiograph) are considered to have

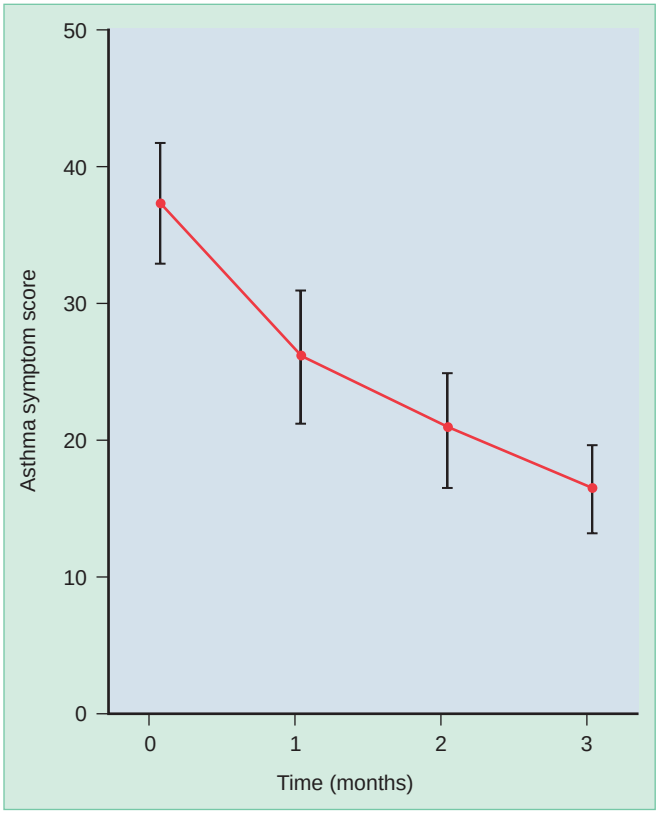


Figure 17–3. Time course of respiratory symptoms in patients with asthma and gastroesophageal reflux disease treated with acid suppression therapy. (Adapted from Harding SM, Richter JE, Guzzo MR, et al: Asthma and gastroesophageal reflux: Acid suppressive therapy improves asthma outcome. Am J Med 100:395-405, 1996.)

chronic cough. Among nonsmoking patients meeting these criteria, GERD is found to be the cause of the cough in 26% to 31% of cases.[120,121] As with asthma, the mechanism by which GERD leads to coughing may be multifactorial. Mechanisms include a vagally mediated esophagotracheobronchial reflex[122,123] and direct microaspiration of peptic contents into the airways.[124] Non-acid reflux may also play a role in contributing to chronic cough. Irwin et al. published the results of a cohort of eight patients with GERD-related cough confirmed by pH monitoring who failed acid-suppression therapy despite normalization of intraesophageal pH. After undergoing antireflux surgery, all patients had improvement in cough.[125] No studies have directly investigated the role of non-acid reflux in patients with chronic cough.

Chronic persistent cough attributable to GERD cannot be diagnosed on the basis of history alone because up to 75% of these patients may deny typical signs or symptoms of reflux.[123,126] The standard test for the diagnosis of GERD-related cough is dual-probe 24-hour esophageal pH monitoring. In addition to documenting reflux, pH testing may establish a temporal relationship between reflux events and cough.[127] Because of the expense and discomfort posed by 24-hour pH monitoring, a trial of empirical PPI therapy is reasonable for patients with chronic cough and a history suggestive of GERD. However, in patients who lack any reflux symptoms and have a normal chest radiograph, ambulatory pH monitoring should be considered before initiating acid-suppression therapy.[112]

Aggressive antisecretory therapy may be successful in treating GERD-related cough. Poe and Kallay developed and tested a protocol in which patients with suspected GERD-related cough were initially treated with high-dose PPIs (e.g., omeprazole, 40 mg). If the patient had dysphagia or did not respond adequately to antisecretory therapy, a prokinetic agent (cisapride or metoclopramide) was added.[121] Among 54 patients with a history suggestive of GERD-related cough, 24 experienced resolution of the cough with PPI therapy. Eighteen required the addition of a promotility agent. After 6 weeks of therapy, resolution was achieved in 95% of responders. Patients who failed to respond to therapy after 2 months underwent a 24-hour pH test to assess for adequacy of acid suppression, and three patients were found to have normal DeMeester scores. This study supports the empirical use of high-dose PPIs for at least 6 weeks, with consideration for the addition of metoclopramide and 24-hour pH monitoring if symptoms do not improve.

Reflux Laryngitis

Among the otolaryngologic disorders associated with GERD, reflux laryngitis is perhaps the most common. Symptoms of reflux laryngitis include excessive throat mucus, chronic throat clearing, chronic cough, hoarseness, sore throat, halitosis, and a globus sensation. As with the other extraesophageal disorders, there is evidence to support more than one mechanism by which reflux leads to laryngitis, including direct exposure of the larynx to gastric acid refluxed through an esophageal-pharyngeal pathway.[128,129] Another postulated mechanism implicates a vagally stimulated chronic cough and throat clearing as a cause of laryngeal injury.[130]

In the diagnosis of reflux laryngitis, other causes of laryngitis should be considered and evaluated. Evaluation should include laryngoscopy (Fig. 17–5), which may show laryngeal edema and erythema, particularly in the posterior aspect of the larynx. Granulation or ulceration may also be seen.[131] Dual-probe pH testing, with one of the probes placed in the pharynx, may document the occurrence of esophagopharyngeal reflux. A high degree of suspicion for GERD should be maintained in patients with laryngitis because the majority of patients with pH-confirmed reflux laryngitis lack the typical symptoms of GERD.[132]

In practice, empirical therapy with antisecretory medication is considered reasonable, although placebo-controlled studies of the efficacy of PPI therapy in this context are few and give conflicting results. On the basis of currently available data, the optimal dose of PPI and optimal length of therapy are unknown.[133] A study by el-

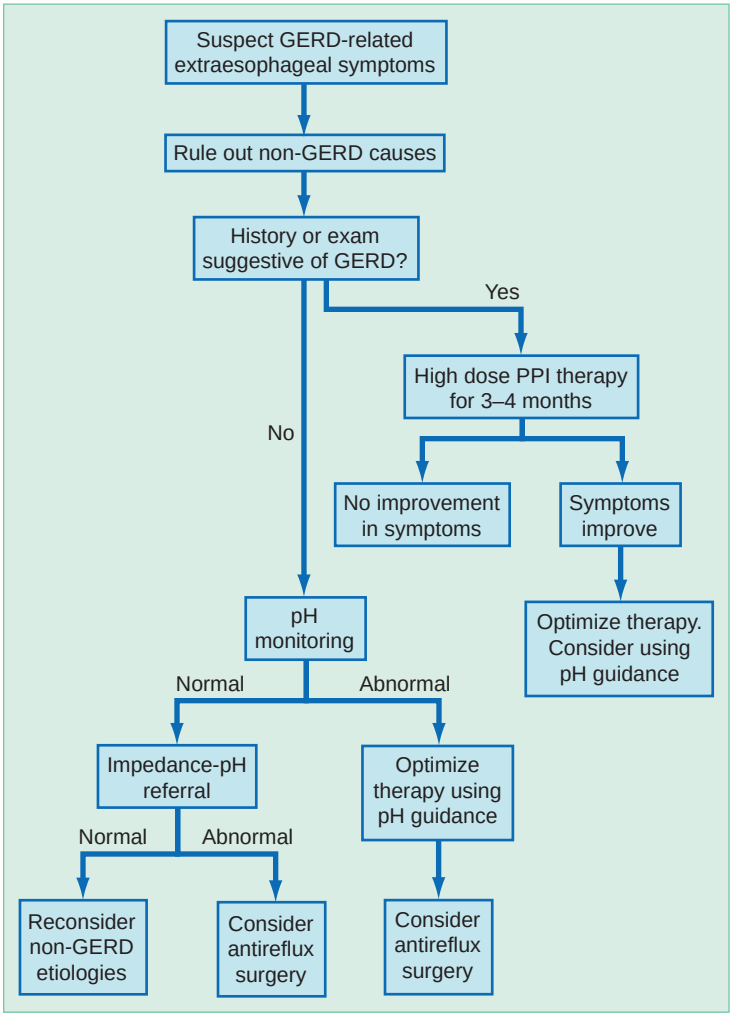
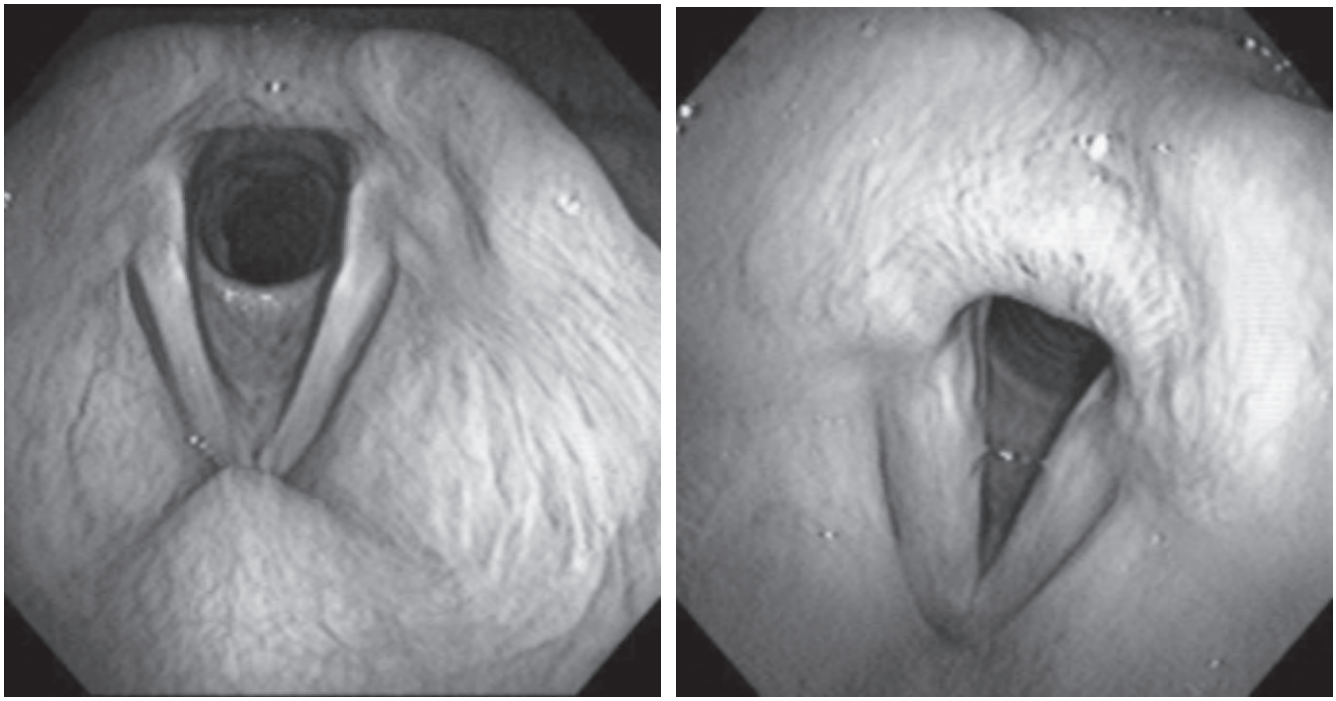


Figure 17–4. A protocol for the approach to treatment of extraesophageal symptoms of gastroesophageal reflux disease (GERD). PPI, proton pump inhibitor.

Serag et al. showed that in patients with reflux laryngitis treated with lansoprazole, 30 mg twice a day, 6 achieved a complete symptomatic response as compared with only 1 of 10 receiving a placebo.[134] A study conducted by Eherer et al. demonstrated similar results in patients given pantoprazole, 40 mg twice daily, but symptomatic improvement also occurred in patients given placebo, thus suggesting a role for watchful waiting in these patients.[135] Although the use of both cisapride and a PPI was associated with an improvement in symptoms in an uncontrolled trial,[136] no controlled studies have demonstrated the efficacy of adding promotility agents.

SUMMARY

Medical therapy for GERD includes both lifestyle modifications and pharmacologic interventions. Although a number of lifestyle modifications play a role in the education of patients with GERD, none of these strategies has been shown to be significantly efficacious when used alone for long-term treatment. Symptomatic relief from GERD can be reliably achieved with a number of agents, including PPIs, H2RAs, and promotility agents. Among the antisecretory therapies, PPIs are the most potent agents for reducing gastric acid production. To achieve the goal of long-term symptom control, lifelong therapy with PPIs may be needed, although various strategies can be used to step down to a less potent agent or reduce the frequency of dosing. In patients in whom erosive esophagitis develops, PPIs produce the highest and most durable remission rates, and lifetime therapy is generally required. Even though medical therapies have not been conclusively shown to prevent Barrett's esophagus and esophageal strictures, they play a significant role in treating underlying GERD symptoms in patients with these disorders. It is hoped that medical therapy may prevent the progression of Barrett's esophagus to dysplasia or adenocarcinoma, although studies have not conclusively demonstrated this effect. Extraesophageal manifestations of GERD include asthma, chronic cough, and laryngitis and continue to present a difficult set of disorders to treat. The diagnosis may not be straightforward because patients often have extraesophageal symptoms as the primary complaint, sometimes in the absence of typical GERD symptoms. Patients with extraesophageal symptoms of GERD generally require a long duration of high-dose acid-suppression therapy. Non-acid reflux may



A B

Figure 17–5. Endoscopic images of the larynx. **A,** The normal larynx, with mobile cords and distinct ventricles. Signs of reflux laryngitis, such as granulation, erythema, edema, or posterior commissure hypertrophy, are not present. **B,** Vocal cord edema in a patient with reflux laryngitis.

also play a role in these disorders, which suggests that promotility agents may need to be added or antireflux surgery may be more appropriate. With the advent of impedance-pH monitoring, future studies are expected to refine the optimal therapy for extraesophageal symptoms.

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Chapter

18

Laparoscopic and Open Nissen Fundoplication

Swee H. Teh · Robert W. O'Rourke · John G. Hunter

Gastroesophageal reflux disease (GERD) is the most common disorder of the esophagus and gastroesophageal junction. With nearly half of Americans experiencing heartburn symptoms at least monthly, GERD is a serious health concern in the Western world. For the 6% to 10% of Americans who describe daily reflux symptoms, GERD increases the risk for esophageal stricture, Barrett's esophagus, and esophageal cancer and has a significant impact on work productivity.[1-3] The modern era of GERD therapy has brought advances in diagnosis and treatment and, subsequently, a better understanding of the pathophysiology of GERD. The single most important factor in the development of GERD is an incompetent lower esophageal sphincter.[4] Progressive dilation plus deterioration of the gastroesophageal valve mechanism results in loss of the antireflux barrier and allows for acid and bile reflux. The goal of antireflux surgery is to re-establish the competency of the lower esophageal sphincter while preserving the patient's normal swallowing capacity.[5]

Improved medical therapies in the form of H_2 receptor antagonists and proton pump inhibitors (PPIs) have brought both symptomatic relief and effective resolution of esophageal inflammation, which may help ameliorate some of the long-term sequelae of GERD, but medical therapy must be continued indefinitely and does not prevent bile reflux. Antireflux surgery provides a permanent anatomic and physiologic cure with symptomatic relief and prevents the adverse consequences of ongoing esophageal exposure to acid and bile refluxate.

The Nissen fundoplication is the gold standard for the operative treatment of GERD. This well-established procedure has proved to be both durable and safe over a period of more than 20 years. With introduction of the laparoscopic approach in the 1990s, the number of Nissen fundoplications performed annually has increased threefold.[6,7] Since Dr. Nissen's original fundoplication in 1937 to protect a gastroesophageal anastomosis, the Nissen fundoplication has undergone many modifications. The principles of modern Nissen fundoplication include secure crural closure and creation of a short (≤2 cm), 360-degree "floppy" fundoplication designed to most closely replicate the normal physiology of the gastroesophageal flap valve.[8]

This chapter discusses the technical aspects of laparoscopic and open abdominal Nissen fundoplication for GERD.

CLINICAL FEATURES

As with all operations, proper patient selection is essential for a successful outcome. A thorough history and physical examination, as well as appropriate laboratory tests, should be completed to establish a diagnosis of GERD and eliminate other potential causes of discomfort. Classic symptoms include heartburn, regurgitation, and dysphagia. The frequency and timing of reflux symptoms, the relationship to meals, symptom exacerbation in the supine or upright position, and difficulty swallowing should be noted. The response to medical therapy and the duration of medical therapy are also recorded.

In addition, patients may have atypical symptoms such as chronic cough, asthma, pulmonary disease, dysphagia, odynophagia, hoarseness, and chest pain. These patients should undergo cardiac evaluation, including a chest radiograph, electrocardiogram, and if indicated, pulmonary function tests, in addition to standard diagnostic evaluation for gastroesophageal reflux. Patients with atypical symptoms and those who fail to respond to medical therapy may show less improvement in symptoms after Nissen fundoplication than those with typical GERD symptoms.[9]

PREOPERATIVE EVALUATION

The preoperative evaluation of patients with GERD should be thorough. At a minimum, patients should undergo a barium swallow and esophagogastroduodenoscopy (EGD). Performance of an esophageal motility study (EMS) is currently a preoperative standard to detect esophageal motility disorders that may lead to troublesome postoperative dysphagia. Although it has been dogma that patients with ineffective esophageal motility (IEM) (mean distal peristaltic amplitude <30 mm Hg or >20% loss of peristalsis) should undergo a partial fundoplication to prevent postoperative dysphagia, recent studies have demonstrated that postoperative dysphagia after Nissen fundoplication is no greater with IEM than with normal esophageal motility.[10] We routinely perform a preoperative EMS because it also allows documentation of a motility "baseline" that may serve for comparison should postoperative dysphagia develop. Twenty-four-hour ambulatory pH monitoring is essential for the evaluation of patients with nonerosive reflux disease (NERD), supraesophageal symptoms, or lack of response to PPI therapy. Patients with typical reflux symptoms and erosive esophagitis (or Barrett's esophagus and peptic stricture) do not routinely need a pH study to prove the diagnosis of reflux preoperatively. In a multivariate analysis of factors predicting a good response to antireflux surgery, the best response to antireflux surgery (98% good to excellent results) occurred in patients who had symptom relief with PPIs, typical GERD symptoms, and a positive 24-hour pH study.[11]

Other new diagnostic devices that will play an increasingly important role in the diagnosis of GERD over the coming decade are the BRAVO pH probe (Medtronics, Minneapolis, MN) and multichannel intraluminal impedance (MII). The BRAVO probe monitors distal esophageal pH and transmits the data to a small external recorder worn on the belt for a duration of up to 48 hours. It has the advantage of being more comfortable than standard 24-hour pH probes. In addition, early data suggest that 48-hour BRAVO monitoring may have greater sensitivity for GERD than standard 24-hour monitoring does.[12] MII has similarly gained significant popularity for the detection of both acid and non-acid GERD. MII measures electrical resistance (impedance) between a series of electrodes on a catheter placed across the gastroesophageal junction and up the esophagus. Air within the esophageal lumen causes an increase in impedance, whereas the presence of liquid refluxate within the esophageal lumen causes a decrease in impedance. By determining the temporal sequence of impedance events, one can establish the directional flow of gas and liquid within the esophagus (i.e., distal flow: swallow; proximal flow: reflux event or belch). By coupling this technology with data from a standard pH probe, one can identify both acid and non-acid refluxate. In part because of lack of standardized analytic software, MII is currently considered a research tool only. However, this technology may become the best method to determine which patients will best respond to surgery. Those with significant symptoms and concomitant reflux events (acid or non-acid) while taking acid-suppression therapy may be the ideal patients for surgical therapy.[13]

INDICATIONS FOR SURGERY

Although several innovative endoscopic methods for treating GERD have achieved modest popularity over the past 5 years, the indications for antireflux surgery have changed little and surgery remains the "gold standard" by which endoscopic procedures should be compared. Box 18–1 lists the primary indications for antireflux surgery.

There is rarely an indication for antireflux surgery in patients with uncomplicated GERD who are satisfied with medical therapy (single-dose or twice-daily PPI). Such patients are usually maintained on medical therapy as long as their symptoms are well controlled. In contrast, antireflux surgery should be seriously considered in patients with severe GERD and symptoms not controlled by medical therapy, patients who would like to avoid lifelong antacid therapy, and those with severe complicated GERD (Barrett's esophagus, ulcer, stricture). In the latter group of patients, surgery may not be necessary if ulcer healing or a 24-hour pH probe while taking medications confirms the absence of acid reflux. However, because elimination of excessive reflux is difficult to achieve in these patients, who have the worst form of GERD, we generally believe that antireflux surgery should be considered. Preoperative endoscopic or medical treatment of esophageal stricture or peptic ulcer disease must be accomplished before surgery. In a patient with esophageal stricture, preoperative dilation to at least 16 mm (48 French) is advisable to minimize the chance that the customary postoperative dysphagia (a result of edema and early postoperative esophageal dysmotility) will be compounded by a tight stricture. If preoperative dilatation to 16 mm is successful—several sessions are sometimes necessary—it is usually possible to extend the

Box 18–1 Primary Indications for Antireflux Surgery

- Patients with esophageal and/or extraesophageal GERD symptoms that are responsive but not completely eliminated by PPIs
- Patients with heartburn eliminated by PPIs but continued non-acid reflux
- Patients with well-documented reflux events preceding symptoms such as chest pain, cough, or wheezing
- Patients with GERD complications such as peptic stricture, Barrett's esophagus, or vocal cord injury while taking PPIs twice a day
- Patients with well-documented GERD who desire to stop chronic PPI use despite excellent symptom control for any reason (e.g., side effects, lifestyle, expense)

dilation intraoperatively to 18 or 20 mm, the standard-size dilators used by surgeons for calibrating the fundoplication.

In certain subgroups of patients with severe GERD, antireflux surgery may not be indicated. Medically complicated, morbidly obese (body mass index >35 kg/m^2) patients with significant GERD should be treated by Roux-en-Y gastric bypass. Patients with Barrett's esophagus and high-grade dysplasia or adenocarcinoma should be treated by esophageal resection. Severe strictures that are not responsive to dilatation therapy should also be treated by esophageal resection. Patients with low-grade dysplasia should be treated with high-dose PPIs for 3 months, after which they should undergo repeat biopsy. Fundoplication may be considered in such patients if subsequent biopsy shows no progression to high-grade dysplasia or carcinoma. Finally, GERD patients with previous gastric surgery should be approached cautiously. GERD in patients after gastric bypass or vertical banded gastroplasty cannot be treated by fundoplication because the fundus has been anatomically disrupted by the previous surgery.

Once a decision is made to perform a surgical antireflux procedure on a patient with GERD, the next step is to decide which type of fundoplication to perform. Recent data support the concept that Nissen fundoplication is effective therapy for GERD and is not associated with significant long-term dysphagia, even in patients with IEM.[14] These data, combined with data suggesting that partial fundoplication is associated with high long-term failure rates,[15] have led to a significant decrease in the application of partial fundoplication in patients with GERD, regardless of esophageal peristaltic function. Currently, only patients with a "named" esophageal motility disorder, such as achalasia or scleroderma, should undergo partial fundoplication. Despite this recent trend toward complete (Nissen) fundoplication in most patients, emerging recent evidence suggests that long-term satisfactory results may be achieved with anterior partial fundoplication.[16] The debate regarding the role of partial fundoplication in the treatment of GERD therefore persists, although most experienced surgeons prefer to perform complete fundoplication in most patients.

PRINCIPLES OF NISSEN FUNDOPLICATION

Basic surgical principles guide the successful performance of Nissen fundoplication, regardless of the approach (laparoscopic or open). Box 18–2 lists the primary principles of Nissen fundoplication.

Box 18–2 Primary Principles of Nissen Fundoplication

- Circumferential crural dissection with preservation of the vagus nerves
- Circumferential dissection of the esophagus at the gastroesophageal junction
- Adequate mobilization of the esophagus (or Collis gastroplasty) to attain 2 to 3 cm of intra-abdominal esophagus without inferior traction
- Crural closure with interrupted sutures
- Gastric fundus mobilization and adequate short gastric vessel division
- Creation of a short (<2 cm), floppy (loose around an 18- to 20-mm dilator) fundoplication anchored to the esophagus in several places

Open Versus Laparoscopic Nissen Fundoplication

Laparoscopic Nissen fundoplication was first reported by Dallemagne et al. in 1991.[17] Since then, several large clinical series of Nissen fundoplication have been reported, including longitudinal studies with long-term follow-up that demonstrate the results of both open and laparoscopic fundoplication to be equivalent.[18-20] Several randomized clinical trials published in the past decade have reached the same conclusion.[18,22-24] The laparoscopic approach is associated with shorter hospital stay, less postoperative pain, fewer wound-related complications, and earlier return to work. Despite these advantages, selection of the open versus the laparoscopic approach should depend on surgeon experience and the patient's previous surgical history. The intraoperative steps of surgical repair are relatively similar in both approaches. Laparoscopic Nissen fundoplication, however, requires that the surgeon possess advanced laparoscopic skills.

The approach to reoperative Nissen fundoplication is somewhat controversial. Some experts advocate that all reoperative surgery be performed through an open approach, but several large series have demonstrated equivalent results with laparoscopic and open reoperation.[25] Laparoscopic reoperation after open surgery, though feasible, may be tedious because the intra-abdominal adhesions associated with open surgery may be formidable.

LAPAROSCOPIC NISSEN FUNDOPLICATION

Position and Port Placement

After induction of general anesthesia, a Foley catheter and pneumatic calf compression devices are applied. The patient is placed in a split-leg position with both arms tucked and secured to the operating table. The surgeon stands between the patient's legs with the primary monitor over the patient's head. The first assistant stands to the patient's left, and the scrub technician stands to the patient's right. Pneumoperitoneum is achieved by inserting a Veress needle at the umbilicus.

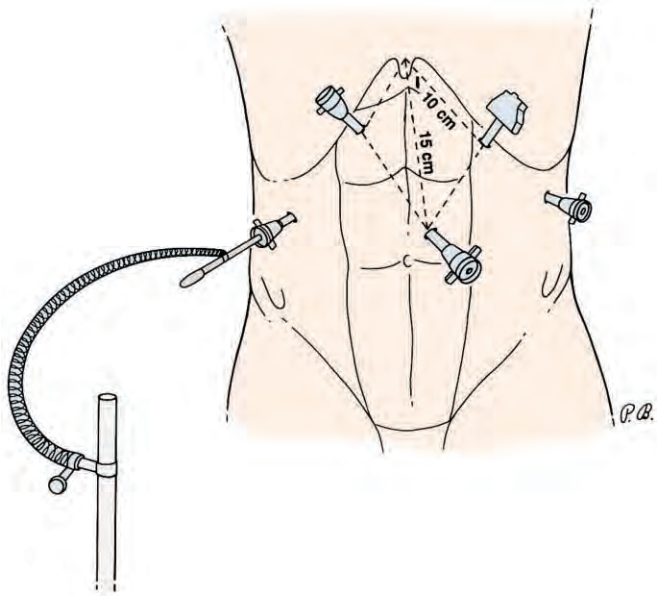

Figure 18–1. Preferred port site position for laparoscopic Nissen fundoplication.

A five-port (two 10-mm ports and three 5-mm ports) technique is used (Fig. 18–1). Additional ports may be placed as necessary. A 10-mm camera port is placed just superior and to the left of the umbilicus, approximately 15 cm below the xiphoid and medial to the inferior epigastric artery. A 45-degree laparoscope is placed through this port. The laparoscope camera may be managed by the first assistant or with a robotic camera holder. A thorough abdominal exploration with the laparoscope is routinely performed before initiating dissection. All secondary ports are placed under direct vision. With the patient in a steep reverse Trendelenburg position, a second port (10 mm) is next placed approximately 11 to 12 cm below the xiphoid process at the left costal margin. The third port (5 mm) is generally placed 8 to 10 cm farther down the left costal margin than the second port. This port should not be placed farther lateral than the anterior axillary line and may be limited by the reflection of the left colon. The fourth port, for liver retraction, is a 5-mm port placed on the right costal margin 12 to 15 cm from the sternal base (depending on the size of the liver). Alternatively, the liver can be retracted with a Nathanson retractor placed high in the subxiphisternal region. Finally, a 5-mm port is placed to the right of midline, at the level of the 10-mm dissecting port, so that it angles through the round ligament internally to lie immediately below the left edge of the liver.

Exposure

A 5-mm articulating liver retractor is placed through the right lateral port under laparoscopic visualization, and the left lobe of the liver is retracted anteriorly and superiorly to expose the hiatus. The right crus and caudate lobe of the liver should be clearly visible through the phrenoesophageal ligament if the liver retraction is adequate. The liver retractor is stabilized with an endoscopic instrument holder attached to the operating table. An atraumatic (Hunter type) grasper is placed through the left lateral port to assist in retraction of the stomach. The epiphrenic fat pad along the lesser curvature just below the esophagogastric junction is used for inferior retraction to minimize the risk of gastric or esophageal injury. The operating surgeon uses an atraumatic grasper in the left hand and a harmonic scalpel or electrosurgical dissecting scissors in the right hand.

Dissection

Lesser Curve

The pars flaccida of the gastrohepatic ligament is opened with the harmonic scalpel or scissors while taking care to preserve the hepatic branch of the vagus nerve, and the stomach is retracted to the patient's left and inferolaterally if possible. Preservation of this hepatic branch of the nerve may prevent impairment of gallbladder motility with subsequent cholelithiasis, although no data exist to support this theory. Nevertheless, some surgeons divide this structure routinely without significant adverse outcomes. In addition to the nerve, an aberrant left hepatic artery may be present in the pars flaccida in up to 13% of patients. If the gastrohepatic ligament is entered above the hepatic branch of the vagus nerve, the chance of encountering the aberrant left hepatic artery is minimal. Preservation of the aberrant left hepatic artery should be attempted if possible. On rare occasion, in the presence of an extremely large hiatal hernia it is necessary to divide the hepatic branch of the vagus or an aberrant left hepatic artery (or both) to reach the base of the right crus of the diaphragm. Clinically significant liver ischemia has not been reported in these circumstances.

Crus

Dissection of the lesser curve is extended superiorly, up to the esophagogastric junction, to reveal the caudate lobe below and expose the hiatus and the right crus of the diaphragm. The peritoneum overlying the right crus is incised, the medial border dissected, and the phrenoesophageal ligament divided along the apex of the hiatus (Fig. 18–2). Dissection is continued across the top of the crural arch until the left crus is exposed. The dissection is then carried down the border of the left crus until the angle of His and the gastric fundus limit further inferior dissection. The anterior vagus nerve crosses the esophagus in this region and should be identified and preserved. Periesophageal mediastinal dissection is initiated bluntly by introducing two round-nosed atraumatic graspers between the right crus and the esophagus and spreading horizontally (9- and 3-o'clock position) with the graspers closed (Fig. 18–3). This step is repeated to the left of the esophagus. The use of thermal devices is limited during mediastinal dissection to avoid undetected injury to the vagus nerves.

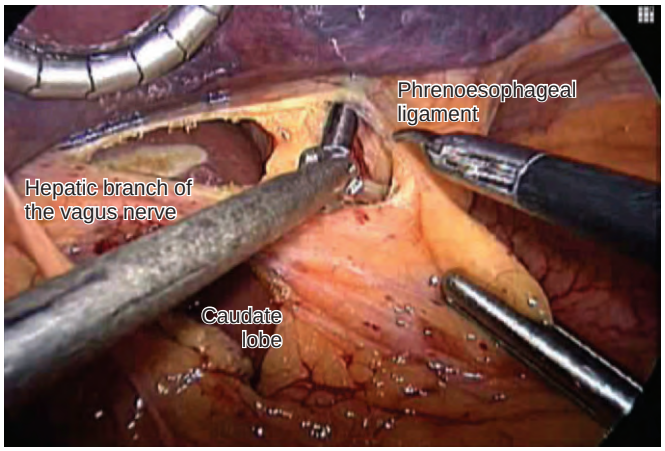

Figure 18–2. Dissection of the lesser curve (extending superiorly) and the phrenoesophageal ligament along the apex of the hiatus.

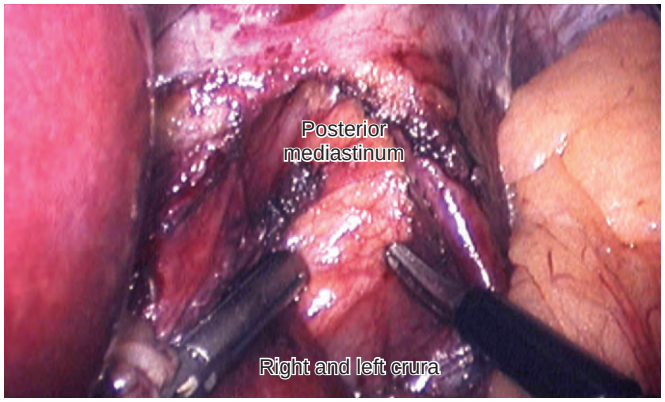

Figure 18–3. Horizontal (9- and 3-o'clock direction) spreading with closed graspers to open the posterior mediastinum.

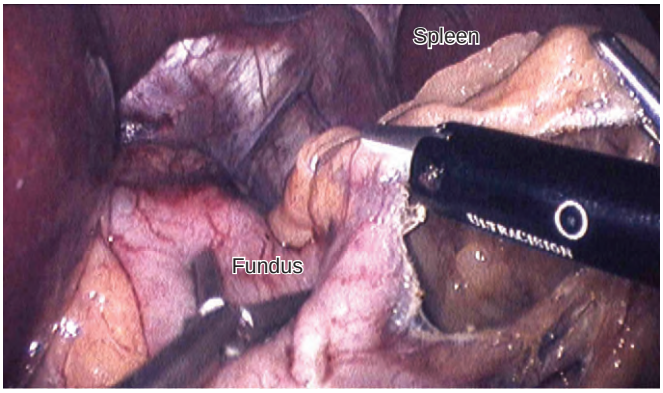

Figure 18–4. Taking down the greater curvature of the stomach by dividing the short gastric vessels.

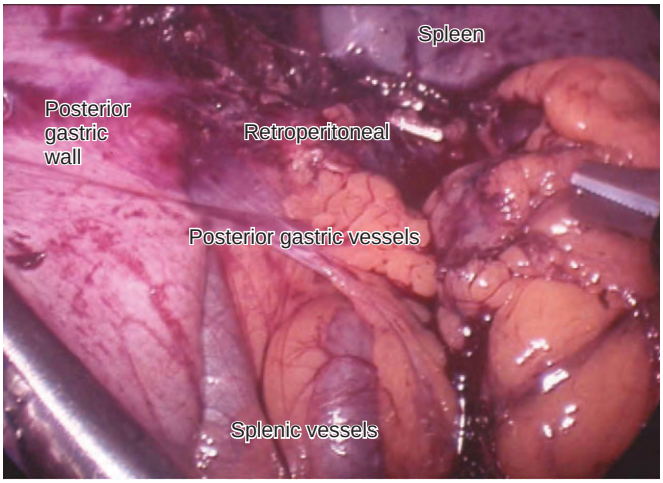

Figure 18–5. Dissection of the retroperitoneal gastrophrenic fold. (Reproduced with permission from Jamie A. Koufman, MD, Voice Institute of New York.)

Fundus and Greater Curve

Dissection of the fundus of the stomach is begun by identifying the point on the greater curvature approximately a third of the distance from the angle of His to the antrum. A convenient landmark for this point is the inferior pole of the spleen or (occasionally visible) the left gastroepiploic artery. With the surgeon's left-hand instrument grasping the stomach adjacent to the greater curvature and retracting posteromedially and the first assistant retracting the greater omentum anterolaterally, the lesser sac is entered with the harmonic scalpel, approximately 5 to 10 mm away from the greater curve of the stomach (Fig. 18–4). The short gastric vessels are divided individually with the harmonic scalpel until the superior pole of the spleen is reached. As one proceeds superiorly, three strategies may help dissection in this area:

1. Expose the superior pole of the spleen with "triangular retraction." The three corners of retraction in the axial plane are the spleen tip, the surgeon's left-hand instrument retracting anteromedially on the anterior wall of the fundus, and the first assistant retracting posteromedially on the posterior wall of the stomach.
2. If the greater omentum obscures the superior pole of the spleen, it should be retracted inferiorly. This may be accomplished by introducing an additional port and grasper in the left flank or placing a "reefing" polypropylene suture in the greater omentum and retracting the omentum through the left lateral port with the two long ends of this suture.
3. Layer the dissection of the vascular structures at the superior pole of the spleen, starting with the visceral peritoneal reflection, then the short gastric vessels, and then the retroperitoneal gastrophrenic tissues. Dividing the pancreaticogastric peritoneal fold and the posterior gastric artery is necessary to fully mobilize the fundus and reach the base of the left crus posteriorly (Fig. 18–5).

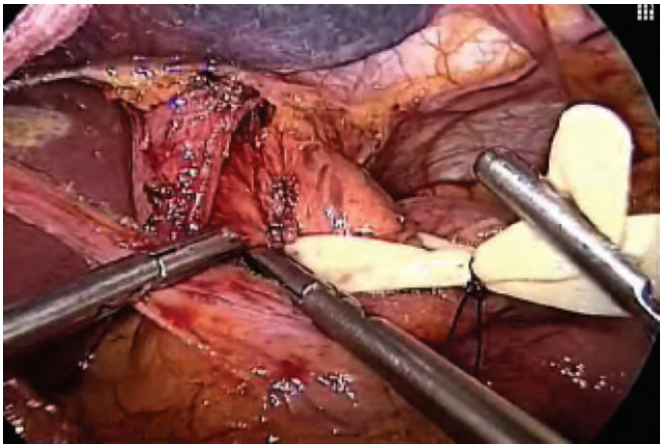

Figure 18–6. Penrose drain around the esophagus and secured with an Endoloop.

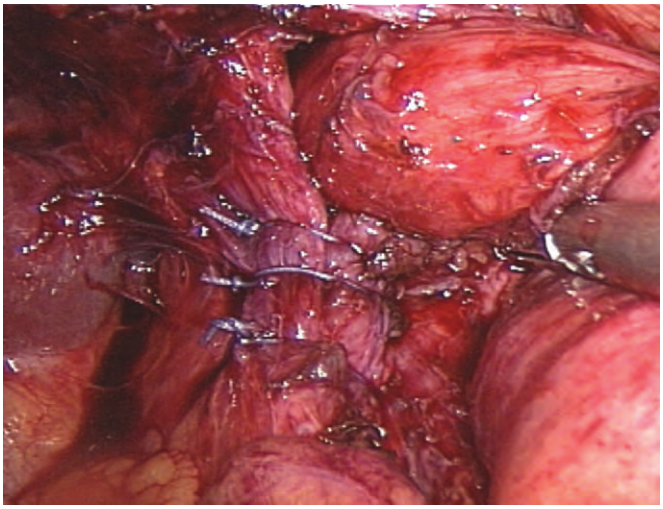

Figure 18–7. Crural closure with nonabsorbable suture starting posteriorly and working anteriorly.

Mediastinal and Posterior Esophagus

At the completion of gastric dissection, the base of the left crus is reached. If the earlier dissection reached the base of the right crus, the plane behind the esophagus is complete. Once this retroesophageal "tunnel" is made, a 4-inch-long, $^1/_4$-inch-wide Penrose drain is passed around the esophagus and secured with an Endoloop (Fig. 18–6). The first assistant places a toothed locking (gallbladder type) grasper on the secured Penrose drain and retracts inferiorly and to the patient's left. The esophagus is freed circumferentially within the mediastinum by blunt dissection. The posterior vagus is encountered adjacent to the esophagus and is generally retracted along with the esophagus. Dissection of the posterior vagus away from the esophagus exposes the vagus to injury later in the dissection. Although most of the mediastinal dissection can be done bluntly, an occasional aortoesophageal artery is encountered (usually high on the left) and should be controlled with the harmonic scalpel. The length of the mediastinal dissection depends on available intra-abdominal esophagus. In the presence of Barrett's esophagus, severe inflammation, stricture, giant hiatal hernia, or previous surgery, the esophagus is often foreshortened and will need extensive high mediastinal dissection or Collis gastroplasty, or both (see later).

To best assess intra-abdominal esophageal length, the Penrose drain is released and the distance from the gastroesophageal junction to the crural closure is measured. At least 2.5 cm of esophagus must be within the abdomen under no tension. If the maximal mediastinal dissection does not adequately reduce more than 2.5 cm of intra-abdominal esophagus, a Collis gastroplasty should be performed.

Repair

Crural Closure

The crura are closed from the right of the esophagus with interrupted nonabsorbable sutures placed 8 to 10 mm apart, 5 to 10 mm back from the crural edge. The peritoneal covering of the crura should be incorporated into the repair, and the sutures should be "staggered" in the anterior-posterior plane on the crura to avoid splitting the crural musculature along the length of the repair. The completed crural closure should be calibrated to the size of the esophagus containing a 56-French esophageal dilator (Fig. 18–7). One cannot close the crura with the dilator in place, but sutures can be added or cut out after the dilator has been used to properly size the crural aperture. To prevent reherniation, the crural closure is often performed with single 1-cm^2 Teflon felt patches, felt strips, or occasionally a piece of absorbable or nonabsorbable mesh placed across the crural closure. Several randomized trials have demonstrated a lower hernia recurrence rate when the closure is buttressed in this fashion.[26,27]

Fundoplication

The fundus is next passed posteriorly from left to right with atraumatic graspers to assess for adequate mobilization. The "shoeshine maneuver" involves sliding the fundoplication back and forth behind the esophagus to confirm good position (Fig. 18–8). One purpose of this maneuver is to confirm that no redundant fundus lies posterior to the esophagus after creation of the fundoplication. Grasping a point too low on the greater curvature may predispose to this error. The fundoplication should not retract significantly when the graspers are released. A 56- or 60-French esophageal dilator is then passed transorally into the stomach by the anesthesiologist under videoscopic vision by the surgeon. Good communication and slow advancement of the dilator are essential to minimize the risk of perforation at the esophagogastric junction. The dilator should pass without resistance. If resistance is encountered, the dilator is removed and a smaller dilator is passed. The size of the dilator is then increased until resistance is noted.

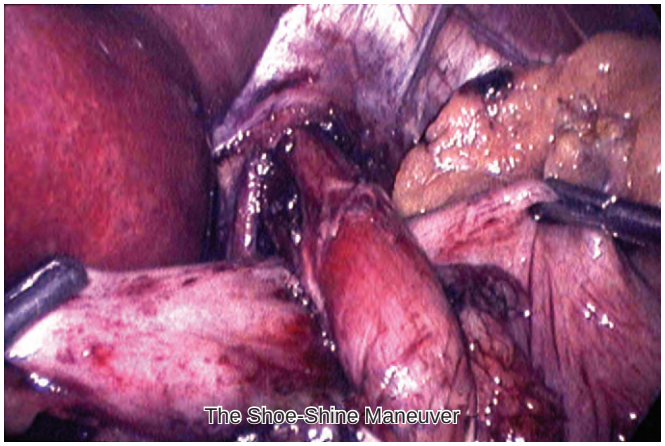

Figure 18–8. The "shoeshine maneuver" to ensure that the fundoplication is in good position without tension.

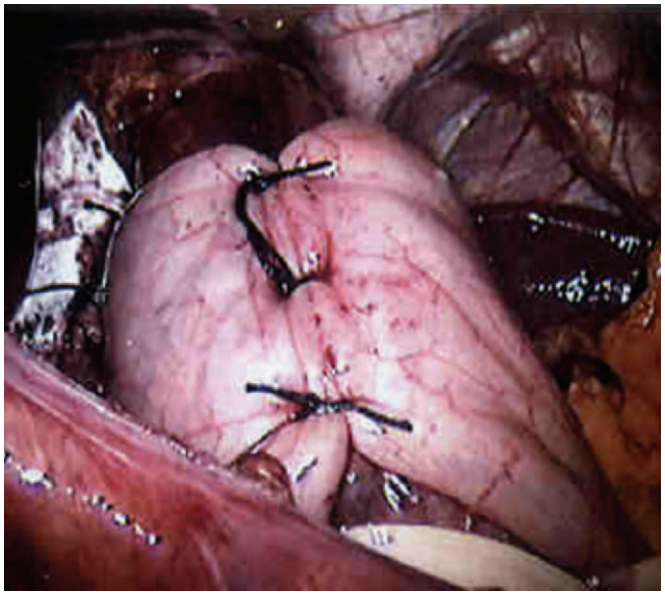

Figure 18–9. The completed Nissen fundoplication with three nonabsorbable sutures 1 cm apart.

After dilator placement, the most superior stitch of the fundoplication is placed 2 cm proximal to the esophagogastric junction with simple interrupted 2-0 nonabsorbable suture; full-thickness bites are taken through each side of the fundoplication and a partial-thickness esophageal bite in between. Two additional sutures are placed 1 cm above and 1 cm below the initial suture to create a 2-cm-long fundoplication that is secured to the esophagus just above the level of the esophagogastric junction (Fig. 18–9). Knots may be tied extracorporeally, but intracorporeal knotting decreases tissue trauma and optimizes knot tension and position. Some authors advocate infradiaphragm fixation of the fundoplication to the crura to prevent reherniation, but there is no evidence that this in any way decreases failure rates.

OPEN NISSEN FUNDOPLICATION

The principal steps in performing an open Nissen fundoplication are similar to the laparoscopic approach. Open Nissen fundoplication is indicated if surgeons do not have adequate laparoscopic experience or patients have dense adhesions because of previous upper gastrointestinal operations. Despite the improved tactile feedback with an open approach, it is important to note that exposure of the hiatus may be less easily achieved than with a laparoscopic approach. The techniques involved in open fundoplication are similar to those in laparoscopic fundoplication; the following sections therefore address only significant differences.

Exploration and Exposure

An upper midline incision with the use of a self-retaining retractor allows good exposure. A liver retractor placed close to the most posterior part of the left lateral lobe of the liver permits improved visualization. Optimal exposure is obtained when the diaphragm is seen to run vertically from the upper end of the incision directly posteriorly to the hiatus.

Lesser Curve

The thin gastrohepatic ligaments are incised, extended superiorly, and carried over the anterior surface of the esophagus as described earlier. Similarly, an aberrant left hepatic artery and hepatic branch of the vagus are protected if encountered in the pars flaccida. The anterior vagus is likewise identified and protected.

Crus

By retracting the lesser curve inferolaterally and to the right, the left crus is exposed. The right crus is dissected bluntly with the left fingers to create a retroesophageal space. A Penrose drain is passed around the lower part of the esophagus, excluding the posterior vagus nerve, and used as a retractor to provide better visualization of the retroesophageal space.

Mediastinal and Posterior Esophagus

With retraction on the Penrose drain, the esophagus can be dissected circumferentially. Similarly, the mediastinal dissection can be carried superiorly.

Fundus and Greater Curve

The loose attachments between the fundus and the left diaphragm are taken down. The short gastric vessels are ligated sequentially with the harmonic scalpel as described earlier or by serial division with clamps and suture.

Repair and Fundoplication

Crural repair and fundoplication are performed as described earlier. A "floppy" Nissen fundoplication requires that the fundic wrap admit the surgeon's index

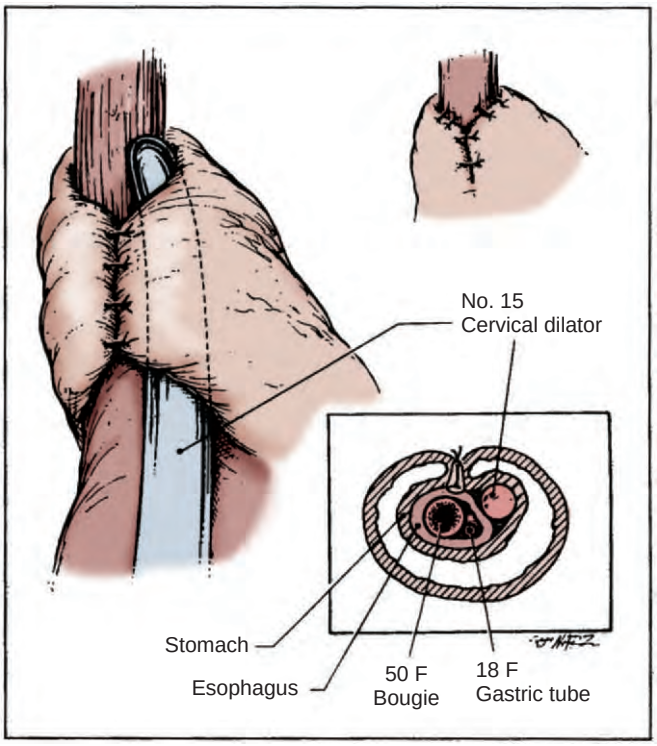

Figure 18–10. The original description of a "floppy" Nissen fundoplication by Donahue and Bombeck et al. in 1977.

finger between the wrap and the esophagus with the dilator in place (Fig. 18–10). Factors that influence the tightness of the wrap are the degree of mobilization of the fundus, the size of the esophageal dilator, and the sutures placed to create the fundoplication.

THE ACQUIRED SHORT ESOPHAGUS

The presence of a short esophagus increases the difficulty of laparoscopic Nissen fundoplication. Up to 20% of surgical failures with Nissen fundoplication are due to the lack of recognition of a short esophagus. A short esophagus is discovered more frequently in patients with esophageal stricture, Barrett's esophagus, and type III paraesophageal hernia. Esophageal foreshortening occurs as a result of recurrent acid peptic injury and subsequent fibrosis of the mediastinal esophagus. Given its pathogenesis, it is not surprising that esophageal stricture is often associated with esophageal foreshortening. Large hiatal hernias may also be associated with a short esophagus as a result of chronic cephalad displacement of the gastroesophageal junction. Preoperative results of barium swallow and EGD may provide an indication of a short esophagus, but no combination of preoperative clinical variables reliably predicts the presence of a short esophagus, and the diagnosis of this entity continues to be made definitively only in the operating room, where it is defined as failure to achieve 2.5 cm of intra-abdominal esophagus after standard mediastinal dissection techniques.

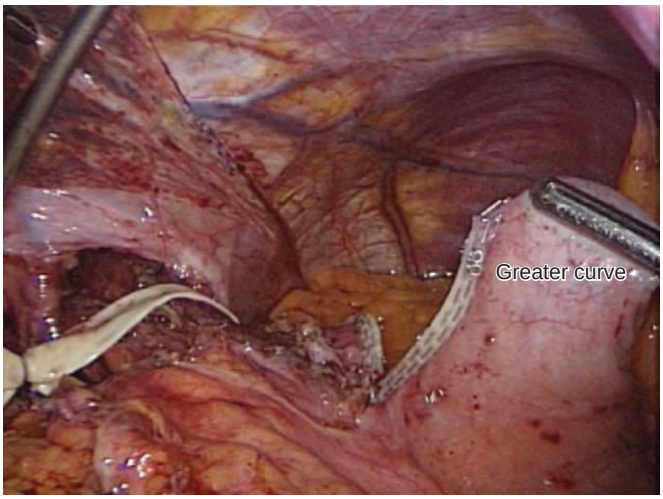

Figure 18–11. Laparoscopic stapling of the fundus from the greater curve toward the lesser curve.

Collis gastroplasty achieves esophageal lengthening by using the gastric cardia to create a neo-esophagus. In open surgery, this can be performed easily by applying a cut staple on the left side and parallel to the esophagus with a 16-mm dilator in place. When a minimally invasive approach is used, the complexity of the procedure is increased. It can be accomplished either by a combined thoracoscopic-laparoscopic approach or by a totally laparoscopic approach.[28,29]

With the esophageal dilator in place, a thoracoscope is inserted through the third intercostal space in the anterior axillary line and passed through the chest until it meets the mediastinal pleura. This is visualized with a laparoscope in place in the abdomen. The thoracoscope is then removed, and a linear stapler is inserted through the same port until it meets the mediastinal pleura at the crura as seen with the laparoscope. Dissection from the abdomen allows for passage of the stapler into the abdomen, which is then applied to the stomach alongside the esophageal bougie at the gastroesophageal junction at the angle of His. Application of this stapler divides the upper part of the stomach from the angle of His distally, along the esophageal dilator, thus creating a neo-esophagus.

The totally laparoscopic approach to a short esophagus has evolved from a method using an EEA circular stapler to our current approach, which involves the use of a linear stapler and creation of a stapled wedge gastroplasty.[30] An esophageal dilator (16 mm) is placed to calibrate the width of the gastric tube. A mark is made 3 cm inferior to the angle of His adjacent to the dilator. The laparoscopic stapled wedge gastroplasty can be performed by applying the laparoscopic stapler horizontally from the greater curve toward the lesser curve with the esophageal dilator in place (Fig. 18–11). The gastroplasty is completed by firing a staple parallel to the dilator in the cranial direction and therefore lengthening the esophagus (Fig. 18–12). The superior portion of the body of the stomach is then used as the wrap. Elements of importance in fashioning the fundoplication include

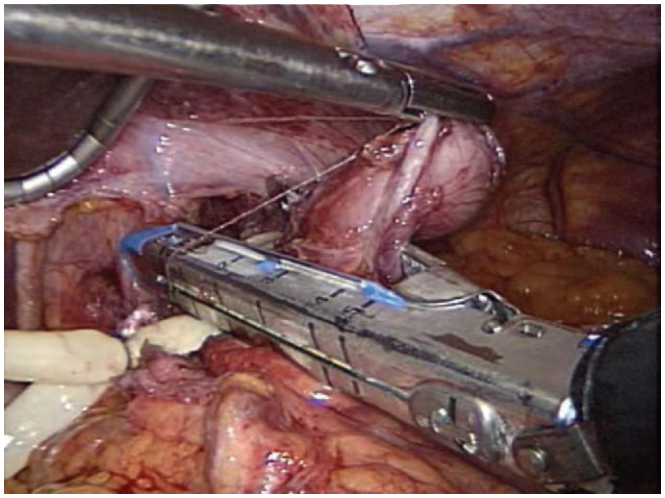

Figure 18–12. Lengthening of the esophagus by laparoscopic stapling parallel to the esophagus (with a dilator in place) in the cranial direction.

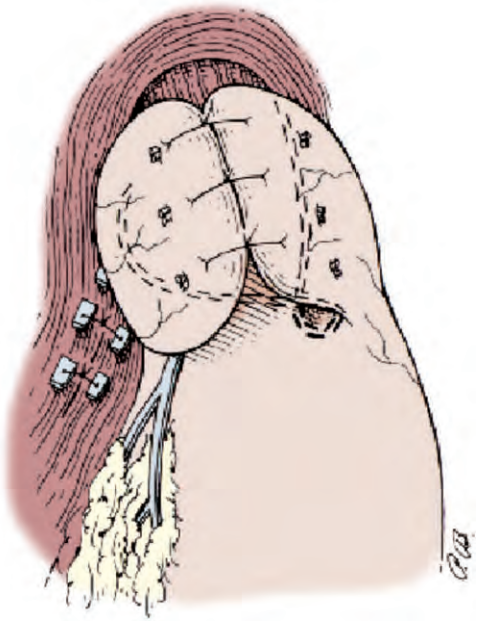

Figure 18–13. Final appearance of the fundoplication with the gastric portion of the staple line placed against the neo-esophagus.

placement of the initial suture of the fundoplication on the esophagus, immediately above the gastroesophageal junction, to ensure that acid-secreting (gastric) mucosa does not reside above the fundoplication. A second element that ensures safety and avoids wrap deformation is to place the gastric portion of the staple line against the neo-esophagus such that the tip of the gastric staple line sits adjacent to the middle suture of the fundoplication on the right side of the esophagus (Fig. 18–13). Before initiating a liquid diet we perform a water-soluble contrast study to ensure that no leak in the staple line is present.

POSTOPERATIVE CARE

A nasogastric tube is unnecessary after laparoscopic Nissen fundoplication. Patients are monitored on the regular floor and start clear liquids once they are awake and alert on the evening of surgery. The diet can be advanced to soft foods the following day. Patients may be dismissed home in 1 to 2 days. Although outpatient laparoscopic Nissen fundoplication has been performed, patient satisfaction is low, and management of pain and nausea may be difficult without parenteral access. Patients are advised to not eat large chunks of unchewed food for about 3 weeks, especially avoiding bread, meat, and raw vegetables. After the first 24 hours, postoperative pain can usually be managed with oral analgesia. We encourage 1-month follow-up; no studies are routine, but a barium swallow serves as an excellent screening test to evaluate postoperative dysphagia or reflux-like symptoms. In brief, if the fundoplication is intact and if a 12.5-mm barium tablet passes without difficulty, it is extremely unlikely that the symptoms are related to a technical deficiency of the repair.

SPECIFIC INTRAOPERATIVE AND POSTOPERATIVE COMPLICATIONS

Intraoperative complications include esophageal perforation, pneumothorax, splenic injury, bleeding, and missed visceral injury. Although these complications occur in less than 2% of all series,[30] the consequences can be grave.[31] Esophageal and gastric perforations occur in approximately 1.5% of cases and should be repaired primarily and buttressed with the fundoplication to minimize the risk for mediastinitis. We delay progression to a solid diet by 5 to 7 days when an esophageal repair has been performed.

Pneumothorax (1% to 5%) is usually self-limited but may cause immediate or delayed hemodynamic or respiratory consequences. When a pneumothorax is detected, we start by making the hole larger (to avoid a tension pneumothorax created by a one-way valve phenomenon). A red rubber catheter is inserted in the abdominal cavity with the tip placed through the rent in the pleura. At the completion of the operation, the wide end of the catheter is pulled out a trocar site and placed under water seal as the lung is re-expanded. A postoperative chest radiograph should be obtained and O_2 saturation monitored.

Splenic injury can take the form of infarction or bleeding. Superior pole infarction can occur with ligation of the short gastric arteries. Occasionally, some of these vessels enter the spleen directly without passing through the hilum and are end arteries to the upper pole. No further intervention is required if the tip of the spleen is infarcted. Rarely do patients have additional pain or fever under these conditions. Splenic bleeding, however, may require conversion to laparotomy and urgent splenectomy (0.5% to 1%). Incidental electrosurgery burns from arcing or inattention can result in delayed perforation and peritonitis. Meticulous dissection and gentle retraction can help prevent injury. An abdominal

survey before closure can help identify any signs of bleeding.

Late complications can take many different forms. Even though Nissen fundoplication has greater than a 90% success rate in eliminating reflux symptoms, over time, new or recurrent foregut symptoms will develop in 2% to 17% of patients. Although some dysphagia, gas bloating, and mild residual esophagitis are not uncommon in the early postoperative period, these symptoms generally resolve by 3 to 6 months; severe or persistent symptoms may indicate failure. Two percent to 6% of patients undergoing antireflux surgery will eventually require a reoperation.[20,25] Reported causes of failure vary significantly between studies, but a slipped or misplaced fundoplication and dehiscence are each responsible in approximately 15% to 30% of patients, transthoracic herniation occurs in 10% to 60%, and tight fundoplication, missed motility disorders, and paraesophageal hernias account for other modes of antireflux surgery failure.

SHORT-TERM RESULTS

The overall short-term results in appropriately selected patients are excellent.[18,32] Minor self-limited symptoms may occur in the postoperative period in some patients. Up to 20% of patients will experience transient dysphagia, which is usually caused by postoperative edema secondary to surgical manipulation of the gastroesophageal junction. These symptoms typically improve without intervention within 6 weeks. EGD or barium swallow is indicated if symptoms persist. Dilatation may provide relief of persistent dysphagia, but reoperation may be indicated in patients who are not responsive to dilatation. The failure rate of Nissen fundoplication is approximately 1% per year.[25,33] Bloating is common in GERD patients, and the severity is not significantly different before or after surgery.[25] Other common symptoms after Nissen fundoplication are early satiety, nausea, and diarrhea. These symptoms are likely to improve with time and tend to respond to nonoperative therapy. Bilateral vagus nerve injury may result in gastroparesis.

LONG-TERM RESULTS

At 5 to 8 years' follow-up, more than 95% of patients report satisfaction with their laparoscopic Nissen fundoplication.[34,35] A minority of patients report persistent dysphagia and bloating. The cause of surgical failure is most often due to (1) complete disruption of the wrap, (2) a slipped Nissen fundoplication (in which part of the stomach lies above and part lies below the fundoplication), or (3) herniation of an intact wrap through the hiatus into the chest.[25,36] Surgical failures may require reoperation.[20,32] Patients should be cautioned that the results of reoperation for GERD are never as favorable as the results after a primary operation and that residual atypical symptoms may persist. Laparoscopic reoperative fundoplication is technically feasible by experienced surgeons.

CONCLUSION

Antireflux surgery is an excellent treatment option for patients with symptoms of GERD that are inadequately treated with medication, for patients who desire to avoid lifelong medical therapy, or for patients with significant complications from acid reflux. The impact of antireflux surgery on progression of Barrett's esophagus is not fully understood, and patients with Barrett's who undergo antireflux surgery still require routine endoscopic surveillance. The introduction of a laparoscopic approach to fundoplication should not alter the operative indications. Finally, to ensure successful surgical outcomes, an understanding of disease pathophysiology, preoperative diagnostic evaluation, appropriate patient selection, and complete familiarity with the various types of antireflux procedures available are essential.

By the time that this volume is in print, effective endoscopic therapies that approximate the outcomes of surgical fundoplication may be available. Regardless of these advances, surgical therapy for GERD will probably continue to play an important role in patients with complicated disease, such as those with large hiatal hernias or a shortened esophagus.

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Chapter

19

Partial Fundoplications

Lee L. Swanström

Subsequent to the incidental discovery of the efficacy of the 360-degree fundoplication as an effective antireflux procedure in the late 1950s, a proliferation of modifications were devised to either address specific physiologies or serve as a "more physiologic" alternative. For the most part, these were either modifications of Nissen's complete wrap that were designed to make it longer lasting or more physiologic or some sort of partial fundoplication. Partial fundoplications were proposed as a less "intense" or competent valve mechanism intended to minimize the common side effects of the original Nissen procedure—dysphagia, gas bloating, inability to vomit, and other complications.[1] Each of these repairs had schools of supporters, and many continue to be used today—particularly if they have made the transition to a laparoscopic application.

TYPES OF REPAIR

Belsey Mark IV Ronald Belsey began development of the repair associated with his name many years before the final publication of version "IV" in 1967.[2] Access for this repair is traditionally via a left thoracotomy, although thoracoscopic access has also been described. The Belsey repair involves mobilization of the distal end of the esophagus and proximal part of the stomach by opening up the hiatus from above and splitting the diaphragm if needed to bring sufficient stomach into the chest. Short gastric vessels are divided only enough to allow the fundus to be brought 270 degrees around the distal esophagus. The fundoplication is fashioned around a 54-French dilator. It is fixed with interrupted sutures to the wall of the esophagus. At completion, the wrapped gastroesophageal junction is reduced below the diaphragm and the crura repaired (Fig. 19–1).

Dor The Dor repair is a 180-degree anterior fundoplication performed via laparotomy or laparoscopy. It was initially described by Jacques Dor in 1962 as an alternative antireflux procedure to the Nissen fundoplication and remains widely used today as the most common antireflux adjunct after Heller myotomy for achalasia or distal diverticula (Fig. 19–2). The most common iteration of the Dor is to bring the greater curvature and anterior fundus up to the left crus and then across the anterior arc of the hiatus. It is frequently fixed to both the right crus and the right side of the esophagus to complete the "wrap."

Toupet Originally described as a more physiologic antireflux repair by its creator, the French surgeon Andre Toupet, this repair was initially a 180-degree posterior fundoplication (Fig. 19–3). It was subsequently modified to a 270-degree wrap for increased valve competency, and posterior crural repair is commonly added as well to minimize the high herniation rate seen in some laparoscopic series. Although this repair used to be little known in North America, the introduction of laparoscopic antireflux surgery has made it the most common repair after Nissen fundoplication.[3]

Watson David Watson and colleagues in Australia have published well-constructed comparative studies of a 90-degree partial fundoplication that seems to produce outcomes similar to those of other repairs.[4,5] This repair emphasizes an acute angle of His with the gastric fundus attached to the left side of the esophagus and the left crus only (Fig. 19–4).

Each type of partial repair, and all of their potential variations, have strong advocates and schools of practice. A very few places advocate partial fundoplication for all patients in an effort to minimize the undesirable side effects of a 360-degree wrap.[6] This school of thought was especially attractive in the early days of laparoscopic fundoplication because it was feared that patients who were undergoing a "minimally invasive" surgery would be particularly unhappy with even transient symptoms of dysphagia, gas bloating, inability to belch, and others.[7] This approach withered somewhat in the face of increasing reports of suboptimal long-term results with partial fundoplication, and today these repairs are used as one of the options for a "tailored" approach, with a Nissen repair being the standard treatment and a partial wrap

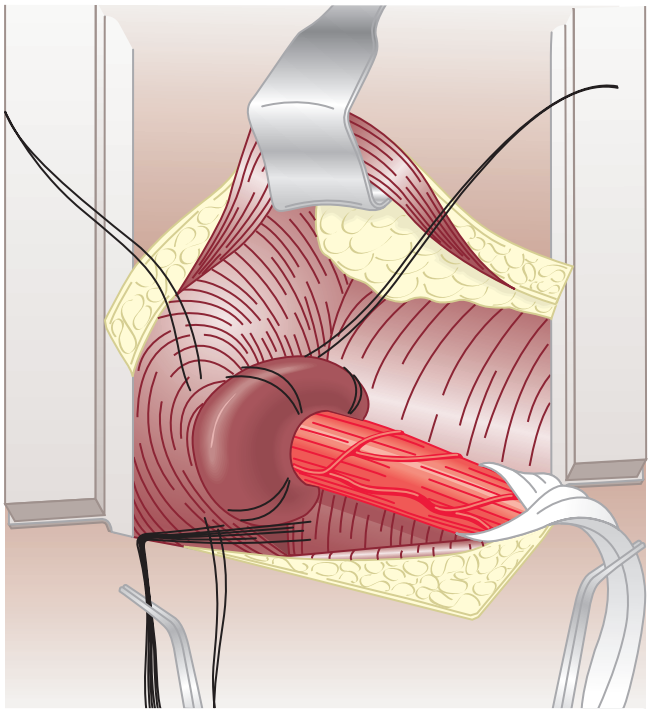


Figure 19–1. The completed Belsey Mark IV repair. (From Nyhus LM, Baker RJ, Fischer JE [eds]: Mastery of Surgery, 3rd ed. Boston, Little, Brown, 1997.)

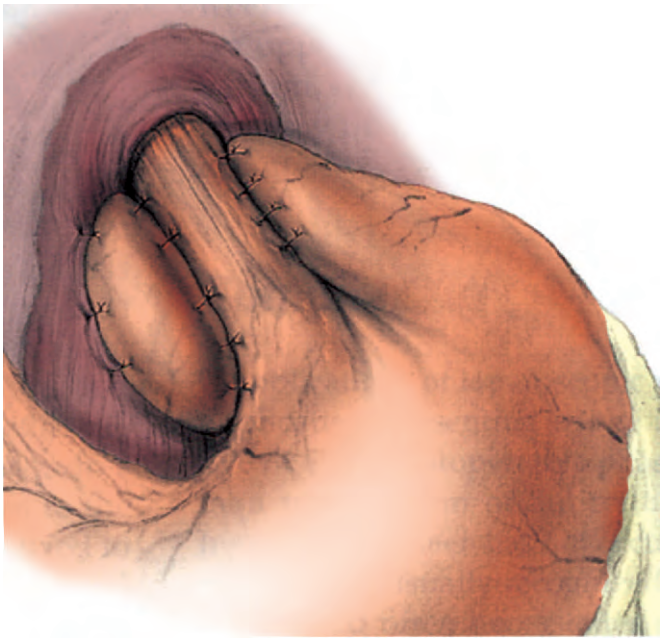


Figure 19–3. A completed 270-degree version of the Toupet fundoplication. (From Soper NJ, Swanström, LL, Eubanks WS [eds]. Mastery of Endoscopic and Laparoscopic Surgery, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2004.)

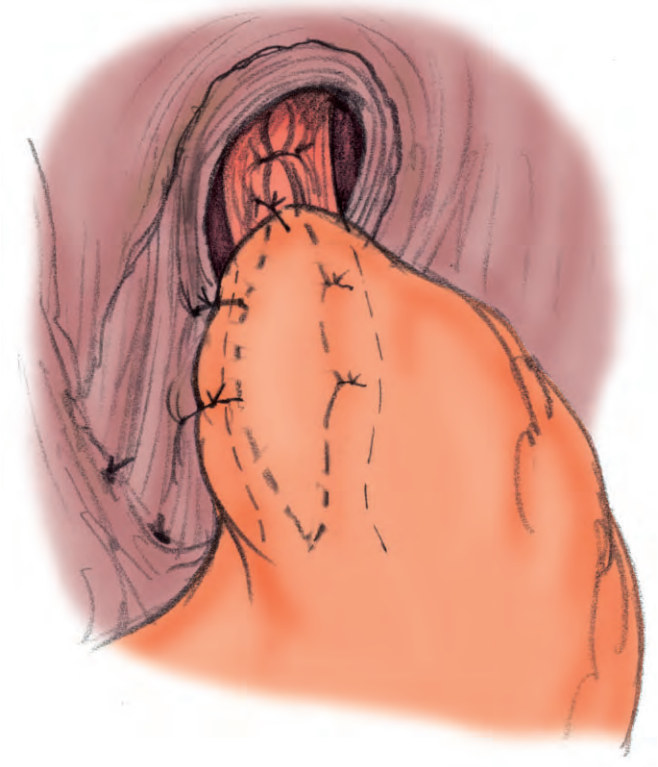


Figure 19–2. The finished Dor fundoplication as an adjunct to Heller myotomy.

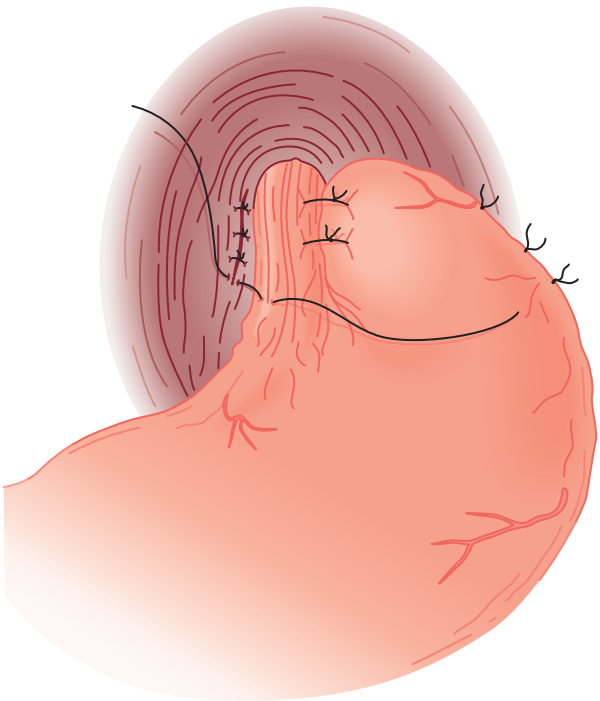


Figure 19–4. The 90-degree anterior fundoplication popularized by D.I. Watson. (From Eubanks WS, Swanström LL, Soper NJ [eds]: Mastery of Endoscopic and Laparoscopic Surgery. Philadelphia, Lippincott Williams & Wilkins, 2000.)

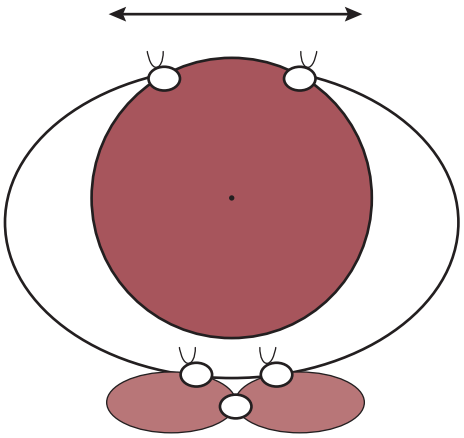


Figure 19–5. One of the differences between complete and partial fundoplications is the "hinge" effect of the exposed esophagus, which reduces the outflow and backflow characteristics of the repair.

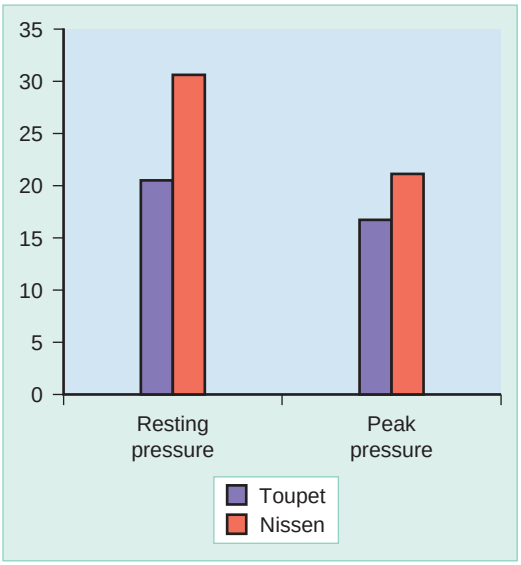


Figure 19–6. The resting and peak pressure of a Toupet fundoplication is lower than that seen with a Nissen fundoplication.

used for particular physiologic findings.[8] The description that follows is based on the use of partial fundoplication as one of the elements of a tailored approach.

MECHANISM

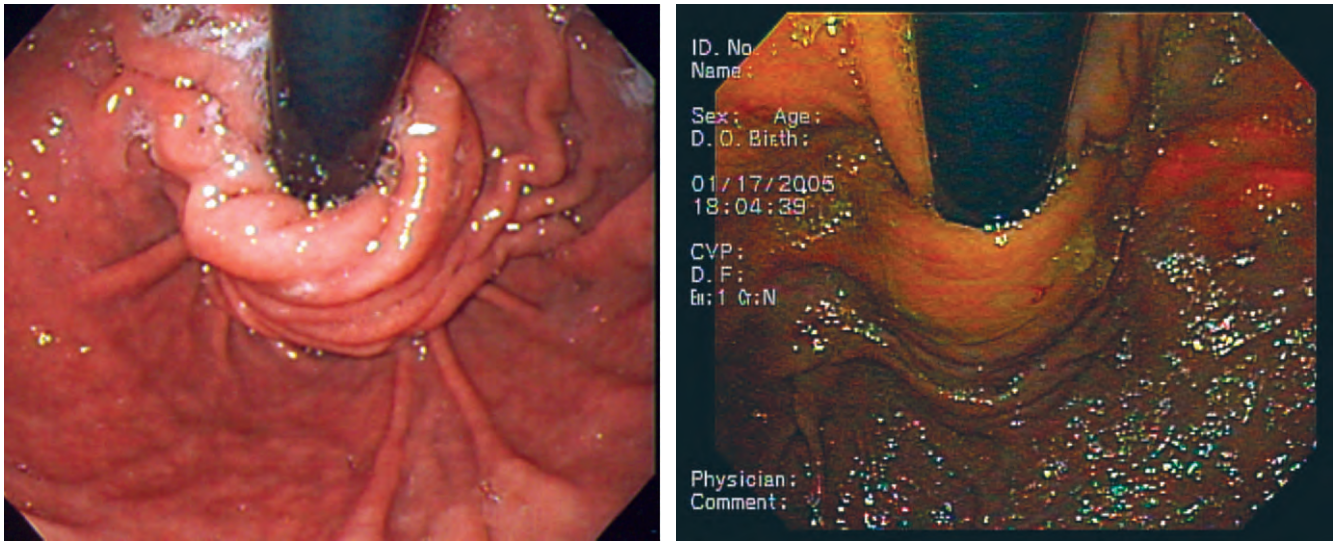
Partial fundoplications, like complete ones, function both by increasing outflow (and therefore "backflow") and resistance of the esophagus (augmentation of the resting pressure of the lower esophageal sphincter) and by restoring an anatomic "flap valve."[9] Outflow resistance, in turn, is a function of two phenomena. The first is the simple physics of resistance, in which the force of resistance to antegrade or retrograde bolus passage is equal to resting pressure times the length of the pressure zone. The second factor is, in effect, a hinge effect in which the uncovered portion of the esophagus common to all partial wraps can still expand easily (Fig. 19–5). This hinge effect allows easier passage of food boluses and easier release of gastric pressure, which can be good, as in belching, or possibly negative, as in continued reflux. It has been well demonstrated that the overall pressure (peak and resting) of a partial wrap is not as high as that seen with a full wrap (Fig. 19–6).[10] All partial fundoplications create a type of flap valve as one of their major mechanisms of action. This valve does, however, have a distinct configuration that distinguishes it from the valve formed with a Nissen repair. This difference can easily be seen on a retroflexed endoscopic view, and once again, the Nissen fundoplication intuitively appears as a more competent, or even super competent, valve configuration (Fig. 19–7).[9]

INDICATIONS AND CONTRAINDICATIONS

As previously discussed, a few centers perform a partial fundoplication for all patients with gastroesophageal reflux disease (GERD). This is, however, definitely a rare approach. For the most part, partial wraps are used for very specific indications and, in most centers, performed in a small minority of reflux patients. As with any antireflux surgery, the patient should actually have gastroesophageal reflux. It must be well documented by history and a thorough work-up as described later. Specific indications for partial repairs include intrinsic physiologic abnormalities that make a Nissen repair unwise; idiosyncratic patient issues, which usually involve the absolute need to belch or vomit; psychological issues that make a Nissen repair ill advised; and intractable failure of a Nissen fundoplication (Table 19–1).

The most common indication for a partial wrap is for esophageal motility disorders (failed peristalsis). Motility disorders are commonly classified as either primary or secondary. Primary disorders have an intrinsic cause (myoneural degeneration) and include named disorders, as well as occasional less well defined disorders. Secondary dysmotility is the result of an extrinsic insult and direct esophageal injury. Although secondary dysmotility may include causes such as caustic ingestion, it is by far most commonly the result of GERD. Distinction between primary and secondary disorders is critical because the treatments are radically different. An intrinsic disorder is best treated with a low-resistance antireflux procedure inasmuch as the defective esophageal pump mechanism can be expected to stay the same or even deteriorate. A secondary dysmotility disorder can be well treated with a standard Nissen repair because the function of the esophagus almost always improves with the prevention of further organ injury.[10,11]

Individual patient physiology can represent a good indication for a partial fundoplication. An example includes patients whose initial complaint is significant dysphagia. If work-up reveals no treatable peptic stricture and GERD symptoms are trivial to the patient, partial



A B

Figure 19–7. **A,** Retroflexed endoscopic view of a Nissen valve. **B,** The same view after a Toupet fundoplication.

Table 19–1 Motility Disorders Treated by Fundoplication

Classification	Disorder	Manometric Characteristics
Primary	Achalasia	No peristalsis, nonrelaxing LES
	Vigorous achalasia	100% simultaneous contractions, nonrelaxing LES
	Diffuse esophageal spasm	High-amplitude, nonperistaltic contractions; normal or hypertensive LES
	Nutcracker esophagus	High-amplitude peristalsis (>180 mm Hg), normal or hypertensive LES
	Hypertensive LES	Normal body motility; high-pressure, possibly poorly relaxing LES
	Ineffective esophageal motility	Low-amplitude (<30 mm Hg) body contractions with all swallows and in all smooth muscle segments
	Nonspecific	Variable abnormal contractions throughout the entire smooth muscle of the esophagus
Secondary	Obstructive	Either low-pressure or high-pressure peristalsis in the distal esophagus
	Caustic ingestion	Decreased contractility throughout the affected segment
	GERD related	Progressively diminished amplitudes in the distal esophagus
	Pseudoachalasia (cancer infiltration)	Immotile esophagus in end-stage cases

GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter.

fundoplication may be a wise choice. Another indication is severe aerophagia. This can be a result of gastroparesis, voluntary behavior such as air swallowing for postlaryngectomy esophageal speech, or unconscious adaptive (or maladaptive) behavior. The later is fairly common in the long-term GERD population but can still lead to crippling gas bloating after Nissen fundoplication if it is severe enough. Finally, some psychological conditions can make a partial wrap a preferred treatment. This category can include known eating disorders such as bulimia or simply the surgeon's analysis that an individual patient is psychologically unable to handle even the transient side effects (dysphagia, inability to belch, gastric distention, and early satiety) common with a Nissen operation.

Contraindications include those common to any surgery—poor cardiac or pulmonary reserve and uncontrolled bleeding dyscrasias. All fundoplication patients should be carefully evaluated before surgery—even if laparoscopic surgery is planned. Conversion to an open procedure is always possible, and the surgery is still an esophageal procedure whether open or closed.

In addition, there are several relative contraindications related to the long-term function of these repairs. Because partial fundoplications offer somewhat less reflux protection, they should be used cautiously, if at all,

Table 19–2 Tests Ordered as Preoperative Evaluation for Reflux Disease

Routine tesst	Upper endoscopy	Rule out malignancy Assess tissue damage Treat strictures Assess anatomy
	Esophageal manometry	Exclude primary esophageal motility problems Determine risk for dysphagia Assess LES status Aid in determination of esophageal length
	24-Hour pH test	Confirm the diagnosis of GERD Quantify the severity of reflux Correlate symptoms Establish a baseline for follow-up
Selective tests	Upper gastrointestinal radiographs	Measure transit time Assess anatomy
	Radionuclide gastric-emptying test	Quantify delayed gastric emptying Observe the gastric contribution to reflux
	Impedance manometry	Non-acid reflux
	Bilitec testing	Bile reflux (duodenal-gastric-esophageal reflux)
	Provocative testing (Bernstein, barostat)	Assess atypical symptoms

GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter.

in patients with severe reflux, particularly those with normal esophageal motility. In a prospective study of the laparoscopic Toupet repair performed on 100 consecutive patients with reflux, it was noted that at 1-year follow-up, 50% of patients with preoperative DeMeester scores of 32 or higher had continued reflux versus 18% of those with scores lower than 32.[12] It is also a relative contraindication to perform a partial fundoplication in a patient with a relatively shortened esophagus because such shortening is typically a sign of chronic severe reflux (Barrett's esophagus, strictures, etc.) or is associated with a large hiatal hernia and shortening makes it difficult to carry out a technically adequate partial fundoplication, which requires at least 4 cm of intra-abdominal esophagus. The one exception is the Belsey repair, which benefits from the ability to extensively mobilize the thoracic esophagus. There are still some indications for an open approach as opposed to a laparoscopic one.[13] Such indications include multiple failed laparoscopic repairs, an extremely hostile abdomen or chest, and perhaps an associated giant paraesophageal hernia. As with any surgery, the approach and the technique should be tailored to the individual patient's physiology and psychology.

PREOPERATIVE EVALUATION

The preoperative evaluation of any reflux patient should be complete and thorough, particularly patients with abnormal physiology who are being considered for partial fundoplication. A structured gastrointestinal history, preferably with a standardized symptoms assessment tool, is extremely important and may help identify patients who should have a partial wrap because of psychological or behavioral issues. Obviously, records of any previous gastrointestinal surgery should be reviewed, as well as copies of all previous foregut testing if at all possible. Not only should the reports of recent tests be reviewed, but the surgeon should also obtain and personally look at the actual physiology tests. Test reports done by nonsurgical investigators often neglect to comment on findings significant to the surgeon. This is particularly the case with upper endoscopy and motility testing, where determination of esophageal length, the size and type of hiatal hernia, and the anatomic appearance or grade of the valve have definite clinical meaning to the surgeon. All patients should undergo upper endoscopy to stage Barrett's esophagus, exclude cancer, grade the valve, assess gastric problems, and exclude findings that may make other studies dangerous, such as diverticula or strictures. Motility should likewise be evaluated in all cases to determine the type of motility disorder, state of the lower esophageal sphincter, and length of the esophagus. Twenty-four-hour pH testing as an absolute prerequisite to surgery is more controversial. We would argue that it should be done in all patients being considered for surgery to exclude those who have no reflux, determine the severity of their reflux, and serve as a baseline for follow-up should postoperative complaints arise. Other tests should be ordered as indicated by the patient's clinical findings or when standard tests fail to delineate the problem (Table 19–2).

SURGICAL TECHNIQUE

Laparoscopic abdominal procedures are typically performed with the patient in a split-leg position with arms outstretched. A basic five-port access pattern is used for

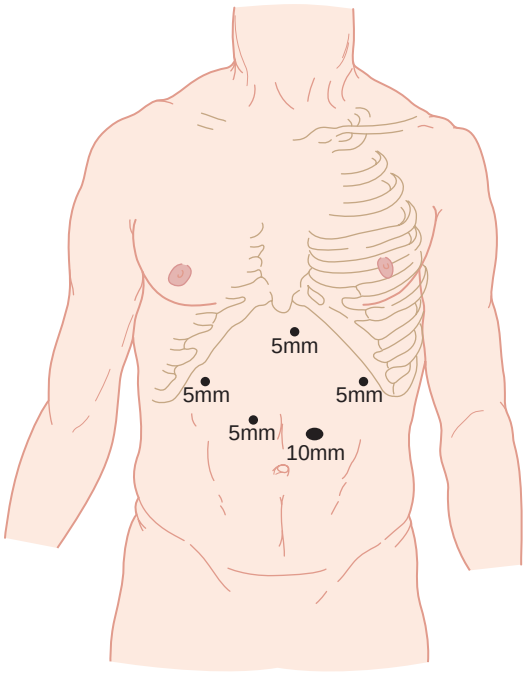


Figure 19–8. Laparoscopic trocar placement for partial fundoplication.

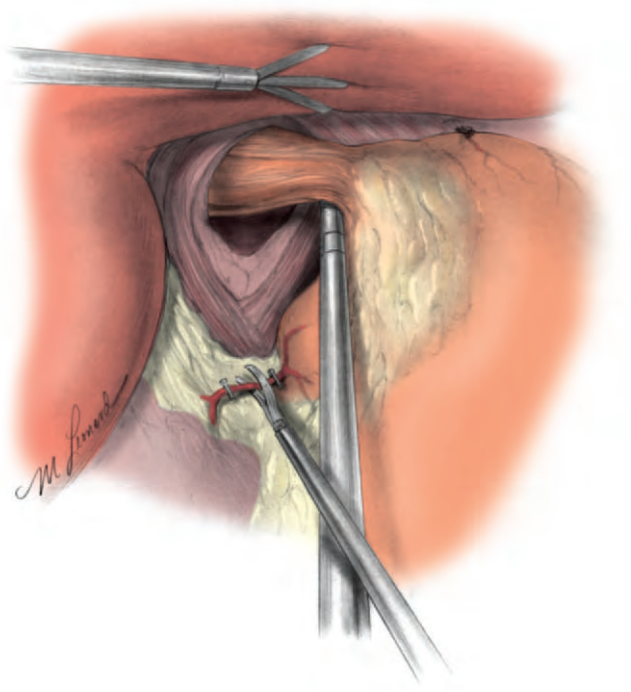


Figure 19–9. Using an angled laparoscope allows a retroesophageal window to be created under direct vision. (From Soper NJ, Swanström, LL, Eubanks WS [eds]: Mastery of Endoscopic and Laparoscopic Surgery, 2nd ed. Philadelphia. Lippincott Williams & Wilkins, 2004.)

any laparoscopic fundoplication (Fig. 19–8). Standard instruments required and some newer time-saving technologies are listed in Table 19–3. Monitors are positioned at the top of the table, and the operating surgeon stands either between the legs of the patient or on the patient's left. The assistant, who holds the laparoscope and retracts, stands on the patient's right or between the legs of the patient.

The left lobe of the liver is elevated without dividing the triangular ligament. The liver retractor is best fixed to a table-mounted retractor holder because secure retraction minimizes trauma to the liver. The assistant retracts the stomach downward and to the patient's left. The hepatogastric ligament is divided while preserving any significant anomalous liver arteries. The phrenoesophageal membrane is "nicked" at the apex of the esophageal hiatus, and blunt dissection is used to gain access to the lower mediastinum. The phrenoesophageal membrane can then be detached from the crura circumferentially with cautery or ultrasonic energy. Care should be taken to avoid stripping the peritoneal covering off of the crura because such stripping will compromise subsequent suture repair. Working from the right side and using the angled laparoscope, a window is created behind the esophagus (Fig. 19–9). The esophageal dissection is carried into the mediastinum via blunt and ultrasonic dissection as far as needed to bring the gastroesophageal junction at least 3 cm into the abdomen. The upper third of the gastric fundus is mobilized by dividing the short gastric vessels and the retrogastric attachments—a technical point that helps minimize tension on even partial fundoplications.

Table 19–3 Instruments for Laparoscopic Partial Fundoplication

Basic instruments	High-resolution laparoscopic camera
	Angled (45- or 30-degree) laparoscope
	Atraumatic liver retractor
	Table-mounted liver retractor holder
	Atraumatic graspers (Glassman)
	5-mm Babcock graspers
	Curved-tip needle holders
	Monopolar cautery scissors
	Multiple clip applier *or* ultrasonic coagulating shears
	Esophageal dilator
Advanced instruments	GIA staplers
	Flexible upper endoscope
	Bipolar scissors
	Clip applier
Optional labor-saving tools	Automatic suturing devices
	Ultrasonic coagulating shears

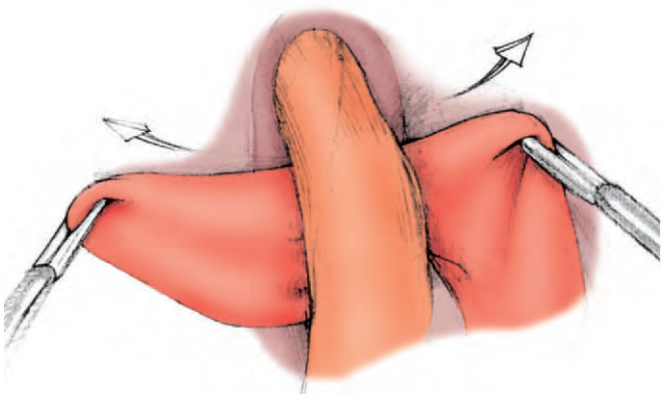


Figure 19–10. The "shoeshine" maneuver ensures that adequate fundus has been mobilized and the correct areas grasped.

Laparoscopic Toupet Procedure

The previously mobilized fundus is grasped from the right and brought behind the esophagus. The greater curvature is grasped on either side, and a "shoeshine" maneuver is performed to ensure that the correct portions of the stomach have been grasped and that the wrap is fully mobilized and loose enough (Fig. 19–10). The assistant then grasps the right side of the wrap and uses it to retract the esophagus to the patient's left. This maneuver exposes the posterior of the hiatus. A loose, nonobstructing hiatal closure is performed with interrupted posterior sutures of heavy woven polyester. Each of these posterior bites includes a slip of the posterior wrap. Additional sutures are placed from the greater curvature of both sides of the wrap to their corresponding crus. The repair is finished by passing a large dilator (54 to 58 French) and tacking the edges of the wrap to the esophagus at the 2- and 10-o'clock positions (see Fig. 19–3). The final result should be a tension-free, 270-degree fundoplication securely fixed to the diaphragm.[14]

Laparoscopic Dor Procedure

One advantage of the Dor anterior fundoplication is the possibility of preserving the posterior phrenoesophageal attachments. This is, of course, only possible if there is no esophageal shortening or hiatal hernia, which would require complete dissection and mobilization. Large hiatal hernias should be loosely closed, either posteriorly if a full dissection was performed or anteriorly if the posterior phrenoesophageal attachments were left intact. It is still preferable to divide the short gastric vessels to ensure the absence of tension on the repair. The Dor repair involves reconstruction of the angle of His by suturing the gastric fundus to the mid left crus. Subsequent sutures from the greater curve to the rim of the hiatus roll the fundus up and over the anterior gastroesophageal junction (see Fig. 19–2). The final result is a 180-degree anterior wrap that is securely fixed to the diaphragm.[15]

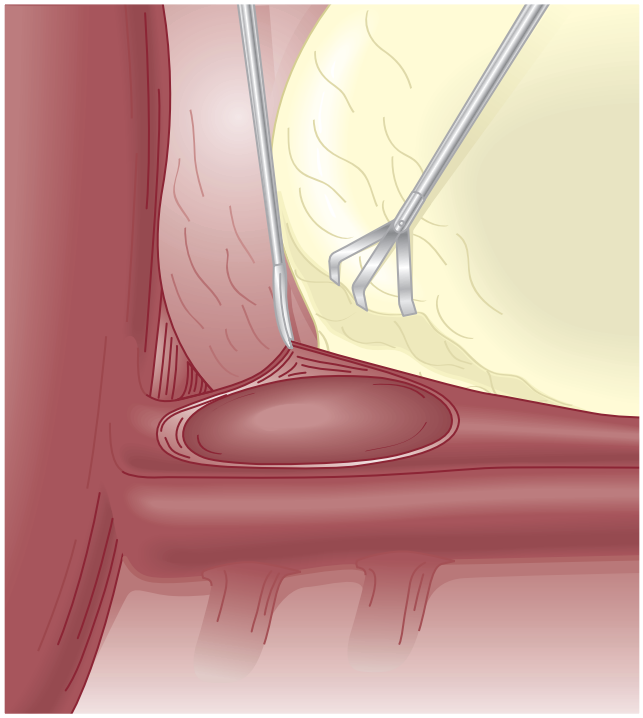


Figure 19–11. The left mediastinal pleura is opened longitudinally to expose the distal esophagus. (From Eubanks WS, Swanström LL, Soper NJ [eds]: Mastery of Endoscopic and Laparoscopic Surgery. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Transthoracic Belsey Mark IV Repair

The Belsey repair is generally performed via a left anterior-lateral thoracotomy, although occasional reports have surfaced of a similar repair done thoracoscopically.[16] Patients undergo general anesthesia with a double-lumen endotracheal tube and indicated monitoring lines. They are positioned in full right lateral decubitus position with care taken to adequately pad and protect dependent parts of the body. A muscle-sparing sixth intercostal incision is made and a self-retaining retractor is placed. The inferior pulmonary ligament is divided with cautery, and the mediastinum overlying the distal esophagus is opened longitudinally (Fig. 19–11). Blunt finger dissection is used to get around the esophagus, and a Penrose drain is placed to allow atraumatic retraction. Dissection is carried distally until the gastroesophageal junction is identified—it may be helpful to identify it via upper endoscopy at this point. The phrenoesophageal membrane is opened with cautery and the stomach is progressively mobilized into the chest by clipping and dividing the short gastric vessels. When adequate stomach wall is free, it is rolled up on the anterior of the esophagus and fixed in place with interrupted

sutures (see Fig. 19–1). When tied, these sutures create a 180-degree partial fundoplication. The fundoplication is then reduced below the diaphragm while mobilizing the esophagus as far proximally as needed to avoid tension. The diaphragm is closed with interrupted nonabsorbable sutures. A chest tube is placed, the thoracotomy is closed in standard manner, and an epidural catheter is placed at the end of surgery for optimal postoperative pain control.[15,17]

POSTOPERATIVE CARE

Patients generally stay in the hospital between 12 and 48 hours for laparoscopic surgery and 3 to 7 days for open surgery. A liquid diet can be started 6 hours after surgery in straightforward cases. In more complex cases (reoperative, myotomy, pyloroplasty, inadvertent gastrotomy, etc.), nothing is allowed orally until a water-soluble upper gastrointestinal radiograph is checked. Patients are advanced to a pureed diet and medications converted to liquid forms or crushed. Patients are instructed to remain on this diet for 2 weeks and then to slowly advance to solids. Care is taken to avoid postoperative nausea and vomiting because acute wrap herniation has been described in this scenario. It is our routine to bring all antireflux surgery patients back for physiology studies 6 to 8 months after surgery. At this visit a gastrointestinal symptoms assessment form is administered and 24-hour pH testing is performed. Upper endoscopy is performed if the patient has dysphagia or had Barrett's esophagus, strictures, or severe esophagitis preoperatively. In patients who had a motility disorder before surgery, an esophageal manometric examination is performed as well to assess the current state of their esophageal function.

RESULTS

A large amount of literature on outcomes has been published over the 40 years that partial fundoplications have been in use. The Belsey repair has lost a great deal of popularity both because of its relatively morbid access and because of outcomes showing lower efficacy than with other repairs (Table 19–4). The Dor repair has an excellent track record when used as an adjunct to Heller myotomy. In one of the larger series of the Dor repair in this capacity, Patti et al. reported an 11% incidence of reflux at 59 months' mean follow-up.[18] These results are typical of the outcomes achieved in most clinical reports of laparoscopic Heller/Dor procedures, which has resulted in it being the most commonly used adjunct to myotomy. Its use as primary antireflux surgery is so rare that there is no contemporary series reporting outcomes for the procedure. The Toupet procedure has become the most commonly used partial fundoplication. It is most often used as an alternative to a Nissen repair in cases of esophageal dysmotility, but there are also series and institutions describing its use as a standard antireflux procedure. Much like the Dor procedure, the Toupet repair works well for postmyotomy patients and for those with significant dysmotility. The results reported with its use as a primary antireflux procedure are conflicting. Several centers have long relied on the posterior partial wrap and report good results.[15,19,20] In addition, there have been three randomized prospective studies favorably comparing partial fundoplication with the "gold standard" Nissen. However, several North American reports have detailed a high rate of valve incompetence and wrap disruption with the Toupet procedure, particularly in patients more severe reflux disease (Table 19–5).[9,21-24]

CONCLUSION

Partial fundoplication has a long and controversial position in the history of antireflux surgery. The advent of laparoscopic approaches—with their increased volume and emphasis on postoperative quality of life—has created a resurgence of interest in partial fundoplication. Early results showing higher failure rates in at least some subsets of reflux patients dampened enthusiasm somewhat for these approaches, but there remain several indications and significant numbers of patients for whom partial wrap remains the best treatment of their reflux. All surgeons interested in an antireflux practice should be familiar with the indications and technical aspects of these procedures.

Table 19–4 Results of the Belsey Mark IV Repair

Author	Study Type	No. Patients	Follow-up (yr)	Success Rate (%) Symptomatic/Objective
Dilling et al. (1977)	Review		4	64/53
Fenton et al. (1997)	Review	276	48.0	82/NA
Alexiou et al. (1999)	Review	90	11	71.9/NA
Champion (2003)*	Review	21	6.2	57/NA
Lerut et al. (1990)	Review	147	5	78/NA

*Thoracoscopic series.
NA, not available.

Table 19–5 Results of Laparoscopic Toupet Antireflux Surgery

Author	Study Type	No. Patients	Follow-up (mo)	Symptomatic/ Objective	Failure Rate Rate(%)
Erenoglu et al. (2003)	Retrospective	118 N 26 T	27.5	+/−	18 N 16 T
Fernando et al. (2002)	Retrospective	163 N 43 T	19.7	+/−	7 N 21 T
Zornig et al. (2002)	Prospective/randomized	100 N 100 T	4	+/+	12 N 10 T
Jobe et al. (2004)	Prospective	100 T	24	+/+	48 T
Zugel et al. (2002)	Retrospective	40 N 122 T	19	+/−	12 N 11 T
Farrell et al. (2001)	Retrospective	591 N 78 T	12	+/−	9 N 21 T

N, Nissen; T, Toupet.

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Chapter

20

Esophageal Replacement for End-Stage Benign Esophageal Disease

Thomas J. Watson

The esophagus is a muscular pump bordered by two sphincters and responsible for only one essential task: the unidirectional movement of ingested food and saliva from the pharynx to the stomach. Prevention of reflux of gastric contents is inherent to this task. Unlike other portions of the gastrointestinal tract, the esophagus has no known endocrine, exocrine, immunologic, digestive, absorptive, or secretory roles. Despite the apparent simplicity of its responsibilities, the esophagus may exhibit derangements in function that can have a profound impact on an individual's overall health and quality of life. In most cases, the symptoms experienced by patients with esophageal disorders are minor, intermittent, and easily controllable with medications and subtle dietary or lifestyle modifications. In more advanced cases, patients may be referred for surgical therapy intended to improve foregut function or correct anatomic abnormalities. In a subset of patients, however, the severity of esophageal dysfunction and associated symptomatology is such that esophageal resection with replacement is the most appropriate option.

Patients who suffer the consequences of severe esophageal disorders or previously failed esophageal surgery are not uncommonly prescribed a myriad of ineffective or marginally beneficial medications in an effort to bring about symptomatic relief. These unfortunate individuals may seek input from multiple medical or surgical specialists in the process of evaluation and treatment. Considerable time and effort may be spent pursuing medical or minimally invasive therapies that despite being low risk, ultimately prove futile. Because previous surgery may have contributed to the problem or is perceived to have contributed, both patients and their treating physicians may be reluctant to consider referral for a repeat attempt at surgical remediation. In addition, complex reoperative esophageal surgery may be viewed as producing significant morbidity or mortality and resulting in marginal long-term functional success. Because of these factors, many patients have exhausted attempts at conservative management at the time of referral to a surgical specialist. The mere fact that the patient finally resorts to surgical evaluation frequently reflects the severity of the underlying pathology, even if a major surgical undertaking is the ultimate solution. Difficult foregut anatomic and functional problems, however, can rarely be successfully remediated through simple means and may require surgical reconstruction.

A major challenge facing esophageal surgeons is the decision whether to attempt fundoplication, myotomy, or other nonextirpative foregut procedure in the setting of advanced disease, especially in the reoperative setting, versus proceeding with the more invasive and potentially morbid option of resection and reconstruction. Despite the desire to avoid a large operation, the surgeon should understand that there are potential adverse consequences to repeat interventions around the esophagus, gastroesophageal junction (GEJ), or stomach that can have a negative impact on the ability to complete successful resection and reconstruction at a later date (Box 20–1). With regard to repeat fundoplication or myotomy, success is highly unlikely after two or three previous failures, depending on the circumstances. Repeated operations in the region of the GEJ can lead to local tissue ischemia and fibrosis, as well as risk iatrogenic vagal nerve injury with its sequelae. Preservation of a scarred and dysfunctional lower esophagus or upper stomach invariably leads to problems with dysphagia, weight loss, or pain. On the other hand, the patient's symptoms must be sufficiently severe to warrant a major extirpative procedure with its inherent risks. Because the functional outcome after esophageal replacement is never normal, the symptomatic result anticipated after esophageal replacement must be realistically assessed and compared

Box 20–1 Reasons to Abandon Attempts at Remedial Foregut Procedures

- Additive morbidity/mortality
- Further tissue damage with additional functional loss and increased adhesion formation
- Loss of blood supply from repeat mobilization with risk of ischemic fibrosis/necrosis
- Risk of iatrogenic vagal nerve injury with its sequelae
- Compromise of potential esophageal replacement organ or organs

Table 20–1 Symptoms of End-Stage Esophageal Disease ($N = 104$)

Symptom	Percent
Dysphagia	90
Regurgitation	57
Heartburn	52
Weight loss	32
Chest pain	25
Epigastric pain	22
Vomiting	20
Cough	18
Nausea	18
Choking	9
Voice change	7
Diarrhea	3
Odynophagia	2
Anorexia	1
Bloating	1

From Watson TJ, DeMeester TR, Kauer WKH, et al: Esophageal replacement for end-stage benign esophageal disease. J Thorac Cardiovasc Surg 115:1241-1249, 1998.

Box 20–2 Mechanisms by Which Benign Esophageal Disease Can Lead to Esophageal Replacement

Inadequate nonoperative therapy

For gastroesophageal reflux disease

- Inadequate acid suppression leading to stricture, bleeding, ulceration, perforation, or fistulization
- Inadequate dilation of reflux-induced stricture
- Necrosis of incarcerated paraesophageal hernia

For achalasia

- Failed Botox injection
- Failed pneumatic dilation

Inadequate surgery

For gastroesophageal reflux disease

- Recurrent hiatal herniation
- Improper fundoplication (e.g., malpositioned/"slipped," too tight, too long, angulated/twisted, excessive crural closure)
- Improper Collis gastroplasty (e.g., too large, excess gastric mucosa above the fundoplication, leakage from the staple/suture line, persistent reflux)
- Iatrogenic vagal nerve injury

For achalasia

- Incomplete myotomy
- Healing of myotomy
- Complete fundoplication
- Paraesophageal herniation
- Iatrogenic vagal nerve injury
- Other technical problems (e.g., angulation, tight hiatus)

Iatrogenic or traumatic injury to the esophagus, stomach, or vagus nerves

- Endoscopic interventions
- Mishaps during attempted endotracheal intubation
- Operations on contiguous organs
- Blunt or penetrating trauma
- Caustic ingestion

Congenital abnormality

End-stage disease at initial evaluation

with the patient's preoperative status, and the magnitude of the anticipated improvements must be weighed against the potential surgical morbidity.

This chapter examines the characteristics of patient populations with end-stage, benign esophageal disease who are being considered for esophagectomy, the principles underlying successful reconstruction of the foregut, and data regarding safety and efficacy of the various reconstructive approaches.

CLINICAL MANIFESTATIONS OF END-STAGE BENIGN ESOPHAGEAL DISEASE

Symptoms in patients with end-stage esophageal disease can be quite variable (Table 20–1). The most common symptom driving the need for surgical intervention is dysphagia, followed by regurgitation and heartburn. Other factors precipitating the need for esophagectomy can be acute hemorrhage, repetitive aspiration, or acute/subacute sepsis from ulceration, perforation, or fistulization (Box 20–2). Finally, foregut continuity may need to be re-established after previous esophageal exclusion/diversion or previously failed reconstruction.

Table 20–2 Nonmalignant Esophageal Conditions Leading to Esophageal Replacement

Diagnosis		No. Patients
End-stage gastroesophageal reflux disease		37
Undilatable stricture	25	
Other	12	
Advanced motility disorder		37
Traumatic or iatrogenic injury or spontaneous perforation		15
Corrosive injury		8
Congenital abnormality		6
Extensive leiomyoma		1

From Watson TJ, DeMeester TR, Kauer WKH, et al: Esophageal replacement for end-stage benign esophageal disease. J Thorac Cardiovasc Surg 115:1241-1249, 1998.

The most common nonmalignant conditions underlying the need for esophageal replacement are end-stage gastroesophageal reflux disease (GERD) and advanced motility disorders, in particular, achalasia (Table 20–2). In some cases, patients first seek medical attention while already manifesting end-stage disease. This fact underscores the ability of individuals to compensate for derangements in alimentary function through dietary, behavioral, and lifestyle modifications when symptoms are mild to moderate, thereby delaying evaluation for prolonged periods, even years. In some cases, disease progresses despite "appropriate" medical or surgical therapy. In other situations, inappropriate or poorly executed therapy can worsen foregut function by exacerbating existing symptoms or inducing new ones. Irreparable injury to the esophagus can occur from blunt or penetrating trauma or caustic ingestion. Iatrogenic injuries to the esophagus or stomach can occur as a result of endoscopic interventions, traumatic airway intubations, or operations on contiguous organs. In the latter case, the vagus nerves may be injured as well. Finally, some patients are initially seen in adulthood with the sequelae of congenital esophageal abnormalities after previous failed attempts at surgical correction.

PREOPERATIVE EVALUATION FOR FOREGUT RECONSTRUCTION

The functional and anatomic status of the foregut is assessed routinely before elective reconstruction by video barium upper gastrointestinal contrast studies, flexible esophagogastroduodenoscopy, and stationary esophageal manometry. Ambulatory esophageal pH monitoring with either a traditional transnasal pH catheter or an implantable Bravo probe (Medtronic, Minneapolis, MN) is performed when documentation of pathologic gastroesophageal reflux is critical to decision making. Other studies, such as radionuclide gastric emptying scans, multichannel intraluminal esophageal impedance tests, or bile monitoring, may be used on a selective basis.

Assessment of the patient's cardiopulmonary reserve is essential before any major surgical undertaking such as esophagectomy. A thorough history is obtained with specific concentration on respiratory difficulties at rest or with exertion, exercise tolerance, chest pain, and fatigability. Physical examination should concentrate on cardiopulmonary findings. When questions exist about coexistent cardiac or pulmonary disease based on the patient's age, comorbid conditions, physical signs, or symptoms, formal physiologic testing should be pursued. Pulmonary function testing, including expiratory flow, lung volumes, and diffusion capacity, can objectify the severity of concomitant obstructive or restrictive lung disease. Lung function should be optimized through smoking cessation, bronchodilators, expectorants, antibiotics, and pulmonary rehabilitation, as necessary. Cardiac imaging and stress testing can elicit subtle changes in cardiac function suggestive of ischemia, cardiomyopathy, or valvular heart disease. When coronary artery or valvular pathology is deemed significant, interventions such as angioplasty, coronary stenting, or even open heart surgery should be completed before elective esophageal surgery in an effort to minimize perioperative risk at the time of esophagectomy.

One advantage of esophagectomy in the setting of benign disease versus malignancy is that surgery can often be delayed pending optimization of cardiopulmonary issues, nutrition, or other comorbid diseases. Although the patient and treating physicians may feel a time pressure to treat an esophageal malignancy, end-stage esophageal disorders tend to be fairly long-standing problems that can be temporized while a thorough work-up is completed and risk factors addressed. Enteral or parenteral support may be pursued if a patient is unable to tolerate an adequate oral diet. Although no absolute thresholds exist for abandoning surgery because of pulmonary or cardiac compromise, such objective information can often assist the surgeon quite significantly in making a decision for or against esophageal reconstruction and in the type of operation chosen.

When the colon is being considered as a potential esophageal substitute, colonoscopy is performed to evaluate the status of the colonic mucosa. Mild diverticular disease is not generally a contraindication to the use of colon as an esophageal replacement, although extensive diverticulosis, frank diverticulitis, or inflammatory fibrosis may preclude colon interposition. Similarly, the presence of a few colonic polyps, whether hyperplastic or adenomatous, that can be removed before surgery does not preclude use of the colon. The presence of extensive polyposis or malignancy, however, is an absolute contraindication.

Some controversy exists regarding the necessity for routine preoperative mesenteric arteriography when colonic interposition is planned. Because the successful

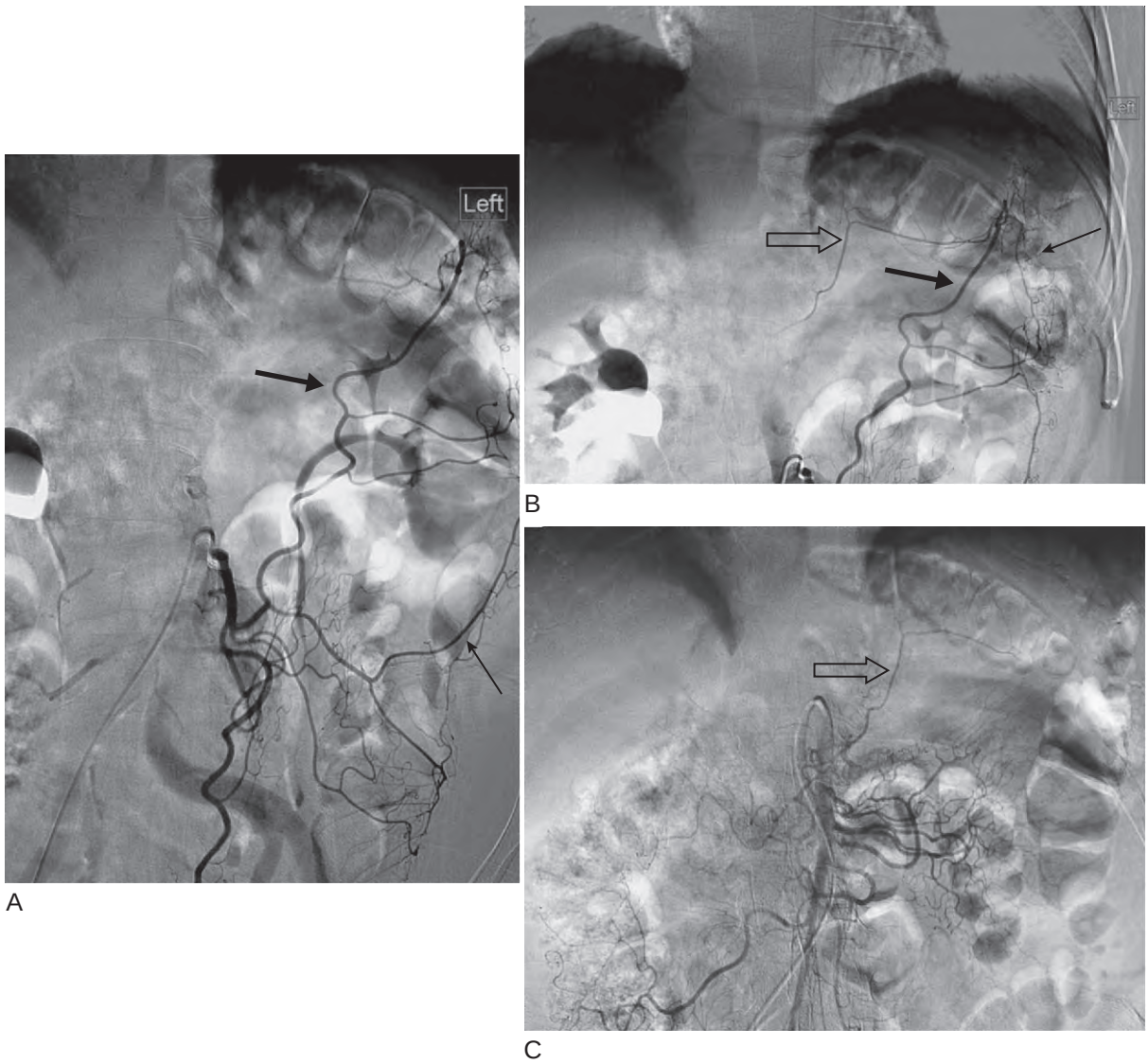


Figure 20–1. Mesenteric arteriogram in preparation for colon interposition. **A** and **B,** Selective injection of the inferior mesenteric artery. Note the ascending branch of the left colic artery *(broad arrows),* on which a left colon interposition is based, and the marginal artery of Drummond *(thin arrow).* **C,** Selective injection of the superior mesenteric artery in the same individual. Note the communication with the arcade from the inferior mesenteric artery *(hollow arrows).*

use of colon critically depends on adequate vasculature, the surgeon should have a low threshold to perform such studies. When arteriography is performed, selective injections of the celiac, superior mesenteric (SMA), and inferior mesenteric (IMA) arteries should be undertaken, including lateral views, with particular attention paid to any anatomic aberrancy. When the left colon is to be used for interposition, the most important angiographic finding is the status of the IMA, especially at its origin, which can be stenosed in elderly individuals or in those with peripheral vascular disease. Because the blood supply of a left colon interposition critically depends on adequate inflow from the IMA, significant stenosis of this vessel is a contraindication to use of the left colon for esophageal reconstruction.[1] A right colon interposition, based on the middle colic branches of the SMA, can be used in this situation because it is not dependent on IMA inflow. Other angiographic features thought important to successful use of the left colon for interposition include a visible ascending branch of the left colic artery, a well-defined anastomosis between the left colic and middle colic systems (along the marginal artery of Drummond), and a single middle colic trunk before division into right and left branches (Fig. 20–1A-C). Because of its more reliable and predictable arterial inflow and venous outflow, not to mention its better size match to the native esophagus, the left colon is generally preferred over the right colon for esophageal replacement.

Because patients undergoing foregut reconstruction have not uncommonly undergone multiple previous

Box 20–3 Features of the Ideal Esophageal Substitute

- Technically simple to construct
- Minimal incisions
- Minimal number of anastomoses
- Adequate length to replace the excised esophageal segment
- Reliable arterial and venous blood supply
- Allows normal swallowing
- Does not alter gastrointestinal function
- Resistant to (or able to prevent) acid reflux
- Durable with no long-term complications

abdominal operations, mesenteric arteriography can help define the resultant vascular anatomy and ascertain that vessels supplying planned esophageal substitutes are patent and not disrupted by previous surgeries. In particular, previous operations involving the greater curvature of the stomach may have disrupted the right gastroepiploic artery, critical to the blood supply of a planned gastric pull-up, or the middle colic artery and marginal artery of Drummond, critical to the blood supply of a planned colon interposition. Preoperative knowledge of such vascular abnormalities can help the surgeon plan surgery and save considerable time and effort during the procedure.

FEATURES OF THE IDEAL ESOPHAGEAL SUBSTITUTE

The goal of foregut reconstruction is return of normal alimentation in a durable fashion with a minimal risk for side effects, morbidity, and mortality. Because no esophageal replacement organ can perfectly replicate normal foregut function, a number of different conduits have been used, each with potential advantages and limitations. None of them fulfills all the criteria of an ideal esophageal substitute, and thus debate continues over which organ is best suited for this purpose (Box 20–3). It is noteworthy that as long ago as 1929, the observation was made that "Judging from the literature, it would seem that every method which ingenuity can invent has been practiced for the purpose of reestablishing the continuity of the esophagus after resection."[2] The field has advanced considerably since the first successful transthoracic esophagectomy performed by Torek in 1913,[3] in which an external rubber tube was placed between an end-esophagostomy and a gastrostomy (Fig. 20–2). Through trial and error with different esophageal replacement strategies and with accumulated experience, certain principles and controversies in foregut reconstruction have evolved.

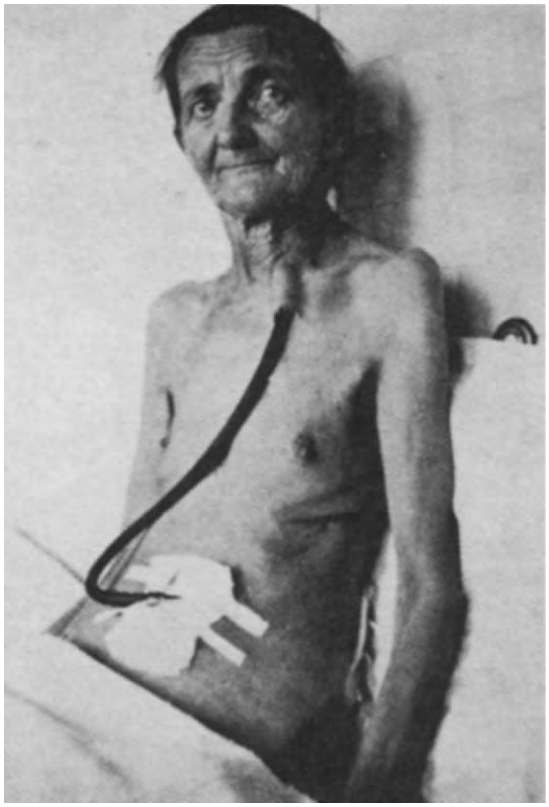


Figure 20–2. Franz Torek's first successful transthoracic esophagectomy patient (1913). An external rubber tube was used to establish continuity between a cervical esophagostomy and a gastrostomy.

CONTROVERSIES IN FOREGUT RECONSTRUCTION FOR BENIGN DISEASE

The debate surrounding foregut reconstruction for benign disease centers on several distinct, though interrelated controversies:

1. Long- versus short-segment esophagectomy
2. Operative approach to esophagectomy and reconstruction
3. Vagal-sparing versus standard esophagectomy
4. Esophageal replacement organ (stomach, jejunum, colon)
5. Esophagectomy as primary therapy for end-stage benign esophageal disease
6. Esophagectomy versus gastrectomy

Long- Versus Short-Segment Esophagectomy

In many cases of severe, end-stage esophageal disease, the significant anatomic or functional defect is localized to the region of the GEJ. Pertinent examples include a nondilatable distal esophageal stricture or failed fundoplication with recurrent hiatal herniation, slipped fundic wrap, and twisting or stenosis at the GEJ (Fig. 20–3).

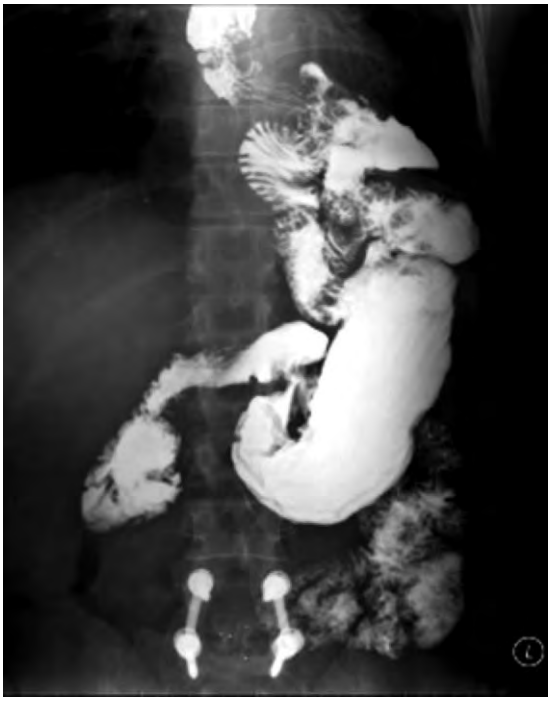


Figure 20–3. Distal esophagectomy and foregut reconstruction with colonic and jejunal interpositions. This patient underwent distal esophagectomy at the age of 7 for a nondilatable esophageal stricture. Reconstruction was initially performed with a colon interposition to the intact stomach. Bleeding from an ulcer within the distal interposed colon developed later, presumably from acid-induced injury, and led to segmental resection of the distal colon interposition and placement of a jejunal interposition between the proximal part of the colon and intact stomach. This barium upper gastrointestinal radiograph demonstrates the resultant reconstruction consisting of esophagus-colon-jejunum-stomach. Significant redundancy and tortuosity developed in the colonic and jejunal interpositions and led to dysphagia and regurgitation. The situation was eventually remediated at 38 years of age by excision of both the colonic and jejunal interpositions with primary esophagogastrostomy.

Another example is end-stage achalasia, with or without previous surgical myotomy or other intervention targeted at the lower esophageal sphincter (LES). In some circumstances, such as with underlying GERD, the esophageal body may demonstrate relatively normal peristalsis in response to swallowing. In other cases, such as with end-stage achalasia, the esophageal body may be relatively dilated and aperistaltic. Even in such cases, however, the esophageal body could be presumed to function no worse than a potential esophageal replacement conduit, which by nature may be similarly dilated and aperistaltic.

In many such cases of end-stage esophageal disease, resection could be limited to the region of the GEJ. Unlike esophageal resection for carcinoma, where the need for a wide resection margin generally mandates excision of a significant portion of the esophageal body, resection for benign disease can theoretically be much more limited. Certain advantages and disadvantages exist for limited esophageal resection versus the more commonly used strategy of resection of a much longer esophageal segment.

Pros of Short-Segment Esophageal Resection

The concept of leaving the majority of the esophagus in situ holds theoretical appeal. Less dissection is necessary to mobilize and resect only the GEJ versus the entirety of the esophagus, with less potential for hemorrhage, third-space fluid losses, or injury to surrounding structures such as the major thoracic blood vessels, thoracic duct, membranous airway, or recurrent laryngeal nerves. When compared with near-total esophagectomy plus cervical esophagogastrostomy, limited distal esophageal resection leaves a longer segment of normal squamous mucosa between the pharynx and stomach, which perhaps acts as a barrier against regurgitation of gastric contents into the pharynx, mouth, or airway. In addition, if the remaining esophagus is functionally normal, common sense would dictate that it is best to leave it intact if at all possible. Finally, limited resection may sometimes be accomplished through a laparotomy alone, thus obviating the need for an additional incision such as a thoracotomy or cervicotomy.

Cons of Short-Segment Esophageal Resection

Traditional teaching holds that limited resection of the GEJ, when reconstructed via primary esophagogastrostomy, is prone to significant gastroesophageal reflux. Low intrathoracic esophagogastric anastomoses (i.e., below approximately the level of the azygous vein) are thought best to be avoided because of this concern. The reason postulated for the increased incidence and severity of reflux in this setting is the high pressure differential between the positive pressure environment of the abdomen and the negative pressure environment of the thorax, exacerbated by loss of the LES barrier. This pressure differential drives gastric contents cephalad.

The extent to which significant gastroesophageal reflux actually occurs after short-segment esophagectomy is a matter of debate. In cases of palliative esophagectomy for advanced esophageal carcinoma, when the patient has a limited life expectancy, the importance of reflux over the ensuing months or few years of the patient's life may not be great. In cases of esophagectomy for benign disease, when life expectancy is measured in many years or decades, the potential adverse consequences of increased gastroesophageal reflux are much more worrisome. Reflux esophagitis, esophageal ulceration, stricture, or intestinal metaplasia may ensue and lead to disabling symptoms, anatomic derangements, or even esophageal carcinoma. In addition, regurgitation, aspiration, and pulmonary injury can lead to significant long-term morbidity. For these reasons, if a short segment of esophagus is resected for benign disease, reconstruction is best completed with a sufficiently long interposition of jejunum or colon between the remaining esophagus and stomach or with a primary Roux-en-Y esophagojejunostomy.

Table 20–3 Late Functional Results in 34 Patients Undergoing Short-Segment Intestinal Interposition of the Distal Esophagus

Grade	Symptoms	Colon	Jejunum
Excellent	Minimal or absent	9	7
Good	Slowed swallowing, occasional regurgitation, or both	4	6
Fair	Dysphagia with some solids, frequent regurgitation or intermittent dilation	3	2
Poor	Nutritional supplementation required	1	
Failure		2	

From Gaissert HA, Mathisen DJ, Grillo HC, et al: Short-segment intestinal interposition of the distal esophagus. J Thorac Cardiovasc Surg 106:860-867, 1993.

An additional issue relative to resection of short segments of the distal esophagus is that the subsequent esophageal anastomosis, whether it be to the stomach, small intestine, or colon, must frequently be intrathoracic in location. Only if there is sufficient length of abdominal esophagus can the subsequent anastomosis be placed in the abdominal compartment. Two potential problems relate to placement of the anastomosis within the thorax. The first is that a thoracotomy or thoracoabdominal incision is generally necessary, with its potential for significant pain, poor cosmetic or functional outcome, necessity for single-lung ventilation during surgery, and the additional time needed to open and close the incision and reposition the patient. Although a transhiatal anastomosis performed with a circular stapling device or thoracoscopic esophageal mobilization and anastomosis may obviate the need for a large thoracic incision, such techniques are not commonly feasible, especially in the setting of a reoperative procedure. The second potential problem is that the consequences of an intrathoracic leak may be more devastating than those resulting from a leak in the neck. Multiple surgical series have reported higher morbidity and mortality associated with intrathoracic esophageal leaks, which can lead to mediastinitis, empyema, and systemic sepsis, although these risks may be decreasing in recent years.[4] Relative to near-total esophagectomy with a cervical anastomosis, which can often be completed without a thoracic incision and places the anastomosis near the thoracic inlet, resection of a limited segment of the distal esophagus frequently carries with it the potential morbidity of both the thoracic incision and the intrathoracic anastomosis.

Clinical Experience with Short-Segment Esophageal Resection

The reported experience with resection of short segments of the distal esophagus for nonmalignant esophageal disease is quite limited. Gaissert et al. reported on 41 patients over a 20-year period at the Massachusetts General Hospital who underwent short-segment interposition of the esophagus with colon or jejunum, most for nonmalignant disease.[5] Colon was used in 22 patients and jejunum in 19. Seventy-six percent of the patients had previously undergone foregut surgical procedures, thus reflecting the severity and complexity of the underlying disease processes. As expected, all patients required a left thoracoabdominal incision or combined left thoracotomy and laparotomy. In the colon interposition group, the major complication rate was 45% with a median hospital stay of 17 days and a mortality of 4.5%. In the jejunal interposition group, the major complication rate was 31% with a median hospital stay of 21 days and a mortality of 10.5%. The overall mortality for the entire surgical series was 7.3%. Late follow-up was available on 34 patients at a mean of 87 months to assess long-term functional outcomes (Table 20–3). Most patients reported satisfactory long-term alimentation, although few claimed normal swallowing. Even though the number of patients was relatively small, the authors found little functional difference between jejunum and colon for the situations encountered, with both providing similar palliation of dysphagia and similar likelihood of regurgitation.

Operative Approach to Esophagectomy and Foregut Reconstruction

Mobilization of the esophagus can be accomplished successfully by open transthoracic, thoracoscopic, or transhiatal routes. In patients with end-stage nonmalignant esophageal disease, the esophagus may be relatively difficult to dissect because of the formation of periesophageal adhesions secondary to transmural fibrosis, previous surgery, or dilation of the esophageal body with neovascularization. Thus, a transthoracic route is often preferable to allow safe dissection under direct visualization.

Transhiatal esophagectomy (THE) has been well described for benign esophageal disease in selected patients. In the largest reported series from the University of Michigan, 1085 esophagectomies were attempted by the transhiatal route, 285 (26%) for benign disease.[6] THE was possible in 98.6% of patients in whom it was attempted, with only 15 patients (1.4%) requiring conversion to open thoracotomy. Reoperation for

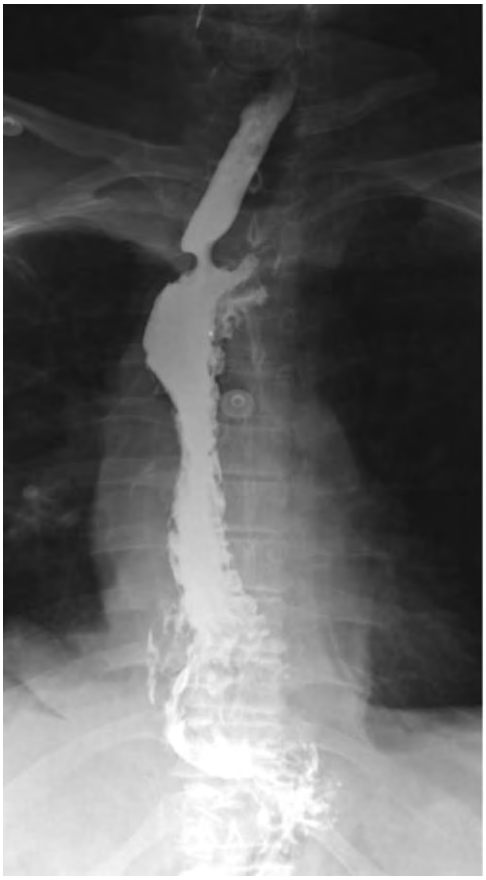


Figure 20–4. Cervical esophagogastric anastomotic stricture after esophagectomy and gastric pull-up.

mediastinal hemorrhage was necessary in five patients within 24 hours of surgery. Of course, such data are from a center with an extensive experience in resection via this approach. Extreme care and considerable judgment are necessary on the part of the operating surgeon to decide on suitable operative candidates. Similarly, the operating surgeon must have a low threshold for conversion to transthoracic resection should adhesions be dense, mobilization prove difficult, or significant bleeding ensue.

THE requires placement of the subsequent esophageal anastomosis in the neck or upper part of the thorax. Although the consequences of an intrathoracic leak are generally worse than those in the neck, the leak rate reported after cervical esophagogastrostomy is generally higher. The University of Michigan group reported a cervical anastomotic leak rate of 13%.[7] The incidence has fallen in recent years, however, with improvements in anastomotic techniques. In their hands, the clinically significant leak rate now falls in the range of 3%.[7]

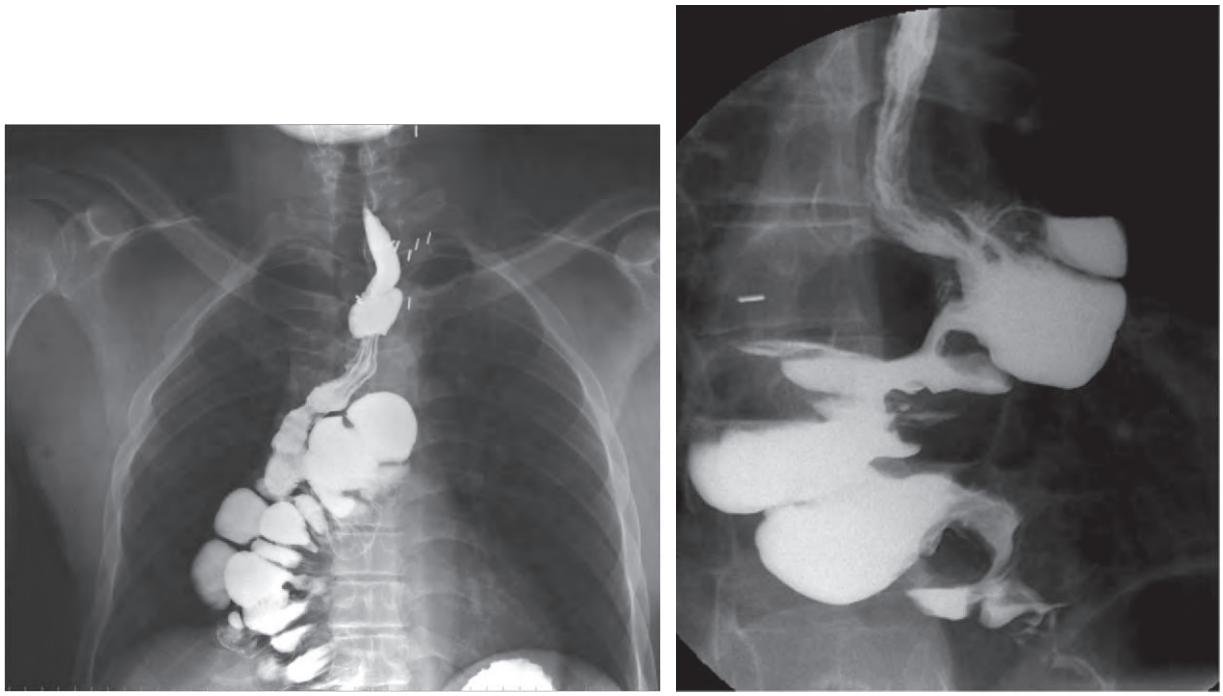
Also of tremendous significance is the incidence of esophagogastric anastomotic strictures developing after cervical esophagogastrostomy (Fig. 20–4). The need for postoperative dilation has been reported to be as high as 77% after THE for benign disease, although it is rarely a disabling, long-term complication.[7] In view of the fact that many patients are referred for foregut reconstruction because of severe dysphagia, however, the persistence of dysphagia after surgery can be a significant adverse outcome.

An issue relevant to foregut reconstruction is the route of passage of the esophageal substitute. Most surgeons prefer to bring the conduit through the posterior mediastinum when it is available for this purpose. The native esophageal bed provides the straightest, shortest, and generally most convenient route for bringing an esophageal replacement conduit to the neck. Of course, this route may not be feasible when the esophagus has previously been resected and the esophageal bed is fibrosed. Another scenario that mandates the use of an alternative route is when the esophagus is bypassed rather than resected. An example of such a situation for benign esophageal disease occurs in the setting of a caustic injury, in which case extensive transmural esophageal inflammation and fibrosis may make esophagectomy hazardous (Fig. 20–5).

When the posterior mediastinum is not suitable for passage of the replacement conduit to the neck, the best available alternative is generally the substernal route. The stomach or colon can usually be brought to the cervical region through the substernal plane, although the jejunum will typically not reach this far when pedicled on its native mesenteric blood supply (Fig. 20–6). Of course, a free jejunal graft with microvascular anastomosis of the arterial inflow and venous outflow can be used to add length to a pedicled jejunal segment. Additionally, an interposed jejunal segment can be "supercharged" by microvascular anastomosis in the neck or upper part of the thorax.

As long as a previous sternotomy has not been performed, a sternotomy is not typically necessary to create an adequate substernal space. Technical details important to successful substernal transposition include a xiphoidectomy to prevent subsequent bony impingement of the conduit, direct dissection and mobilization of the diaphragmatic insertions to the lower part of the sternum to prevent compression in this region, and blunt hand dissection in the substernal plane to create adequate space. Most surgeons add a left hemimanubriectomy with resection of the head of the left clavicle and the head of the left first rib or, at a minimum, resection of the left sternoclavicular joint to create adequate space at the upper thoracic level (Fig. 20–7). Of course, in the setting of a previous sternotomy, a redo sternotomy, with its inherent risks, may be necessary to accomplish a substernal pull-up. Moreover, if a long length of proximal esophagus is available and the chosen esophageal replacement conduit is short, a sternotomy will allow a relatively low anastomosis in an intrathoracic, substernal position. Such an approach may permit a pedicled jejunal interposition or Roux limb of the jejunum to be used with a retrosternal esophagojejunal anastomosis if sufficient esophageal length remains.

Experience has shown that the anastomotic leak rate is higher for substernal conduits than for those brought through the posterior mediastinum. Among the 1030 surviving patients from the University of Michigan series in whom the stomach was positioned in the posterior mediastinum, anastomotic leaks developed in 13% versus



A B

Figure 20–5. Substernal right colon interposition used to bypass a lye-induced esophageal stricture. **A,** Surgery was performed 22 years before this barium radiograph. **B,** Redundancy of the distal colon interposition developed over time.

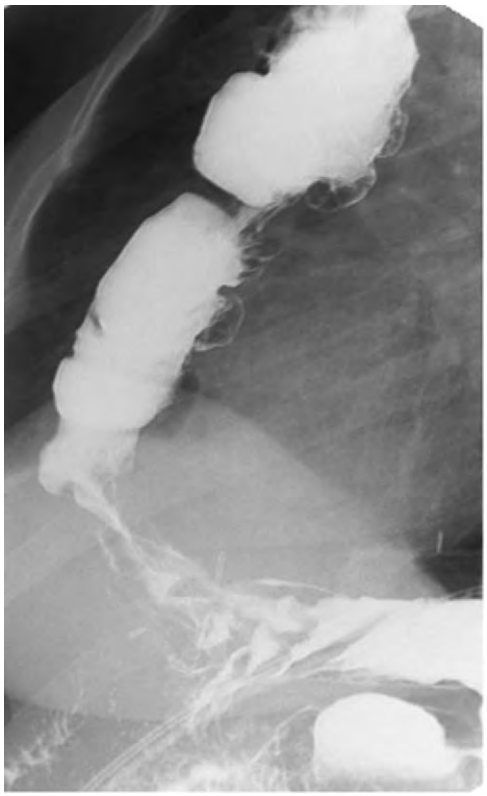
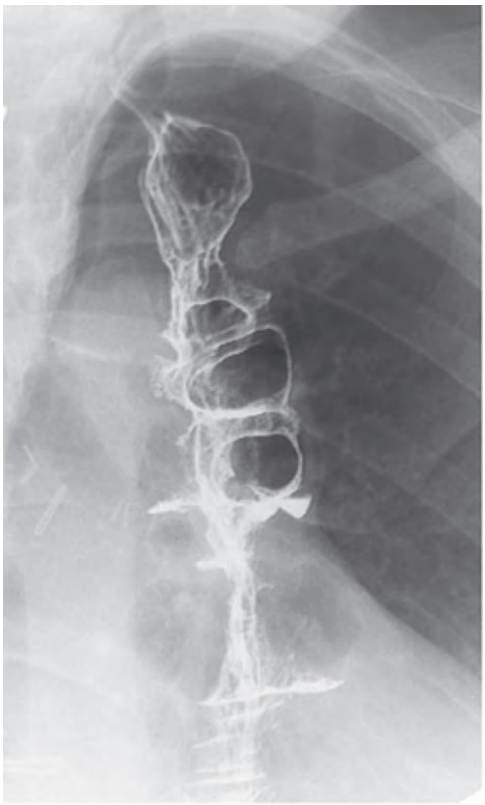


Figure 20–6. Substernal colon interposition. The substernal route was chosen because the patient had undergone resection of a previous gastric pull-up with an end-esophagostomy. The posterior mediastinum was not available for placement of the colon conduit.

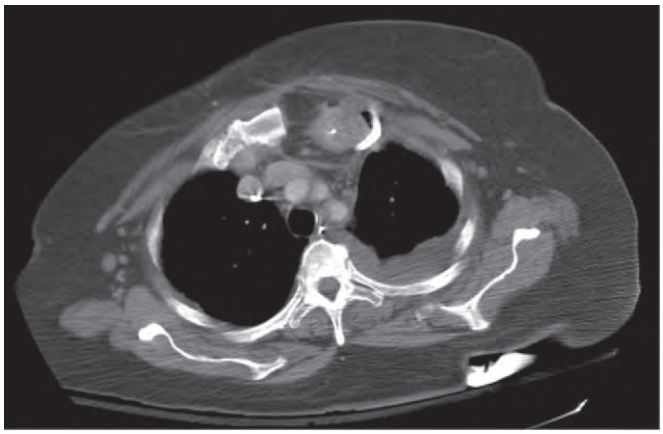
an 86% leak rate in 7 patients reconstructed via retrosternal placement of the stomach.[6] Several mechanisms may explain the higher leak rate associated with a substernal conduit, including the relatively longer route of passage for the conduit plus the potential adverse effect on the blood supply, as well as the relative lack of surrounding soft tissue investment of the anastomosis, which may have a negative impact on wound healing. A substernally passed conduit places the cervical esophageal anastomosis essentially in a subcutaneous location, where it is unsupported during coughing or a Valsalva maneuver early in the postoperative period. On the contrary, when the conduit is placed in the native esophageal bed, the esophageal anastomosis is buttressed by the carotid sheath laterally, the prevertebral fascia posteriorly, and the membranous trachea anteriorly.

An option of last resort for bringing the colon or stomach to the neck is the subcutaneous route. Because of the obvious cosmetic and functional consequences, such a route should be used only when absolutely mandated and should virtually never be necessary. A technique was recently described for the use of tissue expanders to create an adequate subcutaneous space for passage of an esophageal replacement conduit after previous sternotomy.[8]

A final issue relative to colon and jejunal interpositions is whether they are positioned in an isoperistaltic or antiperistaltic fashion. A number of studies have confirmed that such interpositions typically empty by gravity and are not peristaltic.[5,9] Case reports, however, would suggest that over time, an antiperistaltic conduit may propel a food bolus in a retrograde fashion. Most



A



B

Figure 20–7. Substernal colon interposition. **A** and **B,** The left hemimanubrium and head of the left clavicle were resected to create adequate space for passage of the colon.

surgeons therefore prefer to place the esophageal replacement conduit in an isoperistaltic fashion.

Vagal-Sparing Versus Standard Esophagectomy

When esophagectomy is performed for malignancy, the vagus nerves are typically resected because of the potential for transmural spread of tumor and the desire to achieve a complete resection. For nonmalignant conditions leading to esophagectomy, the potential may exist to spare the vagus nerves at the time of resection. Such a vagal-sparing approach assumes, naturally, that the vagus nerves have not been disrupted by previous operative intervention such as myotomy or fundoplication and can be identified and preserved at the time of foregut reconstruction. Many of the side effects after esophagectomy probably relate to the associated vagotomy. By sparing the nerves, the potential exists for less alteration in gastrointestinal function after foregut reconstruction than is the case with a standard approach.

Vagal-sparing esophagectomy was initially reported by Denk in 1913,[10] who used a vein stripper and based the procedure on work performed on human cadavers. Akiyama et al. reintroduced the concept in 1994.[11] Either stomach or colon can be used as the esophageal substitute in this setting.

The technical details of the operation include the creation of a small anterior gastrotomy along the gastric cardia, mobilization and division of the cervical esophagus, passage of a vein stripper of suitable size through the gastrotomy proximally to the cervical esophagus, fixation of the cap of the vein stripper to the divided end of the esophagus by suture ligature, and eversion of the esophagus out of the stomach (Figs. 20–8 and 20–9). In the process the esophagus is stripped from its mediastinal divestments, with a layer of longitudinal esophageal muscle commonly left in situ. The dissection plane is typically quite easy to develop and does not offer much resistance on stripping. Umbilical tape is affixed to the

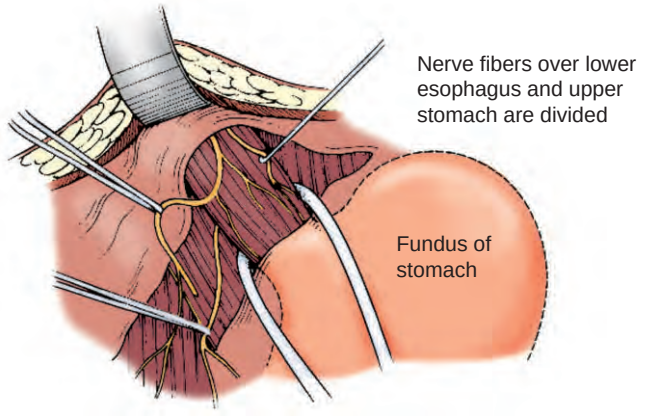


Figure 20–8. Dissection of the abdominal vagal trunks for vagal-sparing transhiatal esophagectomy.

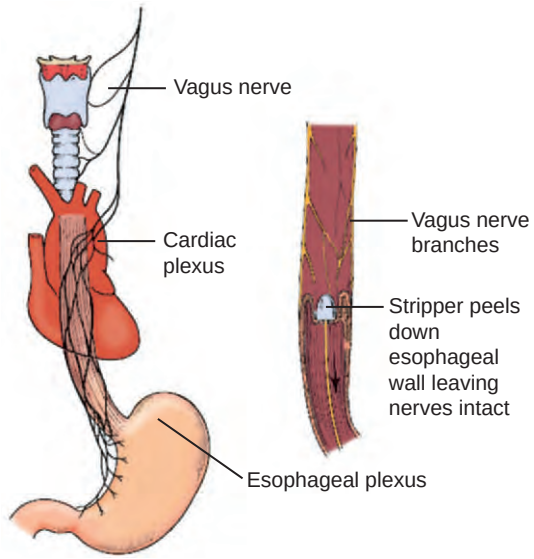


Figure 20–9. The technique of transhiatal vagal-sparing esophagectomy.

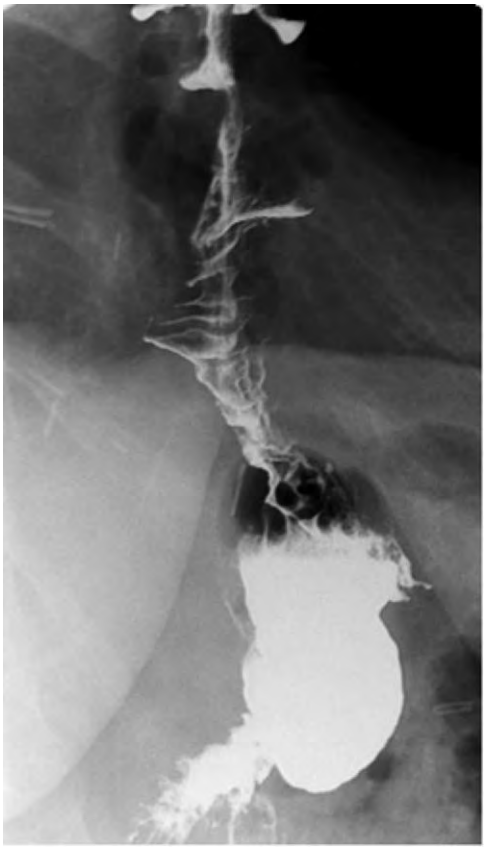


Figure 20–10. Colon interposition anastomosed to the gastric antrum. The proximal part of the stomach was resected to prevent problems with delayed gastric emptying, given that vagotomy was performed as part of a standard esophagectomy.

proximal tip of the esophagus being resected before eversion to allow passage of the tape though the mediastinum. The vagal plexus and main trunks are left intact. The esophagus is then divided near the GEJ. The resultant mediastinal tunnel must be dilated to allow adequate space for passage of the esophageal replacement conduit. Foley catheters with balloons inflated to progressively larger sizes (e.g., 30, 60, 90 ml) can be used for this purpose. The umbilical tape within the mediastinum denotes the proper plane for passage of the replacement organ among the vagal fibers, which can be somewhat web-like. The operation can be performed by open laparotomy or, in experienced hands, by a laparoscopic or hand-assisted technique.

If colon is used for interposition, the colon graft can be passed up through the posterior mediastinum along the path established by the umbilical tape. Anastomosis can then be performed proximally to the esophagus in the neck and distally to the intact stomach. Important differences between the techniques of colon interposition when performed with a vagal-sparing esophagectomy versus a standard esophagectomy are that a pyloroplasty is not necessary because pyloric innervation is preserved and the proximal part of the stomach is left intact. A common practice with colon interposition for malignancy is to resect the proximal two thirds of the stomach, either because of neoplastic involvement or because of the risk for gastroparesis and delayed gastric emptying should the denervated stomach be left intact (Fig. 20–10). By preserving vagal innervation, the stomach should function in normal fashion, thus allowing preservation of the normal gastric reservoir and antral pump.

If stomach is used for esophageal replacement, a highly selective vagotomy along the lesser gastric curvature is necessary to permit mobilization of the conduit. The left gastric artery is left intact in the process. A theoretical advantage of such a technique is better blood supply to the conduit than with a standard gastric pull-up, where the left gastric artery is divided, although this concept has not been proved in the laboratory or clinical settings. The stomach can then be brought to the neck via the posterior mediastinum, as for colon interposition.

Clinical experience with vagal-sparing esophagectomy is fairly limited. One study assessed physiologic parameters and clinical outcomes in patients undergoing vagal-sparing esophagectomy versus those undergoing esophagogastrectomy with colon interposition, standard esophagectomy with gastric pull-up, and asymptomatic normal volunteers.[12] Gastric acid production was assessed by Congo red staining. Vagal secretory function was quantitated by increases in gastric output and rises in serum pancreatic polypeptide levels in response to sham feeding. Vagal motor function was measured by gastric emptying scans and a questionnaire to evaluate dumping symptoms. Gastric reservoir function was estimated by meal capacities and postoperative changes in body mass index (BMI). The results showed that vagal-sparing esophagectomy preserved gastric acid secretion, gastric emptying, meal capacity, and BMI when compared with

esophagogastrectomy plus colon interposition or standard esophagectomy with gastric pull-up. The incidence of dumping in patients undergoing vagal-sparing esophagectomy was 7% (1 of 15 patients), thus suggesting that the vagi were in fact preserved in most individuals. The only significant difference observed in patients who underwent vagal-sparing esophagectomy when compared with normal subjects was the speed with which they ate. This finding is intuitive if one considers that the main difference in operated individuals is the fact that they have a passive, nonperistaltic esophageal replacement conduit that would not be expected to transport food as rapidly as a normally peristaltic esophagus.

Several potential disadvantages of the vagal-sparing approach exist. The surgeon may be unable to ensure that the vagi are in fact preserved and that postoperative gastric emptying will not be an issue. Again, many surgeons would opt to resect the proximal part of the stomach or perform a pyloroplasty (or both) in cases in which the vagi are known to be compromised. The placement of acid-secreting gastric mucosa in juxtaposition to colonic mucosa can be problematic. Cases of colonic mucosal ulceration leading to pain or bleeding have been reported in this situation. Such ulceration would seem less likely when the proximal part of the stomach has been resected and the stomach is vagotomized. Finally, exposure of the hiatus to perform the operation may be technically challenging in obese patients. Whether the advantages of the vagal-sparing approach outweigh its disadvantages awaits further experience with longer follow-up on greater numbers of patients.

Choice of Esophageal Replacement Organ (Stomach, Colon, or Jejunum)

The preferred esophageal substitute is a widely discussed and debated issue. Because most esophagectomies are performed for carcinoma and the patient's life expectancy may be relatively short, the long-term functional outcome after esophageal replacement is often less of an issue in this scenario. In the case of foregut reconstruction for benign disease or early-stage malignancy, where life expectancy may be measured in many years or decades, the issue of the best functioning esophageal substitute is important and remains controversial.

The two organs most commonly used for esophageal replacement are the stomach and the colon. Each organ has been extensively evaluated, and each has its proponents. Closer analysis demonstrates that the stomach and colon possess several theoretical advantages and disadvantages in comparison to each other and to the jejunum.

Proponents of esophageal replacement via gastric pull-up tout the relative ease of gastric mobilization, the need for only a single (esophagogastric) anastomosis, and the relatively quick operative time and return of alimentation. In addition, where expertise exists, the operation can be completed through minimally invasive means, with laparoscopic gastric mobilization and cervical esophagogastrostomy or intrathoracic anastomosis accomplished via thoracoscopy.[13] The published experience with minimally invasive esophagectomy, however, has been predominantly for malignant or pre-malignant disease.

Disadvantages of use of the stomach include loss of the gastric reservoir with the potential for early satiety and dumping, as well as gastroesophageal reflux into the remaining esophageal remnant or pharynx. Placement of the stomach within the negative pressure environment of the thorax, coupled with loss of the normal GEJ antireflux barrier, predisposes the patient to reflux, regurgitation, and aspiration. Although there is general acceptance of the concept that a cervical esophagogastrostomy is less prone to reflux than an intrathoracic anastomosis is, particularly when placed low in the chest, reflux can occur in either scenario and may cause significant symptomatology or induce complications. Placement of gastric mucosa in juxtaposition to squamous esophageal mucosa predisposes the patient to proximal esophagitis, stricture, or Barrett's esophagus (BE) from chronic exposure of the remaining esophageal mucosa to gastric or duodenal content, or to both. A series from Japan demonstrated reflux esophagitis in 44% of patients and Barrett's metaplasia in 12% of patients monitored for more than 2 years after cervical esophagogastrostomy.[14] Another series from Öberg et al. demonstrated the development of metaplastic columnar mucosa within the cervical esophageal remnant in 15 of 32 patients (46.9%) after a gastric pull-up, 3 with intestinal metaplasia.[15] Of note, esophageal columnar metaplasia was more likely to occur in those with Barrett's mucosa resected at the time of esophagectomy than in those without, thus suggesting an underlying genetic predisposition to the development of metaplasia in susceptible individuals. The clinical significance of this metaplastic response, however, is uncertain in that the incidence of cancer in the esophageal remnant after esophagectomy and gastric pull-up is unknown and probably quite low. In contrast, the esophageal mucosa in patients undergoing colon interposition appears to undergo few histologic changes.

The blood supply to the proximal tip of the gastric conduit can be quite tenuous. The incidence of ischemic complications, such as esophagogastric anastomotic leaks or strictures, is relatively high as a result. The anastomotic leak rate after cervical esophagogastrostomy ranges between 3% and 20% in large surgical series.[6,13,16] Orringer and Stirling reported on 145 patients undergoing esophagectomy with gastric pull-up for benign disease.[17] Sixty-five percent of patients required immediate postoperative dilatation and 12% suffered from persistent dysphagia requiring regular anastomotic dilation or a home dilatation regimen. In a more recent publication from the same group, 77% of 251 patients undergoing THE and esophageal replacement with stomach for benign disease have required at least one postoperative anastomotic dilation, whereas only 4% have suffered from severe dysphagia requiring daily or weekly dilations.[6]

With regard to colon interposition (Fig. 20–11), several theoretical advantages have been suggested. The interposed colonic segment separates the remaining esophageal mucosa from acid-producing gastric

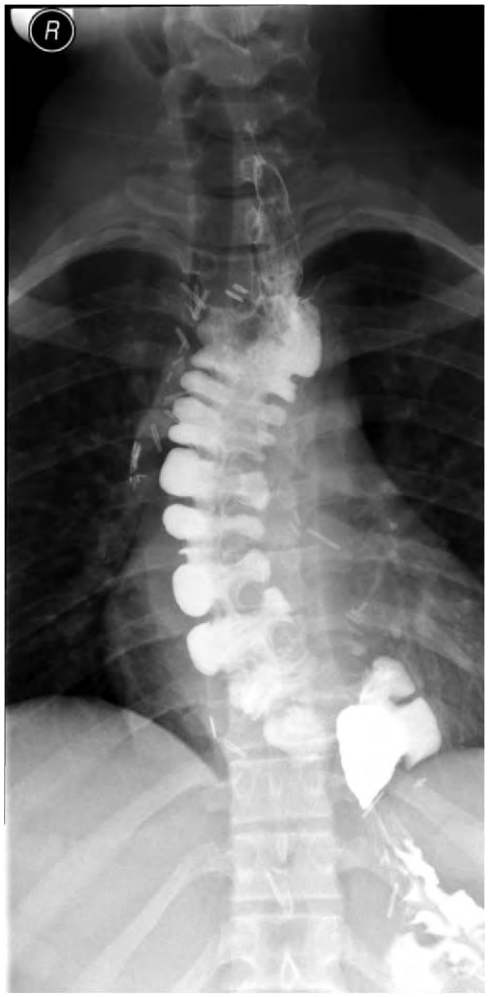


Figure 20–11. Colon interposition brought through the posterior mediastinum. A lye-induced esophageal stricture developed in this patient as a child and was initially treated by esophagectomy and reconstruction with a reserved gastric tube at the age of 6 years. Because the tube never emptied well, surgical remediation was undertaken 8 years later by excision of the gastric pull-up and left colon interposition to the intact gastric antrum.

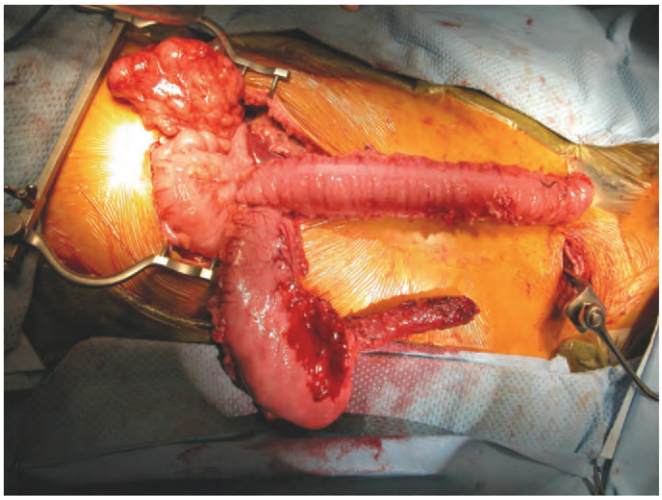


Figure 20–12. Operative photograph of an esophagus resected for a nondilatable lye stricture in a 3-year-old. Reconstruction was completed via a left colon interposition anastomosed distally to the gastric antrum.

mucosa and duodenal contents, as previously stated. The incidence of reflux-induced complications such as esophagitis, stricture, or BE is low. The blood supply to the colon, when mobilized appropriately, is generally quite robust. The incidence of ischemic complications at the esophageal anastomosis, such as leaks or strictures, is also quite low. In 85 patients undergoing colonic interposition for benign disease, Watson et al. reported an esophagocolonic leak rate of 3.5% and a need for postoperative anastomotic dilation in 5%.[16] Both these rates were much less than those after cervical esophagogastrostomy in their series, where anastomotic leaks occurred in 20% and the need for dilation in 30% of patients. Similarly, Briel et al. reported on 395 consecutive patients undergoing esophagectomy for both malignant and benign disease.[18] The development of either anastomotic leak or stricture was analyzed in patients undergoing gastric pull-up versus colonic interposition. Leaks and strictures were more common (14.3% versus 6.1%, $P = .013$; 31.3% versus 8.7%, $P < .0001$, respectively) and strictures were more severe after gastric pull-up.

The colon possesses a reservoir function that allows for a more normal meal capacity. The distal colonic segment and residual stomach remain in the positive pressure environment of the abdomen, thus helping guard against reflux (Figs. 20–12 and 20–13). In some individuals, the stomach is not suitable or available for use as an esophageal substitute. In such cases, the colon may serve the purpose quite well and can be anastomosed distally to a Roux limb of jejunum if the antrum has been resected or there is a significant gastric outlet obstruction. Finally, if the interposed colon becomes dilated or tortuous over the long term, it often can be successfully revised via a tailoring coloplasty or segmental resection.[16,19] A dilated, tortuous, or poorly emptying gastric pull-up, on the other hand, cannot be similarly remediated and requires replacement should significant dysfunction develop.

Disadvantages of the colon as an esophageal substitute are most apparent. The colon must be free of significant pathology, such as extensive diverticulosis, polyposis, or frank malignancy, and must be adequately evaluated and prepared for use, as for elective colon resection. Along with the need for three anastomoses (esophagocolonic, cologastric, and colocolonic), there is an inherently longer operative time with a greater extent of mobilization and dissection than with gastric pull-up. The operation may be technically challenging, especially in terms of preserving arterial inflow and venous drainage of the conduit. Seemingly minor mistakes in judgment or technique can have disastrous consequences with regard to maintenance of adequate vascularity. Leaks or strictures, or both, can occur at any of the anastomoses, and bowel obstruction can occur if the colonic mesentery is not

adequately closed. Minimally invasive techniques for completion of the operation have yet to be mastered. The colon is generally thought to be slower to allow resumption of alimentation than the stomach is. Finally and of great importance is the fact that colon interpositions are known to become dilated or tortuous (or both) when in place for many years. Such redundancy can lead to problems with dysphagia, regurgitation, or aspiration, although surgical remediation is often feasible, as stated earlier (Figs. 20–14 and 20–15).

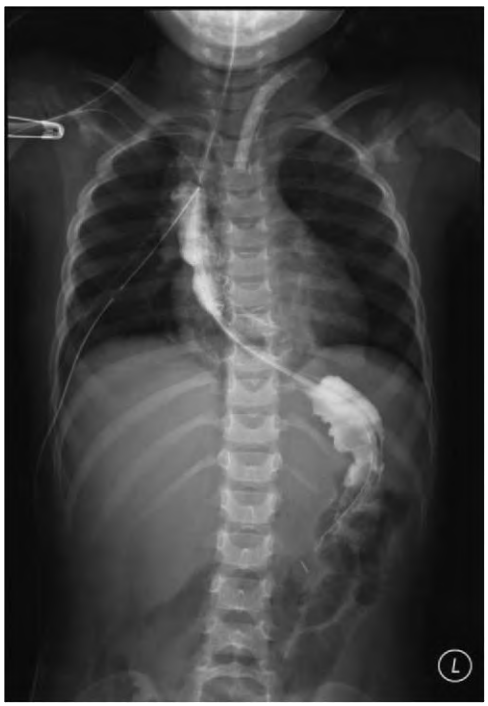
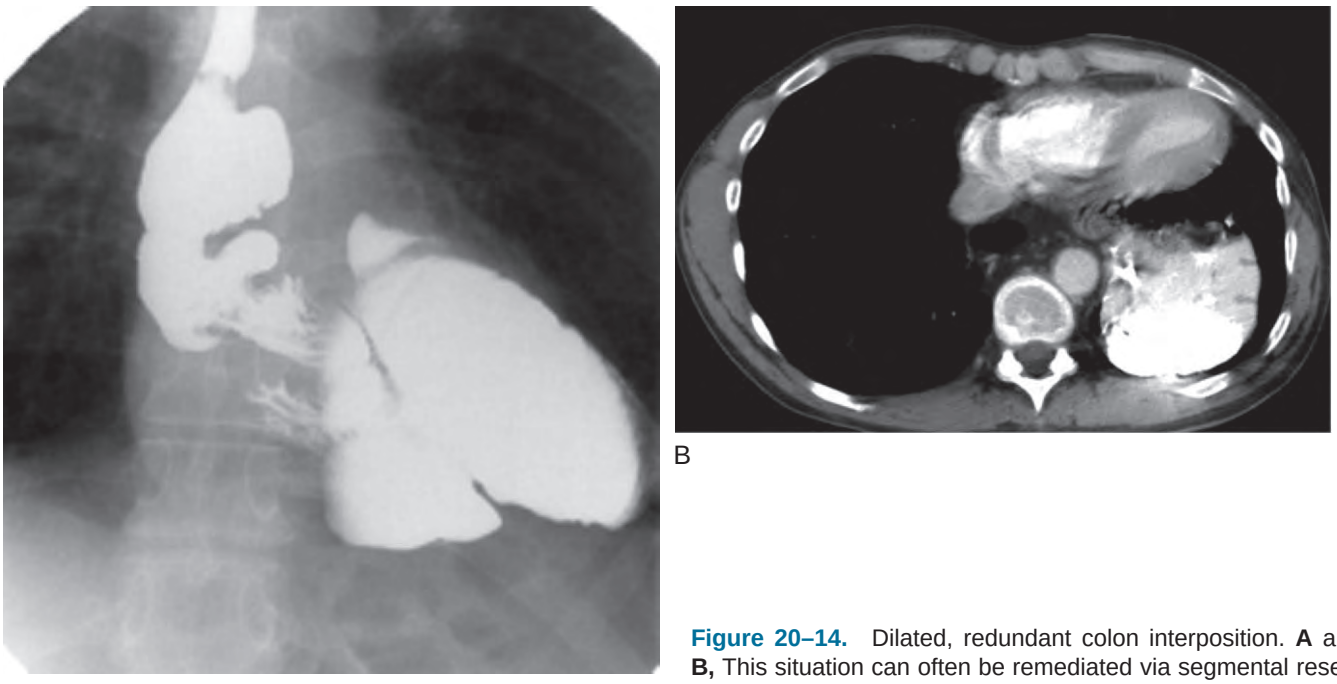


Figure 20–13. Left colon interposition. Postoperative contrast upper gastrointestinal radiograph of the patient in Figure 20–12 demonstrating the intact reconstruction.

Clinical experience with the jejunum as an esophageal substitute is much less than with either the stomach or colon (Fig. 20–16). This fact is largely due to the limited extent to which the jejunum can be brought into the thorax, either as a Roux limb or as a jejunal interposition, because of its short mesentery and tethered blood supply. Of course, a free jejunal interposition can be placed wherever there is suitable arterial inflow and venous outflow, although it is a technically more demanding procedure than the other options because of the need for microvascular anastomoses.

Extensive clinical experience has accumulated from a number of centers using different methods of esophageal reconstruction for end-stage nonmalignant esophageal disease. In the University of Michigan experience with THE for benign disease in 285 patients, the overall hospital mortality was 2.8%.[6] Follow-up data regarding long-term functional results were available in 242 of 251 hospital survivors (96%) at an average of 47 months. Results were considered excellent (completely asymptomatic) in 29%, good (mild symptoms requiring no treatment) in 39%, fair (symptoms requiring occasional treatment such as dilation or antidiarrheal medication) in 28%, and poor (symptoms requiring regular treatment) in 4%.

Curet-Scott et al. reported on the University of Chicago experience with colon interposition for benign disease.[20] Perioperative mortality was 3.8% in the 53



A

B

Figure 20–14. Dilated, redundant colon interposition. **A** and **B,** This situation can often be remediated via segmental resection with reanastomosis or a tailoring coloplasty (or both).

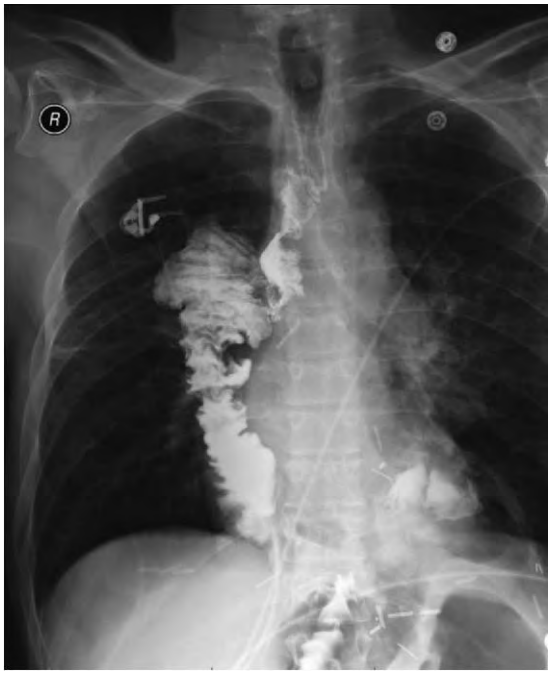


Figure 20–15. Right colon interposition brought through the posterior mediastinum. The intrathoracic portion of the colon is markedly redundant.

patients undergoing surgery, with a 26.4% major complication rate. Follow-up was complete in 83% of patients at an average of 5 years after reconstruction. Results were rated by patients and physicians, with 75% of the patients claiming good or excellent results and 72% classified as having good or excellent results by the physicians. There was, however, a 37% reoperative rate for treatment of delayed gastric emptying, anastomotic stricture, leak, or persistent symptoms. Despite the complication and reoperation rates, the authors stated that colon interposition remained their preferred technique for reconstruction after esophagectomy for benign disease.

At the University of Southern California, 104 patients with benign esophageal disease underwent esophageal reconstruction over a 21-year period.[16] For esophageal replacement, colon was used in 85 patients, stomach in 10, and jejunum in 9. Overall hospital mortality was 2% and the median hospital stay was 17 days. Forty-two patients who were at least 1 year after surgery answered a postoperative questionnaire concerning their long-term functional outcome. Ninety-eight percent of patients reported that the operation improved or cured the symptom driving surgery. Ninety-three percent were satisfied with the outcome of the operation. The number of patients undergoing esophageal reconstruction with stomach or jejunum, however, was too small to allow meaningful comparisons between the different types of reconstructions.

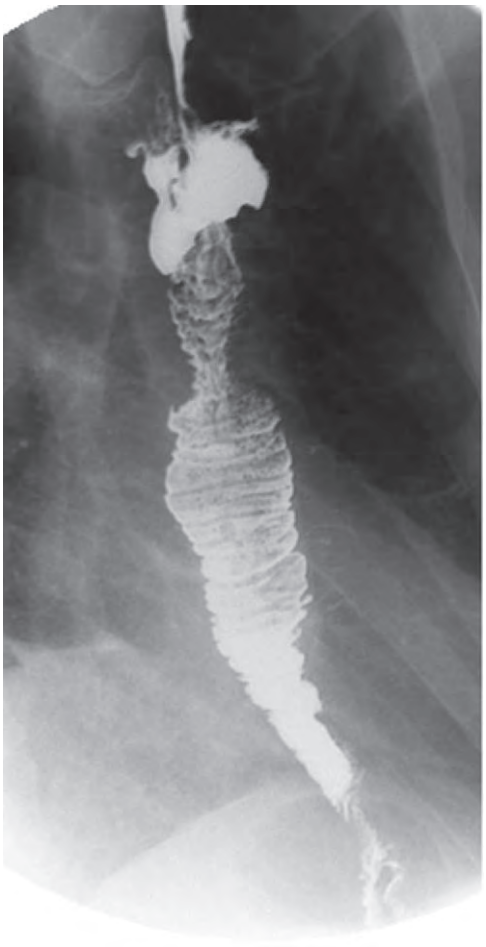
A report from the Mayo Clinic analyzed outcomes in 255 patients undergoing esophagectomy for benign disease between 1956 and 1997.[21] The esophageal substitute was stomach in 66%, colon in 27%, and small bowel in 7%. Perioperative mortality was 5% and morbidity was 56%. Median hospitalization was 14 days. Follow-up was available in 88.6% of patients at a median of 52 months after surgery. Improvement was noted in 77.4% of patients, with functional results classified as excellent in 31.8%, good in 10.2%, fair in 35.4%, and poor in 22.6%. The method of reconstruction did not appear to have an impact on late functional results.

The published reports on esophageal replacement for benign disease inherently reflect an institutional or surgeon-specific bias in terms of the types of reconstructions performed. Randomized trials comparing the different reconstructive options are lacking. Analysis of the published reports reveals that they suffer from a lack of uniform assessment of long-term symptomatic and functional outcomes. The long periods covered in the various reports also make results difficult to interpret in the setting of changing surgeons, refinements in operative technique, and advancements in perioperative care. Firm conclusions, therefore, regarding the optimal operative approach and esophageal replacement conduit for a given patient are lacking.

Esophagectomy as Primary Therapy for End-Stage Benign Esophageal Disease

Fortunately, the need for esophagectomy to treat end-stage motility disorders is rare. As mentioned previously, esophagectomy may be necessary after previous failed esophageal myotomy, fundoplication, or pneumatic dilatation or in patients with major complications such as perforation, ulceration, fistulization, or bleeding. On occasion, a patient is initially seen with an end-stage motility disorder, in the absence of previous interventions or complications, that cannot be remediated by a lesser procedure and requires an esophagectomy as primary therapy. The disease entity that stands as the model in such end-stage cases is achalasia. The largest body of literature, therefore, regarding esophagectomy as primary therapy for end-stage benign esophageal disease relates to achalasia.

Achalasia, though a relatively rare disease, is the most commonly treated of the primary motility disorders. Idiopathic achalasia occurs in approximately 0.5 to 1.0 per 100,000 population per year in the United States and Europe. It is characterized by esophageal body aperistalsis and propulsive failure with absent or incomplete LES relaxation in response to swallowing. The etiology and pathophysiology of achalasia are debated and not well understood but clearly relate to destruction of ganglion cells in the esophageal myenteric plexus of Auerbach, as well as abnormalities within the dorsal motor nucleus of the vagus. Clinically, achalasia is characterized by progressive dysphagia for solids and liquids, regurgitation, and sometimes chest pain or weight loss. Manometrically, achalasia is manifested as loss of LES relaxation in response to wet swallows, a hypertensive LES at rest, esophageal body aperistalsis, and esophageal body pressurization above atmospheric baseline.



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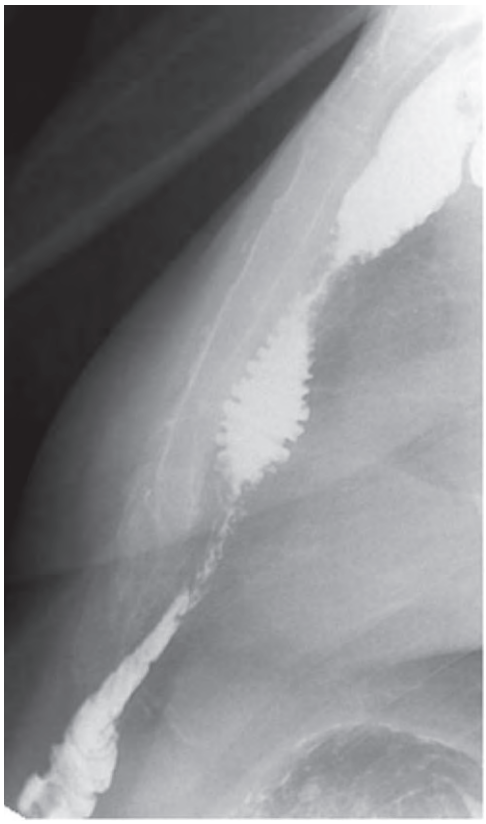
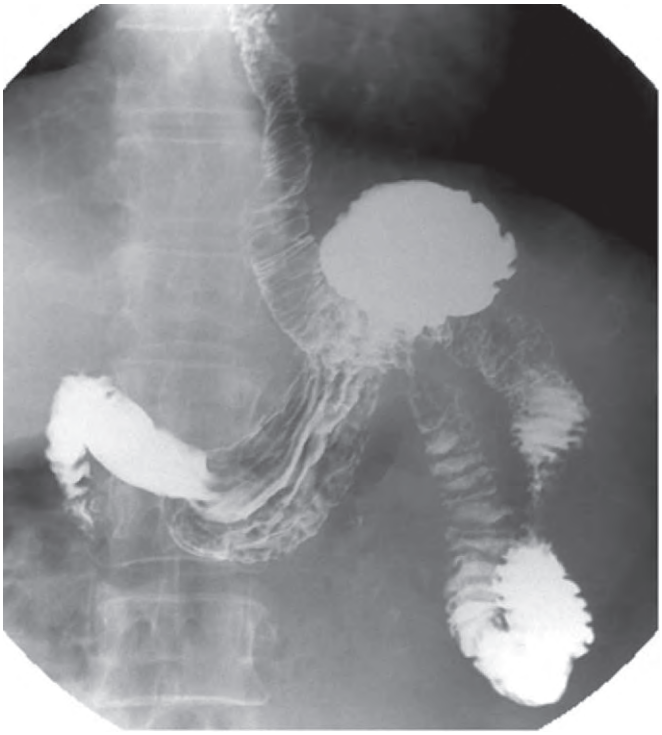


B

Figure 20–16A to **D.** Substernal jejunal interposition. The patient is a 53-year-old born with esophageal atresia. He underwent multiple esophageal operations during infancy, which culminated in a substernal jejunal interposition to the intact stomach approximately 50 years before this radiograph. Current complaints include dysphagia, regurgitation, and cough. Note the significant redundancy of the intra-abdominal segment of jejunum.



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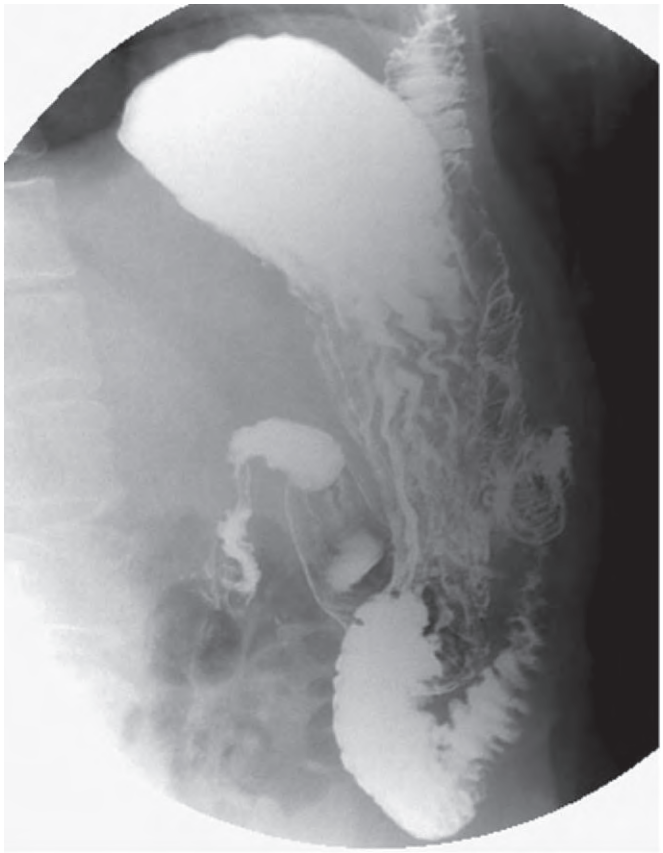

D

Box 20–4 Hallmarks of End-Stage Achalasia

Clinical: Severe dysphagia and/or regurgitation

Radiographic: Massive esophageal dilatation ("megaesophagus") and/or tortuosity ("sigmoid esophagus")

Pathologic: Reduction or absence of ganglion cells with fibrous replacement of the myenteric plexus

From Banbury MK, Rice TW, Goldblum JR, et al: Esophagectomy with gastric reconstruction for achalasia. J Thorac Cardiovasc Surg 117:1077-1084, 1999.

Box 20–5 Mechanisms by Which Achalasia Can Lead to Esophageal Replacement

Ulceration, bleeding, fistulization, perforation

Post-treatment reflux esophagitis/stricture

Development of carcinoma

Inadequate nonoperative therapy (Botox, dilatation)

Inadequate surgery
- Incomplete myotomy
- Healing of myotomy
- Complete fundoplication
- Paraesophageal herniation
- Other technical problems (e.g., angulation, tight hiatus)

End-stage disease at initial evaluation

The accepted therapies for achalasia are aimed at relieving the relative outflow obstruction at the LES and include smooth muscle relaxants, endoscopic botulinum toxin (Botox) injection, pneumatic dilation, and surgical myotomy. The latter can be performed in an open fashion, through the abdomen or thorax, or via minimally invasive approaches, either laparoscopic or thoracoscopic. Myotomy has been described with and without the addition of fundoplication, typically partial.

Therapy for achalasia is palliative, not curative in nature because treatment rarely returns normal function to an aperistaltic esophagus. Outcomes are therefore difficult to assess inasmuch as success is a relative term. In addition, objective outcome measures may not correlate with symptomatic findings.[22] Patients with achalasia typically learn to compensate for symptoms of dysphagia or regurgitation, or both, through a variety of dietary, behavioral, and lifestyle modifications, thus making symptomatic assessment of post-therapy outcome unreliable. Similarly, patients and their treating physicians may underestimate the severity of the physiologic derangements at the time of initial evaluation or after apparently successful intervention. Given these factors, it is no surprise that such patients not uncommonly have the manifestations of end-stage disease, which can be categorized by clinical, radiographic, and pathologic parameters (Box 20–4).

Achalasia may lead to the need for esophageal replacement through a number of mechanisms (Box 20–5). Esophageal stasis can lead to ulceration, bleeding, fistulization, or perforation of the esophageal body. GERD can result from therapy aimed at reducing the competency of the LES and can therefore lead not only to reflux symptoms but also to potential reflux-induced complications such as erosive esophagitis or stricture. Such complications are particularly difficult to correct in the setting of an aperistaltic esophagus. Successful treatment through nonextirpative remediation can be extremely unreliable. Achalasia is a known risk factor for the development of esophageal squamous cell carcinoma, presumably from the chronic esophageal mucosal inflammation associated with stasis esophagitis. Post-treatment gastroesophageal reflux can predispose to esophageal adenocarcinoma as well. Inadequate therapy, whether it is surgical or nonsurgical, can lead to gradual esophageal dilation or tortuosity (or to both), particularly if the patient is not closely monitored for the long term after intervention. As stated, patients tend to compensate for any difficulties encountered in eating and understate the severity of their ongoing symptomatology. For this reason, regular follow-up with the physician, including objective assessment of esophageal structure and function, is recommended indefinitely after therapy. Finally, patients may not be evaluated by the treating specialist until end-stage disease is already present. The fact that this continues to occur is testimony to the degree of compensation that patients can tolerate and the extent to which physiologic derangements can go underappreciated by the patient or primary physician.

With the availability of endoscopic or minimally invasive surgical therapies for achalasia, the question arises whether patients with end-stage achalasia at initial evaluation should ever be treated primarily with esophagectomy. Experience dictates that even significant megaesophagus can be treated with therapy aimed at the LES. As the degree of esophageal body tortuosity increases, however, the chance of success with such treatments diminishes because food must traverse a serpiginous route to reach the stomach. Botox injections in this setting will probably provide minimal, temporary palliation at best. Pneumatic dilation may be technically difficult to accomplish and risks perforation. Laparoscopic myotomy, though minimally invasive, risks potential compromise of the stomach for later use as an esophageal replacement organ and can place the vagus nerves amidst periesophageal fibrosis, thus making subsequent vagal-sparing esophagectomy difficult should the need arise. Primary esophagectomy should be considered when the anatomic and physiologic derangements are sufficiently severe, particularly in the setting of a tortuous or "sigmoid" esophagus. Such a decision requires considerable clinical experience and judgment, with the

Table 20–4 Esophageal Replacement for Achalasia

Institution	Year	No. Patients	Conduit	Mortality (%)	LOS (days)
USC[24]	1995	19	Colon	0	16
Mayo Clinic[25]	1995	37	Stomach: 26 Colon: 6 Small bowel: 5	5.4	12
Cleveland Clinic[26]	1999	32	Stomach	0	14
U. of Michigan[27]	2001	93	Stomach: 91 Colon: 2	2	12.5
Taiwan[28]	2003	9	Colon (short segment)	0	15

LOS, length of stay; USC, University of Southern California.

severity of the patient's symptoms, the anatomic and functional derangements, and associated comorbid conditions taken into account. Common sense would dictate that if any doubt remains about whether a less invasive therapy is indicated, conservative measures should be exhausted before proceeding with the more extensive and irreversible step of foregut resection and reconstruction.

Clinical experience regarding esophagectomy for end-stage achalasia comes from several sources. South American surgeons have extensive experience with primary esophagectomy for Chagas' disease, which has pathophysiologic and anatomic features similar to achalasia. Pinotti et al. reported on primary esophagectomy in 122 patients with Chagas' megaesophagus, with a 4.2% mortality rate and excellent/good functional outcomes in the vast majority.[23] Such experience demonstrates that esophagectomy can be performed safely on appropriately selected patients with end-stage benign megaesophagus.

Data regarding esophagectomy for achalasia come from several centers (Table 20–4). Operative approaches include a mix of transthoracic and transhiatal resections. Depending on institutional biases, patients had their foregut reconstructed with stomach, colon, or small intestine. A recent series from Taiwan reported on short-segment colon interposition for end-stage achalasia performed via a thoracoabdominal incision.[28] Mortality rates run acceptably low in these specialty centers, with lengths of stay consistent with esophagectomy for cancer. Outcomes in these series are reported with mean follow-up intervals of several years (Table 20–5). Given the nonuniformity in methods of assessing symptomatic responses, comparing outcomes across institutions and techniques is difficult. The data would suggest, however, that the vast majority of patients are symptomatically improved by esophageal replacement and are satisfied with the quality of their alimentation after surgery.

With regard to the safety of THE in the setting of megaesophagus, two reported series are noteworthy. Devaney et al. reported on 93 cases of attempted THE for achalasia.[27] Six operations were converted to a thoracotomy, and two patients required urgent thoracotomy for mediastinal hemorrhage within 24 hours of the initial operation. Banbury et al. reported on 32 esophagectomies for achalasia.[26] THE was attempted in 26 of these patients, with 5 converted intraoperatively to thoracotomy and no reoperations for bleeding. The take-home message from these series is that with experience and judgment, THE can be accomplished safely in the setting of megaesophagus, although the surgeon must exercise great care and be quick to convert to thoracotomy should transhiatal dissection prove difficult.

Table 20–5 Outcomes After Esophageal Replacement for Achalasia

Institution	Follow-up (yr)	Outcomes
USC[24]	6.0	93% cured/improved/satisfied
Mayo Clinic[25]	6.3	91.4% excellent/good
Cleveland Clinic[26]	3.6	87% "felt better" than before
U. of Michigan[27]	3.2	93% "felt better" than before
Taiwan[28]	6.0	75% good/25% fair/25% worse

Proximal Gastrectomy or Gastric Bypass as a Remedial Operation for Benign Foregut Disease

The indications for esophageal replacement for nonmalignant conditions and the outcomes after esophagectomy are well studied and elucidated. A number of circumstances arise in which the pathology is localized to

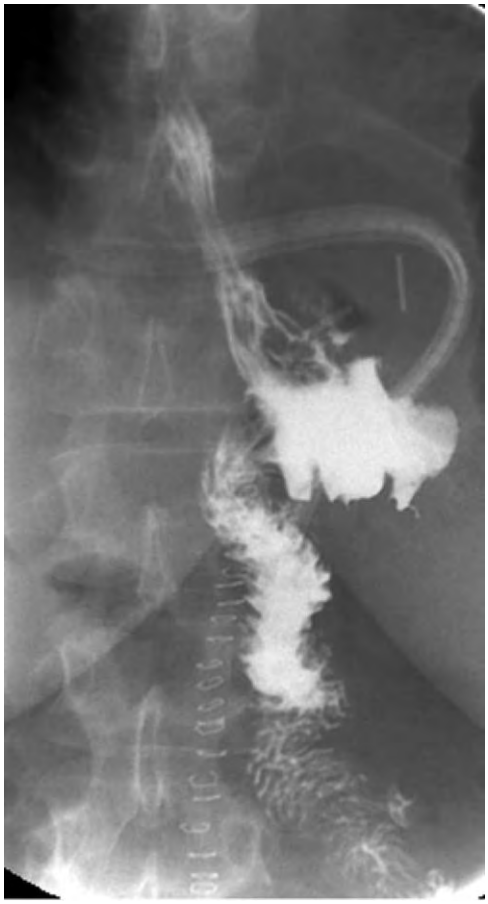

Figure 20–17. Roux-en-Y gastric bypass used as remediation for multiple failed fundoplications.

the GEJ or the upper part of the stomach (or to both), thus raising the question whether reconstruction would best be approached via partial proximal or total gastrectomy rather than esophagectomy. These situations differ from others, such as peptic ulcer disease or bile reflux gastritis, for which distal gastrectomy is an option.

The most notable example in which proximal gastrectomy or Roux-en-Y gastric bypass (RYGBP) is a consideration is in the setting of a failed fundoplication for GERD with or without associated gastroparesis (Fig. 20–17). The decision to attempt repeat fundoplication may be a difficult one in certain situations, particularly after two or more previous fundoplications or after a failed Collis gastroplasty, both of which can be difficult to remediate. In addition, the patient may be overweight or morbidly obese, perhaps contributing to breakdown of a previous operation or recurrence of reflux-related symptoms. The explosion in utilization of RYGBP or related operations for morbid obesity has contributed to the body of knowledge regarding the relative risks and benefits of gastric resection or bypass operations for benign disease.

When compared with esophagectomy, gastric resection or bypass is associated with a number of potential benefits. Obviously, the native esophagus is left intact, which if normally functioning, allows propagation of a food bolus distally and acts as a barrier against the reflux of gastric or intestinal contents into the pharynx or airway. Because surgery is localized to the peritoneal cavity, the operation can typically be completed through a laparotomy alone, thus obviating the need for thoracotomy or cervicotomy. Not uncommonly, end-stage foregut disease is associated with gastric stasis or delayed gastric emptying, which can be addressed via a gastric operation. Finally, in this era of ever-increasing obesity, weight loss from gastric diversion can be a significant associated medical benefit, perhaps even outweighing the symptomatic benefit associated with foregut reconstruction.

An increasing body of literature is evolving regarding the control of GERD in patients undergoing RYGBP for morbid obesity.[29] Such an operation effectively diverts both acid and bile from the esophageal mucosa, with or without the addition of fundoplication or fundopexy. Controversy exists regarding whether fundoplication is more prone to failure in the setting of obesity. Recent reports demonstrate a higher rate of recurrent reflux in obese patients undergoing fundoplication than in overweight or normal-weight individuals.[30] Although other series have not been able to demonstrate such an association, these reports are limited in that they typically analyze results in obese (BMI >30) patients, with relatively few subjects falling in the morbidly obese (BMI >35 to 40) range. In a morbidly obese patient referred specifically for control of GERD, whether fundoplication or RYGBP is the procedure of choice remains unknown, although many surgeons at present are choosing the latter option when the patient so agrees. How best to handle a large hiatal hernia in the setting of morbid obesity and GERD is likewise a matter of debate.

A considerable body of literature also exists regarding distal gastrectomy with Roux-en-Y gastrojejunostomy for control of bile reflux gastritis. In this situation, a sizable proximal gastric remnant is typically left behind, whereas for control of GERD, little to no proximal gastric pouch should be left. Inherent to the success of using a Roux-en-Y bypass to control GERD is the need to eliminate as much acid-secreting mucosa as possible from the upper gastric remnant because the operation works by diversion of acid and bile from the esophageal mucosa rather than by augmentation of the antireflux barrier.

Csendes et al. reported on vagotomy and antrectomy with long-limb Roux-en-Y gastrojejunostomy as the preferred treatment option for patients with long-segment BE.[31] This choice of operation was based on the observations that fundoplication in the setting of BE is associated with a relatively high long-term failure rate and that dysplasia or carcinoma develops in a small proportion of patients with BE during follow-up. Because duodenogastric reflux is common in patients with BE and components of the duodenal refluxate are thought to be carcinogenic or injurious to the esophageal mucosa, antrectomy with Roux-en-Y diversion theoretically diverts the damaging components of the gastric refluxate from the esophageal mucosa. As a result of the added complexity and potential morbidity of such a reconstruction in comparison to fundoplication, especially when the

latter can be performed via a laparoscopic approach, the operation as proposed by Csendes et al. has not gained wide acceptance in the United States and Europe.

An issue of controversy is whether to resect the excluded distal gastric remnant after gastric bypass. Although such a resection is typically not performed in the setting of RYGBP for obesity, resection does appear to reduce or eliminate the potential risk for hemorrhage from the blind gastric pouch, the occurrence of gastrogastric fistulas, the development of marginal ulceration as a result of a retained antrum effect, bacterial overgrowth in the excluded pouch, and the development of a subsequent carcinoma that is not amenable to surveillance.[32] RYGBP with distal gastric resection is clearly more time-consuming and requires more extensive dissection than RYGBP without distal resection does. Whether the benefits of distal gastric resection outweigh the disadvantages merits further study and follow-up.

Little has been written about gastrectomy or RYGBP as a remedial antireflux operation after failed fundoplication in the obese. Raftopoulos et al. reported on seven morbidly obese individuals undergoing revision of an antireflux procedure to laparoscopic RYGBP.[33] The mean operative time was longer than 6 hours. Anastomotic strictures developed in five patients, and two were reexplored for gastric remnant herniation and intestinal obstruction. At a mean follow-up of 24 months, mean excess weight loss was 70.7%, and 70% of comorbid conditions were improved or resolved. In addition, GERD scores were significantly reduced. The authors concluded that laparoscopic RYGBP after failed antireflux surgery in the morbidly obese, though technically challenging, is a feasible and effective treatment of recurrent GERD and is associated with the additional advantages of weight loss and improvement of comorbid conditions.

At the University of Rochester, we have performed 12 RYGBP-type operations as remedial antireflux procedures after failed fundoplications in both normal-weight and obese individuals and have compared our results with those of a cohort of 25 individuals undergoing redo fundoplication.[34] The gastrectomy patients had a higher prevalence of preoperative endoscopic complications of GERD and multiple previous fundoplications than did those undergoing redo fundoplication. Mean symptom severity scores were improved significantly by both gastrectomy and redo fundoplication, but they were not significantly different from each other. Complete relief of the primary symptom was significantly greater after gastrectomy (89% versus 50%, $P = .044$). Overall patient satisfaction was similar in both groups. In-hospital morbidity was higher after gastrectomy than after redo fundoplication (67% versus 16%, $P = .003$), and new-onset dumping developed in two gastrectomy patients. Based on our findings, we concluded that in select patients with severe GERD and multiple previous fundoplications, the symptomatic outcome after gastrectomy is as good as or better than that after redo fundoplication. Gastrectomy is an acceptable treatment option for recurrent symptoms, particularly when another attempt at fundoplication is ill advised, such as in the setting of multiple previous fundoplications or failed Collis gastroplasty. The indications for gastrectomy or RYGBP in the primary or reoperative settings, the pros and cons relative to esophagectomy, and situations in which a repeat attempt at fundoplication should be abandoned still require further elucidation.

CONCLUSIONS

End-stage benign esophageal disease is infrequently encountered in the general medical community. Most hospitals therefore lack the expertise to evaluate and treat patients suffering the manifestations of severe, end-stage esophageal disorders. In such patients, considerable judgment is necessary on the part of the surgeon in deciding when to continue further attempts at remediating foregut dysfunction through medical or surgical means and when to proceed with extirpation and reconstruction. Because the conditions that lead to reconstruction are often not immediately life-threatening, patients frequently remain inadequately treated for long periods before evaluation by a surgical specialist. On the other hand, the risks of a major surgical undertaking must be carefully weighed against the anticipated symptomatic benefit. When the severity of symptoms warrants further intervention and when the patient has been carefully assessed for comorbid disease and performance status, esophageal replacement should be considered. Because a volume-outcome relationship generally exists for esophagectomy, as for other major surgical procedures,[35] patients in need of esophageal replacement should be referred to a center with considerable experience in such types of surgery. Foregut reconstruction for end-stage nonmalignant esophageal disease can be performed safely in selected units with acceptable morbidity, low mortality, and excellent long-term alimentary function. The choice of operative approach and the type of foregut reconstruction should be tailored to the individual patient. With further experience and continued long-term assessment of outcomes, refinements in operative techniques and improvements in results will undoubtedly continue.

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Chapter

21

Endoscopic Antireflux Repairs

Atif Iqbal · Charles J. Filipi · Henry Gale

Gastroesophageal reflux disease (GERD) affects millions of people worldwide. The prevalence of heartburn in a randomly selected adult population is approximately 20%. It is estimated that approximately a third of the adult population in the United States suffers from heartburn on a monthly basis and as many as 10% weekly.[1] Of these, approximately 7% have reflux esophagitis. Management of GERD has gained increasing attention during the past 2 decades because of a high prevalence in Western societies, a better understanding of the pathophysiology, new potent antisecretory drug therapies, the advent of minimally invasive surgery, and new transoral endoscopic therapies.[2] To understand the theoretical or probable mechanism of action of endoscopic antireflux procedures, the anatomy of the gastroesophageal junction (GEJ) and the pathophysiology of GERD as it is understood will be briefly reviewed.

REFLUX PATHOPHYSIOLOGY

Factors Opposing Reflux

The efficacy of the antireflux barrier at the GEJ is dependent on the "lower esophageal sphincter (LES) complex," the geometric profile of the cardia, and their changes as a result of gastric distention. Other factors such as gravity, intraperitoneal pressure, esophageal motility, and the mucosal barrier play a role in reflux prevention but will not be emphasized here.

The Lower Esophageal Sphincter Complex

Competence of the LES is maintained not just by the presence of a high-pressure zone but also by the length of the sphincter and its position relative to the diaphragmatic hiatus. It is known that resistance is directly proportional to the product of its pressure and length. A decrease in the pressure or overall length of the LES or just its abdominal segment predisposes to reflux because it decreases the resistance imposed on the flow of gastric juice or bile from a higher-pressure cavity, the stomach, to a lower-pressure lumen, the esophagus. The most common cause of a permanently defective sphincter is inadequate pressure, but the efficiency of the sphincter can also be nullified by an inadequate abdominal length or an abnormally short overall length.[3]

Geometry of the Cardia and Its Role

The normal angle of His prevents the distending forces generated within the stomach to be transmitted to the LES, thus preventing its subsequent "unfolding."[3] As the normal geometry of the cardia disappears with increasing gastric distention, the gastric forces pull harder on the abdominal segment of the LES and cause it to be "taken up" into the stretching fundus. At a critical length of 1 to 2 cm, lower esophageal sphincter pressure (LESP) drops acutely and reflux occurs.[3] Figure 21–1 shows the circular muscle fiber thickening as proved by Liebermann et al.,[4] and the three circular muscle groups are demonstrated. Each muscle group improves LES tone by sustained contraction. The balance between the circular muscle groups and how they interact at their junctures is not understood; however, the vectors within which they work can be assumed to be in parallel with the fibers as demonstrated in Figure 21–1C and may be relevant to the force applied by the various endoscopic procedures.

Transient Lower Esophageal Sphincter Relaxation or Shortening?

In severe GERD, the LES, or the "high-pressure zone," is virtually nonexistent or greatly reduced. Reflux in this instance is understandable. However, the cause of reflux in milder disease with normal resting LESP is under considerable debate. It is believed that transient LES relaxations (tLESRs), or intermittent spontaneous

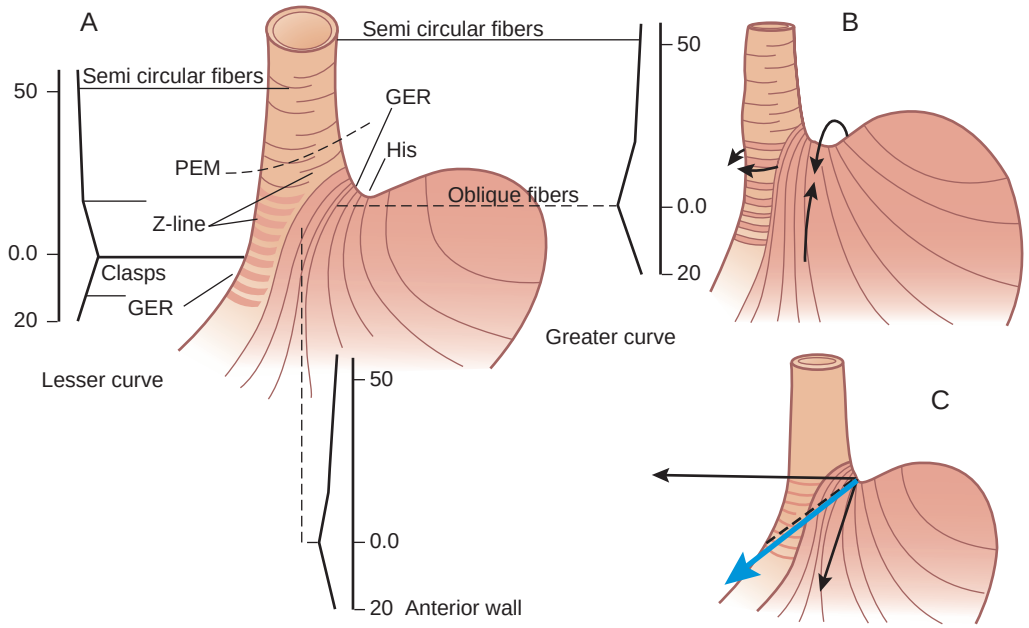

Figure 21–1. Muscle groups of the gastroesophageal junction. **A**, Muscular orientation at the gastroesophageal junction, as described by Liebermann et al.[4] The *arrows* in **B** represent the direction of contraction of the underlying fibers. The *arrows* in **C** represent the vectors, with *black arrows* representing clasp and sling fiber vectors and the *blue arrow* the resultant vector. The length of the *arrows* correspond to the probable forces of contraction. The *dashed line* represents the gastroesophageal ring. GER, gastroesophageal reflux; PEM, phrenoesophageal membrane.

decreases in LESP, are responsible for reflux events.[5-8] Recent electrophysiologic data suggest that the relevant vagal afferent fibers terminate with specialized intraganglionic laminar endings. These deformity-sensitive transducers are lined in series with muscle fibers at the cardia and fundus and are believed to mediate both fundic receptive relaxation and elicitation of tLESRs.[9]

However, on a larger scale, the cause of tLESRs, the frequency of which increases with gastric distention,[4] can also be explained simply by oral intake. Mason et al. have shown that GERD is associated with shortening of LES length secondary to increasing gastric volumes, the so-called transient LES shortening (tLESS).[12] As further evidence, patients with early disease normally experience episodes of esophageal acid exposure shortly after meals. The increased swallowing frequency seen in GERD patients is an effort to neutralize the acid refluxed into their esophagus and is supportive evidence of intraprandial reflux in this population.[3] This, coupled with the ingestion of fatty foods, which delays gastric emptying, explains the rising incidence of GERD in the Western world.

Nissen fundoplication and endoluminal gastroplasty (ELGP)[2] have been shown to prevent LES shortening during gastric distention, thus minimizing GERD. In light of the aforementioned pathophysiologic factors, endoscopic therapies should prevent reflux in the following ways: (1) alter the compliance of the cardia and prevent transient LES shortening/relaxation, (2) increase baseline LES tone or, (3) increase baseline LES length.

Finally, none of the endoluminal therapies effectively reduces the distal end of the esophagus into the abdomen and effects a hiatal hernia repair. Hiatal hernias, even if small, alter the muscular vector force at the GEJ. Sling fibers and perhaps clasp fibers may be spread and stretched more by a hiatal hernia, especially with food intake and elevation of intragastric pressure secondary to Valsalva maneuvers. In addition, the angle of His is obliterated.

TRANSORAL ENDOSCOPIC PROCEDURE BACKGROUND

There has always been discussion and controversy among gastroenterologists and surgeons about treatment options for GERD. The majority of patients with GERD are best treated by proton pump inhibitors (PPIs). However, symptom relapse is common after cessation of treatment because PPIs suppress acid production without affecting the underlying disease mechanism. The rate of relapse reaches 100% in patients with low LESP,[10] and thus many patients must commit to lifelong therapy. Continuous PPI therapy also results in symptom relapse in up to 33% of patients, especially within the first 2 years. Moreover, 50% of patients continue to exhibit low intragastric pH and objective evidence of acid regurgitation despite complete symptomatic control with PPI therapy. Combined impedance-pH testing has highlighted the role of non-acid reflux in GERD. This leaves the patient prone to atypical manifestations of reflux disease, such as pulmonary symptoms, which are difficult to both diagnose and treat. Therefore, PPIs may not be an acceptable option for young patients facing lifelong medication use. There is good evidence that mechanical augmentation of the GEJ by fundoplication is a good

treatment option for patients with severe progressive reflux disease.[3] However, laparoscopic antireflux surgery requires a general anesthetic, hospitalization, and postoperative lifestyle limitations for days to weeks; moreover, it is expensive and associated with postoperative morbidity and even mortality. These limitations, in conjunction with the rising frequency of reflux disease in the Western population, have created the need to develop a less invasive procedure that effectively addresses the underlying problem but is devoid of the shortcomings of the surgical option.

More than 10 years ago, the British gastroenterologist Paul Swain developed a sewing capsule attached to a flexible endoscope to perform limited surgical maneuvers in the gastrointestinal lumen. The idea of minimizing surgical trauma by performing operative procedures within the gastrointestinal tract provided a new perspective. As a consequence, in the past decade an entire spectrum of new endoscopic techniques have been developed for the treatment of GERD.[11] These procedures are listed in Box 21–1. Of these, three novel endoscopic therapies have been approved for use by the Food and Drug Administration. All procedures can be safely performed in an outpatient setting with conscious sedation.

Box 21–1 **Types of Endoluminal Therapy for Gastroesophageal Reflux Disease**

Endoscopic Suturing

- Endoluminal gastroplasty (ELGP/EndoCinch)
- Endoluminal full-thickness plicator (NDO plicator)
- Syntheon ARD plicator

Radiofrequency Energy Delivery

- Stretta procedure

Synthetic Implants/Injections

- Implantable biopolymer (Enteryx)
- Implantable prosthesis (Gatekeeper)
- Implantable Plexiglas microspheres (PMMA)

SELECTION CRITERIA FOR ENDOSCOPIC THERAPY

The general selection criteria that have been used in most trials are shown in Figure 21–2. In addition, specific

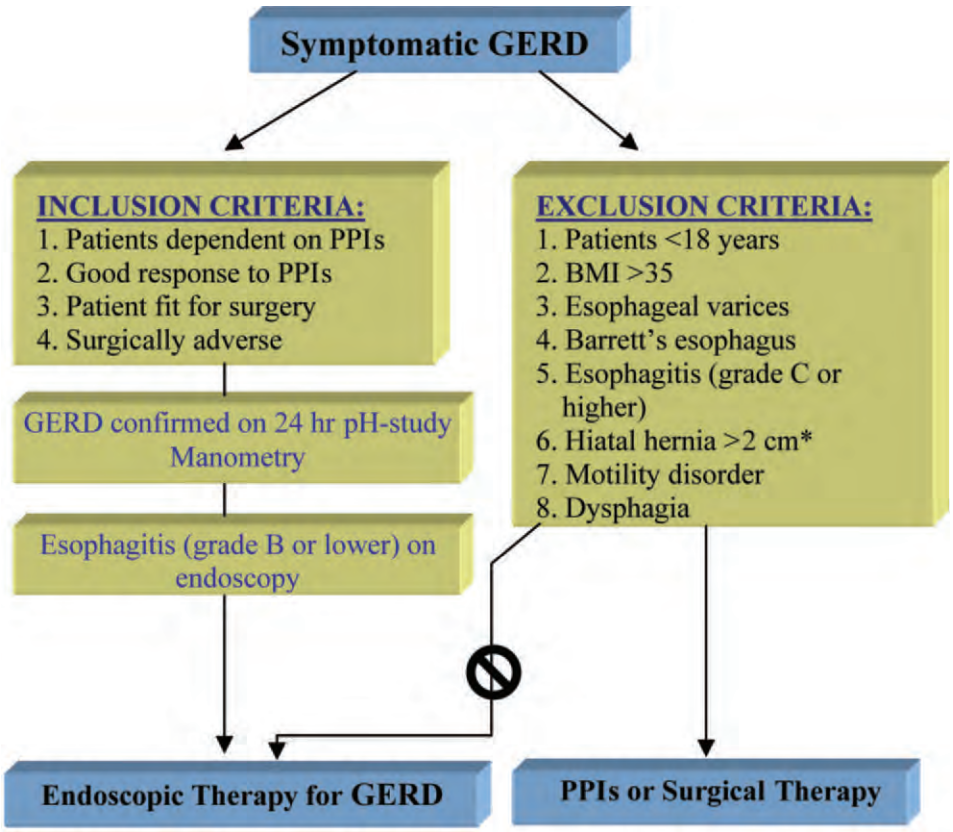

Figure 21–2. Inclusion/exclusion criteria for endoluminal therapies for gastroesophageal reflux disease (GERD). BMI, body mass index; PPIs, proton pump inhibitors. *Recently, some studies have included patients with a hiatal hernia >3 cm and Barrett's esophagus.

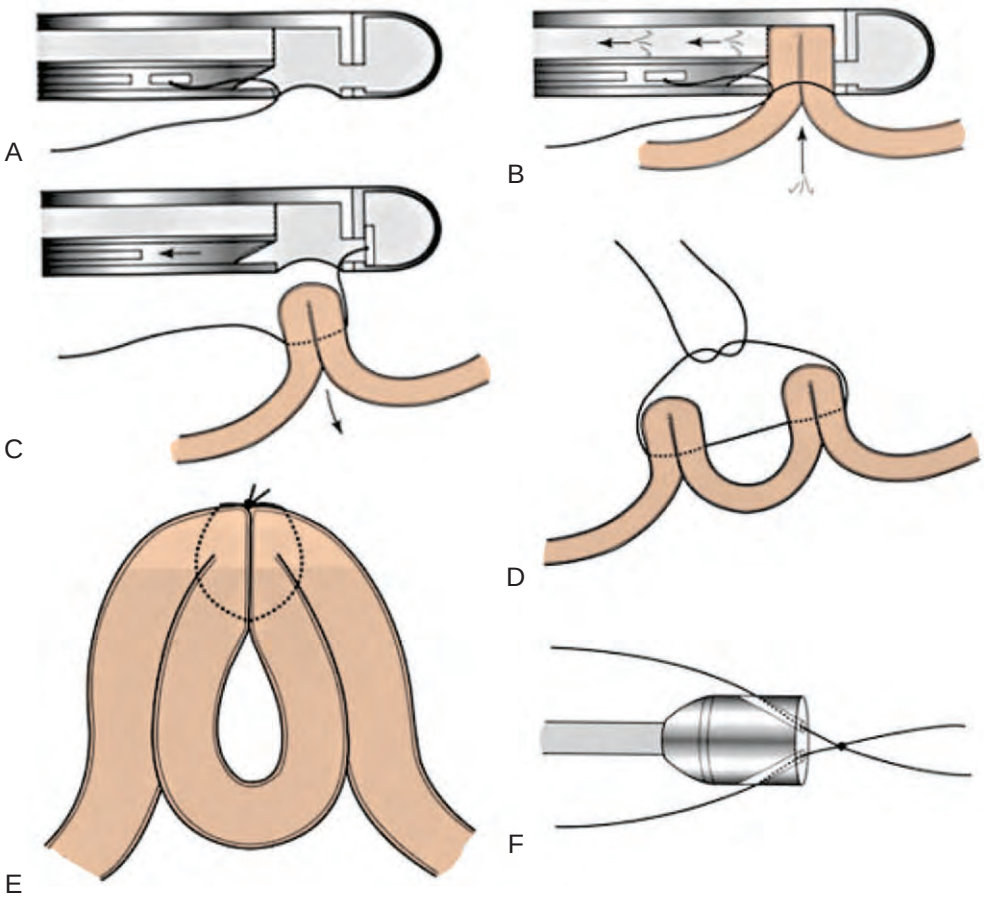

Figure 21–3. **A,** Drawing of a suturing device equipped with a vacuum chamber and a hollow needle in which a suture is attached to a tag. **B,** Tissue is drawn into the chamber by suction. The needle passes through the tissue, and the tag is captured in the distal chamber. **C,** The suction is then released. **D,** The procedure is repeated on an adjacent piece of tissue. **E,** On tightening the knot, the pieces of tissues are approximated. **F,** The suture is cut using a small device with internal knives.

patient selection criteria, if any, are mentioned in discussion of the respective procedures.

ENDOLUMINAL GASTROPLASTY

History

The first endoscopic approach to the GEJ involved the creation of an endoluminal valvuloplasty via a transgastric sewing technique. The valvuloplasty consisted of a full–wall thickness intussusception of the GEJ into the stomach to create a nipple-type valve; the configuration of the valve was maintained with eight staples, and stability was aided by an intramural injection of sodium morrhuate.[2] Safety, durability, and efficacy were tested in baboons.[12]

Swain et al. developed a mechanical aid that allowed passage of a needle and subsequent suture via the biopsy channel of an endoscope.[13] Later, the technique was modified to create plications endoscopically below and at the GEJ for the prevention of GERD.

Procedure

The endoluminal procedure requires a suturing capsule, suture tags, and an anchoring system that secures the suture and cuts the strands (Fig. 21–3). A short, 18-mm-outer-diameter overtube allows repeated intubations (approximately 12) while avoiding trauma to the esophageal mucosa. The choice of sedation depends on the patient's condition and general health. Usually, patients tolerate the procedure with conscious sedation. However, restless patients who have a class II airway require monitored anesthesia, and those with a class III or IV airway require a general anesthetic. Two to four plications are placed either longitudinally (one above the other), radially (next to each other), or spirally within the cardia. Each plication is formed by two stitches placed into the gastric submucosa, approximately 1 cm apart, and then pulled together. The procedure is performed via the following steps. After correct placement of the sewing capsule, suction is applied, the gastric wall is pulled into the hollow chamber of the capsule, and a straight needle loaded with nonabsorbable suture and a T tag is fired through the suctioned tissue. The system is reloaded and a second stitch is placed adjacent to the first. The two stitches are pulled together and cinched by a ceramic plug and ring via a second endoscope. Depending on the expertise of the operator and the number of plications intended, the procedure is completed within 40 to 60 minutes.

The application of cautery on opposing mucosal surfaces before plication may secure tissue apposition and promote long-term adherence. Its efficacy has been proved in pilot studies[14] but needs to be tested in a larger randomized controlled trial.

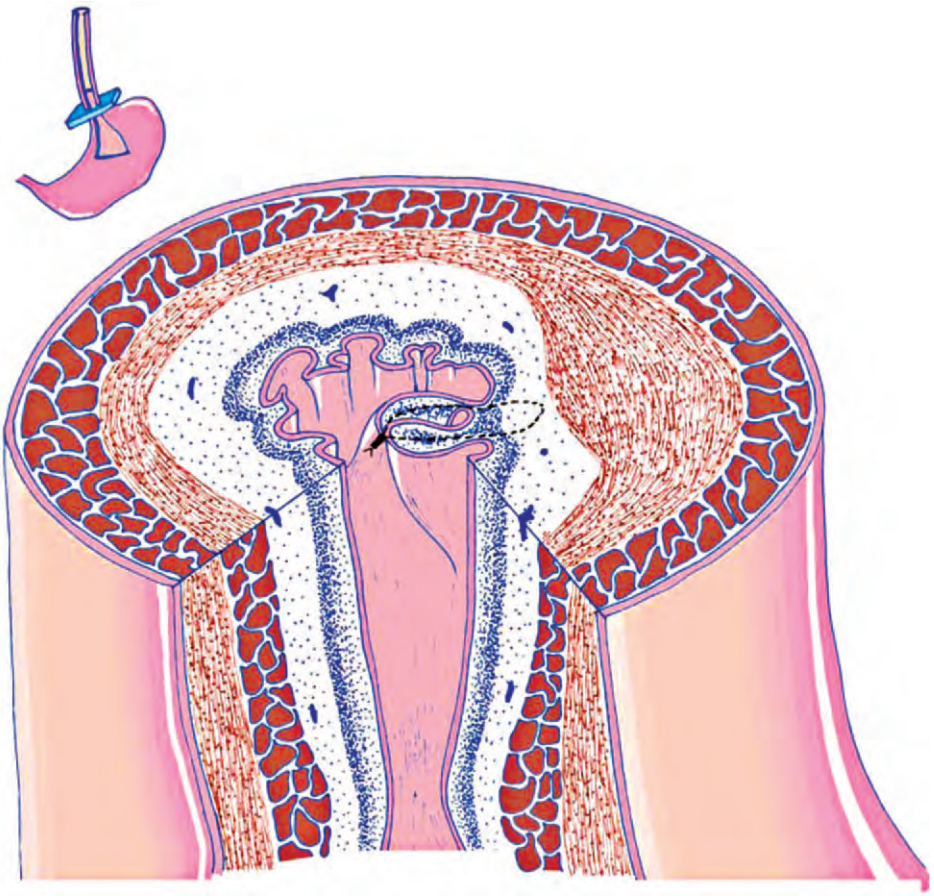

Figure 21–4. Cross-sectional illustration of changes seen with endoluminal gastroplication.

Histologic Changes

In animal models, the device has been shown to place the majority of stitches in the submucosal layer and is believed to do the same in humans. It has been found that everted intraluminal gastroplications do not result in fusion between mucosal folds, irrespective of suture depth. A flat scar is the final outcome and appears to be proportional to the amount of ischemia, foreign body reaction, and suture depth.[15] In a recent publication by Liu et al., ELGP was shown to cause muscular hypertrophy. Eight humans who had symptomatic relief with ELGP and pigs that underwent ELGP were examined by endoscopic ultrasound. The muscularis propria increased by 0.9 mm ($P < .01$) in humans and 2.6 mm by endoscopic ultrasonography and 2.1 mm by autopsy examination in the porcine model.[16] The changes observed with ELGP are shown in cross section in Figure 21–4.

Efficacy

The overall results with ELGP are tabulated in Table 21–1. The pooled data were obtained from 11 studies; however, an effort was made to avoid bias by including only studies that used off-PPI scoring as baseline and intent to treat.

Two multicenter trials are included in Table 21–1 and will be highlighted. In the first trial, 64 patients were randomized to a circumferential or linear plication configuration.[17] All patients were dependent on antisecretory agents and had proven reflux by 24-hour pH monitoring. Manometry and endoscopy were performed to exclude patients with Barrett's esophagus, grade 3 or 4 esophagitis, large hiatal hernias, and an esophageal dysmotility disorder. No difference was found between the plication configuration groups, and postprocedure manometry and endoscopy showed no improvement in LESP or grade of esophagitis. A significant improvement in heartburn and regurgitation scores from baseline occurred, but the pH monitoring results, though significantly improved, showed only a 30% normalization rate.

In a second multicenter study, 85 symptomatic GERD patients not taking PPIs with proven reflux on 24-hour pH monitoring were included.[18] Upper endoscopy and manometry were also performed as baseline. Follow-up was scheduled at 3, 6, 12, and 24 months. Symptom scores and medication use were assessed at each follow-up, and pH-metry was performed at the 3-month follow-up. This study was different from others with respect to inclusion criteria inasmuch as it included patients with grade 3 esophagitis ($n = 10$), hiatal hernia larger than 2 cm ($n = 9$), Barrett's esophagus ($n = 4$), failed fundoplication ($n = 3$), and pulmonary symptoms ($n = 10$). The majority of patients had two plications performed (range, 1 to 3), and most had a circumferential plication (65%), with the remaining receiving a linear configuration (35%).

Table 21–1 Endoluminal Gastroplication: Pooled Results

Variable		≥1 mo		≥3 mo		≥6 mo		≥12 mo		≥24 mo	
GERD-HRQL improvement		—		67%	(56)	69%	(110)	55%	(15)	32%	(31)
Heartburn improvement		89%	(42)	79%	(60)	75%	(160)	74%	(150)	54%	(114)
Regurgitation improvement		78%	(42)	72%	(42)	61%	(42)	55%	(66)	—	
Patients completely off PPIs		68%	(22)	64%	(22)	53%	(57)	40%	(414)	33%	(105)
Patients with ≥50% reduction in PPI use		—		—		82%	(59)	51%	(113)	48%	(105)
Improvement in quality-of-life scores	SF-36 Physical	—		—		16%	(66)	17%	(15)	—	
	SF-36 Mental	—		—		9%	(66)	NS	(15)	—	
	QOLRAD	88%	(22)	85%	(22)	72%	(22)	78%	(22)	—	
LESP improvement		—		NS*	(194)	NS*	(159)	NS*	(21)	—	
LES length improvement		—		NS*	(194)	NS	(130)	NS	(21)	—	
tLESR improvement						Yes	(15)				
Improvement in pH scores	Total time pH <4	—		53%	(170)	26%	(62)	17%*	(15)	—	
	Time upright pH <4	—		NS	(53)	26%	(68)	32%	(21)	—	
	Time supine pH <4	—		NS	(59)	NS	(59)	NS	(59)	—	
	Number of episodes	—		36%	(121)	26%	(29)	33%	(21)	—	
	pH normalization	—		—		NS	(15)	NS	(15)	—	
Healing of esophagitis		—		—		NS	(108)	—		—	
Residual plications		—		86%	(26)	80%	(15)	—		—	
Re-treatment		—		—		11%	(44)	15%	(259)	—	

The results expressed in the majority of studies are shown here. Numbers in parentheses are the numbers of patients studied to obtain the result.
*Signifies disagreement among studies.
GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; LES, lower esophageal sphincter; LESP, LES pressure; NS, change not significant; PPI, proton pump inhibitor; QOLRAD, Quality of Life in Reflux and Dyspepsia questionnaire; SF-36, Short Form-36; tLESR, transient LES relaxation; —, data not available.
Pooled data were obtained from references 17-27.

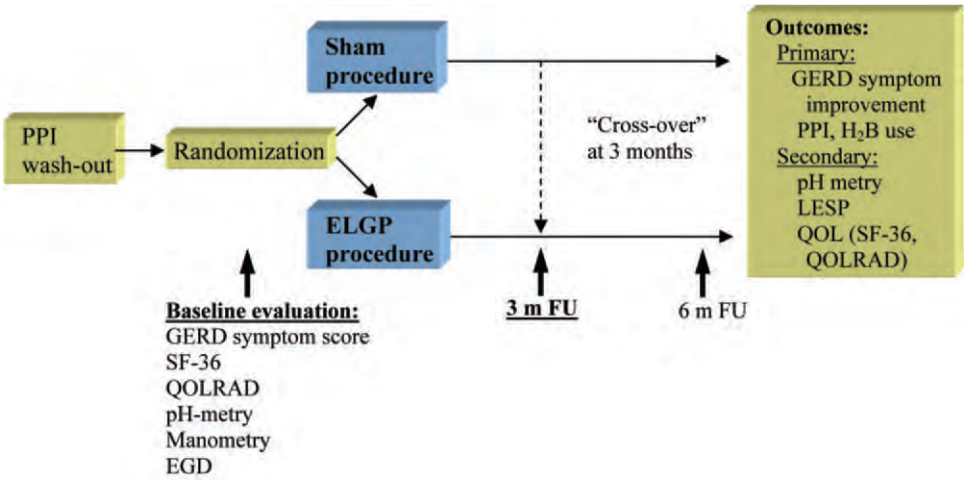

Figure 21–5. Endoluminal gastroplication (ELGP) sham study design. EGD, esophagogastroduodenoscopy; FU, follow-up; GERD, gastroesophageal reflux disease; LESP, lower esophageal sphincter pressure; PPI, proton pump inhibitor; QOL, quality of life; QOLRAD, Quality of Life in Reflux and Dyspepsia; SF-36, Short Form-36.

Twenty-four-month follow-up data demonstrated durable functional improvement and a sustained reduction in antisecretory medication use. Heartburn scores were reduced at both 1- (94%) and 2-year (78%) follow-up. Likewise, PPI use decreased, with 69% of patients using less than 50% of their baseline medication and 41% not taking any PPIs at 2-year follow-up. There was no change in LES length or pressure when measured at 3 months.

A sham-controlled, randomized, blinded single-institution study (n = 34) is under way, and 3-month follow-up is available.[28] The study design for the sham trial is shown in Figure 21–5. The study nurse and patients were blinded to the procedure performed. An overtube and two endoscopes were exchanged in all patients, and the conscious sedation dosing was similar. Four circumferential plications were placed when performing ELGP. At 3-month follow-up, heartburn frequency (69% versus 31%, $P = .03$) and severity (47% versus 17%, P = not significant) were improved in patients who underwent ELGP in comparison to those receiving the sham procedure. A significantly greater number of patients in the plication group discontinued their daily PPI/H_2B (75% versus 25%, $P = .03$). A significant reduction in the percentage of time that the pH was less than 4 was also observed; however, no difference was seen between groups regarding normalization of pH, median LESP, or quality of life. Limitations of this study include a probable type II error, a larger than expected sham effect, inadequate follow-up length, and lack of technique standardization. A randomized controlled trial of larger size with longer follow-up is needed for objective evidence of durable benefit.

Other studies of note have demonstrated a markedly improved quality of life at 1-year follow-up,[19] reduction of the rate of tLESRs by 37% at 6 months in a single-center study,[20] a significant increase in LES length in baboons,[29] and an increase in intra-abdominal but not total length of the LES after placement of three linear plications in dogs by Kadirkamanathan et al.[13]

Changes in Selection Criteria

A significant improvement in symptom scores and pH study results has been observed in 19 patients refractory to medications, although this improvement was less than that seen in other studies.[21] Short-term studies suggest that ELGP can be used as an effective salvage procedure for failed surgical fundoplication,[30,31] but this indication requires further study.

Effect of Plication Configuration and Number

The optimal configuration of plications is not known. In a small and unfortunately underpowered study by Davis et al., 22 patients with proven GERD were randomized to either a helical or a circumferential plication pattern. No difference in outcome was observed between configurations, although a trend in objective results favored the helical pattern.[22] It was proposed that the benefit of ELGP would be sustained at 18-month follow-up, but this was not substantiated, with no difference between groups and only 15% of patients being asymptomatic and not taking antisecretory medication. Raijman et al.[32] reported that the helical plication configuration demonstrated superior results at 6-month follow-up with regard to symptom control and medication use. The prevalence and persistence of these possible advantages are currently subject to investigation. Increasing the number of plications, when using the helical pattern, did not show a significant benefit at either 6- or 12-month follow-up.[22]

Complications

ELGP is generally safe over long-term follow-up and free of serious immediate side effects. The major and minor complications are shown in Table 21–7. Patients are instructed to take only oral fluids for the first 24 hours and to call their physician in the event of any chest pain or symptoms consistent with gastrointestinal bleeding.

Esophageal perforation can occur. Before the U.S. trials, Dr. Paul Swain encountered one patient who required open thoracotomy for a perforation of the esophagus, and in the initial multicenter trial a suture perforation occurred. This patient required 3 days of hospitalization and antibiotics and thereafter made an uneventful recovery. The perforation was thought to be secondary to a suture placed through the esophageal wall that allowed air to escape as evidenced by pneumomediastinum seen on computed tomography. A diatrizoate meglumine (Gastrografin) swallow followed by a barium study showed no extravasation.

Airway assessment is particularly important because hypoxemia and stridor may occur secondary to the overtube. Patients with class III and IV airways are at risk for these complications, whereas class I and II airways do not usually pose any serous problem unless there is a limitation in extension of the head or obesity. Patients who are obese, are combative during the preliminary endoscopy, or have a class IV airway should have either a general anesthetic or propofol sedation with careful monitoring. A dedicated anesthesiologist will improve procedure flow, thereby leading to a significant reduction in procedure time and possibly anesthesia-related complications.[33]

Recommended precautions include a training course for the entire team, preprocedure airway assessment, general anesthesia for combative patients and those with a class IV airway, and examination for active bleeding at the end of the procedure. To avoid a perforation, which is usually due to placement of a full-thickness suture within the esophageal wall, all stitches and plications should be placed below the squamocolumnar junction. If the suturing capsule needle does not retract after penetrating the tissue, the handle with the pusher rod should be disassembled rather than pulling the capsule away from the esophageal wall. Occasionally, the suture loops and locks at the tissue level as the second stitch is being placed. The needle literally goes through a loop and the suture will not slide through the tissue on removal of the endoscope. In this circumstance, the suture should be cut with endoscopic scissors; however, this can be difficult and pullout may be necessary. If tissue accompanies the knot, it should be sent to pathology for frozen section analysis. If the muscularis propria is included in the specimen, an esophagogram should be performed, followed by hospitalization.

Procedure Failure

Studies demonstrate that laparoscopic Nissen fundoplication (LNF) is feasible and effective after failed ELGP.[34,35] Patients should undergo upper gastrointestinal endoscopy before surgery, but suture removal is not necessary. No significant scarring or adhesions have been noted in the esophageal hiatus or inferior mediastinum at LNF, possibly because the stitches do not penetrate beyond the muscularis propria; penetration of the serosa has been shown to induce more scarring.[15] This in itself might contribute to the lack of durability in post-ELGP results. Although the technique is initially effective, long-term symptom control has yet to be established.

An interesting phenomenon that has been experienced by several investigators involved in the initial trials was diminishment of the patient's surgical adversity after ELGP. It appears that some patients, after taking an initial active step to rectify their reflux disorder, become more willing to find a definitive solution. This is potentially a positive effect of all intraluminal antireflux procedures and should be studied.

Alternatively, patients who experience recurrent GERD symptoms after ELGP may benefit from a second procedure. However, one study has demonstrated a significant trend toward earlier onset of recurrent symptoms after repeat ELGP.[23]

Advantages

Easy repeatability, short operative time, early discharge, no morbidity, and symptomatic improvement make ELGP an attractive option. Endoscopic gastroplication has proven short-term efficacy and has been demonstrated to be cost-effective for 1 to 2 years.[36]

Disadvantages

The absence of objective improvement after ELGP is disconcerting. No studies have shown improvement in LES pressure and the grade of esophagitis. pH monitoring results are mixed, but the rate of normalization is only 30% to 40% between studies. The lack of objective evidence of reflux control, in relation to improvement in symptoms, is best explained by a reduced volume of regurgitant confined to the less sensitive distal esophagus. This explanation does not, however, negate the deleterious effect of the acid within the distal esophagus and the chance for progression to complications such as stricture formation or even Barrett's esophagus.

Several studies have compared ELGP and LNF. Comparable improvement in symptom scores, PPI intake, and quality-of-life assessment has been seen. Patients who undergo LNF do have greater physiologic control of esophageal acid reflux, but at the expense of a higher incidence of postprocedure complications.[37] Chandalavada et al. compared 47 ELGP patients with 40 patients who had undergone laparoscopic antireflux surgery. Twelve-month follow-up demonstrated different results.[38] Surgical intervention offered a significantly greater reduction in medication use (87% versus 69%) and greater patient satisfaction (93% versus 66%). Similar patient satisfaction results (96% versus 78%) have also been reported by Velanovich et al.[39] Thus, surgery is superior to ELGP in patient satisfaction and objective improvement in reflux.

Summary

Endoscopic gastroplasty is a safe and moderately effective outpatient procedure that has been demonstrated to significantly improve symptoms and PPI requirements over at least a 1-year period.[19] Symptom relief is acceptable at 6 to 12 months, and the procedure is associated

with minimal discomfort. These results support the use of ELGP in patients who are reluctant to undergo surgery or are at high surgical risk. Good symptomatic results are obtained in part by accuracy in placement of plications, but this seems to be highly operator dependent. Visualization is limited, and thus placement of stitches is difficult, especially after the first plication because of tissue distortion and accumulated blood. Finally standardization of technique has not been achieved. Further device modifications may be of assistance.

ENDOSCOPIC FULL-THICKNESS PLICATOR (NDO PLICATOR)

Current endoscopic suturing techniques usually involve submucosal suture placement, which may limit potential procedure-related complications but may also lead to early suture dehiscence and loss of long-term efficacy. This problem may theoretically be solved by full-thickness suturing or stapling devices that include the use of pledgets. Such an approach may, however, increase the risk for subsequent perforation. A novel technique of applying a full-thickness plication endoscopically has been developed and recently underwent clinical study in a U.S. multicenter trial. Selection criteria were similar to that shown in Figure 21–2.

Procedure

The NDO plicator (Fig. 21–6) is designed to apply a full-thickness pledget-reinforced U stitch near the GEJ with serosa-to-serosa apposition. The system consists of a reusable instrument and a single-use suture-based implant. Additionally, a proprietary endoscopic tissue retractor and a standard overtube are used to perform the procedure. A newer version of the instrument can be passed without an overtube and accepts a small transnasal gastroscope. The instrument passes two needles through tissue at the desired location to place the implant for tissue approximation, plication, and fixation. Controls on the instrument handle actuate the distal end of the device and provide for retroflexion of the distal end, opening and closing of the instrument arms, and delivery of the implant. The instrument contains two dedicated channels, one for insertion of the tissue retractor/plication device, the other for passage of the endoscope.[40] The tissue retractor is designed to engage the deep gastric wall, thereby allowing for creation of the serosa-to-serosa plication. The tissue retractor is configured in a helical fashion and includes a protective outer sheath to stabilize the gastric mucosa while engaging the wall. Typically, the retractor is inserted 1 cm distal to the GEJ, which allows the gastric wall to then be drawn into the arms of the instrument before deployment of the implant.

With the patient under conscious sedation, a gastroscope is passed into the stomach for endoscopic inspection and passage of a guidewire. The plication device is passed into the stomach after removal of the dilator and guidewire. The suture applicator is retroflexed and properly positioned under endoscopic vision. The endoscopic tissue retractor is then inserted to within 1 cm of the GEJ and advanced to the level of the muscularis, which is judged by visible tenting of the

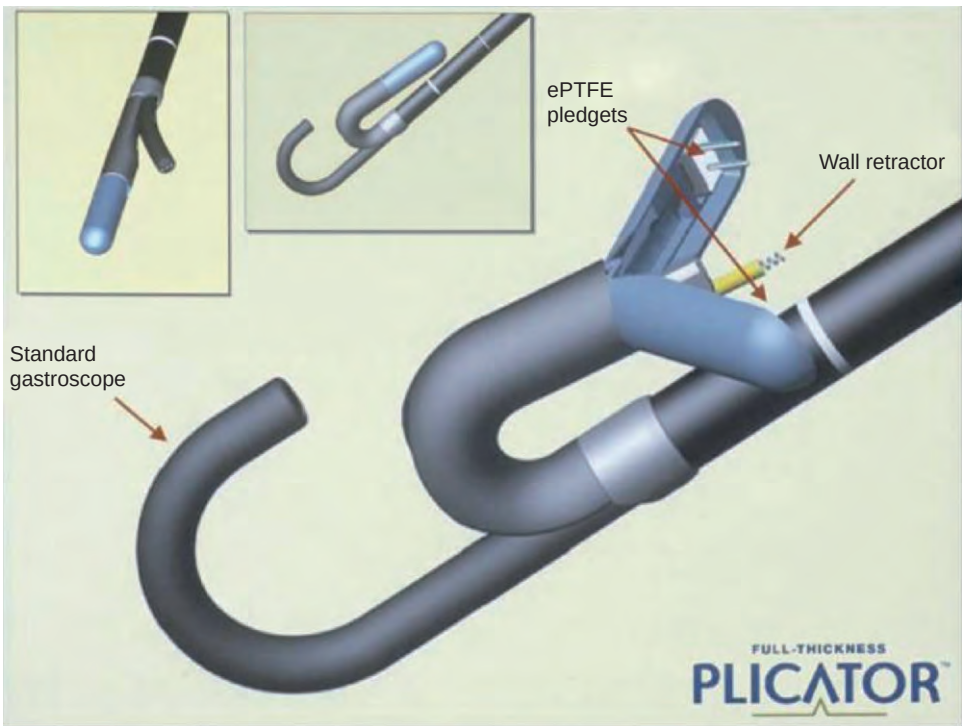

Figure 21–6. The NDO plicator mounted on a small-diameter endoscope. ePTFE, expanded polytetrafluoroethylene.

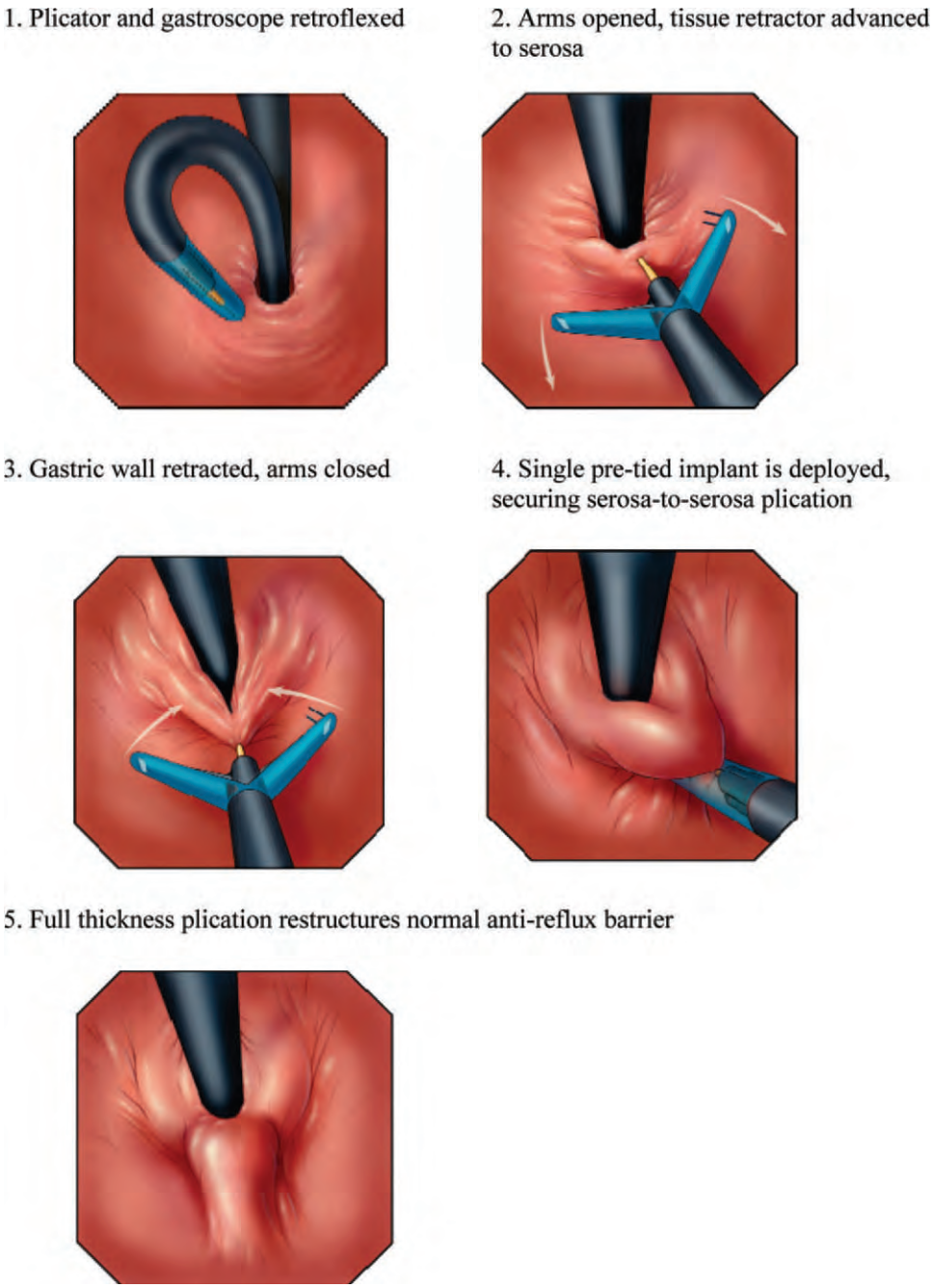

Figure 21–7. Schematic representation of the procedure for application of a full-thickness plication by the NDO plicator.

tissues around the entry point of the retractor. The gastric wall is next retracted and the instrument arms are closed on it. The pre-tied implant is deployed to secure a full-thickness plication. The tissue retractor is removed from the greater curvature side of the GEJ, the jaws are opened, and the entire assembly is removed from the stomach (Fig. 21–7). The approximate procedural time is 15 to 20 minutes.

Efficacy

Pooled results for the NDO plicator are shown in Table 21–2. A multicenter study enrolled 64 patients with symptomatic GERD who were dependent on antisecretory medication and showed evidence of esophageal acid exposure (pH-metry) without an underlying motility disorder. Follow-up was completed at 1, 3, and 6 months after the procedure and showed a significant reduction in GERD symptom scores, medication use, and esophageal acid exposure on 24-hour pH study that persisted at 1-year follow-up. No significant changes in esophageal manometry were noted.[41] At 6-month follow-up, there was a 63% improvement in symptom scores with elimination of PPI therapy in 74% and normalization of pH in 30% of patients. No patient required retreatment during the 6-month follow-up. In this initial trial, one full-thickness plication was used. A pilot study involving seven patients also had similar results but failed

Table 21–2 NDO: Pooled Results

Variable		≥1 mo		≥3 mo		≥6 mo		≥12 mo		≥24 mo
GERD-HRQL improvement		42%	(7)	67%	(68)	63%	(68)	70%	(63)	—
Patients completely off PPIs		—		—		78%	(63)	75%	(58)	—
Improvement in quality-of-life scores	SF-36 Physical	28	(7)	6%	(61)	10%	(61)	31%	(7)	—
	SF-36 Mental	7%	(7)	7%	(61)	5%	(61)	10%	(7)	—
LESP improvement		—		NS	(61)			—		—
LES length improvement		—		NS	(61)			—		—
tLESR improvement							No			
Improvement in pH scores	Total time pH <4	—		—		29%	(43)	—		—
	Number of episodes	—		—		26%	(43)	—		—
	pH normalization	—		—		30%	(43)	—		—
Healing of esophagitis		—		—		NS	(7)	NS	(7)	—
Residual plications		—		—		100%	(7)	—		—
Re-treatment		—		—		0%	(64)	0%	(64)	—

All results displayed are significant. Numbers in parentheses show the number of patients studied to obtain the result.
GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; LES, lower esophageal sphincter; LESP, LES pressure; NS, change not significant; PPI, proton pump inhibitor; SF-36, Short Form-36; tLESR, transient LES relaxation; —, data not available.
Pooled data were obtained from references 40-42.

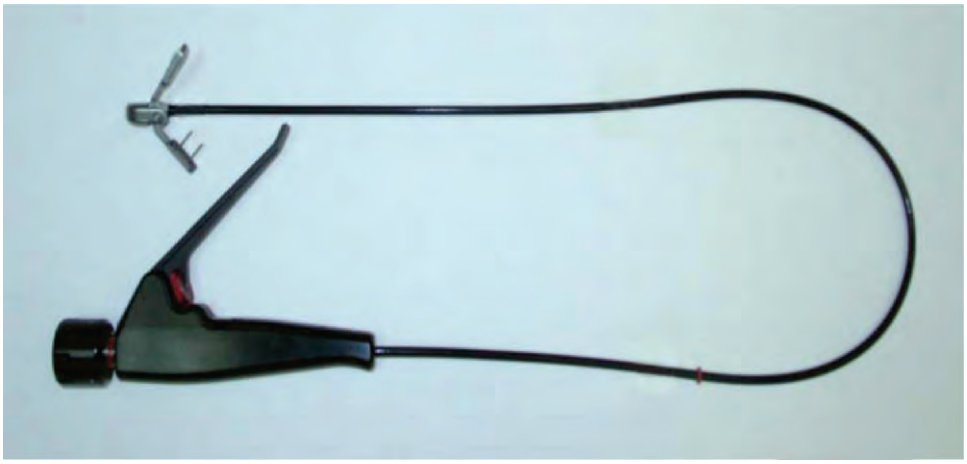

Figure 21–8. Syntheon plicator.

to show objective improvement of reflux.[42] Further studies with single versus multiple plications are anticipated. No sham-controlled trial has yet been completed, but one is being organized.

Complications

The most common complication was sore throat (spontaneously resolving within several days after the procedure). One gastric perforation did occur during the multicenter trial and was managed conservatively.

Summary

A single full-thickness plication placed at the GEJ is effective, reduces symptoms and medication use, and improves esophageal acid exposure. Further studies with longer follow-up will elucidate the safety of this procedure. A sham trial has just been completed. The initial appeal of a full-thickness plication is dampened by the results, but presumably with instrument and technique modification plus further experience, the results will improve.

SYNTHEON ARD PLICATOR

This promising new endoluminal suturing device has the capacity to place two stitches within the gastric wall at once, thus decreasing technical variability between operators (Fig. 21–8). The distance between the two stitches is predetermined. Withdrawal of the device is not necessary after each stitch, which may decrease procedure time and anesthesia-related complications. Results

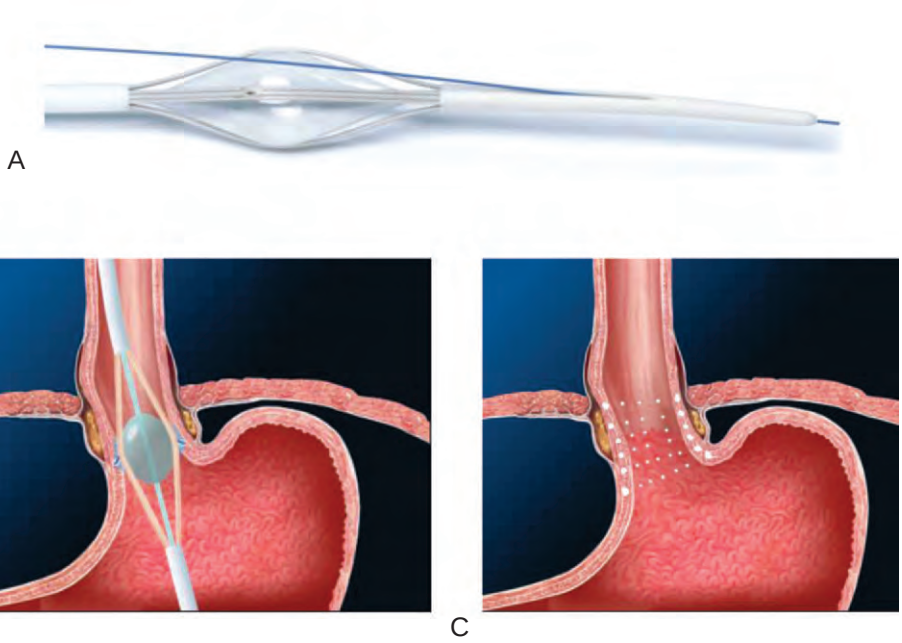

Figure 21–9. **A,** Stretta catheter with guidewire. **B,** Balloon assembly with struts and electrodes extending into the muscularis propria. **C,** A total of 56 lesions are applied as seen in this diagram.

with this device are not yet available, but a multicenter trial is planned. The device does have the ability to place sutures on the lesser curvature side of the GES.

STRETTA PROCEDURE

History

Radiofrequency (RF) energy has been used extensively in medicine since 1921 and is currently being used in the treatment of benign prostatic hypertrophy, cardiac arrhythmias, and metastatic liver lesions. The possibility of RF energy being used for GERD therapy was explored after successful treatment of snoring and sleep apnea. Endoscopic delivery of RF energy to the porcine GEJ was thus investigated and its effects assessed in a pilot study published in 2000.[43]

Patient Selection

RF augmentation of the LES has been widely used. More than 3500 procedures have been performed in the United States alone. Indications in the past have been confined to patients with early reflux disease. The Stretta procedure may have specific utility in morbidly obese patients, in those who have previously undergone gastric resection or a gastric bypass procedure, after a failed LNF,[44] or as an alternative to reoperation after disruption of fundoplication. In a porcine fundoplication disruption model, fluoroscopic guidance improved RF lesion accuracy, and therefore it has been suggested that fluoroscopic guidance be used to ensure probe placement.[45] Patients with failed antireflux surgery and subsequent RF therapy have experienced nonsignificant symptomatic improvement (decrease in heartburn score from 3.33 before the procedure to 2.75 after the procedure); however, patient satisfaction scores are significantly improved.[46] The role of the Stretta procedure in postoperative fundoplication patients remains unclear.

Procedure

The Stretta catheter (Fig. 21–9A) is a flexible, hand-held, disposable, 20-French Savary-style dilator that is used in conjunction with the Curon (Sunnyvale, CA) control module. It is composed of a balloon basket assembly, four nickel titanium electrodes, and suction and irrigation capability. The balloon basket deploys four radially arranged electrodes into the smooth muscle of the GEJ. Tiny thermocouple temperature sensors within the electrodes provide temperature feedback to the RF generator. A target temperature is preselected and the power is automatically discontinued if the temperature exceeds the predetermined threshold. The needles also provide feedback on impedance, which allows the operator to know whether the needles are positioned correctly in the tissue.

The procedure is done under conscious sedation with upper endoscopy performed initially to evaluate the size of the hiatal hernia, if present, to determine the distance to the squamocolumnar junction and to place a guidewire as the endoscope is withdrawn. The catheter is placed over the guidewire into the stomach and withdrawn to the position of needle deployment. The guidewire is removed and suction and irrigation are connected. The balloon at the distal end of the catheter is inflated, the electrodes are deployed, and RF energy is applied for a specific period while monitoring the temperature and impedance levels (see Fig. 21–9B). Continuous cold water irrigation during the procedure prevents mucosal overheating and subsequent surface tissue injury. A first treatment ring of eight lesions is created by rotating the catheter 45 degrees and repeat-

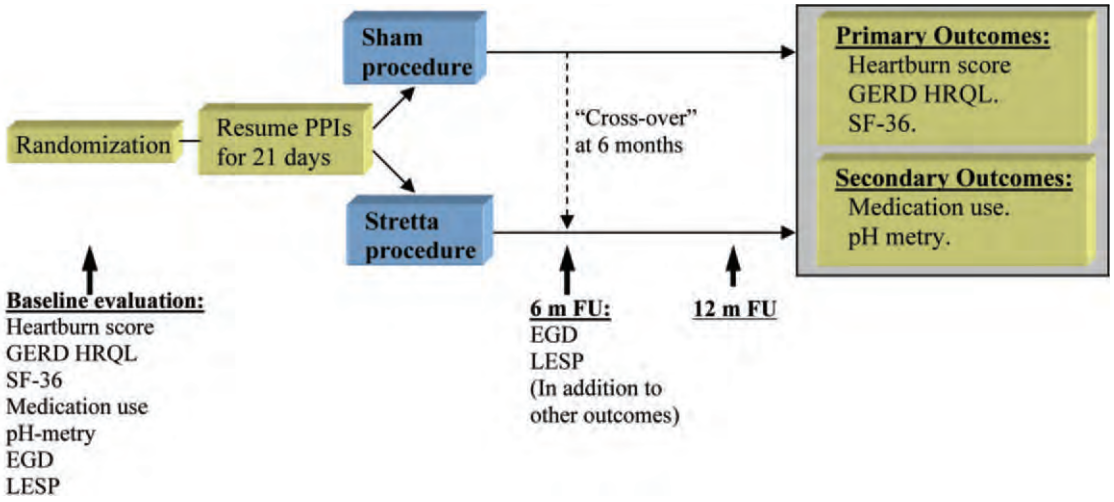

Figure 21–10. The Stretta sham study design. EGD, esophagogastroduodenoscopy; FU, follow-up; GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; LESP, lower esophageal sphincter pressure; PPI, proton pump inhibitor; SF-36, Short Form-36.

ing the same. Four such antegrade rings, each with eight lesions, are created at 0.5-cm intervals to a distance of 1 cm below the GEJ. Two further gastric "pull-back" rings, of 12 lesions each (three sets of deployment each), complete a set of thermal lesions (see Fig. 21–9C). Halfway through the procedure, an endoscope is reintroduced to verify the location of treatments, with subsequent adjustment distally or proximally to prevent superimposition of lesions. After recovery, patients continue their usual antireflux medication for 3 weeks.

It has been proposed that a modified technique be performed if variant anatomy such as a large hiatal hernia (>3 cm) or a failed Nissen fundoplication is present.[47] The modified technique creates six antegrade treatment levels instead of four, beginning 1 cm above the squamocolumnar junction with 5 mm between levels; two sets of lesions are placed at each of the four proximal levels and three sets at the distal two levels.

Histologic Changes

Histologic assessment of porcine specimens has shown focal circular muscle thermal injury with normal mucosa, mild fibrosis, and no inflammation.[46] No randomized study has been completed to document the histologic changes in humans after the Stretta procedure, and the current animal studies suggest different findings. In a study involving 30 pigs, Utley et al. reported histologically normal muscle with occasional focal areas of collagen deposition at 8 weeks' follow-up,[43] whereas in a study involving 11 dogs, Kim et al. reported marked muscular hypertrophy as well as fibrosis within the muscle 7 months after the procedure when compared with control animals.[48] Measurements of the gastric cardia showed a significant (63%) increase in thickness. In animals, the procedure has also been demonstrated to increase LESP and mean muscular wall thickness.[48] Such results have not been proved in humans after the Stretta procedure.[49]

Efficacy

In the initial U.S. open-label trial,[50] 1-year follow-up showed a significant decrease in symptom scores. GERD-specific quality-of-life satisfaction scores and distal acid exposure were significantly improved over the baseline on-medication scores as well. However, normalization of pH monitoring scores did not occur in the majority of patients. In addition, LESP did not increase and esophagitis did not improve significantly at 6-month endoscopic follow-up.

The sham-controlled trial[51] study design is presented in (Fig. 21–10). The data showed significant improvement in symptom scores and quality of life at 6 and 12 months, but at 6 months there was no difference between groups in medication use. The grade of esophagitis did not show improvement, and in fact, grade 2 esophagitis increased in severity in both groups. Similarly, pH scores also failed to show significant improvement, unlike the previous uncontrolled studies.[50,52] The explanation for these findings may be altered sensitivity of the distal esophagus or unusual persistence of the sham effect.

In a registry series,[53] 558 patients underwent the Stretta procedure and experienced a significant improvement in GERD symptom control (from 50% to 90%) and patient satisfaction (from 23% to 86%) at a mean follow-up of 8 months. The onset of GERD relief occurred in less than 2 months in most patients (69%). The treatment effect was durable beyond 1 year, and most patients (51% at 1 year versus 96% before the procedure) were not taking any antisecretory drugs at follow-up. Most studies are limited to short-term follow-up (up to 12 months). For the first time, Torquati et al. reported long-term results in 41 patients, with 83% being highly satisfied at a mean follow-up of 27 months.[54] PPI use was discontinued in 56% of patients and was significantly reduced in 87%. Similarly, Reymunde and Santiage demonstrated significant and sustained improvement in antisecretory drug discontinuation (88%), GERD

Table 21–3 Stretta Procedure: Pooled Results

Variable		≥1 mo		≥3 mo		≥6 mo		≥12 mo		≥24 mo	
GERD-HRQL improvement		67%	(18)	67%	(16)	53%	(219)	65%	(113)	95%	(202)
Heartburn improvement		—		—		52%	(216)	61%	(163)	100%	(202)
Patients completely off PPIs		—		—		65%	(175)	55%	(163)	63%	(332)
Patients with ≥50% reduction in PPI use		—		—		67%	(141)	—		87%	(36)
Improvement in quality-of-life scores	SF-36 Physical	—		—		18%	(202)	20%	(113)	—	
	SF-36 Mental	—		—		14%	(171)	14%	(113)	—	
LESP improvement		—		—		NS*	(211)	—		—	
LES length improvement		—		—		NS	(18)	—		—	
tLESR improvement		—		NS	(36)	24%*	(20)	—		—	
Improvement in pH scores	Total time pH <4	—		53%	(170)	42%*	(180)	36%	(19)	8%	(36)
	Time upright pH <4	—		—		38%	(138)	—		—	
	Time supine pH <4	—		—		48%	(138)	—		—	
	Number of episodes	—		—		32%	(155)	—		—	
	pH normalization	—		—		36%	(22)	—		45%	(22)
Healing of esophagitis		—		—		—		NS	(85)	—	

The results expressed in the majority of studies are shown here. Numbers in parentheses are the numbers of patients studied to obtain the result.

*Signifies disagreement among studies.

GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; LES, lower esophageal sphincter; LESP, LES pressure; NS, change not significant; PPI, proton pump inhibitor; SF-36, Short Form-36; tLESR, transient LES relaxation; —, data not available.

Pooled data were obtained from references 44, 46, 49-52, 54, 57, 58.

symptom scores (82%), and quality-of-life scores (44%) at more than 3 years of follow-up.[55] This encouraging evidence suggests that durability of results is the distinguishing attribute of the Stretta procedure.

Significant improvement in symptom scores and quality of life have also been observed in shorter-term studies.[49,50,53,56] Similarly, decreased PPI use and increased patient satisfaction have been seen consistently.[49,50,56] Most studies fail to demonstrate a beneficial effect of the Stretta procedure on esophagitis, but Triadafilopoulos et al.[52] showed an improvement in esophagitis grade, from 21% with grade 2 esophagitis to 9.3% after the procedure in 43 patients at 6 months. The role of the Stretta procedure in improving extraesophageal manifestations of GERD is still not clear; however, one study[44] suggests that respiratory benefit can be achieved if strict patient selection (abnormal pH study) is followed. Pooled results are shown in Table 21–3.

Complications

The major and minor complications are shown in Table 21–7. The five perforations and two deaths occurred during the learning curve and were due to poor patient selection and technical errors. No major complications were seen in the multicenter trial, and subsequent studies have not shown adverse effects on vagal nerve function or gastric emptying. The incidence and severity of complications observed with this procedure have steadily declined with the introduction of guidewire-directed placement of the Stretta catheter, intense physician training, careful patient selection, provision and adherence to post-treatment guidelines, and standardized post-treatment discharge instructions (including a Stretta card with emergency contacts). The complication rate after the Stretta procedure has been less than 0.6% since introduction of the new technology and 0.13% in the last 12 months.

Recommended Precautions

Operators should check the position if abnormal impedance/temperatures are observed, use correct balloon pressures, control mucosal temperature carefully, minimize balloon pull-back pressure, and avoid nasogastric tube placement for 1 month after the procedure.

Alternatives After Treatment Failure

In the U.S. open-label trial, 5% of the patients elected to undergo fundoplication 6 to 12 months after the Stretta procedure because of an incomplete response or recurrent symptoms. In each case, there was no evidence of extraesophageal tissue abnormality, and the antireflux operation was performed in a normal manner and without difficulty. Richards et al.[44] compared the outcome of patients who underwent the Stretta procedure and those who underwent laparoscopic fundoplication at 6 months and found a comparable and significant improvement in Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire, Short Form-12

(SF-12), and pH scores in both groups. However, medication use was significantly less in patients who had surgery (97% versus 58% not taking PPIs). Both groups were highly satisfied with their procedure. A repeat Stretta procedure is not recommended.

Summary

The Stretta procedure is a promising new endoscopic treatment of GERD. It significantly improves GERD symptoms and quality of life while eliminating the need for PPIs in the majority of patients. RF augmentation of the LES is probably safe, it is well tolerated, and symptom control at 6 to 12 months is acceptable. The future for the Stretta procedure will depend on its durability in long-term follow-up, continued and improved safety, third-party reimbursement, and determination of cost-effectiveness.

SYNTHETIC IMPLANTS/INJECTIONS

History

In the early 1980s, several groups studied the effectiveness of injected collagen or Teflon paste for the treatment of GERD. Most agents were first tested at the urinary bladder neck for female incontinence. Early investigations for the treatment of GERD provided proof of concept and healing of esophagitis in a small number of patients. However, the results were short-lived because of absorption of the collagen and recurrence of symptoms. In addition to these bulk-forming implants, injection therapy with sclerosing agents that induce focal necrosis and fibrosis have similarly been tried. Sodium morrhuate was used in 15 refractory GERD patients, but after a year of follow-up, the authors concluded that the therapy was ineffective.[59]

More recently, various injectable or implantable nonabsorbable biopolymers have been studied. These inert biocompatible substances are easy to place in an outpatient setting under conscious sedation and include Plexiglas spheres in bovine collagen, ethylene vinyl alcohol (Enteryx), and an expandable hydrogel prosthesis (Gatekeeper).

Properties of an Ideal Implant

1. The agent must be in a solution or suspension with viscosity low enough to easily traverse a needle.
2. It must undergo morphologic change, from liquid to a solid or semisolid state, when injected into the LES region. Such changes might be brought about by multiple mechanisms, such as collagen cross-linking as a result of body temperature, swelling of implants by imbibing body water, or an inflammatory response with subsequent collagen entrapment of the implant.
3. The implant and its effects must be durable.
4. It must be able to withstand the physical and chemical forces at the GEJ and resist both dissolution and migration.
5. It must be free of serious side effects and be cost-effective.
6. It must be noncarcinogenic and nonimmunogenic.
7. It must be sterile.
8. The optimal site for placement must be known. The implant commonly flows 1 to 2 cm cephalad or caudad from the injection site.
9. The optimal volume for long-term efficacy must be known. This varies between implants and is still not standardized.

ENTERYX

Enteryx consists of a biocompatible polymer (8% wt/vol ethylene vinyl alcohol polymer [EVOH] with a radiopaque contrast agent dissolved in the organic liquid carrier dimethyl sulfoxide [DMSO]). On contact with tissues or body fluids after injection, the solvent, DMSO, rapidly diffuses and induces precipitation of the polymer (EVOH) as a spongy mass. The low viscosity of Enteryx before dissipation of DMSO permits injection through a 23- to 25-gauge needle. It is not biodegradable and has no antigenic properties. Neither migration through blood vessels or lymphatics nor prosthetic contraction after injection has been observed.[60]

The three components of Enteryx—EVOH, DMSO, and tantalum—have previously been used together medically as a vascular embolization agent and as a membrane for hemodialysis and plasmapheresis. DMSO has been used as a solvent in medical applications since 1964 and is commercially available as the first treatment for interstitial cystitis. Tantalum-impregnated vascular stents have been available for some time.

Patient Selection

Enteryx is a treatment with promise but, like other endoluminal therapies, is lacking objective supportive data. Patients must understand that the procedure is irreversible.[61] Possible future indications for Enteryx include primary therapy for GERD in patients who respond to PPIs but prefer not to take medications daily, salvage therapy for PPI responders to reduce or eliminate daily medications, and salvage therapy for surgical failures.[61]

Enteryx therapy is clearly contraindicated in any individual who does not have physiologically documented GERD by pH study or endoscopic findings. It is also contraindicated in individuals who cannot undergo or tolerate endoscopy and those who have esophageal varices. There is no reported experience with this procedure in individuals with esophageal motility disorders, previous gastric or GERD surgery, scleroderma, Barrett's esophagus, hiatal hernias larger than 3 cm, or a body mass index greater than 35 or in patients who use anticoagulants other than aspirin.[62]

Procedure

The procedure is performed in an endoscopy suite equipped with fluoroscopy. Patients fast overnight and upper endoscopy is performed under conscious seda-

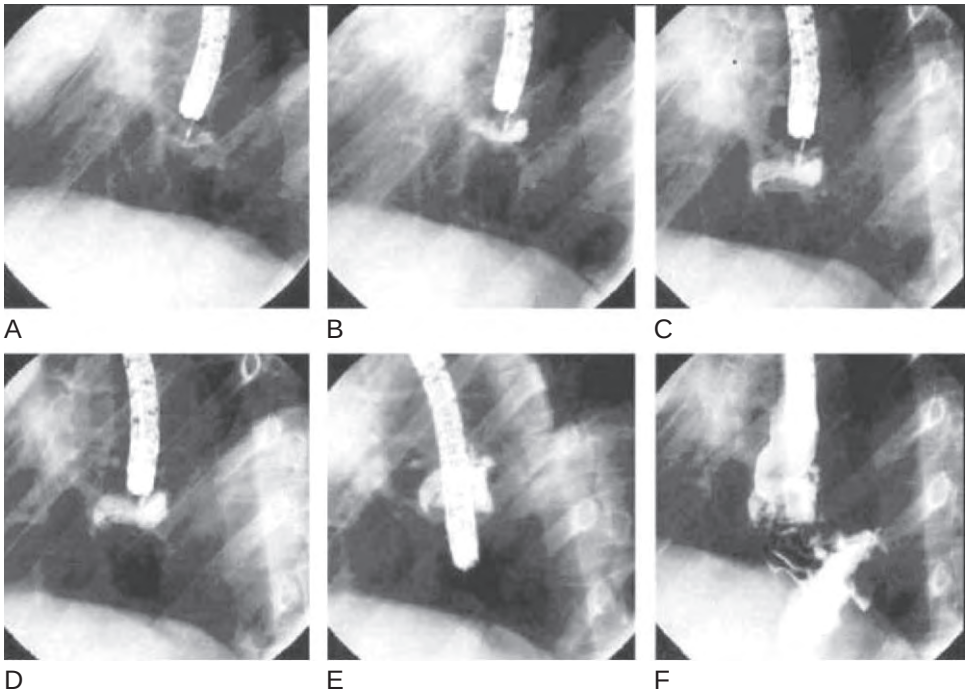

Figure 21–11. Enteryx injection under fluoroscopic control with a resultant prosthetic cuff.

tion. A long-needle catheter is filled with Enteryx after it has been flushed with DMSO to keep it liquefied as long as it stays within the catheter. The prepared injection needle is deployed and advanced into the muscularis propria at the appropriate level of the esophageal wall. The prosthesis is injected at a rate no greater than 1 ml/sec under combined fluoroscopic and endoscopic guidance (Fig. 21–11). The EVOH solidifies within the esophageal wall as the generated heat causes DMSO to dissipate. The injection is stopped if either submucosal or transmural injection is observed. Submucosal accumulation of material is seen endoscopically as a black bulge, and an extramural injection is demonstrated on fluoroscopy as either flow of material beyond the muscularis into the mediastinum or the abdominal cavity or lack of a visible deposit in the esophageal wall. If a circumlinear transverse path of material is visualized under fluoroscopy, the injection is completed at this site with a total of 1 to 2 ml. The procedure is considered satisfactory if 6 to 8 ml of Enteryx is delivered to the muscularis propria circumferentially without a submucosal or transmural injection. After the injection is complete at one site, the needle remains in place for 20 seconds to allow the material to stabilize and solidify and avoid leakage of the prosthesis into the esophageal lumen. Patients are usually discharged 2 to 4 hours after recovery.

Robert et al. reported Enteryx implantation in five pigs without the use of fluoroscopy. Enteryx was consistently deposited into the deep esophageal wall with a high degree of accuracy in a minimal amount of time. Placement was accurate in 85% and was transmural in just one instance. A human trial is under way to confirm these findings.[62]

Histologic Changes

Both gross and histologic examination in animals has shown that the implants persist as encapsulated, firm, smooth, slightly mobile ovoid masses several weeks after implantation. No evidence of pathologic inflammatory changes in the surrounding tissues has been observed.

Efficacy

Enteryx implantation significantly improves quality-of-life scores and medication use.[60,61] No change has been seen in the severity of esophagitis at endoscopy after Enteryx implantation. In general, the structural characteristics of the LES, including its length and pressure, are not altered significantly. Pooled results are shown in Table 21–4.

The 2-year follow-up results of the U.S. multicenter trial, which included 85 patients, were recently published[64] and showed PPI use to be eliminated in 74% of patients at 6-month follow-up. This effect was maintained in 64% of subjects at 2 years, whereas 74% were maintained on less than half their baseline PPI dosage. The improvement in symptom scores was 82% at 6 months and 70% at 2 years. Quality-of-life (SF-36) questionnaires demonstrated an improvement of 6% from baseline at 3 months and 3% at 12 months for the mental score, whereas the improvement in physical score was maintained at 12% at both 6- and 12-month follow-up. pH scores improved with 30% normalization, and there was a small but significant LES length augmentation (1 cm) after therapy.[65] No significant change in LESP was observed. The absence of change in LES resting pressure contrasts with findings from the pilot study, in which a

Table 21–4 Enteryx: Pooled Data

Variable		≥1 mo		≥3 mo		≥6 mo		≥12 mo		≥24 mo	
GERD-HRQL improvement		—		—		83%	(300)	70%	(300)	73%	(64)
Heartburn improvement		75%	(444)	81%	(441)	82%	(511)	71%	(583)	74%	(1985)
Regurgitation improvement		83%	(144)	91%	(141)	87%	(211)	77%	(283)	—	
Patients completely off PPIs		—		81%	(85)	76%	(412)	72%	(393)	65%	(106)
Patients with ≥50% reduction in PPI use		98%	(85)	91%	(141)	89%	(112)	80%	(93)	74%	(106)
Improvement in quality-of-life scores	SF-36 Physical	—		—		12%	(81)	12%	(74)	—	
	SF-36 Mental	—		—		6%	(81)	3%	(74)	—	
	QOLRAD	88%	(22)	85%	(15)	72%	(22)	—		—	
LESP improvement		—		—		NS	(81)	NS	(74)	—	
LES length improvement		—		—		33%	(81)	NS	(74)	—	
tLESR improvement		No									
Improvement in pH scores	Total time pH <4	—		—		27%	(101)	33%	(159)	—	
	Time upright pH <4	—		—		14%	(71)	37%	(261)	—	
	Time supine pH <4	—		—		NS	(71)	50%	(81)	—	
	Number of episodes	—		—		34%	(71)	31%	(160)	—	
	pH normalization	—		—		37%	(71)	38%	(195)	—	
Healing of esophagitis		—		—		—		—		—	
Residual implant volume		—		75%	(81)	—		—		—	
Re-treatment		—		18%	(44)	—		—		—	

All results displayed are significant. Numbers in parentheses are the numbers of patients studied to obtain the result.
GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; LES, lower esophageal sphincter; LESP, LES pressure; NS, change not significant; PPI, proton pump inhibitor; QOLRAD, Quality of Life in Reflux and Dyspepsia questionnaire; SF-36, Short Form-36; tLESR, transient LES relaxation; —, data not available.
Pooled data were obtained from references 64-70.

significant increase in the LESP was observed at 6 months. This may have been due to the inclusion of patients with normal LESP at baseline or the smaller sample size in the pilot study. Importantly, most of the decline in treatment responders during follow-up occurred between 1 and 6 months. Between 6 and 12 months, the proportion of treatment responders remained stable. There was no evidence that the reduction in PPI use after the implant procedure was due to medication shifting.

The decline in residual implant volume seen after 1 month was attributable to sloughing of superficially implanted material until encapsulation was complete. There was no radiographic evidence of implant migration and after 3 months the residual volume remained stable ($P > .1$).[66] Twenty-two percent of patients were re-treated at the 3-month follow-up, 63% of whom improved at the 12-month follow-up, with 58% of patients not taking any PPIs and 5% reducing their PPI use by more than 50% of baseline.[65]

Multicenter randomized controlled sham trials with a "crossover" option starting at 3 months after randomization are currently under way in both Europe and the United States.[71] The European study design is shown in Figure 21–12. An interim report on 56 of the 64 total European patients has been announced with 3 months of follow-up. An improvement in GERD health-related quality of life (HQRL) was seen in 65% of patients in the Enteryx arm versus 21% in the sham arm. The median change in symptom scores was 15 for the Enteryx group and 4 for the sham group. There was also a greater reduction in PPI use (64% versus 33%) and a lower crossover/re-treatment incidence (21% versus 71%) in the Enteryx group than in the sham group. Criteria for both crossover (for controls) and re-treatment (for the Enteryx group) were the same—an off-PPI HQRL score greater than 15.[71]

Johnson et al. reported that the likelihood of a successful clinical outcome is higher with more residual implant volume.[66] They showed that all patients who retained 5 ml of implant material eliminated or reduced PPI use by 50% and that the majority of subjects who retained more than 5 ml of Enteryx achieved a GERD-HRQL score of less than 15. Lehman et al. reported the procedure to be equally effective irrespective of the radiologic pattern evident at the time of implantation.[72] In a study evaluating predictors of outcome for Enteryx, Deviere et al.[73] showed that there was no statistically significant difference in PPI use or pH outcome by gender, but that GERD-HRQL symptom scores were significantly more likely to improve in males (86%; 57/66) than in females (67%; 32/48) ($P = .01$). Finally, Ganz et al. compared the endoscopic findings of patients from the multicenter study at 1-year follow-up with their baseline values (while taking PPIs) and reported that treatment with Enteryx provided improvement in esophagitis

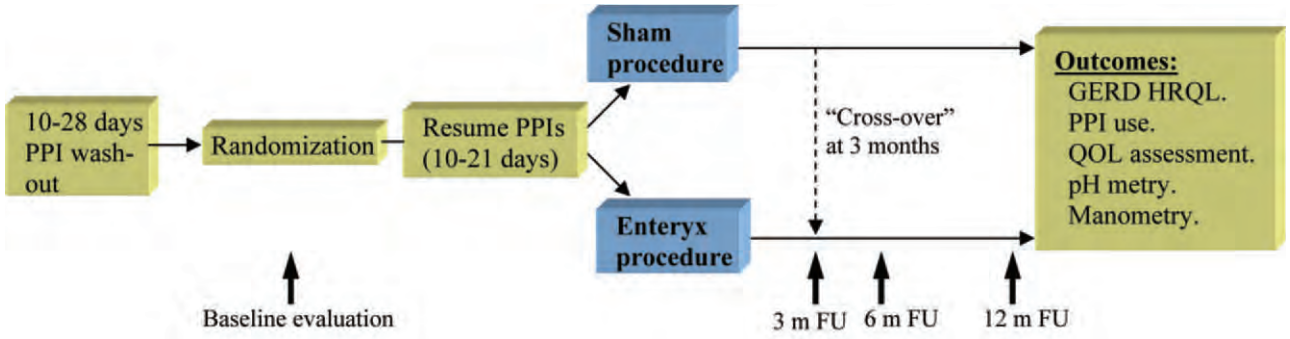

Figure 21–12. Enteryx sham study design. FU, follow-up; GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; PPI, proton pump inhibitor; QOL, quality of life.

scores comparable to that provided by PPI medication.[74,75] This finding, however, has not been supported by other studies.

Complications

Complications are shown in Table 21–7. Recently, one death was reported in a patient as a result of inadvertent injection of Enteryx into the aorta. Further details are not yet available. Two patients experienced pericardial effusion after injection of the prosthesis and subsequently underwent a pericardial window procedure. A pleural effusion developed in two additional patients, but no other problems were recognized.

Recommended Precautions

All operators are required to receive hands-on laboratory training before clinical use. Injection techniques under fluoroscopic control are emphasized, and guidelines for prosthesis preparation are given. Most centers place patients on a liquid diet, followed by a soft diet the day of the procedure and then a normal diet the day after. Maintenance therapy with PPIs is continued for 10 to 14 days after implantation.

Summary

The procedure is uncomplicated and probably safe. Preliminary data are encouraging, although the pH normalization rate and LESP results are similar to those of other endoluminal procedures. Further follow-up is needed, but the present data suggest sustainable efficacy in patients requiring chronic maintenance therapy; however, re-treatment is often necessary. Subsequent to this writing, Boston Scientific withdrew the Enteryx procedure due to further procedural complications. Nevertheless, the lessons learned from this injection form of therapy remain valuable.

GATEKEEPER

Gatekeeper is a dehydrated hydrogel prosthesis implanted into the submucosa of the cardia/LES. It hydrates to 6 × 15-mm cylinder-shaped soft pliable cushions and is removable by endoscopy.[76]

Patient Selection

In addition to the general selection criteria already described, patients with esophageal varices, a peptic stricture, and morbid obesity were excluded from the trials for Gatekeeper.

Procedure

The Gatekeeper device consists of an overtube with separate channels for passage of an endoscope and a long delivery sheath. The overtube is inserted with the patient under conscious sedation. The injection capsule is placed through the overtube to straddle the squamocolumnar junction. A vacuum is created to stabilize the device and to draw the mucosa in. The injection needle is advanced into the submucosa, followed by the injection of 3 to 6 ml of sterile saline until blanching is observed. This is followed by removal of the injection needle and advancement of the needle assembly and delivery sheath into the mucosa, with the delivery sheath left in the submucosal plane. After the needle assembly has been retracted, the prosthesis is inserted into the proximal end of the delivery sheath and advanced to the submucosal level with a pushrod assembly. Up to six hydrogel implants are placed. The implants are small and "sliver"-like when introduced but swell to full size within 24 hours when hydrated. The procedure is shown in Figure 21–13.

Efficacy

In a limited number of patients, the Gatekeeper procedure has been shown to significantly decrease heartburn, improve quality of life and 24-hour pH-metry scores, and decrease medication use.[77] The success rate for implantation is 93%, whereas the procedural success rate was reported at 98.7%.[78] Pooled results for the Gatekeeper are shown in Table 21–5.

After completion of a 6-month pilot study[80] with favorable results, a European multicenter study was initiated.[79] Patients underwent manometry, endoscopy, 24-hour pH-metry, and symptom scoring before and after the proce-

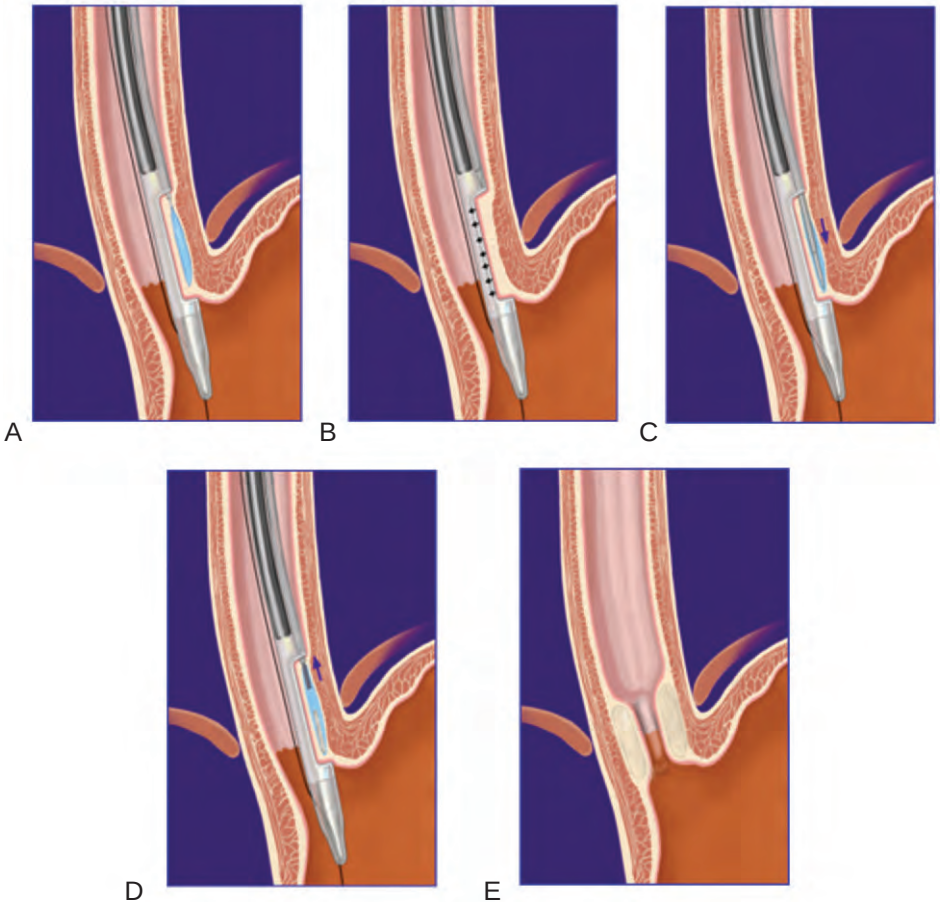

Figure 21–13. **A** to **E,** Gatekeeper procedure.

Table 21–5 Gatekeeper: Pooled Results

Variable		≥1 mo		≥3 mo		≥6 mo	
GERD-HRQL improvement		65%	(55)	65%	(92)	74%	(91)
Regurgitation improvement		81%	(55)	94%	(49)	87%	(49)
Patients completely off PPIs		—		—		58%	(42)
Patients with ≥50% reduction in PPI use		—		—		54%	(67)
Improvement in quality-of-life scores	SF-36 Physical	16%	(61)	19%	(57)	17%	(57)
	SF-36 Mental	3%	(61)	8%	(57)	1%	(57)
LESP improvement		NS	(12)	16%	(78)	36%	(78)
LES length improvement		NS	(12)	—		NS	(78)
Improvement in pH scores	Total time pH <4	NS	(12)	10%*	(11)	32%*	(58)
	Time upright pH <4	—		NS	(27)	45%	(45)
	Time supine pH <4	—		NS	(27)	70%	(45)
	Number of episodes	—		42%	(27)	45%	(45)
	pH normalization	—		—		40%	(45)
Healing of esophagitis		58%	(62)	39%	(37)	45%	(53)
Residual plications		84%	(81)	73%	(69)	71%	(86)
Re-treatment		—		—		16%	(701)

The results expressed in the majority of studies are shown here. Numbers in parentheses are the numbers of patients studied to obtain the result.
*Signifies disagreement among studies.
GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; LES, lower esophageal sphincter; LESP, LES pressure; NS, change not significant; PPI, proton pump inhibitor; SF-36, Short Form-36; —, data not available.
Pooled data were obtained from references 77-79.

dure. The average number of prostheses implanted was 4.3 (2 to 6). The final results showed significant improvement in symptom scores (HRQL score from 24 to 5), quality of life, pH parameters (percent time pH <4, 9.1% to 6.1%), and LESP (8.8 to 13.8 mm Hg) at 6 months.[78] The prosthesis retention rate was 70% at 6 months. Other studies with smaller numbers of patients have failed to demonstrate significant improvement in LESP; however, symptom scores and pH results show consistent improvement.[77,79]

An international, multicenter, randomized sham-controlled Gatekeeper trial has recently commenced.[81] Patients with symptomatic GERD requiring PPI therapy with evidence of GERD on 24-hour pH study and a symptom score greater than 20 while not taking medications are being included in the study. Up to eight implants will be placed circumferentially in the distal LES/cardia, with re-treatment offered to individuals if GERD symptoms persist. The initial 25 patients were lead-in–phase nonrandomized subjects, whereas the next 100 are to be randomized by sealed envelope at a ratio of 2 : 1 implant versus sham. Patients will take antisecretory medications on an as-needed basis.

Complications

The complications reported at 6-month follow-up are shown in Table 21–7.[78] In the largest multicenter study, severe complications developed in 2 of 40 patients (5%), including esophageal perforation caused by overtube placement and severe postprandial nausea (1 week after the procedure) leading to endoscopic removal of the prosthesis at 3 weeks.[78]

Advantages

The Gatekeeper prosthesis is removable by endoscopic means. A needle knife can be used to incise over the edge of the implant, which is then suctioned from its submucosal pocket.[76] Endoscopic ultrasound may be used for exact localization of the prosthesis. Of note, one of the two patients who had the prostheses removed did so 7 months after the procedure. All three prostheses were removed in the other patient 3 weeks after the procedure. No complication was encountered with either patient.

Summary

The Gatekeeper system is a safe and reversible procedure with acceptable to good prosthesis retention. Early results show efficacy on GERD-HRQL, SF-36, and pH monitoring. Many questions still remain unanswered, including its mechanism of action, durability, long-term safety, and placebo effect. A multicenter, randomized, sham-controlled study was initiated. However, the sponsoring company discontinued commercialization due to inefficacy.

PLEXIGLAS

A trial of gelatinous Plexiglas (polymethylmethacrylate [PMMA]) microsphere implants has been published by Feretis et al.[82] A mean volume of 32 ml was implanted submucosally, 1 to 2 cm proximal to the squamocolumnar junction, in 10 patients with a 21-gauge needle. Transient dysphagia was noted in one patient because of excessive implant volume. At a mean follow-up of 7.2 months, there was significant improvement in GERD-related symptoms and 24-hour pH studies (decreased from 24.5 to 7.2), but pH normalization was not seen. Ninety percent of patients were not taking any PPIs at 6-month follow-up. The procedure was found to be safe at short-term follow-up.

Minor and self-limited complications occurred in 4 of 10 patients (40%). Transient dysphagia and gas-bloating syndrome (10%) were thought to be due to excessive treatment with an implantation volume of 39 ml. Plexiglas injection was not associated with local or systemic complications and is not antigenic. PMMA is highly viscous, and therefore an endoscope with a larger biopsy channel that accommodates a large-caliber catheter was used for implantation. Longer follow-up studies are needed.[82] A multicenter study is currently being planned.

GENERAL OVERVIEW

The end points studied in most of the trials are GERD symptoms scores (HRQL), medication use, manometric findings, grade of esophagitis, and 24-hour pH study results. In general, the procedures are safe, with 3 deaths in 9000 to 10,000 cases. At present, the overall complication rates reported for ELGP, the Stretta procedure, Enteryx, and Gatekeeper are 11%, 6%, 6.7%, and 15%, respectively.[78] There is evidence of symptomatic relief with decreased medication use, but failure of an increase in LES length and pressure, healing of esophagitis, and improvement in pH scores. A cost analysis of PPI versus endotherapy for GERD is shown in Figure 21–14. A comparison of the results at 1-year follow-up for all procedures is shown in Table 21–6. An overview of the different endotherapies for GERD is shown in Table 21–7. A comparison of results in patients with EndoCinch, the Stretta procedure, and Enteryx at various follow-up intervals is also depicted in graphic format (Figs. 21–15 to 21–18).

Information on broader clinical applications, a possible spectrum of specific indications, and long-term results regarding the safety, endurance, and outcomes of these procedures has herein been reported. However, long-term efficacy, durability, and therapy-specific patient selection have yet to be elucidated inasmuch as the present literature consists of few publications, most of which are nonrandomized and have small numbers of patients, significant dropout rates, and lack of agreement on end points. To further confuse the issues, most of the larger studies are industry sponsored, and the results are often based on patients who underwent the procedure during the investigator's learning curve. The sham-controlled trials to date have been nonsupportive. The

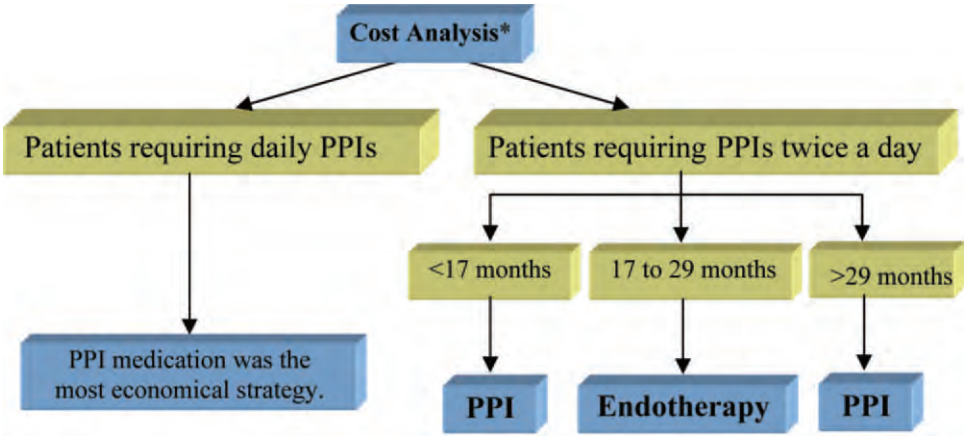

Figure 21–14. Cost analysis of proton pump inhibitor (PPI) therapy versus endotherapy in the treatment of gastroesophageal reflux disease. *Provided endotherapy failure rates remain greater than 20%.

Table 21–6 Endotherapy Result Comparisons: Pooled Data

Trial Results		ELGP	NDO Plicator	Stretta	Enteryx	Gatekeeper*
HDQRL improvement		55%	70%	65%	70%	74%*
Heartburn improvement		74%	—	61%	71%	—
Off PPIs	At 1 yr	40%	75%	55%	72%	58%*
	At >2 yr	33%	—	63%	65%	—
≥50% reduction in PPIs		51%	—	67%	80%	54%*
Quality-of-life improvement	SF-36 Physical	17%	31%	20%	12%	17%*
	SF-36 Mental	None	10%	14%	3%	1.4%*
Time pH <4: improvement		16%†	None	36%	33%	32%*
No. of reflux episode: improvement		33%†	—	None	31%	45%*
pH normalization		25%†	—	—	38%	40%*
LESP improvement		None	None	None†	None	None†
LES length improvement		None	None	None	None†	None
tLESR improvement		Yes	No	Yes	No	No
Healing of esophagitis		None	None	None	None	None
Sham trial		3-mo FU	Being planned	1-yr FU	Under way	Under way

All results are at 1-year follow-up except Gatekeeper. All results are statistically significant.
*Six-month follow-up data.
†Indicates controversy regarding results, but the results presented are the ones shown by the majority of studies.
ELGP, endoluminal gastroplication; FU, follow-up; HDRQL, Heartburn Dysphagic Regurgitation Quality of Life Score; LES, lower esophageal sphincter; LESP, LES pressure; None, change not statistically significant; PPI, proton pump inhibitor; SF-36, Short Form-36; tLESR, transient LES relaxation; —, not available.

Stretta sham trial provided unimpressive data, and the ELGP study was underpowered. Other sham trials are under way or in the planning stage.

PHYSIOLOGIC/ANATOMIC MECHANISMS OF ENDOLUMINAL THERAPIES

In the early stages of disease and in the absence of a hiatal hernia, the geometry and integrity of the cardia are normal. However, in the interprandial period and during periods of gastric stress, such as after meals, gastric distention alters the anatomy and makes the sphincter incompetent, probably because of sphincter shortening, which some term tLESS.[83] Such patients appear to be the ideal population for endoscopic antireflux procedures. LES dysfunction may also be caused by a loss of LES resistance that prevents it from serving as an effective reflux barrier, but this mechanism is seen only in more advanced GERD patients.

Most investigators believe that both the LES complex and the angle of His are crucial in the prevention of GERD. An understanding of the muscle fibers that form and maintain these structures anatomically might provide additional insight into the endoscopic treatment of GERD. Liebermann et al., in a carefully performed study, described the architecture of the GEJ musculature.[4] An oblique "ring" where muscular thickness is

Table 21–7 Procedure Characteristics and Complications: Pooled Data

Variables		EndoCinch	NDO Plicator	Stretta	Enteryx	Gatekeeper
Procedure duration (mean)		68 min	20 min	69 min	33 min	35-60 min
Personnel required		1 physician and 2 assistants	1 physician and 2 assistants	1 physician and 2 assistants	1 physician and 2 assistants	1 physician and 2-3 assistants
Sedation required		Conscious sedation in 82%	NA	Conscious sedation in 100%	Conscious sedation in 100%	NA
Approximate no. of procedures performed		4000	200	4000	2600	225
Major complications	Perforation	0.075%	0.5%	0.125%	0%	0.4%
	Bleeding	0.05%	NA	0.05%	0%	0%
	Hypoxemia	0.075%	0%	0%	0%	0%
	Pleural effusion	0%	0%	0.025%	0.076%	0%
	Pericardial effusion	0%	0%	0%	0.076%	0%
	Aspiration pneumonia	0%	0%	0.05%	0%	0%
	Esophageal abscess	0%	0%	0%	0.038%	0%
	Ulceration over prostheses	0%	0%	0%	0%	0.4%
	Death	0%	0%	0.05%	0.038%	0%
Minor complications		Sore throat (0.35%) Chest soreness (0.17%) Abdominal pain (0.15%) Bloating (0.02%) Transient dysphagia (0.05%) Bronchospasm (0.01%)	NA	Superficial mucosal injury Burn at pad site (0.02%) Transient atrial fibrillation (0.02%) Bloating (0.02%) Gastroparesis and ulcerative esophagitis (0.02%) Low-grade fever Transient dysphagia Transient chest pain Topical anesthesia-related complications (e.g., allergy, hypotension)	Garlic odor for several hours (because of DMSO) Chest pain (82%) Transient dysphagia (13%) Belching/burping Bloating/flatulence Fever	Sore throat (15%) Chest pain (5%) Nausea/vomiting (0.8%) Erosive duodenitis (0.8%) Retrosternal pain (0.4%) Poor sleep (0.4%) Abdominal pain (0.4%) Rash (0.4%) Cough (0.4%)

Complications were obtained from pooled data.
DMSO, dimethyl sulfoxide; NA, not available.

maximal corresponds to the proximal most aspect of the gastric mucosal folds (see Fig. 21–1). This increase in thickness was attributed to an increase in the muscle mass of the inner circular muscle layer. On the lesser curvature side, these muscle bundles split to form semicircular short transverse "clasp" fibers above the gastroesophageal (GE) ring, whereas on the greater curvature side, they spread out as long oblique "sling" fibers. The direction of fibers suggests that the clasp fibers are more likely to contribute more to the barrier effect at the GEJ because the sling fibers are in fact almost parallel to the lesser curvature. As the GE ring is approached, both clasp and sling fibers increase in density and those in the outer coat remain unchanged. These site-specific changes in muscle density suggest that the inner circular ring plays a principal role in maintaining competence at the GEJ whereas the outer layer may be suitable for a more generalized process such as gastric motility.

When the muscular contraction forces being exerted at the GEJ are represented by vectors, one vector is directed transversely from the angle of His toward the lesser curvature (clasp fiber vector) and the other is almost parallel to the lesser curvature (sling fiber vector). The resultant vector obtained is directed obliquely toward the lesser curvature and is parallel to the GE ring outlined by Liebermann et al. (see Fig. 21–1C). The GE ring appears to be the site of maximal resistance to the reflux of gastric contents inasmuch as the cross-sectional thickness of the muscle correlates with increased force of contraction/pressure generated within the lumen, assuming a solid pressure model. The GE ring is oblique, being higher on the greater curvature side, and is thickest posterolaterally.

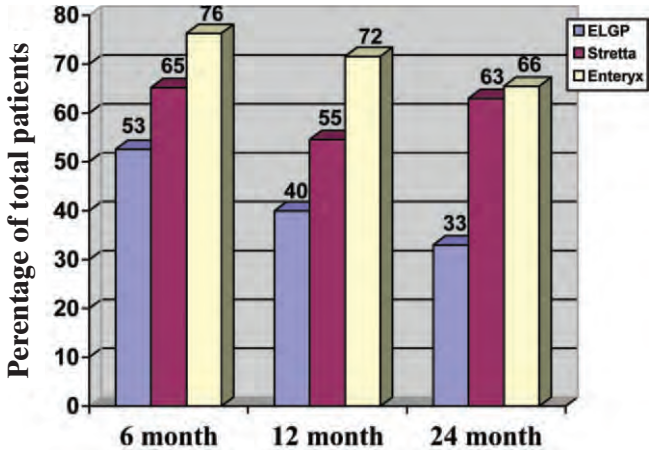

Figure 21–15. Percentage of total patients not taking proton pump inhibitors (PPIs) 6, 12, and 24 months after endoluminal gastroplication (ELGP), Stretta, and Enteryx procedures. All changes are significant when compared with baseline. Pooled data were obtained from references 18-24, 44, 46, 49, 50, 52, 54, 57, 65, 68, 70.

Endoluminal Gastroplasty

EndoCinch therapy has been shown to reduce distal esophageal acid exposure, but it does not eliminate it. The symptomatic improvement can be explained by a lower volume of refluxate reaching the more "sensitive" proximal esophagus. The decreased volume may correspond with a decreased frequency of tLESSs or tLESRs and failure to completely abolish them.

The mechanism by which ELGP improves competence of the GEJ remains unclear. Feitoza et al. demonstrated lack of fusion between the folds when sutures were placed intraluminally in the stomach of rabbits, irrespective of suture depth.[15] The degree of fibrosis, however, increases as the depth increases and is maximal with incorporation of the serosa. Endoscopic manipulation of mucosa before suture placement when performing electrocautery or mucosal resection has improved postoperative tissue healing.[84] ELGP may decrease tLESSs by scar formation.

Secondary scarring may impair the distensibility of the proximal stomach and may also affect neural pathways,

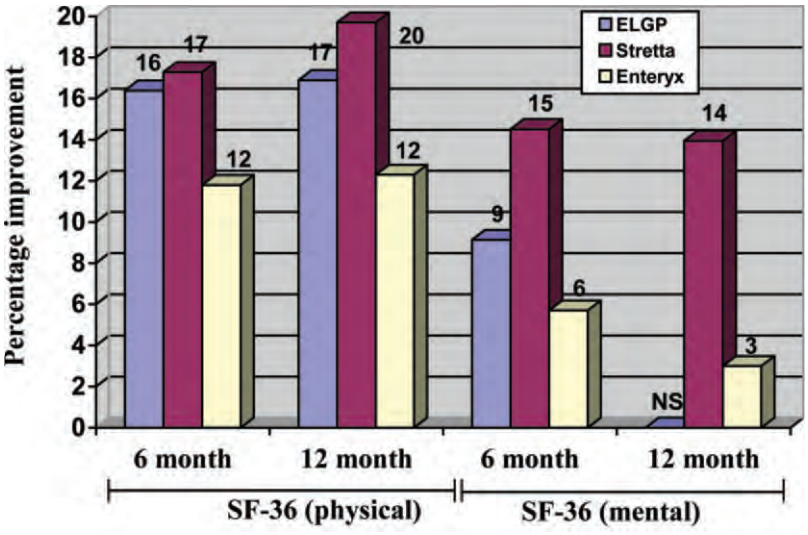

Figure 21–16. Improvement in quality-of-life scores (Short Form-36 [SF-36]), both physical and mental, at 6- and 12-month follow-up intervals after endoluminal gastroplication (ELGP), Stretta, and Enteryx procedures. NS, not significant. All other changes are significant when compared with baseline. Pooled data were obtained from references 17, 20, 50, 51, 52, 57, 65, 66.

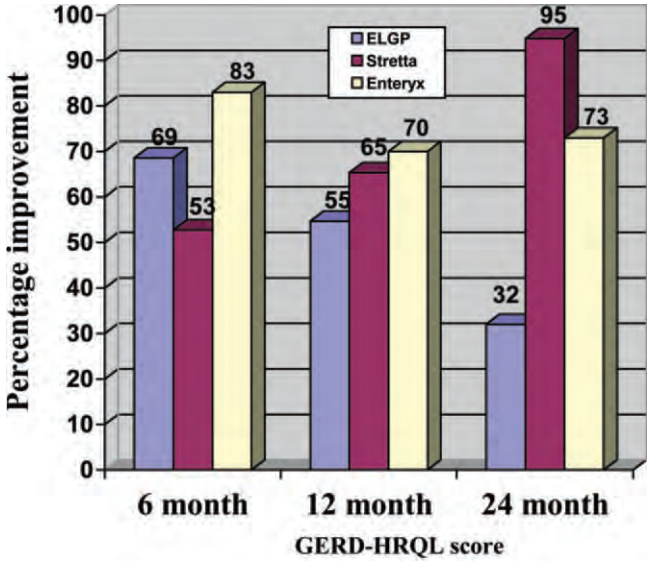

Figure 21–17. Degree of symptomatic improvement at 6-, 12-, and 24-month follow-up intervals after endoluminal gastroplication (ELGP), Stretta, and Enteryx procedures. All changes are significant when compared with baseline. GERD, gastroesophageal reflux disease; HRQL, health-related quality of life. Pooled data were obtained from references 17-22, 24, 25, 46, 50-52, 57, 58, 64, 65, 67-69.

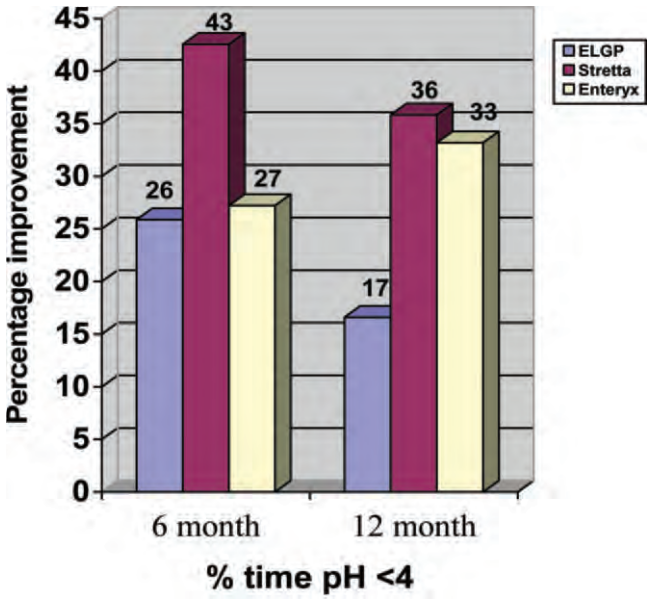

Figure 21–18. Improvement in the percentage of time that the pH is less than 4 at 6- and 12-month follow-up after endoluminal gastroplication (ELGP), Stretta, and Enteryx procedures. Only studies showing significant improvement in pH scores are considered. Pooled data were obtained from references 17, 20, 26, 44, 50, 52, 57, 65, 67, 69.

thereby reducing the rate of tLESRs and tLESSs. Such scar formation, when combined with the fact that ELGP has been shown to result in localized circular muscle hypertrophy in both humans and animals,[16] should lead to increased basal tensile strength and increased resistance to gastric distention.

ELGP increases smooth muscle thickness, but in an indirect fashion. Muscle inclusion within a plication has not been shown with ELGP; thus, muscularis propria gathering occurs rarely, if at all. Tissue apposition is initially realized secondary to mucosal/submucosal gathering, but it dissipates as a result of the lack of mucosal healing and the suture cheese wire effect (the suture seesawing with time through the tissue). The later is presumably caused by peristalsis and additional stressors such as food passage, belching, and vomiting. The scar formation and muscle hypertrophy seen with the current techniques and available devices are not durable and are therefore unable to reduce distal esophageal inflammatory changes and large-volume acid reflux. More strategically placed deeper plications may improve the results. Sling fiber gathering/hypertrophy is less likely to reduce GERD because the number of plications necessary is probably excessive for the technology available. Such may not be the case, however, for the lesser curvature and the underlying clasp fibers. Placement of plications on the GE ring will create hypertrophy apparently in the ideal location, but the exact location of the ring is not possible to identify endoscopically. To be sure of superimposition of plications on the ring, stitches should be applied along the lesser curvature because it is easily identified and close approximation of the capsule to the gastric wall is possible in this location. Placement of plications on the greater curvature is only technically possible 1 cm below the squamocolumnar junction. It is unsafe to go more proximally because suture perforation is more likely and the stomach flairs out more distally, thus making it impossible to place plications accurately since the endoscope with capsule will not work in the retroflexed position. More distally in the antegrade position, the capsule is placed remote from the target area in a partially distended stomach. With this remote position comes inaccuracy because it is impossible to reliably pull in a target area. Plications placed anteriorly or posteriorly are very often difficult to localize for the same reason and certainly do not easily correspond to the obliquity of the GE ring. In Figure 21–19A we propose plications that are more ideally placed to support (create hypertrophy of) the gastroesophageal ring, nature's anatomic point of apparent failure, and to reinforce the important clasp fibers. An additional linear row along the lesser curvature may make this approach the preferred endoscopic technique.

NDO Plicator

The degree of postprocedure inflammatory changes and fibrosis should be greater with a full-thickness plication. Feitoza et al.[15] showed maximal fibrosis with incorporation of serosa in the plication when compared with other depths of suture plication. The retention

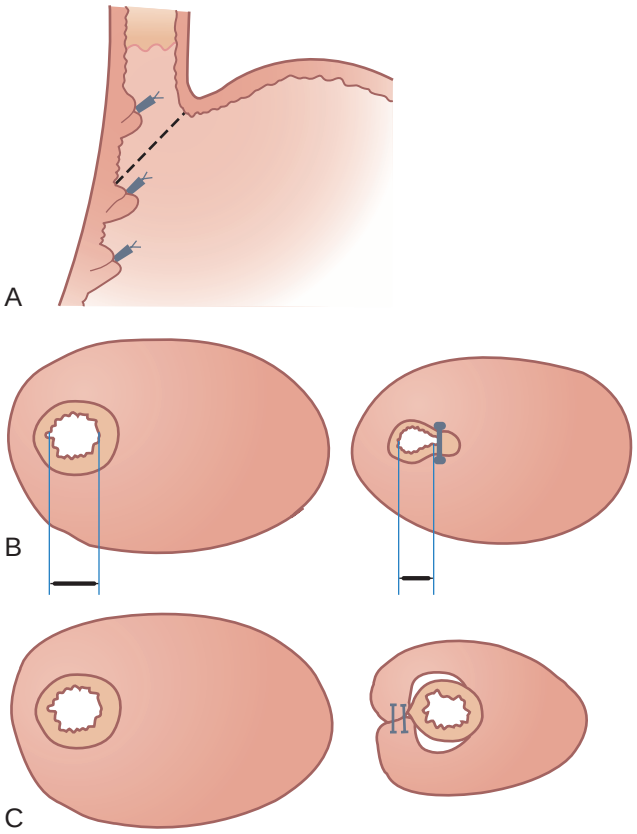

Figure 21–19. **A,** Anterior view of plications overlying the clasp fibers and reinforcing the gastroesophageal ring. **B,** Cross-sectional representation of the gastric lumen before and after the NDO plicator is applied. The plication may strangulate some of the sling fibers on the greater curvature side of the gastroesophageal junction but does decrease the esophageal lumen as indicated by the measurement lines. **C,** Schematic drawing of a Syntheon plication. The underlying clasp fibers may or may not be involved by the plication.

rate for sutures and thus the durability of results should also improve. Lengthening of the intra-abdominal segment of the LES[40] is expected with this technique.

It is our opinion that the full-thickness plication should be placed on the lesser curvature side of the GEJ. In this circumstance, the underlying clasp fiber forces would be reinforced rather than distracted (see Fig. 21–1) as when placing the plication on the greater curvature side of the GEJ. The bottom of the thickened LES and the angle of His are both augmented with the NDO plication, but the overall results of the procedure speak to either insufficient numbers of plications or anatomic/physiologic flaw. Further testing with more plications per patient appears to be in order. The new Syntheon plicator, which places the plication on the lesser curvature side, will also assist in further determining where the full-thickness plications should be applied. The NDO and Syntheon plicators are similar in that they both place a full-thickness U stitch, although the former places it on the greater curvature side of the GEJ and the Syntheon can place it on the lesser curvature side (see Fig. 21–19C). The NDO plicator decreases the internal cross-sectional area of the GEJ, thereby decreasing the pressure being exerted by the luminal contents on the wall, but it may functionally disable some of the muscle fibers distal to the plication as shown in Figure 21–19B. Perhaps more ideal is placement of the deep suture on the lesser curvature, where presumably the anterior and posterior aspects of the fundus are opposed, as in Figure 21–19B. There would appear to be less likelihood of gathering and disrupting the GE ring, and if the inflammatory process is the cause of the muscle hypertrophy, the clasp fibers within the GE ring would be reinforced, whereas with the NDO plicator, the force applied may disrupt rather than ultimately augment the sling fibers.

Stretta Procedure

The unanticipated disparity between symptomatic improvement and acid exposure seen in the sham trial was surprising because acid exposure was expected to be less responsive to a sham effect than either symptom scores or medication use.[51] Previous multicenter studies have shown the contrary. This might be explained by the known poor correlation between GERD symptoms and 24-hour pH monitoring in so far as symptomatic improvement can occur with only slight variations in acid exposure. To explore this discrepancy, patients in the sham trial were divided into responders and nonresponders, depending on their symptomatic improvement. It was found that responders significantly improved their acid exposure when compared with nonresponders, which suggested that decreased acid exposure was accountable for at least part of the symptom improvement in the active treatment group. Alternative explanations proposed in the trial were a residual sham effect on symptoms or altered visceral sensitivity.[51] The later would explain the striking dichotomy between symptom relief and minimal to moderate improvement in acid reflux profiles. Diminished sensitivity may be due to destruction of chemosensitive or mechanosensitive nerve endings.[9]

The underlying mechanism of effect may be explained by multiple changes. First, mechanical alteration and thickening of the LES musculature probably lead to diminished reflux, as shown in the canine model.[48] Second, the progressive tissue remodeling and scar formation observed after the Stretta procedure may contribute to the decreased compliance and increased tensile strength of the GEJ, which also exerts its effect in decreasing tLESRs. This decrease in tLESRs has been shown in both animals and humans.[48,57]

Torquati et al. effectively addressed concerns about the durability of the procedure by reporting significant improvement in symptom scores, PPI use, and patient satisfaction at a mean follow-up of 27 months.[54] This study contradicts the contention that symptomatic improvement with the Stretta procedure is due to desensitization of the esophageal mucosa with a resultant decrease in PPI use but increased mucosal injury as a

result of acid exposure. This was done by showing significant improvement in pH results at 27 months in patients who had responded to therapy. In light of this study, the durability of the procedure might be further increased by strict patient selection and inclusion of only patients who respond to PPIs before the procedure.

Although ablation of vagal afferent pathways of the reflex arc leading to decreased tLESRs has been proposed as a possible mechanism, studies of the pancreatic polypeptide response to sham feeding revealed normal responses, which suggests preservation of the vagal afferents.[49] Moreover, no microscopic or macroscopic evidence of damage to the vagus nerves has been demonstrated thus far except for a porcine model that showed destruction of enteric neural elements after treatment.[43] Delayed gastric emptying occurs in up to 25% of GERD patients and has been shown to improve after Nissen fundoplication. Recently, a study has suggested improvement in gastric emptying after the Stretta procedure, with 93% patients showing significant improvement and 83% complete normalization of gastric emptying.[85] This, in part, might contribute to the efficacy of the Stretta procedure.

Enteryx

Animal studies have shown a significant difference in yield pressure and yield volume with a raised threshold for transient relaxations after Enteryx injection.[86] Animal model findings verify this by showing that Enteryx undergoes fibrous encapsulation without a prolonged active inflammatory response.[86] The fibrous encapsulation may functionally lengthen the LES. The encapsulation/scarring is the probable mechanism of effect, but because the prostheses are placed high in the GEJ and scar formation is dependent on an unreliable distribution of the foreign body, this procedure requires further technical refinement.

The mechanism of action of Enteryx implantation in humans remains to be fully characterized. Enteryx injected circumferentially within and along the muscle layers of the LES incites a localized foreign body reaction and an acute inflammatory response leading to fibrous encapsulation of the Enteryx. Such encapsulation results in decreased LES compliance and distensibility during periods of gastric distention, thus preventing inappropriate LES relaxation/shortening. The "bulking" effect seen with some injectable treatments of urinary incontinence is not apparent for Enteryx because follow-up endoscopy has revealed no evidence of luminal narrowing.

Johnson et al. suggested that the main reasons for an inadequate clinical outcome and lack of durability were either insufficient material injected into the LES or loss of the implant because of sloughing of superficially injected material.[66] They showed that the clinical outcome was associated with the amount of residual implant. Patients with a residual volume of 5 ml had a better symptomatic outcome and greater improvement in medication use.

Gatekeeper

The reasons for failure and success are probably similar to those of the Enteryx procedure, with the exception of bulking and dispersion. The prosthesis does narrow the lumen, even at 6 months' follow-up endoscopy, and is self-contained. The maximum number of prostheses that can be safely applied requires investigation and perhaps manufacturing refinements.

CONCLUSION

Endoluminal therapy is an emerging field with continued prospects that may lead to substantial changes in patient care; however, the goal of such therapy needs to be healing of esophagitis. All studies to date allow the use of PPIs, and most gauge success by the number of patients decreasing their PPI dosage and symptomatic improvement. Meaningful conclusions cannot be made in this instance.

The scientific community needs to wait for industry-independent trials showing endoscopic and 24-hour pH monitoring follow-up data that establish long-term efficacy and prolonged symptomatic benefit. Cost-effectiveness and continued documentation of complications will better define the "true" role of these procedures in the management of GERD patients.

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Part

4

Barrett's Esophagus

Chapter

22

History and Definition of Barrett's Esophagus

Reginald V. N. Lord

The current definition of Barrett's esophagus includes both macroscopic and microscopic criteria. *Macroscopically,* it requires the presence of any length of visible columnar mucosa in the tubular esophagus proximal to the gastroesophageal junction (GEJ). *Microscopically,* the definition requires that true goblet cells be seen, thus establishing the presence of intestinal metaplasia (IM, previously known as specialized epithelial type).[1-6] This definition seems straightforward, but the high frequency of misdiagnosis of Barrett's esophagus indicates the difficulty of accurately identifying it in all cases. Sources of difficulty include changes in the definition of Barrett's, the GEJ,[7] and the cardia, as well as varying terminology for IM that is seen only microscopically, conflicting reports regarding normal histology at the GEJ, and technical difficulties during endoscopy.

The macroscopic component of the diagnosis is usually assessed at endoscopy. The columnar mucosa appears as a homogeneous salmon-colored, reddish, or velvet mucosa distinct from the whiter normal squamous epithelial lining. The columnar mucosa is located proximal to the GEJ, which is defined as the proximal extent of the gastric rugal folds.[8] Columnar mucosa distal to the GEJ is gastric mucosa. IM distal to the GEJ is gastric IM, is associated with *Helicobacter pylori,* and is not related to reflux disease. The columnar mucosa may be either circumferential and project in one or more "tongues" or simply appear as a more irregular or "zigzag" squamocolumnar junction (Z-line) proximal to the GEJ.

It is important to define the GEJ as the proximal extent of the rugal folds rather than as the squamocolumnar junction because the squamocolumnar junction migrates proximally in patients who have gastroesophageal reflux disease, with the greatest cephalad displacement by definition occurring in those with Barrett's esophagus.[9] If the proximal margin of the rugal folds is not distinct, some deflation of the stomach may be needed because with overinflation the folds can flatten out. The endoscopist must make a particular effort to examine the GEJ and squamocolumnar junction in all patients. If there is any doubt about the presence of Barrett's esophagus, biopsy samples should be taken from this area, and the pathology request form should ideally state as accurately as possible the location of the biopsy in relation to the GEJ and squamocolumnar junction. The exact location of a biopsy in relation to the GEJ is sometimes uncertain because of technical difficulties in performing endoscopy. This problem is more likely in patients with a large hiatal hernia, esophagitis, or stricture. It can be helpful in these cases to take an additional specimen from the gastric antrum or body to establish whether gastric *H. pylori* colonization is present. If *H. pylori* is absent, any IM found in the region of the GEJ or squamocolumnar junction is most probably from an area proximal to the GEJ and related to reflux disease. If *H. pylori* is found in the gastric antrum or body, other features can help distinguish esophageal IM from gastric IM, including the presence of esophageal mucosal or

submucosal glands or ducts,[10] the number of eosinophils, clinical features, and esophageal manometry and pH findings.[11,12]

The microscopic criterion for the definition of Barrett's esophagus requires detection of IM, which is defined by the presence of goblet cells. Goblet cells produce and contain mucin and are normally found in the small and large intestine, but not in the esophagus. They are identified on routine hematoxylin and eosin (H&E) staining by their round, weakly basophilic, cytoplasmic vacuole. H&E staining is sufficient to diagnose IM in most cases, but in equivocal cases, staining with alcian blue at pH 2.5 will help distinguish true goblet cells, which display strong positive blue vacuolar staining because of their acid mucin content, from "pseudogoblet" and "columnar blue" cells. Pseudogoblet cells are mucous cells lining the surface and foveolar regions and have cytoplasmic vacuoles containing neutral mucin. Although pseudogoblet cells are typically alcian blue negative, they may be weakly positive ("columnar blue" cells), in which case expert pathologic interpretation relying on cellular morphology will distinguish true goblet cells (IM) from non-IM mucosa. Some recommend selective, rather than routine use of alcian blue staining to confirm the presence of IM seen on H&E sections, thus limiting the likelihood of a false-positive diagnosis of IM because of the presence of alcian blue–positive pseudogoblet cells.[13]

If histopathology confirms the presence of IM, the length of Barrett's esophagus is defined as the distance from the GEJ to the most proximal extent of the macroscopic columnar-lined mucosa. The length of the Barrett's segment is thus not the length of IM. This distinction is important because of the zonation of epithelial types observed within the columnar mucosa.[2,3,5] When IM is present, it is situated most proximally within the columnar mucosa, immediately distal to the squamous mucosa. When IM and nonintestinalized columnar epithelium are both present, the IM is situated at this most cephalad zone, whereas the nonintestinalized epithelium is distal to the IM. Although a lack of zonation has been reported,[4,14] others with a large experience state that when present, IM is always found at the most proximal zone.[13] Consequently, the endoscopist should routinely biopsy this area in patients with suspected Barrett's esophagus.

The presence of Barrett's esophagus was previously defined according to the length of the columnar segment. The 3-cm rule stated that a 3-cm or greater length of macroscopic columnar mucosa was required to diagnose Barrett's esophagus. This rule was first suggested by Cedric Bremner at a 1983 conference in Chicago and was published shortly thereafter by Skinner et al.[15] and by Bremner.[16] Bremner recalls that "the reason why I suggested this was because of Hayward's paper [Hayward J: The lower end of the esophagus. Thorax 16:36-41, 1961]. [Hayward] stated that the normal esophagus could have a 2 cm length of columnar epithelium and so to avoid over-diagnosis of endoscopic Barrett's I suggested that we take 3 cm as the cut-off point" (Cedric Bremner, personal communication, 2005). Confusingly, a 2-cm rule was also used as an alternative to 3 cm.[8] Patients with columnar segments shorter than either of these lengths did not have Barrett's esophagus according to these older definitions.

The presence of IM was recognized as the critical factor for the definition of Barrett's esophagus after it was observed that goblet cells were not normally present in the esophagus and that the risk of malignant change was limited to those with IM.[5,15,17-19] Skinner wrote in 1989, "accordingly we now modify the definition of Barrett's esophagus to include all cases in which the metaplastic goblet cell–type of epithelium is found within the esophageal lumen at any level provided it is in continuity with gastric epithelium distally."[20] The length of the columnar segment is still used to define *long-segment Barrett's esophagus* (LSBE, also known as "traditional" Barrett's), in which the columnar segment is greater than 3 cm (or 2 cm) in length, and *short-segment Barrett's esophagus* (SSBE), in which the columnar segment is less than 3 cm (or 2 cm) in length. SSBE has been estimated as being 10 times more prevalent than LSBE.[21] Patients with LSBE have a greater likelihood of having more severe gastroesophageal reflux than patients with SSBE, as well as an incompetent lower esophageal sphincter,[22] but patients with SSBE are at risk for the development of Barrett's cancers.[23] The risk may be less than that in patients with LSBE, but a significant difference has not been shown.[24]

The term *ultrashort Barrett's esophagus* is a misnomer. It refers to the microscopic finding of IM in patients with no endoscopic columnar-lined esophagus. Because the macroscopic criterion for the definition of Barrett's is not met, these patients do not have Barrett's esophagus. Furthermore, the risk for malignant degeneration in these patients, though not accurately known, is very much less than in patients with Barrett's. A better term for these patients' condition is *cardiac mucosa with intestinal metaplasia* (CIM). This term does not include the words *Barrett's esophagus* and therefore does not have the potential for false alarm that the term *ultrashort-segment Barrett's esophagus* can have, particularly now that many patients research their diagnosis on the Internet.

Cardiac mucosa is a simple, mucinous columnar mucosa with foveolar hyperplasia, no parietal cells, and no goblet cells. It is found in the region of the GEJ in most adults in Western society. When present, it is almost invariably accompanied by an infiltrate of chronic or acute inflammatory cells and may thus be termed *carditis*.[25] In the past, it was believed that a length of cardiac mucosa was normally present in the most proximal section of the stomach, where it divides the gastric oxyntic mucosa from the esophageal squamous mucosa.[26] This prevailing view was challenged by a study suggesting that cardiac mucosa, rather than being a normally occurring mucosa, might be an acquired, metaplastic epithelium that develops in response to the reflux of gastric acid into the esophagus.[27] According to this hypothesis, the histology of a normal GEJ consists of squamous mucosa abutting gastric oxyntic mucosa, or the parietal cell–containing oxyntocardiac mucosa. Subsequent studies have confirmed that this histologic pattern—squamous epithelium directly abutting oxyntic

or oxyntocardiac mucosa—does occur.[28,29] Several lines of evidence indicate that cardiac mucosa is, like Barrett's esophagus, an acquired epithelium that develops in response to gastroesophageal reflux.[30-33] These findings have led to the controversial hypothesis that cardiac mucosa and CIM, though not satisfying the criteria for the definition of Barrett's esophagus, may be early stages in the development of Barrett's esophagus.[34,35]

Using the current definition, the first definite report of Barrett's esophagus was published in 1951 by Lewis H. Bosher, Jr., and Frederick H. Taylor from Barnes Hospital, St. Louis, Missouri.[36] Bosher and Taylor reported a single case, that of an obese 63-year-old woman admitted with severe dysphagia as the primary symptom. Esophagoscopy showed a stricture 23 cm from the incisors, with "heterotopic gastric mucosa" lining the tubular esophagus below this, and the stomach within the abdomen. Esophagectomy was performed to resect the stricture and because it was thought that there was a risk for malignancy. Several photomicrographs are shown in which the "heterotopic gastric mucosa" is clearly IM. Furthermore, the microscopic description notes that the abnormal mucosa was "composed of glands which contained goblet cells. . . ." One photomicrograph shows the transition section where squamous mucosa is abruptly replaced by IM.[36] The authors distinguish their case, in which there was a small, easily reducible hiatal hernia, from "thoracic stomach associated with short esophagus."

Norman Barrett's article "Chronic Peptic Ulcer of the Oesophagus and 'Oesophagitis' " was published in 1950, 1 year before Bosher and Taylor's publication, and is often cited as the first report of Barrett's esophagus (Fig. 22–1).[37] In this article Barrett, who practiced principally at St. Thomas' Hospital, London, reviewed all published cases and contributed four new cases of "chronic peptic ulcer of the oesophagus." He concluded that these esophageal ulcers were chronic gastric ulcers in association with a congenital short esophagus, thereby adding considerably to the confusion regarding their cause.[37] Allison and Johnstone termed these ulcers *Barrett's ulcers*,[38] and the gastric-type epithelium surrounding them came to be known as Barrett's esophagus. The eponymous term *Barrett's esophagus* resulted through no effort of Barrett himself, who used the term *the lower esophagus lined by columnar epithelium* for the title of a 1957 publication in the journal *Surgery*.[39]

Were these ulcers in fact located within a segment of columnar-lined Barrett's esophagus? It is not possible to be certain now, but it is likely that Barrett's cases included some true cases of Barrett's esophagus and also some that were not Barrett's esophagus.[40] By attempting to explain both pathologies as a single entity, Barrett was led into misunderstanding. Two features of the 1950 publication suggest that there may have been at least some true cases of Barrett's esophagus. First, Barrett redefined the esophagus in this article as "that part of the foregut . . . which is lined by squamous epithelium," thus suggesting that he had to resort to redefinition to account for the columnar mucosa within a structure that might otherwise have been esophagus. Second, he stated that "in cases of congenital short oesophagus . . . the bare area is larger than

Figure 22–1. Norman Barrett, senior surgeon at St. Thomas' Hospital, London, in 1958. (Courtesy of Julia Gough.)

usual."[37] With this comment Barrett seems to be attempting to explain the lack of a serosal surface on the columnar-lined gut above the diaphragm. Instead of the rather implausible suggestion that the absence of a serosal surface is due to an exceptionally large bare area of the stomach, it is reasonable to propose that there was no serosa because the columnar-lined intestine was esophagus. Although Barrett did not describe goblet cells within the "histologically gastric" mucosa, which would be expected in a long-segment columnar-lined esophagus, other publications, including the report by Bosher and Taylor, indicate that the pathologic nature of goblet cells in the stomach was not well appreciated at the time.[36] Barrett may thus not have thought it necessary to note the presence of goblet cells.

Other aspects of the publication indicate that at least some of the cases reported did not have Barrett's esophagus. Just as Barrett stated, these patients may have had a chronic peptic ulcer in an intrathoracic stomach, although the underlying abnormality was almost certainly herniation of the stomach through the esophageal hiatus rather than a congenital short esophagus. In support of this, Barrett stated that some cases of "congenital short oesophagus" had a partial covering of peritoneum above the crura (indicating that they were part of the stomach), and the case illustrated shows gastric rugal folds around the ulcer.[37] Finally, there is Barrett's reassessment of these ulcers and the columnar lining that surrounded them. Ten years after the initial report, when he had a greater understanding of esophageal mucosal disease, Barrett wrote, "ulcers that occur in the pouch of

stomach that forms a sliding hiatal hernia are true gastric ulcers (Barrett, 1950) and have nothing to do with reflux."[41] In 1962 he wrote, "some years ago I pointed out that when a piece of stomach passes into a sliding hiatal or a paraesophageal hernia, it is not unusual for a typical peptic ulcer to develop in the abnormally placed segment of the stomach. Such an ulcer (Barrett's ulcer) has the character of a typical gastric ulcer. . . ."[42]

Barrett was thus probably unknowingly describing two different pathologic entities, only one of which was Barrett's esophagus. His other problem was that he erroneously considered that his cases had a congenital short esophagus. This conclusion was not so unreasonable at the time as it appears now because congenital short esophagus was an accepted condition at the time.[7,43-46] Indeed, as late as the 1978 second edition of *Surgery of the Alimentary Tract* by Shackelford there is a section titled "Brachyesophagus (Abnormally Short Esophagus)" with four pages devoted to congenital short esophagus.[47] One of the patients whom Barrett himself had seen was a 13-year-old boy "who had several other congenital deformities."[37] Columnar mucosa was found up to the level of the aortic arch, and the boy died of perforation into a pulmonary vein. Barrett later recognized his (and others') error regarding the congenital short esophagus theory and stated in 1960 that "it would have been better if the term [congenital short esophagus] had never been introduced. . . ."[41]

Allison and Johnstone clarified matters considerably in their 1953 publication "The Oesophagus Lined with Gastric Mucous Membrane."[38] They examined 115 patients with esophageal ulcers and stenosis and found 7 with columnar-lined esophagus, 1 of whom had certain IM. Noting that the columnar segments had no serosal layer but did have esophageal musculature, submucosal glands typical of the esophagus, islands of squamous epithelium, and an esophageal blood supply, they demonstrated the esophageal rather than gastric location of the columnar mucosa. Allison et al. had previously reported on 10 patients with esophageal ulcers, esophageal shortening, and "gastric" mucosa distal to a stricture, but it is not clear that these were cases of columnar-lined esophagus rather than hiatal hernia.[45]

Microscopic examination demonstrating esophageal muscle fibers had also confirmed the true anatomy of the columnar lining in studies conducted in Paris by Jean-Louis Lortat-Jacob and his wife M. Smith-Lortat-Jacob.[48-52] J.-L. Lortat-Jacob created the term *endobrachyesophagus* for the lower esophagus "lined by gastric mucosa."[50] Smith-Lortat-Jacob submitted her thesis on cases of columnar-lined esophagus in 1950, the same year as Barrett's initial publication.[48] "Inspired by his wife's doctoral thesis"[52] and after "a courteous and intelligent 'face à face' across the Channel"[52] with Barrett, J.-L. Lortat-Jacob published his findings in 1957.[49] Stein and Siewert note that the terms *endobrachyesophagus* and *Barrett's esophagus* are used synonymously in Europe.[53]

Is it possible that Barrett's esophagus is a disease that appeared only around the middle of the last century? This seems unlikely because in 1953 Allison and Johnstone found as many as 11 patients with "gastric" mucosa in the esophagus among their 115 patients with esophageal ulcer and stenosis.[38] The prevalence of this disease in recent decades also argues against it being such a new disease. Autopsy studies estimate the prevalence to be 0.4% to 0.9% in the general population[54,55] and 3% to 12% in patients who undergo upper gastrointestinal endoscopy for the investigation of chronic reflux symptoms.[56-59] Endoscopy was not introduced until the late 1860s, but detailed autopsies were commonly performed in the 19th and early 20th centuries. All organs were examined at these autopsies and novel findings were reported regularly. It therefore seems likely that unless Barrett's esophagus was nonexistent or almost so, there should be some reports of columnar-lined esophagus before those of the 1950s. To investigate this hypothesis, some earlier publications that have been classified as early reports of columnar-lined esophagus are reviewed in the following text. These earlier descriptions all focus on esophageal ulcer and are reviewed only because they mention possible instances of columnar mucosa in the esophagus in association with the ulcers.

Alexander "Sandy" Lyall, from the Royal Infirmary and University in Glasgow, was a gifted investigator and physician who reported eight fatal cases of peptic ulcer of the esophagus in 1937.[60] The postmortem report on case 8, a Patrick C. aged 58 years who died of pneumonia but also had a large chronic distal esophageal ulcer, reads: "Closer examination of the mucous membrane in the region of the ulcer showed the presence of a remarkable state of affairs. The intact mucosa separating the lateral edges of the ulcer was found to be heterotopic gastric mucosa which extended as a tongue-shaped process of well-preserved tissue upwards from that of the fundus of the stomach." Microscopic examination showed that "the heterotopic gastric mucosa bore a resemblance to that found normally towards the pyloric end of the stomach, the glands being fairly short and wide. Oxyntic [parietal, HCl-secreting] cells were present, but were comparatively few in number."[60] This description of a tongue of columnar mucosa suggests that the patient had Barrett's esophagus, a possibility that is not excluded by the presence of a small number of parietal cells. Lyall cites articles by Fraenkel, Tileston, and Stewart and Hartfall as prior publications with heterotopic mucosa.

The case reported by Stewart and Hartfall in 1929, though sometimes listed as a report of Barrett's esophagus, is more likely to be one of only islet patches of columnar mucosa. The authors wrote that "a very interesting feature of the case here reported was the presence of two large patches of gastric mucous membrane in the upper oesophagus just below the level of the cricoid cartilage."[61] The illustration shows islets of columnar mucosa, the authors refer to islets, and they reference Schridde and Taylor, who also describe islet patches of columnar mucosa.[62,63] Whether nonislet (Barrett's) columnar-lined esophagus had been present inferior to these islets is unknown because the specimen had undergone extensive postmortem digestion in this region.[61]

In 1879 the great German physician Heinrich Irenaeus Quincke (Fig. 22–2) described three cases of esophageal ulceration with microscopic features

Figure 22–2. Heinrich Irenaeus Quincke, Geheimer Medizinalrath and chair of medicine at Bern and subsequently Kiel. Quincke's 1879 description of columnar mucosa in the esophagus may have been the first report of Barrett's esophagus.

"[usually only found in the stomach or small intestine]."[64,65] This report was perhaps the first of Barrett's esophagus and is also credited as being the first report of a Mallory-Weiss tear. It was one of many contributions by Quincke (1842-1922), whose teachers included Virchow, Heimholtz, and Wilms. Quincke was appointed to the chair in medicine at Bern, Switzerland, at the age of 31 and gave his name to seven medical eponyms. His greatest contribution is considered to be the introduction of lumbar puncture.

Wilder Tileston, from Boston, Massachusetts, reviewed the history of "ulcer of the oesophagus, resembling peptic ulcer of the stomach" in 1906 and noted that they were first described by Albers in 1839, their existence was supported by Rokitansky but denied by Zenker and Birch-Hirschfeld, and the matter was conclusively settled by Quincke's detailed report (1879) of three "clearly proved" cases.[64,66] Tileston excluded all cases reported before Quincke because of uncertainty of diagnosis but reviewed the 41 subsequently published cases and added 3 new cases of peptic ulcer of the esophagus. Microscopic examination was reported in only 14 of these 44 cases, but in 1 of these cases, reported by Fraenkel in 1899, there were "gastric glands present in oesophagus" with an ulcer at the cardioesophageal junction.[66,67] Tileston's first personal case might have had Barrett's esophagus. The patient had a large distal esophageal ulcer with perforation, and on microscopy, "near the edge of the ulcer, in the submucosa, [was] a large group of glands with columnar epithelium, resembling mucous glands in structure." The mucosa was absent because of postmortem digestion. Tileston's other two personal cases—and almost all of the other published cases—are not suggestive of Barrett's esophagus but are seemingly reports of acute esophageal ulcer.[61]

It therefore seems likely, though admittedly uncertain, that Quinke in 1879, Fraenkel in 1899, Tileston in 1906, and Lyall in 1937 reported cases of Barrett's esophagus, and this condition has thus been occurring for more than 100 years. The focus of reports before the 1920s was on associated esophageal pathology, especially esophageal ulcer, lethal conditions were the primary interest, and autopsy was the predominant means of diagnosis. Large autopsy series with detailed examination of all organs were performed and reported. It seems reasonable to conclude that Barrett's esophagus must have been a rare disease before the second half of the 20th century. Lyall's 1 possible case, for example, was found in a series of 1500 postmortem examinations performed over the 4 years in which they "examined specially the oesophaguses."[60] Similarly, Stewart and Hartfall's case of an islet of columnar mucosa "is the first which we have encountered in over 10,000 autopsies performed during the last 18 years," thus suggesting that there were no true cases of Barrett's esophagus among this large number of postmortem examinations.[61] With the more widespread introduction of endoscopy and the consequent increased emphasis on more benign conditions, larger series of esophageal diseases were reported, but there were still very few reports of columnar mucosa in the esophagus, and the possibility that it was not "gastric heterotopia" was not realized until the 1950s. Reasons for the undoubtedly real increase in the incidence of both Barrett's esophagus and esophageal adenocarcinoma since the mid-20th century are beyond the scope of this chapter but discussed elsewhere.[68]

It is similarly difficult to be certain about the first report of Barrett's adenocarcinoma. Morson and Belcher's 1952 report of a case of esophageal adenocarcinoma arising above a columnar-lined esophagus, with the presence of IM noted, is usually credited as being the first definite report,[2] but there are several earlier reports of probable Barrett's-associated adenocarcinoma.[7,69-72] The development of esophageal cancer in association with a chronic "peptic" ulcer of the esophagus was described by Ortmann in 1901,[65] and Tileston wrote in 1906 that he had seen a similar specimen in Vienna.[61,66] Adler clarified the association between Barrett's esophagus and adenocarcinoma.[73]

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Chapter

23

Pathophysiology of the Columnar-Lined Esophagus

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Gastroesophageal reflux disease (GERD) affects an estimated 20% of the population, and with direct and indirect costs exceeding $10 billion annually, it is the costliest gastrointestinal disorder in the United States.[1] Much of this extraordinary sum goes to pay for increasingly more potent and widely prescribed medications to suppress gastric acid production. Although these medications have been proved to relieve heartburn symptoms and heal esophagitis, they have failed to alter the malignant complications of reflux disease. The prevalence of Barrett's esophagus has been increasingly steadily in many Western countries, and in the United States the incidence of esophageal adenocarcinoma continues to increase faster than any other malignancy. Currently, it is outpacing the next closet cancer, melanoma, by a factor of 3.[2]

Because the esophagus is normally lined by squamous mucosa, it is clear that for adenocarcinoma to develop there must be a sequence of events that results in transformation of the normal squamous mucosa into columnar epithelium. This sequence begins with gastroesophageal reflux, and with continued injury, cardiac mucosa replaces the squamous mucosa in the distal esophagus. Subsequently, goblet cells indicative of intestinal metaplasia develop, and when there is a visible segment of columnar mucosa in the distal esophagus that shows intestinal metaplasia on biopsy, the criteria for Barrett's esophagus has been met. Barrett's esophagus is the precursor lesion for one of the most lethal malignancies that occurs in humans, esophageal adenocarcinoma.

DEFINITION

The definition of Barrett's esophagus has undergone many modifications and refinements as our understanding of the pathophysiology of this condition has evolved. In 1950 Dr. Norman Barrett described a columnar-lined foregut structure in the chest that he postulated to be a pouch of stomach that had herniated into the thorax secondary to either scarring or a congenitally shortened esophagus.[3] Shortly thereafter, however, Allison and Johnstone argued that the presence of esophageal submucosal glands indicated that this columnar-lined tubular structure was in fact esophagus.[4] In 1957 Barrett concurred and concluded that the normal squamous lining of the distal esophagus had been replaced by columnar mucosa in these patients.[5] Subsequently, a columnar-lined esophagus became known as Barrett's esophagus.

The first alteration in the definition of Barrett's esophagus came after John Hayward suggested that a junctional or buffer zone of columnar mucosa up to 2 cm in length was normally present at the gastroesophageal junction.[6] Despite the absence of supporting data or proof for this statement in his 1961 publication, Hayward's concept became widely accepted. This prompted concern regarding the potential for overdiagnosis of Barrett's esophagus given that up to 2 cm of columnar mucosa was considered normal, and by the 1980s it was necessary to have a minimum of 3 cm of columnar mucosa in the distal esophagus to make the diagnosis of Barrett's.[7]

Whereas all these modifications focused on the length of the columnar segment, Paull and colleagues introduced an entirely new concept by focusing on the histology of the columnar mucosa of Barrett's esophagus.[8] Using manometrically guided biopsies the authors reported that three types of columnar mucosa could be found in Barrett's esophagus: fundic, cardiac, and intestinal. Despite Paull and colleagues' detailed description, little significance was given to the histology of Barrett's until reports began surfacing in the 1980s that the intestinal type of Barrett's was the only one associated with the development of adenocarcinoma of the esophagus.[7,9,10] The critical importance of the histologic finding of goblet cells within a columnar-lined esophagus was thus

established, and the *definition of Barrett's esophagus* now requires *both* an endoscopically visible segment of columnar lining in the distal esophagus *and* intestinal metaplasia on biopsy. A visible segment of columnar mucosa in the distal esophagus that does not have intestinal metaplasia on biopsy is not considered Barrett's esophagus and should be referred to simply as a columnar-lined esophagus. The premalignant significance of intestinal metaplasia on biopsy has relegated the length of the columnar segment to secondary importance. By current convention, *long-segment Barrett's* has intestinal metaplasia within a columnar-lined segment in the distal esophagus that is 3 cm or greater in length, whereas lengths less than 3 cm are called *short-segment Barrett's*. The finding of intestinal metaplasia within cardiac mucosa from an endoscopically normal-appearing gastroesophageal junction is not considered Barrett's esophagus and, instead, is called *intestinal metaplasia of the cardia (CIM)*.

EPIDEMIOLOGY

The prevalence of Barrett's esophagus appears to be increasing in the Western world. It has been debated whether this increase represents a true rise in incidence or is secondary to a heightened awareness of the dangers of reflux disease among practitioners and increased use of upper endoscopy to evaluate patients with reflux symptoms.[11] The most convincing epidemiologic evidence that the prevalence of Barrett's is actually increasing comes from a recent study in the Netherlands using their Integrated Primary Care Information database, which contains more than 500,000 computerized patient records. In this study there was a linear increase in the diagnosis of Barrett's that was even more pronounced if the increase was based on the number of upper endoscopies performed during the same period (from 19.8/1000 upper endoscopies in 1997 to 40.4/1000 upper endoscopies in 2002).[12] Epidemiologic studies in England have also demonstrated an age-specific increase in the prevalence of Barrett's per 100 upper endoscopies during the years 1982 to 1996.[13]

Thus, there is evidence that the prevalence of Barrett's is increasing, but it is clear that the true prevalence of Barrett's in the population is unknown and probably much higher than what would be expected based on clinical cases diagnosed by upper endoscopy. In one of the few autopsy studies that evaluated the prevalence of Barrett's, Cameron et al. found 376 cases per 100,000 people in Olmsted County, Minnesota.[14] This rate was approximately five times higher than the clinical prevalence of Barrett's in this same area (82.6 per 100,000). Further support for the concern about a large subclinical population of individuals with Barrett's comes from a study conducted in veterans by Gerson and colleagues.[15] They performed upper endoscopy in a group of patients undergoing routine sigmoidoscopy for colorectal cancer screening, none of whom had symptoms of reflux. Although there are obvious limitations to a study primarily involving older, white male military veterans, their finding that 25% of the patients had Barrett's is nonetheless concerning because on the basis of symptoms none of these patients would have been recommended to undergo upper endoscopy. These observations suggest that Barrett's goes undiagnosed in the majority of individuals, either because they ignore minor reflux symptoms or, as the study in veterans suggests, because they are truly asymptomatic.

RISK FACTORS FOR BARRETT'S ESOPHAGUS

Most studies of risk factors have focused on the more definitive end point of adenocarcinoma of the esophagus, and thus there are relatively few studies that specifically evaluate risk factors for Barrett's. However, because Barrett's is the leading risk factor for esophageal adenocarcinoma and both Barrett's and esophageal cancer are linked to gastroesophageal reflux, it is reasonable to extrapolate some of the risk factors defined for adenocarcinoma to Barrett's as well. The most significant risk factor for the development of Barrett's esophagus is longstanding GERD. Case-control studies have shown that individuals with the highest risk for Barrett's esophagus are those in whom reflux symptoms develop at an early age and thus have a long duration of symptoms.[16] Other risk factors for Barrett's esophagus include anatomic and physiologic abnormalities that predispose to severe gastroesophageal reflux, including the presence of a mechanically defective lower esophageal sphincter and a large hiatal hernia.[17] Most significantly, however, the factor that separates patients with reflux *and* Barrett's from those with reflux but *without* Barrett's is the composition of the refluxate, specifically, the presence of bile.[17,18]

Additional risk factors for Barrett's esophagus include age and gender. The prevalence of Barrett's increases in a linear fashion with age, starting at about 20 years old and peaking in the 70- to 79-year-old group.[13] The increase in females appears to start about 20 years later than in males, and the finding that females with Barrett's tend to be older than males with Barrett's has been shown in a number of studies.[13,18] Male gender is also a risk factor for Barrett's, but the explanation for this observation has not been clear until recently. We studied a large and carefully evaluated group of 796 patients with reflux symptoms, including 146 males and 63 females with Barrett's, and found that on average, females had less severe reflux disease than males did. Importantly, females with severe reflux were just as likely to have Barrett's as males with severe reflux, thus suggesting that it is the reduced prevalence of severe reflux rather than any protective effect of being a female that explains the significant sex difference in the prevalence of Barrett's.[18]

Ethnicity is another risk factor for Barrett's esophagus, with white individuals being at highest risk and Asians at the lowest.[19] However, these demographics are changing, perhaps as a result of the spread of fast food and a Western diet around the world. A recent study from Malaysia, where the population is composed equally of Malays, Chinese, and Indians, found an overall 6.2% prevalence of Barrett's, which is similar to that reported

in many Western countries.[20] In another study, the prevalence of Barrett's in Hispanic Americans was found to be similar to that in white Americans.[21] Thus, it is becoming apparent that diet and lifestyle may play a more important role in reflux disease and Barrett's than do biologic differences between ethnic groups, although the lower frequency of Barrett's and esophageal adenocarcinoma in African Americans remains unexplained.[22,23]

The observation that the prevalence of Barrett's increases with advancing age is strong evidence that the condition is acquired. However, the possibility that there is a genetic risk factor for Barrett's esophagus and esophageal adenocarcinoma has emerged after the publication of case reports that describe finding Barrett's in multiple members of the same family and even in identical twins.[24-26] Further support for a genetic link comes from a cohort study by Chak and colleagues, where a positive family history of Barrett's esophagus or esophageal adenocarcinoma was significantly more common in white patients with Barrett's esophagus than in a GERD control group with a negative family history. In this study a positive family history increased the risk for Barrett's by 12-fold.[27] Others, though, have not confirmed this association. Romero et al. noted an increased prevalence of esophagitis in the relatives of Barrett's patients, but they found that increasing age and a longer duration of symptoms were stronger risk factors for Barrett's than a family history of Barrett's esophagus or esophageal adenocarcinoma.[28] Thus, a definitive genetic risk factor or "Barrett's gene" has not been proved to exist; instead, a predilection for severe GERD appears to run in families. There also seems to be individual variations in susceptibility to the development of Barrett's. Support for this concept comes from an intriguing finding by Oberg et al. in a study of the prevalence of cardiac mucosa and Barrett's after esophagectomy.[29] The authors evaluated the residual cervical esophagus above the anastomosis after esophagectomy and gastric pull-up. At the time of surgery the esophageal resection margins were pathologically shown to be squamous mucosa, and on follow-up upper endoscopy the authors found that columnar mucosa had developed in 47% of these patients. Interestingly, the likelihood of finding columnar mucosa above the anastomosis was higher in patients who underwent esophagectomy for adenocarcinoma than in those who underwent it for squamous carcinoma.

Other purported risk factors for reflux, Barrett's esophagus, or esophageal adenocarcinoma include obesity and dietary factors or medications that reduce the resting tone of the lower esophageal sphincter. The association between obesity and reflux disease is well established, but an association between obesity and Barrett's esophagus or esophageal adenocarcinoma has not been conclusively demonstrated.[17,30-33] These findings suggest that although obesity may predispose an individual to reflux disease, it does not appear to be an independent risk factor for Barrett's esophagus or esophageal adenocarcinoma. However, there is evidence linking medications that relax the lower esophageal sphincter with an increased risk for esophageal adenocarcinoma and, by inference, reflux disease and Barrett's.[34] Interestingly, the use of acid-suppression medications has also been linked with a nearly threefold increase in the risk for esophageal adenocarcinoma, even when adjustments were made for the severity of reflux symptoms.[35] Thus, the widespread use of medications that affect gastric acidity and the function of the lower esophageal sphincter may be involved in the increasing prevalence of Barrett's esophagus and esophageal adenocarcinoma.

PATHOPHYSIOLOGY

The development of Barrett's is probably a two-step process. The first step involves the transformation of normal esophageal squamous mucosa to a simple columnar epithelium called cardiac mucosa. This conversion occurs in response to chronic injury produced by repetitive episodes of gastric juice refluxing onto the squamous mucosa. The change from squamous to cardiac mucosa probably occurs relatively quickly, within several years.[29] The second step in the pathophysiology of Barrett's is the development of goblet cells indicative of intestinal metaplasia within the columnar cardiac mucosa. There is evidence that this step proceeds over a period of 5 to 10 years.[29] Once present, Barrett's esophagus can progress to low- and high-grade dysplasia and ultimately to adenocarcinoma. This entire process is commonly described as the Barrett's metaplasia-dysplasia-carcinoma sequence.

Step 1: Metaplastic Columnarization with Cardiac Mucosa

To understand what constitutes a columnar-lined esophagus, an understanding of the anatomy and histology of the normal gastroesophageal junction is required. Unfortunately, the very definition of what is normal in this area remains controversial, with much debate centered on whether cardiac mucosa is normally present at the gastroesophageal junction. Although our understanding is gradually improving, Hayward's remark in 1961 that "the lower end of the oesophagus is a region where the pathology, the physiology, and even the anatomy are not quite clear" remains appropriate even today.[6] In one of the first reports describing the normal gastroesophageal junction, Hayward indicated that a junctional or buffer zone of columnar mucosa was normally interposed between the acid-secreting oxyntic gastric mucosa and the acid-sensitive squamous esophageal mucosa.[6] Though an appealing concept, Hayward provided no data in support of his theory and did not discuss the role of the lower esophageal sphincter, which had been demonstrated to exist before his publication. According to Hayward, this junctional mucosa was "normally" found in a length of up to 2 cm at the gastroesophageal junction. He also noted the following about this junctional mucosa: (1) it was histologically distinct from normal gastric fundic and pyloric epithelium, (2) it did not secrete acid or pepsin but was resistant to both, (3) it was not congenital but acquired, (4) it was mobile and varied in length—creeping progressively higher into the esophagus with continued

gastroesophageal reflux, and (5) it was potentially reversible with correction of reflux. Furthermore, he pointed out that it was located in the esophagus and that it developed in association with gastroesophageal reflux.[6]

Now, over 40 years later, there is still dispute about the histology of the normal gastroesophageal junction. The preponderance of autopsy and clinical biopsy data suggest that in a normal individual, squamous esophageal mucosa transitions directly to oxyntic gastric mucosa at the gastroesophageal junction.[36,37] This situation is present in most children and adults younger than 20 years. However, in older adults, cardiac mucosa can be found in biopsy specimens from the gastroesophageal junction in approximately 50% of individuals, and the prevalence increases with age and the severity of reflux.[38,39] One center still disputes these findings and suggests instead that 1 to 4 mm of cardiac mucosa is a normal finding at the gastroesophageal junction. However, their definition of cardiac mucosa includes columnar cells with glands containing parietal cells, and this casts some doubt on their conclusions.[40,41] Nonetheless, it is clear that Hayward's concept is incorrect and that normally there is no cardiac mucosa or at most 4 mm of cardiac mucosa in the distal esophagus at the gastroesophageal junction. Longer lengths of cardiac mucosa are acquired secondary to chronic gastroesophageal reflux.

Supporting evidence for the concept that cardiac mucosa is acquired is derived from both clinical and experimental studies. Experimental evidence comes from a 1970 study by Bremner and colleagues in which a series of dogs underwent stripping of the distal esophageal squamous mucosa with or without cardioplasty to destroy the function of the lower esophageal sphincter. Squamous re-epithelialization occurred in animals without gastroesophageal reflux, whereas in animals with reflux after cardioplasty, the esophagus was re-epithelialized by a columnar epithelium that lacked submucosal glands and parietal cells—the equivalent of cardiac mucosa in humans.[42] There is also clinical evidence in humans that columnar mucosa can replace normal esophageal squamous epithelium in the setting of gastroesophageal reflux. After esophagectomy with gastric pull-up, reflux of gastric juice into the residual esophagus is common because there is no lower esophageal sphincter and a large hiatal hernia has been created. Postoperative endoscopy has revealed that in many of these patients columnar epithelium histologically identical to cardiac mucosa develops proximal to the anastomosis in the residual esophagus, in what had pathologically been proved to be squamous mucosa at the time of the operation. Several series have shown that this process is common and occurs in 50% or more of patients after esophagectomy with gastric pull-up. Furthermore, cardiac mucosa developed within 2 years of esophagectomy in many patients and was observed to increase in length with longer follow-up.[29,43-46] Importantly, the cardiac mucosa that develops in these patients proximal to the esophagogastric anastomosis has been shown to be biochemically similar to the cardiac mucosa found in unoperated patients at the native gastroesophageal junction.[43]

Additional support for the concept that cardiac mucosa is acquired comes from the fact that it is not found anywhere else in the gastrointestinal tract and, when present at the gastroesophageal junction, is always inflamed and demonstrates reactive changes unrelated to either *Helicobacter pylori* infection or mucosal disease elsewhere in the stomach.[47] This is atypical for normal epithelium. Moreover, the presence of cardiac mucosa can be correlated with objective markers of GERD, including an incompetent lower esophageal sphincter, increased esophageal acid exposure on 24-hour pH monitoring, a hiatal hernia, and erosive esophagitis.[39]

The earliest manifestation of GERD may in fact be the presence of microscopic foci of cardiac mucosa at the gastroesophageal junction. This leads to the question of why the finding of a microscopic length of cardiac mucosa at the gastroesophageal junction is so common, even in patients without the typical reflux symptoms of heartburn or regurgitation. Probably this is related to the pathophysiology of early reflux disease. Evidence is accumulating that reflux disease begins with gastric distention after large and particularly fatty meals. Gastric distention leads to effacement of the lower esophageal sphincter and exposure of the squamous mucosa at the distal extent of the sphincter to gastric juice. The pathophysiology of the gastroesophageal junction has best been studied by Fletcher et al. They noted that the gastric distention that occurs with eating can cause the lower esophageal sphincter to unfold by almost 2 cm in normal volunteers.[48] In addition, they identified an unbuffered acid pocket at the gastroesophageal junction after a meal, a phenomenon they attributed to gastric juice floating on a lipid layer after the ingestion of fatty food. By pulling back a pH catheter before and after a meal they were able to show that the pH step-up corresponding to the functioning lower esophageal sphincter moved proximally with gastric distention secondary to unfolding of the distal portion of the sphincter. By measuring acid exposure with a pH catheter positioned at the squamocolumnar junction and another located 5.5 cm proximal to the squamocolumnar junction, Fletcher et al. demonstrated significantly greater acid exposure at the squamocolumnar junction (median total percent time that the pH was less than 4, 11.7% versus 1.8% 5.5 cm proximal to the squamocolumnar junction).[49] This study confirmed the presence of significant acid exposure at the most distal intrasphincteric segment of the esophagus in patients with otherwise normal acid exposure 5.5 cm proximal to the squamocolumnar junction. These findings were subsequently extended when it was demonstrated that salivary nitrite is rapidly converted to nitric oxide when it comes in contact with gastric acid–containing physiologic levels of ascorbic acid, and this reaction was found to be maximal at the gastroesophageal junction.[50] The levels of nitric oxide generated at the gastroesophageal junction were potentially mutagenic and may play a role in the pathophysiology of this region.

It is likely that continued injury to the distal esophagus and lower esophageal sphincter leads to progressive loss of the abdominal length of the sphincter. What started as transient sphincter unfolding with gastric

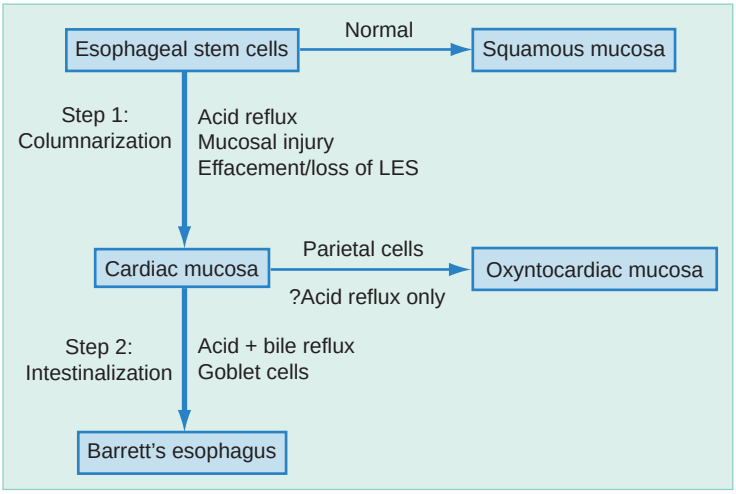

Figure 23–1. Hypothesis for the development of columnar mucosa in the esophagus. LES, lower esophageal sphincter.

distention gradually progresses to permanent sphincter destruction. With destruction of the sphincter, reflux disease is allowed to explode into the esophagus and can lead to an increase in the length of cardiac mucosa, either as tongues or as a circumferential replacement of the distal esophageal squamous mucosa. This leads to progressive migration of the squamocolumnar junction further proximally.[51,52] Confirmation of esophageal submucosal glands deep to areas lined by cardiac mucosa provides clear evidence that the development of cardiac mucosa is occurring in the esophagus in areas previously covered with squamous mucosa and not in the proximal part of the stomach.[52]

The precise details of the molecular mechanism by which squamous mucosa is transformed into cardiac mucosa remain unknown. However, there is probably a critical interaction between normally sequestered esophageal stem cells and an intraluminal stimulus that drives this metaplastic process. Tobey et al. demonstrated that exposure of esophageal squamous mucosa to gastric juice produces dilated intercellular spaces that allow molecules up to 20 kD in size to permeate down to the stem cells in the basal layer.[53] Perhaps the sensation of heartburn occurs as a result of stimulation of sensory afferent nerves by diffusion of hydrochloric acid through these intercellular spaces.[54] These ultrastructural changes occur before gross or microscopic changes become apparent. Thus, one possibility is that factors present in the refluxed juice that gain access to the basal layer stem cells via these dilated intercellular spaces induce a phenotypic transformation such that cardiac columnar mucosal cells rather than squamous cells are produced.

In summary, there is increasing evidence that at a normal gastroesophageal junction, squamous esophageal mucosa transitions directly with oxyntic mucosa of the stomach. Effacement of the lower esophageal sphincter occurs with gastric distention and leads to exposure of the distal esophageal squamous mucosa to acidic gastric juice. In combination perhaps with the generation of nitric oxide from salivary nitrite there is progressive injury to the lower esophageal sphincter, which in some patients leads to destruction of the sphincter and escape of gastric juice proximally into the distal esophagus. The development of dilated intercellular spaces in the squamous epithelium in response to repetitive acid exposure may expose esophageal stem cells to components of the refluxate that stimulate a phenotypic change from squamous to columnar cardiac mucosa. Progression of reflux disease leads to a gradual migration of the squamocolumnar junction proximally and increasing lengths of cardiac mucosa in the distal esophagus.

Pathophysiology—Step 2: Intestinalization of Cardiac Mucosa

Cardiac mucosa is thought to be an unstable epithelium, in part because of the severe inflammatory and reactive changes noted on histologic examination. It is hypothesized that cardiac mucosa progress down one of two possible pathways based on a combination of environmental and genetic factors (Fig. 23–1). One pathway involves the expression of gastric genes and leads to the formation of parietal cells within cardiac mucosa. Gastric differentiation leads to a mucosa called oxyntocardiac mucosa, and this is thought to represent a regressive or favorable change because oxyntocardiac mucosa is not premalignant and appears to be protected from the development of intestinal metaplasia. In the second pathway, expression of intestinal genes causes the formation of goblet cells within cardiac mucosa. In contrast to gastric differentiation, intestinal differentiation represents a progressive or unfavorable change because this mucosa is premalignant. Both oxyntocardiac mucosa and Barrett's esophagus have less inflammation than cardiac mucosa does, which suggests that these mucosal types are more stable epithelia.[55]

The development of goblet cells marks the transformation of cardiac mucosa to intestinal metaplasia. When an endoscopically visible length of this mucosa is present in the esophagus, the definition of Barrett's esophagus has been met. Although gastroesophageal reflux is known to be the primary factor responsible for the

development of Barrett's esophagus, the specific cellular events that lead to the transformation of cardiac mucosa to intestinalized cardiac mucosa are unknown. However, evidence is accumulating that intestinalization requires a specific condition or stimulus and that Barrett's occurs in a stepwise process. The first step, from squamous to cardiac mucosa, probably occurs in response to acid reflux. The second step, development of intestinal metaplasia, probably occurs in response to a different type of luminal insult. Numerous studies have demonstrated that although isolated acid reflux can cause esophagitis, Barrett's esophagus is associated with the presence of a mixture of both acid and bile salts.[56-58] Furthermore, clinical experience dating back 30 years has suggested a role for refluxed bile in the development of intestinal metaplasia. In 1977 Hamilton and Yardley observed the development of columnar mucosa and intestinal metaplasia above the esophagogastric anastomosis in a group of patients after esophagectomy. They noted that "severe symptoms of gastroesophageal reflux and bile staining of the refluxed material were documented only in the group with Barrett's. In addition, pyloroplasty had been performed more commonly in this group."[59] Recently, in two separate analyses of patients who had reflux with and without Barrett's, we found that the factor most associated with the presence of Barrett's esophagus in both males and females with GERD was abnormal bilirubin reflux as determined by Bilitec monitoring.[17,18] Interestingly, although all the patients in these studies had increased esophageal acid exposure by 24-hour pH monitoring, the necessity of acid in the refluxed material for Barrett's to develop is unclear. Scattered reports describing the development of Barrett's esophagus after total gastrectomy have circulated for a number of years, but a recent study clearly documents this process in eight patients at a median of 9 years postoperatively.[60] The authors noted that Barrett's was most likely to develop in patients with a reconstruction that permitted bile reflux into the esophagus. However, only one patient in this series had cardiac mucosa without intestinal metaplasia in the esophagus. This stands in stark contrast to the frequent development of cardiac mucosa in the residual esophagus after esophagectomy with gastric pull-up and supports the concept that cardiac mucosa develops in response to acidic reflux.[60,61]

Fitzgerald and colleagues reported several interesting observations on how the dynamics of mucosal exposure to luminal contents may affect columnar epithelial cell proliferation and differentiation. Using cultured human Barrett's biopsy specimens they demonstrated that continuous exposure to acidic media at pH 3.5 resulted in increased villin expression (a marker for epithelial cell differentiation) and reduced cell proliferation. Villin expression was not detected when the culture media was made more acidic (pH <2.5). In contrast, a dramatic increase in proliferation occurred when the Barrett's tissue was exposed to a short (1 hour) pulse of acidic media (pH 3.5) followed by a return to neutral pH.[62] Clinically, this same group has noted that effective acid suppression results in a shift of Barrett's epithelium away from proliferation toward differentiation.[63] However, the cellular consequences of duodenogastroesophageal reflux in the setting of gastric alkalization with acid-suppression medications were not addressed in this study.

It is hypothesized that the mechanism by which acid and bile interact to cause Barrett's esophagus is related to the ionized state of bile salts.[64] It appears that in a weakly acidic environment certain bile acids are particularly toxic. At a pH in the 3 to 6 range these bile salts are soluble and nonionized and can enter mucosal cells, accumulate, and cause direct cellular injury.[65] When the luminal pH is higher than their pK_a, these same bile acids are ionized and cannot cross the phospholipid membrane. Furthermore, when the luminal pH is lower, as it normally is in the stomach, bile acids precipitate out of solution and are harmless.[66] Thus, it is only at this critical pH range of 3 to 5 that certain bile acids become un-ionized and able to cross the cell membrane. Once inside the cell the pH is 7, and the bile acids become ionized and are trapped inside the cell, where they have been shown to result in mitochondrial injury, cellular toxicity, and mutagenesis.[67-70] Consequently, this midrange gastric pH of 3 to 5 is a danger zone for patients with duodenogastroesophageal reflux.

It remains uncertain whether the transformation of cardiac mucosa to intestinalized cardiac mucosa represents a phenotypic change secondary to the induction of genes or a mutational event within the columnar cells. Mendes de Almeida and colleagues have demonstrated biochemically that both cardiac mucosa and intestinal metaplasia express sucrase-isomaltase and crypt cell antigen—two small intestine marker proteins; however, in this study only three patients with cardiac mucosa were evaluated.[71] Kiron Das has developed a murine monoclonal antibody (DAS-1) that reacts specifically with normal colonic epithelial cells, and he subsequently found that it also reacts with an unknown epitope in Barrett's mucosa.[72] Griffel and colleagues reported that the DAS-1 antibody stained cardiac mucosa without intestinal metaplasia in seven patients and that histologic evidence of intestinalization on repeat biopsy samples later developed in six of the seven patients.[73] Likewise, we noted that the pattern of immunostaining with cytokeratins 7 and 20 was similar in cardiac mucosa and Barrett's.[74] These findings suggest that cardiac mucosa and intestinal metaplasia are biochemically similar and that cardiac mucosa is the precursor of intestinalized columnar epithelium, or Barrett's esophagus.

Currently, Barrett's esophagus is divided into short (<3 cm) and long (≥3 cm) segment types based on the endoscopically determined length of the columnar streak or column in the distal esophagus. Clinically, patients with long-segment Barrett's tend to have more severe reflux disease than do those with short-segment Barrett's. Patients with long-segment Barrett's have a higher prevalence of hiatal hernia, more commonly have a defective lower esophageal sphincter, and demonstrate greater esophageal acid and bilirubin exposure on 24-hour pH and Bilitec monitoring.[56,75] Despite the differences in length, there is evidence that short- and long-segment Barrett's are biochemically similar.[74,76] This finding is supported by the clinical observation that the risk for malignancy is similar in both short- and long-segment Barrett's esophagus.[77]

The presence of goblet cells is the sine qua non of Barrett's esophagus. The likelihood of finding intestinalization correlates with the length of the columnar segment, and once 4 cm of cardiac mucosa is present in the distal esophagus, nearly all patients will be found to have intestinal metaplasia on biopsy.[75,78] However, the location of goblet cells in a columnar-lined segment is not uniform, and often the entire length of columnar esophagus does not demonstrate intestinal metaplasia. Goblet cell density is greatest near the squamocolumnar junction and becomes more variable distally.[55] In other words, if intestinal metaplasia is present within a columnar-lined segment of the esophagus, it will always be present proximally at the squamocolumnar junction. Goblet cells may extend throughout the entire length of the columnar segment, but they might not. Interestingly, the length of Barrett's is determined by the endoscopic length of columnar mucosa and not by the length of mucosa showing intestinal metaplasia. In other words, a 6-cm segment of columnar mucosa with intestinal metaplasia only at the proximal 1 cm is still considered long-segment Barrett's esophagus, but the clinical behavior of this long-segment Barrett's may differ substantially from a 6-cm segment of columnar mucosa with intestinal metaplasia throughout the entire length. The current definition of Barrett's does not take this issue into account.

The time course for the development of goblet cells is uncertain, but it appears to take a minimum of 5 to 10 years.[64,79] Studies involving esophagectomy patients indicate that cardiac mucosa develops rapidly, often within 1 to 2 years. Intestinalization of the columnar segment in these patients occurs significantly later, typically after another 3 to 5 years.[44-46,59,61] These findings may reflect an accelerated course of events because these patients often have significantly greater reflux of acid and bile than the typical patient with GERD does. However, this clinically relevant human model does demonstrate the two-step process of Barrett's, starting with columnarization and subsequently followed by intestinalization in some patients.

The molecular mechanisms by which cardiac mucosa acquires goblet cells remain to be elucidated. However, there is increasing evidence that expression of the homeobox gene *Cdx2* plays a pivotal role. Expression of this gene increases with progression from squamous mucosa with esophagitis to cardiac mucosa and is maximal in the setting of intestinal metaplasia.[80-82] Experimental work suggests that *Cdx2* expression can be modulated by the pH of luminal material.[83] Furthermore, an individual's response to an inflammatory stimulus may also participate in the mucosal adaptation to reflux disease. Fitzgerald et al. have demonstrated that esophagitis and Barrett's esophagus have distinct cytokine profiles that reflect different inflammatory responses to reflux-induced injury.[84] Moreover, even within a given Barrett's segment, the inflammatory response is more severe at the proximal extent near the squamocolumnar junction, which may explain the greater tendency for intestinalization to occur at this location.[85] In addition, the specific cytokine polymorphism of a given individual may influence the development of Barrett's esophagus. Preliminary work from Gough and colleagues, for example, has demonstrated that specific polymorphisms of interleukin-1 receptor antagonist and interleukin-10 are more common in patients with Barrett's than in those with esophagitis.[86] Thus, a genetically determined inflammatory response to reflux may influence the pathway of disease in each individual patient.

In summary, the second step in the formation of Barrett's esophagus involves the development of goblet cells within cardiac mucosa, a reflection of intestinalization of this columnar epithelium. The acquisition of goblet cells appears to be related to the composition of the refluxed material, particularly the presence of bile acids within the refluxed material. If present, goblet cells will always be found at the proximal portion of the columnar segment just distal to the squamocolumnar junction, with decreasing density distally. Goblet cells may or may not extend throughout the entire columnar segment, but identification of a single goblet cell is sufficient to diagnose Barrett's esophagus in the setting of a visible columnar segment in the distal esophagus. The specific genetic events that lead to the transformation of cardiac mucosa to intestinalized cardiac mucosa are unknown, but genes such as *Cdx2* probably participate, and the expression of these genes in response to reflux-induced mucosal injury may be variable in individuals and may influence the response of the mucosa to inflammatory injury.

DYSPLASIA AND MALIGNANT TRANSFORMATION

Barrett's esophagus is a premalignant mucosa and has an increased proliferation rate, decreased apoptosis, and an increased fraction of diploid and aneuploid cells in comparison to normal epithelium.[41,87] The combination of increased proliferation and decreased apoptosis allows genetic abnormalities to develop and accumulate and drives the development of dysplasia and malignant transformation in Barrett's.[88] Whereas nondysplastic Barrett's esophagus is a simple columnar epithelium with homogeneous nuclei arranged close to the basement membrane, dysplasia results in both cytologic and architectural abnormalities, including loss of nuclear polarity, a pleomorphic appearance, and the development of glandular distortion.[89] By convention, four broad categories are used by pathologists to describe the dysplastic process: (1) no dysplasia, (2) indefinite for dysplasia, (3) low-grade dysplasia, and (4) high-grade dysplasia. This classification system was adapted for use in Barrett's esophagus from that used in ulcerative colitis.[90,91] The most significant category, high-grade dysplasia, is characterized by carcinoma in situ with malignant cells that do not invade the lamina propria.

Grading of dysplasia has great clinical utility in stratifying the risk for subsequent cancer in patients with Barrett's, and to date it is the most important predictive marker for the development of invasive adenocarcinoma. However, the ability to grade dysplasia remains a subjective endeavor, particularly outside specialized centers and by those who are not expert gastrointestinal pathologists.[92] Even among focused gastrointestinal

pathologists there is discordance, particularly with regard to the presence of low-grade dysplasia.[93] A new grading system called the Vienna classification has been proposed to reduce interobserver variation, but it has yet to be validated. This lack of precision inherent in histopathologic grading has stimulated efforts to identify more objective molecular and biochemical indicators of an increased risk for progression in patients with Barrett's. It has been demonstrated that in medically treated patients with Barrett's and low-grade dysplasia, the risk for progression is increased in patients with aneuploidy.[94] It is hoped that other molecular markers that are able to better predict which patients with Barrett's are at increased risk for progression will be identified in the future.

Investigating the molecular and genetic pathways by which Barrett's esophagus progresses to dysplasia and cancer not only increases our understanding of the pathophysiology of Barrett's esophagus but also aids in the identification of biomarkers for stratifying risk in an individual patient. It is hoped that ultimately, quantitative measurement of molecular changes will result in more objective end points for assessing the risk for dysplasia and cancer, as well as for assessing response to therapy. Perhaps not surprisingly, however, the genetic events associated with progression of Barrett's esophagus have been found to be diverse and varied. These events can be classified broadly as chromosomal events, characterized by loss or gain of chromosomal regions, molecular events, such as promotor hypermethylation, gene amplification or overexpression, and genetic mutations.[95] The specific changes that occur during progression to dysplasia and malignancy can be classified according to the general principles of carcinogenesis: (1) self-sufficiency and independence from external mitogenic growth signals, (2) insensitivity to antigrowth signals, (3) diminished apoptosis, (4) limitless replicative potential, (5) angiogenic capabilities, and (6) the ability to invade and metastasize.[88] A representative table of such changes studied to date in the Barrett's metaplasia-dysplasia-carcinoma sequence is shown in Table 23–1. Currently, there is no single unifying pathway that fully describes progression through this sequence of events similar to what has been done for sporadic colorectal cancer. Rather, there is increasing evidence that genetic and chromosomal abnormalities randomly accumulate and result in divergent clones of Barrett's mucosa that can progress to cancer. For malignant transformation to occur, it is hypothesized that at least 5 to 10 such genetic changes must accumulate within a given clone of cells.[96-98]

Despite being proposed by Virchow in 1863, the link between inflammation and cancer is only now becoming evident. One example of this link is the development of Barrett's esophagus and adenocarcinoma secondary to gastroesophageal reflux. Recent data indicate that a major mechanism by which reflux-induced inflammation can lead to carcinogenesis is via the nuclear factor-κB (NFκB) pathway, which has also been implicated in hepatocellular carcinoma secondary to hepatitis, cholangiocarcinoma secondary to ductal inflammation, squamous cell carcinoma of the skin, and colorectal carcinoma secondary to ulcerative colitis.[99,100] The NFκB pathway appears to be uniquely positioned to mediate this process because it has been shown to participate in the regulation of immune and inflammatory functions, as well as carcinogenesis. Stimulation of NFκB can occur through numerous factors, including cytokines, oxidants, and immune stimuli, which result in amplification of the inflammatory process. NFκB is responsible for downstream expression of many important and diverse proteins such as proinflammatory cytokines, chemokines, inflammatory enzymes, and adhesion molecules. One such downstream effector is cyclooxygenase-2 (COX-2), the rate-limiting enzyme in arachidonic acid conversion to prostaglandin.

Many investigators have focused on COX-2 in recent years because it appears to mediate the interaction between inflammation and carcinogenesis and has been implicated in multiple important carcinogenic mechanisms, including promotion of proliferation and angiogenesis, as well as inhibition of apoptosis.[101] COX-2 expression is usually undetectable in normal tissue, but it has been found to be up-regulated in Barrett's esophagus and increases in stepwise fashion during the progression to dysplasia and cancer.[102,103] It remains unclear at what point in the metaplasia-dysplasia-carcinoma sequence that COX-2 expression transitions from induced up-regulation secondary to inflammation and becomes permanent overexpression contributing to carcinogenesis. It is possible that COX-2 may play a significant role in the earliest stages of the metaplastic process, even before the development of Barrett's esophagus, because it is also expressed in the squamous epithelium of patients with reflux disease.[104] Recently, we have demonstrated that elevated COX-2 expression in patients with GERD is significantly reduced after antireflux surgery. In fact, it was normalized to levels expressed in control patients without reflux disease (manuscript submitted for publication). This observation demonstrates that increased COX-2 associated with gastroesophageal reflux is reversible. Furthermore, it is the first evidence that antireflux surgery alters gene expression in the esophagus and supports the controversial concept that antireflux surgery can have an impact on the natural history of reflux disease.

NATURAL HISTORY OF BARRETT'S ESOPHAGUS

Although widely accepted that Barrett's esophagus is a premalignant condition, the degree of risk remains uncertain. A meta-analysis by Shaheen et al. of 25 articles published between 1984 and 1998 concluded that the incidence of adenocarcinoma in patients with Barrett's was approximately 0.5% per patient-year, with a range of 0.2% to 2.9%.[105] However, these studies were performed in patients being treated for reflux, including those who underwent antireflux surgery, and thus these estimates may not reflect the true natural history of Barrett's progression. The incidence of low-grade dysplasia is reported to be approximately 4.3% per patient-year and that of high-grade dysplasia, 0.9% per patient-year.[106] Known risk factors for progression to dysplasia and

Table 23–1 Genetic Alterations in the Barrett's Metaplasia-Dysplasia-Carcinoma Sequence

Types of Alterations*	Comment
Abnormal Growth Signals	
Extracellular growth signals	
TGF-β_1	Overexpression, receptor alterations
aFGF, bFGF	Overexpression
TNF-α	Overexpression
TGF-α	Overexpression
Transcellular transducers	
EGFR (erbB-1)	Overexpression
HER2/neu (erbB-2)	Overexpression
Intracellular circuits	
Ras-Raf-MAPK pathway	Ras overexpression, mutations
APC	Inactivation (LOH, mutation, methylation)
Src	Overexpression
Loss of Antigrowth Signals	
Rb pathway	
Rb	Inactivation (LOH, mutation, methylation)
Cyclin D1, E	Overexpression
CDK	Loss of inhibitors
c-myc	Overexpression, aberrant localization
CDK inhibitors	
p16	Inactivation (LOH, mutation, methylation)
p15	Inactivation (LOH)
p27	Inactivation
p21	Inactivation
Loss of Apoptosis	
p53	Inactivation (LOH, mutation)
S-HODE	Reduced expression, proapoptotic
Fas	FasL overexpression, Fas sequestration
Decoy receptor 3	Overexpression, sequesters Fas
COX-2	Overexpression, blocks apoptosis
Bcl-2	Overexpression, inhibits apoptosis
Unlimited Replication	
Telomerase	Overexpression
Angiogenesis	
VEGF	Overexpression
COX-2	Overexpression, induces VEGF
Invasion and Metastasis	
E-cadherin	Reduced expression, aberrant localization
β-Catenin	Aberrant localization, overexpression
CD44	Isoform overexpression
DCC	Inactivation
Urokinase plasminogen activator	Overexpression
Cysteine protease cathepsin B (CTSB)	Overexpression
Src	Overexpression

*The six hallmarks of carcinogenesis. Adapted from Hanahan D, Weinberg RA: The hallmarks of cancer. Cell 100:57-70, 2000.
aFGF, acidic fibroblast growth factor; APC, antigen-presenting cell; bFGF, basic fibroblast growth factor; CDK, cyclin-dependent kinase; COX, cyclooxygenase; DCC, deleted in colon cancer; EGFR, endothelial growth factor receptor; LOH, loss of heterozygosity; MAPK, mitogen-activated protein kinase; Src, sarcoma; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

cancer include hiatal hernia size, the length of Barrett's esophagus, patient age, and the presence of cellular and molecular abnormalities, including abnormal ploidy status and p16 or p53 gene abnormalities.[94,107-110]

The natural history of dysplasia is not well characterized, but the risk for malignancy increases with the development of low- and high-grade dysplasia. The best data come from Reid and colleagues, and in a carefully monitored group of patients they reported that low-grade dysplasia progressed to cancer in 4% over a period of 5 years whereas high-grade dysplasia led to cancer in 61% at 5 years.[94] It is also clear that progression is variable, with some patients progressing at a steady pace over a period of several years and others having stable nondysplastic or low-grade dysplasia in Barrett's esophagus for many years and then rapidly progressing to high-grade dysplasia and cancer. Theisen et al. conducted a review of patients who received follow-up through the entire sequence of Barrett's esophagus, low-grade dysplasia, high-grade dysplasia, and adenocarcinoma to better understand the chronology of these events.[111] In a group of 28 patients with adenocarcinoma, a median of 24 months had passed from the initial diagnosis of Barrett's esophagus. Progression from low-grade to high-grade dysplasia occurred over a median of 11 months. Once high-grade dysplasia was diagnosed, the median time to diagnosis of cancer was 3 months. Although this timeline was variable for each individual, in this cohort of patients who had progression of Barrett's to cancer the process occurred within 3 years. However, because most Barrett's patients do not progress to dysplasia and cancer, the cohort in this retrospective study may not be applicable to all patients. Furthermore, since few of these patients had been in long-term Barrett's surveillance programs, it is not possible to separate prevalent from incident cancers in this group, and the actual month and year that Barrett's developed in each patient is also unknown. Thus, information on progression of Barrett's is largely anecdotal.

SCREENING AND SURVEILLANCE

There are currently no screening protocols for Barrett's esophagus in the United States. Although a history of chronic reflux symptoms in a white male older than 50 years was previously an indication for screening upper endoscopy, this recommendation was recently retracted by the American College of Gastroenterology.[112] The cost versus benefit of endoscopic screening continues to be debated, but perhaps as new technologies emerge such as the Pill-cam there will be lower-cost options that permit cost-effective screening to be performed. The other impediment has been the difficulty in determining appropriate candidates for screening because symptoms of reflux are not a reliable indicator for the presence or absence of reflux-related complications, including Barrett's. Thus, any screening strategy will have to be broadly applied independent of symptoms.

Endoscopic surveillance in patients with a diagnosis of Barrett's is less controversial, yet the cost-effectiveness and timing are debated, and in practice, surveillance in patients is often sporadic.[113,114] The recommended biopsy protocol for surveillance of Barrett's esophagus is four-quadrant biopsies every 2 cm, with specimens taken at 1-cm intervals when high-grade dysplasia is present.[115,116] Occasionally, severe esophagitis may complicate the histologic differentiation of dysplasia versus cellular atypia secondary to inflammation, and repeat biopsy may be necessary after a period of aggressive acid-suppression therapy.

Recognizing the limitations of standard endoscopy, staining techniques have been used in an attempt to increase the sensitivity of diagnosing Barrett's esophagus and dysplasia. Among others, Lugol's iodine, toluene blue, indigo carmine, and methylene blue have been studied. Alternatively, new technologies, including high-magnification chromoendoscopes and a variety of light-scattering techniques, are also being investigated and may aid in recognition of abnormal mucosa and improve biopsy yield.[117] At this time, however, standard endoscopy with systematic four-quadrant biopsy of the columnar-lined esophagus remains the gold standard for the diagnosis and surveillance of Barrett's esophagus.

The recommended time interval for follow-up endoscopy is directly related to the presence or absence of dysplasia. The most recent practice parameters published by the American College of Gastroenterology suggest that when two consecutive endoscopies with biopsy confirm the absence of dysplasia, follow-up endoscopy can be done at 3-year intervals. The finding of low-grade dysplasia escalates follow-up to every 6 months for the first year, followed by annual endoscopy if low-grade dysplasia persists. High-grade dysplasia poses a special problem because of the difficulty with diagnosis and the risk of missing an occult cancer. Thus, the finding of high-grade dysplasia first requires (1) an immediate repeat endoscopy with biopsy every 1 cm to rule out cancer and (2) an expert pathologist consultation to confirm the diagnosis. Continued surveillance for high-grade dysplasia is controversial because it is associated with a significant risk for an occult carcinoma, particularly in long-segment Barrett's or when multifocal high-grade dysplasia is present.[118,119] If surveillance is chosen, it is recommended that it be undertaken every 3 months.[112] Any visible lesion or ulcerated area within a Barrett's segment must be carefully biopsied because of the high risk for associated cancer with these lesions.[118]

Determining appropriate recommendations for surveillance of Barrett's esophagus is difficult given our incomplete understanding of the natural history of this condition. The literature on surveillance and cancer incidence in Barrett's esophagus is compromised by heterogeneous patient groups and referral and publication bias.[105] Despite these uncertainties, surveillance of Barrett's patients has been shown to be beneficial. Patients in whom adenocarcinoma develops within a surveillance program tend to have earlier-stage disease and a better prognosis than do those who have de novo adenocarcinoma with symptoms from local tumor growth.[120-122] Furthermore, the cost of surveillance for Barrett's esophagus compares favorably with the widely accepted protocol of breast cancer detection with

mammography. The cost per life-year saved is $4151 for esophageal adenocarcinoma versus $57,926 for breast cancer.[123]

An interesting dilemma arises in patients who have a columnar-lined segment of esophagus on endoscopy but do not have intestinal metaplasia on histology. This may simply represent a sampling error; however, even if a columnar segment is not intestinalized, there is a significant likelihood that it will become so in the future, particularly when the columnar segment approaches 3 cm in length.[78,124] Most agree that these patients should undergo follow-up endoscopy and biopsy, but consensus on the timing or frequency is lacking.

CONCLUSION

There is increasing evidence that at the normal gastroesophageal junction, esophageal squamous mucosa abuts oxyntic fundic mucosa of the stomach. With exposure to gastric juice the squamous mucosa is injured, and over time it becomes replaced by columnar cardiac mucosa. Deterioration of the lower esophageal sphincter allows reflux to extend up into the esophagus, and the squamocolumnar junction migrates proximally. Although it is likely that acidic gastric juice drives the transformation of squamous mucosa to cardiac mucosa, there is substantial evidence that other components of gastric juice, particularly bile acids, are essential for subsequent intestinalization of the cardiac mucosa to occur.

Barrett's esophagus is a premalignant mucosa, and the risk for malignant transformation is approximately 0.5% per patient-year. The finding of dysplasia is currently the most commonly used indicator of increased malignant risk, but it has high interobserver variability. It is expected that ultimately, molecular markers will prove more helpful than histology in Barrett's, and there are ongoing efforts to determine biomarkers that will better delineate an individual's risk for progression to cancer. Surveillance endoscopy in patients with Barrett's esophagus has proven efficacy, but it is time-consuming and haphazardly applied across the country. Currently, screening endoscopy is not recommended for Barrett's esophagus, but given the dramatic increase in the incidence of esophageal adenocarcinoma, new technologies that permit widespread and cost-effective screening are needed.

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Chapter

24

Surgical Treatment of Barrett's Esophagus

Jeffrey H. Peters

Norman Barrett described the condition that bears his name in 1950.[1] He believed that he was observing a congenitally short esophagus and an intrathoracic stomach.[2] Allison and Johnstone, with careful examination of seven esophagectomy specimens, showed conclusively in 1953 that it was indeed the tubular esophagus lined with columnar epithelium.[3] Despite its 50-year history, many aspects of Barrett's esophagus remain elusive and controversial, including the role of surgical treatment.[4,5] The uncertainty would be of little consequence were it not for the increasing number of, all too often, young men and women, many with few symptoms of gastroesophageal reflux, who have difficulty swallowing and are found to have esophageal adenocarcinoma.

There are five aims of therapy for patients with Barrett's esophagus. Ideally, they should be the same for both operative and nonoperative treatment and include

1. Providing long-term relief of symptoms
2. Allowing healing of reflux-induced esophageal mucosal injury, including stricture formation
3. Preventing progression to more advanced mucosal injury, dysplastic changes, or carcinoma
4. Inducing regression of dysplastic to nondysplastic Barrett's esophagus or intestinalized to nonintestinalized columnar epithelium
5. Completely eliminating and preventing any recurrence of high grade dysplasia

Achieving long-term success in the treatment of Barrett's esophagus can be difficult, particularly in those with long segments. This difficulty is due to the combination of several factors, including the fact that it represents severe gastroesophageal reflux disease (GERD), it is usually associated with large hiatal hernias, and it is a premalignant state. Acid-suppressive medication is increasingly being recognized to be inadequate, and ablative therapies remain difficult, complicated, and investigational. This leaves antireflux surgery as arguably the best treatment option, provided that long-term success can be shown.

RATIONALE FOR ANTIREFLUX SURGERY FOR BARRETT'S ESOPHAGUS

Relief of symptoms remains the primary force driving antireflux surgery in patients with nondysplastic Barrett's esophagus. Healing of esophageal mucosal injury and prevention of disease progression are important secondary goals. In this regard, patients with Barrett's esophagus are no different from the broader population of patients with gastroesophageal reflux. They should be considered for antireflux surgery when patient factors suggest severe disease or predict the need for long-term medical management, both of which are almost always the case in patients with Barrett's esophagus.

Several other factors are increasingly influencing the decision toward surgery, however. The first is the consideration that the ideal end point of treatment may not be simple symptomatic relief but rather elimination of pathologic esophageal acid exposure. This mindset is stimulated by the desire to prevent neoplastic development, together with the results of basic studies on the biology of Barrett's epithelium. These studies have shown disconcerting reflux-induced cellular changes in a Barrett's mucosa organ culture system.[6,7] Fitzgerald et al., for example, found that a dramatic increase in cellular proliferation resulted after Barrett's tissues were exposed to short pulses of acid at pH 3.5. Interestingly, continuous acid exposure had minimal effect. Cellular differentiation was also assessed by quantifying expression of the apical membrane cytoskeletal protein villin, which is important for brush border microvillus assembly. Increased villin expression was found with exposure to acid in a pH range of 3 to 5. Although these in vitro findings may not reflect the situation in vivo, the finding that short pulses of acid induce proliferation suggests that complete and continuous acid suppression is necessary to prevent these abnormal cellular biologic changes. Though theoretically possible with both medical and surgical treatment, complete esophageal acid control is more reliably provided by antireflux surgery.

Table 24–1 Clinical Features of Patients with Barrett's Esophagus and Gastroesophageal Reflux Disease and Esophagogastroduodenoscopy Controls

	Barrett's ($n = 79$)	GERD Controls ($n = 94$)	EGD Controls ($n = 84$)
Duration of symptoms (yr)*	16.4	11.8	13
Mean age at onset*	35.3	43.7	42.7
Esophagitis†	51 (65%)	33 (35%)	24 (29%)
Esophageal ulcer†	17 (22%)	7 (7%)	6 (7%)
Esophageal stricture†	21 (27%)	7 (7%)	5 (6%)
Hiatal hernia†	60 (76%)	41 (44%)	31 (37%)
Severe GERD‡	67 (85%)	55 (59%)	53 (63%)

*$P < .05$ for the Barrett's esophagus group versus either control group (Kruskal-Wallis test).
†Odds ratios for esophagitis, esophageal ulcer, esophageal stricture, and hiatal hernia greater than 3 cm for the Barrett's esophagus group versus either control group.
‡Severe GERD was defined as heartburn so painful that it awoke the patient or prevented sleeping.
Modified from Eisen GM, Sandler RS, Murray S, Gottfried M: The relationship between gastroesophageal reflux disease and its complications with Barrett's esophagus. Am J Gastroenterol 92:27-31, 1997.

Second, it is increasingly being recognized that normalization of esophageal acid exposure with medication is difficult in patients with Barrett's esophagus, even with proton pump inhibitors (PPIs). Sampliner et al. reported that a mean dose of 56 mg of omeprazole was necessary to normalize 24-hour esophageal pH studies after multipolar electrocoagulation.[8] Several studies have shown that nocturnal acid breakthrough resulting in supine GERD is common, even with 20 mg twice daily of PPI therapy.[9,10] Although this nocturnal acid breakthrough period can be reduced by taking a histamine H_2 receptor antagonist before sleep, short pulses of esophageal acid exposure still occur in some patients. Furthermore, once initiated, most patients with Barrett's esophagus will require lifelong treatment with PPIs both to relieve symptoms and to control any coexistent esophagitis or stricture.

Third is the recognition that Barrett's esophagus represents severe end-stage GERD, which will almost certainly require high-dose, lifetime drug therapy. The severity of the disease is demonstrated by clinical, physiologic, and basic biologic findings. A case-controlled epidemiologic study showed that patients with Barrett's esophagus have reflux symptoms at an earlier age and have more severe symptoms than age- and gender-matched GERD or upper endoscopy control patients do[11] (Table 24–1). Complications of reflux, including esophagitis, stricture, and ulceration, also occur more frequently in patients with Barrett's esophagus.[12] Physiologic studies reveal markedly abnormal esophageal acid exposure,[13] an incompetent lower esophageal sphincter,[14] and impaired esophageal body motility in a large majority of patients.[15] Both the frequency and the duration of reflux episodes are increased in comparison to patients with no intestinal metaplasia. Contractility of the esophageal body may be profoundly reduced in patients with Barrett's esophagus, thus resulting in prolonged contact times. The clinical and physiologic severity in patients with short-segment Barrett's esophagus is generally intermediate between those with long-segment Barrett's and those with erosive esophagitis (Table 24–2).[16] Most patients with Barrett's esophagus have a hiatal hernia, which is often larger than in patients with reflux esophagitis without Barrett's.[17]

Studies of the constituents of the refluxate provide further indications that patients with Barrett's esophagus differ significantly from those with GERD without Barrett's esophagus. Patients with Barrett's esophagus are more likely to have mixed reflux of both gastric and duodenal contents into the esophagus.[18] Direct measurement of aspirated bile or measurement of esophageal bilirubin in the distal esophagus as a marker of duodenal juice has shown that duodenoesophageal reflux is significantly more frequent in those with Barrett's esophagus than in those with GERD without Barrett's.[19] A study of 100 patients with GERD found a significant association between the degree of mucosal injury and the presence of duodenogastroesophageal reflux rather than gastroesophageal reflux only.[18] Some animal model studies have indicated that duodenal reflux plays a significant role in esophageal tumor promotion.[20] It is likely that antireflux surgery results in more reproducible and reliable elimination of reflux of both acid and duodenal contents, although long-term outcome studies suggest that as many as 25% of post-Nissen patients will have persistent pathologic esophageal acid exposure confirmed by positive 24-hour pH studies.

OUTCOME OF ANTIREFLUX SURGERY IN PATIENTS WITH BARRETT'S ESOPHAGUS

Antireflux surgery is an excellent treatment option in most patients with Barrett's esophagus. It must be remembered, however, that patients with Barrett's esoph-

Table 24–2 Clinical and Anatomic Characteristics of Varying Degrees of Intestinal Metaplasia of the Esophagus and Gastroesophageal Junction

Characteristic	Total Population *N* (%)	GEJ-SIM *N* (%)	SSBE *N* (%)	LSBE *N* (%)	*P* Value
Sex (M/F)	394/344	25/22	45/19	35/5	.0001
White race	485 (66)	31 (66)	55 (86)	40 (100)	.0011
Hiatal hernia	252 (34)	19 (40)	39 (61)	32 (80)	.0001
Hernia size (cm)	2 (1-9)	2 (1-8)	3 (1-8)	4 (2-7)	.0001
Heartburn	343/550 (62)	20/34 (59)	33/40 (83)	10/16 (63)	.077
Duration of heartburn, yr (range)	2 (0.2-45)	3.5 (0.25-30)	3.5 (0.1-35)	20 (0.16-54)	.009
Esophagitis	110/549 (20)	7/34 (21)	10/40 (45)	3/16 (19)	.003
Dysplasia	0/720	2/47 (4.3)	4/50 (8)	2/13 (15)	
Cancer	0	1/47 (2.1)	1/50 (2)	2/13 (15.4)	
Dysplasia plus cancer	0	3/47 (6.4)	5/50 (10)	4/13 (31)	.043

GEJ-SIM, gastroesophageal junction—specialized intestinal metaplasia; LSBE, long-segment Barrett's esophagus; *N*, number of patients; SSBE, short-segment Barrett's esophagus.
Adapted from Hirota WK, Loughney TM, Lazas DJ, et al: Specialized intestinal metaplasia, dysplasia and cancer of the esophagus and esophagogastric junction; prevalence and clinical data. Gastroenterology 116:277-285, 1999.

agus generally have severe GERD, with its attendant sequelae such as a large hiatal hernia, stricture, shortened esophagus, and poor motility. These anatomic and physiologic features make successful antireflux surgery a particular challenge in this population. Indeed, recent data suggest that antireflux surgery in patients with Barrett's esophagus may not be as successful in the long term as in those without Barrett's. Once the decision for surgery is made, the most important features to identify before surgery are the presence of esophageal shortening, failed esophageal body motility, and dysplasia, each of which has significant bearing on the decision for surgical treatment, as well as the approach and type of antireflux procedure selected.

Choice of Operation

The antireflux procedure of choice is Nissen fundoplication. A laparoscopic approach will be appropriate for most patients, probably 80% to 85%. The remaining 15% to 20% of patients are best approached via open thoracotomy, which allows esophageal lengthening in the presence of a large hiatal hernia and esophageal shortening. Partial fundoplications should be used rarely, if at all in patients with Barrett's esophagus because most studies indicate that they provide inferior reflux control.[21,22] The superior reflux control provided by Nissen fundoplication probably justifies its use in patients with Barrett's esophagus even when disordered or low-amplitude peristalsis is present. The rationale for complete rather than partial fundoplication lies in the increasingly demonstrated importance of completely eliminating pathologic reflux and the prevention of disease progression in Barrett's patients.

Symptomatic Outcome

Studies focusing on the symptomatic outcome of antireflux surgery in patients with Barrett's esophagus document excellent to good results in 72% to 95% of patients 5 years after surgery.[23,24] Several have compared medical and surgical therapy. Attwood et al., in a prospective but nonrandomized study, reported on 45 patients undergoing either medical (26) or surgical (19) treatment of Barrett's esophagus.[25] The groups were similar in age, length of Barrett's segment, percent time with a pH less than 4, and length of follow-up. Mean symptom scores improved dramatically after antireflux surgery. Symptoms of heartburn, dysphagia, or both recurred in 88% of patients treated with medical therapy alone and in 21% after antireflux surgery. Reflux complications, largely the development of an esophageal stricture, occurred in 38% of the medically treated and 16% of the surgically treated patients ($P < .05$) over the 3-year follow-up period. Esophageal adenocarcinoma developed in one patient in each group. They concluded that antireflux surgery was superior to acid suppression for both control of symptoms and prevention of complications in patients with Barrett's esophagus.

Parilla and colleagues recently reported an update of a study originally published in the *British Journal of Surgery* in 1996.[26,27] One hundred one patients were enrolled over an 18-year period (1982 to 2000). Median follow-up was 6 years. Medical therapy consisted of 20 mg of omeprazole (PPI) twice daily since 1992 in all medically treated patients. Surgical therapy consisted of an open 1.5- to 3.0-cm Nissen fundoplication over a 48- to 50-French bougie with division of the short gastric arteries in 39% of patients and crural closure in all. Symptomatic outcomes in the two groups were nearly identical,

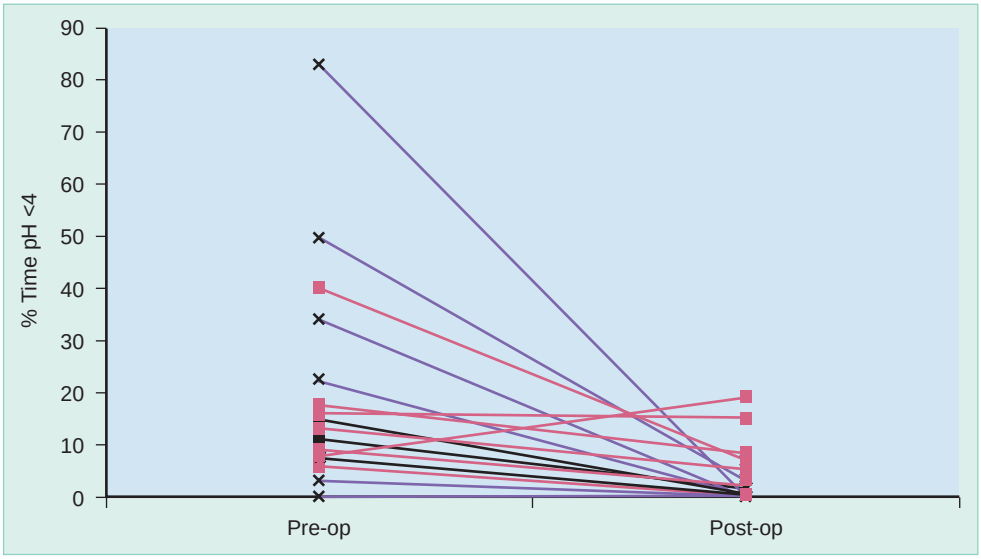

Figure 24–1. Twenty-four-hour distal esophageal pH results before and after Nissen fundoplication in 21 patients with Barrett's esophagus studied preoperatively and postoperatively. (From Hofstetter WA, Peters JH, DeMeester TR, et al: Long term outcome of antireflux surgery in patients with Barrett's esophagus. Ann Surg 234:532-539, 2001.)

although esophagitis, stricture, or both persisted in 20% of the medically treated patients versus only 3% to 7% of those after antireflux surgery. Fifteen percent of patients had abnormal acid exposure after surgery. Although pH data were not routinely collected in patients receiving PPI therapy, in the subgroup of 12 patients who did undergo 24-hour monitoring during treatment, 3 of 12 (25%) had persistently high esophageal acid exposure and most (75%) had persistently high bilirubin exposure.

In contrast, Csendes et al. have suggested that the long-term results of antireflux surgery in patients with Barrett's esophagus may not be as good as previously thought.[28] They reviewed their long-term results with "classic" antireflux surgery in 152 patients with both complicated and uncomplicated Barrett's esophagus. Fifty-four percent of those with uncomplicated Barrett's and 64% of those with Barrett's esophagus complicated by stricture or ulceration were classified as failures when symptoms were assessed 8 years postoperatively. Although this report challenges the long-term results of antireflux surgery in patients with Barrett's esophagus, it suffers from the fact that 85% of the patients were treated with a Hill repair, the results of which should not necessarily be extrapolated to patients undergoing Nissen fundoplication.

The outcome of laparoscopic Nissen fundoplication in patients with Barrett's esophagus has been assessed at 1 to 3 years after surgery. Hofstetter et al. reported the University of Southern California (USC) experience in 85 patients with Barrett's esophagus at a median of 5 years after surgery.[23] Fifty-nine had long-segment and 26 had short-segment Barrett's esophagus, and 50 were treated with a laparoscopic approach. Reflux symptoms were absent in 67 of 85 patients (79%). Recurrent symptoms developed in 18 (21%), and 4 resumed taking daily acid-suppressive medication. Seven patients underwent a secondary repair and were asymptomatic, thus raising the eventual successful outcome to 87%. Postoperative 24-hour pH levels were normal in 17 of 21 (81%) (Fig. 24–1). Ninety-nine percent of the patients considered themselves cured (77%) or improved (22%), and 97% were satisfied with the surgery.

Farrell and colleagues also reported symptomatic outcomes of laparoscopic Nissen fundoplication in 50 patients with both long- and short-segment Barrett's esophagus.[24] Mean scores for heartburn, regurgitation, and dysphagia all improved dramatically after Nissen fundoplication. Importantly, there was no significant decrement in symptom scores when 1-year results were compared with those 2 to 5 years postoperatively. They did find a higher prevalence of "anatomic" failure requiring reoperation in patients with Barrett's esophagus than in non-Barrett's patients with GERD. Others have reported similar results.[29,30]

Objective Measures of Reflux Control

Several studies have documented nearly complete elimination of both acid and alkaline reflux after fundoplication. Stein et al. showed that Nissen fundoplication provides normalization of both acid and bilirubin exposure in virtually all patients with Barrett's esophagus.[31] As mentioned earlier, normalization of duodenogastroesophageal reflux is not achieved with medical acid-suppression therapy. Csendes et al. reported extensive physiologic studies of Barrett's patients after combined fundoplication, highly selective vagotomy, and duodenal-switch bile diversion procedures.[32] Although these authors documented that the combined procedures abolished both acid and duodenogastroesophageal reflux, the extensive nature of the operation limits its appeal. Furthermore, as stated before, a properly performed Nissen fundoplication will prevent gastric juice of any nature from refluxing into the esophagus, thus making the additional procedures unnecessary.

IMPACT OF ANTIREFLUX SURGERY ON THE METAPLASIA-DYSPLASIA-CARCINOMA SEQUENCE

Though by no means proven, a growing body of evidence attests to the ability of fundoplication to protect against dysplasia and invasive malignancy. Several recent studies suggest that effective antireflux surgery may have an impact on the natural history of Barrett's esophagus. The first such evidence came from an analysis of longitudinal follow-up of patients with Barrett's esophagus in the registry of the American College of Gastroenterologists.[33] All patients had nondysplastic, quiescent Barrett's esophagus at initial endoscopy. One hundred fifty-two patients received medical treatment and 29 underwent antireflux surgery. Surveillance endoscopy was performed annually. Dysplasia developed in 30 of 152 patients in the medically treated group (19.7%) and 1 of 29 (3.4%) in the surgical group. A retrospective review of 118 patients with Barrett's esophagus who underwent antireflux surgery at the Mayo Clinic between 1960 and 1990 revealed three cancers occurring over an 18.5-year follow-up period.[34] All were found within the first 3 years after surgery. The fact that the development of adenocarcinoma was clustered in the early years after antireflux surgery and not randomly dispersed throughout the follow-up period strongly suggests that antireflux surgery altered the natural history of the disease, particularly given the fact that once dysplasia has developed, prospective studies show that carcinoma ensues in an average of 3 years. The occurrence of all observed cancers in the first few years suggests that the point of no return in the dysplasia-cancer sequence had already occurred before the time of surgery.

Further evidence that antireflux surgery may alter the natural history of Barrett's esophagus was reported by Katz et al.[35] This Veterans Affairs outcomes group retrospectively reviewed 102 patients undergoing annual surveillance for Barrett's esophagus from 1970 to 1994, for a total of 563 patient-years of follow-up. All specimens with any degree of dysplasia were blinded and rereviewed. New-onset low-grade dysplasia developed in 19 patients, high-grade dysplasia in 4, and adenocarcinoma in 3. Antireflux surgery was associated with a significantly decreased risk for the development of dysplasia, the presence of which persisted in a multivariate analysis that took into account covariables such as age, sex, and smoking. Dysplasia did not develop in any of the 15 patients in this study after antireflux surgery. In the USC review noted earlier, no high-grade dysplasia or cancer developed in 410 patient-years of follow-up.[23] Finally, two prospective randomized studies found less adenocarcinoma in the surgically treated groups. Parilla et al. reported that although the incidence of dysplasia and adenocarcinoma was no different overall, significantly less dysplasia and no adenocarcinoma developed in the subgroup of surgical patients with normal postoperative pH studies.[27] Spechler and associates identified one adenocarcinoma 11 to 13 years after antireflux surgery versus four after medical treatment.[36] Most of these authors concluded that there is a critical need for future trials to explore the role of antireflux surgery in protecting against the development of dysplasia in patients with Barrett's esophagus.

Regression of Barrett's Esophagus After Antireflux Surgery

The common belief that Barrett's epithelium cannot be reversed is probably false. DeMeester et al. reported that after antireflux surgery, loss of intestinal metaplasia in patients with visible Barrett's esophagus was rare but occurred in 73% of patients with nonvisible intestinal metaplasia of the cardia.[37] This finding suggests that the metaplastic process may indeed be reversible if reflux is eliminated early in its process, that the cardiac mucosa is dynamic, and that as opposed to intestinal metaplasia extending several centimeters into the esophagus, intestinal metaplasia of the cardia is more likely to regress after antireflux surgery. Gurski et al. recently reviewed pretreatment and post-treatment endoscopic biopsy samples from 77 Barrett's patients treated surgically and 14 treated with PPIs.[38] Post-treatment histology was classified as having regressed if two consecutive specimens taken more than 6 months apart plus all subsequent specimens showed loss of intestinal metaplasia or loss of dysplasia. Histopathologic regression occurred in 28 of 77 (36.4%) patients after antireflux surgery and in 1 of 14 (7.1%) treated with PPIs alone ($P < .03$). After surgery, regression from low-grade dysplastic to nondysplastic Barrett's epithelium occurred in 17 of 25 (68%) patients and from intestinal metaplasia to no intestinal metaplasia in 11 of 52 (21.2%) (Fig. 24–2). Both types of regression were significantly more common in short-segment (<3 cm) than in long-segment (>3 cm) Barrett's esophagus: 19 of 33 (58%) and 9 of 44 (20%) patients, respectively ($P = .0016$). Eight patients progressed, five from intestinal metaplasia alone to low-grade dysplasia and three from low- to high-grade dysplasia. All those who progressed had long-segment Barrett's esophagus. On multivariable analysis, the presence of short-segment Barrett's esophagus and the type of treatment were significantly associated with regression; age, sex, surgical procedure, and preoperative lower esophageal sphincter and pH characteristics were not. The median time of biopsy-proven regression was 18.5 months after surgery, with 95% occurring within 5 years. Similar findings have been reported by the University of Washington group[39] and Hunter's group.[40] Although these studies do not conclusively prove the ability of antireflux surgery to reverse the changes of early Barrett's esophagus, they do provide encouragement that given early changes, the process may indeed be reversible.

Recent evidence suggests that the development of Barrett's esophagus may even be preventable. Despite being a very difficult hypothesis to study, Öberg et al. monitored a cohort of 69 patients with short-segment, nonintestinalized, columnar-lined esophagus over a median of 5 years of surveillance endoscopy.[14] Forty-nine of the patients were maintained on PPI therapy and 20 underwent antireflux surgery. Intestinal metaplasia was 10 times less likely to develop in these columnar-lined

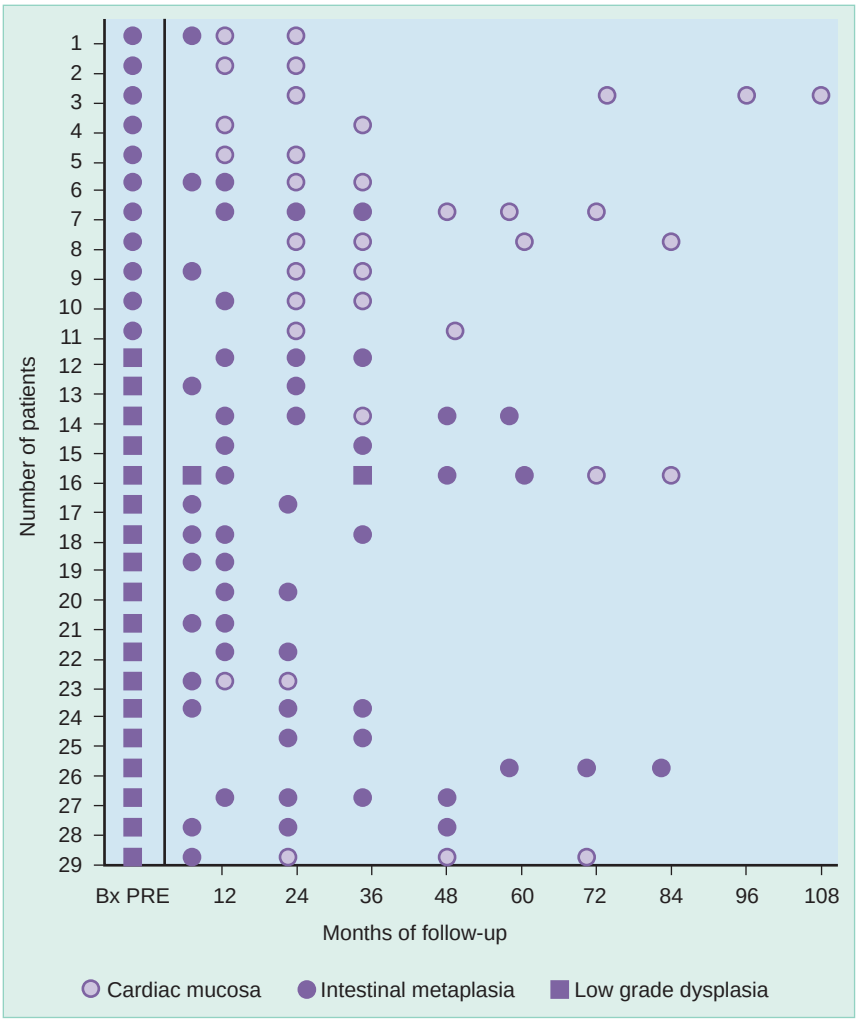

Figure 24–2. Schematic representation of histopathologic regression in 29 patients with Barrett's esophagus. (From Gurski RR, Peters JH, Hagen JA, et al: Barrett's esophagus can and does regress following antireflux surgery; a study of prevalence and predictive features. J Am Coll Surg 196:706-713, 2003.)

esophageal segments in patients treated with antireflux surgery over a follow-up span of nearly 15 years (Fig. 24–3) than in those treated with medical therapy. This rather remarkable observation supports the two-step hypothesis of the development of Barrett's esophagus (cardiac metaplasia followed by intestinal metaplasia) and suggests that the second step can be prevented if reflux disease is recognized and treated early and aggressively.

DYSPLASTIC BARRETT'S ESOPHAGUS

Dysplasia is defined as neoplastic epithelium that is confined within the basement membrane of the gland or epithelium within which it arose. The histopathologic classification of dysplasia in Barrett's epithelium relies on identification of cytologic and tissue architectural changes that were originally described in 1983 for ulcerative colitis[41] and subsequently modified for Barrett's esophagus.[42] Dysplasia is currently classified into four categories: (1) no dysplasia (intestinal metaplasia), (2) indefinite for dysplasia, (3) low-grade dysplasia, and (4) high-grade dysplasia. Before intervention, the diagnosis of high-grade dysplasia should be confirmed by at least two expert pathologists. Unfortunately, there is considerable interobserver disagreement among even expert gastrointestinal pathologists,[43] particularly for the low-grade and indefinite categories. Repeat endoscopy with extensive biopsy should be performed if significant interobserver disagreement is encountered. Endoscopy with four-quadrant biopsy at 1-cm rather than 2-cm intervals within the visible columnar segment is recommended in the presence of dysplastic tissue (Table 24–3).[44] Even with this 1-cm protocol, it is not possible to be certain that cancer is not present in patients with known high-grade dysplasia. Emphasizing this fact is a study by Cameron and Carpenter in which they mapped esophagectomy specimens from 30 patients with high-grade dysplasia or early adenocarcinoma. The median surface area of the adenocarcinomas was 1.1 cm^2, and the three smallest cancers had surface areas of 0.02, 0.3, and 0.4 cm^2.[45]

It can be difficult to distinguish between high-grade dysplasia and well-differentiated intramucosal adenocarcinoma. Most use the term high-grade dysplasia for neoplastic changes involving the epithelium, but not extending into the lamina propria (i.e., superficial to the basement membrane).[46] Neoplastic disease involving the

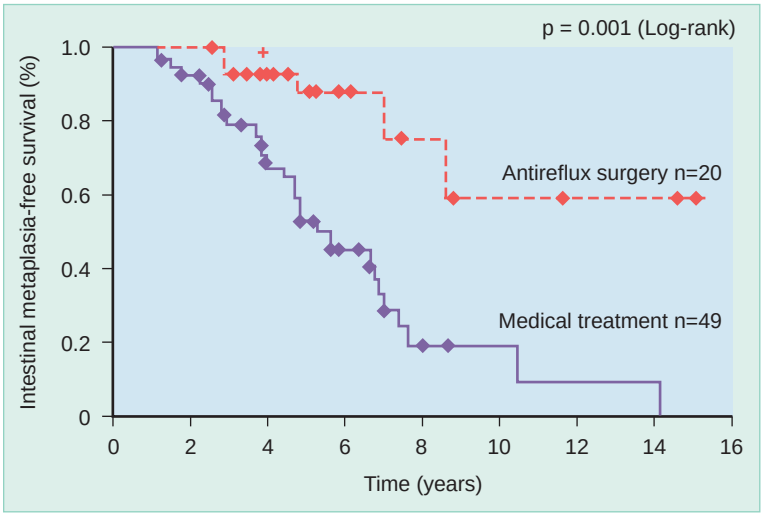

Figure 24–3. Development of intestinal metaplasia in patients' nonintestinalized short segments of columnar-lined esophagus during medical and after surgical therapy for Barrett's esophagus. (From Öberg S, DeMeester TR, Peters JH, et al. The extent of Barrett's esophagus depends on the status of the lower esophageal sphincter and the degree of esophageal acid exposure. J Thorac Cardiovasc Surg 117:572-580, 1999.)

epithelium and lamina propria superficial to the muscularis mucosa is termed intramucosal adenocarcinoma. The term carcinoma in situ has largely been replaced by the term high-grade dysplasia.

The estimated prevalence of low-grade dysplasia in Barrett's esophagus ranges from 15% to 25%, whereas the prevalence of high-grade dysplasia is approximately 5%. The incidence of development of dysplasia is approximately 5% per year (Table 24–4).[47-50] O'Conner et al. prospectively monitored 136 patients for a mean of 4.2 years.[50] Patients with both long-segment (>3 cm, n = 106) and short-segment (<3 cm, n = 30) Barrett's esophagus were included. High-grade dysplasia developed in 4 (2.9%) patients and low-grade dysplasia developed in 24 (17.6%). The median time until the development of low-grade dysplasia was 3.0 years (range, 0.07 to 12.7 years). In another prospective investigation, Levine et al. studied 62 patients with Barrett's esophagus for a mean of 34 months.[51] The authors documented the development of low-grade dysplasia in 10 of 39 patients with no dysplasia on entry into the study, one new case of high-grade dysplasia, and one invasive carcinoma. High-grade dysplasia developed in three patients with low-grade dysplasia at entry.

Table 24–3 Effect of Biopsy Protocol on Endoscopic Detection of Early Cancer in Barrett's Esophagus

Biopsy Protocol	Cancers Detected	% of Total
Visible lesions only	13/26	33
Every 2 cm without visible lesion	15/45	50
Every 2 cm and any visible lesion	32/45	71
Every 1 cm and any visible lesion	45/45	100

Adapted from Reid BJ, Blount PL, Feng Z, Levine DS: Optimizing endoscopic detection of early cancers in Barrett's high-grade dysplasia. Am J Gastroenterology 95:3089-3096, 2000.

Surgical Management of Patients with Low-Grade Dysplasia

Once identified, Barrett's esophagus complicated by dysplasia should be treated aggressively with either PPI medication or fundoplication, preferably Nissen fundoplication. Deciding on the optimum treatment in patients with low-grade dysplasia or a persistent diagnosis of indefinite for dysplasia can be difficult. Because of the possibility of missing higher grades of dysplasia elsewhere in the esophagus as a result of sampling error, the uncertainty at the initial examination of the time from the development of low-grade dysplasia to the development of high-grade dysplasia, and the fact that antireflux surgery alters the anatomy of the gastroesophageal segment such that repeat biopsy may be more difficult, patients with low-grade dysplasia are best managed by continued surveillance for 6 to 12 months before the decision for surgery (Box 24–1). Three- to six-month endoscopic surveillance with four-quadrant biopsy at every 1 cm of the Barrett's segment is the optimal technique. If the dysplastic segment remains stable and no areas of high-grade dysplasia are detected during the surveillance period, antireflux surgery is a good option. If the dysplasia regresses after treatment, the surveillance interval can be extended to 1 year for the first 3 years and then to 2- or 3-year intervals if the regression persists. Surveillance endoscopy after antireflux surgery should be performed by an experienced endoscopist because of the difficulty of obtaining adequate biopsy samples within the fundoplication wrap.

Patients with low-grade dysplasia that persists after antireflux surgery may be the ideal group in which to perform Barrett's ablation or photodynamic therapy.

Table 24–4 Prevalence of the Development of Dysplasia in Studies of Barrett's Esophagus

Author	Barrett's Segment Length	No. of Patients	Mean Follow-up (yr)	No. of Patients Developing Dysplasia	% of Patients Developing Dysplasia/yr
Hameetemen et al.[47]	Long	50	5.2	10	3.8
McCallum et al.[33]	Long	152	4	30	4.9
Ortiz et al.[26]	Long	27	4	6	5.5
Sharma et al.[48]	Short	32	3	5	5.2
Weston[4] et al.[9]	Short	26	1.5	2	5.1
	Long	29	2	6	10.3
O'Conner et al.[50]	Short	30	4.2	4 (all lgd)	13.3
	Long	106	4.2	28 (4 hgd)	26

hgd, high-grade dysplasia; lgd, low-grade dysplasia.

Overholt et al. reported elimination of low-grade dysplasia in 13 of 14 patients with porfimer sodium (Photofrin) photodynamic therapy.[52] Ultrasonic ablation,[53] endoscopic mucosal resection,[54,55] and laser ablation or electrocoagulation[56,57] may also prove suitable treatment for patients with Barrett's low-grade dysplasia. It is worth noting that unsatisfactory results, including progression to malignancy, a high frequency of stricture formation, subsquamous Barrett's esophagus, and reappearance of Barrett's epithelium, have been reported after the use of these newer therapies. These techniques may thus be less suitable for the treatment of patients with high-grade dysplasia.

Box 24–1 Management of Dysplasia

Indefinite for Dysplasia

- Aggressive antireflux therapy (60 mg/day of a proton pump inhibitor plus a nocturnal H_2 blocker)
- Rebiopsy in 3 months

Low-Grade Dysplasia

- Aggressive antireflux therapy
- Monthly surveillance for 6 to 12 months
- Offer antireflux surgery if dysplasia is stable

High-Grade Dysplasia

- Confirmation by two experienced pathologists
- Esophagectomy (? extent)

Operative Management of High-Grade Dysplasia

There are three options for the management of patients with high-grade dysplasia; each has been advocated as the treatment of choice.

1. Endoscopic surveillance until carcinoma is identified
2. Mucosal ablation
3. Esophagectomy

The optimal treatment is controversial, in part because of the fact that the natural history of high-grade dysplasia is uncertain. Prospective studies documenting that a minority of patients progress to detectable adenocarcinoma support a conservative approach to the management of these patients. Watchful waiting, however, involves a time-consuming, labor-intensive, expensive protocol that is impractical in most practice settings. Large cohorts of patients with high-grade dysplasia have now been prospectively monitored at the University of Washington[51,58] and the University of Kansas[59] and retrospectively reviewed at the Hines Veterans Hospital in Chicago.[60] These data clearly show that cancer will be identified (*identified* is a more appropriate term than developed because many of these patients may have had carcinoma for some time before it is detected) in approximately 25% of patients at 1.5 years,[51] 50% at 3 years,[59] and up to 80% 8 years later.[58] The 80% figure should be interpreted in light of the fact that there is a 20% or so error rate in the pathologic diagnosis of high-grade dysplasia. Thus, the natural history of high-grade dysplasia is becoming clear. Most patients will have an invasive adenocarcinoma identified during a 5- to 10-year surveillance period, although a significant minority may not. Though far from perfect, these facts, particularly when viewed in association with p53 and cell cycle (flow cytometry) abnormalities, give the clinician significant information on which to base clinical decisions.

Underscoring these points, a decision analysis study that tested whether esophagectomy or continued surveillance is the optimal treatment for patients with high-grade dysplasia was recently reported in abstract form.[61] Seven strategies were tested, the first being immediate esophagectomy and the remaining six, surveillance for 3, 6, 12, 18, and 24 months and esophagectomy if cancer was identified and, finally, no cancer ever identified. The simulation continued until all patients died of cancer or other causes. A 5-year estimate of 20% to 50% for the development of cancer in patients with high-grade dysplasia was used (quite reasonable in view of the data presented earlier) and included operative mortality and both short- and long-term disability associated with esophagotomy. Immediate esophagectomy was the preferred treatment with all levels of cancer risk anywhere from 10% to 50%. Furthermore, immediate esophagectomy had the greatest gain in quality-adjusted life years. Esophagectomy remained the preferred treatment unless the cancer incidence fell below 3% at 5 years, the operative mortality rose to above 64%, or the quality-adjusted life years after esophagectomy declined to less than 0.5 (0 dead, 1 normal). These rather surprising data lend further credence to the decision for esophagectomy in patients with high-grade dysplasia.

Although efforts at effective ablation of dysplastic Barrett's esophagus have been ongoing for more than a decade, major obstacles remain.[62] Ablation of large segments of Barrett's epithelium is compromised by the fact that residual Barrett's epithelium remains in as many as half the patients and severe complications such as stricture or motility disturbances will develop in 25% to 30%. Effective ablation of small areas of dysplasia, whether by mucosal resection or thermal or photodynamic energy, requires accurate localization. Localization of a nonvisible area containing high-grade dysplasia is presently not possible, although technologies looming on the horizon such as optical coherence tomography may make this a clinical reality. Finally, investigators at the Mayo Clinic Rochester have found that despite the histologic absence of dysplasia after ablation, genetic abnormalities characterizing a premalignant epithelium remain.[63] Ablation is still an elusive goal.

Evidence supporting the performance of esophagectomy in patients with high-grade dysplasia comes from studies of esophagectomy specimens from patients with a preoperative diagnosis of high-grade dysplasia without carcinoma.[64] A report from the Cleveland Clinic that included the use of a jumbo forceps biopsy protocol found adenocarcinoma present in 10 of 28 patients who had a maximum preoperative diagnosis of high-grade dysplasia.[65] Despite the use of a surveillance protocol that entailed four-quadrant biopsy at 1- or 2-cm intervals within the Barrett's segment, the group at the University of California, San Francisco, recently reported that adenocarcinoma was present in the esophagectomy specimens of 4 of 11 patients with a maximum preoperative diagnosis of high-grade dysplasia.[66] Three of the cancer patients had disease not limited to the mucosa and died within 16 months of surgery. Overall, between a third and a half of patients with a maximum diagnosis of high-grade dysplasia will have occult adenocarcinoma. We believe that this fact justifies consideration of esophageal resection in all patients with a definite diagnosis of high-grade dysplasia. It is not possible with the present technology, including endoscopic ultrasound, to differentiate patients who do or do not harbor cancer. Importantly, the combination of regular surveillance and esophagectomy for patients with high-grade dysplasia has been shown to result in the detection of early-stage cancer and consequently high overall survival rates.[67,68] The 5-year survival rate approaches 90% in this setting (Fig. 24–4). When invasive cancer is found, most of these tumors will be limited to the wall of the esophagus, and few will have spread to the regional lymph nodes.

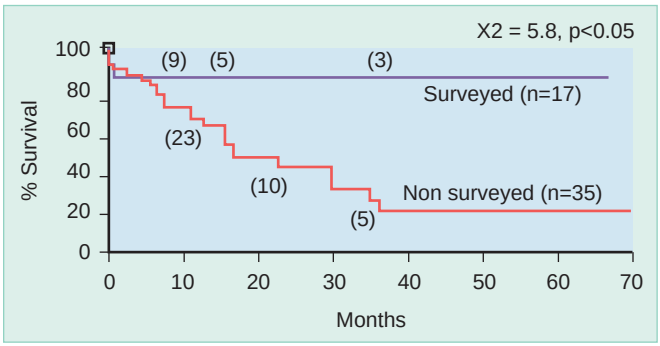

Figure 24–4. Kaplan-Meier survival curves for patients enrolled and not enrolled in an endoscopic surveillance program for Barrett's esophagus. (From Peters JH, Clark GWB, Ireland AP, et al: Outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and non-surveyed patients. J Thorac Cardiovasc Surg 108:813-822, 1994.)

Extent of Resection for High-Grade Dysplasia

The standard surgical resection for patients with high-grade dysplasia includes total esophagectomy with removal of all Barrett's tissue and any potential associated adenocarcinoma. This is usually accomplished by transhiatal or transthoracic esophagectomy, with most expert centers favoring the transhiatal approach. Reconstruction generally requires a posterior mediastinal gastric "pull-up" procedure with placement of the anastomosis in the neck. Intrathoracic anastomoses are to be avoided because of the high prevalence of disabling reflux symptoms after an intrathoracic esophagogastrostomy. The mortality associated with this procedure should be less than 5% and is less than 1% in centers experienced in esophageal surgery. Functional recovery is good to excellent in the vast majority of patients.

Recently, we have used a transhiatal vagal-sparing esophageal stripping procedure, with colon interposition, as a more physiologic alternative to standard transhiatal esophagectomy in patients with high-grade dysplasia.[69] Sparing the vagal nerves improves the functional outcome by eliminating one of the major sources of postoperative alimentary morbidity after esophagectomy, namely, the postvagotomy effects of gastric atony

and diarrhea. Its use is limited, however, to patients in whom there is little or no likelihood of lymph node metastases. Selecting such patients can be difficult. Recent data from our experience indicate that given careful endoscopic examination and biopsy, nodal disease is rare in the absence of a visible lesion.[70] The lymph node status of 10 patients with no endoscopically visible lesion and a biopsy diagnosis of high-grade dysplasia or intramucosal adenocarcinoma was retrospectively reviewed after en bloc esophagectomy. A total of 370 lymph nodes from these 10 patients were examined by both conventional histopathologic and immunohistopathologic methods. Only one lymph node contained metastatic disease. In contrast, 5 of 9 patients with an endoscopically visible lesion and a preoperative diagnosis of either high-grade dysplasia or intramucosal adenocarcinoma had metastasis to regional lymph nodes. If an endoscopically visible lesion is present, the frequency of submucosal disease is high. Because tumors that invade through the muscularis mucosa into the submucosa have a 60% or higher incidence of lymph node metastasis, it seems prudent to perform regional lymph node dissection with esophagectomy for the treatment of visible lesions, regardless of the histologic findings on biopsy (i.e., high-grade dysplasia or intramucosal carcinoma). Recent studies indicate, however, that in early adenocarcinoma in Barrett's esophagus, metastases do not appear to involve the splenic artery nodes and the spleen. Splenic artery dissection and splenectomy are therefore not necessary in this circumstance, nor is extended gastric resection.

Without question, removing the esophagus is a major undertaking often fraught with significant morbidity and mortality. What is often underestimated is the intensity of resources and emotional burden associated with the decision to pursue surveillance every 3 months. When given the option, many patients prefer to eliminate the possibility of development of esophageal adenocarcinoma, even if esophagectomy is the price to do so. Our challenge is to improve the state of the art such that this can be accomplished with as little morbidity as possible. After esophagectomy, average mortality has steadily decreased over the past 2 to 3 decades from higher than 25% to 2% to 4% in most centers. It approaches zero in large series of resection for benign disease[71] (in which patients with high-grade dysplasia can be included) and in units that have specifically focused on preventing death from esophageal resection, such as that in Hong Kong.[72] That being said, as the authors aptly point out, it is arguably the most sensitive surgical procedure to volume-outcome relationships.

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Chapter

25

Endoscopic Ablation of Barrett's Metaplasia and Dysplasia

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BARRETT'S ESOPHAGUS

Barrett's esophagus develops as a result of chronic, pathologic reflux of gastroduodenal contents into the esophagus. The diagnosis is made initially by the endoscopic finding of salmon-colored epithelium in the distal esophagus, followed by histologic confirmation of specialized intestinal columnar epithelium (intestinal metaplasia [IM]) via biopsy.[1,2] Barrett's esophagus is classified by histology as either nondysplastic IM (hereafter IM), low-grade dysplasia (LGD), or high-grade dysplasia (HGD).

Barrett's esophagus is present in 1% to 2% of the adult U.S. population,[2-5] with recent reports suggesting a growing prevalence.[6,7] Rex et al. reported a 6.8% prevalence of IM in a general population of patients undergoing colonoscopy.[6] Among patients who reported symptoms of gastroesophageal reflux disease (GERD) in this study, the prevalence of IM, as might be expected, was even higher (8.6%). Gerson et al. reported a 25% prevalence of IM in a predominantly white, male, non-GERD population (>50 years of age) undergoing sigmoidoscopy.[7] The cause of this observed increase in the number of cases of Barrett's esophagus is unclear, but it may be related to the increase in the prevalence and awareness of GERD, more liberal use of endoscopy, and the broad use of antisecretory medications.

To assess the options available for the management of Barrett's esophagus, specifically, interventions intended to completely eradicate this lesion endoscopically before its progression to HGD or adenocarcinoma, the risk for progression of Barrett's esophagus must first be carefully considered.

RISK OF PROGRESSION TO DYSPLASIA AND ESOPHAGEAL ADENOCARCINOMA

The risk for a patient with nondysplastic Barrett's esophagus to progress to esophageal adenocarcinoma has been reported to be 0.4% to 1.0% per patient per year,[8-10] a risk 30 to 125 times higher than in the general population.[3,4,11] In 2005, according to the American Cancer Society, there were 14,520 new cases of esophageal cancer in the United States, the majority of which were adenocarcinoma, and 13,570 deaths associated with this disease.[12] This figure represents a 300% to 500% rise in U.S. esophageal cancer incidence over the last 30 years, an increase in incidence that surpasses that of all other cancers.[5]

Sharma et al. reported that on initial diagnosis of Barrett's esophagus in 1376 patients (Tables 25–1 and 25–2), LGD (7.3%), HGD (3.0%), or adenocarcinoma (6.0%) had *already* developed in a large number of patients.[8] Thereafter, 618 of the *nondysplastic* IM patients from this series underwent endoscopic surveillance for an average of 4 additional years. During this 4-year interval, a significant number of these previously nondysplastic IM patients progressed to LGD (16.1%), HGD (3.6%), or adenocarcinoma (2.0%). According to these data, the risk for a patient with nondysplastic IM to progress to either HGD or adenocarcinoma, diagnoses for which the standard of care is surgical esophagectomy, is *1.4% per patient per year.* Stated differently, 1 in 71 patients with nondysplastic Barrett's esophagus will have their esophagus removed every year because of the development of HGD or adenocarcinoma.

Table 25–1 Incidence of LGD, HGD, and Cancer at Primary Diagnosis of Barrett's Esophagus

New Case Diagnosis	Number	% of Cases
IM	1376	100
LGD	101	7.3
HGD	42	3.0
Cancer	91	6.7

HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia.
Created from Sharma P, Reker D, Falok G, et al: Progression of Barrett's esophagus to high-grade dysplasia and cancer: Preliminary results of the BEST trial. Gastroenterology 120:A16, 2001.

Table 25–2 Incidence of LGD, HGD, and Cancer in Patients with Nondysplastic Barrett's Esophagus

Diagnosis	Total	% Risk in 4 Years	% Risk per Year
Total IM patients	618	NA	NA
New LGD	100	16.1	4.3
New HGD	22	3.6	0.9
Cancer	12	2.0	0.5

HGD, high-grade dysplasia; IM, intestinal metaplasia; LGD, low-grade dysplasia.
Created from Sharma P, Reker D, Falok G, et al: Progression of Barrett's esophagus to high-grade dysplasia and cancer: Preliminary results of the BEST trial. Gastroenterology 120:A16, 2001.

COLON POLYP/COLON AND RECTAL CARCINOMA VERSUS BARRETT'S ESOPHAGUS/ESOPHAGEAL ADENOCARCINOMA: A "PRECURSOR LESION" COMPARISON

According to the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database for 2005, the lifetime risk for the development of colon and rectal carcinoma (CRC) is 5.7%, whereas that for esophageal cancer is 0.5%.[13] In 2005 there were 145,290 new cases of CRC in the United States and 14,520 new cases of esophageal cancer. Although CRC has a much higher incidence than esophageal cancer (approximately a 10-fold difference), the age-adjusted death rate for CRC is 20.5 per 100,000 population versus 4.4 per 100,000 for esophageal cancer (less than a 5-fold difference). Furthermore, the death rate for CRC in males (all races) is 24.8 per 100,000 versus 7.7 per 100,000 for esophageal cancer (approximately a threefold difference). This dichotomy between the incidence and death rate for CRC and esophageal cancer is due to the difference in 5-year survival rates for the two disease states: 64.1% for CRC versus 14.9% for esophageal cancer, with the latter being one of the lowest 5-year survival rates of any cancer diagnosis.

The risk for progression to CRC in a patient with polyps of the colon[14] and the risk for progression to esophageal adenocarcinoma in a patient with nondysplastic Barrett's esophagus[8-10] are identical—0.5% per patient per year. A patient with Barrett's esophagus, however, has an additional risk, that of HGD (0.9% per patient per year), which results in an aggregate risk of 1.4% per patient per year for the development of a disease state for which the standard of care is esophagectomy.[8]

The surgical intervention for most CRC stages is segmental colectomy or hemicolectomy, and that for most esophageal cancer stages and HGD is esophagectomy. The morbidity and mortality associated with removal of a segment of colon are relatively low, whereas esophagectomy carries a low, but real risk for longer-term complications and death. Mortality rates associated with esophagectomy for invasive cancer are typically 4% to 6%, but several recent reports suggest that in the setting of a patient with HGD it may be significantly lower (0% to 1%). Of note, evidence suggests a significant volume-outcome relationship for esophagectomy in that patients undergoing esophagectomy in small, low-volume hospitals incur a mortality rate as high as 25%.[15,16] A recent study evaluated the mortality associated with esophagectomy in 8657 patients in the United States from 1988 to 2000. Analysis of a random sample of 20% of these cases found that the overall in-hospital mortality rate was 11.3% but was lower in high-volume surgical centers (decreasing to 7.5%).[17] Additionally, several large studies have found that 30% to 50% of patients experienced at least one serious postoperative complication such as pneumonia, myocardial infarction, heart failure, or wound infection and that the average length of hospital stay was at least 2 weeks.[18] Anastomotic strictures requiring dilation occur in 30% to 50% of patients after gastric pull-up, and though a nuisance, they are rarely a significant problem for the patient.[19] Respiratory function may remain depressed for 6 months after esophagectomy.[20] Removal of the gastroesophageal junction and relocation of the stomach remnant into the chest may be associated with refractory gastroesophageal reflux, long-term pulmonary complications, and a risk for recurrence of Barrett's esophagus.[21,22] For these reasons most experts advocate a high intrathoracic or cervical anastomosis, which markedly diminishes these problems. Taken together, these observations suggest that referral to a high-volume center is probably in the patient's best interest.

PREVENTION OF COLON AND RECTAL CARCINOMA AND HIGH-GRADE DYSPLASIA/ADENOCARCINOMA

After the advent of barium radiography of the colon, it was hypothesized that the development of CRC was preceded by malignant transformation of adenomatous

polyps, and subsequently the metaplasia-dysplasia-carcinoma sequence was proposed.[23] Surveillance studies with matched cohorts, such as the National Polyp Study, found that colon carcinoma was significantly less likely to develop in patients undergoing endoscopic removal of adenomatous polyps, a risk reduction that has approximated 80% to 90%.[14] Subsequently, the use of screening colonoscopy plus removal of colon polyps has been recognized as the most effective method for diagnosing and ultimately reducing the risk for development of CRC.[24] Therefore, the paradigm related to colon polyps and prevention of CRC is to (1) screen candidate patients for colon polyps (detect the precursor lesion for CRC) and (2) remove the precursor lesion, which has a 0.5% per patient per year risk for progression to CRC (prevent progression to CRC).

For Barrett's esophagus and prevention of esophageal adenocarcinoma, the current paradigm is clearly different: (1) do not screen patients, but rather detect Barrett's esophagus (precursor lesion for adenocarcinoma) incidentally on endoscopy indicated for GERD symptoms; (2) once detected, do not remove the precursor lesion, even though the lesion incurs a 1.4% per patient per year risk of progressing to HGD or adenocarcinoma; (3) survey patients with nondysplastic Barrett's esophagus every 3 years to detect progression to HGD or adenocarcinoma; and (4) remove the esophagus when HGD or adenocarcinoma is detected.

RATIONALE FOR ENDOSCOPIC REMOVAL OF BARRETT'S METAPLASIA AND DYSPLASIA

Given the elevated inherent risk for progression of nondysplastic Barrett's esophagus to HGD or adenocarcinoma, why then has a conservative "watch and wait" approach been the historic practice paradigm for these patients? The answer may lie in the fact that a technique for safe, effective (complete), and reproducible removal of all IM tissue in a given patient has been quite elusive. The endoluminal techniques that have been studied for removing Barrett's esophagus include circumferential balloon-based radiofrequency ablation,[25-30] photodynamic therapy (PDT),[31-47] endoscopic mucosal resection (EMR),[48-54] laser ablation,[3,55-61] argon plasma coagulation (APC),[3,55,62-73] multipolar electrocoagulation (MPEC),[3,55,74-78] and cryotherapy.[79-81]

There are multiple challenges inherent to achieving safe, effective, and reproducible removal of Barrett's esophagus, and each of these factors must be considered when evaluating a technique for managing this disease: (1) access (the targeted portion of the esophagus is approximately 30 to 40 cm from incisors); (2) the corrugated nature of the esophageal lumen (an uneven epithelial target); (3) mucous and gastric contents affecting the ablative effect of any energy source; (4) esophageal motility, which creates a moving ablation target; and (5) a very limited, tight margin between the ablation being "deep enough" (to the muscularis mucosae) and "too deep" (into the submucosa).

The ideal means to achieve safe, effective, and reproducible ablation of Barrett's esophagus should (1) be feasible for an endoscopist skilled in interventional techniques to perform; (2) be capable of removing all Barrett's epithelium; (3) result in no subsquamous IM (buried glands); (4) have a very low rate of complications, such as stricture formation, bleeding, and perforation; and (5) be well tolerated by the patient, thus enabling repeat therapy as needed for the lifetime of the patient for recurrent (new) or persistent disease, given the chronicity and GERD-related nature of Barrett's esophagus.

What depth of tissue ablation is required to effectively eliminate Barrett's esophagus? Ackroyd et al. reported that the thickness of nondysplastic IM (500 ± 4 μm; range, 390 to 590 μm) is very similar to that of normal squamous epithelium (490 ± 3 μm; range, 420 to 580 μm).[82] This narrow range and tight standard deviation for Barrett's thickness suggest that interpatient and intrapatient variability is very small. This information is promising in that if an ablation technique can be shown to repeatedly and uniformly penetrate at a minimum to the muscularis mucosae (≈700 μm) and at a maximum to the top of the submucosa (≈1000 to 1500 μm), Barrett's epithelium can be reliably and safely removed. Proactive eradication of Barrett's esophagus, if safe and effective, could lead in the long-term to demonstration of a risk reduction for the development of adenocarcinoma.

Thus far we have reviewed the risk inherent for progression of nondysplastic Barrett's esophagus to HGD and adenocarcinoma, the comparison between the "precursor lesions" of colon polyps and nondysplastic Barrett's esophagus, and finally the rationale and ideal requirements for developing an endoprevention paradigm for proactively managing Barrett's esophagus. In the remainder of this chapter we review the presently available techniques for removing and ablating Barrett's esophagus.

CIRCUMFERENTIAL BALLOON-BASED RADIOFREQUENCY ABLATION

The most recently developed tool for ablation of Barrett's esophagus is a balloon-based electrode array (HALO[360] system, BÂRRX Medical, Inc., Sunnyvale, CA) (Figs. 25–1 to 25–5). The balloon is used to dilate the targeted portion of the esophagus to a standardized pressure (0.5 atm), which transiently flattens the esophageal folds and submits the esophageal wall to a standardized tension or stretch. With the esophagus in a dilated state, a high-power, ultrashort (≈300 msec) burst of ablative energy is applied to the epithelium to create a uniform depth of ablation of the muscularis mucosae (≈1000 μm).[25]

The key features of this device that are intended to achieve a uniform ablation depth and wide-field removal of epithelium are (1) very high power (300 W), (2) ultrashort energy delivery time (<300 msec), (3) tightly spaced bipolar electrode array (<250 μm between electrodes), (4) standardized wall tension with balloon dilation, (5) standardized energy density (joules of energy

Figure 25–1. Balloon-based electrode (HALO^{360} Ablation Catheter, BÂRRX Medical, Inc., Sunnyvale, CA). Three-centimeter length with 60 narrowly spaced circumferential electrode bands.

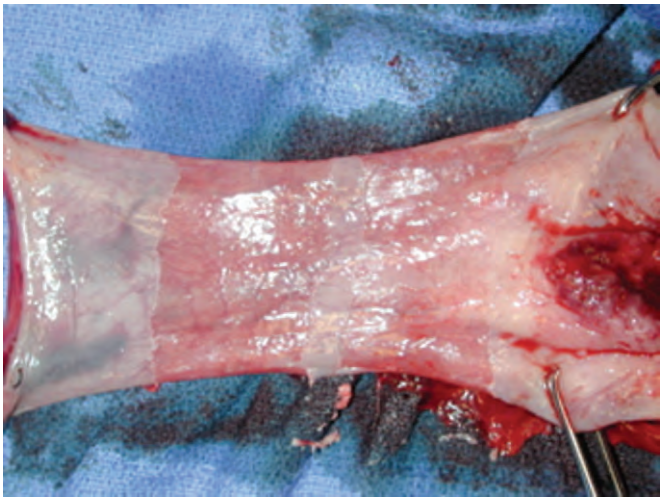


Figure 25–3. Resected human esophagus. Two separate ablation zones delivered via the HALO^{360} system at 10 J/cm^2. Squamous epithelium completely sloughed to the level of the muscularis mucosae.

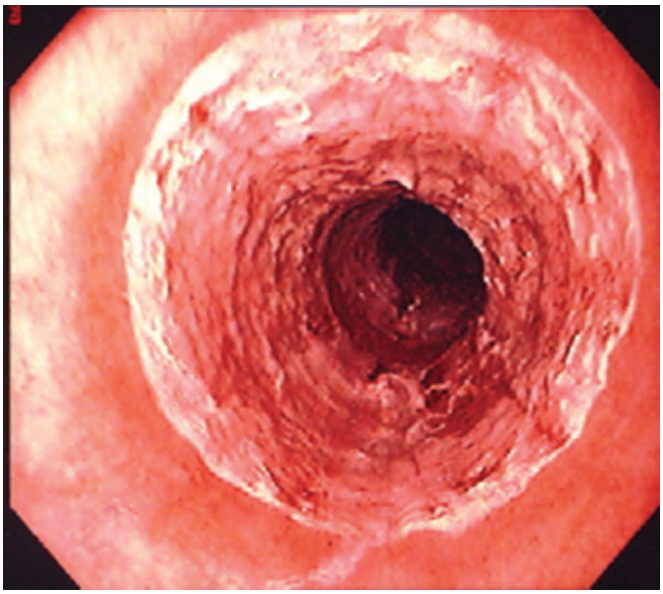
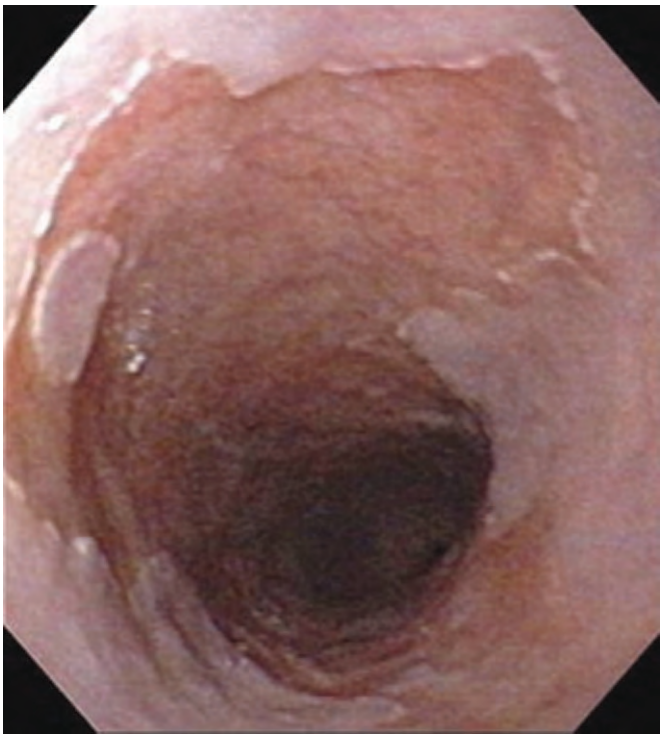


Figure 25–2. Endoscopic appearance after a single ablation with the HALO^{360} system at 12 J/cm^2 in the human esophagus.



Figures 25–4. Human patient with low-grade dysplasia before ablation with the HALO^{360} system.

delivered to each square centimeter of epithelium), and (6) large surface area of the electrode (>30 cm^2).[25]

Why might each of these elements be important? High power (1) enables ultrashort energy delivery time (2), which mitigates the risk of thermal conduction deep into the esophageal wall and prevents injury to the submucosa. Submucosal injury would inevitably lead to stricture formation. Tight bipolar electrode array spacing (3), as assessed by finite element modeling and bench experimentation, further limits the depth of tissue heating. Finite element analysis is a technique to map electrical field and heating characteristics. Changes in esophageal wall tension at the time of energy delivery could adversely affect the ablative effect, and it is therefore important to standardize the balloon inflation pressure (4) in order to control ablation depth. The endoscopist cannot be required to rely on visual evidence of heat-related changes in the epithelium as the end point for ablation. The ablation tool must therefore be automated and

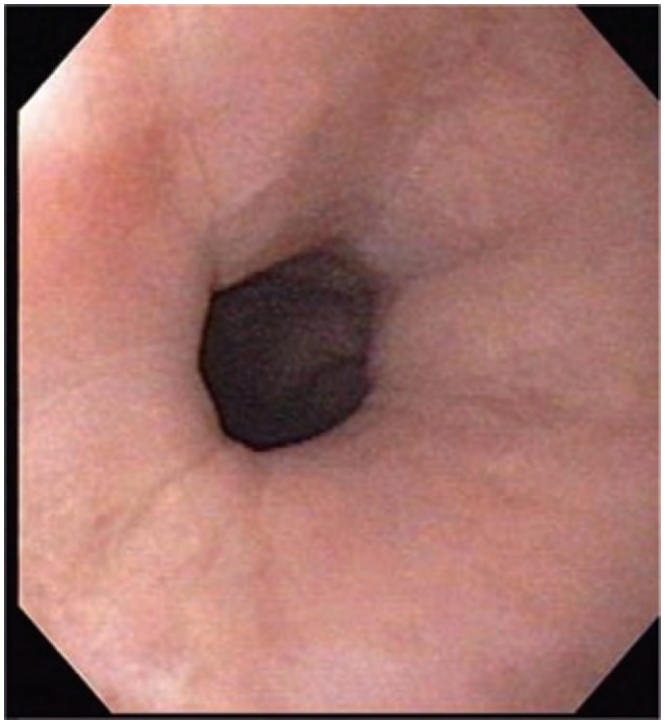


Figure 25–5. Human patient with low-grade dysplasia (LGD) 6 months after ablation with the HALO^{360} system at 12 J/cm^2 delivered twice. Baseline histology showed LGD, whereas all biopsy specimens from 6-month endoscopy showed normal squamous epithelium without subsquamous intestinal metaplasia.

capable of standardizing wall tension and delivering a precise amount of energy (5) to each surface area unit (J/cm^2) to avoid undertreatment or unintended deep tissue injury. Finally, to ablate large areas of Barrett's esophagus, it is necessary to have a large electrode surface area (6), not just a small probe. This device ablates more than 30 cm^2 of epithelium in less than 1 second.

Ganz et al. reported on the use of this ablative device in a porcine model, as well as human esophagectomy patients.[25] Ablation depth was directly related to the energy density delivered, with 8 to 12 J/cm^2 resulting in complete removal of epithelium. There were no strictures and no significant submucosal injury within this energy density range. Deeper injury and subsequent stricture formation were evident at higher energy density settings (>20 J/cm^2). A follow-on evaluation of this device in human subjects undergoing esophagectomy was included in this report. Ablation was performed 1 to 2 days before esophageal resection. Energy density settings of 10 and 12 J/cm^2 were used. Histologic examination revealed that removal of epithelium was complete in all areas of balloon electrode contact. The maximum depth of ablation was the muscularis mucosae, with no submucosal injury, thus corroborating the animal study findings in this energy density dose range.[25]

Dunkin et al. studied the effect of this device in a larger series of patients undergoing esophagectomy who received 10 or 12 J/cm^2 delivered once or twice. Complete removal of the esophageal epithelium without injury to the submucosa or muscularis propria was possible with the balloon-based electrode at 10 J/cm^2 (two overlapped applications in one treatment session) or 12 J/cm^2 (once or twice). A second application did not significantly increase ablation depth, and therefore overlapping ablations zones did not portend a significantly deeper injury.[28]

Sharma et al. reported on the use of this device in the multicenter dosimetry Ablation of Intestinal Metaplasia (AIM-I) trial in patients (N = 32) with nondysplastic IM. The procedure was performed with the use of conscious sedation on an outpatient basis. The median procedure time was 24 minutes. Energy densities evaluated were 8, 10, and 12 J/cm^2 (all delivered once). The procedure was well tolerated and there were no strictures or buried glands. Pathologic examination was performed by a centralized pathology service. After one application, most patients treated with 8 J/cm^2 had residual IM, whereas 10 and 12 J/cm^2 resulted in a respective 40% and 36% complete response (CR) rate (no histologic evidence of IM on four-quadrant biopsies). Given the equivalence of 10 and 12 J/cm^2, all patients were treated a second time with 10 J/cm^2, which resulted in a CR rate of 67% at 1 year.[26]

Fleischer et al. performed a larger follow-on study to AIM-I, deemed AIM-II, which included longer-segment (2 to 6 cm), nondysplastic IM. The median procedure time was 26 minutes. A single energy density setting was evaluated, 10 J/cm^2 (delivered twice). The procedure was well tolerated and there were no strictures or buried glands. At 12 months, the CR rate was 52%. Patients with persistent IM at 1 year typically exhibited focal disease only, in the form of small islands (the average clearance in the group with residual disease was 90%).[30]

Sharma et al. evaluated this device in patients with IM-LGD at 12 J/cm^2 (applied twice). They reported CR rates of 100% for LGD and 60% for IM at 1-year follow-up, with no strictures or buried glands.[27]

In a report by Smith et al., subjects underwent endoluminal ablation of one or two circumferential 3-cm segments of the esophagus that contained IM-HGD with the HALO^{360} system. Treatment settings were randomized to 10, 12, or 14 J/cm^2 and two to six applications. After esophagectomy, multiple sections from each ablation zone were evaluated by hematoxylin-eosin staining and microscopy. The maximum ablation depth was the lamina propria or muscularis mucosae in 10 of 11 specimens. One section treated at the highest energy (14 J/cm^2, four applications) had edema in the submucosa. In the well-overlapped areas of treatment, 91% (10/11) of specimens had no evidence of IM-HGD remaining. In one specimen the majority of IM-HGD was ablated, but small focal areas remained. In three specimens, IM-HGD was found at the edge of the treatment zones where overlap of the multiple energy applications was incomplete. They concluded that complete ablation of IM-HGD in 91% of treatment zones, without excessively deep injury, was possible with this device.[29] As a follow-on to these pilot dysplasia trials, a large, multicenter, randomized, sham-controlled trial is currently

under way to compare ablation with the HALO[360] system plus esomeprazole with a sham ablation plus esomeprazole in patients with LGD or HGD.

PHOTODYNAMIC THERAPY

PDT involves the systemic administration of a photosensitizing pharmaceutical agent followed by the endoscopic delivery of light energy to the affected esophagus. Exposure to this drug-specific wavelength of laser light results in activation of the photosensitizer within esophageal epithelial cells and the subsequent formation of toxic intracellular oxygen metabolites that can result in cell death.[32] Although several photosensitizing agents (both oral and intravenous) have been evaluated for PDT, only porfimer sodium (PORPDT) has received regulatory approval to treat patients with Barrett's esophagus and HGD in the United States.[35]

There have been several published reports regarding the use of PORPDT for the treatment of patients with HGD.[31-43] In the most rigorous and comprehensive clinical trial, recently published by Overholt et al., 208 patients with HGD were randomized to receive either PORPDT plus omeprazole (OM) ($n = 138$) or OM alone ($n = 70$).[31] Average follow-up was 24.2 months. Most patients in the PORPDT group underwent more than one treatment session, with 47% receiving three sessions. There was a significant difference between PORPDT+OM and OM at 18 months for the primary end point (presence of HGD), with 75% of patients receiving PORPDT+OM and 36% of those receiving OM being free of HGD ($P < .0001$). Only 52% of patients receiving PORPDT+OM were free of all IM at any point in the follow-up, whereas 7% of those receiving OM were free of IM.

Patient tolerability was an issue for the PORPDT+OM group, including photosensitivity occurring up to 90 days after injection (69%), esophageal stricture (36%), vomiting (32%), noncardiac chest pain (20%), pyrexia (20%), dysphagia (19%), constipation (13%), dehydration (12%), nausea (11%), and hiccups (10%). No major adverse events occurred in the OM group. Within the PORPDT+OM group, 18 patients (13%) progressed to esophageal adenocarcinoma as compared with 20 patients (29%) in the OM group.

Mayo Clinic researchers have independently reported their experience with PDT in a total of 142 patients (69 patients treated with PORPDT at Jacksonville, FL, and 72 patients treated with either a hematoporphyrin derivative or PORPDT at Rochester, MN).[37,38] The 19- to 20-month follow-up was similar to that of Overholt et al. in that complete elimination of Barrett's mucosa was found in 52% and 35% of patients, respectively, and elimination of HGD in 100% and 88% of patients, respectively. These studies also included the adjunctive use of post-PDT thermal ablation with APC. Stricture rates were 22% and 27%, respectively, comparable to that of Overholt.

The paramount issues that continue to be associated with the use of PDT include patient toxicity (photosensitivity, postablation symptoms), safety (stricture formation, vomiting, pleural effusion, atrial fibrillation),[43] changes in motility after ablation,[44] persistent IM despite elimination of dysplasia in the majority of patients, and subsquamous IM reported in every PDT trial and as high as 51.5% in a recent study.[45]

Triadafilopoulos et al. found that PORPDT followed by surveillance was more cost-effective than esophagectomy for treating HGD despite incurring a greater lifetime cost ($47,310 versus $24,045), mainly because of a higher quality-adjusted length of life associated with PORPDT.[46]

ENDOSCOPIC MUCOSAL RESECTION

EMR techniques have been used to diagnose and treat HGD and carcinoma in selected patients with Barrett's esophagus. EMR is performed via a variety of techniques, such as an endoscopic cap with an internal snare device, a variceal ligation device, or a monofilament snare in conjunction with lifting the mucosa with biopsy forceps.[48] Generally, these resection techniques are performed after an injection into the submucosal layer separates the target mucosa from the deeper muscularis propria layer to mitigate against esophageal perforation. Once snared, coagulative energy is delivered to the snare wire as it is pulled into the cap to cut and coagulate the margins of the specimen. Mucosal resection creates a relatively large excisional mucosal biopsy specimen with a typical diameter of 15 to 20 mm, which allows detailed histologic analysis, including resection margins, provided that the excision specimen is intact and includes the entire lesion.

Ell et al. evaluated the role of EMR in 64 patients with Barrett's esophagus: 61 with early cancer and 3 with HGD.[52] After EMR, complete remission was achieved in 97% of patients who demonstrated the following baseline characteristics: lesion size less than 2 cm, histology showing moderately or well-differentiated adenocarcinoma or HGD, and lesion limited to the mucosa. The complete remission rate was lower (59%) in patients with more advanced baseline findings: lesion size larger than 2 cm and limited to the mucosa, poorly differentiated adenocarcinoma, or infiltration of the submucosa.

Although EMR may be a reasonable technique for primary diagnosis or selective treatment of localized lesions, such as HGD nodules, there are limitations to the extent of mucosa that can be safely resected before toxicity and stricture formation are incurred.[54] Furthermore, EMR is technically demanding for most endoscopists. When used for focal resection of suspicious areas such as nodules, focal nodules, plaques, and intramucosal carcinoma, the residual Barrett's mucosa must still be considered "at risk" for progression to HGD and adenocarcinoma, and subsequent wide-field treatment should be considered.

LASER ABLATION

Laser light sources (light amplification by stimulated emission of radiation) have been used for esophageal mucosal ablation and include neodymium:yttrium-aluminum-garnet (Nd-YAG, 1064 nm), potassium titanyl

phosphate (KTP, 532 nm), and argon dye (514.5 nm). Mucosal depth of ablation and injury depend on the wavelength of the laser light energy used, treatment settings, and target tissue characteristics. Typically, Nd:YAG penetrates most deeply (up to 4 mm), whereas KTP is penetrates least deeply (≈1 mm).[3]

Reports of the use of laser ablation in Barrett's esophagus consist of small case series. In six of these reports,[56-61] complete ablation of all IM was achieved in 0% to 62% of cases after multiple treatment sessions. Buried glands were reported in some studies. Gossner et al. found that 20% of patients had subsquamous IM after laser ablation.[56]

The use of laser ablation has migrated away from primary therapy for Barrett's esophagus toward "spot ablation" salvage for wide-field ablation techniques, such as PDT, that experience high rates of residual focal nondysplastic IM.

ARGON PLASMA COAGULATION

APC is a system that delivers argon gas to the esophageal target epithelium via a through-the-scope catheter. As the gas exits the tip of the catheter, it is exposed to a monopolar electrode that ionizes the gas, which is carried to the tissue via the gas stream, thus returning to a common ground via a dispersive electrode.[3,62] As the energy passes through the epithelium, coagulation occurs. The depth of injury is dependent on the gas flow rate, power setting, duration of application, tissue hydration, and distance from the probe tip to the tissue.[3,62]

This technique has been used by several authors for the treatment of Barrett's esophagus with and without dysplasia.[63-73] Basu et al. reported that the best candidates for thermal ablation therapy are those with shorter segments of IM and good control of gastroesophageal reflux.[64] In this study, however, 44% of patients demonstrated subsquamous IM after treatment.

In 10 published cases series containing a diverse group of 221 patients with and without dysplasia,[63-72] CR rates for IM range widely from 0% to 99%. The observed inconsistency in results may be due to variability in technique, treatment settings, number of ablation sessions, ablation depth with APC, or any combination of these factors. Dulai et al. recently reported a comparison study between APC and MPEC.[73] This study was rigorously controlled with respect to treatment technique, treatment settings, number of treatment sessions, and follow-up, which may explain the more consistent results in comparison to other studies. They reported similar histologic CR rates for IM with APC (58%) and MPEC (65%), with 28 patients per group. The mean number of treatment sessions required to achieve these results was 3.8 (APC) and 2.9 (MPEC), with up to 6 sessions permitted. There was no subsquamous IM found in this study.

Complications related to APC for Barrett's esophagus that have been reported include pneumatosis, pneumoperitoneum, subcutaneous emphysema, pain, ulceration, stricture, bleeding, perforation, and even death.[63-72]

MULTIPOLAR ELECTROCOAGULATION

MPEC involves the delivery of radiofrequency energy to the tissue via a through-the-scope probe that delivers point coagulation to affected tissue. Energy travels between electrodes at the tip of the device and induces tissue coagulation. Like APC, laser ablation, and cryotherapy, the end point for treatment is visual coagulation.[3,55] In five case series,[74-78] 110 patients were treated with MPEC. The reported CR rate for IM ranged from 75% to 100%. Multiple sessions were required to achieve CR in all studies. All studies reported that adverse postablation symptoms were common; specifically, Kovacs et al. found that 41% of patients experienced dysphagia, odynophagia, or chest pain lasting up to 4 days.[76]

As with APC and laser therapy, MPEC is now most commonly used in the management of Barrett's esophagus for focal ablation of persistent IM after ablation with other modalities, such as PDT.

CRYOTHERAPY

Cryotherapy is not a new modality and has been used for tumor management in areas of the body other than the esophagus. More recently, cryotherapy has been studied in a limited manner for ablation of esophageal epithelium.[79,80] Liquid nitrogen is sprayed onto esophageal epithelium via a through-the-scope catheter. Previous attempts at using a "cold probe" were fraught with tissue sticking and ablation depth control. The mechanism of injury appears to include induced apoptosis and cryonecrosis.[81]

In a porcine model (N = 20), liquid nitrogen was sprayed onto squamous epithelium. Exposure time to the spray was varied between 10 and 60 seconds. The authors reported that 95% of the animals demonstrated complete ablation of the epithelium when sacrificed at 2 to 7 days. Stricture formation occurred in 15% of animals and aspiration pneumonia in 5%.[79]

CONCLUSION

Barrett's esophagus is caused by chronic pathologic exposure of the esophagus to gastroduodenal contents. The recurrent injury and resulting inflammation result in a metaplastic change in which the normal squamous lining of the esophagus is replaced by abnormal intestinalized columnar epithelium—a known precursor to esophageal adenocarcinoma. The prevalence of Barrett's esophagus is on the rise, but of much greater concern is the rapid rise in incidence of esophageal adenocarcinoma. For HGD and esophageal adenocarcinoma, surgical esophagectomy is the current standard of care. There is now a role for PDT in patients with HGD, and there are reports of the use of other ablation modalities and EMR for this diagnosis. A randomized sham-controlled trial is under way to evaluate the HALO^{360} balloon-based ablation device for LGD and HGD in an attempt to demonstrate eradication of dysplasia without the associated morbidity of surgery or PDT.

In this chapter we presented data regarding a paradigm that should be considered and supported with continued clinical studies. This paradigm involves proactive endoprevention for Barrett's esophagus containing nondysplastic IM and LGD. Early eradication of this disease, before progression, is a reasonable approach if the technique is safe, reproducible, and effective at removing all diseased tissue.

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Part 5

Esophageal Motility Disorders and Diverticula of the Esophagus

Chapter 26

Disorders of the Pharyngoesophageal Junction

André Duranceau

DEFINITION

Oropharyngeal dysphagia refers to difficulties in swallowing at the pharyngoesophageal level. This high or proximal dysphagia causes three categories of symptoms related to the fact that the oropharynx is involved in the function of swallowing, speech, and respiration. First, difficulty exists in propelling food or liquid from the oral cavity to the cervical esophagus. Regardless of whether the difficulty is initiating swallows, moving the bolus from the mouth to the pharynx, or food incarceration at the cricopharyngeus level, the result is difficulty swallowing. Second, when mechanical or functional obstruction impedes food or liquid transit, the bolus is misdirected back toward the mouth as pharyngo-oral regurgitation or through the nasopharynx as pharyngonasal regurgitation. The third category of symptoms relates to the larynx, with its role in phonation and respiration. Poor coordination plus hypopharyngeal stasis results in laryngeal and tracheal aspiration. The symptom complex of oropharyngeal dysphagia is for the most part associated with neurologic and neuromuscular disease. Idiopathic dysfunction of the upper esophageal sphincter (UES), with or without diverticulum formation, is also a frequent cause of oropharyngeal dysphagia. Previous treatment at the oropharyngeal level, either by surgery or by radiotherapy, may result in proximal dysphagia. Gastroesophageal reflux or transit abnormalities at the gastroesophageal junction may give rise to symptoms referred to the oropharyngeal level. The various causes of oropharyngeal dysphagia are classified in Box 26–1.

Patients with oropharyngeal dysphagia are difficult to assess. However, patients with these symptoms, when carefully selected, can be significantly improved by UES surgery.

The purpose of this chapter is to review the investigation of patients with oropharyngeal symptoms and clarify the role of surgery in managing these patients.

NORMAL FUNCTION

When a swallow is initiated, an organized sequence of events occurs that involves a sweeping action of the tongue, closing of the nasopharynx by the velopharyngeal muscles, and subsequent sequential contractions of the superior, medial, and inferior constrictor muscles. This sequence is difficult to evaluate because of the rapidity and variety of events that take place.

Tactile receptors in the pharynx elicit a series of reflex muscle activities that pull the pharynx up, elevate the hyoid bone, and bring the pharynx forward and upward.

Box 26–1 Etiology of Pharyngoesophageal Dysfunction

- Neurogenic
  - Central
  - Peripheral
- Myogenic
  - End-plate disease
  - Muscular disease
- Idiopathic dysfunction of the UES
  - Isolated UES dysfunction
  - UES dysfunction with a pharyngoesophageal diverticulum (Zenker's)
- Iatrogenic
  - Surgery
  - Radiotherapy
- Distal esophageal dysfunction
  - Gastroesophageal reflux
  - Motor disorders
  - Esophageal obstruction
- Mechanical
  - Intrinsic
  - Extrinsic
- Psychogenic

Respiration ceases, the larynx is closed by the false and true vocal cords, and the epiglottis covers the laryngeal aditus. At the same time, the muscles of the upper middle and lower constrictors, which form a continuous sheet of muscle, are activated sequentially whereas the inferior constrictor remains inhibited during most pharyngeal muscle activity.[1,2]

Pharyngeal swallowing is divided into six phases:

1. When a bolus is present in the oral cavity, the soft palate is opposed to the posterior portion of the tongue, thereby closing the oropharynx.
2. Elevation of the soft palate and hyoid bone occurs while the entire pharynx is raised in a piston-like motion.
3. Active compression of the tongue on the bolus pushes it against and along the hard palate toward the entrance of the oropharynx. The soft palate elevates posteriorly and opposes the constrictor wall, thereby closing the nasopharynx. When the bolus passes the limits of the oropharynx, involuntary deglutition occurs, and the descending wave of peristalsis begins.
4. The hyoid bone reaches maximal elevation, and the larynx elevates to approach the hyoid. At this point the laryngeal vestibule closes, and the epiglottis tilts downward while pharyngeal peristalsis descends toward the hypopharynx.
5. With pharyngeal contraction, approximation of the pharyngeal wall, soft palate, and posterior of the tongue creates a closed chamber where the bolus is squeezed into the hypopharynx and through the open cricopharyngeal sphincter.
6. The pharyngeal airway reopens, and the soft palate, tongue, larynx, and hyoid bone return to their resting positions. The epiglottis springs back to a vertical position, and the laryngeal airway reopens when the pharyngoesophageal junction closes and resumes its elevated resting pressure.[1]

Sokol and associates[3] studied simultaneous cineradiographic and manometric activity of the pharynx and hypopharynx in asymptomatic subjects with the use of continuous perfusion techniques. At rest, the pressure in the pharyngeal cavity is equal to atmospheric pressure. In the hypopharynx, when the pharyngeal wall is collapsed and no air column exists, resting pressure increases progressively to a maximal pressure at the level of the cricopharyngeal muscle. On swallowing, pressure recordings show an initial double pressure peak corresponding to elevation of the laryngopharynx and simultaneous thrust of the tongue (E and I waves). Peak pharyngeal contraction follows these two initial waves; it is a peristaltic sequence starting radiologically as a stripping wave with closure of the velopharyngeal muscles, and it empties the pharyngeal contents into the hypopharynx. In the hypopharynx, the same small double peak is identified on swallowing and is attributed to upward laryngeal movement, tongue thrust, and progression of trapped air or the advancing bolus.

Accurate recording of pharyngeal motor events is not possible with a water-filled or a water-perfused system. For these reasons, Dodds and associates[4] studied human pharyngeal motor function in 12 recordings with an intraluminal strain gauge system. They observed that the pressure was highest in the hypopharynx, with amplitudes on contraction averaging 200 mm Hg. Peak contractions reached 600 mm Hg in one subject. Contraction pressure averaged 100 mm Hg in the oropharynx and 150 mm Hg in the nasopharynx. Wave duration decreased progressively from the nasopharynx to the hypopharynx, from 1.0 to 0.3 second, and peristaltic wave speed ranged between 9 and 25 cm/sec (Fig. 26–1). Observations by Kahrilas et al.[2,5,6] and Castell et al.[7,8] confirmed the difficulty of obtaining precise information on pharyngeal function.

The upper esophageal sphincter is a high-pressure zone 2.5 to 4.5 cm in length.[3] Within this zone is a shorter high-pressure zone, 1 cm long, of maximally elevated pressure that corresponds to the location of the cricopharyngeus muscle. This same pressure profile was described more recently by Kahrilas and Cook as reviewed by Sivarao and Goyal.[9] The cricopharyngeus is a muscle sling attached posteriorly to both laminae of the cricoid cartilage. It exerts its maximal pressure in an anteroposterior direction, at which point it closes the pharyngoesophageal junction and forms a crescentic slit seen at rigid esophagoscopy as the upper limit of the esophagus.

Winans[10] studied the pharyngoesophageal high-pressure zone of 18 human subjects with a special eight-lumen recording catheter that had recording orifices

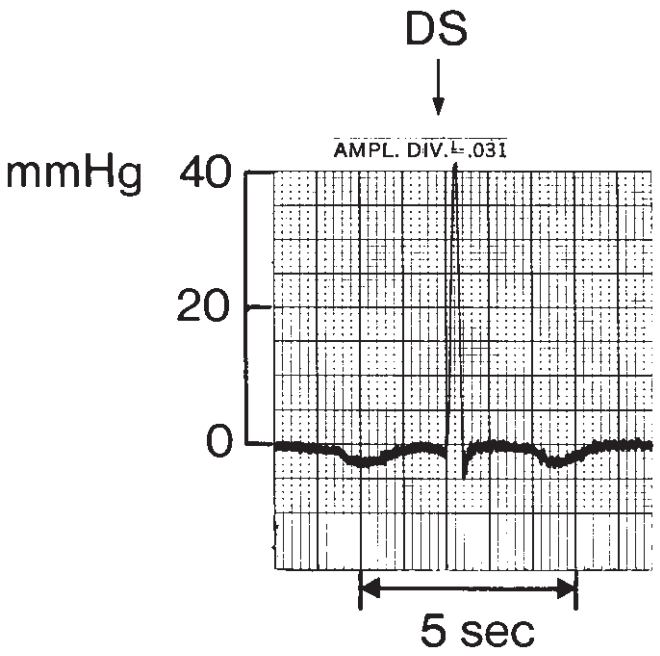


Figure 26–1. Pharyngeal contraction. A powerful single-peak contraction is produced with a duration of 0.4 second. This wave progresses at a speed of 9 to 25 cm/sec. DS, dry swallow.

spaced around its circumference. He observed significant pressure differences related to the position of the recording port, and this led to the concept of sphincter asymmetry (Fig. 26–2). In the UES, the greatest pressure (averaging 100 mm Hg) was recorded from the anterior and posterior orifices. Asoh and Goyal[11] showed that the UES is a high-pressure zone created mainly by the cricopharyngeus and inferior pharyngeal constrictor. They observed that its asymmetry is not only radial but also axial. Pera and colleagues[12] documented a significant decrease in UES resting pressure in patients undergoing sequential surgical myotomy of the cricopharyngeus.

The high-pressure zone of the UES is attributable to continuous active muscle contraction and the elasticity of the surrounding structures. At rest, the cricopharyngeus is a striated muscle that receives its motor nerves from vagal nuclei through the vagi without synaptic interruption. The nerve endings come into direct contact with the motor end plates, and a continuous vagal discharge maintains the tonus of the sphincter at rest.[11,13]

On swallowing, a sequence of relaxations involving the pharyngoesophageal muscle groups is caused by the disappearance of action potentials in the muscle fibers (Fig. 26–3). Forward and upward displacement of the larynx is also involved in the opening mechanism of the sphincter. Although it is generally agreed that the cricopharyngeus is the major component of the UES, its wider pressure zone as observed by Sokol et al.,[3] Winans,[10] Welch et al.,[14] Goyal et al.,[15] and Sivarao and Goyal[9] must be explained by other factors. For instance, the passive elastic force may maintain a closed UES. If the nerve supply to the sphincter is removed, residual closing pressure remains. In addition, the circular muscle of the pharyngoesophageal junction may play a role.[16]

On swallowing, the UES high-pressure zone falls to resting atmospheric pressure and remains open to accommodate bolus transport through the sphincter area. This relaxation is brought about by cessation of vagal nerve stimulation and by vertical upward displacement of the larynx, which pulls the UES for about 2 cm. Full sphincter relaxation is observed for 0.5 to 1.2 seconds, and with passage of the hypopharyngeal contraction, the sphincter closes with a contraction that

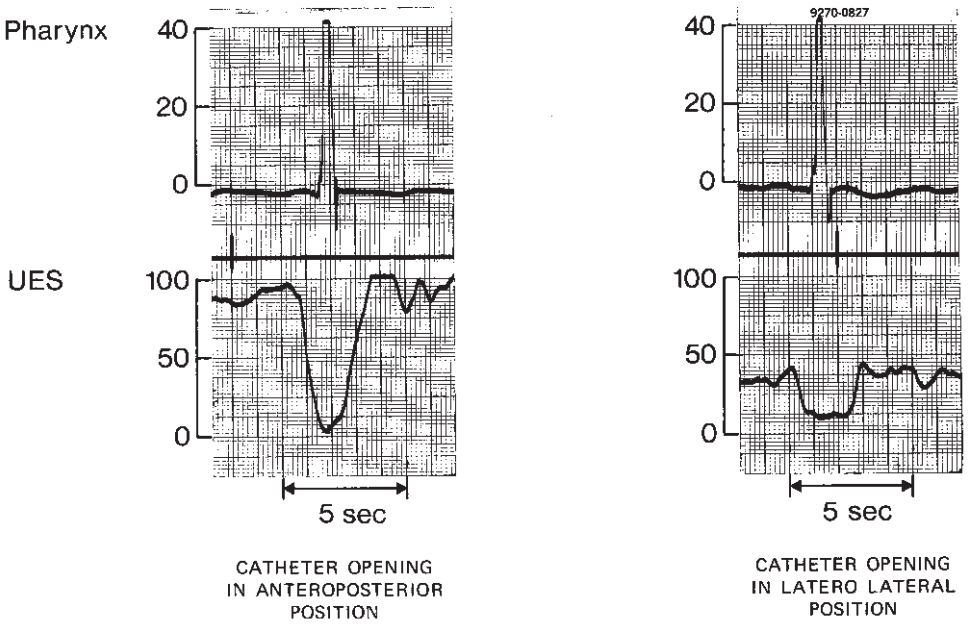


Figure 26–2. Asymmetry of the upper esophageal sphincter (UES). (From Winans CS: The pharyngo-esophageal closure mechanism: A manometric study. Gastroenterology 63:768, 1972, with permission.)

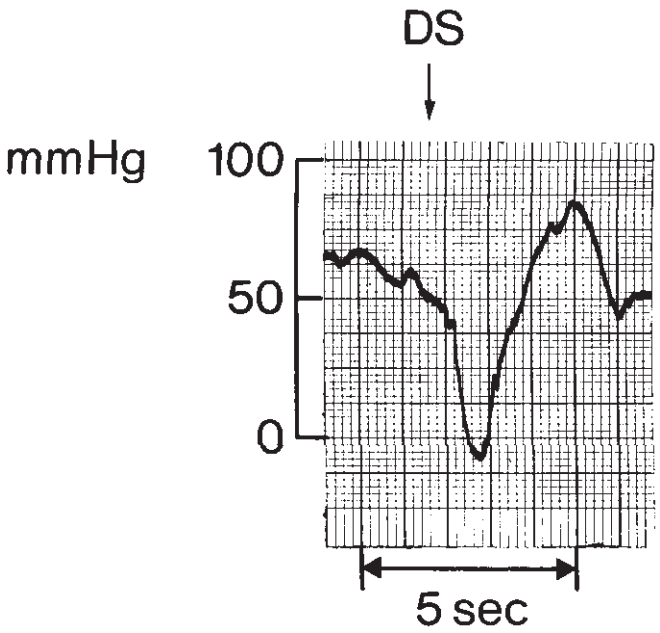


Figure 26–3. The high-pressure zone of the upper esophageal sphincter is caused by continuous active contraction of the cricopharyngeus muscle. DS, dry swallow.

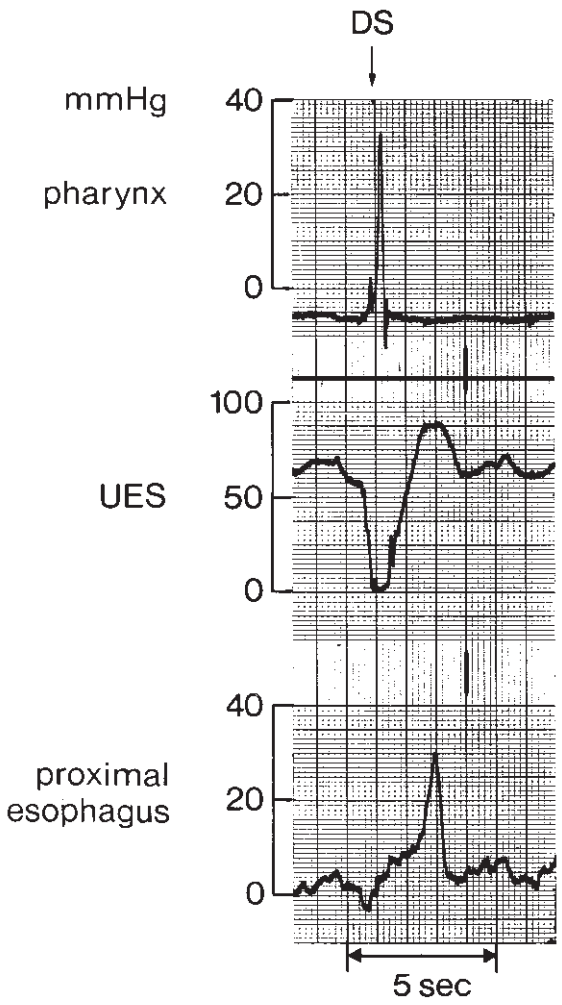


Figure 26–4. Pharynx, upper esophageal sphincter (UES), and cervical esophagus in action. During the rapid single contraction of the pharynx (13 cm), the high-pressure zone of the UES (18 cm) falls to ambient pressure. Passage of the contraction in the hypopharynx closes the sphincter, and the wave continues into the cervical esophagus (23 cm). DS, dry swallow.

creates a pressure that is often twice as high as the resting pressure in the sphincter (Fig. 26–4).

Physiologic evaluation of the UES is difficult because of recording issues. A single side-hole catheter recording must take into account the sphincter asymmetry. The eight-lumen circumferential recording catheter does not follow the upward movement of the sphincter on swallowing. Rapid pull-through techniques record a higher anteroposterior basal tone. A manometric recording device was proposed by Dent[17] and adapted to the UES by Kahrilas et al.[2]; it is a sleeve concept that is thought to record UES pressure behavior despite its movement during deglutition. However, evaluation of relaxation and coordination with pharyngeal contraction remains difficult. Castell and co-workers[7,8] proposed positioning the recording sensor above the high-pressure zone of the sphincter for that purpose, thereby allowing the opened sphincter, in its upward excursion, to be studied.

ASSESSMENT OF OROPHARYNGEAL DYSPHAGIA

Regardless of the cause, patients with oropharyngeal dysphagia must be assessed in a systematic fashion. Methods of investigation of the pharyngoesophageal junction have been reviewed by Cook and Kahrilas[18] and by Sivarao and Goyal.[9]

Clinical assessment of symptoms remains the most important step in classifying the disorder. Though subjective, it helps in obtaining the patient's medical history. The genealogy of transmitted disease can be clarified. For more objectivity, symptoms can be quantified in the manner suggested for reflux disease.[19] This method is summarized in Table 26–1.[20]

Videofluoroscopic evaluation of swallowing is used to detect and analyze functional impairment of the pharyngoesophageal junction. It assesses the response of the oropharynx, palate, proximal airway, and proximal esophagus to swallows of varied volume and consistency and can identify the presence and mechanism of dysfunction. Videofluoroscopy can clarify an inability or delay in initiating swallows, the occurrence of bolus regurgitation or aspiration, or retention of the bolus in the pharynx. Conventional studies are inadequate because of the rapidity of events during the early phase of swallowing. The importance of this type of radiologic assessment is emphasized by the fact that the abnormal function is sometimes confined to one or two frames projected each second.[21] Delineation of specific muscle

Table 26–1 Symptom Score Applied to Oropharyngeal Dysphagia

	1 Point	2 Points	3 Points	4 Points
Frequency	Occasional (<1/mo)	>1/mo, <1/wk	>1/wk, <daily	Daily
Duration	<6 mo	>6 mo, <24 mo	>24 mo, <60 mo	>60 mo
Severity	Mild: nuisance value	Moderate: spoils enjoyment of life	Marked: interferes with living normal life	Severe: terrible experience

For quantification of results: Add frequency and duration and then multiply by severity. Mild symptoms, 1 to 7; moderate symptoms, 8 to 15; marked symptoms, 16 to 23; severe symptoms, 24 to 32.

group abnormalities also requires the assistance of video technology.[22,23] Videofluoroscopic evaluation of swallowing with three-dimensional reconstruction was proposed, used, and perfected by Logemann and Kahrilas.[24]

Manometric evaluation of the entire esophagus must be performed. Assessment of the esophageal body and lower esophageal sphincter will rule out motor disorders and document the quality of lower esophageal sphincter tone. Specific manometric assessment of the UES quantifies the strength of pharyngeal contraction, the completeness of UES relaxation, and the timing of pharyngeal contraction relative to UES relaxation. However, precise recordings are limited in their depiction of events by a number of factors. The radial asymmetry of the sphincter requires multiple port recordings to sum the action of the sphincter[10] or a circumferential pressure-sensing transducer.[8,7] The Dent sleeve is a 6-cm perfused silicone membrane that also has the advantage of recording accurate resting pressure in the UES area.[2] It can record sphincter pressure at any level along the length of the membrane, even if movement displaces the sphincter. Assessment of sphincter relaxation and coordination with pharyngeal contraction is limited in accuracy by the upward movement of the larynx during the recording. Castell and associates[7,8] proposed positioning the recording sensor above the high-pressure zone of the sphincter for that purpose. Despite the sophistication of more recent manometric recordings, true abnormalities in function are undoubtedly underestimated in patients with pharyngoesophageal disorders. Integration of manometric data with fluoroscopic observation of the swallowing events was proposed and performed by Cook and colleagues.[25,26] The main advantage of this technique is detection and measurement of swallowing outcome and identification of subcategories of dysfunction, namely, impaired voluntary swallowing, impaired UES relaxation, and increased outflow resistance. The development of intrabolus pressure gradient recordings helped identify abnormal pathologic constriction in the UES during flow.[27]

Radionuclide pharyngoesophageal transit studies add quantitation to the symptoms. Boluses with different consistencies can be used to measure the poor emptying that results from oropharyngeal dysfunction. It adds to radiologic and manometric data by measuring the end result of any form of therapy that might be used in patients with transit abnormalities between the mouth, pharynx and proximal part of the esophagus.[28]

Endoscopic assessment of a patient with oropharyngeal dysphagia must be undertaken with great care. Anatomic abnormalities must be clearly delineated before any attempt at endoscopic evaluation. Flexible endoscopy can be used if no distortion is present. Any resistance to passage of the instrument should lead to assessment under general anesthesia. Examination under direct vision with a laryngoscope and short rigid esophagoscope should provide detailed visualization of the larynx, pharynx, hypopharynx, and esophageal inlet. No undue effort should be made to penetrate the cervical esophagus if resistance or abnormalities are encountered. Complete assessment of the esophageal body and cardia must be obtained in patients with oropharyngeal dysphagia. However, if any risk is entailed in the evaluation procedures, diagnosis and therapy for the proximal condition must prevail before completing the investigation of the remaining esophagus.

SURGICAL MANAGEMENT

Indications

Cricopharyngeal myotomy is a recognized treatment of patients with dysfunction of the pharyngoesophageal junction secondary to neurologic conditions. Intact voluntary swallowing and the absence of dysphonia are considered important prognostic factors for a successful outcome. In patients with oropharyngeal dysphagia caused by muscle disorders, cricopharyngeal myotomy is performed to remove the obstructive effect of the cricopharyngeus below a pharynx that is unable to mount a proper contraction to push the bolus into the cervical esophagus.

The only treatment available at present for idiopathic dysfunction of the UES and Zenker's diverticulum is surgery. The objective of the operation is to remove the effects of the restrictive myopathy affecting the UES. If the dysfunctional sphincter causes severe symptoms or if there is a symptomatic minute diverticulum present, extensive cricopharyngeal myotomy is completed over the pharyngoesophageal junction. When a diverticulum is present, cricopharyngeal myotomy remains the essen-

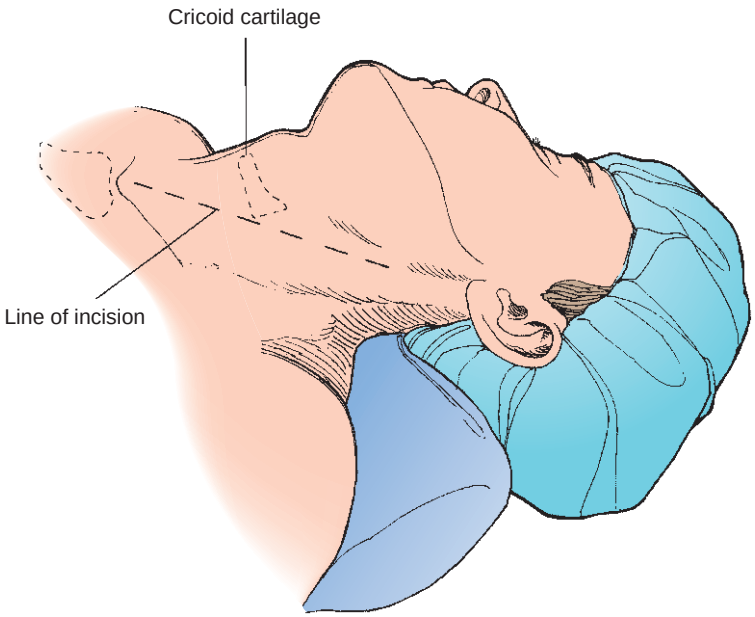


Figure 26–5. Position and incision for the operation. With a pillow under the shoulders, the head is in hyperextension and turned toward the right.

tial focus of treatment, and the diverticulum, seen as a complication of the dysfunction, is either suspended or resected.

Oropharyngeal dysphagia resulting from laryngectomy or from other extensive neck surgery may be encountered in patients so treated. Careful documentation of the UES dysfunction plus exclusion of any mechanical causes for the symptoms is important in these patients.

Operative Technique

Position and Incision

The patient lies in a supine position on the operating table. A pillow is placed under the shoulders to allow the head to be hyperextended and rotated toward the right. The anatomic reference point is the cricoid cartilage, into which the cricopharyngeus inserts. The incision follows the left interior border of the left sternomastoid muscle from the sternal notch to a point a few centimeters under the earlobe (Fig. 26–5).

Access to the Pharyngoesophageal Junction

The plane of access to the retropharyngeal area and to the superior mediastinum is between the large vessel sheath and the thyroid gland (Fig. 26–6A). Progressive division of the cervical tissue layers allows wide exposure of the pharyngoesophageal junction.

First, the subcutaneous tissues and platysma are divided. A branch of the cervical cutaneous nerve usually crosses the middle or proximal part of the incision; if low, the nerve must be divided, which can possibly result in some anesthesia or dysesthesia of the submandibular skin area. If the nerve is more proximal, it may be isolated and retracted for protection.

Next, the sternomastoid muscle is dissected free from the underlying prethyroid muscles and retracted laterally. The omohyoid muscle and both prethyroid muscles are then divided over the entire length of the incision to expose the thyroid gland and large vessels (see Fig. 26–6B).

At this point, the first surgical assistant exerts traction on the thyroid gland, and the middle thyroid vein, if present, is ligated and divided (see Fig. 26–6C). This allows the deep cervical fascia to be put under tension. It is opened proximally behind the pharynx, where the cellular plane between the pharyngeal wall and the prevertebral fascia is first identified. Progressive and careful opening of the fascia along the line of the incision is then completed to expose the interior thyroid artery, which is ligated laterally where it passes behind the carotid artery.

The assistant next retracts upward and contralaterally while exerting an eversion movement on the right side of the laryngeal and pharyngeal structures. The large vessels are retracted laterally to expose the entire posterior pharyngoesophageal junction. When a diverticulum is present and large enough, it can be recognized as a bulge at and below the pharyngoesophageal junction (Fig. 26–7). The recurrent laryngeal nerve is palpated and seen along the trachea just in front of the tracheoesophageal groove; it passes behind branches of the inferior thyroid artery.

Cricopharyngeal Myotomy

Extended cricopharyngeal myotomy of the pharyngoesophageal junction is the preferred technique when treating UES dysfunction of neurologic, muscular, idiopathic, or iatrogenic origin.[29,30]

Low-power diathermy is used on the superficial muscle layers of the posterior wall of the junction to trace

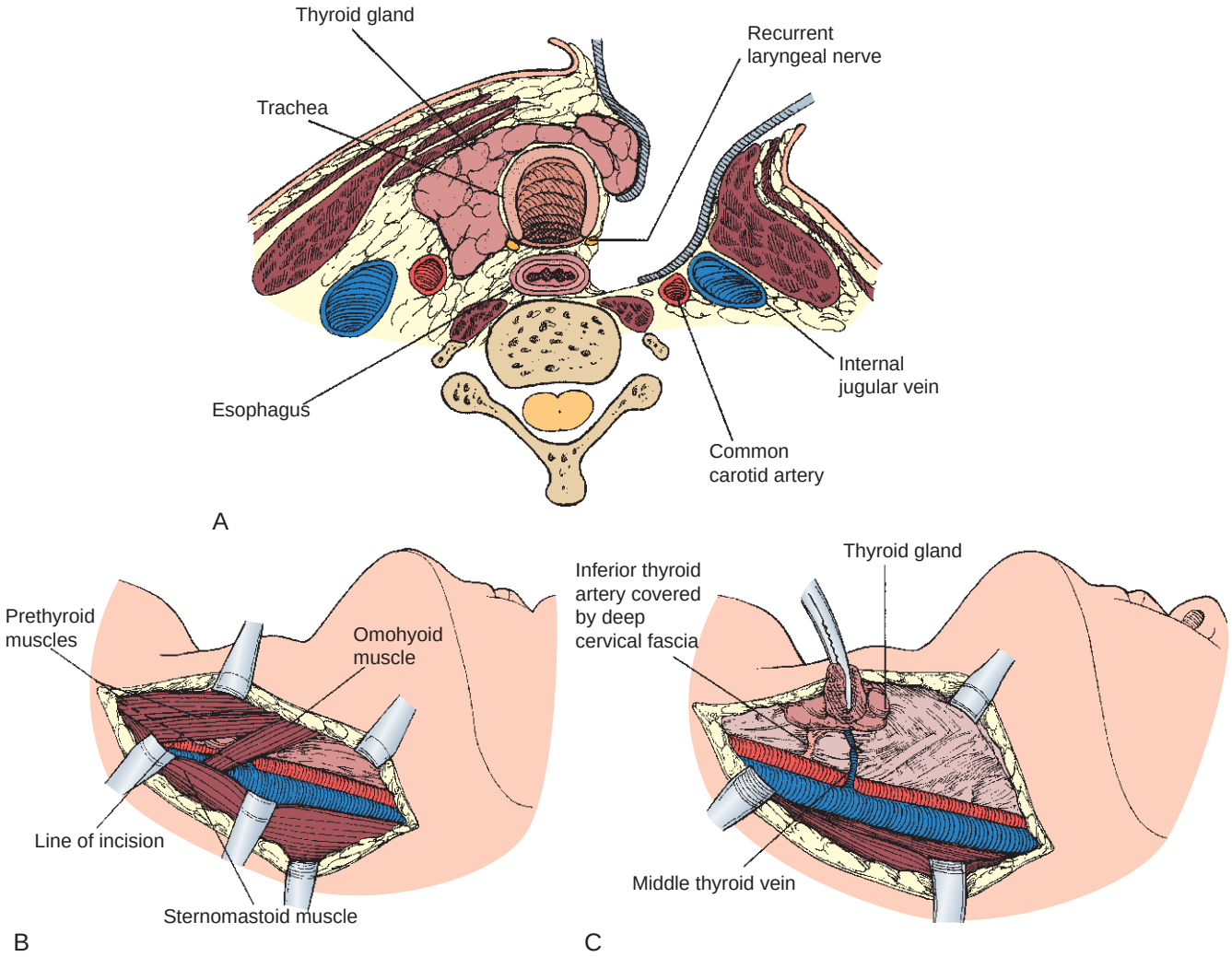


Figure 26–6. **A,** Plane of access to the retropharyngeal space. **B,** The incision is oblique along the anterior border of the sternomastoid muscle. The omohyoid and prethyroid muscles are divided along the length of the incision. **C,** The middle thyroid vein is ligated, the thyroid is retracted toward the right, and the deep cervical fascia is put under tension to be opened proximally behind the pharynx. When the fascia is opened, the inferior thyroid artery is located and ligated.

the intended myotomy. The line of the myotomy is drawn along the right tracheoesophageal groove, which is everted toward the surgeon (Fig. 26–8A). A No. 36 Maloney bougie is passed into the esophagus and serves as a stent during the myotomy. The use of surgical loupes during this part of the operation permits better visualization of fine details while ensuring meticulous hemostasis. With a No. 15 scalpel blade, the myotomy is started on the cervical esophagus and progresses upward. Two to three centimeters of muscularis is divided on the esophagus. When the circular layer is divided, the esophageal mucosa is allowed to protrude between the divided muscle layers. Division of the muscle fibers of the pharyngoesophageal junction is then completed by extending the myotomy 2 cm more proximally.

The cricopharyngeus itself is not a well-identified structure. It corresponds to a thickening of the esophageal musculature at the point where it joins the hypopharyngeal wall. The cricoid cartilage is the reference point for the posterior attachments of the cricopharyngeus. Once cut, the muscle retracts more readily toward the tracheoesophageal groove. An additional 2 cm of thickened muscle is transected on the hypopharynx, for a total myotomy of 6 cm.

After the cricopharyngeal myotomy has been completed, the muscularis is lifted from the underlying mucosa by dissecting a flap of muscle in the fine cellular plane between both layers. A transverse section of this flap is completed distally on the cervical esophagus and proximally at the pharyngeal level. Dissection of the muscularis from the mucosa is more difficult at the pharyngeal level than at the esophageal level because it is more adherent and the presence of a significant submucosal venous plexus may prove troublesome if torn or entered. The dissected flap of muscularis is resected for histologic examination (see Fig. 26–8B).

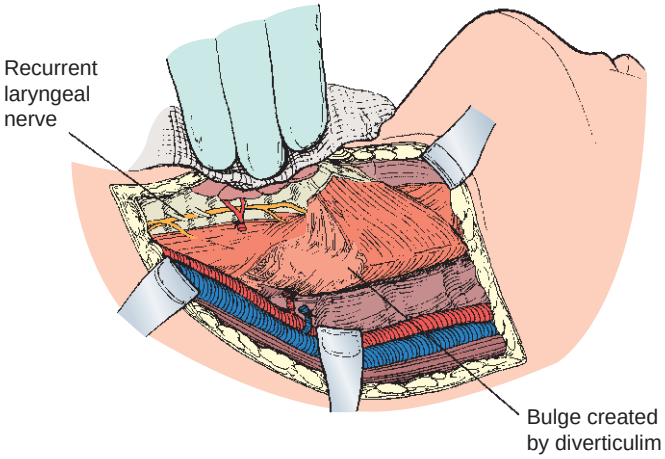


Figure 26–7. The pharyngoesophageal junction can be lifted and everted toward the surgeon. When there is a diverticulum present, it can be perceived as a bulge under adventitial tissues at the junction.

Cricopharyngeal Myotomy for a Pharyngoesophageal Diverticulum (Zenker's)

Minute Diverticula

A very small diverticulum, when symptomatic, is treated by an extended cricopharyngeal myotomy. Once the myotomy is completed, the small diverticulum disappears as part of the freed mucosa.

Established Diverticula (1 to 4 cm)

With the diverticulum freed and uplifted, the myotomy is started in the same manner on the cervical esophagus. The cervical esophageal mucosa is exposed. The cricopharyngeus muscle is then progressively transected (Fig. 26–9A). The muscle fibers are often seen to extend onto the body of the diverticulum itself, and division of these fibers is performed to free the entire collar of the sac. Lateral dissection to the left and right of the pouch allows proximal extension of the myotomy onto the hypopharyngeal wall. Two centimeters of hypopharyngeal muscle is transected with the same muscle flap created and resected for histologic analysis (see Fig. 26–9B).

The tip of the diverticulum left with thicker tissue is then uplifted. Fixation to the posterior pharyngeal wall is accomplished with four to five 3-0 silk sutures; these sutures anchor the thicker part of the diverticulum to the pharyngeal wall. Care is taken to not leave the collar of the sac in a dependent position. The lumen of the diverticulum should not be punctured by sutures to avoid contamination (see Fig. 26–9B).

Large Diverticula

If a pharyngoesophageal diverticulum is too large to uplift and place between the pharynx and prevertebral fascia, it must be resected. In this case, the myotomy is performed in the same way as already described.

With the Maloney bougie well secured in the esophageal lumen, a linear stapler is placed transversely 1 cm above the collar of the diverticulum (Fig. 26–10A). This may occasionally prove cumbersome if proper eversion of the posterior wall is difficult. An angulated linear stapler can be used for easier application. The diverticulum is then resected, with a 1-cm rim of collar tissue left distal to the stapled line. This tissue is uplifted and fixed to the transected muscle of the myotomy zone while leaving no portion of the collar in a dependent position. The myotomy area is left wide open to allow the suture line to heal in eversion and without the effect of a restrictive cricopharyngeus distal to it (see Fig. 26–10B).

Documenting the Integrity of the Mucosa

With the myotomy completed, accompanied by suspension or resection of the diverticulum, the mercury bougie is removed. A nasogastric tube is placed initially at the pharyngoesophageal junction, and 50 ml of air is injected through the tube while the myotomized zone is kept under saline to allow documentation of the integrity of the mucosa (Fig. 26–11).

Drainage and Closure

Nasogastric tube drainage with the tube directed toward the stomach is carried out after integrity of the myotomy site has been tested. The tube remains in place until normal peristalsis has resumed. There are two reasons for gastric drainage: to avoid blind passage of the nasogastric tube in the postoperative period if it should become necessary and to prevent gastric retention and possible regurgitation or vomiting in a patient whose UES has been removed.

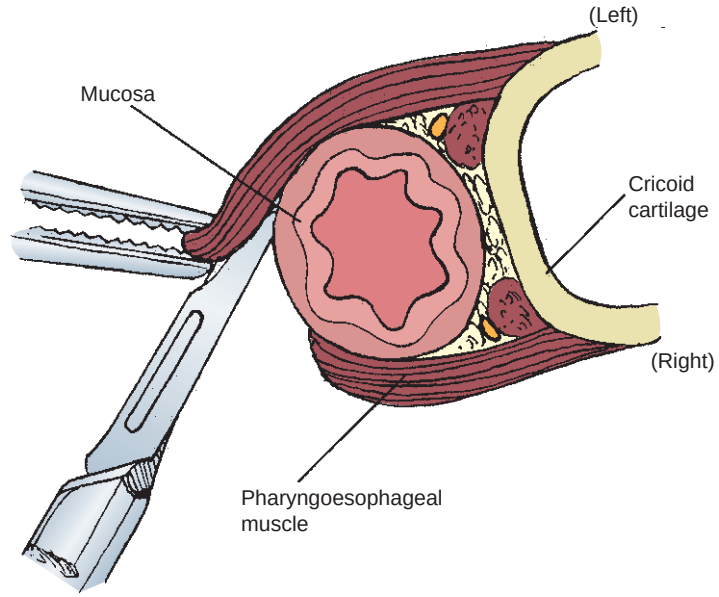
We do not drain the operative site. Wound drainage may be open to discussion, especially if mucosal integrity has been documented. We used to place one Penrose drain at the thoracic inlet level and another behind the myotomized area. However, retrospective analysis of our results revealed a higher wound infection rate, mostly in patients with Zenker's diverticula. For these reasons we decided to not place drains anymore and instead use prophylactic antibiotics effective against aerobes and anaerobes. The wound is closed with a running stitch on the platysma and a resorbable subcuticular stitch on the skin.

Postoperative Care

Patients are mobilized immediately. The nasogastric tube is removed as soon as active peristalsis is documented. A liquid diet is started. Patients are discharged 72 hours after surgery with instructions for a pureed diet the first week and a soft diet during the second week. Normal food intake is then resumed.

Complications

Complications specific to this operation are recurrent laryngeal nerve trauma, hematoma formation, and infection with a salivary fistula. Meticulous technique should



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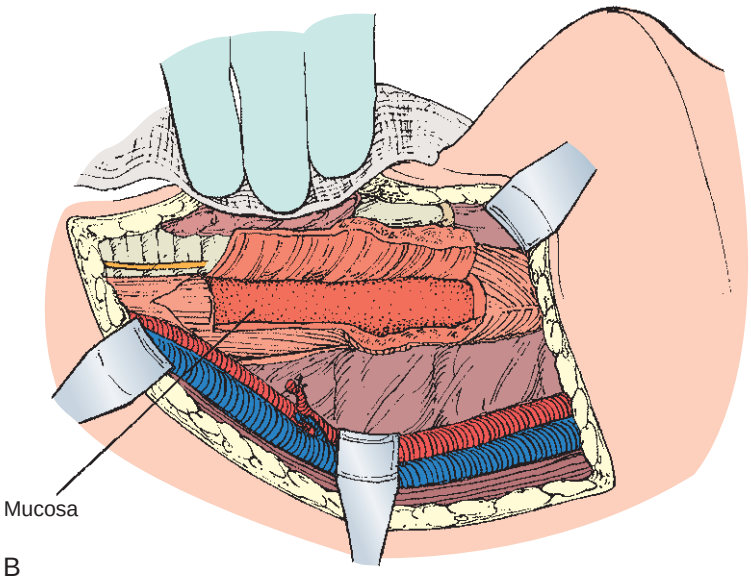


B

Figure 26–8. **A,** With the esophagus and pharynx everted toward the surgeon, the myotomy is started on the right side of the esophagus and the muscle is transected to the mucosal level. **B,** A sequential 6- to 7-cm myotomy is started on the cervical esophagus and then continued on the pharyngoesophageal junction, where the cricopharyngeus is located by identifying the cricoid cartilage. The thicker hypopharyngeal musculature is divided over a span of 2 to 3 cm. Transverse section of the muscle proximally and distally allows dissection of a muscle flap, which is resected for histologic analysis.

prevent all of these complications. Retropharyngeal hematoma, if it occurs, should be evacuated because of the prolonged resorption period in patients with poor swallowing function. When aspiration persists with absent phonation and disappearance of all protective mechanisms, sepsis from pulmonary infection is to be expected. In this extreme situation, we have resorted to permanent tracheostomy with laryngeal excision or exclusion (Fig. 26–12).

Results of Treatment

Neurologic dysphagia results from disruption of the swallowing mechanism in patients with central nervous system diseases or cranial nerve involvement. Stroke is the most frequent cause of this condition. Incoordination between pharyngeal contraction and sphincter relaxation is the pathologic result observed in these patients. It often results in misdirection of the swallowed bolus with pharyngeal and pharyngonasal regurgitation and frequent laryngotracheal aspiration. Complete absence of relaxation of the UES is seen mostly in these patients (Fig. 26–13A to C).

Oropharyngeal symptoms may be improved by myotomy, but they persist to a certain degree. The only significant improvement perceived by these patients is a reduction in aspiration episodes.[30]

When assessed radiologically, laryngeal penetration and tracheal aspiration are still observed frequently, even though the symptoms have improved. Radiologic signs of muscle group dysfunction as a result of the neurologic pathology, such as swallowing apraxia, pharyngeal and

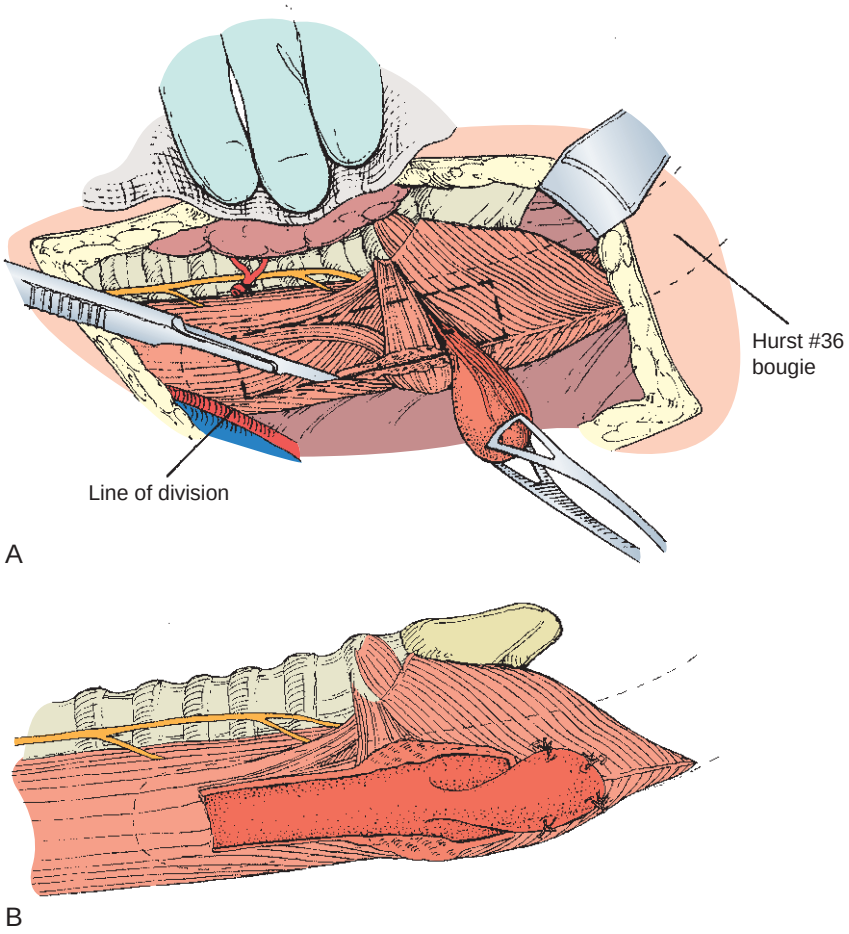


Figure 26–9. **A,** The diverticulum is freed and its tip uplifted and held in a small Duval clamp. A No. 36 bougie is passed into the esophagus and used as a stent. The myotomy is completed around the collar of the diverticulum, and the muscle to be analyzed is resected as described in Figure 26–8. **B,** This moderate-size diverticulum is uplifted and its tip fixed on the musculature of the posterior pharyngeal wall without leaving the collar of the sac in a dependent position.

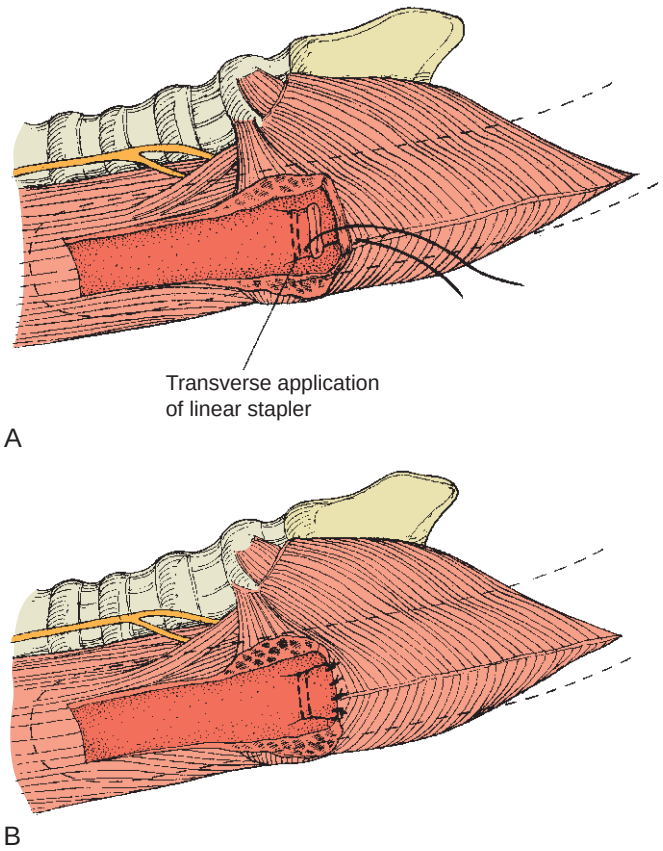


Figure 26–10. **A,** When a diverticulum is large, it is resected. An intraesophageal bougie protects the integrity of the lumen. A linear staple is applied to the collar of the diverticulum. The resection leaves a 1-cm rim of mucosa distal to the stapled line. **B,** The rim of the mucosa is uplifted and fixed on the muscularis of the transected hypopharyngeal wall. The myotomy is left open under the diverticulectomy site.

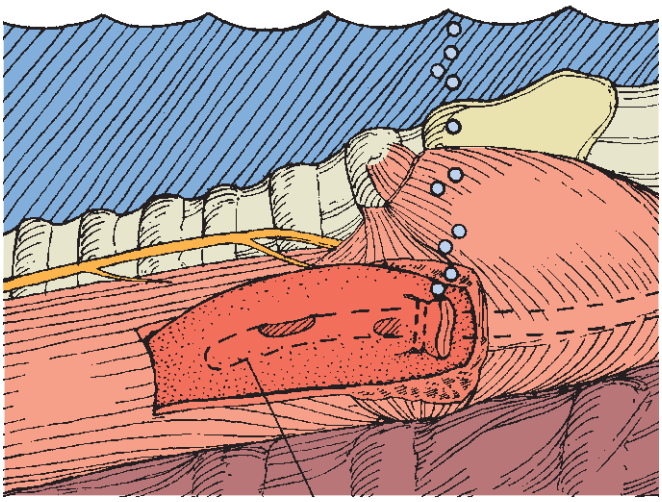


Figure 26–11. Air injected through a nasogastric tube into the submerged esophagus documents the integrity of the myotomized area.

epiglottic incoordination, hypopharyngeal stasis, and aspiration, all persist despite extensive cricopharyngeal myotomy. The functional obstruction and the imprint of the cricopharyngeus observed during the investigation are the only preoperative radiologic signs that are significantly reduced once the myotomy has been completed.

Manometry with specific assessment of the pharyngoesophageal junction shows a significant decrease in resting pressure in the UES, as well as a decrease in the opening time of the sphincter after the operation. These observations have been noted consistently after cricopharyngeal myotomy.[12,31,32] When a single liquid bolus of 10 ml is used for a radionuclide pharyngeal emptying study before and after myotomy, the dysfunction and the resulting emptying capacity are unchanged.

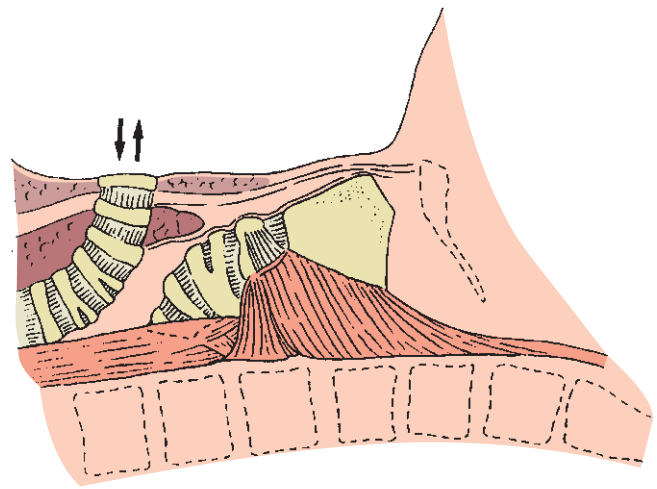


Figure 26–12. In extreme situations when aspiration persists despite an extended myotomy, a permanent tracheostomy with laryngeal exclusion or resection can be offered.

Box 26–2 Prognostic Factors Affecting the Results of Cricopharyngeal Myotomy in Patients with Neurologic Diseases

- Intact voluntary deglutition
- Adequate antepulsion and retropulsion of the tongue
- Normal phonation
- Absent dysarthria

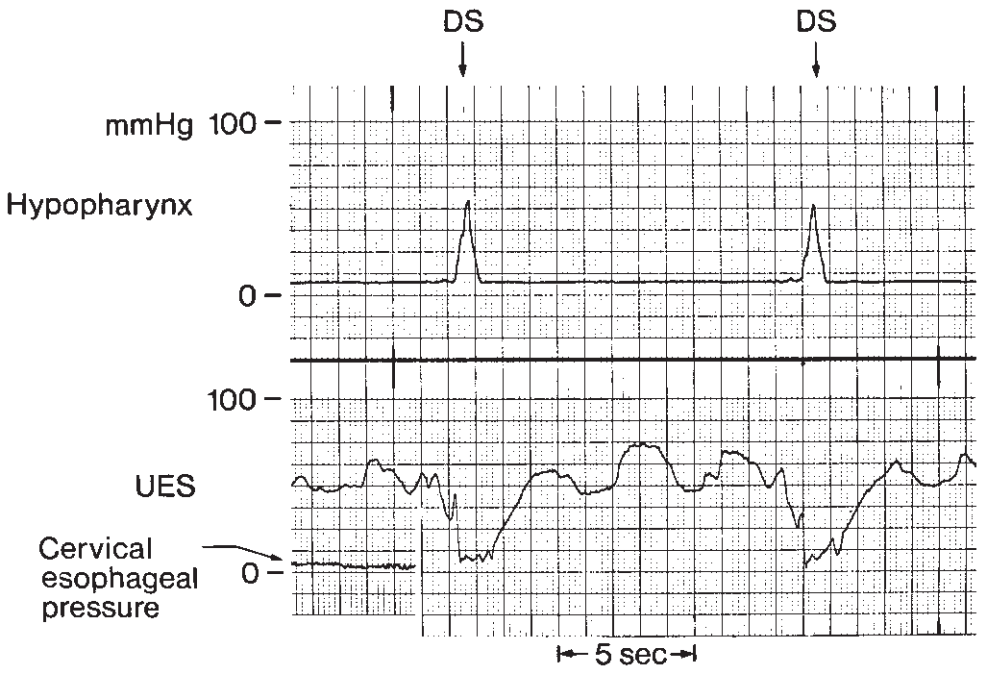
The clinical results of cricopharyngeal myotomy for neurologic dysphagia are influenced by the area of neurologic damage resulting from the stroke or the neurologic lesions. Lesions in the brainstem or from basilar artery thrombosis are associated with significant improvement. Lesions that are more diffuse show a poorer response. Patients with dysphagia from amyotrophic lateral sclerosis and motor neuron disease may have initial improvement, but since these conditions affect mostly the oral phase of deglutition, over time the cricopharyngeal myotomy does not help because the oral-phase abnormalities are untouched. Overall, the clinical improvement rate achieved by cricopharyngeal myotomy for neurologic dysphagia is influenced by the extent and location of damage in the nervous system. Approximately 80% of patients with a cerebrovascular accident are reportedly improved after the operation. When bulbar palsy and bulbar poliomyelitis are responsible for the dysphagia, the reported improvement is around 75%. Fifty percent of patients with amyotrophic lateral sclerosis and motor neuron disease are improved early, but over time the results are poor. Miscellaneous central lesions and bihemispheric damage result in more extensive difficulties that persist despite treatment.

The main prognostic factors for improvement of dysphagia in patients with neurologic disease are summarized in Box 26–2.

Myogenic Dysphagia

Oropharyngeal dysphagia of muscular origin is seen mostly in the oculopharyngeal form of muscular dystrophy. Williams et al.[33] have also studied the biomechanics and treatment outcome of patients with inflammatory myopathy. Oculopharyngeal muscular dystrophy has been investigated mostly in patients of French Canadian origin, in whom this myopathy has been transmitted in an autosomal dominant fashion over the last 12 generations.[34] Families affected by this condition are now found on all continents.

The dysphagia caused by muscular dystrophy is characterized by impaired function of the pharyngeal



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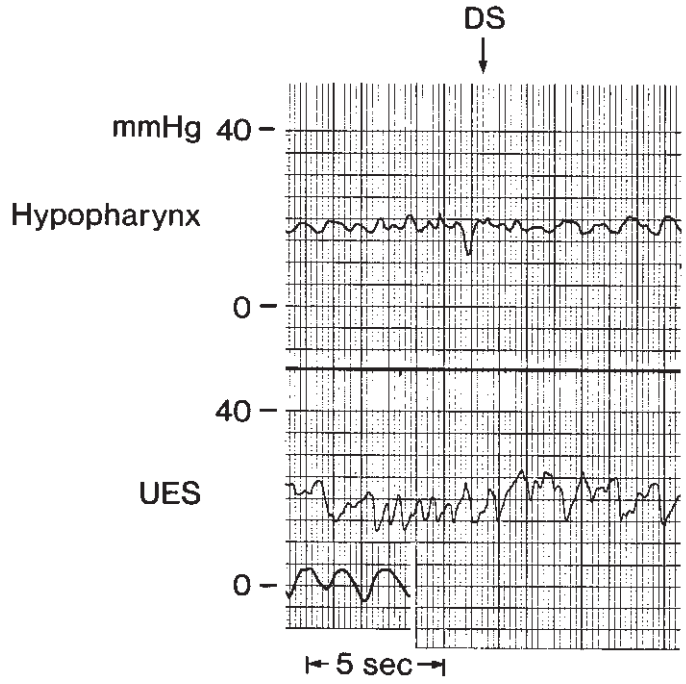

B

Figure 26–13. **A,** Hypopharyngeal contraction with normal relaxation to atmospheric pressure. DS, dry swallow; UES, upper esophageal sphincter. **B,** Achalasia of the UES in neurologic dysphagia.

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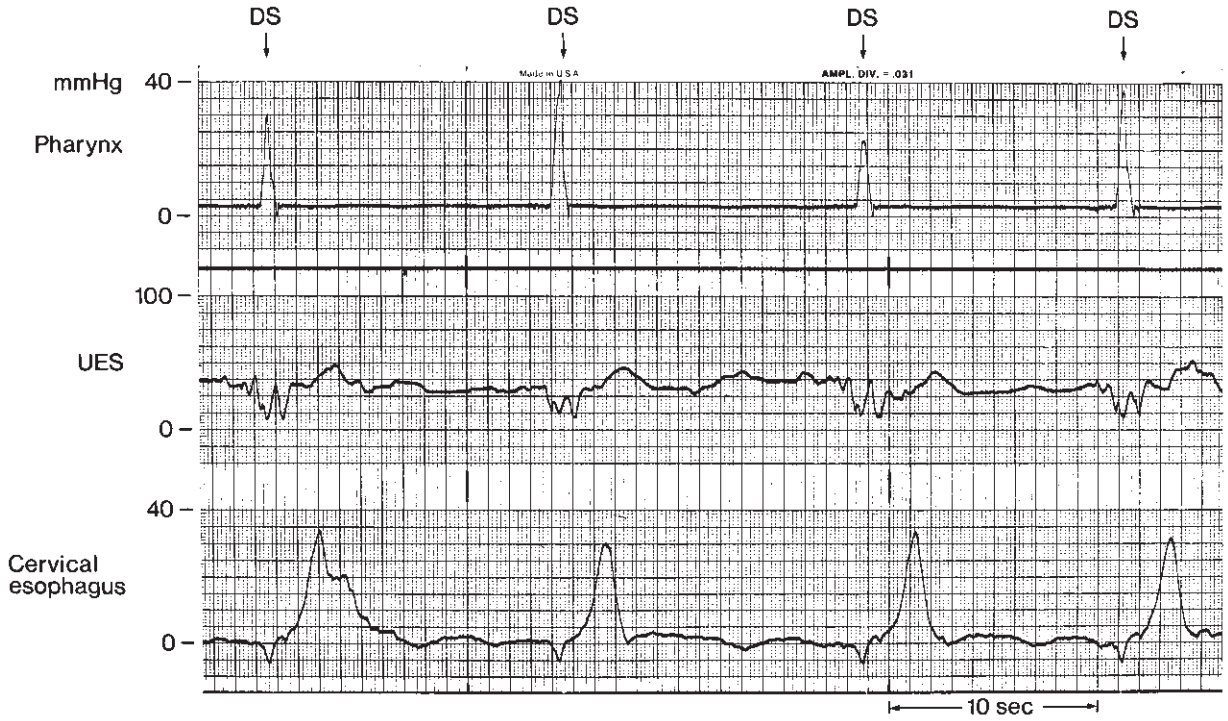


Figure 26–13, cont'd. **C,** Incomplete relaxation of the UES in oropharyngeal dysphagia of neurologic origin.

muscles, which show weak and sluggish contractions. The severity of symptoms is paralleled by the severity of the dysfunction. These symptoms are esophageal and tracheobronchial in location. The dysphagia is identified at the sternal notch level and accompanied by frequent food incarceration at the upper sphincter level with resulting pharyngo-oral regurgitation. The velopharyngeal muscles are affected and incompetent, and pharyngonasal regurgitation results. Laryngeal penetration and tracheal aspiration are reported at mealtime. Saliva pooling in the hypopharynx and aspiration causing bronchorrhea occur during the night. Aspiration pneumonia is frequent. Peripheral muscle groups are affected, with bilateral ptosis usually being evident, as well as voice changes and limb weakness.

Radiologically, hypomotility of the pharynx with stasis of contrast material in the hypopharynx, valleculae, and piriform sinuses is observed frequently. The cricopharyngeus leaves a significant imprint on the radiopaque column on the lateral view in 80% of patients (Fig. 26–14). Aspiration episodes are recorded frequently. Radiologic observations correlate well with radionuclide emptying studies that document the delayed pharyngeal emptying capacity (Fig. 26–15A and B). When studied manometrically by intraluminal transducers, the pharyngoesophageal junction shows low pharyngeal pressure and weak pharyngeal contractions. The UES may have normal resting pressure but exhibits incoordination between a prolonged pharyngeal contraction and an abnormal and incomplete relaxation. Patients with

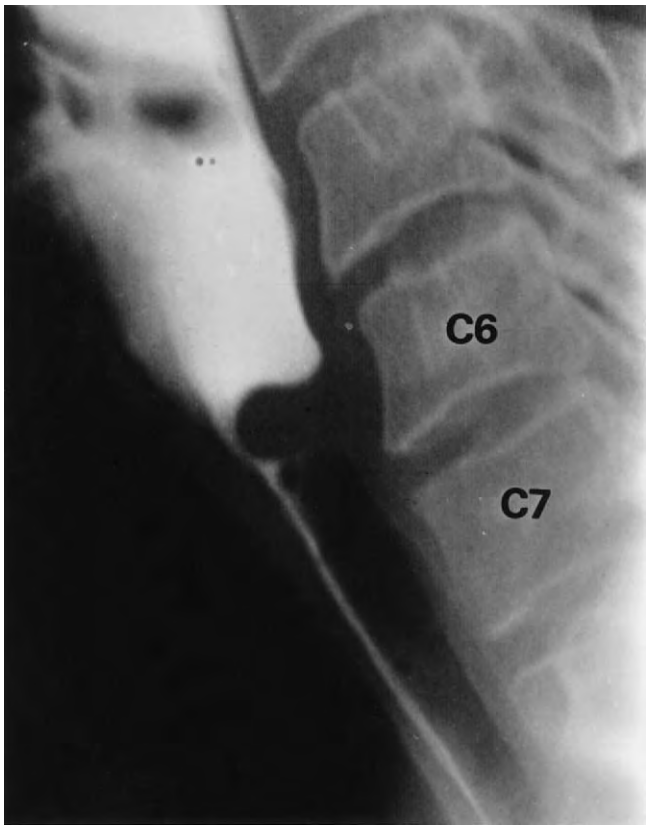


Figure 26–14. Prominent cricopharyngeus closing the esophageal mouth.

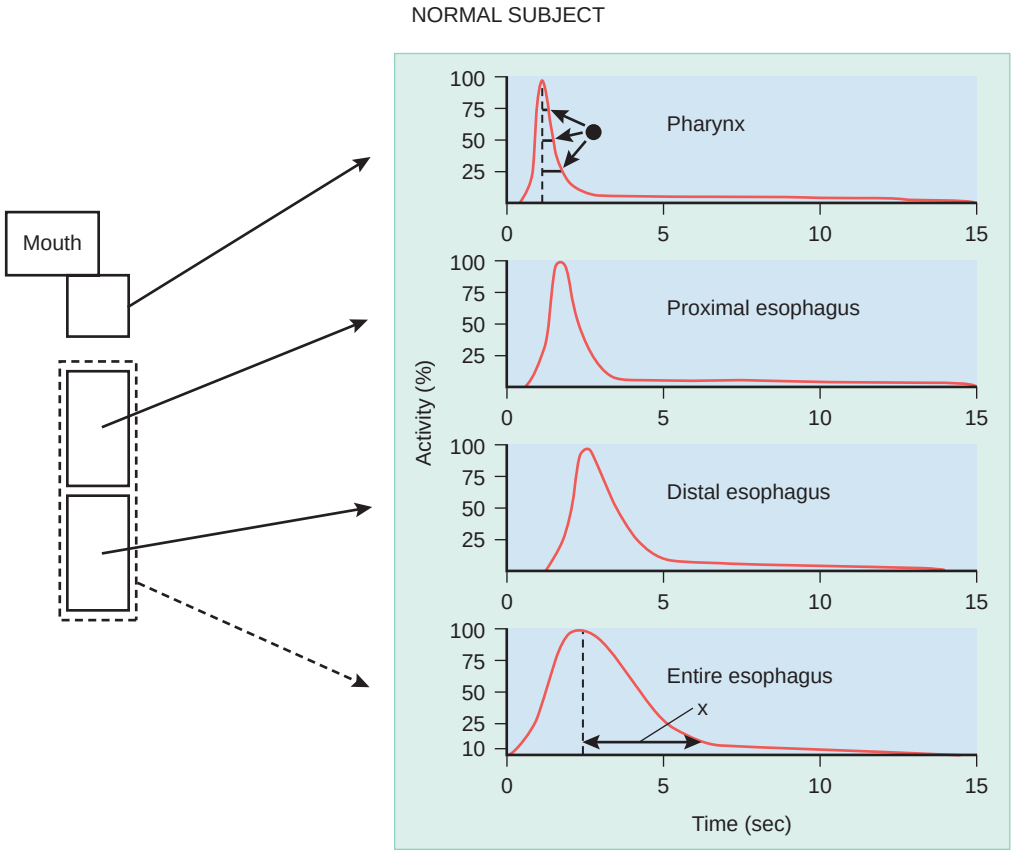


Figure 26–15. **A,** Radionuclide emptying capacity of the pharynx and esophagus in a normal individual. **B,** Radionuclide emptying study in a dystrophy patient. Prolonged retention of the bolus is quantified in the pharynx and esophageal body.

severe symptoms have more abnormalities in their manometric profile.[35]

The cricopharyngeal myotomy offered to these patients adheres to all the technical details described initially by Montgomery in his 1971 publication, the main goal of the operation being to maximally reduce the resistance caused by functional obstruction of the UES. As illustrated, the myotomy ends up as a myectomy involving 6 to 7 cm of the pharyngoesophageal junction because the posterior muscular wall of the junction is completely resected (see Fig. 26–8A and B).

The clinical results of the operation show significant improvement in swallowing comfort in 75% of operated patients. The improvement is appreciated more readily when swallowing solids than when voluntarily swallowing liquids. Tracheobronchial symptoms and nocturnal bronchorrhea improve as well. The stage of the disease and the extent of the muscular pathology and dysfunction affect the results. Patients with poor control of the laryngeal musculature and vocal cords show less improvement because of persistent aspiration. After cricopharyngeal myotomy, pharyngeal emptying scintigrams have documented improvement in clearing of a liquid bolus and in hypopharyngeal stasis.[32] The physiologic basis for improvement in symptoms is the significant reduction in resting pressure of the UES and the significant decrease in relaxation time for sphincter opening, thus suggesting reduced resistance to transit from the pharynx to the esophagus.[36]

Idiopathic Dysfunction of the Upper Esophageal Sphincter

When no identified neurologic disease or dystrophy is present, dysfunction of the UES is called idiopathic. It is then seen as a prominent, functionally obstructing sphincter or as an abnormal cricopharyngeus accompanied by a herniated pouch above the sphincter. Despite being called idiopathic dysfunction, the cricopharyngeus muscle has been documented as being abnormal. Thus, it is more the causes leading to this abnormal UES muscle that remain unexplained.[25,26,37] Patients with just dysfunction of the UES usually have oropharyngeal dysphagia of varying severity. When a diverticulum is present, it is usually found in patients between 60 and 70 years of age. Dysphagia is localized at the cervical level and is usually present at each meal. Regurgitation of freshly ingested food may occur immediately after meals. If the diverticulum is larger, the food tends to remain in the pouch and may be regurgitated or aspirated when the patient is lying down. Aspiration is recorded in 36% of patients with Zenker's diverticula, and 20% will have pulmonary complications.

The diagnosis is confirmed by radiology, with a pouch smaller than 1 cm present in 4% of patients, a diverticulum 1 to 2 cm in size in 20% of patients, and a diverticulum larger than 2 cm in 65% of patients (Fig. 26–16A to C).

Functional studies of the UES have demonstrated a sphincter pressure that was either normal, high, or low, with the type of recording method used having a definite influence on measurements. Incoordination between opening and closing of the cricopharyngeus against pharyngeal contraction was initially suggested.[38] However, sleeve recordings of the UES and measurement of intrabolus pressure in the hypopharynx when a diverticulum is present have been used by Cook et al.[25,26,39] to clarify the pathophysiology of the condition. In addition, they simultaneously observed the opening area of the sphincter on videoradiology. After identifying the restrictive pathology in the sphincter, they documented how the abnormal muscle restricted the opening surface of the esophageal mouth and caused incomplete opening of the sphincter during deglutition with resulting high hypopharyngeal intrabolus pressure. Thus, the progressive outpouching of the mucosa through the muscular wall of the hypopharynx just above the restrictive sphincter is a pulsion diverticulum and must be seen as a complication of the UES dysfunction.

The standard of care, when an established pharyngoesophageal diverticulum has been documented, is surgical.

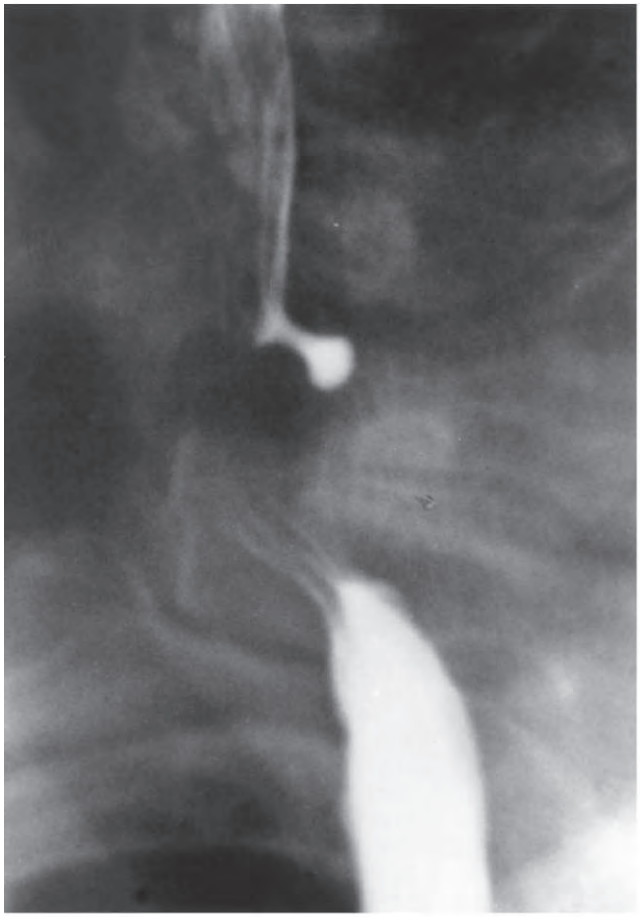
Cricopharyngeal myotomy is the mainstay of treatment to correct an abnormal and restrictive UES. The diverticulum is seen as an anatomic complication of the dysfunctional sphincter, and it is treated according to its size. A simple cricopharyngeal myotomy will cause a minute diverticulum to disappear in the myotomized area (see Fig. 26–8B). Diverticula measuring up to 4 cm can be suspended and fixed on the posterior pharyngeal wall once the myotomy has been completed (see Fig. 26–9B). Diverticula larger than 4 cm usually need to be resected (see Fig. 26–10A and B).

Clinical and functional results are reported as excellent in 95% of treated patients.[37,38,40-42] Shaw and colleagues[43] documented the physiologic effects of the operation on the pharyngoesophageal junction. Myotomy of the junction with either resection or suspension of the diverticulum reduces intrabolus pressure in the hypopharynx to normal and returns the surface opening of the upper sphincter area to normal.

Endoscopic sphincterotomy with the use of a stapling device has been proposed. When performing the technique, the wall between the diverticulum and the esophageal lumen is divided. Use of this device is limited to large diverticula, and functional results have been shown to be acceptable on early follow-up. The remaining dependent pouch at the tip of the stapling line may explain persistent symptoms with this technique.

Oropharyngeal Dysphagia After Neck Surgery

Extensive neck surgery and laryngectomy may distort the muscular function as well as the innervation of the pharyngoesophageal junction. Laryngectomy has been documented to decrease UES resting pressure and reduce the asymmetry of the sphincter.[14,44] Up to 25% of laryngectomized patients may have a spastic sphincter, whereas dysphagia has been documented in nearly 40% of the operated population. Well-documented dysfunction of the UES after laryngectomy or extensive neck surgery may be improved by cricopharyngeal myotomy.



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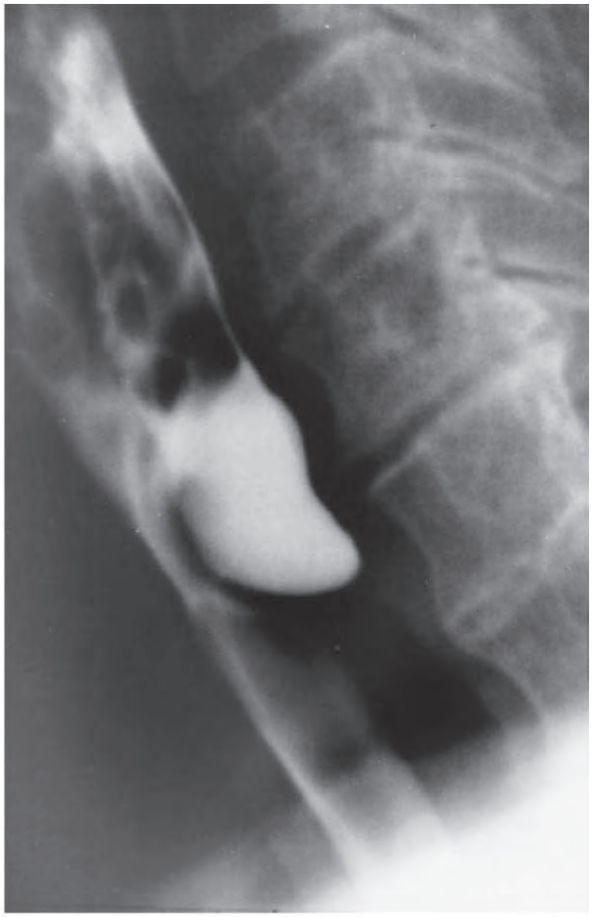

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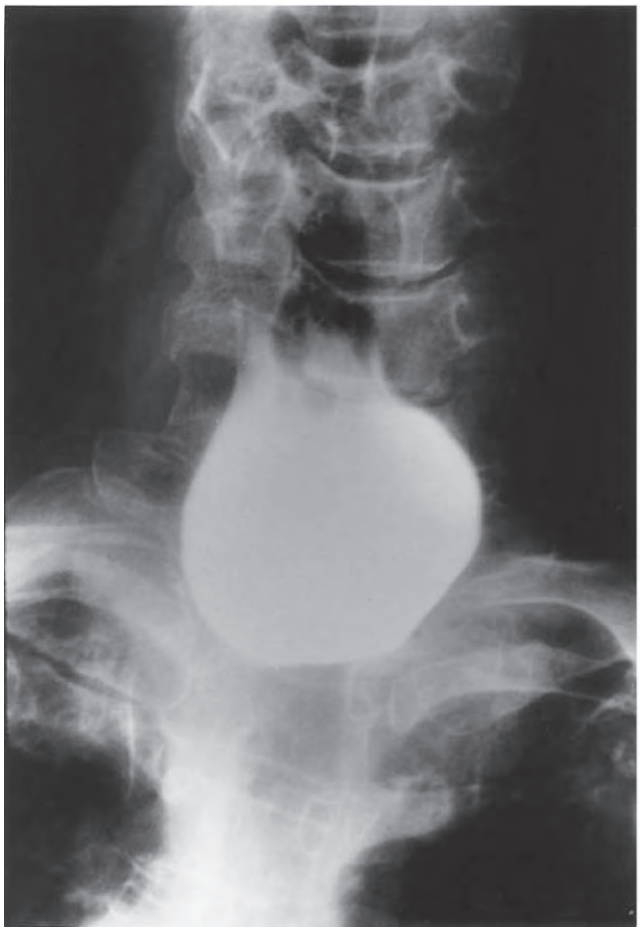

C

Figure 26–16. **A,** A symptomatic minute diverticulum is treated by extended cricopharyngeal myotomy. **B,** A moderate-size diverticulum is treated by cricopharyngeal myotomy, and the diverticulum is suspended and fixed on the posterior pharyngeal wall. **C,** A large diverticulum is usually resected once the cricopharyngeal myotomy has been completed.

Careful evaluation is required because the frequent use of radiotherapy in these patients may well be responsible for their symptoms.

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Chapter

27

Pathophysiology and Treatment of Zenker's Diverticulum

Toni Lerut · Willy Coosemans · Georges Decker · Paul De Leyn · Philippe Nafteux · Dirk Van Raemdonck

Pharyngoesophageal diverticulum was described for the first time as a pathologic entity by Ludlow in 1769.[1] However, it was Zenker who gave his name to this condition through a publication in 1877 in which he reported a series of 27 patients.[2] Already at that time Zenker presumed that the pouch is the consequence of "forces within the lumen acting against a restriction," a hypothesis that is indeed close to the modern understanding of its pathogenesis and remarkable because both endoscopy and radiology had yet to be invented. However, the mechanistic compression theory as a cause of symptoms would prevail until far into the 20th century and dominate therapeutic strategy as well (diverticulectomy). Only during the last decennia of the 20th century, thanks to new developments in imaging, endoscopy, manometry, and manofluorography, has better insight into the pathogenesis of Zenker's diverticulum (ZD) emerged and led to fundamental changes in the therapeutic strategy (myotomy of the cricopharyngeal muscle).

PHYSIOLOGY AND PHYSIOPATHOLOGY

ZD is defined as a blowout of the mucosa through a so-called locus minoris resistentiae on the posterior wall at the transition zone between the hypopharynx and the esophagus (Killian's triangle).[3] The proximal and lateral borders of this zone are the horizontal cricopharyngeal muscle distally and the oblique fibers of the thyropharyngeal muscle, which is part of the constrictor pharyngeus inferior muscle. At rest, the upper esophageal sphincter (UES) is closed because of tonic contraction. Within milliseconds after swallowing, a transient interruption of the muscle contraction relaxes the UES and allows passage of the bolus into the upper part of the esophagus. During this process the larynx moves forward and upward to facilitate opening of the relaxed sphincter.

At manometry it appears that UES pressure drops before its opening is visualized on simultaneous fluoroscopy. Conversely, manometric contraction precedes fluoroscopically visualized closure.

UES function also seems to be influenced by bolus volume. Kahrilas et al. showed that gradual bolus volumes modify movement and relaxation of the UES.[4] The larger the swallowed volume, the wider and longer the opening and the greater the oral motion of the UES.

The exact cause of the development of ZD remains unclear, and several hypotheses have been presented over time. For years the most widely accepted mechanism of development of ZD has been a functional disturbance of the pharyngoesophageal segment. Increased resting pressure of the sphincter, lack of complete relaxation, and in particular, incoordination between the hypopharynx and the sphincter have all been considered to play a role. The most frequently accepted hypothesis in this respect was that of premature relaxation and closure of the UES during swallowing as shown by Ellis and colleagues.[5] Cook et al.,[6] however, using a sleeve catheter for manometry and simultaneous videoradiography, found no difference between the timing of pharyngeal contraction and sphincter relaxation in patients with ZD and a control group. Nonetheless, they did find a significantly reduced sphincter opening in patients with greater intrabolus pressure. They concluded that ZD is a disorder of diminished UES opening, with increased hypopharyngeal pressure probably accounting for development of the diverticulum. Subsequent histologic examination of biopsy specimens taken at the time of surgery indicated

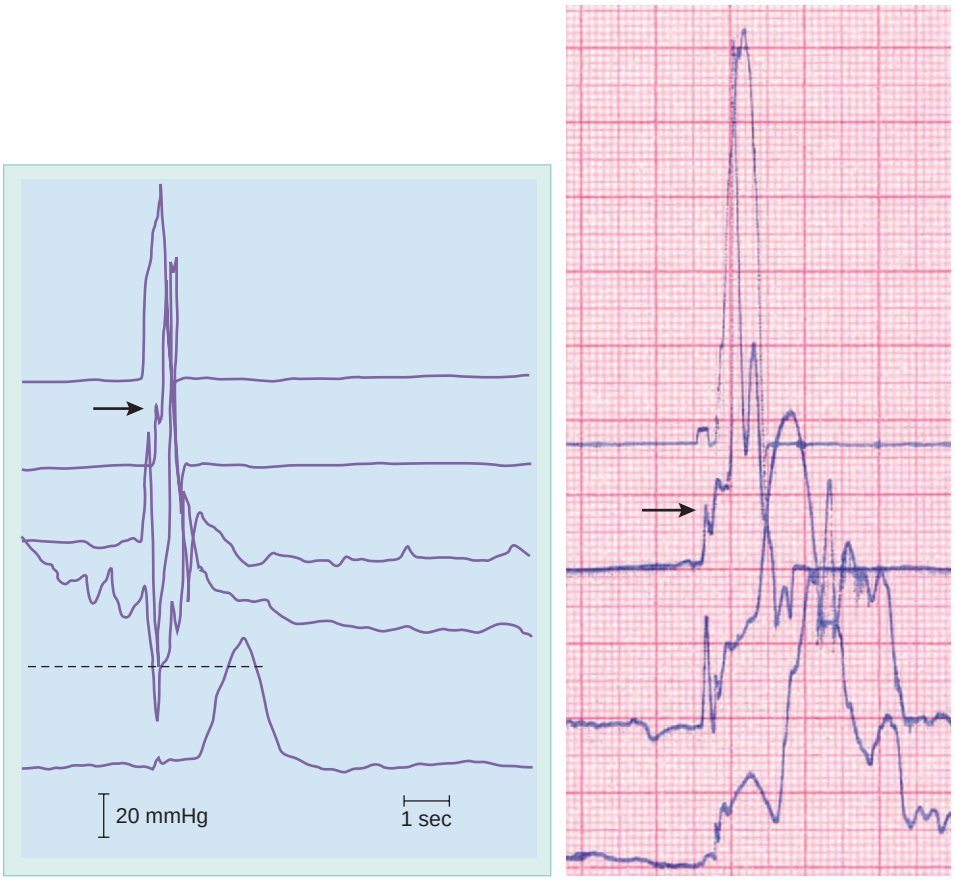


Figure 27–1. A, Manometric tracing of the upper esophageal sphincter (UES) in a healthy volunteer showing complete relaxation of the sphincter. The *arrow* indicates intrabolus pressure. **B,** Manometric tracing of the UES in a patient with Zenker's diverticulum indicating no relaxation of the sphincter. The *arrow* indicates the "shoulder" of increased intrabolus pressure. (Courtesy of E. Dejaeger.)

degenerative changes. They postulated that these degenerative muscle changes prevent the sphincter from opening completely because of lack of sufficient elasticity. The lack of compliance is reflected by the appearance of a "shoulder," or higher pressure, on manometric tracings when the bolus arrives (Fig. 27–1). This lack-of-compliance theory has been endorsed by our own studies on biopsy specimens harvested from a group of patients with ZD and a group of controls. Contractility, enzymohistochemistry, immunohistochemistry, and biochemistry studies were performed.[7]

Contractility Studies

Contractility studies showed a clear difference between diverticulum and control specimens (Table 27–1). In the diverticulum group, all the specimens had a slower and weaker contraction curve with a lower amplitude, a longer time to peak twitch, and a much longer relaxation half-time (Fig. 27–2). The values are statistically significant for the time to peak twitch, relaxation half-time, and increment in velocity of force, thus indicating reduced absolute force and slower contraction in patients with ZD.

The data obtained from pathologic, enzymohistochemical, and immunohistochemical analysis demonstrate an obvious disturbance of all analyzed parameters in ZD as compared with the control group (Table 27–2). In particular, atrophy, hypertrophy, size variation, necrosis, fibrosis, inflammation, and central nuclei were observed (Fig. 27–3). Ragged red fibers (abnormal accumulation of mitochondria) were seen frequently, and the presence of nemaline rods (abnormal densification of the Z-band) was occasionally noted. All changes were important enough to be considered pathologic. Only in two patients (5%) were all of the aforementioned normal. The distribution of fiber types was—with one exception—predominantly type I fiber, with an estimated 70% type I and 30% type II in the ZD group. In the control group, type II predominated in three specimens, whereas type II was predominant in some bundles in three other specimens (Fig. 27–4). Acetylcholinesterase and neurofilament staining showed a heterogeneous and weak pattern when compared with controls, at least in 75% of the 44 specimens. In most cases, more than 50% of the individual fibers did not stain (Fig. 27–5). In 10 patients, a biopsy specimen was taken from below the cricopharyngeal muscle at the level of the cervical esophageal muscle wall; in 8, it was combined with biopsy of the sternocleidomastoid muscle—all patients, of course, underwent cricopharyngeal muscle biopsy. The sternocleidomastoid biopsies were all strictly normal. Type II fiber clearly predominates (75% to

Table 27–1 Contractility Studies in 5 Controls and 5 Patients' with Zenker's Diverticulum

	TPT (msec)	½ RT (msec)	Amp (g)	DP/DT (g/msec)
Control	84	70	8.3	0.2
	72	70	1.4	0.05
	123	165	3	0.06
	61.5	123	6	0.08
	172	193	4.1	0.5
Total	102.5	124		0.32
	(±45.2)	(±55.4)		(±0.01)
ZD	324	188.0	0.9	0.006
	126	120	1.2	0.07
	490	312	0.7	0.01
	126	178	0.8	0.05
	72	193	0.5	0.01
Total	225	189		0.03
	(±156)	(±66)	(±0.001)	
	$P < .05$	$P < .05$	$P < .05$	

Amp, amplitude; DP/DT, force velocity increment; ½ RT, relaxation half-time; TPT, time to peak twitch; ZD, Zenker's diverticulum.

Table 27–2 Enzymohistochemical and Enzymoimmunologic Findings in 15 Control Specimens and 62 Zenker's Diverticulum Specimens

Dominant Fiber Type	Hypertrophy	Atrophy	Necrosis	Size Variation	Fibrosis	Central Nucleus	Inflammation	Nemaline Rods	Ragged Red Fibers	Acetylcholine-sterase	Neurofila-ments
Control											
I: 9 II: 3 II: in some bundles: 3	1/15	1/15	0/15	2/15	2/15	1/15		0/15	0/15	2/15	0/9
Zenker's Diverticulum											
I: 40	32/41	37/41	33/41	40/41	31/41	30/41	21/41	4/41	23/41	33/44	33/44

The denominator gives the number of patients in whom a given parameter was examined.

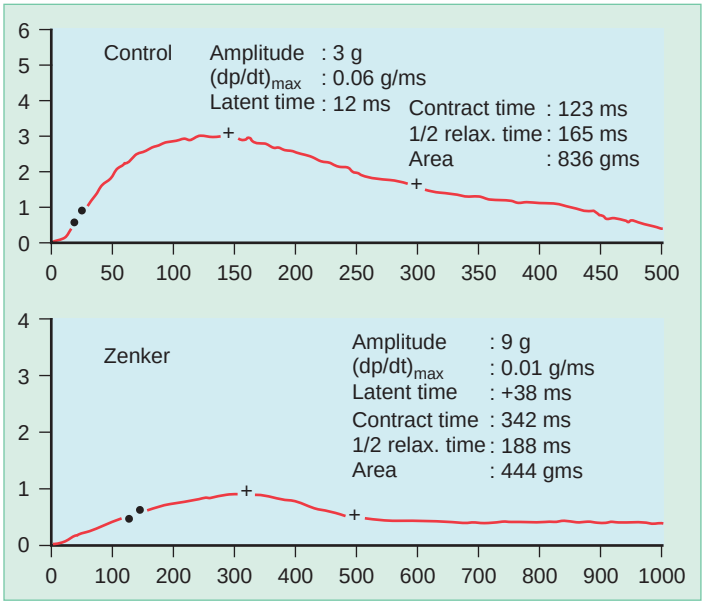
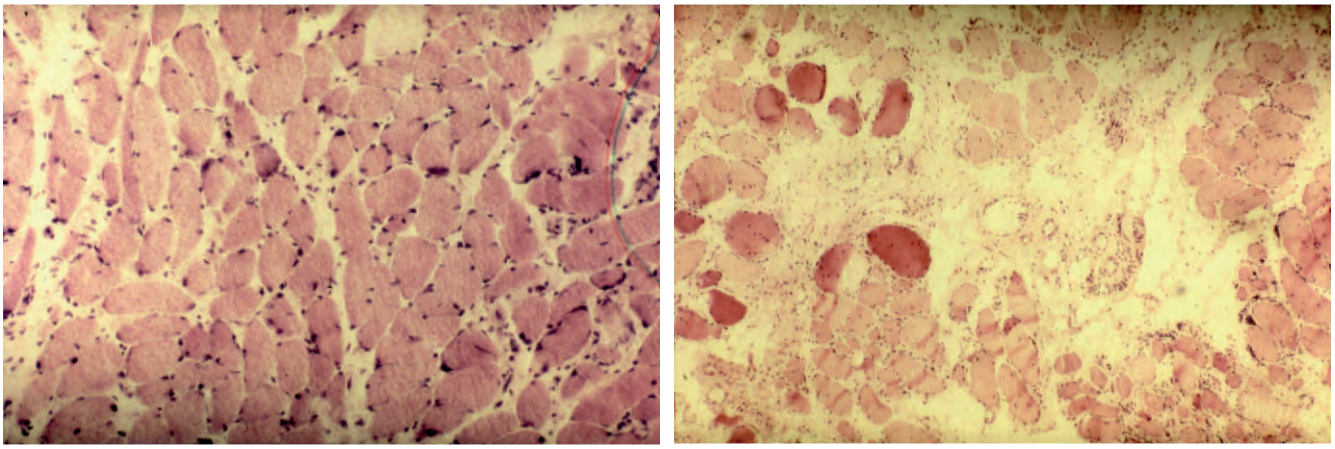
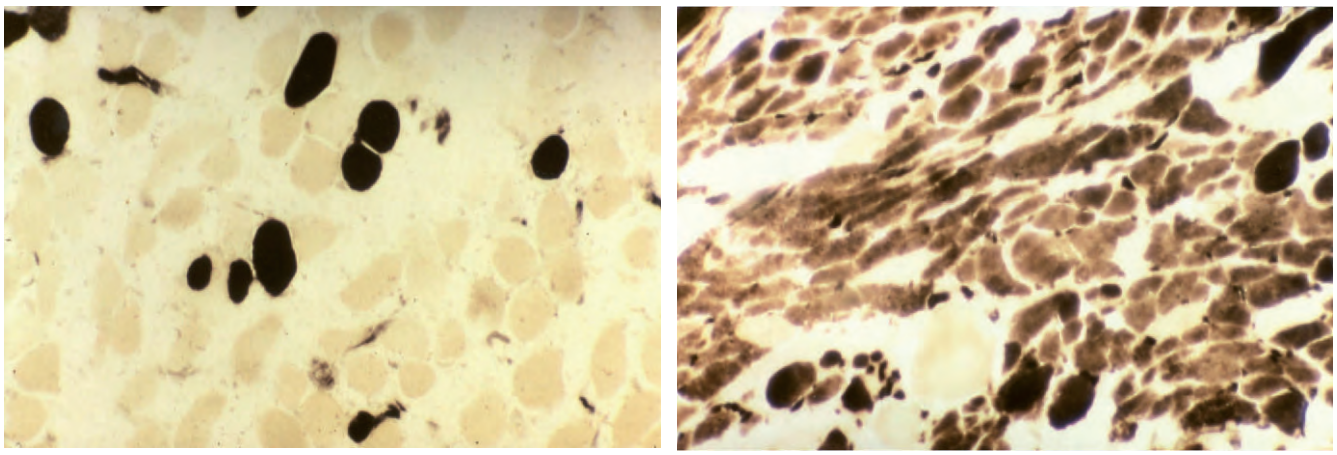


Figure 27–2. Contractility pattern of the cricopharyngeal muscle in a control specimen and Zenker's diverticulum.



A B

Figure 27–3. **A,** Control specimen (hematoxylin-eosin [H&E] stain, ×10). **B,** Diverticulum specimen (H&E, ×10). An irregular pattern of inflammation, increased fibrotic tissue, size variation, and necrosis is evident in the diverticulum specimen. Contrast with the regular-shaped organization of the muscle fibers without necrosis or inflammation in the control specimen.



A B

Figure 27–4. **A,** Control specimen (ATPase stain, pH 4.3, ×10). **B,** Diverticulum specimen (ATPase stain, pH 4.3, ×10). The control specimen shows a predominance of pale-colored type II fibers, whereas in the diverticulum specimen, dark-stained type I fibers dominate.

25%). The cervical esophageal muscle biopsies showed exactly the same pathologic changes, although somewhat less pronounced, as described for the cricopharyngeal muscle.

Enzymohistochemical studies, as well as electron microscopic studies, suggested the presence of abnormal accumulation of mitochondria. Our further studies have therefore been focusing on the biochemical aspects of biopsy specimens.[8] Concentrations of adenosine triphosphatase (ATPase) and nicotinamide adenine dinucleotide (NAD), an essential coenzyme for oxidative phosphorylation, were analyzed. This analysis was performed by high-performance liquid chromatography on samples of cricopharyngeal muscle from 14 patients with ZD and 6 controls (Table 27–3).

ATPase was found to be significantly reduced in the cricopharyngeal muscle of patients with ZD (5.8 μmol/g dry weight) when compared with the ATPase content of cricopharyngeal muscle from controls (10.4 μmol/g dry weight, $P = .0033$). NAD was equally significantly reduced in the cricopharyngeal muscle of patients with ZD (0.54 versus 0.903 μmol/g dry weight, $P = .0011$), thus suggesting deficient ATPase synthesis.

To exclude possible bias in values caused by the increase in fibrosis and subsequent decrease in the absolute amount of muscle fiber per gram dry weight, a study of creatine phosphokinase was performed. Creatine phosphokinase is an excellent measure of the absolute amount of muscle tissue present in a given biopsy specimen. There was no difference in creatine

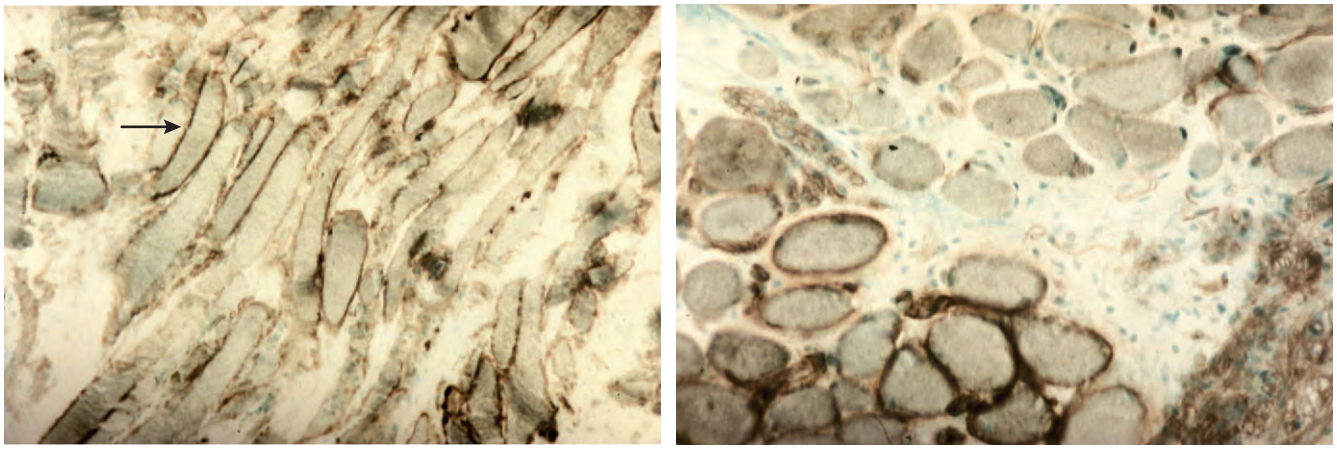


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Figure 27–5. **A,** Control specimen (acetylcholinesterase stain, ×25). **B,** Diverticulum specimen (acetylcholinesterase stain, ×25). The dark-colored fibers represent the acetylcholinesterase staining. There is much more pronounced staining *(arrow)* in the control specimen **(A)** than in the diverticulum specimen **(B).**

Table 27–3 Biochemical Results

	n	ATPase, µmol/g Dry Weight	*n*	NAD, µmol/g Dry Weight	*n*	Creatine Phosphokinase, U/mg Dry Weight
Cricopharyngeus—ZD	14	5.8 (±2.9) ($P = .033$)	9	0.54 ($P = .0011$)	3	1.9 (±1)
Cricopharyngeus—control	6	10.4 (±2.2)	6	0.903	3	2 (±1.6)
Sternocleidomastoid—ZD	10	12.1 (±4.8)				
Sternocleidomastoid control	6	17 (±1.7)				

Standard deviations are in parentheses.
ATPase, adenosine triphosphatase; NAD, nicotinamide adenine dinucleotide; ZD, Zenker's diverticulum.

phosphokinase in cricopharyngeus muscle tissue from ZD patients and controls. These data strongly suggest that for the same amount of muscle tissue, ATPase and the energy charge are indeed deficient in the cricopharyngeal muscle of patients with ZD.

These studies seem to implicate both neurogenic and myogenic abnormalities as a potential underlying cause of the UES dysfunction. Further work performed by Venturi et al.[9] indicates a significantly higher collagen content in both the cricopharyngeal muscle and the muscularis propria of the esophagus below the cricopharyngeal muscle than in a control group. In the cricopharyngeal muscle, ratios of isodesmosine to desmosine and collagen to elastin were significantly higher in patients with ZD than in controls. These data, as well as our own data, indicate that both the cricopharyngeal muscle and the upper part of the striated cervical esophageal muscle are involved in the pathogenesis of ZD. These findings therefore support extension of the myotomy into the muscle of the proximal cervical esophagus below the cricopharyngeal muscle.

Most likely, no single pathogenic mechanism is solely responsible for the development of ZD. However, at this stage, poor UES compliance rather than cricopharyngeal incoordination appears to be the most plausible explanation. The increasing precision of imaging techniques, endoscopy, manometry, and manofluorography[10] has further endorsed the contention that ZD should be considered a pulsion diverticulum secondary to an underlying disturbance in function of the cricopharyngeal muscle and a so-called proximal UES. Gastroesophageal reflux has been implicated by some authors on the basis of a high prevalence of pathologic reflux in the ZD population. Chronic reflux of acidic gastric contents is thought to cause chronic damage to the cricopharyngeal muscle over time. However, this hypothesis has not been validated.[11] Dysfunction of the cricopharyngeal muscle is playing a premier role in the manifestation of symptoms, although the presence of the pouch, especially a larger one, is also contributing to the symptomatology.

Table 27–4 Zenker's Diverticulum: Clinical Features and Symptoms

Age (Mean, 68; Low, 38; High, 93)	
50% >70 years	
20% >80 years	
Symptoms (Mean Duration, 37.4 Months)	
Dysphagia	80%
Regurgitation	58%
Choking	20%
Coughing	18%
Globus sensation	21%
Weight loss	23%
Others	14%
Associated Pathology	
Pulmonary infection	37%
Upper gastrointestinal pathology	60%
Documented reflux	44%
Other comorbid conditions	52%

These results are from our personal experience ($N = 325$).

SYMPTOMATOLOGY

The lack of compliance by the cricopharyngeal muscle and UES causes dysphagia (intrinsic dysphagia), the cardinal symptom, together with choking. Distention of the pouch by the incoming bolus and accumulation of food particles in the pouch may aggravate the sensation of dysphagia (extrinsic dysphagia). Regurgitation of undigested food particles, abnormal noise during swallowing, halitosis, the rare event of a visible swelling in the neck, and ear, nose, and throat symptoms are all manifestations of ZD (Table 27–4). Spontaneous evolution may result in life-threatening complications, in particular, cachexia or recurrent pulmonary infection and progression to end-stage respiratory insufficiency as a result of chronic aspiration. These complications are even more life-threatening inasmuch as ZD is a condition of the third age, with more than 50% of patients being older than 70 years and more than 20% being older than 80 years at the time of diagnosis.

One has to be aware that over 50% of patients have synchronous or metachronous complaints or documented pathologic changes of the upper gastrointestinal tract (or both). In particular, hiatal hernia and gastroesophageal reflux have to be looked for because of their high association with ZD. From our own material it appeared that 44% of the patients had pathologic reflux on 24-hour pH study or grade II or higher esophagitis at endoscopy.[7] These figures indicate that a full investigation of the upper gastrointestinal tract is mandatory in every patient with ZD, and if present, such associated pathologic change (e.g., gastroesophageal reflux) has to be treated "lege artis" (using the correct methods and procedures).

TREATMENT

Treatment is indicated for any symptomatic ZD. A variety of techniques are presently available and are discussed briefly.

Diverticulectomy and Diverticulopexy

Through a cervicotomy, preferably left sided, the diverticulum is identified and, after dissection of the pouch down to its neck, resected (diverticulectomy). The development of stapling devices that allow resection after staples have been fired has resulted in a clear decrease in the incidence of postoperative salivary fistula, the most important surgical complication. Nevertheless, data from the literature indicate an incidence of salivary fistula varying between 1% and 25%.[12,13] Moreover, because of a bare staple line on a fragile structure such as the mucosa, there is a tendency to wait somewhat longer before starting oral feeding. This delay will, of course, have a direct impact on the hospital stay, which in itself may increase the risk for comorbid conditions, especially in geriatric patients, and eventually result in an even longer hospital stay and possibly mortality.

To decrease the risk for postoperative leakage with a possibly fatal outcome, a technique has been developed by which the pouch is turned upside down after dissection and suspended on the prevertebral fascia of the cervical spine. This technique is called diverticulopexy.[14] Its main advantage is the fact that the esophageal lumen is not opened, thereby allowing patients to resume oral feeding the very same day or the day after the operation and thus resulting in a substantial decrease in hospital stay and a virtually nonexistent incidence of salivary fistula.

The Importance of Myotomy

Several authors have noticed recurrence of symptoms and pouch in a number of patients treated by simple diverticulectomy or diverticulopexy. Depending on the intensity of the follow-up and technical examinations applied, the recurrence rate after simple resection/diverticulopexy is reported to be between 2.5% and 20%.[13,14] It appears that recurrence is a slow process that requires several years. As a result, symptomatic recurrence will most likely not become apparent in very elderly patients.

In our own experience, it appeared that after simple diverticulectomy, which was the preferred method between 1953 and 1975, the incidence of symptomatic recurrence increased over time.[15] As a result of better understanding of the physiopathology, an increasing number of authors have underlined the importance of adding extramucosal myotomy of the cricopharyngeal muscle and proximal cervical striated muscle when performing either diverticulectomy or diverticulopexy (Figs. 27–6 and 27–7).[7,16] Although a randomized study has never been performed, there seems to be a consensus today that extramucosal myotomy is as an essential step in the treatment of ZD.

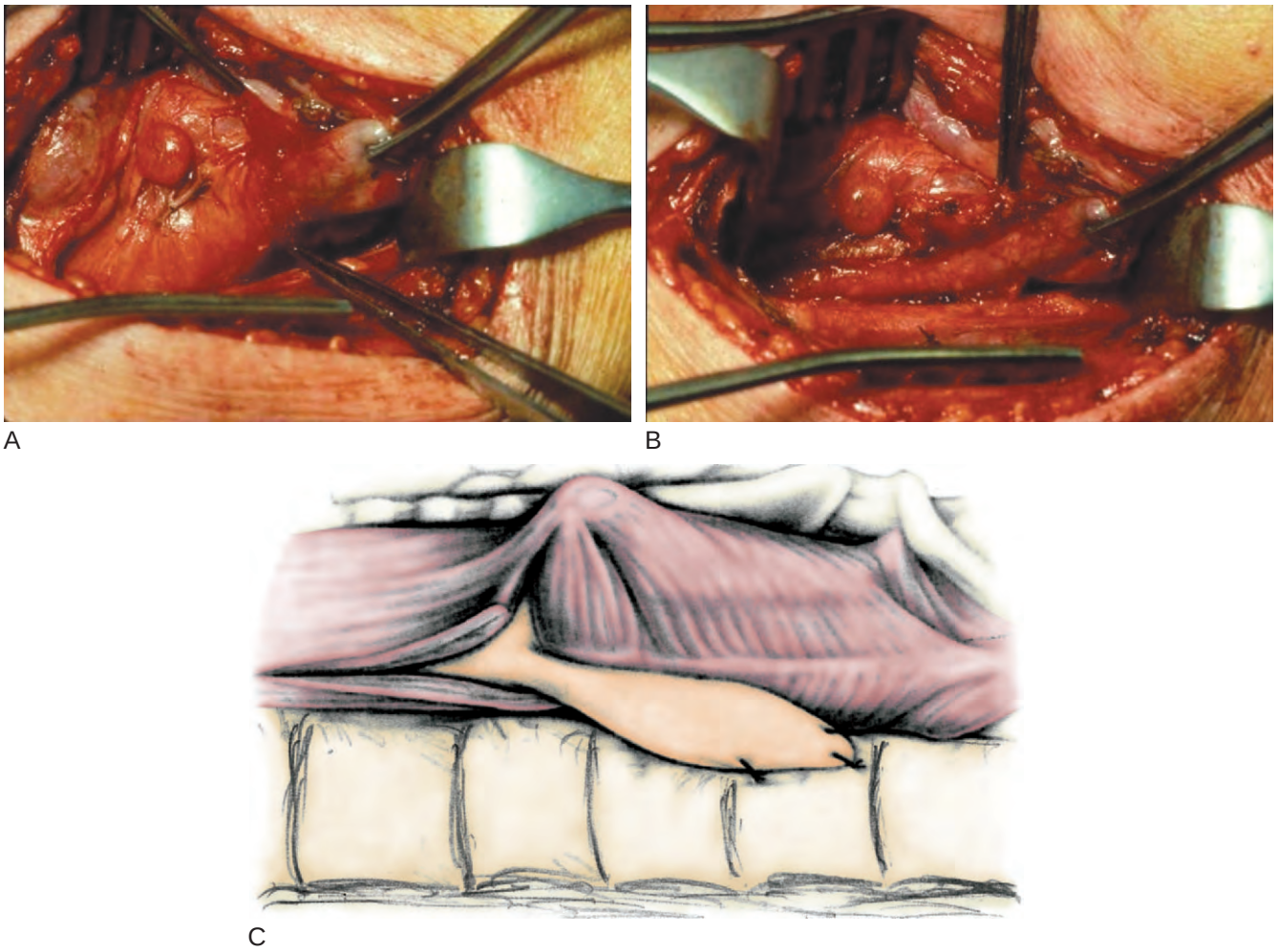

Figure 27–6. Myotomy and diverticulopexy in Zenker's diverticulum. **A,** The diverticulum is clearly visible. The forceps point toward the proximal border of the cricopharyngeal muscle. **B,** Same patient after performing a longitudinal extramucosal myotomy of the cricopharyngeal muscle and the proximal striated cervical muscle. **C,** Schema of the operation illustrating the diverticulopexy fixed to the prevertebral fascia.

With small diverticula (<2 cm), performance of solely extramucosal myotomy suffices to completely relieve the symptoms, which in itself seems to confirm the importance of the myotomy.

Endoscopic Techniques

The concept of an endoscopic approach dates back to the beginning of the 20th century. In 1917, Moscher described a technique by which the common wall between the esophagus and the pouch (the so-called cricopharyngeal bar) could be divided via an endoscopic approach.[17] Initially, the method resulted in high postoperative mortality. In 1960, Dohlman and Mattsson substantially improved this technique[18] by using a fixed rigid esophageal scope to allow better visualization of the cricopharyngeal bar and applying electrocoagulation. More recently, further refinement was obtained by replacing electrocoagulation with laser therapy and using magnifying devices.[19] The advantages of the endoscopic approach are evident: no open external approach and therefore less surgical trauma, shorter length of narcosis, and earlier resumption of feeding. The downside of the method is the fact that the cricopharyngeal bar can be incised only over a short distance because of the risk for perforation and subsequent mediastinitis. As a result, several sessions will be required in a substantial number of patients to eventually achieve complete symptomatic relief, but at the risk of higher morbidity.

However, with the introduction of videoscopic surgery, a method was developed by which a stapler is introduced through an endoscopic approach and an esophagodiverticulostomy is performed. After a sufficiently long myotomy of the cricopharyngeal bar and proximal cervical esophageal muscle, the anterior wall of the pouch and the posterior wall of the cervical esophagus are stapled along the line of transection (Fig. 27–8).[20-23] In addition to the myotomy, this method also enlarges the communication with the esophageal lumen of the

pouch. This technique is clearly much more in alignment with the concept of a sufficiently long myotomy but without increasing the risk for a salivary fistula.

Negative aspects of the technique are the already documented risk for instrumental perforation and occasional leakage. Another disadvantage is that the pouch remains in its place and, despite enlargement of its basis, a so-called cul-de-sac persists. This may result in the accumulation of alimentary particles at the bottom of the pouch and potentially cause regurgitation, coughing, or aspiration. Furthermore, it is evident that in a number of patients—10% to 15%—the method is not applicable, such as patients with ankylosis of the jaw, a prominent dental arch, and cervical kyphosis making hyperextension impossible. Finally, the procedure is difficult, if not impossible in patients with a diverticulum smaller than 3 cm because of the difficulty of introducing the stapler into the small pouch and the potential for an inadequate myotomy. Conversely, with a very large diverticula (>6 cm), several staples need to be fired, which might result in a too long a transection of the dorsal cervical esophageal wall and the eventual creation of a cloaca.

More recently, the endoscopic technique has been further refined to allow the use of flexible endoscopy, and thus there is the potential for treatment on ambulatory basis.[24,25]

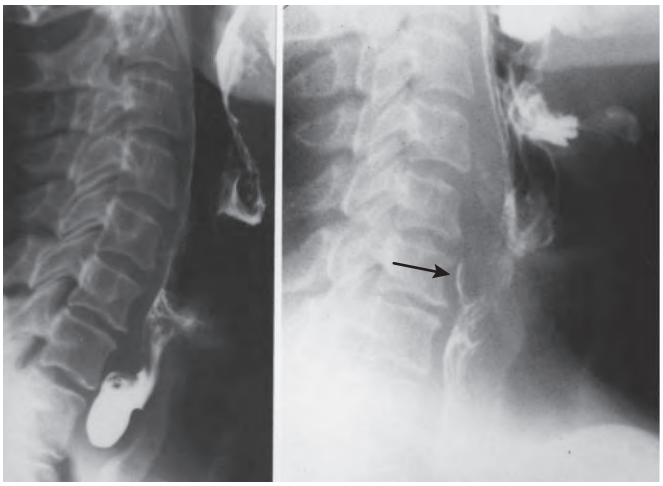

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Figure 27–7. **A,** Zenker's diverticulum: preoperative appearance with a contrast study. **B,** Same patient after extramucosal myotomy and diverticulopexy with free passage of the contrast material. The suspended diverticulum is visible as a small contrast line *(arrow).*

RESULTS

Our Experience with 325 Patients

At our institution, the treatment of choice initially consisted of simple diverticulectomy. Between 1955 and 1975, 36 patients were treated in this manner. There was no postoperative mortality. Seven surviving patients were studied in long-term follow-up. One patient had a symptomatic stenosis. Another experienced symptomatic recurrence 16 years after surgery.[15] From 1975 to December 2003, 289 patients were operated on. Postoperative mortality was 0%.

The overall morbidity in this series is 8.5%, but it gradually decreased over the years to the point that it was 5.8% in 138 patients treated during the last 10 years. Overall in the series of 289 patients, three contained fistulas (0.1%) and three lesions of the recurrent nerve

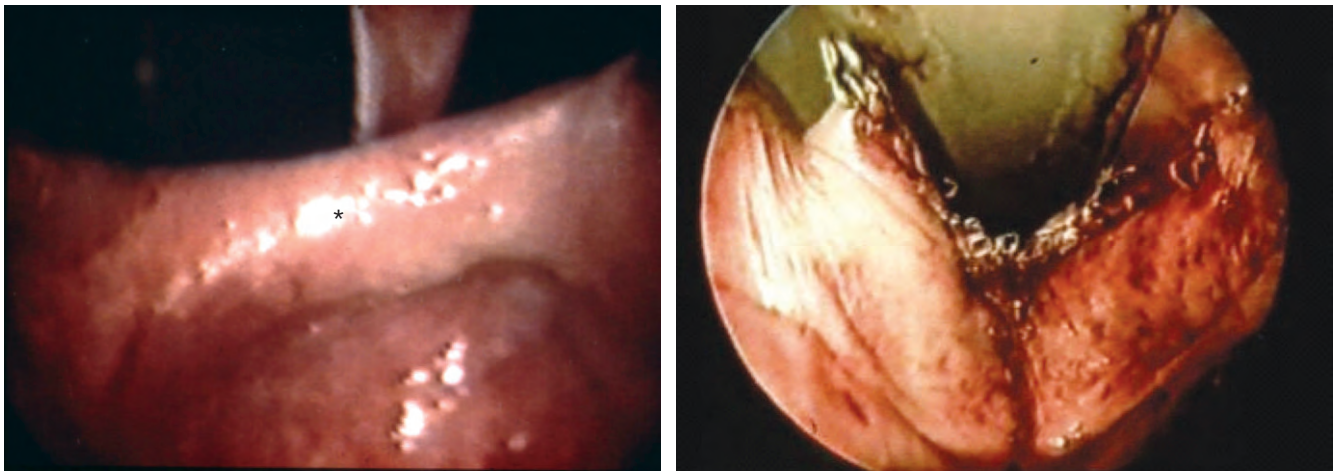

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Figure 27–8. Endoscopic approach. **A,** A cricopharyngeal bar *(asterisk)* is crossing the picture. The bottom of the picture shows the sac of the diverticulum. The upper part shows the entrance of the esophagus and the nasogastric tube in place in the esophagus. **B,** Same patient with an esophagodiverticulostomy after firing the endostapler. Note the V shape caused by retraction of the cricopharyngeal muscle.

(0.1%) with temporary vocal cord paralysis (Table 27–5) occurred. In addition, the mean hospital stay sharply decreased over the years from 8.3 days during the 1970s and mid-1980s to 2.6 days in the past 10 years. Typically, a contrast study is performed the day after surgery, and if no evidence of leakage is seen, normal oral alimentation is resumed and the patient is discharged.

The treatment of choice is extramucosal myotomy of the cricopharyngeal muscle and proximal cervical striated muscle combined with diverticulopexy. This type of operation has been performed in 265 patients; in 9 a simple myotomy was performed, the diverticulum itself being too small for diverticulopexy. In 4 patients, myotomy was combined with diverticulectomy, the reason being residual impaction of barium contrast material in the diverticulum. Finally, in 11 patients a videoendoscopic esophagodiverticulostomy was performed. An extended follow-up study was conducted twice over the years. The first analysis consisted of 178 patients in whom a myotomy plus diverticulopexy was performed between 1975 and 1996. Excellent to very good results were achieved in 90.6%. Eighty-five percent of the patients considered themselves totally asymptomatic. A fair to bad result was recorded in 3.4%. One patient had to undergo surgery again. In this patient a primary muscular disorder was considered the probable cause of the recurrent symptoms.

In these series a group of 28 patients who had been operated on more than 10 years previously were analyzed. Twenty-seven patients were completely asymptomatic. Between 1993 and August 2003, 138 patients were operated on and evaluated by means of a detailed questionnaire or outpatient clinic follow-up, or both. Excellent to very good results were obtained in 94% of the patients. Five patients (3.8%) had a fair result, three of them because of persistent symptoms of gastroesophageal reflux disease.

Of this group of 138 patients, 12 (8.7%) had been referred after previous endoscopic or open intervention. Redo interventions consisted of extramucosal myotomy and diverticulopexy in 11 and videoendoscopic esophagodiverticulostomy in 1. Excellent to very good results were achieved in 87% of this subgroup of patients.

In this series of 138 patients, 11 were treated by videoendoscopic esophagodiverticulostomy within the framework of a prospective study. There were no postoperative complications, but in further follow-up, recurrence of dysphagia and choking developed in two patients (Table 27–6). This appeared to be the consequence of a fibrotic tissue bar hampering passage of a solid bolus (Fig. 27–9). A redo intervention was performed, again via an endoscopic approach. Both patients remained asymptomatic afterward. As a result of these complications, the prospective study was interrupted and the treatment of choice today remains an open approach with myotomy and diverticulopexy because with both methods (open and endoscopic), resumption of oral alimentation can be started the day after surgery and the mean hospital stay is equally short. In other words, it appears that a videoendoscopic technique had no extra advantage with respect to resumption of oral alimentation and hospital stay.

Table 27–5 Zenker's Diverticulum: Postoperative Complications

Complication	Number
Temporary speech symptoms	6
Infection/abscess	4
Pneumonia	3
Recurrent nerve paralysis	3
Hematoma	2
Fistula	3
Respiratory insufficiency	1
Thoracic duct leak	1
Other	3
Postoperative mortality	0

Results from the Literature

Among many publications dealing with the treatment of ZD, a substantial number are providing only fragmentary results and also lack accurate information, such as the seriousness of complications and the improvement in preoperative symptoms. In addition, the definition of

Table 27–6 Results of a Prospective Study to Evaluate Diverticuloesophagectomy

Type of Procedure	No. of Preoperative Complications	No. of Postoperative Complications	Late Complications	Final Outcome
Open ($n = 9$)	—	Hematoma: 1	—	Excellent: 9
Endoscope ($n = 11$)	Subcutaneous emphysema: 1	Left vocal cord paresis: 1	Hematemesis: 1 Dysphagia Slight: 1 Moderate: 2	Excellent: 4 Good: 5 Fair: 2

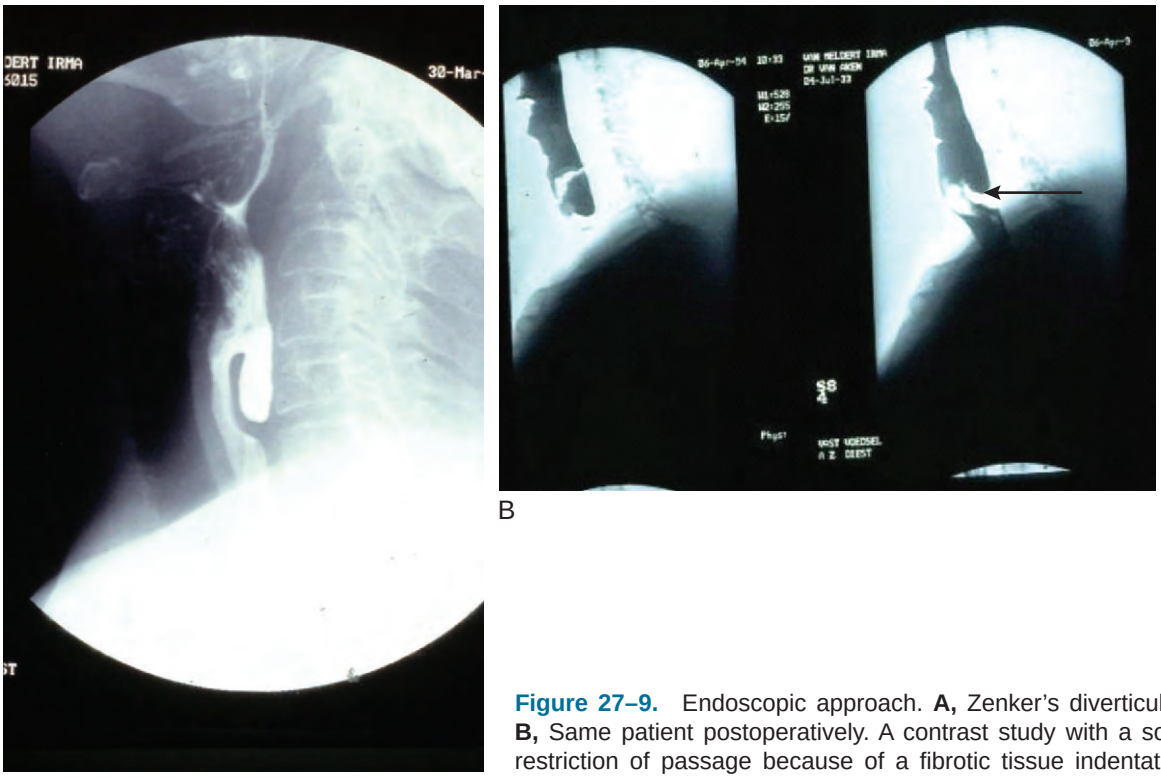

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Figure 27–9. Endoscopic approach. **A,** Zenker's diverticulum preoperatively. **B,** Same patient postoperatively. A contrast study with a solid bolus indicates restriction of passage because of a fibrotic tissue indentation into the lumen *(arrow).*

recurrence when using the videoendoscopic approach lacks precision because the diverticulum by definition remains in place. Moreover, it is often unclear whether the redo surgery was incorporated as a recurrence in the results section when describing the final outcome. In analysis of the literature, one has to also take into consideration the date of publication, especially when studying the results of an open approach. Indeed, over the years, the progress of surgery in general and the improvement in perioperative management have undoubtedly resulted in a substantial decrease in surgical complications as reflected by more recent publications over the last decade. Tables 27–7 and 27–8 present an overview of the most relevant and larger series in the more recent literature dealing with ZD.[26-52]

The results of this overview indicate the consistent progress with regard to postoperative mortality during the last 2 decades. Mortality today is indeed very low. Morbidity seems to be similar for the different therapeutic approaches and is generally considered rather minor. It appears, however, that a videoendoscopic approach more frequently results in a need for reintervention and a clear and higher incidence of recurrence or insufficient control of symptoms. The incidence of total control of symptoms is clearly higher when using an open approach that includes myotomy than when using a videoendoscopic approach, in particular, endoscopic stapling, and this finding is also reflected in two comparative studies described in Table 27–9.[13,52]

WHICH TREATMENT?

Nowadays, ZD can be treated safely with a very low postoperative mortality rate irrespective of the type of treatment modality used. Equally irrespective of the treatment modality, oral alimentation can be started the day after (possibly the same day as) surgery with a very short mean hospital stay. In fact, the hospital stay is determined by the patient's comorbid conditions. This comorbidity can be serious and life-threatening inasmuch as ZD is indeed a condition of the third age. Precisely because of this fact, the goal of treatment of ZD is to provide a definitive solution with a single intervention for this often serious medical and social problem. Therefore, the treatment of choice is an approach or technique that in the long run offers the optimal guarantee for an excellent (i.e., totally asymptomatic) result.

Cosmetic considerations related to scar visibility are obsolete because in fact the scar is limited and barely visible after complete healing.

Data from the literature and in particular our own data seem to favor an open approach with extramucosal myotomy of the cricopharyngeal muscle and the proximal cervical striated muscle, combined with a diverticulopexy, as the technique of choice.

In occasional patients with contraindication to narcosis or open surgery, an endoscopic treatment modality may be the preferred method. Evidently, experience and mastery of the different techniques available are of paramount importance in determining the indication, type of treatment, and overall outcome.

Table 27–7 Open Approach

Author	Publication Year	Time Period	Method	*N*	Complications (%)	Mortality (%)	Results (%) Asymptomatic, Very Good	Partial Improvement	Recurrence
Payne[26]	1992	1944-1978	D, DM, M	888	7.9	2	82	11	3.6
Laing[27]	1995	1979-1988	DM	67	16.4	NA	92.5	7.5	3
GEEMO multicenter report[8]	1996	1960-1982	D: 184	390	21		94		4.9
			DM: 121		10				4.9
			PM: 55		12.7	1.5			1.8
			M: 26		0				NA
			P: 4		0				7.6
Bonafede[28]	1997	1976-1993	M, DM, PM	87	24	3.5	78	13	NA
Zbaren[29]	1999	1987-1997	D, DM	66	15	1.5	77	11	6
Feussner[30]	1999	1982-1998	PM, DM	140	4.2	1	>90		0.8
Leporrier[31]	2001	1988-1998	DM, PM	40	17,5	0	92	8	0
Jougon[32]	2003	1987-2000	DM	73	4	0	99	1	0
Colombo-Benkmann[33]	2003	1985-1995	D, DM	79	15	0	76	19	2.5
Lerut	2004	1975-2003	PM, M, MD	289	8.5	0	94.2	3.8	0.03
Total				2119	10.5	1.4%			3.5%

D, diverticulectomy; GEEMO, Group Européen d'Etude des Maladies de l'Oesophage; M, myotomy; NA, not announced; P, diverticulopexy.

Table 27–8 Endoscopic Approach

Author	Publication Year	Time Period	Method	*N*	Complications (%)	Mortality (%)	Results (%)		Recurrence (%)
							Asymptomatic, Very Good	Partial Improvement	
Van Overbeek[19]	1994	1964-1992	Caut/CO_2L	545	6.7	1	90.6	8.6	NA
Ishioka[24]	1995	1982-1992	Caut	42	4.8	0	92.9	7.1	7.1
Von Doersten[34]	1997	1985-1994	Caut	40	25	0	92.5		0
Hashiba[35]	1999	Since 1978	Caut	47	14.9	0	96		4.3
Lippert[36]	2000	1984-1996	CO_2L	60	10	0	73	21	10
Nyrop[37]	2000	1989-1999	CO_2L	61	13.3	0	70	22	13
Mattinger[38]	2002	1974-1998	CO_2L	52	13.5	1	84.6		15.4
Krespi[39]	2002	1989-2001	CO_2L	83	4.8	0	85.5	11	7.5
Total				930	8.7	0.02			7.2
Peracchia[40]	1998	1992-1996	ESD	95	0	0	92.2	7.8	5.4
Van Eeden[41]	1999	1996-1997	ESD	18	5.9	0	53	35	NA
Cook[42]	2000	1995-1999	ESD	74	5	0	71	24	8.7
Luscher[43]	2000	1997-1998	ESD	23	4.3	0	76	14	4.3
Philippsen[44]	2000	1996-1996	ESD	14	0	0	57	21	NA
Sood[45]	2000	1992-1999	ESD	44	4.5	1	70	24	9
Jaramillo[46]	2001	1996-1999	ESD	32	3.7	0	80		7.4
Stoeckli[47]	2001	1997-2000	ESD	30	27	0	96		NA
Counter[48]	2002	1993-1997	ESD	31	9.7	0	50	44	22
Raut[49]	2002	1994-1998	ESD	25	8	0	48		32
Chang[50]	2003	1995-2001	ESD	150	12.7	0	73.3	22	11.8
Chiari[51]	2003	1997-2001	ESD	39	10	0	71	20	10.9
Total				575	7.8	0.02			10.9

Caut, electrocauterization; CO_2L, CO_2 laser; ESD, endoscopic stapler diverticulostomy.

Table 27–9 Comparative Studies of Long-Term Results

	Excellent Results		Excellent to Good Results	
	Open	Endoscopic	Open	Endoscopic
Gutschow, 2002[13] (1984-2002)	$n = 47$	$n = 28$	$n = 84$	$n = 79$
Diverticulum <3 cm	85%	25% ($P < .003$)	98%	57% ($P < .001$)
Diverticulum ≥3 cm	86%	56% ($P < .004$)	97%	88% ($P < .04$)
Zaninotto, 2003[52] (1993-2001)	$n = 34$	$n = 24$		
	100%	87.5% ($P < .05$)		

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Chapter

28

Epidemiology, Pathophysiology, and Clinical Features of Achalasia

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Achalasia is a primary motility disorder of the esophagus characterized by aperistalsis and failure of the lower esophageal sphincter (LES) to relax appropriately in response to swallowing.[1] It is a chronic benign disease that is a common cause of dysphagia, yet its cause remains poorly understood. Sir Thomas Willis provided the first documented case report of achalasia in 1674, when he described his experience with esophageal dilation with a whalebone in a patient who had dysphagia and a dilated esophagus. To this day, the cornerstone of treatment of achalasia remains relief of the functional obstruction at the level of the gastroesophageal junction. In 1927, Hurst coined the term esophageal *achalasia*, meaning absence of relaxation, specifically, inadequate LES relaxation in the absence of mechanical obstruction.[2]

EPIDEMIOLOGY

The epidemiology of achalasia has not been thoroughly studied. The incidence of achalasia worldwide is estimated at 0.5 to 1 per 100,000 persons per year. It can occur at any age but has a peak incidence between the ages of 30 and 60 and is exceedingly rare in the first 2 decades of life.[3] In the University of California, San Francisco (UCSF), experience, the median age at diagnosis was 48 years (Fig. 28–1). Men and women are equally affected, with no ethnic predisposition to the disease.[4] There have been reports of "familial achalasia," but these cases represent less than 1% of cases in the literature and do not seem to follow any mendelian inheritance pattern.[5] The triple-A syndrome, or Allgrove's disease, is a rare condition consisting of achalasia, alacrima, and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency. Severe skeletal and autonomic neuropathy, cerebellar dysfunction, and cognitive defects are also part of the syndrome.[6] The disease almost always occurs in the first decade of life, and dysphagia is an early symptom. Most children have hypoglycemic or hypotensive episodes from adrenal insufficiency. Neurologic deterioration commonly occurs in the second or third decade of life. The syndrome follows an autosomal recessive inheritance pattern with variable penetrance. A genetic linkage analysis of families with triple-A syndrome has linked the disease to markers on 12q13, and recently, mutations have been localized to the *AAAS* gene.[6] Although achalasia significantly increases the risk for esophageal cancer, longitudinal studies indicate that achalasia does not affect life expectancy. The mean age of death of patients with achalasia in one series was 80 years, thus suggesting a relatively low frequency of esophageal cancer.[2]

PATHOGENESIS

The defining pathologic feature of achalasia is progressive inflammation and selective loss of the inhibitory myenteric neurons in Auerbach's plexus of the esophagus that normally secrete vasoactive intestinal polypeptide and nitric oxide. This results in failure of relaxation of the LES and aperistalsis of the esophageal body with subsequent functional obstruction at the level of the gastroesophageal junction and gradual dilatation of the esophagus.[7] Based on animal models and clinical observation, some authors have suggested that the primary event in achalasia is LES dysfunction with resulting outflow obstruction and secondary esophageal dilatation and loss of peristalsis.[2,7,8] According to this theory, relief of LES obstruction early in the disease would reverse the loss of peristalsis. Little et al. demonstrated that banding of the gastroesophageal junction in a feline model resulted in loss of peristalsis that was reversed with relief

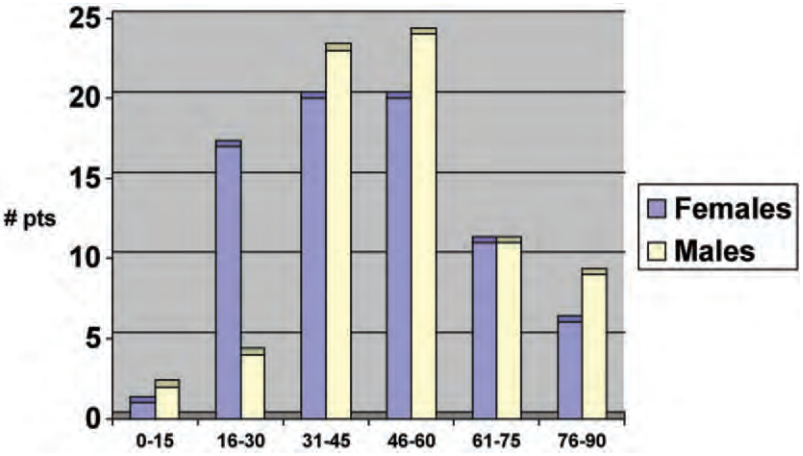

Figure 28–1. Age distribution in 148 untreated patients with achalasia.

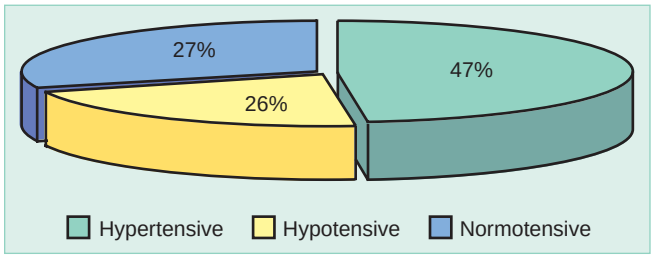

Figure 28–2. Lower esophageal sphincter pressure in untreated patients with esophageal achalasia.

of the obstruction.[9] Parilla described some return of peristalsis in patients after myotomy, which occurred more frequently in those who had a shorter duration of symptoms.[10] In our experience of 173 patients undergoing minimally invasive myotomy for achalasia, we found no return of peristalsis after treatment. Furthermore, the duration of symptoms at the time of myotomy had no effect on the outcome of the operation.[11] The theory of primary LES dysfunction is further flawed by the well-documented observation that less than 50% of patients with achalasia have a hypertensive LES. In fact, 25% of untreated patients with achalasia have a hypotensive LES (Fig. 28–2).[12] It is difficult to fathom that a hypotensive LES can produce a functional obstruction sufficient to cause aperistalsis.

The pathogenesis of achalasia remains elusive despite an understanding of the physiology of the disease. Overall, there is progressive esophageal dilation above the LES ranging from minimal dilation in early achalasia to an esophageal diameter of 10 to 14 cm in patients with long-standing disease. Mucosal changes, namely, ulceration and fibrotic thickening, can be present because of stasis of food and esophagitis. Histologically, neuritis and ganglionitis are seen early in the disease, with fibrosis gradually replacing the myenteric plexus in the esophageal body. Consequently, there is a marked decrease in intramuscular small nerve fibers and neurotransmitter-carrying vesicles in the remaining fibers.[7] Wallerian degenerative changes have been described in the vagus nerve and dorsal motor nucleus of the vagus, and some investigators have reported impaired gastric acid secretion in patients with achalasia as a result.[13] Immunohistochemical studies show a marked inflammatory response mediated by cytotoxic T cells early in the disease, thus leading to the possibility of an infectious or autoimmune-mediated cause. The striking similarity of achalasia with Chagas' disease has further supported an infectious cause of primary achalasia. Although herpes simplex virus type 1 (HSV-1), HSV-2, polio, human papillomavirus, and measles have all been proposed as candidates in initiating the immune response, no infectious pathogens have been convincingly isolated from tissue samples either by electron microscopy or by polymerase chain reaction amplification.

HSV has been a prime candidate because of its neurotropic proclivity in other diseases such as trigeminal and facial neuritis. Recently, Castaglinolo et al. demonstrated that exposure of esophageal mononuclear cells isolated from the LES of patients with achalasia to HSV-1 antigens in vitro led to significantly elevated mononuclear cell proliferation and interferon-γ production when compared with controls. Based on this finding, they speculated that HSV-1 might initiate the inflammatory reaction leading to achalasia.[14] This result supports a causal relationship between HSV and achalasia, though not conclusively.

Certain class II major histocompatibility complex (MHC) antigens such as HLA-DQw1, HLA-DQB1, and HLA-DRB1 have been associated with achalasia.[15,16] A class II HLA association has been observed in autoimmune diseases such as rheumatoid arthritis and autoimmune endocrinopathies. Other postinfectious diseases, such as postgonococcal arthritis, have been linked to specific MHC antigens, although typically to class I alleles.[16] Also supporting an autoimmune cause is the presence of autoantibodies to myenteric plexus neurons in the serum of 39% to 64% of patients with achalasia versus 0% to 6% of healthy controls and patients with other esophageal disorders.[17,18]

Most consider the esophagopathy of achalasia and Chagas' disease to be clinically identical. Chagas' disease results from infection by the parasite *Trypanosoma cruzi* and is endemic to Central and South America, especially

Brazil, Venezuela, and northern Argentina. In chronic Chagas' disease there is progressive destruction of ganglion cells throughout the body, including the gastrointestinal tract. This neuropathy results in disturbed peristalsis leading to stasis and dilation predominantly in the esophagus, duodenum, and colon. Megaesophagus is present in 60% to 70% of patients with chronic Chagas' disease. The radiographic and manometric findings of patients with Chagas' disease are identical to those of patients with primary achalasia. Although primary achalasia and Chagas' disease are widely considered to be indistinguishable, some subtle differences between the two diseases do exist. In Chagas' disease there is denervation of both inhibitory and excitatory myenteric nerves, as opposed to the selective inhibitory neuronal loss seen in primary achalasia. Patients with Chagas' disease demonstrate hyposensitivity of the LES to gastrin, as opposed to hypersensitivity in primary achalasia. Finally, basal LES pressure is lower in Chagas' disease than in primary achalasia.[19] Because of more limited access to medical attention in developing nations where Chagas' disease is prevalent, there is typically a longer duration of symptoms and more pronounced esophageal dilation in these patients at the time of initial evaluation.[19]

CLINICAL FEATURES

The cardinal symptom of achalasia is dysphagia, which is present in almost all patients at the time of diagnosis. Most patients have had symptoms for more than 5 years before the diagnosis of achalasia is made and typically accommodate to their dysphagia by eating smaller quantities of food, avoiding solid food such as meat and bread, and drinking liquids with their meals. Often, patients are incorrectly given another diagnosis, most commonly gastroesophageal reflux disease (GERD), before eventually undergoing esophageal function tests that document achalasia. In our experience, 69% of untreated patients were taking acid-suppressing medications at the time of referral to our center.[4]

As the esophagus dilates, it becomes a reservoir of undigested food, and in severe cases it empties only when sufficient hydrostatic pressure is generated. Because of stasis in the esophagus, regurgitation occurs in 76% of patients, and 52% complain of heartburn.[4] Heartburn is due to stasis and fermentation of the food, and halitosis is a common complaint. Aspiration occurs usually at night when the patient is recumbent and can cause nocturnal cough, pneumonia, and pulmonary abscess.

Chest pain was present in 41% of patients referred to our center, even though it was never considered the main complaint.[4] The pain is probably due to esophageal wall distention, stasis esophagitis, or *Candida* esophagitis. Contrary to common belief, it is not related to younger age, shorter duration of symptoms, or the manometric finding of vigorous achalasia.[20]

Weight loss was present in 35% of patients with achalasia in the UCSF experience. It is usually due to an inability of the esophagus to empty and to *sitophobia,* or fear of eating. The average weight loss was 20 lb. Twenty percent of patients lost 1 to 15 lb, 7% lost 16 to 30 lb, and 8% lost more than 30 lb.[4] Severe weight loss over a short period in elderly patients should raise the suspicion of malignancy-induced or secondary achalasia.[2]

DIAGNOSTIC EVALUATION

Once the diagnosis of achalasia is suspected, a contrast esophagogram should be obtained. This test often shows distal esophageal narrowing (bird beak), an air-fluid level, slow emptying of the barium, and esophageal dilatation. Among our patients, the esophageal diameter was less than 4 cm in 30%, 4 to 6 cm in 50%, and greater than 6 cm in 16%. A sigmoid esophagus was present in 4% of patients and a hiatal hernia in 6%.[4]

The gold standard for the diagnosis of achalasia is esophageal manometry, which should be performed on all patients before initiating therapy. The defining manometric abnormality is lack of peristalsis of the esophageal body, as manifested by simultaneous, nonpropulsive contractions (Fig. 28–3). Impaired LES relaxation with swallowing is seen in 87% of patients. *Vigorous achalasia* is defined as the presence of nonpropulsive contractions with an amplitude greater than 37 mm Hg. Overall, there is no significant difference in age, sex, or duration of symptoms between patient with classic and vigorous achalasia or between patients with and without chest pain (Table 28–1).[20]

A hypertensive LES has been widely considered essential for the diagnosis of achalasia. However, many investigators have documented a hypertensive LES in only 50% of patients with achalasia. In our series of 145 untreated patients, only 43% of patients with achalasia had a hypertensive LES (>24 mm Hg), whereas 32% had a normotensive LES (14 to 24 mm Hg) and 25% had a hypotensive LES (<14 mm Hg) (see Fig. 28–2). In our experience, preoperative LES pressure did not affect the outcome of laparoscopic Heller myotomy.[12] In patients with a hypotensive LES and aperistalsis, it is important to differentiate achalasia from scleroderma. In contrast to patients with achalasia, those with scleroderma will frequently have a wide-open gastroesophageal junction on esophagography, a distal stricture or evidence of esophagitis on endoscopy, and evidence of GERD on pH monitoring.

Upper endoscopy should always be performed to exclude other disease such as cancer, peptic stricture, and scleroderma. In primary achalasia, the esophageal mucosa is usually normal, although there may be some esophagitis because of retained food. The endoscope should pass through the gastroesophageal junction without marked resistance. In previously treated patients, 24-hour esophageal pH monitoring differentiates heartburn secondary to real reflux from heartburn caused by stasis and fermentation of food in the distal esophagus.[21]

SECONDARY ACHALASIA

Secondary achalasia refers to esophageal motility abnormalities that are similar to achalasia but caused by other disease entities, most commonly malignancy and occa-

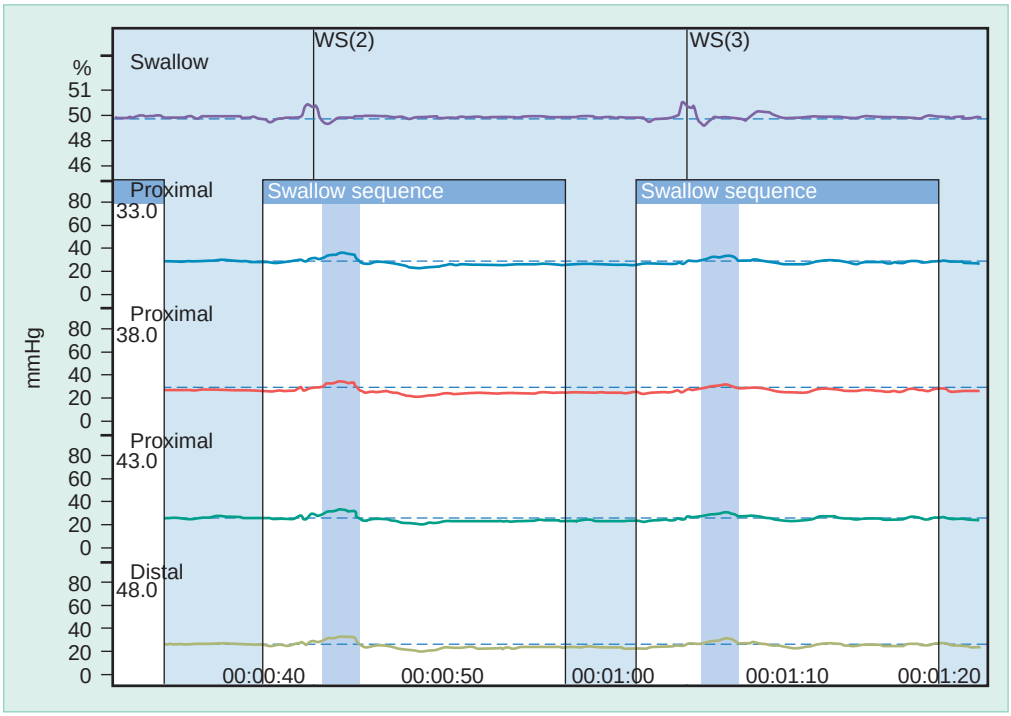

Figure 28–3. Classic manometric findings in achalasia. Esophageal peristalsis is absent.

Table 28–1 Classic Versus Vigorous Achalasia

	Patients with Chest Pain ($n = 117$)	Patients Without Chest Pain ($n = 94$)	*P* Value
Age (yr)	49 ± 16	51 ± 14	NS
Sex (F/M)	56/61	41/53	NS
Duration of symptoms (mo)	71 ± 91	67 ± 67	NS
Dysphagia (score 0-4)	2.7 ± 1.4	2.6 ± 1.5	NS
Regurgitation (score 0-4)	1.8 ± 1.4	2.0 ± 1.5	NS
Esophageal diameter (cm)	4.5 ± 0.7	4.3 ± 0.8	NS
LES pressure (mm Hg)	15 ± 9	17 ± 11	NS
LES relaxation (% patients)	46	37	NS
Absent	44	52	NS
Partial	10	11	NS
Complete			
Vigorous achalasia	50	47	NS

From Perretta S, Fisichella PM, Galvani C, et al: Achalasia and chest pain: Effect of laparoscopic Heller myotomy. J Gastrointest Surg 7:595-598, 2003.

sionally intestinal pseudo-obstruction, postvagotomy states, amyloidosis, and sarcoidosis.

Malignancy-induced achalasia, often referred to as *pseudoachalasia,* accounts for up to 4% of patients with manometric findings of achalasia and is caused by adenocarcinoma of the gastric cardia in 75% of cases. The pathophysiology of pseudoachalasia involves direct tumor infiltration into the myenteric plexus causing denervation similar to that seen in primary achalasia.[22] Malignant distal esophageal strictures caused by tumors involving the gastroesophageal junction and tumors involving the vagus nerve can similarly give rise to pseudoachalasia. Distant cancers such as prostate and pancreatic cancer have been reported to cause secondary achalasia via a paraneoplastic neuropathy. Age older than 60 years, duration of symptoms less than 1 year, and significant weight loss should raise suspicion of malignancy.[2] Endoscopic ultrasonography

or computed tomography can help establish the diagnosis.

COMPLICATIONS OF ACHALASIA

Esophagitis is caused by irritation from stasis and by infection. Epiphrenic diverticula represent pulsion diverticula secondary to increased intraesophageal pressure. In addition, there is an association between achalasia and the development of squamous cell esophageal cancer, presumably because of chronic mucosal irritation. Achalasia patients in whom esophageal cancer develops typically complain of worsening dysphagia 15 to 30 years after their initial symptoms. The incidence of cancer varies widely in the literature from 0.3% to 20%.[2,7] In the most comprehensive prospective endoscopic surveillance study published to date, Meijssen et al. monitored 195 patients with achalasia by surveillance endoscopy for more than 10 years after endoscopic dilatation. Esophageal cancer developed in three patients, for a 1.5% incidence of cancer over the 10-year study, a 33-fold increased risk in comparison to historical controls.[23] Brucher et al. reported a 3.2% incidence of esophageal carcinoma in 124 patients with achalasia observed over a median of 5.6 years. The cancer developed 18 to 42 years after the patients experienced symptoms. Fifty percent of the cancers were early stage, and long-term survival was similar to that of esophageal cancer in patients without achalasia.[24] The effect of surgical myotomy or endoscopic therapies on decreasing the risk for cancer by decreasing the amount of esophageal stasis and mucosal irritation is unknown.

Surgical myotomy and endoscopic treatments of achalasia may also increase the risk for esophageal adenocarcinoma because of disruption of the LES with resulting gastroesophageal reflux and the development of Barrett's esophagus. GERD is documented by 24-hour pH monitoring in about a third of patients after endoscopic dilatation,[25] in 38% to 60% of patients after Heller myotomy without fundoplication,[21,25] but in only 8% to 15% with the addition of a partial fundoplication.[21,26] Overall, patients in whom Barrett's esophagus is diagnosed have an estimated 0.5% annual risk for esophageal cancer. The incidence of Barrett's esophagus and esophageal cancer is not well studied in patients undergoing surgical and endoscopic treatment of achalasia. In one series of 46 patients who underwent surgical myotomy without fundoplication, Barrett's esophagus developed in 9% on long-term follow-up.[27] Of the 30 patients in the literature with Barrett's esophagus and achalasia, adenocarcinoma developed in 25% after a mean follow-up of 22 years following treatment.[28] It is important to stress that this group of patients was not treated with laparoscopic Heller myotomy and fundoplication, the current surgical standard of care. Longer follow-up is necessary to accurately determine the incidence of Barrett's esophagus and esophageal adenocarcinoma after surgical myotomy with fundoplication for achalasia.

Patients who have previously been treated for achalasia and complain of recurrent dysphagia should undergo a complete evaluation, including barium swallow, upper endoscopy, esophageal manometry, and pH monitoring. Treatment should be tailored to the findings of these tests. For asymptomatic patients, the recommended frequency of surveillance endoscopy is debatable and not based on controlled studies.

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Chapter

29

Laparoscopic Esophageal Myotomy: Techniques and Results

Dave R. Lal ▪ Brant K. Oelschlager

Achalasia is a rare primary esophageal motor disorder characterized by ineffective relaxation of the lower esophageal sphincter (LES) and concomitant loss of esophageal peristalsis. The clinical manifestations of achalasia include progressive dysphagia and varying degrees of regurgitation, aspiration, chest pain, and weight loss. The reported incidence in the United States is 0.5 to 1 per 100,000. Although achalasia can occur at any age, a majority of patients are between the ages of 20 and 50 years. There is no gender preponderance.

Although the cause of achalasia is unknown, histologic examination of affected esophagi demonstrate myenteric inflammation with loss of ganglion cells and fibrosis of the myenteric plexus.[1] This destruction is probably autoimmune regulated because T lymphocytes predominate in the inflammatory infiltrate surrounding the myenteric plexus.[2] Additional research has shown achalasia patients to have decreased nitric oxide synthase in the myenteric plexus, which contributes to reduced nitric oxide production.[3] Nitric oxide is a key factor in gastrointestinal smooth muscle relaxation, including the LES.

Though first described more than 300 years ago, treatment of achalasia has evolved from dilatation with a whale bone to open and minimally invasive surgical myotomy, pneumatic dilatation, and botulinum toxin A (Botox) injection. This chapter discusses the medical and surgical management of achalasia.

DIAGNOSIS

Patients typically complain of a slow progression of dysphagia, first to solids and then to liquids. The dysphagia is usually accompanied by regurgitation, mild weight loss, and chest pain/discomfort associated with eating. Most patients relate a sensation of food getting stuck in their esophagus. Some adopt maneuvers, including standing and raising their arms above their heads, in an effort to use gravity to propel food into the stomach. Because of poor esophageal clearance, regurgitation of undigested food is common after meals and when lying supine. This regurgitation can lead to recurrent aspiration, pneumonia, and vocal hoarseness. Although patients complain of reflux, it is usually not due to gastric acid secretions but rather fermentation of undigested food that is pooled in the esophagus. Therefore, acid-suppressive medications provide little relief. In older patients (>55 years), those with a shorter duration of symptoms (<6 months), or those with more profound weight loss (>15 lb), it is crucial to rule out pseudoachalasia (presence of a distal esophageal tumor) as the cause of the symptoms.

The preferred initial diagnostic test for most patients with progressive dysphagia is a barium swallow. This inexpensive and readily available study reveals impaired peristalsis, a dilated esophagus, and the pathognomonic smooth tapering at the gastroesophageal (GE) junction commonly termed a "bird's beak" (Fig. 29–1A and B). In long-standing achalasia, the esophagus can become dilated and tortuous and has been termed sigmoid-shaped esophagus or megaesophagus (see Fig. 29–1C).

Manometry is required to diagnose achalasia. Manometric findings include failure of the LES to relax with deglutition and aperistalsis of the esophageal body. LES pressure is typically elevated (>40 mm Hg) but may be normal. Motor activity in the esophagus consists of low-amplitude (<40 mm Hg) simultaneous contractions. Occasionally, high-amplitude simultaneous contractions are seen, and these patients are classified as having vigorous achalasia.

Endoscopy is necessary to exclude pseudoachalasia and evaluate for atypical anatomy. Characteristic findings

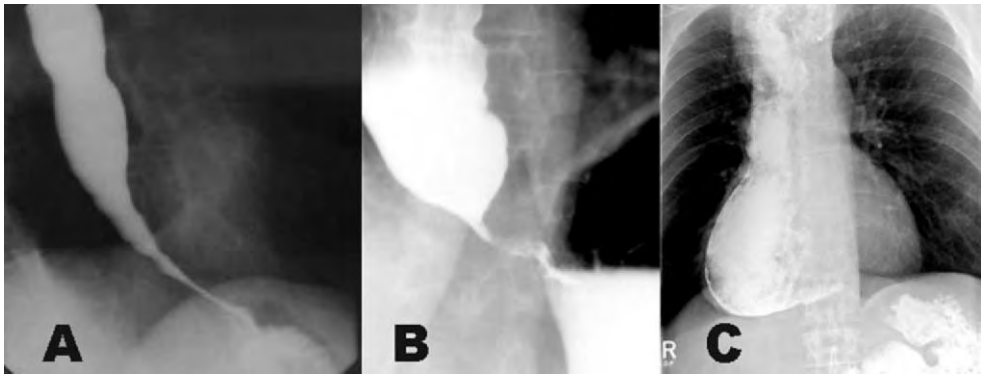

Figure 29–1. Barium esophagograms of patients with varying stages of achalasia. All demonstrate the smooth tapering of the distal end of the esophagus termed a bird's beak. **A,** Early achalasia. Note the minimal esophageal dilatation. **B,** More typical esophagogram depicting a dilated esophagus in a patient with achalasia. **C,** Dilated and tortuous esophagus typically seen in patients with long-standing achalasia, termed megaesophagus or sigmoid-shaped esophagus. (Courtesy of Charles A. Rohrmann, Jr., M.D., University of Washington School of Medicine, Seattle.)

include a dilated esophagus with failure of the LES to open on insufflation and minimal resistance to passage of the scope through the GE junction. Retention of food and debris in the esophagus is common. Patients with achalasia have a 16-fold increased rate of esophageal cancer (typically squamous cell); thus, all mucosal abnormalities must be sampled by biopsy.[4] If concern for pseudoachalasia persists, computed tomography or endoscopic ultrasound (or both) should be added.

MEDICAL THERAPY

Pharmacologic Treatment

Nitrates and calcium channel blockers have been used with various degrees of success. Relief of symptoms is usually transient, limited to early or mild achalasia, and associated with side effects, including peripheral edema, dizziness, and headaches. Recently, sildenafil, a phosphodiesterase-5 inhibitor, has been shown to relax the LES.[5,6] The mechanism of action involves inhibition of phosphodiesterase-5, which results in increased nitric oxide and cyclic guanosine monophosphate within the LES. Like other pharmacologic treatments, sildenafil's effects last approximately 2 to 8 hours, and it may cause significant side effects. We occasionally prescribe pharmacologic therapy for short-term relief of severe symptoms in patients awaiting surgical myotomy.

Botulinum Toxin

Botox inhibits muscle contraction by blocking acetylcholine release from presynaptic nerve terminals. Treatments involve multiple injections around the GE junction via an endoscope. Although the initial success rate is high, long-term relief is not sustained. Zaninotto et al.[7] have published the only randomized controlled trial comparing Botox with surgical myotomy. In this trial, patients randomized to receive Botox underwent two sessions of Botox injection within a 1-month period. Both techniques provided similar relief at 6 months. Prolonged follow-up at 2 years revealed that 87.5% of patients in the surgical group remained symptom-free whereas only 34% remained so in the Botox group ($P = .05$). Previous Botox injections in patients undergoing surgical myotomy can lead to increased difficulty finding and dissecting the submucosal plane and a higher perforation rate.[8,9] Botox treatment should be reserved for patients unable to withstand surgery or unwilling to undergo an invasive procedure.

Pneumatic Dilatation

Pneumatic dilatation is performed under endoscopic or fluoroscopic guidance. The technique involves the inflation of polyethylene balloons, usually starting at 30 mm and progressing stepwise to 35 mm and occasionally to 40 mm. Inflation of the balloon and subsequent stretching of the distal esophagus result in fracture of the LES circular muscle. Patients typically undergo conscious sedation and have the procedure performed as an outpatient. Patients are observed after the procedure for approximately 6 hours to monitor for the reported 2% risk for esophageal perforation.[10] At 1 year, most authors have reported success rates around 70% for pneumatic dilatation. Dobrucali et al.[11] monitored their patients long-term and found that 54% continued to be symptom-free at 5 years. In comparison, Junginger et al.[12] reported on the long-term outcome in patients undergoing surgical myotomy. At a median of 88 months, 96% of the patients reported a very good or good outcome and 92% related no or very rare dysphagia. Similarly, Bonavina et al.[13] observed their Heller myotomy patients for a median of 64 months; 94% related their outcomes as excellent or good. In contrast to Botox injections, previous pneumatic dilatation does not hinder surgical myotomy.[8]

SURGICAL THERAPY

Approach

Before the introduction of minimal access surgery, Heller myotomies were routinely performed via a left thoracotomy. In the early 1990s, as minimally invasive techniques were developed, thoracoscopic cardiomyotomy was first described. The benefits of this minimally invasive technique were decreased postoperative pain and shorter hospital stay without compromise in relief of dysphagia.[14,15] Multiple factors in the mid-1990s led to the change in surgical approach from thoracoscopy to laparoscopy. First, surgeons were performing increased numbers of laparoscopic fundoplications and became more adept at operating on and around the esophagus and hiatus. Second, it became clear that extending the myotomy well onto the stomach was critical to consistent and durable relief of dysphagia.[16] Third, even with limited gastric myotomy, the incidence of postoperative reflux was high with the thoracoscopic approach. Additionally, laparoscopy avoided a double-lumen endotracheal tube and the need for single-lung ventilation and a postoperative chest tube. Multiple studies have affirmed the superiority of laparoscopic Heller myotomy by demonstrating shorter operative times and hospital stay with decreased postoperative dysphagia and reflux in comparison to the thoracoscopic approach.[16-18]

LAPAROSCOPIC HELLER MYOTOMY

Patient Positioning and Preparation

Patients are placed in a modified lithotomy position with a bean bag beneath them and both arms tucked at the sides. The bean bag overhangs the edge of the operative table to allow the formation of a saddle around the patient's perineum. This technique secures the positioning. The operative surgeon stands between the patient's legs with the assistant at the patient's left side. Monitors should be located ergonomically above the patient's head.

Port Placement

Initial access is obtained at the costal margin in the left upper quadrant. After establishing pneumoperitoneum with a Veress needle, a Visiport trocar (United States Surgical Corporation, Norwalk, CT) is inserted near the umbilicus. The abdomen is examined and four working ports are then placed under direct visualization, as shown in Figure 29–2. It is important to note that landmarks change with abdominal insufflation; therefore, port site markings should be performed after insufflation and visually checked intracorporeally to ensure proper reach and ergonomics. The camera port is placed approximately 10 to 12 cm inferior to the left upper quadrant port and 4 cm left of midline. The remaining ports include a 5-mm trocar in the right upper quadrant for the surgeon's left hand, a 10-mm trocar in the left lower quadrant for the assistant's right hand, and a 10-mm trocar in the right lateral quadrant for a liver retractor. After port placement, the patient is placed in steep reverse Trendelenburg positioning. Our preference for liver retraction is a paddle retractor that can be secured to the operative table with a Bookwalter retractor post and flexible arm (Codman, Raynham, MA). Alternatively, a 5-mm subxiphoid incision can be made and a Nathanson liver retractor (Cook, Bloomington, IN) used. A 10-mm 30-degree angled laparoscope provides superior visualization.

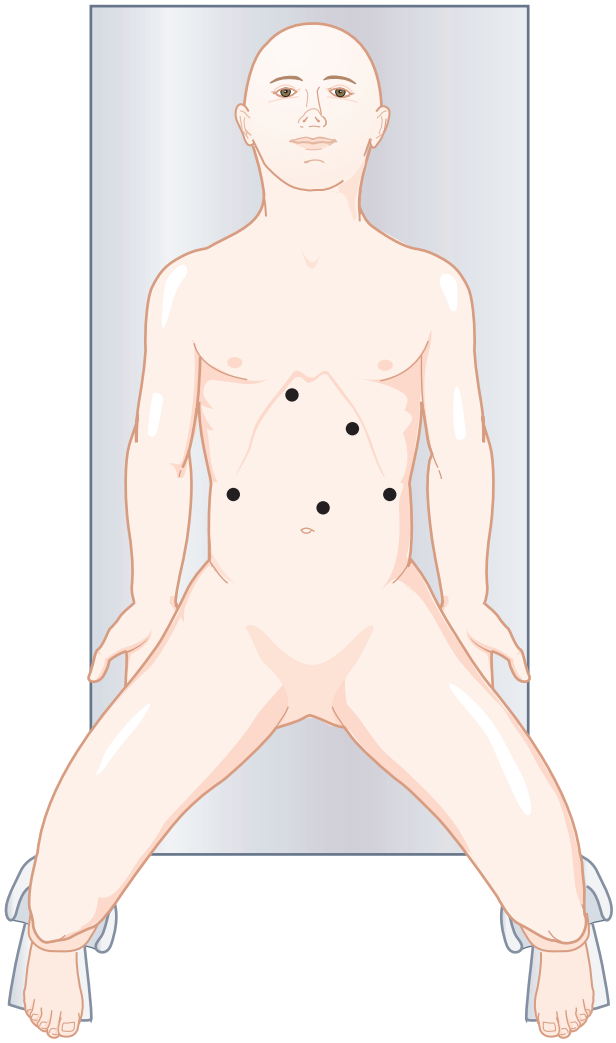

Figure 29–2. Patient positioning and port placement. (From Woltman TA, Oelschlager BK, Pellegrini CA: Achalasia. Surg Clin North Am 85:483-493, 2005, with permission.)

Operative Steps

Our initial approach involves dividing the left phrenoesophageal and phrenogastric ligaments to allow exposure of the left crus. Next, we mobilize the gastric fundus for later fundoplication. An ultrasonic dissector is used to divide the short gastric vessels, beginning at the inferior pole of the spleen and continuing superiorly to the

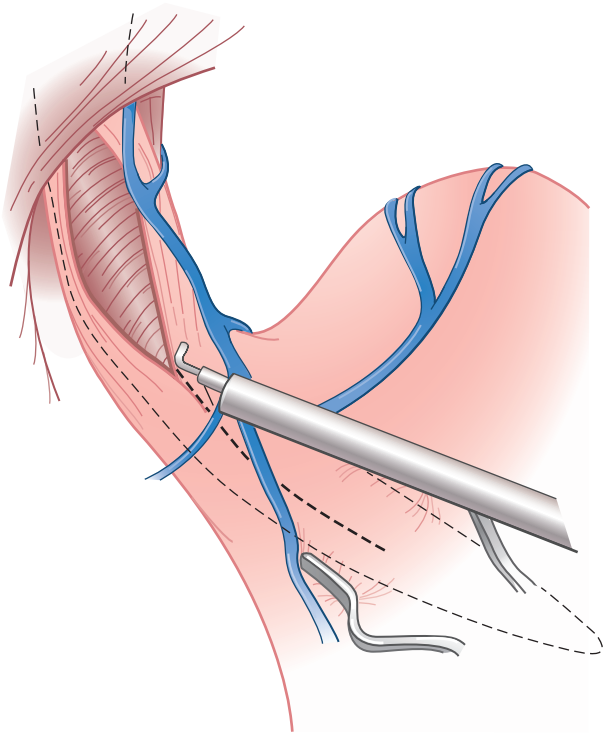

Figure 29–3. Laparoscopic Heller myotomy. A hook cautery is used to divide the outer longitudinal esophageal muscle for exposure of the underlying circular muscle. The *dashed line* in the background represents a lighted bougie in correct placement. A Babcock retractor is placed around the bougie and retracted caudally with slight tension on the esophageal muscle layers. (From Ali A, Pellegrini CA: Laparoscopic myotomy technique and efficacy in treating achalasia. Gastrointest Endosc Clin N Am 11:353, 2001, with permission.)

previously exposed left crus. The posterior attachments between the proximal part of the stomach and the retroperitoneum are also divided. Once the proximal stomach has been adequately mobilized to permit tension-free fundoplication, attention is turned to the gastrohepatic ligament. An avascular area close to the liver is incised and the incision carried craniad toward the esophageal hiatus to expose the right crus. Care is taken to preserve the nerves of Latarjet and aberrant vessels such as an accessory or replaced left hepatic artery. The anterior phrenoesophageal ligament and peritoneum overlying the anterior abdominal esophagus are divided while being cognizant of the underlying anterior vagus nerve. A posterior esophageal window is created to allow for a Toupet fundoplication. This is accomplished by dissecting to the base of the right crus under the esophagus and finding the confluence of the right and left crura. During this step the posterior vagus should be visualized and protected.

Adequate mediastinal esophageal mobilization is crucial for a long esophageal myotomy and tension-free fundoplication. If necessary, a Penrose drain may be placed around the GE junction and used to retract the esophagus caudally and laterally during hiatal and transmediastinal esophageal mobilization. Before the myotomy can be performed, a clear path must be made across the GE junction. We resect the cardioesophageal fat pad to the left of the anterior vagus nerve and at the same time mobilize the vagus off the esophagus. This allows a straight plane to perform the myotomy.

Essential to performing the myotomy is excellent visualization and exposure. A lighted 52-French bougie is placed in the body of the stomach; it serves to both illuminate the esophagus and muscle layers and provide a stable platform to perform the myotomy. A Babcock retractor is then draped over the bougie at the GE junction and retracted caudally. This motion exposes the anterior of the esophagus and myotomy path, and places the esophageal muscle fibers under slight tension, which aids in their identification and division. The myotomy is begun approximately 3 cm below the GE junction with an L-shaped hook electrocautery device. During the myotomy, electrocautery should be avoided unless absolutely necessary. Individual muscle fibers are divided by hooking them and applying gentle upward traction. Bleeding from the muscle or submucosa is controlled with pressure and time. These steps are important to avoid delayed perforation from unrecognized thermal mucosal injury. The longitudinal muscle fibers are divided first to expose the underlying circular muscle (Fig. 29–3). Once the circular muscles are divided, a mucosal plane is reached with smooth, white, bulging mucosa (Fig. 29–4). This plane is then carried cephalad onto the esophagus for a length of 6 to 8 cm. The entire myotomy therefore spans approximately 9 to 11 cm (3 cm below the GE junction to 6 to 8 cm above the GE junction). The most difficult dissection involves the 3-cm myotomy on the stomach. In this area, the plane of dissection becomes blurred with intervening sling muscular fibers, and the underlying gastric mucosa is thinner, thereby increasing the risk for perforation. Mucosal perforations are repaired with fine (4-0 or 5-0) absorbable monofilament suture and rarely require further intervention. Endoscopy can be used to evaluate the myotomy and check for a missed perforation.

After satisfactory cardioesophageal myotomy, we perform a Toupet fundoplication. The posterior fundus of the stomach is brought around the esophagus and secured to the right crus and the right cut edge of the myotomy. In a similar (in fact mirror image) fashion, the anterior fundus of the stomach is sutured to the left crus and left cut edge of the myotomy (Fig. 29–5). Rarely, patients with large hiatal hernias require curapexy closure of the hiatus. If we have an esophageal perforation, we perform an anterior (Dor) fundoplication to buttress the repair.

Postoperative Management

Typically, patients receive liquids the evening of their operation. They are then advanced to a soft diet and discharged the following day. It is important to treat nausea aggressively with antiemetics. Patients are advised to avoid strenuous activity and heavy lifting for 4 to 6 weeks.

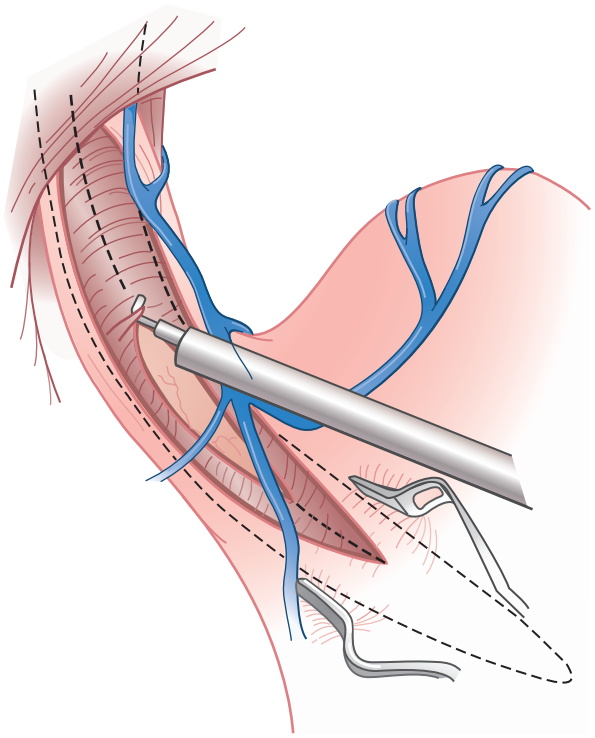

Figure 29–4. Laparoscopic Heller myotomy. Division of the inner circular muscle layer reveals the bulging underlying esophageal mucosa. Note the long length of the myotomy both distally onto the stomach and proximally on the esophagus. (From Ali A, Pellegrini CA: Laparoscopic myotomy technique and efficacy in treating achalasia. Gastrointest Endosc Clin N Am 11:353, 2001, with permission.)

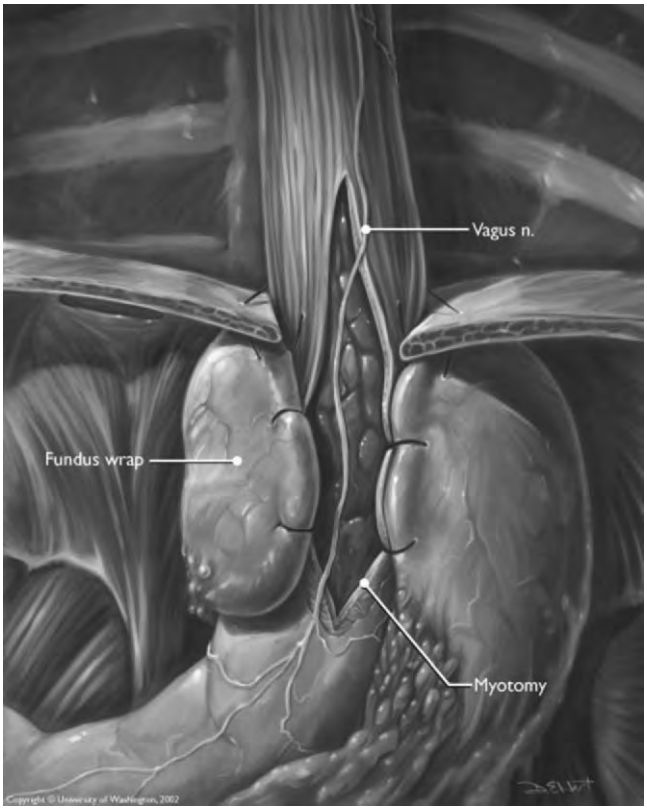

Figure 29–5. Completed laparoscopic Heller myotomy with posterior (Toupet) fundoplication. (Courtesy of the University of Washington, Seattle, with permission.)

A majority of patients resume normal activities within 1 to 2 weeks and a regular diet in 2 to 6 weeks.

CONTROVERSIES

Length of the Myotomy

The exact length and dimensions of the esophageal myotomy have been a source of debate. Multiple authors have shown a correlation between relief of dysphagia and length of myotomy carried onto the stomach. We first noted this association in our thoracoscopic group of patients in whom the myotomy extended 0.5 cm onto the gastric wall. The rate of persistent dysphagia was 27% as a result of the incomplete myotomy.[16] A critical flaw in the thoracoscopic approach is its inherent inability to perform an extended distal myotomy onto the stomach. Therefore, we switched our technique to a laparoscopic approach and incorporated a myotomy carried out 1 to 1.5 cm on the gastric wall. This additional length of myotomy distally decreased the postoperative dysphagia rate to 11%.[16] Similarly, Ramacciato et al.[19] compared outcomes in patients treated with thoracoscopic and laparoscopic Heller myotomy. In their study, myotomies were carried onto the stomach for a distance of 1 cm in the thoracoscopic group and 2 cm in the laparoscopic group. They found that the thoracoscopic group had significantly more dysphagia than the laparoscopic group did (37.5% versus 5.8%, respectively, $P = .04$). Additionally, the median postoperative basal LES pressure was 15.5 mm Hg in the thoracoscopic group and 10.5 mm Hg in the laparoscopic group ($P = .0001$).

In 1998, our group hypothesized that postoperative dysphagia could be further decreased with an extended myotomy carried 3 cm distal to the GE junction. We compared outcomes in extended myotomy patients and those undergoing a short myotomy 1 to 1.5 cm onto the gastric wall. Our data clearly showed that an extended myotomy resulted in significantly less severity and frequency of postoperative dysphagia than a short myotomy did ($P = .001$ for both).[20] The frequency of postoperative heartburn, regurgitation, and chest pain was no different in patients with either an extended or short myotomy ($P = .36$, $P = .19$, $P = .71$, respectively). Additionally, postoperative 24-hour pH studies demonstrated no difference in proximal or distal esophageal acid exposure between extended and short myotomy ($P = .55$ and $P = .96$, respectively). These studies highlight the shortcomings of the thoracoscopic approach and importance of an extended distal myotomy.

Antireflux Procedure

Whether an antireflux procedure should be performed at the time of a Heller myotomy has been the most controversial surgical issue in the treatment of achalasia. Such is no longer the case; with few exceptions, an antireflux procedure should be performed. Performing a cardiomyotomy, in the vast majority of cases, renders the primary barrier to gastroesophageal reflux (GER) ineffective. Thus, a partial fundoplication that does not inhibit bolus transit from the aperistaltic esophagus into the stomach but diminishes GER would seem intuitive.

It has been shown that patients with achalasia have decreased esophageal chemoreceptors and therefore do not sense acid reflux as much as normal subjects do.[21] This is probably the reason for the low frequency of postoperative GER reported by patients treated with Heller myotomy and no antireflux procedure. Although the GER remains silent to the patient, continuous acid exposure of the esophagus can lead to peptic strictures, Barrett's esophagus, and esophageal cancer.[4] Proponents of cardiomyotomy without fundoplication cite their shorter operative times, diminished risk of causing dysphagia, and ease with which GER can be treated with modern acid-suppression medication.

We and others have long since said that an antireflux procedure was necessary to reduce the high rate of GER and could be done without increasing the rate of dysphagia.[12,13,16,18] Until recently, only meta-analysis and nonrandomized studies were available to base one's decisions. Richards et al.,[22] previous objectors to the need for an antireflux procedure, recently published the only prospective randomized double-blind study specifically addressing whether an antireflux procedure is necessary. In their study, 43 patients were randomized to undergo Heller myotomy alone or Heller myotomy plus Dor fundoplication. The addition of an antireflux procedure to Heller myotomy clearly decreased the incidence of GER (ninefold) without increasing the rate of dysphagia. In a comparison of the two groups, the incidence of pathologic GER was 47.6% in the Heller-only group and 9.1% in the Heller-plus-Dor group ($P = .005$). Distal esophageal acid exposure was significantly greater in the Heller group than in the Heller-plus-Dor group, 4.9% versus 0.4%, respectively ($P = .001$). The median postoperative LES pressure was 13.7 mm Hg in the Heller group and 13.9 mm Hg in the Heller-plus-Dor group. Subjectively, patients undergoing Heller-only and Heller-plus-Dor procedures reported similar decreases in the median dysphagia score (9 versus 8, $P = .79$). There are now few surgeons who do not perform an antireflux procedure after myotomy.

Fundoplication Technique

Because of the aperistaltic esophagus in achalasia patients, a complete 360-degree wrap is typically avoided. A majority of surgeons perform either an anterior (Dor) or a posterior (Toupet) 270-degree fundoplication. The advantage of the Dor fundoplication is its technical ease because it avoids extensive gastric mobilization and is able to buttress small mucosal perforations created during myotomy. A Toupet fundoplication inherently splays the myotomy edges apart, which theoretically prevents fibrosis between them and recurrent dysphagia. A small nonrandomized study showed that patients undergoing Toupet fundoplication had less postoperative reflux than did patients undergoing Dor fundoplication.[18] It is the authors' choice to perform a Toupet fundoplication for these advantages, although until a good randomized control trial comparing Dor with Toupet fundoplication is performed, this controversy will continue.

Sigmoid-Shaped Esophagus or Megaesophagus

Megaesophagus represents end-stage achalasia because the combination of an aperistaltic esophagus and failure of LES relaxation leads to progressive esophageal dilatation and lengthening with time (see Fig. 29–1C).[23] Previously, it was suggested that patients with megaesophagus be treated by esophagectomy rather than myotomy,[24-26] the rationale being that dilated, elongated, and often tortuous aperistaltic esophagi do not empty sufficiently to improve dysphagia, even when the LES is disrupted. As a result of the drastic decrease in morbidity with minimally invasive approaches, many surgeons have elected to attempt a myotomy first. Recently, two studies have demonstrated good postoperative results in patients with megaesophagus treated by Heller myotomy. The obvious advantage of a Heller myotomy is avoidance of the morbidity and mortality associated with esophagectomy. Patti et al.[27] performed laparoscopic Heller myotomy on patients who had a dilated esophagus (>6 cm) with a straight-axis configuration and a sigmoid-shaped configuration. They reported no increased difficulty in performing the surgery, no increase in complications, and excellent relief of dysphagia in both groups. Overall, 92% of patients in the study reported an excellent or good postoperative outcome. Likewise, Mineo and Pompeo[28] studied 14 patients with a sigmoid esophagus treated with a Heller myotomy. With a median follow-up of 85 months, excellent or good results were reported by 72%, and no patient required an esophagectomy. Postoperative dysphagia and regurgitation scores decreased significantly ($P = .002$ and $P = .001$, respectively) and were equivalent to postoperative scores from a nondilated esophagus group undergoing Heller myotomy. Health-related quality of life evaluated with a Short Form-36 questionnaire indicated statistically improved general health, social function, and mental health. Interestingly, esophageal width was found to narrow with time, on average 10 mm in 24 months.

COMPLICATIONS

Early complications are fortunately uncommon and include intraoperative esophageal perforation, pneumothorax, bleeding, intra-abdominal abscess, and

wound infection. The esophageal perforation rate has been reported to be between 0% and 7% in most major studies.[22,29] Once identified, perforations are repaired by reapproximating the esophageal mucosa and buttressing the repair with an anterior (Dor) fundoplication. The Dor fundoplication is created by positioning the gastric fundus over (anterior to) the myotomy and perforation site. The fundus of the stomach is secured with sutures to the right and left crura, as well as the transected edges of the esophageal myotomy (Fig. 29–6).

Other complications occur in less than 3% of cases.[30] Pneumothorax typically develops when a rent is made in the pleura during mediastinal esophageal mobilization. If identified intraoperatively, the pleural defect may be primarily repaired with a suture or, if small, an endoclip. Rarely does the pneumothorax cause respiratory or circulatory embarrassment. If physiologic problems do occur, a majority resolve by decreasing the insufflation pressure to less than 10 mm Hg; if unsuccessful, a tube thoracostomy may be required. An asymptomatic pneumothorax discovered on a postoperative chest radiograph should be treated with oxygen supplementation via nasal cannula or face mask. These pneumothoraces resolve quickly because the carbon dioxide is rapidly absorbed by the body.

Late complications include recurrent dysphagia and GER. Postoperative dysphagia may be due to incomplete myotomy, perihiatal scarring, progressive dysmotility of the esophagus, peptic stricture, and obstructing tumor. Work-up of these patients should include esophagography, endoscopy, and repeat manometry. The most likely reason for recurrence of dysphagia is incomplete myotomy. As stated previously, we have found that extended myotomy significantly reduces postoperative dysphagia without increased GER.[20] Zaninotto et al.[31] reported on their experience with the development of dysphagia after laparoscopic Heller myotomy. Of 113 patients studied, 10 (8.8%) were considered surgical failures because of recurrent dysphagia or chest pain. Postoperative testing (performed on nine patients) identified that seven patients failed because of an incomplete myotomy distally, one for an incomplete myotomy proximally, and one as a result of megaesophagus, with the last cause being unknown. All patients underwent endoscopic pneumatic dilatation with 35- or 40-mm balloons inflated to a median of 6 psi for 1 minute. Seventy-eight percent of patients experienced complete resolution of their dysphagia or chest pain. The remainder underwent redo surgical myotomy. Likewise, Patti et al.[32] found that a majority of their postoperative failures were due to incomplete myotomy. These studies demonstrate that postoperative dysphagia is most likely due to incomplete myotomy and further support our group's advocacy of extended myotomy. Persistent dysphagia after surgery should first be approached with endoscopic dilatation and, if this fails, redo surgery.

As discussed earlier, symptomatic GER is rare in patients after Heller myotomy. However, if patients undergoing Heller myotomy without fundoplication are studied postoperatively, a significant amount will have pathologic acid reflux. Although it typically remains clinically silent, it does predispose the patient to Barrett's esophagus, peptic strictures, and cancer. It is therefore imperative that measures to minimize GER be implemented whether it is symptomatic or not. As discussed earlier, the most effective method of reducing GER is to perform a fundoplication in conjunction with myotomy. Six months after surgery, we study all patients with a 24-hour pH monitor to detect asymptomatic GER. Patients found to have abnormal esophageal acid exposure are placed on a regimen of proton pump inhibitors and monitored.

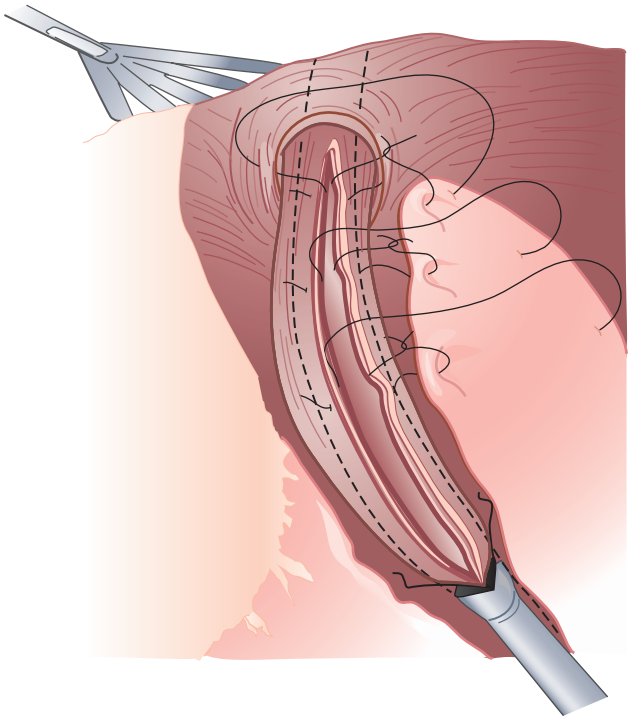

Figure 29–6. Laparoscopic Heller myotomy with anterior (Dor) fundoplication. The anterior fundus is sutured to the myotomy edges and both crura. (From Yim APC, Hazelrigg SR, Izzat MB, et al [eds]: Minimal Access Cardiothoracic Surgery. Philadelphia, WB Saunders, 2000, p 258.)

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Chapter

30

Diffuse and Segmental Esophageal Spasm, Nutcracker Esophagus, and Hypertensive Lower Esophageal Sphincter

Tasha A. K. Gandamihardja · Cedric G. Bremner

This group of spastic conditions usually first comes to medical attention because of a history of chest pain, dysphagia, or both and often challenges the clinician with respect to making a correct diagnosis and initiating effective treatment. The cause and mechanism of the abnormalities remain unknown, but there has been progress in their management. Although radiologic investigation may suggest the diagnosis of a motility disorder, esophageal manometry, endoscopy, and pH testing are essential to give a precise appraisal of the problem.

DIFFUSE AND SEGMENTAL ESOPHAGEAL SPASM

Diffuse and segmental esophageal spasms are rare conditions. They are characterized by symptoms of substernal pain, dysphagia, or both; the radiographic appearance of localized, nonprogressive swallow responses (tertiary contractions); and an increased incidence of nonperistaltic contractions recorded on intraluminal manometry. The condition was first described by Osgood in 1889 as esophagismus.[1] In 1967, Fleshler described the syndrome of diffuse esophageal spasm (DES) as a clinical syndrome.[2] The chest pain or dysphagia may be precipitated by the ingestion of hot or cold foods, or it may occur spontaneously. Chest pain may be the predominant symptom and is sometimes indistinguishable from cardiac-type pain. Dysphagia may be less pronounced and intermittent in occurrence. This difference in symptomatology separates esophageal spasm from achalasia, where dysphagia usually predominates.

The etiology of esophageal spasm is unclear. It has been suggested that the esophagus of patients with DES produces a hypersensitive response to cholinergic and hormonal stimulation, probably mediated by neural dysfunction.[3] A genetic link has also been proposed. The basic motor abnormality is a rapid progression of esophageal contractions down the esophagus without the normal latency gradient.

Investigations

Endoscopy Endoscopic examination is necessary to exclude an associated hiatal hernia or esophagitis.

Radiology Radiologic investigations may be normal in patients with DES and thus do not exclude the diagnosis. A variety of radiologic appearances have been described, such as "corkscrew" or rosary-bead esophagus (Fig. 30–1), segmental spasm, and pseudodiverticulosis, but in most cases the diagnosis is not obvious. Spasm may cause compartmentalization of the esophagus with resulting epiphrenic or midesophageal diverticula. Incomplete or absent primary peristalsis and mild to severe tertiary contractions have been described in about 70% of patients.[4] Impaired LES opening has also been reported.[5]

Manometry Manometry is essential for the diagnosis of esophageal spasm (Table 30–1). The criteria for

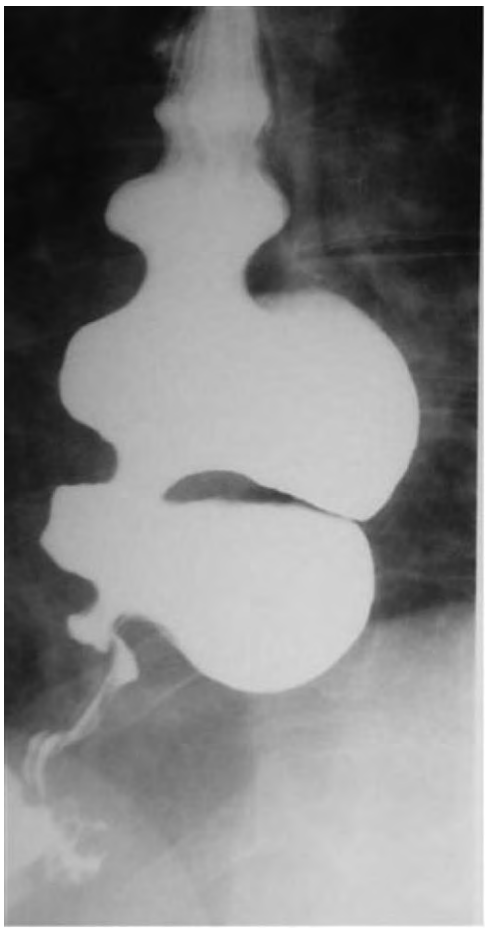

Figure 30–1. "Corkscrew esophagus" seen on a barium study of a patient who complained of dysphagia and chest pain.

diagnosis require that simultaneous swallow responses be present in at least three fifths of the esophageal body in 20% or more of wet swallows (Fig. 30–2).[6] It is important to appreciate that in esophageal spasm, the esophagus retains a degree of peristaltic contractions whereas in achalasia, there is no peristalsis. Because of this "misnomer," a plea has been made to describe the condition as "distal" esophageal spasm.[7] Furthermore, although DES has also been described as a motility disorder characterized by high-amplitude contractions, such contractions are not seen frequently. In one study, associated manometric features were repetitive (>3 peaks) contractions in 67% of subjects, high-amplitude contractions in 33%, spontaneous activity in 22%, prolonged duration of contractions in 11%, and LES abnormalities in 5%.[8] Other classic manometric findings include simultaneous multipeaked and repetitive responses to swallows (see Table 30–1).

Standard stationary esophageal manometry may, however, fail to detect the spasms, whereas ambulatory manometry may be more successful.[9]

Simultaneous contractions can occur in other diseases, such as achalasia, gastroesophageal reflux disease (GERD), diabetes, alcoholism, and connective tissue diseases. These conditions need to be ruled out before embarking on any possible surgical procedure.

pH Studies Many patients with manometric findings of DES describe symptoms of gastroesophageal reflux. Some argue that the esophageal spasm in these patients is a consequence of acid exposure,[10] whereas others have argued that the aperistaltic nature of the esophagus causes poor clearance and hence retention of acid.[6] Reflux-induced and idiopathic DES cannot be differentiated on manometric features alone. Differentiation between GERD and DES may be based on the persistence of chest pain and dysphagia while the patients are taking acid-suppression therapy. Thus, in this group of patients, combined pH monitoring with simultaneous ambulatory

Table 30–1 Manometric Features of Primary Esophageal Motility Disorders

Disorder	Lower Esophageal Sphincter	Esophageal Body
Diffuse esophageal spasm	May be abnormal	>20% simultaneous contractions Other features may be present: Repetitive (>2 peaks) contractions Prolonged duration Spontaneous contractions High-amplitude contractions Intermittent normal peristalsis
Nutcracker esophagus	May be hypertensive	High-amplitude contractions (mean >180 mm Hg) Other features may be present: Prolonged duration (mean >6 sec) Normal peristaltic progression
Hypertensive lower esophageal sphincter	Baseline elevated (>27 mm Hg) Normal relaxation or mild elevation of residual pressure	Normal peristaltic progression Ramp bolus pressure may be increased distally

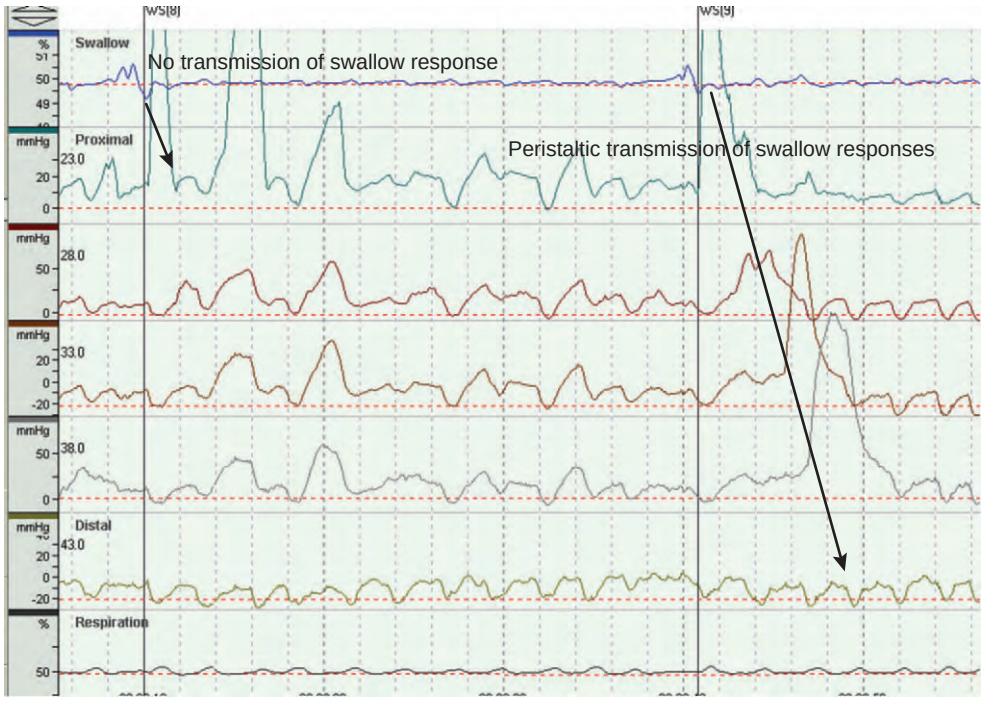

Figure 30–2. Manometric recording in a patient with diffuse esophageal spasm. The first swallow resulted in simultaneous swallow responses seen in the five channels, which are each 5 cm apart in the body of the esophagus. The second swallow, however, resulted in a normal peristaltic response. More than 20% simultaneous contractions with intermittent peristaltic contractions is required for the diagnosis of diffuse esophageal spasm.

24-hour esophageal motility studies may help differentiate the two conditions.

Treatment

Medical treatment of DES includes the use of muscle relaxants such as calcium channel blockers and nitrates. Psychosomatic treatment with antidepressants has been proposed as an effective mode of treatment because anxiety and depression have been found to be prevalent in this group of patients.[3] The use of endoscopically administered botulinum toxin provides initial symptom relief; however, repeated injections are usually necessary.[11] Medical treatment is generally geared toward symptom control, and the results are variable.

Surgery focuses on the mechanical dysfunction aspect of the condition, where bolus transit down the esophagus is restricted because of the presence of a functional obstruction resulting from simultaneous contractions as well as decreased muscle compliance.

Ambulatory motility studies performed during meals in patients with symptoms of dysphagia have shown that an association exists between increased simultaneous waveforms and decreased contraction amplitude of peristaltic waves. It has been shown that the presence of 75% or more simultaneous waveforms on ambulatory motility studies during meals is a good indication for surgical myotomy.[6] The presence of chest pain alone is not a sufficient indication for myotomy. Myotomy of the esophageal body relieves dysphagia by reducing the amplitude of esophageal contractions and the frequency of simultaneous, double-peaked and multipeaked, high-amplitude and long-duration contractions.[6]

The extent of the myotomy should be predetermined from the preoperative manometry study. The upper limit of the myotomy is still a contentious issue among surgeons. To minimize outflow resistance, the lower limit usually extends distally across the lower esophageal sphincter (LES). This, however, eliminates the role of the sphincter as an antireflux barrier, and as a result an antireflux procedure needs to be performed to prevent reflux of stomach contents into the esophagus. A complete fundoplication will offer too much resistance (about 20 mm Hg) to esophageal emptying, and thus partial fundoplications have been preferred. A Dor or a modified Belsey procedure has been found to improve eating ability and significantly reduce the severity of chest pain, dysphagia, heartburn, and regurgitation.[6,12-14] In one study a Toupet fundoplication was reported to provide better relief from postoperative dysphagia.[15]

These procedures can now be carried out thoracoscopically or laparoscopically.

NUTCRACKER ESOPHAGUS

Nutcracker esophagus is a condition first described in 1979.[16] The majority of patients have chest pain, although dysphagia and symptoms of GERD may also be reported. The chest pain may be difficult to distinguish from cardiac pain, just as with DES. These patients are therefore often seen first by a cardiologist to rule out a cardiac cause before further referral. It is difficult to differentiate various esophageal motility disorders on the basis of symptoms alone, and thus further investigations are warranted.

The condition is characterized by high-amplitude peristaltic contractions in the distal end of the esophagus, with peak amplitudes greater than 2 SD above normal values recorded in individual laboratories (i.e., greater than 180 mm Hg), or a prolonged duration

of contractions (or both).[17] The term "super squeezer" has also been used to describe the esophagus in this condition.

The etiology and pathogenesis of nutcracker esophagus is unclear. A few reports have documented the progression of nutcracker esophagus to achalasia, thus raising the question of whether it may be an abnormality occurring early in a spectrum of motility disorders that ends with achalasia.[18,19] Patients have been noted to have higher levels of somatization, anxiety, and depression, similar to those with esophageal spasm and irritable bowel syndrome. The similarities in symptoms suggest a possible generalized functional disorder in these patients.

Patients with nutcracker esophagus and chest pain have been found to have a low threshold for pain when their symptoms are reproduced by balloon distention. Furthermore, the esophageal reactivity to balloon distention is higher in these patients than in controls. The hypersensitivity and stiffness of the esophagus may play a role in the pathogenesis of chest pain in this condition.[20]

Recently, it has been suggested that gastroesophageal reflux may play an important role in the pathogenesis of nutcracker esophagus. A study found that 70% of patients with nutcracker esophagus had increased esophageal acid exposure with esophagitis and a positive symptom index.[21] The majority of patients with nutcracker esophagus and chest pain, however, did not have classic reflux symptoms. Among the patients who did suffer from GERD symptoms, 76% either improved after acid-suppression therapy or were symptom-free at an average of 10.7 months' follow-up. The authors concluded that patients with nutcracker esophagus may represent a subgroup of patients with acid reflux different from that in other reflux patients, given the lack of typical GERD symptoms. An important note, however, is that in this study nutcracker esophagus was defined as manometric contractions greater than 180 mm Hg at any level of the esophagus, rather than just the distal level used by the conventional definition.

Investigations

Endoscopy Endoscopic examination is necessary to rule out associated pathology such as hiatal hernia and esophagitis.

Radiology Barium studies are invariably normal. Occasionally, hiatal hernias are detected.

Manometry Manometry is essential for the diagnosis of nutcracker esophagus. Contraction amplitudes must exceed 2 SD above normal values determined for individual laboratories, be present in the two distal channels, and be peristaltic in waveform (Fig. 30–3). Other features seen in nutcracker esophagus include a prolonged duration of contractions (Fig. 30–4)[17] and a hypertensive sphincter, both of which are not required for the diagnosis.

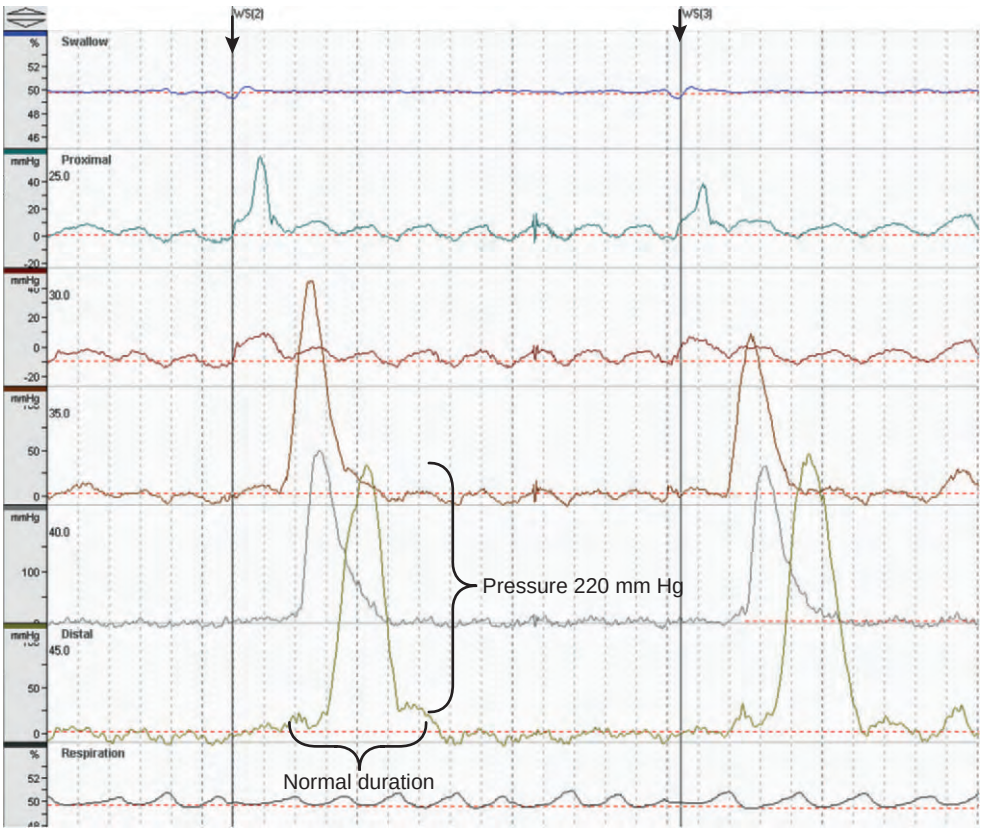

Figure 30–3. Manometric features of a nutcracker esophagus. High-amplitude, peristaltic responses to wet swallows were recorded in the distal three channels, which are each 5 cm apart. Contractions are of normal duration.

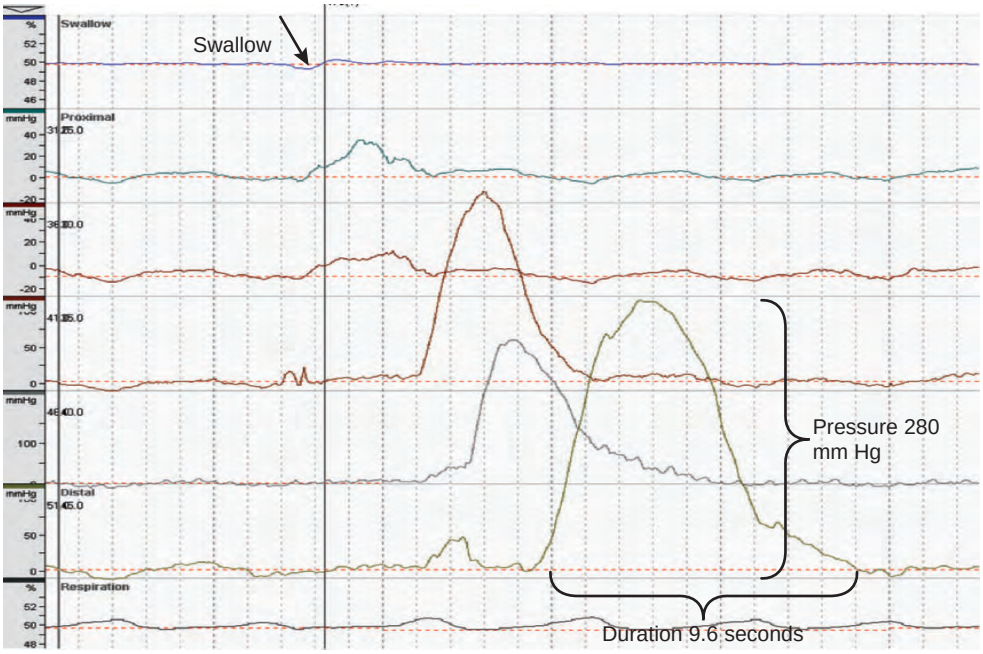

Figure 30–4. Nutcracker esophagus. On wet swallows, high-amplitude contractions are seen in the distal two channels (>180 mm Hg). The responses also have a prolonged duration (>6 seconds).

Of interest, when patients with nutcracker esophagus are monitored, changes in their manometric features may be seen. In one follow-up study, more than 50% of patients with nutcracker esophagus retained the initial manometric diagnosis and 33% had a change to segmental high-amplitude contractions.[17] Manometric changes to those typical of other esophageal motility disorders, such as DES and achalasia, and even to normal tracings have also been reported.[18,22-24]

Treatment

Medical treatment has produced variable results. The calcium channel blocker nifedipine has been shown to decrease esophageal contraction amplitude, but without associated improvement in symptoms,[25] whereas diltiazem has been shown to improve symptoms.[26]

Sildenafil, an inhibitor of phosphodiesterase type 5, has recently been shown to be a potential alternative treatment of nutcracker esophagus. It promotes guanosine 3′,5′-cyclic monophosphate accumulation, which then phosphorylates other intracellular signaling molecules to stimulate either smooth muscle relaxation or reduction in muscle excitability.[27] Sildenafil has been shown to decrease LES pressure and the amplitude of distal esophageal peristaltic pressure responses to swallows. However, the reduction in resting pressure was of short duration, which may limit the usefulness of this treatment.

Based on the high prevalence of GERD in patients with nutcracker esophagus, gastroesophageal reflux rather than an esophageal motility disorder has been suggested to be the cause of the chest pain experienced by patients. A recent double-blind, placebo-controlled, crossover study using the proton pump inhibitor lansoprazole as a means of acid-suppression therapy did not, however, produce significantly better pain relief than placebo did. Furthermore, no motility pattern change was seen during the study.[28] The role of acid in the pathogenesis of nutcracker esophagus needs further investigation.

Surgical treatment of nutcracker esophagus should therefore be undertaken with caution. A long myotomy performed because of the presence of chest pain and the finding of high-amplitude peristaltic contractions may aggravate the symptoms by rendering the esophagus aperistaltic. The chest pain may not be relieved, and dysphagia may result from the aperistalsis after the myotomy.

The observation that many patients improve with time has suggested a stress-related or psychological phenomenon playing a role in the pathogenesis of symptoms in these patients.

HYPERTENSIVE LOWER ESOPHAGEAL SPHINCTER

Hypertensive lower esophageal sphincter (HLES) is a primary motility disorder that was first described in 1960 by Code et al.[29] This condition is uncommon and, in order of frequency in our laboratory, is second to achalasia.

Typically, patients have symptoms of dysphagia (37% to 100%) and chest pain (33% to 100%).[30-36] These patients may also have the classic GERD symptoms of heartburn, regurgitation,[31,36] and epigastric pain.[30] In addition, it has been noted that patients with HLES have more of a nervous predisposition and display higher levels of anxiety and somatization.[1,35]

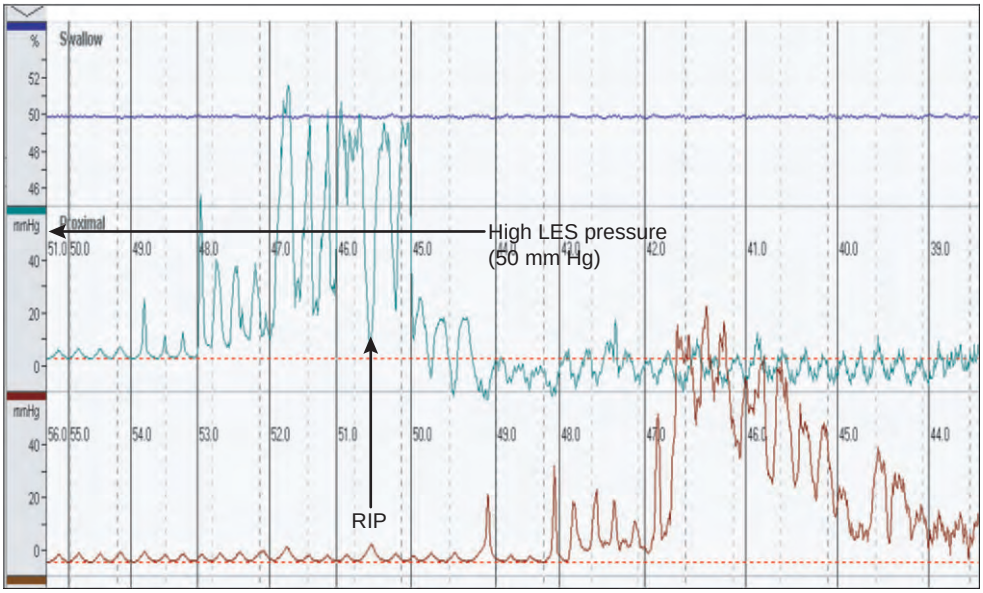

Figure 30–5. Manometric features of a hypertensive lower esophageal sphincter (LES). A pressure of 50 mm Hg was recorded in this stationary pull-through study of the LES. The pressure was measured at the midrespiratory phase at the respiratory inversion point (RIP). The upper limit of pressure at this point is 26 mm Hg.

Investigation

A thorough investigation is required to assist in the diagnosis of HLES.

Radiology Barium esophagography studies are either normal or demonstrate slight narrowing at the gastroesophageal junction.[35] Both upper gastrointestinal endoscopic studies and radionuclide solid esophageal emptying studies[37] are reported to be typically normal.

Manometry Esophageal manometry is essential for the diagnosis of this condition. HLES is characterized manometrically by the following:

- An elevated resting pressure in the LES that exceeds the upper limit of normal measured in a series of volunteers (Fig. 30–5). In Dr. DeMeester's laboratory at the University of Southern California, the upper limit of normal is 26 mm Hg, whereas in Dr. Castell's laboratory, it is 45 mm Hg.[38]
- Normal peristalsis of the esophageal body, thus distinguishing it from achalasia and DES.
- Incomplete LES relaxation (62% in our series),[31] although previously reported to be normal (Figs. 30–6 and 30–7).
- Increase in intrabolus pressure in the body of the esophagus. This, together with the presence of residual relaxation pressure (incomplete relaxation), suggests outflow obstruction.[31]

pH Studies Gastroesophageal reflux can occur in the presence of a hypertensive sphincter,[32,37] and approximately 25% of patients with HLES have been shown to have a positive 24-hour pH test. Transient LES relaxations are thought to be the cause of this paradoxical phenomenon.

The association between HLES and GERD is unclear, although fewer reflux episodes and a significantly lower total and supine percentage of time with the pH lower than 4 have been shown to occur in GERD patients with HLES than in those with symptoms of GERD alone.[30,37] Accordingly, the presence of HLES in patients with GERD may offer a protective barrier against refluxate and prevent the development of advanced grades of esophagitis.

Thus, to rule out GERD, pH studies are essential in patients with HLES.

Treatment

Treatment of HLES remains controversial. Previously, both medical and surgical options have focused mainly on reducing LES pressure. Medical drugs as the first line of symptomatic treatment have included the use of muscle relaxants such as calcium channel blockers, nitroglycerin, and nifedipine, with Botox injections and pneumatic dilatation reserved for resistant cases. However, the results of these treatment modalities are variable and often short-lived.

The recent demonstration of gastroesophageal acid reflux in patients with HLES has now challenged physicians to modify treatment modalities to suit individual needs. When HLES patients have GERD symptoms together with an abnormal ambulatory pH score, acid reflux therapy has been found to be effective therapy.[31,36] For the few nonresponders, an antireflux operation has been reported to result in a successful outcome. Nissen fundoplication performed in patients with HLES and GERD/type III hiatal hernia has been shown in one study to relieve symptoms of chest pain and dysphagia in all of the patients studied, with a good or excellent outcome in 81% of patients.[39]

On the other hand, when HLES is present without evidence of gastroesophageal reflux, LES myotomy with partial fundoplication has been shown to be effective

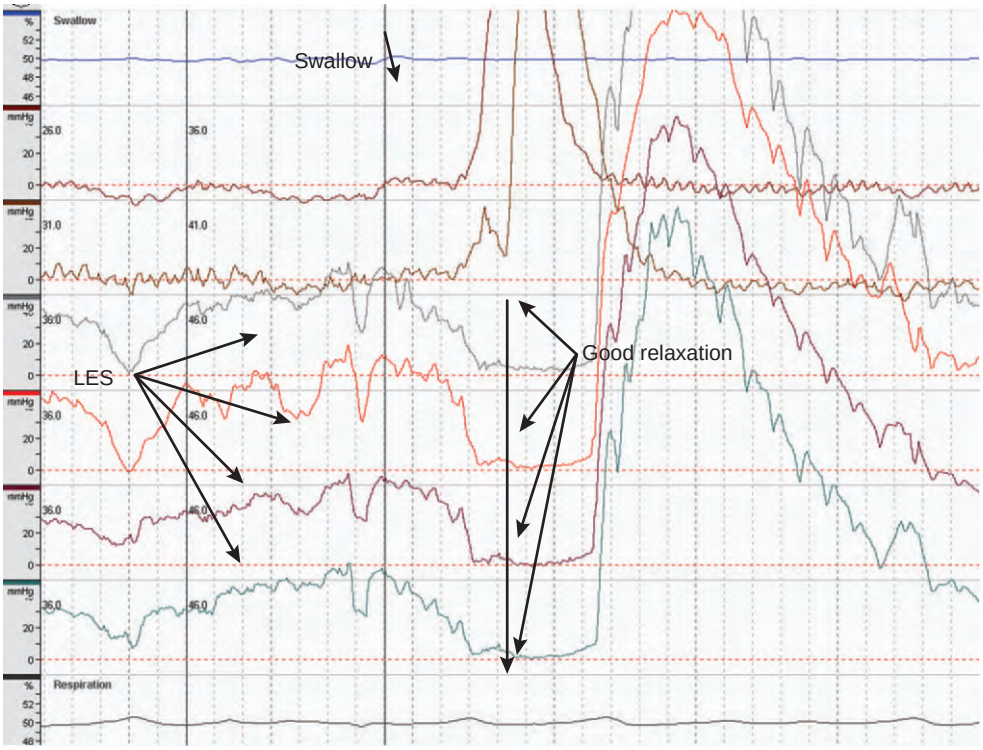

Figure 30–6. Swallow study in a lower esophageal sphincter (LES) that is hypertensive. LES pressure is recorded in channels 3 to 6, which are all at the same level in the sphincter. The sphincter relaxes to baseline during swallowing, thus confirming complete relaxation.

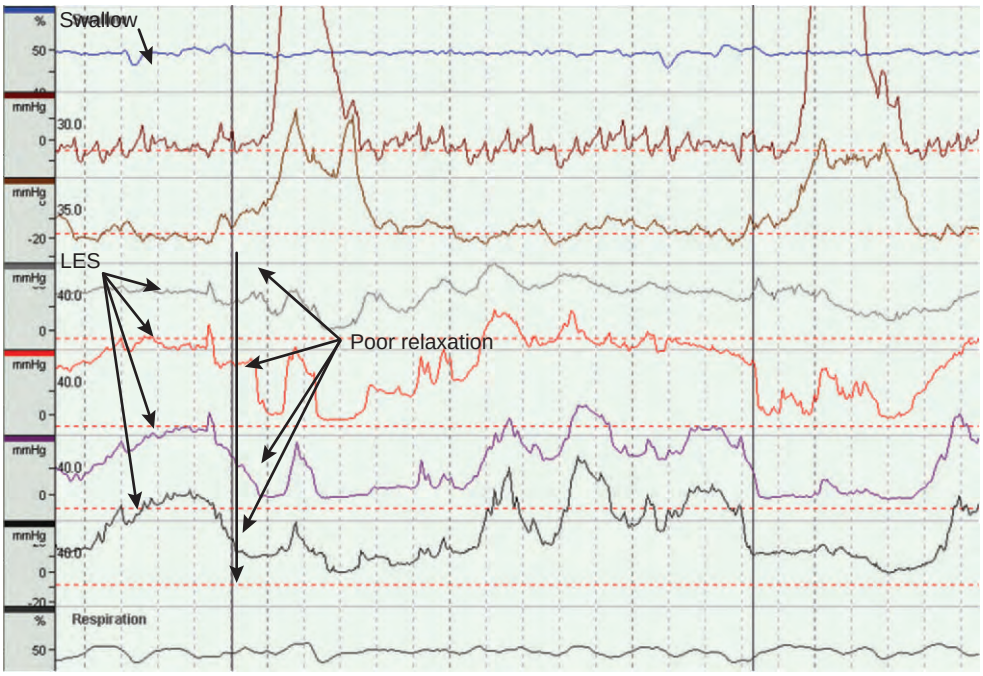

Figure 30–7. Manometric features of a hypertensive lower esophageal sphincter (LES), as seen in the distal four channels. The manometry catheter used for this recording has four radial sensors at the same level. Relaxation of the sphincter in this patient was poor. Good esophageal body contractions are noted in the proximal channels, which are 5 cm and 10 cm above the upper border of the LES.

therapy,[39,40] thus supporting a possible primary sphincter dysfunction. Because these patients have normal esophageal body motility, there is no reason why a complete fundoplication should not be performed at the time of the myotomy. This procedure is now accomplished in most patients by a laparoscopic approach.

Patients with HLES are a heterogeneous group, and treatment should be guided by both clinical investigations and symptoms at initial evaluation.

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Chapter

31

Surgical Management of Esophageal Diverticula

Luigi Bonavina

Esophageal diverticula are epithelial-lined protrusions of the gut wall that remain in continuity with the lumen. They can occur at any level from the pharynx to the cardia and are generally acquired. An anatomic classification consisting of three categories (pharyngoesophageal, midesophageal, epiphrenic) is most commonly adopted, although the classic Rokitanski classification (pulsion and traction) still provides useful clues to the pathogenesis. Most esophageal diverticula are of the pulsion type and lack a muscular coat ("false" diverticula). Only midesophageal diverticula are of the traction type and have been considered "true" diverticula because they contain all layers of the esophageal wall. It has long been speculated that esophageal motor abnormalities are involved in the pathogenesis of diverticula, but the evidence remains inconclusive. Management of esophageal diverticula is dictated by the main clinical manifestations, most commonly dysphagia and regurgitation. Respiratory symptoms frequently occur in elderly patients, even in the absence of esophageal complaints, and require surgical therapy to prevent life-threatening episodes of aspiration.

PHARYNGOESOPHAGEAL (ZENKER'S) DIVERTICULUM

Pathophysiology

Toward the end of the 19th century, Zenker[1] formulated the hypothesis that a pharyngoesophageal diverticulum is caused by increased hypopharyngeal pressure producing herniation through an area of structural weakness, specifically, the junction of the inferior pharyngeal constrictor and the cricopharyngeus muscle, also known as Killian's triangle. Subsequent radiologic observations of a posterior indentation below the neck of the sac led to application of the term *cricopharyngeal achalasia*,[2] although manometric studies of patients with Zenker's diverticulum have often shown normal upper esophageal sphincter relaxation. Later, a reflex spasm of the cricopharyngeus muscle caused by presumed gastroesophageal reflux was implicated in the pathogenesis of the diverticulum.[3] An incoordination between pharyngeal and cricopharyngeal activity, with temporal premature contractions of the upper esophageal sphincter, was demonstrated by several investigators.[4-8] Other studies have focused on degeneration of the cricopharyngeal muscle,[9-12] with interstitial fibrosis being the main histologic finding.

Recent studies support the hypothesis that fibrosis of the cricopharyngeal muscle impairs upper esophageal sphincter opening by decreasing wall compliance. The reduced opening causes increased hypopharyngeal bolus pressure to compensate for the decreased cross-sectional area and maintain trans-sphincteric flow, and it can lead to the formation of a pulsion diverticulum through the weak Killian's triangle. Cook and colleagues[13] compared patients with Zenker's diverticulum and control subjects via simultaneous videoradiography and manometry. They were able to document significantly reduced sphincter opening and greater intrabolus pressure in patients with Zenker's diverticulum. They concluded that the primary abnormality in patients with Zenker's diverticulum is incomplete upper esophageal sphincter opening rather than abnormal coordination between pharyngeal contraction and upper esophageal sphincter relaxation or opening.

Thus, the act of swallowing in the presence of cricopharyngeal dysfunction, combined with the usual pressure phenomena during deglutition, is believed to generate sufficient transmural pressure to allow mucosal herniation (pulsion diverticulum) through an anatomically weak point in the posterior of the pharynx above the cricopharyngeus muscle. Because of the recurrent nature of the pressure involved and the constant distention of the sac with ingested material, the diverticulum progressively enlarges and descends toward the posterior

and left lateral side of the neck.[14] Selective filling of the sac may compress and angulate the adjacent esophagus anteriorly. These anatomic changes obstruct swallowing. Moreover, because the neck of the diverticulum is above the cricopharyngeus, spontaneous emptying of the diverticulum is unimpeded and often associated with laryngotracheal aspiration, as well as pharyngo-oral regurgitation.

Symptoms and Diagnosis

Although a pharyngoesophageal diverticulum may be asymptomatic, symptoms develop early in the course of the disease in most patients. Once the pouch is established, it progresses in size (Figs. 31–1 and 31–2) and severity of symptoms and complications. Symptoms consist of cervical esophageal dysphagia, noisy deglutition, halitosis, and spontaneous regurgitation with or without coughing or choking episodes. The regurgitated food is characteristically undigested. If the condition is neglected, weight loss, hoarseness, asthma, respiratory insufficiency, and pulmonary infection leading to abscess are all potential complications. A gurgling mass may be appreciated in the left cervical region. The main complications of Zenker's diverticulum are nutritional and respiratory. Carcinoma arising in a pharyngoesophageal diverticulum is extremely uncommon.[15] Perforation of the diverticulum may occur after esophagoscopy, attempts at tracheal intubation, or accidental ingestion of a foreign body.

The diagnosis is confirmed by radiographic barium swallow with lateral views, which demonstrate posterior outpouching of the hypopharyngeal wall. Manometry is of little clinical value. Upper gastrointestinal endoscopy is useful to measure the longitudinal extension of the pouch and to exclude the presence of associated foregut disorders. However, the endoscopist should be warned of the possibility of a pharyngoesophageal diverticulum because of the risk for instrumental perforation. If passage of the endoscope under direct vision is unsuccessful, a guidewire can be inserted under fluoroscopic control through the esophageal inlet and the endoscope can be gently pushed over the instrument.

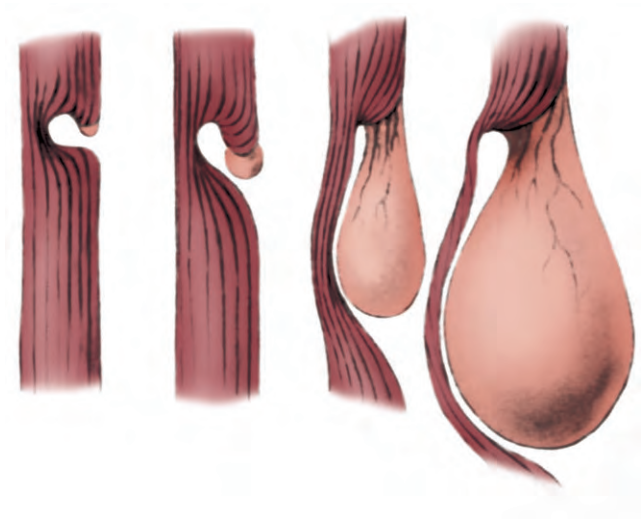

Figure 31–1. Evolution of a pharyngoesophageal diverticulum from small to large. Note the prominence of the cricopharyngeus muscle within the spur between the esophagus and diverticulum.

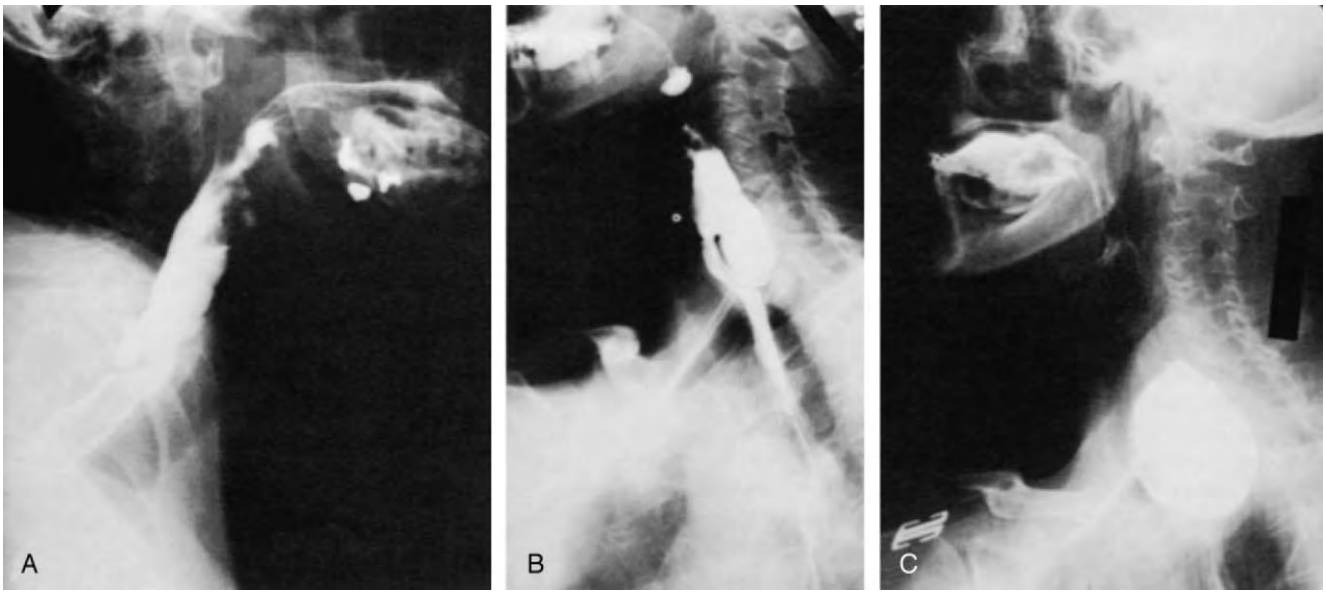

Figure 31–2. Radiographic appearance of various sizes of pharyngoesophageal diverticula. **A,** Small. **B,** Moderate. **C,** Large. (**A** and **C** From Payne WS: Diverticula of the esophagus. In Payne WS, Olsen AM [eds]: The Esophagus. Philadelphia, Lea & Febiger, 1974; **B** from Payne WS, Clagett OT: Pharyngeal and esophageal diverticula. Curr Probl Surg 23:1-31, 1965.)

Treatment

Treatment of Zenker's diverticulum is indicated, regardless of its size, to relieve the disabling symptoms of oropharyngeal dysphagia and pharyngo-oral regurgitation and to prevent the life-threatening complication of aspiration pneumonia. The tendency of the pouch to progressively enlarge and the possible, though rare development of squamous cell carcinoma represent additional arguments in favor of early treatment.[15] Treatment is best done on an elective basis while the pouch is small or of moderate size and before complications have occurred. Advanced age is not a contraindication to surgical treatment. A recent review of patients 75 years or older who underwent surgical treatment of Zenker's diverticulum demonstrated an improvement rate of 94% with no operative death.[16] However, the nutritional status and respiratory condition of elderly patients with severe dysphagia and repetitive hypoxic episodes of aspiration are of special concern; in such circumstances, nutritional support and respiratory physiotherapy may be indicated before proceeding with surgical therapy. It has long been postulated that gastroesophageal reflux is common in patients with Zenker's diverticulum and that priority should be given to surgical correction of the reflux to prevent postoperative aspiration.[17] In most circumstances, medical treatment with proton pump inhibitors is effective for the treatment of mild degrees of gastroesophageal reflux, thus allowing the surgeon to proceed primarily with treatment of the diverticulum when the main complaint is obstructive dysphagia. If necessary, however, an antireflux repair can safely be performed during the same operative session.

Evolution of Current Management

Treatment of Zenker's diverticulum has evolved through a better understanding of the underlying pathophysiology of the disease. Surgical attempts to treat a disorder of the pharyngoesophageal junction date back to the past century, when Nicoladoni established a fistula to empty a Zenker diverticulum of its contents.[18] The first successful diverticulum resection was performed by Wheeler in 1885. This procedure was subsequently abandoned because of a high rate of leakage from the suture line and was replaced by a complicated two-stage operation to allow a more controlled salivary fistula. However, by the 1950s, almost all surgical therapy for Zenker's diverticulum used the one-stage technique of primary resection and closure.[19] Although the addition of cricopharyngeal myotomy to resection of the diverticulum had first been proposed by Aubin in 1936, it was not recognized until a few decades later that correction of the functional obstruction caused by the upper esophageal sphincter is an important component of the surgical procedure.[20] The objective documentation of increased intrabolus pressure resulting from inadequate sphincter opening[13] has strengthened the opinion of most esophageal surgeons that cricopharyngeal myotomy, alone or combined with resection or suspension of the diverticulum,[7] is an essential part of the surgical procedure irrespective of the presence of a manometric abnormality. Myotomy alone can be sufficient to treat small diverticula,[21] whereas myotomy combined with resection of the diverticulum has become the technique of choice for diverticula larger than 2 cm.[22]

An endoscopic approach to Zenker's diverticulum was first attempted almost a century ago by Mosher.[23] He divided the septum between the esophagus and the pouch with punch forceps, but this procedure was soon abandoned. The concept of endoscopically creating a common cavity between the esophagus and the pouch was restored to favor by Dohlman and Mattsson,[24] who introduced diathermy, and by van Overbeek,[25] who introduced laser treatment. Recent developments in minimally invasive surgery have led to the use of linear endoscopic stapling devices to suture and then divide the septum formed by the opposing walls of the esophagus and the diverticulum, a procedure that appears to be simpler and safer than electrocoagulation or laser therapy.[26,27]

Methods and Results of Surgical Therapy

The operation can be performed under general or locoregional anesthesia.[28] The patient is positioned supine on the operating table with a small pillow under the shoulders. The head is hyperextended and turned slightly to the right side. The neck is draped from the chin to below the clavicles. An oblique skin incision centered at the level of the cricoid cartilage is made along the anterior border of the left sternocleidomastoid muscle. The subcutaneous tissue and platysma are divided with cautery. The pharynx and cervical esophagus are exposed by retracting the sternocleidomastoid and carotid sheath laterally and the larynx and thyroid gland medially. Care is taken to not injure the recurrent laryngeal nerve, which runs in the tracheoesophageal groove. The diverticulum can be recognized as arising from the posterior wall of the pharynx at a point just above the level where the omohyoid muscle crosses the incision (Fig. 31–3). The pouch is grasped with Duval forceps and retracted cephalad. The loose connective tissue surrounding the diverticulum is carefully dissected to identify its neck on the posterior pharyngeal wall. The transverse fibers of the cricopharyngeal muscle can be identified just below the neck of the diverticulum. At this point, a right-angle forceps can be used to develop a dissection plane inferiorly between the muscularis and the mucosa, and the myotomy is performed with a No. 15 blade or curved scissors. Most sacs smaller than 2 cm simply disappear after the myotomy (Fig. 31–4). For diverticula between 2 and 4 cm, the myotomy is initiated at the neck of the diverticulum and extended inferiorly for about 4 cm (Fig. 31–5A). Simultaneously, a small peanut dissector is used to retract the muscle borders laterally. The diverticulum can be transected by the cut-and-sew technique and the mucosal defect closed with interrupted 4-0 PDS or Biosyn sutures. Larger diverticula should be resected with a TA stapling device, which improves the speed and safety of closure (see Fig. 31–5B and C). A 36-French bougie or an endoscope can be left

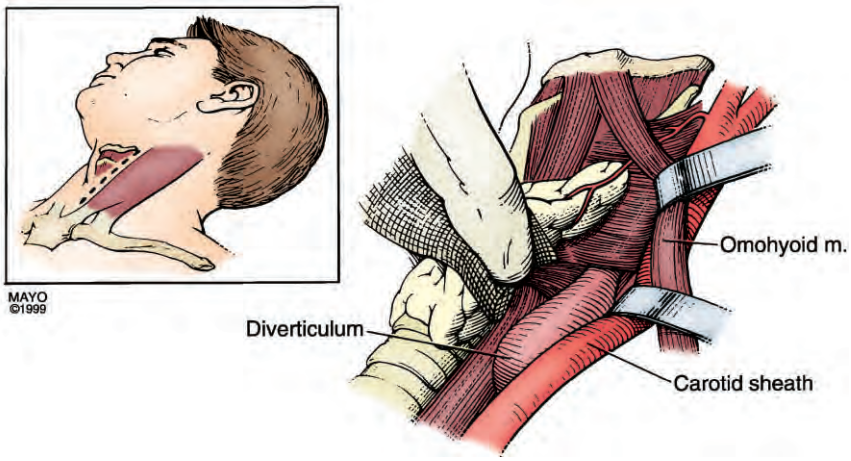

Figure 31–3. Surgical exposure of the retropharyngeal space is gained through an oblique left cervical incision oriented along the anterior border of the sternomastoid muscle *(inset)*. Retraction of the sternomastoid and carotid sheath laterally and the thyroid, pharynx, and larynx medially provides the necessary exposure of the diverticulum, which is located at a cervical level where the omohyoid crosses the surgical field. (Note that the omohyoid has been retracted cephalad to show the diverticulum.) (© Mayo Clinic, 1999.)

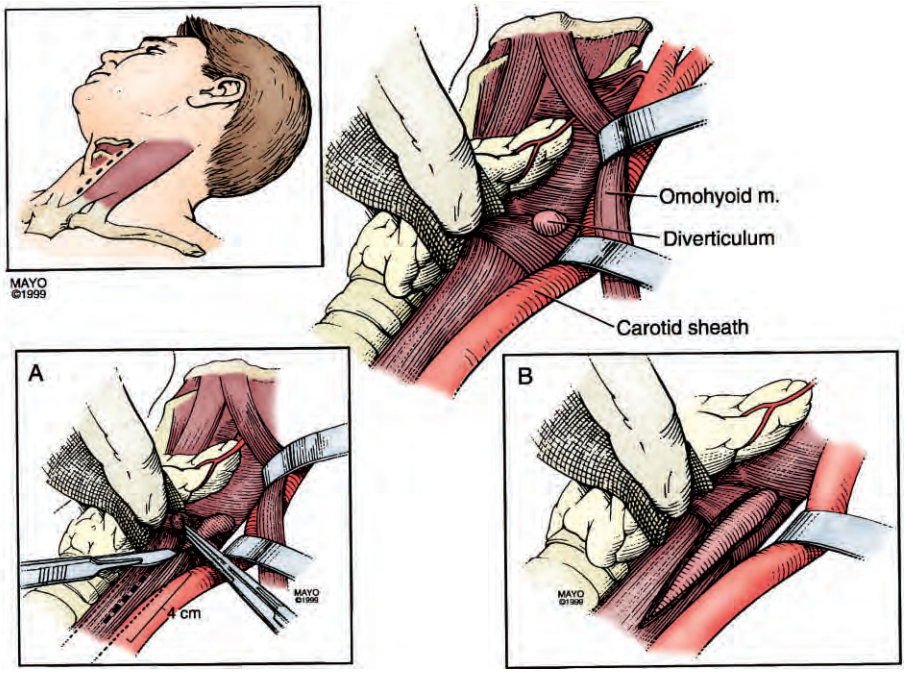

Figure 31–4. After connective tissue is dissected from the mucosal sac to identify the defect in the posterior pharyngeal wall, a posterior midline extramucosal myotomy is performed with a scalpel from the neck of the small sac inferiorly for a distance of 4 cm **(A).** After retraction of the edges of the cut muscle with a peanut dissector, an almond-shaped diffuse bulge of mucosa through the myotomy is seen **(B).** After the myotomy, the small diverticulum disappears. (© Mayo Clinic, 1999.)

in place to prevent narrowing of the lumen while the stapling device is applied. A the end of the operation, a standard nasogastric tube is applied, and a Penrose drain is placed in the retropharyngeal space.

A diatrizoate meglumine (Gastrografin) contrast study is performed the following day, and if satisfactory, the diet is resumed. The drain is removed 48 hours after the operation and the patient discharged home on the third postoperative day. If evidence of a mucosal leak is found on the radiographic study or if signs of excessive wound drainage develop, the drain is left in place, and the patient is fed nothing by mouth for 7 to 10 days. If repeat radiographs show persistent leakage, a central venous access is inserted and parenteral nutrition started to restore a positive nitrogen balance. Within 2 weeks it is usually possible, with either fistula sealing or a well-established drainage tract, to begin oral feeding. The drain can be eventually removed with the expectation that the fistula will close spontaneously.

The results of the one-stage pharyngoesophageal diverticulectomy have been highly satisfactory. More than 800 patients were treated at the Mayo Clinic by this means, and the operative mortality rate was 1.4%.[19] The chief complications were recurrent nerve palsy (2.8%) and salivary fistula (2.5%). Generally, these complications clear spontaneously in a matter of days or weeks. In a 5- to 14-year follow-up of 164 patients, Welsh and Payne[29] found that 93% either were asymptomatic or had such rare and mild symptoms that they could be classified as having an excellent (82%) or a good (11%) result. Only 11 (7%) of the 164 had poor results, with or without anatomic recurrence, and required additional treatment. More recently, cricopharyngeal myotomy has been incorporated with equally satisfactory results. Late follow-up

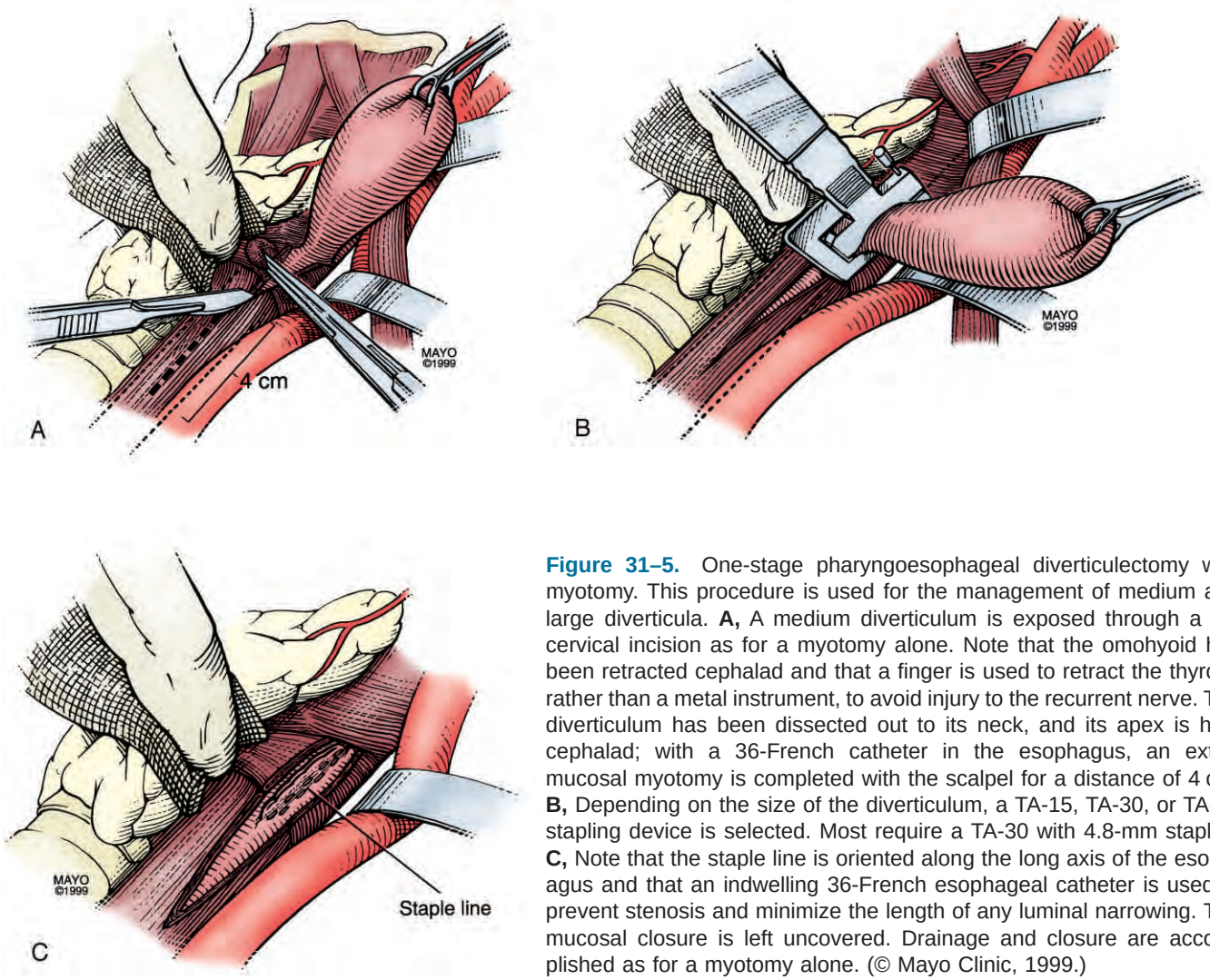

Figure 31–5. One-stage pharyngoesophageal diverticulectomy with myotomy. This procedure is used for the management of medium and large diverticula. **A,** A medium diverticulum is exposed through a left cervical incision as for a myotomy alone. Note that the omohyoid has been retracted cephalad and that a finger is used to retract the thyroid, rather than a metal instrument, to avoid injury to the recurrent nerve. The diverticulum has been dissected out to its neck, and its apex is held cephalad; with a 36-French catheter in the esophagus, an extramucosal myotomy is completed with the scalpel for a distance of 4 cm. **B,** Depending on the size of the diverticulum, a TA-15, TA-30, or TA-55 stapling device is selected. Most require a TA-30 with 4.8-mm staples. **C,** Note that the staple line is oriented along the long axis of the esophagus and that an indwelling 36-French esophageal catheter is used to prevent stenosis and minimize the length of any luminal narrowing. The mucosal closure is left uncovered. Drainage and closure are accomplished as for a myotomy alone. (© Mayo Clinic, 1999.)

results of Payne and Reynolds[30] show little change in the incidence of late pouch recurrence. Any radiographic recurrence was less likely to be symptomatic if the initial diverticulectomy was accompanied by myotomy. A similar outcome with no postoperative mortality, minimal morbidity, and very good to excellent results in 96% of patients has been reported in Europe.[22,31]

Two reviews on reoperation for recurrent pharyngoesophageal diverticula have clearly indicated an increased risk for early postoperative morbidity.[32,33] Reoperation on the upper esophageal sphincter can be a technical challenge because previous surgery often results in obliterated tissue planes and friable esophageal mucosa. The use of an indwelling bougie is particularly helpful, both as a landmark for the esophagus and as a stent over which the repair can be accomplished without fear of entering the esophageal lumen.[34]

Methods and Results of Endoscopic Therapy

The operation is routinely performed under general endotracheal anesthesia. The surgeon sits behind the patient's head. The hypopharynx is entered with a modified Weerda diverticuloscope (Storz), which is gently pushed under vision behind the endotracheal tube. The instrument is held in place with a scope holder and a chest support (Fig. 31–6). A 5-mm wide-angle 0-degree telescope is inserted and connected to a cold-light source and to a videocamera to obtain a magnified view of the operative field on a television screen. The two self-retracting valves of the diverticuloscope, which can be approximated and angulated to fit the patient's hypopharyngeal anatomy, are then allowed to enter the diverticulum and the esophageal lumen, respectively. The septum between the esophagus and the diverticulum is therefore centered in the operative field. The longitudinal extension of the diverticulum can be checked with a graduated rod. This maneuver also allows the pouch to be straightened and the common wall to be elongated. A linear stapling device (ETS35, Ethicon Endo-Surgery) is used to divide the septum. The anvil is placed in the lumen of the diverticulum and the cartridge of staples in the lumen of the cervical esophagus. The instrument jaws are placed across the septum along the midline before firing (Fig. 31–7). With a single application of the endostapler, the

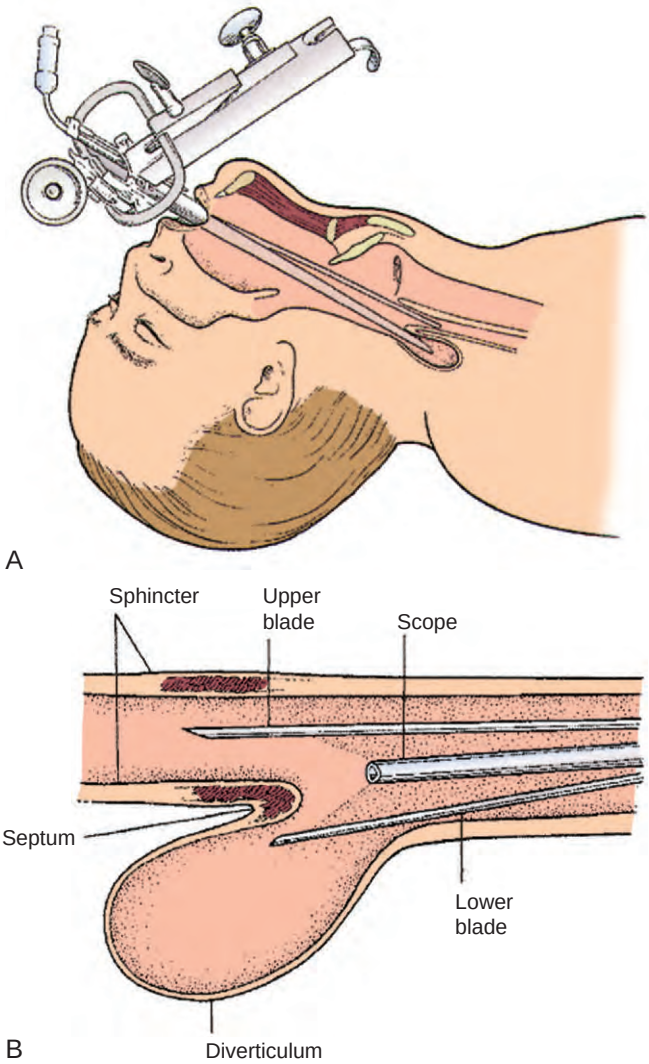

Figure 31–6. **A,** Position of the Weerda diverticuloscope. **B,** Visualization of the septum interposed between the esophagus and diverticulum.

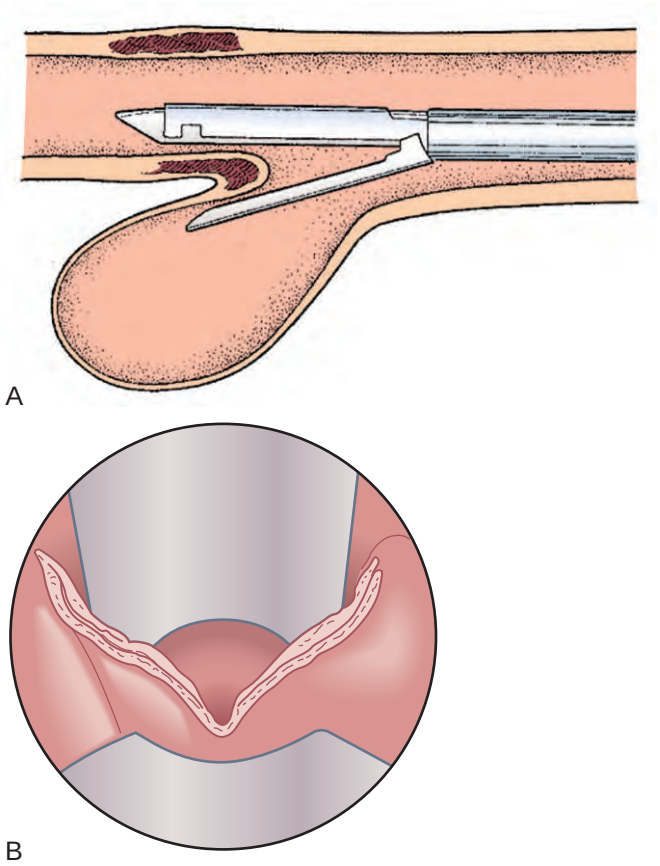

Figure 31–7. **A,** Suture and section of the septum with a linear endostapler. **B,** Frontal view of the divided septum. A common cavity has been created.

posterior esophageal wall is sutured to the wall of the diverticulum, and the tissue is transected between three rows of staples on each side. Multiple stapler applications may be necessary, depending on the size of the diverticulum. Coagulating endosurgical scissors may be used to complete the section at the distal end of the staple line. After removal of the stapler, the two wound edges retract laterally because of division of the cricopharyngeal muscle (see Fig. 31–7). Finally, the suture line is checked for hemostasis. The procedure requires a few minutes, and a nasogastric tube is not necessary. A Gastrografin swallow study is performed on the first postoperative day. The patient is then allowed to drink and eat and is discharged from the hospital 24 hours after surgery.

When compared with the conventional surgical operation, advantages of the endosurgical approach include absence of a skin incision, shorter operative time, minimal or absent postoperative pain, quicker resumption of oral feeding, and shorter hospital stay. An additional advantage of this technique may be expected in patients who had undergone surgery in the left side of the neck or who have a recurrent diverticulum after a conventional operation.[35] In such circumstances, the conventional operation may pose a major technical challenge to the surgeon and is associated with a high risk for leakage or recurrent nerve palsy. On the other hand, the endoscopic approach may prove impossible in patients in whom neck hyperextension is limited and in those with reduced opening capacity of the mouth. Dental injury may occur as a result of difficult handling of the diverticuloscope in this setting. The best indication for the endosurgical technique is a medium-sized diverticulum 3 to 6 cm in length in which at least two staple cartridges can be applied and an adequate cricopharyngeal myotomy can be expected. A diverticulum smaller than 2 cm is a formal contraindication to the endosurgical approach because the common wall is too short to accommodate one cartridge of staples and allow complete division of the sphincter. This would result in an incomplete myotomy with persistent dysphagia.[36]

No prospective clinical trials have compared the endosurgical with the conventional surgical approach for the management of Zenker's diverticulum. Data from retrospective series or prospectively recorded case series con-

sistently show that a satisfactory outcome is obtained in 96% of patients undergoing the endosurgical operation, with a 6% recurrence or persistence rate.[37] However, a retrospective comparison of endoscopic treatment with the stapler or laser against open surgery showed that only 75% of patients treated endoscopically were symptom-free at follow-up, as opposed to 97% of patients who underwent open surgery.[38]

EPIPHRENIC DIVERTICULUM

Pulsion diverticula can develop at any level of the esophageal body but have a predilection for the distal 10 cm. Epiphrenic diverticula generally project from the right posterior wall of the esophagus. The ratio of epiphrenic to pharyngoesophageal diverticula is 1 to 3.[39] However, the exact prevalence of this condition is unknown because asymptomatic cases are not usually discovered. Most epiphrenic diverticula are found in middle-aged or elderly patients, and male patients have a slight preponderance. Multiple diverticula can occur in up to 20% of cases.

Pathophysiology

With the advent of manometric studies, it has become evident that functional obstruction of the distal end of the esophagus may be not only the cause of the diverticulum but also a major cause of symptoms. Achalasia, diffuse esophageal spasm, hypertensive lower esophageal sphincter, and nonspecific motor abnormalities have all been seen in as many as two thirds of patients with epiphrenic diverticula.[40] It is inferred that increased motor activity and abnormal lower esophageal sphincter relaxation produce zones of increased intraluminal pressure through which outpouchings occur.[41-44] Therefore, the concept that epiphrenic diverticula are complications of esophageal motility disorders rather than primary anatomic abnormalities has gained widespread acceptance.

Symptoms and Diagnosis

The symptoms most commonly reported in patients with epiphrenic diverticula are dysphagia and regurgitation. Dysphagia is sometimes associated with esophageal obstruction. Regurgitation of indigested food is characteristically of large volume, frequently occurs at night, and is often precipitated by a change in position. Retrosternal pain or heartburn, or both, can be reported, and it may be difficult to determine whether these complaints are related to the motor disorder, the diverticulum itself, or coexisting gastroesophageal reflux disease. Pulmonary complications from aspiration occur in 24% to 45% of patients,[45,46] but this phenomenon is probably underestimated. Conversely, many patients with epiphrenic diverticula do not have definite symptoms. The diverticulum is often an incidental finding on barium swallow performed for unrelated reasons. Complications such as ulceration, bleeding, and spontaneous perforation are rare and may be due to caustic pills lodging in the pouch. Primary squamous cell carcinoma has been noted with epiphrenic diverticula, as have rare benign neoplasms, particularly leiomyoma.[39]

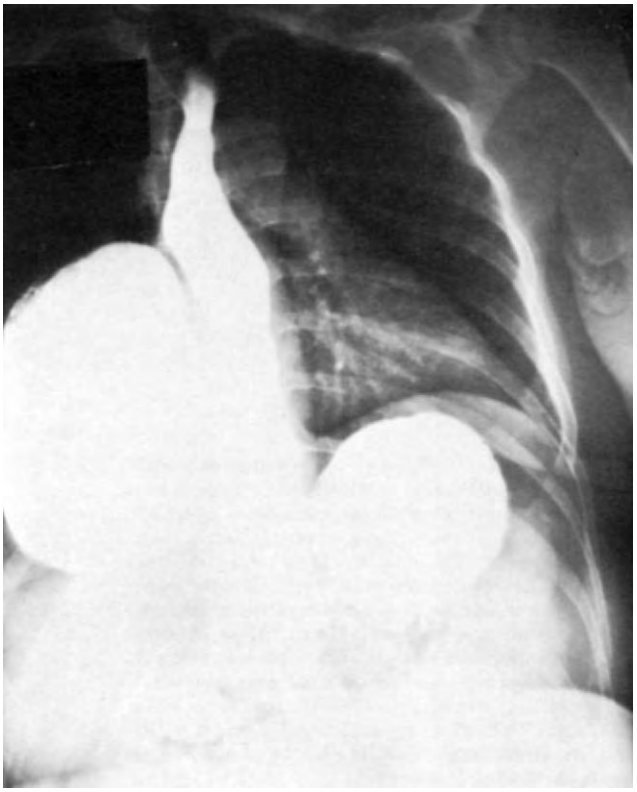

Figure 31–8. Esophagus with a huge epiphrenic diverticulum occupying about half of the right thorax. Note the associated sliding esophageal hiatal hernia. (From Payne WS: Esophageal diverticula. In Shields TW [ed]: General Thoracic Surgery, 3rd ed. Philadelphia, Lea & Febiger, 1983, p 859.)

The diagnosis of epiphrenic diverticulum is established by a barium swallow study. The diverticulum appears as a round structure with a diameter of 1 to 5 cm (Fig. 31–8). Giant diverticula are rarely seen but can be larger than 10 cm. Patients with incapacitating symptoms should be further studied by esophagoscopy and esophageal manometry. Esophagoscopy allows evaluation of the mucosa for the presence of esophagitis and is also of value to detect associated lesions such as carcinoma, stricture, or hiatal hernia. In addition, the size and position of the diverticular neck can be precisely assessed, and this may be relevant if a laparoscopic surgical approach is planned. Esophageal manometry is crucial to assess the presence of an underlying motility disorder. The manometric findings may help determine the length of esophagomyotomy required to relieve the functional obstruction. Twenty-four-hour ambulatory motility testing can be helpful if the results of standard manometry are normal or indefinite.[45] If gastroesophageal reflux is suspected, a 24-hour pH study can also be performed to evaluate esophageal acid exposure. If not confirmed, the symptoms thought to be related to reflux may be caused by other conditions,

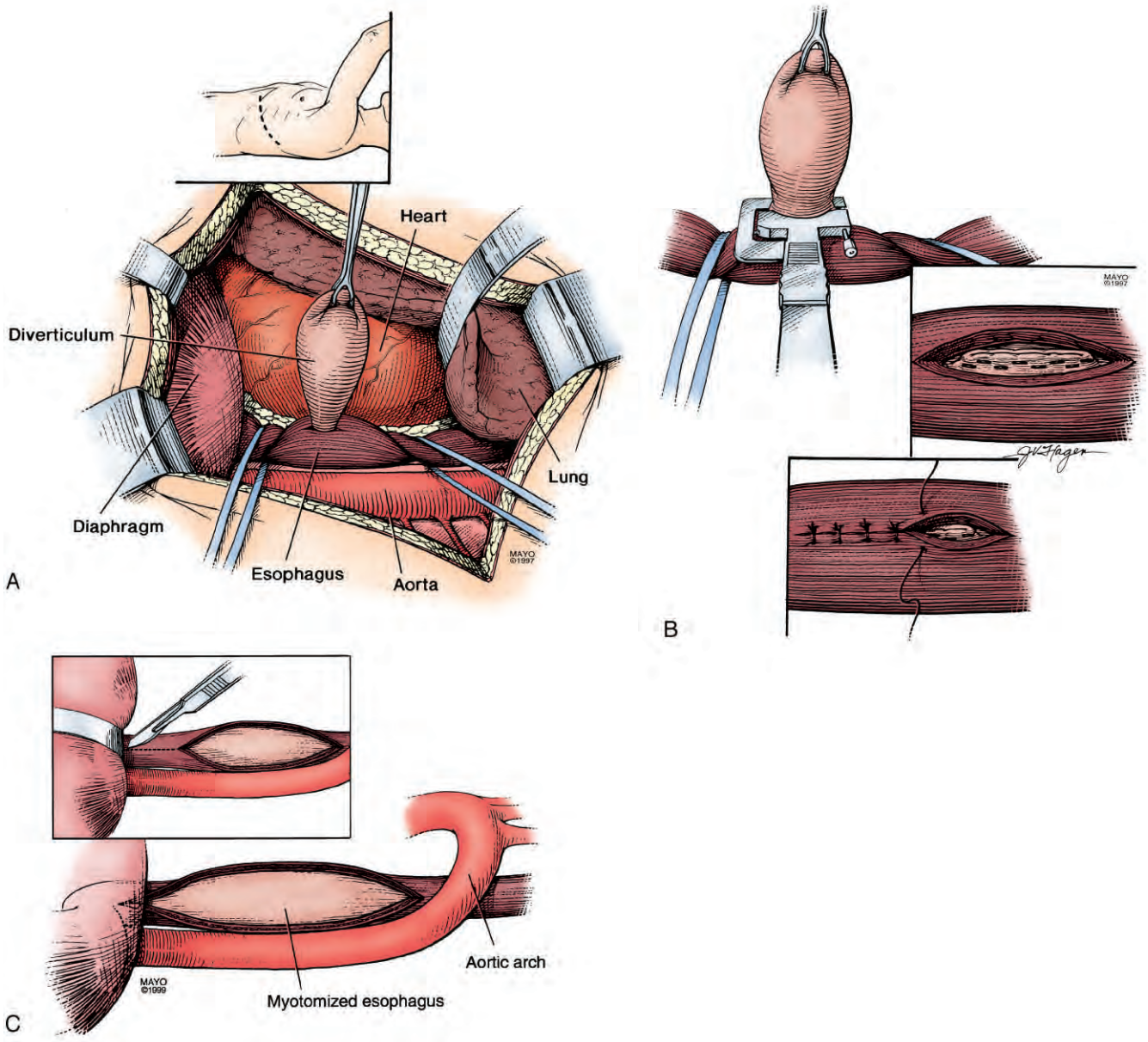

Figure 31–9. Surgical management of a pulsion diverticulum of the lower portion of the esophagus. Placement of the left posterolateral thoracotomy incision is shown in the *inset.* Exposure of the diverticulum is obtained when the chest is entered through the bed of the unresected left eighth rib. Note that the esophagus has been delivered from its mediastinal bed, tape has been passed around the esophagus, and the esophagus has been rotated to bring the diverticulum into view. The neck of the mucosal diverticulum has been dissected to identify the defect in the esophageal muscular wall **(A).** A TA stapling device is used to transect and close the diverticulum, followed by closure of the esophageal musculature over a mucosal suture line **(B).** The site of the diverticular incision has been rotated back to the right and is not visible. A long esophagomyotomy extending from the esophagogastric junction to the aortic arch has been performed. The musculature of the esophagus has been freed from about 50% of the circumference of the esophageal mucosal tube to allow the mucosa to bulge through the muscular incision **(C).** (© Mayo Clinic, 1999.)

such as abnormal motility or regurgitation of diverticular contents.

Treatment

Most patients with epiphrenic diverticula are asymptomatic and do not require treatment. Simple medical measures often provide good temporary control in mildly symptomatic patients. Benacci and associates,[47] reporting a series of 112 patients, described the natural history of the condition in a group of 47 asymptomatic individuals who did not undergo surgical therapy. Twenty of these patients were monitored for a median of 4 years (range, 1 to 17 years), and all remained symptom-free. Fifteen additional patients had mild symptoms without surgical intervention, and in none of them did incapac-

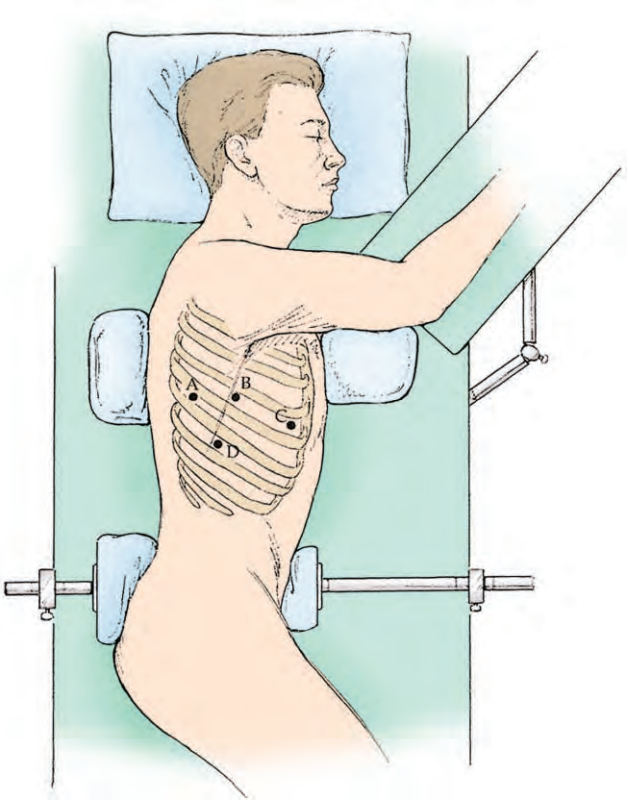

Figure 31–10. Port position for thoracoscopic resection of an esophageal diverticulum.

itating symptoms develop during follow-up (median, 11 years; range, 1 to 25 years). Although only half the patients with asymptomatic or mildly symptomatic disease had long-term follow-up available for review, progressive symptoms or complications did not develop in any of them. Therefore, patients with minimal symptoms should be managed conservatively and monitored at regular intervals. Neither size nor dependent location of the diverticulum usually correlates with symptoms. If symptoms are incapacitating or recurrent respiratory complications from aspiration are reported or suspected, surgical therapy is mandatory. Most esophageal surgeons agree that the ideal operation should include diverticulectomy, myotomy, and an antireflux repair. Streitz et al. have advocated selective use of myotomy in patients with documented motor abnormalities.[48]

Methods and Results of Surgical Therapy

The standard surgical technique consists of a diverticulectomy in conjunction with a long extramucosal esophagomyotomy, preferably through a left transthoracic approach (Fig. 31–9). The sac is mobilized and the diverticulectomy is performed longitudinally over an endoluminal bougie with a linear stapling device. The muscular wall is usually closed over the diverticular stump. An esophagomyotomy is performed not only to prevent suture line rupture and recurrence of the pouch but also to relieve symptoms from the underlying motor disorder. The esophagomyotomy is performed opposite the site of the diverticulectomy and should be carried onto the stomach for a few millimeters. Controversy persists regarding whether all patients undergoing an esophagomyotomy should have a concomitant antireflux procedure. When preoperative gastroesophageal reflux or hiatal hernia is present, a modified Belsey Mark IV fundoplication should be performed.[49]

A reasonable alternative to the conventional operation is an epiphrenic diverticulectomy performed through either a thoracoscopic or a laparoscopic approach. The right thoracoscopic access has been chosen because the majority of pouches develop from the right side of the esophagus and are adherent to the right pleura or diaphragm, or both.[50,51] To overcome the difficulty of performing an esophagomyotomy from this side of the chest, it has also been suggested that pneumatic dilation of the lower esophageal sphincter be performed before the operation in patients with documented manometric abnormalities.[50] A double-lumen endotracheal tube is used to allow right lung retraction. The patient is placed in the left lateral decubitus position. Four ports are required: one for the camera, one for the lung retractor, and two for the operating devices (Fig. 31–10). Dissection is begun by taking down the inferior pulmonary ligament and freeing the right lower lobe to the level of the inferior pulmonary vein. The pleura overlying the esophagus is incised, and the right lateral aspect of the esophagus is dissected for a length of about 10 cm. Moderate insufflation and transillumination through an esophagoscope facilitate both dissection and resection of the diverticulum. The pouch can be grasped with a Babcock clamp and gentle traction applied to facilitate identification of the diverticular neck (Fig. 31–11). Once completely dissected, the diverticulum is excised with a reticulating linear endostapler (EndoGIA II) with a blue cartridge. The stapler must be oriented parallel to the longitudinal axis of the esophagus (see Fig. 31–11). If this step is unsatisfactory, a video-assisted approach can be used by performing a small thoracotomy and inserting a hand to assist in stapler orientation. One or two cartridges of staples are usually necessary. Endoscopic visualization is helpful to check placement of the stapler after closure of the jaws, as well to inspect the integrity of the suture line after resection. The muscle layer is closed over the mucosal suture with interrupted sutures of PDS or Biosyn. A standard chest tube is placed. A Gastrografin swallow study is performed on day 4, and the nasogastric tube is removed.

More recently, a laparoscopic approach has been advocated in an effort to simplify alignment of the stapler and facilitate performance of myotomy and fundoplication.[52] The patient is placed on the operating table in the lithotomy position with a 20-degree reverse Trendelenburg inclination. The surgeon stands between the legs. Pneumoperitoneum is established and five operating ports are placed in the upper part of the abdomen. After incision of the phrenoesophageal membrane, the dissection is begun on the right crus of the diaphragm. The esophagus is encircled with a Penrose drain for traction. Mediastinal dissection is performed bluntly close to the

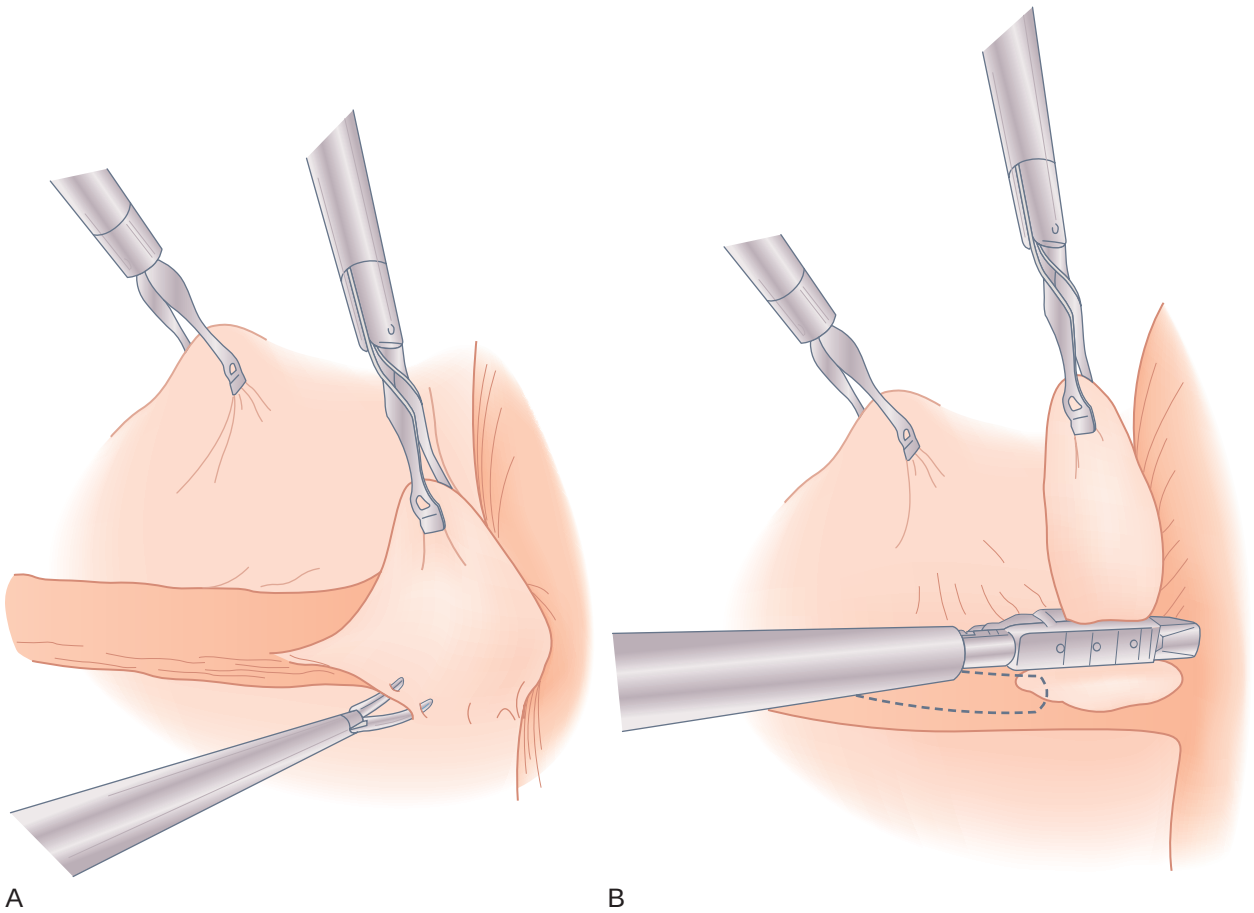

Figure 31–11. **A,** Dissection of an epiphrenic diverticulum through a right thoracoscopic approach. **B,** Application of the reticulating endostapler to the neck of the diverticulum.

esophageal wall until the diverticular pouch is reached. Moderate insufflation and transillumination through an endoluminal esophagoscope facilitate dissection of the diverticulum and identification of its neck. The pouch must be thoroughly cleaned of all adhesions. A reticulating linear endostapler (EndoGIA II) with a blue cartridge is introduced through the trocar in the left upper quadrant and applied parallel to the esophageal axis (Fig. 31–12). The stapler jaws are closed under endoscopic control. Further stapler application may be necessary to remove the diverticulum. The integrity of the suture line must be checked endoscopically, and then a few interrupted PDS or Biosyn sutures are placed to close the muscular wall. A Heller myotomy is performed on the opposite side of the esophageal wall with ultrasonic scissors. The myotomy is extended distally for about 2 cm on the gastric side with a sharpened hook (Fig. 31–13). A posterior hiatoplasty is performed with interrupted sutures. A Dor fundoplication is constructed by suturing the anterior fundic wall to the edges of the myotomy. The cranial sutures also attach the fundus to the anterior crura. A Penrose drain is placed in the subhepatic space. A Gastrografin swallow study is performed on postoperative day 4, and the nasogastric tube is removed.

Surgical treatment of an epiphrenic diverticulum results in resolution of symptoms in most patients. However, the operative risks are significant. Among the 33 patients who underwent transthoracic resection of an epiphrenic diverticulum at the Mayo Clinic between 1975 and 1991, the mortality rate was 9%.[47] Death was caused by a clinically significant leak in two patients and by respiratory failure from aspiration during a Gastrografin swallow in the third individual. Six esophageal leaks occurred, four of which were benign and asymptomatic. Based on these data, operative intervention for asymptomatic or minimally symptomatic epiphrenic diverticula should be discouraged.[53] Although failure to perform myotomy in conjunction with diverticulectomy may be associated with suture line disruption and postoperative death, these sequelae are not inevitable results of its omission. Nevertheless, most esophageal surgeons agree that every effort should be made to correct associated esophageal disorders in order to minimize complications. Early radiographic examination of the esophagus before oral feeding is mandatory in the postoperative management of these patients. If leakage is documented, parenteral feeding should be continued for at least 3 weeks along with nasogastric aspiration, proton pump inhibitors, and antibiotics.

The long-term results of the operation are acceptable and durable. Patients are generally symptom-free if associated esophageal conditions have been adequately dealt

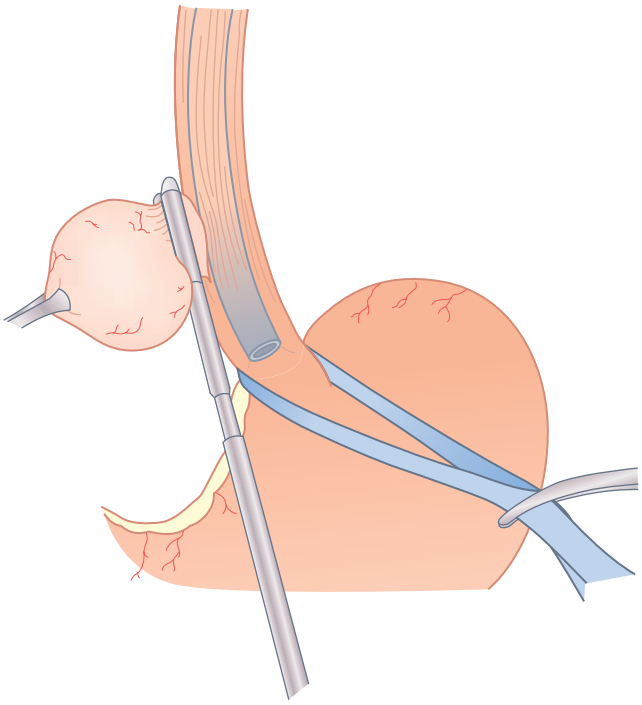

Figure 31–12. Stapled resection of an epiphrenic diverticulum through a laparoscopic approach.

with during the operation. In the Mayo Clinic study,[47] the long-term follow-up ranged from 4 months to 15 years, with a median of 6.9 years. No recurrent diverticulum was observed. The overall results were good or excellent in 22 patients (76%), fair in 5 (17%), and poor in 2 (7%).

Sufficient data are not yet available to definitely recommend the minimally invasive surgical approach. Only small case series or case reports are found in the literature, and these procedures have been performed in just a few centers worldwide. Limitations of the right thoracoscopic approach include the fulcrum effect of thoracoports, difficult alignment of the stapler along the esophageal axis, and the impossibility of performing a distal myotomy from the right side of the chest. Theoretically, a video-assisted approach and patient repositioning for a laparoscopic myotomy and Dor fundoplication could overcome these limitations. The complete laparoscopic approach may represent the ideal procedure for patients with a truly distal epiphrenic diverticulum, but the short- and long-term results of this procedure are still awaited.[54,55]

MIDESOPHAGEAL DIVERTICULA

Midesophageal diverticula are traditionally thought to be caused by external "traction" in patients with mediastinal fibrosis or chronic lymphadenopathy from tuberculosis or histoplasmosis. In exceptional circumstances, mid-

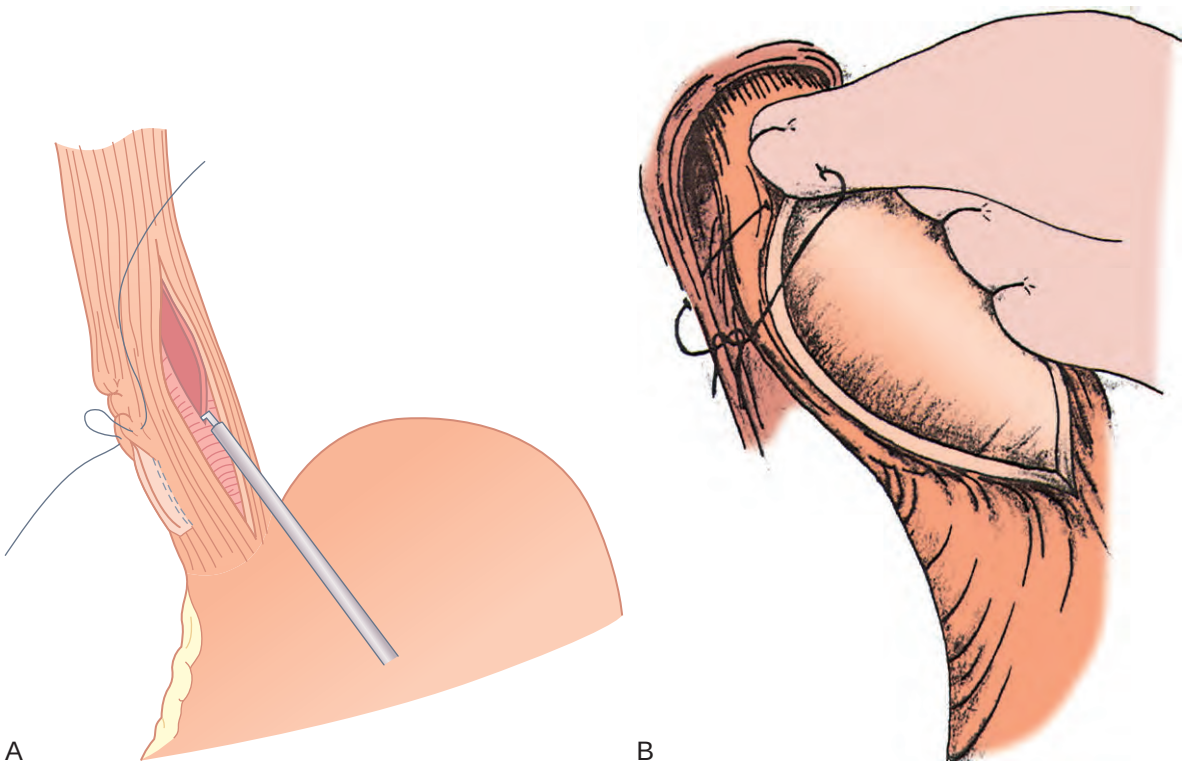

Figure 31–13. **A,** Heller myotomy performed on the opposite esophageal wall of the stapled line and extending for about 2 cm on the gastric side. **B,** A Dor fundoplication is constructed by suturing the anterior fundic wall to the edges of the myotomy.

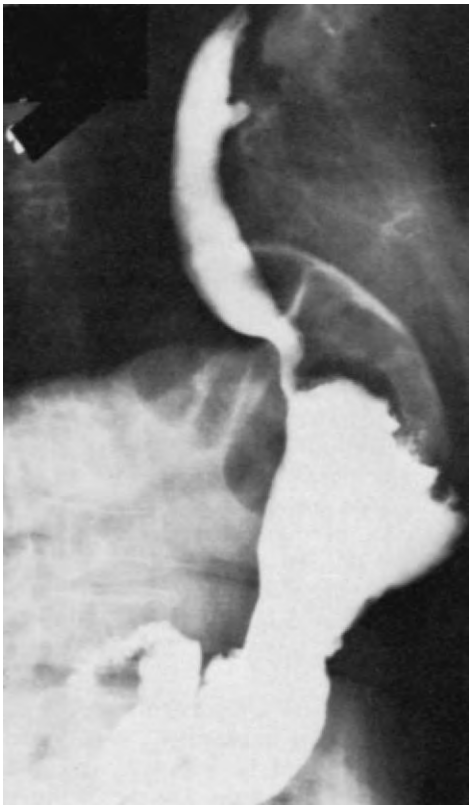

Figure 31–14. Esophagus with a traction diverticulum in the middle third of the thoracic portion in relation to the subcarinal lymph nodes. The patient was asymptomatic. (From Payne WS: Diverticula of the esophagus. In Payne WS, Olsen AM [eds]: The Esophagus. Philadelphia, Lea & Febiger, 1974, p 207.)

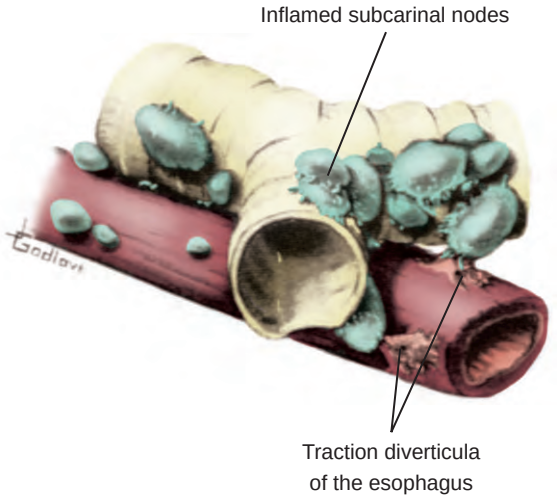

Figure 31–15. Traction diverticula of the esophagus occur most commonly in the middle third of the thoracic portion of the esophagus in relation to the granulomatous subcarinal lymph nodes. Note how the esophageal wall is tented by inflammatory lymph nodes. (From Payne WS, Clagett OT: Pharyngeal and esophageal diverticula. Curr Probl Surg 23:1-31, 1965.)

esophageal diverticula may be congenital and result from an abortive tracheoesophageal fistula or a foregut duplication that has established permanent communication with the esophageal lumen.[17] Because all layers are affected, these diverticula are considered to be "true" as opposed to the "false," pulsion-type diverticula in which only the mucosa is represented. Most traction diverticula arise within 4 to 5 cm proximal or distal to the carina and are associated with granulomatous diseases of the subcarinal lymph nodes (Figs. 31–14 and 31–15).[56] Inflamed nodes become anchored to the esophagus, and the contracting scar tissue tents up the esophageal wall to form a conical outpouching. With the progressive decline in the incidence of granulomatous disease of the mediastinum in the Western world, a pulsion theory became prominent and emphasized endoluminal forces secondary to motility disorders as the main pathogenetic mechanism of parabronchial diverticula,[57] analogous to epiphrenic diverticula. Nowadays, any pouch sited anywhere in the course of the esophageal body should be regarded as a pulsion diverticulum until proved otherwise.[44]

Occasionally, patients may complain of dysphagia, retrosternal discomfort, and regurgitation. However, the majority of midesophageal traction diverticula are totally asymptomatic and likely to remain so. In most circumstances, they appear to be incidental findings during esophageal radiography or endoscopy. It is thought that because of their wide-mouthed configuration and dependent drainage, they remain stable in size without causing symptoms. Carcinoma arising from a parabronchial diverticulum has rarely been reported.[58]

Complications of traction diverticula include bleeding and fistulas with the airways. Because of their rarity, precise diagnosis is often delayed or missed. Erosion of neighboring major blood vessels can produce massive upper gastrointestinal bleeding. More frequently, the hemorrhage is caused by friable granulation tissue or erosion of small bronchial or esophageal vessels.[59] Demonstration of a complication such as an acquired tracheobronchial esophageal fistula[60] may be delayed when the manifestation is recurrent pneumonia without the classic "swallow-cough" sequence. Esophageal radiography sometimes fails to define such a fistula unless the patient is in the prone position during examination. An alternative diagnostic technique consists of the simultaneous instillation of methylene blue in the esophagus during bronchoscopy. However, many patients suspected of having a fistula are actually aspirating ingested material through the larynx as a consequence of pharyngoesophageal incoordination. Surgical therapy consists of division of the fistula tract, closure of the esophagus in layers over an indwelling bougie, and closure of the airway (Fig. 31–16). A right thoracotomy is the approach of choice. Because of previously inflamed lymph nodes, extreme scarring is to be expected. Attention must be directed to correcting the distal esophageal obstruction if present. The risk for a recurrent fistula with the airways

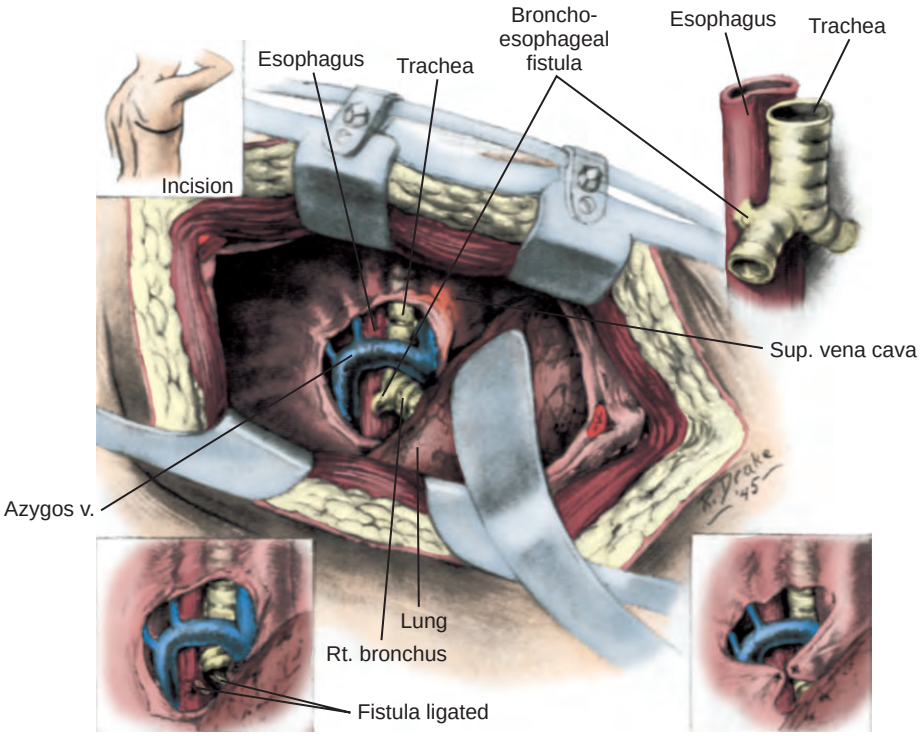

Figure 31–16. Technique for closing an acquired esophagobronchial fistula as a complication of a traction diverticulum of the esophagus. A right posterolateral thoracotomy incision *(upper left inset)* is made. For surgical exposure, the lung has been retracted anteriorly. Note the relationship of the esophagus, right main bronchus, and fistula to the neighboring sutures *(center).* The fistula before division and after division and ligation is seen in the *upper right* and *lower left insets.* The *lower right inset* shows the method of interposing pedicles of the mediastinal pleura between esophageal and bronchial closure. (From Payne WS, Clagett OT: Pharyngeal and esophageal diverticula. Curr Probl Surg 23: 1-31, 1965.)

is best minimized by the interposition of an intercostal muscle flap.

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Part 6

Neoplasms of the Esophagus

Chapter 32

Epidemiology, Risk Factors, and Clinical Manifestations of Esophageal Carcinoma

Daniel Vallböhmer · Jan Brabender · Paul M. Schneider · Arnulf H. Hölscher

Esophageal cancer is one of the deadliest malignant tumors worldwide. During the last 30 years significant changes have occurred in the epidemiologic pattern of this disease, and recent studies have identified several risk factors for the development of esophageal cancer. These new findings serve as the focus of this chapter.

In 2005, esophageal cancer will be diagnosed in an estimated 14,520 people in the United States.[1] Of these, squamous cell carcinoma and adenocarcinoma are the most common types of primary esophageal malignancies.[2] Although esophageal cancer is uncommon, the incidence of esophageal adenocarcinoma in particular has increased dramatically over the last 25 years in the United States and large parts of Europe.[3-7]

Until the 1970s esophageal adenocarcinoma was a rare diagnosis worldwide. From 1926 to 1976, four large surgical series reported that only 0.8% to 3.7% of esophageal malignancies were adenocarcinoma and that squamous cell carcinoma overwhelmingly outnumbered adenocarcinoma.[5,7] Subsequently, the incidence of esophageal adenocarcinoma has increased rapidly in the Western world. In fact, the rate of increase in adenocarcinoma of the esophagus is greater than that of any other major malignancy in the United States (Fig. 32–1).[5] The absolute incidence increased approximately sixfold from 3.8 per million in 1973 to 1975 to 23.3 per million in 2001. For the same period (1975 to 2001), the incidence of squamous cell carcinoma of the esophagus fell from 31 to 19 per million (Fig. 32–2).[5]

Despite the fact that the incidence of esophageal adenocarcinoma has increased, it remains a relatively uncommon malignancy. The number of new cases per 100,000 white males in Western countries varies between 1 and 5, with the highest incidence in Great Britain, followed by Australia.[7] Other countries with relatively high-incidence populations are the United States and the Netherlands, whereas the incidence remains low in Eastern Europe and Scandinavia.[6]

MORTALITY/PROGNOSIS OF PATIENTS WITH ESOPHAGEAL CANCER

Esophageal cancer is expected to account for 13,570 cancer deaths in the United States in 2005.[1] Despite recent progress, esophageal cancer remains a highly lethal malignancy. The overall 5-year survival rate has increased from 4% in the 1970s to merely 14% currently.[8] With complete surgical removal of the tumor, the 5-year survival rate is 50% to 80% for stage I disease, 30% to

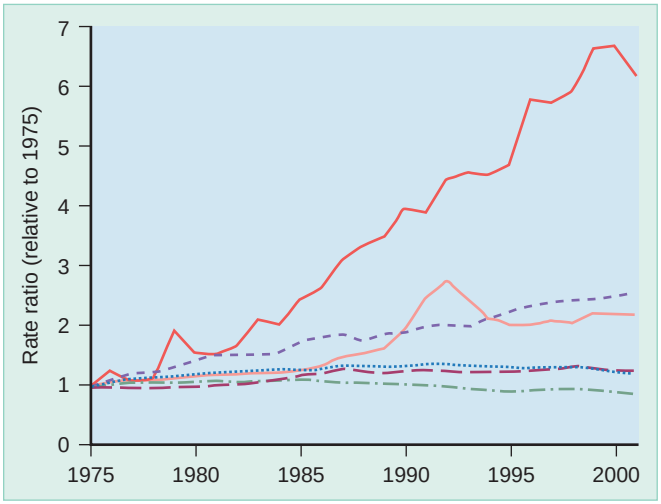


Figure 32–1. Relative change in incidence of esophageal adenocarcinoma and other malignancies (1975 to 2001). Data are from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age adjustment using the 2000 U.S. standard population. Baseline was the average incidence between 1973 and 1975. *Dark orange line,* esophageal adenocarcinoma; *purple short dashed line,* melanoma; *light orange line,* prostate cancer; *red dashed line,* breast cancer; *blue dotted line,* lung cancer; *green dashed and dotted line,* colorectal cancer. (From Pohl H, Welch HG: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 97:142-146, 2005.)

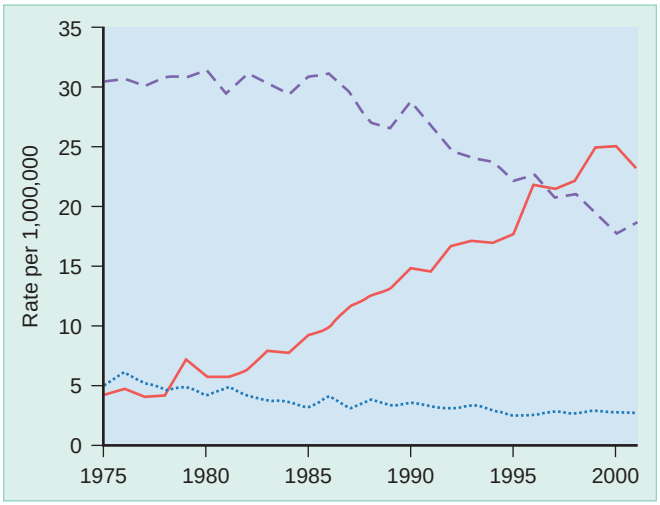


Figure 32–2. Histology and esophageal cancer incidence (1975 to 2001). Data are from the National Cancer Institute's Surveillance, Epidemiology, and End Results program with age adjustment using the 2000 U.S. standard population. *Dark orange line,* adenocarcinoma; *purple dashed line,* squamous cell carcinoma; *blue dotted line,* not otherwise specified. (From Pohl H, Welch HG: The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 97:142-146, 2005.)

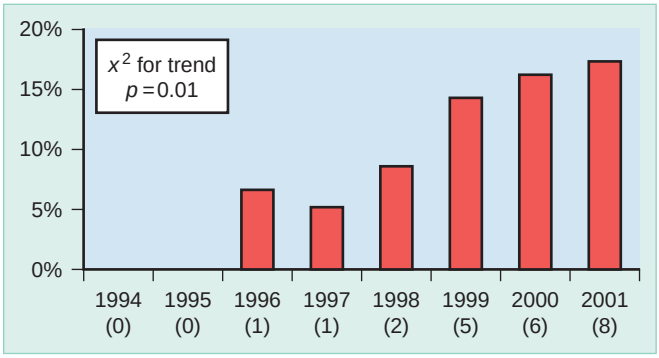


Figure 32–3. Incidence of esophageal adenocarcinoma in patients 50 years or younger at the University of Southern California. (From Portale G, Peters JH, Hsieh CC, et al: Esophageal adenocarcinoma in patients < or = 50 years old: Delayed diagnosis and advanced disease at presentation. Am Surg 70:954-958, 2004.)

40% for stage IIA disease, 10% to 30% for stage IIB disease, and 10% to 15% for stage III disease.[8]

AGE, SEX, AND RACE DISTRIBUTION

The incidence of esophageal adenocarcinoma increases with age, with a median age at diagnosis of 55 to 60 years and a striking male preponderance (7:1).[4,6] Interestingly, Portale et al. reported an increasing number of young patients with esophageal adenocarcinoma during the past decade at their institution (Fig. 32–3).[9] In this study consisting of 263 consecutive patients with resectable esophageal adenocarcinoma, 32 (12.2%) were 50 years or younger. It was found that these younger patients usually sought medical attention because of dysphagia, were symptomatic for a longer time before diagnosis, and had more advanced disease than older patients did. With appropriate aggressive treatment, survival was found to be similar, thus suggesting that liberal use of endoscopy and an aggressive diagnostic approach are paramount in young patients with dysphagia/symptoms of gastroesophageal reflux disease (GERD).

Esophageal adenocarcinoma incidence rates vary markedly by ethnicity. Kubo et al. recently analyzed the multiethnic and gender variability of the incidence of esophageal and cardia adenocarcinoma by using Surveillance, Epidemiology, and End Results cancer registry data between 1992 and 1998.[10] They demonstrated that white males' esophageal adenocarcinoma rate (4.2 per 100,000 population per year) was double that of Hispanics and fourfold higher than that of blacks, Asians, and Native Americans and that female rates were much lower than male rates for all ethnicities. Similar to esophageal adenocarcinoma, cardia adenocarcinoma rates were highest in white males (3.4 per 100,000 population per year). However, the ethnic differences were much less and female rates were comparable for almost all ethnicities, except Native Americans. In addition, it was found that the incidence rates of esophageal adeno-

Table 32–1 Risk Factors for Esophageal Adenocarcinoma and Squamous Cell Carcinoma

	Esophageal Adenocarcinoma	Esophageal Squamous Cell Carcinoma
Age	↑	↑
Alcohol	0	↑
Caucasian race	↑	↓
Cholecystectomy	↑	0
Fruit and vegetables	↓	↓
Gastroesophageal reflux disease/Barrett's esophagus	↑	0
Helicobacter pylori infection	↓	?
Low socioeconomic status	↓	↑
Lower sphincter–relaxing medications	↑	0
Male sex	↑	↑
Nonsteroidal anti-inflammatory drugs	↓	↓
Obesity	↑	↓
Tobacco	↑	↑

↑, positive association; ↓, negative association; 0, no association.

carcinoma increased significantly only in whites and not in the other ethnic groups whereas cardia cancer rates did not increase for any ethnicity during this period. These findings suggest that cardia and esophageal adenocarcinomas are biologically distinct entities or that the incidence rate of cardia cancer represents a blending of gastric and esophageal carcinoma incidence rates. Current putative risk factors do not adequately explain this substantial variability.

Squamous cell cancer of the esophagus also has a male preponderance, with rates two to four times higher in males than in females.[4,6] In contrast to adenocarcinoma, squamous cell cancer incidence rates were highest in blacks (8.8 per 100,000 population per year) and Asians (3.9 per 100,000 population per year), and they were stable or declined for all ethnicities between 1992 and 1998, which could be influenced by the different socioeconomic variables existing between these ethnic groups.[10]

RISK FACTORS FOR SQUAMOUS CELL CANCER AND ADENOCARCINOMA

Obesity

Obesity is a risk factor for a number of gastrointestinal malignancies (Table 32–1). Calle et al. examined the relationship between body mass index (BMI) for men and women in 1982 and the risk for death from all cancers and from cancer at individual sites in a prospectively studied population of more than 900,000 U.S. adults (404,576 men and 495,477 women) who were free of cancer at enrollment.[11] They demonstrated that increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites, including esophageal cancer (Fig. 32–4). In particular, those with the greatest BMI (≥40) had death rates from all cancers combined that were 52% higher for men and 62% higher for women than for people of normal weight. In men, the relative risk for death was 1.52, and in women, the relative risk was 1.62. It is suggested that obesity, which increases the incidence of GERD, might result in an increase in the incidence of Barrett's esophagus, the most important risk factor for esophageal adenocarcinoma, thereby leading to a higher risk for the development of esophageal adenocarinoma.[3,12] In contrast, it is noted that esophageal squamous cell cancer decreases with increasing BMI.

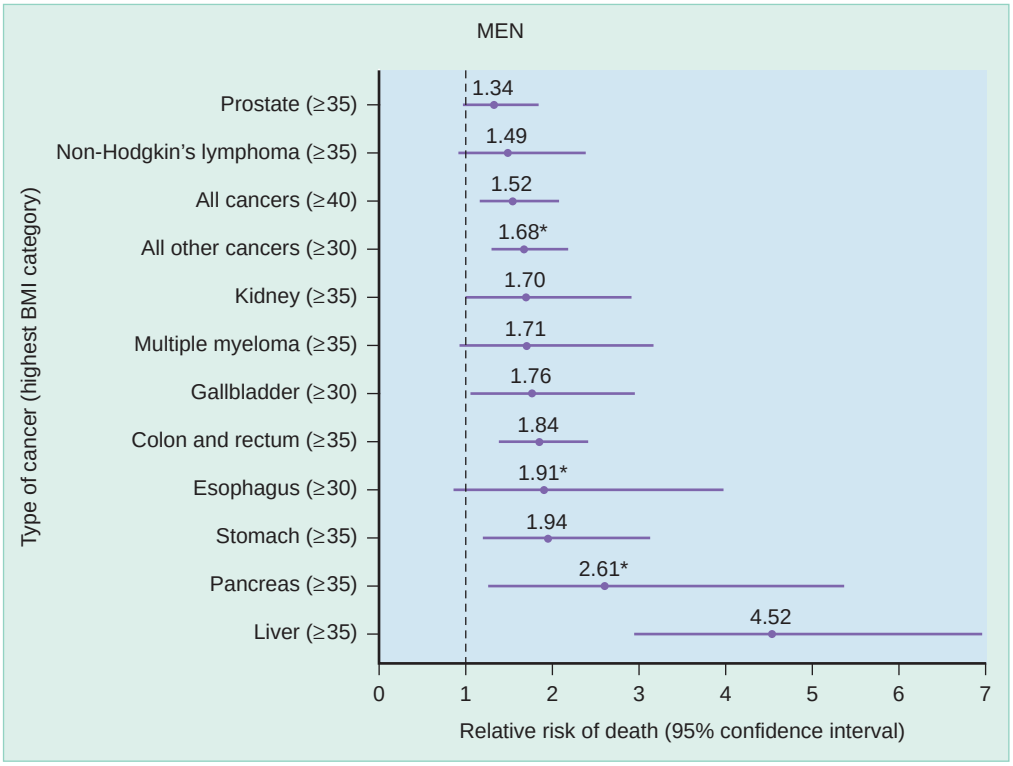
Tobacco and Alcohol

Tobacco smoking and alcohol exposure have been identified as strong, independent risk factors for squamous cell cancer of the esophagus, but the risk depends mainly on the duration of smoking and the amount of alcohol consumed.[13,14] Cessation of smoking for 5 years reduces the risk by 50%, and abstinence from alcohol for at least 10 years reduces the risk to levels of nondrinkers.

For esophageal adenocarcinoma, smoking seems to be merely a moderate risk factor and alcohol consumption is not associated with an increased risk for this type of cancer.[15,16]

Diet and Nutrition

Squamous cell cancer and adenocarcinoma seem to be influenced by diet and nutrition in the same way. It has been shown that high intake of fruits and vegetables reduce the risk for both histologic types.[17-20] For example, Bollscheiler et al. demonstrated that low intake of vitamins C and E correlates significantly with the development of squamous cell carcinoma and adenocarcinoma.[20] Evidence suggests that in particular the



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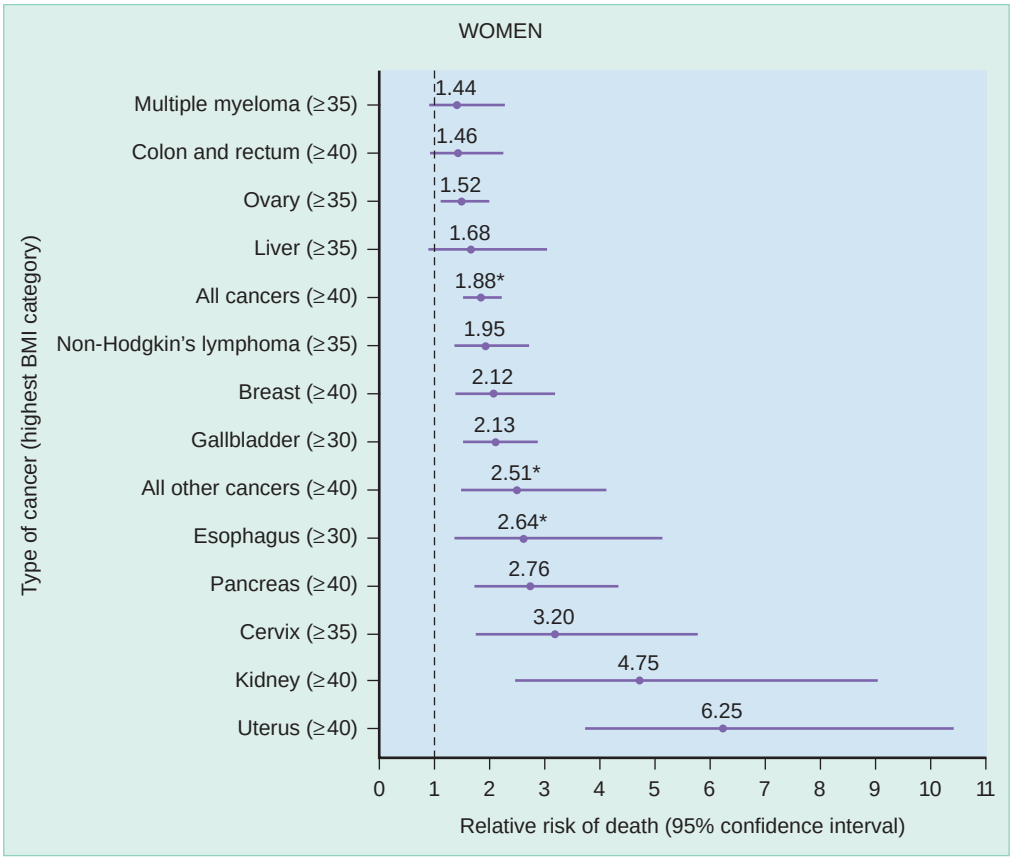

B

Figure 32–4. **A,** Summary of mortality from cancer according to body mass index for U.S. men in the Cancer Prevention Study II, 1982 through 1998. **B,** Summary of mortality from cancer according to body mass index for U.S. women in the Cancer Prevention Study II, 1982 through 1998. (From Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 24;348:1625-1638, 2003.)

antioxidants in these dietary items seem to provide the protective effect.[21]

Nonsteroidal Anti-inflammatory Drugs

Cyclooxygenase-2 (COX-2) has been implicated as an important enzyme in the early development of several gastrointestinal cancers, including esophageal cancer.[22] COX-2 may contribute to cancer growth through several mechanisms, including increasing cells' longevity via inhibition of apoptosis and stimulation of angiogenesis.[23] Previous studies found an association between increased COX-2 expression and the development/progression of Barrett's esophagus, a premalignant condition of the esophagus strongly associated with esophageal adenocarcinoma.[24,25] Interestingly, epidemiologic studies suggest that the long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenases, are associated with a reduced risk for cancer, including both squamous cell cancer and adenocarcinoma of the esophagus.[26,27] Recently, Corley et al. performed a systematic review with a meta-analysis of nine observational studies consisting of 1813 cancer patients to evaluate the association of aspirin/NSAID use and esophageal cancer.[28] They described a significant protective association between the use of aspirin/NSAIDs and esophageal cancer and found that both intermittent and frequent medication use was protective. Therefore, aspirin/NSAIDs could protect against esophageal adenocarcinoma either by preventing the development of its primary precursor (i.e., Barrett's esophagus) or by diminishing the likelihood of Barrett's esophagus progressing to adenocarcinoma.

RISK FACTORS SPECIFIC TO ESOPHAGEAL ADENOCARCINOMA

Gastroesophageal Reflux Disease

GERD is a common disease that affects up to 30% of the Western population on a monthly basis. Its role in the development of esophageal adenocarcinoma has been investigated recently in several large epidemiologic studies. Lagergren et al. described a strong association between the risk for esophageal cancer and symptomatic GERD.[29] In this Swedish population-based, nationwide case-control study, 189 patients with esophageal adenocarcinoma and 820 control subjects were included. In persons with long-standing and severe symptoms of reflux, the odds ratio was 43.5 for esophageal adenocarcinoma. However, also in persons with recurrent symptoms of reflux occurring at least once per week, the risk for esophageal adenocarcinoma was increased eightfold. In a medical record–based case control-study by Chow et al. that included 196 patients with esophageal or cardia adenocarcinoma, a significantly twofold increased risk was found in persons with a recorded history of GERD, hiatal hernia, esophagitis/esophageal ulcer, or difficulty swallowing.[30] These results were validated in a case-control study of similar design in the United States.[31] Finally, a Swedish cohort study of 65,000 male patients with a discharge diagnosis of heartburn, hiatal hernia, or esophagitis analyzed the relationship between GERD and esophageal adenocarcinoma.[32] The investigators reported a ninefold increased risk for esophageal adenocarcinoma in patients with endoscopic evidence of esophagitis.

Barrett's Esophagus

Barrett's esophagus is a condition in which the normal squamous epithelium of the distal end of the esophagus is replaced with metaplastic specialized intestinal-type epithelium as a sequela of chronic GERD.[33] This metaplastic condition is the most important risk factor for esophageal adenocarcinoma. In studies with a large sample size, the risk for development of esophageal adenocarcinoma was 30- to 60-fold higher in patients with Barrett's esophagus than in the general population.[6] Cameron et al. performed one of the earliest retrospective studies evaluating the malignant potential of Barrett's esophagus. In 18 of 122 patients, adenocarcinoma of the esophagus and Barrett's esophagus were found simultaneously, whereas in the remaining 104 patients, esophageal adenocarcinoma developed in 2 after a mean interval of 8.5 years.[34] In a Dutch prospective follow-up study by Hameeteman et al., 50 patients with Barrett's esophagus, without carcinoma at entrance to the study, were evaluated for a period of 1.5 to 14 years (mean, 5.2 years) to determine the dysplastic/malignant potential of Barrett's esophagus.[35] At the end of the observation period dysplasia had been found in 13 patients, in 10 scored as low grade and in 3 as high-grade, and adenocarcinoma had developed in another 5 patients. These data demonstrate that Barrett's esophagus is a premalignant condition that predisposes to the development of esophageal adenocarcinoma.

Lower Sphincter–Relaxing Medications

Several drugs are able to relax the lower esophageal sphincter and are thought to thereby increase the risk for development of esophageal adenocarcinoma because of an increase in the incidence of GERD. A Swedish case-control study tested the possible association between the use of sphincter-relaxing medications, such as nitroglycerin, anticholinergics, β-adrenergic agonists, aminophyllines, and benzodiazepines, and the risk for esophageal adenocarcinoma.[36] It was found that past use of sphincter-relaxing drugs was positively associated with risk for esophageal adenocarcinoma and that the association almost disappeared after adjustment for reflux symptoms, thus suggesting that promotion of reflux is the link between the use of sphincter-relaxing drugs and esophageal adenocarcinoma.

Helicobacter pylori Infection

Eradication of *H. pylori* is an effective strategy for chemoprevention of gastric cancer.[37] However, evidence

suggests that such eradication is associated with a higher risk for esophageal adenocarcinoma. Two clinical studies, by Chow et al. and Simán et al., found that infection with *H. pylori* decreased the risk for esophageal cancer by 60% and by 50% to 80%, respectively.[38,39] The mechanism of this protective effect is still unclear. It is hypothesized that *H. pylori* infection induces atrophic gastritis and possibly increased intragastric ammonia production leading to protection against esophageal adenocarcinoma.[40]

WHY IS THE EPIDEMIOLOGY CHANGING?

Although the incidence of esophageal adenocarcinoma is rising dramatically, the reasons for this observation are still controversial. The increase may represent a true rise in disease burden; nevertheless, it may also be the result of overdiagnosis or reclassification. Pohl and Welch have recently examined the incidence, stage distribution, and disease-specific mortality of esophageal adenocarcinoma to determine whether the dramatic increase in incidence of this malignant disease represents merely overdiagnosis or reclassification or constitutes a real increase in disease burden.[5] They found that the distribution of esophageal cancer in general has changed and that the only location of disease manifestation with a rising incidence is the lower third of the esophagus, the typical location of adenocarcinoma, which suggests that reclassification of squamous cell cancer is unlikely to explain the change in epidemiology. In addition, they described an increased incidence of adjacent cardia cancer, thus demonstrating that even reclassification of cardia cancer is also unlikely to influence the rising incidence of esophageal adenocarcinoma. Finally, they excluded overdiagnosis as a factor influencing the rising incidence because in the last 30 years there has been just a minor change in the proportion of patients with localized disease and at the same time the mortality associated with esophageal adenocarcinoma has increased more than sevenfold. Therefore, they concluded that the increase in this cancer type represents a true increase in disease burden, thus suggesting that changes in the prevalence of known risk factors, specifically, GERD, obesity, or a decrease in *H. pylori* infection, might be possible explanations for the changing epidemiology. Nevertheless, if these risk factors contribute mainly to the increase in esophageal cancer, their incidence should also have risen in the last decades. Especially for GERD, thought to be one of the strongest risk factors, there is unfortunately a lack of data, so the future goal is to more carefully analyze the epidemiology of risk factors for esophageal cancer to ultimately prevent this disease in the future.

CLINICAL MANIFESTATIONS

Early symptoms in patients with esophageal cancer are normally absent. Therefore, at the time of diagnosis more than 50% of patients have an unresectable tumor or visible metastases.[8] The most common symptom in patients with this malignant tumor is dysphagia (74%). In addition, 57% of patients complain of weight loss and 17% of odynophagia (pain on swallowing food and liquids) at the time of diagnosis.[41] Other possible symptoms are cough, dyspnea, hoarseness, and pain (back, retrosternal, or abdominal). For patients with esophageal adenocarcinoma, Leers et al. recently confirmed that chronic GERD is a frequent factor in the clinical history of patients with this malignant disease.[42] Of the 117 patients included in this study, 86% reported having had heartburn or regurgitation at least several times in their lives. Moreover, 46% of the patients had reflux symptoms daily.

Usually, physical examination is unremarkable. However, if patients have metastatic disease, lymphadenopathy in the head and neck area, hepatomegaly, and pleural effusion can occur.

More recently, endoscopic surveillance of patients with Barrett's esophagus, the most important risk factor for esophageal adenocarcinoma, is becoming established. The rationale for this surveillance is twofold: to detect progression of disease to cancer and to allow early intervention while cure is still likely.[43] Peters et al. analyzed the clinical outcome of adenocarcinoma arising in Barrett's esophagus in endoscopically surveyed and nonsurveyed patients.[44] They reported that patients referred from surveillance programs for Barrett's esophagus have a better outcome and earlier stage than nonsurveyed patients do. Normally, these patients do not have the typical symptoms, such as dysphagia or weight loss, at the time of diagnosis but rather complain about typical reflux symptoms.

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Chapter

33

Esophageal Cancer: Current Staging Classifications and Techniques, Endoscopic Ultrasound, and Laparoscopic and Thoracoscopic Staging

Simon Law

Accurate staging serves three purposes: prognostication, source of information for stage-directed therapies, and quality control in clinical trials. Staging methods have evolved over the years, and there are now many staging techniques at our disposal, both invasive and noninvasive. Although these technologies undoubtedly have improved accuracy, the optimal methods remain controversial. Treatment strategies for esophageal cancer have also changed. A variety of endoscopic and surgical techniques and multimodality therapies are available to individual patients. Accurate staging assumes more importance for stage-directed therapy. This chapter details the current staging classifications and methods for esophageal cancer and highlights some of the difficulties and controversies.

STAGING SYSTEMS

Ideally, a staging system for cancer should be simple and easy to apply, provide sufficiently accurate and useful stratification of patients into different prognostic groups, and guide treatment. Unfortunately, no perfect system exists and constant modifications are required, depending on the knowledge gained. Currently, there are two main staging systems for esophageal cancer: the tumor-node-metastasis (TNM) system of the Union Internationale Contre le Cancer (UICC)[1] and the American Joint Committee on Cancer (AJCC),[2] which are uniform, and the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus advocated by the Japanese Society for Esophageal Diseases (JSED).[3]

Anatomic Subsites

Both systems divide the esophagus into anatomic segments for ease of classification (Fig. 33–1):

1. The cervical esophagus extends from the esophageal orifice (lower border of the cricoid cartilage) to the sternal notch (or thoracic inlet), which corresponds to approximately 18 cm from the upper incisor teeth.
2. The upper thoracic esophagus extends from the sternal notch to the tracheal bifurcation and measures approximately 24 cm from the upper incisor teeth.
3. The middle thoracic esophagus is the proximal half of the two equal portions between the tracheal bifurcation and the esophagogastric junction; it corresponds to roughly 32 cm measured from the upper incisor.
4. The lower thoracic esophagus is the thoracic part of the distal half of the two equal portions between the tracheal bifurcation and the esophagogastric junction.
5. The abdominal esophagus is the abdominal part of the distal half of the two equal portions between

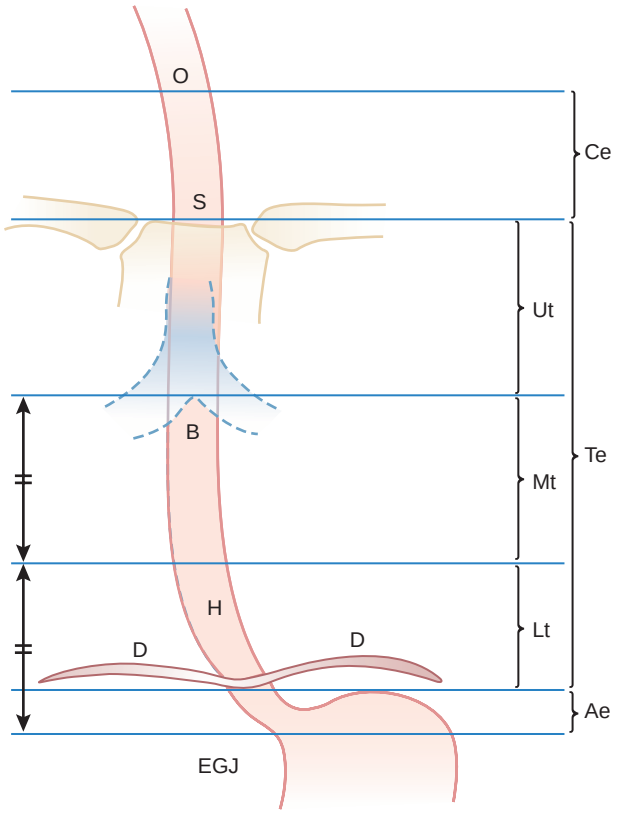

Figure 33–1. Description of the different levels of esophageal tumor. Ce, cervical esophagus; Te, thoracic esophagus; Ut, upper third; Mt, middle third; Lt, lower third; Ae, abdominal esophagus; EGJ, esophagogastric junction; O, esophagus; S, sternal notch; B, tracheal bifurcation; D, diaphragm; H, hiatus.

the tracheal bifurcation and the esophagogastric junction. The esophagogastric junction approximates 40 cm measured from the upper incisor.

Definitions of Depth of Tumor Infiltration (T Stage)

The depth of tumor infiltration classified by the Japanese system addresses the following:

1. TX: Depth of tumor invasion not able to be assessed
2. T0: No evidence of primary tumor
3. Tis: Carcinoma in situ (EP)
4. T1a: Invasion to the lamina propria mucosae (lpm) or up to but not beyond the muscularis mucosae (mm)
5. T1b: Invasion to but not beyond the submucosa (sm)
6. T2: Invasion to but not beyond the muscularis propria (mp)
7. T3: Invasion to the esophageal adventitia (Ad)
8. T4: Invasion to adjacent organs

In the current AJCC/UICC system, although T1 lesions are not subdivided into T1a and T1b officially, it is clear that T1a and T1b tumors are prognostically different in that T1b lesions are associated with a substantial chance of lymph node metastasis, so the nomenclature T1a and T1b is widely used. Studies on early cancer also indicate that subdivisions of mucosal and submucosal cancer are possible. Mucosal cancer is separated into intraepithelial cancer (m1), tumor involving the lamina propria (m2), and cancer penetrating the lamina muscularis mucosae (m3). Progressive depths of submucosal infiltration (sm1 to sm3) also indicate escalating chance of metastasis. This is increasingly of relevance, especially when high-frequency endoscopic ultrasound (EUS) and endoscopic mucosal resection techniques are used. In the Japanese system, "superficial cancers" are defined as carcinomas limited to the submucosal layer, whereas "early-stage cancers" are referred to as carcinomas with invasion into the mucosal layer but without metastasis (Tis N0 M0 and T1a N0 M0).

Box 33–1 **Regional Lymph Nodes for Esophageal Cancer According to the American Joint Committee on Cancer TNM Classification**

Cervical Esophagus

- Scalene
- Internal jugular
- Upper and lower cervical
- Periesophageal
- Supraclavicular

Intrathoracic Esophagus (Upper, Middle, and Lower)

- Upper periesophageal (above the azygous vein)
- Subcarinal
- Lower periesophageal (below the azygous vein)

Gastroesophageal Junction

- Lower esophageal (below the azygous vein)
- Diaphragmatic
- Pericardial
- Left gastric
- Celiac

Nodal Metastases (N Stage)

The most controversial aspect in TNM staging is the classification of nodal metastases. Both the AJCC/UICC and the JSED systems use a topographic description of nodal metastases. The AJCC/UICC system is simpler and essentially regards periesophageal, mediastinal, and perigastric lymph node stations as "regional." For cervical esophageal cancer, only lymph nodes in the neck are regarded as regional (Box 33–1). For intrathoracic

tumors, the celiac and cervical lymph nodes are classified as M1 disease, with subdivision into M1a and M1b depending on the site of the primary tumor. The latter also includes visceral organ metastases. The TNM stage groupings are shown in Table 33–1. A lymph node map that extends the nomenclature and numbering system used for the staging of non–small cell lung cancer has been suggested by the AJCC and is included in the staging manual (Fig. 33–2). In the Japanese system, lymph node stations are expanded in addition to that used for gastric cancer staging in Japan (Fig. 33–3 and Table 33–2). This system is substantially more complicated than that proposed by the AJCC. Lymph node stations are classified into N0 to N4, and just like gastric cancer, assignment of the N category depends on the location of the primary tumor (Table 33–3). Moreover, when pathologic information is available, the pN category is modified according to the number of lymph nodes found involved. For one to three metastatic nodes, no revision of the pN value is necessary; for four to seven nodal metastases, the pN value is modified upward by an increment of 1 (not beyond N4 cases); and when eight or more nodes are involved, a correction factor of 2 is used (not beyond N4). Thus, for example, in a patient found to have pN1 disease (by location), if eight nodes are found to be positive, the pN1 category is upgraded to pN3. Implicit within the staging system is that a minimum of four nodes need to be examined to allow this modification of the pN value. The final TNM combinations in different stages are shown in Figure 33–4. Lymph node stations are sometimes also classified according to a system proposed by Akiyama based on his extensive experience in three-field lymphadenectomy; it includes seven anatomic regions (Table 33–4). This system, however, has not been adopted by the JSED.

Table 33–1 Stage Groupings for Esophageal Cancer According to the AJCC TNM Classification

T: Primary tumor
- Tx Tumor cannot be assessed
- Tis In situ carcinoma
- T1 Tumor invades the lamina propria or submucosa; does not breach the submucosa
- T2 Tumor invades into but not beyond the muscularis propria
- T3 Tumor invades the adventitia but not the adjacent structure
- T4 Tumor invades the adjacent structure

N: Regional lymph nodes
- NX Regional nodal status cannot be assessed
- N0 No regional lymph node involvement
- N1 Regional lymph node involved

M: Distant metastases
- MX Distant metastases cannot be assessed
- M0 No distant metastasis
- M1a Upper thoracic esophagus with metastases to the cervical nodes
  Lower thoracic esophagus with metastases to the celiac nodes
- M1b Upper thoracic esophagus with metastases to other nonregional nodes or other distant sites
  Lower thoracic esophagus with metastases to other nonregional nodes or other distant sites
  Middle thoracic esophagus with metastases to the cervical, celiac, or other nonregional nodes or other distant sites

Stage Groupings

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
	T3	N0	M0
Stage IIb	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	N0-N1	M0
Stage IVa	Any T	Any N	M1a
Stage IVb	Any T	Any N	M1b

From American Joint Committee on Cancer: AJCC Cancer Staging Manual. New York, Springer, 2002, pp 91-95.

Cancer Around the Gastroesophageal Junction

For cancer around the gastroesophageal junction, a classification system proposed by Siewert and Stein is increasingly being used.[4] This system aims at subclassifying adenocarcinomas found within 5 cm proximal and distal to the anatomic gastroesophageal junction and is therefore of particular relevance in the West, where Barrett's esophagus and adenocarcinoma of the lower esophagus and gastric cardia are prevalent.[5,6] The system classifies tumors as type I to type III (esophageal, cardiac, and subcardiac), depending on the relative extent of involvement of either the esophagus or stomach (Fig. 33–5). The three types of cancers are different in patient demographics, possible cause, histopathologic features, and prognosis. Different treatment strategies are also advocated.[7] Further validation of this classification is needed to determine its reliability. In the East, where Barrett's esophagus and adenocarcinomas of the esophagus are uncommon, the system is perhaps less relevant[8]; lower esophageal cancers are mostly squamous, and there is no doubt about their cellular origin. Subcardiac cancers should probably be regarded as primarily gastric cancers. Classification and treatment of type II cancers centered on the gastroesophageal junction are most controversial, and it is uncertain whether they should be staged as gastric or esophageal tumors.[9]

In the Japanese classification, depending on the relative extent of involvement of the esophagus and stomach, a simple descriptive method of EG, E = G, and GE is used. Realizing the problem of classification of junctional tumors, the assignment of nodal stations into N1 to N4

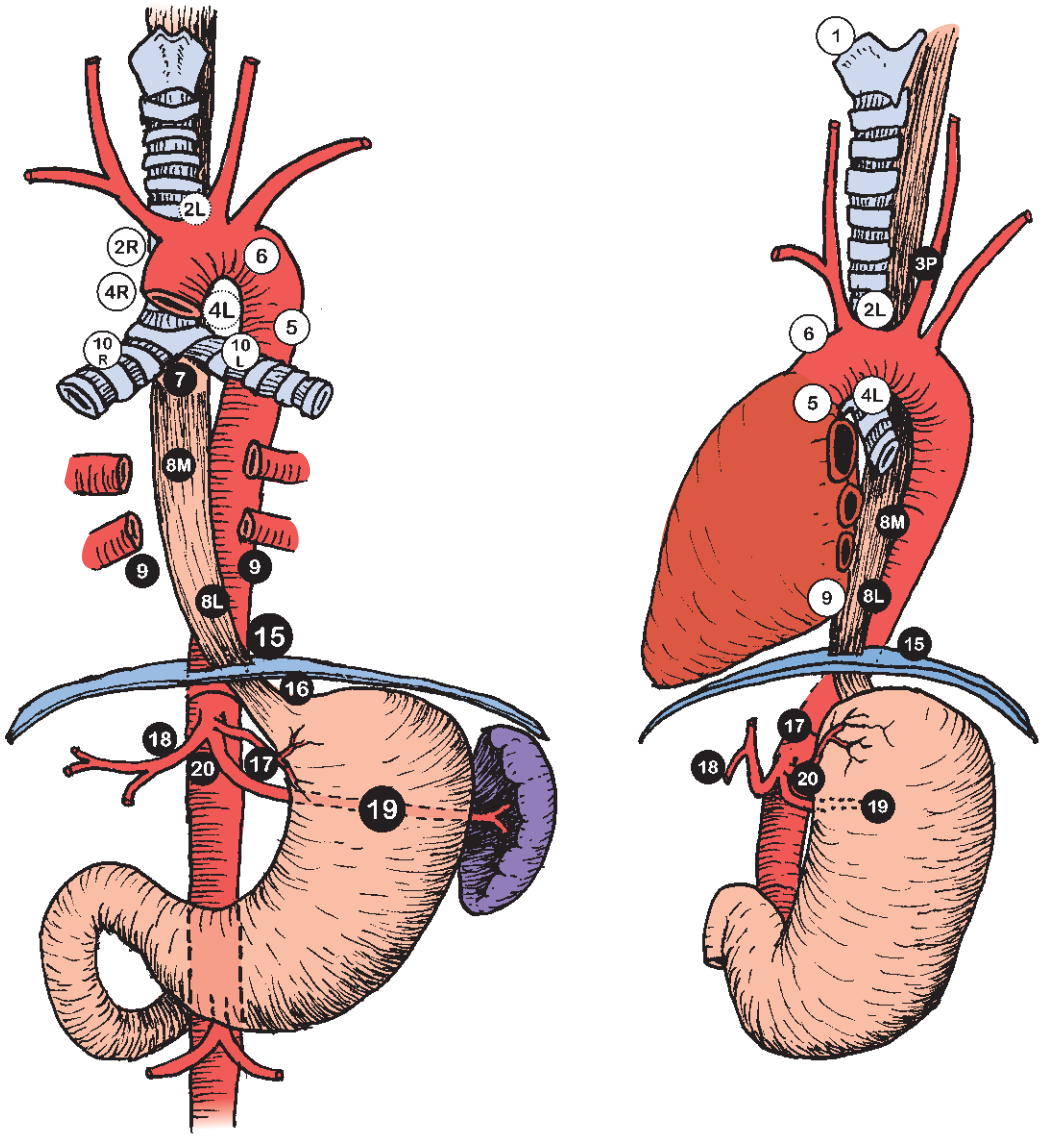

Figure 33–2. Lymph node stations suggested by the American Joint Committee on Cancer manual. 1, Supraclavicular; 2R, right upper paratracheal nodes; 2L, left upper paratracheal nodes; 3P, posterior mediastinal nodes; 4R, right lower paratracheal nodes; 4L, left lower paratracheal nodes; 5, aortopulmonary nodes; 6, anterior mediastinal nodes; 7, subcarinal nodes; 8M, middle paraesophageal nodes; 8L, lower paraesophageal nodes; 9, pulmonary ligament nodes; 10R, right tracheobronchial nodes; 10L, left tracheobronchial nodes; 15, diaphragmatic nodes; 16, paracardial nodes; 17, left gastric nodes; 18, common hepatic nodes; 19, splenic nodes; 20, celiac nodes.

for these cancers is described as "tentative" by the JSED.[3] According to the Japanese Classification of Gastric Carcinoma endorsed by the Japanese Gastric Cancer Association, lymph node groupings also change when a cardia or proximal gastric cancer invades the esophagus.[10] To add to the confusion, the current Japanese gastric cancer nodal stations are classified from N0 to N3, whereas for esophageal cancer, the classification extends to N4. It is also observed that if the AJCC/UICC gastric cancer staging system is going to be used for type II or III cancers, assignment of nodal metastases changes from a topographic to a numerical one: N0 disease indicates no nodal disease, N1 is used for 1 to 6 involved regional nodes, N2 for 7 to 15 nodes, and N3 for more than 15 involved nodes. The nomenclature of tumors around this area is therefore far from settled. Further work is urgently required to accurately reflect uniform and accurate staging of tumors around the gastroesophageal junction.

Which Staging System Should Be Used?

There is little disagreement with regard to T stage because it is reproducible and clear evidence of progressive metastatic potential and prognosis can be

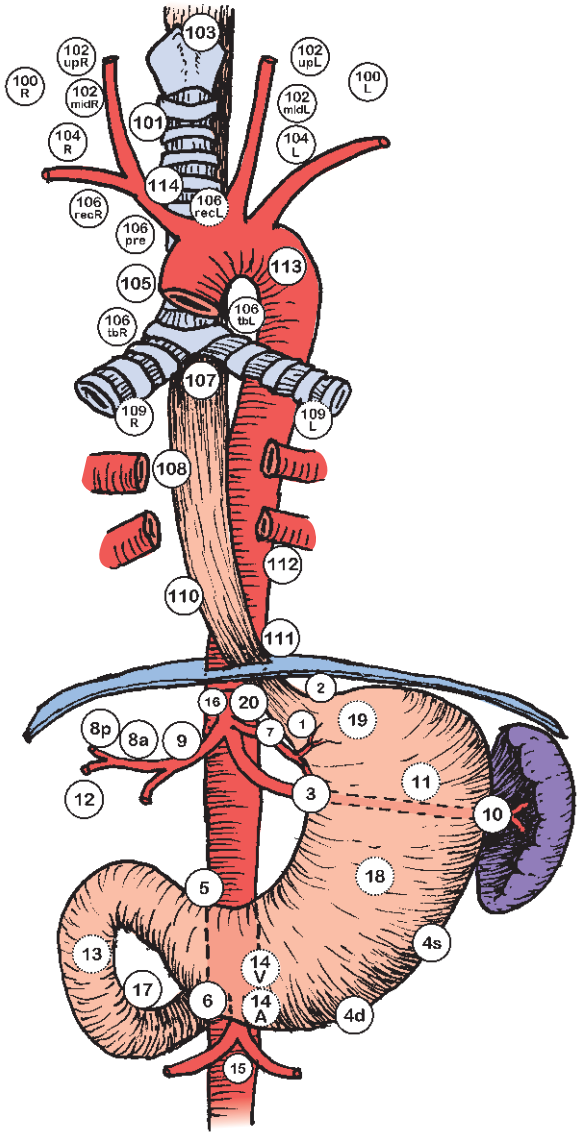

Figure 33–3. Lymph node stations according to the Japanese Society for Esophageal Diseases.

demonstrated; accordingly, the AJCC/UICC and the Japanese system do not differ. How to classify nodal metastases and stage groupings is most controversial. Both systems use a topographic assignment for lymph node stations. The AJCC/UICC system is clearly simpler to apply. The problem with the Japanese method is that more detailed and meticulous handling of the surgical specimen is required. When a pathologic stage is assigned from esophagectomy specimens, close cooperation between the surgeon and pathologist is essential. In Japan, it is customary that individual lymph nodes be dissected from the surgical specimen by the operating surgeon before the specimen is sent to the pathologist, thereby ensuring topographic accuracy. In most Western practices this is not performed, and more reliance is placed on the pathologist. It is clear that the extent of lymphadenectomy and the thoroughness of the pathologist's examination of the specimen together determine the number of lymph nodes retrieved; additional technique such as fat clearing also increases the yield.[11] At the author's institution, tissue at individual stations is dissected out and labeled for the pathologist to examine, but individual lymph nodes are not dissected out of the connective tissue and fat. This may be a practical compromise to ensure topographic accuracy without being too time-consuming for the surgeons.

The AJCC system is more widely used internationally. Assignment of nodal stations to simply N0 and N1 is perhaps oversimplified. The N1 versus M1a versus M1b descriptors also do not accurately identify prognostically different groups.[12] Currently, celiac lymph nodes are classified as M1a for lower thoracic esophageal tumors. Clearly, better survival can be achieved, with an approximately 10% or higher chance of cure at 5 years after surgical resection, as opposed to the more dismal prognosis with visceral metastases. Similarly, in patients with cervical nodal metastases, cervical lymphadenectomy can also result in long-term cure, especially when three-field lymphadenectomy is performed.[13]

The number of metastatic lymph nodes is recognized as an important prognostic factor. The TNM classification of gastric and colorectal cancer has already incorporated the number of lymph nodes in the pN classification category. Using the number of lymph nodes for staging implies a minimum number of retrieved nodes for histopathologic examination. The UICC recommends a minimum of 6 retrieved lymph nodes for an accurate nodal classification of esophageal cancer, 15 or more nodes for gastric cancer, and 12 or more for colorectal cancer.[1] Other authors have suggested a total of 12 for esophageal cancer.[14] The number of nodes resected is often used as a surrogate for quality control of lymphadenectomy. As already discussed, this reflects not only the extensiveness of the lymphadenectomy but also the manner in which the surgical specimens are handled and the conscientiousness of the pathologist. The Japanese style of specimen processing will invariably lead to more nodes examined, regardless of the extent of lymphadenectomy. This aside, various cutoff points of prognostic importance have been reported for the number of involved nodes: 0 or 1 versus 2 or more,[15] 0 versus 1 to 2 versus 3 or more,[12] 0 or 1 versus 2 to 7 versus 8 or more,[16] 1 to 4 versus 5 or more,[17-24] 0 versus 1 to 3 versus 4 or more,[25] 0 to 5 versus 6 or more,[26] and 1 to 7 versus 8 or more[27]; in addition, as used by the current Japanese system, cutoff points include 0 versus 1 to 3 versus 4 to 7 versus 8 or more.[3] The variety of combinations shows that although the number of involved nodes is recognized to be important, it is difficult to find a consensus. Other than the number of nodes, the lymph node ratio (number of positive nodes divided by the number sampled) was also found to have prognostic value.[28,29]

Modification of the current TNM staging system is clearly desirable, and various revisions have been suggested.[22-26] The AJCC task force for esophageal cancer strongly considered changing the TNM staging system for the latest version; however, it was thought that there were insufficient published data to support a proposal for a new system that would be widely accepted.[30]

Table 33–2 Lymph Node Stations According to the Japanese Society for Esophageal Diseases

Cervical and Mediastinal Lymph Nodes		Abdominal Lymph Nodes	
No.	**Definition**	**No.**	**Definition**
100	Superficial lymph nodes of the neck	1	Right cardial lymph nodes
101	Cervical paraesophageal lymph nodes	2	Left cardial lymph nodes
102	Deep cervical lymph nodes	3	Lymph nodes along the lesser curvature
103	Peripharyngeal lymph nodes	4	Lymph nodes along the greater curvature
104	Supraclavicular lymph nodes	5	Suprapyloric lymph nodes
105	Upper thoracic paraesophageal lymph nodes	6	Infrapyloric lymph nodes
106	Thoracic paratracheal lymph nodes	7	Lymph nodes along the left gastric artery
106-rec	Recurrent nerve lymph nodes	8	Lymph nodes along the common hepatic artery
106-rec L	Left recurrent nerve lymph nodes	9	Lymph nodes along the celiac artery
106-rec R	Right recurrent nerve lymph nodes	10	Lymph nodes at the splenic hilum
106-pre	Pretracheal lymph nodes	11	Lymph nodes along the splenic artery
106-tb	Tracheobronchial lymph nodes	12	Lymph nodes in the hepatoduodenal ligament
106-tb L	Left tracheobronchial lymph nodes	13	Lymph nodes on the posterior surface of the pancreatic head
106-tb R	Right tracheobronchial lymph nodes	14	Lymph nodes at the root of the mesentery
107	Subcarinal lymph nodes	14A	Lymph nodes along the superior mesenteric artery
108	Middle thoracic paraesophageal lymph nodes	14V	Lymph nodes along the superior mesenteric vein
109	Main bronchus lymph nodes (formerly: pulmonary hilar lymph nodes)	15	Lymph nodes along the middle colic artery
110	Lower thoracic paraesophageal lymph nodes	16	Lymph nodes around the abdominal aorta
111	Supradiaphragmatic lymph nodes (formerly: diaphragmatic lymph nodes)	17	Lymph nodes on the anterior surface of the pancreatic head
112	Posterior mediastinal lymph nodes	18	Lymph nodes along the inferior margin of the pancreas
113	Ligamentum arteriosum lymph nodes (Botallo's lymph nodes)	19	Infradiaphragmatic lymph nodes
114	Anterior mediastinal lymph nodes	20	Lymph nodes in the esophageal hiatus of the diaphragm

For more detailed subdivisions of individual lymph node groups, refer to the staging manual of the Japanese Society for Esophageal Diseases.

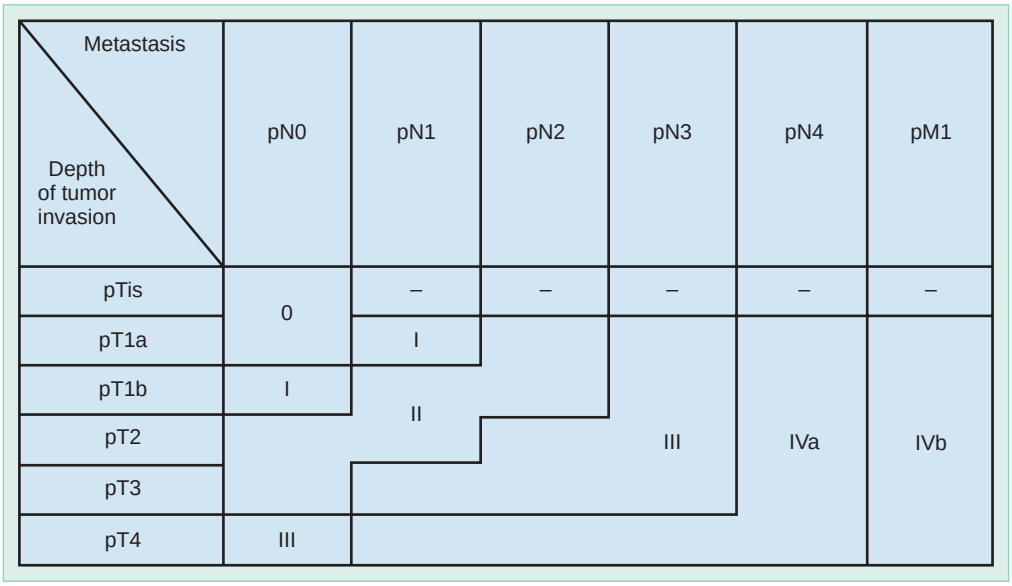

Figure 33–4. Stage groupings according to the Japanese Society for Esophageal Diseases.

Table 33–3 Lymph Node Groups by Location of the Primary Tumor According to the Japanese Society for Esophageal Diseases

Tumor Location		N1	N2	N3	N4
Cervical esophagus (Ce)		101, 104	102, 106-rec	100, 103, 105, 106-tbL, 107, 108	106-pre, 106-tbR, 109, 110, 111, 112, 113, 114, 1, 2, 3, and others
Thoracic esophagus (Te)	Upper (Ut)	105, 101, 106-rec	104, 106-tbL, 107, 108, 109	102-mid, 106-pre, 106-tbR, 110, 111, 112, 1, 2, 3, 7	100, 102-up, 103, 113, 114, 4, 5, 6, 8, 9, 20, and others
	Middle (Mt)	108, 106-rec	101, 105, 106-tbL, 107, 109, 110, 1, 2, 3, 7	104, 111, 112, 20	100, 102, 103, 106-pre, 106-tbR, 113, 114, 4, 5, 6, 8, 9, and others
	Lower (Lt)	110, 1, 2	106-rec, 107, 108, 109, 111, 112, 3, 7, 20	101, 105, 106-tbL, 9, 19	101, 102, 103, 104, 106-pre, 106-tbR, 113, 114, 4, 5, 6, 8, 10, and others
Abdominal esophagus (Ae)		1, 2, 3, 20	110, 111, 7, 9, (4), (10), (11), 19	108, 5, 8, (112)	100, 101, 102, 103, 104, 105, 106, 107, 109, 113, 114, 6, and others
Esophagogastric junction*	EG E = G GE	1, 2, 3	7, 9, 10, 11, (110), (111), (4)	108, 5, 6, 8, (112), (12), (13), (14)	100, 101, 102, 103, 104, 105, 106, 107, 109, 15, 16, and others

For lymph nodes in parentheses, the D category is not affected by excision or nonexcision of these lymph nodes.
*Lymph node groups of the esophagogastric junction are tentative.

Table 33–4 Lymph Node Groups as Described by Akiyama

Anatomic Site	Lymph Node Group
Cervical nodes	Deep lateral nodes (spinal accessory chain) Deep external nodes Deep internal nodes (recurrent nerve chain)
Superior mediastinal nodes	Recurrent nerve chain Paratracheal nodes Brachiocephalic artery nodes Paraesophageal nodes Infra-aortic arch nodes
Middle mediastinal nodes	Tracheal bifurcation nodes Pulmonary hilar nodes Paraesophageal nodes
Lower mediastinal nodes	Paraesophageal nodes Diaphragmatic nodes
Superior gastric nodes nodes	Pericardiac nodes Lesser curvature nodes Left gastric artery nodes
Celiac axis nodes Common hepatic artery nodes	

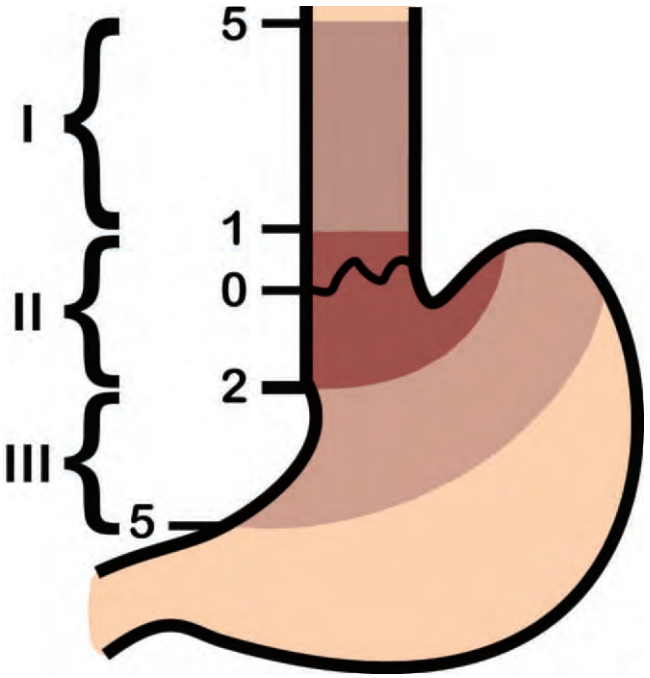

Figure 33–5. Siewert and Stein's classification of adenocarcinomas around the gastroesophageal junction. Type I, esophageal; type II, cardiac; type III, subcardiac.

The TNM system remains the most widely used, although the detailed topographic Japanese classification does have its merits. With the increasing amount of data accumulated, future changes in staging are inevitable. How best to integrate a topographic as well as a numerical component for nodal metastases remains to be determined. The minimal number and the stations of sampled lymph nodes required for adequate nodal staging, the optimal cutoff points for involved lymph nodes, the topographic locations of nodal stations that impart prognostic value, and whether the M1 category should be reserved for visceral metastases only are just some issues that need clarification. Because the incidence of lower esophageal and junctional adenocarcinoma is increasing while that of distal gastric cancer is decreasing, some concordance between staging of gastric, gastroesophageal junction, and lower esophageal adenocarcinoma is also desirable.

TNM Residual Tumor Classification

The R classification, an axillary classification within the TNM system, denotes the absence or presence of residual tumor after treatment and describes residual tumor as macroscopic or microscopic in amount.[31] The R category considers residual tumor at the primary tumor site, in the regional lymph nodes, and at distant sites. It may be used after surgical resection alone or after various combinations of nonoperative treatment. The R categories are defined as follows:

RX: The presence of residual tumor not able to be assessed
R0: No residual tumor
R1: Microscopic residual tumor
R2: Macroscopic residual tumor

R2 cases can be subdivided into R2a, in which there is no microscopic confirmation of residual tumor, and R2b, in which microscopic confirmation is available. The R1 category is reserved exclusively for cases in which residual tumor is found by histologic examination. This may apply to biopsy sampling of the regional tissue at the site of resection or a distant site at the time of surgery. It also applies to microscopic examination of the resection margins of the surgical resection specimen by the pathologist. In resected esophageal cancer specimens, the proximal and distal margins, as well as the lateral margins, should be examined pathologically for residual disease. Involvement of any margins despite gross macroscopic clearance at the time of surgery indicates an R1 resection. R1 should be used only if histologic examination reveals that the tumor is transected,[31] although some investigators have reported involvement of microscopic tumor within 1 mm or less of the resection margin as R1, and such cases are associated with a worse prognosis.[32] In tumor resection specimens from patients who have undergone lymphadenectomy, the "marginal" node is the one near the resection margin that is most distant from the primary tumor. Involvement of such a "marginal" or "apical" node, however, does not influence the R category. The R category naturally correlates with the stage of disease; the likelihood of palliative resection (R1-R2) migrates with advancing stage of disease, but R0 resections can also be performed for stage IV disease, provided that the metastatic lesion is resected as well.

Aside from stage, the R category is perhaps the strongest prognostic factor. It is also important with regard to quality assurance in oncologic treatment and facilitates comparison of treatment results if applied in a consistent manner. The need for additional treatment planning also depends heavily on the R category. This treatment-related variable should be carefully assessed and documented.

STAGING METHODS

Clinical staging requires a thorough physical examination and additional imaging methods. The physical sign indicative of metastatic disease that is most likely found is a palpable metastatic lymph node in the neck, particularly around the paratracheal region. Hoarseness of voice suggests recurrent laryngeal nerve palsy and thus signifies either direct tumor involvement or metastatic lymph nodes. Hepatomegaly with liver metastases is found only in very advanced disease. A simple chest radiograph may show metastases. Solitary lesions, however, may more likely indicate a primary pulmonary lesion.

Specific methods in clinical staging involve barium contrast studies, bronchoscopy, computed tomography (CT), percutaneous ultrasound of cervical lymph nodes with or without fine-needle aspiration (FNA) cytology, EUS with or without FNA, 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET), and laparoscopy or thoracoscopy (or both).

Barium Contrast Study

Typical features on a barium contrast study include mucosal irregularity and shouldering, narrowing of the lumen, and proximal dilatation of the esophagus (Fig. 33–6). It gives a longitudinal graphic view of the tumor in relation to other mediastinal structures, especially the trachea and main bronchi. It is a useful guide to the endoscopist and the surgeon, and in addition, it is sensitive in depicting tracheal-airway fistulas. Tortuosity, angulation, axis deviation from the midline, sinus formation, and fistulation to the bronchial tree are signs indicative of advanced tumor that has traversed the adventitia and involved the neighboring fixed organs.[33]

Endoscopic Examination

A classification of the macroscopic endoscopic appearance of esophageal cancer is in use by the JSED.[3] Superficial tumors are classified into type 0-I (superficial and protruding), type 0-II (superficial and flat), and type 0-III (superficial and distinctly depressed). Advanced tumors are classified as type 1 (localized protruding), type 2 (ulcerative and localized), type 3 (ulcerative

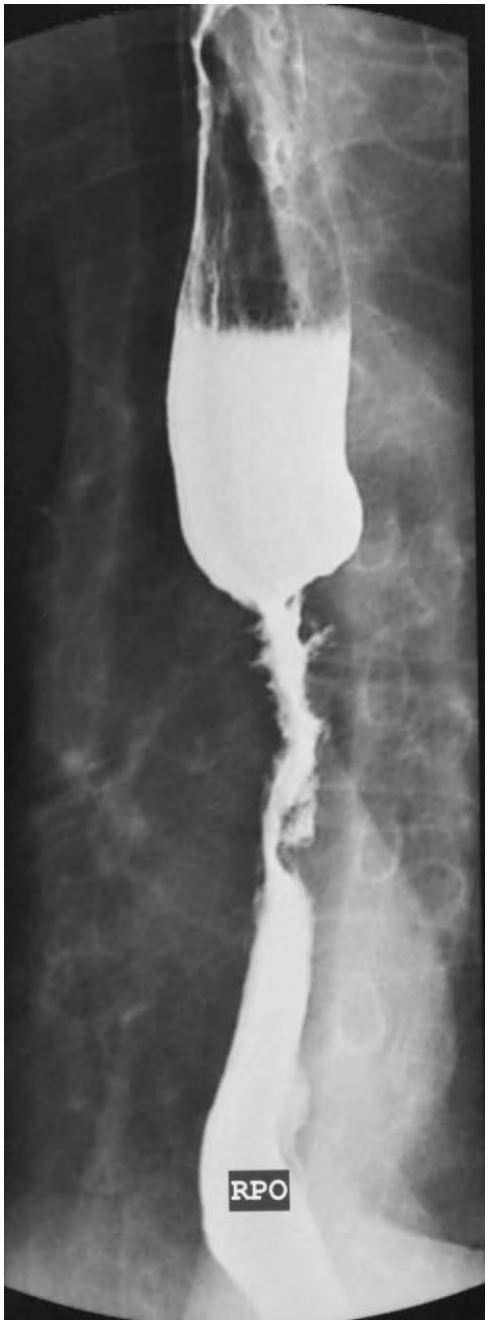

Figure 33–6. Barium contrast study showing a mid-esophageal tumor. Tumor stenosis with proximal dilatation of the esophagus is evident. The small sinuses are also suggestive of advanced infiltrative disease. RPO, right posterior oblique view.

and infiltrative), type 4 (diffusely infiltrative), and type 5 (miscellaneous type). Types 0-I, 0-II, 1, 4, and 5 are further divided into subtypes. Corresponding barium contrast appearances are also included in the classification.

In a study of 209 patients correlating the UICC's T stage with the JSED's endoscopic categories, it was shown that endoscopic assessment was both sensitive (78%) and specific (93%) in predicting the local extent of tumor (overall accuracy, 89%). Detailed analysis showed good sensitivity for type 0 (83%), which corresponds to T1 carcinoma, and for types 3 and 4 (82% and 83%), which represent T3 and T4 tumors. In endoscopic type 1 and type 2, the concordance with T stage (T2) was weak, with a sensitivity of 52%.[34]

Indirect information can be gained on the T stage and N stage by endoscopy alone. Esophageal tumors that are sufficiently large to cause luminal stenosis tend to be T3 and T4 lesions.[35] A tumor length greater than 5 cm is also predictive of T3 cancer with a sensitivity of 89%, specificity of 92%, positive predictive value (PPV) of 89%, and negative predictive value (NPV) of 92%.[36] Because advancing T stage correlates strongly with the presence of regional lymph node metastases, advanced-disease stage can often be inferred in patients with nontraversable tumors. In one study, 21 of 79 patients (26.6%) had high-grade malignant strictures precluding endosonographic examination without preceding esophageal dilatation. Nineteen of the 21 patients (90.5%) had stage III or IV disease by histopathologic examination of the surgical specimen.[37] Endoscopy alone, however, cannot distinguish T3 from T4 tumors, nor can distant metastases such as celiac lymph node or visceral metastases be predicted.

Endoscopic examination allows biopsy of the tumor, with or without brush cytology, to increase the diagnostic yield. In early tumors especially, Lugol's iodine chromoendoscopy is invaluable in localizing the extent of disease, in addition to directing biopsy at other dysplastic areas. Normal mucosa with its glycogen content should stain brown, with suspicious areas left unstained for directed biopsy. In patients with high-grade stenosis, endoscopically guided nasogastric tube insertion for tube feeding can be performed in the same setting.

Bronchoscopy

Use of the fiberoptic endoscope allows histologic confirmation of the cancer by biopsy or brush cytology. Flexible bronchoscopy is performed to assess tumor involvement of the tracheobronchial tree, especially tumors in the mid and upper portions of the esophagus. Signs of involvement include a widened carina, external compression, tumor infiltration, and fistulization. The last two signs contraindicate resection.[38] The gross macroscopic bronchoscopic appearance may not be accurate, and biopsy plus brush cytology is recommended. In one study involving patients with supracarinal cancer, endoluminal tumor mass, protrusion of the posterior tracheal wall, and signs of mucosal invasion were visible in 5.9%, 28.6%, and 4.1% of bronchoscopic examinations, respectively. However, in only 8.6% of 220 bronchoscopic examinations was cancer invasion proved by biopsy or cytology. Bronchoscopy excluded 18.1% of otherwise potentially operable patients from surgery because of airway invasion, with an overall accuracy of 93.3%.[39]

Bronchoscopic ultrasound has been investigated as a staging tool. The diagnosis of tracheobronchial invasion was based on an interruption in the most external hyper-

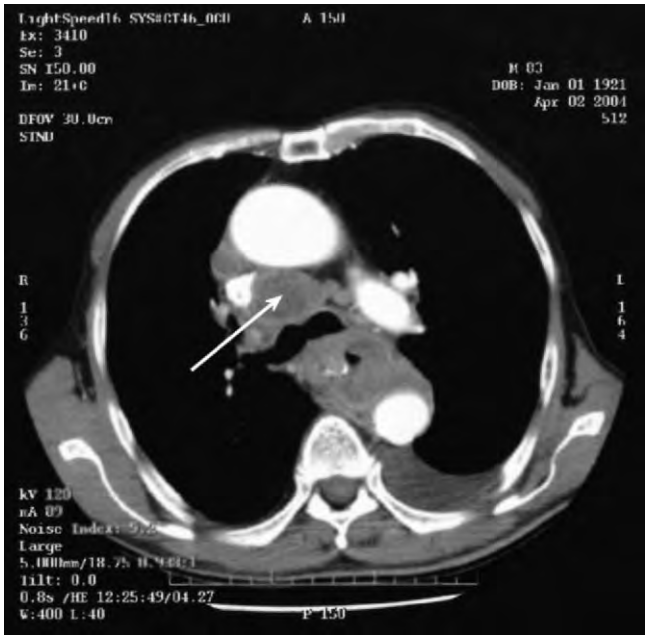

Figure 33–7. Computed tomography scan showing a midthoracic esophageal cancer with suspicious aortic infiltration, as well as a large precarinal lymph node *(arrow).*

echoic layer of the tracheobronchus (corresponding to its adventitia). In one study, of 26 patients determined to be invasion-free by bronchoscopic ultrasound, only 2 had invasion, as compared with 7 of 22 patients who had invasion after CT scans had suggested that they did not. The examination had no complication.[40] The technique, however, is not commonly performed.

Computed Tomography

The main value of CT in staging esophageal cancer lies in its ability to detect distant disease, such as in the liver, lungs, bone, and kidneys. When a metastasis to the liver is larger than 2 cm, the sensitivity of diagnosis is 70% to 80%, although it drops to approximately 50% when it is less than 1 cm.[41] With adenocarcinoma of the gastroesophageal junction and gastric cardia, peritoneal metastases are more likely than with squamous cell cancer of the tubular esophagus. CT scanning is inferior to laparoscopy in detecting peritoneal metastases.[42] Solitary lung metastases are rare in patients with esophageal carcinoma[43] and, thus, when seen on CT, are more likely to be primary lung cancer or benign nodules and should be investigated as such.

CT cannot reliably distinguish the various T stages, and its use lies in the diagnosis of T4 disease (Fig. 33–7). One study showed that the sensitivity and specificity of CT in detecting T4 disease were 25% and 94%, respectively.[44] Obliteration of the fat plane between the esophagus and the aorta, trachea and bronchi, and pericardium is suggestive of invasion, but the paucity of fat in cachectic patients makes this criterion unreliable. Thickening or indentation of the normally flat membranous trachea and left main bronchus is also suggestive of invasion, but it should always be confirmed by bronchoscopic examination. When the area of contact between the esophagus and the aorta extends for more than 90 degree of the circumference, an 80% accuracy of infiltration was reported,[45] but this is by no means absolute and the accuracy is inferior to that of EUS.

The sensitivity of detecting mediastinal and abdominal nodal involvement is suboptimal with CT because only size alone can be used as a diagnostic criterion. Intrathoracic and abdominal nodes greater than 1 cm are enlarged, and supraclavicular nodes with a short axis greater than 0.5 cm and retrocrural nodes greater than 0.6 cm are pathologic.[46] However, normal-sized lymph nodes may contain metastatic deposits, and enlargement of lymph nodes may be due to reactive and inflammatory hyperplasia. Recent studies using high-resolution helical CT scanning have demonstrated sensitivities of 11% to 77% and specificities of 71% to 95% for the detection of regional nodal disease.[47,48] CT is relatively insensitive in detecting celiac axis lymphadenopathy. Experience with magnetic resonance imaging (MRI) has shown limitations similar to those of CT, especially with respect to the low detection rate of mediastinal lymph nodes.[49]

Percutaneous and Endoscopic Ultrasound

Percutaneous ultrasound has a specific role in diagnosing cervical lymph node involvement, especially for squamous cell cancer, because the incidence of lymph node metastases in the neck is high, given the more proximal location of the tumor. Although lymph nodes are abundant in the neck (more than 300 in a normal adult), normal nodes are difficult to visualize because they are isoechoic to the surrounding fat. Sonographic examination of cervical lymph nodes usually begins with visualization of the common carotid artery and internal jugular vein at the base of the neck. Axial scans, transverse to the vessels, are performed in a cephalad direction. Nodes are viewed in relation to the carotid and jugular vein. Level IV, III, and II nodes are sequentially visualized anterior to and level V posterior to the vessels. Adenopathy can be a result of underlying inflammation in up to 50% of cases, whereas 20% to 40% of normal-sized nodes may harbor metastases; thus ultrasound-guided FNA is essential.

In a large study involving 519 patients, cervical lymph node metastasis was detected in 30.8% of patients (160/519). The sensitivity, specificity, and accuracy of ultrasound diagnosis in patients who underwent subsequent cervical lymphadenectomy were 74.5%, 94.1%, and 87.6%, respectively. In those who did not undergo neck dissection, the chance of cervical nodal recurrence was low at less than 5%.[50]

EUS is the only imaging modality able to distinguish the various layers of the esophageal wall, usually seen as five alternating hyperechoic and hypoecheoic layers (Fig. 33–8). Three general types of echoendoscopes can be used for staging: (1) a radial scanning endoscope, which provides a 360-degree view of the esophageal wall and surrounding tissues; it can operate at 5 to 20 MHz;

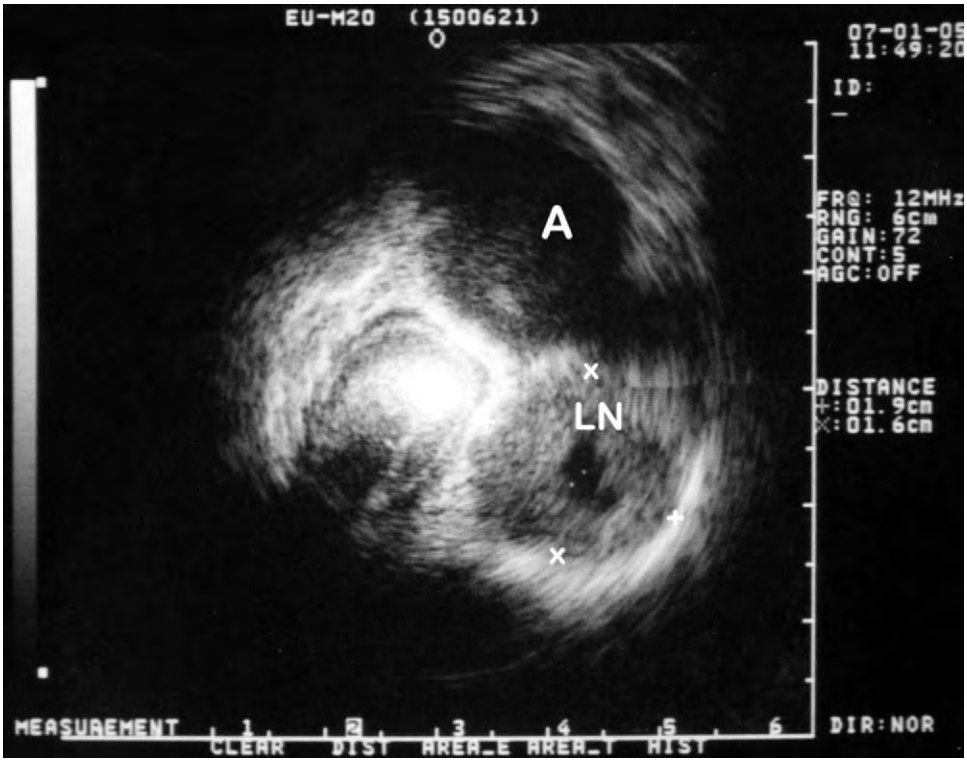

Figure 33–8. Endoscopic ultrasound image with a 12-MHz miniprobe placed at the gastroesophageal junction showing the aorta (A) and a large 2-cm adjacent lymph node (LN) with central necrosis. (Courtesy of K. E. Kwok, The University of Hong Kong.)

(2) EUS miniprobes, which can be passed through the accessory channel of the endoscope and provide 360-degree imaging at 12, 20, and 30 MHz; the high-frequency probes provide excellent resolution of the esophageal wall but have limited penetration and are best used for imaging superficial cancers; and (3) curved linear-array transducer endoscopes, which are primarily used for ultrasound guidance during FNA procedures such as sampling of the celiac lymph nodes; the lack of a 360-degree view makes it less user-friendly for T staging. The resolution and depth of penetration vary with the frequency of the ultrasound: at a frequency of 7.5 MHz, the depth of penetration is 9 cm with a resolution of 0.2 mm; the corresponding figures are 3 cm and 0.1 mm for 12 MHz.

The accuracy of EUS in locoregional staging is not questioned. The accuracy of EUS in T and N staging averages 85% and 75% versus 58% and 54% for CT.[51] Sensitivity and specificity tend to vary by T stage, with improved sensitivity as the T stage increases. In one series, the sensitivity was 58% for less than T2, 59% for T2, and 91% for greater than T2 disease.[52] A review of the literature shows variation in accuracy for T stage, as follows: 75% to 82% for T1, 64% to 82% for T2, 89% to 94% for T3, and 88% to 100% for T4.[53] One main limitation of EUS is an inability to pass the endoscope through the tumor stricture, which occurs in about a third of patients.[53-56] Although earlier studies suggested that dilatation would result in up to a 25% chance of perforation without much gain in diagnostic information,[35,37] more recent results show that dilatation can be performed safely, with the success rate of complete examination depending on the extent of dilatation: 36% for 11 to 12.8 mm and 87% for 14 to 16 mm.[57] An alternative is to use miniprobes; with a 6-French, 12.5-MHz miniprobe, overall accuracy in assessment of tumor infiltration depth and nodal disease is 90% and 78%, respectively.[58]

The use of higher-frequency echo-ultrasound allows fine distinction of early mucosal and submucosal esophageal cancer into intraepithelial cancer (m1), tumor involving the lamina propria (m2), tumor penetrating the lamina muscularis mucosae (m3), and various degree of submucosal infiltration (sm1 to sm3). The diagnostic accuracy was 80% when the muscularis mucosae was seen.[59] Such information is of particular importance when endoscopic mucosal resection is a treatment option for early cancer or for the detection of submucosal invasion, high-grade dysplasia, or carcinoma in situ in Barrett's esophagus.[60]

Ultrasonographic features of lymph nodes that suggest malignant involvement include echo-poor (hypoechoic) structure, sharply demarcated borders, rounded contour, and size greater than 10 mm, in increasing order of importance.[61] The four features just described, when each is present alone, may be inaccurate in diagnosing metastatic lymph nodes, but when all four are present, the accuracy reaches 80%. However, one study showed that all four features were present in only 25% of malignant nodes.[62] A collective review showed that the overall accuracy of staging nodal disease was 77%.[51]

Accuracy may differ for different lymph node locations. Its sensitivity is highest for the cervical and upper thoracic paraesophageal, infracarinal, left paratracheal, and recurrent laryngeal nodes. It is best with the para-

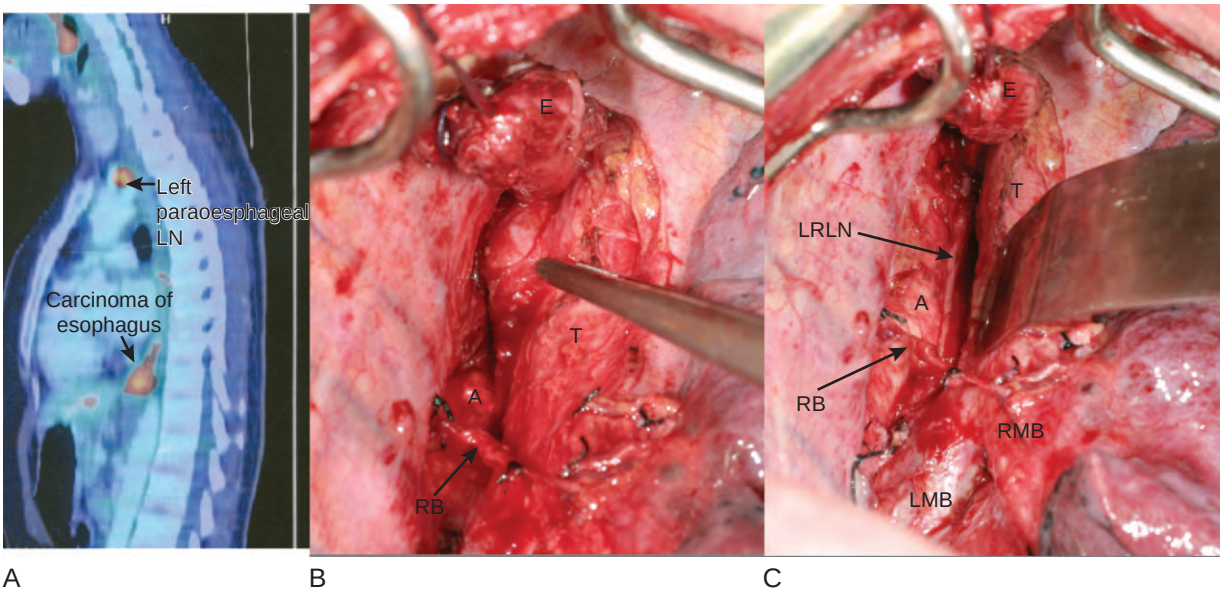

Figure 33–9. **A,** Positron emission tomography scan showing a patient with a lower esophageal tumor and a metastatic lymph node (LN) in the superior mediastinum. **B,** Operative photograph showing the lymph node identified in the left paratracheal area on the left recurrent laryngeal nerve. The forceps are pointing at the enlarged lymph node. A, aortic arch; E, esophageal stump; RB, right bronchial artery; T, trachea. **C,** Operative photograph showing the mediastinum after resection of the lymph node and mediastinal dissection. A, aortic arch; E, esophageal stump; LMB, left main bronchus; LRLN, left recurrent laryngeal nerve; RB, right bronchial artery; RMB, right main bronchus; T, trachea.

esophageal nodes and varies inversely with the axial distance of the nodes from the esophageal axis[63]; this is obviously related to the limited depth of penetration of EUS.

The availability of EUS-guided FNA increases the diagnostic accuracy of staging nodal disease because actual cytologic examination can be added to mere descriptive features (size, shape, border, and internal echo pattern). EUS-FNA is not ideal for detecting lymph nodes when the path of the needle may traverse through the primary tumor, in which case contamination by the primary tumor can lead to false-positive results. However, it is mostly distant nodes that are of importance, such as the celiac lymph nodes, for which even helical CT scanning is suboptimal in discerning.[44] EUS is better in identifying the celiac nodes, and EUS-guided FNA can help confirm the diagnosis. In a large series of 102 patients, the sensitivity of EUS in detecting celiac lymph nodes was 77%; specificity, 85%; NPV, 71%; and PPV, 89%.[64] In another report, when EUS-FNA was compared with CT, of 20 patients who satisfied the criteria for EUS-guided FNA directed toward the celiac nodes, 18 (90%) were positive for malignancy. CT was able to detect only 6 (30%) of the 20 cases of suspicious celiac lymph nodes, 5 (83%) of which were positive for malignancy by FNA.[65]

Combining cervical ultrasound and EUS can be highly accurate. In 329 patients who underwent esophagectomy, one-to-one comparisons between preoperative ultrasound, EUS, and histologic diagnosis were performed. The accuracy of combined ultrasound was 80.2% for regional lymph nodes, 91.5% for distant lymph nodes, and 74.4% in overall stage groupings. When the number of metastatic nodes was classified into subdivisions of 0, 1 to 3, 4 to 7, and ≥8, accuracy rates were 83.8%, 59.7%, 43.3%, and 96%, respectively. More importantly, the preoperative combined ultrasound separation into the number of involved lymph node showed prognostic stratification close to the histologic diagnosis.[66] This type of examination of both the location and number of nodes with one-to-one comparisons with histologic findings does require experience and meticulous attention to detail, and such expertise may not be widely available.

FDG-PET Scans

The main limitations of CT in esophageal cancer staging are its insensitivity in diagnosing unresectability (T4 disease) and its inability to identify metastases in normal-sized lymph nodes. FDG-PET scans, by using the differential glucose metabolism of cancer, provide a functional assessment of lymph nodes even though they are not enlarged. PET scanning is gaining popularity in esophageal cancer staging,[67,68] and as more data have accumulated, the role of PET scanning is becoming clearer (Fig. 33–9).

For detection of a primary tumor, the sensitivity of PET ranges from 78% to 95%, with most false-negative tests occurring in patients with T1 or small T2 tumors,[47,69] thus suggesting limitations in spatial resolution of the PET imaging device, currently around 5 to 8 mm, as the cause of nonvisualization. Adenocarcinomas of the gas-

troesophageal junction and proximal part of the stomach sometimes show limited or absent FDG accumulation, regardless of tumor volume (FDG nonavidity). Some investigators have observed this phenomenon in as many as 20% of these patients, which seems to be related to the diffusely growing subtype and poorly differentiated tumors.[70]

PET does not provide enough definition of the esophageal wall and thus has no value in T staging. For locoregional nodal metastases, its spatial resolution is also insufficient to separate the primary tumor from juxtatumoral lymph nodes because of interference from the primary tumor, and thus most studies demonstrate poor sensitivity.[69,71] This is especially true for nodes in the middle and lower mediastinum, where most primary tumors are found. In one study, the sensitivity of PET for detecting cervical, upper thoracic, and abdominal nodes was 78%, 82%, and 60% respectively, but it was only 38% and 0%, respectively, for the mid and lower mediastinum.[47] The specificity of PET in detecting regional nodes is usually much better, with specificities of 95% to 100% reported.[69,71] The low rate of false-positive findings is important in preoperative staging.

The main utility of PET scanning seems to lie in its ability to detect distant metastases. Luketich and colleagues reported 69% sensitivity, 93.4% specificity, and 84% accuracy in detecting metastases with PET as compared with 46.1% sensitivity, 73.8% specificity, and 63% accuracy with CT.[68] Similar results were shown by others.[70]

A recent meta-analysis of 12 publications on the use of PET in esophageal cancer showed that the pooled sensitivity and specificity for the detection of locoregional metastases were 0.51 (95% confidence interval [CI], 0.34 to 0.69) and 0.84 (95% CI, 0.76 to 0.91), respectively. The PPV and NPV were 0.60 and 0.46, respectively. For distant metastases, the pooled sensitivity and specificity were 0.67 (95% CI, 0.58 to 0.76) and 0.97 (95% CI, 0.90 to 1.0), respectively. The corresponding PPV and NPV were 0.92 and 0.83. When 2 studies (out of 11) that had particularly low sensitivities for the detection of distant metastases were excluded (probably because they included more early tumors), the pooled sensitivity improved to 0.72 and the specificity to 0.95.[72] Specifically for the celiac nodes, the sensitivity, specificity, PPV, and NPV ranged from 53% to 98%, 77% to 100%, 79% to 100%, and 82% to 100%, respectively. This study highlights that the accuracy of PET in detecting locoregional nodes is only moderate. EUS-FNA may be better in this regard. PET is, however, more useful for picking up distant nodal and visceral metastases. Its specificity is especially high.

The diagnostic yield of PET for the detection of unsuspected metastases in early-stage disease (Tis, T1) may be low because the chance of lymph node metastases increases with increasing T stage. Cost-effectiveness in this setting is uncertain. It seems that PET should be performed in patients in whom standard staging methods (CT and EUS) demonstrate no distant metastatic disease. In such cases, PET may improve the detection of metastatic disease and thus change the management strategy.

Thoracoscopy and Laparoscopy

Thoracoscopy and laparoscopy have their advocates. Thoracoscopic staging usually involves a right-sided approach, with opening of the mediastinal pleura from below the subclavian vessels to the inferior pulmonary vein; lymph node sampling is then performed. Sometimes left-sided thoracoscopy is also performed to sample lymph nodes at the aortopulmonary window. Laparoscopic staging can include celiac lymph node biopsy, collection of peritoneal fluid for cytologic examination, and the use of laparoscopic ultrasound for detecting liver metastases. In a study of 53 patients whose staging included conventional CT and EUS, minimally invasive staging reassigned a lower stage in 10 patients and a more advanced stage in 7 patients (32.1%).[73] The multiinstitutional study CALGB 9380 (Cancer and Leukemia Group B) reported on combined thoracoscopic and laparoscopic staging in 113 patients; the strategy was feasible in 73% of patients. Thoracoscopy and laparoscopy identified nodes or metastatic disease missed by CT in 50% of patients, by MRI in 40%, and by EUS in 30%. Although no deaths or major complications occurred, it did involve general anesthesia, one-lung anesthesia, a median operating time of 210 minutes, and a hospital stay of 3 days.[74]

The chance of metastases in the abdomen is considerably greater with adenocarcinoma of the lower esophagus and gastric cardia than with squamous cell cancer of the esophagus. Laparoscopy can be of use in diagnosing abdominal metastases such as peritoneal secondaries or identifying unsuspected cirrhosis, which is a relative contraindication to surgical resection for some investigators. Its value is minimal for more proximally located tumors.[75]

One recent study looked at the cost-effectiveness of different combinations of staging methods, including CT, EUS, PET, and thoracoscopy and laparoscopy. Although PET plus EUS-FNA was the most accurate staging combination, it was more expensive than CT plus EUS-FNA. Even though thoracoscopy and laparoscopy could identify some additional patients with advanced disease, the yield was small.[76] The study suggests that initial PET staging is indicated, and if no metastatic disease is identified, EUS with or without FNA should be performed. The limitations of these models include the selected patient population studied and assumptions regarding how patients with certain disease stages are treated. The controversies of M1a versus M1b disease and the significance of celiac node involvement have already been discussed. Given that PET scanning is still not widely available, it seems that CT and EUS should be the initial staging modalities, with PET indicated especially for patients found to have locally advanced tumor with no distant metastases. The invasiveness and cost of thoracoscopy and laparoscopy and the constantly improving noninvasive methods such as PET scanning make the use of minimally invasive staging less attractive. It should be reserved for patients in whom positive confirmation of metastatic disease not otherwise obtained is essential in deciding on treatment.

Therapy Monitoring

After nonsurgical treatment or neoadjuvant therapy, reassessment of tumor stage is unreliable because it is difficult to distinguish fibrosis, inflammation, and true histologic response. Often, epithelialization occurs despite residual tumor present in the wall of the esophagus. Biopsy of the mucosa will result in a false complete response. Neither CT nor EUS is accurate with regard to assessing response. EUS was only 27% to 48% and 38% to 71% accurate in assessing T stage and N stage, respectively.[77,78] In a study involving the use of CT scans, CT after chemoradiotherapy accurately staged the T classification in only 42%, over-staged 36% of patients, and under-staged 20%. CT had a sensitivity of 65%, a specificity of 33%, a PPV of 58%, and an NPV of 41% in evaluating the pathologic tumor response.[79]

Metabolic imaging with PET scanning holds promise. Brücher and colleagues reported PET after chemoradiation in patients with locally advanced squamous cell cancer.[80] Twenty-seven patients were assessed before and after chemoradiation. Responders were defined as having histologic findings of a complete response or 10% or less viable cells in the surgical specimen. In responders, FDG uptake decreased by 72%, whereas in nonresponders, it was reduced by 42%. A receiver operating characteristics analysis indicated that at a threshold of a 52% decrease in FDG uptake, the sensitivity in detecting a response was 100%, with a corresponding specificity of 55%. The PPV and NPV were 72% and 100%. These data imply that PET is excellent in identifying nonresponders. Nonresponders also had significantly worse survival after resection than responders did.

Flamens and colleagues also demonstrated the value of PET for evaluation of response. PET responders were defined as patients with complete or almost complete normalization of FDG uptake at the primary tumor site, together with complete normalization of all lymph node metastases seen on PET before chemoradiation. Serial PET had a predictive accuracy of 78% for a major response, with a sensitivity of 71% and a specificity of 82%.[81] False negativity (overestimation of response) is due to residual micrometastatic cancer foci falling below the detection threshold; thus, the sensitivity and PPV of a completely normal postinduction PET scan for the diagnosis of a complete pathologic response were only 67% and 50%, respectively. False positivity (underestimation of response) usually occurs at the primary tumor site, where inflammatory reactions may increase FDG uptake.

A recent comparative study using PET, CT, and EUS for the identification of pathologic responders after neoadjuvant therapy also showed that PET is more accurate for the prediction of response and survival than CT and EUS are. A postchemoradiation PET standard uptake value (SUV) of 4 or greater had the highest accuracy for pathologic response (76%). The inability to detect a complete histologic response, however, was again evident.[82]

Taking the potential use of PET further, it has been investigated as a means of predicting response early in the course of multimodal treatment. Weber and colleagues studied 40 patients with adenocarcinoma of the lower esophagus and gastric cardia (type I and II tumors). All patients had T3-4 Nx M0 disease. Chemotherapy was given, and PET was performed before and 14 days into treatment. Clinical response was assessed by a 50% or greater reduction in tumor length and wall thickness, and in those who underwent resection, histopathologic major response was also assessed. The reduction in tumor FDG uptake after 14 days of therapy was significantly different between responding (−54% ± 17%) and nonresponding tumors (−15% ± 21%). Optimal differentiation was achieved with a cutoff value of a 35% reduction in initial FDG uptake. Applying this cutoff value as a criterion for a metabolic response predicted clinical response with a sensitivity and specificity of 93% (14 of 15 patients) and 95% (21 of 22), respectively. Histopathologically complete or subtotal tumor regression was achieved in 53% (8 of 15) of the patients with a metabolic response but in only 5% (1 of 22) of those without a metabolic response. Patients without a metabolic response were also characterized by significantly shorter time to progression/recurrence and shorter overall survival.[83]

In a similar study by the same group, 38 patients with squamous cell cancer of the esophagus of stage cT3 cN0/+ cM0 were treated by chemoradiation. Patients underwent PET before therapy ($n = 38$), 2 weeks after initiation of therapy ($n = 27$), and preoperatively (3 to 4 weeks after chemoradiotherapy; $n = 38$). In histopathologic responders (<10% viable cells in the resected specimen), the decrease in SUV from baseline to day 14 was 44% ± 15%, whereas it was only 21% ± 14% in nonresponders ($P = .0055$). Metabolic changes at this time point were also correlated with patient survival ($P = .011$). The two studies described showed that changes in tumor metabolic activity after 14 days of preoperative treatment significantly correlated with tumor response and patient survival. PET might be used to identify nonresponders early during neoadjuvant treatment, thereby allowing for early modifications of the protocol. Thus, further cost and morbidity can be avoided in patients with little chance of a positive response.[84]

STAGE-DIRECTED THERAPY

The information derived from the staging methods described is useful only if a stage-directed therapy strategy is used. From the foregoing discussions, it seems clear that although the current stage segregation into stage I to IV has prognostic significance, further refinement is much needed. The separation of M1a and M1b, the significance of celiac or cervical lymph nodes, and the redefinitions of nodal disease are obvious controversies. Staging methods have improved accuracies, but the current techniques are unreliable in providing the precise number and location of nodal metastases. As a consequence, some surgeons even regard lymph node status (especially locoregional ones) as unimportant for deciding whether a primary resection should be

performed because it cannot be predicted with sufficient accuracy preoperatively and, furthermore, regional nodes are resected routinely during esophagectomy.[85]

The assumption of benefit from stage-directed therapy is intuitive and reasonable and is obviously true for extreme cases such as T1a disease versus stage IV disease with visceral metastases. The finer distinction of patients into intermediate stages is difficult. It is even more controversial to consider the many options and combinations of treatments for each stage of disease, for which more studies are required to provide convincing evidence. Accurate staging is the prerequisite of quality control in clinical trials.

There is no doubt that staging methods will further improve and refinement of stage classification will evolve. As molecular techniques are coming of age, molecular classification may eventually be incorporated into tumor staging systems as well. The challenge is to constantly modify our treatment strategies according to new knowledge gained to give the best results to our patients.

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Chapter

34

Carcinoma of the Esophagus and Gastroesophageal Junction

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Carcinoma of the esophagus and gastroesophageal junction (GEJ) remains one of the most difficult problems facing surgeons. Though relatively uncommon, these tumors are historically associated with a high mortality rate because of both the late stage of disease at initial evaluation and the many challenges associated with their treatment. Changes in the epidemiology of esophageal cancer have provided an opportunity for early detection, which together with the availability of new treatment modalities, has increased the number of patients who can be offered potentially curative surgical resection. At the same time, several controversies have arisen regarding the optimal treatment strategy. A number of new unproven therapeutic approaches have been advocated for patients with early cancer, such as mucosal ablation[1,2] and endoscopic mucosal resection.[3] For patients with more advanced-stage tumors, neoadjuvant chemoradiotherapy has been broadly applied despite the lack of clear evidence of benefit.[4-9] In some centers, the need for surgical resection at all has been questioned, with definitive chemoradiotherapy being offered instead. When surgery is performed, controversy persists regarding the extent of resection necessary,[10-14] and much of the debate has centered on the benefits of systematic lymph node dissection. This chapter reviews the current approach to the diagnosis and management of esophageal cancer, with an emphasis on improvements in clinical and pathologic staging. When combined with a better understanding of the natural history of disease, a logical and tailored treatment plan can be developed.

HISTORY

The history of surgery in the management of esophageal cancer is largely limited to the past century. Although tumors of the esophagus were recognized as early as the 12th century, attempts at surgical resection were not recorded until the late 19th century. The early experience was limited to resection of cervical esophageal cancer because of the risk for fatal pneumothorax associated with operations in the chest. After advancements in surgical and anesthetic techniques, most notably the availability of intratracheal administration of anesthetic gases, the first successful resection of an intrathoracic esophageal cancer was performed in the United States by Torek in 1913.[15] Gastrointestinal continuity was reestablished in this patient with the use of an extracorporeal tube. The first resection followed by reconstruction with esophagogastrostomy was performed in Japan by Ohsawa in 1932,[16] and it was popularized in the United States by Adams and Phemister at the University of Chicago in 1938.[17] Large series published in the mid-1940s detailed the risk associated with these early attempts at resection, with operative mortality rates as high as 60%.[18,19]

The history of radiation therapy for esophageal cancer is also relatively recent. First applied in the early 1920s, radiation therapy with crude delivery systems was associated with poor results and a high complication rate. In the latter half of the 20th century, the availability of more sophisticated equipment led to a rapid increase in the use of radiation therapy. At the same time, a variety of

chemotherapeutic agents became available, which have increasingly been used alone or in combination with radiation therapy or surgery. To date, none of these combinations of therapies have been convincingly demonstrated to be superior to surgical resection alone, although the use of combined-modality therapy continues to increase.

EPIDEMIOLOGY

Esophageal cancer is the sixth leading cause of cancer death in the world,[20] although it remains relatively uncommon in North America. The most recent data available from the Surveillance, Epidemiology and End Results program of the National Cancer Institute indicate that 14,250 new esophageal cancers were diagnosed in the United States in the year 2004,[21] which represents 1% of all cancers and approximately 6% of gastrointestinal malignancies. Despite its relative rarity, the death rate remains high,[22] with an estimated 13,300 deaths attributed to esophageal cancer annually. This figure represents 2.4% of all cancer mortality and 10% of all deaths from gastrointestinal malignancy. It is four times more common in men than women, and in the United States it is three times more common in black than in white individuals.[23]

A dramatic change has occurred in the epidemiology of esophageal cancer over the past 2 decades.[24] The incidence of adenocarcinoma has risen faster than that of any other malignancy, and as a result it has replaced squamous cell carcinoma as the most common esophageal malignancy in most Western countries.[25] Although squamous cell carcinoma remains the most common type of esophageal cancer around the globe, particularly in developing areas such as the Caspian littoral region of Iran, northern China, and South Africa, the incidence of squamous cell cancer has fallen in the United States from 31 to 19 per million population between 1975 and 2001. During this same period, the incidence of adenocarcinoma has increased nearly 600% to 23.3 per million in 2001.[26]

There are clear differences in the epidemiologic profiles of patients with squamous cell carcinoma and adenocarcinoma of the esophagus. Esophageal adenocarcinoma is more common in white males and is strongly associated with a history of chronic gastroesophageal reflux disease (GERD). It also tends to occur at a younger age. In contrast, squamous cell carcinoma is more common in minority populations, including Asian and black Americans, and is more strongly associated with tobacco and alcohol consumption.

ETIOLOGY

The cause of esophageal cancer is unknown, but several clearly defined risk factors and associated medical conditions have been identified (Table 34–1).

Squamous Cell Carcinoma

Tobacco and alcohol consumption are the most well recognized risk factors for squamous cell carcinoma of the esophagus. Case-control studies have shown that smoking is associated with a 2.3 to 15.5 relative risk for the development of squamous cell carcinoma, with regular consumption of alcohol bestowing a 2.5 to 19 relative risk. The effects of these agents appear to be synergistic.[27] Because these risk factors are associated with other aerodigestive malignancies, a patient with a history of previous lung or head and neck cancer carries an increased risk. The risk for a synchronous or metachronous esophageal cancer in a patient with a primary head and neck malignancy has been estimated to be between 3% and 9%.

Other conditions associated with chronic irritation of the esophagus that have been associated with an increased risk for squamous cell cancer of the esophagus include achalasia, caustic injury, and tylosis. Longstanding achalasia results in chronic stasis of food and saliva, which leads to fermentation and lowering of the pH of the esophagus to near gastric levels.[28] Over a period of 20 years or more such chronic irritation gives rise to the development of squamous cell carcinoma in approximately 5% to 10% of patients with achalasia.[29,30] Chronic irritation is also present in patients with a history of lye ingestion. Squamous cell carcinoma has been reported to occur in 1% to 5% of these individuals, usually 30 to 40 years after the episode of lye ingestion.[31,32] Irradiation of the esophagus has also been identified as a risk factor for squamous cell cancer of the esophagus, although the absolute risk appears to be small. Finally, tylosis (nonepidermolytic palmoplantar keratoderma), a rare, autosomal dominant disorder characterized by hyperkeratosis of the squamous epithelium of the palms and plantar surfaces of the feet, has been associated with an increased frequency of squamous cell carcinoma. Papillomas of the esophagus develop in these patients, and the risk for development of esophageal cancer has been estimated to be as high as 70%.[33]

Table 34–1 Risk Factors Associated with Esophageal Carcinoma

Squamous cell carcinoma	Tobacco use
	Alcohol consumption
	History of head and neck cancer
	Achalasia
	Caustic injury
	Tylosis
Adenocarcinoma	Chronic gastrointestinal reflux disease
	Obesity
	Diet deficient in fruits and vegetables
	Diet high in animal protein and cholesterol

Adenocarcinoma

The primary risk factor for esophageal adenocarcinoma is the presence of GERD. The best evidence of this relationship comes from a population-based study by Lagergren and associates.[34] Patients with reflux symptoms occurring more than three times a week had a 17-fold higher risk for adenocarcinoma, with a similarly increased risk in patients with higher reflux symptom scores and a duration of symptoms of more than 20 years. When combined, a patient with frequent severe reflux symptoms of prolonged duration had a nearly 44-fold higher risk for cancer. Other less well defined risk factors for esophageal adenocarcinoma include obesity and a diet deficient in fruits and vegetables. A diet rich in animal protein and cholesterol also appears to increase the risk for esophageal adenocarcinoma.[35,36]

Adenocarcinoma is unique among upper gastrointestinal malignancies in that a well-defined precursor lesion—Barrett's esophagus—has been identified. Barrett's esophagus is a condition associated with GERD in which there is a metaplastic transformation from the normal squamous epithelium in the distal esophagus to glandular epithelium with evidence of specialized intestinal metaplasia. It is a condition that was initially described in the late 1800s but has received heightened attention since the recognition by Hawe et al.[37] in 1973 that it was a precursor to the development of esophageal adenocarcinoma. Since then, the pathophysiologic mechanisms that lead to the development of Barrett's esophagus have been well defined. In addition, the histologic sequence of progression from reflux injury to cardiac metaplasia and reflux carditis, intestinal metaplasia, dysplasia, and ultimately, adenocarcinoma has been well described.[38] Recognition of this relationship between Barrett's esophagus (a known complication of GERD) and adenocarcinoma of the distal esophagus and GEJ has linked one of the most deadly malignancies known to humanity to the most common upper gastrointestinal disorder in Western civilization. Awareness of this relationship has resulted in another important recent change in the epidemiology of esophageal cancer—a documented increase in the number of esophageal cancers[39] detected at an early stage through early endoscopy in patients with reflux symptoms and the performance of surveillance endoscopy in those with Barrett's esophagus. The precise risk for the development of adenocarcinoma in patients with Barrett's esophagus is unknown, with recent estimates of 0.2% to 2.1% per year for patients without dysplasia, which translates into a lifetime risk for cancer that is 30 to 125 times greater than that of the general population.[40]

PATHOLOGY

The vast majority of esophageal neoplasms are malignant. Squamous cell carcinoma and adenocarcinoma account for over 90% of primary esophageal malignancies, with an assortment of other malignancies accounting for the remainder (Box 34–1). It has been estimated that metastatic lesions may actually outnumber primary esophageal malignancies, with metastatic melanoma, breast cancer, and lung cancer being the most common cell types.[41] Using autopsy data, Antler and associates[42] estimated that 4.5% of primary lung cancers had metastases to the esophagus that were not by direct extension. With more than 177,000 new lung cancers in 2004, this would amount to nearly 8000 patients with esophageal metastases from lung cancer alone, but most of these metastases are not clinically significant.

Box 34–1 Pathology of Esophageal Malignancies

- Squamous cell carcinoma
- Adenocarcinoma
- Leiomyosarcoma
- Melanoma
- Metastatic lesions

Squamous Cell Carcinoma

Grossly, squamous cell carcinoma usually appears as an exophytic lesion with a large fungating mass in the esophageal lumen, although a variant has been described that is manifested as an endophytic lesion with extensive submucosal spread and stricture formation. Multicentric tumors occur in 15% to 20% of cases. Whether they represent synchronous tumors or intramural metastases is controversial. Histologically, squamous cell cancers are composed of epithelial cells with characteristic intracellular bridges. Well-differentiated tumors have little nuclear pleomorphism and well-formed squamous pearls, whereas moderate to poorly differentiated tumors have considerable nuclear pleomorphism, and they may lack keratinization and intracellular bridges (Fig. 34–1).

Squamous cell cancers are distributed throughout the length of the esophagus. These tumors are located in the proximal third of the esophagus in 20% to 40%, the middle third in 50% to 60%, and the distal third in 10% to 20%. Tumors located in the proximal and middle thirds of the esophagus may involve the tracheobronchial tree by direct extension in up to 40%, with malignant tracheoesophageal fistula reported in 10% to 15%. In the confined space of the mediastinum, advanced proximal tumors may involve the recurrent laryngeal nerve, larynx, or thoracic duct. Middle third tumors can also invade the aorta and pericardium, whereas distal third tumors can involve the diaphragm, liver, and stomach.

Regional lymph node metastases are common in patients with squamous cell carcinoma, with the likelihood increasing as the tumor invades more deeply into the wall of the esophagus. For tumors confined to the mucosa, lymph node involvement is relatively rare (<5%), but with tumor invasion into the submucosa, node involvement is evident in 10% to 40% of patients.[43,44] The frequency of node involvement increases to 60% for tumors invading the muscularis

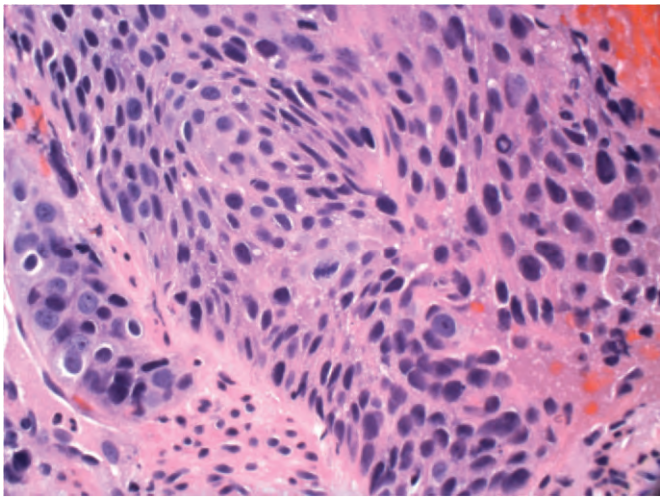

Figure 34–1. Photomicrograph of squamous cell carcinoma of the esophagus. (Courtesy of Dr. P. Chandrasoma, University of Southern California.)

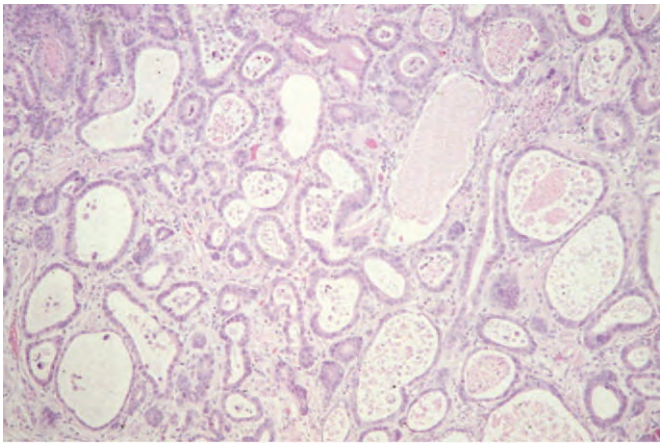

Figure 34–2. Photomicrograph of adenocarcinoma of the esophagus. (Courtesy of Dr. P. Chandrasoma, University of Southern California.)

propria and exceeds 80% in patients with transmural tumors.[45] The pattern of lymph node spread is not predictable because of the extensive lymphatic drainage system of the esophagus. Nodes far removed from the primary tumor may contain metastases, with abdominal lymph node involvement reported in up to 40% of patients with upper third tumors and a similar rate of cervical node involvement in patients with advanced tumors in the distal esophagus.[46]

Adenocarcinoma

Adenocarcinoma of the esophagus is most commonly manifested as a visible lesion grossly indistinguishable from the appearance of other types of tumors. They can be polypoid (5% to 10%), flat (10% to 15%), fungating (20% to 25%), or infiltrative (40% to 50%).[47] Upward of 40% to 60% of patients will have Barrett's mucosa identified in the resected esophagus, and it is believed that in the remainder Barrett's mucosa was present initially but was overgrown by the advancing tumor.[48] Histologically, these tumors are composed of irregularly shaped glands made up of cuboidal to columnar cells that infiltrate into the various layers of the esophageal wall. In the most poorly differentiated tumors, sheets of poorly formed glandular elements with signet ring cells can be found (Fig. 34–2).

The likelihood of lymph node spread in esophageal adenocarcinoma also depends on the depth of tumor invasion. The risk for node metastases is approximately 5% when the tumor is confined to the mucosa and 30% to 50% when it invades the submucosa.[49] Once the tumor penetrates the muscularis propria, more than 80% have at least one involved node.[50] The pattern of node dissemination is also not predictable, although involvement of the cervical nodes appears to be less frequent than in patients with distal esophageal squamous cell cancer.

CLINICAL FEATURES

Esophageal cancer is typically initially detected in the sixth or seventh decade of life. Although dysphagia remains the most common initial symptom, heightened awareness of the relationship between reflux and esophageal adenocarcinoma has resulted in early diagnosis before the onset of dysphagia in an increasing number of patients. The reasons for evaluation in a consecutive series of 263 patients with esophageal adenocarcinoma are listed in Table 34–2.[51] Of note, more than half these patients had their cancer diagnosed at the time of endoscopy performed for indications other than dysphagia. In a third, endoscopy was performed for worsening foregut symptoms or for surveillance of known Barrett's esophagus. Occult bleeding and patient request accounted for another 18%. As might be expected, the symptom of dysphagia was associated with the presence of an advanced-stage tumor, whereas patients with other indications for endoscopy were more likely to have early tumors.

Weight loss is common in patients with esophageal cancer, and it is often more profound than in other types of cancer because of the combined systemic effects of malignancy and the obstructive effects of the tumor itself. Chest pain and odynophagia are also common, particularly in patients with bulkier tumors. These symptoms may arise from spasms occurring above an obstructing tumor or from ulceration of the esophagus. Ulceration of the tumor can also result in hematemesis, melena, or anemia. Less commonly, chest pain and odynophagia may arise from direct tumor extension into adjacent mediastinal structures. More advanced tumors may cause symptoms of hoarseness as a result of invasion of the recurrent laryngeal nerve, cough secondary to invasion of the airway, and aspiration pneumonia as a result of a malignant tracheoesophageal fistula.

Table 34–2 Comparison of Indication for Endoscopy and Pathologic Tumor Stage

Reason for Endoscopy:	*N*	Stage I (*n* = 97)	Stage II-IV (*n* = 166)	*P* Value
Dysphagia	129	20 (21)	109 (66)	<.0001
Barrett's surveillance	44	38 (39)	6 (4)	<.0001
Worsening of foregut symptoms	42	18 (19)	24 (14)	.39
Occult bleeding	32	12 (12)	20 (12)	1.0
Patient request	16	9 (9)	7 (4)	.11

Data are expressed as numbers of patients (%).

DIAGNOSIS

The diagnosis of esophageal cancer should be considered in any patient who complains of dysphagia. Evaluation should begin with a careful history and physical examination, followed by laboratory investigations, appropriate radiographic studies, and upper gastrointestinal endoscopy. The possibility of metastatic spread should be considered in a patient with profound weight loss or bone pain. Respiratory symptoms such as hoarseness, cough, or a history of aspiration pneumonia may indicate the presence of local tumor extension into adjacent mediastinal structures, which may preclude attempts at resection. Palpable cervical or supraclavicular adenopathy or a palpable nodular liver may indicate the presence of metastases. The history and physical examination should also focus on the patient's cardiopulmonary and nutritional status to anticipate the need for further preoperative functional assessment and nutritional supplementation.

Laboratory investigations should include a complete blood count because of the possibility of ulceration and bleeding. Liver function tests and measurement of the serum alkaline phosphatase level should also be performed to screen for metastatic disease to the liver or bone. In addition, the carcinoembryonic antigen (CEA) level should be measured in patients with adenocarcinoma. Though not diagnostic of esophageal adenocarcinoma, when elevated the CEA level can be useful in monitoring the results of therapy and the development of recurrence.[52]

EVALUATION

Chest Radiography

Chest radiography may be abnormal in as many as 50% of patients with locally advanced esophageal cancer, although the findings are generally nonspecific. An air-fluid level may be evident in patients with total or nearly total obstruction. Locoregionally advanced disease may also be evident by the presence of a soft tissue mass or bulky mediastinal adenopathy. In addition, a chest radiograph may reveal the presence of lung metastases or a pleural effusion.

Barium Esophagography

A contrast esophagogram provides useful information regarding the location of the tumor and an indication of the length of the primary tumor. The usual appearance of a lower third esophageal cancer is shown in Figure 34–3. The esophagogram typically reveals an irregular mucosal abnormality with dilatation of the proximal esophagus. By themselves, however, these findings are not diagnostic of cancer because benign strictures and esophageal dilatation in achalasia can have a similar appearance. Occasionally, a fistulous tract involving the tracheobronchial tree can be identified.

Upper Gastrointestinal Endoscopy

Evaluation of patients suspected of having esophageal cancer should always include endoscopy. In patients with dysphagia, the tumor is easily recognizable as a friable exophytic mass that is often ulcerated. Earlier-stage tumors may be more difficult to recognize, and biopsy should be performed on any abnormal-appearing mucosa. Careful attention should be paid to the possibility of synchronous lesions, especially in patients with squamous cell carcinoma.

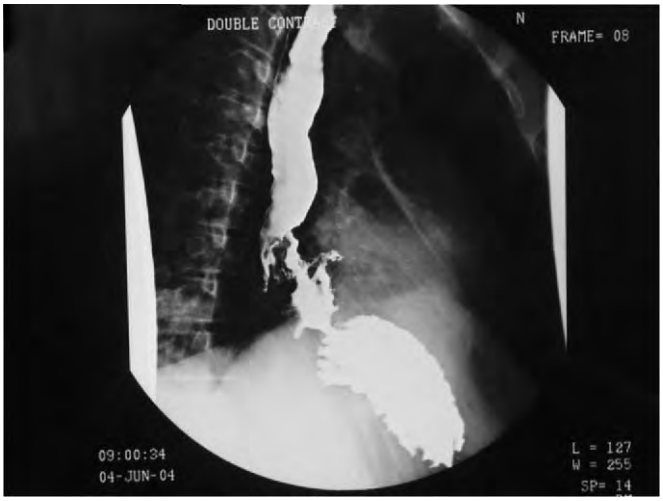

Figure 34–3. Esophagogram demonstrating a tumor at the gastroesophageal junction.

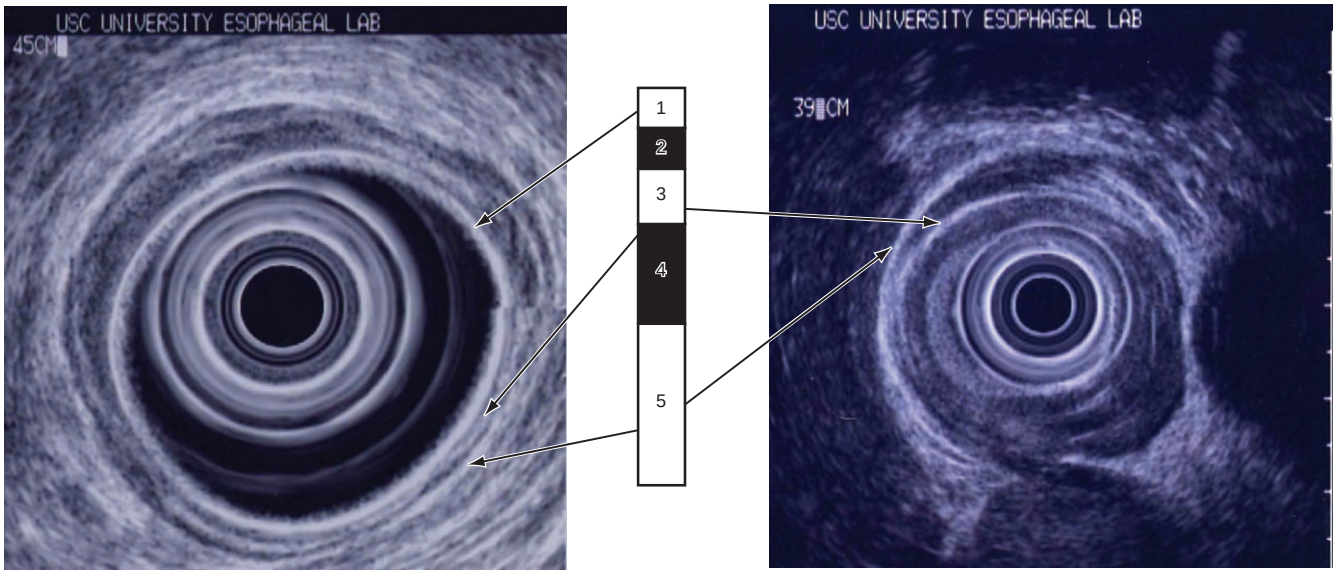

Figure 34–4. Endoscopic ultrasound appearance of a normal esophagus *(left)* and a T3 esophageal cancer *(right).* The layers of the esophagus appear as alternating white (hyperechoic) and black (hypoechoic) rings. The first hyperechoic layer represents the mucosa (epithelium and lamina propria). The first hypoechoic or black ring represents the muscularis mucosa. The third layer is hyperechoic and represents the submucosa. The fourth layer is hypoechoic and identifies the muscularis propria. The last layer is hyperechoic and identifies periesophageal tissue. The tumor seen at 4 o'clock shows disruption of the third and fifth layers.

The endoscopic length of the tumor can provide useful information regarding the likelihood of lymph node involvement or systemic spread, or both. Tumors less than 5.0 cm in length are more likely to be T1 or T2 tumors, whereas tumors longer than 5 cm are more likely to be T3 or greater.[53] Patients found to have a high-grade luminal stenosis that precludes passage of an adult endoscope likewise have a greater likelihood of locally advanced tumor invasion.[54] Eloubeidi et al.[55] have shown that tumor length is also predictive of survival in the absence of nodal disease, with longer tumors associated with poorer survival.

Measurement of the distance between the tumor and the incisors provides useful information for treatment planning. The relationship between the tumor mass and important structures such as the cricopharyngeus, aortic arch, left main bronchus, and diaphragm can be determined. When the endoscope can be passed beyond the tumor, the stomach and duodenum should be examined. This evaluation should include a retroflexion maneuver to assess the fundus and cardia region of the stomach, which can be involved in a patient with a distal third cancer.

The diagnosis of esophageal cancer is usually made on the basis of biopsy samples obtained at the time of flexible endoscopy. The use of jumbo biopsy forceps increases the accuracy of endoscopic biopsy, but biopsy can be negative even when carefully performed, especially in patients with a tight stenosis. In these patients, careful dilatation before biopsy and brush cytology will usually establish the diagnosis. In a malnourished patient, consideration should be given to placement of a percutaneous gastrostomy tube at the time of endoscopy.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is the best diagnostic tool available to assess the locoregional extent of disease. Introduced in the 1980s in Japan and the Netherlands for squamous cell carcinoma of the esophagus, it has recently grown in popularity in the United States for staging esophageal adenocarcinoma. The depth of tumor penetration of the esophageal wall and the presence of lymph node involvement can be assessed with an ultrasound probe attached to the tip of a flexible endoscope. The standard EUS probe uses ultrasound frequencies between 7.5 and 12 MHz. The typical appearance of a normal esophageal wall and the appearance of an invasive cancer are shown in Figure 34–4. Esophageal cancer appears as an irregular hypoechoic area of disruption of the normal esophageal wall architecture. Lymph nodes are categorized into three groups based on their appearance on EUS. Type 1 lymph nodes are poorly defined with diffuse homogeneous ultrasound echoes. These nodes are considered benign. Type 2 lymph nodes appear as well-defined structures with weak, relatively sonolucent echoes. Type 3 lymph nodes appear as well-defined structures with strong internal echoes and notching. Type 2 and 3 lymph nodes are considered malignant.

The accuracy of EUS in staging esophageal cancer has recently been reviewed.[56] EUS is 75% to 82% accurate in detecting T1 tumors, 64% to 85% accurate for T2 tumors, and 87% to 94% accurate for T3 disease. The accuracy of detecting invasion of adjacent structures approaches 100%. EUS is less accurate in assessing the depth of invasion for earlier-stage tumors because of difficulty distinguishing between intramucosal (T1a) and

submucosal (T1b) invasion. This issue is of great importance inasmuch as alternatives to standard esophageal resection are increasingly being advocated, especially for patients with disease limited to the mucosa. In this setting, EUS has an accuracy of less than 20%.[57] It has been suggested that the use of higher-frequency ultrasound probes may increase the diagnostic accuracy of EUS in earlier-stage disease, but at present data are limited.[58,59] Endoscopic mucosal resection (EMR) may be a useful adjunct in staging these patients. Small mucosal abnormalities can be excised in their entirety via EMR so that a larger piece of tissue can be obtained for histologic evaluation to determine tumor depth. This approach has been shown to accurately predict tumor depth in all patients in a small series of patients who underwent EMR followed by esophagectomy.[60]

When locoregional nodes are assessed by EUS before esophagectomy and lymphadenectomy, the accuracy of identifying a malignant node ranges from 70% to 85%. The sensitivity of EUS in detecting node involvement ranges from 80% to 89%, but the specificity is only 50% to 75%. Fine-needle aspiration biopsy may improve these results. Given the relatively high false-positive rate of EUS assessment of lymph node involvement, caution should be exercised in basing important treatment decisions on the results of EUS.

Bronchoscopy

Bronchoscopic evaluation is mandatory for any patient with symptoms suggestive of airway invasion, such as cough or aspiration. In addition, all patients with a tumor located in proximity to the airway should undergo bronchoscopy. Bulky tumors in this location commonly cause a bulge in the membranous trachea or bronchus, although this finding does not always indicate invasion of the wall of the airway. Airway invasion should be suspected when the mucosa of the tracheobronchial tree is edematous or if it bleeds easily when contacted. Fixation of the mucosa on rigid bronchoscopy usually indicates invasion. Biopsy specimens should be obtained in this setting.

Computed Tomography of the Chest and Abdomen

Computed tomography (CT) remains a useful radiographic tool for evaluating a patient with esophageal cancer. It not only provides important information regarding the size of the primary tumor and the status of the mediastinal lymph nodes but also allows for assessment of the lungs, liver, and adrenal glands for metastases. The thickness of the tumor and its length can be estimated by CT. The normal esophageal wall is rarely more than 5 mm, and an asymmetric, thickened esophagus can be identified on CT in more than two thirds of patients with esophageal cancer.[61] However, the depth of invasion cannot be determined as accurately with CT as with EUS. Tumor depth is accurately predicted in only 30% to 50% in most series with a sensitivity of 43% to 73% and a specificity of only 15% to 52%.[62] CT is generally better at distinguishing T4 from earlier-stage tumors. With the use of criteria such as obliteration of fat planes, thickening of adjacent tissue, and greater than 90 degrees of contact, direct invasion to an adjacent organ can be identified. Tracheobronchial invasion can be identified accurately in more than 85%, and aortic wall invasion can be detected in more than 80%. It has also been reported that performance of a CT scan in the prone position may enhance the accuracy of CT staging.[63] However, caution should still be exercised in precluding surgical resection based on radiologic criteria alone.

Computerized axial tomography is generally considered to be less accurate in determining lymph node involvement than other modalities such as EUS. Although many authors consider lymph nodes greater than 1 cm in size to be malignant, the actual size of the lymph node does not always correlate with pathologic review. In patients assessed with CT and the results compared with findings on esophagectomy and lymphadenectomy specimens, the overall accuracy was 65%, with a sensitivity of 60% and a specificity of 74%.[64]

Assessment for Metastases

The need for routine diagnostic tests to search for asymptomatic metastatic disease remains controversial. Scintigraphic studies such as a liver-spleen scan or a bone scan are rarely useful because they are relatively insensitive and seldom positive in patients without symptoms of metastases. In addition, benign abnormalities that can mimic metastases on bone scan are present in many patients, thus leading to additional and often costly investigations.

The broad availability of positron emission tomography (PET) has led to an improved ability to detect otherwise occult metastatic disease and can result in an alteration in clinical staging in as many as 20% of patients with esophageal cancer.[65,66] In a recent series of consecutive patients with esophageal cancer undergoing PET scanning, 12% were found to have otherwise unsuspected metastases, including metastases to nonregional lymph nodes and to other distant sites. As with other staging modalities, false-positive results can occur with PET, and therefore confirmatory biopsy specimens should always be obtained.

PET can also be used to identify regional lymph node involvement. In studies comparing CT, EUS, and PET scanning, PET appears to be more accurate in nodal staging than CT is, but it may be less accurate than EUS.[64] In studies in which PET findings were compared with lymph node histology after esophagectomy with formal lymphadenectomy, the accuracy of PET scanning was lower.[67] The major limitation in PET scan detection of mediastinal nodal involvement relates to the intense hypermetabolism present in the primary tumor, which tends to obscure activity in nodes in close proximity to the tumor mass. These are, of course, the nodes most likely to be involved. In addition, there are size limitations in the identification of lymph nodes with PET scanning, with an increasing false-negative rate for nodes

smaller than 8 mm. The use of combined PET/CT appears to improve the accuracy of detecting node involvement, but false-positive and false-negative test results remain a problem.

Minimally Invasive Surgery for Staging Esophageal Cancer

Minimally invasive surgery using laparoscopy with or without thoracoscopy (MIS staging) has been proposed as an approach to staging esophageal cancer. The feasibility of this approach was recently evaluated in the Intergroup Trial CALGB 9380 (Cancer and Leukemia Group B).[68] In this trial, patients with esophageal carcinoma underwent comprehensive noninvasive staging with CT, EUS, and magnetic resonance imaging (MRI) and were then further staged with thoracoscopy and laparoscopy within 6 weeks of clinical staging. Overall, only 14% of patients had positive lymph nodes identified that were not detected by noninvasive testing. In addition, of the 13 patients identified as N0 on MIS staging, 3 (23%) had lymph node involvement at the time of resection, thus indicating that false-negative MIS staging may be quite common. The authors reported a median operating time of 210 minutes (40 to 865) and median length of stay of 3 days (1 to 35). No data on the complications or the ease or difficulty at the time of resection were reported. Although MIS staging may be feasible in as many as 73%, it does not appear to add much benefit over noninvasive testing, and the results do not appear to alter treatment in most patients. Many centers have abandoned MIS staging for these reasons and because of additional resource consumption.[69]

STAGING SYSTEM FOR ESOPHAGEAL CANCER

American Joint Committee on Cancer Staging System

Esophageal cancer is staged by using the tumor, nodal, and metastasis (TNM) system of categorization according to the American Joint Committee on Cancer (AJCC).[70] The goals of clinical staging are to determine the prognosis and allow selection of the most appropriate therapy. In the current staging system, the esophagus is divided into four regions. The cervical esophagus is defined as extending from the cricopharyngeus to the level of the thoracic inlet, which corresponds to a distance of approximately 18 cm from the incisors. The upper third of the thoracic esophagus is defined as extending from the thoracic inlet to the carina, which is located approximately 24 cm from the incisors. Middle third tumors are defined as those located between the carina and a point half the distance between the carina and the GEJ. The lower third of the esophagus extends from this point to the GEJ, located between 32 and 40 cm from the incisors.

Tumors are classified with the TNM system in accordance with the definitions listed in Table 34–3. T1 tumors invade into but not through the submucosa. These tumors are often subclassified as T1a and T1b for tumors limited to the lamina propria and submucosa, respectively, although this is not a component of the recognized staging system in use today. A tumor that invades into but not through the muscularis propria is designated a T2 lesion. Tumors that invade beyond the muscularis propria into the adjacent adventitia are classified as T3 tumors, whereas tumors that invade adjacent structures are classified as T4.

Lymph node status is classified according to the presence or absence of regional node involvement. Regional nodes are defined differently for tumors in different locations in the esophagus (Table 34–4). For tumors located in the cervical esophagus, the cervical, supraclavicular, and upper periesophageal lymph nodes are considered regional nodes. For tumors located in the GEJ, the periesophageal nodes below the azygos vein and the diaphragmatic, pericardial, left gastric, and celiac nodes are all considered to be regional nodes. The current staging system classifies involvement of any nonregional nodes as M1a disease. However, recent observations have questioned the validity of this practice, which has led to the suggestion that a category of N2 disease be added to better classify these tumors for prognostic purposes.

Combinations of TNM classifications are grouped into stages (Table 34–5). Stage 0 includes carcinoma in situ in the absence of node involvement or distant metastatic disease. Stage I tumors are limited to the lamina propria or submucosa in the absence of node involvement or distant metastases. T2 and T3 tumors without node involvement or distant metastases are classified as stage IIA. Tumors that are confined to the wall of the esophagus (i.e., T1 and T2 tumors) with regional node involvement are classified as stage IIB disease. Stage III includes T3 tumors with regional node involvement, as well as any

Table 34–3 TNM Descriptors

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria or submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the adventitia
T4	Tumor invades adjacent structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
Distant Metastases (M)	
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Table 34–4 Definitions of Regional and Nonregional Lymph Node Involvement by Tumor Location

Tumors of the Lower Thoracic Esophagus	
Regional lymph nodes	Nonregional lymph nodes (M1a)
Upper periesophageal nodes (above the azygos vein)	Celiac nodes
Subcarinal nodes	
Lower periesophageal nodes (below the azygos vein)	
Tumors of the Midthoracic Esophagus	
Regional lymph nodes	Nonregional lymph nodes (M1a)
Upper periesophageal nodes (above the azygos vein)	Not applicable
Subcarinal nodes	
Lower periesophageal nodes (below the azygos vein)	
Tumors of the Upper Thoracic Esophagus	
Regional lymph nodes	Nonregional lymph nodes (M1a)
Upper periesophageal nodes (above the azygos vein)	Cervical nodes
Subcarinal nodes	
Lower periesophageal nodes (below the azygos vein)	

T4 tumor irrespective of node status. Stage IV tumors are classified in two groups: stage IVA for M1a tumors and stage IVB for M1b disease.

Inadequacies in the Current Staging System

The adequacy of the current staging system for esophageal cancer has been called into question for a number of reasons. First, it does not fully consider adenocarcinomas that arise at the GEJ. According to the current definitions, a tumor arising in the region of the GEJ that involves less than 2 cm of the esophagus is classified as a proximal gastric cancer without consideration of the presence or absence of associated Barrett's epithelium, which most authorities consider a clear indication of the esophageal origin of these tumors. Second, it classifies "nonregional" lymph nodes in quite general terms while assigning tumors with metastases to these nodes as stage IV disease, which is considered unresectable. Third, the staging system does not consider the number of metastatic lymph nodes, a factor identified in several recent studies as being of prognostic importance. Finally, analysis of the performance of the current staging system in patients undergoing resection has shown that survival estimates do not differ significantly between several stage groups (i.e., the survival probabilities are not distinctive) and that TNM combinations included in the same stage grouping are dissimilar (i.e., the survival probabilities are not homogeneous).[45]

Table 34–5 Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Clear epidemiologic evidence suggests that adenocarcinoma of the GEJ should be considered distinct from other types of gastric cancer. These so-called cardia cancers are increasing in frequency in Western countries at a time when other types of gastric cancer are clearly on the decline. In addition, identified risk factors and patient demographics more closely resemble those of esophageal than gastric cancer. Most importantly, a high percentage of these patients will have Barrett's-type intestinal epithelium in the distal esophagus, thus suggesting a common pathophysiology. Unless there is extensive gastric involvement, these tumors are approached the same from a therapeutic standpoint as well, with similar outcomes. All these facts suggest that tumors arising at or above the GEJ should be considered with adenocarcinomas arising higher in the tubular esophagus.

The classification of nonregional node involvement as metastatic disease stems from Japanese data limited to patients with squamous cell carcinoma. Although there is little doubt that survival in patients with involvement of nonregional nodes is worse than in patients with only regional nodes involved, it is also clear that survival in patients with nonregional node involvement is significantly better than the 4- to 6-month median survival reported in patients with visceral metastases.[71] Several recent publications have demonstrated 5-year survival rates as high as 17% in patients with squamous cell carcinoma when nonregional nodes are involved.[72,73] In a recent review of our experience with en bloc resections performed for distal esophageal adenocarcinoma,[74] 26 patients had distant node involvement, including 16 with involved celiac nodes. Survival rates at 5 years in these patients with stage IV disease according to the current staging system were 33% and 29%, respectively.

The current staging system also fails to account for the prognostic importance of the extent of lymph node involvement. Rather, lymph node status is considered to be a dichotomous variable despite reports from centers around the world documenting the importance of both the number of positive lymph nodes and the ratio of positive lymph nodes to the number of nodes removed. In 1982, Skinner and co-workers[14] first recognized the prognostic importance of the number of involved nodes and suggested a revised classification system in which limited node disease was defined by the presence of two or fewer

node metastases. Skinner later revised this recommendation to a threshold of four or fewer node metastases based on subsequent analysis of additional patients undergoing en bloc resection.[75] Since that time, reports from several other investigators have reached similar conclusions.[71,74,76]

Classification according to the lymph node ratio (the number of nodes with metastases divided by the number of nodes removed) has also been proposed as being more accurate for prognostic purposes. Roder and colleagues[77] used a lymph node ratio of 20%, whereas more recent studies[55,78] would suggest that a lymph node ratio of 10% better stratifies patients with regard to survival. In our recently reported series of 100 en bloc resections for adenocarcinoma,[74] we found that the lymph node ratio appears to best stratify patients from the standpoint of 5-year survival. The 5-year survival rate was 92% for N0 disease versus only 18% in the setting of metastases to more than 10% of the nodes removed. Patients with node metastases and a lymph node ratio of less than 10% had an intermediate survival of 47%.

More recently, we have used immunohistochemistry (IHC) in an attempt to better classify patients with regard to lymph node involvement.[79] Twenty patients who had metastases to less than 10% of the nodes removed had IHC performed on all of the nodes removed. Overall, the 5-year survival rate in this group of patients was 55%. Additional node metastases were identified by IHC in 14 patients. When the number of IHC-detected node metastases was added to the number detected by hematoxylin-eosin staining and the lymph node ratio remained less than 10%, the survival rate was 77% at 5 years. In contrast, when the additional metastases detected by IHC resulted in a lymph node ratio of greater than 10%, the survival rate at 5 years was only 14%. Together, these observations have led to the suggestion that the lymph node staging system be revised such that patients with limited node involvement would be classified as N1 and patients with extensive nodal involvement as N2 disease.

The final inadequacy of the current staging system relates to the lack of distinctiveness and homogeneity of the stage groupings. This issue has been addressed in a recent review by Rice and colleagues[76] of their experience in 480 patients who underwent resection alone for esophageal cancer. They found a lack of homogeneity in the T1 classification and noted significant survival differences for tumors limited to the lamina propria (T1a) versus those that involved the submucosa (T1b). For reasons outlined in the preceding paragraph, they also noted a lack of homogeneity in patients with N1 disease, with a significant decrease in survival as the number of regional node metastases increased. In addition, these authors demonstrated a lack of distinctiveness between several of the stage groupings as currently defined. Although significant differences in survival were found between stages I, IIA, and III, they found no difference in survival between stage IIB, III, and IV disease. Based on these findings, they and others[71,76,80] have called for revision of the staging groupings in use for esophageal cancer (Table 34–6).

MANAGEMENT

Over the past 2 decades, management of esophageal cancer in Western countries has changed from the treatment of patients with advanced squamous cell carcinoma to those with earlier-stage esophageal adenocarcinoma occurring in the setting of Barrett's esophagus. The combination of increasing numbers of patients with very early-stage tumors along with the perceived high risk for mortality and morbidity associated with esophageal resection has spurred interest in a number of new and unproven therapeutic approaches, such as mucosal ablation and EMR. At the same time, patients with more advanced-stage tumors are increasingly being treated with combined-modality therapy (neoadjuvant chemoradiotherapy) despite a lack of clear evidence of the superiority of this approach. In some centers, the need for surgical resection is being questioned, with definitive chemoradiotherapy offered as primary therapy.[81] In addition, when surgery is performed, controversy persists in regard to the extent of resection necessary, with much of

Table 34–6 Proposed Revisions to the Staging Classification for Esophageal Cancer

Stage	Korst et al.[71]	Rice et al.[76]	Ellis et al.[80]
0	T0 N0 M0, Tis N0 M0	N/A	T1 N0 M0
I	T1 N0 M0, T2 N0 M0	Tis, T1a N0 M0	T1 N1 M0, T2 N0 M0
IIA	T3 N0 M0 T1 N1 M0	T1b N0 M0, T1a N1 M0, T2 N0 M0	T2 N1 M0, T3 N0 M0
IIB	T2 N1 M0 T3 N1 M0		
III	T1-3 N2 M0	T3 N0 M0, T1b/T2 N1 M0, T3 N1 M0, T4 N0 M0	T3 N1 M0, Any T N2 M0
IV	T4 Any N M0 Any T Any N M1	T4 N1 M0, Any T N2 M0, Any T Any N M1	Any T Any N M1

the debate focused on the benefits of formal lymph node dissection.

Proponents of alternatives to primary resection cite as justification high surgical mortality rates of 10% to 15% and low 5-year survival rates of 20% to 25% after surgery. These statements, based largely on past experience with squamous cell cancer, give the perception that surgery is not curative in most patients with esophageal carcinoma and suggest that surgical therapy is no longer central in the treatment of these patients because the survival benefits are outweighed by the risks of resection. However, recent observations[51,82] suggest that the outcomes of surgical resection in the present era of improvements in perioperative care, which has resulted in increasing numbers of tumors being diagnosed at an earlier stage, are much better than commonly quoted, with overall survival rates after surgery approaching 50% and operative mortality rates of less than 5%.

Surgical Therapy

Surgical resection remains the primary mode of therapy for patients with cancer of the esophagus in the absence of systemic metastases. Surgery offers the highest likelihood of cure for patients with localized disease, and it can offer quality palliation for patients with more advanced disease. To obtain the best results, management of esophageal carcinoma should be individualized on the basis of a combination of factors, including the physiologic status of the patient, tumor location, and the stage of disease.

Patient Assessment

Esophageal cancer is a disease that occurs predominantly in the sixth and seventh decades of life. However, advanced age alone should not be considered a contraindication to esophageal resection. Although the risk for mortality is higher in patients older than 70 years, this increased risk is due to the higher frequency of comorbid medical conditions such as heart, liver, and kidney disease in the elderly population rather than age per se.[83] It is important to note that when operative mortality is excluded, long-term survival after resection in the elderly population is similar to that observed in younger patients. As a result, patients in their 80s and 90s can be considered candidates for potentially curative resection, but particular attention needs to be paid to the preoperative assessment of these patients.

The strong etiologic relationship between cancer of the esophagus and alcohol and tobacco use makes it imperative that patients be carefully screened for the presence of cardiovascular, pulmonary, and hepatic dysfunction regardless of their age. It has been estimated that between 20% and 30% of patients with esophageal cancer will have evidence of cardiovascular disease if carefully screened.[84] This evaluation should include noninvasive screening for coronary artery disease by either stress echocardiography or thallium imaging. In most patients, proper preoperative evaluation and perioperative management will allow the patient to undergo resection. The preoperative evaluation should also include pulmonary function testing and arterial blood gas analysis. Patients with significant impairment in the forced expiratory volume at 1 second (FEV_1 <1 L) and those with chronic bronchitis are at increased risk for respiratory complications after surgery.[85,86] The presence of hypercapnia ($PaCO_2$ >45 mm Hg) or hypoxemia (PaO_2 <55 mm Hg) is also associated with an increased risk for complications. Finally, cirrhosis of the liver is not uncommon in patients with esophageal cancer, particularly those with squamous cell carcinoma. Well-compensated cirrhosis (Child's classification A) alone is not a contraindication to resection of an otherwise curable cancer, but care should be exercised when considering resection in the setting of more advanced stages of cirrhosis.

Tumor location is also an important factor in selecting the most appropriate therapy for an individual patient. Tumors in the cervical esophagus and the upper third of the thoracic esophagus are less amenable to complete en bloc resection because of the comparatively close proximity of these tumors to the airway and important vascular structures. As a result, these tumors are preferentially treated by either definitive chemoradiotherapy or chemoradiation therapy followed by resection of any residual disease. For tumors of the lower esophagus and GEJ, selection of patients for surgical resection is based on the results of a complete clinical staging evaluation. A selective therapeutic approach that we have used is summarized in Figure 34–5.

Extent of Resection for Early Esophageal Adenocarcinoma

Because of the perceived high risk for morbidity and mortality associated with esophagectomy, a number of alternatives to resection have been proposed, particularly in patients with very early-stage tumors. Such alternatives include EMR, mucosal ablation via photodynamic therapy, and limited-resection techniques such as vagal-sparing esophagectomy (VSE). These treatments all focus on removal or destruction of the esophageal lesion only and do not include lymph node dissection. As a result, they are applicable only in situations in which the risk of lymph node involvement is very low. Patients with early-stage tumors, most often detected in the course of surveillance programs for Barrett's esophagus, are potential candidates for these alternative therapies. It has been shown that when a tumor is limited to the lamina propria (T1a tumors), the risk for lymph node metastases is very low. We have identified 2 patients, each with a single involved lymph node, out of 58 (3.4%) who underwent esophageal resection for a tumor limited to the lamina propria. In both patients, the involved node was located at the GEJ in immediate proximity to the tumor. When submucosal invasion is present, between 30% and 50% will have evidence of lymph node involvement,[74,87] which argues strongly for the need to perform a formal node dissection. As previously mentioned, it is difficult to reliably differentiate between these subgroups of T1 disease on clinical grounds. Even when EUS is performed, the accuracy of categorization between T1a and T1b disease

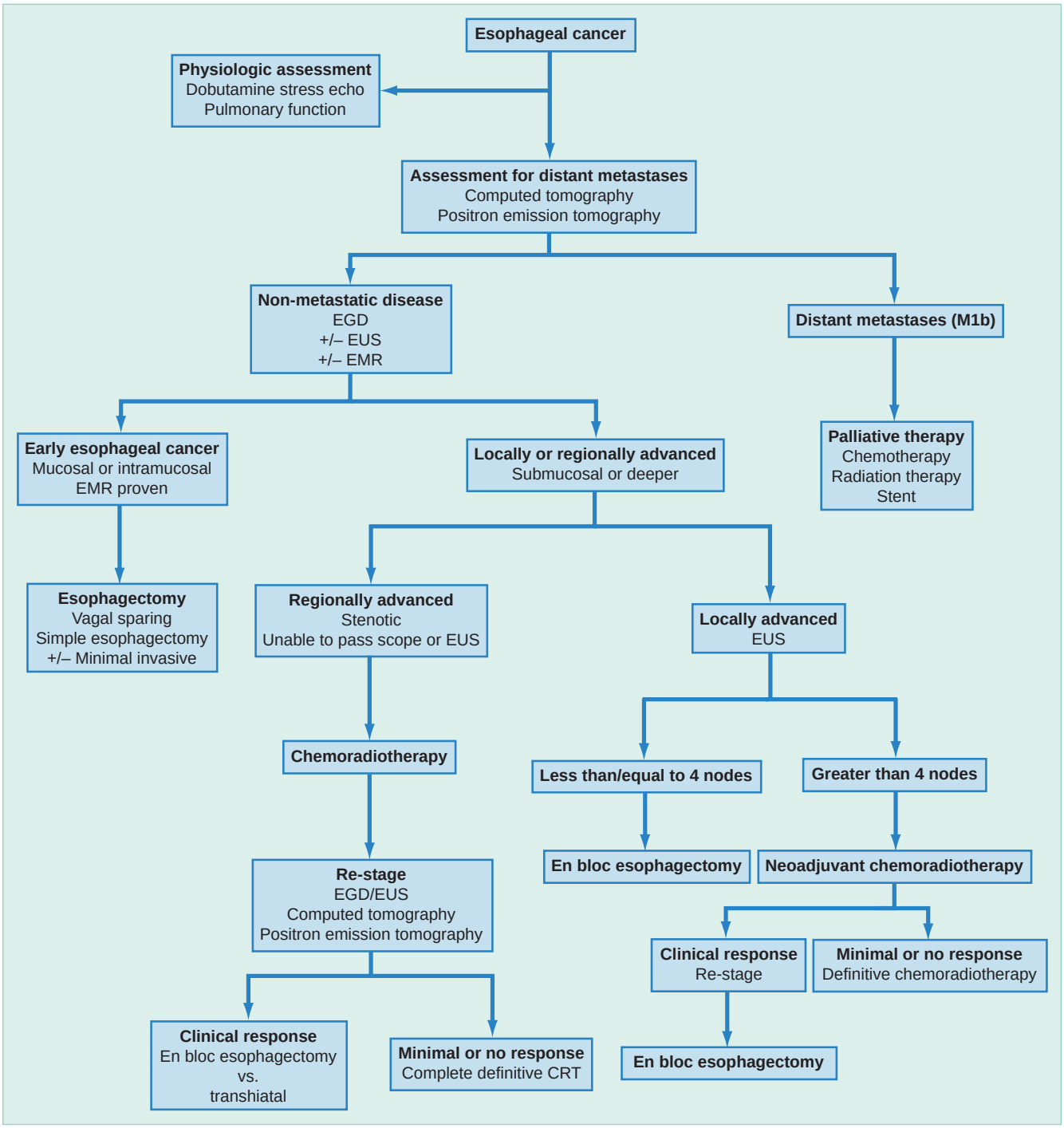

Figure 34–5. Therapeutic approach to esophageal cancer. CRT, chemoradiotherapy; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasonography.

is no better than 20% to 30%.[56,88] We have recently described the utility of the endoscopic appearance of the Barrett's segment in differentiating between these early T1a and T1b tumors.[89] When no lesion is visible in the Barrett's mucosa and biopsy indicates the presence of intramucosal carcinoma, 80% have a tumor confined to the lamina propria. In contrast, when a lesion is visible, three quarters have a tumor that invades into the submucosa or beyond, and over half have node involvement. The former are potential candidates for more limited therapy, whereas the latter clearly need a formal cancer operation. More recently, we have performed EMR in patients with a visible lesion in an attempt to accurately determine the depth of invasion.[60] When EMR confirms the presence of a tumor limited to the lamina propria, treatment can be limited to removal of the esophagus

Table 34–7 Relationship between Tumor Depth and Lymph Node Status

Tumor Depth	Prevalence of Node Metastases* (%)	Number of Involved Nodes† (Median [IQR])	Number with 1-4 Involved Nodes‡ (%)	Number with >4 Involved Nodes§ (%)
Intramucosal	1/16 (6.25)	2 (N/A)	1/16 (6.25)	0/16 (0)
Submucosal	5/16 (31.25)	1 (N/A)	4/16 (25)	1/16 (6.25)
Intramuscular	10/13 (76.92)	2 (1-4)	9/13 (69.23)	1/13 (7.69)
Transmural	47/55 (85.45)	5 (3-13.5)	22/55 (40)	25/55 (40)

*$\chi^2 = 42.0$, $P < .0001$ (chi-square test for trend).
†$\chi^2 = 11.02$, $P = 0.0116$ (Kruskal-Wallis); includes only patients with involved nodes.
‡$\chi^2 = 13.64$, $P = .0035$ (chi-square test for trend).
§$\chi^2 = 21.38$, $P < .0001$ (chi-square test for trend).
IQR, interquartile range.

without the need for formal lymph node dissection. In these patients, we advocate VSE.

Technique of Vagal-Sparing Esophagectomy The technique of VSE was developed to avoid the morbidity associated with division of the vagal nerves during standard esophagectomy.[90] The intent of the operation is to make esophagectomy more acceptable therapy to patients with end-stage benign disease and early malignant disease by avoiding some of the common gastrointestinal side effects of a standard esophagectomy.

VSE is performed through an upper midline abdominal incision and a second incision in the left side of the neck. The abdominal operation begins with identification of both the anterior and posterior vagus nerves. The nerves are encircled with tape for retraction purposes, and the nerve trunks are mobilized from the GEJ by a limited highly selective vagotomy. The proximal part of the stomach is transected with a linear stapling device above this point. When the stomach is to be used for reconstruction, the highly selective vagotomy is simply continued distally on the stomach to provide for greater mobility and creation of the gastric tube without injury to the vagus nerves.

The esophagus is then exposed in the neck and mobilized into the thoracic inlet where it can be divided as low as possible to preserve length for construction of the anastomosis. A gastrotomy is then made proximal to the point of gastric division, and a vein stripper is passed retrogradely up the esophagus. A stout ligature is applied around the esophagus and the vein stripper in the neck incision, and the esophagus is divided just above this point. The vein stripper is then used to remove the thoracic esophagus in an inverting fashion. After dilation of the esophageal bed with a 90-ml Foley catheter, the alimentary tract is reconstructed with either a colon interposition or a gastric pull-up.

We have compared the functional outcome of VSE with the results of standard transhiatal esophagectomy with gastric pull-up and esophagectomy with colon interposition.[91] Vagal secretory function was better preserved after VSE, as was vagal motor function. Gastric reservoir function was also more normal, and there was a significantly lower frequency of dumping and diarrhea after VSE. To date, experience with this technique in more than 100 patients with tumors confined to the lamina propria has confirmed the excellent quality of life after VSE, and in no patient has recurrent disease developed.

Extent of Resection for Localized Esophageal Cancer

Once the tumor has penetrated the submucosal layer, about half the patients will have node metastases. More than 80% of patients with invasion of the muscularis propria will have at least one involved lymph node.[49] In the event of transmural invasion, node involvement will be present in over 85%, and the median number of involved nodes and the proportion of patients with more than four involved nodes will increase (Table 34–7).[74] These patients, who have locoregionally advanced tumors, should be considered for resection based on the time-honored principles of surgical oncology, which emphasize the importance of complete resection. It is our preference to offer these patients en bloc resection.

Technique of En Bloc Esophagectomy The en bloc procedure is performed through an initial right thoracotomy followed by a midline laparotomy. The proximal anastomosis is performed through an incision made in the left side of the neck. The thoracic dissection includes removal of the azygos vein with its associated nodes, the thoracic duct, and the low paratracheal, subcarinal, paraesophageal, and parahiatal nodes in continuity with the resected esophagus. The block of tissue removed is bounded laterally on each side by the excised mediastinal pleura, anteriorly by the pericardium and membranous trachea, and posteriorly by the aorta and vertebral bodies.

The procedure begins with the patient in the left lateral decubitus position, and a posterolateral thoracotomy is performed with entry into the chest through the seventh or eighth intercostal space. The pleura over-

lying the lateral aspect of the vertebral bodies is incised from the level of the azygos arch to the diaphragm, and the intercostal veins are divided between ligatures as they enter the azygos vein. A dissection plane is then created by following each intercostal artery to reach the adventitial plane of the aorta. Blunt dissection continues across the anterior surface of the aorta until the left mediastinal pleura is reached. One or more hemiazygos communicating veins need to be ligated as they pass behind the aorta.

The anterior mediastinal dissection is performed along the posterior aspect of the pericardium, which is not removed unless the tumor is adherent. Once the left mediastinal pleura is reached, a vertical incision is made in the pleura just behind the pericardium and along the anterior aspect of the aorta at the limits of the previously created posterior dissection. The thoracic esophagus is then encircled with a Penrose drain for traction. The dissection plane along the anterior aspect of the aorta is then continued cephalad to a point just above the azygos arch, where the dissection is transitioned to the wall of the esophagus. In this transition, the right vagus nerve and the bronchial artery are divided. The anterior dissection is then continued cephalad along the pericardium until the subcarinal nodes are encountered. Careful dissection along the right main bronchus up to the carina and then distally along the left main bronchus allows removal of the entire subcarinal node packet in continuity with the resected esophagus. At this point, the anterior dissection is also transitioned to the wall of the esophagus by dividing the left vagus nerve. Blunt dissection from this point proximally should be performed as far as possible into the base of the neck to facilitate the later dissection.

As the en bloc dissection proceeds caudally, the thoracic surface of the diaphragm is reached. This should be incised with cautery to incorporate a portion of the esophageal hiatus with the specimen. The mediastinal tissue posteriorly just above the diaphragm includes the thoracic duct, which must be ligated carefully to prevent the development of chylothorax. A heavy silk ligature should be placed so that it incorporates all of the tissue anterior to the vertebral body and lateral to the aorta and esophagus. This ligature will also contain the azygos vein as it traverses the diaphragm, and the upper end of this vein is ligated flush with its confluence with the superior vena cava. The chest is closed after placement of a suction drain.

The abdominal portion of the operation begins at the porta hepatis, where all of the lymph node–bearing tissue overlying the hepatic arterial trunk and the portal vein is removed. This dissection is continued proximally along the hepatic artery to its origin from the celiac axis. The retroperitoneal tissue above the pancreas overlying the right crus of the diaphragm is dissected medially and superiorly so that it remains attached to the esophagectomy specimen. Attention is then turned to the greater curvature of the stomach, where the gastrocolic omentum is divided with preservation of the gastroepiploic arcade. This dissection should begin distally at the level of the pylorus and continue proximally to include division of the short gastric vessels. The use of a Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH) greatly facilitates this dissection. The short gastric vessels should be divided as close as possible to the spleen to preserve as many collateral vessels to the fundus as possible. The gastric fundus is rotated to the right to continue the dissection in the retroperitoneum, and all the node-bearing tissue above the splenic artery and overlying the left crus of the diaphragm is removed. The musculature of the diaphragmatic hiatus is then incised to meet the incision made in the diaphragm during the thoracic dissection. By retracting the stomach anteriorly, ample exposure of the celiac axis can be achieved to allow ligation of the coronary vein and the left gastric artery at its origin. A Kocher maneuver should be performed to allow maximum mobility of the stomach.

Exposure of the cervical esophagus is accomplished through an oblique left neck incision placed along the anterior border of the sternocleidomastoid muscle. This incision should extend from the sternal notch to a point half way to the ear lobe. The omohyoid, sternohyoid, and sternothyroid muscles are divided laterally. A dissection plane is then created between the contents of the carotid sheath and the trachea and esophagus to reach the prevertebral fascia. The inferior thyroid artery is divided between ligatures. Dissection is then continued posterior to the esophagus down into the thoracic inlet, where the dissection plane created during the thoracotomy is reached. The esophagus is encircled with a Penrose drain, and the upper thoracic esophagus is delivered up into the neck. A linear stapler is used to divide the esophagus as low as possible, and the specimen is removed through the abdomen.

Reconstruction is performed either by creation of a gastric tube after wide resection of the gastric cardia down to the fourth vein on the lesser curvature of the stomach or by using an isoperistaltic colon interposition based on the left colic artery. The gastric tube is created with a linear stapling device. This staple line should begin on the upper fundus at least 5 cm from the distal limit of the tumor and should continue to a point along the lesser curvature corresponding to the fourth or fifth branch of the left gastric artery. We prefer to oversew this staple line with a running absorbable suture to minimize the risk for a leak. A pyloromyotomy is then performed to aid in drainage from the vagotomized stomach. If an isoperistaltic colon interposition is used, the abdominal dissection also includes removal of the proximal two thirds of the stomach, the omentum, and the lymph nodes along the proximal two thirds of the greater curvature of the stomach.

Choice of Reconstruction The choice of reconstruction by gastric pull-up or colon interposition is based on several factors. Generally, when the primary tumor is large or involves the proximal part of the stomach to a significant degree, a colon interposition should be performed to ensure adequate margins. However, in the setting of intrinsic colonic disease (polyps, diverticula, etc.) or variations in vascular supply that preclude use of the colon, a gastric pull-up or small intestinal interposition should be used.

In most patients undergoing resection for esophageal cancer, reconstruction is performed with a gastric conduit. The blood supply is very dependable, and only a single anastomosis is required. The major disadvantages of using the stomach include the complete lack of peristaltic activity and the tendency for persistent reflux into the remaining cervical esophagus that is directly connected to the acid-secreting stomach. In long-term survivors, this ongoing reflux can result in the development of recurrent Barrett's esophagus.[92] The need to preserve length may also result in more limited margins, especially for large or very distal tumors, which can result in local recurrence. As a result, with extensive involvement of the upper part of the stomach or in patients with a high expectation for long-term survival, we prefer to use an isoperistaltic left colon interposition.

The gastric pull-up is performed by wrapping the previously created gastric tube in a bowel bag to facilitate atraumatic passage to the neck. Care should be exercised to avoid excessive tension on the stomach or its gastroepiploic arcade during this maneuver, and twisting of the stomach must be avoided. The anastomosis is performed between the remaining cervical esophagus and the anterior wall of the gastric pull-up. We prefer to use a single-layer technique with placement of 4-0 monofilament absorbable sutures and tie the knots in the lumen. The last three or four sutures are placed in a modified Gambee fashion to achieve mucosal inversion. Gentle retraction on the gastric conduit from within the abdomen will remove redundancy in the gastric pull-up. Several nonabsorbable sutures should be placed between the stomach and the left diaphragmatic crus to prevent herniation of the stomach back into the thorax. A nasogastric tube is then carefully passed, a drain is placed in the neck, and the cervical wound is closed.

When a colon interposition is performed, the proximal part of the stomach is removed with the esophagectomy specimen by dividing the stomach at the level of the antrum. Leaving more denervated stomach can lead to gastric stasis and does not result in improved gastrointestinal function. The ascending colon and descending colon are mobilized completely. The segment of colon to be interposed derives its arterial supply from the ascending branch of the left colic artery and usually corresponds to the segment extending from the mid transverse colon to the proximal descending colon. This segment is mobilized by dissecting the middle colic artery back to its origin from the superior mesenteric artery, where it arises as a single trunk in most patients. After the middle colic artery and vein are temporarily occluded to ensure adequate collateral flow through the marginal artery, these vessels are ligated and divided.

The apex of the arc portended by the vascular pedicle is then marked with a suture, and the distance from this point to the neck is measured with umbilical tape. This tape is used to measure proximally from the first marking stitch to determine the point of transection of the proximal part of the colon. The divided colon is then passed through the bed of the resected esophagus wrapped in a bowel bag, and a single-layer monofilament anastomosis is performed to the remaining cervical esophagus. Traction is gently applied to the colon from within the abdomen to eliminate redundancy, and the colon is secured to the left crus of the diaphragm with a nonabsorbable suture.

The colon is then divided with a linear stapler 5 to 10 cm below the point where it enters the abdomen. Care should be exercised to not leave too long an intra-abdominal segment of colon because this will result in food retention. The mesentery should be divided immediately adjacent to the wall of the colon to avoid injury to the vascular pedicle. A two-layered anastomosis is then performed between the proximal divided colon and the antrum, and colon continuity is restored by a standard colocolostomy.

We routinely perform a catheter jejunostomy to provide for early postoperative feeding and to avoid the need for parenteral nutrition in the event of postoperative complications such as an anastomotic leak. The jejunostomy catheter is removed when the patient is able to maintain weight by oral feedings, usually 3 to 4 weeks postoperatively.

Transhiatal Esophagectomy Transhiatal esophagectomy has been advocated as an alternative to en bloc resection. Proponents cite lower morbidity and mortality rates associated with this approach, which eliminates the potentially debilitating thoracotomy incision.

Technique of Transhiatal Esophagectomy The procedure is performed through a midline laparotomy and an incision in the left side of the neck. Although an abdominal dissection similar to that described for the en bloc procedure can be performed, including the lymph nodes along the hepatic artery, the celiac trunk, and the left gastric artery and lesser curvature of the stomach, removal of the lower mediastinal lymph nodes is limited in this approach.

The operation begins with an abdominal lymph node dissection and gastric mobilization identical to that described for the en bloc procedure. After the stomach has been completely mobilized, the musculature of the esophageal hiatus is incised circumferentially. This not only ensures removal of any potentially involved parahiatal nodes but also enlarges the hiatal opening to facilitate the lower mediastinal dissection. The cervical esophagus is then exposed as described earlier.

Placement of appropriate retractors through the esophageal hiatus allows dissection of the lower thoracic esophagus under direct vision. This allows removal of many of the potentially involved periesophageal nodes from the lower mediastinum. When the limits of dissection under direct vision are reached, a hand is inserted into the mediastinum behind the esophagus. A relatively avascular plane can be developed that can reach the level of fingers of the opposite hand inserted in the neck incision behind the esophagus. A similar relatively avascular plane can then be developed anterior to the esophagus by working from both the abdomen and the neck. The lateral attachments on the left are dissected by reaching through the mediastinum posterior to the esophagus up into the neck incision. The index finger and thumb can then be used to bluntly dissect downward along the left

side of the esophagus. In the lower mediastinum the vagal nerve trunks, which are separated from the esophagus by this maneuver, can be divided under direct vision after applying a large vascular clip. The right lateral attachments are mobilized in a similar manner by passing the right hand anterior to the esophagus and using the thumb and index finger to bluntly dissect the right lateral attachments. The upper thoracic esophagus is then delivered into the cervical wound, and it is divided with a linear stapling device as low as possible in the neck. The thoracic esophagus is then pulled down into the abdomen, the stomach is divided, and reconstruction is accomplished as described earlier.

Postoperative Care

Patients are routinely extubated at the completion of the operation, and they are admitted directly to the intensive care unit, where they are observed for 2 to 3 days after surgery. During the first 72 hours after surgery, patients are supported with a minimal amount of intravenous crystalloid and dextrose solutions. Continuous infusions of dopamine (3 µg/kg/min) and nitroglycerin (5 to 20 mg/min) are administered to aid graft perfusion. Albumin is used liberally to support blood pressure and urine output. A thoracic epidural catheter placed before the operation is used for postoperative pain management. This encourages early ambulation and assists in pulmonary toilet. Broad-spectrum antibiotics are continued for 24 hours after the operation.

After 72 hours, patients without complications are transferred to ward-level care. The infusions of dopamine and nitroglycerin are discontinued. Jejunal feedings are started at 15 ml/hr and increased by 15 ml daily until the target goal rate is achieved. Early mobilization and aggressive chest physiotherapy are continued on the ward. The nasogastric tube is removed when drainage is minimal and bowel function has returned. We routinely obtain a videoesophagogram 7 days after surgery to check for anastomotic leak and delayed conduit emptying. An oral diet, beginning with clear liquids and advanced to a soft diet over a period of 2 to 3 days, is gradually instituted with the patient sitting during and for 90 minutes after the meal. During this transition and after discharge, jejunal feedings are delivered at night to provide approximately 1000 calories until the patient is able to maintain hydration, weight, and nutrition with oral intake.

Complications

Despite recent improvements in perioperative management, postoperative morbidity and mortality after esophagectomy for cancer remain significant. These are large, technically demanding operations that are often performed on patients with compromised cardiopulmonary function. Nutritional disturbances are also common because of the combined effects of the cancer itself and the obstructing mass in the esophagus.

Complications occurring in a recent series of resections performed for esophageal adenocarcinoma are summarized in Table 34–8.[51] Overall, 62% experienced at least one complication. Pulmonary complications, including pneumonia, acute respiratory distress syndrome requiring prolonged intubation, pleural effusion, and empyema, are among the most common complications and occurred in 23%. These complications can be minimized by early ambulation and careful attention to adequate pain control. Prevention of aspiration can be achieved by keeping the patient in the semi-upright position at all times and by meticulous attention to maintaining a functioning nasogastric tube. When necessary, a minitracheostomy can provide invaluable assistance in clearing retained secretions.

Cardiac complications occur in approximately 17% of patients, with the development of atrial fibrillation accounting for the majority of these complications. Though generally self-limited, they do require cardiac monitoring and treatment, which can prolong the intensive care unit stay. There is no evidence that prophylactic administration of antiarrhythmic drugs reduces the development of atrial fibrillation, although they are commonly used.

Table 34–8 Perioperative Complications Occurring in 263 Consecutive Resections for Esophageal Adenocarcinoma

Complication	*n*
Respiratory	61 (23%)
Pneumonia	25
Prolonged intubation	15
Empyema	5
Pleural effusion	16
Cardiovascular	44 (17%)
Arrhythmias	42
Myocardial infarction	2
Anastomotic	36 (14%)
Leak	31
Graft ischemia	5
Chylothorax	8 (3%)
Deep vein thrombosis/pulmonary embolism	9 (3%)
Gastrointestinal bleeding	1 (<1%)
Sepsis	4 (2%)
Urinary tract infection	3 (1%)
Wound infection	10 (4%)
Reoperation	30 (11%)
Abdominal bleeding	5
Anastomotic leak/graft necrosis	6
Sepsis/bowel infarction	3
Thoracic duct ligation	3
Empyema or continuous thoracic drainage	6
Fascial rupture/wound infection	7
Others	4 (2%)

Anastomotic complications occur in 10% to 30% of patients, depending on the type of reconstruction performed. They appear to be more common after the use of neoadjuvant therapy, in patients with diabetes and hypertension, and in the obese.[93] Most of these leaks can be managed with local drainage and administration of antibiotics, as long as the vascular supply to the reconstruction is adequate. We recommend early endoscopy in any patient who is known or suspected to have a leak to exclude potentially life-threatening conduit ischemia, which can be present in as many as 14% of patients with an anastomotic leak.

Results

The goals of surgery in patients with esophageal cancer include elimination of dysphagia and improvement in long-term survival. Esophageal resection with reconstruction successfully achieves palliation of dysphagia in 80% to 90% of patients, but strictures do occur in 10% to 15% and may require intermittent dilatation. Weight loss, which is present in the vast majority of patients before surgery, is reversed in the majority, and most patients are able to return to work. Other potential complications of untreated esophageal cancer such as tumor pain, hemorrhage, and the development of an esophagorespiratory fistula can also be prevented.

Long-term survival after esophagectomy depends on a number of factors, such as the depth of tumor invasion, the number of involved lymph nodes, and the location of the tumor in the esophagus. The prognosis is better for tumors of the cervical esophagus and for those located at the GEJ than for tumors located in the thoracic esophagus. The impact of the type of resection performed on long-term survival remains a subject of debate. Although the results of single-institution series seem to indicate improved survival after en bloc resection, to date no prospective randomized trial has been reported with sufficient sample size to answer this question definitively.

We have recently reviewed our experience with 100 consecutive en bloc resections performed for esophageal adenocarcinoma.[74] Despite the fact that 55% had transmural invasion and node metastases were present in 63%, the overall survival rate at 5 years was 52%. Survival by AJCC stage is shown in Table 34–9. The survival rate after en bloc resection was higher than 94% for stage I disease, with an approximately 80% survival rate in patients with stage II disease. Even when stage III or IV disease was present, en bloc resection achieved long-term survival in approximately 25%. Similar results have been reported in several other relatively large single-institution series. Altorki and Skinner reported a 5-year survival rate of 40% in a series of 111 patients in which 60% had lymph node involvement and 59% had T3 or T4 disease.[94] The survival rate in patients with stage III disease was 39%. Collard and colleagues[95] have also reported a large experience with en bloc resection in a series of 235 patients, half of whom had N1 disease and more than 62% had T3 or T4 disease. The survival rate at 5 years was 49%, with 30% of the 98 patients with stage III disease surviving 5 years or more.

Table 34–9 Survival According to AJCC Stage Grouping

Stage (No. Patients)	Survival (%)
I (26)	94.4
IIa (9)	80.0*
IIb (11)	77.1†
III (32)	24.3‡
IV (16)	28.7

*P = NS for stage IIa versus stage IIb.
†P = .005 for stage IIb versus stage III.
‡P = NS for stage III versus stage IV.
AJCC, American Joint Committee on Cancer; NS, not significant.

A number of reports published recently have described the results of transhiatal esophagectomy. The overall 5-year survival rate has been reported at 18% to 27%,[96,97] with 10% to 15% survival rates in patients with stage III disease. Four recently published retrospective series compared survival after transhiatal and en bloc resection at a single institution.[13,97-99] Three of them reported improved survival after en bloc resection.

Proponents of transhiatal esophagectomy argue that the apparent benefit in overall survival associated with en bloc resection can be explained by the selection of patients with more favorable tumors for en bloc resection. They also explain the differences in survival by stage that have consistently been reported as being due to stage migration, which results from the more thorough lymph node sampling that undoubtedly occurs during an en bloc procedure. To address this question, Altorki et al.[13] reported outcomes after en bloc and transhiatal resection performed in patients with T3 N1 (stage III) disease. In this group of patients, stage migration cannot occur because all have locally advanced tumors with lymph node involvement. They reported a 4-year survival rate of 35% after en bloc resection, which was significantly better than the 11% survival rate observed after transhiatal esophagectomy. Ultimately, this debate can be resolved only by the completion of a large randomized controlled trial. To date, only one such trial has been reported, that by Hulscher and colleagues.[100] In this moderate-sized trial of 220 patients, the survival rate after en bloc resection was 39%, as opposed to a 27% survival rate after transhiatal esophagectomy. This difference, which amounted to a 44% improvement in survival after en bloc resection, was of borderline statistical significance (P = .08), thus suggesting that the study may have been underpowered.

There can be little doubt that the en bloc esophagectomy is a technically demanding operation that requires considerably more time to complete than standard esophagectomy does. A dedicated team of specialists is necessary to perform the procedure and to care for the patient after the operation to achieve acceptable morbidity and mortality rates. The technical expertise required to perform the surgery is demanding, and the

learning curve is steep. Care after the operation is constant and complex for 10 to 14 days, but on occasion it can be much longer. In view of these issues, it is doubtful that the procedure will gain widespread acceptance until a prospective randomized trial is accomplished to show the benefit of the en bloc procedure. If such a study were to show the superiority of en bloc resection, it should be done in only a few select centers capable of organizing a team to perform the procedure and committed to providing care after the procedure.

The Role of Neoadjuvant Therapy

Increasingly, management of esophageal cancer has focused on multimodality therapy, with neoadjuvant chemoradiotherapy being administered to nearly all patients in many centers. This approach has made its way into the mainstream treatment of esophageal cancer despite the clear lack of convincing evidence of the superiority of this approach. The concept of neoadjuvant therapy in esophageal cancer was spurred by a general disappointment in the results of standard resections, which historically resulted in survival rates of 20% or less at 5 years. Rather than pursue more aggressive surgery, many centers chose to combine chemotherapy and radiation treatment with surgical resection in an attempt to increase the cure rate. Several phase II trials conducted in the early 1990s reported complete response rates of 10% to 20%, with improvement in survival in comparison to historical controls.[101-104]

This enthusiasm should have been tempered by awareness of the limitations of phase II trials. In particular, comparison with historical controls is known to introduce bias. The changes that have occurred in the epidemiology of esophageal cancer over the past several decades are well documented and have clearly resulted in detection of increasing numbers of cancers at an earlier, more curable stage. The results of surgical therapy also appear to be improving. The morbidity and mortality associated with surgery have declined, and our ability to deal with many side effects associated with treatment has also improved. For these and other reasons, the importance of the so-called historical control bias, which has been recognized since the 1950s, cannot be overemphasized.

As a result of these phase II trials, a number of randomized controlled trials have been conducted to assess the potential impact of combined-modality therapy for esophageal cancer. To date, the results of nine such trials have been reported. Of these, only one trial[9] was limited to patients with adenocarcinoma, whereas five trials included only patients with squamous cell cancer and three included tumors of both cell types. Only two of these trials have shown a benefit with routine administration of preoperative therapy. In each of these positive trials, a detailed review suggests several significant flaws.

The first randomized controlled trial to report improved survival with neoadjuvant therapy was published by Walsh et al. in 1996.[9] They reported the outcome in approximately 50 patients randomized to receive either preoperative 5-fluorouracil and cisplatin chemotherapy along with 40 cGy of external beam radiotherapy or surgical resection alone. They reported improved median survival (16 months versus 11 months) and better survival at 3 years after multimodality therapy. The major flaw in this study was the strikingly poor results achieved with surgery alone. They reported a 3-year survival rate of 6%, which is well below that reported in any recent surgical series. A detailed review of the manuscript reveals several possible explanations for the poor results reported for surgery alone. First, there was no standardization of surgical technique across the study centers, with at least five different operations being performed, depending on local preference. Second, the study also included proximal gastric cancers. Third, the prevalence of nodal metastases was nearly twofold higher in the surgery arm of the trial (82% versus 42%), thus suggesting that more advanced-staged tumors were randomized to surgical resection alone.

The only other randomized trial to report improved survival with neoadjuvant therapy was the Medical Research Council trial reported in 2002.[105] Approximately 400 patients were randomized to surgical resection alone or to 5-fluorouracil and cisplatin chemotherapy, followed by surgery. Radiation therapy was administered at the discretion of the study center. In this trial, 2-year survival was significantly better in the neoadjuvant therapy arm (43% versus 34%). Detailed review of the results of this trial raises several questions. First, the improved survival reported amounts to nine more patients surviving 2 years or more in the neoadjuvant therapy arm. However, there is evidence that the two groups may not have been comparable because the surgery-alone arm included 22 more patients with T4 tumors, 5 more patients with incomplete (R1) surgical resections, 22 more patients with lymph node involvement, and 18 more patients with distant lymph node involvement. Patients in the surgery-alone group were also more likely to have gross residual disease left behind (R2 resection), and in 13% of these patients no resection was performed. Combined, 26% of the surgery-alone group either had no resection or had incomplete resection as compared with a rate of only 14% in the neoadjuvant therapy arm. This difference in the extent of disease present may explain the difference in survival observed.

One consistent observation in nearly all reports of the outcome of neoadjuvant therapy has been the observation that patients who respond to neoadjuvant therapy have significantly better survival than nonresponders do. This observation has led to the use of response to therapy as a selection criterion in some centers for proceeding with surgical resection. Although it appears likely that neoadjuvant therapy does indeed benefit patients who respond, this implies that nonresponders fare correspondingly worse, particularly in the studies that report no difference in overall survival in comparison to surgery alone. There are at least two possible explanations for the reduced survival observed in patients who fail to respond to neoadjuvant therapy. First, it should be noted that the response rate to any particular chemotherapy regimen is at best 25% to 35%. In the remaining patients, the tumor is essentially left untreated during the 2 or 3

months that neoadjuvant therapy is given. During this period, the tumor may progress and these patients would probably have been better off if they had undergone resection initially. Administration of chemotherapy that has a significant impact on natural immunity without killing the patient's tumor cells may result in reduced protection from potential tumor metastases. The second possible explanation for reduced survival in nonresponders is that response to therapy may simply be a marker for tumors with less aggressive biologic behavior and therefore a better prognosis. If this is true, it is hardly an endorsement for the benefits of neoadjuvant therapy because it implies that the treatment itself was not of benefit. There are clinical data to suggest that such may be the case. In a randomized controlled trial involving 147 patients with squamous cell cancer, Law and coworkers[106] reported no difference in overall survival when neoadjuvant therapy was compared with surgical resection alone. As many others have shown, survival was better in patients who responded to neoadjuvant therapy than in those who did not. However, they also showed that patients who responded to neoadjuvant therapy had significantly smaller tumors on endoscopy at the time of randomization and had clinically earlier-stage tumors. In a report of the outcome of combined-modality therapy administered in a nonrandomized setting, Jiao et al.[107] showed that N status on MIS staging was the strongest predictor of response to neoadjuvant therapy, with a response rate of nearly 60% in patients with N0 disease versus only 15% when node metastases were present. Taken together, these observations suggest that response to therapy may be as much an indicator of a more favorable tumor as an indicator of a true benefit of the therapy administered.

Some evidence in the literature suggests that certain patients may be harmed by the routine administration of neoadjuvant therapy. Using a complicated statistical modeling approach, Rice and colleagues[108] have shown that survival in patients with clinical N1 disease that was down-staged to N0 disease after neoadjuvant therapy was similar to those staged N0 who had surgery alone, thus suggesting a benefit of combined-modality therapy in these patients. However, they also showed that survival was worse in patients with clinical N1 disease after neoadjuvant therapy if they failed to respond than in patients with similar clinical stage tumors that were treated by surgical resection alone. Using a similar statistical modeling approach in another publication,[109] the same group reported improved survival after neoadjuvant therapy in patients with clinical T3 N0 disease and in those with N1 disease if they responded to therapy. However, they concluded that survival was worse after neoadjuvant therapy in patients with clinical T1 or T2 tumors than would be expected had they undergone surgical resection alone.

SUMMARY

Changes in the diagnosis, evaluation, and treatment of carcinoma of the esophagus and GEJ have resulted in an improved prognosis for patients with this uncommon but deadly disease. Recent changes in epidemiology combined with a heightened awareness of the association between reflux, Barrett's metaplasia, and esophageal adenocarcinoma have allowed for earlier recognition and treatment. A more sophisticated approach to invasive and noninvasive preoperative staging with endoscopy, EUS, CT, and PET scanning has improved the selection of patients for a variety of treatment modalities. A tailored approach to the management of these patients can result in an overall 5-year survival rate greater than 50%, a dramatic improvement over the dismal results reported in the past.

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Chapter

35

Palliative Treatment of Carcinoma of the Esophagus

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Despite advances in staging and in oncologic and surgical treatment of esophageal and junctional tumors, 5-year survival rates remain stubbornly between 10% and 15% at best. Thus, the majority of patients with these cancers will require some form of palliative treatment. As a result of unacceptably high postoperative mortality and morbidity, health commissioning bodies in both the United States and the United Kingdom have directed centralization of esophageal resection to centers performing a "high" volume of resectional surgery (in the United States, centers with more than 10 resections per annum; in the United Kingdom, units serving greater than 1 million population). It is enigmatic that no direction or resources have been allocated to the palliative treatment of such patients, who represent the majority of patients and for whom the appropriate choice of treatment is essential.

Patients requiring palliation fall into two groups: those who for reasons of metastatic disease, age, comorbid condition, or choice are unsuitable for radical surgery or chemoradiotherapy and those who have undergone treatment with curative intent but the disease recurs. The goals of palliative treatment are, first, to relieve the specific symptoms of dysphagia, mediastinal pain, and bleeding and, second, to delay death as a result of metastatic disease with minimal comorbidity. These goals must be accomplished within a few months inasmuch as 60% or more will have died within 6 months of diagnosis.[1]

Selection of palliative treatment must be individualized for each patient and be based on the physical characteristics and location of the tumor, the performance status and age of the patient, tumor burden, and expected survival. Other considerations are the availability of home support, traveling time between home and hospital, and finally, the local facilities and expertise at the hospital of treatment. These decisions can be difficult and should not be made by individual clinicians in isolation. In the United Kingdom National Health Service, all upper gastrointestinal cancer patients (whether undergoing curative or palliative treatment) are discussed at a weekly multidisciplinary team (MDT) meeting. The upper gastrointestinal MDT meeting is attended by upper gastrointestinal surgeons, gastroenterologists, radiologists, oncologists, histopathologists, and palliative care and cancer specialist nurses. The central figure in these meetings is the upper gastrointestinal cancer nurse specialist, who acts as the patient's advocate and the point of contact for the patient.

ASSESSMENT OF PATIENTS REQUIRING PALLIATIVE TREATMENT

The scope of clinical and laboratory investigations depends on the individual patient's circumstances. For example, an 80-year-old patient with ischemic heart disease, a 5-cm tumor causing grade IV dysphagia, and 5 hours' traveling time from the treatment center may best be served by a "one-off" treatment, such as a self-expanding stent or brachytherapy. Such a patient may require a full blood count and electrolyte assay to enable transfusion or rehydration to be delivered concurrently. Computed tomography (CT) and endoscopic ultrasound are superfluous and will not alter the management. A 50-year-old patient, however, with good performance status and celiac nodal or hepatic secondaries may require tumor staging by CT to further assess the metastatic load, as well as appropriate biochemistry evaluation to determine whether nephrotoxic chemotherapy may be administered.

Careful assessment must be made of the patient's dentition and ability to swallow. The site, length, and nature of the tumor (e.g., whether it crosses the cardia, is scirrhous or exophytic, and is single or multifocal) must be evaluated. This is best done endoscopically, although barium studies can assist when tumor growth precludes

Box 35–1 Palliation of Malignant Dysphagia

Endoscopically Delivered

- Bougienage (dilatation)—can be rigid pulsion dilators such as the Savary-Gilliard or balloon dilators
- Chemical—alcohol injection
- Stents—self-expanding metal stents (SEMS). Stents can be covered/uncovered/impregnated with a chemotherapeutic agent
- Thermal energy
  - Nd-YAG laser
  - Argon beam coagulation (ABC)
  - Bipolar cautery (Bicap)
  - Photodynamic therapy (PDT)

Oncologic Treatment

- Radiotherapy
  - External beam
  - Brachytherapy
- Chemotherapy
  - Single agent
  - Multiagent

Surgical

- Palliative resection
- Bypass surgery
- Exclusion therapy and nutrition.

endoscopic assessment of the distal extent and dilatation is contraindicated.

Psychological support is paramount for patients with malignant dysphagia. This devastating symptom adversely affects quality of life and is embarrassing for both the patient and relatives in the social context of eating a meal.

The various methods available for palliation of malignant dysphagia are presented in Box 35–1. Table 35–1 lists the advantages and disadvantages of each method. Many of the treatments can be administered concurrently, with improved results—for example, external beam radiotherapy can enhance the effects of laser ablation of esophageal cancer.[2] The concept of one treatment being appropriate for all patients has been abandoned.

ENDOSCOPIC METHODS OF PALLIATION

Alcohol Sclerotherapy

Small (0.5 to 1 ml) aliquots of 98% ethanol can be injected sequentially into the tumor with an endoscopic varices needle. This method is cheap, readily available, and repeatable. Most patients experience some discomfort during and shortly after injection and require supportive analgesia. Randomized studies[3] have compared alcohol therapy with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser ablation: both treatments produced similar improvement in dysphagia scores, but further treatments were required at the same time intervals (approximately 30 to 42 days). Return to feeding was achieved in similar proportion (laser, 88%; alcohol, 78%). The alcohol-treated group took a few days longer to begin normal feeding, probably because of the time needed to achieve tumor necrosis. Failure to relieve dysphagia—as indicated by stent insertion—was equivalent at around 12%.

Chemotherapeutic drugs (mitomycin C, bleomycin, cisplatin, and doxorubicin) have also been injected directly into esophageal tumors in the form of a gel matrix, but this technique has not gained widespread acceptance.

Bougienage

The first dilators were made of wax, hence the term "bougie" from the name of the Algerian town of Bougiyah, the medieval capital of the wax trade. The first description of their use took place 4 centuries ago. Mercury-filled dilators were introduced in 1915, but not until the development of fluoroscopically controlled, guidewire-assisted olive dilators in the 1950s (Eder-Puestow) was effective dilatation of neoplastic strictures possible. The subsequent development of hollow-core polyvinyl dilators (Savary-Gilliard) and through-the-scope (TTS) balloon dilators further refined these techniques.

The introduction of safe expansile metal prostheses has tended to supersede palliative esophageal dilatation for the relief of malignant dysphagia, although the latter remains a helpful initial approach in up to 90% of patients for whom a period of reasonable swallowing may be achieved.

Poiseuille's law and equation relate volume flow in a cylindrical tube model to the fourth power of the vessel's radius. Thus, a small decrease in the diameter of the esophagus by encroaching tumor can rapidly lead to worsening dysphagia and vice versa. A small improvement in luminal diameter may therefore be temporarily helpful. The technique of either bougienage or TTS balloon dilatation is simple and inexpensive and can easily be accomplished as a day (office) case, and the equipment is widely available. Although esophageal dilatation alone may effectively and safely palliate stenosis secondary to carcinoma, the effect is only temporary, particularly with carcinomas that are more scirrhous, for which the technique may need to be repeated every 10 to 14 days. Thus, even though up to 90% of patients will achieve palliation, the length of time before another dilatation is required is variable and unpredictable. Any initial savings over a prosthesis may therefore be lost by the need for repeat dilatation and, on rare occasion, by an inpatient stay after perforation. This complication may approach an incidence of 5% with neoplastic strictures and, though a major setback in any patient, is a

Table 35–1 Advantages and Disadvantages of Methods for Palliation of Malignant Dysphagia

Method	Advantages	Disadvantage
Bougienage	"Office" based Simple and inexpensive Readily available	Repeated treatments necessary Temporary relief of symptoms Risk of perforation
Stent	Short stay Simple Readily available "Treats" perforation/fistula Single treatment	Expensive May be painful Tumor overgrowth Stent slippage
Alcohol injection	"Office" based Inexpensive Readily available	Least reliable in efficacy Not beneficial for long tumors Repeated treatment necessary
Nd-YAG laser	Effective for exophytic, short tumors Office based	Expensive capital outlay Repeated treatments necessary Risk of post-treatment hemorrhage and perforation Not widely available
Argon beam coagulation	"Office" based Inexpensive Effective with short superficial tumors Less penetrative power than laser (less risk of perforation)	Repeated treatments Less effective with long, extensive tumors
Photodynamic therapy	"Office" based Prolonged length of effect Effective for long, tortuous tumors	Not readily available Photosensitivity
Radiotherapy		
Brachytherapy	Single treatment Successful with short tumors	Not widely available Esophageal lumen patency required No use with long tumors Time lag to efficacy
External beam	Reasonably effective	Wide effect Certain degree of patient fitness needed Repeated visits to hospital Time lag to efficacy
Chemotherapy	Effective with systemic disease	May require venous infusion and portable pump Toxic gastrointestinal and hematologic side effects Requires frequent monitoring

disaster for those in whom curative surgery is still a possibility because such patients can be rendered incurable by this complication. Preoperative dilatation in such potentially operable patients should either be avoided or be undertaken with particular caution.

Role of Esophageal Prostheses as Palliation for Obstructing Carcinoma

The alternative approach to dilatation, or placement of a per oral prosthesis, provides for more long-lasting palliation. Though originally placed surgically via a "pull-through" technique, the procedure was associated with high morbidity and mortality. The advent of fiberoptic endoscopy led to the development of pulsion techniques of placing a plastic prosthesis over a guidewire under fluoroscopic control. A number of different prostheses became available, usually manufactured from radioresistant, radiopaque latex, rubber, or polyvinyl chloride that was reinforced with a nylon or metal coil to prevent kinking and included a proximal and distal flange to help prevent migration. These tubes were unpleasant and sometimes traumatic to place for both the patient and operator. The tumor frequently required maximal dilatation to 54 or 58 French before placement because a large "rammer" tube with an outside diameter of 30 mm was necessary to hold the endoprosthesis in place as the flanged wand was deployed to release the prosthesis in the required position. The procedure caused high morbidity in approximately 20% of patients with esophageal perforation rates of about 10%. Procedure-

related mortality was usually less than 8% but could be as high as 25%. Despite these limitations, however, such plastic stents have provided effective palliation with relief of dysphagia for semisolid food in up to 90% of patients. Studies to determine whether combining modalities such as laser plus intubation were somewhat equivocal, with little advantage over each technique used singly.

The development of a new class of endoprostheses in the early 1990s was a major breakthrough. An expansile tube manufactured from metal mesh, compressed and restrained on a delivery device of small diameter, meant that maximal esophageal dilatation was no longer required before deployment. The ability of these self-expanding metal stents (SEMS) to expand to a large diameter also offered the prospect of rapid and effective palliation and other benefits with minimal morbidity and mortality. The high initial cost of these stents (≈1250 Euros each) in comparison to plastic stents is more than compensated for by their ease of placement, reduced procedure time, reduction in morbidity and mortality, and decreased hospital stay, thus making them highly cost-effective.[4] One study showed that 4 weeks after insertion, the cost associated with SEMS and plastic endoprostheses was not significantly different.[5]

SEMS have been compared with other palliative modalities, including laser therapy and brachytherapy. A randomized trial of laser therapy alone versus uncovered stents seemed to favor uncovered stents for palliation of dysphagia.[6] However, a trial of single-dose brachytherapy seemed to give better long-term relief of dysphagia with fewer complications, although relief of dysphagia was more rapid with a stent.[7] Initial studies with stents impregnated with chemotherapeutic agents have, however, been disappointing.[8]

Stent designs vary. Although some original stents (e.g., Ultraflex) were bare mesh, which had the advantage of better anchoring properties,[9] there were problems with occasional rapid stent occlusion by tumor ingrowth. The use of covered stents has been shown to result in a reduction in the need for subsequent endoscopic procedures,[9,10] and their use is now standard practice. These stents have expanded flanges or flared ends to minimize migration, are simple to deploy, and are available in varying lengths. Studies comparing various types of covered stents in various locations indicate equal efficacy and complication rates for the different types of stents available.[11,12] Some authors have suggested that stenting for tumors of the distal esophagus and gastric cardia may be associated with a greater number of problems, particularly migration of the stent.[13,14] However, a randomized prospective comparison of the Flamingo Wallstent and Ultraflex for lower third tumors, including those across the gastroesophageal junction, failed to demonstrate any difference in efficacy or complication rates. There was, however, a suggestion that the lower end of the more flexible Ultraflex was less likely to impinge on the gastric wall and cause outlet obstruction.[12]

SEMS are effective not only for intrinsic esophageal neoplasms but also for extrinsic compression from mediastinal tumors and esophagobronchial fistulas. In this particular situation, nitinol-covered stents (e.g., Ultraflex) may be preferable to stainless steel–covered stents (e.g., Flamingo Wallstents) because they seemed to more frequently provide complete esophageal fistula sealing.[15]

Tumors of the cervical esophagus present a particular problem and can be difficult to manage.[16] Stents deployed too near the cricopharyngeus may cause odynophagia and a permanent foreign body sensation, and thus accurate placement is essential. Using stents that release proximally (e.g., Ultraflex) may be helpful in this situation. Similarly, with this proviso, stent placement after esophagectomy is also feasible.

Technique

Placement of SEMS is usually performed as a day case, either endoscopically with fluoroscopic control or radiologically. The patient is normally sedated with a benzodiazepine hypnotic, with or without throat spray and opioid analgesia, depending on the operator's preferences. The upper and lower margins of the tumor need to be demarcated, which is most conveniently accomplished by placing external skin markers under fluoroscopy. For endoscopic placement, impassable strictures may require gentle dilatation before passage of the endoscope and placement of a stiff guidewire into the distal antrum/proximal duodenum. The stent is advanced across the stricture, preferably leaving a covered margin of 1 cm distally and 2 cm proximally. Radiopaque markers on the stent release system allow accurate placement (Fig. 35–1). Releasing mechanisms vary in type and complexity. The Flamingo Wallstent has an outer constraining sheath that is retracted. This has the advantage of allowing resheathing and adjustment of prosthesis position, provided that not more than 50% of the stent has been deployed. The Ultraflex stent is constrained by a circumferential thread that is deployed by pulling on the suture ring. However, this stent is now available with a sheathing mechanism (Figs. 35–2 to 35–4). After release of the stent, the position can be checked with contrast or endoscopically (Fig. 35–5); in the absence of clinical indications of perforation, the patient is allowed to drink 2 hours later and to start a soft diet after 6 to 8 hours. Full expansion of the stent may take several hours, depending on the degree of stenosis and rigidity of the tumor.

Chest pain is common as the stent expands, but other than this, early complications are rare. If immediate perforation occurs, such as after initial dilatation, the operator should continue to deploy the stent to seal the perforation. In this case, a subsequent water-soluble contrast study to ensure that there is no continuing leak is necessary before allowing the patient anything by mouth.

The major disadvantages of the technique remain stent migration and tumor overgrowth at the proximal or distal ends of the prosthesis (Fig. 35–6). Stents that migrate into the stomach can usually be left in situ without complication or risk. If they do require removal, it is best achieved by passing a snare to the middle of the stent, compressing it, and pulling it upward in an inverted "V." If a stent has slipped, thereby allowing tumor to once again obstruct the lumen, or if tumor overgrowth occurs, a further stent can usually be

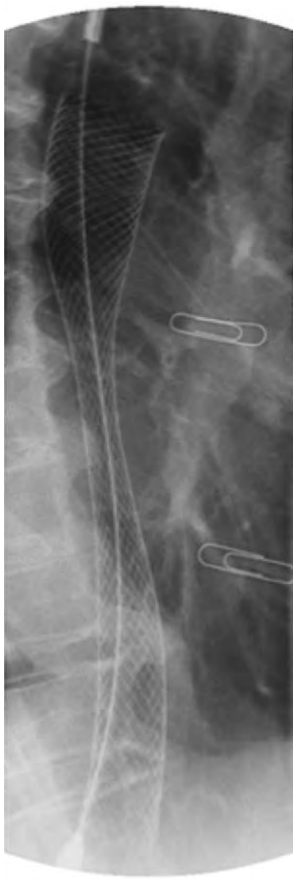

Figure 35–1. Radiograph of a deployed Flamingo stent crossing an esophageal tumor. The narrowing of the stent is at the area of the tumor. The paper clips are placed on the patient's skin and mark the proximal and distal extent of the tumor before stent deployment.

Figure 35–2. Ultraflex stent before deployment showing a retaining suture.

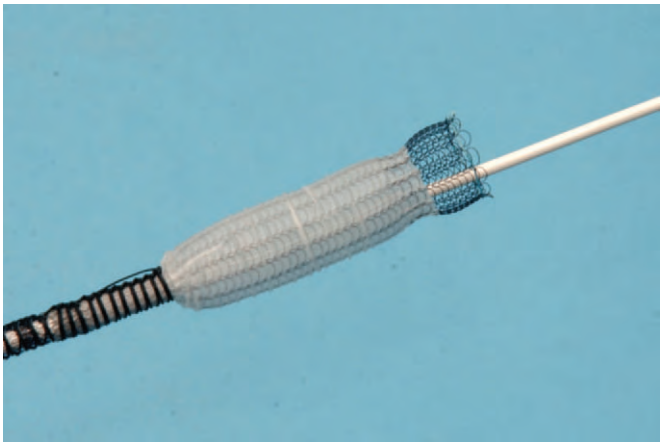

Figure 35–3. Ultraflex stent showing traction on the thread-releasing suture with stent release.

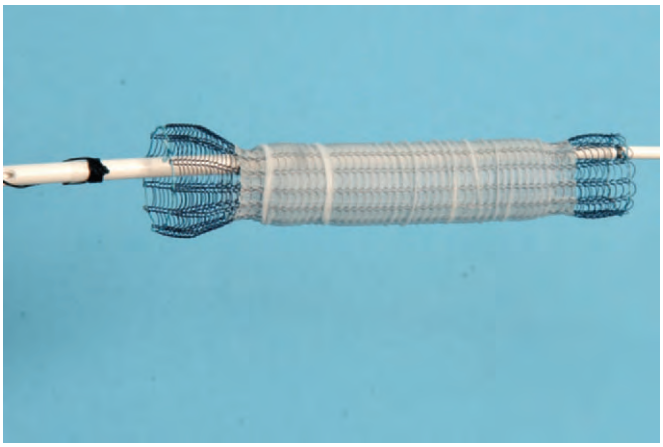

Figure 35–4. Ultraflex stent fully deployed.

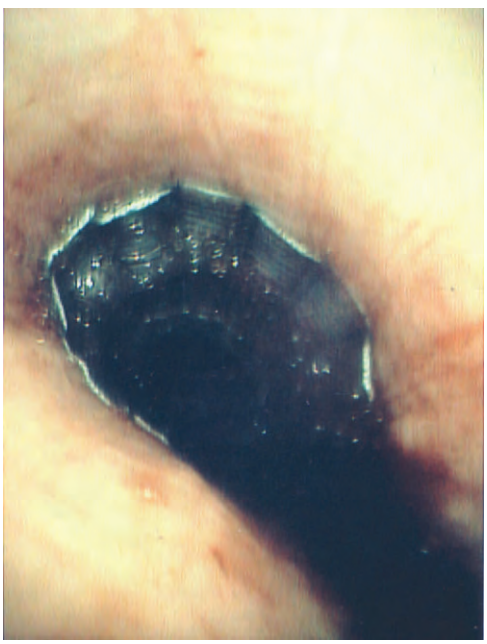

Figure 35–5. Endoscopic appearance of the proximal end of the stent after deployment.

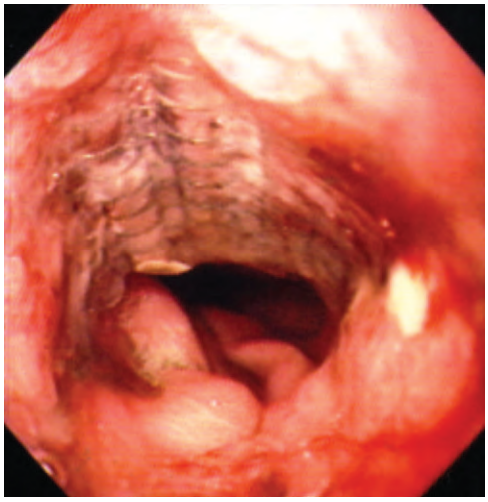

Figure 35–6. Endoscopic appearance of a tumor growing through an uncovered Ultraflex stent.

"piggy-backed" onto the original stent without difficulty. Laser, argon, or alcohol injection therapy can also be used for tumor overgrowth.

Special Considerations

Esophageal dilatation results in transient but significant bacteremia, and prophylactic antibiotics should be given to patients at moderate or high risk for endocarditis. Patients with friable tumors who are taking anticoagulants can bleed significantly after dilatation, and depending on the risks and circumstances, it may be appropriate to consider withdrawing or reversing oral anticoagulation before the procedure.

Stents placed across the gastroesophageal junction will allow free reflux of gastric contents into the esophagus. This can be a significant problem, not only initially but also in the longer term.[14] All patients should be placed on a long-term regimen of acid inhibition. To minimize such reflux, stents with antireflux mechanisms, usually a windsock-type valve at the lower end, have been developed and are reported to be effective in this situation.[17] However, a randomized trial has failed to demonstrate benefit over a standard open stent.[18]

Because stents do not usually allow completely normal swallowing of all solid food, it is essential that all patients with an esophageal stent have reasonable dentition to allow effective mastication. It is also useful to advise patients to disrupt food boluses with carbonated drinks every two to three mouthfuls to minimize the possibility of bolus impaction of the stent. Should bolus impaction fail to resolve spontaneously, endoscopic disimpaction is usually necessary.

Thermal Treatment

Heat can be used to destroy esophageal tumors. The three most common methods are argon beam coagulation (ABC), bipolar diathermy, and laser treatment.

Argon Beam Coagulation

ABC relies on the electrical ionization of argon gas, which is conducted down an argon coagulation probe passed through the endoscope instrument channel. A readily visible white/blue light is produced. The argon beam has a penetration depth of 2 to 3 mm, less than that of an Nd:YAG laser, and thus the risk for esophageal perforation is less but the number of treatments required may be more. The preferred method is to commence treatment distally; some patients may require prior esophageal dilatation. Heindorff et al.[19] from Denmark reported complete recannulation in one treatment session in 58% of 83 patients undergoing ABC; 26% required repeat treatments (average of six) at approximately 25- to 30-day intervals. Two thirds of patients maintained esophageal patency until the time of death, but in this study a third required stenting. Perforation can occur with ABC in approximately 2% of patient treatments.[20] Thus, ABC, perhaps unfairly, can be called a poor man's laser; when compared with the Nd:YAG laser, its advantages are relatively low capital and revenue costs and a slightly lower risk for esophageal perforation, but against these advantages must be weighed the increased number of treatment sessions required to maintain luminal patency.

Bipolar Electrocoagulation

Bipolar electrocoagulation uses olives of varying diameter mounted onto a semiflexible shaft that is passed over an endoscopic guidewire previously inserted into the stomach. An electric current is passed through the olive, which is placed at the level of the tumor. The applied current generates heat and produces tumor necrosis over a depth of 2 to 4 mm as the olive is pulled back through the tumor. This system is particularly suited to treat circumferential tumors because contact with normal esophageal tissue may result in perforation and fistulation. In a comparison of bipolar electrocoagulation and Nd:YAG laser treatment, approximately 85% of both groups experienced improvement in swallowing. Bipolar electrocoagulation is particularly suited for long circumferential tumors.

Nd:YAG Laser

The light energy of the laser is converted to heat by molecular agitation of tissue. The greater the absorption of light, the greater the molecular agitation and the greater the depth of tissue destruction. The usual depth of penetration of the Nd:YAG laser is up to 4 to 5 mm.

The preferred method of laser cannulization of esophageal tumors is retrograde therapy. Pretreatment lumen dilatation may be necessary in up to a third of patients to enable the endoscope to pass down the length of the tumor so that distal treatment can be performed first. In this manner the entire length of tumor can be treated in one session. Prograde treatment may result in an increased perforation rate.

Laser treatment is particularly indicated for short (<5 cm) exophytic tumors arising in the tubular

esophagus. It has now become one of the standard treatments and may provide good palliation until death in up to 75% of patients.[21]

In a recent prospective study from Scotland of 948 patients undergoing palliative treatment of esophageal cancer, the laser was used in 117.[1] Trials comparing laser with stents and laser with bipolar coagulation have demonstrated similar efficacy, but morbidity and mortality were greater in patients in whom stents were used.

Complications of laser therapy include perforation (1% to 10%), although dilatation before laser treatment may be partially responsible for this. Perforation may be more common in those in whom laser treatment followed radiotherapy. Hemorrhage and tracheoesophageal fistula have been reported, as has stricture formation, especially in patients with submucosal lesions. An analysis of 350 patients treated by laser alone showed that tumor length, histologic type, and site had no effect on either survival or relief of dysphagia; the worse the dysphagia score at initial evaluation, the poorer the survival.[22]

The effect of laser therapy can be enhanced by chemotherapy with epirubicin, cisplatin, and 5-fluorouracil (5-FU); this combination resulted in increased survival in comparison to laser alone and laser plus 5-FU/folic acid, in addition to no additional laser treatments being needed until the time of death.[22] The combination of external beam radiotherapy[2] or brachytherapy[23] and laser treatment can markedly reduce the requirement for further endoscopic therapy. Laser treatment may need to be repeated on average every 4 weeks, and tumor progression may require stent insertion (up to 27%).[22]

Lasers have been compared with SEMS in a randomized trial.[24] This study showed longer survival (125 days) in the laser group than in the stent group (68 days). The median hospital stay and cost of treatment (largely related to overnight hospital admission) for the laser group were twice that for the stent group. This study reported equally disappointing results in the relief of dysphagia 1 month after treatment in both the stent and laser groups but noted that pain was more prominent in the stent group.

Endoscopic Photodynamic Therapy

In photodynamic therapy (PDT) an exogenous synthetic photosensitizer is administered orally or intravenously, and after 2 to 3 days, during which time the photosensitizer accumulates in the malignant tissues (as well as normal tissues), light of appropriate wavelength is directed at the tumor by means of an endoscopic or a windowed balloon. The excited photosensitizer damages the mitochondrial and lysosome membranes and thereby induces cellular destruction. A randomized trial has shown PDT to be as effective as the Nd:YAG laser in the initial relief of dysphagia, but the effect was more long lasting in the PDT group[25] and may last up to 80 days.[26] Perforations were more common after laser treatment (7%) than after PDT (1%).

PDT is useful in patients with completely obstructed tumors, long and tortuous tumors, and high cervical tumors in which it is difficult to use a laser probe. The depth of tumor destruction is very predictable after PDT therapy.

PDT is not widely available, thus limiting its potential for use. Moreover, natural light exposure may cause skin photosensitivity in up to 20%, but this problem can be reduced by the use of endogenous photosynthesizers. PDT application in selected patients may have dramatic results.

ONCOLOGIC MANAGEMENT

Options

Various treatment modalities can be implemented for the palliation of esophageal cancer, including radiotherapy (external beam and brachytherapy), chemoradiation, and chemotherapy. All have their place.

External beam radiotherapy and brachytherapy can be effective in palliating symptoms attributable to the primary disease, and in recent years chemoradiation has become an additional option. Locally advanced and disseminated disease can be helped by systemic chemotherapy. It can be given as a single agent or as combination therapy.

Patients who are not fit enough to tolerate active treatment can still benefit from best supportive care. Appropriate medications such as antiemetics, appetite stimulants, analgesics, and blood transfusions, given together with psychological and social support, can significantly improve the quality of life of terminally ill patients.

Radiotherapy

Patient Selection

Patients with predominantly local symptoms such as mediastinal pain, dysphagia, and local bleeding are likely to benefit most from local therapy. Radiation therapy is frequently the most appropriate choice in such circumstances.

Improvement in symptoms will often only occur over a number of weeks. Hence for patients with very severe dysphagia, stent insertion achieves a more immediate improvement in swallowing and is more appropriate. Radiotherapy may be offered subsequently should symptoms recur with the stent in situ.

Frail patients will frequently be offered relatively low-dose radiation schedules that may still provide meaningful palliation of symptoms for a period. Patients with good performance status but whose tumor is not suitable for radical therapy (usually because of the length and position of the tumor or regional or distant spread) can at times be offered higher-dose schedules, often with combined external beam radiotherapy and brachytherapy or sometimes combined with chemotherapy. These treatments may achieve more prolonged control of symptoms. The balance of risks and benefits with such interventions in the noncurative setting must be carefully weighed.

External Beam Radiotherapy

External beam therapy involves the application of radiation from an external source onto appropriate target areas within the patient. When used as a simple palliative treatment, it is relatively quick and easy to plan, verify, and deliver. All procedures are minimally invasive for the patient and involve a short visit to the simulator (either CT for virtual simulation where the tumor can be viewed directly on a planning CT scan or conventional simulation with real-time diagnostic x-ray image intensified screening and a barium swallow to visualize the tumor stricture), with a typical low-dose regimen consisting of 5 to 10 daily treatments. Each session takes approximately 10 to 15 minutes to set up and deliver.

This treatment is appropriate for patients with a bulky tumor (because the bulk of the disease can easily be encompassed in the irradiated volume), mediastinal pain, or a stricture that significantly interferes with the practicalities of administering brachytherapy. Disadvantages include the requirement for several visits to the radiotherapy department for treatment. In addition, adjacent noninvaded normal tissues may be irradiated and damaged. Modern radiotherapy technique includes shaping the radiation field to the shape of the tumor by excluding normal tissues with blocks or multileaf collimators. This is known as simple conformal radiotherapy. External beam radiotherapy has been shown to provide palliation of dysphagia in approximately 70% to 80% of patients and is effective until death in 50%. An increased dosage may achieve greater palliation by combining external beam therapy with local brachytherapy.

Brachytherapy

Intraluminal brachytherapy involves the insertion of a radioactive source into the lumen of the esophagus via an endoscope or nasogastric tube. Modern high-dose-rate (HDR) brachytherapy can deliver high doses of radiation over short periods, thereby allowing acceptable time for palliative treatment of patients. The usual isotope is iridium 192, and the dose is generally prescribed for treatment at a distance of 1 cm from the source. This treatment is practical and convenient for patients, who can often be treated in a single treatment session. Elderly patients (unless very frail) may prefer this. Moreover, since radiation is administered to the site of the tumor intraluminally, this treatment allows a high dose to be delivered to the tumor site with minimal irradiation of the surrounding normal tissues because of rapid falloff of the dose. This limits toxicity and is particularly suitable for patients with exophytic disease.

The major limitation of brachytherapy is the effective treatment distance. Treatment with ^{192}Ir is suboptimal at a distance greater than 1 cm; as a consequence, very thick tumors will be undertreated at their periphery.

Sources are usually introduced via a nasogastric tube. More frail patients can find the invasive nature of this treatment rather distressing. Furthermore, such treatment may not be technically feasible if the patient has a very tight stricture through which the introducing equipment cannot be passed; these patients require pretreatment dilation.

Homs et al.[27] reviewed 149 patients in a retrospective analysis. Patients were treated with HDR brachytherapy in one or two sessions at a median dose of 15 Gy. Six weeks after treatment, dysphagia scores had improved, although dysphagia had not improved in 51 patients. Procedure-related events occurred in 11 patients (7%), and late complications such as fistulas or retrosternal pain developed in 12 (8%). Procedure-related mortality occurred in 2%. At follow-up, 55 (37%) patients suffered recurrent dysphagia, and 34 (23%) required insertion of a stent.

A prospective randomized trial using HDR brachytherapy as the sole modality for palliation of advanced esophageal carcinoma was performed by the International Atomic Agency.[28] Two hundred thirty-two patients with inoperable squamous cell carcinoma of the esophagus were randomized to receive 18 Gy in three fractions or 16 Gy in two fractions on alternate days. The median overall dysphagia-free survival for the whole group was 7.1 months, and the median overall survival for the whole group was 7.9 months.

Combined Radiation Therapy

The combination of brachytherapy and external beam radiation therapy may offer effective palliation with acceptable complication rates.

Hujala et al.[29] reported on 40 patients with inoperable esophageal cancer treated with combined external (median dose, 40 Gy in 20 fractions) and intraluminal (median dose, 10 Gy in 4 fractions, on average 1 week after external beam radiotherapy) radiation therapy. Forty percent of patients attained immediate symptomatic relief, and no major complications were encountered.

Similarly, Sharma et al.[30] assessed 58 patients with advanced or recurrent esophageal carcinoma. Thirty-eight patients received intraluminal brachytherapy alone, and 20 received a combination of external beam radiotherapy and brachytherapy. Overall improvement in swallowing was seen in 22 patients (38%). The median dysphagia-free survival was 10 months. The overall complication rate was 30%. Strictures developed in 9 (16%) patients, ulceration in 6 (10%), and fistulas in 3 (5%).

Several trials have showed less favorable outcomes—particularly in the curative setting. The RTOG 92-07 trial[31] investigated 75 patients with carcinoma of the thoracic esophagus. Patients received a combined-modality regimen of 5-FU and cisplatin during weeks 1, 5, 8, and 11 concurrently with 50 Gy of external beam radiotherapy, followed by a boost during cycle 3 of chemotherapy with intraluminal brachytherapy—either at a low dose rate (19 patients not included in the final analysis because of low accrual) or at a high dose rate (56 patients, treatment given in weekly 5-Gy fractions during weeks 8, 9, and 10). The complete response rate was high at 73%, with a median follow-up of only 11 months. However, local failure occurred in 27% of patients. Acute toxicity was marked, with 58% having grade 3 toxicity and 26% grade 4, and treatment-related deaths occurred in 8%. In view of such toxicity, higher treatment doses

are not suitable for palliation and can be considered in the curative setting only with considerable caution.

Chemoradiation

Chemoradiation combines radiation therapy with chemotherapy. It can offer the benefits available from both modalities and can increase the effectiveness of radiotherapy. Chemoradiation can have an important role in the management of unresectable esophageal cancer both for palliation of dysphagia and for longer-term disease control. This more aggressive approach verges toward giving radical regimens to incurable patients and is not considered appropriate by some authors. However, patients with good performance status, minimal comorbidity, and incurable disease may well benefit from a more intensive treatment regimen aimed at longer-term palliation than that achievable with the standard short-course palliative radiotherapy.

The practicalities of treatment planning and attendance over prolonged periods, together with probable toxicities (in the form of acute esophagitis, pneumonitis, and pericarditis with longer-term strictures and fistulas, as well as chemotherapy-induced toxicities), must be considered. Toleration of the side effects of treatment must be balanced against presumptive gain of symptom relief and longer-term benefit. All must be evaluated before undertaking complex treatments that may offer minimal improvement of symptoms over that derived from a simple and short treatment course. Modern radiotherapy techniques using conformal radiotherapy make this approach more appropriate for some patients.

Chemoradiation for suitable patients has been shown to be superior to external beam radiation alone. It is now standard practice to use 5-FU (by continuous infusion on days 1 to 4 and 29 to 33 and cisplatin on days 1 and 29), with concurrent external beam irradiation.

Two thirds of patients obtain palliation of dysphagia until death, but disadvantages of chemoradiation are the time taken to achieve palliation (up to 6 weeks) and discontinuation of chemotherapy as a result of toxicity (up to 25%).

Chemotherapy

Patient Selection

Chemotherapy is appropriate for patients who have symptoms from disseminated disease. The object in this situation is to palliate symptoms and improved quality of life rather than cure the disease. Local symptoms may also be palliated by chemotherapeutic agents, particularly if the tumor has become tolerant of radiation.

Therapy is chosen to suit the patient's fitness and tolerability of the toxicity profile. Different cytotoxic agents have differing toxicity profiles, and the physician and patient must together examine the risks and benefits of treatments. Side effects include general fatigue and malaise, myelosuppression with a risk for neutropenic sepsis, gastrointestinal problems (nausea, vomiting, and diarrhea), mucositis, hair loss, neurotoxicity, and renal toxicity among others.

Administration of cytotoxic drugs to patients with recurrent or metastatic carcinoma of the esophagus is often challenging. Such patients may be elderly with comorbid conditions. Their nutritional status is often poor, and their tumor burden is also frequently high. These factors together result in poor performance status and an impaired ability to tolerate treatment.

Each cycle of chemotherapy will consist of one or more drugs over a period of 3 or 4 weeks. Bolus administration of cytotoxic drugs will usually be given in a chemotherapy suite. Some regimens require continual administration as a protracted central infusion via an ambulatory device.

Regular review should be undertaken by the physician throughout the treatment period. Before each new cycle of chemotherapy the patient's toleration of treatment should be assessed.

Response to Treatment

Response is measured both subjectively and objectively. General well-being, pain control, level of fatigue, appetite, and swallowing ability are assessed. These subjective indices can be formalized by using quality-of life questionnaires, dysphagia scores, and pain scores and by analyzing analgesic requirements. Objective measurement of response is advisable midway through a course of treatment. CT images should be reviewed with the use of standard RECIST (response evaluation criteria in solid tumors) criteria. Direct visualization via endoscopy is helpful.

Ensuring an adequate response is essential. If one particular chemotherapeutic regimen is found to be ineffective, alternative regimens should be considered.

Over the last 25 years, many trials have investigated systemic therapy for esophageal cancer, but no regimen has evolved into the gold standard for patients with advanced disease. Several agents have shown modest activity when used alone, but in combination their activity is improved, with acceptable toxicity profiles.

Single-Agent Chemotherapy

Certain chemotherapeutic agents have been shown to be active against esophageal cancer when used alone, but response rates have been modest, with approximately 20% achieving brief symptomatic relief.

Combination Chemotherapy

Combination chemotherapy, though offering an improved response rate over single-agent treatment, may be limited in applicability.

Modern combination regimens include irinotecan and cisplatin. These agents were combined in view of their differing mechanisms of action and toxicity profiles. Ilson et al. used weekly cisplatin and irinotecan to treat 35 patients with advanced esophageal cancer and observed a 57% response rate.[32] The median duration of response was 4.2 months, the median survival was 14.6 months, and toxicity was acceptable; dysphagia and quality of life were improved in the majority of patients.

Several helpful chemotherapy regimens are available for patients with advanced esophageal cancer. Worthwhile benefits in quality of life, including relief of dysphagia in 60% to 80% of patients, can be achieved. Cisplatin-based therapy remains the most favored approach to treatment. The addition of newer drugs, such as irinotecan and paclitaxel, appears to achieve higher response rates, albeit with limited durations of response and increased toxicity.

New Agents

A most recent approach to cancer treatment lies in the production of agents that are designed to target specific molecules involved in potentially important oncologic processes, such as cell cycling, apoptosis, and angiogenesis. Such agents could theoretically produce greater disease responses without excessive toxicity. For example, bevacizumab, a recombinant humanized monoclonal antibody to vascular endothelial growth factor, which already has a place in the management of colorectal carcinoma, is currently being investigated in combination with radiotherapy for esophageal cancer and with irinotecan and cisplatin for gastric and gastroesophageal cancer.[33]

Similarly, the epidermal growth factor pathway is thought to be of importance in the pathogenesis of upper gastrointestinal malignancies.[34] Investigation of inhibitors of this pathway is ongoing.

Oncologic Treatment in Practice

Patients with Prominent Local Symptoms Such as Dysphagia, Pain, and Bleeding

Dysphagia can have a major impact on patient quality of life. Not only is nutritional status compromised with symptoms of general weakness and malaise, but social situations involving meals may also be difficult. Improvement of swallowing by localized therapy can have a major impact on the physical and psychological welfare of such patients.

A patient with a locally advanced esophageal tumor deemed unsuitable for more intensive radical therapy would be palliated with a simple course of palliative radiotherapy (either 20 Gy in 5 fractions or 30 Gy in 10 fractions). Radiotherapy can be planned in the conventional simulator, with patients in the supine position, their arms by their side, the use of a barium swallow, and the field edge placed to give a margin 5 cm superior and inferior and 2 cm lateral to the gross tumor volume, or a virtual simulation program using a CT planning scan to localize the tumor can be deployed (Fig. 35–7). This can allow slightly smaller fields to be used because it permits the physician to be more confident of the tumor position. The usual field arrangement is a parallel opposed pair with the dose directed at the midplane.

A patient with good performance status and minimal comorbidity but unsuitable for radical chemoradiation could be offered a treatment schedule consisting of external beam radiotherapy with or without a brachytherapy boost to the tumor bed. Such a regimen could be 30 Gy in 10 daily fractions or 40 Gy in 20 daily fractions, followed by a brachytherapy boost of 10 Gy at 1 cm 1 to 2 weeks later.

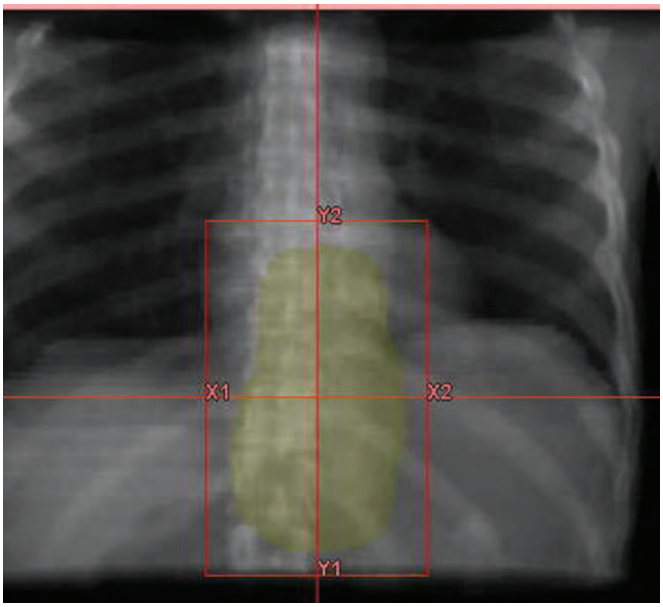

Figure 35–7. Palliative radiation field demonstrated on a digitally reconstructed radiograph. Field borders encompass the contoured volume of the tumor plus an appropriate margin. (Courtesy of Dr. R. Bulusu.)

If the patient found traveling to the radiotherapy center troublesome and had an exophytic tumor such that brachytherapy could be appropriate for palliation, a single high-dose Selectron treatment could planned in the simulator with a barium swallow used for tumor localization. Radiotherapy would be delivered as a single HDR microSelectron treatment of 15 Gy at 1 cm.

If the patient was found to require rapid palliation within a few days because of severe dysphagia, radiotherapy may be considered less suitable than other approaches such as a stent or laser therapy, both of which would have a more immediate effect.

Patients with Systemic Symptoms

Patients with symptoms from disseminated disease such as nausea and malaise, respiratory symptoms from diffuse disease, or pain not amenable to focal irradiation should be offered systemic treatment in the form of chemotherapy. Performance status and comorbid conditions need to be considered when evaluating the tolerability of treatment. Diverse regimens with differing toxicities will be appropriate for various patients, and decisions must be made by both physicians and patients regarding the acceptability of toxicities as a result of treatment.

Best supportive care is appropriate for more frail patients with multiple existing comorbid conditions in whom the benefits of chemotherapy will be outweighed by the potential additional morbidity involved.

Surgical Therapy for Palliation

Before the development of endoscopic means of palliation, intraluminal esophageal stents were pulled through the esophagus into the stomach at laparotomy. Patients with esophageal obstruction were also treated by substernal or subcutaneous colonic interposition or, as a last desperate measure, by cervical esophagostomy and feeding gastrostomy.

The postoperative mortality and length of survival were such that these heroic and fruitless operations have no role in the 21st century when less invasive means of palliation are available.

On rare occasion it may be necessary to place an enteral feeding device to permit maintenance of nutrition when other palliation has failed or when the side effects of palliative treatment (e.g., radiation esophagitis) inhibit oral intake. This situation is most commonly encountered in younger patients who may wish to sustain nutrition for as long a period as possible.

Management of Terminal Patients

The terminal stages of locally advanced cancer of the esophagus are distressing for patients and caregivers. Patients may suffer intractable cough, aspiration, mediastinal pain, and an inability to swallow saliva. Management of the terminally ill is best undertaken by palliative care specialist doctors and nurses. Patients may need ambulatory opioid pumps, portable suction devices, and antisecretory medication. If oral intake is impossible, medication may need to be delivered by transdermal patch or per rectum.

SUMMARY

Palliation of esophageal cancer poses greater challenges than the management of potentially curable disease. It is as necessary to concentrate the care of these patients in centers that have a large range of treatments available and where sufficient experience may be gained as it is to centralize surgery in hospitals performing high volumes of resections.

ROLE OF THE UPPER GASTROINTESTINAL CLINICAL NURSE SPECIALIST

Patient Advocate/Support

The optimum time for the relationship between the clinical nurse specialist (CNS) and the patient to start is at diagnosis. Support at this time is crucial in enabling the patient and family to gain some control over the situation. Once an association is established, then acting as the patient advocate can become the focus. This is an important aspect of care because the majority of patients with upper gastrointestinal malignancy are elderly and tend to be very accepting of the treatment and advice given by the doctor. Patients who start a relationship at this emotionally vulnerable time were found to value the relationship as being meaningful for themselves as well as their family because it developed at a significant life-changing event. A substantial part of the responsibility of a CNS is to support both the patient and the family through this disease, including nurturing the development and maintenance of hope. By achieving this, the nurse is able to bring about balance in the everyday changing life and enable a family to cope with the profound effect of the diagnosis of a terminal cancer.

The support of a health care professional empowers the patient to gain control by providing information to preserve a balance of knowledge, thereby letting patients hope for the best yet prepare for the worst. Doing so involves not only listening but also hearing what is not said in order to formulate a bigger picture of the individual and family. Individual knowledge of the patient's unique environment and culture is also necessary to achieve this goal. The specialist nurse can then use this knowledge to obtain resources that may be required, such as information, financial help, or psychological support. If this is realized, patients will be able to move forward with a positive attitude and visualize themselves as cancer survivors.

Planning is crucial after the diagnosis of a life-threatening illness, and it is the role of the health care team to be involved in this so that the plans made are realistic and in line with the patient's ability and life expectations.

Teacher/Educator

Once the initial shock of a cancer diagnosis is overcome, the majority of patients and caregivers require information, both about the disease and about the proposed treatment plan. Most patients and caregivers regard the CNS as the person with time to share and discuss the choice of treatment and the implications of this choice. Being part of the MDT enables the CNS to shape any treatment plan to a patient's requirement and inform the patient of the latest decision. The need for information continues throughout the cancer journey and emphasizes the importance of the nurse/patient relationship. Often, patients will contact the CNS after treatment to check progress or to receive advice. Written information to back up verbal discussion is always useful because it gives the patient something to reflect on and provokes questions. A patient who is distressed at the diagnosis and treatment can use the booklet to inform family and prevent seemingly endless repeated conversations. It is important that use of medical terminology be minimal and a low reading level be assumed.

Clinical Expert/Promoter of Quality Care

Someone with additional in-depth knowledge of a condition is in a prime position to influence the care that the patient and caregivers receive while undertaking treatment. This area of a CNS role can in some instances provide the key to the patient's cancer journey and enable it to be tailored where possible to individual needs. Gastrointestinal cancer has huge social implica-

tions for patients.[35] Living with cancer requires both physical and emotional strength. Use of nutritional supplements plus frequent meals is the key to weight maintenance and gain. The palliation achieved by stent use has enabled nutrition and hydration to continue in patients with severely advanced disease. This often simple measure goes some way to achieving calmness in both the patient and caregiver because most find the "starvation" aspect of this disease distressing.

Included within this area are the development and encouragement of patient support groups. These groups provide help to patients by patients. Every health care professional should reflect that "the true" expert of a condition is a person who has undergone a similar experience and can therefore fully empathize with the sufferer.

Researcher/Change Agent

Evidence-based practice is now recognized as the way to change clinical nursing practice. This may involve auditing a service (especially a newly developed one) to assess achievements and instigate changes to meet patient requirements.

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Chapter

36

Multimodality Treatment of Esophageal Cancer

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Carcinoma of the esophagus is the fifth most common neoplasm of the digestive system, and it carries an alarmingly high fatality rate. According to recent data from the American Cancer Society, it is estimated that 14,520 new cases of esophageal carcinoma will be diagnosed in the United States in 2005, with estimated deaths of 13,570. In the last several decades treatment modalities and diagnostic imaging for esophageal carcinomas have undergone rapid transformation. Despite this progress, disease-free and overall survival has shown little improvement.[1] Adenocarcinoma is now considered the most common histologic type in North America and Europe, but squamous cell cancer of the esophagus still constitutes the majority of esophageal tumors in other parts of the world. Although controversy remains regarding the relative prognosis and efficacy of various treatment modalities for esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC), most of the relevant studies in the past 20 years have either focused on SCC primarily or combined both histologies in the same study. To the extent that previous reports have described similar responses to therapy for both cell types and there have been no randomized studies that have proved such to be incorrect, we will discuss the treatment of esophageal cancer in general, with mention of the specific histology when available, the caveat to the reader being that the biologic activity of distal EAC and gastroesophageal junction tumor is quite possibly very distinct from that of proximal esophageal and mid-esophageal SCC.

RATIONALE FOR MULTIMODALITY TREATMENT

Historically, radiotherapy was the primary treatment of cancer of the esophagus, especially over the first 2 decades of the last century, but cure was considered a spurious event. The role of esophagectomy evolved in the 1930s. Since then, with progress in anesthetic and surgical techniques, resection became the treatment of choice and relative gold standard for patients with localized disease. However, the more recent evolution in the understanding of cancer biology, en bloc resection techniques, and advances in critical care has failed to significantly improve the survival of patients with locally advanced disease over the past 30 years. It is known that most patients with esophageal cancer will have advanced disease at initial evaluation. Although patients would benefit from aggressive surgical therapy if their disease were detected at an early stage, we currently lack an effective screening modality for esophageal malignancy. Because of the modest results achieved with surgery alone, the lack of effective early detection strategies, and the fact that other treatment modalities have been shown to have efficacy to a certain extent, multimodality treatment became the focus of interest for several trials in an attempt to investigate the role and timing of each treatment method.

TREATMENT MODALITY

Radiation Therapy

Preoperative Radiation Therapy

At the turn of the last century, radiotherapy was considered the primary method of treatment of esophageal cancer. First applied as radium bougies and then as kilovoltage external beam therapy, radiation was shown to have the ability to down-stage tumors, achieve an occasional complete pathologic response, and sterilize areas outside the operative field. However, toxicity such as pulmonary fibrosis was a frequent complication of this treatment modality. Although radiation was originally applied as an alternative to esophagectomy, later treatment efforts sought to improve on the results of surgery with the use of preoperative or postoperative radiation treatment.

Table 36–1 Randomized Trials of Preoperative Radiation Therapy for Esophageal Cancer

Investigators	Year	Histology	Total Patients	Treatment	5-Year Survival (%)	*P* Value
Launois	1981	SCC	124	Surgery + XRT (40 Gy)	9.5	NS
				Surgery alone	11.5	NS
Gignoux (EORTC)	1987	SCC	208	Surgery + XRT (30 Gy)	10	NS
				Surgery alone	9	NS
Wang	1989	SCC	206	Surgery + XRT (40 Gy)	35	NS
				Surgery alone	30	NS
Arnott	1992	SCC/EAC	176	Surgery + XRT (20 Gy)	9	NS
				Surgery alone	17	NS

EAC, esophageal adenocarcinoma; EORTC, European Organization for Research and Treatment of Cancer; NS, not significant; SCC, squamous cell carcinomas; XRT, x-ray therapy.

Nonrandomized Trials of Preoperative Radiation Therapy Several nonrandomized trials have assessed preoperative radiation therapy, the earliest of which was conducted in 1970 by Akakura and colleagues and more recently by Liu in 1986.[2,3] These trials focused mainly on SCC, and the therapeutic approach ranged from hyperfractionated to hypofractionated radiation therapy in doses ranging from 20 to 64 Gy. Many of the uncontrolled trials showed significant improvement in resection rates and overall survival that was attributed to the additional radiation therapy. These studies were the basis for the subsequent randomized controlled trials that follow.

Randomized Trials of Preoperative Radiation Therapy The apparent success of the nonrandomized trials encouraged investigators to conduct several randomized prospective trials to establish whether preoperative radiotherapy (20 to 40 Gy) could have a role in decreasing local recurrence and improving survival in patients with esophageal cancer. These trials are summarized in Table 36–1.

Launois et al. (1981) randomized a total of 124 patients with SCC to preoperative radiation versus esophagectomy only.[4] The regimen involved 40 Gy of radiation over a period of 8 to 12 days, followed by surgery. This study resulted in no statistical significance in 5-year survival rates, which were 9.5% in the irradiated group versus 11.5% in the nonirradiated group. Moreover, the toxicity seen with the intense regimen of intermediate-dose radiotherapy resulted in a higher complication rate in the combined-therapy group.

In 1987, the European Organization for Research and Treatment of Cancer (EORTC, published by Gignoux et al.) randomized 208 patients with esophageal SCC to receive an intermediate dose of 33 Gy of preoperative radiation followed by surgery versus esophagectomy only.[5] The investigators found no differences in resectability between the groups, and postresectional pathologic analysis did not demonstrate convincing evidence of down-staging. At a mean follow-up of 3.6 years, this trial demonstrated no difference in overall survival: 49 weeks for the combined-treatment group and 48 weeks for surgery only (P = .943). A subset analysis revealed that patients without lymph node involvement who underwent complete resection also received no survival benefit from the addition of radiation (P = .846). The study did show benefit in patients with upper third neoplasms, whose mean survival was 161 weeks versus 97 weeks, thus favoring preoperative therapy (P = .04). In addition, a lower local failure rate was observed in patients randomized to the treatment arm (46%; P = .045), although attention should be focused on a very high local recurrence rate of 67% in the surgery-only arm of the study.

In a randomized trial from China, Wang et al. (1989) assigned a total of 206 patients to 40-Gy radiation and esophagectomy versus esophagectomy only.[6] The results showed a similar incidence of complete resection in both groups, and the overall 5-year survival rate was 35% in the radiation-plus-surgery arm versus 30% in the surgery-only arm. Despite the 5% trend, the improvement in survival was not significant. The authors noted that patients with a significant physiologic response to therapy (grade 3 to 4 esophagitis) had a higher survival rate in subgroup analysis and concluded that more effective radiation doses may be needed to confer an advantage.

From the United Kingdom, Arnott and colleagues (1992) performed a study involving 176 patients that also failed to demonstrate any survival benefit of low-dose preoperative radiotherapy.[7] Patients with SCC and EAC were randomized to receive 20 Gy of radiation followed by surgery versus esophageal resection alone. Five-year survival rates were 9% and 17%, respectively (P = NS), with a median survival of 8 months in both arms. The investigators identified by proportional hazard analysis that lymph node involvement, high tumor grade, and male sex were adverse prognostic features.

In 1998, Arnott et al. performed a summary meta-analysis that included 1147 patients, all of whom were enrolled in randomized trials and had adequate long-term follow-up.[8] They concluded that based on the existing trials, there was no clear evidence that preoperative radiation therapy could improve the survival of patients

Table 36–2 Randomized Trials of Postoperative Radiation Therapy (40-60 Gy) for Esophageal Cancer

Authors	Year	Histology	Total Patients	Treatment	Median Survival (mo)	3-Year Survival (%)	*P* Value
Teneiere	1991	SCC	221	Surgery + XRT	18	19*	NS
				Surgery alone	18	19*	
Fok	1993	SCC/EAC	130	Surgery + XRT	8.7	11	.02
				Surgery alone	15	22	
		Curative (subset)		Surgery + XRT	15	24	NS
				Surgery alone	21	28	
		Palliative (subset)		Surgery + XRT	7	0	.09
				Surgery alone	12	15	
Zieran	1995	SCC	68	Surgery + XRT	—	22	NS
				Surgery alone	—	20	
Xiao	2003	SCC/EAC	495	Surgery + XRT	—	43.5	NS
				Surgery alone	—	50.9	
		Stage III (subset analysis)	272	Surgery + XRT	—	35.1*	.0027
				Surgery alone	—	13.1*	

*Five-year survival rate.
EAC, esophageal adenocarcinoma; NS, not significant; SCC, squamous cell carcinomas; XRT, x-ray therapy.

with resectable esophageal carcinoma. Furthermore, there may be a modest improvement in survival of 3% to 4%, but a much larger trial or meta-analysis would need to be performed to confirm that this potential benefit would be statistically significant.

Despite the number of well-performed trials and inclusion of many patients, these trials have been noted to have several limiting factors. First, the inclusion of patients with differing histology and tumor location may have interfered with the outcomes. Second, although the use of low-dose radiation therapy as opposed to intermediate- or high-dose radiation in the preoperative setting may have resulted in fewer complications, the dose may not have been high enough to confer any significant biologic antitumor activity. Some investigators have argued that intermediate- to high-dose preoperative radiation therapy is necessary to observe a significant response in esophageal carcinomas, which may explain the lack of survival benefit seen when low-dose radiation therapy was used.

Postoperative Radiation Therapy

Temporal reports pointed to a high locoregional failure rate after esophagectomy with or without preoperative radiation. The toxicity of effective neoadjuvant radiation therapy and the apparent lack of locoregional control in patients with locally advanced disease who were treated with surgery alone led investigators to consider adjuvant radiotherapy. This modality of radiation therapy would be delivered at higher levels (40 to 60 Gy) in the postoperative period with less concern for the perioperative mortality that was previously thought to complicate the combination of intermediate- to high-dose radiation followed by esophagectomy. Postoperative radiation therapy was considered in the late 1960s, and a few small nonrandomized studies reported efficacy with this regimen. Because it had never been examined in a randomized controlled setting, beginning in the late 1980s several prospective trials were performed with the hypothesis that adjuvant radiation therapy could sterilize the mediastinum, achieve better local control, and therefore improve survival. These trials are summarized in Table 36–2.

In a large multicenter randomized adjuvant radiation trial reported by Teniere et al., 221 patients with squamous esophageal carcinomas were randomized to esophagectomy alone or esophagectomy with 45- to 55-Gy adjuvant radiation therapy.[9] At a follow-up of at least 3 years, the actuarial 5-year survival rate was similar at 19%, with a median survival of 18 months in both groups. Regional recurrence was significantly lower in patients receiving radiation therapy ($P < .02$); however, this difference occurred only in the subset of patients who were found to have no lymph node involvement. Patients with nodal disease spread showed no locoregional or survival benefit with intermediate-dose adjuvant radiation in this trial.

In 1993, Fok and co-workers from Hong Kong published a prospective, randomized trial involving 130 patients with SCC or adenocarcinoma of the esophagus in which the addition of adjuvant radiation therapy was compared with esophagectomy alone.[10] The two groups were subdivided into curative resection (CR) and palliative resection (PR). PR patients were defined as those who underwent R1 or R2 resection or whose pathologic examination revealed tumor infiltration beyond the esophagus or gross regional or distant lymph node involvement. In the curative arm (CR versus CR + radiation), no benefit in median survival was demonstrated. Actually, survival rates were lower in the postoperative radiation group, and this trend reached statistical significance when the whole study group was compared (CR and PR versus CR + radiation and PR + radiation;

$P = .02$). Local control was similar in the CR and CR + radiation patients, with a 10% versus 13% failure rate, respectively. In the PR versus PR + radiation group, the difference in the local recurrence rate reached statistical significance (46% versus 20%, $P = .04$). As one would expect, there were no differences in the incidence of distant failure found in the analyses. The investigators attributed the lower survival to the higher postoperative complication rates in the combination-treatment arm. This study established that radiotherapy may have some local control benefit in patients with locally advanced disease, but this benefit comes at the expense of high toxicity.

Zieren and colleagues published a study in 1995 on 68 patients with clinical stage II to IV SCC of the esophagus.[11] The treatment group underwent surgical resection followed by 56 Gy of adjuvant radiation therapy; the control group received surgical resection only. At a follow-up of at least 18 months, the 3-year survival rates were similar (22% versus 20% respectively). There were no differences in locoregional control, distant metastases, or elapsed time to failure between the two treatment groups. The authors concluded that adjuvant radiation was not justified in patients with "curative" surgery, although there could be a role for it in palliation.

In an ethically controversial trial, Xiao and co-workers (2003) demonstrated survival benefits with postoperative radiation therapy in patients with stage III esophageal cancer and positive lymph nodes.[12] In this large trial of 495 patients with SCC and EAC, 275 were randomized to surgery alone and 220 to surgery followed by 50- to 60-Gy radiation. The authors excluded 54 patients from the analysis who received lower-dose radiation treatment (<40 Gy) for several medical and social reasons, which later became a limitation of this trial.[12] The overall 5-year survival rates were 31.7% and 41.3%, respectively ($P = .45$). However, the 5-year survival rates of patients with lymph node involvement were 14.7% and 29.2%, respectively ($P = .0698$). Furthermore, the 5-year survival rates of subgroup stage III patients were 13.1% and 35.1%, respectively ($P = .0027$). Despite the significant findings, this trial generated a great deal of controversy because patients were not informed that they were part of a research study. In addition, this trial was criticized for the timing of randomization after resection, which introduced a significant selection bias in the study. The exclusion of 54 patients who received low-dose radiation (<40 Gy) further limits the conclusions that were reached in this trial.

Chemotherapy

There are several theoretical reasons to offer patients with esophageal cancer systemic chemotherapy. Distant failure is a common event leading to death in patients with esophageal cancer. Chemotherapy can potentially treat undetectable micrometastasis, and there is evidence that it can improve locoregional control. Neoadjuvant systemic chemotherapy has been shown to increase R0 resection rates and may down-stage unresectable (T4) tumors, thus rendering patients potential candidates for resection. Combination chemotherapy has been found to have synergistic effects with radiation therapy. Finally, the response to preoperative systemic chemotherapy serves as a marker that can be used to influence later treatment.

Platinum-based chemotherapy has been the foundation for modern systemic treatment of esophageal carcinoma, hence its ubiquitous use in recent prospective randomized trials involving the use of chemotherapy. The results of many phase II studies using cisplatin and other agents in combination chemotherapy have been encouraging. In some experiences, chemotherapy has demonstrated clinical response in up to 50% of patients.[13] There have also been reports of complete pathologic response in up to 22% of patients who received chemotherapy alone.[14]

Randomized Trials of Preoperative Chemotherapy

Preoperative chemotherapy was compared with surgery alone in several prospective randomized trials that included patients with SCC and EAC. A summary of these trials is presented in Table 36–3.

In a small randomized trial, Roth et al. (1988) evaluated the role of perioperative cisplatin-based chemotherapy and esophagectomy versus surgery alone. Patients with mid-distal SCC (T4 and M1 patients excluded) were randomized to receive preoperative and postoperative systemic cisplatin, vinblastine, and bleomycin ($n = 19$) versus surgery only ($n = 20$).[15] With minimal dosage adjustment, all patients in the treatment arm tolerated the chemotherapy regimen. The frequency of complications and treatment-related mortality was similar in both groups. The complete resection rate was not statistically different between the treatment and control groups, although the trend favored the treatment group, which attained a higher percentage of patients with histologically negative resection margins (35% versus 21%). Despite a difference in the 3-year survival rate in the treatment and control groups (25% versus 5%, respectively; $P = .34$), median survival was 9 months for both groups; therefore no statistical difference was seen. The major contribution of this study was that the subset of patients who had a major or complete response to chemotherapy (47% and 5%, respectively) was shown to have a longer median survival than that of nonresponders (20 versus 6 months, $P = .008$). The responding patients also compared favorably with the surgery-only arm (8.6 months, $P = .05$). Despite the impact of response to chemotherapy, this study was limited by its small number of patients.

Likewise, Schlag (1992) assigned patients with SCC to cisplatin and 5-fluorouracil (5-FU) followed by surgery ($n = 29$) versus surgery only ($n = 40$). Although operative mortality was higher in the treatment arm than in the surgery-alone arm (21% versus 12%, respectively), there was no difference in overall median survival (8 versus 9 months, respectively).[16] Similar to Roth and colleagues' trial, this analysis demonstrated no survival benefit and was limited by the small number of patients.

Table 36–3 Randomized Trials of Preoperative Chemotherapy Versus Surgery Alone for Esophageal Cancer

Investigators	Year	Histology	Total Patients	Agent	3-Year Survival (%)	Median Survival (mo)	*P* Value
Roth	1988	SCC	39	Cisplatin, Vb, Bleo	25	9	NS
				None	5	9	
Schlag	1992	SCC	69	Cisplatin, 5-FU	—	8	NS
				None	—	9	
Law	1997	SCC	147	Cisplatin, 5-FU	44*	17	NS
				None	31*	13	
Kelsen	1998	SCC + EAC	440	Cisplatin, 5-FU	23	15	NS
				None	26	16	
Ancona	2001	SCC	96	Cisplatin, 5-FU	44	25	NS
				None	41	24	
MRCOCWP	2002	SCC + EAC + UD	802	Cisplatin, 5-FU	43*	16.8	<.005
				None	34*	13.3	

*Survival rates in the MRCOCWP trial were 2-year survival rates.
Bleo, bleomycin; EAC, esophageal adenocarcinoma; 5-FU, 5-fluorouracil; MRCOCWP, Medical Research Council Oesophageal Cancer Working Party; SCC, squamous cell carcinoma; UD, undifferentiated carcinoma; Vb, vinblastine.

In another trial using a similar regimen, Law et al. (1997) demonstrated no survival benefit with neoadjuvant chemotherapy.[17] In their trial, patients received cisplatin and 5-FU followed by esophagectomy (n = 74) versus esophagectomy alone (n = 73). Two-year survival rates were 44% in the treatment arm and 31% in the surgery-alone arm; median survival was 17 months and 13 months, respectively. Neither was statistically significant. A trial of 96 patients reported by Ancona et al. (2001) echoed these results. Equal numbers of patients received preoperative cisplatin and 5-FU and then esophagectomy (n = 48) or surgery alone (n = 48).[18] Three-year survival rates in the treatment arm versus surgery-alone arm were 44% and 41%, respectively, with a median survival of 25 and 24 months, respectively.

As part of the North America Intergroup Trial, Kelsen and colleagues (1998) conducted one of the largest trials (Trial 0113) on preoperative and postoperative chemotherapy in patients with SCC of the esophagus and EAC.[19] Of 440 treated patients, 227 underwent immediate esophagectomy and 213 were treated with 5-FU and cisplatin followed by esophagectomy. Endoscopic ultrasound was not uniformly used as a staging modality; therefore, response to chemotherapy in this trial was measured with barium contrast studies of the esophagus. Compliance was low: 66% completed the preoperative schedule and 38% were able to complete the postoperative regimen. Reported results showed that in both arms surgeons achieved a similar R0 resection rate (62% versus 59%, respectively). At a median follow-up of 55.4 months, the 3-year overall survival rate in the treatment group was 23% versus 26% in those who received surgery only (P = .74), and the median survival was 15 versus 16 months, respectively (P = .53). Disease-free survival was equivalent as well. Subset analyses revealed no difference in the survival of patients with SCC or EAC, and patients who were considered to have undergone curative procedures faired no differently with or without the addition of chemotherapy. The addition of chemotherapy also failed to achieve better local control in this trial. Locoregional failure rates were 32% and 31% (P = NS) in the treatment and control arms of this trial, respectively. Distant failure was recorded in 41% versus 50% (P = NS). The study is criticized for its relatively low compliance rate and the high locoregional failure rate seen in both arms of the study.

The only large phase III trial to show survival benefit with the addition of chemotherapy to surgery in patients with esophageal cancer was reported in the Medical Research Council (MRC) trial from the United Kingdom. In the largest trial addressing the role of preoperative chemotherapy, the MRC trial (2002) randomized 802 patients to receive preoperative chemotherapy followed by surgery versus esophagectomy only.[20] The chemotherapy regimen consisted of two cycles, 3 weeks apart, of cisplatin (80 mg/m^2) and continuous infusion of 5-FU (1000 mg/m^2). In contrast to many of the previous trials, patients in the chemotherapy arm tolerated their treatment well enough to achieve a compliance rate of 86%. The results showed a benefit in R0 resection rates for those who received preoperative chemotherapy (60% versus 54%; P < .001). At a median follow-up of 37 months, 2-year survival rates for the preoperative treatment group versus surgery alone were 43% and 34%, respectively (P = .004), with a median survival of 16.8 and 13.3 months, respectively. Although 9% of patients in each arm underwent preoperative external beam irradiation, this did not affect the differences seen in overall survival when reanalyzed with exclusion of these patients.

Overall, the two largest trials addressing the role of neoadjuvant chemotherapy in the treatment of

Table 36–4 Randomized Trials of Postoperative Chemotherapy for Esophageal Cancer

Investigators	Year	Histology	Total Patients	Treatment	5-Year Survival (%)	Median Survival (mo)	*P* Value
Pouliquen*	1996	SCC	120	Cisplatin + 5-FU	—	13	—
				Surgery alone	—	14	—
JCOG9204	2003	SCC	242	Cisplatin + 5-FU	52	—	0.13
				Surgery alone	61	—	
Armanios (phase II)	2004	EAC	59	Cisplatin and paclitaxel	60†	31	N/A

*Resections performed in this trial were for palliative purposes only.
†Two-year survival rate.
EAC, esophageal adenocarcinoma; 5-FU, 5-fluorouracil; JCOG, Japan Clinical Oncology Group; N/A, not applicable; SCC, squamous cell carcinoma.

potentially curative esophageal cancer have reported conflicting results, which does not fully support the use of this treatment modality.

The potential benefit of preoperative chemotherapy was evaluated in a meta-analysis of 1976 patients from 11 randomized clinical trials by Urschel et al. in 2003.[21] In this meta-analysis, neoadjuvant chemotherapy followed by esophagectomy did not achieve any survival benefit at up to 3 years. The authors offered two potential reasons for the failure of neoadjuvant chemotherapy to improve survival in patients with operable esophageal cancer. First, the current chemotherapeutic agents are not potent enough to treat micrometastasis. Second, treatment-related toxicities might hinder the effectiveness of preoperative chemotherapy. Although the rate of R0 resection was higher in patients treated with chemotherapy before surgery, the overall resection rate favored surgery alone (odds ratio, 1.71; 95% confidence interval [CI], 1.22 to 2.4; $P = .002$). This last finding is significant and is reiterated throughout many of the neoadjuvant trials.

Postoperative Chemotherapy

Despite the relative failure of preoperative and perioperative chemotherapy in previous trials, questions remained regarding the potential benefit of chemotherapy in the treatment of resectable esophageal cancer. Proponents of neoadjuvant therapy cite reasons mentioned in the previous text. Others argued that postoperative therapy could increase survival by allowing the selection of patients who were most likely to benefit from therapy while avoiding additional toxic therapy in those who had been shown to potentially derive the least amount of benefit. Table 36–4 summarizes the following studies.

Pouliquen et al. published the results of a multicenter, randomized study from France in 1996 that examined the role of additional chemotherapy after palliative surgical resection of esophageal SCC.[22] In this study, 120 patients who underwent esophagectomy and were found to have pathologic N1 disease, incomplete resections (R1-2), or distant metastasis (M1) were randomized to receive postoperative chemotherapy with cisplatin and 5-FU to a maximum of eight cycles versus observation. In each group, patients were subdivided in the analysis into stratum I (N1) and stratum II (R1-2, M1). Compliance was considered excellent at 87%. The results showed no significant differences in survival. Median survival in the treated versus the untreated group was 13 and 14 months, respectively. Stratum I patients had a median survival of 20 months and an actuarial overall 5-year survival rate of 13%, with values similar in the treated and observed groups. Stratum II patients had a 0% 5-year survival rate, and there was no difference in the median survival in the treated and observed groups. The authors concluded that postoperative chemotherapy conferred no additional benefit to either subset of patients but did significantly decrease the treated patients' quality of life. There was 8% mortality attributed to adjuvant treatment in this study.

As part of the Japan Clinical Oncology Group study, Ando et al. (2003) reported a multicenter trial (JCOG9204) involving 242 patients with American Joint Committee on Cancer stage I to IV esophageal SCC.[23] In this randomized, phase III trial, 122 patients received surgery alone and 120 underwent surgery followed by two courses of cisplatin and 5-FU within 2 months of surgery. Full compliance with therapy was noted in 75% of patients, which was accomplished with limited treatment toxicity. Reported end points of the study after 63 months' median follow-up were 5-year disease-free survival, which was 45% for surgery versus 55% for esophagectomy plus adjuvant chemotherapy ($P = .037$), and 5-year overall survival, which was 52% versus 61%, respectively ($P = .13$). Subset analyses revealed that the disease-free benefit was observed only in the N1 group (38% versus 52%; $P = .04$) and not in the N0 patients (76% versus 70%; $P = .43$). This divergence between disease-free survival and overall survival may reflect a potential benefit of better local control achieved by the N1 population. Another explanation is that within this

Table 36–5 Studies Investigating Definitive Chemoradiation Therapy for Esophageal Cancer

Investigators	Year	Histology	Total Patients	Treatment	Median Survival (mo)	2-Year Survival (%)	*P* Value
RTOG 85-01	1992	SCC + EAC	121	Cisplatin + 5-FU + 50 Gy	12.5	38	.001
				64 Gy	8.9	10	
RTOG 90-12 (phase II)	1999	SCC	38	5-FU + cisplatin followed by 5-FU + cisplatin and 64 Gy	20*	20	—

*Five-year survival rate.
EAC, esophageal adenocarcinoma; 5-FU, 5-fluorouracil; RTOG, Radiation Oncology Therapy Group; SCC, squamous cell carcinoma.

multicenter trial, the extent of lymph node dissection differed significantly among participating institutions, which may have introduced a selection bias in the study via a stage migration effect.

A recent phase II trial reported by Armanios et al. in 2004 focused on adjuvant chemotherapy in patients with completely resected adenocarcinoma of the distal esophagus and gastroesophageal junction. In this multicenter trial, 59 patients with T2-4, N0-1, R0 disease were entered into the study, 89% (49/55) of whom had lymph node involvement.[24] Patients received intravenous cisplatin and paclitaxel every 21 days for four cycles. Compliance was noted at 84% for all four courses, and grade 3 or 4 toxicity developed in 54% (32/59) while on treatment. Median follow-up was 4 years with a 2-year overall survival rate of 60%. This was compared with historical controls and found to be significantly different ($P = .0008$). The pattern of first recurrence was at a distant site in 58% of patients and locoregional in 9%. In the light of the encouraging results of this study, the authors proposed validating these result in a randomized trial setting. In addition, they pointed out the disappointing systemic control offered by chemotherapy.

Chemoradiation

Definitive Therapy

Concern regarding the high morbidity and mortality rates associated with esophagectomy led investigators to consider chemoradiation therapy as definitive treatment of esophageal cancer. The synergistic antitumor effects and encouraging results seen with cervical esophageal SCC when using alternative therapies were valid reasons to apply this combined-treatment approach to other types of esophageal neoplasms.

Several nonrandomized trials investigating concurrent chemotherapy and radiation therapy demonstrated feasibility despite a high toxicity rate. Combination chemotherapy with concurrent radiation therapy was later found to achieve better survival in nonsurgical patients with esophageal SCC and EAC than chemotherapy or radiation alone was, and this finding forms the basis for modern combined-therapy trials. A summary of these trials is in presented in Table 36–5.

Herskovic and colleagues (1992) conducted an important prospective randomized Intergroup Trial (RTOG 85-01) comparing combined chemotherapy with concurrent radiation versus radiation therapy only. In this trial patients with SCC and EAC, T1-3, N0-1, M0 of the thoracic esophagus, were randomized to receive combined 5-FU (1000 mg/m^2) and cisplatin (75 mg/m^2) plus concurrent 50-Gy radiotherapy ($n = 61$) versus 64-Gy radiation therapy alone ($n = 60$). At a median follow-up of 17.9 months, significant survival advantages were demonstrated in the combination-treatment group. One-year and 2-year survival rates in the radiation-only group were 33% and 10%, respectively, versus 50% and 38%, respectively ($P < .001$), in the combined-therapy group. Median survival in both groups was 12.5 and 8.9 months, respectively. Despite high local recurrence rates in both groups, local and distant recurrent rates were significantly lower in the combination-treatment group.[25] The study was halted after accrual of 121 patients because of the obvious benefit of combined therapy over radiation alone. Not surprisingly, treatment-related toxicity was significantly higher in the combined-treatment arm (20% versus 3% rate of life-threatening toxicity). The authors concluded that the improvement seen in overall survival and local control comes at the cost of toxicity.

Long-term follow-up of RTOG 85-01 was published in 1999 by Cooper et al. After early termination of the accrual phase of the study, 73 more nonrandomized patients who received combined therapy were added.[14] At a minimum of 5 years of follow-up, 26% of the randomized and 14% of the nonrandomized patients in the combined modality group were alive versus 0% in the radiation-only arm ($P < .001$). Within the randomized patient group, 22% survived at least 8 years, and no deaths after 5 years were attributed to esophageal cancer. There was a trend toward longer survival in patients with SCC than in those with EAC (21% versus 13%), but this difference was not significant. Five-year survival rates in the randomized and nonrandomized patients receiving combined treatment were 26% and 14%, respectively; however, no patients survived 5 years in the radiation group. Toxicity, again, played a significant role in the

delivery of treatment. Eight percent of the combined-treatment group had life-threatening side effects, and 2% died directly as a result of therapy, but there were no "late" toxic effects; patients who survived longer than 90 days had no more toxicity than the radiation-alone group did. This study showed that cure was possible without surgical intervention and that the incidence of cure rivaled the dismal results from surgery published in a review by Earlam and Cunha-Melo in 1980 (4% 5-year overall survival).[26]

To improve the local control results of the RTOG 85-01 trial, a proposal to intensify the dose of radiation and chemotherapy was made. Minsky et al. (1999), as part of Intergroup Trial 0122 (RTOG 90-12), published the results of a trial in which 45 patients were entered into a single-arm study, 38 of whom were eligible.[27] Patients with proximal to distal, T1-4, N0-1, M0 esophageal SCC were treated with three cycles of induction cisplatin (100 mg/m^2/day) and 5-FU (1000 mg/m^2/day), followed by an additional two cycles of 5-FU (1000 mg/m^2/day) and cisplatin (75 mg/m^2) with concurrent radiation treatment to a dose of 64 Gy. Treatment compliance was 69% for the induction phase, and 48% received the full radiation protocol. Reported complete response (radiographic) rates were 47%. After a median follow-up of 59 months, this trial failed to show an improvement in the locoregional failure rate seen in the original RTOG 85-01 trial. The actuarial 5-year survival rate was 20% with a median survival of 20 months. Shortcomings of the study included treatment-related mortality in 9% and the fact that 39% of the treated patients had T1-2 N0 disease. Despite any drawbacks, this study helped establish the basis of 50.4 Gy as an appropriate dose for definitive or neoadjuvant radiation therapy and re-emphasized the high complete response rate attainable with induction chemotherapy followed by concurrent chemoradiotherapy. This later became the platform for many trials involving surgery as well.

RTOG 92-07 was a study expanded from the 85-01 trial that was conducted to examine the role of additional brachytherapy in a phase I/II trial involving 49 patients with stage T1-2, Nx-1, M0 esophageal cancer that was limited to the thoracic esophagus. Adenocarcinoma was included in this trial (6%), although it was predominantly a study of esophageal SCC. Treatment consisted of concurrent radiotherapy to 50 Gy with two cycles of 5-FU and cisplatin. Two weeks after completion of external beam therapy, patients received an esophageal brachytherapy boost up to 15 or 20 Gy. Compliance with the concurrent chemoradiotherapy was excellent at 96% but dropped off to 69% (34/49) for the additional esophageal brachytherapy. The results showed no improvement over the RTOG 85-01 trial results in terms of tumor response, local control, or survival. There were, however, six cases (12% overall, 18% of treated patients) of treatment-related esophageal fistulas, which were ultimately fatal in three patients.

In a departure from the general direction that the field was moving, Sykes et al. (1998) published a manuscript on the use of definitive radiotherapy alone for the treatment of clinically localized esophageal SCC and EAC.[28] This was a descriptive cohort study of 101 patients who were treated definitively with radiation because they were medically unfit for resection or they chose radiation over surgery. A little over half the patients had disease localized to the mid to lower third of the esophagus, and 10% had adenocarcinoma. Radiotherapy was given over a period of 3 weeks to a total dose of 45 to 52.5 Gy, and treatment-related toxicity was considered tolerable. In this study the 5-year survival rate was 21% with a median survival of 15 months. Patients who lived longer than 3 years had significantly more involvement of the middle and lower esophagus than the upper. It appears that the results of this study have not been duplicated elsewhere.

Finally, a recent study in Germany published by Stahl and colleagues in 2005 sought to evaluate the additional benefit of surgery with chemoradiotherapy.[29] In a phase III trial, 172 patients were randomized to receive neoadjuvant induction chemotherapy, followed by concurrent chemoradiotherapy, followed by either observation or surgery. Inclusion was limited to patients with locally advanced (T3-4, N0-1, M0) upper to middle esophageal SCC. Their results showed that locoregional control was significantly better with the addition of surgery, but this failed to translate into a statistically significant survival advantage. Notable limitations of this study include the 66% eventual resection rate on an intent-to-treat basis of the patients randomized to the surgery arm, again emphasizing the lower overall resection rate of patients who undergo neoadjuvant therapy.

In summary, chemoradiation therapy without esophagectomy has a potential role in the treatment of locally advanced or metastatic disease. The standard of care for resectable esophageal cancer is still complete esophageal resection when possible, although the additional benefit of surgery in patients who have persistent locoregional disease or have had a complete response after induction therapy and concurrent chemoradiotherapy is also a study end point of an ongoing multi-institutional phase II trial (RTOG 0246).

Preoperative Chemoradiation for Esophageal Cancer

Trials of definitive chemoradiation therapy demonstrated improved complete response rates and survival benefits over single-therapy modalities, but they continued to be hampered by high local recurrence. This led several investigators to use all three modalities in an attempt to improve survival through better local control. Mixed results were generated in the various nonrandomized trials. In almost all, cisplatin-based combination therapy was administered along with intermediate- to high-dose radiation therapy. Several international investigators have conducted prospective randomized trials consisting of chemoradiation therapy preceding esophageal resection, all of which except one have shown no survival benefit. A summary of these trials is presented in Table 36–6.

Nonrandomized Trials of Preoperative Chemoradiation for Esophageal Cancer In a nonrandomized trial, Donington et al. (2004) presented a single-institution

Table 36–6 Randomized Trials of Preoperative Chemoradiation Therapy for Esophageal Cancer

Investigator	Year	Histology	Total Patients	Treatment	Median Survival (mo)	3-Year Survival (%)	*P* Value
Nygaard	1992	SCC	88	Surgery alone	7.5	9	NS
				Cisplatin/bleo + 35 Gy	7.5	17	
Le Prise	1994	SCC	86	Surgery alone	10	13.8	NS
				Cisplatin/5-FU + 20 Gy	10	19.2	
Apinop	1994	SCC	69	Surgery alone	7.4	10*	NS
				Cisplatin/5-FU + 40 Gy	9.7	24*	
Walsh	1996	EAC	113	Surgery alone	11	6	.01
				Cisplatin/5-FU + 40 Gy	16	32	
Bosset	1997	SCC	282	Surgery alone	18.6	37	NS
				Cisplatin + 37 Gy	18.6	39	
Urba	2001	SCC + EAC	100	Surgery alone	17.6	16	NS
				Cisplatin/Vb/5-FU + 45 Gy	16.9	30	
Burmeister	2002	SCC	256	Surgery alone	19	—	NS
				Cisplatin/5-FU + 35 Gy	22	—	

*Five-year survival rates
Bleo, bleomycin; EAC, adenocarcinoma; 5-FU, 5-fluoruracil; NS, not significant; SCC, squamous cell cancer; Vb, vinblastine.

study evaluating 75 patients with clinical stage III EAC.[30] Forty-seven patients received treatment with concurrent chemoradiation (50.4 Gy and two cycles of 5-FU plus cisplatin) followed by surgery, and 28 patients underwent esophageal resection only. Nineteen percent of patients who were treated with combined-modality therapy also underwent esophageal brachytherapy. The combined-treatment modality resulted in a 26% pathologic complete response rate. Positive margins were found more frequently in patients who did not undergo chemoradiotherapy (18% versus 4%), a finding mentioned in several other trials, but this trend was not statistically significant. At a median follow-up of 20 months, the authors concluded that there was no benefit to this trial of neoadjuvant chemoradiotherapy, citing 3-year disease-free survival rates in the combined-treatment and surgery-alone groups of 29% and 33%, respectively ($P = .51$). The 3-year overall survival rate was similar (42%) in both arms as well ($P = .70$).

Randomized Trials of Preoperative Chemoradiation for Esophageal Cancer Several randomized trials have been conducted to explore the role of chemoradiotherapy in resectable esophageal neoplasms. Only one of the numerous published randomized controlled trials has demonstrated a survival benefit with multimodality treatment. A summary of these trials is presented in Table 36–6.

Nygaard and colleagues conducted the first trial of this sort in Sweden in 1992 on 88 patients with esophageal SCC.[31] Forty-one patients underwent surgery only and 47 received chemotherapy consisting of cisplatin and bleomycin with radiation therapy followed by esophagectomy. R0 resection was accomplished in only 50% of cases in the treatment group. Although the mortality rate was higher in the neoadjuvant treatment group (24% versus 13%, respectively), median survival was similar at 7.5 months. The 3-year survival rate showed a trend favoring the neoadjuvant group (17% versus 9%, respectively), but it failed to reach statistical significance, and the trial therefore failed to demonstrate any survival benefit with the additional therapy. The question of whether to blame the study design and small patient numbers for the lack of significant findings or the lack of effective therapeutic alternatives was left to future studies.

Likewise, in 1994 Le Prise et al. published the results of a randomized trial in patients with SCC of the esophagus in which surgery alone was compared with preoperative chemoradiotherapy followed by surgery. In this trial, patients received *sequential* neoadjuvant chemoradiotherapy with 20-Gy radiation and cisplatin (100 mg/m^2)/5-FU (600 mg/m^2) followed by surgery ($n = 41$) versus surgery alone ($n = 45$).[32] In the combination-therapy arm, 95% of the patients completed their treatment course. There was a 10% complete response rate. At a short median follow-up of 16 months, the survival difference was not significant (3-year survival rates of 19.2% and 13.8%, respectively; $P = .10$). The limitations of this trial included small numbers of accrued patients, short follow-up, and a relatively low dose of preoperative radiation.

In the same year, Apinop et al. published the results of a similar trial involving 69 patients with locoregional, resectable, middle to distal esophageal SCC treated with preoperative cisplatin (100 mg/m^2) and 5-FU (1000 mg/m^2/day) plus 40 Gy of concurrent radiation

therapy followed by esophagectomy in the treatment arm.[33] The 5-year survival rates in the combination group and surgery group were 24% and 10%, respectively, with a median survival of 9.7 and 7.4 months ($P = .4$). Again, a trend in survival was not demonstrated statistically in this small trial, and the overall survival in the surgery arm was low. However, subset analysis of this trial revealed that a partial or complete response to combined treatment had a favorable significant impact on survival ($P = .001$).

In 1997, Bosset et al. conducted a larger randomized trial that included 282 patients with esophageal SCC treated by esophagectomy alone ($n = 139$) versus esophagectomy after chemoradiotherapy ($n = 143$).[34] The preoperative treatment included cisplatin (80 mg/m^2) only with concurrent radiotherapy (37 Gy). At a median follow-up of 55 months, disease-free survival was found to be significantly longer in the combined-treatment group ($P = .003$); however, no overall survival benefit was demonstrated. In fact, both treatment groups shared similar median survival (18.6 months). Though not generally seen in other trials, the postoperative mortality rate in this trial was significantly higher in the combination-therapy group than in the surgery arm of this study (16.7% versus 5%; $P = .012$). The investigators proposed that higher doses of radiation (37 Gy), malnutrition (weight loss), and immunosuppression were potential reasons for the increased number of postoperative deaths.

Unlike the previously mentioned randomized trials that were mainly limited to esophageal SCC, there have been two randomized trials investigating the role of neoadjuvant chemoradiotherapy for both esophageal SCC and EAC. In 2001, Urba et al. from the University of Michigan published a randomized trial that included 100 patients with esophageal carcinoma (75% EAC/25% SCC) at all levels.[35] They compared concurrent chemoradiotherapy followed by transhiatal esophagectomy with surgery alone. The preoperative chemotherapy in this trial consisted of cisplatin (20 mg/m^2/day), 5-FU (300 mg/m^2/day), and vinblastine (1 mg/m^2/day); the radiation was given to a dose of 45 Gy. At a substantial follow-up of 8.2 years the neoadjuvant treatment arm did not show any improvement in survival over surgery alone (median survival of 17 months in both groups). Although the 3-year overall survival rate in the chemoradiation group was superior by 14%, this was not statistically significant (30% versus 16%, respectively; $P = .15$). Disease-free survival echoed this trend. The local-regional failure rate, however, was significantly lower in the combination-therapy group (19% versus 42%; $P = .02$), but this had no bearing on the outcome. To put this in perspective, the concurrent incidence of distant disease relapse was similar for both groups, thus implying that although local control may have been improved by chemoradiotherapy, there was no effect on distant metastasis and overall survival. This randomized trial is unique for fair randomization in both arms in terms of patient histopathology; however, locoregional failure in the surgery arm is considered to be higher than that seen in previously published reports. Complicating this issue is the fact that locoregional failure is defined differently by different authors and is notoriously difficult information to obtain. The design of this trial may also have played a role in the negative findings of the study.

Several other small phase II trials tested a similar model of 5-FU, cisplatin, and concurrent radiotherapy. Some added induction chemotherapy before chemoradiotherapy, and this may improve locoregional control in locally advanced cases of esophageal cancer. All of them reported a relatively high incidence of compliance, R0 resection, and complete pathologic response, but they were also hampered by high locoregional or distant recurrence rates (or both). Although not all of them were designed to compare long-term survival, of those that were, none were able to show a significant benefit with the additional therapy.[36-41] The most notable finding in these trials was the improvement in survival seen in patients who demonstrate a complete or major response (no residual or microscopic disease seen on pathologic examination). Within the subset of patients who respond, survival in those with a down-staged post-treatment pathologic stage is similar to that of similarly staged patients treated with surgery alone.[42]

Walsh and colleagues (1996) from Ireland have been the only group to show a survival benefit for neoadjuvant chemoradiotherapy in patients with resectable EAC.[43] In this trial patients were randomized to receive preoperative 5-FU (15 mg/kg/day) and cisplatin (75 mg/m^2) with concurrent radiation (40 Gy) followed by surgery ($n = 58$) or surgery alone ($n = 55$). Patients randomized to the combined-treatment group had a favorable outcome when compared with patients who underwent esophagectomy only (3-year survival rate of 32% versus 6%, respectively; $P = .01$). However, this trial was heavily criticized for several aspects. First, the authors were inconsistent in their method of staging. Second, several patients included in the surgery-alone arm were stage IV. Third, the overall survival rate of patients randomized to the esophagectomy-only arm was 6% at 3 years, which is considered to be significantly lower than other reported experiences for esophageal resection. Fourth, there were statistical inconsistencies within the paper. Last, this trial had a relatively short median follow-up of 10 months.

In summary, randomized controlled trials using chemoradiation improved locoregional control and achieved a complete pathologic response in 26% to 47%, and in selected patients with an excellent response to neoadjuvant therapy, survival was more favorable. Overall, however, the results are conflicted regarding any potential survival benefit with this treatment modality, and there have been no definitive results to conclude that one modality is superior to the other.

META-ANALYSES

A comprehensive and well-presented series of meta-analyses was performed by Malthaner et al. (2004) to investigate the effect of surgery alone versus all other treatments in patients with resectable esophageal cancer.[44] In this publication, 34 randomized controlled trials and 6 meta-analyses were integrated into several

basic treatment approaches. The authors referred to Arnott's meta-analysis (2000) of 1147 patients from five trials, which showed a hazard ratio for death of 0.89 (95% CI, 0.78 to 1.01; $P = .062$) for preoperative radiation therapy and esophagectomy versus esophagectomy only.[8] When postoperative radiation therapy plus surgery was compared with esophageal resection alone, there was no significant difference in survival at 1 year (overall risk ratio, 1.23; 95% CI, 0.95 to 1.59; $P = .11$). Of seven randomized trials examining preoperative chemotherapy and surgery versus surgery alone, the meta-analysis showed no difference in mortality risk at 1 year (relative risk ratio, 1.00; 95% CI, 0.83 to 1.19; $P = .98$). A separate meta-analysis investigating the utility of preoperative and postoperative chemotherapy plus surgery versus surgery alone did not detect any difference in mortality at 1 year (risk ratio, 0.99; 95% CI, 0.81 to 1.21; $P = .93$). Furthermore, no survival difference was noted at 3 years when the meta-analysis examined postoperative chemotherapy and surgery versus surgery alone (risk ratio, 0.94; 95% CI, 0.74 to 1.18; $P = .59$). Although the previous analyses of combined monotherapy and surgery demonstrated no survival benefit, a meta-analysis of trials investigating combined preoperative chemoradiation and surgery noted a decrease in 3-year mortality and better local control but a lower resection rate than with surgery alone (risk ratio, 0.87; 95% CI, 0.80 to 0.96; $P = .004$). These results were similar to those reported in meta-analyses performed by Fiorica et al. and Urschel et al. on neoadjuvant chemoradiotherapy.[21,45] However, the most recent meta-analysis, that by Greer et al. in 2005, weighted the observations of the individual studies according to their mean follow-up.[46] This analysis concluded that there may be a small survival benefit with neoadjuvant chemoradiation followed by surgery versus surgery alone, but this benefit did not reach statistical significance (risk ratio, 0.86; CI, 0.74 to 1.01; $P = .07$). The most interesting findings of this meta-analysis are that despite the fact that most of the randomized trials limited enrollment to clinically early disease, there was a lower overall rate of completion of therapy in the treatment arm (72% to 97%) than in the surgery-only arm (100%).

Postoperative Chemoradiation

Because one of the major drawbacks of chemoradiotherapy is toxicity, which may have led to the decrease in the overall resection rate in the previous studies, investigators attempted to focus additional therapy on a subgroup of patients who were thought to benefit most from the treatment. Ajani et al. from the University of Texas M.D. Anderson Cancer Center established the feasibility of this approach in a phase I/II study conducted on 35 patients with resectable adenocarcinoma of the esophagus and GE junction.[13] All patients received a total of six courses of chemotherapy (etoposide, 5-FU, and cisplatin) divided into two courses preoperatively and three to four courses postoperatively. Adjuvant radiation treatment was given if patients had positive margins or gross residual disease. There were no deaths related to esophagectomy, chemotherapy, or radiation treatment. The toxicities related to chemotherapy were moderate.

Several modern studies using this type of treatment protocol have been published; two have shown benefit with this treatment whereas other smaller studies have not. Rice et al. from the Cleveland Clinic randomized 83 patients with SCC or EAC to esophagectomy followed by adjuvant chemoradiation therapy versus esophagectomy only.[47] The stages were varied (pT1-4, pN0-1, pM0-1a). Of 83 patients, 31 patients with locoregionally advanced disease (pT1-4, pN0-1, pM0-1a) underwent esophageal resection and received postoperative cisplatin/5-FU and radiation, and 52 patients with advance disease (pT1-4, pN0-1, pM0-1b) received esophageal resection only. This trial demonstrated that patients with locoregionally advanced disease who received adjuvant chemoradiation had better median survival (28 versus 15 months, respectively; $P = .05$) and recurrence-free survival (22 versus 11 months, respectively; $P = .04$) than did those who underwent surgery alone. Another randomized study by Bédard et al. (2001) revealed in a multivariate model that adjuvant chemoradiotherapy was an independent predictor of survival and that overall median survival was improved (47.5 versus 14 months, respectively; $P = .001$).[48]

In summary, postoperative chemoradiotherapy remains a treatment option for patients who are at high risk for locoregional recurrence, and it may have benefit in a selected subgroup of patients. Difficulty with the administration of adjuvant therapy after undergoing esophagectomy may limit the overall efficacy of this modality.

NEW TREATMENT MODALITIES

Numerous trials have been performed to investigate the role and timing of esophagectomy, systemic chemotherapy, and radiation therapy. Combined-treatment modalities have resulted in improved 3-year mortality and complete resection rates in selected patient populations. On the other hand, the overall outcome of esophageal cancer remains dismal. This highlights the importance of considering new approaches to treatment, such as molecular-based targeted therapy. Evidence is evolving to demonstrate that biologic inhibitors can be potential adjuncts to our current armamentarium of treatment.

Cyclooxygenase-2 Inhibitors

Cyclooxygenase-2 (COX-2) is an inducible form of the COX enzyme that leads to the synthesis of prostaglandins. COX-2 is regulated by a variety of oncogenes and growth factors. An increasing body of evidence is supporting the fact that COX-2 contributes to the development of cancer, hence the utility of COX-2 inhibitors as a molecular target for the treatment and prevention of esophageal cancer. Two National Cancer Institute–sponsored trials are under way to evaluate the use of COX-2 inhibitors in reversing the dysplastic effect of Barrett's esophagus and its effect in a thermally ablated esophagus. Phase II trials (published in abstract form) using COX-2 inhibitors as part of the preoperative

chemotherapy for locally advanced esophageal cancer have suggested a possible response to treatment. Unfortunately, recent reports of cardiac toxicity with COX-2 inhibitors may limit the ability to complete important ongoing trials. Diversion to inhibiting alternative pathways that ultimately lead to a common cascade are under way. It may be that derivative compounds such as dimethyl celecoxib could provide similar antitumor effect with a different safety profile.

Tumor Necrosis Factor

There is great interest in tumor necrosis factor-α (TNF-α) for its known immune response effect in causing severe tumor necrosis. Ongoing phase I/II protocols are taking place in which all patients will receive 5-FU, cisplatin, and 45-Gy external beam radiation therapy, followed by esophagectomy. A TNF-α–incorporated adenoviral vector will be injected in patients in a dose-escalating manner. Phase II will treat 50 patients in a single arm with preoperative chemoradiation therapy along with TNF-α biologic injection.

Epidermal Growth Factor Receptor

Epidermal growth factor receptors (EGFRs) are transmembrane glycoproteins with tyrosine kinase activity that play an important role in cell proliferation. Overexpression of EGFR has been found in several malignancies, including bladder, head and neck, breast, gastric, and colorectal carcinoma. In addition, several reports have identified EGFRs in normal esophagus, Barrett's esophagus, and poorly differentiated esophageal carcinoma. In an analysis of 38 patients with resectable esophageal carcinoma, Wilkinson and colleagues (2004) performed immunohistochemical analysis on paraffin-embedded tissue samples with the use of EGFR monoclonal antibodies.[49] In this interesting analysis, 13 of 23 patients with poorly differentiated esophageal cancer stained positive for EGFR ($P = .02$). Furthermore, it appears that EGFR correlates with outcome as evidenced by disease recurrence in 6 of 13 EGFR-positive patients ($P = .06$). Molecular target agents such as tyrosine kinase inhibitors are potential implications of this study for those who overexpress EGFR.

SUMMARY

A plethora of publications in the literature support or refute various modalities of treatment of SCC and adenocarcinoma of the esophagus. Surgery is the treatment of choice for early localized esophageal cancer. It appears that there is little role for combined perioperative monotherapy and surgery in patients with resectable lesions. Chemoradiotherapy may be beneficial in patients who have locally advanced disease, and the addition of surgical intervention in patients with locally advanced disease and a poor response to multimodality therapy should be considered palliative given the high incidence of regional and distant metastasis and poor overall outcome in that group. Limited current evidence shows some survival advantage to chemoradiation in the aftermath of esophagectomy, but this finding lacks the validation of a larger prospective randomized controlled trial.

As our understanding of esophageal cancer therapy evolves, the deficits remaining in esophageal cancer treatment modalities are becoming clearer. Careful staging, whether invasive or noninvasive, performed by contemporary investigators has helped us develop some understanding of the biology of this disease and has taught us that it is appropriate to approach the treatment of each patient with a stage-based algorithm.[50-52] Ultimately, the question remains whether current multimodality therapy is merely compensating for inadequate patient selection for surgery (a stage migration effect) or inadequate locoregional control (or both). If this were true, we may see improvement only in locoregional control with a marginal benefit on overall survival, and this is consistent with the trend of the relevant studies that we have reviewed. Certainly, future therapeutic effort needs to be directed at relatively chemoresistant and systemic disease. Further improvement in the overall treatment-related outcomes for esophageal cancer will depend on the innovation of novel molecular-based and biologic therapeutic agents and performance of statistically sound, well-constructed collaborative trials.

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Chapter

37

Benign Tumors and Cysts of the Esophagus

Richard F. Heitmiller · Molly M. Buzdon

Benign tumors and cysts of the esophagus are rare. A review of the literature does not indicate a change in their overall incidence or the distribution of specific types of tumors and cysts. No new classification schemes have been adopted. The majority of benign esophageal tumors and cysts continue to be small and produce no symptoms. Most are still found incidentally.

On the other hand, there have been dramatic advances in our ability to diagnose these lesions once they are identified. Historically, one of the most common indications for surgical resection was uncertainty of pathologic diagnosis. Such is no longer the case. Endoscopic esophageal ultrasound, transesophageal biopsy methods, and the digital imaging techniques of computed tomography (CT) and magnetic resonance imaging (MRI) with three-dimensional reconstruction result in a specific clinical diagnosis, often a pathologic diagnosis, with a high degree of confidence. Surgeons now have considerably more information available to determine which patients should undergo resection versus observation.

Another advancement in the management of patients with benign esophageal tumors and cysts is the introduction and refinement of endoscopic and minimally invasive methods to resect these lesions. Historically, surgical resection was accomplished by a standard thoracotomy approach that was safe and effective but a major surgical insult for a patient with a benign and generally asymptomatic lesion. Currently, increasing reports are documenting endoscopic resection of these lesions, especially those with a mucosal or intraluminal component. Intramural-extramucosal lesions can now frequently be resected with minimally invasive thoracoscopic and laparoscopic techniques.

Finally, pathologists have been able to study the molecular genetic profile of benign esophageal tumors to individually define tumor diagnosis and pathogenesis.

OVERVIEW

Incidence

Patterson[1] identified only 62 reported cases of benign esophageal tumors over the 215-year period 1717 to 1932. In separate autopsy series, Moersch and Harrington,[2] and Plachta[3] reported a prevalence of benign esophageal tumors and cysts of 0.59% (44/7459) and 0.45% (90/19,982), respectively. More recently, Attah and Hajdu identified only 26 benign esophageal tumors out of 15,454 autopsies over a 30-year review period.[4] The autopsy review by Plachta[3] best summarizes the overall characteristics of benign esophageal tumors and cysts. In that review, of the total 504 esophageal tumors identified at autopsy, 82% were malignant and 18% benign. Benign tumors were more common in males than females. The mean age of patients was 45 and 68 years for symptomatic and asymptomatic patients, respectively, although the age range was broad (22 to 92 years). Of the 90 benign esophageal tumors, the most common were leiomyomas in 49 (54%) patients, polyps in 23 (26%), cysts in 3 (3%), hemangiomas in 3 (3%), and papillomas in 2 (2%). There was a slightly increased prevalence of benign tumors involving the lower third of the esophagus.

Symptoms

Choong and Meyers[5] reported five clinical patterns in patients with benign esophageal tumors: asymptomatic, intraluminal obstruction, extramural extension with involvement of adjacent mediastinal structures, regurgitation of a pedunculated tumor, and mucosal ulceration with bleeding. Despite the fact that benign esophageal tumors may attain significant size, most patients are asymptomatic. Though uncommon, dysphagia is the second most common symptom. The reported incidence

of dysphagia from benign esophageal tumors ranges from 0.075% to 0.14%.[2] Extraluminal compression of the adjacent airway results in cough and wheezing symptoms. Regurgitation of a pedunculated tumor is most commonly seen in patients with fibrovascular polyps. Bleeding is uncommon but has been reported in conjunction with esophageal hemangiomas.

Surgery

Ten percent (9 of 90) of patients with benign tumors required surgical treatment in Plachta's series.[3] More recent reports suggest that benign esophageal tumors and cysts are an infrequent indication for esophagectomy. Davis and Heitmiller[6] performed 45 esophagectomies for benign disease in which benign tumor was the indication in only 2 (4%) patients. The pathologic examination findings for these two cases were leiomyoma and melanotic schwannoma. Benign tumor was not an indication for transhiatal esophagectomy in any of the 166 cases reviewed by Orringer and Stirling.[7] In an operative series of 20 patients by Mansour et al.,[8] there were 13 leiomyomas, 4 cysts, 2 polyps, and 1 granular cell myoblastoma.

HISTORY

Sussius[9] is credited with the first description of a benign esophageal tumor, a leiomyoma, in 1559. Since that time there has been slowly accumulating experience with benign esophageal tumors and cysts, thus reflecting the infrequent occurrence of this pathologic condition. The first pathologic description of a leiomyoma is attributed to Virchow[10] in 1863. One of the earliest studies evaluating the prevalence of benign esophageal tumors was by Vinson et al.[11] from the Mayo Clinic in 1926. Of 4000 patients with dysphagia evaluated at the clinic, only 3 were found to have benign esophageal tumors as the cause of their symptoms. The infrequent occurrence was further established by Patterson[1] in 1932, who identified only 61 reported cases of benign esophageal tumor and cyst over the preceding 215 years. This fact is now a well-known characteristic of these tumors.

Although the majority of patients with benign esophageal tumors are asymptomatic, many of the early reports involved symptomatic patients. Arrowsmith[12] (1877) described a patient with a benign polypoid esophageal growth that resulted in such severe dysphagia that the patient died of malnutrition. Moersch and Harrington[2] (1944) noted that only 1 of 15 patients was asymptomatic. This undoubtedly reflects the fact that these reports antedated modern endoscopic and radiographic methods, which have since increased the probability of diagnosis of asymptomatic lesions.

One of the first reports of treatment was by Vater[13] in 1750, who described a patient whose esophageal polyp spontaneously separated and was regurgitated. In 1818, Dubois[14] successfully ligated a polypoid intraluminal esophageal neoplasm that later separated while the patient was sleeping and led to regurgitation, aspiration, and asphyxiation. Mackenzie[13] described two patients whose tumor was removed with a probang, which is a long flexible rod with a sponge at one end. The first open surgical removal of a benign tumor is generally attributed to Oshawa[15] in 1933; however, Storey and Adams[16] identified a report 1 year earlier by Sauerbruch[17] of transpleural resection of a leiomyoma. The first successful surgery in the United States is attributed to Churchill[18] in 1937.

The most recent chapter in this historical review is still being written. The introduction of minimally invasive surgical methods approximately 25 years ago has challenged open surgical approaches for resecting benign esophageal tumors and cysts. Furthermore, as outlined in the beginning of the chapter, our ability to specifically diagnose these tumors and cysts, once they are identified, by endoscopic ultrasound (EUS), transesophageal endoscopic biopsy, and digital radiographic imaging methods has dramatically evolved. Finally, pathologists have been able to study the molecular genetic profile of benign esophageal tumors to determine their specific diagnosis and pathogenesis.

CLASSIFICATION

Three classification schemes have been proposed and are summarized in Box 37–1. The first classification system, advocated by both Sweet et al.[19] and Moersch and Harrington,[2] is based on both clinical and gross pathologic findings. They organized tumors according to the esophageal layer—mucosa, submucosa, and muscularis—from which they originated. The second is an anatomic classification attributed to Nemir et al.[20] in which esophageal tumors are organized by cell of origin into epithelial, nonepithelial, and heterotopic tumors. The third approach classifies benign tumors and cysts by location and clinical (radiographic and endoscopic) appearance. One example of this third approach, cited by Reed[21] and attributed to Herrera,[22] classifies tumors as intraluminal, intramural, and extramural. Another example, advocated by Avezzano et al.,[23] classifies tumors

Box 37–1 Proposed Classification Schemes for Benign Esophageal Tumors

Classification by esophageal layer of origin[2,19]
- Mucosal
- Submucosal
- Muscularis

Classification by anatomic site of origin[20]
- Epithelial
- Nonepithelial
- Heterotopic

Classification by location and clinical appearance[21-23]
- Intramural/extramucosal
- Intraluminal/mucosal
- Cysts and duplications

Table 37–1 Esophageal Mesenchymal Tumors

Features	Schwannoma	Leiomyoma	GIST
Histology	Moderately cellular Peripheral lymphoid cuff	Eosinophilic cytoplasm	Highly cellular Spindle cells Basophilic appearance
Molecular genetic markers	+S-100, GFAP –CD117, CD34, SMA	+Desmin, SMA –CD117, CD34	+CD117, CD34
Gender ratio (M:F)	1:1	2:1	2:1
Mean age (yr)	54	35	63
Malignant potential	Lowest	Mixed	Highest

GFAP, glial fibrillary acidic protein; GIST, gastrointestinal stromal tumor; SMA, smooth muscle actin.
Data from references 22-29.

into two groups, intramural-extramucosal and mucosal-intraluminal. These two similar schemes are combined into the third classification based on clinical findings. The following description of specific benign tumors and cysts of the esophagus is organized according to this last classification scheme.

INTRAMURAL/EXTRAMUCOSAL

Mesenchymal Tumors

Previously, each benign esophageal tumor was thought to originate independently from precursor cells within the esophageal wall. For example, leiomyomas were thought to arise from smooth muscle cells of the muscularis mucosa, muscularis propria, vascular smooth muscle cells, or embryonic rest cells within the esophageal wall. However, increasing molecular genetic data indicate a common mesenchymal cell of origin for the three benign tumors *leiomyoma, gastrointestinal stromal tumor* (GIST), and *schwannoma.* Table 37–1 summarizes the histologic, immunohistochemical, and clinical characteristics of these three tumors.[22-29] Schwannomas are the least common of the three. They are positive for S-100 protein and glial fibrillary acidic protein (GFAP) but negative for CD117, smooth muscle actin (SMA), and CD34. Malignant potential is the lowest for the three mesenchymal tumors. Leiomyoma is the most common mesenchymal tumor. These tumors are positive for desmin and SMA but negative for CD117 and CD34. Malignant potential is closely related to tumor size. A large tumor, or documented growth, suggests a higher malignant potential. GIST is uncommon in the esophagus but more common than schwannoma. GIST is positive for CD117 and CD34. It has the highest malignant potential of mesenchymal tumors. The risk for malignancy, as with leiomyoma, increases with tumor size and with documented growth. However, even a smaller GIST with low mitotic activity can result in metastatic tumor recurrence, and reports indicate that a characteristic of all these tumors is expression of c-kit (CD117 antigen). The actual mesenchymal cell of origin is not known with certainty, but resemblance to the interstitial cells of Cajal, which regulate gut peristalsis, suggests that they are the common cell of origin for these tumors. These cells retain the ability to grow and differentiate into smooth muscle cell (leiomyoma), stromal cell (GIST), and neural sheath (schwannoma) tumors. The terminology for these tumors remains confusing. Many still refer to each separately, whereas others call them *stromal tumors.* In this chapter they are grouped together as mesenchymal tumors in acknowledgment of their common mesenchymal cell of origin.

Leiomyoma

Leiomyoma accounts for approximately two thirds of all benign esophageal tumors. There have been many excellent reviews of the clinical and pathologic features of esophageal leiomyomas, including those by Storey and Adams,[16] Seremetis et al.,[10] Sweet et al.,[19] Posthlethwaite and Musser,[30] and Hatch et al.[31] The most recent comprehensive review, that by Lee et al.,[32] includes the time period 1900 to 2003. All these reviews present a picture of esophageal leiomyoma that is remarkably consistent.

Despite the fact that leiomyoma is the most common benign esophageal tumor, it is rare, with a reported incidence of 0.005% to 7.9% in autopsy series. Clinically, the prevalence is less because many tumors are small and remain undetected. Esophageal cancer is 50 times more common than leiomyoma. There is no evidence suggesting that the true, overall incidence is changing. The peak incidence at manifestation is between 30 and 50 years of age for both men and women (Fig. 37–1). The youngest and oldest reported patients are 9 and 83 years of age. Leiomyoma is more common in men than women with a ratio of 2 : 1.

Anatomically, leiomyomas are most commonly located in the lower two thirds of the esophagus. In the review by Hatch et al.,[31] the frequency of tumors in the upper, middle, and lower third of the esophagus was 8.5%, 38.2%, and 46.5%, respectively. An additional 6.8% of tumors involved both the lower third of the esophagus and the proximal part of the stomach. Leiomyomas most

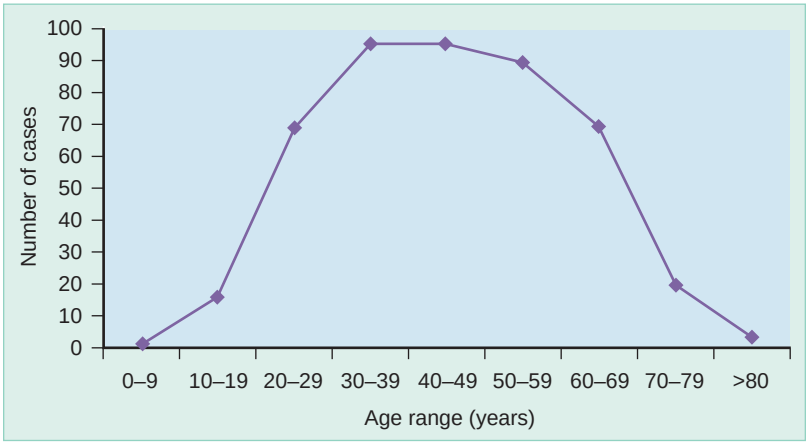

Figure 37–1. Leiomyoma: age at diagnosis.

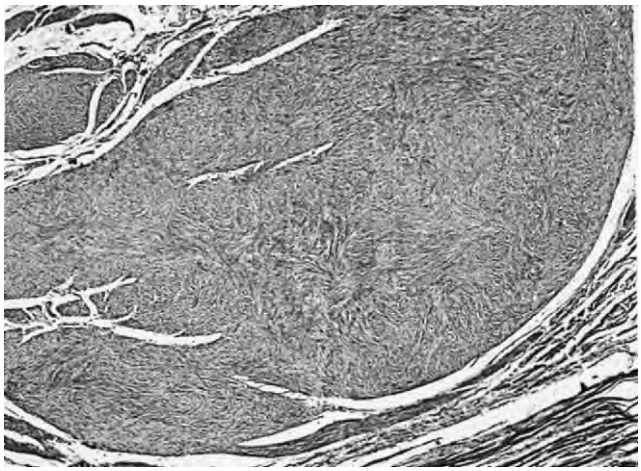

Figure 37–2. Photomicrograph of an intramural circumscribed leiomyoma demonstrating uniform spindle cells arranged in fascicles or whorls.

Table 37–2 Esophageal Leiomyoma: Major Symptoms

Symptom	Prevalence
Dysphagia	47.5%
Pain	45%
Pyrosis	40%
Weight loss	24%
Duration of symptoms	30% >5 yr
	30% >2 yr
	40% 11 mo*

*Average length of symptoms.
From Seremetis MG, Lyons WS, DeGuzman VC, Peabody JW: Leiomyomata of the esophagus. Cancer 38:2166-2177, 1976, with permission.

commonly occur as an extramucosal-intramural mass (72.4%), which is why they are included in this section; however, they may also be manifested as an extraluminal mass (19%) extending outside the esophagus into the mediastinum or as an intraluminal, polypoid mass (8.6%). Most tumors involve only a portion of the circumference of the esophageal wall, but 13% of leiomyomas are annular and involve the entire circumference of the bowel wall.

Leiomyomas are firm, rubbery, encapsulated masses that can assume many shapes—some uniform and others bizarre. Round, oval, spiral, horseshoe, and annular masses have been reported. Half these tumors are less than 5 cm in diameter, and 85% are less than 10 cm in diameter. Tumors ranging in size from several millimeters to 29 cm in diameter have been reported. Tumors exceeding 1000 g are termed giant. The histologic appearance demonstrates uniform spindle cells arranged in fascicles or whorls (Fig. 37–2). The vast majority of leiomyomas are solitary (97%). In some cases, the entire smooth muscle portion of the esophagus is filled with confluent small tumors, a condition termed leiomyomatosis.

Conditions that have historically been associated with esophageal leiomyoma include hiatal hernia, diverticulum, and achalasia. Amer et al.[33] documented esophageal motility disorders, distinct from achalasia, in four patients whose motility patterns normalized after removal of leiomyoma. The association of leiomyoma with esophageal motility disorders might be expected given that these tumors originate from the interstitial cells of Cajal, which are responsible for gastrointestinal motility. Other disorders that should be considered in the differential diagnosis of leiomyoma include esophageal cancer, other benign esophageal tumors or cysts, vascular anomalies, and lung and mediastinal tumors.

The symptoms related to leiomyoma, comprehensively reviewed by Seremetis et al.,[10] continue to be valid today and are listed in Table 37–2. Approximately half the patients with leiomyomas are asymptomatic. When symptoms are present, dysphagia and pain predominate. The pain is usually retrosternal or epigastric and is often

described as a feeling of pressure. Unlike leiomyoma originating in the stomach, bleeding is rare. The patient's symptoms are of long duration. Sixty percent of patients reported symptoms for 2 years or longer. The remaining 40% of patients had symptoms for an average of 11 months. Storey and Adams[16] emphasized that in a symptomatic patient, multiple symptoms were the rule. They also noted that respiratory symptoms, including cough, dyspnea, or both, occurred in 10% of patients. Sweet et al.[19] identified tumor size as the single most important factor in determining the likelihood and severity of symptoms. In one report of a 13-year-old girl with hypertrophic osteoarthropathy and esophageal leiomyoma, the osteoarthropathy regressed rapidly after removal of the leiomyoma.[34]

There are no symptoms that specifically indicate that a patient has a leiomyoma. Fifty percent of patients with esophageal leiomyoma are asymptomatic. Often the symptoms, when present, are vague in their description and time of onset. Sometimes it is not even clear that the symptoms are related to the esophageal tumor. Therefore, diagnosis requires endoscopic or radiographic imaging.

Historically, most leiomyomas were identified as an incidental finding of an extramucosal, intramural esophageal mass on esophagoscopy. Even though a benign tumor was suspected, early surgical intervention was recommended because of the uncertainty in diagnosis. As mentioned in the beginning of the chapter, advances in diagnostic methods now result in the ability to diagnose the nature and extent of benign esophageal tumors with considerably greater confidence. As a result, patients can be appropriately triaged to surgical therapy versus observation.

Most esophageal leiomyomas cannot be visualized on plain chest films. Larger tumors, especially those that extend outside the esophageal wall, may be identified as a mediastinal mass.[35] On occasion, these tumors have been reported to contain focal areas of punctate calcification that could be identified in the posterior mediastinum on plain films.[36]

The characteristic features of leiomyomas on barium esophagography have been well described.[9,37-39] Oral contrast studies demonstrate a segmental lesion that focally impinges on the column of swallowed contrast (Fig. 37–3). This crescent-shaped tumor generally has half its mass in the esophageal wall and the rest extending into the lumen. The junction of the mass with the esophageal wall demonstrates sharp margins (approaching 90 degrees). There is little obstruction to flow of contrast. The mucosa overlying the mass is intact but smooth, as though it is stretched over the tumor. The mucosa on the opposite wall is intact. Proximal esophageal dilatation is unusual. Tumors near or involving the esophagogastric margin are often larger and angulate and flatten the esophageal lumen. Tumors near the esophagogastric junction may impair esophageal emptying, result in esophageal dilatation, and simulate achalasia. On CT most leiomyomas appear as eccentric, focal esophageal wall thickening. This finding has not been specific for leiomyoma, although radiologists are making progress in correlating CT findings with the specific pathologic diagnosis of benign esophageal tumors.[40] Administration of oral contrast helps in visualizing intramural esophageal leiomyomas. CT scanning is most helpful in evaluating larger tumors, especially those that extend outside the esophageal wall, to assess the interface between tumor and mediastinum.

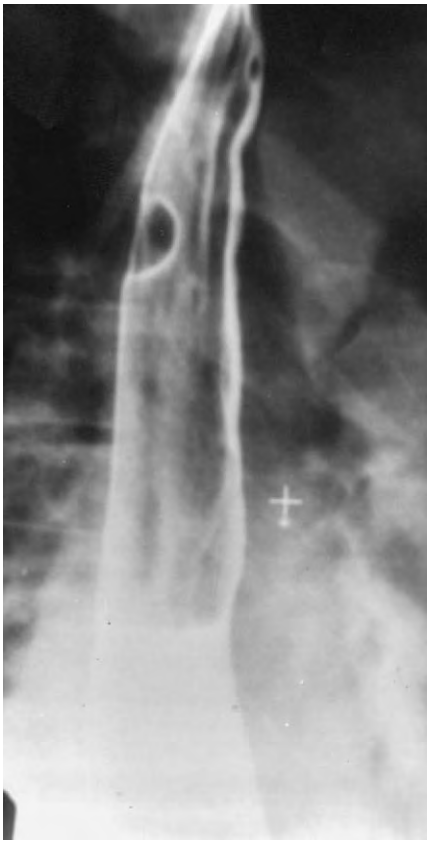

Figure 37–3. Contrast esophagogram demonstrating the characteristic findings of a leiomyoma.

The endoscopic characteristics of leiomyoma have also been well described[9,41] and include (1) a segmental tumor bulge into the lumen, (2) an intact overlying esophageal mucosa, (3) narrowing of the esophageal lumen without obstruction, and (4) a movable mass (Fig. 37–4). Ulceration of the mucosa overlying a benign esophageal leiomyoma is rare. In the past, endoscopic biopsy of extraluminal esophageal lesions was avoided for fear of bleeding or perforation. However, the safety of transendoscopic needle aspiration for cytologic evaluation is now well established. Often, a needle biopsy is performed in conjunction with EUS to more accurately establish the anatomy of the target lesion.

EUS has become instrumental in improving the diagnostic and staging accuracy of esophageal tumors. Rice[42] has classified benign esophageal tumors according to the five EUS esophageal layers. This classification is reproduced in Table 37–3. Leiomyomas are identified as arising from the fourth layer, or the muscularis propria. According to Rice, leiomyomas may arise from the muscularis mucosae in the second EUS layer, but they do so

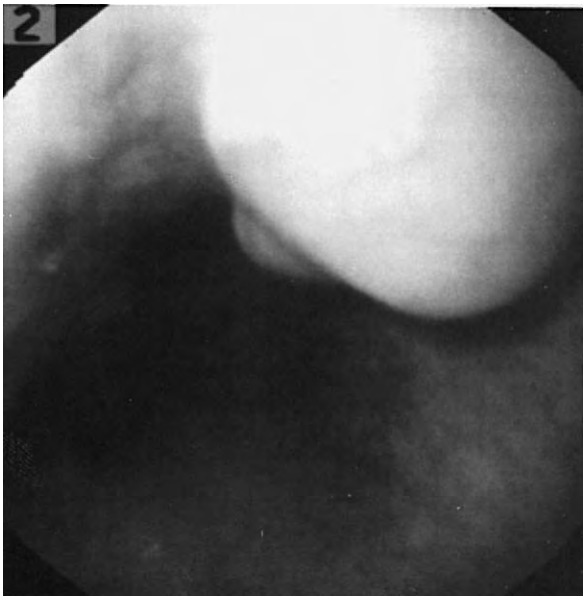

Figure 37–4. Endoscopic appearance of a leiomyoma illustrating the segmental tumor bulge, intact overlying mucosa, and luminal narrowing without obstruction.

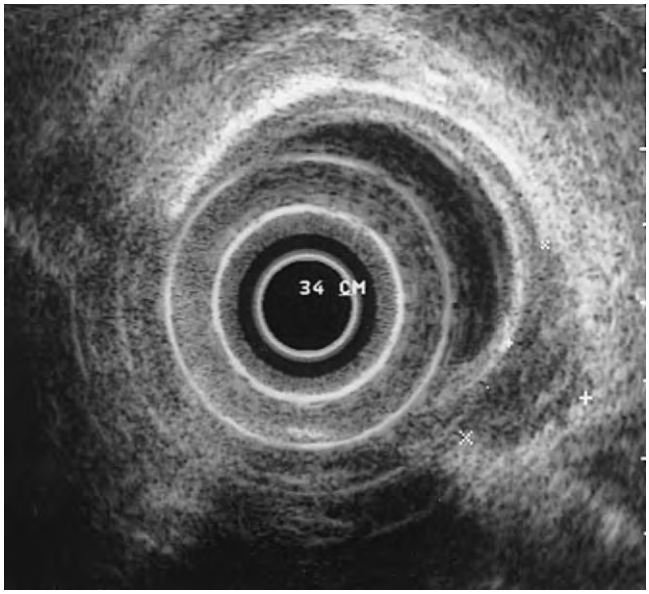

Figure 37–5. Endoscopic ultrasound of a leiomyoma demonstrating the size and location of the tumor. The tumor borders are marked by the three scan markers (*, x, +).

Table 37–3 Correlation of Endosonographic Layer and Pathology

Endoscopic Ultrasound Layer	Esophageal Tumor	Esophageal Cyst
First/second layer (mucosa and deep mucosa)	Squamous papilloma Fibrovascular polyp Granular cell tumor	Retention cyst
Third layer (submucosa)	Lipoma Fibroma Neurofibroma Granular cell tumor	
Fourth layer (muscularis propria)	Leiomyoma*	Cysts and duplications
Fifth		Cysts and duplications

*Leiomyomas most commonly arise as extraluminal/intramural masses. However, they may be manifested as intraluminal polypoid masses or with extraesophageal extension.

From Rice TW: Benign esophageal tumors: Esophagoscopy and endoscopic esophageal ultrasound. Semin Thorac Cardiovasc Surg 15:20-26, 2003.

only rarely. Therefore, EUS *location* of the tumor assists in the differential diagnosis. EUS can identify the size, shape, and extent of the tumor. It can identify lesions that would be too small to see by contrast esophagography or CT. In addition to location, the specific EUS *pattern* of leiomyoma is characteristic and includes a hypoechoic, homogeneous, well-demarcated mass with no associated lymphadenopathy (Fig. 37–5). EUS findings that are atypical for a benign leiomyoma include larger size (>4 cm), irregular margins, nonhomogeneous echoic pattern, and regional lymphadenopathy.

Historically, identification of an extraluminal-intramural esophageal mass was an indication for surgery because of the uncertainty of specific diagnosis and the inability to monitor the size of the lesion over time. Now, however, EUS and chest CT have increased the diagnostic accuracy and safety of nonoperative surveillance. Additionally, it is now well established that malignant degeneration of a benign leiomyoma is a very rare event generally heralded by a change in tumor size. Factors that need to be considered when selecting a patient for nonoperative management include tumor size, location, and patient symptoms. Leiomyomas that are small, extramucosal-intramural, without associated lymphadenopathy, and in asymptomatic patients may be observed without surgery. What size constitutes a "small" leiomyoma is not defined in the literature. Samphire et al.[43] consider small to be 2 cm or less. The principle of

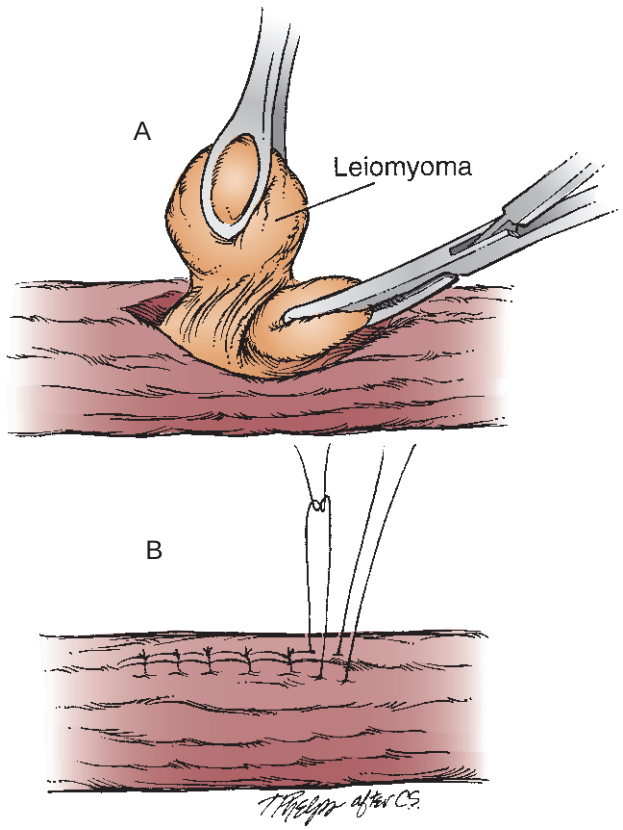

Figure 37–6. The technique of enucleation is illustrated. **A,** The esophageal muscular fibers are split and the leiomyoma is bluntly extracted from the esophageal wall. **B,** Once removed, the muscular defect is reapproximated.

nonoperative management is to monitor patients for the onset of symptoms or a change in size of the esophageal tumor. EUS, performed every 1 to 2 years, with or without chest CT, most accurately tracks tumor size.

Indications for resection include symptoms, uncertainty of diagnosis, larger size, mucosal erosion, regional lymph node enlargement, and tumor growth. Open resection has been the standard approach to resecting leiomyomas, but it is recently being challenged by minimally invasive and endoscopic methods. Lower third esophageal tumors are approached with a left thoracotomy. Tumors near the esophagogastric junction may be resected via laparotomy and a transhiatal approach. Leiomyomas proximal to the lower third are approach by right thoracotomy. In all cases, the tumor is localized visually and by palpation. The esophageal muscle is then split over the mass, which is then delivered from the muscular wall in a technique termed "enucleation" (Fig. 37–6). The mucosa is not generally involved, and intramural leiomyomas may be removed without entering the esophageal lumen. Once the mass is removed and the mucosa is inspected to ensure that it has not been inadvertently opened, the muscular fibers are reapproximated with interrupted sutures.

Resection of leiomyoma by the minimally invasive methods of thoracoscopy and laparoscopy is now well established. The same technique as for open surgery is used to enucleate the tumor from the muscular wall. Samphire et al.[43] published an excellent description of thoracoscopic and laparoscopic enucleation of leiomyoma. More recently, Elli et al.[44] reported the successful use of robotic-assisted thoracoscopic resection of leiomyoma. Lee et al.[32] described an endoscopic-assisted method of enucleation called "combined endoluminal intracavitary thoracoscopic enucleation," or the "balloon push-out" method. At the time of thoracoscopy, an intraluminal balloon attached to an esophagoscope is inflated at the level of the leiomyoma and pushes the tumor outward toward the operating surgeon, thereby facilitating resection.

Several methods have been reported in which benign esophageal tumors are resected solely by endoscopic techniques. If an esophageal leiomyoma is intraluminal and polypoid, it may be removed via standard endoscopic polypectomy methods. Kinney and Waxman[45] reported their experience and reviewed the literature on a technique called endoscopic mucosal resection. In this method, a sclerotherapy needle is inserted into the esophageal wall under the submucosal tumor. Saline injection causes the tumor to protrude into the lumen in a polypoid fashion. The mass is then resected by standard polypectomy methods. Sun et al.[46] used suction on the submucosal tumor to pull it into the esophageal lumen, where it was "banded" at its base. Later, the tumor sloughed free into the gastrointestinal tract and the mucosal defect healed without further intervention. Park et al.[47] described an endoscopic, electrocautery method of resecting submucosal tumors. The technique results in successful but "piecemeal" resection of the tumor.

In some patients with diffuse esophageal leiomyomatosis or with particularly large tumors (>8 cm in size), esophagectomy is required. Esophagectomy is reported to be indicated in 10% of patients or less. Standard surgical techniques are used. Particular care should be taken to minimize the risk for postoperative gastroesophageal reflux.

In their collective review, Lee et al.[32] tabulated the results of resecting esophageal leiomyomas by thoracotomy, minimally invasive surgery, and endoscopic methods for the time period 1984 to 2001. With open thoracotomy, operative mortality for enucleation ranged from 0% to 1.3%. Complications were uncommon and minor, and 89% to 94% of patients were symptom-free 5 years after surgery. An earlier report by Rendina et al.[48] noted a mortality of 10.5% if esophagectomy was required. In one of the larger series reported to date by Bonavina et al.,[49] of 66 patients, 95.5% were managed by enucleation and 4.5% required esophagectomy. Enucleation was performed by thoracotomy in 50 (79%), laparotomy in 5 (8%), and videothoracoscopy in 8 (13%) patients. Indications for esophagectomy were either diffuse disease or large size. In their series there were no deaths. The number of cases reported in which leiomyomas are enucleated by thoracoscopy and laparoscopy is limited. However, it seems as though these approaches lower operative mortality in comparison to open methods, with similar favorable long-term outcomes. Whether the reduction in reported mortality is

secondary to the minimally invasive methods or patient selection is not clear. The greatest danger with the use of minimally invasive methods is mucosal damage. When identified, it can be closed without conversion to an open approach. It is speculated that the application of robotic systems, with three-dimensional computer imaging, will further improve results. Endoscopic methods are new, and the number of reported cases and length of follow-up are limited. However, no deaths have been reported. Bleeding and symptoms from iatrogenic mucosal ulceration are the most prevalent problems encountered. Local recurrence, presumably from incomplete tumor resection, is the primary long-term concern. Overall, the data suggest a continued decline in operative mortality in the management of these tumors in adults.

Leiomyomas rarely develop in patients younger than 10 to 12 years.[21,50] In the pediatric age group, leiomyoma is more common in girls, and there is diffuse esophageal involvement in more than 91% of patients. Dysphagia is the most common initial symptom. Patients are often thought to have achalasia. Because of the diffuse nature of the disease in children, treatment requires esophagectomy in most patients. Operative mortality in pediatric patients is higher (21%), undoubtedly reflecting the greater percentage of esophagectomies required for these younger patients.[21,50]

Gastrointestinal Stromal Tumor

GISTs are mesenchymal tumors with specific molecular genetic features that differentiate them from leiomyomas and schwannomas.[25-29] These tumors most commonly develop in patients 40 years or older. They occur with equal frequency in both men and women. GISTs may occur anywhere along the gastrointestinal tract; however, they are most common in the stomach (60%). Less than 5% of GISTs are found in the esophagus. Benign tumors exceed malignant forms by a margin of 10:1. GISTs are firm, solid masses that on histologic examination demonstrate spindle cell morphology. Histologic differentiation between benign and malignant tumors is based on the presence and number of mitotic figures per high-power field (HPF). Tumors with 5 to 10 mitotic figures per HPF, or size greater than 10 cm in diameter, are considered to have high malignant potential. Even tumors with low mitotic counts per HPF are capable of generating metastatic disease.

Symptoms, diagnostic methods, and treatment options are the same as just discussed for leiomyoma.[40]

Tumor size is the best factor to determine whether to recommend surgery or observation. In general, tumor diameter greater than 5 cm, growth under observation, or symptoms are indications for surgical resection. Small GISTs can be enucleated by open or minimally invasive techniques as previously discussed. Larger GISTs, because of their adherence to the esophageal mucosa and their malignant potential, often require esophagectomy.

Schwannoma

Schwannomas are the least common of the esophageal mesenchymal tumors. The small number of reported cases makes it difficult to generalize about the patient characteristics of these tumors. The reported age range of patients is 47 to 62 years. No gender preponderance is noted. Grossly, schwannomas are tan masses that are firm and rubbery. Histologically, these tumors exhibit moderate cellularity and a characteristic peripheral rim of lymphoid cells. Some esophageal schwannomas have associated melanin pigmentation. Immunohistochemical studies demonstrate that these tumors are positive for S-100 protein and GFAP but negative for c-kit, CD34, and SMA.

Symptoms and diagnostic methods are similar to those for leiomyoma. Treatment options are to observe or resect these tumors. Resection options are the same as those described for leiomyoma. Of note, the majority of schwannomas are benign. Tumor size is the best predictor of malignant potential. The bigger the tumor, the greater the chance that it will be malignant. Post-treatment outcome is related to completeness of resection and whether the tumor is benign or malignant.[51-55]

Granular Cell Tumor

Granular cell tumor (GCT), also known as granular cell myoblastoma, is a rare submucosal tumor that infrequently involves the esophagus. Esophageal GCT and leiomyoma are both intramural submucosal tumors and share many clinical features, including initial symptoms, diagnostic work-up, and treatment options. Abrikossof is credited with the first description of an esophageal GCT in 1931.[9] GCT may occur in any organ system but is most commonly seen in the submucosa of the tongue (40%), skin (30%), breast (15%), and gastrointestinal tract (5%).[56-58] Most GCTs are benign; malignant GCTs account for only 2% to 3% of overall cases. Reports have documented both a male[59] and a female[56] preponderance of this tumor. More likely, GCT occurs equally in both sexes.[9] The average age at the time of diagnosis is 40 to 44 years. Despite accumulating experience with GCT, there is still controversy regarding its specific cell of origin, differentiation into benign and malignant tumor, and recommendations for optimal management.

The prevailing opinion is that GCT arises from neural cells within the esophageal wall. GCT cells have electron microscopic features similar to those of Schwann cells and stain for the neural proteins S-100 and neuron-specific enolase.[9,21] Only 1% to 2% of GCTs are found in the esophagus. Most GCTs, 50% to 63%, are located in the distal end of the esophagus. Multiple esophageal GCTs are reported in 20% of patients. When the esophagus is involved, it is the sole organ site in the majority of cases; however, in 5% to 14% of patients, GCT is identified in multiple organ sites.[56,60] Grossly, the tumor arises in the submucosa and protrudes into the esophageal lumen. GCTs have a characteristic pale yellow color. The overlying esophageal mucosa is intact, but it is often so translucent that it appears absent. Microscopically, tumor cells are pale staining with small nuclei and abundant cytoplasm that is characteristically granular in appearance (Fig. 37–7). The overlying mucosa shows pseudoepitheliomatous hyperplasia. There are no

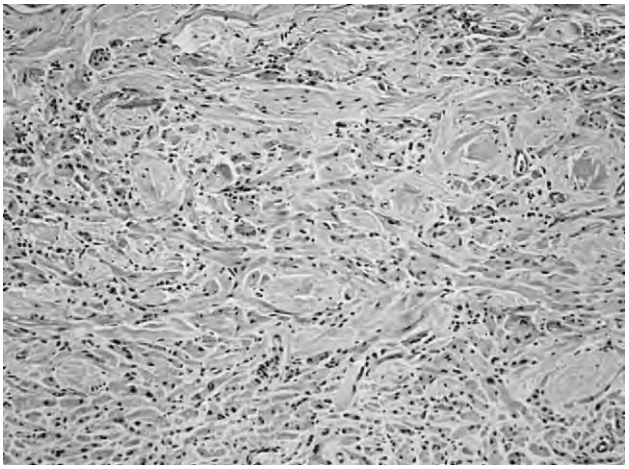

Figure 37–7. Photomicrograph of a granular cell tumor that has relatively uniform plump spindle cells containing coarsely granular eosinophilic cytoplasm.

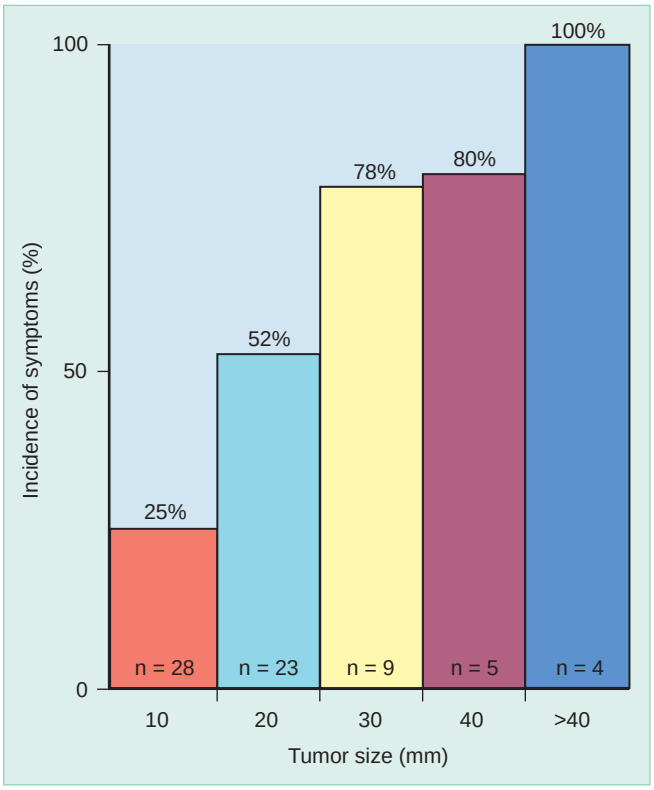

Figure 37–8. Incidence of symptoms as a function of granular cell tumor size. (From Coutinho DS, Soga J, Yoshikawa T, et al: Granular cell tumors of the esophagus: A report of two cases and review of the literature. Am J Gastroenterol 80:758-762, 1985, with permission.)

characteristic histologic findings defining malignant GCT. The diagnosis of benign versus malignant GCT is made on the basis of *both* clinical and histologic findings. Both local invasion and metastases have been reported with malignant GCT.

There are great similarities in the symptoms of esophageal GCT and leiomyoma. Symptoms include dysphagia, retrosternal pain or vague discomfort, and less frequently, nausea and vomiting. Fifty percent of patients with GCT are asymptomatic. Coutinho et al.[59] have demonstrated nicely that the frequency of symptoms is directly related to tumor size, as shown in Figure 37–8. In their series the frequency of symptoms in patients with tumors 10 mm or less, 11 to 20 mm, 21 to 30 mm, and 31 to 40 mm was 25%, 52.2%, 77.7%, and 80%, respectively. The differential diagnosis for patients with suspected GCT includes other benign esophageal tumors and malignant carcinoma.

As with patients with leiomyoma, the diagnosis is best made by contrast esophagography and endoscopy. A barium esophagogram demonstrates a smooth-walled filling defect impinging on the esophageal lumen. Smaller tumors are difficult to identify radiographically, whereas larger tumors may result in high-grade esophageal obstruction. Endoscopically, the tumor is visible as a yellowish "molar-shaped" polypoid lesion protruding into the lumen.[61] Endoscopic biopsy of these tumors is often nondiagnostic. EUS is helpful in defining the site of origin and the extent of these tumors. Tada et al.[61] described the EUS findings of esophageal GCT as hyperechoic solid masses surrounded by hypoechoic submucosa without continuity to the muscularis propria.

Management of patients with GCT remains controversial. Postlethwaite and Lowe[9] have argued that these tumors should be treated aggressively with surgical removal on diagnosis because of the inability to distinguish between benign and malignant tumors. Others have advocated conservative management with endoscopic follow-up for smaller, asymptomatic tumors.[62] These authors site the low frequency of malignancy and availability of the tumor for endoscopic surveillance as justification for conservative management. This issue remains unresolved. There is agreement that symptomatic tumors or any tumor demonstrating rapid tumor growth is an indication for removal. Treatment in the past was limited to transthoracic excision; however, successful endoscopic mucosal resection has been described in several reports.[61,63-65] One report of endoscopic alcohol injection of a GCT under EUS guidance has been described,[66] as well as yttrium-aluminum-garnet (YAG) laser and argon plasma coagulation.[67,68]

Hemangioma

Hemangiomas are benign vascular tumors that originate from the esophageal submucosa. They are rare, with less than 100 reported cases in the literature. In Platcha's series,[3] hemangioma accounted for 3% of all benign esophageal tumors. Gentry et al.[69] found that only 11 of 261 (4.2%) gastrointestinal vascular tumors were located in the esophagus. The first description of an esophageal hemangioma, treated by radium application, is credited to Vinson et al.[70] in 1927. There are no data defining the demographics of patients with esophageal hemangioma. Riemenschneider and Klassen[71] noted a slight male

preponderance and an age range from newborn infants to 72 years. They can also occur in association with Rendu-Osler-Weber syndrome as multiple esophageal hemangiomatosis.[72]

The gross appearance of hemangioma is a bluish polypoid mass arising from the submucosa of the esophageal wall. Some hemangiomas are small and form simple cystic masses. Others can become quite large with multinodularity. The tumor is noncircumferential and may involve the esophagus anywhere along its length. In a review of 58 patients, Govoni[73] noted that the majority of hemangiomas were located in the middle or distal portion of the esophagus. Microscopically, there is proliferation of benign vascular spaces of a cavernous nature. Multinodular masses demonstrate fibrous septation. The overlying mucosa is intact.

Symptoms include dysphagia, hemorrhage, and substernal pain or discomfort. In adults,[71] symptoms may be of relatively short duration (2 months) or may be chronic (7 years). Dysphagia tends to be mild, even with larger masses, because of the compressible, noncircumferential nature of these tumors. The hemorrhage produced by rupture may be massive and even fatal. Approximately a third to a half of patients with hemangioma are asymptomatic.

Hemangiomas are manifested as well-defined submucosal tumors on barium esophagography. A bluish, polypoid submucosal lesion is seen endoscopically. The mass is compressible endoscopically, and biopsy is not recommended.[74] EUS has been used to identify and "stage" these vascular tumors. In contrast to leiomyoma or GCT, CT is particularly helpful in making the diagnosis and planning treatment of hemangiomas.[75] MRI has also been described in the diagnosis of hemangioma, especially for larger tumors.

A wide variety of treatments have been proposed to manage esophageal hemangioma, including endoscopic resection,[76] YAG laser fulgaration,[77] sclerotherapy,[78] radiation therapy, and open or videothoracoscopic resection.[79] Surgical resection can usually be performed by either local resection or enucleation, although esophagectomy is occasionally required. The surgical procedures are safe with a mortality of approximately 2%.[9] There are no reports of recurrence after surgical resection. The results of endoscopic resection are limited to case reports but seem reasonable over a limited follow-up.

Other Intramural Tumors

All benign esophageal tumors are uncommon. The most common intramural tumors, leiomyoma, GCT, and hemangioma, have been separately discussed. Other rare intramural esophageal tumors have been reported. To be complete, they will be briefly covered in this section.

Rhabdomyomas are tumors of the striated skeletal muscle of the upper third of the esophagus. They are rare, and not enough patients have been identified to determine the clinical characteristics of these tumors. Lipomas and fibromas usually protrude into the esophageal lumen as a polyp, but they may form submucosal masses. Schwannomas share many pathologic and clinical features with leiomyoma. Both tumors arise from the interstitial stem cells of Cajal. Schwannomas produce the same symptoms as leiomyoma and are diagnosed in the same fashion. Recommended treatment is surgical enucleation. Endoscopic resection has been reported only once in the literature.[80]

Lipomas occur rarely as tumors of the submucosa and are usually found incidentally. They appear as a soft, pale yellow tumor with intact overlying mucosa. When evaluated by EUS, they are hyperechoic, homogeneous lesions that are confined to the submucosal layer. Biopsy samples are difficult to obtain because lipomas do not involve the mucosa. They do not require treatment or further follow-up because they have no malignant potential.[42]

Underlying submucosal inflammation can lead to inflammatory pseudotumors. These reactive pseudoneoplastic processes can occur throughout the body.[81] They may result from an underlying injury, such as perforation or the postoperative healing process, or can be secondary to an autoimmune disorder or subclinical infection. Epstein-Barr virus has also been implicated in the formation of these pseudotumors.[82-84] These tumors are composed of reactive blood vessels, fibroblasts, and polycellular inflammatory cells. Because they are submucosal lesions, biopsy may be inconclusive. Occasionally, they may cause ulceration of the overlying mucosa. Treatment strategies have included surgical excision or systemic corticosteroids, although the latter results in a high recurrence rate and is not without side effects.[85]

Congenital ectopic rests of pancreatic, thyroid, and parathyroid tissue have been reported in the esophageal wall.[9] In some cases this tissue has been hormonally active. In such cases, treatment is local resection or enucleation.

INTRALUMINAL/MUCOSAL

Fibrovascular Polyp

Fibrovascular polyps are the second most common benign esophageal tumor and the most common intraluminal tumor. Jang et al.[86] reported 56 cases in the literature in 1969. Fibrovascular polyp is a term that includes a broad range of specific intraluminal polyps, including fibromas, fibrolipomas, myomas, myxofibromas, pedunculated lipomas, and fibroepithelial polyps. The pathogenesis, clinical features, work-up, and treatment options are similar regardless of the specific histologic type of polyp. Though not proven, it is hypothesized that these polyps begin as a region of submucosal thickening that elongates into the esophageal lumen as a result of esophageal peristaltic action to form a polyp. Polyps most commonly originate from the proximal part of the esophagus just distal to the cricopharyngeus. They may achieve large size and result in esophageal dilatation or be long enough to reach into the stomach. The most dramatic clinical feature of fibrovascular polyps is their potential for regurgitation out through the oropharynx, where they may be reswallowed, severed by biting and expectorated, or aspirated.

Table 37–4 Age and Sex of 55 Patients with Fibrovascular Polyps

Age (yr)	Men	Women
20-29	3	5
30-39	3	3
40-49	6	1
50-59	11	4
60-69	8	4
70-79	5	0
80-89	2	0

From Posthlethwaite RW, Lowe JE: Benign tumors and cysts of the esophagus. In Zuidema GD, Orringer MB (eds): Shackelford's Surgery of the Alimentary Tract, vol 1, 4th ed. Philadelphia, WB Saunders, 1996, pp 369-386.

Avezzano et al.[23] reported a male preponderance (75%) and a peak prevalence in the sixth and seventh decades. Posthlethwaite and Lowe[9] commented that polyps were seen in older men (average age, 54.7 years) and younger women (average age, 43.4). In their series, 69% of patients were men (Table 37–4).

Grossly, these polyps are cylindrical-shaped masses attached by a stalk to the esophageal wall, usually of the proximal esophagus. Polyps range in size from less than 1 cm to greater than 20 cm in length. The average size is 5 cm.[87] Polyps may be long enough that they extend into the stomach, where acid results in focal ulceration. A polyp's diameter may be wide enough that it results in esophageal dilatation. Multiple polyps have been reported. The site of origin within the esophagus is cervical, upper thoracic, middle, and lower esophageal in 80%, 2%, 8%, and 10%, respectively.[9] Histologically, these polyps are composed of mature fibrous tissue with varying amounts of vascularity and adipose tissue. Which of these three components is most prominent determines the specific name for the polyp (e.g., fibrolipoma, myxofibroma). Polyps are covered by intact, smooth mucosa. No malignant degeneration of these polyps has been reported, although at least one case of a coexisting squamous cell carcinoma has been identified.[87]

Aside from identifying a regurgitated polyp, no physical findings are characteristic of these tumors. Potential symptoms include intermittent dysphagia, regurgitation of the polyp, and respiratory symptoms. Polyps that extend into the stomach may ulcerate and bleed and thereby result in anemia and symptoms related to anemia. Levine et al.[88] reported that dysphagia (87%) and respiratory symptoms (25%) were most common. Regurgitation of the polyp into the mouth was noted in only 12% of patients. In their experience, the average duration of symptoms was 17 months; however, 44% of patients had symptoms for 6 months or less. Up to 30% of patients have been reported to be asymptomatic. Barium esophagography demonstrates a polypoid filling defect that may be seen to move within the esophageal lumen with a swallow. High-grade obstruction is uncommon. Larger polyps may cause esophageal dilatation mimicking achalasia. Polyps may be missed on endoscopy because most originate in the proximal esophagus and are covered by normal mucosa. EUS demonstrates an echo-dense intraluminal polyp.[87] Findings on CT vary, depending on the amount of adipose and fibrovascular tissue. Polyps that contain a mixture of fibrovascular and adipose tissue appear as a heterogenous mass on CT, whereas those with a majority of adipose tissue appear as a fat-density lesion expanding the lumen of the esophagus, with a thin rim of contrast surrounding the polyp.[88] The differential diagnosis for a patient suspected of having a fibrovascular polyp includes polypoid schwannoma, leiomyoma, and hamartoma.

Treatment is resection of the polyp, including its point of origin and attachment. Historically, this has been accomplished by open surgical techniques in which the esophageal wall is opened, preferably 180 degrees opposite the base of the polyp, and the polyp and stalk excised along with a small cuff of mucosa. The mucosal defect is reapproximated and the esophagotomy closed. The procedure is performed via a cervical incision for proximal tumors and thoracotomy for more distal lesions. Endoscopic removal has been reported for polyps without excessive vascularity. Unless the polyp base is completely removed, however, local recurrence is possible. Treatment by either method is safe. No treatment-related deaths have been reported.[23]

Squamous Papilloma

Squamous papilloma is a rare, benign neoplastic disorder involving the esophageal mucosa. Autopsy series show a frequency of 0.01% to 0.04% of the general population.[89] Adler et al.[90] are credited with the first histologic description in 1959. Papillomas occur in males more frequently than females (2:1). Age at diagnosis ranges from 40 to 70 years. The etiology of papillomas is not known. Gastrointestinal reflux or other chronic mucosal irritation has been proposed as a potential cause. Human papillomavirus (HPV) is found in varying degrees in these tumors. Odze et al.[91] reported that 13 of 26 papillomas evaluated were positive for HPV, most commonly HPV type 16. Others[92-95] have found a more rare association of HPV with squamous papilloma, in the range of 0% to 4% of cases, even when tested by polymerase chain reaction. It is proposed that their etiology is multifactorial and may be a synergistic effect of mucosal irritation and HPV. There has been only one case report[96] of malignant degeneration associated with papillomavirus. Cases of progressive, fatal systemic dissemination have been reported.[97]

Papillomas are usually solitary, sessile lesions involving the distal end of the esophagus. Most lesions are small, less than 1 cm in diameter. Microscopically, papillomas are composed of a central core of connective tissue covered with hyperplastic squamous cells (Fig. 37–9).

The majority of patients with papillomas are asymptomatic, but some may complain of mild dysphagia. Because of an association of papillomas with gastroesophageal reflux and peptic ulcer disease,[90] some patients may initially be evaluated indirectly for

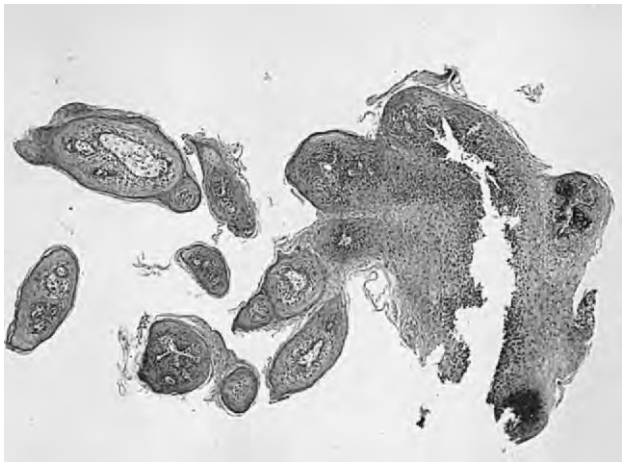

Figure 37–9. Photomicrograph of squamous papilloma showing no dysplastic squamous epithelium with a central core of connective tissue.

symptoms of these associated disorders. There are no characteristic findings on physical examination. Endoscopically, fleshy pink lesions, either sessile or pedunculated, are seen, usually in the distal end of the esophagus. Visually, the lesions may be mistaken for squamous carcinoma. The diagnosis is confirmed by biopsy. No further diagnostic or staging work-up has been advocated.

On the basis of published reports it is not clear whether these lesions should be observed or aggressively resected. Certainly, the diagnosis must first be confirmed and cancer ruled out by biopsy. If a lesion is localized and pedunculated, it should most likely be resected endoscopically and the patient monitored. Papillomas have been noted to recur and spread after treatment by laser fulguration, endoscopic resection, or surgical excision. Because of the risk of seeding, recurrence, or proliferation of disease, Politoske[92] concluded that papillomas should be removed with as little manipulation as possible.

CYSTS AND DUPLICATIONS

Cysts and duplications are included together because they share similar etiology, clinical and radiographic findings, and treatment options. Autopsy studies of the general population estimate the incidence of esophageal cysts to be 1 in 8200 patients.[98] Ten percent to 15% of all gastrointestinal duplications are esophageal in origin. Cysts are more commonly diagnosed in males than females and in children than adults. Cysts and duplications account for approximately 0.5% to 3.3% of all benign esophageal tumors. In children, however, duplications have been shown to account for 12% of mediastinal masses. It is estimated that only 25% to 30% of cysts occur in adults.[3,99,100] Posthlethwaite and Lowe[9] demonstrated a biphasic age distribution for patients with cysts. Forty-one percent of cases occurred in patients younger than 9 years, and 38% occurred in patients between the ages of 20 and 49 years. The first

Box 37–2 Classification of Esophageal Cysts

- Congenital
  - Duplication
  - Bronchogenic
  - Gastric
  - Inclusion
- Other
  - Neuroenteric
- Acquired
  - Retention (single or multiple)

Modified from Arbona JL, Fazzi GF, Mayoral J: Congenital esophageal cysts: Case report and review of the literature. Am J Gastroenterol 79:177-182, 1984.

description of a cyst is credited to Blassius in 1711, and the first surgical resection of a cyst was reported by Sauerbruch and Fick in 1931.[9] Arbona et al.[99] proposed a classification of esophageal cysts that is most commonly cited (Box 37–2).

Cysts and duplications are congenital in origin. One theory states that the early foregut is lined by ciliated columnar epithelium that grows and obliterates the lumen. Vacuoles are then secreted and subsequently coalesce, line up, and form the bowel lumen. It is postulated that single vacuoles become separated, remain within the esophageal wall, and develop into duplications or cysts.[21,99,101] Another theory has been advocated by Hutchison and Thomson.[100] Because the endodermal tube that is destined to form the gut is part of the yolk sac or archenteron, they propose that all developmental gastrointestinal cysts should be labeled "archenteric cysts." According to their theory, at an early stage in development, a *segment* of endoderm becomes separated and fails to become incorporated into the developing gut. This segment retains its endodermal competence and therefore directs the mesoderm to form surrounding muscular wall. However, because it is displaced, its histologic differentiation is less precise, thus accounting for the diversity of mucosal linings that these developmental cysts are noted to have.

Esophageal cysts are classified as duplications[21,99,101] if the cyst (1) is located within the esophageal wall, (2) is covered by two muscular layers, and (3) is lined by squamous epithelium or embryonic epithelium (columnar, pseudostratified, ciliated). Duplications are usually round, but they may be elongated tubular structures. The average diameter of spherical duplications is 4.5 cm. They are most frequently found in the lower part of the esophagus. In the collective series by Arbona et al.,[99] the location was the lower, middle, and upper esophagus in 60%, 17%, and 23%, respectively. A case of an esophageal duplication cyst manifested as an abdominal mass has been reported. Esophageal duplications can be associated with duplications elsewhere in the gastrointestinal tract. Duplication cysts are not linked to vertebral abnormalities. Malignancies arising in duplications are rare but have been reported in the literature.[102]

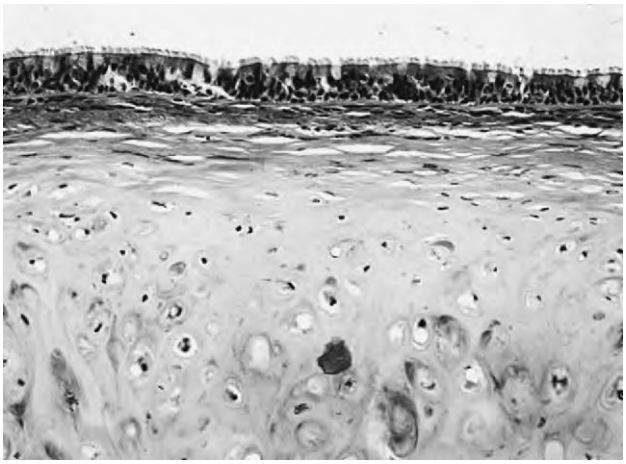

Figure 37–10. Photomicrograph of a bronchogenic cyst wall showing mature cartilage and respiratory-type pseudostratified ciliated columnar epithelium.

Bronchogenic cysts arising from the esophagus are rare.[99] These cysts are caused by an abnormality in lung bud separation from the primitive foregut. Cells from this evolving lung bud become sequestered within the esophageal wall and develop into a bronchogenic cyst. Pathologically, these cysts are located within the esophageal wall and contain cartilage (Fig. 37–10). Bronchogenic cysts are found within the middle and lower thirds of the esophagus and are not associated with vertebral anomalies. No neoplastic changes have been reported.

Gastric cysts are postulated to arise from cells that are destined to become stomach but fail to descend and remain within the esophageal wall. To be classified as a gastric cyst, it must be located within the esophageal wall, contain a muscular wall, and be lined with gastric mucosa.[99] Mucosal hydrochloric acid and enzyme production with ulceration and hemorrhage has been described.

Inclusion cysts are intramural cysts that contain respiratory or squamous epithelium, are not covered by muscle, and do not contain cartilage. They can therefore be differentiated from bronchogenic and duplication cysts. Arbona et al.[99] reported inclusion cyst location to be in the lower, middle, or upper esophagus in 66%, 24%, and 10% of patients, respectively. Cyst size ranged from 0.5 to 20 cm. They are not associated with vertebral abnormalities.

Neuroenteric cysts, also known as posterior mediastinal duplication cysts, arise during notochord separation from the foregut endoderm. At the time of separation, an endodermal diverticulum may form that remains fused to the esophagus or attached to it by a stalk and develops into a cyst. Neuroenteric cysts are found in the posterior mediastinum, are covered by muscle, and are lined by a variety of gastrointestinal mucosa.[99] Split notochord syndrome is described as a neuroenteric cyst associated with vertebral anomalies.[103] The vertebral anomalies may not be at the same level as the cyst.

The normal esophagus contains mucosal and submucosal glands that may coalesce to form acquired cysts. They may be single or multiple. If multiple, it is referred to as esophagitis cystica. These cysts range in size from a few millimeters to 3 cm in diameter and are located in the upper third of the esophagus.

No findings on physical examination are characteristic of cysts and duplications. Symptoms are related to size, location, and patient age. Respiratory symptoms, including cough and wheezing, are more common in children. Gastrointestinal symptoms, including dysphagia, epigastric and substernal pain, and anorexia and nausea, are more common in adults. The prevalence of gastroesophageal reflux seems to be increased in patients with cysts and duplications. According to Cioffi et al.,[104] 37% of patients are asymptomatic on initial evaluation. There has been one report of an acute rupture of an esophageal duplication cyst.[105] Findings on contrast esophagography and esophagoscopy are similar to those in patients with leiomyoma in which a smooth-walled submucosal mass is identified. EUS is helpful in defining the anatomy and establishing the diagnosis. CT is also helpful for both making the diagnosis and planning surgical therapy. MRI can likewise aid in diagnosis, with duplication cysts appearing as high–signal intensity structures on T2-weighted images.[106,107]

Management options include observation, aspiration, and surgical resection. Each option has advocates. Indications for resection include control of symptoms, increase in cyst size, and exclusion of malignancy. Surgically, cysts may be enucleated in a fashion similar to that used for leiomyoma. The procedure has been performed by open thoracotomy, video-assisted thoracoscopic, and laparoscopic techniques.[108]

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Part 7

Miscellaneous Esophageal Conditions

Chapter 38

Perforation of the Esophagus

Dennis Blom

Perforation of the esophagus remains a highly lethal condition that constitutes a true surgical emergency. Successful management demands immediate diagnosis, sound clinical judgment, and institution of appropriate therapies.

The majority of perforations are iatrogenic and caused by instrumental rupture during diagnostic or therapeutic procedures. Spontaneous perforation, often referred to as Boerhaave's syndrome, is the etiologic cause in only 15% of such patients. Less common causes include penetration of the esophageal wall by a swallowed foreign body or trauma.[1] Pain is a striking and consistent symptom and strongly suggests that an esophageal rupture has occurred, particularly if located in the cervical area after instrumentation of the esophagus or in a substernal location in a patient with a history of recent vomiting. When subcutaneous emphysema is also present, the diagnosis is almost certain. The outcome of an esophageal perforation depends on four factors: (1) the cause and location of the perforation, (2) the underlying esophageal disorder, (3) the interval to diagnosis and treatment, and (4) patient comorbid conditions.

HISTORICAL BACKGROUND

In 1724, Hermann Boerhaave, a Dutch physician and one of Europe's leading physicians of the time, published the first description of spontaneous rupture of the esophagus after performing an autopsy on Barron van Wassenaer, the Grand Admiral of the Dutch navy. The admiral suffered from indigestion after large meals and often ingested emetics to induce vomiting for relief. The vivid description of his symptoms gives a lasting impression of the pain induced by spontaneous esophageal rupture: "But while he was sitting upon a chair trying to vomit, even though he did not feel any illness thus far, he suddenly gave forth a horrifying cry at which all the servants ran and they heard him complaining that something near the upper end of his stomach was ruptured, torn, or dislocated." He suggested that the pain was such that "in the most certain and vivid manner, death was coming and inevitable." He died within 24 hours. Boerhaave's autopsy demonstrated rupture of the lower third of the esophagus with free perforation into both pleural cavities. Boerhaave stated, "When it recurs again it can be recognized with the help of this description but cannot be remedied by the assistance from the medical profession." This statement was true for over 200 years, until the first successful repair of an esophageal perforation was reported separately by Barrett and by Olsen and Clagett in 1947.[2,3]

ETIOLOGY

The most common cause of esophageal perforation today is iatrogenic perforation secondary to medical instrumentation. In a comprehensive review of the literature, including 511 perforations, Jones and Ginsberg found that 43% were due to instrumentation of the esophagus, 19% were due to trauma, 16% were spontaneous, 8% were caused by operative injury, 7% were a result of foreign bodies, and 7% were due to tumors and other miscellaneous causes (Table 38–1).[1]

Table 38–1 Causes of Esophageal Perforation in 511 Patients in the Literature

Cause	Percent
Instrumentation	43
Trauma	19
Spontaneous	16
Surgical	8
Foreign bodies	7
Tumor	4
Other	3

From Jones WG, Ginsberg R: Esophageal perforation: A continuing challenge. Ann Thorac Surg 53:534, 1992.

Diagnostic flexible esophagogastroduodenoscopy is a common procedure that is associated with low morbidity and mortality. A survey of more than 14,000 flexible endoscopies in England revealed a 0.05% incidence of perforation and a 0.008% mortality rate.[4] Rigid endoscopy carries a higher risk (0.8% to 1.1%).[5] An American Society of Gastrointestinal Endoscopy survey estimated an overall esophageal perforation rate after flexible upper endoscopy of 0.03% with an associated mortality of 0.001%.[6] The incidence increased to 0.4% after bougienage and 0.3% after pneumatic balloon dilatation. The incidence of perforation also increased to 4% when dilatation is performed for the treatment of achalasia and to 10% with dilatation of malignant strictures.[7,8] Endoscopic thermal therapy for gastrointestinal bleeding is associated with a 1% to 2% incidence of esophageal perforation, whereas palliative ablative procedures are associated with a 5% incidence and esophageal stents with a 5% to 25% incidence.[9,10] When perforation occurs secondary to diagnostic endoscopy, it is usually at the cricopharyngeus muscle; however, when therapeutic dilatation is performed, the location of the perforation is generally at or just proximal to the esophageal stenosis.

Spontaneous rupture, regardless of the cause (vomiting, weightlifting, excessive coughing, Heimlich maneuver, seizures, defecation, child birth), is secondary to the barotrauma associated with a sudden increase in intra-abdominal pressure.[11] If the upper esophageal sphincter fails to relax, this sudden increase in intra-abdominal pressure, frequently exceeding 200 mm Hg, can be completely transmitted into the thoracic esophagus, usually through a defective intrathoracic lower esophageal sphincter. Fifty percent of patients have concomitant gastroesophageal reflux disease, thus suggesting that decreased resistance to the transmission of abdominal pressure into the thoracic esophagus is a factor in the pathophysiology of the lesion. Because extragastric pressure remains almost equal to intragastric pressure, stretching of the gastric wall is minimal. The amount of pressure transmitted to the esophagus varies considerably, depending on the position of the gastroesophageal junction. When the gastroesophageal junction is in the abdomen and exposed to intra-abdominal pressure, the pressure transmitted to the esophagus is much less than when the junction is exposed to the negative thoracic pressure. In the latter situation, the lower esophageal pressure will frequently equal intragastric pressure if the glottis remains closed. Cadaver studies have shown that when this pressure exceeds 150 mm Hg, rupture of the esophagus is apt to occur. When a hiatal hernia is present and the sphincter remains exposed to abdominal pressure, the lesion produced is usually a Mallory-Weiss mucosal tear, and bleeding rather than perforation is the problem. This is due to stretching of the supradiaphragmatic portion of the gastric wall. In this situation the hernia sac represent an extension of the abdominal cavity, and the gastroesophageal junction remains exposed to abdominal pressure.

Trauma-related esophageal perforation is uncommon and may be categorized into blunt or penetrating injury. Perforation of the esophagus secondary to blunt trauma is rare (0.001%) and usually secondary to direct force or spinal fracture,[12] probably because of its posterior, well-protected location and the high lethality of these injuries when adjacent vital structures are also injured. Esophageal perforation as a result of blunt trauma most commonly occurs at the cervical esophagus and is often associated with other neck injuries.[13] Blunt trauma to the distal esophagus is exceedingly rare, with fewer than a dozen cases reported in the world literature.[14] Penetrating esophageal perforations caused by knife and missile injuries are more frequent than blunt perforation but are still relatively uncommon.[13] They too are almost always associated with other injuries and are often fatal.

Perforation of the esophagus can inadvertently occur during any esophageal, periesophageal, or gastric operation. Recently, laparoscopic foregut surgery has surged in popularity, and perforation during such surgery has been reported. Three mechanisms of injury accounted for a series of 17 gastric and esophageal laparoscopic perforations: improper retroesophageal dissection, passage of the bougie or nasogastric tube, and suture pull-through. Most injuries were repaired laparoscopically.[15]

Esophageal perforations secondary to the ingestion of foreign bodies most often occur at the normal acute angulations or physiologic narrowing of the esophagus, with the cricopharyngeus muscle being the most common location. Tumors, ingestion of caustic substances, retained pills, infections, severe peptic esophagitis, and Barrett's ulceration have all been reported as a cause of esophageal perforation.

CLINICAL FINDINGS

The clinical manifestation of esophageal perforation depends on three factors: (1) the location of the perforation, (2) the size of the perforation (i.e., the degree of surrounding contamination), and (3) the time elapsed since injury (i.e., the degree of surrounding inflammatory response, infection, and sepsis).

Patients with cervical esophageal perforation routinely complain of cervical pain, dysphagia, and odyno-

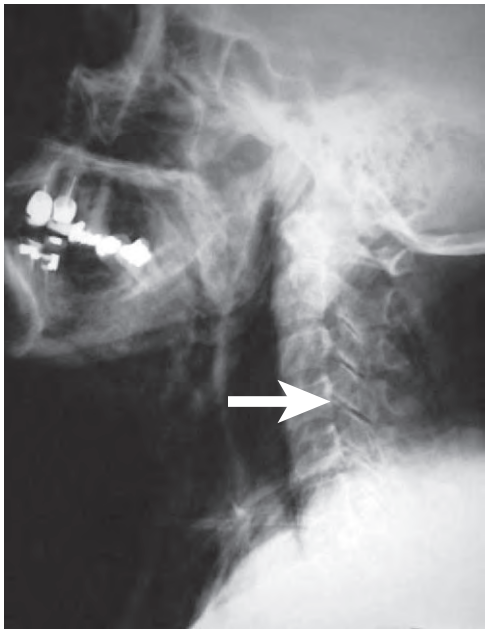

Figure 38–1. Chest roentgenogram showing air in the deep muscles of the neck after perforation of the esophagus *(arrow).* This is often the earliest sign of perforation and can be present without evidence of air in the mediastinum.

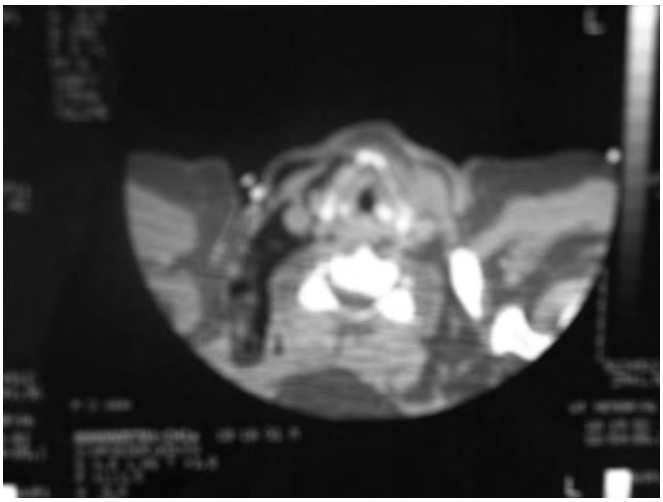

Figure 38–2. Computed tomography scan of a patient with a cervical perforation of the esophagus illustrating air in the deep muscle planes of the neck.

phagia. The pain is made worse by swallowing and movement, especially flexion of the neck. The neck is tender to examination, and crepitus is often noted. Fever usually develops early, and pleural effusions develop later, after 24 hours (Figs. 38–1 and 38–2).

Spontaneous rupture of the esophagus is often associated with a poor outcome and survival because of delay in recognition and treatment. Although there is generally a recent history of esophageal instrumentation, surgery, or vomiting, approximately 50% of patients have an atypical history, and in a small number of patients the injury occurs silently without any antecedent history. When the condition is visualized on a chest roentgenogram as air or an effusion in the pleural space, it is often misdiagnosed as pneumothorax or pancreatitis (Fig. 38–3). An elevated serum amylase level caused by extrusion of saliva through the perforation may fix the diagnosis of pancreatitis in the mind of an unwary physician. If the chest roentgenogram is normal, the diagnosis is often confused with myocardial infarction or a dissecting aneurysm.

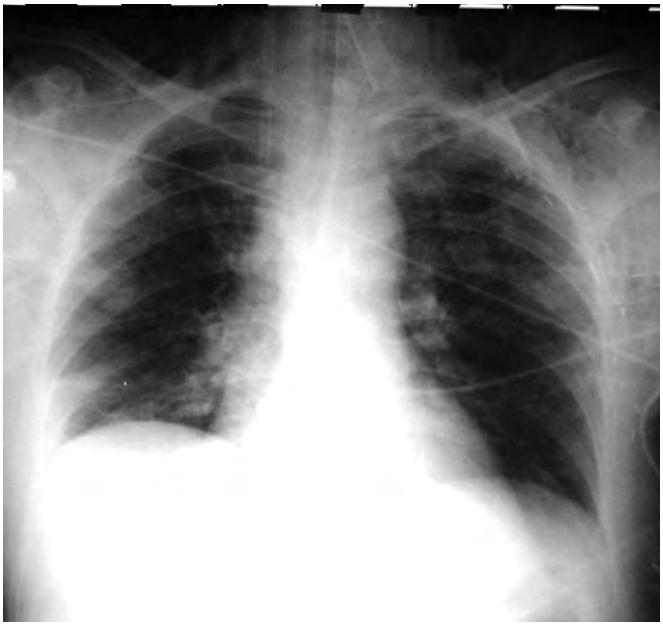

Figure 38–3. Chest radiograph of a patient with spontaneous thoracic esophageal perforation and subcutaneous emphysema.

Spontaneous rupture usually occurs on the left side of the distal esophagus into the left pleural cavity or just above the gastroesophageal junction. These patients are typically male (85%), 40 to 60 years of age, who have a history of recent emesis. Mackler's triad of thoracic pain, vomiting, and cervical subcutaneous emphysema is less reliable for the diagnosis of spontaneous esophageal perforation than once thought, and its absence should not exclude the diagnosis. Forty percent or more of patients will not exhibit this classic triad. Hematemesis is rare and, if present, is of small volume relative to the massive upper gastrointestinal bleeding associated with a Mallory-Weiss tear. Thoracic perforations cause substernal and epigastric pain. Mediastinal emphysema and pleural effusions are common, but early cervical subcutaneous emphysema is noted in only 20% or less of patients. Fever and sepsis develop with increasing contamination and inflammation of the mediastinum and pleural cavities. If left untreated, fulminant mediastinitis and hemorrhagic necrosis will develop and lead to an ever-increasing systemic inflammatory response,

multiorgan failure, and cardiopulmonary collapse. Patients with an abdominal perforation have epigastric abdominal pain that is also often referred to the back and left shoulder; with time, signs of peritoneal irritation (rebound tenderness, muscle spasm, abdominal wall rigidity) and generalized peritonitis can develop.

DIAGNOSIS

Esophageal perforation, particularly spontaneous rupture of the esophagus, continues to be associated with poor survival because of the delay in recognition and treatment. The most important factor contributing to a delay in diagnosis is failure to consider esophageal perforation as a diagnostic possibility. All patients complaining of pain after endoscopy, especially if therapeutic dilatation was performed, should be suspected of having a perforation until proved otherwise. The diagnosis of Boerhaave's syndrome can be more elusive. The differential diagnosis includes perforated ulcer, acute pancreatitis, myocardial infarction, pneumonia, Mallory-Weiss tear, pneumothorax, dissecting aortic aneurysm, or incarcerated paraesophageal hernia. A careful history, physical examination, and appropriate laboratory tests should raise suspicion of esophageal perforation, exclude most of these incorrect diagnoses, and direct the clinician to the appropriate confirmatory radiologic studies.

Regardless of the cause, an urgent posteroanterior and lateral chest radiograph should be obtained. Abnormalities on the chest radiograph can be variable, depending on the time interval between the perforation and the roentgenographic examination, the site of the perforation, and the integrity of the mediastinal pleura (see Fig. 38–3). Mediastinal emphysema, a strong indicator of perforation, is present in only 40% of patients and usually takes at least 1 hour to develop. Mediastinal widening secondary to edema may not occur for several hours. Cervical emphysema is common with cervical perforation and mediastinal emphysema is rare; the converse is true for thoracic perforations. Frequently, air will be visible on a neck radiograph in the erector spinae muscles before it can be palpated or seen on a chest roentgenogram (see Fig. 38–1). The integrity of the mediastinal pleura influences the roentgenographic abnormality. Rupture of the pleura results in pneumothorax in 77% of patients. In approximately 70% of these patients the perforation is on the left side, 20% are right sided, and 10% are bilateral. If pleural integrity is maintained, mediastinal emphysema appears rapidly rather than pneumothorax. A pleural effusion secondary to inflammation of the mediastinum occurs late. In approximately 10% of patients the chest roentgenogram will remain normal.[16] The diagnosis is usually confirmed with a contrast esophagogram. This technique will demonstrate extravasation in 90% of patients (Fig. 38–4). The initial use of a water-soluble medium such as diatrizoate meglumine (Gastrografin) is preferred to prevent extravasation of barium into the mediastinum or pleura. If no leak is seen, a barium study should follow. Patients at high risk for aspiration should have a barium esophagogram as their first study because of the risk for pulmonary edema from water-soluble contrast. Of concern is the reported 10% false-negative rate, which may be due to performing the roentgenographic study with the patient in the upright position. When upright, the passage of water-soluble contrast material can be too rapid to demonstrate a small perforation. The studies should be done with the patient in the right lateral decubitus position with water-soluble contrast followed by barium (see Fig. 38–4). In this position the contrast material fills the whole length of the esophagus, thereby allowing the site of perforation and its interconnecting cavities to be illustrated. One should not hesitate to repeat the radiographic evaluation if clinical suspicion remains high for perforation despite a negative work-up originally.

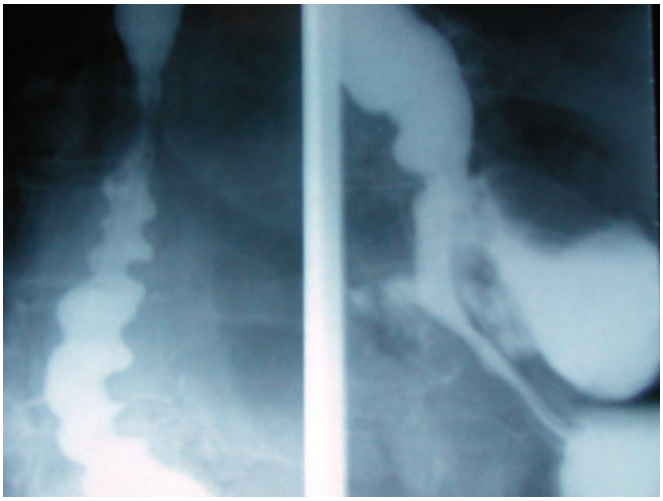

Figure 38–4. Roentgenographic study using water-soluble contrast material in a patient with a perforation of the esophagus. The patient is placed in the lateral decubitus position with the left side up to allow complete filling of the esophagus and demonstration of the defect.

Computed tomography (CT) and esophagoscopy are also useful in complicated, equivocal cases or when an esophagogram is unavailable.[17]

CT is often the first imaging modality used in patients with severe chest pain. Subtle findings such as mediastinal gas or fluid, esophageal thickening, or small pleural effusions may suggest the diagnosis of esophageal perforation. CT scanning may be particularly useful to rule out other pathologic changes and causes of chest pain, and its sensitivity can be increased with the use of dilute oral contrast (Fig. 38–5).[17]

Flexible esophagoscopy is generally underused because of fear of extending the injury. It can provide important information about the location and extent of injury, the presence of coexisting disease, and the condition of surrounding tissues. Risks should be minimal if performed by an experienced surgeon prepared to definitively manage the esophageal perforation, either nonoperatively (Fig. 38–6) or surgically.

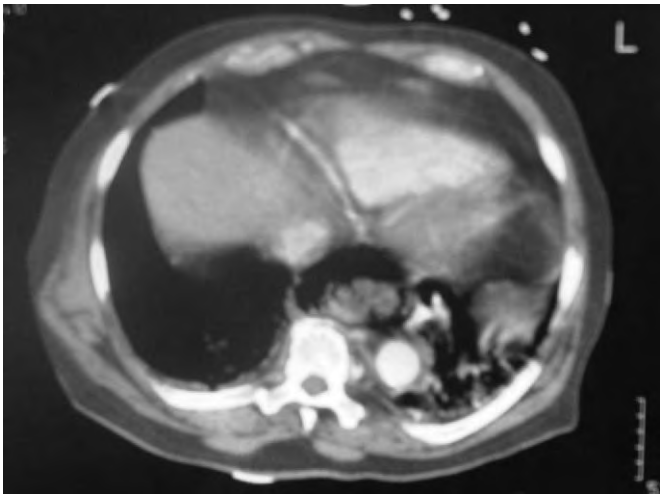

Figure 38–5. Abdominal computed tomography scan revealing mediastinal air and pneumothorax secondary to thoracic esophageal perforation.

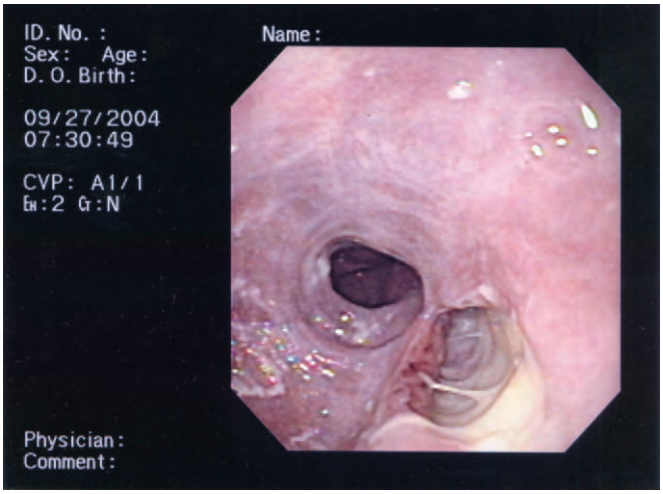

Figure 38–6. Esophagoscopy illustrating a large contained spontaneous esophageal perforation. The patient was successfully managed with nonoperative therapy.

MANAGEMENT OF ESOPHAGEAL PERFORATION

A tailored approach is critical to the successful management of esophageal perforation (Fig. 38–7). The outcome depends on the location of the perforation, the extent of tissue destruction, and the degree of inflammation and sepsis present, which is determined by the time interval between injury and initiation of treatment and the presence of underlying esophageal disorders. Treatment options include nonoperative therapy; periesophageal drainage alone; primary repair, with or without autologous tissue reinforcement; esophageal resection; and exclusion and diversion in continuity.

Regardless of the treatment modality, the goals of treatment must include (1) prevention of continued contamination, (2) elimination and control of infection, (3) maintenance of the patient's nutritional status, and (4) restoration of the integrity and continuity of the alimentary tract.

Once esophageal perforation is suspected, immediate resuscitation should be initiated and consists of (1) discontinuation of all oral intake, (2) judicious placement of a nasogastric tube to decompress the stomach and decrease continued contamination, (3) aggressive intravenous volume support, and (4) broad-spectrum antibiotics with coverage of aerobic and anaerobic oral flora and fungi.

Nonoperative Therapy

Nonoperative management of esophageal perforation has been advocated and can be successful in select situations.[18-24] The choice of nonoperative therapy requires skillful and continuous clinical judgment and necessitates careful roentgenographic or endoscopic examination of the esophagus (or both).[10,11] This course of management usually follows a injury recognized during dilatation of esophageal strictures or pneumatic dilatation for achalasia or when there has been a significant delay in diagnosis with minimal symptoms and no signs of sepsis. Nonoperative management should not be used in patients who have free perforations into the pleural space or peritoneal cavity. Cameron and colleagues originally proposed criteria for nonoperative management of esophageal perforation in 1979, and they were updated by Altorjay et al. in 1997. These criteria include (1) intramural perforation; (2) transmural perforation that is not within the abdomen, is shown to be contained within the mediastinum, and drains well back into the esophagus; (3) perforation that is not associated with obstructive esophageal disease or malignancy; and (4) mild symptoms and minimal evidence of clinical sepsis.[18,19] If these conditions are met, it is reasonable to treat the patient with nothing by mouth, total parenteral nutrition, antibiotics, and intravenous proton pump inhibitors or H_2 receptor antagonists (or both) to inhibit acid secretion and diminish pepsin activity. Oral intake is resumed in 7 to 14 days, depending on subsequent roentgenographic findings. It is imperative that patients treated in this manner be continuously monitored and frequently reassessed for signs of physical deterioration. Operative intervention should be performed immediately if any of the criteria for continued nonoperative management are no longer met.[18,19]

Recently, the use of covered self-expandable stents has been reported for the conservative treatment of esophageal perforation in highly selected patients. Covered and self-expandable stents may be indicated and particularly useful in patients with extensive defects, in those with multiple comorbid conditions, and in the critically ill.[25-27]

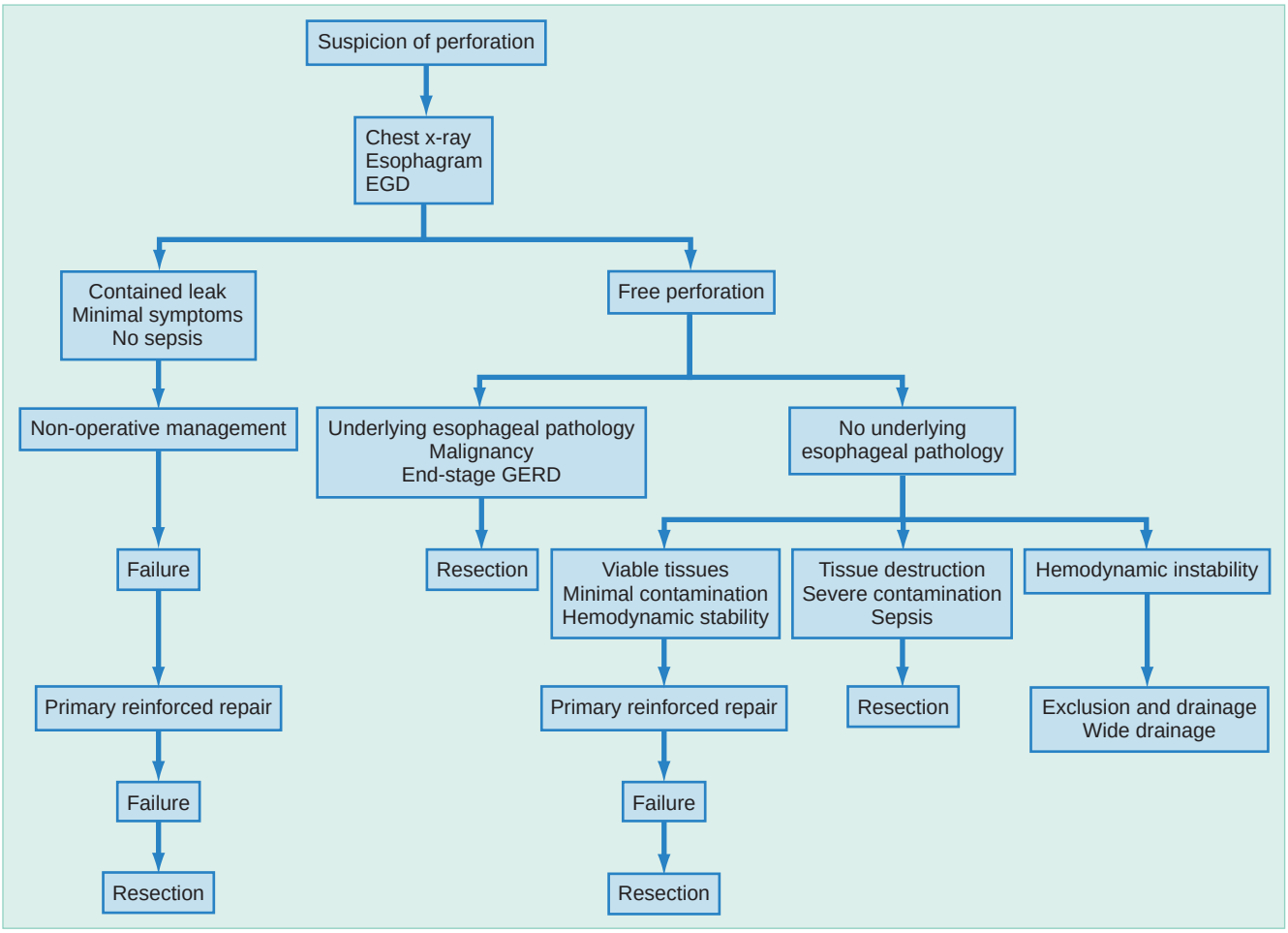

Figure 38–7. Treatment algorithm for esophageal perforation. EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease.

Surgical Management of Cervical Esophageal Perforation

Perforation of the cervical esophagus is seldom lethal. Most patients are candidates for cervical exploration and closure of the defect or drainage alone.[20,28-30] It is controversial whether closure offers any advantage over drainage alone.[1] In some instances, nonoperative approaches may suffice.[31]

Most cervical esophageal perforations can be surgically managed through a cervical approach using a longitudinal incision made along the anterior border of the left sternocleidomastoid muscle. The pharynx and cervical esophagus are exposed by retracting the sternocleidomastoid muscle and carotid sheath laterally and the thyroid and larynx medially. Routine division of the omohyoid, sternothyroid, and sternohyoid muscles gives ideal exposure. The middle thyroid vein and inferior thyroid arteries are identified and divided. The recurrent laryngeal nerve can be found as it courses in the tracheoesophageal groove, just anterior to the inferior thyroid artery. Retraction in this area is avoided. The esophagus is identified at the thoracic inlet as it overlies the spine and is dissected circumferentially. The perforation is usually evident at this stage of the dissection. In the absence of severe inflammation, the perforation should be closed. A short myotomy is performed and the mucosal edges are trimmed. The mucosa is then approximated with interrupted sutures and the muscle layer closed separately. Placement of a closed suction drain and closure of the wound complete the procedure.

Surgical Management of Intrathoracic and Intra-abdominal Esophageal Perforations

The key to optimal management of a free thoracic or intra-abdominal esophageal perforation is not only early diagnosis but also immediate initiation of appropriate treatment. Recently, several investigators have documented a decline in mortality, both overall and in early and late treatment groups. Reeder et al. from the University of Chicago reported an overall survival rate of 91%, a 10% increase from the 81% reported a decade earlier from the same institution. The survival rate with early treatment improved from 91% to 95%, whereas

after late treatment it increased from 71% to 86%. The combination of improved critical care, antibiotics, parenteral nutrition, and surgical treatments most likely accounts for these improved outcomes.[32]

Early Treatment

Review of the literature indicates that the most favorable outcome is usually obtained after primary closure of a thoracic or abdominal esophageal perforation within 24 hours of the injury. Such treatment results in the survival of more than 90% of patients. All therapies instituted after 24 hours result in significantly decreased survival.[20,28,30,33-37]

To achieve adequate exposure of upper and middle thoracic esophageal perforations, a right-sided thoracotomy should be performed through the fourth or fifth intercostal space. However, the most common area of spontaneous perforation is the left lateral wall of the esophagus just above the gastroesophageal junction.[1] Perforation of the lower esophagus is best approached through a left thoracotomy performed through the sixth or seventh intercostal space. The principles of successful surgical therapy must include débridement of all mediastinal and esophageal devitalized tissue, with anastomosis performed only between healthy mucosa, submucosa, and muscularis (Fig. 38–8). The proximal part of the stomach is pulled up into the chest, and the soiled fat pad at the gastroesophageal junction is removed. To visualize the entire mucosal defect it is essential to incise the muscularis both proximal and distal to the mucosal tear. Failure to completely visualize the injury can lead to inadequate repair, recurrence, and fistula formation. At this point, if nasogastric decompression has not been achieved, a tube can be placed under direct vision, palpation, or both. The edges of the mucosa are trimmed and closed, which can be accomplished with a surgical stapler, with a two-layer interrupted closure, or in one layer with a modified Gambi stitch (Figs. 38–9 and 38–10). If there is concern about causing esophageal stenosis, closure can be performed over a 40- to 46-French Maloney bougie. The anastomosis should then be reinforced or buttressed with healthy tissue such as the pleura, diaphragm, or stomach (Fig. 38–11). Separate anterior and posterior chest tubes are placed to adequately drain the thorax, and the thoracotomy is closed.

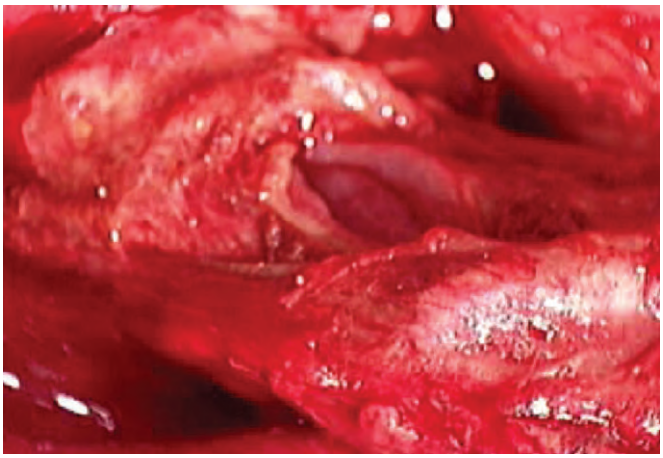

Figure 38–8. Spontaneous thoracic esophageal perforation. Notice the débridement to healthy tissue in preparation for closure.

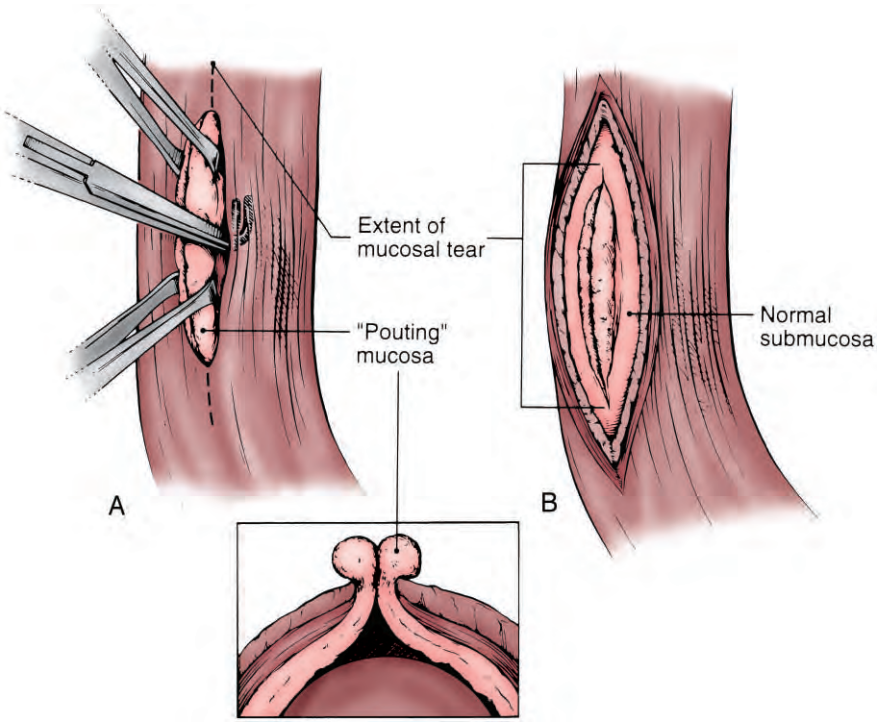

Figure 38–9. Primary repair of esophageal perforation illustrating exposure of the perforation. **A,** Extension of the muscular tear proximal and distal to the injury to allow complete exposure of the mucosal defect. The *inset* demonstrates the damaged pouting mucosa initially seen on inspection of the injury. **B,** Mobilization of the submucosa away from the muscular coat to allow exposure of the defect surrounded by normal submucosa and both the proximal and distal extent of the mucosal injury by extension of the muscular tear. (From Whyte RI, Iannettoni MD, Orringer MB: Intrathoracic esophageal perforation—the merit of primary repair. J Thorac Cardiovasc Surg 109:140, 1995.)

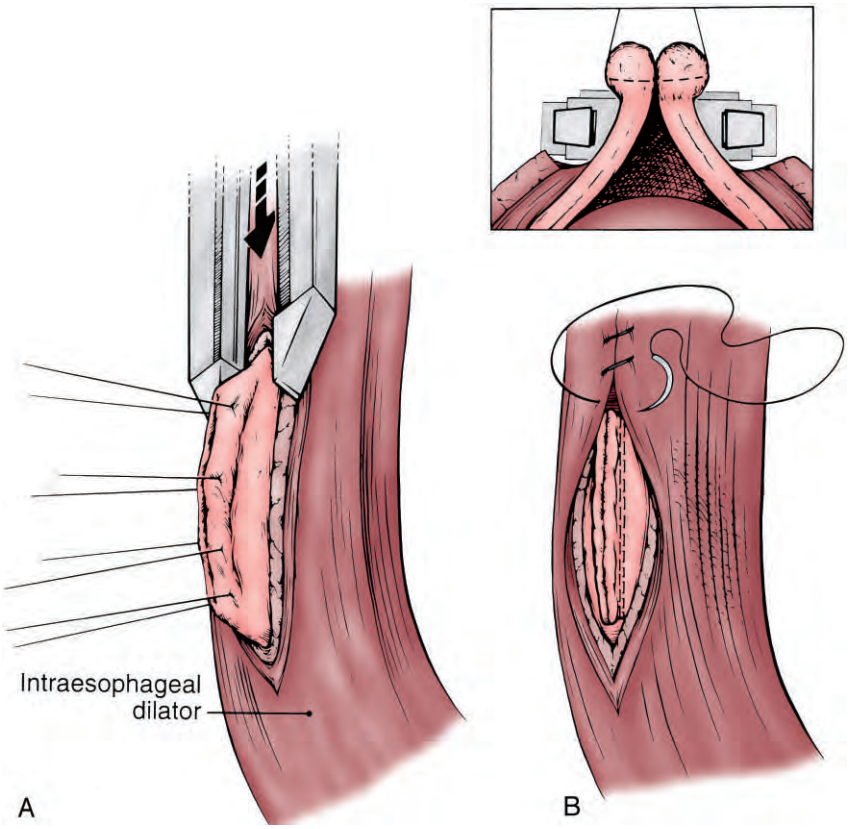

Figure 38–10. Technique of primary repair of esophageal perforation illustrating **(A)** closure of the defect with a GIA surgical stapler after mobilization and exposure of the mucosal and submucosal tear beyond the muscular tear and **(B)** approximation of the muscular coat over the suture line with running absorbable suture. The stapler is applied over an intraesophageal bougie *(inset)* to healthy mucosa and submucosa, not to the inflamed edges of the defect. (From Whyte RI, Iannettoni MD, Orringer MB: Intrathoracic esophageal perforation—the merit of primary repair. J Thorac Cardiovasc Surg 109:140, 1995.)

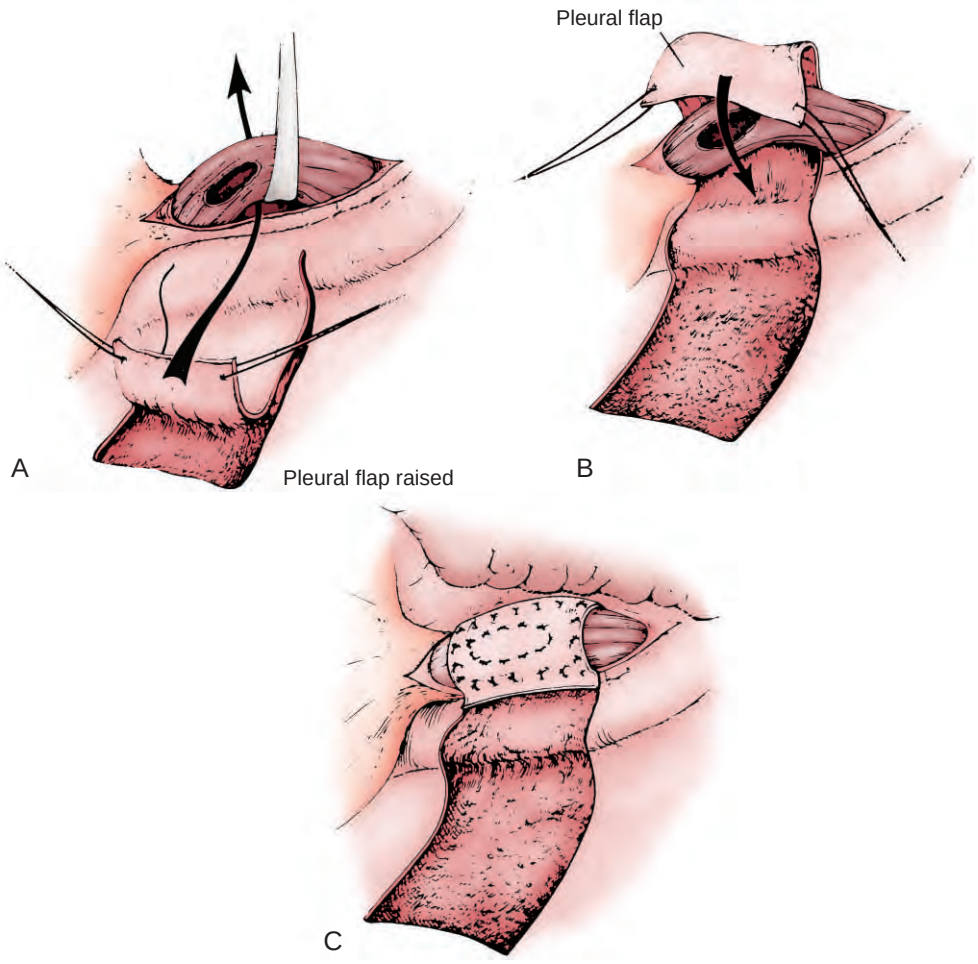

Figure 38–11. Pleural flap patch closure of a large esophageal defect. **A,** After mobilization of the esophagus, a pleural flap is raised. **B,** The flap is placed around the esophagus so that it covers the perforation. **C,** The flap is sutured to itself. Sutures are placed above and below at the margins of the flap as well as the perforation itself to tack the pleura firmly to the esophageal muscularis. (From Gricco HC, Wilkins FW: Esophageal repair following late diagnosis of intrathoracic perforation. Ann Thorac Cardiovasc Surg 20:337, 1975, by permission of The Society of Thoracic Surgeons.)

Late Treatment

Esophageal perforation with late or delayed diagnosis/treatment results in increased mediastinal contamination, inflammation, tissue destruction, and hemodynamic instability. These factors make primary repair more difficult and prone to failure. A primary reinforced repair remains the procedure of choice, regardless of the time interval between injury and repair, if the principles previously described can be followed.[38] In the setting of extensive esophageal damage, mediastinitis, or severe underlying esophageal disease, esophagectomy is the best option.

Salo et al. reviewed 34 patients with esophageal perforations greater than 24 hours old. Nineteen of these patients underwent primary repair with drainage and 15 underwent primary esophagectomy. Hospital mortality was 68% in the group treated by closure and drainage and 13% in patients after esophagectomy. They concluded that esophagectomy is superior to primary repair in the setting of esophageal perforation with mediastinal sepsis.[39]

Esophagectomy can be accomplished through either a transhiatal or a transthoracic approach. The contaminated mediastinum is widely drained with closed suction drainage or chest tubes (or both). A gastrostomy and feeding jejunostomy are created for decompression and enteral nutrition. As much normal esophagus as possible should be saved before performing a cervical esophagostomy. In some situations the retained esophagus may be so long that it can be tunneled subcutaneously to exit on the anterior of the chest and saved for later reconstitution of alimentary tract continuity (Fig. 38–12). Recovery from sepsis is often immediate and dramatic as reflected by a marked change in the patient's course in 24 hours. On recovery from sepsis the patient is discharged and returns on a subsequent date for reconstruction with a substernal gastric or colonic interposition.[40] Failure to apply such aggressive therapy can result in mortality in excess of 50% in patients in whom the diagnosis has been delayed.[41]

In patients deemed unsuitable for resection because of hemodynamic instability and sepsis, an esophageal exclusion and diversion procedure with wide drainage of the mediastinum, stapled or ligated occlusion of the lower esophagus, and the formation of a cervical esophagostomy is preferred and can be performed quickly (Fig. 38–13). Gastrostomy and feeding jejunostomy may or may not be performed again, depending on the situation.[42-44]

In extreme cases, control of the esophageal fistula with a Silastic drain or T-tube and wide pleural drainage alone may be necessary.[45-46]

A free intra-abdominal esophageal perforation can lead to peritoneal contamination, peritonitis, and sepsis. However, if recognized early, abdominal perforation is associated with an excellent prognosis. The principles of repair are the same as for thoracic perforations, except that access may be gained through a celiotomy. The contaminated cavity (mediastinum, abdomen) is widely drained, and the injury is débrided, exposed, closed, and buttressed with a fundoplication or omental graft (Figs. 38–14 to 38–16). Enteral access by gastrostomy, tube jejunostomy, or both may also be performed.[47]

Esophageal perforation that occurs during laparoscopic foregut procedures and is recognized intraoperatively can be successfully repaired by primary closure and reinforcement with excellent outcomes. Schauer et al. reported 0% mortality, 0% postoperative leaks, and a mean hospital stay of 4.5 days in their patients who experienced a laparoscopic perforation recognized and repaired at the initial procedure. On short-term follow-up these patients reported no dysphagia or recurrence of their reflux symptoms. This outcome is in contrast to

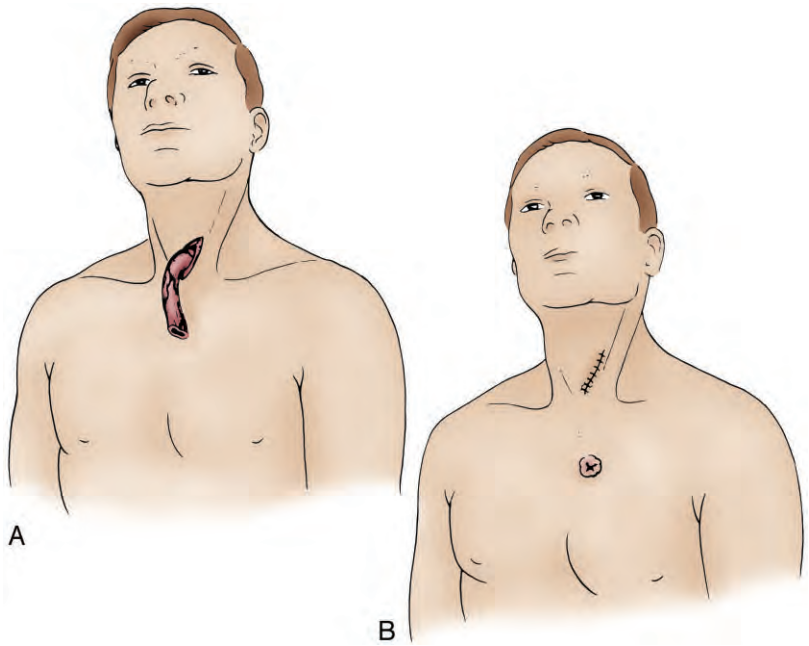

Figure 38–12. Construction of an anterior thoracic esophagostomy to preserve maximal length of esophagus. **A,** The mobilized thoracic esophagus is placed on the anterior chest wall to determine the location of the stoma. **B,** The esophagus is then tunneled subcutaneously and the esophagostomy is constructed. Stomal appliances are easily applied to the flat surface of the chest, and the additional esophageal length provided by the technique often facilitates later reconstruction. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma. Philadelphia, JB Lippincott, 1984, with permission.)

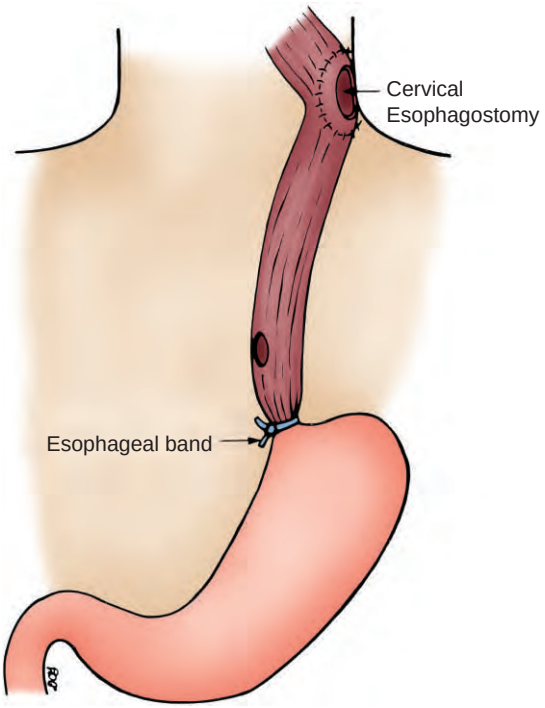

Figure 38–13. Technique of esophageal exclusion. A side cervical esophagostomy diverts oral secretions. Reflux of gastric and biliary secretions is prevented by umbilical tape tied at the gastroesophageal junction. The tape is tied tightly enough to obstruct the lumen but not tight enough to cause mural ischemia. The vagus nerves are not included in the tie but lie superficial to it. (From Brewer LA III, Carter R, Mulder GA, Styles QR: Options in the management of perforations of the esophagus. Am J Surg 152:62, 1986.)

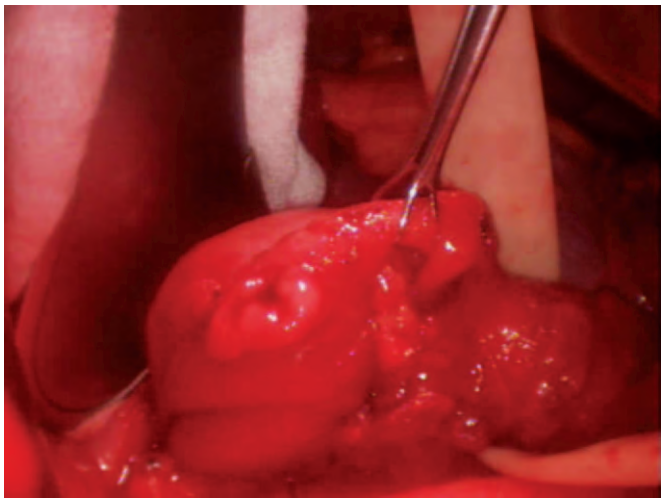

Figure 38–14. Perforation secondary to dilation, just below the gastroesophageal junction, in a patient with a hiatal hernia and esophageal stricture.

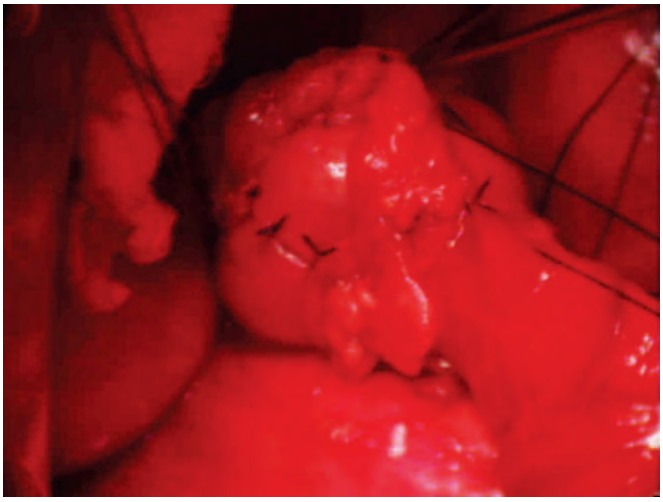

Figure 38–15. Perforation seen in Figure 38–14 after primary closure in two layers.

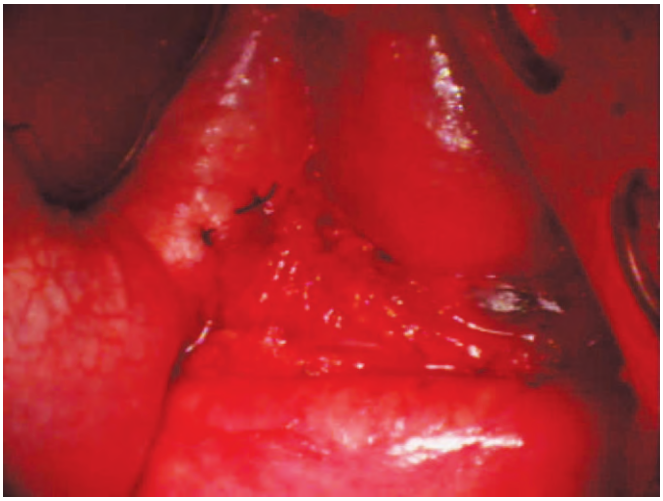

Figure 38–16. Repair of the perforation in Figure 38–14 after reinforcement of the closure with an omental graft.

a 17% mortality in patients with a delayed diagnosis. Laparoscopic or thoracoscopic repair of these perforations can be achieved with good results, depending on the location of the perforation and the laparoscopic skill of the surgeon.[15] However, conversion to open repair is recommended in the majority of these cases, given the unforgiving nature of the esophageal wall, and should always be considered wise surgical judgment.

PERFORATION ASSOCIATED WITH ESOPHAGEAL DISEASE

Primary repair of an esophageal perforation in a patient with preexisting esophageal disease is often much more complex and can carry a much worse prognosis. Pathologic change that leads to distal esophageal obstruction

will invariably lead to failure of a primary esophageal repair for perforation. It is therefore mandatory that the preexisting esophageal disorder be remedied at the same time as the perforation.[30,48,49]

Management of Esophageal Perforation After Dilation Therapy for Achalasia

Perforation of the esophagus after pneumatic dilatation for idiopathic motor disorders, specifically achalasia, requires special consideration, with treatment directed at both the perforation and the underlying esophageal disorder. For perforations that are contained within a localized region of the mediastinum and associated with minimal signs and symptoms, an initial course of nonoperative therapy is warranted as previously discussed. Free perforations require prompt surgical intervention. Again, the surgical principles discussed in previous sections apply: (1) prevention of continued contamination, (2) elimination and control of infection, (3) maintenance of the patient's nutritional status, and (4) restoration of the integrity and continuity of the alimentary tract. The procedure is usually performed via a left thoracotomy. The mucosal edges are débrided and the mucosa closed with interrupted suture. Importantly, a myotomy that extends 2 to 3 cm distal to the gastroesophageal junction on the gastric cardia and 3 to 4 cm proximal onto the body of the esophagus must be performed on the side opposite the perforation. The repair is then buttressed with a partial fundoplication such as a Dor, Thal patch, or Belsey Mark IV. Given prompt diagnosis and definitive treatment of the underlying esophageal motility disorder, the results of primary repair for esophageal perforation are excellent.

End-Stage Gastroesophageal Reflux, Intractable Strictures, Dysmotility, and Malignancy

In the situation of esophageal perforation associated with gastroesophageal reflux, intractable strictures, severe dysmotility (such as end-stage achalasia with esophageal tortuosity), caustic strictures, extensive devitalized tissue, or malignancy, esophageal resection is the procedure of choice. Primary repair, in this setting, often leads to decreased survival and increased subsequent morbidity when compared with primary resection.[28,36,48] Iannettoni et al. from the University of Michigan reported on the poor functional outcomes of 25 patients treated by primary repair for esophageal perforation in the presence of severe esophageal disease or strictures. Thirteen of these patients required at least one further operative treatment, and at least a third of the patients experienced chronic dysphagia requiring repeated dilatation or resection and reconstruction.[50] Esophageal resection can again be performed via a transthoracic or transhiatal approach. In a properly selected, stable patient, immediate reconstruction with a gastric graft and cervical esophagogastric anastomosis is possible and results in an excellent outcome.[51-53]

SUMMARY

Successful management of esophageal perforation continues to be a clinical challenge. Despite improvements in diagnostic, supportive, and surgical techniques since Boerhaave's classic description, mortality remains high. The most important aspect of management is consideration of esophageal perforation as a diagnostic possibility, aggressive resuscitation, and prompt surgical intervention tailored to the site of perforation, the presence of underlying esophageal disorder, the amount of surrounding contamination, and the condition of the patient.

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Chapter

39

Esophageal Caustic Injury

Peter F. Crookes

It was simple fire in a liquid form.

Mark Twain, *Tom Sawyer*, Chapter 12

HISTORY OF CAUSTIC INGESTION

Ingestion of poison either accidentally or with suicidal or homicidal intent has been known to humanity for thousands of years. The locally damaging effect of caustics or corrosives on the foregut has also been known for a long time.[1] Shakespeare records how Portia, the wife of Brutus, committed suicide by ingesting fire.[2] For the past 100 years two major subgroups of patients have continued to challenge health care agencies after caustic ingestion: children, who ingest caustic agents accidentally, and adults, who ingest them with suicidal intent. Accidental ingestion also occurs in adults and is more common in retarded or intoxicated individuals.

Children are at risk because cleaning materials, the most common toxic agents, are by convention kept in a cupboard beneath the kitchen sink. Toddlers who are unable to reach higher cupboards have easy access to these materials. It was a particular problem in the past because they were frequently kept in bottles resembling lemonade containers. The natural curiosity of children, combined with a proclivity to eat or drink anything in sight, made this a serious hazard. In the past 80 years, passionate lobbying has brought about federally mandated changes in the labeling and packaging of these materials by requiring them to be dispensed in characteristically shaped containers with childproof lids, as well as reducing their toxicity. However, the range of potentially injurious substances in a typical kitchen remains very large. The overall effect of these social changes has nevertheless been a significant reduction in the incidence and severity of accidental caustic ingestion in the United States, with the secondary consequence that most modern information now comes from countries where legislation is less restrictive, such as Turkey, India, France, and Eastern Europe.

Suicidal ingestion of caustic agents has also decreased in severity in the United States. As a mechanism of attempted suicide, caustic ingestion lags far behind ingestion of medications, gunshot wounds, leaping from a height, and hanging. However, in other cultures where firearms and pharmaceuticals are less readily available, caustic ingestion remains a significant social problem. The spectrum of ingested substances is a function of availability. In the Netherlands, for example, glacial acetic acid is commonly used by the Indonesian population. Within that community, suicidal ingestion of glacial acetic acid is frequent, with a high rate of complications and mortality.[3] In India, hydrochloric acid is widely used as a cheap toilet cleaner and is the agent most frequently swallowed in suicide attempts.[4] In the United States, glacial acetic acid and concentrated hydrochloric acid are not readily available, and cleaning agents are the most frequent caustic substances swallowed. The Toxic Exposure Surveillance System reported a total of 211,077 cleaning agent exposure incidents during 2003, of which exposure to hypochlorite (bleach) vastly outnumbered all other agents, with only one fatality reported in more than 52,000 exposures.[5]

PATHOPHYSIOLOGY

The injury inflicted by swallowed caustic substances is related to the nature of the agent and the amount swallowed. Accidental ingestion is associated with the consumption of lesser quantities because after the first gulp the patient will expectorate or try to dilute the agent, whereas in a deliberate suicide attempt, the initial revulsion and discomfort are ignored. Furthermore, in suicidal ingestions the patient may be socially isolated at the time and may delay seeking medical attention. In general, caustic alkali causes more profound injury than acid does because acid produces coagulative necrosis, which acts as a kind of barrier to limit deeper levels of injury, whereas alkali tends to cause liquefactive necrosis, thereby allowing deeper penetration.[6,7]

Phases of Injury

The initial contact with the toxic agent on the mucosa causes inflammation, which if severe leads to necrosis in the first 24 hours. Experimental studies have shown that severe transmural injury can develop after exposure to strong alkali (pH > 12) for even 1 second.[7-9] Thus, although the final outcome is very dependent on access to timely and expert medical treatment, the extent of injury is determined within a very short time of ingestion. Extensive thrombosis of submucosal vessels is observable at 48 hours, with inevitable necrosis of the mucosa. Although acid materials may produce an eschar that limits esophageal damage, they tend to induce pylorospasm and as a result lead to more severe gastric damage with the development of antropyloric strictures. Acid appears to be the causative agent in most cases of gastric stricture after caustic ingestion.

Purely esophageal damage is deeper with strong alkali agents. In the second and third week, granulation tissue begins to replace the necrotic slough, and the process of stricturing begins. It is in the period 4 to 14 days after injury when the esophagus is most likely to be perforated by endoscopy or dilation, and the traditional recommendation is therefore to avoid instrumentation of the esophagus at that time.

Spectrum of pH

The pH of the ingested material is a major factor in determining the extent of injury. The most severe damage is inflicted by strong alkalis such as sodium hydroxide. Lye is a nonspecific term used to describe any strong alkali used for making soap. It is found in drain cleaners such as Drano and Liquid-Plumr. The pH of these preparations is typically between 13 and 14. Floor stripper has a pH between 11 and 12, and household ammonia has a pH of 11. Most domestic cleaning products are much less alkaline, including Clorox (sodium hypochlorite) with a pH of 9, and cause correspondingly less damage. Strong acids are not commonly used in this country, but the concentrated hydrochloric acid used as a toilet cleaner in India has a pH of zero. Because the stomach physiologically contains hydrochloric acid in the pH range 1.2 to 1.5 and episodes of acid reflux in the pH range 2 to 3 are common in the esophagus, it may be wondered why concentrated hydrochloric acid is so damaging. It must be remembered that the household form is more than 10 times as concentrated as the physiologic form. In a normal stomach the presence of a low pH causes feedback inhibition of acid production. When a large quantity of concentrated HCl is ingested, pyloric spasm causes retention of the material in the antrum, where it overwhelms the normal defense mechanism.

Conceptually, the injury can be thought of in three categories:

1. Mild injuries, which involve only the mucosa and heal without sequelae
2. Moderate injuries, which heal with an esophageal stricture
3. Severe transmural injuries, which cause full-thickness damage leading to perforation acutely or dense, undilatable strictures in the recovery phase that require major foregut resection to restore the ability to eat

CLINICAL FEATURES

In the mildest form of injury, the patient goes to the emergency department (ED) with a history of caustic ingestion and reports only minor symptoms such as a sore throat or no symptoms at all. There may be normal mucosa or mild erythema in the oropharynx, but the voice is normal, patients can swallow their own saliva, and there is no systemic toxicity. This is commonly the situation with children.

With a substantial ingestion, the edema is more profound, and the patient is frequently drooling saliva, has a hoarse voice, is in severe distress with dysphagia, chest pain, and vomiting, and has tachycardia and leukocytosis. The oropharyngeal mucosa and lips may show ulceration or adherent sloughing. The more extensive the ingestion, the more likely that there will be full-thickness injury to the oropharynx, the tubular esophagus, and the stomach and surrounding organs. Hematemesis may indicate erosion into a major blood vessel. Abdominal tenderness is an ominous sign suggesting gastric necrosis.

Development of Strictures

With injury deeper than the mucosa, a stricture will develop in most patients in the recovery period. The location of the stricture depends on the rapidity with which the toxic material was transported down the esophagus. Damage tends to be maximal at areas of natural narrowing, such as the cricopharyngeal sphincter or the site of the left main bronchus. For reasons mentioned earlier, gastric stricture tends to be a consequence of concentrated acid consumption.[10]

PRINCIPLES OF MANAGEMENT

Management of caustic ingestion can be conveniently subdivided into three phases:

The *early phase,* which begins with arrival at the ED, deals with immediate assessment of the extent of injury, early resuscitation, and the disposition of the patient, whether to be discharged, admitted to the floor for observation, or sent to the intensive care unit (ICU) or directly to the operating room.

The *intermediate phase* involves managing the patient through the acute episode in the hospital by dealing with such issues as sepsis, aspiration, the need to maintain nutrition, and steering the patient though a potentially complicated postoperative course after resection of the esophagus, stomach, or both.

The *chronic phase* is aimed at restoring function once the patient has recovered from the acute attack and may

involve elements such as psychosocial support and counseling and treatment of depression, nutritional support, repeated endoscopy for strictures, and major reconstructive surgery of the oropharynx and upper digestive tract.

EMERGENCY DEPARTMENT MANAGEMENT

Before any decision about disposition can be made, a basic clinical assessment must be carried out. Try to identify what and how much of the material the patient ingested. In children and ill or intoxicated adults, ask the accompanying family or friend. Assess the previous psychiatric background.

Examination follows the ABCs for any serious emergency. Check the airway. Stridor, coughing, drooling, and inability to speak are all signs of airway compromise, and the respiratory rate and the use of accessory muscles will give a warning of the need for intubation. Establish intravenous access in all symptomatic patients because they may sequester large amounts of extracellular fluid in the mediastinum and become hypotensive. Look at the oral mucosa, tongue, and pharynx for erythema and ulceration. More severe damage causes an adherent black or gray slough. Examine the neck for crepitus and tenderness and the abdomen for tenderness. Provide the patient with a suction catheter if drooling. Check routine chemistry and the blood count. These studies are useful as a baseline if the patient needs to be admitted. In all symptomatic cases it is wise to obtain immediate plain films of the chest and abdomen to look for signs of pneumothorax, pneumomediastinum, or pneumoperitoneum.

The results of this immediate clinical assessment will dictate whether the patient can be discharged home, whether endoscopy should be performed in the ED before the patient is either discharged or admitted, or whether the patient requires ICU admission or urgent surgery. The most severely ill patients with systemic signs (fever, tachycardia, leukocytosis, metabolic acidosis, and difficulty maintaining an airway) should be admitted to the ICU, resuscitated urgently, and have the endoscopic assessment performed under general anesthesia in the operating room.

Early Discharge

Prompt discharge with a follow-up appointment is appropriate only for a few patients who report no symptoms and have normal mental status. The patient should be afebrile and not have any tachycardia or abdominal tenderness on examination. Endoscopy is performed on all others. Patients with minimal systemic disturbance and no oral lesions on visual inspection may undergo endoscopy in the ED because if no damage is seen, it is reasonable to discharge them from the ED. The risk of any damage subsequently occurring is extremely low.

Follow-up of patients discharged early from the ED should involve social or psychiatric services. The parents of children who have ingested caustic agents are often plagued by guilt and may themselves need support. In others, neglect amounting to abuse may be responsible, and social services may need to assess the potential for other forms of abuse.[11]

Psychosocial support is also important for adult patients who may have fallen out with their families and whose social isolation may have led to the underlying depression that precipitated the ingestion episode.

Endoscopic Assessment

Endoscopy is the single most valuable diagnostic tool in planning the management of patients after caustic ingestion. It is indicated for all but the most trivial injuries. Significant esophageal damage can be present without any signs of oropharyngeal injury. Symptoms are important in identifying even trivial injuries, and several studies have clearly shown that a patient who is asymptomatic on initial evaluation will not have significant damage detected by endoscopy.[12] Thus, all symptomatic patients should be examined endoscopically. It used to be asserted that the endoscope should not be advanced past the first sign of injury, presumably because of a risk of worsening the damage, but this advice stemmed from the days of rigid endoscopy, and modern flexible narrow-caliber endoscopes passed with gentleness by a skilled operator do not increase the risk for perforation. The examination may be performed in the ED under sedation in patients with mild symptoms, but when the patient has mental status changes, is simultaneously intoxicated, or has drooling and difficulty swallowing, it is preferable to perform endoscopy under general anesthesia with airway protection in the operating room.

As a result of endoscopy, the injury can be classified into one of three major categories (Box 39–1). First-degree burns, or mere erythema, heal without incident. Second-degree burns tend to heal by stricturing. Third-degree burns are characterized by full-thickness necrosis and may require immediate esophagectomy if extensive.

Box 39–1 Endoscopic Grading of Caustic Injury

Grade 1: mucosal edema or hyperemia

Grade 2
- A: Friability, erosions, exudates
- B: As grade 2A plus deep or circumferential ulceration

Grade 3
- A: Scattered areas of necrosis with black or gray discoloration
- B: Extensive areas of necrosis

IN-PATIENT MANAGEMENT

Resuscitation

A patient with clinical or endoscopic signs of more severe injury will be admitted. Therapy is initially directed toward resuscitation and supportive management. Broad-spectrum antibiotics are generally recommended for moderate and severe injuries, but no controlled data are available because most workers report their own protocol. The oropharynx and esophagus are home to many virulent bacteria, and a damaged esophagus quickly becomes invaded, with the potential for systemic sepsis. Consequently, broad-spectrum antibiotics active against oral and intestinal flora are administered and should include gram-positive and anaerobic coverage, such as penicillin and metronidazole.

The patient should have nothing by mouth (NPO). Do not attempt to induce vomiting because any toxic material will cause damage on the way up, just as it did on the way down. Do not attempt to neutralize the material because thermal damage may be induced by the subsequent exothermic reaction.

Imaging Studies

Barium or contrast studies are of little value and may precipitate aspiration. Some recent work has rekindled interest in using a suspension of sucralfate labeled with technetium 99m to detect ulceration in the damaged esophagus. This method has good correlation with the endoscopic appearance because sucralfate adheres to ulcerated mucosa. It may be valuable in uncooperative children, in whom the risks associated with endoscopy and general anesthesia may be avoided.[13]

Steroids

The value of systemic steroids has been debated for years, but the general advice, based on a single randomized controlled trial in 1990, is that they confer no advantage.[14,15] Other recent nonrandomized series suggest that stenosis is reduced, but at the expense of a higher incidence of gastrointestinal hemorrhage.[16]

Acid Suppression

Acid suppression has been generally recommended to avoid exacerbation of the esophageal injury by superimposed gastroesophageal reflux (GER). Not only does the esophageal injury result in damage to the lower esophageal sphincter mechanism and lead to esophageal shortening, but GER can also be induced or aggravated by injury to the stomach as a result of pyloric stenosis.[17] Intravenous H_2 blockers are recommended for patients with NPO status. Thereafter, when oral liquids are tolerated, proton pump inhibitors are effective.

Stenting

Early dilation and stenting are sometimes recommended as a means to reduce the severity of future strictures. It seems intuitive that if contraction of collagen could be prevented in the first few weeks after injury, stricture severity could be reduced.[18] However, migration, bleeding, and tissue ingrowth sometimes requiring esophagectomy to remove the stent have all been reported, and the progression to stricture is likely to be determined by the initial injury rather than the treatment.

Early Stages of Recovery

Strictures begins within the first 2 to 3 weeks and may progress rapidly. Historically, dilation was associated with a high risk for perforation (Chevalier Jackson was fond of quoting the aphorism of Trousseau that “those who live by the bougie die by the bougie”), and a major advance in the management of severe caustic injuries in children was the introduction of Tucker’s retrograde bougie technique.[19] This technique required the patient to swallow a string, which was retrieved at the time of creation of a gastrostomy. The gastrostomy was used for feeding, as well as for passing fusiform bougies over the string to dilate the stricture from below. Although passing retrograde bougies over a guide reduced the incidence of esophageal perforation, the large gastrostomy needed for passage of these bougies created troublesome skin problems. In recent times flexible endoscopy and through-the-scope balloon dilation have become the most common treatment, but passing Savary-type bougies over an endoscopically placed guidewire is also effective and considerably cheaper.

Maintenance of Nutrition

Throughout the patient’s hospital course and early recovery period when numerous dilations are being performed, there is a serious risk for malnutrition as a result of the severe catabolic state and the fact that the priorities of the medical team are directed to immediately life-threatening considerations. Consequently, attention to nutrition is in danger of being overlooked. Patients may be fed via an indwelling nasogastric tube for fairly short periods, but long-term tolerance of this method is poor, and gastrostomy or jejunostomy is more commonly used. Gastrostomy may be performed endoscopically (percutaneous endoscopic gastrostomy [PEG]), but it should not be performed if the stomach is itself badly inflamed or if it is anticipated that the stomach is going to be used for eventual esophageal replacement. In this situation a feeding jejunostomy is superior, but bolus feeding by syringe is not tolerated in the jejunum, and instead, continuous infusion via a pump is required. A typical patient will need 30 kcal/kg/day, and because most enteral feeding formulas contain 1 kcal/ml, an average patient will require 2000 to 2500 ml/day, or 90 to 100 ml/hr over a 24-hour period. As the patient becomes more mobile, it is possible to cycle the tube feedings to deliver the same total amount over a shorter period, but rates above

160 ml/hr are often associated with discomfort and crampy abdominal pain. Total parenteral nutrition may be used but is associated with a risk for bacterial translocation, liver impairment, and acalculous cholecystitis, and thus the gastrointestinal tract should be used if possible.

Management of Severe Injuries

Patients with full-thickness injury to the foregut are at risk for serious systemic sepsis and extension of the injury to adjacent organs: the colon, pancreas, and duodenum in the abdomen and the tracheobronchial tree in the chest.[20,21] The combination of a systemic disturbance with hemodynamic instability (marked tachycardia or hypotension, oliguria, fever, and leukocytosis) and extensive injury on endoscopy is a strong indication to proceed to the operating room. One recent report of caustic ingestion injuries from Taiwan compared arterial blood gas data in patients who required surgery with those who did not. Acidosis was a prominent feature of the group requiring surgery (mean pH of 7.22, mean base excess of −12.0), but in the group treated conservatively, the mean pH was 7.38 with a mean base excess of −1.8. A marked acidosis therefore appeared to indicate a severe injury.[22] Some surgeons advocate laparoscopy because of the ease with which a rapid assessment of the stomach serosa can be made, and if no resection is required, a feeding jejunostomy is easily inserted. If the stomach shows signs of necrosis, the esophagus is also profoundly damaged and subtotal esophagectomy and total gastrectomy should be performed to prevent the spread of mediastinal or peritoneal sepsis.[23] The surgical details of esophagectomy are discussed elsewhere in this volume (Chapter 42). This might seem a radical step so early in the course of the illness, but it has the clear advantage of removing the major source of continued infection, and when performed early, it is a relatively easy and atraumatic operation. Although no level 1 evidence is available, several workers have noted that mortality and morbidity are reduced after the adoption of an aggressive surgical approach.[24] The stomach is mobilized in the abdomen and the distal esophagus mobilized though the hiatus by dividing the phrenoesophageal membrane and separating the distal esophagus from the right and left crura. The neck is then explored via an incision along the border of the left sternocleidomastoid muscle and the esophagus carefully mobilized away from the trachea. After dividing the omohyoid muscle and detaching the strap muscles close to their attachment to the manubrium and sternoclavicular joint, the esophagus is easily identified as the trachea and larynx are retracted medially and the carotid sheath laterally. As in all operations on the cervical esophagus, care must be taken to protect the recurrent laryngeal nerve, which lies in the sulcus between the trachea and esophagus and is at risk during mobilization of the anterior aspect of the esophagus. Once the cervical esophagus is safely encircled, a varicose vein stripper is inserted from the cardia up into the proximal end of the esophagus, the esophagus is transected in the neck, and the distal end is ligated around the vein stripper. By careful and gentle traction, the esophagus can then be stripped out of the mediastinum with minimal blood loss and negligible mediastinal trauma. No attempt at reconstruction is made; the proximal end of the esophagus is brought out as a spit fistula, the duodenum is stapled off, and a feeding jejunostomy is inserted. The patient usually recovers quite quickly from this procedure, and subsequent definitive reconstruction is carried out electively many months later. Attention is paid to nutrition and psychological support in the interim. In time, the opening of the esophagostomy is likely to scar down. This process often continues for a year or more, and early reconstruction before the process is complete will risk the creation of a dense anastomotic stricture, which can be as difficult to manage as a typical corrosive stricture.

THE CHRONIC PHASE: RESTORATION OF FUNCTION

In patients who survive the initial crisis, the third phase of treatment involves either repetitive dilation of strictures in the preserved esophagus or surgical reconstruction.

Chronic Dilation

Several schemes have been devised to classify the severity and extent of caustic strictures, but in practice, the major distinction is between dilatable and nondilatable strictures. Some strictures are so severe that there is total luminal occlusion or they are so narrow and tortuous that dilation simply cannot be achieved with safety. In these patients, reconstruction is the only option. Milder strictures may be palliated by frequent dilation, but even these strictures have a higher incidence of perforation and require more frequent dilation than typical peptic strictures do. The study of Broor et al., in which the outcome of dilation was compared in 51 patients with caustic ingestion and 39 with peptic strictures, is instructive: of nine perforations in the series of dilations, eight occurred in the caustic group.[25] Another study from Korea using balloon dilation reported a 32% incidence of perforation. It is therefore clear that dilation is associated with significant morbidity in this population.[26] Many patients who survive the initial episode subsequently have severe strictures that can be physically dilated with some restoration of swallowing, but it is required so frequently, sometimes twice weekly, that recovery of normal life is impossible. Elective esophageal replacement may then be considered with expectation of good quality of life.

Intractable Esophageal Stricture

Resection or Bypass?

Unless the esophagus was resected at the time of the initial episode of ingestion, the surgeon has the option of simply bypassing the strictured esophagus and leaving

it in situ. In most instances it is possible to bring up the esophageal substitute via a substernal route and perform the proximal anastomosis in the neck or pharynx. Esophageal bypass avoids the need to dissect out a densely scarred esophagus with the attendant risk of injury to the great vessels, thoracic duct, and the trachea or left main bronchus and the inevitable consequence of vagal injury. The disadvantage of bypass is that the remaining esophagus is prone to undergo cystic dilation, with occasional rupture.[27] It is inaccessible to endoscopic examination. If it is not disconnected from the stomach, it may be subject to severe acid reflux without the buffering effect of saliva. Finally, the esophagus has an increased risk for cancer after caustic injury. The magnitude of the risk is debated, but it is alleged that the risk is 1000 times that of the general population. It tends to occur many years after the injury, often more than 30 years later.[28,29] Many published reports do not distinguish between cancer in the portion of the esophagus in the food stream and cancer in the bypassed segment. It has been argued that the increased mortality as a consequence of attempted resection outweighs the theoretical advantage of reducing the cancer risk. Resection of the esophagus after transmural caustic injury can be a formidable undertaking. Thoracotomy is usually required because the dense periesophageal scarring, as a result of both the injury itself and possibly superimposed microperforations from numerous dilations, is difficult and dangerous to resect via the transhiatal route. Although the balance of evidence cannot be dogmatically determined, it can be confidently asserted that if esophagectomy is to be performed, it should be done in a high-volume center where experienced surgeons and intensive care is available.

Choice of Esophageal Substitute

There is an ongoing debate among esophageal surgeons about the relative merits of colon interposition versus gastric pull-up to replace a damaged esophagus. This debate is of most relevance to esophageal cancer, and the considerations are dealt with in detail elsewhere in this book. Gastric pull-up requires only one anastomosis, is generally quicker, and is increasingly being performed laparoscopically. However, the functional results tend to deteriorate over time with the development of symptomatic reflux, stricture, and columnar metaplasia above the anastomosis in the proximal esophageal remnant. In contrast, colon interposition is a more extensive procedure that requires three anastomoses, but the functional results remain stable or improve with time. We have recently shown in a long-term study of anastomotic stricture after esophagectomy that colon interposition is associated with a lower incidence of stricture than gastric pull-up.[30] When applied to caustic stricture, there are even stronger grounds for preferring colon interposition because the stomach has often been damaged by the caustic agent and is scarred and foreshortened.

Unusual cases occur in which both the stomach and the transverse colon have been damaged by the injury or resected before the ingestion episode. In such cases the right colon and terminal ileum may be available. If the colonic damage is extensive, recourse must then be made to the use of jejunum. The short mesentery of the jejunum generally precludes a jejunal limb from reaching to the cervical esophagus or pharynx. It is best to bring the limb of jejunum into the middle or upper mediastinum and then bridge the gap by harvesting a free flap of jejunum and anastomosing the artery and vein to the external carotid and jugular vein, respectively. The distal end may be anastomosed to the upper limit of the Roux limb of the jejunum, but it may be wise to let the free flap mature and the blood supply develop for several weeks before performing the proximal anastomosis in the pharynx.

One technique that was performed in the days before colon interposition or other gastrointestinal transposition procedures was the use of skin flaps. Early attempts with pedicled cervical skin flaps were associated with a very high failure rate because of leakage and stricture. A myocutaneous flap harvested from the pectoralis major muscle and based on the pectoral branch of the acromiothoracic artery may be tunneled under the clavicle and sutured into a pharyngeal defect, but this flap is too bulky to be used for a circumferential defect. As a general rule, these methods are of historical interest only and have been superseded because of the relative ease and reliability of reconstruction with the gastrointestinal tract.

Strictures in the Cervical Esophagus and Below

When the pharynx and laryngeal mechanism are spared and the esophageal stricture is located well below the cricopharyngeus, surgical treatment differs little from the standard principles of esophageal replacement for other more common diseases, with the caveat that a transthoracic rather than transhiatal approach is preferred (Fig. 39–1). The technique of colon interposition as described by DeMeester et al. in 1988 has never been bettered.[31] Certain important principles apply to the postoperative care of any patient after esophagectomy, including careful attention to fluid balance to avoid pulmonary overload, constant awareness of the high risk for aspiration, and vigilance to detect early signs of sepsis. Caustic ingestion is associated with an especially high risk for the development of an anastomotic stricture,[32] for several reasons. First, scarring in the proximal esophageal stump may continue to progress for more than 1 year after the initial insult. If there are strong clinical grounds for definitive surgical reconstruction during the first few months, care must be taken to resect well proximal to the strictured portion. Second, there may be tension on the anastomosis. Two techniques to reduce this tension are important: (1) a sufficiently long piece of colon should be mobilized by dividing the colon proximally so that it will reach high in the neck with ease, and (2) when using the substernal route, it is very helpful to excise the left half of the manubrium and the most distal portion of the left clavicle. This maneuver removes the risk of creating an anastomosis in a tight, crowded space.

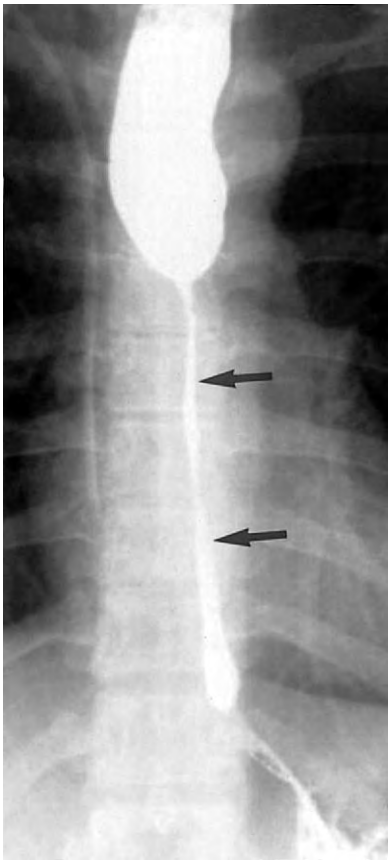

Figure 39–1. Stricture in the mid and distal portion of the esophagus, where conventional techniques of esophagectomy and reconstruction can bring about a good result.

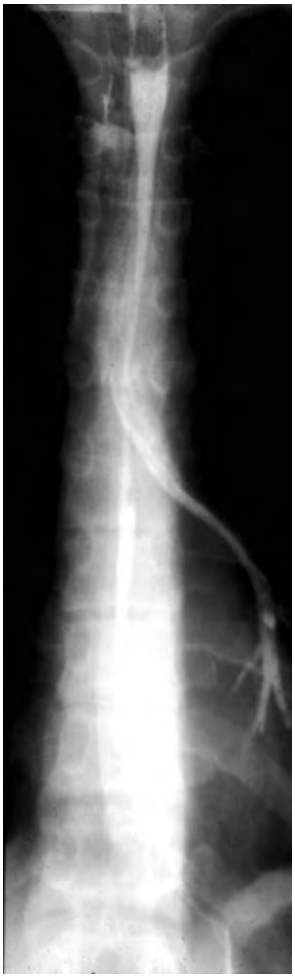

Figure 39–2. Stricture high in the cervical esophagus that was associated with an anastomotic stricture after colon interposition.

It is important to divide the clavicle medially, just lateral to the sternoclavicular joint, so that the costoclavicular ligament remains intact. This avoids the unsightly protrusion of the unattached clavicle.

One further technique to reduce the risk for anastomotic stricture is to perform it in two stages, as advocated by Ergun et al.[32] In this method the colon is generously mobilized and passed substernally up to the neck, where it is left in situ for 3 months, during which time it is claimed that the blood supply improves and thereby allows a safer definitive anastomosis in the neck. The authors report a stricture rate of 11%, which compares favorably with rates of 13% to 60% reported by other workers.

Oropharyngeal Stricture

Strictures high in the esophagus and pharynx are much harder to manage than those in the tubular esophagus or stomach (Fig. 39–2) because of the difficulty of restoring swallowing without creating intractable aspiration. A laryngeal or subglottic stricture is characterized by progressive dysphonia that eventually mandates tracheostomy. Injuries of this degree are easily recognized clinically by the presence of limited jaw opening and an inability to protrude the tongue as a consequence of fibrosis of the tongue base. Direct laryngoscopy shows that the epiglottis is scarred, deformed, and adherent to the pharyngeal wall. The vallecula and one or both piriform sinuses may be occluded by scarring. The epiglottis may be liberated by laser therapy, but scarring frequently redevelops. During this time the patient requires a tracheostomy. Most such patients are unable to phonate properly, and the voice is reduced to barely audible inarticulate squeaks. In this situation the chance of restoration of speech is so remote that the patient is better off with a primary laryngectomy and end tracheostomy. Once this key decision is made, a colon interposition or gastric pull-up can then be performed to the base of the tongue, and even the impaired pharyngeal apparatus that remains can generally be sufficient to permit the patient to have adequate swallowing for maintenance of nutrition without tube feeding. In the rehabilitation period the patient will need the services of a speech pathologist who specializes in laryngectomized patients, and some external mechanical larynx or the

creation of a Bloom-Singer valve may be helpful in restoring the ability to communicate.

For patients with pharyngeal involvement but limited damage to the laryngeal mechanism, the ultimate goal of therapy is preservation of both swallowing and speech. The problem is not the physical provision of a conduit; it is the intractable aspiration that occurs. If both piriform sinuses are open, the prognosis for safe swallowing is relatively good. If one piriform sinus is preserved, it may still be possible to perform a safe anastomosis. When both are occluded by scarring, the larynx is also severely damaged. Many ingenious surgical solutions have been proposed, including anastomosis to the piriform sinus as advocated by Tran Ba Huy and Celerier[33] and pharyngocoloplasty as described by Popovici, a Romanian surgeon with a personal series of 253 esophageal reconstructions for caustic injury. Most of this extensive experience is available only in the French literature, but a summary is available in English.[34,35]

LONG-TERM CONSEQUENCES

The economic impact of serious caustic injuries is very significant. Young children with extensive injuries often remain in the hospital for several months and require numerous surgical and diagnostic procedures and anesthetics. The burden on their parents, who may have to move closer to a major referral center, is also very great. In adults with extensive injuries, prolonged ICU stay (averaging 58 days in the study by Cattan et al.) and the necessity for repeated interventions by surgeons, radiologists, and gastroenterologists are responsible for huge expenses that are rarely recouped by private institutions.[20]

In addition to the economic consequences, it has also been shown that there is an astonishingly high incidence, about 50%, of behavioral and educational problems in children who survive and that over a quarter of their families break up in the wake of the protracted period of stress.[36] In adults the risk for repeated suicide attempts is a real one, especially in the depressing situation in which a sequence of complications necessitates numerous additional surgeries. These considerations validate all the effort expended by lobbying groups to reduce the ease with which these devastating injuries occur.

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Chapter

40

Paraesophageal and Other Complex Diaphragmatic Hernias

Matthew M. Hutter ▪ David W. Rattner

Paraesophageal hernias (PEHs) merit consideration as a separate entity from the more common sliding hiatal hernia (HH) because they are associated with life-threatening complications such as strangulation, necrosis, and perforation of the stomach. As a result of the perceived high rate of complications and the high mortality of emergency surgery in this setting, surgical dogma has been to repair PEHs on diagnosis. Recent evidence, however, questions this dogma, and evidence-based guidelines recommend watchful waiting for elderly patients who are asymptomatic or minimally symptomatic. Only patients who are symptomatic require operative repair.

The principal components of surgery for PEH include reduction of the herniated stomach and other organs below the diaphragm, restoration of an intra-abdominal segment of esophagus, excision of the hernia sac, and repair of the defect in the diaphragm. Controversy exists regarding the best approach (laparoscopic versus transabdominal versus transthoracic), the need for routine fundoplication, the role of prosthetic mesh, the benefits of gastropexy, and the prevalence of the "short esophagus." These controversies are examined in this chapter.

Although this chapter focuses on PEH, it also discusses other complex hernias of the diaphragm, including

- Traumatic hernias
- Postoperative diaphragmatic hernias
- Parahiatal hernias
- Congenital diaphragmatic hernias in adults

CLASSIFICATION AND PATHOPHYSIOLOGY

All HHs are characterized by a portion—if not all—of the stomach protruding through an enlarged esophageal hiatus into the chest. HHs are thought to be caused by the combined forces of age, stress (negative intrathoracic pressure and positive intra-abdominal pressure), and degenerative processes on the diaphragm. HHs can be classified into four types, depending on the anatomic location of the gastroesophageal (GE) junction and the extent of herniated stomach or other organs (Fig. 40–1).

A *type I* hernia is known as a sliding HH and is characterized by upward displacement of the GE junction into the posterior mediastinum. The stomach remains in its usual longitudinal alignment (see Fig. 40–1). The development of an HH appears to be related to age and to structural deterioration of the phrenoesophageal membrane over time.[1] This deterioration is probably due to repetitive upward stretching of the phrenoesophageal membrane during swallowing, as well as the combined force of negative intrathoracic pressure and positive intra-abdominal pressure. This postulate is supported by the fact that power lifters, who develop high intra-abdominal pressure during weight training, have a higher incidence of sliding HH than do non-weightlifting age-matched controls.[2] A higher incidence of HH has also been found in people with inguinal hernias.[3] Although the majority of patients with HH are asymptomatic, the prevalence and size of the sliding HH correlate with increasing severity of reflux disease.[4]

Type II and *type III* hernias are known as paraesophageal hernias (see Fig. 40–1). Type II—a "true" PEH—is defined by a normally positioned intra-abdominal GE junction with upward herniation of the stomach alongside it. A type III hernia is known as a "mixed" hernia and is characterized by displacement of both the GE junction and a large portion of the stomach cephalad into the posterior mediastinum. The difference between a type I or sliding HH and a type III or mixed PEH is that with a type III hernia, a portion of the stomach lies cephalad to the GE junction.

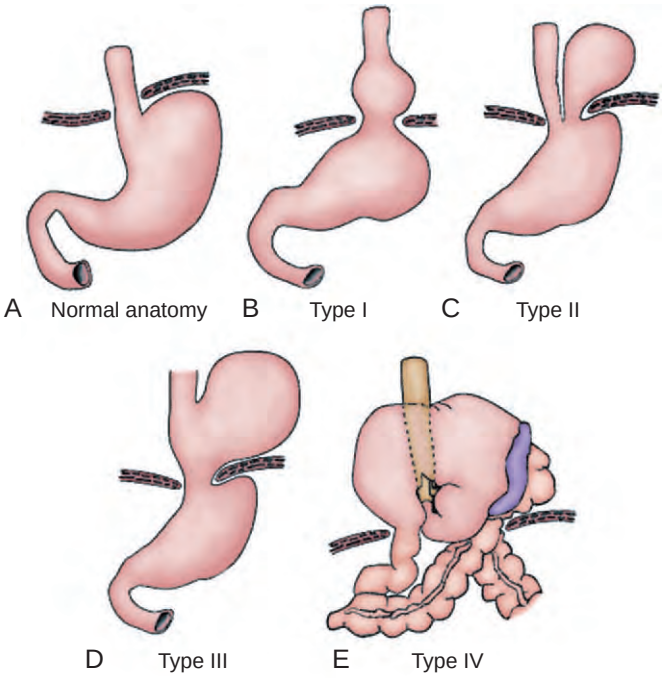


Figure 40–1. Types of hiatal hernia. **A,** Normal anatomy. **B,** Type I: sliding hiatal hernia. **C,** Type II: "true" paraesophageal hernia. **D,** Type III: "mixed" paraesophageal hernia. **E,** Type IV: paraesophageal hernia containing other intra-abdominal organs. (From Duranceau A, Jamieson GG: Hiatal hernia and gastroesophageal reflux. In Sabiston DC Jr [ed]: Textbook of Surgery and the Biological Basis of Modern Surgical Practice, 15th ed. Philadelphia, WB Saunders, 1997, p 775.)

A PEH develops when there is a defect, possibly congenital, in the esophageal hiatus anterior to the esophagus.[5] Persistent posterior fixation of the GE junction is the essential difference between a PEH and a sliding HH. A type III or mixed hernia probably starts as a sliding HH, and over time as the hiatus enlarges, more and more of the fundus and body of the stomach herniate into the chest. Alternatively, a type III hernia could start as a type II hernia, with eventual migration of the GE junction cephalad.

In a *type IV* hernia, the esophageal hiatus has dilated to such an extent that the hernia sac also contains other organs such as the spleen, colon, or small bowel (see Fig. 40–1). Because of this altered anatomy, bowel obstruction and other complications may develop. PEHs initially develop on the left anterior aspect of the esophageal hiatus. The anterior gastric wall, or perhaps the epiphrenic fat pad itself, serves as a lead point, with the remainder of the stomach rolling up into the chest over time. The fundus must gain enough mobility from its intra-abdominal attachments to travel cephalad into the chest. This mobility is obtained by laxity in the gastrocolic and gastrosplenic ligaments, which normally help secure the stomach below the diaphragm. It is this laxity that allows volvulus to develop. Volvulus occurs when the stomach twists on itself, and this twisting leads to obstruction of the stomach or esophagus and potentially perforation.

Two types of volvulus can occur: organoaxial and mesentericoaxial (Fig. 40–2). In organoaxial volvulus, the greater curvature of the stomach moves anterior to the lesser curve, along the axis of the organ. In mesentericoaxial volvulus, which is less common, the stomach rotates along its transverse axis. Gastric strangulation develops if the blood supply is compromised by distention of the herniated contents or a 360-degree twist of the stomach.

PREVALENCE

The actual prevalence of HH in the overall population is not known. Most patients are asymptomatic. Upper gastrointestinal (GI) barium studies in patients with GI complaints identify some type of HH in 15% of cases. The majority of hernias identified are incidental radiographic findings.

Greater than 95% of HHs are type I or sliding hernias. Less than 5% are PEHs. Of all PEHs, type III is the most common and is found more than 90% of the time,[6] type II is found 3.5% to 14% of the time, and type IV is the least common and occurs in only 2% to 5% of all PEHs.[4]

PEHs are four times more likely to develop in women than in men. The incidence of PEH increases with advancing age. Patients with PEH are on average significantly older than those with sliding HH: a mean of 61 years versus 48 years.[7] Familial cases of HH have been well documented and have an autosomal dominant mode of transmission.[8]

SYMPTOMS

Upward of 50% of patients with PEH are considered to be asymptomatic, although many of the symptoms are minor and may be overlooked. When patients are questioned carefully, 89% will actually have symptoms related to their hernia.[9] Symptoms include chest pain, epigastric pain, dysphagia, postprandial fullness, heartburn, regurgitation, vomiting, weight loss, anemia, and respiratory symptoms (Table 40–1).

When compared with a sliding HH, symptoms of dysphagia and postprandial fullness are more common with a PEH. The symptoms of heartburn and regurgitation that can be present with a sliding HH can also be present with a PEH and thus do not differentiate between the two.

Incarceration and Strangulation

The most serious complications of PEH are incarceration with obstruction of the stomach and gastric strangulation. Even mild dilation from incarceration with obstruction can lead to relative ischemia, ulceration, perforation, and ultimately sepsis. Borchardt's triad consists of chest pain, retching with an inability to vomit, and an inability to pass a nasogastric tube. This triad indicates an incarcerated intrathoracic stomach and is a true sur-

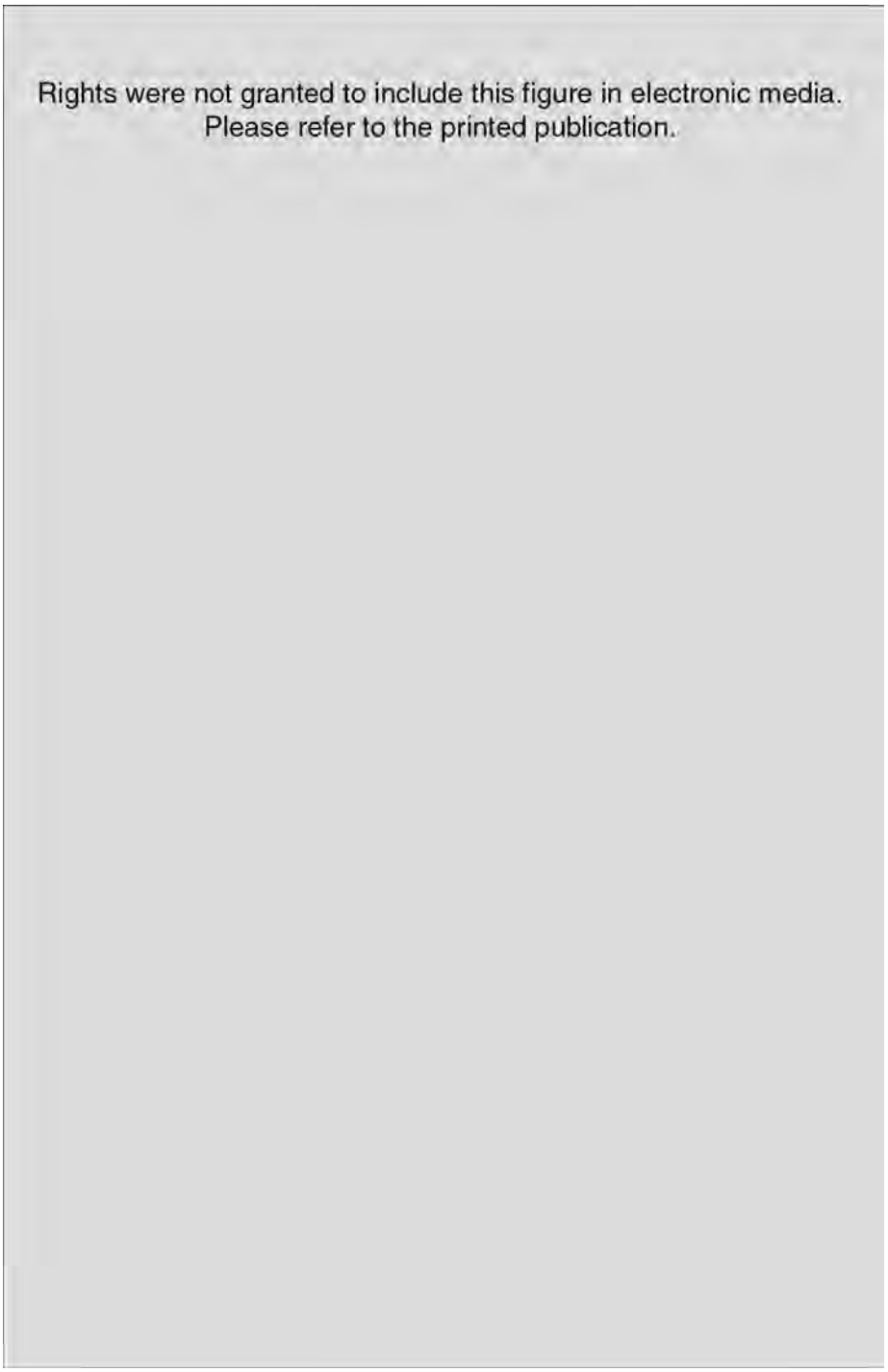


Figure 40–2. Gastric volvulus associated with paraesophageal hernias. *Top,* Organoaxial volvulus. Volvulus occurring along the longitudinal axis of the stomach leads to a true "upside down" stomach. The stomach becomes obstructed at both the cardia and the pyloroduodenal area. This type of gastric volvulus is the most common. *Bottom,* Mesentericoaxial volvulus. Folding of the stomach on itself along the transverse axis leads to pyloroantral obstruction. (From Menguy R: Surgical management of large paraesophageal hernia with complete intrathoracic stomach. World J Surg 12:416, 1988.)

gical emergency. It is often misdiagnosed as a myocardial infarction. Without timely surgical intervention, a life-threatening situation soon develops.

Compression of the Esophagus or Stomach

In a large PEH, symptoms are usually caused by the mechanical forces of the displaced stomach. In patients with organoaxial volvulus, or an "upside-down stomach," both the GE junction and the pylorus are relatively fixed (see Fig. 40–2). Distention of a gastric volvulus is akin to wringing out a towel. The fluid trapped in the stomach leads to nausea, pain, and vomiting. As the stomach distends, the esophagus may be compressed and give rise to dysphagia or chest pain. Some patients complain of spitting up foamy fluid, or oral secretions that could not transit the obstructed GE junction. Interestingly, many patients with long-standing heartburn relate that their heartburn resolved at or about the same time that they began to complain of mechanically related symptoms such as postprandial "dry heaves" or chest pain. Vomit-

Table 40–1 Paraesophageal Hernias: Preoperative Symptoms and Findings

Typical heartburn	47%
Dysphagia	35%
Epigastric pain	26%
Vomiting	23%
Anemia	21%
Barrett's epithelium	13%
Aspiration	7%

Caveat: Many paraesophageal hernias are asymptomatic.
From Pierre AF, Luketich JD, Fernando HC, et al: Results of laparoscopic repair of giant paraesophageal hernias: 200 consecutive patients. Ann Thorac Surg 74:1909-1915, 2002.

ing is usually intermittent, but persistent vomiting suggests incarceration of the stomach.

Bleeding

Hematemesis or anemia is evident in about a third of patients with PEH. Bleeding can be caused by ischemia of the gastric mucosa or by "riding ulcers," otherwise known as "Cameron's ulcers." Cameron's ulcers are due to the constant abrasive force as the stomach rubs against or is pinched by the diaphragmatic hiatus.[10] The continuous movement of the stomach and esophagus as they travel up and down with respiration and swallowing compounds the problem. Anemia from a PEH resolves in 92% of patients after surgical repair.

Pulmonary Symptoms

Pulmonary symptoms associated with PEH include dyspnea because of the restrictive effects created by abdominal organs in the chest, pain with inspiration, or chronic cough. Recurrent aspiration from regurgitation can lead to pneumonia or a restrictive pulmonary disease.[11] With operative repair of the hernia, significant improvements in objective measurements of pulmonary function are usually achieved.[12]

DIAGNOSIS AND PREOPERATIVE EVALUATION

Although some patients have the symptoms just described, many are asymptomatic or minimally symptomatic. Physical examination can be remarkable for decreased breath sounds or dullness to percussion on the left side of the chest. Bowel sounds can often be auscultated in the chest in a person with a type IV HH. PEHs in asymptomatic or minimally symptomatic individuals are found during radiographic or endoscopic evaluations performed for other reasons.

Radiographic Studies

Chest radiographs often show opacity in the left side of the chest or an air-fluid level behind the cardiac silhouette. The lateral view usually demonstrates this opacity best (Fig. 40–3). A nasogastric tube that coils in the stomach can be used to demonstrate that this opacity is indeed an intrathoracic stomach. *Computed tomography* (CT) scans show these anatomic abnormalities with much more precision and can demonstrate whether other abdominal organs have migrated above the diaphragm as well. An *upper GI barium swallow* can be quite useful to assess anatomic detail, and it provides the diagnosis in almost all cases (Fig. 40–4). An upper GI study is also the best way to determine the location of the GE junction, which can help differentiate between a type II and type III hernia.

Endoscopy

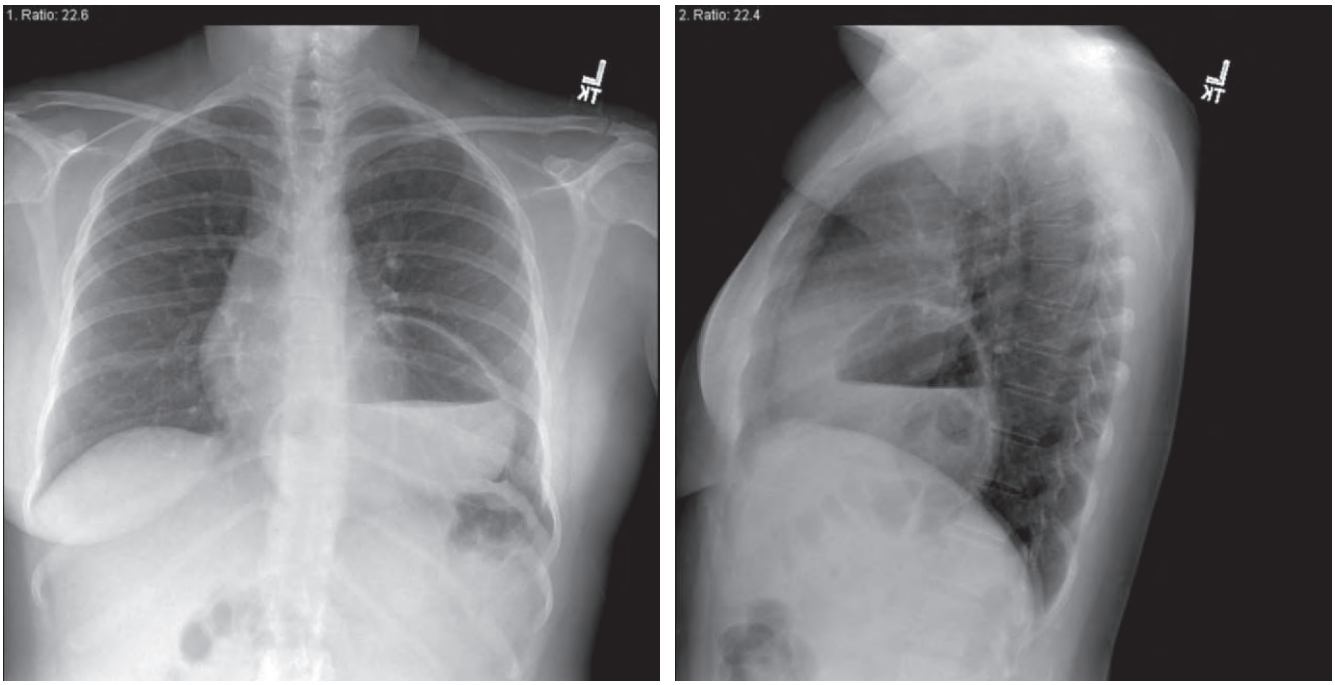
Flexible fiberoptic endoscopy can be used to readily diagnose a PEH during retroflexed evaluation of the GE junction. Diagnostic findings of a type II PEH include a second orifice next to the GE junction and gastric rugal folds extending up into the opening. A type III PEH shows a gastric pouch extending above the diaphragm with the GE junction entering partway up the side of this pouch. Having the patient sniff can help identify the crura. Endoscopy can also be used to identify other intraluminal abnormalities, including ulcerations, gastritis, esophagitis, Barrett's esophagus, and mucosal-based neoplasms.

Manometry and 24-Hour pH Monitoring

Manometry and 24-hour pH monitoring are not very useful because the anatomic distortion of a PEH invariably makes the findings from these studies abnormal. We rely on fluoroscopic evaluation for a crude measure of esophageal motility. Because many patients are elderly, esophageal peristalsis is often abnormal, and thus symptomatology (presence or absence of dysphagia) is the best predictor of whether a patient will tolerate a full fundoplication. We recommend an antireflux procedure in most circumstances (see "Role of Fundoplication," later).

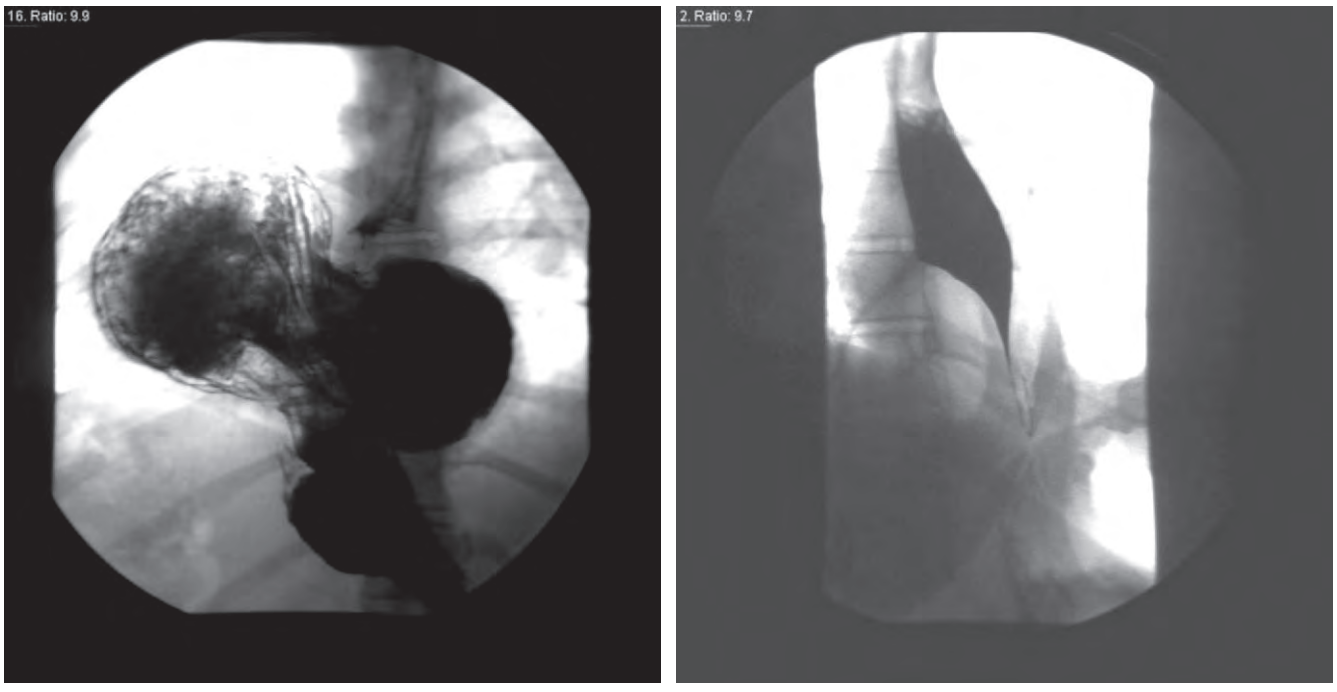
TREATMENT

Because PEH is an anatomic abnormality, no medical treatment can correct it. Although symptoms of gastroesophageal reflux disease (GERD) may be alleviated by acid suppression, the symptoms caused by mechanical forces such as ulceration, vomiting, and postprandial chest pain respond only to surgical restoration of normal anatomy. Endoscopic gastropexy has been described for use in the highest-risk patients; in this procedure the hernia is reduced with a gastroscope and fixed intra-abdominally with a double percutaneous endoscopic gastrostomy (PEG) technique, with or without laparoscopic assistance.[13] However, surgical repair remains the mainstay of treatment of PEH.



A B

Figure 40–3. Posteroanterior **(A)** and lateral **(B)** chest radiographs in a patient with a paraesophageal hernia. Notice the large air-fluid level behind the cardiac silhouette as a result of the intrathoracic stomach.



A B

Figure 40–4. Barium swallow in a patient with a paraesophageal hernia (same patient as in Fig. 40–3). **A,** Most of the stomach is in an intrathoracic position. **B,** Esophageal narrowing caused by compression from the intrathoracic portion of the stomach.

Indications

Traditional surgical teaching recommended operative reduction and repair of all PEHs once diagnosed, unless the patient was unfit for general anesthesia. The perceived need for prophylactic repair in all patients with a PEH is based on the theory that the mechanical complications leading to catastrophic life-threatening complications can occur without warning. This dogma was established in 1967 after publication of the classic report by Skinner and Belsey, who observed 21 patients without surgery.[14] Six of these 21 patients (29%) died of causes related to their PEH, including strangulation, perforation, bleeding, and acute dilation of the stomach. The authors concluded that elective surgery, with a 1% mortality rate, was preferable to the high mortality rate of emergency surgery.[14] This study, even though based on a small number of patients, was thought to characterize the natural history of PEH, as well as the morbidity and mortality associated with elective and emergency operations, and helped determine surgical practice for decades.

More recent evidence suggests that the risk of observing asymptomatic patients is much less, and therefore elective surgery should be reserved for symptomatic patients. In a 1993 article by Allen et al., 23 patients with a PEH who were asymptomatic were monitored for 20 years, and in only 4 of them did symptoms eventually develop.[15]

A recent study examined the outcomes of watchful waiting versus elective laparoscopic PEH repair in asymptomatic or minimally symptomatic patients.[16] This study used a Markov Monte Carlo decision analytic model based on pooled data from all published studies in this field and on nationwide, population-based data from the Nationwide Inpatient Sample. The authors found that published articles overestimated the mortality associated with emergency surgery when compared with the population-based data—17% versus 5.4%. Mortality with elective surgery was 1.4% in the population-based study. The annual probability of the development of acute symptoms requiring emergency surgery with the watchful waiting strategy was 1.1%. Using data for laparoscopic PEH repair as the benchmark for surgical treatment, this study concluded that routine elective repair would benefit only one in five patients. Furthermore, elective laparoscopic hernia repair in asymptomatic patients might actually decrease the quality-adjusted life expectancy for patients 65 years and older. Because progression of symptoms is slow and emergency surgery is seldom necessary, watchful waiting is the preferred approach for patients with large but relatively asymptomatic PEHs. Along with these landmark studies, multiple other current esophageal surgeons favor a nonoperative approach for asymptomatic patients.[9,15,17,18,19]

In contrast to asymptomatic patients, individuals who have either obstructive symptoms, bleeding, or complications of GERD associated with a PEH should undergo surgical repair. These patients are clearly the subgroup at risk for the development of life-threatening complications requiring emergency surgery. Elderly, high-risk patients who are symptomatic require specific consideration. Complex judgment is required to balance the risk associated with surgery, the type of surgical approach, and the extent of the procedure performed.

Surgical Approach

PEHs can be reduced and repaired from either a transthoracic or transabdominal approach. It would be optimal if the surgeon caring for patients with PEH were trained in all approaches and could truly individualize the approach to each patient's unique anatomy and risk profile. This, however, is rarely true in real-life practice. We do not believe that one operation is appropriate for all PEHs and use the following guidelines to select the approach. We preferentially repair PEH with a laparoscopic approach because of the high success rate and lower morbidity than with laparotomy or thoracotomy. This approach requires excellent advanced laparoscopic suturing and dissecting skills. In experienced hands, mobilization of the esophagus to the aortic arch can be routinely accomplished and a Collis gastroplasty added if necessary. In inexperienced hands, however, this is the most dangerous approach. Laparoscopic PEH repair is much more difficult than a routine laparoscopic antireflux operation and should probably not be attempted by the occasional laparoscopic surgeon. It is best if the operation is performed by an adequately trained surgeon so that the patient has the best chance for a safe and effective treatment.

Not all patients are good candidates for laparoscopic PEH repair. Those who have previously undergone open HH repair or laparoscopic PEH repair and obese patients are poor candidates for the laparoscopic approach. This group of patients is probably best approached transthoracically. Proponents of the transthoracic approach argue that it allows for complete esophageal mobilization and the best exposure for dissection of the hernia sac. A thoracotomy also provides easy exposure to perform a Collis gastroplasty. Disadvantages include the morbidity of a thoracotomy with incisional discomfort, pulmonary complications, and prolonged length of stay, as well as difficulty assessing the intra-abdominal organs. In our practice, open transabdominal approaches are reserved for patients being treated by gastropexy only. We believe that laparoscopic visualization is superior to that obtained via laparotomy—especially as one tries to work cephalad through the hiatus. Therefore, there is little advantage of laparotomy over laparoscopy in experienced hands if one chooses a transabdominal approach.

Laparoscopic Approach

Laparoscopic PEH repair confers the typical benefits of minimally invasive surgery—less blood loss and less third spacing of fluids, fewer pulmonary complications, and quicker recovery from surgery. This benefit is magnified in patients with PEHs, who tend to be elderly and debilitated and may not tolerate a thoracotomy or laparotomy well. The laparoscopic approach has additional unique advantages in that the view of the operative field is

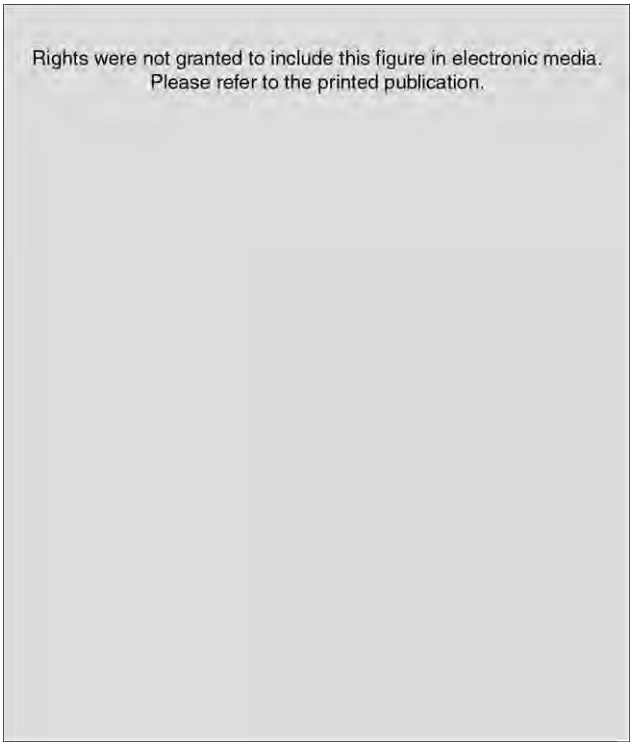


Figure 40–5. Trocar placement for laparoscopic paraesophageal hernia repair. A five-trocar technique is generally used, with two 10-mm trocars and three 5-mm trocars. (Adapted from Hutter MM, Mulvihill SJ: Laparoscopic management of pancreatic pseudocysts. In Zucker KA [ed]: Surgical Laparoscopy, 2nd ed. Philadelphia, JB Lippincott, 2001, p 647.)

magnified, thereby facilitating precise identification of tissue planes and vessels. Insufflation of CO_2 frequently establishes the correct dissection plane as one separates the peritoneal and pleural components of the hernia sac. The use of an angled scope also allows visualization of the mediastinum that cannot be obtained via laparotomy.

The disadvantages of a laparoscopic approach are the long learning curve and the need for advanced laparoscopic experience to perform this difficult operation safely and effectively. Some state that 30 to 50 laparoscopic fundoplications should be performed before attempting a laparoscopic PEH repair.[9] Such experience makes it easier to identify the anatomy, safely dissect the hernia sac from the mediastinum, and accurately place the crural sutures deep in the crura close to the aorta.

Laparoscopic Technique

The patient is placed supine, with the surgeon on the patient's right side. A five-port technique is used, with the initial 10-mm port placed via an open technique a few centimeters to the left of the midline and a few centimeters above the umbilicus (Fig. 40–5). Pneumoperitoneum is established, and a 10-mm 30-degree scope is used. A 10-mm port is placed in the left subcostal region, one or two fingerbreadths below the rib, a 5-mm trocar is placed inferior to this in the left anterior axillary line, a second 5-mm port is placed one hand's-breadth to the right of the camera port and a bit cephalad, and a third 5-mm port is placed on the right in the anterior axillary line for the liver retractor. Using atraumatic graspers, the stomach is grasped and traction is placed on it in an attempt to reduce it. The gastrohepatic ligament can be opened, and then ultrasonic coagulating shears can be used to incise the peritoneum at the anterolateral edge of the hiatus (Fig. 40–6). It is critical at this point in the procedure that the natural tissue plane that exists between the peritoneal and pleural layers of the hernia sac be developed. This plane is frequently areolar and bloodless. In patients who are highly symptomatic, however, inflammation can develop and make it more difficult to establish this plane. Once the plane is established, it can be carried circumferentially around the sac. Small vessels should be coagulated with the ultrasonic shears or cautery. At the cephalad margin one should identify the vagi and then roll the sac down into the abdomen. A laparoscopic peanut can be helpful for this blunt dissection (Fig. 40–7). Pneumothorax may develop during this dissection if the pleura itself is violated. Ordinarily, it is not of any consequence because the patient is being maintained on positive pressure ventilation. However, if the patient is hypovolemic or inadequately relaxed, tension pneumothorax can develop. Depressurizing the CO_2 in the abdomen will ameliorate this problem until volume status and anesthesia depth are corrected. Once complete dissection of the sac is performed, the sac is excised close to its attachment to the GE junction and removed so that it does not interfere with the subsequent repair. The anterior and posterior vagus nerves should be identified during the dissection and preserved during excision of the sac. If there is concern about the location of the vagus nerves or the sac is very thick and vascular, it is better to leave some excess sac than risk injury to the nerves or esophagus. It is, however, essential that the sac be completely detached from the crura and mediastinum. Residual attachments of the sac to the hiatus will lead to recurrence. With a rubber drain or tape around the esophagus, extensive mediastinal dissection with mobilization of the esophagus to the level of the aortic arch can be performed. The goal is to restore a suitable length (2.5 cm) of tension-free esophagus in the abdomen. The length should be measured with the esophagus unstretched and at the level where the crura are to be closed. The crura are then reapproximated with 0-Ethibond (Ethicon, Somerville, NJ) sutures tied over felt pledgets (Fig. 40–8). The left-handed grasper is placed on the left side of the aorta, and the needle is inserted through the base of the left crus. The needle can then be bounced off this grasper, which protects the aorta while ensuring that the suture gets a deep enough bite through the base of the crus. The sutures are placed starting caudally and tied, and additional pledgeted sutures are applied until only a 1-cm gap remains in the undistended esophageal hiatus. It is often helpful to lower the pressure of the

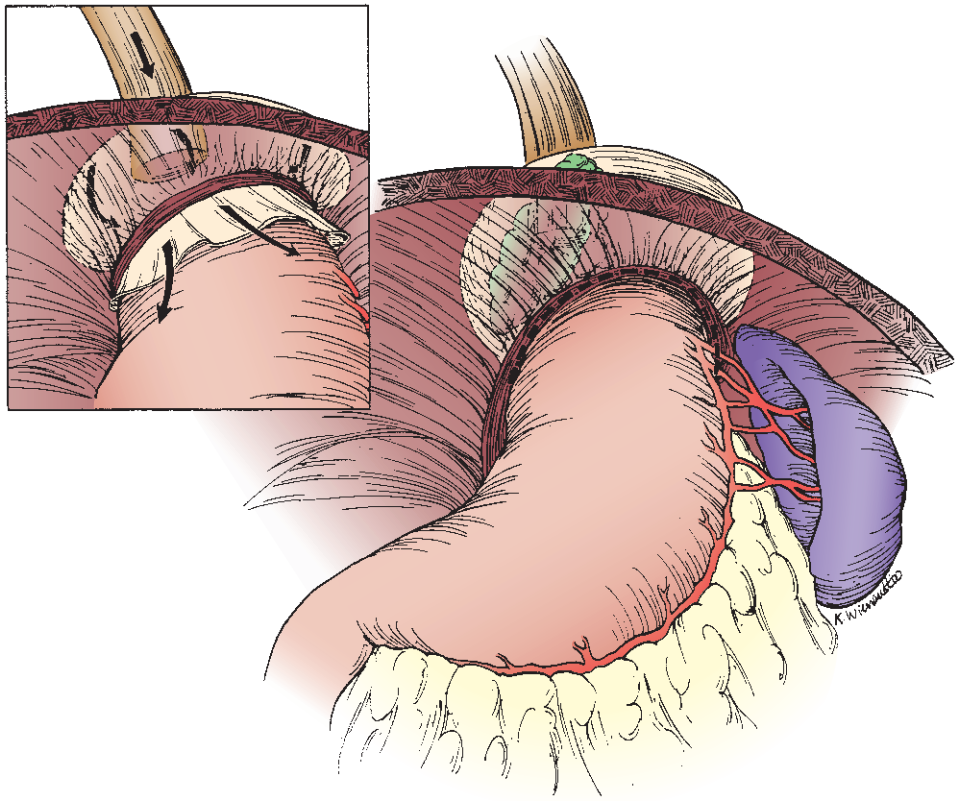


Figure 40–6. Laparoscopic dissection of the hernia sac. The gastrohepatic ligament can be opened, and then ultrasonic coagulating shears can be used to incise the peritoneum at the anterolateral edge of the hiatus (see *dotted line*). It is critical at this point in the procedure to develop the natural tissue plane that exists between the peritoneal and pleural layers of the hernia sac. This plane is often areolar and bloodless. (From Lee R, Donahue PE: Paraesophageal hiatal hernia. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. St Louis, CV Mosby, 2001, p 44.)

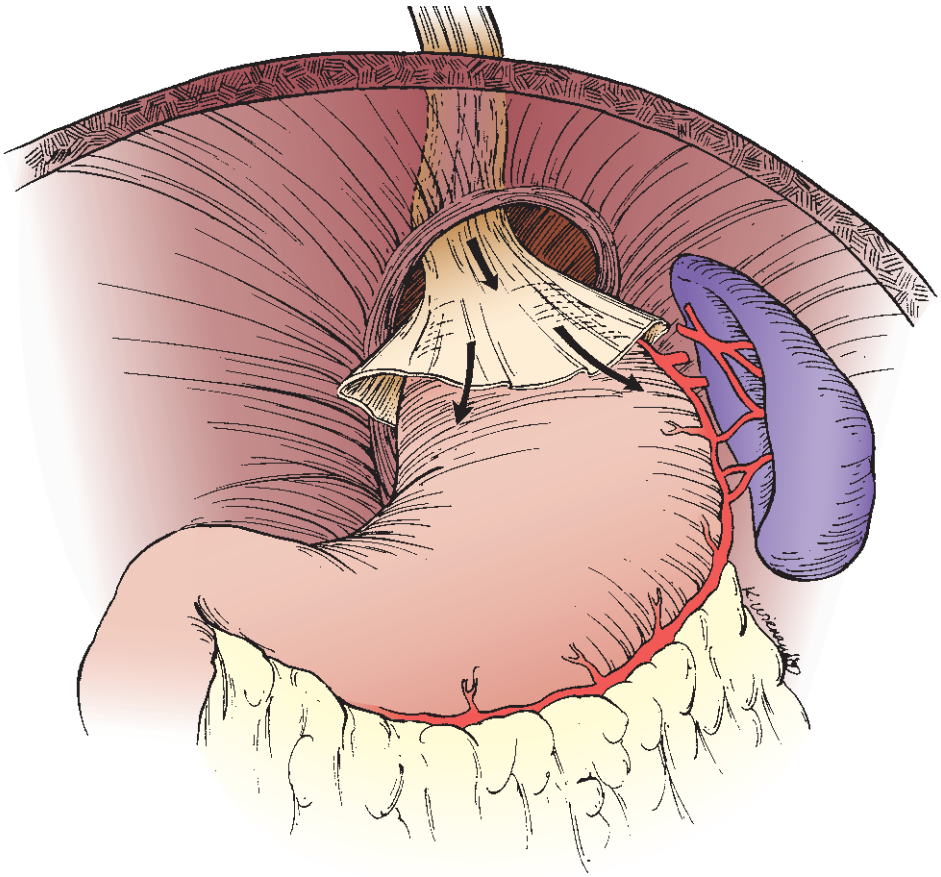


Figure 40–7. Laparoscopic dissection of the hernia sac (continued). The hernia sac is dissected circumferentially and seems to "tumble" down into the abdomen with gentle blunt dissection in the mediastinum with a laparoscopic peanut. (From Lee R, Donahue PE: Paraesophageal hiatal hernia. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. St Louis, CV Mosby, 2001, p 45.)

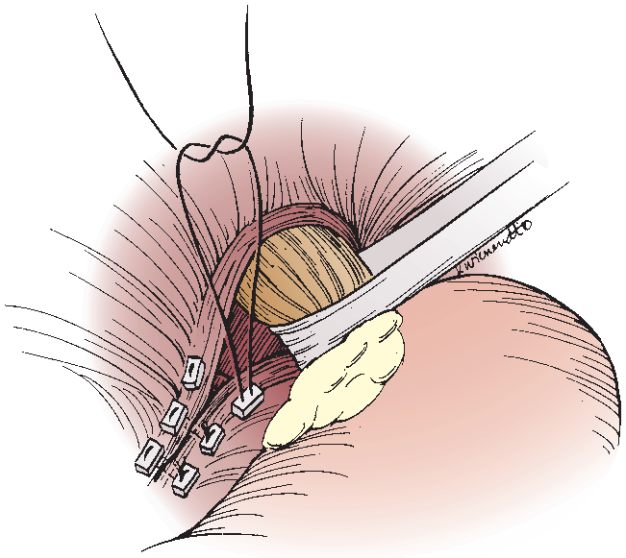


Figure 40–8. Crural closure. The crura are closed with simple interrupted pledgeted 0 braided polyester suture. Starting posteriorly, additional sutures are placed until there is a 1-cm space below the undistended esophagus. (From Lee R, Donahue PE: Paraesophageal hiatal hernia. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. St Louis, CV Mosby, 2001, p 46.)

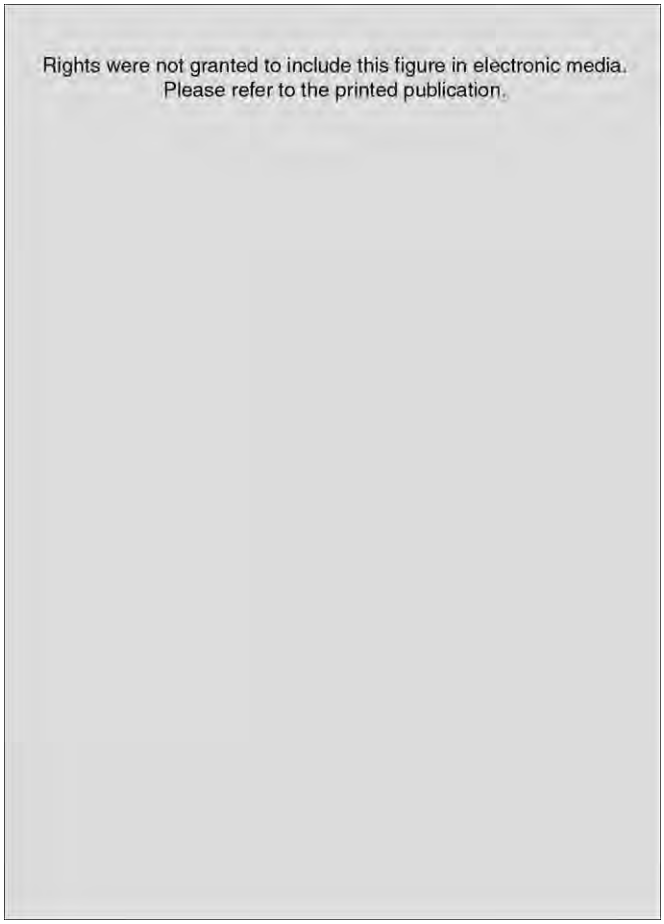


Figure 40–9. Completed Toupet fundoplication. Eight sutures are placed. Over a 54-French bougie, the top two sutures (one on the right, one on the left) include the esophagus, the fundus, and the edge of the crus. Two other sutures are placed on each side of the esophagus and include just the esophagus and fundus. One must be careful to avoid the anterior vagus nerve. Three crural sutures are seen toward the right on this diagram, and two sutures are placed posteriorly (not depicted) from the back of the wrap to the crural closure. In total, there are four points of fixation of the wrap to the crura. (From Champion JK, McKernan JB: Laparoscopic Toupet fundoplication. In Zucker KA [ed]: Surgical Laparoscopy, 2nd ed. Philadelphia, JB Lippincott, 2001, p 406.)

pneumoperitoneum to 8 to 10 mm Hg while closing the crura. The highest short gastric vessels are then divided, and either a 360-degree (Nissen) fundoplication or a 240-degree (Toupet) fundoplication is created (Fig. 40–9). In elderly patients or those with severe dysmotility seen on videoesophagograms, we prefer a partial fundoplication. The Toupet fundoplication also has the advantage of providing four points of fixation of the wrap to the crura. On completion of the repair, upper GI endoscopy can be useful if there is concern of esophageal injury or leak. We routinely perform an anterior gastropexy with two transfascial sutures of 2-0 Prolene (Ethicon, Somerville, NJ) at the conclusion of the repair.

A swallow study may be obtained on the first postoperative day to rule out leakage and reherniation if the dissection was difficult. Antiemetics should be given as part of the anesthetic and postoperative routine to prevent vomiting or retching. Clear liquids are started on the first postoperative day, and the patient is discharged home with instructions to start a full liquid diet on the second postoperative day and continue it for 1 week, at which time the diet is slowly advanced.

OUTCOMES

Outcomes of PEH repair reported in the literature are from a few high-volume, tertiary care centers that specialize in these procedures. Data from low-volume centers and population-based data are not available. The following results must therefore be interpreted with caution because they are not necessarily generalizable to all situations where these procedures are being performed.

Thoracic Approach The largest series using a thoracic approach was recently reported by Patel et al. from the University of Michigan.[20] A Collis gastroplasty was performed in 96% of their 240 cases. With a 42-month mean follow-up, the mortality rate was 1.7% and the complication rate was 8.5%, including three leaks. Nineteen (8%) anatomic recurrences were documented, 8 (3.3%) of which required reoperation. Maziach et al. from the University of Toronto reported a series of 94 cases, with 97% done transthoracically and 80% undergoing gastroplasty.[21] With a 94-month mean follow-up, the mor-

tality rate was 2%, the major complication rate was 19%, including four leaks, and 2% required reoperation for recurrence.

Abdominal Approach In 2000, Geha et al. from the University of Illinois reported on 100 patients, 82 of whom were treated by an abdominal approach.[22] Two percent also required a Collis gastroplasty. There were two deaths in patients undergoing emergency operations and none in the elective group, with no recurrences. Williamson et al. from the Lahey Clinic reported on 119 patients with PEHs who underwent a transabdominal repair.[23] Follow-up in this study was for a median of 61.5 months, the mortality rate was 1.7%, and the complication rate was 11.8%. Eleven percent had symptomatic recurrences.

Laparoscopic Approach Pierre et al. from the University of Pittsburgh reported on 200 patients undergoing laparoscopic repair.[24] Fifty-six percent underwent a Collis gastroplasty, and 11% received polytetrafluoroethylene (PTFE) patches. With an 18-month median follow-up, the mortality rate was 0.5%, the complication rate was 28%, including six (3%) leaks, and 2.5% required reoperation for recurrence. Other laparoscopic series by Diaz et al. at Washington University ($N = 116$),[25] Andujar et al. from Allegheny Health System ($N = 166$),[26] and Mattar et al. from Emory ($N = 136$)[27] show similar mortality rates of 0% to 2.2% and complication rates of 4% to 10%. Gastroplasty was performed in less than 5% of these cases. Recurrence rates seen radiographically were as high as 22% to 33%; however, recurrences requiring reoperation occurred only at a rate of 2% to 3%. Many of the radiographically detected recurrences were small sliding HHs and were not thought to be clinically significant.

Laparoscopic Versus Open Repair Two single-institution studies retrospectively compared laparoscopic with open repair. Hashemi et al. at the University of Southern California (USC) looked at 54 patients: half underwent a laparoscopic procedure, a quarter underwent laparotomy, and a quarter underwent thoracotomy.[28] Although symptomatic outcomes were similar in both groups, 42% of the laparoscopic group had a recurrence on videoesophagography as compared with 15% in the open repair group. Schauer et al. at the University of Pittsburgh compared 95 consecutive cases, 70 performed laparoscopically and 25 performed with an open technique (19 transabdominal, 4 transthoracic).[29] The laparoscopic group had a significant reduction in blood loss, intensive care unit stay, ileus, hospital stay, and overall morbidity in comparison to the open group. Multiple studies also suggest that laparoscopic repair of PEH is successful and safe and leads to a shorter hospital stay with lower costs and greater patient satisfaction than with the open technique.[13,30-48]

The major concern about laparoscopic hernia repair is the recurrence rate. As mentioned earlier, the USC group reported a 42% reherniation rate in the laparoscopic group detected by videoesophagography as opposed to 15% in the open group.[28] The other laparoscopic series also show high anatomic recurrence rates ranging from 22% to 30%. Despite this high radiographic recurrence rate, only 2% to 3% require operative repair for these recurrences, similar to the rate in the open studies. The high recurrence rates seen in the laparoscopic series may reflect the difficulty of placing sutures deeply into the crura or relaxed patient selection criteria such that patients who were considered unfit for thoracotomy were triaged to laparoscopic surgeons.

CONTROVERSIES

Role of Fundoplication

Controversy persists over whether to add an antireflux procedure to hiatal herniorrhaphy in patients with PEH.

There are many reasons to perform an antireflux procedure during PEH repair. First, an antireflux operation such as a Nissen, Toupet, Hill, or Belsey procedure can help hold the stomach in an intra-abdominal position. The bulky nature of the wrap or the suture fixation to the crura (or both) makes it more difficult for the stomach to reherniate into the chest. Second, it is very difficult to preoperatively assess which patients will have reflux symptoms once the hernia is reduced. Preoperative symptoms may be due to the distorted anatomy and poor esophageal clearance rather than reflux per se. Preoperative testing with pH probes and manometry in these patients does not provide much practical information because of the effects of their quite abnormal anatomy, as discussed earlier.

Third, the functionality of the GE junction is likely to be compromised by the operative dissection and reconstruction necessary to reduce the hernia sac and repair the hiatus. Even if function of GE junction were normal preoperatively, complete dissection of the hernia sac and mobilization of the esophagus mandate destruction of the posterior esophageal attachments, thereby predisposing to the development of reflux. Failure to perform an antireflux procedure can lead to symptomatic postoperative reflux in 20% to 40% of patients.[41]

The disadvantages of performing a fundoplication include additional time in the operating room and the added risk of complications specific to the fundoplication, such as dysphagia. However, because adequate dissection and crural closure have already been performed, we find that the addition of an antireflux procedure adds little time or morbidity. The risk of creating dysphagia or relative obstruction in a patient with inadequate esophageal motility is lessened by the liberal use of Toupet fundoplication. Furthermore, not all postoperative dysphagia is caused by the fundoplication—overly tight closure of the hiatus or severe postoperative fibrosis can also lead to dysphagia.

Prevalence of the "Short Esophagus"

Controversy persists over the need for an esophageal lengthening procedure in the repair of a PEH, mostly because of differing opinions about the prevalence of a "short esophagus." Most agree that a 2- to 3-cm

segment of esophagus must be restored to the abdomen to perform an appropriate antireflux procedure. However, there is great controversy over how often this is encountered.

The prevalence of a "short esophagus" seems to be mostly related to the surgeon's perspective, the surgical approach, and how much effort the surgeon is willing to put forth in fully mobilizing the esophagus. The need for a Collis gastroplasty during PEH repair ranges from 0% in some series to as high as 96% in other series. Transthoracic series have the highest rates, whereas laparoscopic series have the lowest rates. Proponents of the liberal use of Collis gastroplasty point to the low recurrence rate of PEH attributable to decreased tension on the esophagus.

Patel et al., in their series of 240 patients undergoing transthoracic repair, performed an esophageal lengthening Collis gastroplasty in 96%.[20] In another large series of patients with large PEHs approached through the chest, the presence of a shortened esophagus requiring Collis gastroplasty was noted in 75 of 94 patients (80%).[21] One laparoscopic series has shown the need for Collis gastroplasty in 27% of cases.[31] Most series report that a shortened esophagus is present in approximately 10% of cases, although not all require gastroplasty.[48] In most laparoscopic series, gastroplasty is necessary in only 1% to 4% of cases.

There is no doubt that in certain circumstances a shortened esophagus does exist. Urbach et al. found that preoperative risk factors associated with finding a shortened esophagus requiring gastroplasty included the presence of a stricture, PEH, Barrett's esophagus, and redo antireflux surgery.[49] Repeated dilations or past perforations can also be risk factors.

Despite the added length of neo-esophagus created by the Collis gastroplasty, there are concerns about its liberal application, including the risk of placing gastric mucosa above the level of the newly created esophageal sphincter. There is also concern about leaks and bleeding from the staple line. Furthermore, when the short gastric vessels are divided, as is routine in laparoscopic approaches, the proximal end of the gastroplasty can become ischemic and result in a stricture or leak.

We have found that with adequate circumferential dissection of the hernia sac and extensive mediastinal dissection of the esophagus, the prevalence of a truly "short" esophagus is quite low. What appeared initially to be a short esophagus can usually be brought easily into the abdomen after adequate dissection and mobilization. Others have also shown that with such mediastinal dissection, highly selective rather than liberal use of Collis gastroplasty is appropriate.[50,51]

Need for Gastropexy or Gastrostomy

Gastrostomy and gastropexy have been suggested for patients who do not undergo an antireflux procedure, especially an elderly or debilitated patient who might not tolerate an extensive operation. Gastropexy helps keep the reduced stomach in an intra-abdominal position and can help reduce the chance of postoperative volvulus. It can be especially helpful as an adjunct to a repair with posterior fixation. Gastrostomy can do the same, but it can also allow for gastric decompression to permit a chronically incarcerated stomach time to regain its functionality. Because of the little risk and additional effort involved, anterior gastropexy should be added even if a fundoplication is performed.

Use of Prosthetic Mesh

It is tempting to draw on lessons learned from inguinal and ventral hernia repair and conclude that prosthetic mesh should be more widely used in repairing PEHs. However, the concern that the repetitive motions of swallowing and breathing will cause the mesh to erode into the GI tract over time, as happened with the Angelchik device,[52] should be taken seriously. Ideally, the crura should be closed under as little tension as possible. Prosthetic patches have been used to achieve a tension-free repair, but many surgeons are currently reluctant to use them near the GE junction. Although long-term results are not available, short- and medium-term results are extremely promising, with a recurrence rate close to zero when a prosthetic patch is used.

Multiple techniques have been described for patch placement, and both absorbable and nonabsorbable prostheses have been used.[53-65] A circular prosthesis that surrounds the esophagus with a keyhole cut out has been used with both polypropylene[56,57] and PTFE.[61] An A-shaped PTFE mesh patch that surrounds the crura has likewise been described.[59] Patches can also be used to buttress the crural repair without encircling the esophagus.

A randomized controlled trial of PTFE patch repair versus simple cruroplasty was conducted in patients undergoing laparoscopic Nissen fundoplication with a hiatal defect measuring 8 cm or greater, with 36 patients in each group.[65] A 3-cm keyhole was cut in a 13 × 10-cm PTFE patch for the esophagus to pass through, and the patch was secured to the diaphragm and crura with a straight hernia stapler. The study showed a marked decrease in recurrence rate in the prosthetic patch group—there were eight recurrences (22%) in the simple cruroplasty group and no recurrences in the PTFE patch group ($P < .006$).[65] At a mean follow-up of 3.3 years, there have been no erosions, strictures, or infections in the PTFE group.

Case series using polypropylene patches have reported no recurrences. Carlson et al. reported on 44 patients with large HHs and an intrathoracic stomach operated on through an open transabdominal approach using a keyholed polypropylene patch.[57] With a mean follow-up of 52 months, there were no clinical recurrences; however, one erosion was reported in a complicated patient. Granderath et al. from Austria used a polypropylene patch to buttress the crural closure rather than cutting a keyhole from the mesh via a laparoscopic approach performed on 24 patients undergoing redo laparoscopic antireflux procedures.[56] They found no recurrences with barium swallow at 1-year follow-up and no erosions or infections.

Overall, these series are quite encouraging regarding the application of prosthetic patches. The use of prosthetic patches to buttress PEH repairs is likely to evolve rapidly as longer-term data become available and newer studies report on the use of other prosthetic materials, including dual-sided expanded polytetrafluoroethylene (ePTFE), polypropylene coated with ePTFE or other nonadherent coating, and biodegradable patches. If erosion or other complications of the prosthetic patches do not develop over time, they should be used more liberally for large hiatal defects. Given the dynamic nature of the GE junction and the motion that occurs with swallowing and respiration, we remain concerned about keyhole mesh patches and the long-term potential complication of erosion—despite the fact that the short-term results as just described do not suggest erosion to be an issue. At this point we prefer to either make a relaxing incision in the diaphragm[17] or buttress the caudal extent of the crural closure as described by Granderath et al. to prevent the mesh from coming directly into contact with the esophagus.[56]

OTHER COMPLEX DIAPHRAGMATIC HERNIAS

Traumatic Hernias

Traumatic hernias can be caused by blunt force or penetrating objects, and management depends on whether they are identified acutely or in delayed fashion. Seventy-five percent of published traumatic hernias are due to blunt trauma, although the rate at a specific trauma center depends on the mix of penetrating versus blunt trauma in that specific geographic region.[66] Approximately 1% of patients admitted to the hospital after blunt trauma have a diaphragmatic injury: 69% are left-sided injuries, 24% are right sided, and 1.5% are bilateral. Fourteen percent are diagnosed in delayed fashion, and of the remaining cases, half are identified preoperatively and half during exploration. The mortality rate after an acute diagnosis is 3% to 17%, depending on the mechanism and associated injuries.[66,67]

In blunt trauma, rupture is usually due to increased intra-abdominal pressure related to falls or motor vehicle accidents. Diaphragmatic rupture generally occurs at the apex of the diaphragm in this situation.

Traumatic rupture of the diaphragm can be a diagnostic challenge. The diagnosis depends on a high index of suspicion, careful evaluation of the chest radiograph and CT scans, and meticulous inspection of the diaphragm when operating for concurrent injuries.[66] Although there have been advances in imaging the diaphragm,[68] no specific radiographic study can rule out a diaphragmatic injury, especially with penetrating trauma. The incidence of occult diaphragmatic injury with penetrating trauma to the lower left side of the chest is high, approximately 24%.[69] Delay in diagnosis with penetrating trauma increases mortality significantly—from 3% in the acute setting to 25% in the delayed group.[67] Therefore, some trauma surgeons recommend delayed laparoscopy in patients with left lower chest penetrating injuries if they do not otherwise have an indication for celiotomy.[69]

The surgical approach for repair of a diaphragmatic injury can be through either the abdomen or the chest. In the acute setting, most trauma surgeons use an abdominal approach because greater than 89% will have an associated abdominal injury.[66] Patients with a delayed diagnosis usually have significant adhesions to the intrathoracic organs, so a transthoracic approach should be considered. The surgical approach in a patient with a delayed diagnosis is controversial, but one must be prepared to operate on both sides of the diaphragm when undertaking such a case. Laparoscopic exploration and repair have also been undertaken in both the acute and chronic phases.[69-71] Creating a pneumoperitoneum when there is a diaphragmatic rupture can lead to a tension pneumothorax, so one must be prepared to decompress the chest urgently if necessary.

To fix the hernia defect, suture repair with interrupted, large nonabsorbable sutures is recommended. Direct suture repair is usually possible in the acute setting. In the chronic setting, a prosthetic patch is generally used. A chronic defect can be hard to close without a patch, and because the defect is not usually right at the GE junction, there is less concern about erosion by the patch.

Postoperative Diaphragmatic Hernias

Postoperative diaphragmatic hernias are due to alterations in the normal anatomy from surgical dissection of the hiatus. They may occur as a result of previous hernia repairs in this region, antireflux procedures, esophagomyotomy, partial gastrectomy, misguided chest tubes, or thoracoabdominal incisions in which the diaphragm is taken down.

After laparoscopic Nissen fundoplication, an iatrogenic PEH can develop in up to 6.3% of cases.[72] Early dysphagia after fundoplication can be caused by wrap herniation, which can readily be confirmed with a barium swallow. Symptomatic patients should undergo repair immediately. A laparoscopic repair is usually possible, although one must be prepared to perform an open procedure.[73]

Parahiatal Hernias

Parahiatal hernias are fleetingly rare, and some question their existence altogether in the absence of operative manipulation or trauma. A parahiatal hernia by definition arises lateral to the crural musculature, not through the esophageal hiatus itself. The clinical findings can be indistinguishable from those of a PEH.[74] Repair is similar to the repair of a PEH and can be performed laparoscopically or through an open approach.[74,75]

Congenital Diaphragmatic Hernias

Bochdalek hernias and Morgagni hernias occur as a result of incomplete embryologic development of the

diaphragm. Most are repaired in children; however, 5% are found in adults.[76]

Bochdalek Hernias Bochdalek hernias, otherwise known as posterolateral hernias, account for 85% of congenital hernias. They occur on the left side 80% of the time. These hernias are diagnosed and repaired in children the majority of the time. Primary closure of small hernias can be performed with interrupted mattress sutures of nonabsorbable material, or larger defects can be repaired with a prosthetic patch. Both open and laparoscopic approaches have been described.[76]

Morgagni Hernias Foramen of Morgagni hernias, retrosternal hernias, and Larrey's hernias all describe the same entity and occur in the triangular space between the muscle fibers that make up the diaphragm; they extend from the xiphisternum and the costal margin to the central tendon of the diaphragm.[77] These hernias are thought to be due to congenital defects or absence of fusion of the muscle fibers in the diaphragm that is made worse by increased intra-abdominal pressure. Ninety percent are right sided because the pericardium itself prevents left-sided hernias.[78] Foramen of Morgagni hernias account for 3% to 4% of diaphragmatic hernias requiring surgery in both adults and children. Patients are usually asymptomatic, but anterior mediastinal masses are found incidentally on chest radiographs. Prompt surgical repair after diagnosis is prudent to avoid incarceration or strangulation of abdominal organs. A transabdominal route is the preferred choice. Although these hernias can be repaired laparoscopically, fixation of mesh and the use of tacks require skill and discretion to gain adequate fixation anteriorly and to not injure the pericardium and heart along the left margin of the defect. Prosthetic mesh is generally required to repair the defect.

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Chapter

41

Congenital Disorders of the Esophagus

R. Cartland Burns

The purpose of this chapter is to familiarize surgeons with common congenital problems of the esophagus, to understand the embryologic events leading to formation of the defect, and to understand the surgical principles of caring for children with these anomalies. The primary congenital disorders of the esophagus are those that result from failure of formation (esophageal atresia [EA]), incomplete separation of the aerodigestive tract (tracheoesophageal fistula [TEF] and cleft), duplication, stenosis, and external compression (vascular ring).

EMBRYOLOGY AND ANATOMIC CONSIDERATIONS

Comprehension of the embryologic development of the esophagus serves to improve understanding of the congenital diseases that affect the esophagus, in addition to providing a framework to understand the essential anatomic considerations that have a bearing on important surgical principles useful for the treatment of these disorders. This topic is covered in detail elsewhere and is only briefly mentioned here.

The median ventral diverticulum (eventually forming the trachea) begins to form during the third week after conception (day 22 to 23), and the stomach forms sequentially in a posterior position. The esophagus develops from the endodermal tissue between these two structures. The trachea and esophagus elongate during the next 10 days, and separation of the two structures proceeds in a cranial direction to complete division of the esophagus and trachea by day 34 to 36. The esophagus has attained its full length by day 49 and continues to grow rapidly during the first postnatal years (Fig. 41–1).[1]

During the course of development the lumen of the esophagus becomes nearly filled with epithelial cells by the eighth week. A single lumen is restored by the process of vacuolization, perhaps mediated by regulated apoptosis as is suspected in other portions of the gastrointestinal tract.[2-4]

Sympathetic innervation is derived from mediastinal branches of the thoracic sympathetic trunk and from the celiac plexus. Parasympathetic innervation arises from the vagus nerve.[4] Vascular supply in the upper esophagus is derived from branches arising from the inferior thyroid artery, and the lower esophagus is supplied by segmental branches arising directly from the aorta.

ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

Historical Points

Esophageal and tracheoesophageal atresia has captured the fascination of the medical community since it was first described in 1670, when Durston described pure EA.[5,6] Proximal EA with distal TEF was subsequently described by Thomas Gibson in 1697.[7] Despite knowledge of the anomaly, no surgical treatment was effective until 1939, when Ladd and Leven, working independently, performed a staged approach to feeding via gastrostomy, division of the fistula, and eventual reconstruction with a skin tube created on the anterior chest wall.[5,8] Before this time, all reported attempts at correction were met with uniform mortality.[9] Subsequent work by Cameron Haight in 1941 resulted in the first successful primary repair accomplished by thoracotomy. He later modified the approach to the extrapleural route, which remains the most popular approach even today.[10,11] Recently, reports are demonstrating the feasibility of the thoracoscopic approach for the surgical management of EA-TEF.[12,13]

Development

Developmental understanding of the malformation is largely limited to animal models demonstrating the

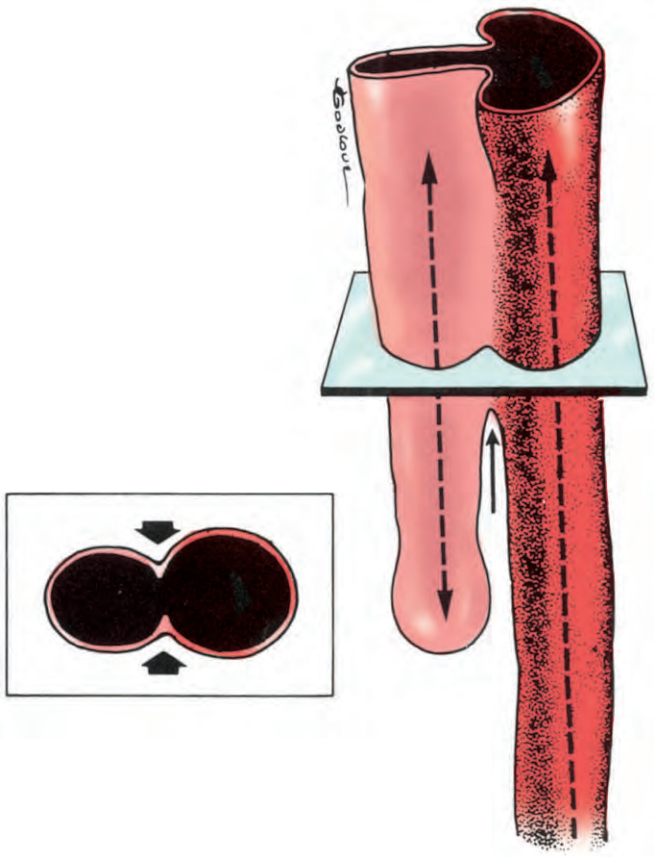

Figure 41–1. The trachea *(red)* forms as a diverticulum from the primitive foregut, and both structures elongate. Two cellular ridges form *(inset)* and divide the two structures into the trachea *(red)* and esophagus *(pink)*. This process begins at the caudal end and proceeds in a cranial direction *(arrow)*. (From Skandalakis J, Gray S: Embryology for Surgeons. 2nd ed. Baltimore, Williams & Wilkins, 1994, p 65.)

lesion. These malformations are primarily induced by exposure to the teratogen doxorubicin (Adriamycin),[14,15] and EA and foregut duplications develop in the embryo in a dose-related manner. The effect of the anthracycline antibiotic on apoptosis seems relevant to the restoration of a continuous lumen in this animal model.[16] Various candidate genes regulating these processes appear to be the HOX D group and the SHH and GLI signaling pathway, which have also been linked to anomalies in the VACTERL constellation (vertebral, anorectal, cardiac, tracheoesophageal, renal, and limb anomalies).[11]

Classification

EA and TEF occur in a predictable pattern and are categorized by anatomic variation as described by Gross in his classic textbook.[17] In this volume, Gross described six anatomic variations of the esophageal anomaly, demonstrated in Figure 41–2. Type C, proximal EA and distal TEF, is the most common and represents 85% of cases. Pure atresia (type A), though less common (6%), may present a greater surgical challenge because of inadequate esophageal length for repair. The upper pouch fistulas in types B and D may be overlooked because of attention focused on the atretic esophagus. They will subsequently be found when persistent coughing and symptoms of aspiration prompt investigation. Similarly, TEF without atresia (type E) is characterized by symptoms of gastroesophageal reflux (GER) and choking spells with feeding. Type F congenital esophageal stenosis arises from various embryologic errors and is discussed in detail later.

Associated Abnormalities

As many as 50% of children with EA or TEF (or both) will have other important anomalies.[18-24] In many cases the associated anomalies will have a greater impact on the overall prognosis for the child than the foregut anomaly. Accordingly, it is important to conduct a thorough investigation for such abnormalities. Anomalies associated with EA include those found in the VACTERL constellation of anomalies,[25,26] as well as several other less common deformities.

Holder[27] and subsequently Dunn et al.[28] reported that associated anomalies were most common in pure EA without fistula and least common in cases of H-type TEF without atresia. These anomalies involve, in order of frequency, the cardiovascular (ventricular septal defect most common), gastrointestinal (imperforate anus, duodenal and other atresia, malrotation), and genitourinary systems (hypospadias, cryptorchidism, renal malformation, urinary obstruction and exstrophies).

The CHARGE association is seen in 2% of patients with EA[29] and includes coloboma, heart defects, choanal atresia, mental retardation, genital hypoplasia, and ear anomalies.

Esophageal anomalies may be seen in patients with Down's syndrome, and in these cases one must investigate for evidence of duodenal atresia, cardiac defects, and Hirschsprung's disease.

Tracheomalacia is common in children with EA and may be mild with insignificant clinical findings or may be severe enough to result in respiratory compromise. The upper part of the trachea is the most commonly involved area and corresponds to the area adjacent to the obstructed upper pouch of the esophagus. The commonly accepted mechanism is pressure-induced malacia from the dilated upper pouch, and it is associated with a deficiency of tracheal cartilage. The tracheomalacia will typically improve in time after correction of the atresia, but it may be problematic, with stridor requiring treatment. Usual management includes careful attention to feeding, avoidance of aspiration, and evaluation for GER, which will exacerbate the condition. Tracheal suspension (aortopexy) is occasionally needed in severe cases and improves the tracheal obstruction by lifting the aorta and its attachments to the trachea anteriorly. This maneuver creates an external "stent" that relieves the obstructive symptoms.

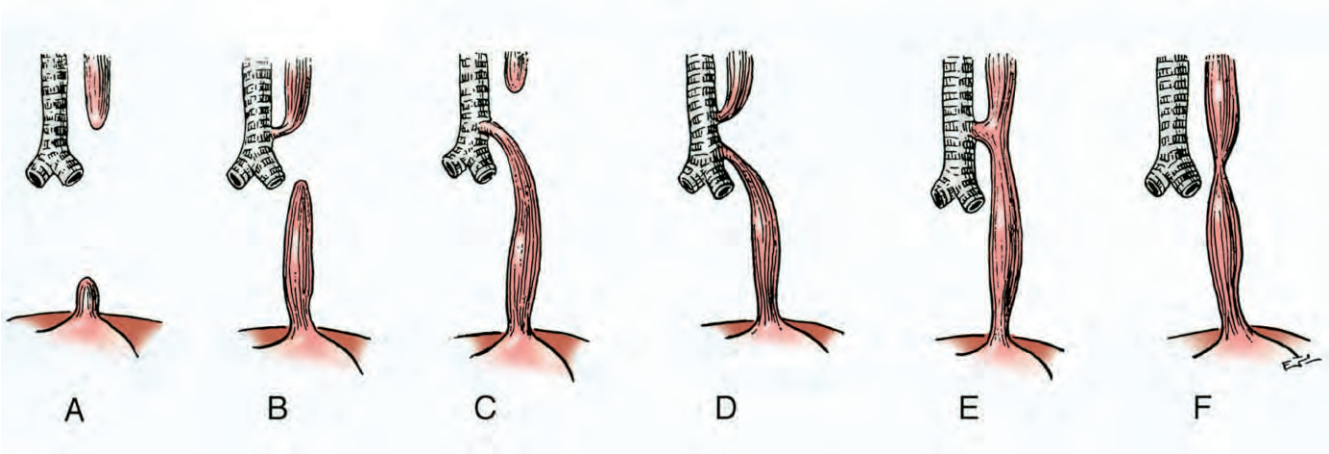

Figure 41–2. Classic stratification of the most common varieties of esophageal atresia and tracheoesophageal fistula as outlined by Robert Gross in 1953. **A,** Pure esophageal atresia without fistula, also called "long-gap" atresia. **B,** Esophageal atresia with a proximal tracheoesophageal fistula. **C,** The most common anatomic relationship of esophageal atresia and distal tracheoesophageal fistula. **D,** Esophageal atresia with both proximal and distal tracheoesophageal fistulas. This variety may be more common than once reported, and an upper pouch fistula is always suspected. **E,** Tracheoesophageal fistula without atresia. Also known as an H-type fistula, this lesion is usually high in the trachea and generally approachable through a cervical incision. **F,** Congenital esophageal stenosis. (From Gross RE: Atresia of the esophagus. In Gross RE [ed]: The Surgery of Infancy and Childhood. Philadelphia, WB Saunders, 1953, p 76.)

Clinical Findings and Diagnostic Evaluation

Prenatal diagnosis is becoming more common and more accurate.[30-32] The ultrasound findings of a dilated upper esophagus, small stomach, and polyhydramnios are all suggestive of EA. When EA is suspected in the antenatal period, it is desirable to offer the family counseling by a pediatric surgeon, neonatologist, and geneticist. These parents may wish to consider amniocentesis or chorionic villus sampling. At the very least, they can be educated about the diagnosis, associated anomalies, and treatment options and possibilities before the delivery, when the diagnosis of anomalies can be overwhelming.

The newborn's clinical symptoms are related to the anatomic findings. EA results in failure to swallow saliva, apparent marked salivation, and drooling. Attempts at feeding are accompanied by coughing, choking, and regurgitation of undigested milk or formula. These events are usually followed by the attempted passage of nasogastric or orogastric tubes, which are met with resistance and are seen to be coiled in the upper pouch on chest radiographs. Radiographs will demonstrate a gasless abdomen in patients with pure EA (Fig. 41–3) or air in the abdomen in those with atresia and TEF (Fig. 41–4). Abdominal distention may be present in children with TEF, but not with pure atresia. In patients with distal intestinal atresia (duodenal atresia, small bowel atresia, imperforate anus), the abdominal distention may be marked and can cause respiratory compromise. Isolated TEF is associated with coughing, choking, and apparent aspiration episodes with every feeding.

Diagnostic evaluation should give consideration to confirmation of the presence of EA, which may be as simple as an inability to pass an orogastric tube with the tip coiled in the upper pouch. A plain radiograph will confirm this location, demonstrate the presence or absence of air in the intestine, and identify vertebral anomalies. Barium may be instilled into the upper pouch (diluted, 1 ml) to confirm the diagnosis, but it is not frequently necessary. This study may demonstrate an upper pouch fistula, although it has been shown to have a significant rate of inaccuracy, and a great deal of care is required to avoid aspiration through the larynx and resultant soiling of the lungs. Because associated anomalies are common, preoperative studies should include a thorough physical examination, echocardiogram, and renal ultrasound. Chromosome analysis may be considered if not completed in the prenatal period.

Management Considerations

The presence of EA or TEF is not a surgical emergency, but it does require diligence in protection of the infant's lungs because tracheobronchial aspiration is common and can contribute to significant pulmonary complications, including pneumonitis. Aspiration of saliva can occur via the larynx or aspiration of gastric contents via the distal TEF. The upper pouch saliva is suctioned with an orogastric sump tube to clear secretions. The oral route is preferred because infants are obligate nasal breathers and the nasal route risks compromising the airway. Gastric reflux through the distal TEF is reduced by maintaining the infant in an upright, preferably prone position. Spontaneous ventilation is preferred to prevent continuous gaseous distention of the stomach. On occasions when intubation and mechanical ventilation are required, low inspiratory pressures are preferred. These and all surgical neonates require 10% dextrose solutions to prevent hypoglycemia, as well as careful attention to

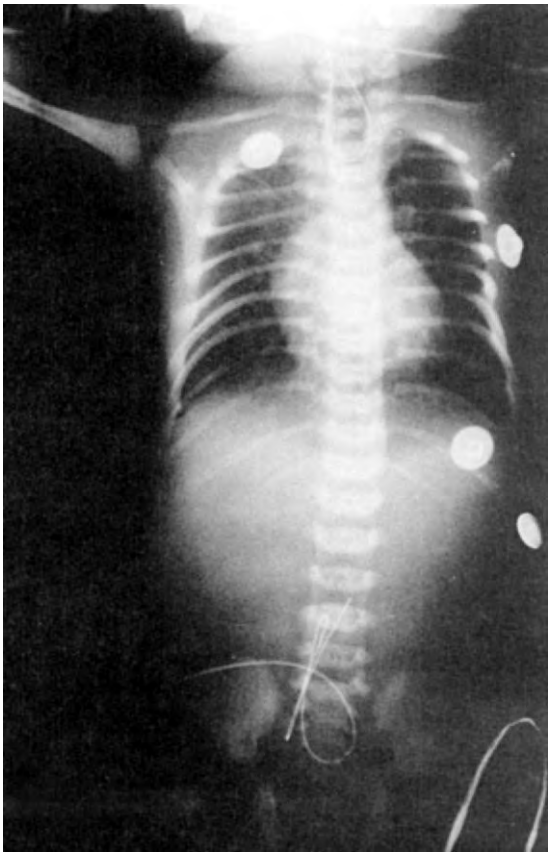

Figure 41–3. Typical radiograph in an infant with esophageal atresia demonstrating the orogastric tube coiled in the atretic proximal esophagus without a patent tracheoesophageal fistula as shown by the gasless abdomen. (From Ashcraft KW, Murphy JP, Sharp RJ, et al [eds]: Pediatric Surgery, 3rd ed. Philadelphia, WB Saunders, 2000, p 353.)

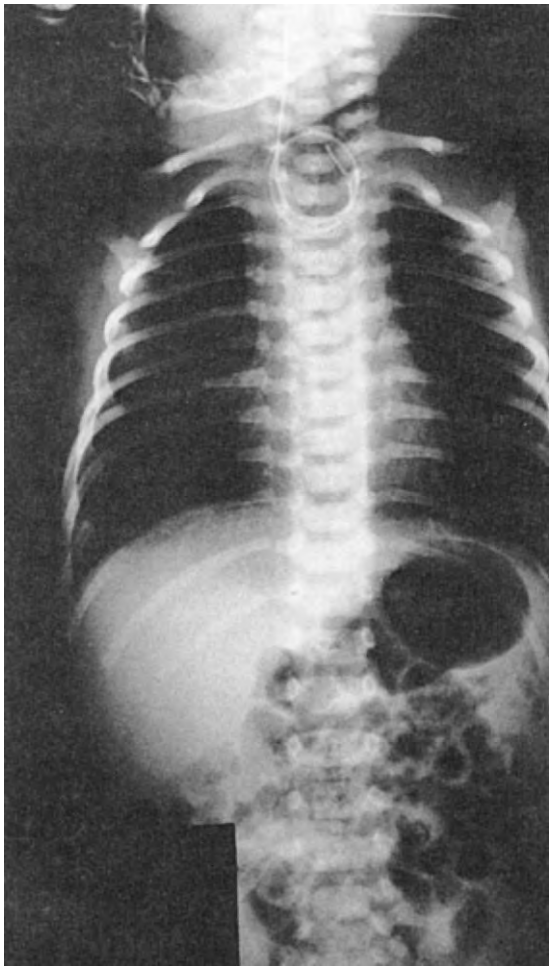

Figure 41–4. Radiograph illustrating esophageal atresia with the orogastric tube coiled in the atretic upper esophageal pouch. Air in the bowel indicates a distal tracheoesophageal fistula. This radiograph does not exclude the presence of the upper pouch fistula seen in type B. (From Ashcraft KW, Murphy JP, Sharp RJ, et al [eds]: Pediatric Surgery, 3rd ed. Philadelphia, WB Saunders, 2000, p 353.)

maintenance of electrolyte balance. Perioperative broad-spectrum antibiotics are instituted as well. In some instances, children with long-gap atresia have been allowed to be cared for at home before definitive repair, which may be delayed for months after birth.[33-35]

Preoperative evaluation will allow identification of pertinent associated anomalies, some of which will adversely affect the outcome of an infant with EA. Historically, Waterston's criteria were used to separate infants into risk groups based on prematurity and associated anomalies.[36] This classification scheme was highly relevant when it was developed; however, modern surgical and neonatal care has shifted focus to alternative considerations in perioperative planning. Several recent studies have shown that physiologic status, specifically respiratory status and life-threatening anomalies, are the primary prognostic factors in the current treatment of EA and TEF.[37-39] With these guidelines, current success rates in children without life-threatening associated anomalies and with good respiratory function approach 100% with primary division of TEF and repair of EA. In children with associated cardiac anomalies and low birth weight (<1500 g), perioperative risk is much greater, with only a 22% survival rate.[40]

Operative Management

Proximal EA with distal TEF is usually managed by primary division of the fistula and repair of the atretic esophagus. Division of the TEF allows more controlled ventilation and prevents further soiling of the tracheobronchial tree, whereas repair of the EA reconstitutes gastrointestinal tract continuity. Many surgeons prefer rigid bronchoscopy at the outset of the proposed repair of the anomaly to assess for the presence of a proximal pouch fistula. The operative strategy is coordinated with the anesthesiologist, and a right thoracotomy is preferred in the usual case of a left-sided aortic arch. Either left main stem intubation or low-volume ventilation is helpful for posterior mediastinal exposure. The child is placed in the decubitus position, and a muscle-sparing thoracotomy is performed in the fourth or fifth intercostal space. The latissimus dorsi and serratus anterior muscles are mobilized off the chest wall, and the intercostal space is identified. The intercostal muscle is

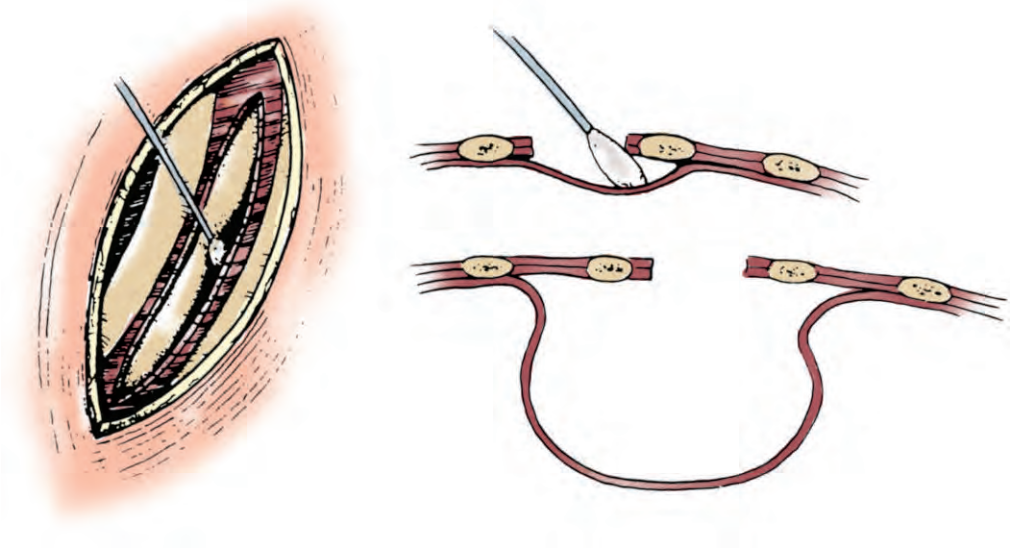

Figure 41–5. After dividing the intercostal muscles, the parietal pleura is encountered and protected. By gentle dissection, the parietal pleura is separated from the chest wall and a retropleural plane is developed. The retropleural plane allows easy control of the ipsilateral lung during dissection and prevents intrapleural soiling in the event of an anastomotic leak.

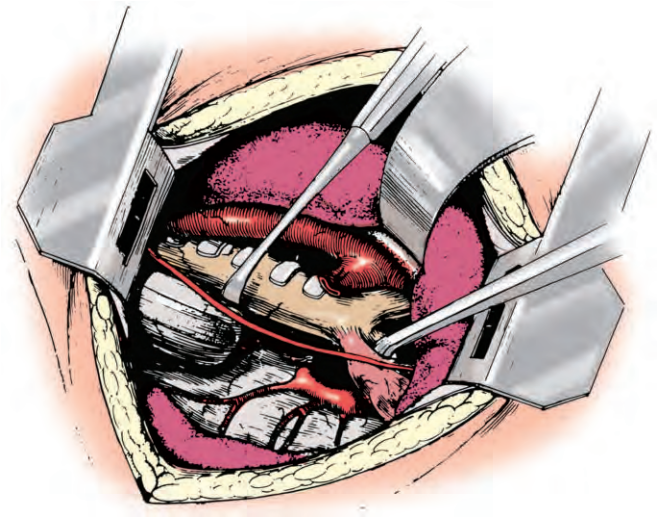

Figure 41–6. The azygos vein is identified and divided near its junction with the superior vena cava. The location of the azygos vein directs the surgeon to the region of the tracheal carina, where a distal tracheoesophageal fistula is usually found. The tracheal anatomy is carefully confirmed to avoid erroneous division of a bronchus.

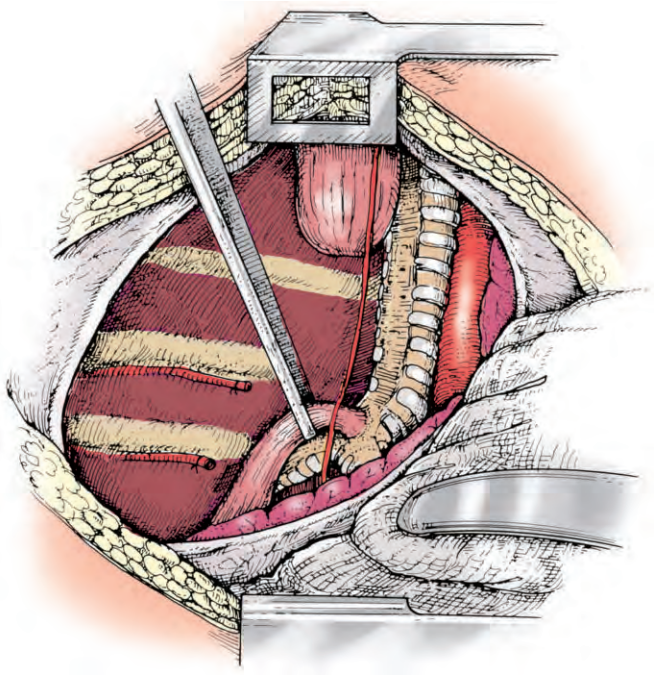

Figure 41–7. The tracheoesophageal fistula is dissected to allow control of the fistula near the trachea. A vessel loop allows traction on the fistula, which will immediately improve ventilation. The vagus nerve (if found) is carefully preserved. (From Ashcraft KW: Atlas of Pediatric Surgery. Philadelphia, WB Saunders, 1994, p 40.)

divided with care to avoid pleural violation. A retropleural dissection is conducted carefully to mobilize nearly the entire lateral and posterior aspect of the chest (Fig. 41–5). The azygos vein is encountered and divided between ligatures (Fig. 41–6). The distal TEF can be identified at this point and is usually distended with air at each inspiration. The distal portion of the esophagus is dissected circumferentially at the level of the fistula and encircled with a vessel loop (Fig. 41–7). At this point the surgeon can occlude the fistula and the anesthesiologist will confirm adequate (usually improved) ventilation. The fistula is divided with absorbable monofilament sutures on the trachea while taking care to not deprive the trachea of an adequate lumen nor retain an esophageal remnant as a tracheal diverticulum (Fig. 41–8). The distal esophagus is controlled with a fine suture, and attention is turned to locating and mobilizing the proximal esophagus. The proximal esophagus is mobilized as widely as possible to allow a tension-free anastomosis (Fig. 41–9). Mobilization of the distal esophagus has traditionally been discouraged, although recent

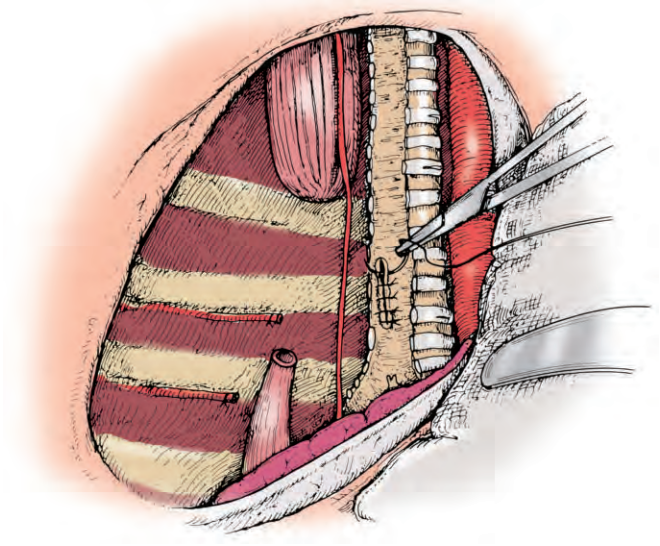

Figure 41–8. The tracheoesophageal fistula is divided at the junction with the trachea by sequential transection and suture repair of the trachea. This is performed sequentially to avoid the development of a large air leak complicating ventilation. The trachea is repaired with absorbable monofilament sutures to avoid narrowing the trachea or preserving a tracheal diverticulum. (From Ashcraft KW: Atlas of Pediatric Surgery. Philadelphia, WB Saunders, 1994, p 41.)

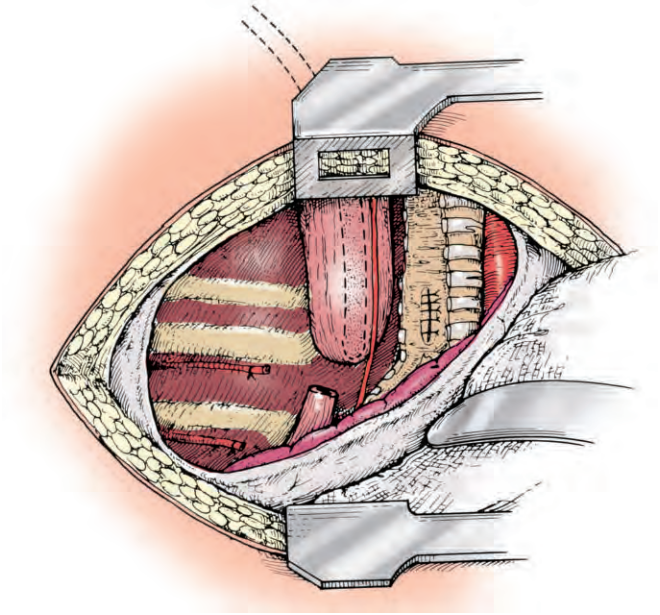

Figure 41–9. The upper pouch is mobilized with the assistance of the anesthesiologist by placing an orogastric tube into the upper pouch and distending the upper part of the esophagus. The two ends of the esophagus are assessed for feasibility of primary anastomosis. (From Ashcraft KW: Atlas of Pediatric Surgery. Philadelphia, WB Saunders, 1994, p 41.)

reports indicate that distal mobilization can be performed safely.[41] End-to-end anastomosis is accomplished with interrupted absorbable sutures (Fig. 41–10). A transanastomotic nasogastric or orogastric tube may or may not be placed at this time, depending on surgeon preference. A retropleural drain is generally used to control possible anastomotic leaks.

Primary repair of both deformities is ideal; however, in children with significant risk factors, division of the fistula may be undertaken as a primary procedure and gastrostomy performed for access to the distal gastrointestinal tract for nutritional management. In this case, the distal esophagus is secured to the prevertebral fascia to prevent retraction and to aid in identifying this structure at subsequent reconstruction.

Pure EA is frequently associated with a long gap between the proximal and distal atretic segments. The gap may prohibit primary repair of the deformity, and such children are usually managed with an initial gastrostomy for enteral feeding access.[42] Delayed repair is then planned, with consideration for mobilization of both the proximal and distal segments. The literature is replete with descriptions of innovative techniques and operative strategies for the management of patients with long-gap EA, thus bearing witness to the fact that it presents a true surgical challenge. Several techniques have been proposed for increasing the length of the proximal esophagus, such as bougienage[43] or intraoperative myotomy of either the upper pouch, the lower pouch, or both.[44-49] Some authors have reported success with creation of a fistula between the proximal and distal

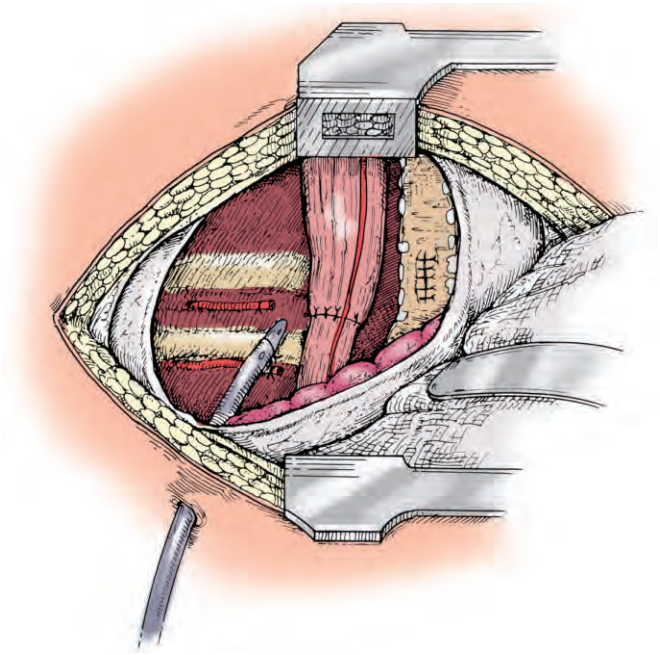

Figure 41–10. A primary repair is achieved with an accurate single-layer anastomosis created with interrupted, absorbable sutures. The posterior row of sutures is preplaced and then tied with the assistant holding traction to release tension from the anastomosis. The anterior row of sutures is then placed and tied. A tube thoracostomy is placed near the anastomosis to control a possible anastomotic leak. Some prefer to suture the tube in place with fast-absorbing suture. (From Ashcraft KW: Atlas of Pediatric Surgery. Philadelphia, WB Saunders, 1994, p 43.)

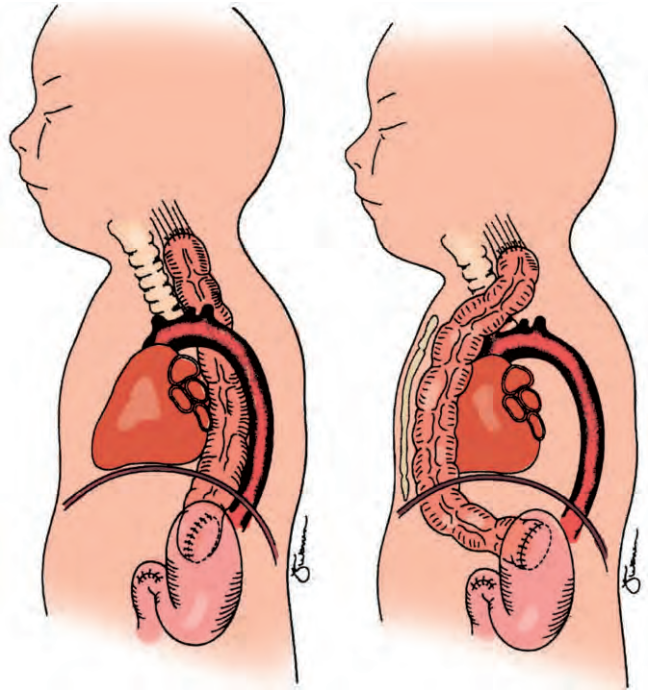

Figure 41–11. Colonic interposition has been used successfully as a replacement esophageal conduit and is shown in the substernal position, as well as in the preferred native esophageal position in the posterior mediastinum. (From Dillon PA: Esophagus. In Oldham KT, Colombani PM, Foglia RP, et al [eds]: Principles and Practice of Pediatric Surgery, vol 2. Philadelphia, Lippincott, Williams, & Wilkins, 2005, p 1034.)

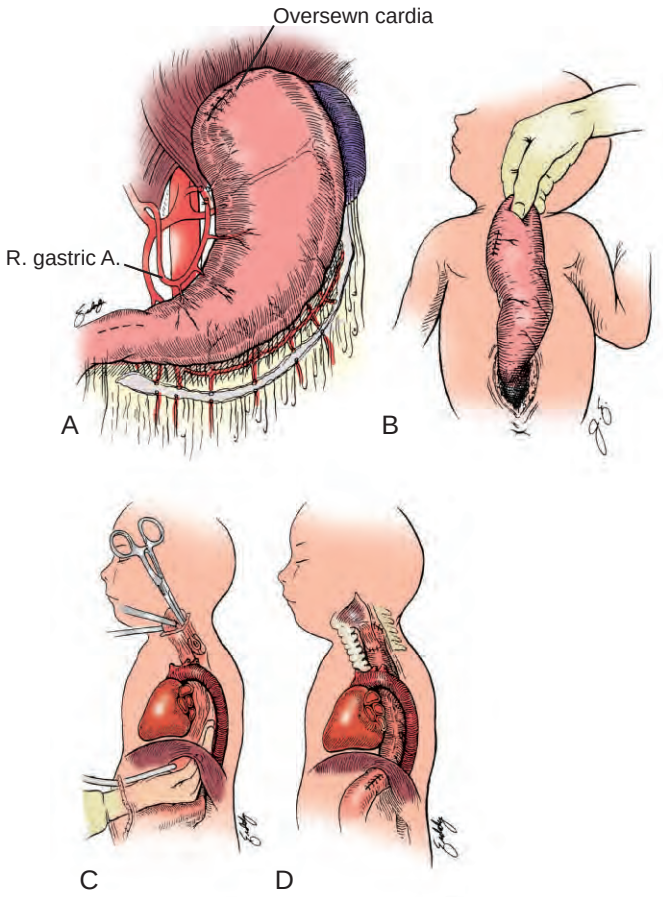

Figure 41–12. **A** to **D,** Gastric transposition has been used to replace the missing esophagus and, with extensive mobilization, will reach into the neck. The vagus nerves are sacrificed, thus necessitating pyloroplasty. (From Dillon PA: Esophagus. In Oldham KT, Colombani PM, Foglia RP, et al [eds]: Principles and Practice of Pediatric Surgery, vol 2. Philadelphia, Lippincott, Williams, & Wilkins, 2005, p 1035.)

ends of the esophagus and subsequently dilating the tract.[50] Recently, several reports have demonstrated success with the technique of mobilizing the proximal and distal esophagus, followed by placement of external sutures tethering the ends to a button. The button is subsequently tightened to produce tension on the esophagus and stretch the atretic segments into proximity, followed by primary anastomosis.[51-54] Still other authors have promoted primary repair of the atretic segments regardless of the amount of tension on the anastomosis.[55,56] The multiplicity of techniques and reports supports the conventional wisdom that the native esophagus remains the preferred conduit for the thoracic gastrointestinal tract; however, the occasion does arise in which replacement is required. In such cases the literature describes acceptable outcomes with the interposition of colon (Fig. 41–11), small bowel, or gastric conduit (Figs. 41–12 and 41–13).[57-64]

Recent reports have described thoracoscopic repair of EA and TEF.[12,13,65] The procedure has been proved to be safe and effective, but it requires a specialized unit with a dedicated endoscopic surgical team. The occasional laparoscopist will find the procedure tedious and will probably not reproduce the current excellent outcomes offered by the open procedure.

Complications

Complications associated with repair of EA and TEF can be considered to be either perioperative or late in nature. Perioperative complications are limited primarily to anastomotic leak or disruption. This complication occurs in approximately 15% of patients and usually responds (95%) to simple drainage, which is generally established at the time of anastomosis.[66-68] The development of an anastomotic leak is usually due to inaccurate surgical technique, poor perfusion, or excessive tension on the anastomosis. These factors can generally be avoided, but in some cases they are inevitable and a leak will occur. An anastomotic leak is diagnosed by detecting the presence of pneumothorax or pleural effusion in the first 24 to 48 hours postoperatively or by a leak on an esophagogram performed routinely at 5 to 7 days postoperatively before instituting enteral feeding. The principles of management of an anastomotic leak include adequate drainage and nutritional repletion with parenteral nutrition. These children are maintained

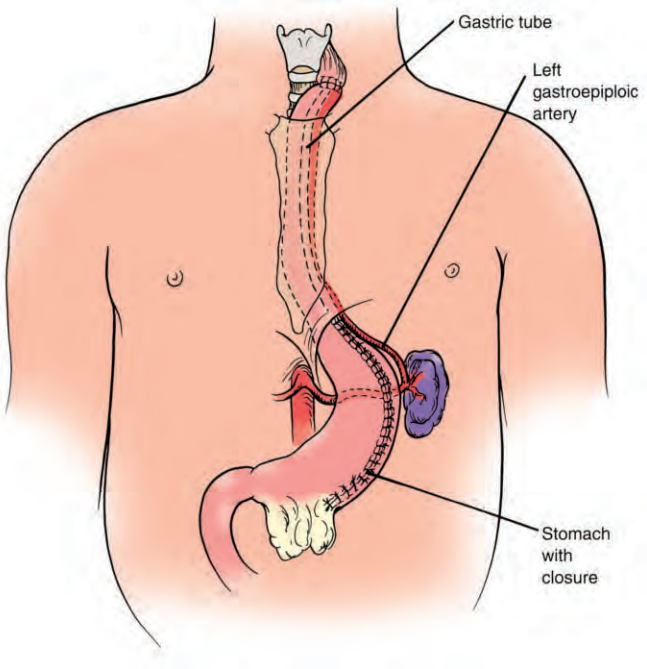

Figure 41–13. The reversed gastric tube can be fashioned from the greater curvature of the stomach and may be mobilized to reach the upper pouch in the neck. (From Dillon PA: Esophagus. In Oldham KT, Colombani PM, Foglia RP, et al [eds]: Principles and Practice of Pediatric Surgery, vol 2. Philadelphia, Lippincott, Williams, & Wilkins, 2005, p 1036.)

on antibiotics for the duration of the leak. Even large leaks are successfully managed with conservative techniques and rarely require a reoperation.

Later complications include anastomotic stricture, which in many cases is a secondary complication after an anastomotic leak. Stricture may also occur as a result of GER, and a stricture that does not respond rapidly to treatment should alert the surgeon to consider treatment of GER by fundoplication.[69] The incidence of stricture is reported to be as high as 40%.[70] An anastomotic stricture is suspected when there is impaction of food, feeding intolerance, or dysphagia. The diagnosis is confirmed by either esophagography or esophagoscopy, which may also be therapeutic. Treatment consists of dilation, and the type of dilator is based on surgeon preference. Dilators include those passed antegrade, such as a Maloney- or Savary-type bougie. Pneumatic dilation is also available and may offer the advantage of fluoroscopic guidance; when the balloon is filled with contrast material, it provides a dynamic view of the stricture and dilation.[70] If dilation is unsuccessful, the surgeon should consider the possibility of GER being a contributing factor, and contrast studies and pH monitoring should be performed before considering local resection and anastomosis.

Recurrent TEF usually occurs in association with an anastomotic leak (approximately 10%)[71-73] and is probably related to local inflammation and poor healing of the primary lesion. A high index of suspicion is needed to identify a recurrent TEF because the symptoms may be nonspecific. These children generally have symptoms of coughing, choking, and feeding intolerance. Recurrent pneumonia is also seen with recurrent TEF. If suspected, the diagnosis is pursued by contrast esophagography, esophagoscopy, and bronchoscopy. Once the diagnosis is confirmed, treatment options must be considered. Options for the management of recurrent TEF include repeat thoracotomy for very early recurrence. The operative management of this lesion should include repeat division of the fistula, repair of the esophagus and trachea, and placement of tissue between the two structures. The choice of tissue is variable and has included an intercostal muscle flap, pleural flap, pericardium, and azygos vein. Recent innovative techniques have been described and include cauterization, fibrin glue, and histoacryl glue.[72,74-79]

Tracheomalacia is commonly associated with EA and TEF and may result in respiratory symptoms, including expiratory stridor or a barking-type cough.[80] These children may have symptoms ranging from noisy breathing to apneic spells leading to life-threatening events. The trachea lacks its normal rigidity because of one of several causes, and this allows the trachea to collapse under the positive pressure of expiration or straining. The traditional wisdom regarding tracheomalacia associated with EA and TEF holds that the dilated upper pouch of the esophagus exerts pressure on the posterior wall of the trachea and causes the trachea to be easily deformable.[81,82] Further information has found a high incidence of primary tracheal defects in patients with EA/TEF and thus raises support for consideration of tracheomalacia as a primary airway defect.[83] Suspicion of tracheomalacia can be confirmed by bronchoscopy with spontaneous ventilation (Fig. 41–14) or by radiographic means.[84-87] Although most children with tracheomalacia will improve with time, those with severe manifestations require intervention. The primary form of treatment is aortopexy to achieve elevation of the vascular structures anteriorly for relief of pressure on the trachea. This can be accomplished by direct suturing (Figs. 41–15 and 41–16), a pericardial sling, or more recently, thoracoscopic techniques.[88-92] Occasionally, a child will fail to respond to vascular suspension and will require a tracheostomy, and tracheal stenting has been used with limited success.[93-95]

ESOPHAGEAL DUPLICATION

Esophageal duplication cysts represent anomalous structures arising from the primitive foregut and are frequently described as dorsal enteric remnants.[96] These remnants arise from the foregut early during development and may be found as cystic structures in the superior mediastinum or more commonly in the posterior mediastinum. The cyst may be lined with any type of epithelium found in the foregut structures, including ciliated respiratory epithelium and enteric (commonly gastric) mucosa.[97-100] The gastric mucosal remnants may secrete acid and cause the cyst to erode into adjacent structures. Most commonly, these cysts do not communicate with the lumen of the esophagus, although mus-

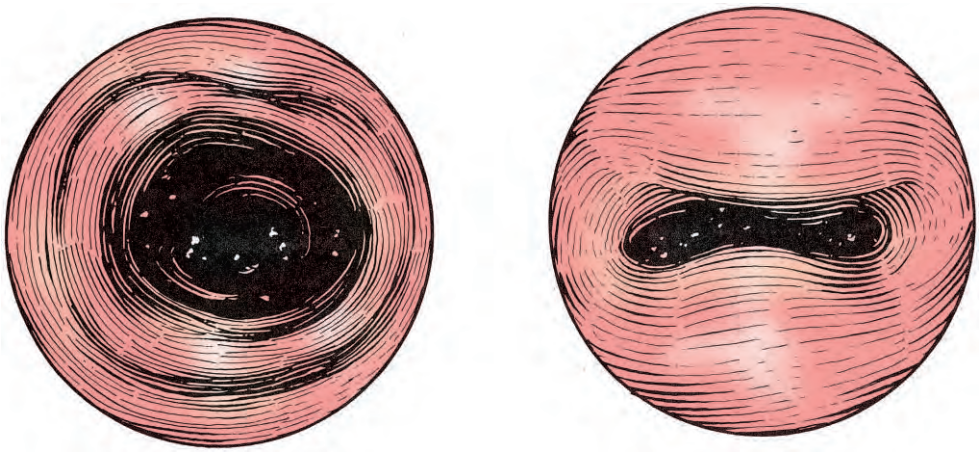

Figure 41–14. Bronchoscopic evaluation of a patient with tracheomalacia reveals a compromised lumen; this is demonstrated during spontaneous ventilation as positive pressure holds the lumen in a distended position and may lead to error in diagnosis. Insufficient tracheal rings may be identified as well. Some prefer to complete the aortopexy under bronchoscopic guidance to confirm correction of the compression. (From Rob and Smith's Operative Surgery: Pediatric Surgery, 4th ed. Boston, Butterworth, 1988, p 126.)

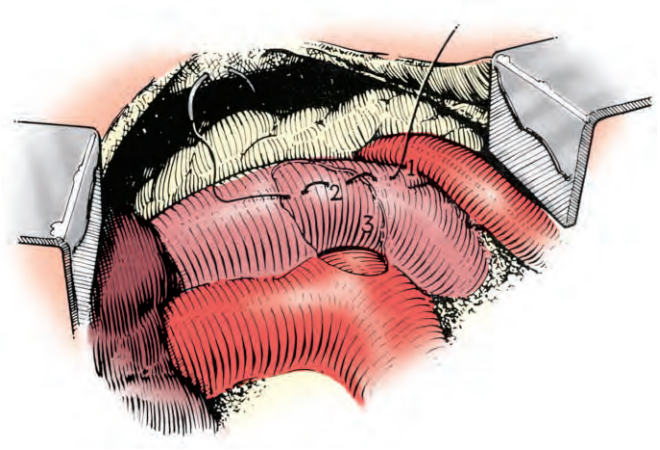

Figure 41–15. The aorta is mobilized anteriorly through the pericardium, and usually three sutures are placed partial thickness into the aorta. Care is taken to avoid dissection of the tissues between the vascular structures and the trachea because these fibrous attachments are necessary to create the lift or external stenting of the trachea. (From Rob and Smith's Operative Surgery: Pediatric Surgery, 4th ed. Boston, Butterworth, 1988, p 129.)

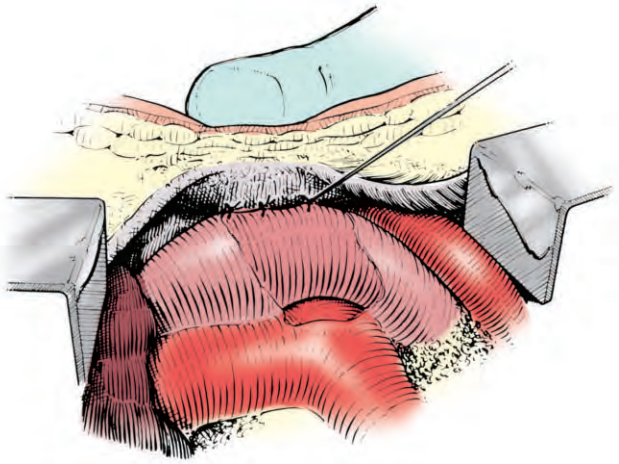

Figure 41–16. The sutures are tied to complete the aortopexy. The aorta is approximated to the posterior of the sternum. This is usually accomplished while the assistant is depressing the sternum to avoid excessive traction on any of the aortic sutures. (From Rob and Smith's Operative Surgery: Pediatric Surgery, 4th ed. Boston, Butterworth, 1988, p 129.)

cularis mucosae may be shared. A cleavage plane usually exists between the two structures.

These abnormalities are associated with vertebral anomalies in as many as 50% of cases, and there is nearly a 50% incidence of associated additional intestinal duplications. In some cases the lesion will cross the diaphragm, and a cyst manifested as a thoracic duplication will be originating from below the diaphragm.[101] Additionally, the cyst may be associated with a vertebral anomaly, with extension into the spinal canal, and it is then termed a neurenteric cyst.[102] Because the preoperative evaluation usually focuses on the chest, the surgeon must remain vigilant about the possibility of transdiaphragm extension.[96,97,102]

Symptoms attributed to these lesions depend on the size of the cyst and the pressure of the mass on surrounding structures.[103] Such symptoms usually include airway irritation (cough, dyspnea), failure to thrive, or esophageal symptoms (dysphagia, chest pain). Cysts containing gastric mucosa may give rise to hemorrhage or perforation as a result of ulceration. Occasionally, the gastric mucosa will cause erosions into the lung, bronchi, or esophagus. In these cases, pulmonary hemorrhage or hematemesis may develop.[104]

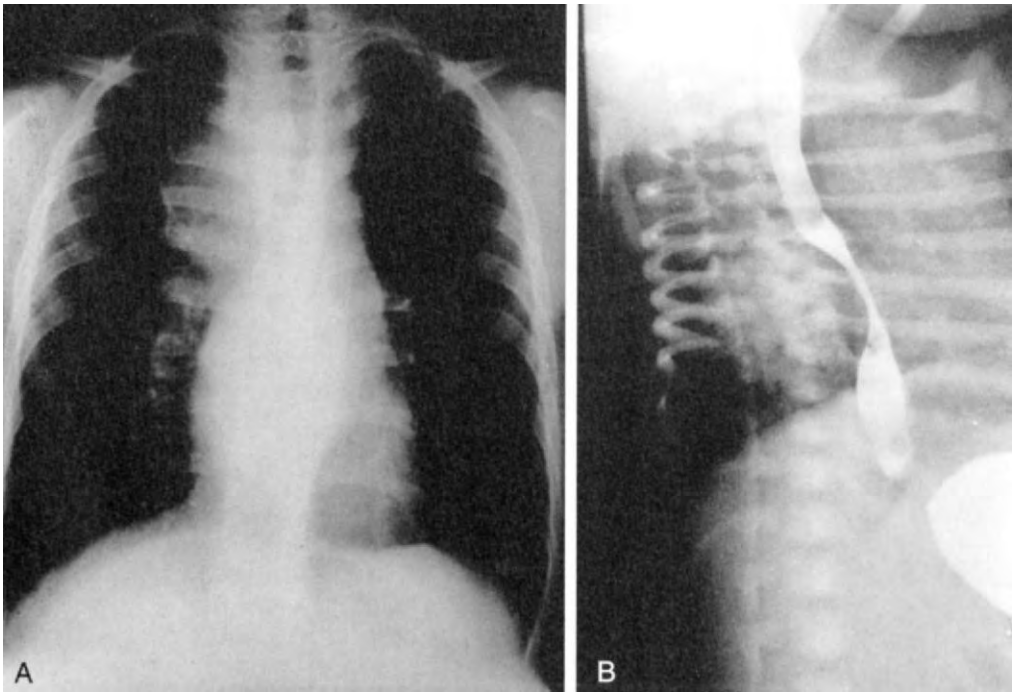

Figure 41–17. A child with vague respiratory symptoms or solid food dysphagia is found to have a mediastinal mass on a plain chest radiograph **(A).** The esophagus is deformed by the mass as seen on the contrast study **(B).** (From Ashcraft KW, Murphy JP, Sharp RJ, et al [eds]: Pediatric Surgery, 3rd ed. Philadelphia, WB Saunders, 2000, p 320.)

Evaluation

Duplication cysts are generally found on plain radiographs as part of the evaluation for vague respiratory or esophageal symptoms. Physical examination findings are rarely specific, and radiographs show a clearly defined spherical or ovoid mass in the mediastinum. Esophagography is usually performed and reveals a deformation of the esophagus caused by the cyst in proximity to the esophagus (Fig. 41–17). Computed tomography or magnetic resonance imaging further defines the lesion and allows preoperative planning.[105-111]

Treatment

The preferred management of thoracic enteric duplications is excision (Fig. 41–18). The approach is usually transpleural and can be safely accomplished by thoracotomy, as described for the treatment of EA, or by thoracoscopic techniques for surgeons accustomed to advanced thoracoscopy.[106,112] The principles of surgical therapy for these cysts demand complete excision to avoid the complication of retained gastric mucosa leading to further erosion. When the muscularis is inseparable from the esophagus, it may be allowed to remain; however, the entire mucosa must be excised. During dissection, one may find that erosion is present and the mass may be densely adherent or eroded into surrounding lung parenchyma or bronchial structures. Rarely, this will necessitate pulmonary lobectomy to complete the resection. As mentioned earlier, lesions with transdiaphragm extension are usually amputated in the chest, and the abdominal portion is dealt with separately.

CONGENITAL ESOPHAGEAL STENOSIS

Congenital esophageal stenosis (CES) caused by a developmental defect is a rare disorder and occurs in only 1 per 25,000 to 50,000 live births. The deformity is associated with other anomalies in nearly a quarter of patients, including primarily EA or TEF, anorectal malformations, hypospadias, and craniofacial malformations.[113,114]

True CES is not associated with GER and is a developmental defect categorized into one of three types.[115]

A *tracheobronchial remnant* (TBR) is the most common type of CES and results from errors in separation of the enteric and respiratory foregut structures during early fetal development (fourth week of gestation).[116] Respiratory remnants are retained in the esophagus and are usually manifested as a cartilaginous rest causing obstruction of the esophagus. These lesions are most commonly found in the distal third of the esophagus and result in dysphagia or feeding intolerance. The occurrence of TBR in association with EA is well described, and such remnants are usually found in the distal end of the esophagus.[117,118]

Idiopathic fibromuscular hypertrophy (FMH) or stenosis is nearly as common as TBR and develops as a result of hypertrophy of submucosal muscle and fibrous tissue. The overlying mucosa is normal. The cause of FMH is unclear, and it has been compared with the findings associated with pyloric stenosis, although there is no clear relationship. This lesion usually occurs in the middle third of the esophagus and again is characterized by dysphagia and feeding intolerance. FMH may involve a short segment of stenosis or may extend as long as 4 cm and result in an hourglass shape on contrast esophagography.

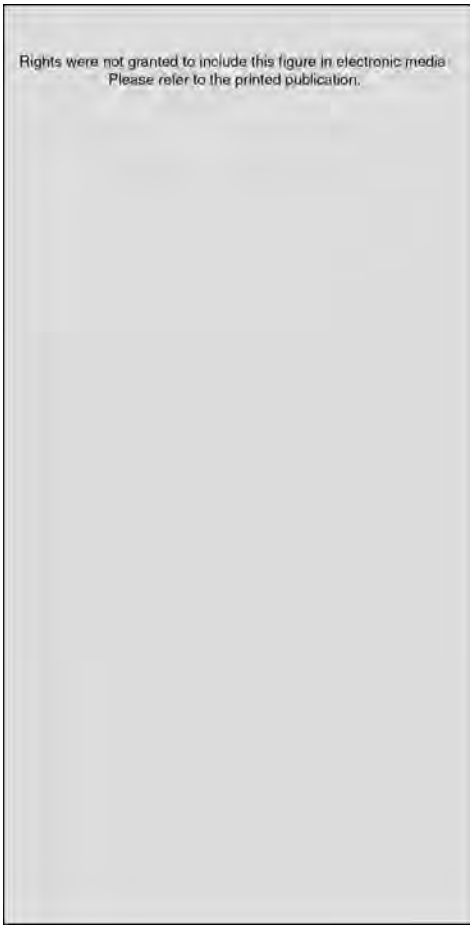

Figure 41–18. A duplication cyst arises from the muscular wall of the esophagus and rarely communicates with the lumen of the esophagus **(A).** The cyst is mobilized from the esophagus, with the esophageal mucosa left intact. If necessary, only the mucosal lining of the cyst is removed to avoid entry into the lumen of the esophagus **(B** and **C).** The muscular remnants are closed over the esophageal defect to prevent perforation or the development of a diverticulum **(D).** (From Raffensperger JG, ed: Swenson's Pediatric Surgery, 5th ed. Norwalk, CT, Appleton & Lange, 1990.)

A *congenital membranous web (CMW) or diaphragm* occurs less frequently and may represent an incomplete form of EA. This lesion occurs in the middle third of the esophagus and appears as a short segment of incomplete obstruction. The web is generally found when children begin to take solid foods at approximately 6 months of age because the web usually allows the passage of liquids.

Diagnostic evaluation of CES is important because the three varieties of this anomaly require different forms of therapy. A child with feeding intolerance should undergo contrast esophagography, which will demonstrate narrowing of the esophagus. The character of the narrowing is helpful in determining the type of obstruction. Both FMH and CMW usually occur in the middle third of the esophagus, and TBR is most common in the distal third. FMH may be a longer narrowing with an hourglass impression, whereas CMW is narrow with a small opening in the web that is usually eccentric. TBR will be seen as a short-segment stenosis in the lower esophagus. If esophagoscopy is performed, the TBR will be found to be an unyielding distal obstruction, whereas FMH will usually permit passage of the esophagoscope. CMW will be seen as a mucosal-lined obstruction with a small pinhole opening.[113,119,120] Recently, ultrasound has been used for the evaluation of CES and may provide some useful information in differentiating the type of CES.[121]

Treatment options usually begin with attempts at dilation with either bougie dilators or pneumatic dilators, depending on surgeon preference. Several reports have demonstrated successful results with dilation alone for FMH, and this is generally the therapy of choice. The risk of perforation appears low, and although dilation may be repeated on several occasions, the outcome is usually good. CMW has been treated with dilation as well; however, resection or division of the web is much more likely to be needed to achieve good functional results. The web may be divided or ablated endoscopically, thus avoiding thoracotomy. TBR does not respond well to dilation, and although it is safe to attempt dilation, this course of treatment is rarely successful. Because TBR is usually a short-segment obstruction, it is generally amenable to resection and anastomosis, although there are reports of enucleation of the cartilaginous bar without esophageal resection. TBR may be located very near the lower esophageal sphincter, and resection may therefore interfere with its function. In these cases, consideration should be given to antireflux procedures.[113,122-124]

The outcome of CES is generally very good, although associated anomalies have an impact, as do chromosomal defects.

VASCULAR COMPRESSION

Compression of the esophagus can be caused by aberrant vascular structures commonly referred to as vascular rings. These anomalies are usually related to a double aortic arch encircling both the trachea and esophagus (Fig. 41–19), a right aortic arch and ligamentum arteriosum encircling both the trachea and esophagus, or an aberrant right subclavian artery arising from the left and passing behind either the trachea or esophagus (Fig. 41–20). In each anomaly, the aberrant vascular structure compresses the esophagus and thereby results in dyspahgia.[125-127]

The diagnosis is based on historical factors and imaging studies. The symptoms are primarily related to dysphagia, especially when starting solid foods, or they may be associated with tracheal compression manifested by inspiratory stridor or recurrent pneumonia. The site of compression is at the level of the aortic arch, and contrast esophagography shows a winding or steeply angled compression in the case of an aberrant subclavian artery. This lesion can be differentiated from CES by contrast esophagography, echocardiography, or more recently, magnetic resonance angiography.[128-130]

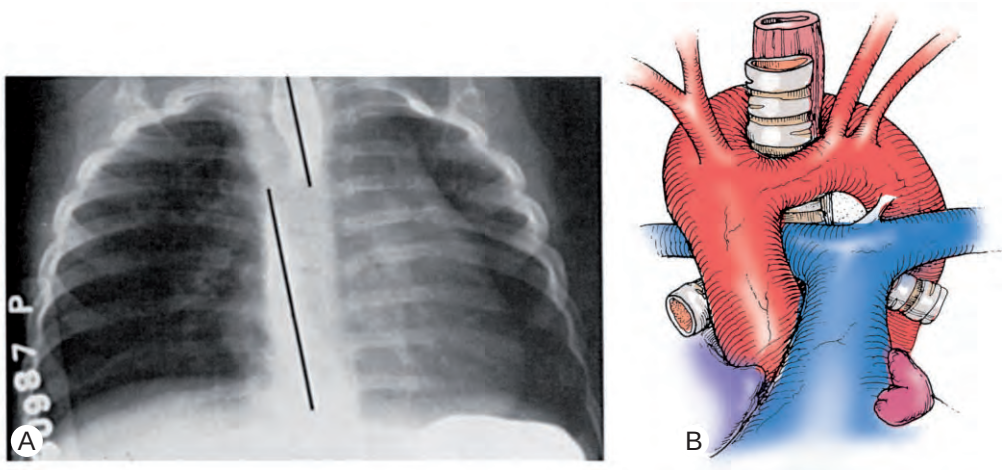

Figure 41–19. Vascular compression of the esophagus is seen on a contrast esophagogram as an angulated obstruction **(A).** The anatomic relationships of the double aortic arch depict the cause of esophageal obstruction, as seen in **B.** (From Ashcraft KW, Murphy JP, Sharp RJ, et al [eds]: Pediatric Surgery, 3rd ed. Philadelphia, WB Saunders, 2000, p 343.)

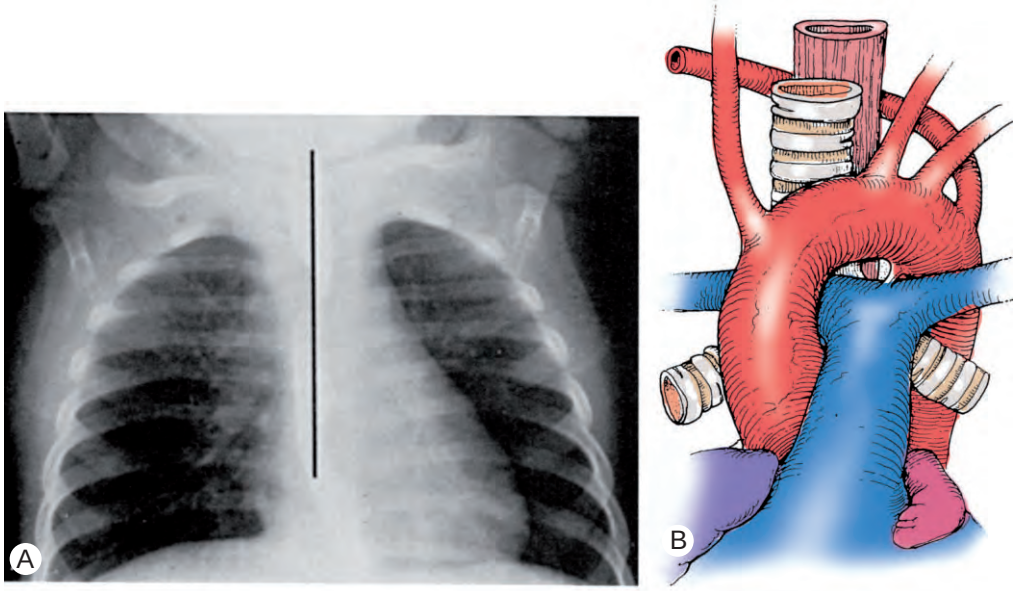

Figure 41–20. A and **B,** The anatomic relationships of an aberrant subclavian artery demonstrate the mechanism of esophageal compression resulting in solid food dysphagia. (From Ashcraft KW, Murphy JP, Sharp RJ, et al [eds]: Pediatric Surgery, 3rd ed. Philadelphia, WB Saunders, 2000, p 343.)

Treatment

Vascular compression of the esophagus is treated by division of the offending vessel through an anterolateral thoracotomy. Each anomaly is evaluated individually; however, the usual approach is to divide the smallest vessel or the aberrant vessel. In cases of double aortic arch, when the left (anterior) arch is small, the left arch is divided distal to the left subclavian artery; alternatively, in patients with a smaller right (posterior) arch, it is divided near the junction with the descending aorta. In those with equal-sized arches, the right (posterior) arch is divided. In either case the operation includes division of the ligamentum arteriosum or ductus arteriosus and lysis of the fibrous tissue between the trachea and esophagus to release the constriction around the esophagus.

In cases of persistent right aortic arch with left ligamentum arteriosum, the approach includes division of the ligamentum arteriosum and lysis of the fibrous tissue surrounding the esophagus and trachea.

An aberrant right subclavian artery causing symptoms of dysphagia should be divided at its origin from the aorta, and it can usually be approached through a posterolateral thoracotomy, unlike the previous lesions.[125,130-134]

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Chapter

42

Techniques of Esophageal Reconstruction

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Esophageal resection and reconstruction remain a major therapeutic challenge for surgeons involved in the care of patients with benign and malignant disease of the esophagus. Despite major advances in postoperative care, operative mortality rates worldwide remain unacceptably high. Much of the operative mortality is related to the complications of anastomotic leak. "Acceptable" leak rates of 8% to 10% are still reported today. With whatever conduit is chosen, the operation requires careful planning and preparation of the patient, strict attention to technical details of the operation, and dedicated postoperative care. Resection and reconstruction are inevitable for malignant disease, but every attempt should be made to preserve the native esophagus in patients with benign disease because no esophageal substitute achieves "normal" swallowing comparable to that of the esophagus.

In the final analysis, a general thoracic surgeon must be thoroughly familiar not only with the technical aspects of various visceral esophageal substitutes but also with the appropriate selection of a particular conduit under specific circumstances. Accordingly, this chapter is intended to provide both details of surgical technique and the physiologic concepts that constitute the basis for selection of a particular organ for creation of a replacement "esophagus" (esophagoplasty).

HISTORICAL BACKGROUND

The first successful resection of the cervical esophagus was reported by Czerny in 1877.[1] Torek is credited with the first resection of the thoracic esophagus in 1913.[2] Successful resection plus intrathoracic reconstruction of the esophagus was reported by Oshawa in 1933.[3] Sweet and Churchill in 1942 reported a three-layer technique of anastomosis that gave results superior to those of many contemporary reports today.[4] Sweet's series in 1954 of 141 patients with an operative mortality rate of 15% and a leak rate of 1.4% was remarkable for its time and is still acceptable by today's standards.[5] In 1946, Ivor Lewis popularized the laparotomy and right thoracotomy approach for tumors of the middle third of the esophagus—an approach that still bears his name.[6] Mahoney and Sherman published their results of colon replacement after total esophagectomy in 1954.[7] Replacement of the distal esophagus with a short-segment colon interposition was reported in 1965 by Belsey[8] and with jejunum by Brain in 1967.[9] As recently as 1990, Muller et al. in another collective review reported that the overall operative mortality for curative and palliative resection of the esophagus was 11% and 19%, respectively.[10] Mathisen and associates reported an operative mortality rate of 2.9% and no leaks at the Massachusetts General Hospital.[11] Others have reported similar excellent results from single institutions, but it is obvious that the challenge still remains.

OPTIONS IN REPLACING THE ESOPHAGUS

Surgeons involved in the care of patients with esophageal disease should be familiar with all the conduits available for esophageal replacement. Individual circumstances may dictate the choice of substitute, or unexpected operative findings may cause a change in plan. The surgeon should be flexible enough to tailor the choice of substitute to suit the patient and the underlying disease process. Many factors dictate which option is chosen: benign or malignant disease, availability of conduit, comorbid conditions such as chronic obstructive pulmonary disease or vascular occlusive disease, steroid-dependent conditions, previous irradiation, and ultimately, the surgeon's preference. Some methods of reconstruction, such as antethoracic skin tubes or prosthetic replacements, are primarily of historical significance but should be remembered for the rare patient for whom no other option is available. Other methods, such

as the reversed gastric tube, are suitable alternatives but have never gained popularity.

The three standard visceral substitutes used for replacing the esophagus, in the order of both frequency and preference, are the stomach, colon, and jejunum.

Stomach

The liberal blood supply of the stomach makes it the most reliable organ for use in intrathoracic replacement of the esophagus. Of its five feeding arterial sources, the left gastric artery, the left gastroepiploic artery, and the short gastric arteries may be divided, with the right gastric and right gastroepiploic arteries left to supply the entire transpositioned stomach. Division of these arteries is possible because of the presence of extensive intrinsic collaterals within the gastric wall. A second reason for the reliability of the stomach in replacement of the esophagus is its size and contour, which after total division of the greater and lesser omenta and lateral peritoneal liberation of the duodenal sweep (Kocher's maneuver), permit the stomach to be brought to the neck. When maximum length is required, the true fundus of the stomach should be used for anastomosis rather than the gastroesophageal junction. Skeletonizing the lesser curve also gives added length with little ischemic risk. Moreover, use of the stomach for esophageal replacement requires only a single anastomosis, either in the chest or in the neck. Use of the stomach also allows for a portion of the omentum to be used to wrap the anastomosis. The stomach can be transposed by either the posterior mediastinal route in the bed of the native esophagus or the substernal route. The posterior mediastinal route is the preferred route in most patients.

Colon

The colon may be used for extended lengths of esophageal replacement or for bypass (i.e., when it is necessary to reach to the neck). When the left colon is selected and placed in an isoperistaltic direction, it derives its blood supply from the inferior mesenteric artery through the left colic artery. If the antiperistaltic direction is used, the midcolic artery becomes the feeding source. When shorter segments of colon are required, the transverse colon based on the middle colic artery and the splenic flexure supplied by the left colic artery are the primary options. Although the right colon can be used in some circumstances, the lack of a reliable marginal artery and its limited mobility make it an option only when others have been exhausted.

Jejunum

The jejunum is most frequently used as a short segment replacing the distal esophagus, more often in benign disease and particularly for reflux acid-peptic stricture. In these cases, the proximal jejunum is used as a short interposition graft with a segment beginning just distal to the first jejunal arterial branch from the superior mesenteric artery. In asthenic patients with a long jejunal mesentery, the jejunum may be brought to a level above the aortic arch, and in young children particularly, it may even reach all the way to the cervical level. More often, however, when such length is mandated by the lack of other available options, arterial and venous augmentation may be necessary, such as an internal mammary artery–to–jejunal artery anastomosis. For short-segment replacement of the cervical esophagus, a free *autograft* of small intestine may be used; arterial and venous anastomoses are accomplished by conventional microvascular techniques to, for example, the superior thyroid artery and the anterior facial vein.

Specific factors ultimately come into play in selection of the viscus used to replace the esophagus, including (1) availability, related to previous surgical resections; (2) anomalous anatomic variants, particularly in blood supply; (3) possible pathologic processes in the viscus under consideration; (4) technical reliability of the vascular supply necessary for appropriate anastomotic healing; and (5) always, the experience of the operating surgeon.

Throughout this discussion, emphasis is placed repeatedly on blood supply. *The first and foremost requisite for successful replacement of the esophagus is adequate circulation, both arterial input and venous drainage, in the substituting organ.* An anastomosis cannot heal by primary intention in the absence of reliable circulation in both ends to be joined.

TECHNICAL VARIABLES

In addition to selection of the viscus to be used for esophageal replacement, the surgeon has three other choices to consider when planning the ideal technical operation: (1) the surgical approach, (2) the route for replacement of the new "esophagus," and (3) the level of the anastomosis.

Placement of Incision

For distal partial esophagectomy and anastomosis below the aortic arch, there is almost general agreement on use of a left transthoracic or thoracoabdominal incision. With upward paravertebral extension and Sweet's double-rib resection (or double intercostal incisions), the left-sided approach can be extended to any level of the intrathoracic esophagus if necessary, although dissection of large carcinomas at the level of the aortic arch may pose technical challenges.

For midesophageal carcinomas, the conventional approach is use of the double incisions of Lewis: a midline laparotomy for gastric mobilization and a high right-sided posterolateral thoracotomy for esophageal dissection and execution of a high intrathoracic anastomosis. This operative approach may be extended to include a third, cervical incision to allow resection of a greater length of proximal esophageus and a cervical anastomosis as described by McKeown.[12]

Yet another surgical approach is the transhiatal esophagectomy of Orringer, in which a high midline

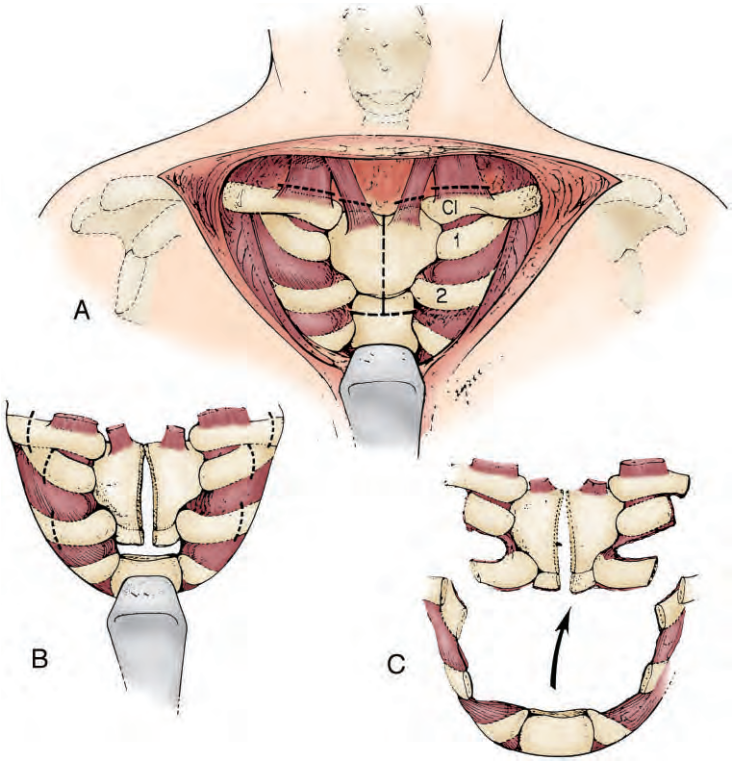

Figure 42–1. **A,** The anterior cervical skin and platysma are elevated inferiorly over the pectoral fascia, especially in the midline. The sternocleidomastoid muscle is detached from the sternal and clavicular attachments. **B** and **C,** Resection of a plate of sternum, clavicle, and the first and second ribs. Usually, the left half is all that is required to enlarge the thoracic inlet, but both sides may be needed in special circumstances.

laparotomy and transhiatal dissection are combined with a cervical incision to allow proximal esophageal dissection and performance of the anastomosis.[13] Extensive division of the hiatus allows greater visualization of the distal esophagus. Partial resection of the manubrium and the first and second ribs (Fig. 42–1) permits better visualization and dissection of the cervicothoracic esophagus in some patients. Both these techniques allow esophagectomy to be performed under direct visualization in most patients.

Finally, the rapidly advancing technology of laparoscopy has been applied to esophageal disease. Both a transhiatal technique and a method involving thoracoscopic mobilization of the esophagus have been described.[14,15] Both involve a cervical anastomosis. Initial reports have demonstrated minimally invasive esophagectomy to have outcomes similar to those of most open procedures and potentially shorter hospital stay with better quality of life. With improving instruments and advancing robotic technology, minimally invasive esophagectomy may come to occupy a more prominent role in the management of esophageal carcinoma.

Route of Replacement

Four options are available when choosing the route of replacement: (1) posterior mediastinal through the bed of the resected esophagus; (2) anterior mediastinal in the retrosternal position; (3) lateral transpleural, usually behind the lung root; and (4) the antethoracic or presternal subcutaneous route. The fourth choice has never achieved universal popularity, primarily because of cosmetic considerations.

The orthotopic posterior mediastinal route for placement of the conduit is the most widely used if the esophagus has been removed. It is the shortest and most direct route and does not require dissection and preparation of the second port of access.

The retrosternal route is used most commonly for bypass of the esophagus when it has been decided, because of tumor unresectability, condition of the patient, or staging, to not resect the esophagus. This choice may require enlarging the thoracic inlet by resecting the head of the clavicle and the anterior end of the first rib to ensure adequacy of room for the replacement and to be certain that there is no compression of the essential vascular supply (see Fig. 42–1). The retrosternal route is noted to be longer than posterior mediastinal positioning by 2 to 3 cm.

The transpleural route is seldom used but may be necessary if the usual anterior mediastinal route has been transgressed by a previous median sternotomy, particularly for an open cardiac surgical operation.

Level of Anastomosis

If the transhiatal approach to esophagectomy is used, there is no option; the anastomosis is always performed at the cervical level. Likewise, the three-incision technique for near-total removal of the esophagus uses a cervical anastomosis. However, if distal esophagectomy is planned, a decision regarding the level of anastomosis is paramount. A level must be chosen that permits complete removal of the tumor with a negative resection margin. It must also allow construction of a secure anastomosis with full visual exposure. Because of these con-

siderations, intrathoracic anastomoses at the middle to high level are better accomplished from the right-sided thoracic approach.

The most important aspect of a successful esophagectomy and replacement (at least in terms of postoperative recovery) is performance of a safe, intact anastomosis. *The technical goal of all esophageal surgeons is a zero anastomotic leakage rate.*

GUIDELINES IN MAKING THE CHOICE

For malignant disease in particular, the stomach is the most reliable replacement for the esophagus. Its intrinsic blood supply is the most extensive and the stomach's pliability allows it to reach any necessary level. It has stood the test of time and has now been in general use since the 1938 report of Adams and Phemister.[16] The principal drawback in using the stomach is the development of reflux esophagitis resulting in stricture at or above the anastomosis. Although pyloric drainage procedures and anastomosis-wrapping techniques are used to minimize the possibility of damaging reflux, practice has shown that the higher the anastomosis is placed, the less likely the development of esophagitis.

In patients with a nondilatable peptic stricture of the distal esophagus, interposition of a segment of intestine is the preferred method of replacement after esophageal resection. The choice between colon and jejunum is mainly one of the surgeon's preference and experience. Either organ can provide a satisfactory physiologic "barrier" against ongoing gastroesophageal reflux while maintaining the entire stomach in its normal abdominal anatomic location. An esophagogastric anastomosis, particularly at the distal esophageal level for reflux peptic disease, is fraught with a high incidence of postoperative esophagitis and the danger of possible life-threatening nocturnal tracheobronchial aspiration. On the other hand, in elderly or medically compromised patients, the esophagogastric distal anastomosis may be used because of the expedience of the procedure and the reliability of the circulation.

For a long esophageal replacement in patients with benign disease (i.e., usually stricture, either peptic or corrosive), the colon is given first consideration. Its reliable marginal arterial circulation, especially between the left branch of the middle colic and the left colic arteries, permits isoperistaltic replacement of the left colon all the way through the posterior mediastinal esophageal bed to the level of the neck. An alternative route, even after resection, is placement through a retrosternal tunnel.

For esophageal bypass without resection, the colon is also the viscus of choice. It is placed behind the sternum unless obliteration of the anterior mediastinum by previous surgery, mediastinal irradiation, or malignant disease requires transpleural replacement. The side and position (in front of or behind the root of the lung) are the surgeon's choice. Bypass rather than esophageal resection may be selected because of either the extent of an invasive carcinoma or the physiologic status of the patient, both of which may prevent successful transpleural resection. In addition, some general thoracic surgeons prefer to stage a procedure in the event of corrosive destruction of the esophagus by first performing a looping esophageal bypass and, later, esophageal resection.

STUDIES USEFUL IN THE DECISION-MAKING PROCESS

A viscus cannot be used to replace the esophagus unless it is intrinsically healthy (i.e., free of its own disease) and has an adequate arterial supply and venous return. The three methods used to assess these characteristics are (1) endoscopy, (2) arteriography, and (3) barium contrast radiology.

Endoscopy

Endoscopy provides the greatest amount of information when it can be applied appropriately. For instance, if the fiberoptic esophagogastroscope can be negotiated through an esophageal carcinoma or stricture, it provides information about (1) the presence or absence of a second carcinoma, (2) the presence or absence of peptic ulceration or gastritis, and (3) the adequacy of the pyloric channel. In evaluating the colon for use as replacement of the esophagus, colonoscopy is essential. It provides the opportunity for total inspection and thus eliminates the possibility of the presence of a polyp, small carcinoma, or other unsuspected lesion in either the substitute viscus or the residual colon that does not participate in the replacement. It may not provide information about diverticulitis unless it is extensive or actually obstructive.

Arteriography

There is room for a difference of opinion about the need for arteriography. The arterial supply of the stomach is abundant because of its five primary vessels, and its intrinsic network of interconnecting communications is so extensive that arteriography is not necessary. Anomalies in arterial supply are neither too common nor sufficiently severe to cause concern, even with the necessary disconnection from the adjacent omentum, spleen, colon, and celiac axis. For the colon, however, the situation is quite the opposite. The adequacy of the segmental arterial supply is inconstant. First, atherosclerotic involvement of the colonic vessels is common, particularly in the older population so frequently affected by esophageal carcinoma. The origin of the inferior mesenteric artery is a particular site of atherosclerotic narrowing. Second, the variety and frequency of anomalies in colonic blood supply require clarification before a decision can be made about (1) the utility of the colon as a replacement of the esophagus and (2) which portion to use. Numerous variants have been identified by careful anatomic dissection, and anomalies have been found in more than 10% of patients studied by mesenteric arteriography as reported by Sonneland and colleagues.[17] The

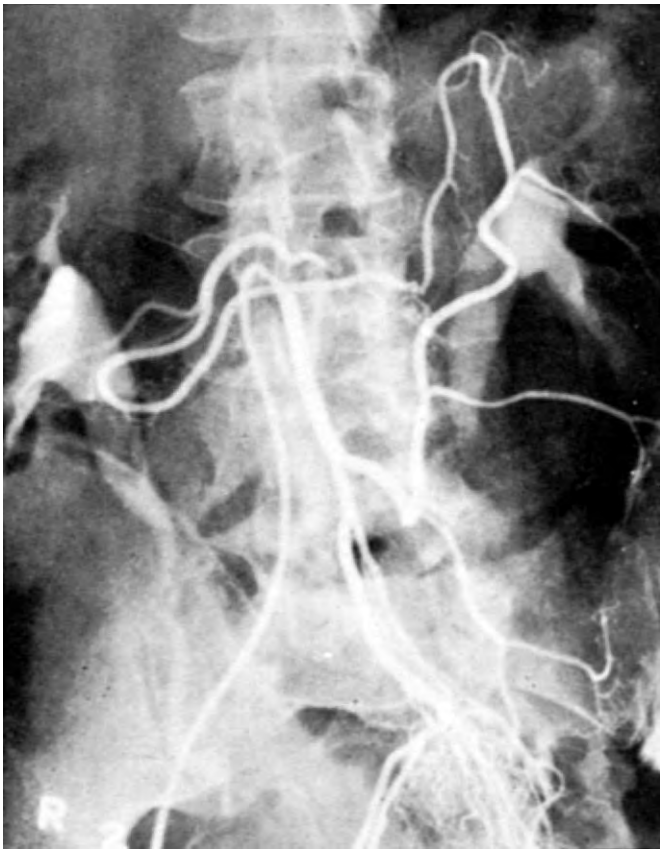

Figure 42–2. This inferior mesenteric arteriogram demonstrates filling of the left colic artery around the splenic flexure, through the anastomotic branch to the middle colic artery, and even (overlying the right renal pelvis) to the right branch of the middle colic artery and the hepatic flexure. This anatomy ensures successful use of the left hemicolon for esophagocoloplasty.

point of strategic interest is the marginal communication between the left branch of the middle colic artery and the ascending portion of the left colic artery (Fig. 42–2). Successful use of the left colon depends on this critical marginal artery. The distribution of the right colic artery is inconsistent, and an unreliable communication with the right branch of the middle colic artery or the ileocolic artery makes selection of the right colon sometimes risky. The true benefit of colonic arteriography lies in the fact that it provides a clear anatomic "road map" *preoperatively* to eliminate any surprise or confusion in the operating room. The most common useful arteriographic findings are stenosis at the origin of the inferior mesenteric artery, inadequacy of the marginal artery, failure of communication of the right and left branches of the middle colic artery, and a short trunk of the middle colic artery precluding access and division. Knowledge of these findings before surgery saves considerable time intraoperatively. A complete study includes transfemoral retrograde catheter opacification of the inferior mesenteric artery, the superior mesenteric artery, *and* the celiac axis. Complications of such a study in experienced radiographic hands are uncommon.

Barium Contrast Radiography

The contrast barium esophagogram still provides a good "road map" for the surgeon to assess the length of tumor involvement, proximity of the tumor to the aortic arch, and involvement of the lesser curve of the stomach. It is especially helpful in making a decision between the thoracoabdominal approach and the Ivor Lewis approach. A contrast barium enema is helpful to rule out neoplasms and extensive diverticulosis when considering use of the colon.

A concluding point in this section on diagnostic studies is that none of the three studies is actually applicable to the jejunum. The jejunum has a consistent blood supply and is always long enough, at least for short esophageal replacement. It is not accessible to endoscopy. The detail provided by a small bowel barium follow-through examination is marginal. For these reasons, indeed, many surgeons give the jejunum preference as the viscus for replacement of the esophagus.

ESOPHAGOGASTROSTOMY

The surgical technique for esophageal replacement by the stomach is best considered by reducing it to its component steps: (1) mobilization of the stomach, (2) lengthening of the stomach, (3) drainage of the stomach, (4) transposition of the stomach, and (5) anastomosis. Each step is described here with a preferred method of performance and the reason why it is performed in this manner. The actual esophageal dissection is described elsewhere.

Mobilization of the Stomach

Detaching the stomach from its complicated intra-abdominal anatomic relationships requires full operative exposure, which is best achieved by performing a standard upper midline laparotomy (used for combined incisions, including the abdominal–right thoracic and the transhiatal-cervical) or a left thoracoabdominal incision (used for distal esophageal resections). Although the stomach may be detached for distal esophagectomy via a strictly transthoracic, transdiaphragmatic approach, this method does not provide optimal exposure.

The initial step in mobilizing the stomach is division of the greater omentum outside the gastroepiploic arcade, which is formed by the right gastroepiploic artery from the gastroduodenal artery at the pyloric end of the stomach and the left gastroepiploic artery from the splenic artery toward the proximal end of the stomach. This division is facilitated by grasping the transverse colon, lifting it out of the incision distally, and entering the lesser omental sac at a point where the omentum is thinnest and most transparent, usually at the midpoint of the stomach or slightly to its left. The dissection is carried all the way to the level of the pylorus, with division of the small omental branches of the epiploic arcade. These vessels may be coagulated, clipped, or tied. The use of fine ligatures is preferred to avoid any retrograde coagulum, which might compromise the integrity

of the gastroepiploic arcade, and to avoid metal clips, which might compromise the clarity of detail of any subsequent computed tomography scan. The dissection is then directed toward the spleen, where the left gastroepiploic artery is ligated at the upper end of the arcade above the segmental artery to the stomach.

The short gastric (gastrolienal) arteries are divided carefully between hemostatic clamps and ligated securely. The more proximal of these vessels may be quite short and require the application of suture ligatures. Ligatures on the stomach must be tied securely because there have been instances in which these ties slipped off when the stomach later became distended in the thorax. Finally, there is a posterior branch from the splenic artery to the posterior aspect of the cardia that is very constant; division of this branch completes the liberation of the greater curvature.

The reflection of peritoneum at the esophagogastric junction is divided, and blunt finger or right-angled clamp dissection permits the surgeon to encircle the abdominal esophagus. Circumferential passage of an empty Penrose rubber drain allows upward traction on this end of the stomach during dissection of the lesser curvature. If the entire stomach is to be used to replace the esophagus, the vagus nerves are divided at this point. If the proximal part of the stomach itself is to be resected, the branches of the vagus nerves are included when the stomach is transected. The rather avascular, thin gastrohepatic omentum is entered low on the stomach, and a second Penrose drain is passed around the stomach at about the level of the incisura to permit downward traction during dissection of the lesser curvature.

Attention is directed toward exposing the origin of the left gastric artery at the trifurcation of the celiac axis. This structure is approached most easily from the posterior aspect of the stomach, which is elevated to the right by the assistant applying traction on the two Penrose drains. It is necessary to divide the filmy, avascular adhesions between the back of the stomach and the retroperitoneum that extend from the pylorus to the superior edge of the pancreas. At this point, the celiac axis and its three branches can be identified by palpation as the left thumb and forefinger encircle what is left of the lesser curvature attachments. The left gastric artery is exposed by sharp dissection. It is doubly ligated at its origin with heavy nonabsorbable suture material, such as No. 0 silk. The first ligature is placed and tied firmly before the artery is actually divided so that should the ligature break during tying, a freely spurting major artery is avoided. Two hemostatic clamps are then applied distal to this first ligature, and the artery is divided between them. A stitch is placed on the left gastric artery 5 mm distal to the first tie. The artery on the gastric side is managed best with a secure stitch ligature. The left gastric vein is usually identified separate from the artery and is handled in similar fashion. The tissue remaining now includes branches of the vagus nerves and the sympathetic chains, which extend upward to the Penrose tape previously placed to encircle the esophagogastric junction; this tissue is divided between clamps and suture-ligated because vessels frequently arise from the undersurface of the liver to the highest point on the lesser curvature.

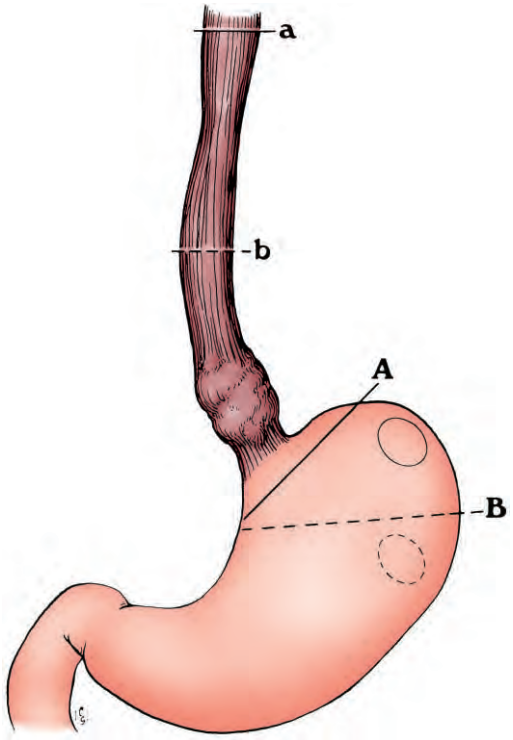

Figure 42–3. The gastric fundus should be preserved (A) to maximize gastric length, which will permit extension of the gastric tube to the neck (a) if necessary. For a distal lesion where only a portion of the esophagus need be resected (b), it is important not to assume adequate gastric length and prematurely amputate the gastric fundus (B). A complete *circle* indicates the proposed esophagogastric site.

The stomach is now free except for the duodenum with the right gastric and right gastroepiploic arteries and the esophagus with its two vagus nerves. Depending on the procedure, the stomach is now handled in one of two ways:

1. If the primary operation is a distal esophagogastrectomy, the nodes along the left gastric artery and celiac axis have been dissected carefully so that they remain in continuity with the stomach. The stomach is transected *from* a point on the greater curvature opposite the level of emergence of the left gastroepiploic artery *to* a point on the lesser curvature below the lowest branch of the left gastric artery with the GIA or TA90 stapler (Fig. 42–3). The lesser curvature point of transection may actually be carried distally to a point below the incisura. The stapled gastric margin is turned in with interrupted No. 4-0 silk Lembert sutures.
2. If the operation planned is a more proximal esophagectomy of the Ivor Lewis type, nothing further need be done at this point. Transection of the stomach at the cardia is carried out once the stomach is drawn through an enlarged hiatus into the right hemithorax after the right thoracic esophageal dissection. This method allows less

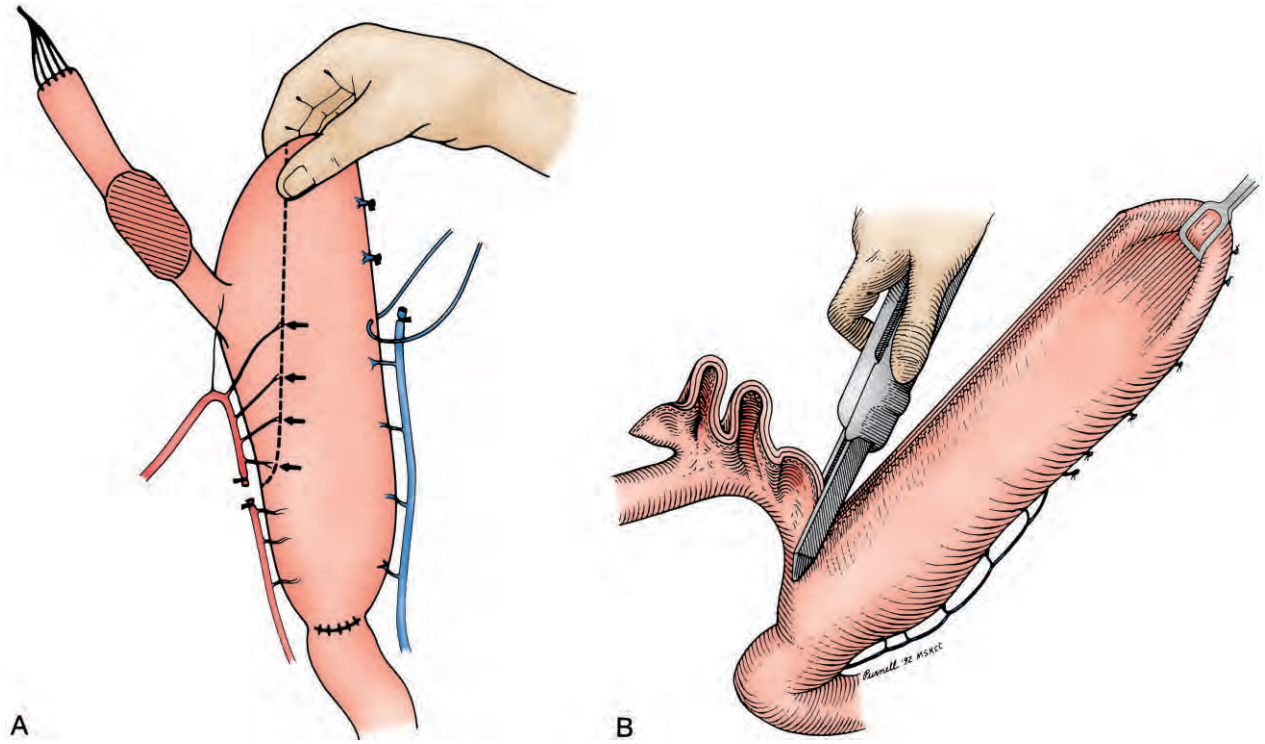

Figure 42–4. **A,** This illustration demonstrates both removal of the lesser curvature of the stomach and elongation of the stomach by traction on the greater curvature. The subsequent esophagogastric anastomosis will be made to a point toward the greater curvature from the surgeon's thumb. (From Akiyama H: Surgery for carcinoma of the esophagus. Curr Probl Surg 17:56, 1980.) **B,** Multiple applications of the GIA-60 stapler are used to "unfold" the lesser curvature and achieve maximal length of the gastric tube. (From Shriver CD, Spiro RH, Burt M: A new technique of gastric pull-through. Surg Gynecol Obstet 177:519, 1993.)

opportunity for possible torsion of the stomach as it is drawn upward. The operator must be careful to not pull the stomach too tightly when mobilizing it into the chest, which could result in compression by the hiatus or in redundancy of the stomach in the chest with resultant poor emptying.

Lengthening of the Stomach

After completion of the dissection just described, lengthening of the stomach is achieved by right lateral peritoneal pancreaticoduodenal mobilization, the so-called Kocher maneuver. It is begun distal to the pylorus along the second portion of the duodenum, with particular care taken to preserve the right gastric artery and to remain anterior to the common bile duct. The peritoneum alone is divided, and the dissection is carried around the C curve of the duodenum along the inferior margin of its third portion. The duodenum can then be dissected free posteriorly by blunt dissection behind the pancreas and in front of the inferior vena cava. The Kocher maneuver permits the duodenum to assume an almost vertical axis as the stomach is drawn up into the thorax. This allows the stomach to reach the cervical level with the pylorus then lying at the level of the diaphragmatic hiatus.

Akiyama has described resection of the lesser curvature of the stomach to gain additional length (Fig. 42–4A).[18] This maneuver may be needed to remove a lymphatic drainage siphon, but aside from dividing both anterior and posterior branches of the left gastric artery individually, excision of the lesser curvature is not usually necessary to gain length. This procedure can be accomplished by use of the linear stapler (see Fig. 42–4B).

Because of the peculiar shape of the stomach, maximal length is obtained by applying upward traction on a point high on the greater curvature of the stomach, actually the highest point of the fundus (see Fig. 42–4A). The location of this point is determined by moving the right thumb and forefinger along on the greater curvature while applying upward traction to find the point providing maximal length.

Drainage of the Stomach

Opinion regarding the necessity for a pyloric drainage procedure after esophagectomy is varied. Actual practice is largely the result of personal experience. There are staunch supporters of routine pyloric drainage and those who favor it only when pyloric obstruction is encountered.

Huang and colleagues, in a prospective study of pyloroplasty versus no pyloroplasty after esophagectomy, showed no difference in gastric emptying time.[19] If gastric outlet obstruction at the level of the pylorus per-

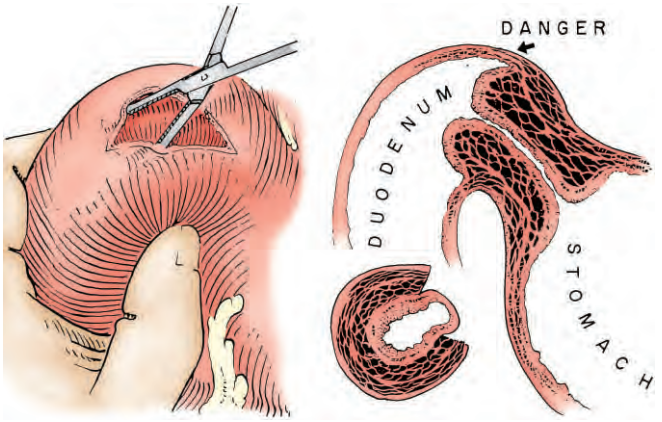

Figure 42–5. Pyloromyotomy. The 3-cm incision across the pylorus provides complete exposure of the sphincter muscle for division down to the mucosal layer. Fine hemostatic forceps are helpful in this dissection. The principal risk of entry into the duodenum is shown in the cross section at the *right,* where the duodenal mucosa covers the undersurface of the pyloric muscle at the duodenal aspect.

sists, surgical intervention is invariably required. This can be difficult in a patient after esophagogastrectomy, especially if an Ivor Lewis or transhiatal approach has been used, because the pylorus is usually located at or near the hiatus, thus making exposure difficult. Balloon dilation may be successful in patients who have undergone a pyloromyotomy and failed conservative measures for correction of gastric outlet obstruction.

From a physiologic standpoint, a gastric drainage procedure makes sense. In the early clinical experience with vagotomy for peptic ulcer disease, it became clear that obstructive symptoms were encountered frequently when vagotomy was performed without a drainage procedure. After esophagectomy, gastric stasis may be observed when the anastomosis is examined radiologically at the initial postoperative study. Because gastroesophageal reflux is common after an intrathoracic anastomosis of the esophagus and stomach and peptic stricture is always a possibility, most experienced general thoracic surgeons now perform a drainage procedure.

A pyloromyotomy is preferred by most. It does not detract from the length of the stomach when the stomach must be brought to the neck, and the pylorus retains some of its barrier capacity against the reflux of bile and pancreatic juice into the stomach (Fig. 42–5). Performance of a complete pyloromyotomy is not always an easy technical task. The best teachers of the proper technique are pediatric surgeons, who gain considerable experience from the Ramstedt-Fredet operation for hypertrophic pyloric stenosis.

The myotomy is limited to 3 cm. Transfixion sutures of silk around the pyloric vein on either side of the myotomy site facilitate exposure by reducing bleeding and permitting lateral traction. With the left hand placed behind the gastroduodenal junction and lifting the pyloric channel forward, the incision is begun directly over the easily palpable pyloric muscle with an unused No. 15 Bard-Parker blade. The surgeon's thumb retracts the muscle downward as it is divided while the assistant provides countertraction upward. When the submucosal plane is reached, the myotomy incision is carried onto the first portion of the duodenum, which presents the only real danger of entry into the lumen. The last muscle fibers are often best separated with good exposure and light and the use of fine, vertically cutting scissors.

If entry into the duodenum does occur, the safest course of action is to convert the procedure to a pyloroplasty. The Heineke-Mikulicz method of closure suffices, again limiting the length of the incision to no more than 2 to 3 cm. Continuous fine inverting chromic catgut or polyglycolic acid sutures are used for closure of the inner layer, and interrupted Lembert sutures of fine silk are used for the reinforcing, outer layer. A single-layer closure is also acceptable. Tacking a portion of adjacent residual omentum over the pyloromyotomy or pyloroplasty provides an additional safety measure against subsequent leakage.

Transposition of the Stomach

If the esophagus has been removed, the stomach is placed in the posterior mediastinal or orthotopic position. If a bypassing conduit is planned, a retrosternal tunnel must be constructed to allow anterior mediastinal transposition of the stomach.[20] Of the various placement options for the stomach, the orthotopic position is the shortest. Ngan and Wong measured the distances of the various positions used for gastric replacement of the esophagus.[21] The orthotopic route was an average of 2 cm less than the retrosternal route; the latter was an additional 2 cm less than the presternal subcutaneous route of passage.

The Ivor Lewis right-sided thoracotomy approach to esophageal dissection permits the mobilized stomach to be drawn gently through the hiatus into the orthotopic position. Then after confirming that torsion of the stomach has not occurred, the cardia or more distal part of the stomach is transected with a GIA or TA90 stapler, and the staple line is inverted with interrupted fine silk Lembert sutures.

If the retrosternal route is chosen, the diaphragmatic attachments to the back of the sternum are sharply divided, and this avascular opening is gradually dilated from the width of two fingers to a size that permits upward passage of the entire hand (Fig. 42–6). With the palm upward, the areolar tissue and pleural membrane are swept gently from the midline to the patient's left until the plane of dissection developed through a left oblique cervical incision is encountered. The left pleural membrane does not approach as close to the midline as the right does, and therefore blunt dissection to the left is less likely to result in entering the pleura. Hemodynamics must be monitored carefully to watch for hypotension or arrhythmia. If symptoms develop, the hand must immediately be withdrawn and blunt dissection continued only when the changes resolve. If either pleural space is entered, placement of a thoracostomy tube (No. 28 Argyle) is required. A portable chest radiograph is always taken before the patient is moved from the operating table because an unsuspected pneumothorax can be managed easily in the operating room.

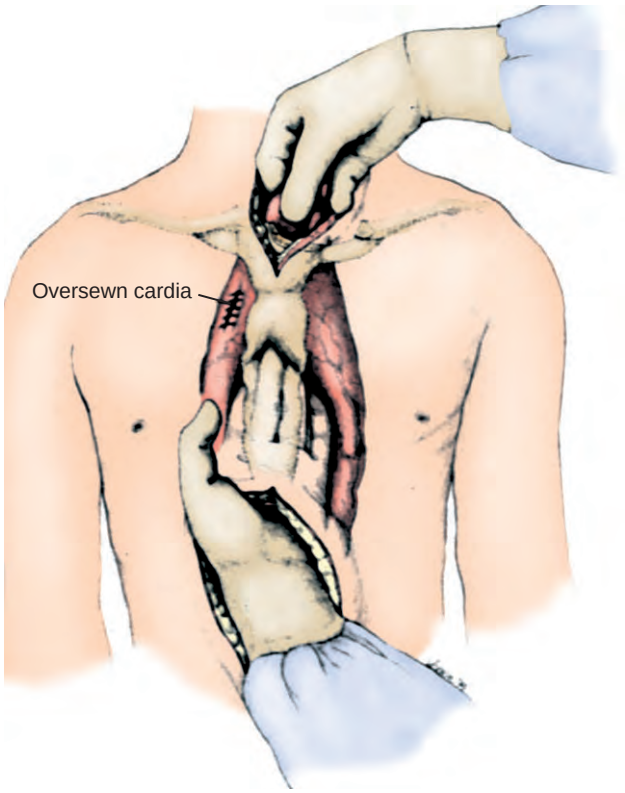

Figure 42–6. The retrosternal tunnel has been bluntly dissected with the finger so that the entire hand can be extended upward in the anterior mediastinum. This figure illustrates passage of the stomach through this tunnel to the thoracic inlet and the cervical incision. Note that the thoracic inlet has been enlarged by resection of the inner end of the clavicle and a portion of the manubrium. (From Orringer MB, Sloan H: Substomal gastric bypass of the excluded thoracic esophagus for palliation of esophageal carcinoma. J Thorac Cardiovasc Surg 70:836, 1975.)

Anastomosis

In patients undergoing esophageal resection, the anastomosis may be placed below the aortic arch (as in a left-sided thoracoabdominal approach for carcinoma of the cardia or very distal esophagus), at the apex of the right hemithorax (as in the conventional Ivor Lewis approach), or in the neck for subtotal esophagectomy. If an anterior mediastinal approach is used, the anastomosis must be placed in the neck. This procedure may actually be the most critical part of the operation. In our experience at Massachusetts General Hospital, the esophagogastric anastomosis is sufficiently secure that placing it in the mediastinum is not a concern. Thus, placement of the anastomosis in the neck is dictated *solely* by the extent of disease, not by fear of possible leakage at the anastomotic suture line.

For more than 50 years we have used a two-layer anastomosis of interrupted fine (4-0) silk. Meticulous attention to detail is required in this technique. No clamps of any sort are permitted on the edges of the anastomotic tissue. The cutting cautery is not used to transect the esophagus; only a new sharp scalpel blade is used. There must be no tension on the respective edges of the esophagus and stomach. Placement of a given stitch is guided by gentle traction on the preceding one, and the edges are handled as little as possible with forceps. The interrupted technique prevents purse-stringing of the anastomosis and allows patent capillaries to extend to the precise edges of the anastomosed structures.

The details of the anastomosis have previously been described by Wilkins[22] and by Mathisen and colleagues.[11] It is an end-to-side (esophagus-to-stomach) technique. A point on the stomach is selected on its anterior aspect at least 2 cm from the gastric transection line in what was the fundus of the stomach and toward the greater curvature. A small circle (the size of a nickel) is scored in the gastric serosa with a scalpel. This maneuver exposes the intramural plexus of vessels, which are then individually suture-ligated with fine silk, thus minimizing ooze and preserving a bloodless field for suture placement (Fig. 42–7). With the specimen still attached to the esophagus at this point, the esophagus is reflected proximally to expose the area of planned transection. A long right-angled occluding clamp is placed just distal to the planned anastomotic line (i.e., toward the specimen). The clamp assists in providing exact exposure of the anastomosis and at the same time prevents spillage of gastric contents or tumor cells from the specimen.

1. The first row of 4-0 silk sutures is an outer posterior row placed in horizontal mattress fashion between the muscularis of the esophagus and the seromuscular layer of the stomach (see Fig. 42–7A). Four to six of these sutures are placed first and then tied carefully, always drawing the stomach upward to the esophagus by positioning the tying left forefinger above the point of actual approximation. The esophagus is a fixed structure that cannot be brought down distally, and its muscular coats are fragile and do not hold sutures as well as those of the stomach. The outer posterior row of sutures covers only about a third of the circumference to allow better exposure when placing the next layer. The corner ties are left long and marked with hemostats.
2. The esophagus is then opened with a scalpel 4 to 5 mm distal to the initial row of stitches, and the incision is extended around each corner. The mucosal layer of stomach is incised, and the scored button is removed. The pinkish gray esophageal mucosa is exposed carefully (it tends to retract) by spreading (not grasping) the opening in the esophagus. The inner posterior stitches, also 4-0 silk, are placed and tied as one proceeds (see Fig. 42–7B). Each stitch is placed about 5 mm back from the cut edge on either structure. The needle must be pulled through each edge separately because trying to include both edges in one pass of the needle causes tearing. The use of atraumatic grasping forceps is necessary to place the first stitch, but subsequent grasping of mucosa is usually unnecessary. Elevation of the previous stitch guides placement of the next. The entire posterior mucosal row is

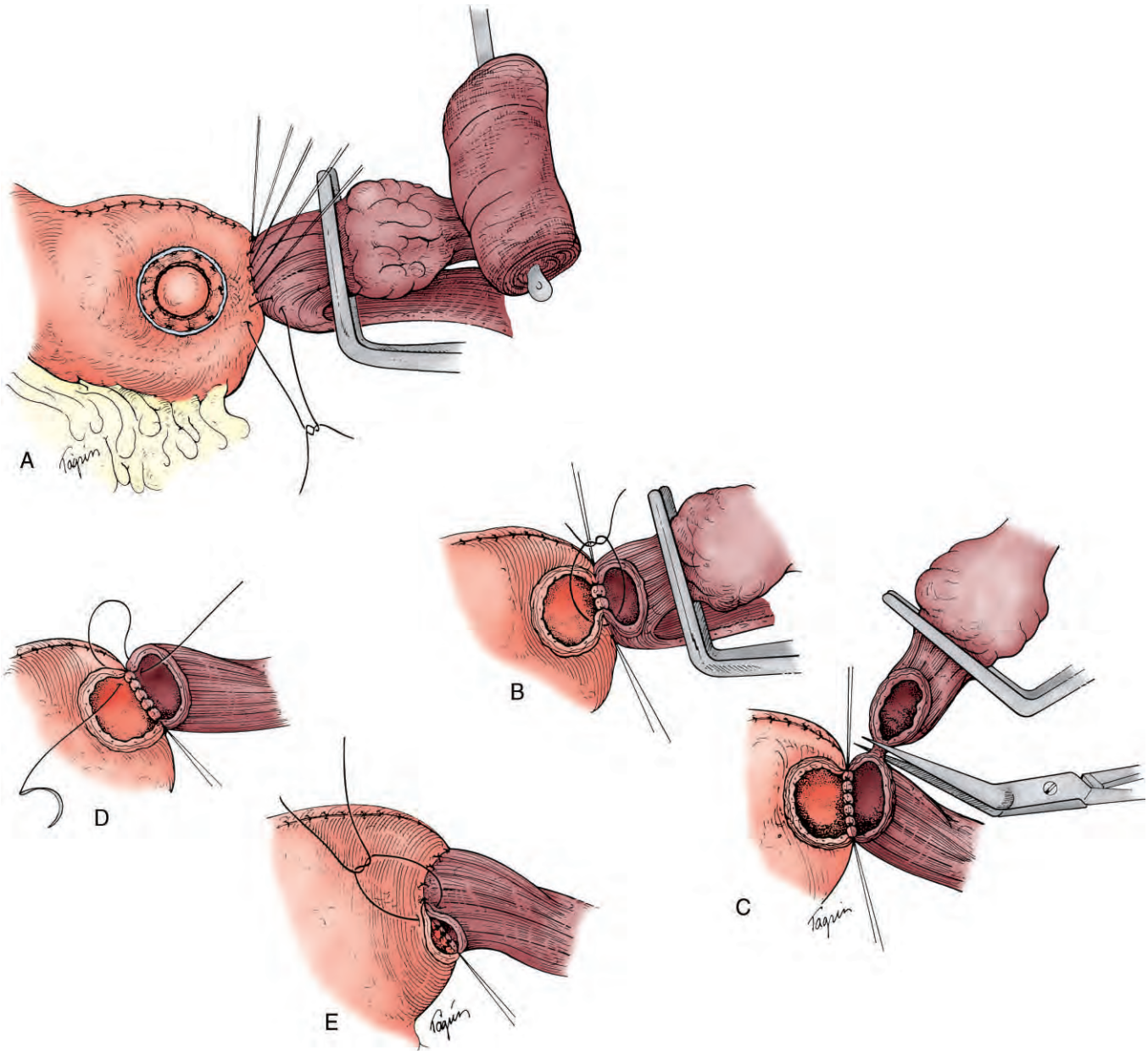

Figure 42–7. **A,** The first step in the Sweet anastomosis developed at the Massachusetts General Hospital. An end-to-side anastomosis is being initiated with excision of a button of gastric wall. This button must not be placed too close to the gastric turn-in. The button can actually be placed quite close to the greater curvature, often between the last two branches of the gastroepiploic arcade. The outer posterior row of the anastomosis is being performed with interrupted mattress sutures of fine silk placed across the longitudinal muscle fibers of the esophagus. Our preference is to place all these sutures before tying. **B,** The gastric button has been excised. With the specimen still attached and excluded with the right-angle clamp, the mucosae of the esophagus and stomach are approximated with interrupted fine silk sutures. **C,** Completion of the posterior inner row and excision of the specimen. **D,** The corner of the anastomosis is being turned to begin the anterior row of sutures. These are placed, again in interrupted fashion, with the knots tied on the inside. **E,** Completion of the anastomosis with mattress sutures of interrupted silk in the outer anterior row. Each suture approximates the muscularis of the esophagus to the seromuscular layer of the stomach. These sutures are placed in horizontal mattress fashion (not as actually shown) so that there is less risk of cutting through. (From Mathisen DJ, Grillo HC, Wilkins EW Jr, et al: Transthoracic esophagectomy: A safe approach to carcinoma of the esophagus. Ann Thorac Surg 45:137, 1988.)

completed, with the corner sutures left uncut. Transection of the esophagus is now completed, and the specimen is removed (see Fig. 42–7C). The nasogastric tube is directed downward through the anastomosis to the level of the gastric antrum and is fixed by the anesthetist to the patient's nose.

3. The anterior inner row is continued in interrupted fashion, with the stitches placed so that the knots are always tied within the lumen (see Fig. 42–7D). The assistant holds the previous tie down and away as each subsequent stitch is secured. This method allows complete inversion of the mucosal layer. The previous suture is then cut after tying each subsequent stitch. This row of sutures is tied from either end toward the middle so that a final horizontal mattress suture can be placed to complete the anterior mucosal row.
4. The outer anterior row is placed in horizontal mattress fashion over what is left, which is about two thirds of the circumference (see Fig. 42–7E). The serosa of the stomach is brought as much as 1 cm above the inner mucosal layer. Because the anastomosis has been placed 2 cm or more down the apex of the stomach posteriorly and the stomach has been folded upward anteriorly, a valve-like luminal orifice has been created that helps minimize the possibility of gastroesophageal reflux. The stomach is suspended by a series of nonabsorbable sutures to the fascia overlying the thoracic spine. This minimizes the possibility of downward drag of a potentially full stomach on the fragile anastomosis.

Whether the esophagogastrectomy is performed as a replacement of the esophagus or as a bypass of it, it may be accompanied by placement of a feeding jejunostomy. The jejunostomy is used for feeding purposes if there is any difficulty with the anastomosis or delay in postoperative gastric emptying. It also provides access for immediate postoperative substantive caloric feeding, obviates the need for total intravenous parenteral nutrition, and promotes healing at the anastomotic sites by providing a catabolic state for the patient.

One week after surgery, barium swallow is used to evaluate the esophagogastric anastomosis and gastric emptying. If there are no issues, the patient is allowed small amounts of clear liquids. Gastric dilatation must be evaluated by chest radiography as oral intake commences. If delayed gastric emptying is identified, oral intake should be stopped and nasogastric decompression instituted. A prokinetic agent such as metoclopramide (Reglan) should be started. A second trial of oral liquids should be attempted several days later. If the patient fails again, balloon dilatation of the pylorus should be considered. The jejunostomy tube is usually removed at the first postoperative visit (1 month).

Functional Results

Despite the vast experience with the stomach as an esophageal substitute, little information is available on long-term functional results. Orringer and associates have reported the early and late results of transhiatal esophagectomy in patients with benign and malignant disease.[23] As they note, functional results are better demonstrated in patients undergoing surgery for benign disease because of longer survival data. Among patients with benign disease who underwent esophagectomy, data have been accumulated on 242 patients over an average of 47 months. The overall functional result in patients with benign disease was reported as excellent in 29% (asymptomatic), good in 39% (mild symptoms requiring no intervention), fair in 28% (occasional episodes of dumping or requiring occasional dilatation), and poor in 4% (requiring regular treatment).

Orringer et al. also reported on 721 patients at an average of 29 months after transhiatal esophagectomy for esophageal cancer.[23] The overall functional results were reported as excellent, or asymptomatic, in 54% of patients. The results were reported as good in 28%, fair in 15%, and poor in 3% of patients.

ESOPHAGOCOLOPLASTY

The term *esophagocoloplasty* is used arbitrarily in this section to denote either replacement or bypass of the esophagus by colon. As clearly described already, the stomach is the first choice for replacing the esophagus. However, when the stomach has previously been removed, even partially, the colon is the viscus of choice. In addition, when bypass of an unresectable esophageal carcinoma is required, the colon offers the best possibility of providing successful palliation. An advantage to colon grafts is the length available, but colon interposition can cause significant morbidity and is a technically complex procedure. The specific indications for esophagocoloplasty are presented in Box 42–1.

Box 42–1 Indications for Esophagocoloplasty

Malignant Tumors

- Replacement of esophagus after gastrectomy
- Bypass of unresectable carcinoma
- Palliation of esophagotracheal or bronchial fistula
- Staged complex esophageal resections

Benign Conditions

- Staged bypass of caustic esophageal stricture
- Esophageal atresia (congenital) when primary anastomosis is not feasible
- Bypass of a long peptic esophageal stricture in a physiologically impaired patient

Preoperative Preparation

Emphasis has already been placed on evaluating the colon by colonoscopy, mesenteric arteriography, and barium enema. Of these, evaluation of the colon's arterial blood supply by arteriography is the most vital because it provides important detail on the variable colic arteries. In older patients, the presence of atherosclerotic plaque is also identified by these studies. Any of a number of major mesenteric arterial anomalies may be identified. Although in most cases the details of this anatomy can be worked out by intraoperative transillumination of the colonic mesentery, arteriographic study saves both time and confusion during the actual conduct of the operation.

Adequate colon preparation is essential to primary healing of the esophagocolic anastomosis in the neck, where spillage of residual fecal contents must be avoided. Mechanical cleansing of the colon is accomplished with polyethylene glycol (GoLYTELY), and enemas are rarely required and should not be administered within 12 to 18 hours before surgery. Oral antibiotics are favored by some, with 1 g of neomycin and 1 g of erythromycin every 4 hours for three doses being the most common regimen. Broad-spectrum antibiotics are initiated parenterally on call to the operating theater, and maintenance doses are continued in bolus intravenous fashion during the procedure and 48 hours after.

The route of reconstruction must be considered. The posterior mediastinal route for placement of the conduit is often available after esophageal resection. However, when it has been decided, because of tumor unresectability or the condition of the patient, to not resect the esophagus, a retrosternal approach may be taken (described in the next section). In addition, the subcutaneous route may be necessary if the usual anterior mediastinal route has been transgressed by a previous median sternotomy, particularly for an open cardiac surgical operation. This approach requires a mandatory ventral hernia to allow the colon to enter the subcutaneous tissue of the chest. Finally, a transpleural route may be used with the colon passing through the esophageal hiatus and pleural space.

Operative Technique

Retrosternal positioning of the colonic bypass is ideally suited to a two-team approach, an abdominal team and a cervical team. The cervical team should delay incision until the exploratory findings in the abdomen are clearly favorable: (1) absence of major intra-abdominal metastatic disease and (2) the presence of a suitable length of colon with a proper arterial blood supply and venous drainage. The abdominal mobilization of the colon described subsequently is the same for any of the routes or reconstructions.

Standard endotracheal anesthesia is used and the patient is placed supine on the operating table with the head turned to the right. Hyperextension of the neck is achieved with elevation of the shoulders by a thyroid bag. The operative field is prepared from the left mastoid process to the symphysis pubis. A nasogastric tube is passed to the point of esophageal obstruction or into the stomach.

Abdominal Team

A long midline or left paramedian laparotomy incision is used that extends from the xiphoid process to below the umbilicus. Careful exploration is needed to search for hepatic metastases, left gastric artery–celiac axis node metastases, peritoneal or omental implants of tumor, a possible second gastric carcinoma, or other unsuspected intra-abdominal processes.

The colon is then mobilized from the ascending to the sigmoid level. Freeing the colon from the omentum and from the right and left peritoneal reflections is not difficult but must be accomplished carefully. The general surgical background of the thoracic surgeon is a helpful attribute. Important points in this dissection are, in order of approach, (1) total detachment of the omentum from the colon, leaving it attached to the stomach but preserving the midcolic vessels as the posterior leaf of the omentum is peeled off the transverse mesocolon; (2) mobilization of the splenic flexure without injury to the spleen, a process that is more easily accomplished after the left peritoneal reflection has been incised, thereby permitting downward traction on both the transverse and descending colon; and (3) freeing of the hepatic flexure from the duodenum and retroperitoneal structures in the right upper quadrant.

This subtotal freeing of the colon now permits it to be elevated for appropriate transillumination and visualization of all colic vessels. The left hemicolon is preferred for use as the bypassing conduit because of its more reliable blood supply and an advantageous size match. The marginal artery between the left branch of the midcolic artery and the ascending portion of the left colic artery is critical, and its presence and adequacy on the preoperative arteriogram must be verified (see Fig. 42–2). The midcolic artery is no less critical. Because the length of the necessary colon bypass takes one to the hepatic fixture, a bifurcation of the midcolic artery well out from its superior mesenteric arterial source is required; a bifid origin of the right and left branches of the midcolic artery does not permit retrograde blood flow all the way from the left colic artery to the hepatic flexure. *Isoperistaltic placement of the colon segment is preferred* (Fig. 42–8).

To use the left colic artery as the source of blood supply, the midcolic vessels are now divided at their origin from the superior mesenteric vessels and doubly ligated (Fig. 42–9). For complete mobility of the hepatic flexure, the right colic vessels must also often be divided. The distance from the point where the colon is tethered by the left colic artery is measured to the level of the midneck. The distance is then measured around the colon toward the hepatic flexure, and the appropriate transection point is carefully identified. The colon is divided with the GIA stapler both at this point and at the juncture of the descending and sigmoid colon. The colon can then be passed behind the stomach through a wide aperture made in the avascular gastrohepatic omentum. This maneuver allows the left colic artery and

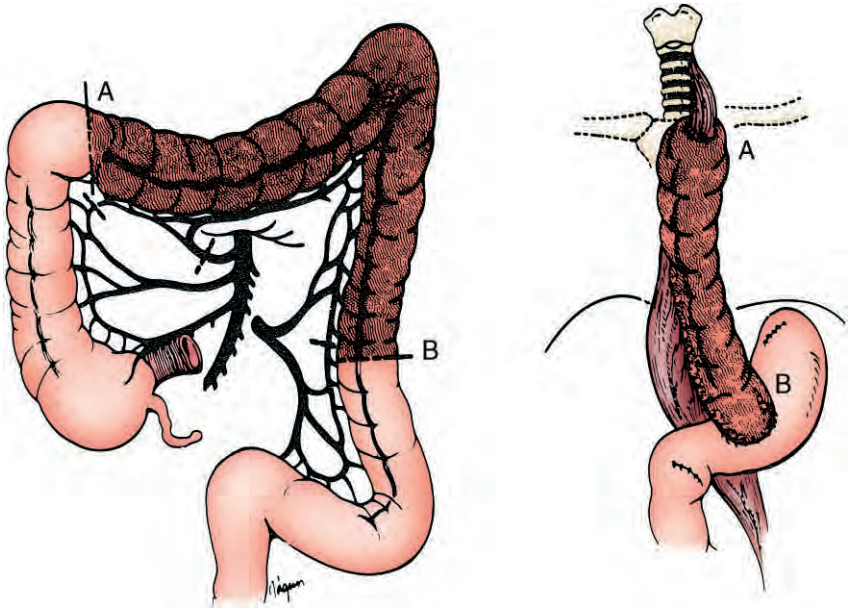

Figure 42–8. Schematic illustration showing use of the left colon to replace the esophagus. Points A and B are determined by the length of colon necessary to reach the neck. The left colic artery provides the blood supply. The middle colic artery is divided. The colon is placed, always, in isoperistaltic fashion such that the segment near the hepatic flexure is anastomosed to the esophagus in the neck and the end near the sigmoid colon is attached to the antrum of the stomach in the abdomen.

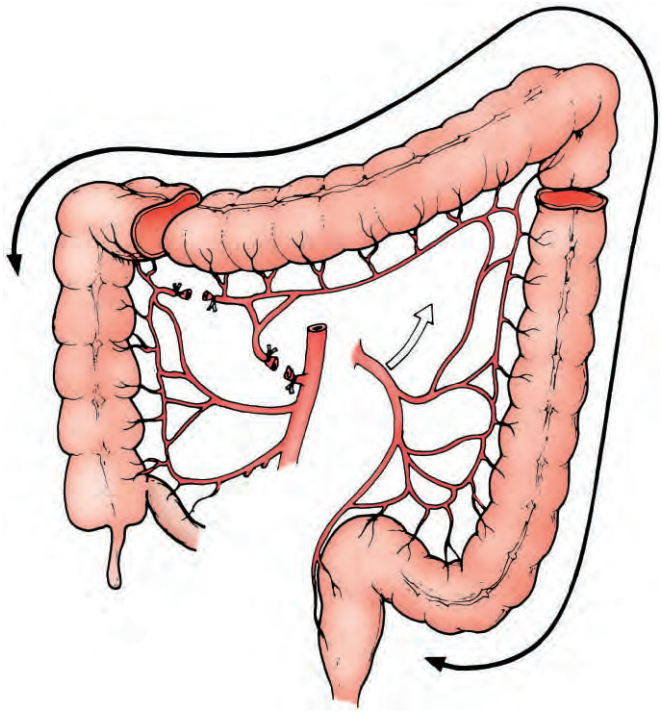

Figure 42–9. The long line with *arrows* at both ends illustrates the extent of colon to be freed for left colon replacement of the esophagus. Blood supply is provided through the inferior mesenteric artery, the left colic artery, and the anastomotic branch connecting the middle colic artery. The middle colic artery has been divided near its origin from the superior mesenteric artery.

vein to extend the shortest distance and prevents angulation or potential compression by a dependent full stomach.

The mobilized residual abdominal colon can now be reanastomosed. Our preference has been to use an end-to-end, two-layer, inverting anastomosis of interrupted fine silk and running catgut suture. An important detail is closure of the colon mesentery to minimize the likelihood of internal herniation of small intestine. This closure usually lies slightly caudad to the ligament of Treitz and often requires approximation of the mesentery to the posterior peritoneum.

With a viable colon segment, the second team can begin the cervical incision and the abdominal team can start to bluntly develop the retrosternal tunnel. Particular attention is paid to the thoracic inlet portion of this tunnel, and it should be big enough to admit four fingers. The inlet can be enlarged if necessary as described earlier (see Fig. 42–1). The colon segment is then gently drawn upward by means of a guiding heavy silk thread, with care taken to keep its mesentery on the right without any twisting. An impediment in venous return may result in subsequent venous thrombosis and failure of the colon bypass. Viability of the upper end of the segment must be verified not only by visual inspection of its color but also by palpable observation of arterial pulsation, by the application of a Doppler probe, or by incisional demonstration of arterial blood flow.

The cologastric anastomosis is carried out in end-to-side fashion to the anterior aspect of the midportion of the stomach with an inner layer of running 4-0 catgut and an outer layer of interrupted 4-0 silk suture.

The pylorus is palpated to determine the need for a pyloric drainage procedure (an opportunity is available at the time of cologastric anastomosis to palpate the pylorus from within). In general, pyloric drainage is required only if the esophagus is being removed and the

vagus nerves divided; a simple bypass does not compromise gastric innervation, and stasis is not likely to be an issue.

Gastric decompression is provided by a Stamm gastrostomy placed proximal to the cologastric anastomosis. A No. 18 Foley catheter works effectively and is brought out through a stab incision placed laterally in the left upper quadrant. The stomach is secured to the anterior peritoneum in four quadrants around the tube with 3-0 silk sutures.

Cervical Team

A left-sided oblique cervical incision is a useful approach to the cervical esophagus. It requires dividing the omohyoid muscle, retracting the sternocleidomastoid muscle laterally, dividing the inferior thyroid artery and often the middle thyroid vein, detaching the sternal insertions of the peritracheal muscles, and entering the avascular prevertebral plane. The esophagus is readily apparent by palpation of its inlaying nasogastric tube.

The esophagus is encircled, with care taken to not damage the membranous portion of the trachea or the recurrent laryngeal nerves. Even unilateral vocal cord palsy enhances the possibility of postoperative aspiration. The mobilized esophagus is transected 2 to 3 cm distal to the cricopharyngeus and its proximal end marked with silk sutures at the corners and left open without clamping. The distal end is turned in with two layers, one stapled and the second with inverting 4-0 interrupted silk sutures.

The critical esophagocolic anastomosis is carried out in end-to-end fashion with two layers of inverting, interrupted 4-0 silk. The actual suture material is not as important as the two-layer, interrupted technique. Use of the left colon minimizes the size discrepancy between the two lumens, and proper interval spacing of the sutures or the addition of a short vertical incision at the end of the esophagus permits an anastomosis with no redundant tissue. The nasogastric tube, withdrawn to transect the esophagus, is replaced distally into the colon bypass before completing the anterior row of sutures: It provides evacuation of colonic air, monitors postoperative bleeding, and minimizes the potential for tracheal aspiration. The nasogastric tube is routinely left in overnight and removed on postoperative day 1.

The neck is closed without drains unless there is persistent oozing or contamination (the abdominal incision has now been closed by the abdominal team). A portable chest radiograph is obtained before the endotracheal tube is removed, and pneumothorax is decompressed by means of a thoracostomy tube.

Postoperative Care

The most important consideration in postoperative management is viability of the colon bypass segment. An extremely reliable indicator that the segment may be compromised is a persistently high fever. Endoscopy is hazardous because of the fresh anastomosis, and the appearance of the mucosa is not always a consistent indicator of viability. The best method of assessing the colon conduit is a second-look operation. The neck incision can be opened easily under local anesthesia, and the upper end of the colon segment can be inspected directly. If the segment is nonviable, the entire colon bypass must be immediately removed from its retrosternal location. A necrotic colon persisting in the anterior mediastinum is a source of possible death. In one case of failed colon bypass in our experience, the residual viable colon was brought up subcutaneously, and the resultant gap was ultimately bridged with a free jejunal autograft.

Feedings are begun by gastrostomy on the second day with the patient fed in a semierect position to minimize possible gastrocolic reflux. A barium esophagogram is carried out on the seventh postoperative day. Oral feeding is then begun gradually if the anastomosis proves to be intact.

Table 42–1 Indications for Colon Esophageal Bypass

Diagnosis	No. of Patients
Neoplastic	88
Esophageal cancer	78
Proximal gastric cancer	3
Laryngeal cancer	3
Thyroid cancer	3
Malignant carcinoid	1
Non-neoplastic	48
Stricture	35
Caustic	16
Peptic	14
Radiation	5
Congenital atresia	10
Motility disorder	3

From Wain JC: Long segment colon interposition. Semin Thorac Cardiovasc Surg 4:336, 1992.

Results

Wain reported our results with long-segment colon substitution of the esophagus in 136 patients.[24] Indications were neoplasms in 88 and non-neoplastic disorders in 48 (Table 24–1). The left colon was used in 100 of 136 (74%) and the right colon in 36 of 136 (26%). Major acute complications included graft ischemia (4 of 100 with the left colon, 8 of 36 with the right colon) and cervical anastomotic leak (Table 24–2). Thirty-day operative mortality rates were 16% in the neoplastic group and 0% in the non-neoplastic group (Table 24–3). The differences in operative mortality between benign and malignant disease were corroborated in a review by Postlethwait (Table 24–4).[25] Late complications included proximal anastomotic stenosis (eight), graft redundancy (four), bile reflux (two), and esophageal mucocele (one). Among operative survivors, excellent function (no dysphagia, stable weight) was obtained in 88% (107

of 122), good function (mild dysphagia, stable weight) in 10% (12 of 122), and poor results in only 2.5% (3 of 122).

Wain and colleagues further analyzed 52 patients who had undergone long-segment colon interposition for acquired disease.[26] Pneumonia was the most frequent complication, and it occurred in 24 patients. Graft ischemia was noted in 5 patient (3 of 46 with left colon interposition and 2 of 6 patients with right colon interposition), and late complications included anastomotic strictures in 24 patients, all managed with dilatation. Episodes of aspiration pneumonia were noted in three patients more than 6 months after the procedure. Median survival was 11.5 years, and 11 of 50 patients maintained their weight. A modified diet for aspiration or moderate dysphagia was necessary in 33 of 50 patients. Five patients required continuous enteral feeding to maintain weight.

Redundancy of the colon in the chest or abdomen is a potentially serious complication. In a group of 69 long-segment colon interpositions, Jeyasingham et al. noted a 25% incidence of colonic redundancy.[27] Of the group of patients, supra-aortic redundancy developed in 4, supradiaphragmatic redundancy in 11, and subdiaphragmatic redundancy in 7. The authors hypothesized that as a thin-walled structure the colon dilated in response to negative intrathoracic pressure above potentially obstructing landmarks. Of the patients in whom redundancy developed, 15 required operative intervention.

Colon bypass requires precise attention to technical detail for a successful outcome. The major complications and causes of operative mortality are often related to technical failure. When successful, the colon has proved to be an effective conduit with which to replace the esophagus.

Table 42–2 Acute Complications of Colon Esophageal Bypass

Diagnosis	No. of Patients
Technical	
Graft ischemia	12
Left colon	4
Right colon	8
Cervical anastomotic leak	8
Vocal cord paresis	3
Acute nonvascular perforation	1
Sternal necrosis	1
Other	
Pneumonia	15
Wound infection	9
Small bowel obstruction	4
Pulmonary embolism	2
Cholecystitis	1

From Wain JC: Long segment colon interposition. Semin Thorac Cardiovasc Surg 4:336, 1992.

Table 42–3 Cause of Operative Mortality in Long-Segment Colon Bypass for Neoplasm

Cause	No. of Patients
Colon necrosis	7
Respiratory failure	5
Metastatic disease	1
Sudden cardiac death	1

From Wain JC: Long segment colon interposition. Semin Thorac Cardiovasc Surg 4:336, 1992.

ESOPHAGOJEJUNOPLASTY

Jejunum represents the third alternative for esophageal replacement. As a replacement, it can be used in one of three ways: (1) as an interposition graft retaining its vascular supply with branches from the superior mesenteric artery and vein, (2) as a Roux-en-Y limb, or (3) as an autograft. Jejunum is most frequently used as a short-segment interposition graft after resection of a distal esophageal stricture, although it may also be used to restore continuity after distal esophagectomy for carcinoma when the stomach has previously been removed. The anatomy of its mesentery makes long-segment interposition difficult, although in children, a Roux-en-Y loop readily reaches the neck. As an autograft, it is used for resection of short

Table 42–4 Colon Interposition Operative Mortality

	Benign		Malignant	
	No. of Patients	Deaths (%)	No. of Patients	Deaths (%)
Through 1961	54	11.1	78	21.8
Through 1971	655	7.5	245	24.5
Through 1981	474	4.9	367	16.6
Total	1183	6.8	690	20.0

From Postlethwait RW: Surgery of the Esophagus, 2nd ed. Norwalk, CT, Appleton-Century-Crofts, 1986, p 505.

cervical esophageal segments containing carcinoma, after extensive cervical trauma involving damage to the esophagus, or for augmentation of a failed colonic esophageal bypass.

Interposition

The short jejunal interposition for distal esophageal resections is described here because it is the most common application of esophagojejunoplasty. A left-sided thoracoabdominal incision provides the exposure necessary for both the esophageal procedure and preparation of the jejunum. The proximal part of the jejunum is identified and lifted out of the abdomen for transillumination of its mesentery (Fig. 42–10). The first jejunal artery is identified and preserved to maintain vascular integrity of the 10 to 12 cm of jejunum adjacent to the ligament of Treitz. After determining the length of jejunum needed, the upper three or four jejunal arteries to this measured segment are exposed. With the help of the transilluminating light, these arteries are isolated and occluded sequentially with atraumatic bulldog clamps to test the reliability of one jejunal artery to provide circulation to this segment. The peritoneum is reflected carefully from either side of the mesentery outward to the primary anastomotic arcade, the tissue intervening between the jejunal arteries is incised, and the necessary jejunal arteries and veins are divided and securely ligated with 2-0 silk. For longer reaches of the jejunal segment, one or two points on the secondary anastomotic arcade may require division (Fig. 42–11).

The jejunal segment is now separated from normal intestinal continuity by proximal and distal applications of the GIA stapler. The pedicled segment to be interposed is then brought through the transverse mesocolon. Because the segment has a proclivity to retain its curved axis, the stapled proximal end of the segment is turned in with interrupted 3-0 silk Lembert sutures. The distal end of the jejunal segment is anastomosed first to the posterior aspect of the fundus of the stomach with a two-layer technique of interrupted 4-0 silk and continuous 4-0 chromic catgut. The esophagojejunal anastomosis is carried out in end-to-side fashion at a point 2 cm away from the jejunal turn-in on its antimesenteric border (Fig. 42–12). This is done with the same technique of two inverting layers of interrupted silk suture as

Figure 42–10. Transillumination of the jejunum demonstrates the jejunal branches of the superior mesenteric artery and permits selection of an appropriate one for reliable blood supply to the segment to be used in esophagojejunoplasty.

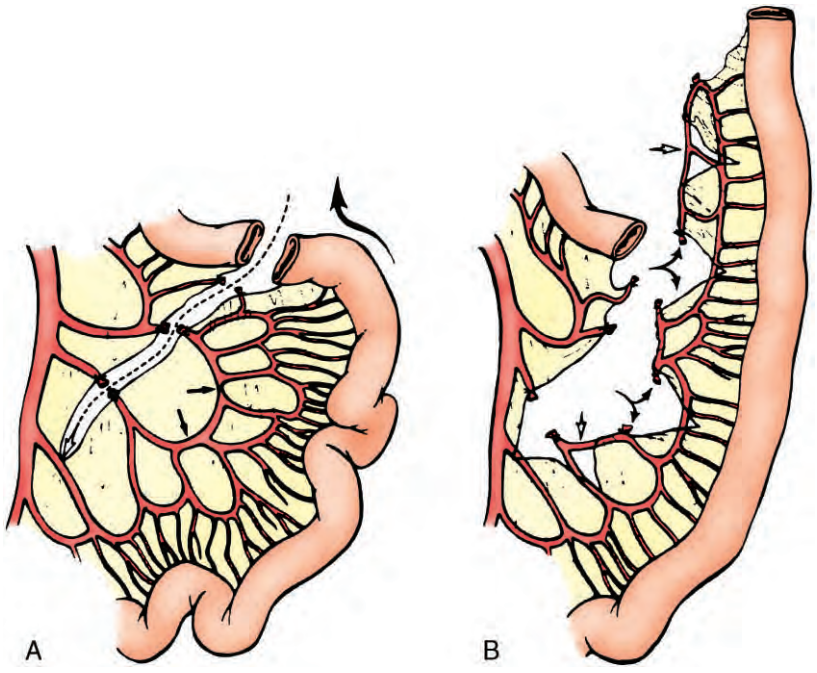

Figure 42–11. **A** and **B,** Diagrammatic illustration of (1) preservation of the highest jejunal artery, (2) division of the next three jejunal arteries, and (3) two points of division of a secondary arcade in **B.** Particular care must be taken that an arcade exists from the feeding arterial source (in this case, the fourth jejunal artery) all the way to the transected margin. (From Ring WS, Varco RL, L'Heureux PR, et al: Esophageal replacement with jejunum in children: An 18 to 33 year follow-up. J Thorac Cardiovasc Surg 83:918, 1982.)

Figure 42–12. A-D, Methods of reconstruction using jejunum. (From Postlethwait RW: Surgery of the Esophagus, 2nd ed. Norwalk, CT, Appleton-Century-Crofts, 1986, p 500, with permission.)

described in the section on esophagogastrostomy. An end-to-end anastomosis constructed with an outer layer of silk and an inner running catgut suture restores jejunal continuity.

Roux-en-Y Limb

When there is no stomach for jejunal interposition, a Roux-en-Y jejunal limb may be used. This procedure involves only two anastomoses—esophagojejunal and an end-to-side jejunojejunal—instead of the three needed for an interposed segment. The higher the jejunum must reach in the chest or even to the neck, the more jejunal arteries that must be divided to provide adequate length of the Roux-en-Y limb. Unfortunately, this requirement increases the possibility of vascular failure at the tip of the jejunal segment and explains why jejunum is generally considered the third choice for esophageal replacement. Ring and associates state that jejunum is the first choice in children, but their illustrations (Fig. 42–13) show a process of staging the esophagojejunal anastomosis with an unanastomosed jejunal stoma in the neck in the first stage, presumably planned to be certain of its viability, and subsequent esophagojejunal anastomosis.[28]

In cervical esophagojejunoplasty, there is always the option of vascular enhancement by microvascular anastomosis of the internal mammary artery or a branch of a carotid artery to the jejunal mesentery arterial arcade. A suitable draining vein must also be identified and anastomosed under these circumstances. Payne and Fisher described a unique experience with "free jejunal transfer circulatory augmentation of pedicled intestinal inter-

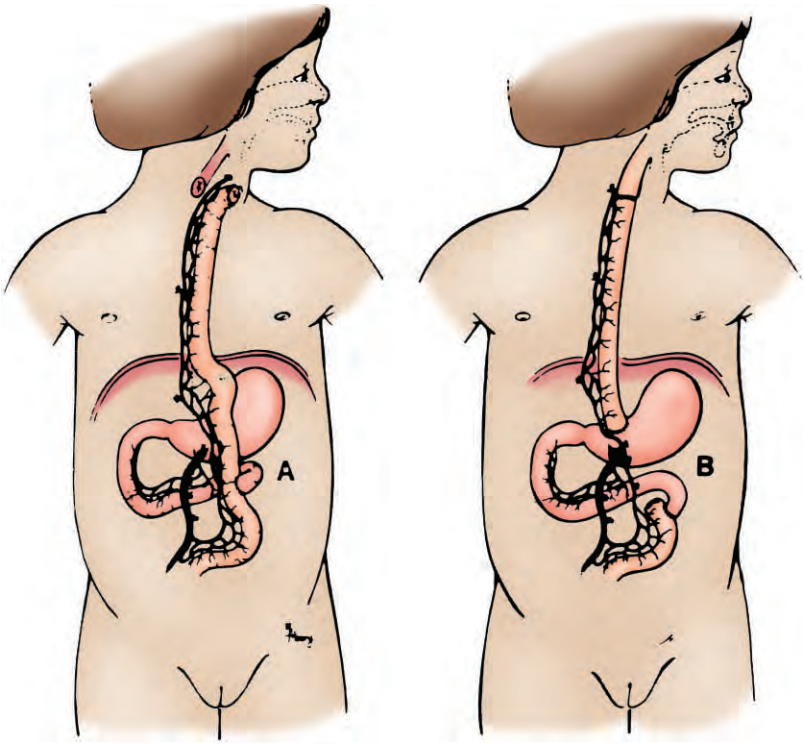

Figure 42–13. Use of the jejunum to replace the esophagus in a child. The jejunum readily reaches the neck. **A,** The proximal end of the jejunum is brought out as a cervical stoma to permit secondary performance of the esophagojejunal anastomosis. **B,** The distal end of the jejunum has been divided and anastomosed to the antrum of the stomach and the cervical anastomosis completed. (From Ring WS, Varco RL, L'Heureux PR, et al: Esophageal replacement with jejunum in children: An 18 to 33 year follow-up. J Thorac Cardiovasc Surg 83:918, 1982.)

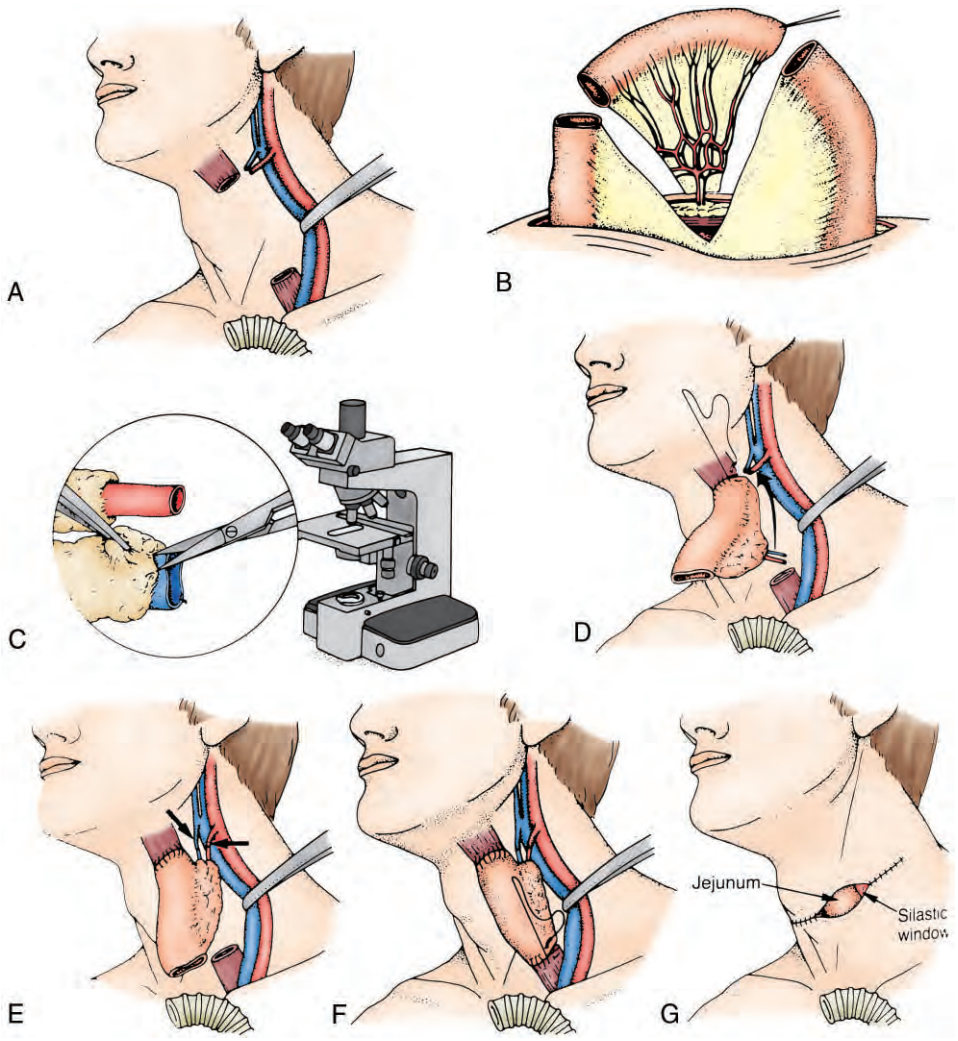

Figure 42–14. Reconstruction of the cervical esophagus with a free jejunal graft according to the technique described by Hester et al. (1980). **A,** Tumor extirpation and neck dissection are completed. **B,** After abdominal exploration, a suitable segment of proximal jejunum is isolated on its pedicle, and the bowel is divided proximally and distally while ensuring that the only blood supply to the segment is through the pedicle. **C,** The artery and vein of the chosen segment are cleaned of adventitia with use of the operating microscope. **D,** The proximal bowel anastomosis is completed with interrupted 3-0 Vicryl sutures. **E,** The arterial and venous anastomoses to the chosen donor vessels are done. **F,** The distal bowel anastomosis is completed with interrupted 3-0 Vicryl sutures. **G,** A small window of dimethicone (Silastic) sheeting is left over the jejunum to allow close postoperative observation of the replant. (From Skinner DB, Belsey RHR: Management of Esophageal Disease. Philadelphia, WB Saunders, 1988.)

positions using microvascular surgery," in which the details of a number of variants of esophagojejunoplasty are described to solve unusual problems of cervical esophageal replacement.[29] When contemplating the use of jejunum for a long-segment replacement of the esophagus, such as to the cervical level, a thoracic surgeon he would be well advised to consult a microvascular surgical practitioner to prepare for the possible need for circulatory augmentation.

Free Transfer

Two teams accomplish the free transfer procedure most expeditiously. Attention in this discussion is focused on the abdominal procurement ("harvesting") team. Through a routine laparotomy, a suitable segment of jejunum is selected, preferably at least 40 cm distal to the ligament of Treitz (Fig. 42–14B). The principal issue in selecting the site is obtaining an appropriate length of a jejunal artery and vein for later vascular anastomosis. The character of the bowel itself is an additional consideration in that it must have adequate caliber and be free of intrinsic disease. Once the length of jejunum needed is determined, it is transected proximally and distally with a GIA stapler. The mesentery is divided in a V fashion to the origin of the perfusing vessels. The isolated segment is now allowed to perfuse until the cervical team is prepared to carry out the actual transfer (see Fig. 42–14A). Meanwhile, jejunal continuity is re-established by end-to-end anastomosis as described in the preceding section.

The jejunal autograft, with the artery and vein carefully occluded by noncrushing bulldog clamps, is moved to the cervical incision. The segment is placed in the cervical esophageal bed in an isoperistaltic fashion. The proximal jejunal anastomosis is performed first to the cervical esophagus or hypopharynx with two layers of inverting interrupted 4-0 silk as described for esophagogastrostomy (see Fig. 42–14D). This provides enough fixation and stability to allow performance of the two microvascular anastomoses without concern for tension or torsion. A suitable neck artery (the inferior thyroid, transverse cervical, or common carotid artery itself) is used for the vascular anastomosis, which is performed with 10-0 nylon monofilament sutures under the operating microscope (see Fig. 42–14E). The microvascular bulldog clamps are released, and the jejunal autograft is allowed to perfuse. A two-layer anastomosis of the distal

jejunum to the esophagus is then completed, again using inverting, interrupted fine silk sutures (see Fig. 42–14F). Finally, venous anastomosis to the facial vein, the middle thyroid vein, or one of the jugular veins is carried out.

The cervical incision is usually closed without drainage. A thermistor probe has been used as a method of monitoring viability of the jejunal graft. Alternatively, a Silastic "window" can be used for direct observation of the jejunal segment for 24 to 48 hours and then primarily closed once viability is ascertained (see Fig. 42–14G). It is preferred that a nasogastric tube not be allowed to pass through the cervical jejunum; gastric drainage can be accomplished with a gastrostomy tube.

SHORT-SEGMENT COLON INTERPOSITION

Short-segment colon interposition is an alternative to jejunal interposition of the distal esophagus. Preparation of the patient and colon is as described for long-segment colon interposition. Because extensive length is not required, more options exist, and arteriography is not as critical. The most popular segment of colon to use for distal esophageal replacement is an isoperistaltic segment of the distal transverse colon or the descending left colon based on the ascending branch of the left colic artery.

The operation is usually performed through an extended left thoracoabdominal incision to allow mobilization of the colon segment, resection of the diseased distal esophagus, and anastomosis of the colon segment to the distal esophagus and posterior wall of the stomach. Left colon segments are based on the ascending branch of the left colic artery. Transverse colon segments are based on the middle colic artery. The colon segment should be isoperistaltic. In our experience, the left colon was used more commonly ($n = 19$) than the transverse colon ($n = 3$).[6] The length of colon segment needed is mobilized, and the vascular pedicle is identified but not skeletonized. The bowel is divided with staplers and the colon segment placed in a posterior mediastinal position while avoiding tension or torsion of the vascular pedicle. The proximal anastomosis is end to end with a two-layered closure of interrupted 4-0 silk. The distal anastomosis is end to side, most commonly to the posterior gastric wall. This allows the colon to be positioned in a more direct, straight path than an anastomosis to the anterior gastric wall does. At least 12 cm of colon is desirable to prevent reflux. A nasogastric tube through the colonic segment is used initially, and gastrostomy or jejunostomy is performed when indicated. The hiatus is carefully tacked to the colon to prevent herniation of abdominal contents. A gastric drainage procedure is always performed.

Results of Short-Segment Colon and Jejunal Interposition

Jurkiewicz and Paletta recounted their experience with 130 free jejunal interpositions and reported a graft sur-

Table 42–5 Indications for Short-Segment Intestinal Interposition of the Distal Esophagus

Diagnosis	No. of Patients
Gastroesophageal reflux disease	34
Failed antireflux repair	21
Nondilatable stricture	9
Complication of treatment of chalasia	2
Complication of myotomy for motility disorder	1
Complication of intrathoracic esophagogastrostomy	1
Esophageal moniliasis with stricture	2
Barrett's esophagus with carcinoma in situ	2
Leak from esophagotomy	1
Carcinoma of the esophagus	1
Leiomyosarcoma of the esophagus	1

From Gaissert HA, Mathisen DJ, Grillo HC, et al: Short segment intestinal interposition of the distal esophagus. J Thorac Cardiovasc Surg 106:860, 1993.

Table 42–6 Major Complications After Intestinal Interposition

Complication	No. of Patients
Colon	
Pneumonia/acute respiratory distress syndrome	4*
Graft perforation	1
Colon perforation, subphrenic abscess	1
Chylothorax	1
Pulmonary edema	1
Pulmonary embolus	1
Deep vein thrombosis	1
Jejunum	
Pneumonia	3
Graft necrosis	1*
Gastric perforation	1
Paraparesis, aortoenteric erosion	1
Transient recurrent nerve injury	1
Myocardial infarction	1*

*Cause of operative mortality.
From Gaissert HA, Mathisen DJ, Grillo HC, et al: Short segment intestinal interposition of the distal esophagus. J Thorac Cardiovasc Surg 106:860, 1993.

vival rate of 92%.[30] The operative mortality rate was 5%. The main cause of graft failure is often arterial or venous insufficiency, and if graft failure does occurs, a second attempt with another free jejunal graft should be made, with success rates of 50% to 75% being attained. A pharyngocutaneous fistula is a common postoperative complication that was reported in 33 of 101 patients in Jurkiewicz and Paletta's series. Twenty-four of these fistulas closed spontaneously; the others were managed by a second graft or simple drainage.

Gaissert and associates published our results with jejunal (19 patients) and short-segment colon (22 patients) interposition of the distal esophagus.[31] Indications for intestinal interposition are listed in Table 42–5. Multiple previous operations were common and had occurred in more than 75% of patients. Major complications developed in 45% of patients (10 of 22) after colon interposition, and the hospital mortality rate was 4.5% (Table 42–6). Major complications after jejunal interposition occurred in 31% of patients, and the hospital mortality rate was 10.9%. Late functional results in 32 patients with a mean follow-up of 87 months were excellent in 26, fair in 5, and poor in 1.

Intestinal interposition is a technically demanding procedure that requires strict attention to detail to avoid catastrophic complications and ensure the greatest chance for success.

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Chapter

43

Complications of Esophageal Surgery

Andrew C. Chang · Mark B. Orringer

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Many of the complications of esophageal surgery are directly related to specific features of esophageal anatomy and physiology. Detailed knowledge and thorough understanding of these characteristics by the surgeon are essential to identify potential pitfalls of esophageal surgery and avert complications before they occur. When performing esophagoscopy, for example, one must bear in mind the three naturally occurring sites of esophageal narrowing: the upper esophageal introitus, or the cricopharyngeal sphincter; the level of the aortic arch and left main stem bronchus; and the esophagogastric junction (Fig. 43–1). The rigid esophagoscope must be manipulated appropriately through these points of narrowing to minimize the risk for injury during esophagoscopy. One distinct feature of esophageal anatomy is its unusually fatty submucosa, which allows greater mobility of the overlying squamous mucosa. When performing an esophageal anastomosis manually, meticulous technique is essential to ensure such that every suture transfixes the mucosal edge, which at times may retract more than 1 cm from the cut esophageal margin (Fig. 43–2). The esophagus is also unique in the gastrointestinal tract because it lacks a serosal layer. The soft and often tenuous muscle holds sutures poorly and cannot be relied on to maintain a fundoplication, for example, unless the associated submucosa is transfixed by the esophageal stitch.

The esophagus is nourished by four to six paired aortic esophageal arteries, as well as collateral circulation from the inferior thyroid, intercostal and bronchial, inferior phrenic, and left gastric arteries. The segmental "poor" blood supply of the esophagus has frequently been incriminated as the cause of anastomotic disruption. However, the submucosal collateral circulation of the esophagus is extensive, and even after the cardia has been divided and the intrathoracic esophagus mobilized completely out of the chest, the distal end of the esophagus maintains good arterial bleeding as long as the inferior thyroid arteries remain intact. Poor technique, not poor blood supply, is the more likely explanation for the complication of esophageal anastomotic disruption. Finally, the parasympathetic innervation of the esophagus is supplied by the vagus nerves, and the recurrent laryngeal nerve supplies the upper portion of the esophagus. Recurrent laryngeal nerve injury during esophageal surgery may result in one of the most devastating complications, cricopharyngeal muscle dysfunction with subsequent incapacitating cervical dysphagia and aspiration pneumonia.[1] Similarly, injury to the vagal nerve trunks during distal esophageal operations may produce neurogenic dysphagia or gastric atony and pylorospasm, which are very troublesome complications after esophageal surgery.

Physiologic considerations influence other complications of surgery on the esophagus. The pathophysiology of gastroesophageal reflux and secondary reflux esophagitis directly influences the results of antireflux surgery and hence the complication of recurrent reflux. For example, it has been demonstrated that the incidence of recurrent reflux in patients undergoing the standard Belsey Mark IV transthoracic hiatal hernia repair in the presence of esophagitis or stricture is between 25% and 75%.[2,3] In patients with intramural inflammation and esophageal shortening secondary to reflux esophagitis, the esophageal sutures of the Belsey repair may not be reliable, and tension on the repair to reduce the requisite 3 to 5 cm of distal esophagus below the diaphragm sets the stage for recurrence of the hernia (Fig. 43–3). These same considerations apply to the Nissen fundoplication and the Hill posterior gastropexy, which also aim to restore an intra-abdominal segment of distal esophagus and require esophageal or periesophageal sutures (Fig. 43–4). To avert the complication of disruption of the repair as a consequence of (1) the

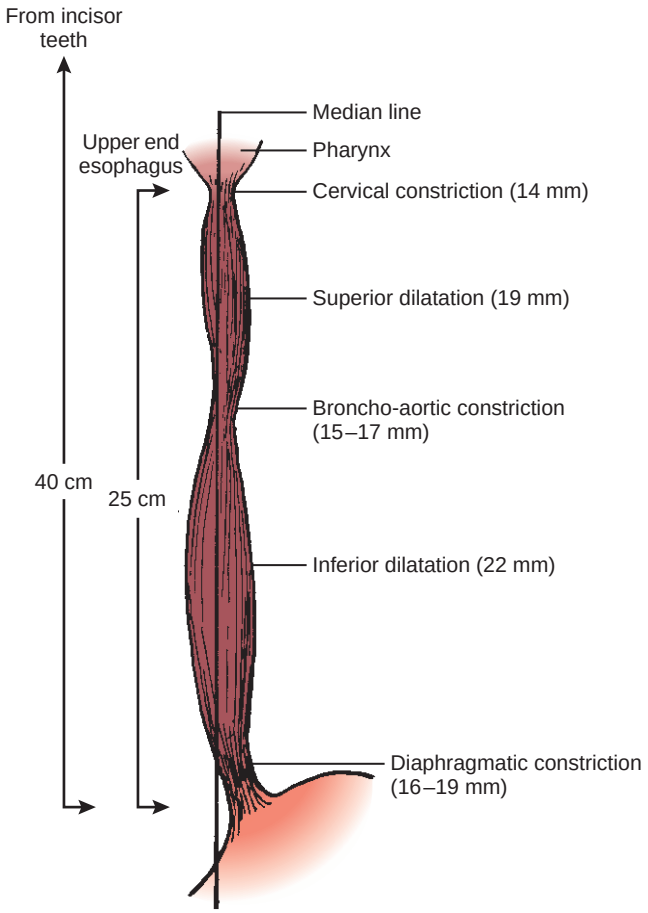

Figure 43–1. Normal esophageal constrictions, dilatations, and measurements. (From Shackelford RT [ed]: Surgery of the Alimentary Tract, vol 1, 2nd ed. Philadelphia, WB Saunders, 1978.)

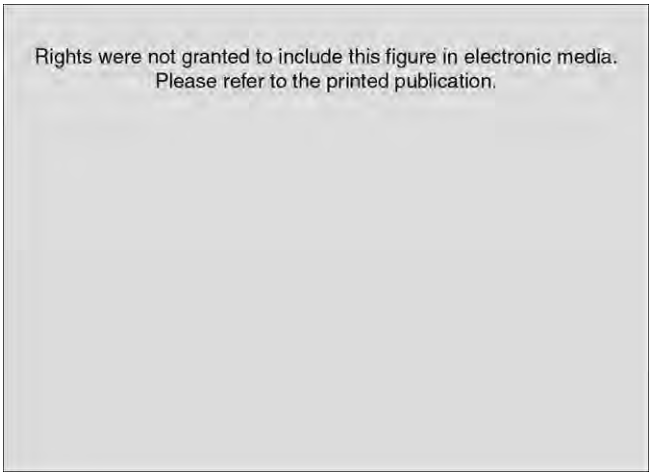

Figure 43–2. Failure of an esophageal anastomotic suture to transfix the mucosa is a function of the fatty submucosa, which permits mobility of the overlying mucosa and allows it to retract. The mucosa must be identified and deliberately transfixed with each suture placed to achieve mucosal apposition and avoid an anastomotic leak. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 303.)

need to suture an inflamed esophagus and (2) tension on the repair, the esophagus-lengthening Collis gastroplasty can be combined with fundoplication.[4-6] The gastroplasty tube functions as a new distal esophagus and provides healthy, resilient tissue (i.e., the gastric wall) around which to perform the fundoplication. Furthermore, the additional "esophageal length" provided by the gastroplasty tube reduces tension on the repair. The presence of reflux esophagitis and a peptic stricture also complicates an antireflux procedure if the stricture is perforated during attempted dilation.

An intrathoracic esophagogastric anastomotic leak, perhaps the most dreaded complication of esophageal surgery, in part owes its morbidity to associated gastroesophageal reflux. An intrathoracic esophagogastric anastomosis is almost invariably associated with the development of reflux esophagitis, in contrast to a cervical esophagogastric anastomosis, which is rarely associated with clinically significant reflux. Although it has been argued that with appropriate attention to detail, an intrathoracic esophagogastric anastomosis can be performed reliably and with an exceedingly low morbidity rate,[7] the potential for an anastomotic leak and secondary mediastinitis cannot be eliminated totally, and this fact perhaps more than anything else has influenced our current "defensive posture" that the best esophagogastric anastomosis is a cervical anastomosis because the consequence of a leak is a salivary fistula and not life-threatening mediastinitis and sepsis.

Gastroesophageal reflux after esophageal resection and esophagogastric anastomosis may be responsible for life-threatening aspiration of gastric contents into the tracheobronchial tree in the early postoperative period. For this reason, initial decompression of the intrathoracic stomach with a nasogastric tube and placement of the patient in a 45-degree head-up position are important. Similarly, because of the potential for regurgitation and aspiration after eating, patients who have a fresh esophagogastric anastomosis should not be permitted to undergo postural drainage as part of their postoperative pulmonary physiotherapy within 1 to 2 hours of mealtime.

The potential pulmonary complications, primarily aspiration pneumonia, resulting from esophageal obstruction secondary to a variety of causes cannot be overestimated. Particularly in a patient with megaesophagus as a result of advanced achalasia, the risk for massive regurgitation and aspiration on induction of general anesthesia is enormous. Awareness of this possibility dictates the need for esophageal decompression and emptying by nasogastric tube in these patients before rapid-sequence induction of general anesthesia and endotracheal intubation.

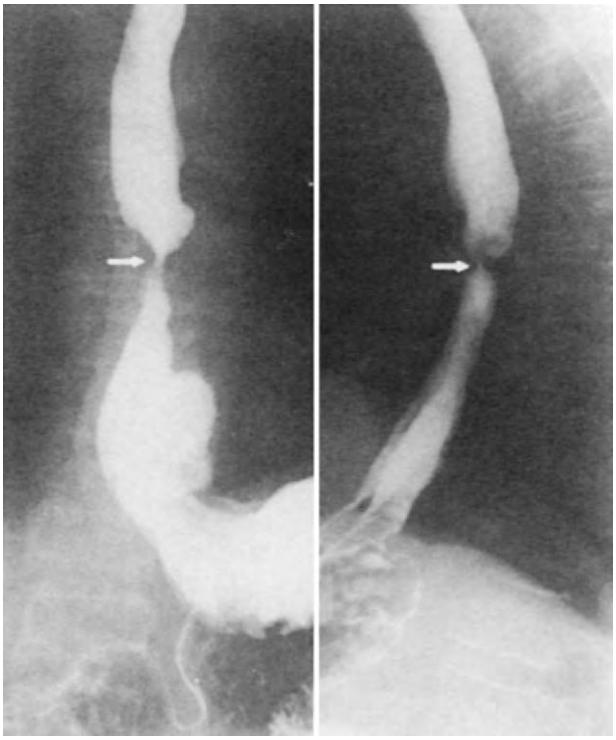

Figure 43–3. Posteroanterior *(left)* and lateral *(right)* views from a barium swallow examination showing a sliding hiatal hernia with a midesophageal stricture *(arrow)* at the squamocolumnar junction in a patient with Barrett's esophagus. Standard antireflux operations (Hill, Belsey, or Nissen) require reduction below the diaphragm of not only the esophagogastric junction but also the distal 3 to 5 cm of esophagus. The esophageal shortening and periesophageal fibrosis secondary to reflux esophagitis in this patient prevented a tension-free standard repair.

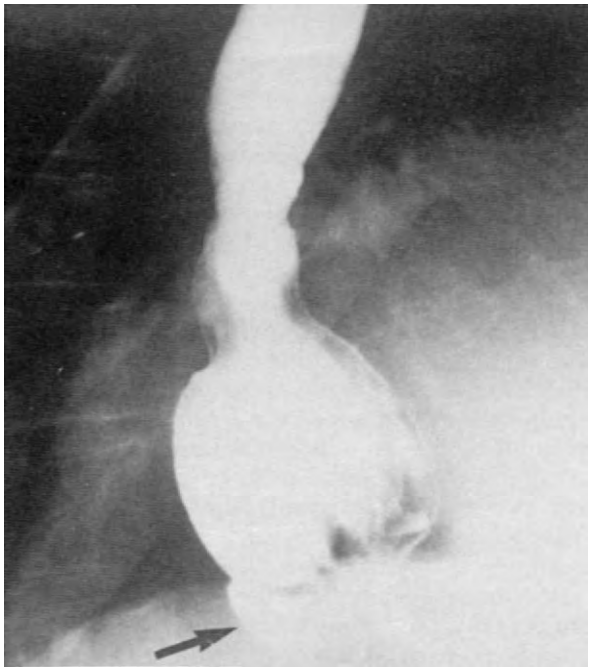

Figure 43–4. Slipped Nissen fundoplication in a patient who was operated on for reflux complicated by a short esophagus and stricture. Tension on the repair resulted in subsequent disruption of it. The proximal part of the stomach has herniated through the fundoplication *(arrow)* and is seen above the level of the diaphragm.

ESOPHAGEAL PERFORATION

Perforation of the thoracic esophagus, with resultant mediastinitis, poses a devastating threat. Regardless of the cause of perforation (Box 43–1), delay in recognition and definitive management increases concomitant mortality and morbidity. Repair of an acute esophageal tear in an otherwise normal esophagus within 6 to 8 hours carries a risk of morbidity that is essentially the same as that imposed by elective esophagotomy and primary esophageal closure. If operative intervention is delayed beyond this early period, local inflammation greatly jeopardizes primary healing of the esophageal tear and mortality rises dramatically.[8-10]

Esophageal instrumentation accounts for the large majority of iatrogenic perforations, with the cricopharyngeal area most commonly injured (Fig. 43–5). Perforation of the mid and distal esophageal segments is most likely to occur after biopsy or dilatation. Spontaneous perforation usually occurs after straining (Boerhaave's syndrome), with rupture involving the left posterior aspect of the distal esophagus.[11]

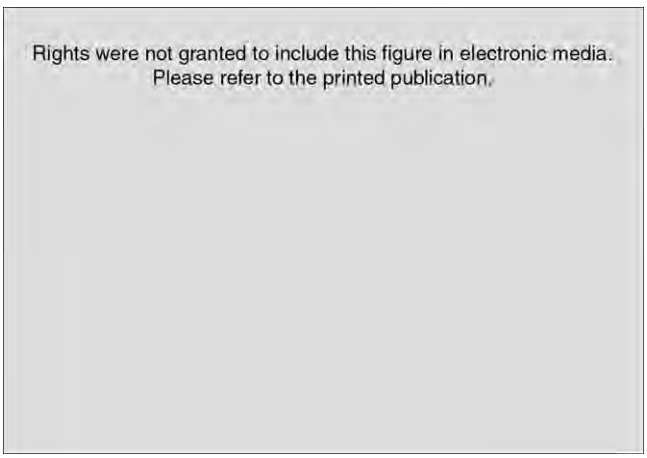

Figure 43–5. Mechanism of endoscopic cervical esophageal perforation. In performing rigid esophagoscopy, it is essential that a gentle, steady lifting force *(arrow)* be exerted to displace the larynx and cricoid cartilage forward. Failure to overcome the natural pull of the upper esophageal sphincter against the cricoid cartilage results in a typical posterior perforation *(inset)* (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 309.)

Box 43–1 Causes of Esophageal Perforation

Instrumental

- Endoscopy
  - Direct injury
  - Injury occurring during removal of a foreign body
- Dilatation
- Intubation (esophageal, endotracheal)

Noninstrumental

- Barogenic trauma
  - Postemetic
  - Blunt chest or abdominal trauma
  - Other (e.g., labor, convulsion, defecation)
- Penetrating neck, chest, or abdominal trauma
- Postoperative
  - Anastomotic disruption
  - Devascularization after pulmonary resection, vagotomy, or repair of hiatal hernia
- Injury after ingestion of a caustic agent
- Erosion by adjacent infection with a resultant fistula involving the tracheobronchial tree, pericardium, pleural cavity, or aorta
- Pathologic
  - Severe reflux esophagitis
  - Candidal, herpetic, and opportunistic infection

Diagnosis

Patients with esophageal perforation typically have pain directly referred from the site of injury. The presence of mediastinal air or hydropneumothorax on a chest radiograph in a patient suspected of having a perforation is confirmatory. However, a normal chest radiograph does not exclude the possibility of esophageal perforation. Not every esophageal tear is a full-thickness disruption. For example, pneumatic dilatation of the esophagus for achalasia may result in a tear of the distal esophageal mucosa and submucosa. Air insufflation through a flexible esophagoscope may result in mediastinal, cervical, or subcutaneous air, thereby exaggerating the extent of injury. After esophagoscopy or an esophageal operation, postoperative pain or fever should be considered to be caused by esophageal perforation until proved otherwise. Contrast esophagography should be performed immediately to limit any further delay in establishing proper drainage or definitive repair, or both. Water-soluble contrast esophagography, followed by dilute barium, best identifies the site of perforation (Fig. 43–6) and establishes whether the perforation is communicating with either the pleural or peritoneal cavities or is confined to the mediastinum.

Treatment

Once the diagnosis of esophageal perforation is established, oral intake by the patient should cease. Aggressive intravenous fluid resuscitation, facilitated by using either a central venous pressure catheter or a pulmonary artery catheter, is indicated if there is hypovolemia associated with an intrathoracic perforation. Broad-spectrum antibiotic coverage is initiated. The presence of carious teeth increases the risk for morbidity in patients with esophageal injury because of the virulence of swallowed oral bacteria. Thus, oral hygiene should not be neglected in a patient with an esophageal perforation.

There is controversy about the best method of treatment of patients with esophageal perforations. Nonoperative "conservative" therapy is successful in some patients with esophageal perforation, primarily those with preexisting periesophageal and mediastinal fibrosis that contains the injury. Thus, for an esophageal disruption in which contrast material extends only a few millimeters from the esophageal lumen and the patient is doing well clinically, antibiotic therapy, chest tube drainage as indicated, and observation may suffice.[12-14] More frequently, however, a successful outcome after esophageal perforation requires surgical intervention (Fig. 43–7).

Perforation of the cervical and upper thoracic esophagus is approached through an oblique cervical incision that parallels the anterior border of the left sternocleidomastoid muscle (Fig. 43–8). The sternocleidomastoid muscle and carotid sheath are retracted laterally and the trachea and thyroid gland medially. If the perforation can be identified, it is closed with absorbable polyglycolic acid sutures. If the injury cannot be visualized adequately for repair, the retroesophageal prevertebral space is dissected bluntly with the finger and the superior mediastinum is drained with two 1-inch Penrose drains brought out through the neck wound. Esophageal perforations at the level of the tracheal bifurcation can generally be treated successfully with such a cervical approach. Midthoracic esophageal perforations must be approached through a right thoracotomy, and those of the distal third of the esophagus are approached through a left thoracotomy.

Traditional surgical dogma teaches that esophageal perforations beyond 6 to 12 hours in duration are virtually impossible to repair primarily because the pouting inflamed mucosa at the edge of the tear holds sutures poorly. Isolated reports, however, have emphasized that even after a marked delay in repair, successful closure of the esophageal injury may be possible.[8,15] Several groups have found that the majority of esophageal tears can in fact be repaired successfully with meticulous surgical technique that includes identification of adjacent submucosa by dissecting away the overlying muscle, definition of the limits of the mucosal tear (Fig. 43–9), reapproximation of the disrupted mucosa and submucosa with a surgical stapler (Auto Suture Endo GIA II Stapler, U.S. Surgical Corporation, Auto Suture Company Division, Norwalk, CT),[16] and reapproximation of the muscle over the staple suture line (Fig. 43–10). Limited esophagomyotomy performed 180

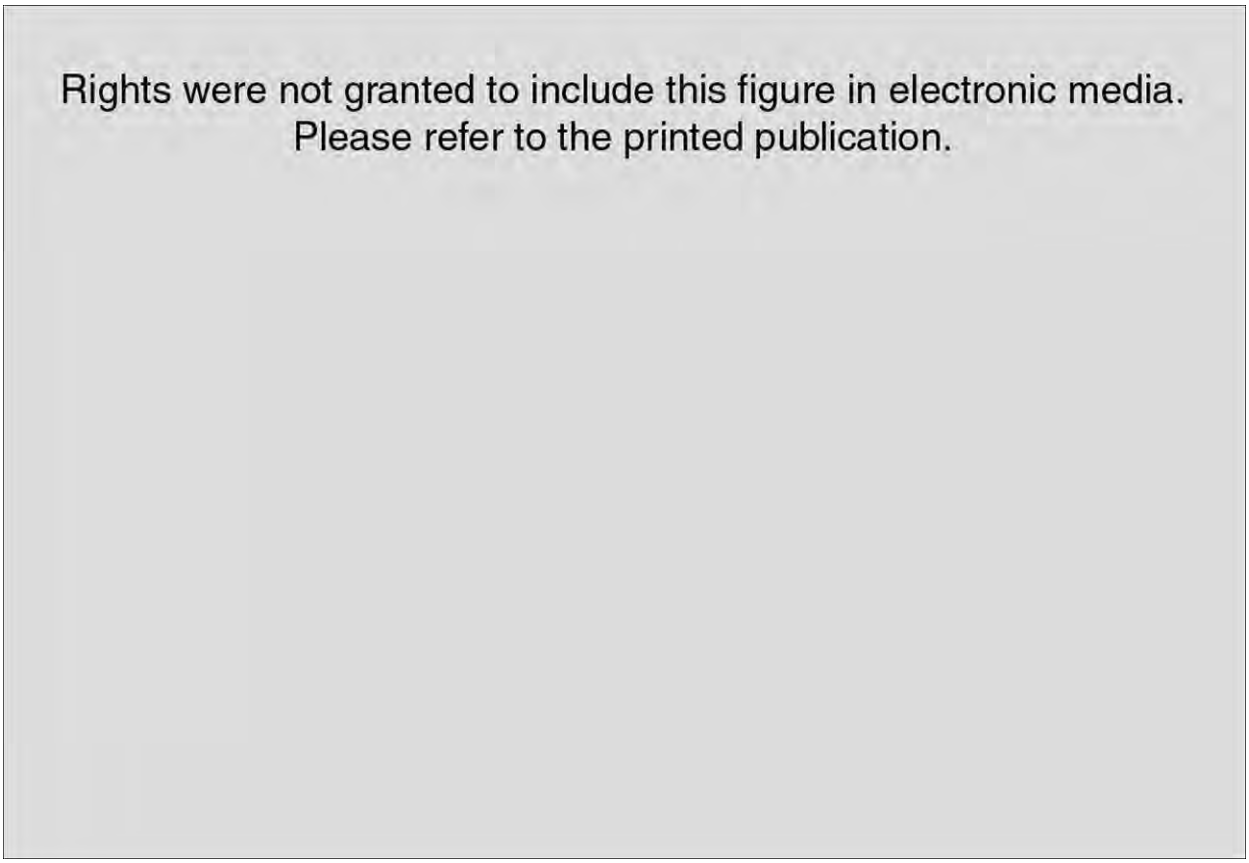

Figure 43–6. Posteroanterior *(left)* and lateral *(center)* views from a diatrizoate meglumine (Gastrografin) esophagogram in a patient with acute caustic injury that was incorrectly dilated prematurely within 10 days of caustic ingestion. There was still acute inflammation in this esophagus, and the patient had fever and chest pain after dilation. Despite the negative Gastrografin swallow, dilute barium was administered *(right),* and a perforation *(arrow)* of the midesophagus was demonstrated. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 312.)

degrees opposite the site of injury may permit enough advancement of adjacent esophageal wall for adequate repair of the perforation.[17] In patients with chronic mediastinitis and pleural reaction, the adjacent mediastinal pleura is thickened and provides an excellent flap with which to reinforce the esophageal suture line. Alternatively, if insufficient parietal pleural thickening is available to provide adequate support for the suture line, reinforcement with a pedicled intercostal muscle flap, omentum, pericardium, visceral pleura, or diaphragm can be carried out.[18,19] The mediastinal pleura must be opened from the apex of the chest to the diaphragm to permit wide drainage of the mediastinum. After copious irrigation of the mediastinum and pleural cavity and decortication of any acute fibrinous exudate that may have formed over the lung, a large-bore chest tube is left near the esophageal suture line so that if disruption occurs, the result will be an esophagopleural cutaneous fistula.

When treating an esophageal perforation, associated esophageal disease cannot be ignored. Thus, a perforation proximal to a carcinoma or a caustic or reflux stricture may necessitate emergency esophagectomy with either primary or delayed esophageal reconstruction. In patients with an esophageal perforation and a long-standing history of reflux stricture, postoperative dysphagia requiring repeated esophageal dilatation is more likely to develop. In this subset of patients, consideration should be given to primary esophagectomy if their physiologic status at the time of surgery permits.[20] Alternatively, if it is possible to dilate a benign stricture intraoperatively to relieve the distal obstruction, closure of a proximal esophageal perforation may be successful. A subsequent disruption of the esophageal closure may still eventually heal if dilatation of the associated stricture is continued. A perforated pulsion diverticulum of the esophagus may be resected within several hours of the injury. The associated obstruction must be dealt with and the esophageal neuromotor dysfunction responsible for formation of the pouch relieved by performing a concomitant esophagomyotomy.

PROCEDURAL COMPLICATIONS

Esophagoscopy

Technologic advances in the development of flexible fiberoptic instruments have greatly facilitated the

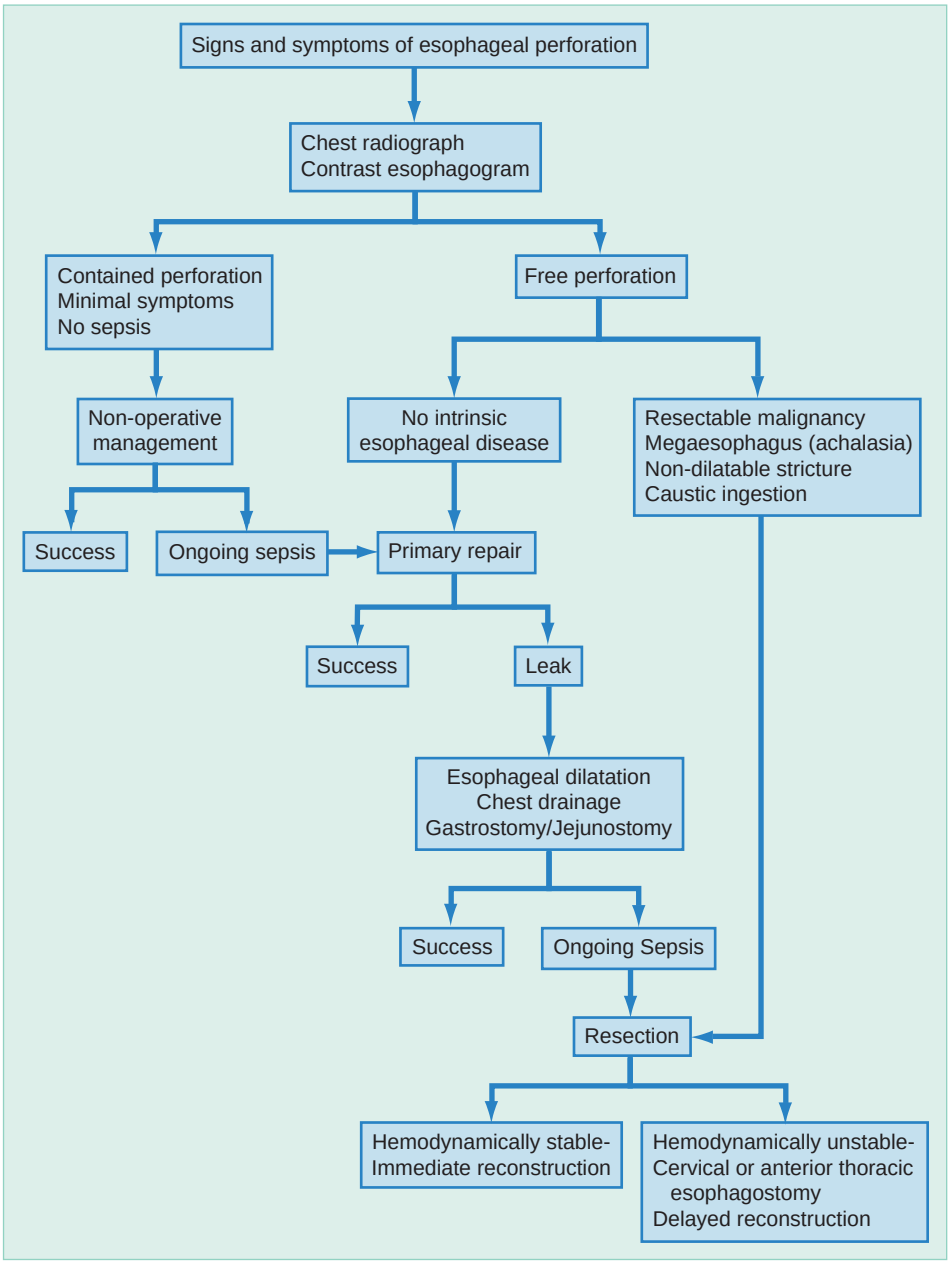

Figure 43–7. Treatment algorithm for esophageal perforation. (From Chang AC, Iannettoni MD: Complications of esophageal surgery. In Mulholland MW, Doherty GA [eds]: Complications in Surgery. Philadelphia, Lippincott Williams & Wilkins, 2006.)

performance of esophagogastroscopy, particularly with the advent of endoscopic ultrasound. Furthermore, there has been a concomitant increase in the number of these studies being performed on an outpatient basis. The consequences of esophageal disruption, however, have not changed. Perforation occurs in 0.8% of all patients during flexible upper endoscopy, with rates as high as 4% in patients undergoing esophageal dilatation.[21] Perforation after rigid esophagoscopy can occur in as many as 5% of patients after therapeutic procedures (e.g., biopsy, dilatation, or removal of a foreign body) and in up to 1.5% of patients after rigid esophagoscopy alone.[22] To avoid perforation during esophagoscopy, certain basic principles must be acknowledged:

1. Adequate preoperative and intraoperative sedation and anesthesia are mandatory. In some cases, general anesthesia is the only means of creating acceptable conditions for performing esophagoscopy for both the patient and the surgeon.
2. Esophagoscopy should not be carried out unless a barium esophagogram has been performed and reviewed by the endoscopist. The barium swallow provides information about preexisting disease and its expected location (Fig. 43–11). For example, a Zenker diverticulum identified on a contrast esophagogram should be expected to be encountered at the level of the upper esophageal sphincter, approximately 15 cm from the upper

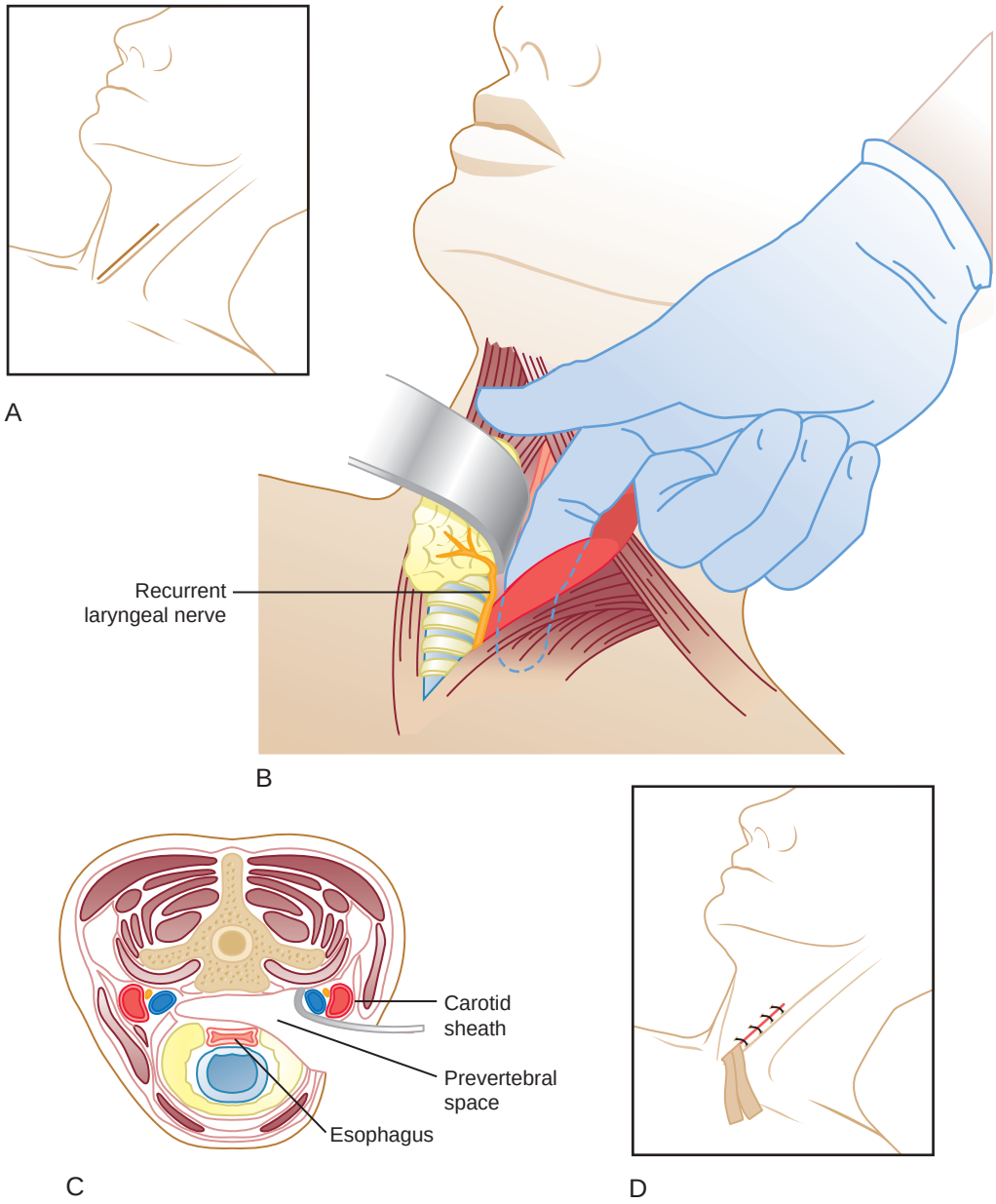

Figure 43–8. Surgical approach to a perforated cervical esophagus. **A,** Skin incision along the anterior border of the left sternocleidomastoid muscle from the level of the cricoid cartilage to the sternal notch. **B,** Blunt dissection into the superior mediastinum along the prevertebral fascia medial to the sternocleidomastoid muscle and carotid sheath. Injury to the recurrent laryngeal nerve in the tracheoesophageal groove must be avoided. **C,** Schematic view of the prevertebral space to be drained. **D,** Placement of two 1-inch rubber drains to allow establishment of an esophagocutaneous fistula. (From Orringer MB: The mediastinum. In Nora PF [ed]: Nora's Operative Surgery, 3rd ed. Philadelphia, WB Saunders, 1990, p 374.)

incisors. A midesophageal carcinoma at the level of the tracheal bifurcation is encountered approximately 25 cm from the upper incisors. An epiphrenic diverticulum is encountered before the esophagoscope reaches the esophagogastric junction at a point 40 cm from the upper incisors. Perforation of a cervical esophageal diverticulum or a midesophageal stricture cannot be justified because the endoscopist was unaware of these lesions as a result of neither obtaining nor personally reviewing a barium swallow examination beforehand.

3. Failure to introduce the rigid esophagoscope properly through the upper esophageal sphincter may result in a perforation. The cricopharyngeus muscle originates from the cricoid cartilage, and the natural "pull" of this muscle against the cartilage will result in a posterior perforation unless the larynx is "lifted" anteriorly as the esophagoscope is advanced.

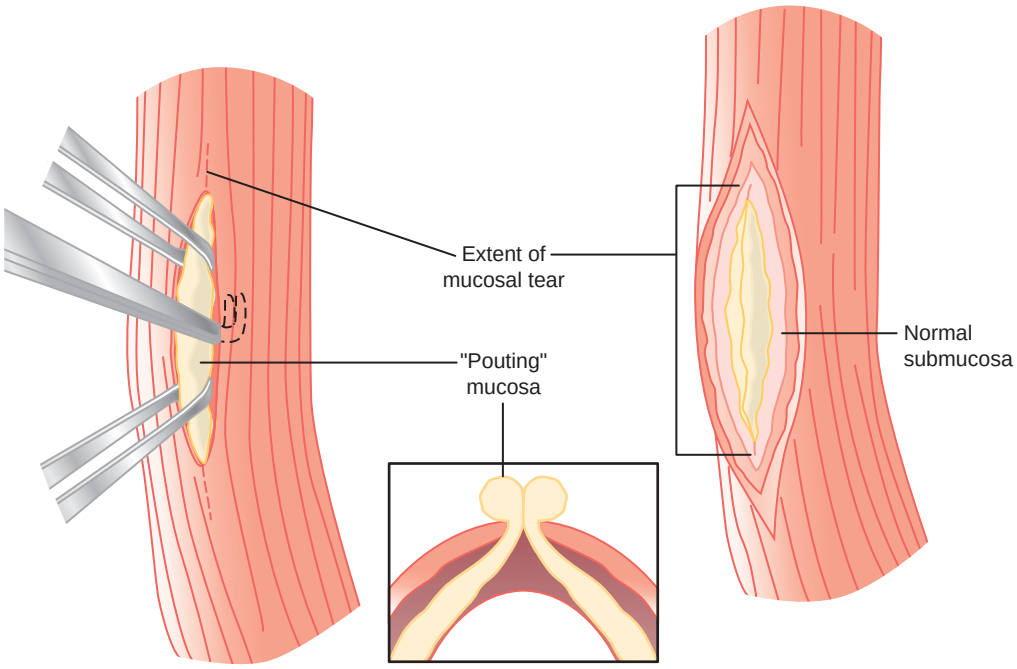

Figure 43–9. Technique of primary repair of an esophageal perforation. Mucosa at the site of the tear *(inset)* is grasped with Allis clamps **(A),** and the adjacent esophageal muscle is mobilized around the entire tear until 1 cm of normal submucosa is exposed around the defect **(B).** (From Whyte RI, Iannettoni MD, Orringer MB: Intrathoracic perforation: The merit of primary repair. J Thorac Cardiovasc Surg 109:140, 1995.)

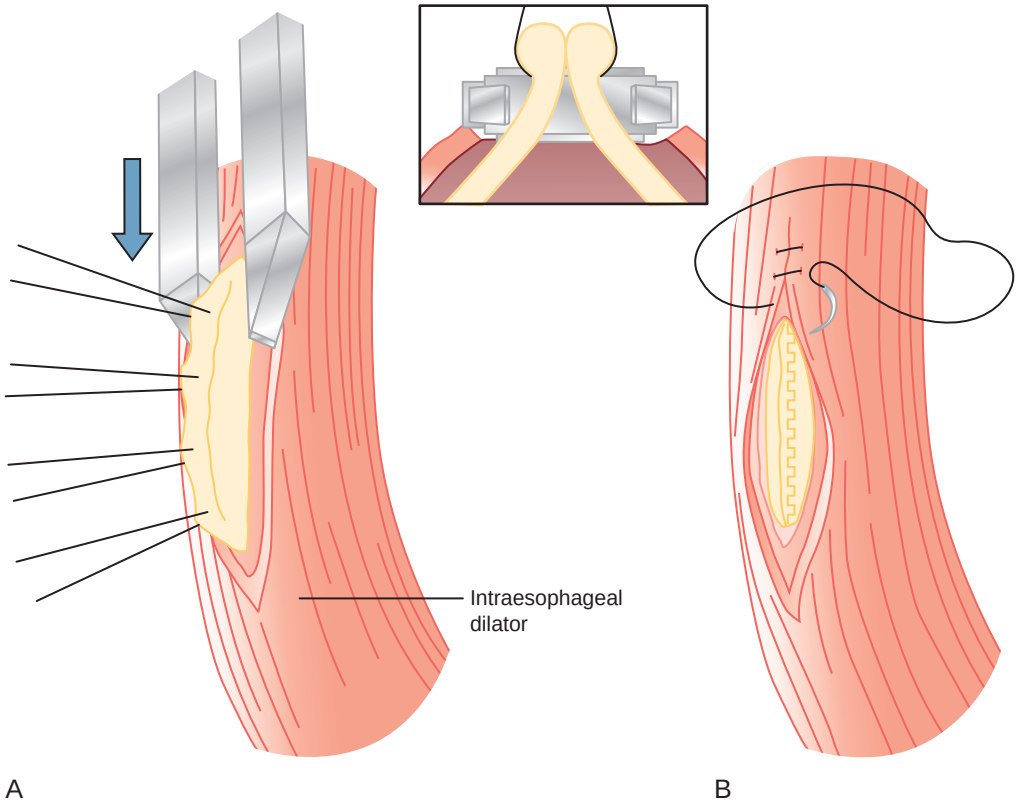

Figure 43–10. Technique of primary repair of an esophageal perforation (continuation of Fig. 43-9). Traction sutures placed along the inflamed mucosal edge of the tear elevate the submucosa so that an Endo GIA II cartridge (3.5-mm staples) can be applied and deployed. The esophageal lumen is maintained by passage of an intraesophageal dilator (**A** and *inset*). The staple line is covered by approximating the adjacent muscle with running absorbable suture **(B).** (From Whyte RI, Iannettoni MD, Orringer MB: Intrathoracic perforation: The merit of primary repair. J Thorac Cardiovasc Surg, 109:140, 1995.)

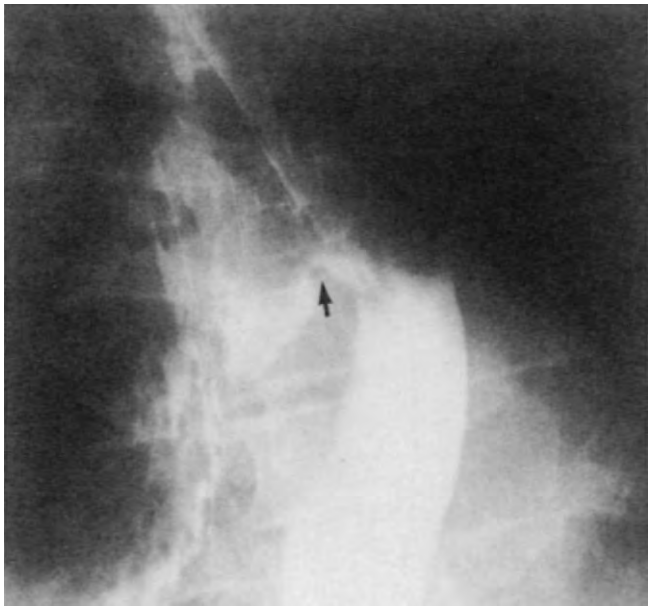

Figure 43–11. Gastrografin swallow showing a midesophageal perforation *(arrow)* after rigid esophagoscopy in a patient who had dysphagia. An outside "normal" barium swallow report had been accepted, and esophagoscopy was performed without the endoscopist seeing the contrast study. In this patient, a large subcarinal mass of lymph nodes secondary to sarcoidosis was displacing the esophagus to the left, as is evident in this posteroanterior view. Without knowledge of this abnormal course of the esophagus in this patient, the esophagoscope was advanced, and a perforation occurred. The surgeon performing esophagoscopy is responsible for seeing the barium swallow examination in the patient before passing the esophagoscope.

4. The esophagoscope should not be advanced unless the lumen is visible.
5. As the esophagoscope is advanced, adjustment must be made for the natural course of the esophagus. Because the distal esophagus courses anteriorly and to the left as it joins the stomach, the instrument must be angled toward the right side of the patient's mouth and the occiput of the head lowered as the esophagoscope is advanced into the distal end of the esophagus, particularly when performing rigid endoscopy.
6. The initial dilatation of a tight esophageal stricture is frequently painful, and adequate sedation and anesthesia are important to minimize patient discomfort and allow the surgeon to concentrate on the visual field. When a rigid esophagoscope is used for this initial evaluation, flexible gum-tipped Jackson bougies are inserted through the stricture under direct vision, and the pliability and extent of the stenosis are assessed. With a mild "soft" stenosis, dilatation by advancing the esophagoscope through the stenosis might be possible. With firmer, high-grade strictures, it is safer to pass progressively larger dilators through the narrowing. This can be accomplished by using the Savary-Gilliard guidewire and dilating system, under fluoroscopic guidance, or Maloney tapered esophageal dilators. The latter instruments are our preference for repeated outpatient dilatations of esophageal strictures; they do not require the sedation or anesthesia that is necessary when endoscopic balloon dilatations are performed.

Box 43–2 Complications of Hiatal Herniorrhaphy

Intraoperative Complications

- Perforation
- Vagus nerve injury
- Hemorrhage
  - Splenic laceration
  - Short gastric vessel

Postoperative Complications

- Perforation
  - Stricture
  - Suture placement
- Dysphagia
  - Mechanical
    - Tight hiatal closure
    - Excessive fundoplication
    - Inadequate gastroplasty
  - Edema
  - Gastric atony, pylorospasm
- Early anatomic recurrence
  - Crural repair disruption
- Functional
  - Postvagotomy diarrhea
  - Ileus
- Cardiac tamponade
- Chylothorax
- Pleural effusion
- Incisional pain

Modified from Patel HJ, Tan BT, Yee J, et al: A twenty-five year experience with open primary transthoracic repair of paraesophageal hiatal hernia. J Thorac Cardiovasc Surg 127:843, 2004.

Hiatal Hernia Repair

Hiatal herniorrhaphy, though conceptually quite simple, can result in a number of serious complications (Box 43–2). Acute esophageal perforation can occur when concomitant esophagoscopy is performed during an antireflux operation or when a distal esophageal stricture is disrupted during intraoperative dilatation. A delayed perforation, usually within 1 week of surgery, may occur

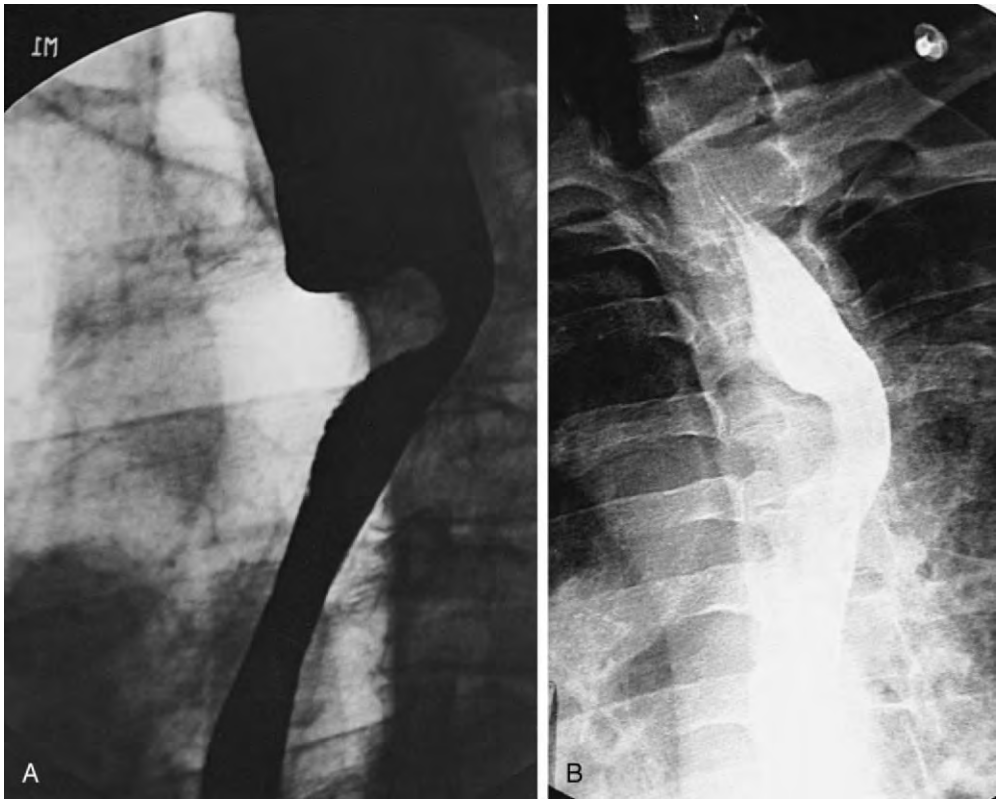

Figure 43–12. A, Barium swallow examination in a 49-year-old man who was treated for a gunshot wound in the esophagus and trachea 23 years earlier. At that operation, the tracheal and esophageal holes were débrided and repaired, and the esophagus was incorrectly wrapped circumferentially with a mobilized intercostal muscle pedicle. Subsequent regeneration of cartilage from the perichondrium of the intercostal pedicle resulted in severe dysphagia and the high-grade upper esophageal stenosis with proximal esophageal dilation that is shown. **B,** Postoperative barium swallow after a repeat right thoracotomy and partial resection of the encircling cartilaginous and muscle ring. The lumen was greatly improved, and the dysphagia was relieved.

when esophageal sutures placed too deeply during the repair result in local mural necrosis.

Acute esophageal tears recognized intraoperatively should be approached transthoracically and repaired and the esophageal suture line reinforced either with the fundoplication if the tear is in the distal esophagus or with pedicled anterior mediastinal fat or a pedicled intercostal muscle flap if the tear is higher. When an intercostal muscle pedicle is used to reinforce an esophageal suture line, it should be sutured to the esophagus as an onlay patch, not placed circumferentially around the esophagus; otherwise, regeneration of bone or cartilage from the perichondrium or periosteum mobilized with the flap may result in a late obstructing ring around the esophagus (Fig. 43–12). When a reflux stricture is perforated during attempted dilation at the time of a planned antireflux operation, unless the involved tissues are relatively healthy and amenable to repair, resectional therapy is generally a better option. Although most reflux strictures can be dilated and many regress after an antireflux procedure has been carried out, disruption of a stricture during attempted dilation is one of the definitions of an "undilatable" stricture that justifies esophageal resection. Our preference in this situation is to proceed with transthoracic esophagectomy and then reposition the patient supine and carry out a cervical esophagogastric anastomosis. Several additional options for the treatment of a disrupted distal stricture are available. Unfortunately, none is without its associated morbidity. The Thal fundic patch esophagoplasty uses adjacent gastric fundus to "patch" the opened narrowed esophagus. This procedure not only relies on healing of the opened, inflamed distal esophagus to which the stomach is sutured but also requires the addition of an intrathoracic fundoplication (Thal-Woodward procedure) to control gastroesophageal reflux, in effect, creating an iatrogenic paraesophageal hiatal hernia. The high incidence of suture line disruption and mechanical complications associated with this operation condemns its use. For the same reason, we oppose the use of an intrathoracic fundoplication (without a Thal procedure) to control reflux (Fig. 43–13). The complications of such an approach outweigh its benefits.

Gastric ulceration may complicate 3% to 10% of fundoplications and may occur with both supradiaphragmatic fundic wraps and intra-abdominal fundoplications. In the former, one is dealing with a complication of an iatrogenic paraesophageal hiatal hernia, and operative repair is generally indicated. In the latter, ulceration may be due to relative ischemia in the wrap, and treatment with H_2 receptor blockers, proton pump inhibitors, or cytoprotective agents may suffice.

The development of fever, chest pain, or respiratory distress during the first week after a hiatal hernia operation mandates a contrast study, and if a distal esophageal perforation is diagnosed, treatment usually involves reoperation. The site of the perforation is identified intraoperatively, at times by insufflating air through a nasogastric tube. A leak from an intra-abdominal fundoplication suture may be closed and reinforced with adjacent omentum. If the leak is in the chest, pedicled anterior mediastinal fat, intercostal muscle, or pleura is used to reinforce the closure through a transthoracic approach. A jejunostomy feeding tube should be placed

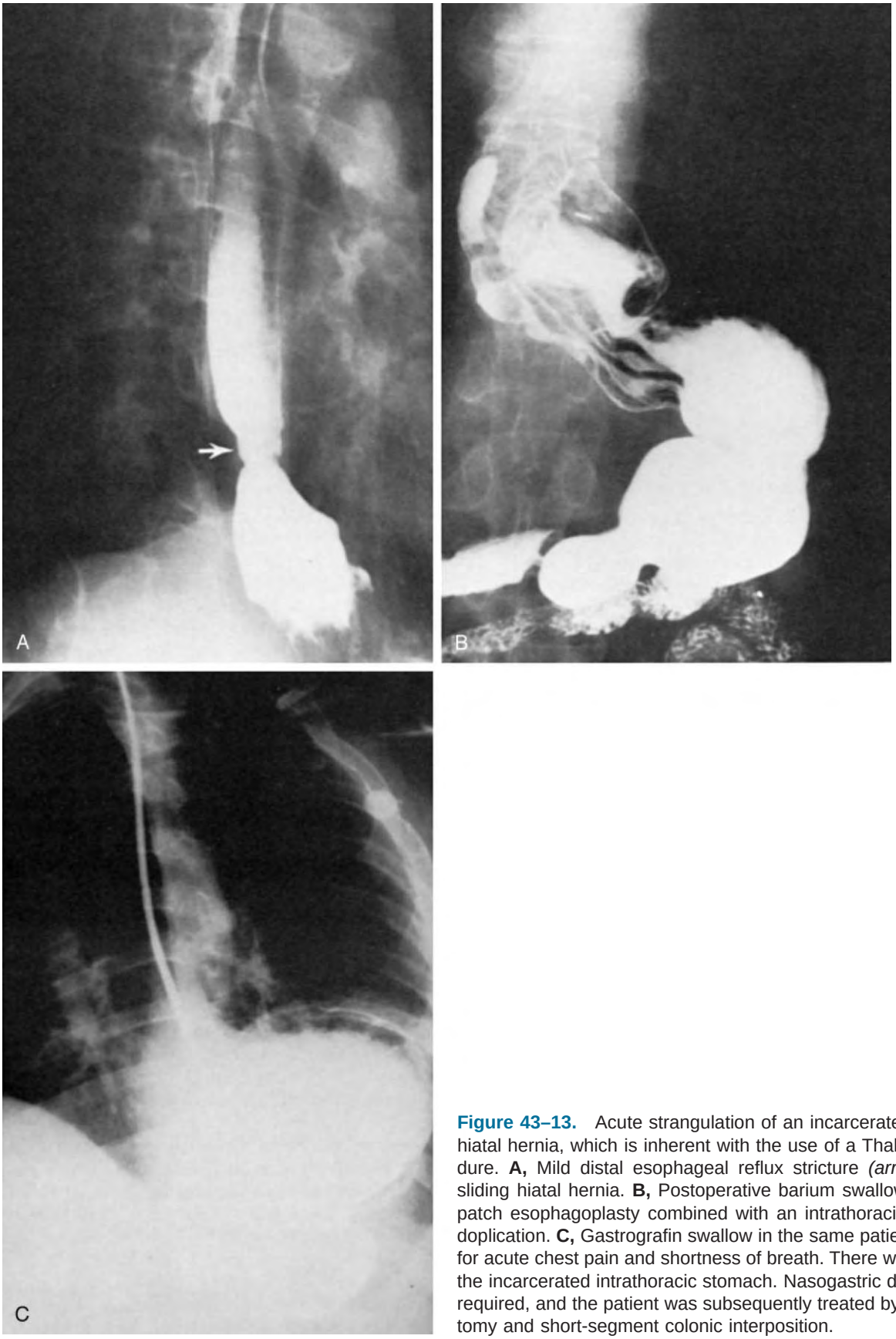

Figure 43–13. Acute strangulation of an incarcerated paraesophageal hiatal hernia, which is inherent with the use of a Thal-Woodward procedure. **A,** Mild distal esophageal reflux stricture *(arrow)* proximal to a sliding hiatal hernia. **B,** Postoperative barium swallow after Thal fundic patch esophagoplasty combined with an intrathoracic Nissen-type fundoplication. **C,** Gastrografin swallow in the same patient when evaluated for acute chest pain and shortness of breath. There was gross dilation of the incarcerated intrathoracic stomach. Nasogastric decompression was required, and the patient was subsequently treated by distal esophagectomy and short-segment colonic interposition.

to allow nutritional support and unimpeded ambulation in case the repair is unsuccessful and an esophageal fistula ensues. Either a large-bore chest tube should be left near the thoracic esophageal repair or a drain should be placed near the transabdominally repaired fundoplication to ensure external drainage of a recurrent fistula. There have been recent reports suggesting the use of self-expanding Silastic-covered esophageal stents for the treatment of postoperative esophageal leaks because of the touted ability to remove or reposition such devices once healing is complete. However, long-term follow-up is not readily available. In a normal-caliber esophagus, such devices appear to be more prone to distal migration into the stomach. Furthermore, the radial force exerted by these stents when placed in a pathologically narrowed esophagus may result in relative ischemia with possible extension of the esophageal injury and enlargement of the esophageal leak. The use of such devices should therefore be undertaken with caution and reserved for patients who are otherwise not suitable candidates for surgery.[23]

Low retrosternal dysphagia after an antireflux operation may have one of several causes: (1) distal esophageal edema after intraoperative manipulation, (2) distal esophageal motor dysfunction as a result of manipulation of the vagus nerves, (3) obstruction caused by too tight a fundoplication, (4) or obstruction from excessive closure of the hiatus. Performance of the fundoplication over at least a 54-French intraesophageal dilator minimizes the likelihood of this latter complication. Dysphagia after truncal vagotomy has been recognized for more than 40 years, and it is apparent that esophageal neuromotor dysfunction may follow manipulation of the vagus nerves at the level of the distal esophagus. This complication after antireflux surgery is more likely with a transthoracic than with a transabdominal repair because both exposure and displacement of the main vagal trunks are more frequent with the former approach. Such patients have dysphagia immediately after the antireflux procedure. On barium swallow examination, the distal esophagus is tapered and empties poorly, similar to the picture of achalasia or esophageal spasm. Reassurance plus maintenance of a soft diet for several days is usually adequate therapy, although passage of an esophageal dilator is at times required for relief. This problem typically subsides spontaneously, but occasionally reoperation, takedown of the repair, and at times even esophageal resection may be needed.

Another complication of intraoperative vagus nerve injury occurring during hiatal hernia repair is impaired gastric motility or pylorospasm resulting in delayed gastric emptying and secondary gastric dilation. This complication has direct implications for the long-term success of hiatal hernia repair because sustained gastric dilation in conjunction with a competent distal esophageal sphincter mechanism may eventually result in disruption of the esophageal sutures used to construct the fundoplication and failure of the repair. When gastric dilation develops immediately after surgery in a patient who has undergone an antireflux operation, a 7- to 10-day trial of gastric decompression with a nasogastric tube is indicated. At times, an anticholinergic (e.g., atropine, 0.4 mg either per os or intramuscularly every 4 to 6 hours) may relieve the associated pylorospasm. However, this problem should not be permitted to persist indefinitely, and it is best to perform an early gastric drainage procedure (pyloromyotomy or pyloroplasty) than to risk recurrent gastroesophageal reflux. Finally, vagal nerve injury may result in varying degrees of "dumping syndrome" (i.e., postprandial diarrhea, cramping, abdominal pain, nausea, diaphoresis, palpitations). This problem generally subsides within a few months, but at times long-term management with antidiarrheal medication and dietary restriction may be required.

Chylothorax after an antireflux procedure may result from injury to the thoracic duct, which passes from the abdomen through the aortic hiatus and then courses in the lower part of the chest anterior to the spine between the esophagus and the aorta. Injury may occur during mobilization of the cardia or during placement of the crural sutures. This complication is heralded by prolonged chest tube drainage after a transthoracic repair, and the true cause of this serosanguineous drainage may not become apparent until the patient's diet is liberalized and its fat content increases. If chylothorax is present, the oral administration of 60 to 90 ml of cream for 4 to 6 hours will result in chest tube drainage of opalescent and milky chyle. The diagnosis can also be established by staining the fluid with Sudan R, which stains the globules of fat. Determination of cholesterol and triglyceride levels in the fluid is not usually necessary. A cholesterol-triglyceride ratio of less than 1 is characteristic of a chylous effusion, whereas nonchylous effusions have a ratio of greater than 1. In most cases, chylothorax after hiatal hernia repair can be managed nonoperatively by administering a low-residue elemental diet and maintaining prolonged chest tube suction. If the output of chyle remains significant (>400 to 600 ml per consecutive 8-hour periods) after 7 to 10 days of this treatment, reoperation with identification and ligation of the injured thoracic duct is indicated.

Acute postoperative hemorrhage after an antireflux operation is most often the result of bleeding from an unsecured divided short gastric vessel along the high greater curvature of the stomach. This possibility should always be borne in mind as the short gastric vessels are divided and ligated before performing a fundoplication. Hemorrhage from these vessels may be a particularly treacherous complication after transthoracic hiatal hernia repair because the resulting hypovolemic shock may be attributed to other causes (e.g., myocardial infarction) when there is minimal chest tube drainage and the chest roentgenogram shows no hemothorax. The proper course of therapy is abdominal exploration, evacuation of the blood, and ligation of the bleeding vessel. Splenic injury also occurs in a small percentage of patients undergoing antireflux surgery, particularly during reoperations. The incidence of splenic injury is slightly higher with transabdominal than with transthoracic antireflux operations, particularly in obese patients. Rarely, postoperative hemorrhage is manifested as a pericardial effusion causing tamponade and cardiopulmonary collapse. This complication may arise from avulsion of an epicardial vessel, disruption of pericardial

adhesions during esophageal mobilization for repair of a large hiatal hernia, or inadvertent injury to the myocardium during placement of diaphragmatic crural sutures. Rapid diagnosis by surface echocardiography followed by sternotomy, relief of tamponade, and repair of the bleeding vessel is indicated.[24]

Before the patient is discharged from the hospital after an antireflux operation, a barium swallow examination should be routinely performed to document the postoperative appearance of the reconstructed esophagogastric junction. At times, this contrast study may reveal a "silent" localized extravasation of contrast material at the site of one of the fundoplication sutures that was placed too deeply. If the patient is asymptomatic and the "leak" is very small, no therapy may be required because the supporting fundoplication has prevented a more major disruption. A far more disconcerting radiographic finding on a "routine" postoperative barium swallow obtained before discharge is asymptomatic migration of the fundoplication or gastric fundus into the chest as a result of disruption of the posterior crural repair (Fig. 43–14). This iatrogenic paraesophageal hiatal hernia is subject to the same mechanical complications of paraesophageal herniation as in a patient who has had no surgery. Reoperation is necessary to reduce the fundoplication back into the abdomen and to replace the posterior crural sutures if they have pulled through the crural muscle (or to narrow the hiatus further if they have not) before postoperative adhesions form between the herniated stomach and adjacent tissues and make any subsequent repair more complicated. It may be difficult to tell an asymptomatic patient recovering from an antireflux operation that a reoperation is necessary, but conservative management of this problem is ill advised.

Controversy remains regarding the role of surgical therapy in patients with complications of gastroesophageal reflux disease, particularly Barrett's esophagus. Both symptoms and the requirement for antisecretory medications decrease significantly after an antireflux operation.[25] However, no long-term data are available regarding regression of Barrett's esophagus, regarded as a precursor lesion to esophageal adenocarcinoma. Currently, patients with Barrett's esophagus who are undergoing hiatal herniorrhaphy should continue to be monitored by routine surveillance esophagoscopy with biopsy to screen for progression from metaplasia to dysplasia and esophageal adenocarcinoma.[26]

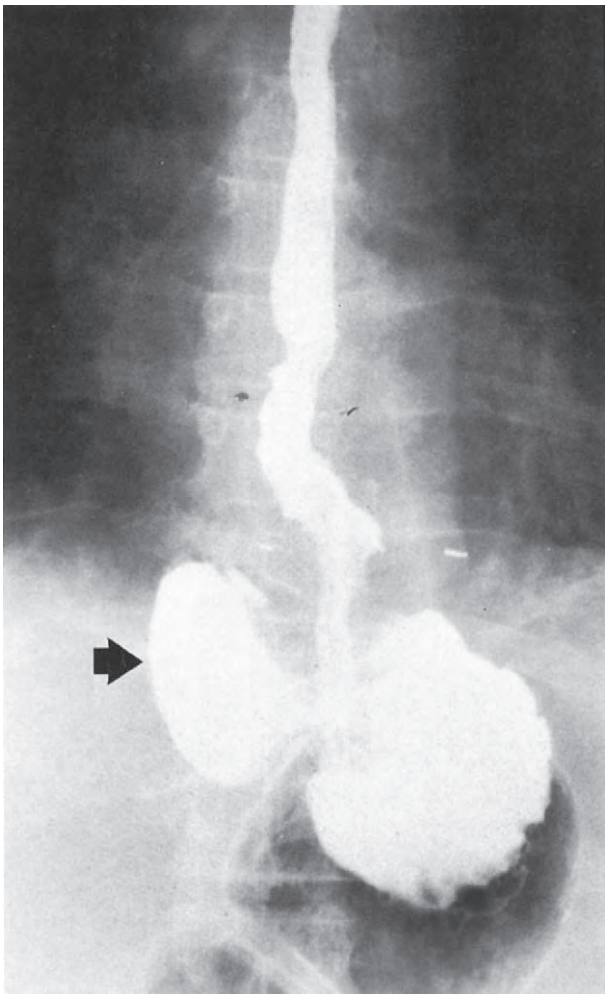

Figure 43–14. Asymptomatic partial migration of the fundoplication into the chest through the diaphragmatic hiatus 1 week after a Collis-Nissen hiatal hernia repair (the *arrow* indicates the portion of fundoplication above the diaphragm). Although asymptomatic, this patient underwent a reoperation, with the fundoplication reduced and secured below the diaphragm and the hiatus narrowed further to prevent later potential complications of this paraesophageal hernia. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield, LJ [ed]: Complications in Surgery and Trauma. Philadelphia, JB Lippincott, 1984, p 275.)

Laparoscopic Antireflux/ Hiatal Hernia Surgery

Since 1991, when the first reports of laparoscopic antireflux surgery were published, minimally invasive surgical approaches to the diaphragmatic esophageal hiatus have been used with increasing frequency. Although mortality rates for laparoscopic fundoplication have been low (0% to 1.4%), early morbidity rates are acceptable, and conversion rates to an open procedure range from 0% to 14%, the learning curve for this operation is substantial.[27]

In obese patients, in those with intra-abdominal adhesions from previous surgery, or in those with an unusually large left hepatic lobe, visualization of the operative field may be so difficult that persistence in performing the "closed" operation may be frankly dangerous. The latter factors remain indications for open transthoracic hiatal hernia repair. Perforations of the distal esophagus or gastric fundus have been reported during laparoscopic fundoplication. Blind dissection posterior to the esophagus should be avoided to prevent this complication. When recognized at the time of or soon after surgery, laparoscopic repair is feasible, but conversion to an open procedure may be the best option.

Early postoperative dysphagia may result from an overly tight fundoplication, which is more likely to occur with minimally invasive procedures because tactile sensation cannot be used to assess the tightness of the wrap. Performance of the fundoplication over at least a size 54-French Maloney dilator minimizes the likelihood of this complication. Postoperative dysphagia as a result of fibrotic stenosis of the muscular esophageal hiatus, attributed to diathermy injury during esophageal dissection, has also been reported and treated with laparoscopic hiatal division. Persistent dysphagia after a laparoscopic fundoplication that is refractory to dilatation therapy may necessitate reoperation, takedown of the wrap, and construction of a looser fundoplication. The authors' approach for such reoperative procedures is transthoracic, generally with a combined esophageal-lengthening Collis gastroplasty and Nissen fundoplication. Additional complications of laparoscopic fundoplication include pneumothorax or pneumomediastinum from CO_2 tracking into the chest during the operation, incisional hernia at a port site, and herniation of the fundoplication through the diaphragmatic hiatus (particularly when the crura were not approximated well or at all at the time of the original operation).

As enthusiasm for laparoscopic fundoplication has grown, this approach has also been used to repair large paraesophageal hiatal hernias, which are often associated with an attenuated, abnormally wide esophageal hiatus in an obese patient. In 1983, Pearson and associates emphasized that esophageal shortening is common in these patients, most of whom have combined sliding and paraesophageal hiatus hernias, and they used the combined Collis gastroplasty–fundoplication operation liberally in this group.[28,29] With the laparoscopic approach one cannot assess the degree of tension on the distal esophagus that results from reduction of the esophagogastric junction below the diaphragm because, again, direct manual palpation of the esophagus is not possible. Furthermore, with the diaphragms pushed abnormally upward by CO_2 insufflation into the abdomen during the operation, a false sense of ease of reduction of the esophagogastric junction into the abdomen may occur. Although several groups have developed minimally invasive techniques for combined Collis gastroplasty and fundoplication with acceptable short-term results,[30,31] our group believes that most large combined sliding and paraesophageal hiatal hernias should be approached through the chest with an open operation, generally a combined Collis gastroplasty and Nissen fundoplication. The increasing number of fundoplications that have "slipped" through the hiatus into the chest after laparoscopic repair probably reflect, at least in part, a lack of recognition by the original surgeon that there was unacceptable tension on the repair. Recurrent herniation of an intact or a partially disrupted fundoplication is the most common reason for failure of laparoscopic fundoplication. Body habitus is another important but often overlooked factor in recurrence after laparoscopic (or any) antireflux operations; obesity is present in a significant number of patients who experience disruption of repairs.

Another laparoscopic technique for the repair of paraesophageal hiatal hernias involves the use of mesh to close the diaphragmatic defect. This is an ill-conceived operation because the constant diaphragmatic motion against the adjacent esophagus at the hiatus may result in esophageal or gastric erosion and perforation. This approach is mentioned only to condemn its use.

Esophageal Resection and Visceral Esophageal Substitution

In almost every large series of patients undergoing a traditional esophageal resection and substitution with either stomach or intestine, the leading causes of death are (1) respiratory insufficiency associated with the physiologic insult of a combined thoracic and abdominal operation and (2) sepsis from mediastinitis secondary to disruption of an intrathoracic anastomosis. As a result, our group has adopted a general policy of performing no intrathoracic esophageal anastomoses and prefers a cervical esophagogastric anastomosis instead. A cervical esophagogastric anastomotic leak generally represents little more acute morbidity than a salivary fistula, and spontaneous closure with local wound care is the rule. Our group has reported a dramatic reduction in the incidence of postoperative cervical esophagogastric anastomotic leak to less than 3% with a side-to-side stapled cervical esophagogastric anastomosis[32] constructed with the Auto Suture Endo GIA II Stapler. The authors have also found that a transhiatal esophagectomy without thoracotomy plus a cervical esophagogastric anastomosis is applicable in most patients requiring esophageal resection and reconstruction for both benign and malignant disease. This procedure minimizes the operative insult to the patient by avoiding a thoracotomy. The incidence of postoperative pulmonary complications is thereby reduced, and the possibility of mediastinitis resulting from an intrathoracic leak is virtually eliminated.

The authors recommend the use of a 14-French rubber catheter feeding jejunostomy tube secured in place with a Witzel maneuver, not a "needle catheter" jejunostomy, in every patient undergoing esophagectomy and esophageal reconstruction. The jejunostomy tube is regarded as an "insurance policy" in case anastomotic disruption necessitates an alternative means of nourishment. If use of the tube is not required postoperatively, it is removed after several weeks. Alternatively, if an anastomotic leak occurs, a feeding jejunostomy tube is safer and more effective in providing calories than intravenous hyperalimentation.

Anastomotic Leak

After completion of a cervical esophageal anastomosis, the neck wound is closed loosely with only four or five 4-0 sutures over a ¼-inch Penrose drain placed adjacent to the anastomosis. If an anastomotic leak does occur, the neck wound is opened at the bedside in its entirety, and the wound is gently packed with gauze. The size of the leak can be estimated by having the patient drink water and evaluating the amount that escapes from the neck

wound with a disposable bedside suction catheter. Generally, within several days of opening the wound, the drainage diminishes considerably, and the patient may resume oral intake while maintaining steady gentle pressure over the wound to occlude the fistula. Passage of tapered Maloney dilators (generally 40 and 46 French) at the bedside during the first week after drainage of the cervical fistula ensures that no element of obstruction from either local edema or spasm contributes to continued drainage of the fistula.[33] More than 98% of cervical esophagogastric anastomotic leaks are small and respond to the open drainage and packing as described. A small proportion, however, are associated with catastrophic complications: major gastric tip necrosis necessitating takedown of the anastomosis, construction of a cervical esophagostomy, and resection of nonviable stomach; vertebral body osteomyelitis; epidural abscess with resultant paraplegia; pulmonary microabscesses from an internal jugular vein abscess; and tracheoesophagogastric anastomotic fistula.[34]

Early disruption of an intrathoracic esophageal anastomosis occurring within the first 10 critical days after surgery is characterized by the signs and symptoms of mediastinitis: fever, chest pain, tachycardia, tachypnea, respiratory distress, peripheral cyanosis, vasoconstriction, hypotension, and shock. When coupled with a chest roentgenogram that demonstrates hydrothorax or pneumothorax, there is little question about the diagnosis. The diagnosis should nonetheless be confirmed with a contrast study. In an otherwise asymptomatic patient found to have a small (<1 cm) contained anastomotic leak on a routine postoperative barium swallow, observation alone may be sufficient. In most cases, however, anastomotic disruption warrants urgent re-exploration, irrigation of the chest and mediastinum, repair of the fistula if possible, and chest tube drainage. A localized anastomotic leak with viable adjacent tissue may be amenable to direct suture repair. A pedicled flap of anterior mediastinal fat, an intercostal muscle flap, pleura, or omentum should be mobilized to reinforce the repair. Decompression of the esophageal substitute with a nasogastric tube, placement of a jejunostomy tube for nutritional support, and appropriate antibiotics complete the therapy. After removal of the chest tubes, a barium swallow examination should be performed 10 days after the reoperation to be certain that healing has occurred. If disruption of the anastomosis recurs, a controlled esophagopleural cutaneous fistula should be established. Rib resection with placement of a large-bore drainage tube adjacent to the fistula may be required to ensure that all drainage from the esophageal leak can flow freely out of the chest. Gastric contents that are aspirated through the nasogastric tube can be returned to the alimentary tract through the jejunostomy tube to minimize electrolyte imbalance and to simplify fluid and electrolyte replacement.

During re-exploration of the chest for a disrupted esophageal anastomosis, extensive local necrosis of the tissue with a major anastomotic dehiscence mandates takedown of the anastomosis, resection of nonviable stomach, and replacement of the remaining stomach into the abdomen. Only nonviable distal esophagus should be resected. However, a diverting lateral cervical esophagostomy with oversewing of the divided proximal intrathoracic esophagus should not be attempted. Not only is disruption of the intrathoracic esophageal suture line likely, but if subsequent reconstruction is possible, management of the remaining segment of intrathoracic esophagus also presents a considerable technical problem. The best alternative is to mobilize the esophagus circumferentially well into the neck through the thoracic incision. After the thoracotomy is closed, an end esophagostomy, with the patient returned to the supine position, should be performed. As indicated earlier, the submucosal collateral circulation of the esophagus is excellent, and most of the length of the thoracic esophagus will remain viable as long as at least one inferior thyroid artery remains intact. Therefore, after delivering the divided thoracic esophagus out of the neck incision, the maximum length of remaining esophagus should be preserved to facilitate later reconstruction. This is achieved by developing a subcutaneous tunnel anteriorly to the left clavicle onto the chest wall and constructing an anterior thoracic esophagostomy. An esophagostomy stoma placed on the relatively flat upper anterior chest wall is much more easily cared for by the patient because a stomal appliance is more readily adapted to this location than to the usual site of a standard cervical esophagostomy (Fig. 43–15). A feeding jejunostomy is, of course, required until later esophageal reconstruction can be performed.

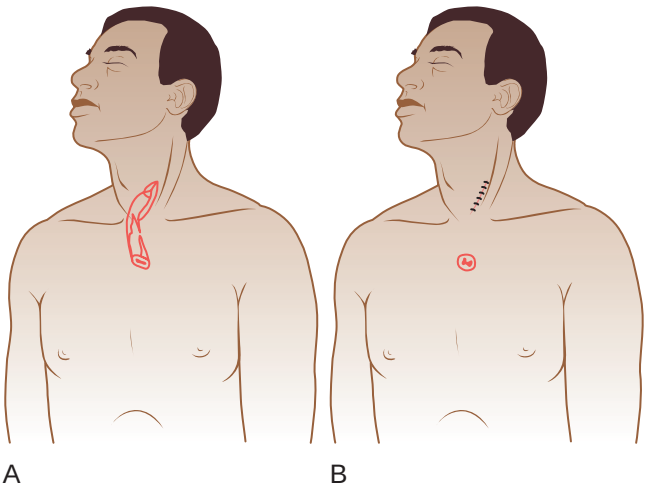

Figure 43–15. Construction of an anterior thoracic esophagostomy instead of a traditional end cervical esophagostomy. **A,** The mobilized thoracic esophagus is placed on the anterior chest wall so that the location of the stoma can be determined. **B,** All viable remaining esophagus is preserved and tunneled subcutaneously, and an end anterior thoracic esophagostomy is constructed. Stomal appliances are readily applied to the flat anterior surface of the chest, and when performing a later colon interposition, 7 to 12 cm of esophagus is available for the reconstruction. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 317.)

When colon or jejunum has been used to replace the esophagus and necrosis of the graft is documented at re-exploration for an anastomotic leak, there is similarly little recourse but to remove the nonviable graft and insert a feeding tube. If the patient survives the sequelae of the mediastinal sepsis, later reconstruction can be considered.

Anastomotic Stricture

Although the management of a cervical anastomotic leak is generally straightforward and seldom associated with death, the long-term sequelae of a cervical leak are far from inconsequential. As many as 50% of cervical esophagogastric anastomotic leaks result in an anastomotic stricture as healing occurs, which is an unsatisfactory outcome of an operation that is intended to provide comfortable swallowing. The implications are similar in patients who survive an intrathoracic esophageal anastomotic leak. Our group has previously reported an anastomotic leak rate averaging 13% in nearly 1100 transhiatal esophagectomy patients at the University of Michigan, with subsequent anastomotic strictures developing in nearly half of these patients,[35] consistent with reports in the literature for the incidence of both anastomotic leak (5% to 26%) and stenosis (10% to 31%).[36-38] Without question, prevention of an anastomotic leak is the key to a successful functional outcome in these patients. In our initial experience with the side-to-side stapled cervical esophagogastric anastomosis, which has been associated with an anastomotic leak rate of less than 3%, we observed a dramatic reduction in the need for late postoperative anastomotic dilatations.[32]

In a patient who has experienced an esophageal anastomotic leak, early passage of a 46-French or larger dilator within 1 week of drainage is carried out to maintain a satisfactory lumen and prevent late high-grade stenosis. A cervical fistula generally heals within 7 to 10 days of external drainage. When the patient returns for follow-up within 2 weeks of discharge, a 46-French or larger Maloney dilator is passed through the anastomosis. If the patient has no dysphagia and there is no resistance to passage of the dilator, the need for subsequent dilatations is dictated by the return of cervical dysphagia. In patients with anastomotic narrowing that prevents the free passage of a 46-French or larger Maloney dilator, a more aggressive program of esophageal dilatation is undertaken. With an early program of weekly dilatations, anastomotic healing in a patent configuration is often achieved. Patients whose anastomotic stricture produces resistance as the dilator is passed may need more frequent dilatations. In this situation, the patient is taught over a period of several weeks to pass a 46- or 48-French dilator with the assistance of a family member or friend. Once facility with passage of the dilator is achieved, the patient is issued a dilator with instructions to pass it daily for 1 week, then every other day for 1 week, and then at increasingly longer intervals until the longest duration between dilatations without recurrence of dysphagia can be established. With this aggressive initial program of dilatation, long-term comfortable swallowing with little or no need for subsequent dilatations is generally achieved. Few patients require anastomotic revision. Occasionally, endoscopic injection of steroids into a refractory anastomotic scar facilitates the management of this problem.[39,40]

Pulmonary Complications

Respiratory insufficiency after esophageal resection and reconstruction is exceedingly common and is associated with a mortality rate of up to 40%.[41,42] Patients with esophageal squamous cell cancer, particularly those treated with preoperative chemoradiation, may have a greater risk for postoperative pulmonary morbidity, including pleural effusion, pneumonia, and respiratory insufficiency after esophagectomy.[43] A vital part of minimizing postoperative pulmonary complications after esophageal resection and reconstruction is rigorous preoperative pulmonary physiotherapy. The authors insist on total abstinence from cigarette smoking for a minimum of 3 weeks before esophagectomy. Home use of an incentive inspirometer and instruction in deep-breathing exercises are also begun 3 weeks preoperatively. This investment of time and energy in improving the patient's preoperative respiratory status is repeatedly rewarded by a lower incidence of postoperative pulmonary complications after esophageal resection and reconstruction. Postoperatively, patients are extubated immediately after surgery and resume pulmonary physiotherapy as early as possible. Adequate postoperative analgesia, particularly epidural anesthesia, is of great value in minimizing postoperative pulmonary problems.

One of the most disastrous complications after esophageal resection is the development of a fistula between the tracheobronchial tree and either the esophagus or the esophageal substitute, generally at the anastomotic site. Among 207 patients with malignant esophagorespiratory fistulas treated at the Memorial Sloan-Kettering Cancer Center in New York, Burt and associates reported 13 patients in whom fistulas developed after resection for esophageal carcinoma.[44] Once a fistula between the airway and adjacent alimentary tract develops, there is little option other than to prevent continued contamination of the respiratory tree by identifying and dividing the fistula and repairing the airway, generally a major undertaking in a desperately ill patient.

Gastric Outlet Obstruction

The need for a routine gastric drainage procedure after the vagotomy that inevitably accompanies esophagectomy has been debated. It has been shown, for example, that most patients who undergo esophagectomy and esophagogastric anastomosis without a concomitant drainage procedure do not have difficulty with gastric outlet obstruction.[45,46] However, in a prospective trial in which 200 patients undergoing esophageal resection were randomized to receive either pyloroplasty or no gastric drainage procedure, gastric emptying was found to be four times longer in those who did not have a pyloroplasty.[47] Adverse postprandial symptoms were less frequent in those who had a drainage procedure, and there was no morbidity from the pyloroplasty. For the

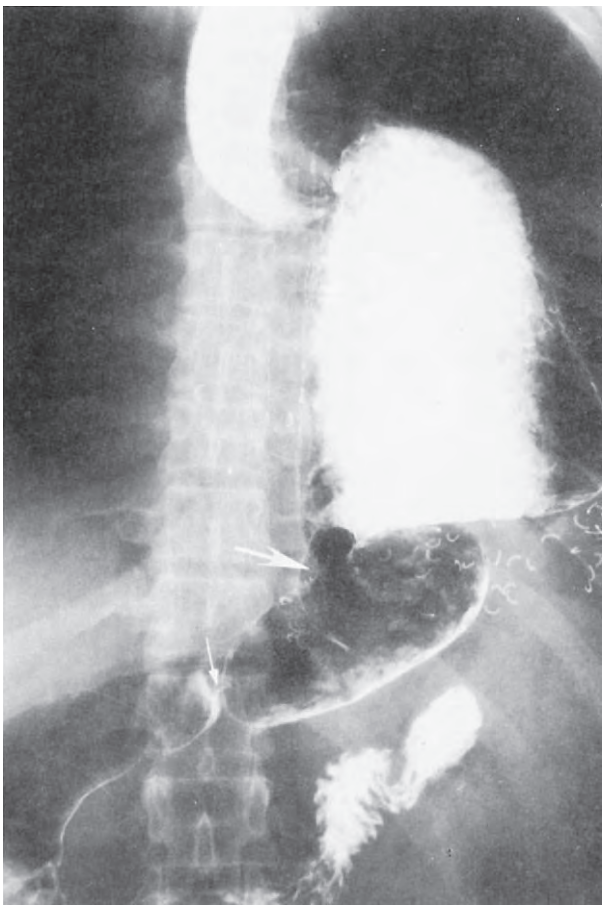

Figure 43–16. Barium study in a patient with regurgitation and dilatation of the intrathoracic stomach after esophagectomy for distal-third carcinoma. This complication was the result of two technical errors: failure to enlarge the diaphragmatic hiatus sufficiently, with resultant relative obstruction at the diaphragmatic hiatus *(large arrow),* and failure to perform a gastric drainage procedure, with resultant pyloric obstruction *(small arrow).* (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 318.)

occasional patient in whom significant gastric outlet obstruction does develop after esophageal resection (Fig. 43–16), the outcome may be disastrous: aspiration pneumonia and impaired nutrition because of an inability to eat. Furthermore, a reoperation to perform a drainage procedure may be very difficult after the stomach has been mobilized into the chest. For these reasons, the authors advocate performance of a gastric drainage procedure in every patient undergoing esophagectomy and esophageal reconstruction; our preference is a Ramstedt-type extramucosal pyloromyotomy, which avoids the intra-abdominal suture line of a pyloroplasty. After performing the pyloromyotomy, silver clip markers placed at the level of the pylorus aid in interpreting the subsequent radiologic studies used to evaluate gastric emptying. In more than 1500 such pyloromyotomies performed during esophageal bypass or replacement with stomach, our group has experienced one leak postoperatively. This leak resulted in fatal peritonitis. Intrathoracic gastric outlet obstruction may also result from failure to enlarge the diaphragmatic hiatus adequately before mobilizing the stomach into the chest. The diaphragmatic hiatus should accommodate at least three fingers comfortably alongside the mobilized stomach to prevent this complication.

Diaphragmatic Hiatal Obstruction or Herniation

Not only must the hiatus be enlarged sufficiently to prevent the esophageal substitute from becoming obstructed at the level of the diaphragm, but the esophageal replacement, whether stomach or intestine, should also be carefully sutured to the edge of the diaphragmatic hiatus to prevent subsequent herniation of abdominal viscera through the hiatus and into the chest (Fig. 43–17). As our group and others have observed, this complication may occur acutely within the first several days after surgery or years after the esophagectomy.[48,49] Such a hernia may be an asymptomatic finding on a postoperative chest roentgenogram on which intestinal gas is seen above the level of the hiatus, or the patient may have vague left upper quadrant abdominal or lower thoracic discomfort, nausea, and vomiting, as is the case with chronic traumatic diaphragmatic hernias. Because the risk for incarceration and strangulation of the herniated viscera is substantial, reduction of the hernia is advised. Herniation of intestine through the diaphragmatic hiatus after esophagectomy can generally be repaired transabdominally. In the case of chronic traumatic diaphragmatic hernias, the opening in the diaphragm is relatively small, and the herniated viscera may become adherent to adjacent intrathoracic structures and require a transthoracic approach for reduction. The majority of herniations of intestine alongside the intrathoracic stomach, on the other hand, occur through a relatively patulous hiatus. Reduction of the hernia and narrowing of the hiatus are readily achieved through the abdomen. As is the case with other complications that follow esophageal surgery, this situation can also generally be prevented. When the esophageal substitute has been brought through the diaphragmatic hiatus and the anastomosis has been completed, several heavy diaphragmatic crural sutures should be used to narrow the hiatus so that it admits three fingers alongside the stomach or colon. Then a few interrupted sutures should be placed between the edge of the diaphragmatic hiatus and the visceral esophageal substitute to limit the migration of other intra-abdominal viscera through the hiatus into the chest. Finally, the divided triangular ligament of the mobilized liver should be sutured to the edge of the hiatus to provide one additional barrier to herniation at this site.

Chylothorax

Because of the proximity of the thoracic duct and the esophagus, chylothorax after esophagectomy is a recognized complication. Ligation of the divided

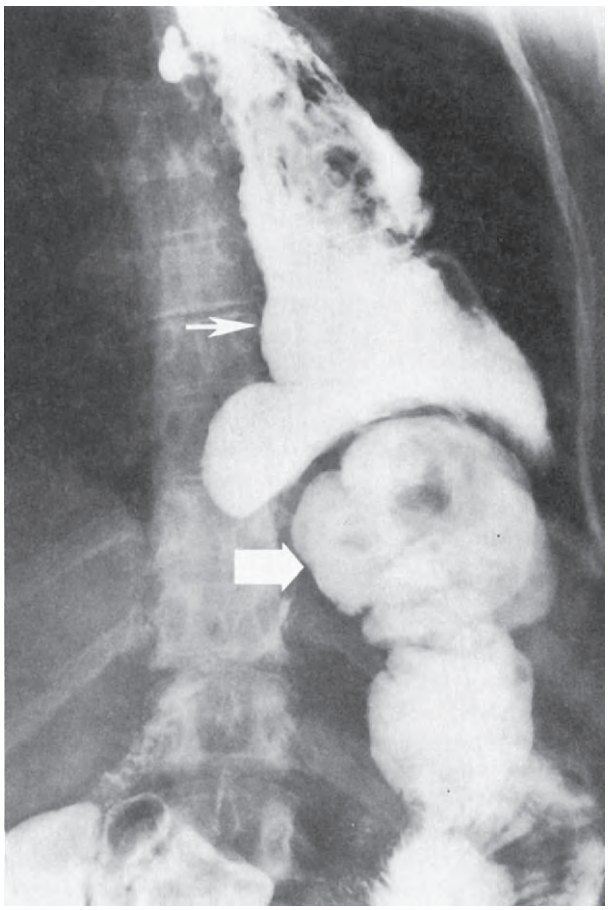

Figure 43–17. Herniation of the splenic flexure of the colon *(large arrow)* through the diaphragmatic hiatus after esophageal replacement with stomach for a caustic stricture. No sutures had been placed between the intrathoracic stomach *(small arrow)* and the edge of the diaphragmatic hiatus to prevent this complication. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 318.)

periesophageal tissues at the time of esophagectomy minimizes this complication. When compared with the relatively healthy patient who sustains a chylothorax after aortic surgery, however, this complication in a debilitated patient with esophageal obstruction is not well tolerated, with reported mortality as high as 50%.[50,51] Patients with chronic esophageal obstruction are already nutritionally depleted. Further loss of protein-rich chyle is not well tolerated. Only a few days should be expended in trying to treat this complication nonoperatively. With aggressive operative intervention and direct ligation of the point of thoracic duct injury, patient salvage is the rule.[52] Thoracic duct ligation at the point where the thoracic duct emerges through the diaphragmatic hiatus can be accomplished by either right posterolateral thoracotomy or video-assisted thoracoscopic surgery.

Pancreatitis

Postoperative pancreatitis may occur after esophagectomy as a result of pancreatic injury during performance of either the Kocher maneuver or gastric mobilization. The possibility should be suspected in patients in whom unexplained fever, respiratory distress, or prolonged ileus develops after esophagectomy. The diagnosis is confirmed by determining serum amylase and lipase levels. Standard treatment of pancreatitis with nasogastric tube decompression of the gastrointestinal tract and administration of intravenous fluids is usually sufficient, although progression to fatal hemorrhagic pancreatitis may ensue.

Splenic Injury

Injury to the spleen may occur during esophagectomy, particularly during mobilization of the stomach for esophageal replacement. Careful avoidance of undue traction on the short gastric vessels during gastric mobilization and early division of adhesions between the stomach and the spleen on opening the abdomen minimize this complication. Routine splenectomy as part of the "cancer operation" for esophageal carcinoma is not advocated because splenectomy is associated with a well-documented increased morbidity of its own.

Peripheral Atheroembolism

Thromboembolic sequelae after transhiatal esophagectomy have been reported in two patients and attributed to inadvertent dislodgement of debris from the diseased aorta in the process of mobilizing the esophagus through the diaphragmatic hiatus.[53] This complication has not been encountered by our group in a combined experience totaling more than 1500 transhiatal esophagectomies.

Complications of Substernal Esophageal Replacement

Several unique complications of esophageal replacement are related to retrosternal placement of the esophageal substitute. The most obvious is potential obstruction at the level of the retrosternal neohiatus because of failure to create an adequate opening (Fig. 43–18). When creating a retrosternal tunnel, it is our practice to dilate this space until the entire hand and forearm can be inserted retrosternally to ensure sufficient room for either the stomach or the colon. Compression along with obstruction of the retrosternal esophageal substitute at the superior opening into the anterior mediastinum is a function of the posterior prominence of the clavicular head, which narrows the anterior thoracic inlet. For this reason, when performing a retrosternal interposition of stomach or colon, which requires relocation of the cervical esophagus anteriorly from its usual position to the left and posterior to the trachea, the medial third of the left clavicle, the adjacent manubrium, and usually the medial first left rib as well should be resected to ensure an adequate opening into the anterior mediastinum.

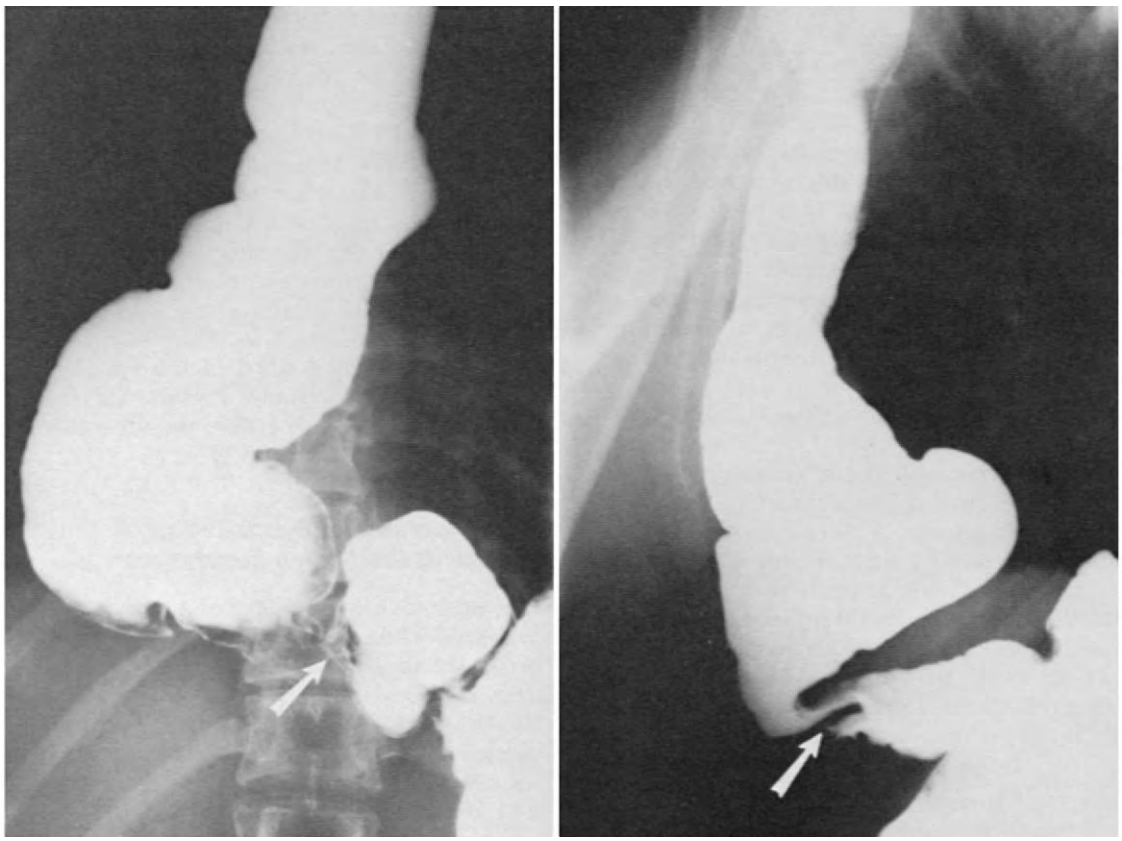

Figure 43–18. Posteroanterior *(left)* and lateral *(right)* views from a barium swallow showing early postoperative obstruction of a retrosternal colonic interposition at the level of the diaphragm *(arrows)* as a result of failure to create an adequate opening in the diaphragm.

Complications of Bypassing or Excluding the Native Esophagus

Management of the diseased native esophagus is controversial when performing retrosternal replacement of the esophagus. An esophagus that is severely strictured from a caustic injury, for example, may simply be left in the posterior mediastinum and bypassed with a retrosternal colon. The potential complications arising from the residual diseased esophagus, however, mandate that it be removed whenever possible. The small but definite increased risk for late development of carcinoma in the caustic strictured esophagus is a less compelling reason to resect it than the potential for subsequent reflux esophagitis. A caustic injury may destroy the lower esophageal sphincter mechanism as a result of subsequent fibrosis, and reflux symptoms and severe esophagitis in the native esophagus may develop in such a patient undergoing substernal colon interposition (Fig. 43–19).

Although substernal bypass of the excluded esophagus with either stomach or colon has been used for the treatment of both benign and malignant disease, the complications from such an approach are appreciable. The excluded esophagus may become a giant posterior mediastinal mucocele that causes respiratory distress as a result of tracheobronchial compression (Fig. 43–20). Of more immediate concern in the postoperative period is the incidence of disruption of the distal end of the excluded esophagus with a resultant left subphrenic abscess. When esophageal replacement is necessary for benign disease, the authors advocate resection of the esophagus. It is always preferable to place the esophageal substitute in the posterior mediastinum in the original esophageal bed because (1) this is the shortest distance between the neck and the abdominal cavity; (2) if subsequent anastomotic dilation is required, it is far safer and more direct to perform it when one does not have to negotiate the anterior angulation of a cervical esophagus that has been anastomosed to a retrosternal graft; and (3) the incidence of postoperative cervical anastomotic leak is lower. In the original esophageal bed in the neck, the anastomosis is buttressed by adjacent tissues: the spine posteriorly, the carotid sheath laterally, the trachea medially, and the strap muscles anteriorly. An esophageal anastomosis to a retrosternal colon or stomach is basically subcutaneous in the neck and is relatively unsupported. Coughing or a Valsalva maneuver against a closed upper esophageal sphincter results in distention of the retrosternal esophageal substitute with increased pressure on the anastomosis and a higher anastomotic leak rate. If esophageal bypass is performed in

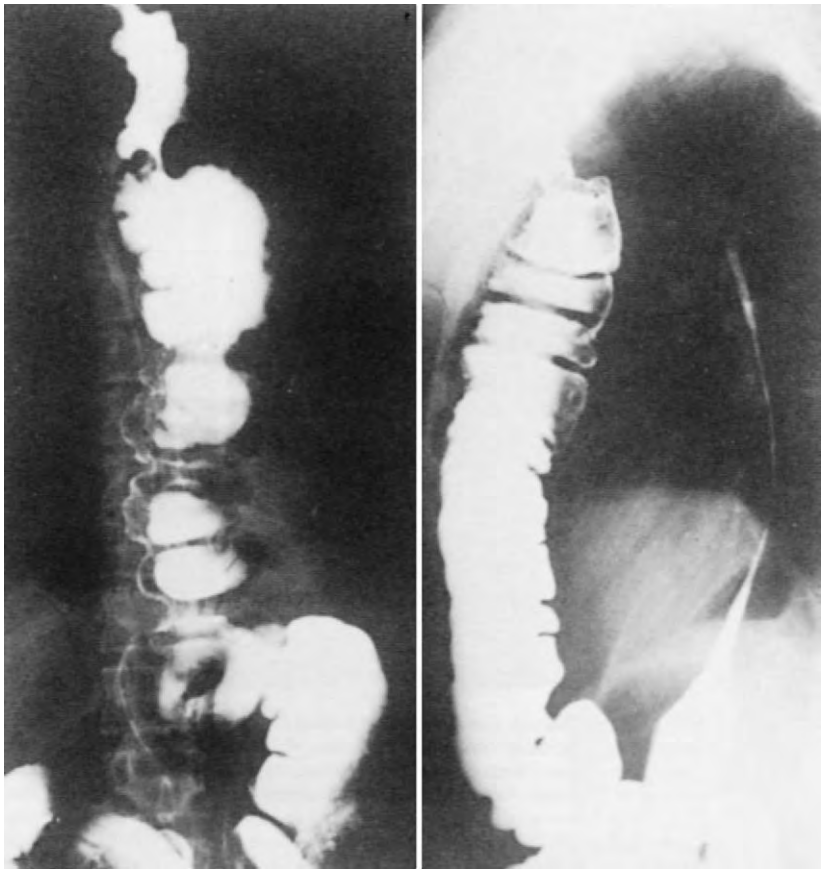

Figure 43–19. Posteroanterior *(left)* and lateral *(right)* views from a barium swallow performed in a patient who had undergone a retrosternal colonic bypass for a caustic esophageal stricture 4 years earlier. This patient had experienced severe reflux symptoms for 2 years before being evaluated for upper gastrointestinal bleeding secondary to reflux esophagitis. The lateral film shows simultaneous opacification of both the colon graft and the native esophagus, which filled as a result of a grossly incompetent lower esophageal sphincter. Resection of the native esophagus was required to relieve the severe reflux esophagitis.

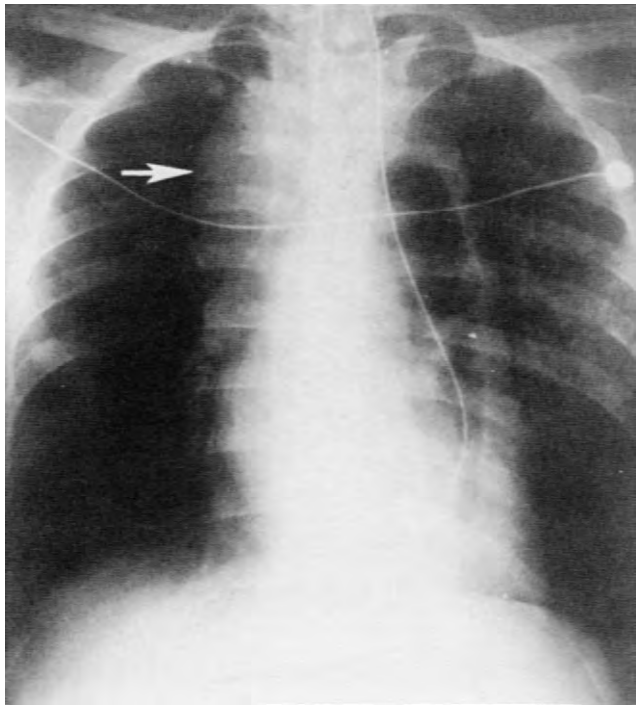

Figure 43–20. Posteroanterior chest roentgenogram in a 27-year-old man being evaluated for acute respiratory distress 2 years after undergoing substernal gastric bypass of the excluded thoracic esophagus for a caustic stricture. The patient had compression of the tracheobronchial tree by a huge posterior mediastinal mucocele *(arrow)* that had formed in the excluded esophagus. An endotracheal tube was required to relieve the airway obstruction. A nasogastric tube is seen in the retrosternally placed stomach. A right-sided thoracotomy and resection of the dilated esophagus were carried out.

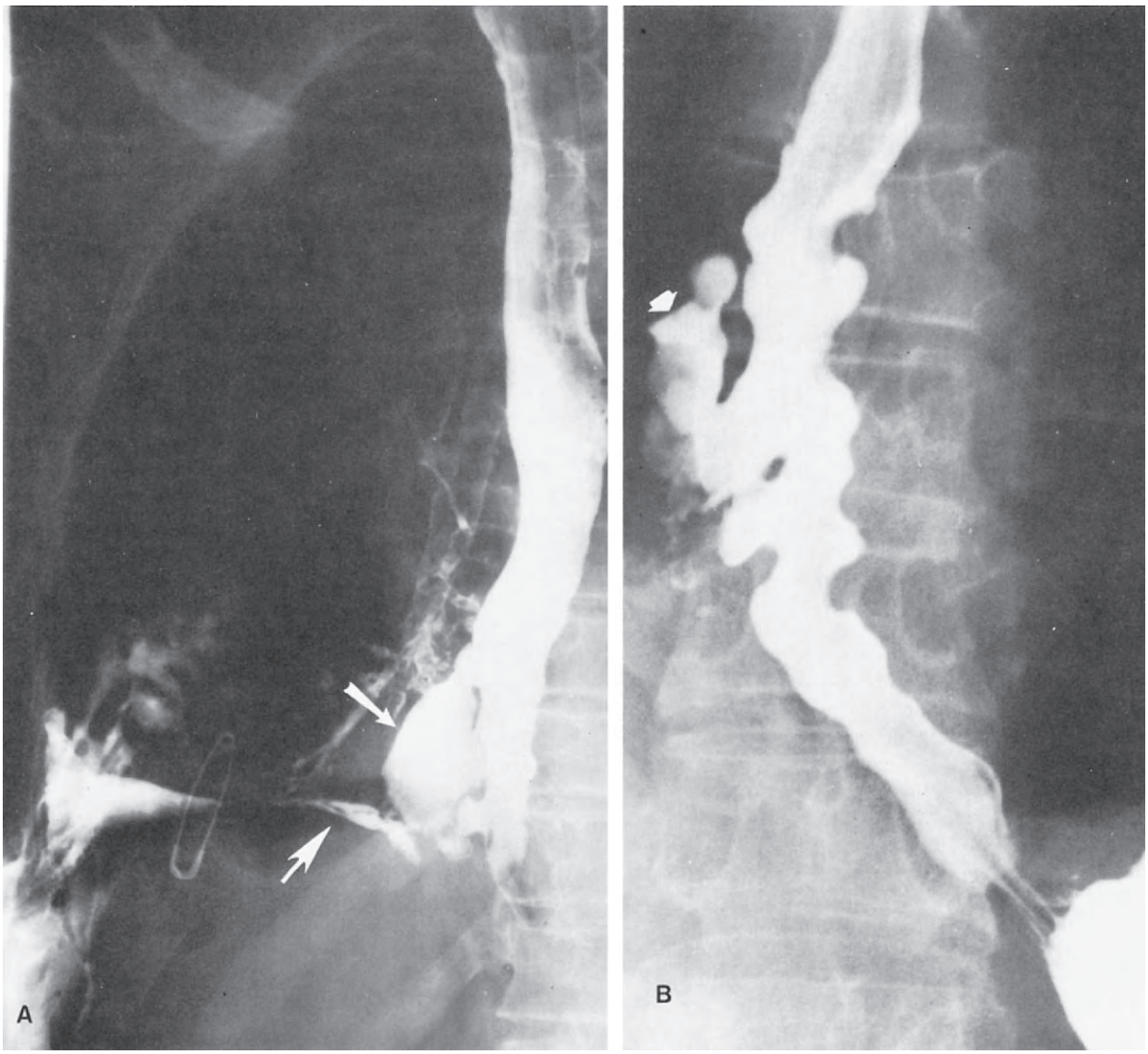

Figure 43–21. **A,** This esophagogram shows an esophagopleural cutaneous fistula *(large arrow)* and a recurrent esophageal diverticulum *(small arrow)* in a patient who had previously undergone resection of the diverticulum without esophagomyotomy. **B,** The patient's underlying esophageal neuromotor problem is evident in this view from the same study, which shows a typical corkscrew esophagus. The relative obstruction secondary to intermittent spasm distal to the esophageal suture line had not been relieved when the diverticulum was resected; hence disruption of the suture line with fistula formation and recurrence of the diverticulum *(arrow)* followed. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 320.)

patients with unresectable esophageal carcinoma, the distal esophagus should be decompressed into a Roux-en-Y limb or jejunum rather than excluded.[54,55]

Esophageal Diverticulectomy

Pulsion diverticula of the esophagus, whether oropharyngeal (Zenker's diverticulum) or intrathoracic, result from associated distal esophageal obstruction, most often neuromotor dysfunction. Thus, if the underlying neuromotor abnormality responsible for formation of the diverticulum is not addressed at the time of diverticulectomy, failure to relieve the distal obstruction may result in disruption of the suture line (Figs. 43–21 and 43–22). After resection of a diverticulum, the esophagus should be insufflated with air through an indwelling nasogastric tube positioned within the esophagus, and an air leak should be looked for by immersing the pouting esophageal submucosa in saline solution (Fig. 43–23). The most opportune time to treat such a pinhole leak is at the time of surgery, and a single 5-0 monofilament stitch may avert a great deal of postoperative morbidity. Alternatively, if a cervical esophageal leak occurs after

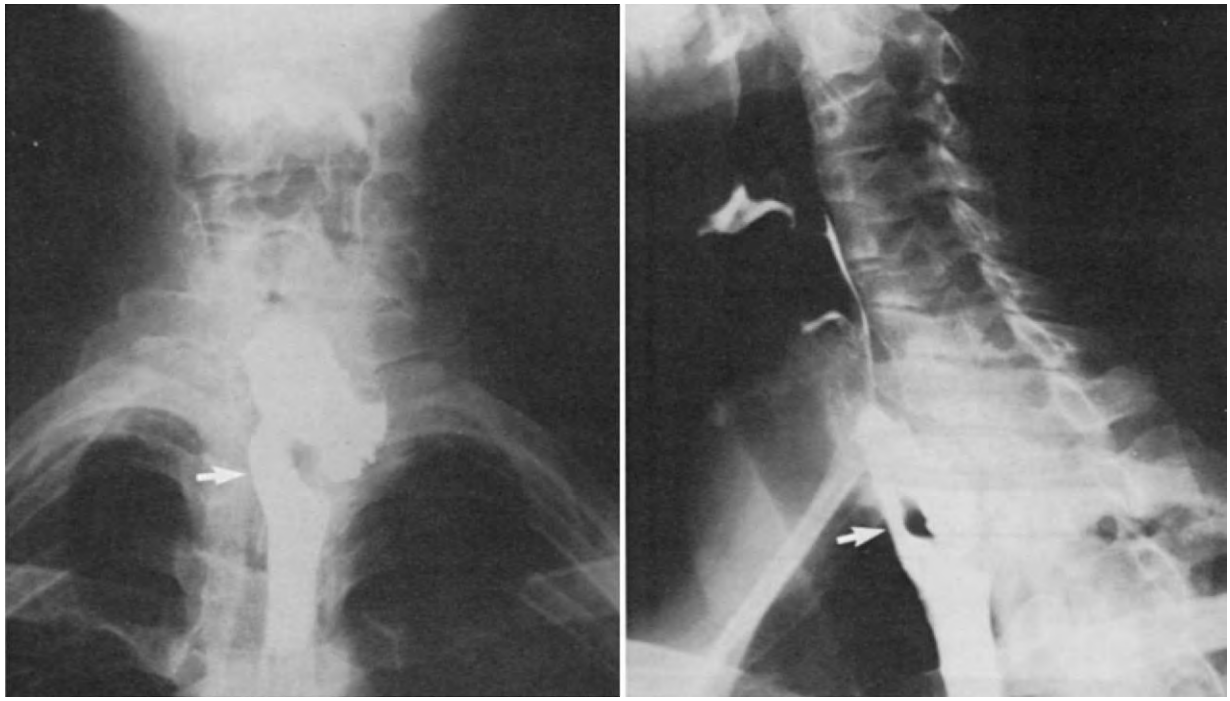

Figure 43–22. Posteroanterior *(left)* and lateral *(right)* views of a barium swallow in a patient with a recurrent Zenker diverticulum after two previous diverticulectomies, each one complicated by disruption of the suture line and an esophagocutaneous fistula. The undivided cricopharyngeus muscle *(arrow)* causing the obstruction distal to the pouch is evident. An esophagomyotomy to relieve this neuromotor dysfunction causing the obstruction had not been performed. A third diverticulectomy, this time combined with esophagomyotomy, resulted in relief of dysphagia. The diverticulum has not recurred after 10 years of follow-up.

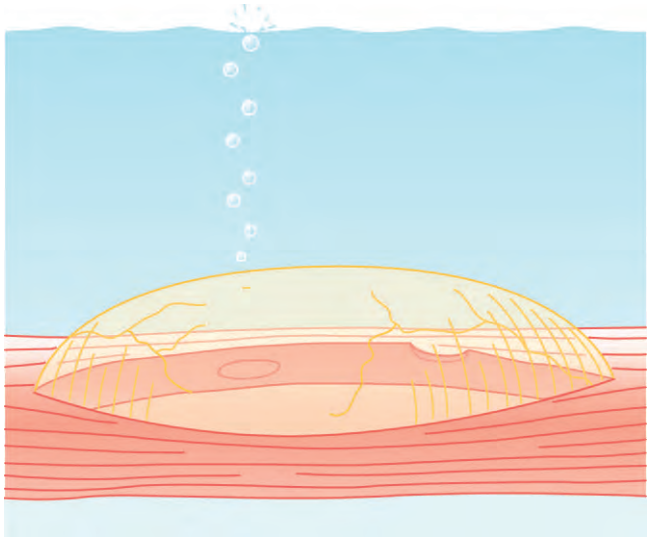

Figure 43–23. Testing for inadvertent esophageal perforation after esophagomyotomy. The esophageal mucosa is distended by insufflating air down an intraesophageal nasogastric tube. Air bubbles escaping from the esophagus submerged under saline indicate a perforation. (From Orringer MB: Complications of esophageal surgery and trauma. In Greenfield LJ [ed]: Complications in Surgery and Trauma, 2nd ed. Philadelphia, JB Lippincott, 1990, p 322.)

diverticulectomy and esophagomyotomy, the neck wound must be opened, irrigated, and drained, as described earlier for the treatment of cervical anastomotic disruption. Nutrition may be maintained with either nasogastric feedings or total parenteral support. Broad-spectrum antibiotics are administered. With an adequate esophagomyotomy that has relieved the distal obstruction, the incidence of leak from a diverticulectomy suture line should be exceedingly low. If a cervical salivary fistula does occur, however, spontaneous closure within 7 to 10 days should be expected. If an intrathoracic esophageal suture line leak occurs within several days of diverticulectomy, immediate re-exploration of the chest with closure of the fistula and reinforcement with anterior mediastinal fat, adjacent pleura, intercostal muscle, or omentum is indicated.

Esophagomyotomy for Achalasia or Esophageal Spasm

The megaesophagus of achalasia may contain 1 to 2 L of stagnant intraesophageal contents. Induction of general anesthesia in such a patient represents the most dangerous part of the operation. Because a nasogastric tube interferes with deep breathing and adequate clearing of pulmonary secretions, one should not use an intraesophageal nasogastric tube for several days preopera-

tively to decompress the dilated esophagus. Rather, the patient is restricted to a clear liquid diet for 2 days before the operation, and then immediately before induction of general anesthesia, with the patient in a sitting position, a nasogastric tube is passed, and the esophagus is aspirated and evacuated. Rapid-sequence induction of anesthesia is then carried out while constant pressure is maintained on the cricoid cartilage to prevent regurgitation of esophageal contents into the pharynx until the endotracheal tube balloon is inflated. Once the airway is protected, rigid esophagoscopy is carried out, and the esophagus is evacuated and irrigated.

After completion of the esophagomyotomy, integrity of the esophageal mucosa is documented by insufflating air into the esophagus through an indwelling intraesophageal nasogastric tube. As described earlier, identification plus closure of an inadvertent esophageal injury at this point is far simpler than when the perforation is detected hours to days after surgery. Patients with achalasia are frequently referred for surgery after failed pneumatic dilatation or, more recently, unsuccessful intrasphincteric injection of botulinum toxin. These previous endoscopic interventions may increase the difficulty of identifying tissue planes at the time of subsequent esophagomyotomy. In particular, patients who have previously undergone botulinum toxin injection and obtained some relief of achalasia symptoms are more likely to have periesophageal fibrosis and, consequently, a greater risk, as high as 50%, for esophageal perforation during esophagomyotomy and less palliation of their symptoms after surgery. Periesophageal fibrosis was less prevalent in patients who had previously been treated by pneumatic dilatation, and it did not appear to affect surgical outcomes after esophagomyotomy.[56,57]

Regardless of the approach used, potential complications exist and may require reoperation in 10% to 15% of patients after esophagomyotomy. If a complete distal esophagomyotomy is not performed and the obstruction relieved, dysphagia and regurgitation will continue in the immediate postoperative period and a reoperation may be necessary.[58] Alternatively, if the esophagomyotomy is carried onto the stomach to ensure adequate relief of the esophageal obstruction, the uncoordinated lower esophageal sphincter may be converted to an incompetent one, with ensuing long-term complications of reflux esophagitis. Furthermore, a "long" esophagomyotomy, greater than 5 cm with extension onto the stomach, has been associated with "diverticularization" of the mucosa in long-term follow-up.[59,60]

Controversy exists about the need for a concomitant antireflux procedure with the distal esophagomyotomy, which may render the lower esophageal sphincter incompetent.[61-63] With a few notable exceptions, the majority of esophageal surgeons now advocate partial fundoplication to prevent the subsequent development of gastroesophageal reflux after esophagomyotomy for achalasia.[64] A Belsey-type partial fundoplication has been recommended when esophagomyotomy is approached transthoracically, whereas Toupet (posterior) or Dor (anterior) fundoplasty is typically recommended after transabdominal esophagomyotomy. When performing a fundoplication to ensure lower esophageal sphincter competence in an atonic esophagus, care must be exercised to avoid subsequent obstruction as a result of overaggressive fundoplication.

Among the more difficult problems of surgery for achalasia is the development of recurrent dysphagia and regurgitation secondary to esophageal obstruction occurring 1 or more years after a previous esophagomyotomy. Although esophagomyotomy has become the standard surgical approach to patients with achalasia, in those with a tortuous megaesophagus and a supradiaphragmatic pouch of esophagus, delayed esophageal emptying may occur even after a satisfactory esophagomyotomy. Furthermore, a patient who has undergone a previous esophagomyotomy and has recurrent symptoms has only a 40% to 70% chance of experiencing a good result from a "redo" esophagomyotomy.[65,66] Finally, esophagomyotomy remains a palliative operation for patients with esophageal motor disorders involving the body of the esophagus and lower esophageal sphincter. Patients with achalasia remain at risk for the development of esophageal squamous cell carcinoma and should undergo routine surveillance upper endoscopy after esophagomyotomy. In patients with either recurrent or persistent symptoms of achalasia, with or without associated reflux esophagitis, esophagectomy may provide the best option by eliminating the esophageal obstruction as well as the potential for the late development of carcinoma.[67]

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Part

8

Hernia

Chapter

44

Femoral Hernia

Daniel E. Swartz ▪ Edward L. Felix

A femoral hernia (Greek *hernios*, offshoot or bud) is a protrusion of preperitoneal fat, bladder, or peritoneal sac with or without intraperitoneal contents through the femoral ring. It becomes clinically evident once the exit of the femoral canal, or the femoral orifice, is breached. Accounting for 2% to 8% of adult groin hernias, a femoral hernia is three to five times more common in women than men, rarely occurs in children, and is most commonly seen in patients between the ages of 40 and 70 years, with a peak incidence during the sixth decade. Since the laparoscopic era, the reported incidence of femoral hernia has increased to 11% of groin hernias.[1,2] Approximately 27,000 femoral herniorrhaphies are performed annually in the United States.

ANATOMY

The femoral canal is an elliptically shaped inverted cone measuring approximately 2 cm in length that extends from the femoral ring superomedially to the femoral orifice inferolaterally (Fig. 44–1A and B). Located just medial to the femoral vessels, it is lined by the transversalis fascia and normally contains lymphatics, adipose tissue, and commonly the lymph node of Cloquet (Fig. 44–2). The femoral ring, or entrance to the canal, is lined by the iliopubic tract anterosuperiorly after it crosses anterior to the femoral vessels. The fibers of the iliopubic tract spread out in a fan-shaped manner, the superior fibers of which curve posteriorly, insert into the superior ramus, and form the medial margin of the ring. The inferior fibers of the iliopubic tract descend vertically to join the fascia lata and form the medial wall of the femoral canal. The femoral ring, furthermore, is bordered inferoposteriorly by Cooper's ligament and laterally by the femoral sheath. The femoral canal is enveloped by the fascia lata, with the superficial layer forming the anterior wall and the deep layer forming the posterior wall. The medial wall of the canal is composed of the descending fibers of the iliopubic tract and fascia lata, which are supported by the lacunar (Gimbernat's) ligament. The femoral canal normally ends blindly; however, when a femoral hernia is present, an opening known as the femoral orifice is created. The femoral orifice is bounded posteriorly by the pectineal fascia, laterally by the femoral sheath, anteriorly by the superior cornu of the fascia lata, and medially by the fan-shaped fibers of the iliopubic tract.[3,4]

HISTORY

Femoral hernia was first distinguished from inguinal hernia by Guy de Chauliac in 1363 in his text *Chirugia Magna*.[5] It was further described by Barbette in 1687, but the first detailed account of femoral canal anatomy was not recorded until 1817 by Cloquet.[6] There are three classic approaches to a femoral hernia: femoral, inguinal, and preperitoneal. The femoral approach was first described by Socin in 1879. He performed high ligation of the sac alone and noted a high recurrence rate. Bassini, in 1885, used a femoral approach to close the femoral ring with suture. He sutured the inguinal ligament to the pectineal fascia and lacunar ligament. Marcy,

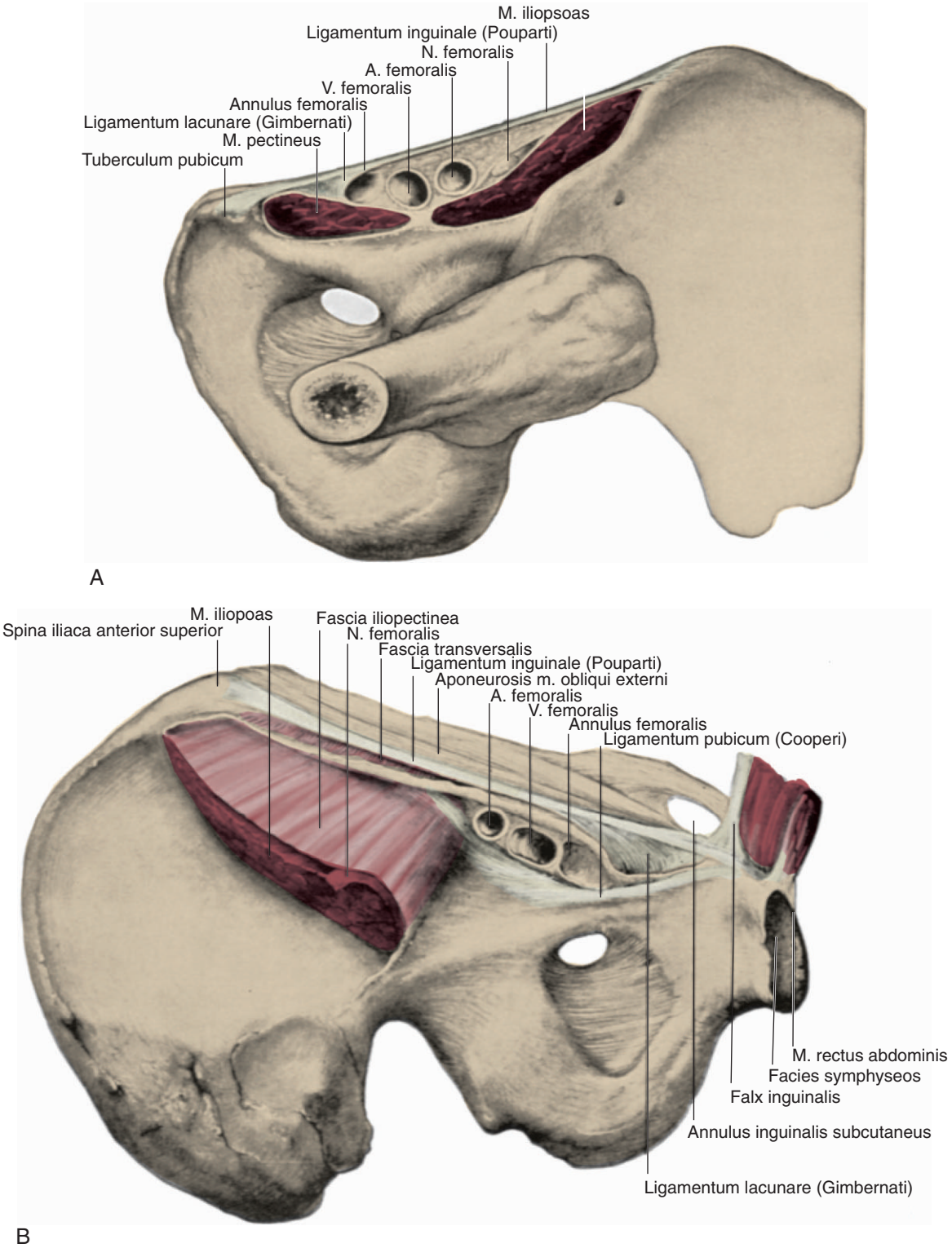

Figure 44–1. Bone and ligamentous anatomy of the femoral canal and related structures as viewed from the thigh **(A)** and from the pelvis **(B).**

in 1892, used a purse-string suture to close the femoral ring.[7] It was not until 1974 that a tension-free repair with a cylindrical roll of polypropylene mesh to plug the femoral canal was described by Lichtenstein and Shore.[12] This approach was subsequently modified by others, including Gilbert, Rutkow and Robbins, and Bendavid.[4,8,9]

The inguinal approach to a femoral hernia was first described by Annandale in 1876.[10] His repair consisted of high ligation of the sac. The first repair approximating

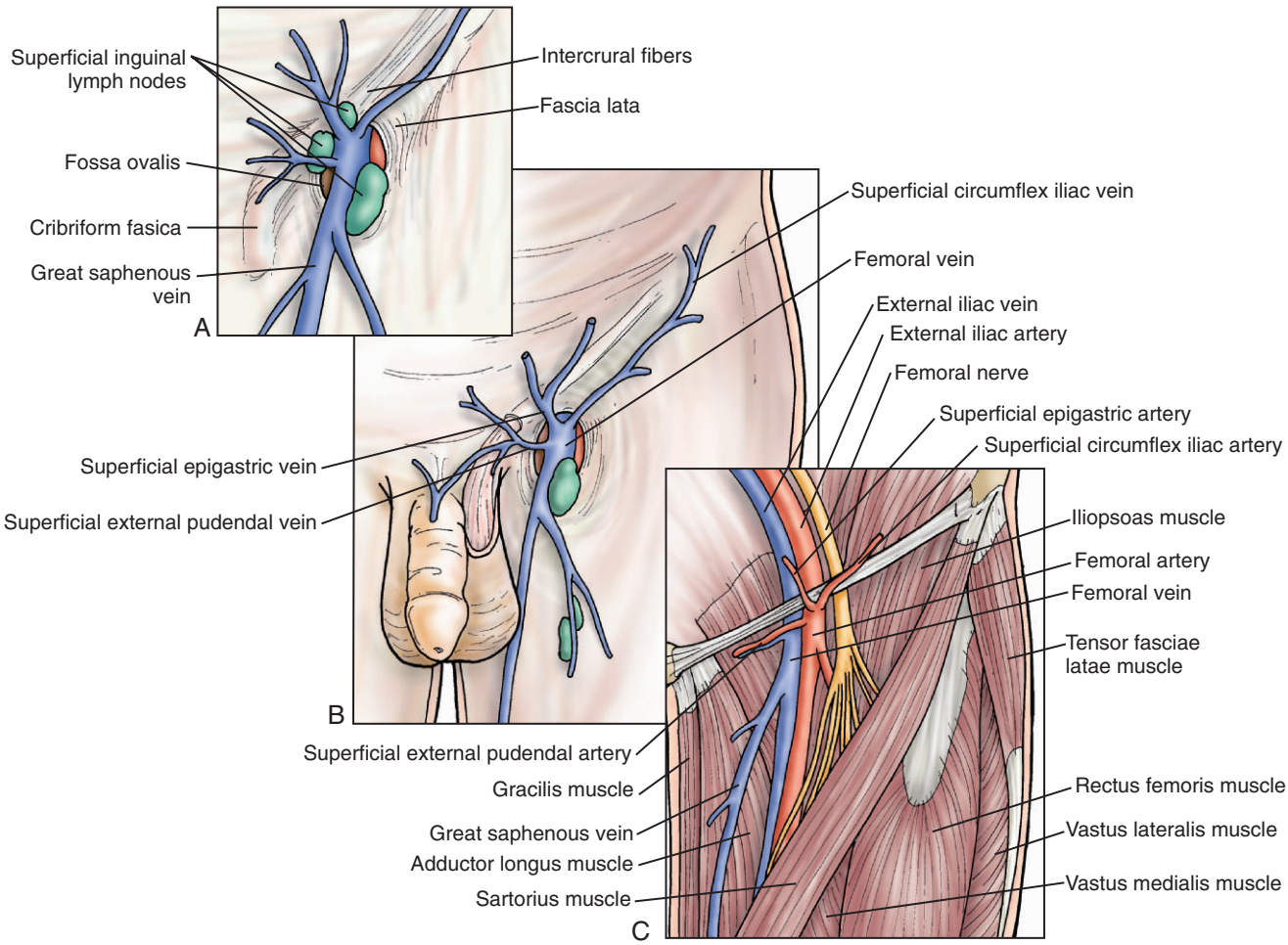

Figure 44–2. Superficial inguinofemoral dissection. **A,** Relationship of the fossa ovalis to the deep fascia of the thigh, the inguinal ligament, and the superficial vessels. **B,** The fossa ovalis cleared of the lymphatic contents and the cribriform fascia. **C,** Exposure of the contents of the femoral trigone (of Scarpa) after all superficial structures and the deep fascia have been removed.

Cooper's ligament to the inguinal ligament was described by Ruggi in 1892. Later, Moschowicz included an inguinal floor repair to reduce the potential for recurrence of an inguinal hernia.[11] Lotheissen first described using Cooper's ligament to repair a ruptured inguinal ligament during inguinal herniorrhaphy in 1898, and this technique was later popularized by McVay and Anson in 1942 as an anatomic repair of femoral and direct inguinal hernias. They astutely noted that the transversus abdominis muscle and transversalis fascia inserted onto Cooper's ligament and not the inguinal ligament. This repair became widely accepted and more recently has included placement of prosthetic mesh plugs via the femoral ring to obliterate the canal.[4,8,9,12]

The preperitoneal approach was first described by Annandale in 1876 and further advanced by Cheatle[13] (1920) and later Henry[14] (1936) through a low midline incision. The linea alba was carefully divided with the peritoneum left intact, and the plane of dissection was bluntly created by separating the peritoneum from the bladder and pelvic brim. McEvedy used an oblique incision over the lateral border of the rectus sheath to access this plane and sutured the conjoined tendon to Cooper's ligament in 1950. Nyhus et al. (1960) advanced this procedure by using a transverse incision cephalad to the superior border of the pubis to expose the femoral ring. The hernia was reduced, the sac ligated, and the repair performed by approximating Cooper's ligament to the iliopubic tract. They later modified the technique by buttressing the repair with polypropylene mesh and reduced the recurrence rate to less than 1 %.[15] In 1973, Stoppa et al. used a posterior midline approach to place a large sheet of polyester mesh bilaterally.[16] A unilateral preperitoneal hernia repair using ring-supported mesh inserted through a small 2- to 3-cm incision was subsequently popularized by Kugel.[17]

The first laparoscopic transabdominal preperitoneal (TAPP) inguinal hernia repair using a mesh plug and polypropylene buttress was reported by Schultz et al. in 1990.[18] By 1993, Felix and others demonstrated that the plug was unnecessary with a laparoscopic approach and that a large sheet of mesh covering all potential hernia

sites was the key to the repair.[19] The preperitoneal approach, whether open or laparoscopic, is different from the inguinal or femoral approaches in that it repairs the entire posterior floor, including the femoral defect, in all patients. In 1993, McKernan and Laws reported the first laparoscopic totally extraperitoneal (TEP) approach mimicking the open technique of Stoppa.[20] A laparoscopic intraperitoneal onlay mesh was described around the same time but was quickly abandoned because of intra-abdominal adhesions and a high recurrence rate.[5]

ETIOLOGY

A femoral hernia was initially thought to be of congenital origin with a preformed peritoneal sac. Careful anatomic studies by Keith in 1923, however, led to abandonment of this theory.[21] The acquired theory is now the most widely accepted. It proposes elevated intra-abdominal pressure as the causative factor, such as during pregnancy, constipation, and bronchitis. Preperitoneal fat is displaced through the femoral ring and may pull peritoneum with it and thereby create a sac. The normally closed femoral orifice is then opened. Femoral hernias may also be produced iatrogenically when a conventional Bassini repair under tension distorts and opens the femoral ring.

DIAGNOSIS

The classic manifestation is pain or a lump in the groin, or both. Physical examination often reveals a small nonreducible mass below the inguinal ligament. The differential diagnosis includes inguinal hernia, lymphadenopathy, lipoma, and pseudohernia. A femoral pseudohernia is a nonpathologic entity seen in extremely thin patients with bilateral masses below the inguinal ligament and medial to the femoral vessels that resolve on recumbency. The cause is accentuation of a normal fat pad and Cloquet's lymph node, which normally reside in the femoral canal, and no treatment is necessary.[6]

The presence of an incarcerated hernia in the groin should immediately raise suspicion that it is a femoral hernia because incarcerated femoral hernias outnumber all other incarcerated abdominal wall hernias combined.[4] Differentiating between a femoral and an inguinal hernia, although difficult at times, is important. The likelihood of strangulation at 3 and 21 months is 20% and 45% for femoral and only 3% and 4.5% for inguinal hernias, respectively,[22] and strangulation is associated with a mortality rate of 6% to 23%.[4] The sensitivity and positive predictive value of physical examination by surgeons have been shown to be only 50% and 37.5%, respectively.[22] There have been reports of the use of contrast herniography, color Doppler ultrasound, and computed tomography to diagnose femoral hernias, but no rigorous study has been performed to determine their accuracy.[23-26] Physical examination therefore remains the mainstay of preoperative diagnosis.

Nyhus described two ways to differentiate femoral from inguinal hernias: first, the pubic tubercle will be felt superior and medial to a femoral hernia; in contrast, it will be felt inferior and lateral to an inguinal hernia. Second, with the hernia reduced, the examiner places a finger at the medial end of the inguinal ligament and has the patient cough. A femoral hernia will appear below the finger, whereas an inguinal hernia will appear above it.[27] Another method is to follow the adductor longus tendon caudally from the inguinal ligament and place fingers lateral to the tendon (one fingerbreadth medial to the femoral artery) and have the patient cough. The presence of a bulge suggests that it is an inguinal hernia because a femoral hernia should stay reduced.[22]

TREATMENT

As previously discussed, there are three basic approaches to treatment: femoral, inguinal, and preperitoneal, the latter of which includes open and laparoscopic approaches. Suture, mesh, or both may be used in all three approaches. Each technique has advantages and disadvantages, but in the hands of skilled and experienced surgeons, each has been shown to have low complication and recurrence rates. With a nonincarcerated, nonstrangulated femoral hernia, any of the techniques may be applied; with incarceration or strangulation, however, the femoral and laparoscopic TEP repairs should be avoided. Although a majority of surgeons have espoused the open inguinal approach in the presence of incarceration and strangulation, the authors prefer a laparoscopic TAPP approach. In the presence of strangulation, bowel resection will be required and prosthetic mesh should be avoided. Franklin et al. have recently reported using a biologic mesh composed of porcine small intestinal submucosa (Surgisis, Cook Surgical, Bloomington, IN) intraperitoneally to repair strangulated inguinal and incisional hernias. Even with gross contamination, the authors reported no mesh-related complications or recurrences in 58 hernia repairs with a 19-month follow-up.[28] Further studies are needed before advocating the routine use of mesh for strangulated or contaminated hernias.

The femoral approach is the simplest, requires the least dissection, and may be performed with local anesthesia (Fig. 44–3). This approach is most appropriate for a nonincarcerated, nonstrangulated femoral hernia and for high-risk surgical patients. Incarcerated hernias have been treated in this manner, although it can be difficult because visualization of femoral ring anatomy is poor. After making an inguinal or subinguinal incision, the subcutaneous fascia is divided to reveal the intact external oblique aponeurosis. The hernia sac, located just inferior to the aponeurosis, is dissected, opened, and emptied. If the hernia is incarcerated, it may be released by incising the lacunar (Gimbernat's) ligament medially and, failing that, the inguinal ligament. With the femoral approach this is often a blind maneuver and a counteringuinal incision may be required for better visualization. Once the hernia is free, the sac is opened, the contents are inspected and returned to the abdominal cavity, and the sac is ligated. The femoral canal is obliterated either with sutures or with a cylindrical polypropy-

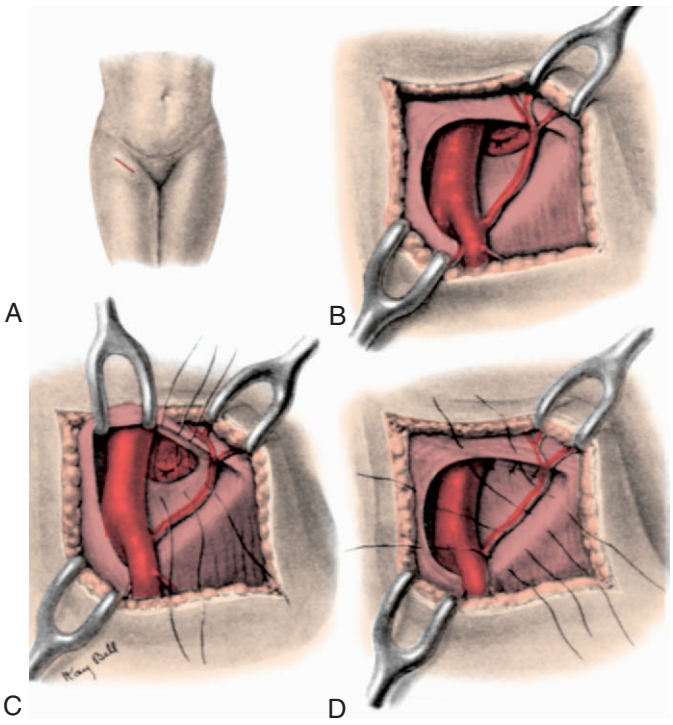

Figure 44–3. The femoral approach to repair of a right femoral hernia with suture. **A,** Incision. **B,** Dissection of the femoral orifice and canal. **C,** Placement of nonabsorbable sutures between the inguinal ligament, fascia lata, and pectineal fascia. **D,** View of the completed repair.

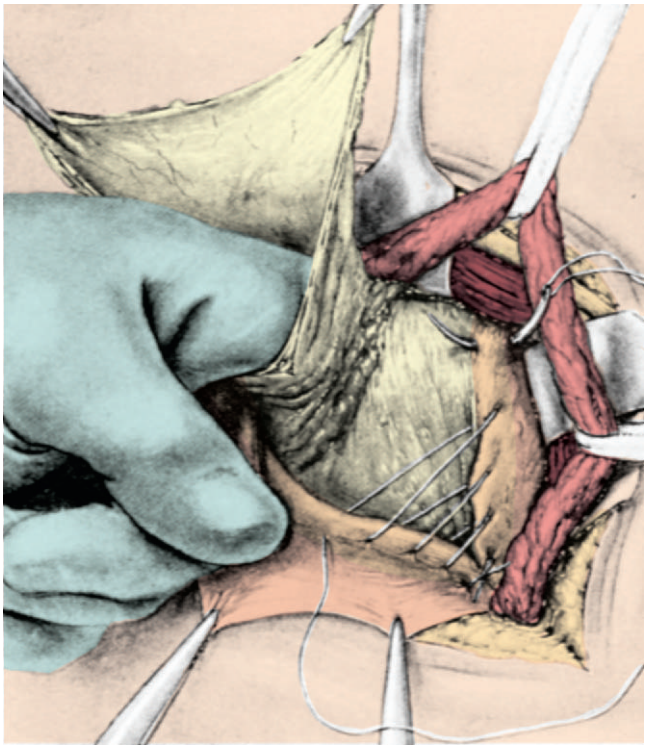

Figure 44–4. Examination for a concomitant femoral hernia during inguinal hernia repair. Examination for a concomitant inguinal hernia during repair of a femoral hernia should similarly be performed.

lene mesh plug placed within the femoral canal and sutured to the inguinal ligament, fascia lata, and pectineal fascia.[12]

The excellent exposure of the femoral ring provided by the classic inguinal approach facilitates release of the incarcerated hernia, as well as the opportunity to resect gangrenous intestine. An inguinal incision is made in the skin and carried down through the subcutaneous layers. The external oblique aponeurosis is opened in the line of its fibers from the cephalad aspect of the external ring medially until the internal ring is exposed laterally. The external oblique aponeurosis is cleared of the cremasteric muscle attachments, and the cord structures are mobilized. Careful examination of the cord and inguinal floor is necessary to exclude the presence of a concomitant inguinal hernia (Fig. 44–4). The floor of the inguinal canal (transversalis fascia) is opened and the femoral hernia sac exposed. If necessary, an aberrant obturator artery may be ligated at this point. In the event of an incarcerated hernia, the contents of the sac must be examined for viability after the hernia is reduced. An incarceration is released by dividing the fibers of the iliopubic tract and lacunar ligament at the medial edge of the femoral ring. In rare cases the inguinal ligament must be divided, but this should be avoided if possible because of the increased likelihood of recurrence. Once the contents of the hernia sac are examined and returned to the abdominal cavity, the sac is ligated at the level of the peritoneal cavity and the repair is performed.

It can be done either by suture approximation of the iliopubic tract to Cooper's ligament (Fig. 44–5) or, preferably, in the absence of strangulation, by polypropylene mesh repair to obliterate the femoral ring and canal. This may be achieved with several shapes of plugs, including cylindrical,[12] umbrella,[5] or dart with a base[29] fashioned to the inguinal ligament and iliopubic tract anteriorly, Cooper's ligament posteriorly, the femoral sheath laterally, and the iliopubic tract and lacunar ligament medially with nonabsorbable suture. Inguinal herniorrhaphy should be included to prevent an iatrogenic hernia.[11] Because of reports of chronic pain after the use of mesh plug repairs,[30] Amid at the Lichtenstein Hernia Institute has abandoned the use of plugs in favor of a polypropylene mesh sheet that covers the femoral ring in addition to the inguinal floor.[31]

The open, preperitoneal approach remains popular[13-16] because it permits excellent exposure, it allows for rapid intraperitoneal access to control any strangulated viscera, and mesh permits repair of all three potential hernia sites, including a femoral hernia (Fig. 44–6). Access is through a transverse lower abdominal incision 3 cm cephalad to the typical inguinal incision. The subcutaneous fascia is dissected to expose the anterior rectus sheath and external oblique aponeurosis. The anterior rectus sheath is divided cephalad to the internal ring, and the rectus abdominis is retracted medially to expose the posterior inguinal wall. The sac is carefully reduced while maintaining control of the contents for

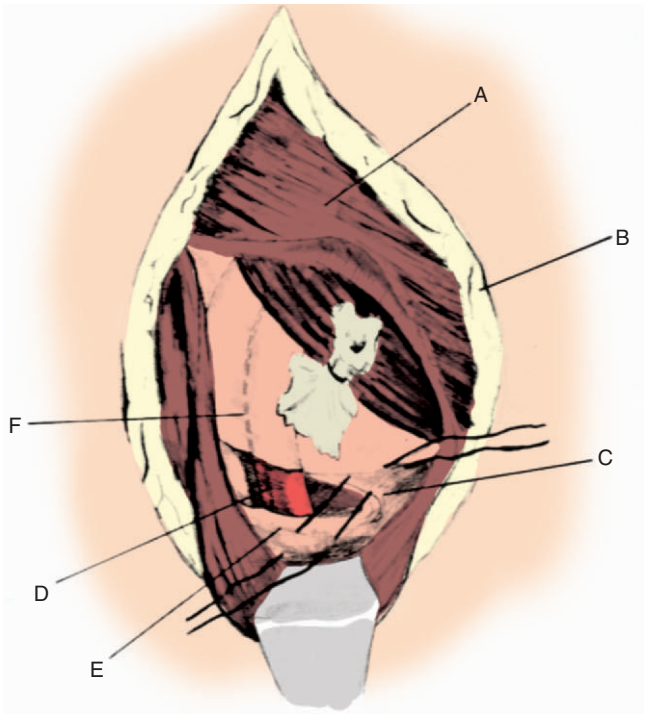

Figure 44–5. Inguinal approach to repair of a femoral hernia using suture approximation of the iliopubic tract to Cooper's ligament. Closure of the peritoneum (sac excision and ligation) has already been performed.

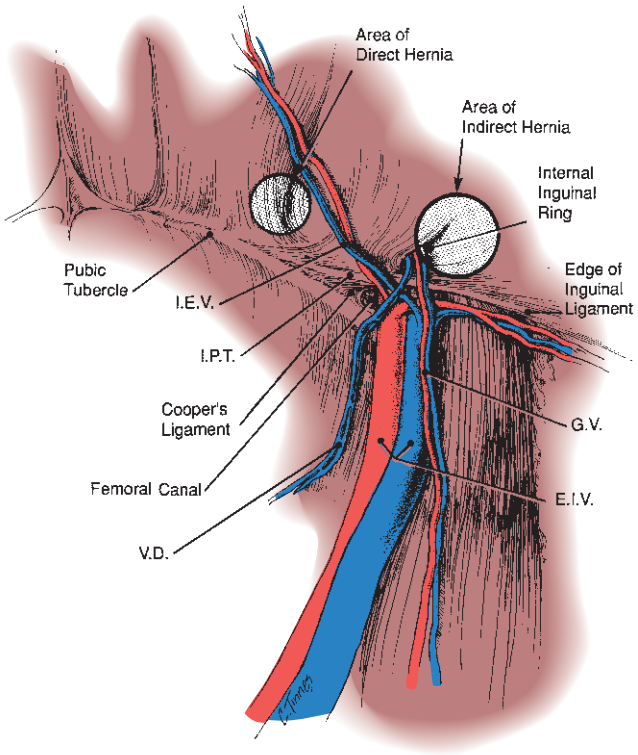

Figure 44–6. Schematic view of the extraperitoneal anatomy as seen from the open or laparoscopic preperitoneal approach. Direct and indirect hernia spaces, as well as the femoral canal, are shown. E.I.V., external iliac vein; I.E.V., inferior epigastric vessel; I.P.T., iliopubic tract.

examination. If the hernia is incarcerated, an incision through the iliopubic tract where the fibers insert onto Cooper's ligament at the medial border of the femoral ring should release it. Once strangulation is excluded by opening the sac and examining its contents, the peritoneum is closed. Small primary femoral hernias (Nyhus type IIIC) can be repaired with three to five nonabsorbable sutures approximating the iliopubic tract to Cooper's ligament. Large, recurrent, or complex femoral hernias (Nyhus type IV) can be repaired in the same manner but usually require a mesh buttress. Alternatively, they may be repaired with mesh without suture approximation of the femoral ring. Polypropylene mesh is placed as a sheet that covers the femoral ring and the direct and indirect spaces with a 2- to 3-cm overlap.

The Kugel repair is the newest modification of the preperitoneal approach. A ring-reinforced double layer of polypropylene mesh (Davol, Cranston, RI) is placed in the preperitoneal space through a small 3-cm oblique incision by blunt finger dissection.[17] Today, mesh repairs are preferred by most surgeons, but in the presence of contamination or strangulation, prosthetic material should be avoided.

The laparoscopic approach to hernia repair has become increasingly popular with advanced laparoscopic surgeons. The technique combines the benefits of laparoscopic procedures (reduced postoperative pain and early return to activities) and the preperitoneal approach (excellent exposure, easy intraperitoneal access for visceral examination or resection, and coverage of all three potential groin hernia sites with a single sheet of mesh). There are two accepted techniques: TAPP and TEP (Fig. 44–7). Many surgeons favor the TEP technique for elective repairs because it avoids potential intraperitoneal complications, but the TAPP technique is equally acceptable.[2] Most surgeons perform TAPP repairs for hernias with incarceration or strangulation because of improved visibility and control of incarcerated viscera, but Ferzli et al. have suggested that the TEP technique can also be used.[32] If necessary, bowel resection may be performed either laparoscopically or with conventional laparotomy, depending on the experience of the surgeon.

The TEP technique involves dissection of the preperitoneal space and the cord structures beyond the separation of the vas deferens and testicular vessels, as well as any hernia within the indirect, direct, or femoral spaces.[19] The peritoneum must be dissected back so that it lies completely posterior to the inferior edge of the mesh. When a TAPP technique is used, the peritoneum is opened 2 cm superior to the internal ring and is dissected down to expose all three potential groin hernia sites. After completing the hernia repair, a TAPP technique requires careful reapproximation of the peritoneum. Whether a TAPP or TEP technique is used, incarcerated femoral hernias are released by dividing the superomedial aspect of the femoral ring where the

Table 44–1 Recurrence Rates After Primary Femoral Hernia Repair

Author	Year	*N*	Approach	Follow-up	Recurrence (%)
Amid[3]	1994	200	Femoral, mesh plug	1-15 yr	0.5
Bendavid[4]	1994	329	Inguinal, mesh plug	—	1.8
Felix[2]	1997	85	TAPP, TEP	2 yr (median)	0
Glassow[36]	1985	1138	Femoral, suture	—	1.9
Hachisuka[7]	2003	67	Femoral, mesh	—	1.5
Hernandez[37]	2000	51	TAPP	1 yr	0
Kapiris[38]	2001	19	TAPP	3.75 yr	0
Swarnkar[39]	2003	43	Femoral, mesh plug	2 yr (median)	0
Trabucco[29]	1994	40	Femoral, mesh dart	1-4 yr	2.5

TAPP, transabdominal preperitoneal; TEP, totally extraperitoneal.

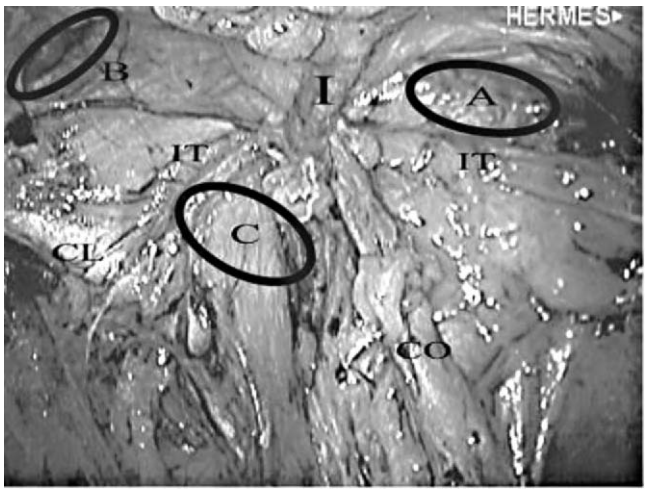

Figure 44–7. View of the extraperitoneal anatomy during a laparoscopic totally extraperitoneal technique. A, direct hernia; B, indirect space; C, femoral space; CL, Cooper's ligament; CO, spermatic cord structures; I, inferior epigastric vessels; IT, iliopubic tract medial and lateral to the inferior epigastric vessels.

iliopubic tract inserts into Cooper's ligament. Once all the dissection is completed, a polypropylene mesh is placed over the entire floor. The mesh may be fixed in place with anchors or placed without fixation. The authors' preferred technique is the use of preformed mesh (Bard 3-D Max) that conforms to the pelvis and does not require fixation.[33,34]

RESULTS

A comprehensive list of primary femoral hernia repair studies and their outcomes is presented in Table 44–1. Swarnkar et al. reported no recurrences to a median 2-year follow-up in 43 femoral hernias repaired via a femoral approach with a polypropylene mesh plug.[35] Trabucco reported a single recurrence (2.5%) with a 1- to 4-year follow-up in 40 femoral hernias repaired via dart-shaped polypropylene mesh plugs through an inguinal approach.[29] Bendavid fashions an umbrella-shaped polypropylene mesh placed via an inguinal approach and has reported a 1.8% recurrence rate in 329 repairs.[4] Glassow has reported repair of 1138 primary femoral hernias by suture via a femoral approach, with 21 recurrences (1.9%).[36]

Hernandez-Richter and colleagues reported no recurrences in a 12-month follow-up of 51 femoral hernias repaired by a laparoscopic TAPP technique.[37] Kapiris et al. retrospectively reported the outcomes of laparoscopic TAPP repairs in 3017 patients over a 7-year period, including 16 femoral hernia repairs. The authors reported 22 recurrences for a rate of 0.72%, but only 5 recurrences in the last 3205 patients when a larger (10 × 15 cm) sheet of mesh was used.[38] Felix and associates reported using both TEP and TAPP techniques to repair 1173 groin hernias, 16 of were pure femoral hernias and 69 had a femoral component to an inguinal hernia. Of these 85 femoral hernias, there were no recurrences over a 2-year median follow-up.[2] In another series of 90 recurrent inguinal hernias repaired laparoscopically with TAPP and TEP techniques, 8 hernias had a femoral component, and no re-recurrences were discovered during a median 14-month follow-up.[39]

COMMENTARY

The incidence of femoral hernias is relatively rare when compared with that of inguinal hernias. Femoral hernias account for 2% to 8% of all groin hernias. Differentiating femoral from inguinal hernias preoperatively is an inexact science, and definitive diagnosis requires surgical examination. Crawford et al. found that a preoperative diagnosis of groin hernia was incorrect 56% of the time in 253 patients, with ipsilateral femoral hernias and contralateral inguinal and femoral hernias frequently being missed.[1] Unlike the unnecessary attempt to distinguish indirect from direct inguinal hernias preoperatively because both spaces are examined and repaired with an anterior approach, unsuspected femoral hernias may be missed with an anterior approach and lead to a

"femoral" recurrence of the groin hernia repair. Mikkelsen et al. reviewed the Danish surgical database of 34,849 groin hernias repaired over a 3-year period and noted that the incidence of "recurrent" femoral hernia after inguinal herniorrhaphy was 15 times higher than the rate of primary femoral hernias found in that population.[40] The main advantage of the preperitoneal approach, open or laparoscopic, is the ability of the surgeon to accurately examine for and repair all groin hernias at the same time, hence potentially eliminating all missed hernias.

Surgeons at our center routinely perform laparoscopic repair of all groin hernias unless there is a contraindication such as anesthetic risk or obliteration of the preperitoneal space as a result of previous surgery or irradiation. Routine use of the laparoscope has led to the discovery of unsuspected femoral hernias in up to 11% of patients undergoing inguinal herniorrhaphy,[1,2] which suggests that the commonly touted femoral hernia rate of 2% to 8% underestimates its true incidence. Laparoscopic groin hernia repair requires extensive experience on the part of the surgeon in both TAPP and TEP techniques and has a significant learning curve.[41,42] Previous studies have found that severe complications, though rare, occur more frequently with laparoscopic than with open repair.[41,43-45] However, other series reported by experienced surgeons demonstrate low complication rates and recurrence rates of 0% to 2%, comparable to those in the open literature.[46-48] The preperitoneal approach, whether open or laparoscopic, is the preferred approach for recurrent femoral hernias because the femoral approach is associated with a 10% recurrence rate.[35] The approach that each surgeon uses should be based on the clinical situation, as well as the surgeon's experience and results. The aim of this chapter has been to provide a review of the commonly used repairs and a framework with which to select the most appropriate one.

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Chapter

45

Basic Features of Groin Hernia and Its Repair

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HISTORY

The earliest written records dealing with inguinal hernias (*hernios* in Greek = budding) date back to approximately 1500 BC. Early operations involved ligation of the sac and cord at the level of the external ring with excision of the sac, cord, and testis. Celsus (3 to 64 AD) is credited with bringing the more advanced Greek medicine to Rome (Greco-Roman Era, 460 BC to 467 AD). Notable figures such as Herophilus, Erasistratus, Heliodorus, and Galen, influenced by Hippocrates, "the father of medicine," and Aristotle, "the philosopher," performed and wrote about hernia surgery with a scientific understanding of anatomy and the use of anesthesia and hemostasis by ligature. During medieval times—the "Dark Ages" (Middle Ages, 476 AD to the 15th century)—the technical advances of Alexandrian and Greco-Roman surgery were largely lost. Surgery was usually performed by barbers, most of whom were ignorant and often illiterate. Hot cautery devices were commonly used to destroy tissue and control bleeding as the art of tying off a bleeding vessel disappeared. The use of any type of anesthesia was absent, and mutilation of the testicle and castration were thought to be necessary to cure a hernia. Needless to say, complications from these brutal methods were numerous.

The Renaissance (15th through mid-17th centuries) heralded many improvements for society, and surgery was no exception. Ambroise Pare is considered by many to be the father of modern surgery. Among many contributions was his understanding of the importance of ligating vessels to control bleeding instead of hot oil or cautery. The use of anesthesia was reinstated for inguinal hernia surgery, and preserving the testicle became an essential part of the operation as described by Casper Stromayr in 1559. The 18th century surgeon/anatomists were the first to publish treatises with illustrations based on detailed anatomic dissections. Sir Percivall Pott's *Treatise on Ruptures* refuted the older theories concerning the cause of hernias and methods of treatment (Fig. 45–1). While being the first to describe congenital hernias, he also gave a detailed description of the operative repair of incarcerated and strangulated hernias. Richter, a German surgeon, described the partial enterocele strangulation that still bears his name in *Abhandlung von den Bruchen,* one of the best-written hernia treatises of that time. A French contemporary, Alexis Littre, described herniation of a Meckel diverticulum. Jean Louis Petit recommended surgical repair of strangulated hernias only and described an external herniotomy without entering the sac, an operation that is eponymously linked to him. He also described the inferior lumbar triangle formed by the latissimus dorsi muscle, external oblique muscle, and iliac crest. It was John Hunter who renamed the lacunar ligament as Gimbernat's ligament after the Spanish anatomist described his technique of incision of the lacunar ligament for reduction of femoral hernia contents. Camper, a physician and philosopher, was the first to describe the processus vaginalis and the superficial fascia laying over the subcutaneous tissue in his *Icones Herniarum.*[1]

By the first decade of the 19th century, giants such as Astley Cooper, Franz Hesselbach, and Antonio Scarpa produced high-quality anatomy atlases that facilitated the development of modern hernia repairs. Marcy, an American surgeon and pupil of Lister, was the first to recognize the importance of the transversalis fascia and closing the internal ring when repairing an inguinal hernia. Furthermore, he emphasized the need for antisepsis. Edoardo Bassini, another pupil of Lister, described his technique of dissecting and ligating the sac high in the retroperitoneal space after dividing the transversalis fascia and emphasized the importance of including the transversalis fascia in his posterior wall buttress, which

Figure 45–1. Percivall Pott (1714-1788) gave a detailed description of the operative repair of incarcerated and strangulated hernias, among many other contributions to the field. (From Rutkow IM: A selective history of hernia surgery in the late eighteenth century: The treatises of Percivall Pott, Jean Louis Petit, D. August Gottlieb Richter, Don Antonio de Gimbernat, and Pieter Camper. Surg Clin North Am 83:1021-1044, 2003.)

involved suturing the internal oblique and transversus abdominis with the upper layer of the transversalis fascia in one layer (Bassini's famous triple layer!) to the lower leaf of the transversalis fascia and the inguinal ligament with interrupted silk sutures.[2] His final results published in 1894, with a 100% follow-up at 5 years, revealed 8 recurrences in 206 operations with no operative mortality.[3] These phenomenal results have earned him the title of Father of Modern Herniorrhaphy.

Unfortunately, the results achieved by Bassini were not reproduced when his operation was adopted by the general surgical community. Protégés of Bassini have pointed out that modifications in the technique decreased its effectiveness. Perhaps most notable was omission of division of the transversalis fascia in favor of blindly grasping tissue beneath the internal oblique muscle and sewing it to the inguinal ligament. The basis of this modification was fear of bladder or neurologic injury, or both, caused by entering the preperitoneal space. This "good stuff to good stuff" approach did not result in an entirely reproducible procedure because of the variability of what was actually grasped by the Allis forceps. The only Bassini modification that offered consistently comparable results was the multilayered Shouldice repair, reported by surgeons at the Shouldice Clinic in Toronto. However, this operation was hard to teach because of difficulty understanding what was really being sewn to what. Unless specifically trained at the Shouldice Clinic with an opportunity to work with the surgeons there, the various layers in the medial flap are not reliably identified by surgeons to develop the multiple suture lines.

Proponents of prosthetic material began to express the opinion that these materials might be the solution for achieving the holy grail of a "tension-free" repair as early as the 1950s. However, the vast majority of surgeons were disinclined to use foreign material for an inguinal hernia repair because of fear of infection, erosion into surrounding structures, rejection, cost, and even carcinogenesis. By the late 1980s it had become clear that these complications were not common and that the recurrence rate after nonprosthetic herniorrhaphies was much higher than generally appreciated, especially outside specialized centers (population-based studies). Modern hernia specialists such as Lichtenstein in 1986 and Gilbert in 1987 reported their techniques of "tensionless and sutureless" repairs, which involved placing a synthetic polypropylene mesh either deep to or in front of the repaired transversalis fascia in addition to using a rolled-up strip of mesh to plug wide hernial defects. Surgeons at the Lichtenstein Institute initially applied their technique only for the repair of complicated groin hernias (large direct, pantaloon, and recurrent hernias). It was their observation of the low recurrence rate in this group that led them to apply the technique universally.

The preperitoneal space can also be used to repair an inguinal hernia. An open preperitoneal procedure was described by the ancient Hindus to relieve cases of strangulated hernia. Fruchard is credited with development of the concept that the root cause of all groin hernias is failure of the transversalis fascia to retain the peritoneum and its contents. The basis of preperitoneal repairs is to reinforce the space between the peritoneum and the transversalis fascia, thereby re-establishing the ability of the transversalis fascia to retain intra-abdominal viscera. In this model the difference between direct, indirect, and femoral hernias looses its significance because all hernias are treated the same by covering the entire myopectineal orifice. There are several different ways for the surgeon to enter the preperitoneal space for the purpose of performing the repair there. Read and Rives favor an anterior approach through a conventional groin incision. In contrast, Nyhus, Condon, and Wantz in the United States and Stoppa and others in France have been strong proponents of an extraperitoneal posterior approach, either a midline, high transverse or Pfannenstiel incision, especially for complicated or recurrent hernias. The introduction of therapeutic laparoscopy into general surgery in the early 1990s made a transabdominal approach to the same space more attractive.

EMBRYOLOGY

The processus vaginalis is a peritoneal diverticulum in the embryonic lower anterior abdominal wall that traverses the inguinal canal; in males it forms the tunica vaginalis testis. In the eighth week of fetal life, the processus vaginalis is open into the inguinal canal with an extraperitoneal gubernaculum, a mesenchymal column of tissue that connects the fetal testis to the developing scrotum and plays a role in testicular descent. The primitive testis and metanephros lie close together near the

pelvic brim. As the trunk of the fetus elongates, the kidney migrates upward and the testis follows its anchoring gubernaculum downward. By the third trimester, it is located behind the processus vaginalis. At birth, 60% of infants still have an open processus. This figure drops by half after the first month. Although a persistent processus vaginalis is associated with an indirect inguinal hernia, it is important to realize that the processus vaginalis remains open in 25% of adult men, in most of whom an inguinal hernia never develops.[4] A persistent processus vaginalis in females is known as the canal of Nuck.

NATURAL HISTORY

It is impossible to obtain a completely accurate picture of the natural history of inguinal hernias because of the difficulty of finding a whole group of untreated patients. Most surgeons would repair a hernia at diagnosis, even if asymptomatic, to avoid potential complications. The commonly quoted 4% to 6% lifetime risk for strangulation of an inguinal hernia is probably more the result of speculation than fact. A probability of 0.037 hernia-related complications per patient per year was determined by studying a group of hernia patients from a Paris truss clinic in the 19th century at a time before inguinal herniorrhaphy was routinely performed. A similar figure was noted in a more recent Colombian government study. Using life table analysis and the probability calculated from these two studies, the lifetime risk for a hernia accident in an 18-year-old man is 20%, or 1 in 5 patients; for a 72-year-old, it is 4.0%, or 1 in 25 patients. Hair and colleagues provided some data concerning the likelihood of pain or incarceration by examining a prospectively maintained database of 699 patients.[5] Using Kaplan-Meier estimates, they were able to calculate that the probability of pain developing by 10 years was 90%, but this seemed to have minimal clinical significance because leisure activity was affected in only 29% and just 13% of the employed patients had to take time off of work because of hernia-related symptoms. Similarly, the cumulative probability of a hernia becoming irreducible rose from 6.5% at 12 months to 30% by 10 years, but only 10 patients in their series required an emergency operation and only 2 had to have strangulated contents resected. The U.S. Agency for Healthcare Related Quality of Life, in conjunction with the American College of Surgeons, sponsored a comprehensive clinical trial to compare a strategy of observation for asymptomatic patients with routine repair. The results of this study showed, on a 2-year observation period, that watchful waiting in minimally symptomatic patients is an acceptable option, and delaying repair until symptoms increase is safe because incarceration or strangulation occur rarely.[5a]

INCIDENCE

Seventy-five percent of all abdominal wall hernias occur in the groin. Approximately 750,000 inguinal herniorrhaphies are performed annually in the United States, with indirect hernias outnumbering direct hernias by about 2:1. Reliable figures concerning the incidence and prevalence of hernias are not readily available, the major reason being a lack of objective criteria to consistently make an accurate diagnosis. The prevalence of an inguinal hernia in a male is clearly age dependent. In a recent study 32% of male children weighing less than 1500 g required a hernia operation by the age of 8 years. For an adult male, the incidence increases steadily with age and has been reported to approach 50% for men older than 75 years. Abramson and colleagues from Israel published a particularly helpful paper dealing with inguinal hernia epidemiology. They studied 455 men with inguinal hernias from a settlement community in the early 1950s. The patients were a mixture of native-born Israelis and immigrant Europeans, Americans, Asians, and Africans and were therefore thought to be representative of the population as a whole. From this group they were able to calculate a current prevalence rate (excluding repaired hernias) of 18% and a lifetime prevalence rate (including repaired hernias) of 24%.[6] However, it should be noted that there is considerable variance in reporting. A recent study by Akin et al.[7] in adult male military recruits revealed a 3.2% prevalence, much lower than that reported by Abramson et al.[6]

ETIOLOGY, BIOCHEMICAL BASIS, AND MECHANICAL STRESS

The cause of an inguinal hernia is undoubtedly multifactorial. In the evolution from a quadruped to a biped, the unprotected groin has become more vulnerable to changes in intra-abdominal pressure. Physical exertion is probably less important than commonly believed, as suggested by the fact that athletes and weightlifters do not seem to have an excessive incidence of inguinal hernias. Russel proposed the so-called saccular theory based on the presence of a patent processus vaginalis as the cause of an indirect inguinal hernia.[8] Opponents of this theory point out that autopsy studies have shown that patients can have a patent processus without clinical evidence of hernia and, conversely, that patients with an obliterated processus vaginalis have been noted to have an abdominal wall defect lateral to the epigastric vessels. Increased intra-abdominal pressure and relative weakness of the posterior inguinal wall are thought to be important in the development of direct inguinal hernias. Increased intra-abdominal pressure and the size and shape of the femoral ring contribute to the development of femoral hernias. Although the femoral vein laterally and Cooper's ligament inferiorly are fairly constant boundaries of the femoral ring, variations in attachment of the iliopubic tract anteriorly and medially account for the development of femoral hernias. The iliopubic tract normally inserts for a distance of 1 to 2 cm along the pectinate line between the pubic tubercle and the midportion of the superior pubic ramus. A femoral hernia can result if the insertion is less than 1 to 2 cm or if it is shifted medially. The myopectineal orifice is an area bounded

superiorly by the internal oblique and transversus abdominis muscles, medially by the rectus muscle and sheath, laterally by the iliopsoas muscle, and inferiorly by Cooper's ligament. This funnel-shaped orifice is lined in its entirety by the fascia transversalis. As noted previously, Fruchaud's concept states that the fundamental cause of all groin hernias is failure of the transversalis fascia to retain the peritoneum. This led to the development of operations by some of his better-known students, such as Rives and Stoppa, in which a barrier (e.g., a mesh) was placed between the transversalis fascia and the peritoneum (i.e., the preperitoneal space) to address all types of groin hernias, thus rendering the distinction between direct indirect and femoral hernias less meaningful.

Familial predisposition and the role of connective tissue diseases in hernia development have received considerable attention in recent years. Various connective tissue disorders, such as osteogenesis imperfecta, Marfan's syndrome, Ehlers-Danlos syndrome, and congenital hip dislocation, are associated with hernias. Autosomal dominant polycystic kidney disease is characterized by abnormal production of extracellular matrix (ECM) and a 43% incidence of hernias. Individuals with hypermobile joints (e.g., circus contortionists) have been shown to have an abnormal increase in type III collagen and an increased risk for hernias. A similar phenomenon is observed in smokers.

Research at the molecular level has uncovered disturbances in collagen metabolism that are believed to contribute to hernia disease and high recurrence rates. Read performed biopsies of the rectus sheaths from adults with inguinal hernias. He found that equal-sized biopsy specimens were lighter in patients with hernias. He went on to show a striking decrease in hydroxyproline (a surrogate for collagen) in the hernia patients. Hydroxyproline makes up about 80% of the rectus sheath. Subsequently, he showed that fibroblasts cultured from the anterior rectus sheath of patients with inguinal hernias proliferated only half as well as those from individuals without herniation. The patients with direct herniation in this study had the longest generation time in the reproduction of fibroblasts. Furthermore, he demonstrated decreased incorporation of radioactive proline in the rectus sheath samples of individuals with hernias and a reduced hydroxyproline-to-proline ratio. Peacock and Madden suggested that the metabolic abnormality in patients with inguinal herniation might involve increased collagenolysis.[9] Cannon and Read coined the term "metastatic emphysema" based on their finding that elastase activity was increased in patients with direct hernias and elastase inhibitory activity measured by serum antitrypsin levels was decreased, with remarkably low levels seen in smokers.[10] Further evidence of the role of collagen abnormality is the increased incidence of inguinal herniation in patients with lathyrism and several congenital connective tissue diseases.

Recent studies dealing with the development of a hernia have focused on the ECM. The ECM is in a dynamic balance of synthesis and degradation by matrix metalloproteinases (MMPs). Within the transversalis fascia, an alteration in collagen composition leads to increased tissue elasticity. Whereas type I collagen confers predominantly tensile strength, type III collagen consists of thinner fibers and is regarded as a temporary matrix during tissue remodeling. A decreased ratio of type I to type III collagen can be detected in fascial and skin specimens from patients with incisional hernia disease at both the mRNA and protein levels. Further analysis of the collagen content of mesh samples that were removed at the time of repair of a recurrence demonstrated a significantly decreased collagen type I–to–type III ratio. The MMP family consists of zinc-dependent proteases secreted as latent proenzymes with substrate specificity.[11] Recent studies by Bellon et al. revealed MMP-2 overexpression in the fibroblasts of patients with direct inguinal hernias, whereas Klinge et al. detected MMP-13 overexpression in patients with recurrent inguinal hernias.[12,13]

Herniogenetics is rapidly developing as a science and has the goal of unraveling the secrets of genes that might contribute to the tendency for development of an inguinal hernia. Currently, hernia disease is believed to be a polygenetic trait, with penetrance of the hernia phenotype being dependent on complex interactions between environmental factors and multiple genes. The most likely candidate genes for genetic studies are those that are responsible for the production of fibrillar type I and type III collagen and MMPs. Polymorphisms occurring not only within the coding sequences but also within the regulatory and promoter sequences might be of importance in disease manifestation. Microarray analysis of ECM-related genes in patients with hernias and healthy subjects will help determine the susceptibility genes for hernia development.

Bendavid has recently proposed a "unified theory" of hernia formation that links anatomic, chemical, genetic, environmental, and metabolic etiologies of inguinal hernias. He makes the point that the final common denominator in all these proposed etiologies is the collagen matrix.[14]

ANATOMY

A surgeon who is attempting to repair a hernia with an open technique as opposed to one using a laparoscopic approach views the abdominal wall anatomy differently. Surgical anatomy is discussed from both perspectives in this chapter. The abdominal wall spans the space between the lower ribs and the pelvis. The diaphragm is the superior border of the abdominal cavity, whereas inferiorly the abdominal cavity is continuous with the pelvic cavity. The anterior abdominal wall is formed above by the lowest ribs and below by the rectus abdominis, external oblique, internal oblique, and transversus abdominis muscles and their aponeuroses. Posteriorly, the abdominal wall is made up in the midline of the lumbar vertebrae and their intervertebral disks; laterally, the gap between the 12th rib and the upper part of the pelvis is bridged by the psoas muscles, quadratus lumborum muscles, and the aponeurosis of the transversus abdominis muscles.

Anterior Abdominal Wall

Skin, Fascia, Vessels, and Nerves

The lines of cleavage in the skin run horizontally around the trunk, and this is clinically important when planning operative incisions. Camper's fascia is the superficial fatty layer that lies below the skin; it is continuous below with the outer layers of fascia covering the perineum and genitalia and also contains the dartos muscle fibers of the scrotum. The superficial circumflex iliac and superficial epigastric vessels, tributaries of the femoral vessels, are the major blood vessels of the superficial fascia. The lymphatic channels that traverse this fascia drain to the axillary nodes above the umbilicus and to the inguinal nodes below. The lymphatic channels cross the inguinal ligament and are potentially located in the surgical field for an inguinal herniorrhaphy. A second fascial layer in the superficial abdominal wall is the deep fascia of Scarpa, which is composed of compressed fibrous components of the superficial fascia. After forming the suspensory ligament of the penis (or clitoris), it fuses with the membranous layer of the superficial fascia, or Colles' fascia, in the perineum. Scarpa's fascia is thin and fades out above and laterally, where it becomes continuous with the superficial fascia of the thorax and back, respectively. Scarpa's fascia also fuses with the deep fascia investing the external oblique muscle. This fascia is bound inferiorly to the inguinal ligament and pubis before continuing onto the thigh, where it blends with the fascia lata to seal the space beneath and inferior to the inguinal ligament, which is the inferior portion of the myopectineal orifice. This portion of the inguinal region includes Hesselbach's triangle superiorly and is therefore the weakest aspect of the groin.

The cutaneous nerve supply to the anterior abdominal wall is derived from the anterior rami of the lower six thoracic and the first lumbar nerves in the familiar dermatomal pattern. Because of considerable overlap in dermatomal fields, disruption of one of these nerves is rarely clinically significant in postoperative patients. The cutaneous branches reach the subcutaneous layer by coursing between the flat lateral muscles and by piercing the sheath of the rectus abdominis.

Muscles, Ligaments, and Aponeurosis

The great lateral muscles of the anterior abdominal wall are composed of large aponeuroses and variable amounts of muscle. From exterior to interior they are the external oblique, internal oblique, and transversus abdominis. On either side of the midline anteriorly are the wide vertical muscles, the rectus abdominis muscles. The aponeuroses of the lateral muscles form the sheath of the rectus abdominis. The linea alba is the midline decussation of the three aponeuroses. In the lower part of the rectus sheath there may be a small muscle called the pyramidalis. The cremaster muscle is derived from the lower fibers of the internal oblique and passes inferiorly, covering the spermatic cord.

External Oblique Muscle and Associated Ligaments

The external oblique arises from the posterior aspect of the lower eight ribs (Fig. 45–2). The direction of the muscle fibers varies from nearly horizontal in its upper portion to oblique in the middle and lower portions. The fibers fan out and insert into the xiphoid process, linea alba, pubic crest, pubic tubercle, and anterior half of the iliac crest. The obliquely arranged anteroinferior fibers of insertion fold on themselves to form the inguinal ligament. The most posterior fibers passing down to the iliac crest form a posterior free border, which together with the anterior fibers of the latissimus dorsi and the iliac crest form the inferior lumbar triangle of Petit.

The more medial fibers of the external oblique aponeurosis divide into medial and lateral crura and form the superficial inguinal ring. The spermatic cord (or round ligament), the ilioinguinal nerve, and the genital branch of the genitofemoral nerve pass through this opening. The crural margins give origin to the external spermatic fascia.

The inguinal ligament is important because of its role as both a landmark and an integral component of many groin hernia repairs. It is the incurved free edge of the external oblique aponeurosis between its origin on the iliac crest and its insertion at the pubis. The ligament has a caudally directed convexity as a consequence of its connection to the fascia lata of the thigh. The ligament bridges the muscular and vascular structures that leave the pelvis inferiorly. This area deep to and above the inguinal ligament, including Hasselbach's triangle (see later), is called the *myopectineal orifice*. At its insertion to the pubic tubercle, the fibers of the inguinal ligament flare out in a fan-like fashion and fuse with the anterior rectus sheath and fibers from the opposite inguinal ligament along the upper border of the pubic bone to form the superior pubic ligament. The inguinal ligament continues downward to the superior pubic ramus to form the lacunar (Gimbernat's) ligament and courses laterally along the pectineal line as Cooper's ligament.

Internal Oblique and Transversus Muscles and Aponeurosis

The internal oblique is also a broad, thin, muscular sheet that lies deep to the external oblique. It arises from the lumbar fascia, the anterior two thirds of the iliac crest, and the lateral two thirds of the inguinal ligament. The muscle is inserted into the lower three ribs and their costal cartilages, the xiphoid process, the linea alba, and the symphysis pubis (Fig. 45–3). The transversus muscle runs horizontally deep to the internal oblique. It arises from the deep surface of the lower six costal cartilages, the lumbar fascia, the anterior two thirds of the iliac crest, and the lateral third of the inguinal ligament. The medial aponeurotic fibers of the transversus abdominis contribute to the rectus sheath and insert on the pecten pubis and the crest of the pubis to form the falx inguinalis. These fibers are infrequently joined by a

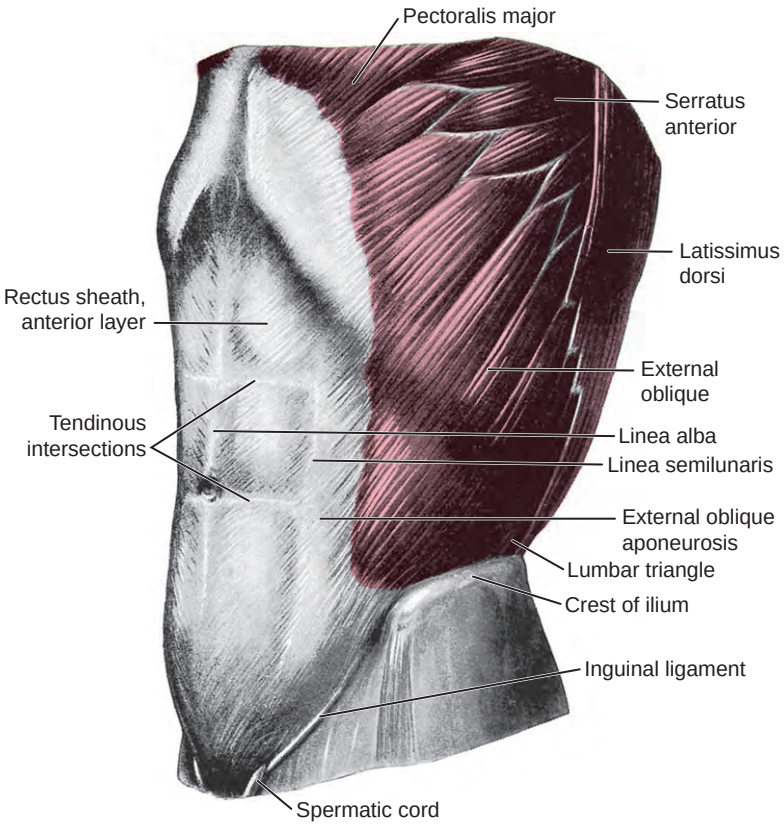


Figure 45–2. Left anterolateral view of the abdominal wall muscles showing the anterior rectus and external oblique muscles. (From Standring S: Gray's Anatomy: The Anatomical Basis of Clinical Practice, 39th ed. London, England, Churchill Livingstone, 2005. Fig 67.8, p 1108.)

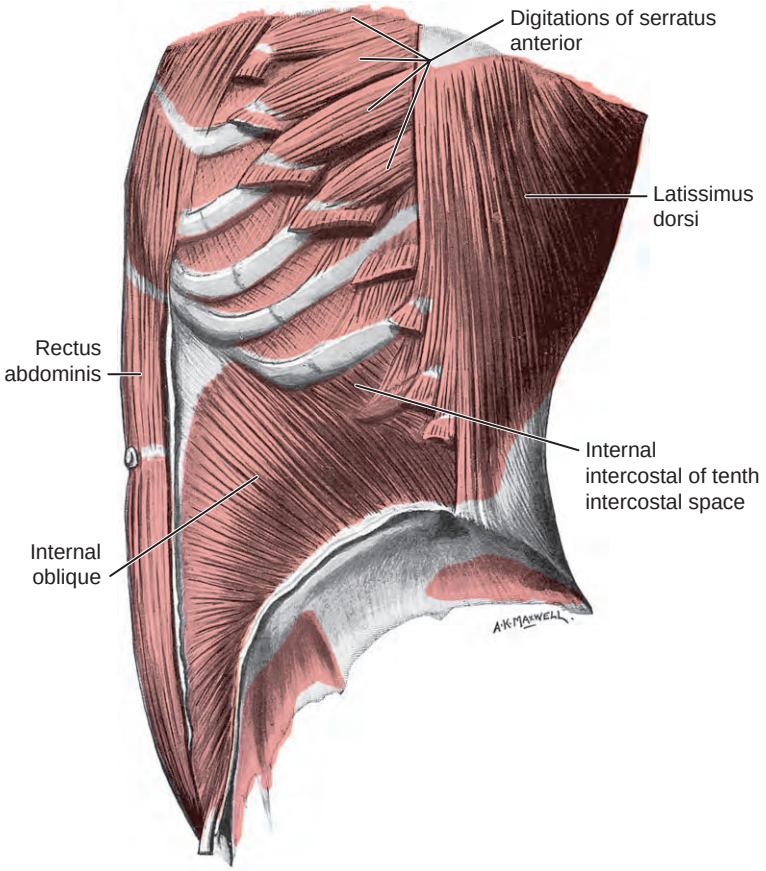


Figure 45–3. Left anterolateral view of the abdominal wall with the external oblique and anterior rectus muscles removed to show the internal oblique muscle. (From Standring S: Gray's Anatomy: The Anatomical Basis of Clinical Practice, 39th ed. London, England, Churchill Livingstone, 2005. Fig 67.9, p 1108.)

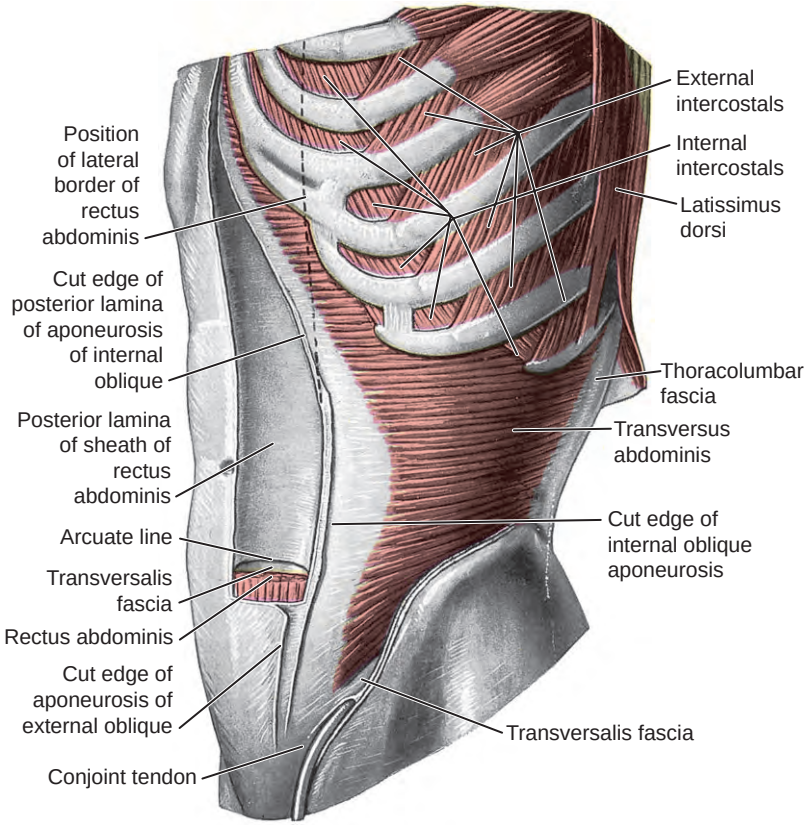


Figure 45–4. Left anterolateral view of the abdominal wall muscles with the rectus and internal oblique muscles removed to show the posterior rectus sheet, transversus abdominis muscles, and conjoint tendon. (From Standring S: Gray's Anatomy: The Anatomical Basis of Clinical Practice, 39th ed. London, England, Churchill Livingstone, 2005. Fig 67.11, p 1109.)

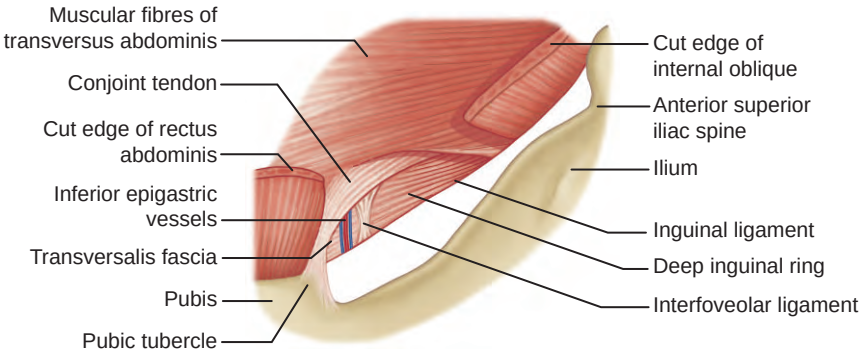


Figure 45–5. Anterior view of the muscles of the groin area (the internal oblique has been removed and the conjoint tendon is highlighted). (From Standring S: Gray's Anatomy: The Anatomical Basis of Clinical Practice, 39th ed. London, England, Churchill Livingstone, 2005. Fig 67.16, p 1111.)

portion of the internal oblique aponeurosis; only then is a true conjoint tendon formed (Fig. 45–4). What is commonly referred to as the conjoint tendon in many texts might better be termed the aponeurotic arch. Contraction of the transversus abdominis causes this structure to move down toward the inguinal ligament in a kind of shutter mechanism that reinforces the weakest area of the groin when intra-abdominal pressure is elevated (Fig. 45–5).[15]

Rectus Abdominis and Rectus Sheath

The rectus abdominis is a long muscle that arises from the symphysis pubis and pubic crest and is inserted into the fifth, sixth, and seventh costal cartilages and the xiphoid process (see Fig. 45–2). Three tendinous intersections, one at the xiphoid, one at the umbilicus, and one halfway between the two, usually divide it segmentally. The rectus sheath is a long fibrous sheath that encloses the rectus abdominis and pyramidalis muscle (a small muscle found in front of the lower part of the rectus abdominis). Above the costal margin the anterior wall is formed by the external oblique aponeurosis, and the fifth, sixth, and seventh costal cartilages and their intercostal spaces form the posterior wall. Between the costal margin and the anterior superior iliac spine, the internal oblique aponeurosis splits to enclose the rectus muscle. The external oblique muscle is directed in front and the transversus aponeurosis is directed behind the muscle. Between the level of the anterior superior iliac spine and the pubis, the sheath does not have a posterior wall and the aponeurosis of all three muscles forms

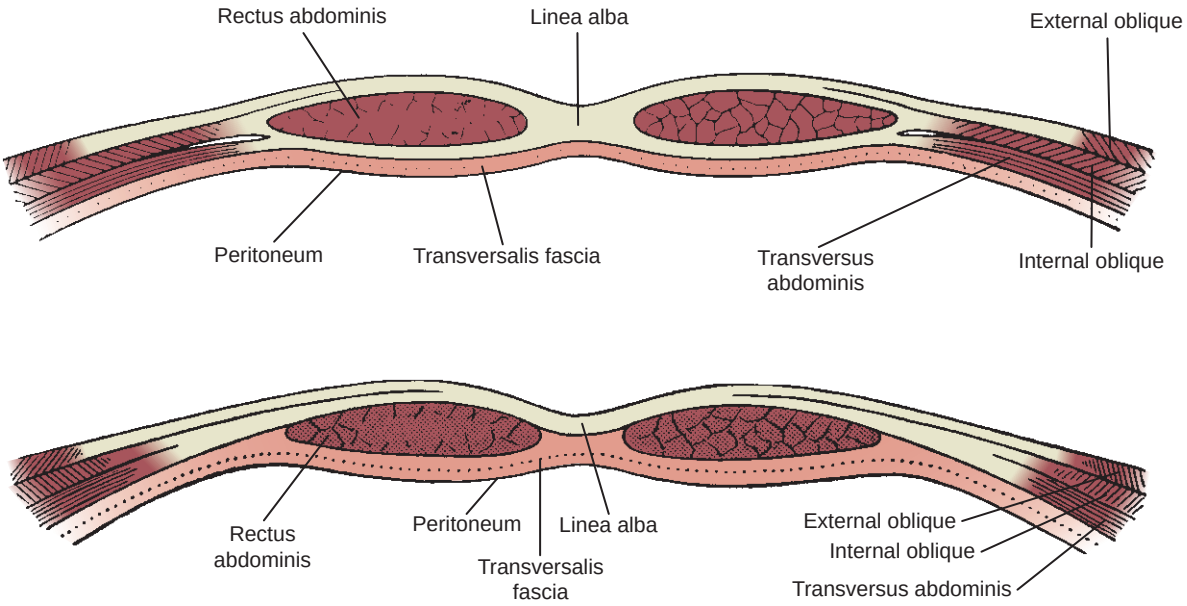


Figure 45–6. Transverse view of the abdominal wall above and below the arcuate line. (From Standring S: Gray's Anatomy: The Anatomical Basis of Clinical Practice, 39th ed. London, England, Churchill Livingstone, 2005, p 1105.)

the anterior wall. The curved free lower border of the posterior wall is called the arcuate line, and it allows passage of the deep inferior epigastric vessels into the sheath (Fig. 45–6).

Laparoscopic Anatomy of the Inguinal Region

Surgeon preparation for laparoscopic herniorrhaphy mandates relearning inguinal anatomy from the preperitoneal perspective.[16] Surgeons unaccustomed to the unique viewpoint encountered during laparoscopic procedures find the images to be quite disorienting. The anatomy of the groin area and anterior wall can easily be mastered if several relatively consistent anatomic landmarks are noted. Details of laparoscopic anatomy are discussed in Chapter 46, Laparoscopic Inguinal Hernia Repair, and only a brief overview follows here.

Deep Aspects of the Anterior Abdominal Wall, Peritoneal Folds, and Associated Structures

Distending the peritoneal cavity with gas allows identification of the umbilical peritoneal folds, which are prominent and easily identifiable landmarks in most individuals. The single median umbilical fold extends from the umbilicus to the urinary bladder and covers the fibrous remnant of the allantois, the urachus. The urachus may be partially or completely patent and may open onto the umbilical scar in newborns or form a cystic remnant along the course of the median umbilical ligament. The medial umbilical fold, on either side, is formed by the underlying obliterated portion of the fetal umbilical artery, a branch of the anterior division of the internal iliac artery. The patent proximal portion of this artery supplies the superior vesical artery to the bladder. The lateral umbilical fold covers the inferior epigastric arteries as they course toward the posterior rectus sheath, which they enter approximately at the level of the arcuate line. The *supravesical fossa* is the depression found between the medial and median umbilical ligaments. This is also the site for hernias of the same name. The *medial fossa* is the space between the medial and lateral ligaments and is the site of direct inguinal hernias. The *lateral fossa* is less well delineated than the others. The lateral umbilical ligament and the rectus abdominis form the medial border of the fossa. This fossa does not have a lateral border; rather, the concavity slowly attenuates and is the site of congenital or indirect inguinal hernias.

Nerve injury during laparoscopic hernia repair may cause considerable and often persistent postoperative pain. The iliohypogastric, ilioinguinal, genitofemoral, lateral femoral cutaneous, and femoral nerves are all at risk. Two anatomic danger zones in regard to nerve and vessel injury are described and must be avoided. The first danger zone is the so-called *triangle of doom*, which is an area bounded laterally by the gonadal vessels and medially by the vas deferens with its apex orientated superiorly at the internal ring. The inferior border is arbitrary because it is the interface between dissected and nondissected peritoneum after preperitoneal dissection (Fig. 45–7). Within this triangle are the external iliac artery and vein, the deep circumflex iliac vein, the genital branch of the genitofemoral nerve, and the femoral nerve. The second anatomic danger zone is referred to as the *triangle of pain* or the *electrical hazard zone*. The medial border is constant and is formed by the internal spermatic vessels. It is questionably accurate to call this zone a triangle inasmuch as the lateral and inferior borders are nebulous because the entire space lateral to the internal spermatic vessels where critical nerves pass is included. The "triangle" contains the lateral femoral cutaneous nerve, the femoral branch of the

Figure 45–7. **A,** Preperitoneal view of the right side of the groin depicting the so-called triangle of doom (A) and the triangle of pain or the electrical hazard zone (B). **B,** Cadaveric preparation showing the structures included within these triangles that could be damaged during preperitoneal herniorrhaphy. AP, anterior pubic branch and iliopubic vein; B, bladder (reflected posteriorly); CI, common iliac artery; CL, Cooper's ligament; DC, deep circumflex iliac vessels; ES, external spermatic vessels; FB, femoral branch of the genitofemoral nerve; FN, femoral nerve; GB, genital branch of the genitofemoral nerve; GN, genitofemoral nerve; IA, external iliac artery; IE, inferior epigastric vessels; IL, ilioinguinal nerve; IM, musculus iliacus; IP, iliopubic tract; IPA, iliopectineal arch; IS, internal spermatic vessels; IV, external iliac vein; LC, lateral femoral cutaneous nerve; LV, iliolumbar vessels; PB, anastomotic pubic branch; PM, musculus psoas major; RP, retropubic vein; U, ureter; UA, umbilical artery; VD, vas deferens. (From Greene FL, Ponsky JL: Endoscopic Surgery. Philadelphia, WB Saunders, 1994, p 365.)

genitofemoral nerve, and the femoral nerve. Avoidance of electrosurgical energy, dissection, or the application of staples within these triangles is crucial to prevent nerve injury, entrapment, or vascular injury. The genitofemoral nerve is especially at risk during laparoscopic herniorrhaphy, as is the lateral femoral cutaneous nerve.

Transversalis Fascia and Its Derivatives

Harrison in 1922 was the first to stress the importance of the fascia transversalis in the pathology and repair of inguinal hernias. The transversalis fascia is a continuous sheet that extends throughout the extraperitoneal space. It is defined as the deep or endoabdominal fascia covering the internal surface of the transversus abdominis, the iliacus, the psoas muscles, the obturator internus, and portions of the periosteum. One variant of this convention is the use of terms specific to the muscle covered by the fascia (e.g., obturator fascia). Most hernia specialists believe that the transversalis fascia is bilaminar. There is a posterior fatty preperitoneal component (referred to as the preperitoneal fascia by some) and an anterior lamina that is adherent to the deep surface of the transversus and rectus abdominis muscles. The transversalis fascia is essentially a vascular envelope that encloses between these two laminae the arterial and venous plexuses that supply the muscles of this region (Fig. 45–8). The extraperitoneal space of Bogros lies behind the posterior lamina. It is important that in any preperitoneal approach the prosthesis be placed deep to the posterior lamina of the transversalis fascia, but superficial to the vas deferens and the parietalized spermatic vessels lying in the extraperitoneal fat.

At its attachments to the pubis and at points where it is penetrated by neurovascular or cord structures the transversalis fascia thickens to form important derivatives: the iliopectineal arch, the iliopubic tract, and the crura of the deep inguinal ring. The superior and inferior crura form a sling around the deep inguinal ring, a structure shaped like a "monk's hood." When the transversus abdominis contracts, the crura of the ring are pulled upward and laterally, which results in a valvular action that helps prevent the formation of an indirect hernia. With the increasing use of laparoscopy the iliopubic tract has become a more important surgical landmark. It is the thickened band of transversalis fascia formed at the zone of transition between the deep surfaces of the iliac and transversus abdominis muscles. It is not obviously visible in every patient from a laparoscopic perspective, but its location should be immediately known to the surgeon because of its constant relationship to other landmarks in the area. Anatomically, the tract courses parallel to the more superficially located inguinal ligament and is attached to the iliac crest laterally and the pubic tubercle medially. It forms a portion of the inferior crus of the deep ring and the anterior and medial walls of the femoral sheath. The tract fuses with the inguinal ligament to form a portion of the inferior wall of the inguinal canal. The pectineal ligament is reinforced by fibers of the iliopubic tract that are reflected downward off the pubic tubercle. The branches of the lumbar plexus run inferior to this tract. In fully 42% of

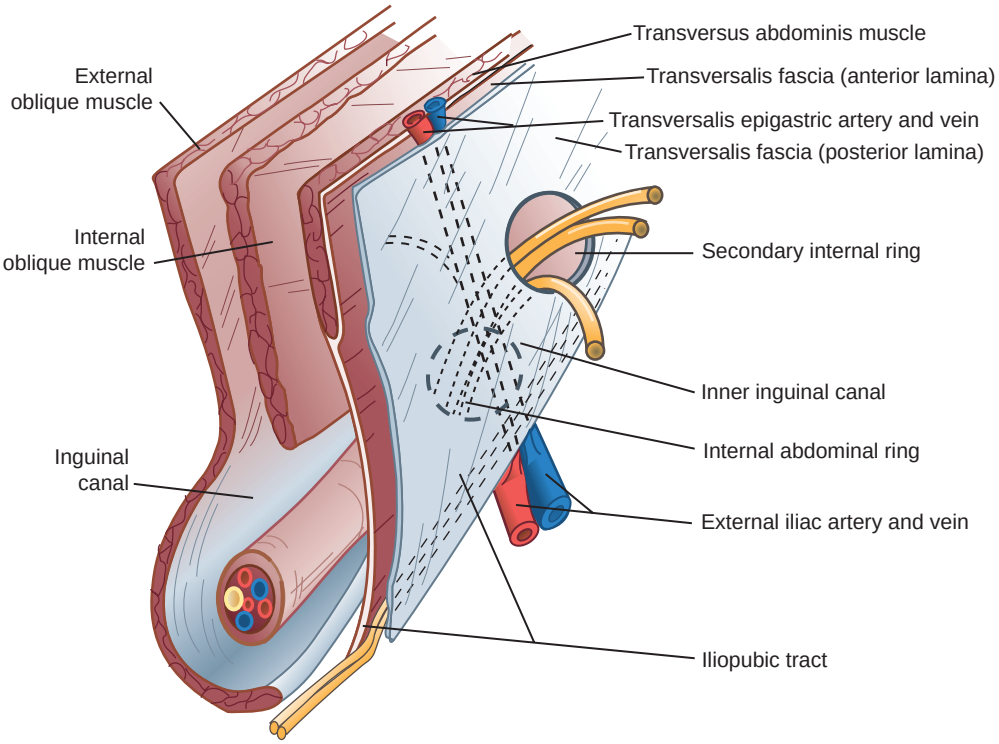


Figure 45–8. Parasagittal view of the right midinguinal area demonstrating the two laminae of the transversalis fascia. (From Read RC: The transversalis and peritoneal fasciae—a re-evaluation. In Nyhus LM, Condon RE [eds]: Hernia, 4th ed. Philadelphia, JB Lippincott, 1995, pp 57-63.)

examined specimens in a recent study, the iliopubic tract was a substantial structure suitable for use in hernia repair. The iliopectineal arch, also a derivative of the fascia transversalis, separates the vascular compartment (lacuna vasorum) containing the femoral vessels from the neuromuscular compartment (lacuna musculorum) containing the iliopsoas muscle, femoral nerve, and lateral femoral cutaneous nerve. It joins the iliopubic tract in contributing to the femoral sheath. The femoral sheath itself is a downward protrusion into the thigh of the fascial envelope lining the abdominal walls, as previously alluded to. The sheath surrounds the femoral vessels and lymphatics for about 1 inch below the inguinal ligament. The vascular compartment is further divided by septa into compartments for the vessels and the femoral branch of the genitofemoral nerves. The medial border of the femoral sheath follows the transversus abdominis aponeurosis to its insertion just lateral to that of the lacunar ligament and extends inferiorly to eventually fuse with the medial septum and adventitia of the femoral vein. The resultant cone-shaped cul-de-sac is the femoral canal, which often contains a large lymph node referred to as Cloquet's node. The femoral ring is the extraperitoneal opening of the canal. Its boundaries are the lacunar ligament medially, the femoral vein and its connective tissue septum laterally, the inguinal ligament anteriorly, and Cooper's ligament posteriorly reinforced by fibers from the iliopubic tract. The roof of the femoral ring (i.e., the iliopubic tract) is not reinforced by the tough transversalis fascia, which is diverted to form the femoral sheath in this location, and this predisposes to hernia formation, especially in female subjects (see Fig. 45–8).

Hesselbach's Triangle and the Spermatic Cord

The inguinal (Hesselbach's) triangle is formed by the rectus abdominis medially, the inferior epigastric vessels superolaterally, and the inguinal ligament at the base. It is the site of direct inguinal herniation. Only the peritoneum and transversalis fascia cover the triangle in this area. The aponeurotic arch, which is formed from the transversus abdominis muscle, crosses the apex of this triangle and reinforces this area of weakness when one strains. A high arch may predispose to the formation of direct inguinal hernias by offering less reinforcement. The cord structures include the ductus deferens, the pampiniform venous plexus, the testicular artery, and the genital branch of the genitofemoral nerve, a branch of the lumbar plexus.

Innervation and Blood Supply of the Abdominal Wall

The lumbar plexus is formed in the psoas muscle from the anterior rami of the upper four lumbar nerves. The branches of the plexus emerge from the lateral and medial borders of the muscle and its anterior surface. The iliohypogastric, ilioinguinal, lateral cutaneous nerve of the thigh, and femoral nerves emerge from the lateral border of the psoas, in that order from above downward. The genitofemoral nerve is the most anterior of the nerves encountered. The genital branch travels with the spermatic cord and ultimately innervates the cremaster muscle and the lateral aspect of the scrotum. Most studies show that the branches of the lumbar plexus destined for the thigh run beneath the iliopubic tract, which

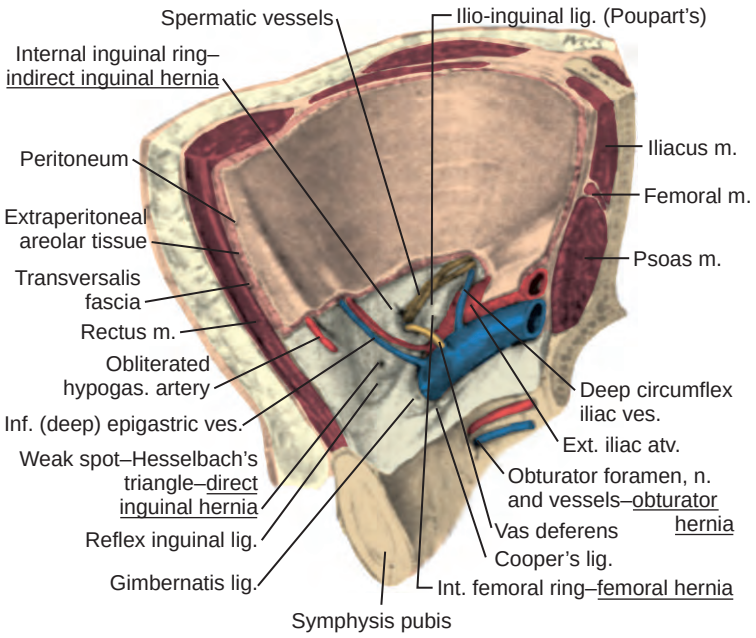


Figure 45–9. Posterior and sagittal view of the right inguinal area demonstrating the inguinal, femoral, and obturator orifices and their relationships. (From Read RC: Basic features of abdominal wall herniation and its repair. In Zuidema GD, Yeo CJ [eds]: Shackelford's Surgery of the Alimentary Tract, vol 5, 5th ed. Philadelphia, WB Saunders, 2002, p 92.)

has important implications for a surgeon working in the preperitoneal space. This is not universally accepted, however, because anomalous routes for some of the nerves above the iliopubic tract have been described. The femoral branch of the genitofemoral nerve innervates the proximal midthigh skin. The iliohypogastric and ilioinguinal nerves (L1) enter the lateral and anterior abdominal walls. The iliohypogastric nerve crosses the iliac fossa just inferior to the kidney and pierces the transversus abdominis. The subsequent course of the nerve carries it between the transversus and the internal oblique until it pierces the aponeurosis of both obliques just above the external inguinal ring. The ilioinguinal nerve normally crosses the iliac fossa just inferior to the iliohypogastric nerve. The nerve pierces the transversus and internal oblique above the iliac crest and subsequently enters the inguinal canal. The iliohypogastric nerve supplies the skin of the lower part of the anterior abdominal wall, and the ilioinguinal nerve passes through the inguinal canal to supply the skin of the groin and the scrotum or labium majus. The lateral cutaneous nerve crosses the iliac fossa under the iliac fascia and pierces the inguinal ligament to enter the thigh. The femoral nerve lies immediately below the lateral aspect of the psoas muscle and is not routinely encountered in laparoscopic surgery, although there are some reports of injury to this nerve.

The primary blood supply to the deep anterior abdominal wall is from the inferior epigastric artery, a branch of the external iliac artery. Aberrant obturator vessels may arise from the inferior epigastric vessels, arch inferiorly over Cooper's ligament, and join the normal obturator circulation to form the corona mortis; copious bleeding can result during careless dissection of Cooper's ligament or when one attempts to release a tight femoral hernial neck by incising the lacunar ligament. It is questionable whether the finding of a corona mortis should be considered anomalous because the variant is so common. Other veins in this area are larger than the accompanying arteries and are also prone to injury. The external iliac artery and vein are the vessels in the vascular compartment of the deep inguinal region. The deep circumflex iliac artery and vein pierce the transversalis fascia and run along the iliac fossa to anastomose with the deep lumbar system. As they course along the iliopubic tract, they can be inadvertently stapled or otherwise injured during laparoscopic herniorrhaphy (Fig. 45–9).

SYMPTOMS AND DIAGNOSIS

Patients with groin hernias have a wide range of clinical manifestations ranging from no symptoms at all to a life-threatening condition caused by strangulation of incarcerated intestinal contents. Asymptomatic patients are detected during routine physical examination or seek medical attention for a painless groin bulge. Indirect hernias are more likely to produce symptoms than direct ones are, with patients describing a heavy feeling or dragging sensation that tends to be worse as the day wears on. Radiation of pain into the testicle is not rare. Although some patients describe the pain as intermittent, others complain of a sharper pain that is either localized or diffuse. It is important to distinguish groin strain with a coexistent asymptomatic hernia from a truly symptomatic hernia. If the hernia is improperly determined to be a cause of the patient's pain, the stage is set for a postherniorrhaphy pain syndrome.

Physical examination is the best way to determine the presence or absence of an inguinal hernia. The diagnosis may be obvious by simple inspection when a visible bulge is present. Nonvisible hernias require digital examination of the inguinal canal, which is best done in both

the lying and standing positions. This invagination test helps distinguish a true hernia from a normal expansile bulge of muscle. Classic teaching is that an indirect hernia will push against the fingertip whereas a direct hernia will push against the pulp of the finger. Many authors, however, do not believe that direct and indirect inguinal hernias can be distinguished clinically.[17] The ring occlusion test is based on the premise that fingertip pressure over the midinguinal point will prevent an indirect hernia from protruding but will not be able to control a direct hernia. The differential diagnosis for groin hernias includes groin malignancies, ectopic and undescended testicles, psoas abscess, epididymitis, hydrocele, enlarged lymph nodes, saphenous varix, and femoral aneurysms.

Almost all groin hernias in women are either indirect or femoral. The stronger transversalis fascia in the floor of the inguinal canal, as a result of childbearing, makes direct herniation unusual. The indirect sac is the nonobliterated portion of the prenatal peritoneal evagination, known in females as the canal of Nuck, that runs along and partly covers the round ligament. In repair of these hernias most authors recommend ligation of both the sac and the round ligament at the level of the deep ring and anchoring of the round ligament stump to the internal oblique for support of the uterus. A femoral hernia appears as a swelling below the inguinal ligament and just lateral to the pubic tubercle. Femoral hernias need to be distinguished from a prominent femoral fat pad, the so-called femoral pseudohernia. Femoral hernias account for less than 10% of all groin hernias, but 40% are initially manifested as emergencies because of incarceration or strangulation. They are more common in older patients and in men who have previously undergone an inguinal hernia repair. Although the absolute number of femoral hernias in males and females is about the same, the incidence in females is four times that in males because of the lower overall frequency of groin hernia in women (male-to-female ratio of 7:1)

Sliding hernias constitute about 1.5% of all inguinal hernias. One wall of the sac, the posterior and lateral, is formed by a hollow viscus, usually the cecum on the right and the sigmoid colon on the left. The bladder may be present. The danger of these hernias is that the viscus may be mistaken for a sac and opened. They occur more commonly in the elderly, especially those with long-standing herniation. Characteristically, they can be only partially reduced during physical examination. A preperitoneal approach to the groin, whether open or laparoscopic, enables easier reduction and repair of these difficult hernias.

Irreducibility and incarceration may persist for years or decades without great inconvenience as a result of adhesions developing between the contents and the sac. Recent onset of incarceration is a potentially dangerous condition because it may result in strangulation and gangrene of the contents and is an indication for urgent repair. Bowel obstruction is more common in indirect, recurrent, and femoral hernias and is of the closed loop type. As a result of blockage at both the entry and exit of the intestine at the level of the internal ring, the pressure in the intestinal lumen and accompanying vasculature and lymphatics cannot be dissipated, and perforation and gangrene of the bowel follow in neglected cases. Plain roentgenograms of the abdomen can be diagnostic. Taxis can be attempted in the absence of signs of strangulation. Taxis is performed with the patient sedated and in the Trendelenburg position. The hernia sac neck is grasped with one hand while the other applies pressure on the most distal part of the hernia. The goal is to elongate the neck of the hernia so that the contents of the hernial sac can be reduced with a rocking movement. Mere pressure on the most distal part of the hernia causes bulging of the hernia contents around the neck, which can occlude the neck and prevent reduction. Taxis should be performed only by a surgeon who is willing to observe the patient after successful reduction because of the slight possibility that gangrenous bowel might be reduced into the abdomen, viable hernia contents might be perforated, or the phenomenon known as en masse reduction might occur, which is defined as displacement of a hernia mass without relief of incarceration or strangulation secondary to a constricting fibrous ring. Strangulation is a life-threatening condition. The irreducible hernia is tense and tender, and the overlying skin may be discolored with a reddish or bluish tinge. The patient is often febrile, dehydrated, and toxic. Laboratory investigations often reveal metabolic acidosis and leukocytosis with a left shift.

Radiologic investigations are sometimes warranted to correctly diagnose the cause of groin pain. Herniography, though invasive, helps avoid unnecessary surgical exploration. Ultrasound is useful, especially in acute manifestations of groin swelling, to distinguish incarcerated bowel from acute lymphadenitis. It is, however, operator dependent.

Cross-sectional imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) are increasingly being used for the investigation of groin pain and swelling. Hernias are visualized as anteroposterior ballooning of the inguinal canal with simultaneous protrusion of fat or bowel. Van den Berg et al. looked at a group of patients scheduled to undergo elective laparoscopic herniorrhaphy for either unilateral or bilateral hernias detected on physical examination.[18] Blinded interpreters examined ultrasound and MRI scans and looked at not only the affected but also the opposite side; laparoscopy was considered the final arbitrator of the groin pathology on either side. The sensitivity and specificity were 74.5% and 96.3% for physical examination, 92.7% and 81.5% for ultrasound, and 94.5% and 96.3% for MRI. With the development of fast imaging scanners that allow dynamic imaging during straining, the addition of intraperitoneal contrast, and tweaking of the best weighting for images along with improved understanding of the technology, MRI is likely to become the imaging modality of choice in investigating groin pathology.

CLASSIFICATION

Surgeons have traditionally classified inguinal hernias as direct or indirect and groin hernias as inguinal or

Table 45–1 Inguinal Hernia Classification Systems

Modified	Traditional	Nyhus-Stoppa	Modified Gilbert	Schumpelick/Aachen
IA	Indirect small	I	1	L1
IB	Indirect medium	II	2	L2
IC	Indirect large	IIIB	3	L3
IIA	Direct small	IIIA	5	M1
IIB	Direct medium	IIIA	—	M2
IIC	Direct large	—	4	M3
III	Combined	IIIB	6	Mc
IV	Femoral	IIIC	7	F
0	Other	—	—	—
R	Recurrent	IV A, B, C, D	—	—

femoral, and that is the convention used in this chapter. However, this classification is not universally accepted, with many surgeons considering the terms groin hernia and inguinal hernia to be synonymous and inclusive of direct, indirect, and femoral hernias. Although it was Cooper who devised the concept of direct and indirect, it was Hesselbach who used the inferior epigastric vessels as the defining boundary between these two areas. With the advent of a new generation of herniorrhaphies in the 1950s there arose interest in devising a more scientific classification of groin hernias. Harkins developed a grading system to classify groin hernias. Grade I consists of indirect infant hernias, whereas grade 2 represents simple indirect hernias in older children and healthy young adults. Grade 3 hernias are "intermediate" types of hernia (larger indirect hernias, inguinal hernias in young adults or small hernias in older patients with strong tissue, or direct inguinal hernias in older patients with strong tissue or narrow necks). Grade 4 hernias include recurrent, femoral, direct, and indirect hernias not specifically falling within the earlier grades.

The primary purpose of a classification system for any disease is to stratify for severity so that reasonable comparisons can be made between various treatment strategies. However, with the multiplicity of operative techniques and approaches for repair of groin hernias, no single classification system has been accepted by all practitioners. The reason why it is so difficult to develop a classification system that all surgeons can agree on is that in the final analysis, physical examination represents an important component and no one has been able to eliminate its subjectivity. The more commonly applied classification systems are summarized in Table 45–1. The advantage of the modified traditional classification system, as proposed by Zollinger, is that it includes all the classes or grades within the other commonly used classification systems.[19] It separates the Nyhus IIIA and IIIB groups into distinct components, and it accounts for the direct (medium) hernias missing from Gilbert's system (Fig. 45–10). Finally, the modified traditional method allows for an "other" group rather than forcing the user to imprecisely classify an unusual hernia and separately classifies recurrent hernias, as does Nyhus. Kingsnorth has developed a clinical classification system that groups patients according to grades of predicted technical difficulty. A score of 2 to 8 for prediction of the grade of difficulty of repair can be generated from the size of the hernia (H1 to H4) and the subscapular skin fold (F1 to F4) and enables preoperative stratification into groups of difficulty to match the competency level of the operator. The subscapular skin fold thickness correlates well with groin fat thickness, a marker of technical difficulty.[20] Future classification systems will probably include modifiers such as contents, associated abnormality, and reducibility of the hernia and will also be applicable from a laparoscopic perspective.

SURGERY

Indications and Alternatives

Strangulation and bowel obstruction are sometimes referred to as hernia accidents and are absolute indications for surgery. Unlike an adhesive bowel obstruction, obstruction caused by an inguinal hernia is almost never partial. Therefore, semiurgent surgery is indicated. Resuscitation includes bowel decompression, intravenous fluids to correct dehydration and electrolyte imbalance and ensure optimal urine output, followed by immediate surgery. All significantly symptomatic hernias should be repaired to improve quality of life.[21] Nonoperative treatment is applicable only for asymptomatic and minimally symptomatic hernias. Patients are counseled about the signs and symptoms of complications from their hernia so that they may promptly contact their physician in case of an adverse event. Nonoperative treatment remains controversial, and most standard surgical texts continue to recommend surgical repair of all inguinal hernias at diagnosis. However, a recent randomized controlled trial has provided strong evidence that supervised observation is safe.[5a] Women early in pregnancy should undergo surgery, whereas those who are about to deliver should have their hernia dealt with after delivery. Infants and young children should undergo prompt repair of groin herniation because their

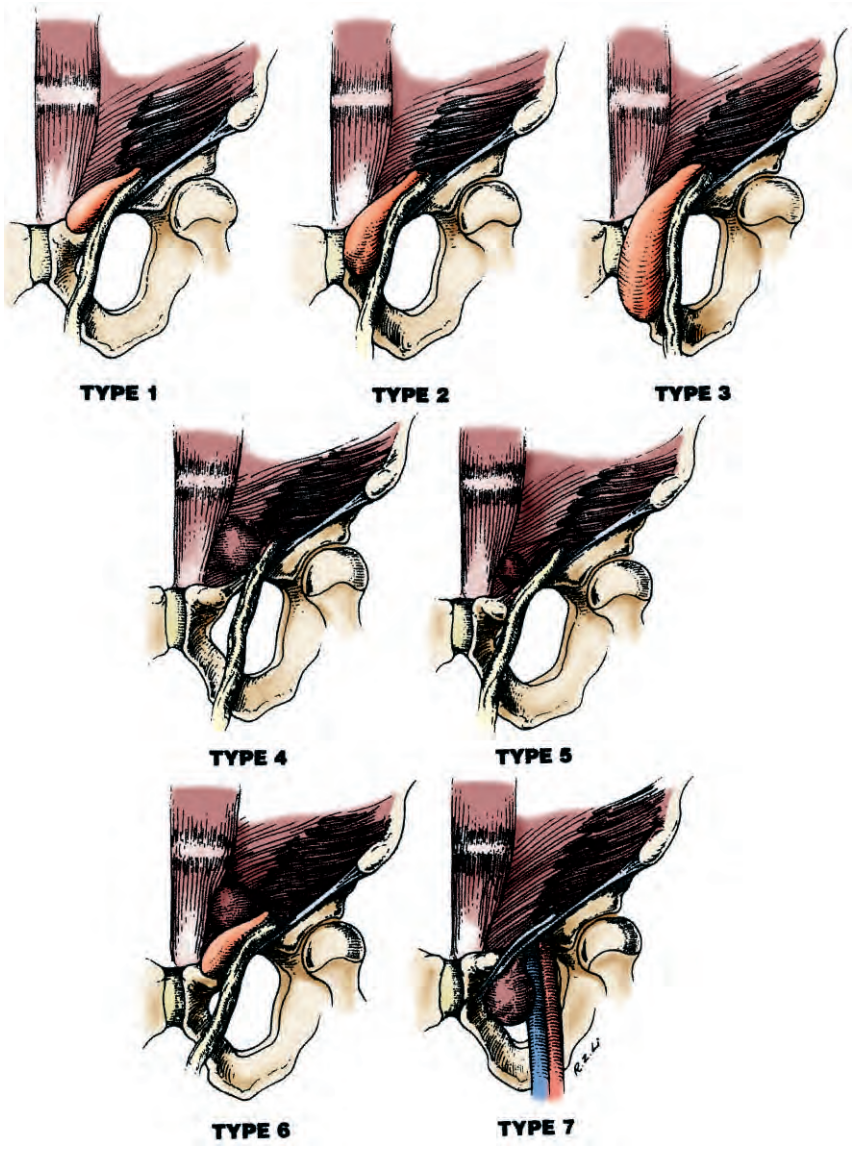


Figure 45–10. Gilbert's hernia classification (From Rutkow IM, Robbins AW: Classification systems and groin hernias. Surg Clin North Am 78:1122-1124, 1998.)

clinical course is unpredictable. Patients starting peritoneal dialysis commonly became more symptomatic, and therefore prophylactic herniorrhaphy is a good option. Predisposing pathologies of hernia accidents, such as liver disease with ascites and colon cancer, should be considered in the appropriate clinical setting.

A truss is a mechanical appliance consisting of a belt with a pad that is applied to the groin after spontaneous or manual reduction of a hernia and has been used for centuries (Fig. 45–11). It serves to maintain reduction and possibly prevents enlargement of the hernia. There are insufficient studies to determine how effective trusses actually are and whether they are as good as surgery for control of symptoms. Most patients find them cumbersome to use and difficult to keep clean. With prolonged use, atrophy of the spermatic cord has been reported, and eventual surgical repair is made more difficult because of fibrosis of the tissues. However, some patients do achieve symptomatic relief.

Preoperative Preparation

Most patients require no special preparation and can be safely treated as outpatients (day care surgery). Significant comorbid illness should be addressed, as with any surgical procedure. A single dose of preoperative intravenous antibiotics is preferred by many, especially if a prosthesis is to be used. However, there is no conclusive evidence that administration of antibiotics decreases the incidence of wound infection. With large groin hernias, one must be cognizant of the fact that replacement of hernia contents into the abdominal cavity during herniorrhaphy could be followed by respiratory embarrassment or abdominal compartment syndrome, or both. The term "loss of domain" refers to this clinical scenario and can be addressed by establishment of pneumoperitoneum in preparation for hernia surgery. A CT scan allows the surgeon to determine the extent of domain loss and make a final decision about the need for pneu-

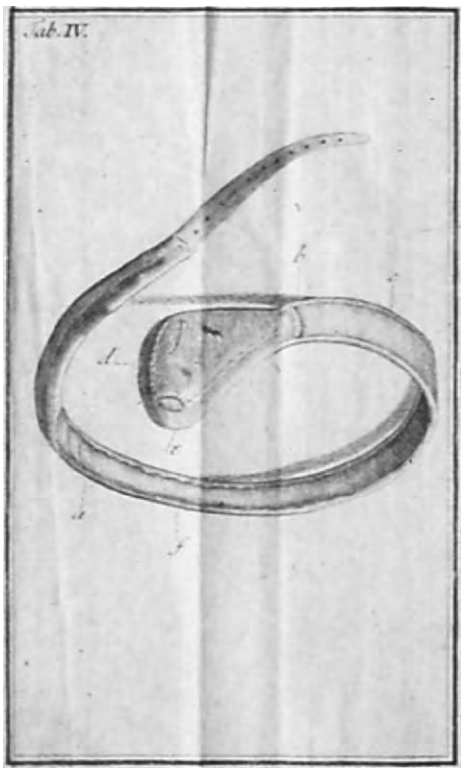


Figure 45–11. Illustration of an older style truss from the 18th century. (From Rutkow IM: A selective history of hernia surgery in the late eighteenth century: The treatises of Percivall Pott, Jean Louis Petit, D. August Gottlieb Richter, Don Antonio de Gimbernat, and Pieter Camper. Surg Clin North Am 83:1021-1044, 2003.)

moperitoneum. The objective of pneumoperitoneum, which is applied in successive sessions, is to increase the amount of room in the peritoneal cavity. Many techniques have been described, including daily needle puncture, placement of an indwelling catheter by a percutaneous system or minilaparotomy, or a completely implanted system involving a tunneled peritoneal catheter and a venous access reservoir. Room air is inflated into the abdominal cavity on a once- or twice-daily timetable to patient tolerance as determined by abdominal discomfort or shortness of breath. Usually, 1 to 2 L is insufflated at each session. Upright chest roentgenography is useful because the level of the diaphragm is a measurable objective monitor.

Potential complications include infection and visceral or vascular injury during placement of the catheter. Furthermore, pneumoperitoneum is not always successful because the insufflated air may preferentially enter the hernia sac and have minimal effect on the abdominal cavity. In addition, pneumoperitoneum has been shown to diminish lower extremity venous return, which could translate into a higher risk for thromboembolic complications. Deep venous thrombosis prophylaxis is prudent when one is considering this approach.

Box 45–1 Cumberland's Characteristics of the Ideal Prosthetic Material

- Not modified physically by tissue fluid
- Chemically inert
- Not carcinogenic
- Does not cause an allergic or hypersensitivity response
- Resistant to mechanical strain
- Pliable and therefore moldable
- Easily sterilized

Anesthesia

Although general anesthesia is almost always recommended for laparoscopic hernia repairs, the choice of anesthesia for open inguinal herniorrhaphy depends on the personal preference of the surgeon. Local anesthesia, when used in adequate doses and far enough in advance, proves very effective, especially in combination with short-acting amnesic and anxiolytic agents such as propofol. The local anesthetic should be injected before preparing and draping the patient for best results. One of the biggest advantages of local anesthesia is that the patient can be aroused from sedation at intervals to perform Valsalva maneuvers and test the repair. Regional anesthesia in the form of spinal or epidural anesthesia can also be used successfully in experienced hands. If general anesthesia is used, a local anesthetic should be administered at the end of the procedure as an adjunct to reduce postoperative pain.

Choice of Prosthetic Material

As far back as 1878, Billroth envisioned that prosthetic material would be the best solution for the problem of inguinal herniation. Numerous randomized comparative trials, as well as meta-analyses and comprehensive reviews, have unequivocally proved the superiority of prosthetic repairs over pure tissue repairs in terms of recurrence.[22] Tissue repairs are associated with an irreducible recurrence rate of 5% to 10%. The modern era of hernia repair has seen a progressive decrease in recurrence rates because of improvement in surgical technique and prosthetics. Most authorities agree that prosthetic herniorrhaphy will decrease the recurrence rate by approximately 50% when compared with tissue methods. The properties of the ideal prosthetic material are listed in Box 45–1.[23] Materials that have emerged as suitable for routine use in hernia surgery and fulfill Cumberland's classic ideal characteristics include polypropylene, either monofilament (Marlex, Prolene) or polyfilament (Surgipro), Dacron (Mersilene), and

expanded polytetrafluoroethylene (ePTFE) (Gore-Tex). An absorbable prosthesis has no role in groin hernia surgery. The newer biologic prostheses made of human cadaver skin, porcine cross-linked dermal collagen, or porcine small intestinal submucosa are more expensive and have no proven advantage over synthetic prostheses in uncomplicated groin hernia surgery. However, they can be useful in infected groin hernia wounds.[24,25] Recently, the development of prostheses that modulate ECM expression by incorporating basic fibroblast growth factor has attracted the attention of investigators.[26]

Although foreign body reaction, infection, erosion into surrounding structures, rejection, increased incidence of postherniorrhaphy pain, and even carcinogenesis remained an early concern with the use of prostheses, after nearly 50 years of use it is obvious that these fears are without foundation. Metal prostheses have largely been abandoned in the United States because of many of the aforementioned complications. Cost of prostheses is still an issue in many parts of the world, but with the skyrocketing increases in overall operating room charges in the West, the cost of the mesh pales in significance. The incidence of postherniorrhaphy pain is lower with mesh repairs than with pure tissue repairs. When it occurs, however, it can occasionally be relieved by removal of the prosthesis. Sarcomatous transformation has been observed in animals after polypropylene implantation; however, no such transformation has been noted in humans, but one should remain vigilant. Another issue that has recently emerged is the possibility of injury to the vas deferens caused by a reaction to a prosthesis that resulted in infertility in a small subset of patients. This consideration demands careful follow-up. Ironically, one of the major arguments for the routine use of mesh in inguinal hernia surgery is to preserve fertility. The theory is that by decreasing the generally accepted recurrence rate in the general population from 10% to 15%, as seen with the Bassini repair and its variants, to less than 5% with the mesh tension-free approach, reoperative surgery with its heavy toll of testicular loss is avoided.

Approaches to Repair of Groin Hernias

Groin hernia repairs can be performed conventionally (anterior or preperitoneal) or laparoscopically. For conventional operations one can use a prosthesis or a pure tissue technique for repair. Whereas prosthetic approaches are by definition tension-free, avoidance of tension in nonprosthetic repairs is accomplished by relaxing incisions. Table 45–2 summarizes the more common herniorrhaphy procedures. Numerous modifications of inguinal hernia repairs, usually associated with a specific surgeon's name, have been described over time. Laparoscopic herniorrhaphy is dealt with in Chapter 46, Laparoscopic Inguinal Hernia Repair.

Conventional Anterior, Nonprosthetic

Many elements are common to all of the herniorrhaphy procedures, and they will be summarized initially in this section. Subsequently, the distinguishing features of prominent individual operations will be presented.

The initial skin incision is horizontal along the lines of Langer for cosmetic reasons. The incision is deepened through Camper's and Scarpa's fascia to the external oblique aponeurosis. This structure is incised medially to and through the external ring. The superior flap of the external oblique is bluntly swept off the internal oblique muscle laterally and superiorly. The ilioinguinal and iliohypogastric nerves are identified and preserved. The cord structures are then separated from the inferior flap of the external oblique aponeurosis by blunt dissection to expose the shelving edge of the inguinal ligament and the iliopubic tract. The cord structures are lifted en masse with the fingers at the pubic tubercle so that the index finger can be passed underneath to meet the index finger of the other hand. A Penrose drain is placed around the cord for retraction. Most surgeons would now avoid complete division of the cremasteric muscle and instead open it longitudinally to expose the inguinal floor. This avoids testicular descent in the postoperative period. High ligation of the sac performed by formal

Table 45–2 Commonly Recognized Conventional Inguinal Hernia Repairs

	Anterior	Preperitoneal		Combined
Nonprosthetic	Marcy Bassini Moloney darn Shouldice McVay-Cooper's ligament repair Miscellaneous	Original Nyhus-Condon (historical interest only now)		
Prosthetic	Lichtenstein tension-free Hernioplasty Mesh plug and patch	Anterior approach Read-Rives	Posterior approach GPRVS Kugel Nyhus-Condon	Bilayer repair

GPRVS, great prosthesis for reinforcement of the visceral sac.

division and transfixion or simply inverting the sac into the preperitoneal space follows. The latter technique avoids injury to unrecognized incarcerated sac structures and decreases the risk for adhesive complications. It is questionable whether pain is lessened by the simple inversion technique, which avoids incision of the richly innervated peritoneum. A small indirect inguinal hernia sac is completely mobilized and excised or inverted into the preperitoneal space. For a larger indirect hernia or an inguinal-scrotal hernia, the sac should be divided in the inguinal canal. The proximal end can be inverted or excised, but the distal end should not be removed to avoid injury to the testicular blood supply. The anterior wall of this distal sac needs to be opened as far distally as convenient. Contrary to popular opinion in the urologic literature, this technique does not increase the incidence of hydrocele formation. Tanner described a relaxing incision in the anterior rectus sheath that extends from the pubic tubercle superiorly for a variable distance as determined by the tension. This incision works by allowing the various components of the abdominal wall to displace laterally and inferiorly. The rectus muscle itself is strong enough to prevent future herniation. The external oblique fascia is closed to reconstruct the superficial ring tight enough to avoid a so-called industrial hernia, but loose enough to avoid strangulation of the cord structures. The term industrial hernia refers to the presence of a dilated external ring that an inexperienced examiner confuses with a hernia.

The Bassini Repair The Bassini repair involves division of the cremaster muscle lengthwise, followed by resection of the indirect sac while simultaneously exposing the floor of the inguinal canal to assess for a direct hernia. The transversalis fascia in the floor of the inguinal canal is divided along its full length. This ensures adequate inspection for a femoral hernia and results in preparation of the deepest layer of Bassini's famous triple layer (the transversalis fascia, the transversus abdominis, and the internal oblique muscle). After high ligation of the sac, the posterior wall is reconstructed by suturing this triple layer medially to the inguinal ligament and possibly the iliopubic tract laterally. Classically, the first stitch in the repair includes the triple layer superiorly and the periosteum of the medial side of the pubic tubercle along with the rectus sheath. Most surgeons would now avoid the periosteum of the pubic tubercle to decrease the incidence of osteitis pubis. Laterally, the repair ends with closure of the internal ring. In the classic Bassini procedure the suture material used for the repair was silk placed in interrupted fashion. As described earlier, the Bassini operation could be considered a preperitoneal repair, but the American version does not involve opening the transversalis fascia (inguinal floor), hence its classification as a conventional anterior procedure. In lieu of opening the floor, forceps are used to blindly grasp tissue in the hope of including the transversalis fascia and the transversus abdominis muscle. The layer is then sutured along with the internal oblique muscle to the reflected part of the inguinal ligament. Because of anatomic variations among individuals, the structures grasped superiorly are not always consistent. Students of Bassini believe that it is this variability that accounts for the inferior results achieved with this procedure in North America.[27,28] Perhaps the need to develop better herniorrhaphies would not have been so pressing if Bassini's operation had been practiced as he described it. The McVay Cooper's repair is similar to the Bassini repair except that Cooper's ligament is used instead of the inguinal ligament for the medial portion of the repair. Interrupted sutures beginning at the pubic tubercle and continuing laterally along Cooper's ligament progressively narrow the femoral ring, and this is the most common application (i.e., treatment of a femoral hernia). The last stitch into Cooper's ligament is known as a transition stitch and it includes the inguinal ligament. The stitch effectively narrows the femoral ring and allows a step-up to the inguinal ligament over the femoral vessels so that the repair can be continued laterally similar to the Bassini procedure. A Tanner slide (a relaxing incision on the anterior rectus sheath) is essential because there is considerable tension associated with this repair. It is indicated for the repair of femoral hernias or large direct inguinal hernias with extensive destruction of the inguinal floor when a mesh would be contraindicated, such as infection.

The Moloney Darn The Moloney darn and its variant the Abramson darn use nonabsorbable suture to form a meshwork over the inguinal floor. The interstices of this meshwork fill with fibrous connective tissue that buttresses the weakened area of the inguinal canal. The initial layer consists of a continuous nylon suture to appose the transversalis fascia and the transversus abdominis, rectus, and internal oblique muscles medially to the reflected portion of the inguinal ligament laterally, similar to a Bassini repair. A difference is that the first suture is continued into the muscle about the cord, woven in and out to form reinforcement around the cord, and finally tied to the inguinal ligament on the lateral side of the internal ring. The darn is a second layer with sutures applied in a crisscross fashion through muscular tissue medially to the inguinal ligament. Abramson stresses the importance of leaving the suture loose and not forcing the edges of the repair together during the darn, thereby allowing a "tension-free" repair and maintaining the meshwork structure.[29] The darn must be carried well over the medial edge of the inguinal canal onto the anterior rectus sheath.

The Shouldice Technique The Shouldice Clinic in Toronto serves as a model specialty clinic where hernia repairs are combined with weight reduction and exercise programs. The initial approach is similar to the Bassini repair, with particular importance placed on freeing the cord from its surrounding adhesions, resection of the cremaster muscle, high dissection of the hernia sac, and division of the fascia transversalis. Continuous monofilament steel wire is used to repair the floor to ensure even distribution of tension and avoid the defects that could potentially occur between interrupted sutures. The repair is started at the pubic tubercle by approximating the iliopubic tract laterally to the undersurface of the lateral edge of the rectus muscle. The suture is

continued laterally to approximate the iliopubic tract to the medial flap, which is made up of the transversalis fascia, transversus abdominis, and internal oblique. The running suture is continued to the internal ring, where the lateral stump of the cremaster muscle is picked up to form a new internal ring. The direction of the suture line is then reversed toward the pubic tubercle to approximate the medial edge of the internal oblique and transversus abdominis muscles to Poupart's ligament, and the wire is tied to itself. The second wire suture is started near the internal ring and approximates the internal oblique and transversus muscles to a band of external oblique aponeurosis superficial and parallel to the inguinal ligament, in effect creating a second artificial inguinal ligament. The suture is then reversed and a fourth suture line is constructed in a similar manner, superficial to the third line. The cribriform fascia is always incised in the thigh, parallel to the inguinal ligament, to make the inner side of the lower flap of the external oblique aponeurosis available for these multiple layers. When performed by experienced surgeons at the Shouldice Clinic, the operation has a recurrence rate of less than 1% and was the gold standard against which other operations were compared. The major criticisms are that it is difficult to teach and it is hard for surgeons to understand what is really being sewn to what. This is further compounded by the fact that modifications outside the Shouldice Clinic have resulted in different versions.

Conventional Anterior, Prosthetic

Lichtenstein Technique The Lichtenstein Clinic is dedicated to hernia repairs. The herniorrhaphy is performed under local anesthesia with sedation. The initial steps are similar to those of the Bassini repair. After the external oblique aponeurosis has been opened from just lateral to the internal ring through the external ring, the upper leaf is freed from the underlying anterior rectus sheath and internal oblique aponeurosis in an avascular plane from a point at least 2 cm medial to the pubic tubercle to the anterior superior iliac spine laterally. The cord with its cremaster is swept off the pubic tubercle and separated from the inguinal floor. The ilioinguinal nerve, external spermatic vessels, and genital branch of the genitofemoral nerve all remain with the cord structures. The effect is to create a large space for eventual placement of the prosthesis and at the same time provide excellent visualization of the nerves.

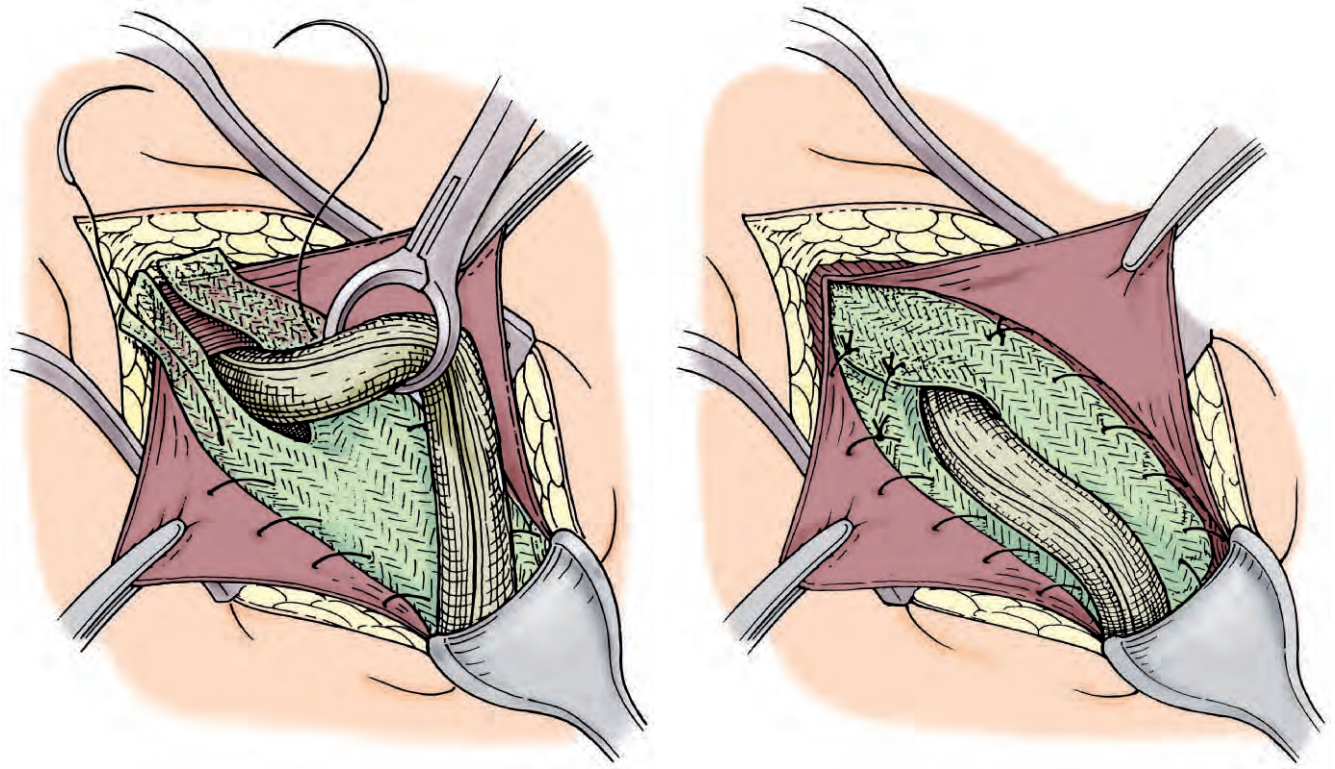
High ligation is performed by dissecting the sac from the surrounding cord structures after incising the cremaster muscle longitudinally. Direct hernias are separated from the surrounding structures and reduced back into the preperitoneal space. Dividing the superficial layers of the neck of the sac circumferentially facilitates reduction and aids in maintaining the reduction while the prosthesis is being placed. A suture can also be placed to allow the repair to proceed unencumbered by the sac protruding into the operative field. A mesh prosthesis with a minimum size of 15 by 8 cm is positioned over the inguinal floor. The medial end is rounded to correspond to the patient's anatomy and secured to the anterior rectus sheath a minimum of 2 cm medial to the pubic tubercle. The mesh is secured on either side of the pubic tubercle, and then the suture is continued along the shelving edge in a running locking fashion. The suture is tied at the internal ring.

Two tails, a wide one (two thirds) above and a narrower (one third) below, are created by making a slit at the lateral end of the mesh. The tails are positioned around the cord structures and placed beneath the external oblique laterally, with the upper tail placed on top of the lower. The lower edge of the superior tail is anchored to the lower edge of the inferior tail by a single suture to re-create the shutter valve at the internal ring. This step is considered crucial for preventing the indirect hernia recurrence that is seen when simple reapproximation of the tails is performed. This shutter valve suture should also pass through the shelving edge to allow the mesh to buckle medially over the direct space and avoid tension when the patient stands upright. A few interrupted sutures are then placed to secure the superior and medial aspects of the mesh to the underlying internal oblique and fascia (Fig. 45–12A and B). Care should be taken to avoid placing anchoring suture through the iliohypogastric nerve. Sufficient laxity should be maintained in the prosthesis to account for the difference in tension between the supine and prone positions and to compensate for mesh shrinkage. The only potential drawback of this procedure is that a femoral hernia could be missed because the inguinal floor is not opened. If one is detected, the posterior surface of the mesh is sutured to Cooper's ligament after the inferior edge has been attached to the inguinal ligament.

Plug and Patch (Rutkow) Technique The mesh plug technique was developed by Gilbert and then modified by Robbins and Rutkow.[30,31] The sac is dissected away from the surrounding structures and reduced into the preperitoneal space after a standard anterior approach. A plug made of rolled polypropylene mesh or prefabricated in the configuration of a flower is inserted into the defect and secured to its edges by interrupted suture. Millikan suggests that the internal petals be sewn to the preperitoneal side of the ring of the defect, which forces the outside of the prosthesis underneath the inner side of the defect and makes it act like a preperitoneal underlay. For an indirect hernia, the plug is held in place with three or four sutures around the defect (Fig. 45–13). For direct hernias, the transversalis fascia is opened to facilitate plug placement (Fig. 45–14). The patch portion is optional and involves placing a flat piece of polypropylene in the conventional inguinal space so that it widely overlaps the plug in a fashion similar to the Lichtenstein procedure (Fig. 45–15). The technique is not only fast but also easy to teach in both academic and private centers.

Conventional Preperitoneal Prosthetic

The key to preperitoneal prosthetic repairs is placement of a large prosthesis in the preperitoneal space between the transversalis fascia and the peritoneum, in effect replacing the transversalis fascia. This preperitoneal



A B

Figure 45–12. Lichtenstein repair. **A,** One of the sutures demonstrates approximation of the inferior edge of the prosthesis to the inguinal ligament. The second suture will include the inferior surface of the superior tail and the inferior surface of the inferior tail just lateral to the internal ring, as well as the inguinal ligament, to create a shutter valve. (From Surg Clin North Am 83:1110-1111, 2003.) **B,** The "shutter" valve has been completed, and the superior and medial surfaces have been sutured to the underlying internal oblique muscle and anterior rectus sheath, respectively. This older illustration shows continuous suture on the superior medial border of the prosthesis, but interrupted sutures are now preferred by most surgeons to minimize the incidence of nerve entrapment. (From Kurzer M, Belsham PA, Kark AE: The Lichtenstein repair for groin hernias. Surg Clin North Am 83:1099-1117, 2003. Courtesy of Gillian Lee.)

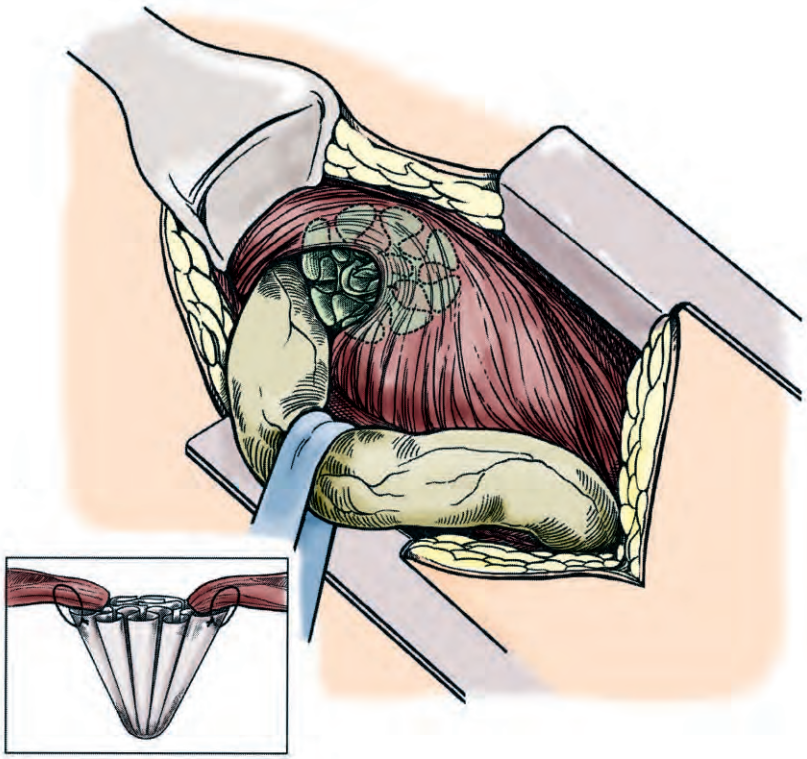


Figure 45–13. Plug and patch technique: plug placement for an indirect inguinal hernia. The *inset* shows a sagittal view of the implanted plug. (From Rutkow IM: The PerFix plug repair for groin hernias. Surg Clin North Am 83:1079-1098, 2003.)

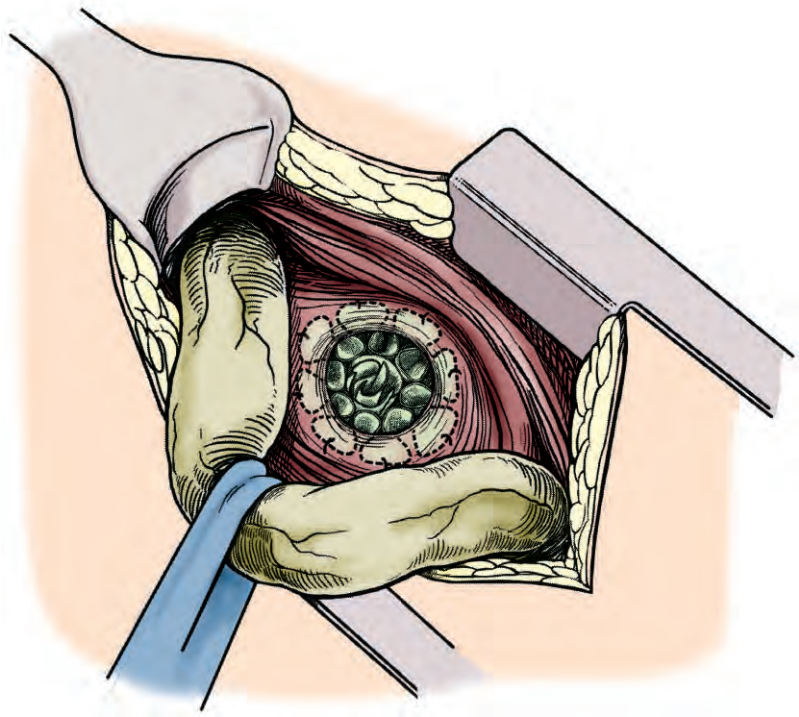


Figure 45–14. Plug and patch technique: plug placement for a direct inguinal hernia. (From Rutkow IM: The PerFix plug repair for groin hernias. Surg Clin North Am 83:1079-1098, 2003.)

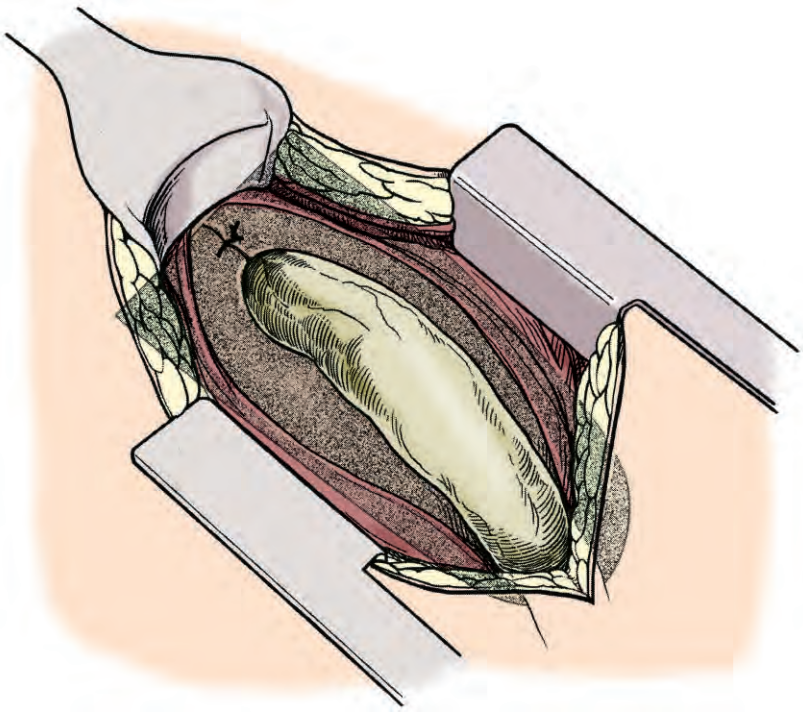


Figure 45–15. Tails of the mesh encircling the spermatic cord. One or two sutures are placed where the tails of the mesh cross lateral to the cord to ensure a snug fit. (From Kurzer M, Belsham PA, Kark AE: The Lichtenstein repair for groin hernias. Surg Clin North Am 83:1099-1117, 2003. Courtesy of Gillian Lee.)

space can be entered from either the anterior or the posterior aspect. In the anterior approach a groin incision is made and the space is entered directly through the inguinal floor. A midline, Pfannenstiel, or paramedian incision can be used to enter the space from the posterior aspect. The transabdominal approach as advocated by LaRoque has returned to popularity because of the ease of entering the space laparoscopically.

Anterior Approach (Read/Rives) This operation starts like a classic Bassini procedure, including opening the inguinal floor. The inferior epigastric vessels are identified and the preperitoneal space is completely dissected. The spermatic cord is parietalized by separating the ductus deferens from the spermatic vessels. A 12- by 16-cm mesh is positioned in the preperitoneal space deep to the inferior epigastric vessels and secured with three

sutures: one each to the pubic tubercle, Cooper's ligament, and the psoas laterally. The transversalis fascia is closed over the prosthesis and the cord structures replaced before closure.

Posterior Approach

Great Prosthesis for Reinforcement of the Visceral Sac The procedures described by Wantz, Stoppa, and Rives are grouped together under the heading of great prosthesis for reinforcement of the visceral sac because they have only minor variations. These repairs are used for bilateral hernias, recurrent hernias, and diffuse abdominal wall weakness associated with collagen disorders. A lower midline, transverse or Pfannensteil incision can be used according to surgeon preference. If a transverse incision is chosen, it should extend from the midline 8 to 9 cm in each direction laterally and 2 to 3 cm below the level of the anterior superior iliac spine, but above the level of the internal ring. The anterior rectus sheath and the oblique muscles are incised for the length of the skin incision. The lower flap of these structures is retracted inferiorly toward the pubis. The preperitoneal space is entered by incising the fascia transversalis along the lateral edge of the rectus muscle or by incising the fascia overlying the space of Retzius. The preperitoneal space is completely dissected to a point lateral to the anterior superior iliac spine. The symphysis pubis, Cooper's ligament, and iliopubic tract are identified. The spermatic cord is "parietalized" (completely dissected) to provide adequate length to displace it laterally. Direct sacs are reduced in the course of this dissection. Indirect sacs are mobilized from the cord structures and reduced back into the peritoneal cavity. Large sacs may be difficult to mobilize and may be divided so that the distal part of the sac is left in situ and the proximal portion of the sac is dissected away from the cord structures. Care should be taken during the course of this dissection to avoid damage to the testicular vessels. It must be particularly emphasized that the dissection should proceed in the relatively avascular plane between the fascia transversalis and the peritoneum to avoid a bloody procedure.

Stoppa and Wantz recommend that the abdominal wall defect be left alone, but other surgeons prefer to plicate the fascia transversalis in the defect by suturing it to Cooper's ligament to prevent a bulge caused by a seroma in the undisturbed sac.

The next step is placement of the prosthesis. Dacron mesh is preferred over polypropylene by many European surgeons because they believe that it conforms better to the preperitoneal space. The size of the prosthesis for unilateral repairs is approximately the distance between the umbilicus and the anterior superior iliac spine minus 1 cm for the width, with the height being approximately 14 cm. Because of his extensive parietalization of the cord structures, Stoppa does not think that it is necessary to split the prosthesis laterally to accommodate the cord structures, and this avoids potential recurrence through the keyhole. Wantz recommends cutting the prosthesis eccentrically, with the lateral side longer than the medial, to achieve the best fit in the preperitoneal space. Rignault, on the other hand, prefers a keyhole defect in the mesh to encircle the spermatic cord in the belief that this technique provides the prosthesis with enough security that fixation sutures or tacks can be avoided. Minimizing fixation in this area is important because of the numerous anatomic elements in the preperitoneal space that could be inadvertently damaged during suture or tack placement. For Wantz's technique, three absorbable sutures are used to attach the superior border of the prosthesis to the anterior abdominal wall well above the defect. The three sutures are placed near the linea alba, semilunar line, and anterior superior iliac spine in a medial-to-lateral direction. A Reverdin suture needle facilitates such placement. Subsequently, the mesh is positioned to cover the iliac fossa and the parietalized cord structures and iliopsoas muscle laterally; the pubic ramus, obturator fossa, and iliac vessels medially; and the space of Retzius in the middle. The size of the mesh for the Stoppa technique to repair bilateral hernias is the distance between the two anterior superior iliac spines minus 2 cm for the width, and the height is equal to the distance between the umbilicus and the pubis. The wound is closed in layers.[32]

Nyhus/Condon (Iliopubic Tract Repair) These two authorities performed extensive cadaver dissections and pointed out the importance of the iliopubic tract. A transverse lower abdominal incision is made two fingerbreadths above the pubic symphysis. The anterior rectus sheath is opened on its lateral side to allow the rectus muscle to be retracted medially, and the two oblique and the transversus abdominis muscles are incised to expose the fascia transversalis. A combination of sharp and blunt dissection inferiorly opens the preperitoneal space and exposes the posterior inguinal floor. Direct or indirect defects are repaired similarly after the peritoneal sac has been reduced or divided and closed proximally. The transverse aponeurotic arch is sutured to the iliopubic tract inferiorly, with Cooper's ligament occasionally included in the medial portion of the repair. The internal ring, if large, is also narrowed by placing a suture lateral to it. For femoral hernias the iliopubic tract is sutured to Cooper's ligament. Once the defect has been formally repaired, a tailored mesh prosthesis can be sutured to Cooper's ligament and the transversalis fascia for reinforcement.[33]

Kugel/Ugahary Repair These operations were devised to compete with laparoscopy by using a small 2- to 3-cm skin incision 2 to 3 cm above the internal ring. Kugel locates this point by making an oblique incision one third lateral and two thirds medial to a point halfway between the anterior superior iliac spine and the pubic tubercle. The incision is deepened through the external oblique aponeurosis, and the internal oblique fibers are bluntly spread. The transversalis fascia is opened vertically about 3 cm, but the internal ring is not violated. The inferior epigastric vessels are identified to ensure that the dissection is in the correct plane. The vessels are left adherent to the overlying transversalis fascia. The cord structures are thoroughly parietalized, and anatomic landmarks, including the iliac vessels, Cooper's ligament, pubic bone, and hernia defect, are identified by palpa-

tion. Most direct and small indirect sacs are reduced by such dissection; large indirect sacs are often divided with the distal end being left in situ while the proximal end is reduced. A specifically designed 8- by 12-cm prosthesis made of two pieces of polypropylene is deformed and fit through the small incision. It then springs open to regain its normal shape and provides wide overlap of the myopectineal orifice. Ugahary's operation is similar, but a special prosthesis is not needed.[34,35]

Combination Anterior and Preperitoneal Approaches (Bilayer Technique)

This repair depends on a dumbbell-shaped device consisting of two flat pieces of polypropylene mesh connected by a cylinder of the same material. The basis of this design is to take advantage of the benefits of both the anterior and posterior approaches, with prosthetic material being placed in both the preperitoneal space and the conventional inguinal canal. The preperitoneal space is entered through the hernia defect. The deep layer of the prosthesis is deployed in the preperitoneal space, whereas the superficial layer of the device occupies the conventional anterior space in a manner similar to the Lichtenstein repair. It is slit laterally to accommodate the cord structures and then sutured with three or four interrupted sutures to the area of the pubic tubercle, the middle of the inguinal ligament, and the internal oblique muscle.

COMPLICATIONS

Complications specific to laparoscopic herniorrhaphy are presented in Chapter 46, Laparoscopic Inguinal Hernia Repair. General complications such as urinary retention, paralytic ileus, and cardiorespiratory compromise can follow any operative procedure, and inguinal herniorrhaphy is no exception.[36,37] The most common is urinary retention, especially after general anesthesia. Complications specific to the herniorrhaphy itself are summarized in Box 45–2.

Box 45–2 Postherniorrhaphy Complications After Conventional Repair

- Recurrence
- Chronic groin pain
  - Nociceptive
  - Neuropathic
- Cord and testicular
  - Hematoma
  - Ischemic orchitis
  - Testicular atrophy
  - Injury to the vas deferens
  - Hydrocele
  - Testicular descent
- Bowel and bladder injury
- Osteitis pubis
- Prosthetic complications
  - Contraction
  - Erosion
  - Infection
  - Rejection
  - Fracture
- Miscellaneous complications
  - Seroma
  - Hematoma
  - Wound infection
- General complications

Chronic Postherniorrhaphy Pain Syndromes

Chronic postherniorrhaphy groin pain is defined as pain that lasts longer than 3 months after hernia repair. The overall incidence is about 25%, with 10% fitting the definition of moderate or severe pain that prevents the subject from returning to the preoperative level of functioning or is frankly incapacitating. Patients are difficult to categorize because of the heterogeneous description of their pain; nevertheless, an attempt should be made to assign them to one of two groups to help determine therapeutic options: (1) nociceptive pain caused by tissue injury, which is further subdivided into somatic and visceral, and (2) neuropathic pain secondary to nerve damage.

Somatic pain is usually caused by damage to ligaments, tendons, and muscles and includes osteitis pubis and adductor tenoperiostitis. Visceral pain refers to specific visceral dysfunction such as dysejaculation and urinary dysfunction. The principles of treating patients with nociceptive pain are similar to those for patients with groin pain but no obvious hernia.

Division, stretching, contusion, crushing, entrapment, or electrical injury to the nerve causes neuropathic groin pain. The nerves most commonly injured during conventional herniorrhaphy are the ilioinguinal and iliohypogastric. The classic manifestation is pain or paresthesia (or both) in the distribution of one of the major nerves. Precise diagnosis of nerve involvement is difficult because of dermatomal overlap. Physical activity aggravates the pain, and a recumbent position with hip flexion relieves it. Reassurance plus conservative treatment with anti-inflammatory medications and local nerve blocks is preferred initially. At least 1 year of conservative treatment should be tried before offering neuroma excision or neurectomy.

Recurrent Hernias

The hernia recurrence rate with the use of prosthetic material is less than 1%. This rate is probably an

underestimation of the problem because patients frequently do not return to their original surgeon. It still translates to a hefty number because of the size of the denominator. A recurrent hernia is usually manifested as a bulge with a cough impulse. Occasionally, the initial symptom is pain. In this situation, a consistent definition of recurrent hernia does not exist because of difficulty differentiating a lipoma of the cord, a seroma, or an expansile bulge of the internal oblique muscle from true hernia recurrence. Imaging in the form of CT, MRI, or ultrasound should be obtained to unequivocally document recurrence. Causes of recurrence include (1) failure to perform high ligation or reduce the peritoneal sac with an indirect hernia, (2) inadequate closure of the internal ring, (3) missed hernias, (4) continuing failure of the floor of the canal, and (5) infection. The general principle for managing recurrent hernias depends on the original repair. The logical approach is to perform herniorrhaphy in the space that has not been dissected. If the patient has previously undergone a conventional repair, a preperitoneal repair is best chosen. On the other hand, if the index operation was a preperitoneal one, a repair that is performed in the conventional inguinal space is best.

Cord and Testicular Injury

Ischemic orchitis is defined as postoperative inflammation of the testicle that occurs within 1 to 5 days after surgery. It is thought to result from thrombosis of veins draining the testicle secondary to extensive dissection of the spermatic cord. It is much more common after repair of recurrent hernias. Initial symptoms include a low-grade fever with painful enlargement of the testicle. Management is supportive and consists of scrotal support and anti-inflammatory agents. Ischemic orchitis usually resolves without sequelae but may occasionally progress to testicular atrophy. It is generally accepted that dividing rather than excising large indirect inguinal-scrotal hernia sacs and leaving the distal part of the sac open in situ can decrease the incidence of testicular complications.

The dysejaculation syndrome is defined as a burning, searing, painful sensation occurring just before, during, or after ejaculation (or any combination). A stenotic lesion in the vas deferens probably causes it. The condition is usually self-limited, and thus the initial treatment is expectant. Injury to both vasa is a potentially devastating complication after bilateral hernia repair. If injury to the vas is recognized during herniorrhaphy, reanastomosis should be attempted if paternity is an issue. Even unilateral injury to the vas can result in infertility as a result of the development of sperm antibodies in response to extravasated sperm. Scrotal hematomas can occur after herniorrhaphy as a consequence of cremasteric or vascular hemostatic errors. Postherniorrhaphy hydroceles can develop, but the cause is not known. Although the urologic literature suggests that hydroceles develop as a result of the practice of leaving the distal sac in situ, most experienced hernia surgeons do not accept this theory. Treatment is the same as for any other hydrocele.

Prosthetic Complications

Shrinkage of prosthetic material because of scarification of the recipient's tissues should be anticipated during herniorrhaphy. Sufficient overlap in anticipation of 20% contracture is recommended. Mesh migration of polypropylene plugs into nearby organs such as the bladder has been reported but is rare. Intra-abdominal placement of a mesh prosthesis should be avoided in favor of an ePTFE or biologic prosthesis to avoid fistulation or bowel obstruction. Local erosion into cord structures has been reported. Rejection because of allergic reactions is extremely rare and is probably a manifestation of chronic infection. The ideal prosthetic material characteristics are enunciated in Box 45–1.

Bowel and Bladder Injury

Bladder and bowel injury is unusual with conventional anterior herniorrhaphy unless a sliding hernia goes unrecognized during repair. The bladder is at much greater risk during preperitoneal procedures, especially in the setting of previous surgery in the space of Retzius. Previous surgery in this space can be considered a relative contraindication to preperitoneal repair. Bladder injuries need to be repaired in two layers with absorbable suture, followed by extended Foley decompression until a cystogram confirms bladder integrity.

Wound Infection

The groin appears to be a protected area inasmuch as wound infection after inguinal herniorrhaphy occurs in less than 5% of patients. However, this figure may be an underestimation of the true incidence because of a delayed manifestation in many cases. In a recent study from the United Kingdom, the median interval between repair and infection was 4 months (range, 2 weeks to 39 months).[38] Most surgeons in North America would recommend prophylactic broad-spectrum antibiotics, although studies by the Cochrane group have shown no benefit.[39] Whereas infection after nonprosthetic repairs can be managed by open drainage and dressing changes, prosthetic removal is commonly required in addition to routine wound care after prosthetic procedures. In general, ePTFE prostheses always have to be removed, but true meshes can on occasion be salvaged with conservative wound care and antibiotic treatment. The late recurrence rate is much higher after a postoperative wound infection.

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Chapter

46

Laparoscopic Inguinal Hernia Repair

Varun Puri · Alene J. Wright · Robert J. Fitzgibbons, Jr.

Laparoscopic techniques and procedures were introduced into mainstream general surgery in the 1980s with the development of laparoscopic cholecystectomy. Since then, the laparoscopic approach has been adapted for numerous conventional general surgical operations, and many ingenious surgeons have devised new operations using videoscopic principles. Inguinal hernia surgery is no exception. The two most commonly performed laparoscopic inguinal hernia repairs, the *transabdominal preperitoneal* (TAPP) repair and the *totally extraperitoneal* (TEP) repair, have been modeled after the conventional open preperitoneal inguinal hernia repairs. The *intraperitoneal onlay mesh* (IPOM) repair, however, is a novel laparoscopic approach and is the only truly minimally invasive laparoscopic herniorrhaphy because radical dissection of the preperitoneal space is avoided. The other advancement that has defined the development of modern-day hernia surgery, though not limited to laparoscopic techniques, is the development of newer and better prosthetics.

APPLIED ANATOMY OF THE REGION

A detailed understanding of the anatomy of the deep inguinal region and the posterior aspect of the anterior abdominal wall is necessary to perform a laparoscopic inguinal hernia repair. Mastery of this knowledge is especially important because the region contains a number of major blood vessels and nerves that may be exposed to injury. Anatomic background descriptions for traditional repairs have defined the anatomy from the superficial to the deep aspect because this is the perspective that the surgeon will use when performing a herniorrhaphy. Understanding the same from the opposite perspective was the first challenge that laparoscopists faced. What follows is a description of the anatomy from the peritoneal surface to the skin.

Peritoneal Folds and Fascia Transversalis

The umbilical folds in most patients are quite prominent and easily identified. They have been referred to as ligaments in some texts but do not possess the true structure of a ligament. The unpaired median umbilical fold covers the urachus, the fibrous remnant of the fetal allantois, and extends from the urinary bladder to the umbilicus. The urachus may be patent for a variable length along its course, usually close to the urinary bladder in adults and close to the umbilicus in children. The paired medial umbilical folds are created by the obliterated fetal umbilical arteries. The artery, like the urachus, may be patent in its proximal course and may contribute to the superior vesical artery. The paired lateral umbilical folds are created by the peritoneal coverings over the inferior epigastric vessels. The inferior epigastric artery arises from the external iliac artery and supplies the anterior abdominal wall. It enters the rectus sheath at about the level of the arcuate line. Injury to this vessel may occur during accessory trocar placement. The fossa lying between the median and medial umbilical folds is called the supravesical fossa. The fossa formed between the medial and lateral ligaments is the medial fossa and is the site of direct inguinal hernias. The lateral fossa extends lateral to the lateral umbilical fold and is the site of indirect inguinal hernias (Fig. 46–1).

The transversalis fascia is the deep or endoabdominal fascia covering the internal surface of the transversus abdominis, iliacus, psoas, and obturator internus muscles and portions of the periosteum of the pelvis. Some authors believe that this fascia consists of two layers or laminae. The importance of the transversalis fascia for laparoscopic hernia surgeons is due to its derivatives or analogues: the iliopectineal arch, iliopubic tract, and crura of the deep inguinal ring. The iliopectineal arch, a condensation of the transversalis fascia, is situated at the medial border of the iliacus muscle and is continuous with the fascia iliaca, or the endoabdominal fascia

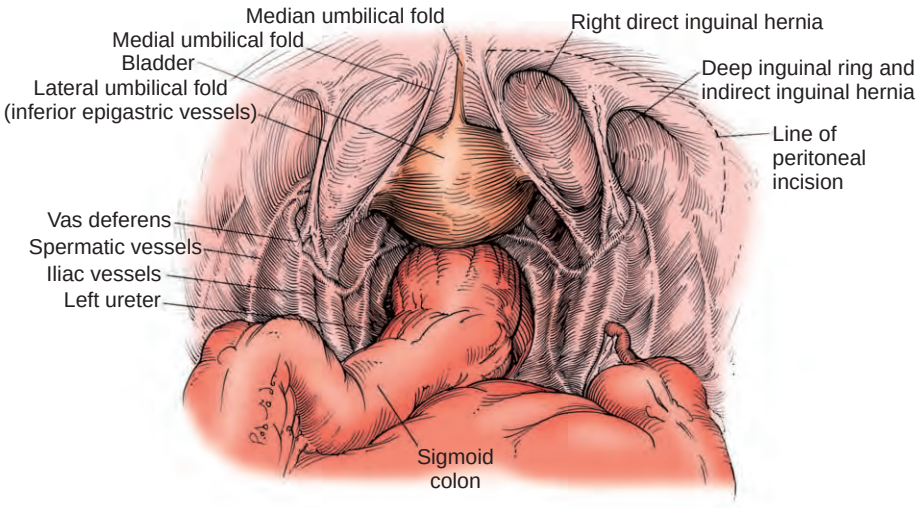

Figure 46–1. Laparoscopic view of groin anatomy before incision of the peritoneum. (From Eubanks S: Hernias. In Sabiston DC Jr, Lyerly HK [eds]: Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 15th ed. Philadelphia, WB Saunders, 1997, p 1226.)

covering the iliacus. The iliopectineal arch divides the vascular compartment containing the iliac vessels from the neuromuscular compartment containing the iliopsoas muscle, femoral nerve, and lateral femoral cutaneous nerve. The iliopubic tract is a condensation of the transversalis fascia that is attached to the iliac crest laterally, crosses over the femoral vessels, and inserts on the pubic tubercle medially. It serves as an important landmark for laparoscopic surgeons, and its location should always be established during preperitoneal dissection. Branches of the lumbar plexus (T12, S1-S4) are located inferior to this tract. Mesh fixation or excessive dissection in this location can lead to nerve damage/entrapment and result in long-term morbidity. The superior and inferior crura of the deep inguinal ring are derived from the transversalis fascia and form a fascial sling. When the transversus abdominis contracts, the crura of the deep ring are pulled upward and laterally, thereby creating a valve-like action at the deep ring that prevents the formation of indirect hernias.

Important Nerves and Vessels

The lumbar plexus is formed by nerve roots from the 12th thoracic and 1st through 4th lumbar nerves. Five branches of this plexus, which have cutaneous innervation, can be seen to course across the iliacus muscle and are encountered during laparoscopic inguinal hernia repair (Fig. 46–2). The nerve branches, which may quite variable in course in different subjects, lie in the so-called triangle of pain bordered medially by the psoas muscle, anteriorly and inferiorly by the iliopubic tract, and laterally by the iliac crest.[1] This region lateral to the spermatic cord and posterior to the level of the iliopubic tract, where the cutaneous nerves reside, has also been referred to as the "electrical hazard zone."[2] The use of electrocautery is best avoided in this area.

The most anterior nerve seen is the genitofemoral nerve. The genital branch travels with the spermatic cord and innervates the cremaster muscle and the medial aspect of the scrotum, whereas the femoral branch innervates the skin of the proximal aspect of the midthigh. The femoral nerve lies deep to the lateral psoas muscle and is not routinely encountered during dissection. The lateral femoral cutaneous nerve crosses the iliac fossa deep to the iliacus fascia and the iliopubic tract and pierces the inguinal ligament to enter the thigh. The iliohypogastric nerve arises from the first lumbar trunk and courses across the iliac fossa to pierce the transversus abdominis. It then courses between the transversus and internal oblique muscles and becomes superficial by piercing the aponeuroses of both the internal and external oblique muscles just above the superficial inguinal ring. The ilioinguinal nerve, also arising from the first lumbar nerve root, runs parallel and just inferior to the iliohypogastric nerve in the iliac fossa. It usually pierces the transversus abdominis and internal oblique muscles to eventually enter the inguinal canal.

The inferior epigastric artery, a branch of the external iliac artery, supplies the deep anterior abdominal wall (Fig. 46–3). In some individuals, more frequently than previously thought, an artery called the "aberrant" obturator artery arises from the inferior epigastric artery, arches over Cooper's ligament, and joins the "normal" obturator artery to complete a vascular ring. It is referred to as the "corona mortis." Injury to this ring may be sustained while working in the region of Cooper's ligament and results in severe bleeding. The internal spermatic vessels and the ductus deferens approach the deep inguinal ring from different directions. As the two structures approach, they form the apex of the "triangle of doom,"[3] so called because deep to it, hidden under the peritoneum and transversalis fascia, are the external iliac vessels. Identification of the ductus deferens may not be easy in all subjects, thus rendering it and the adjacent iliac vessels at risk during mesh fixation. Another vessel of some importance in this region is the deep circumflex artery. Its origin may be variable, but it usually courses along the iliopubic tract, pierces the transversalis fascia, and runs across the iliac fossa. It may sustain injury during mesh fixation close to the iliopubic tract.

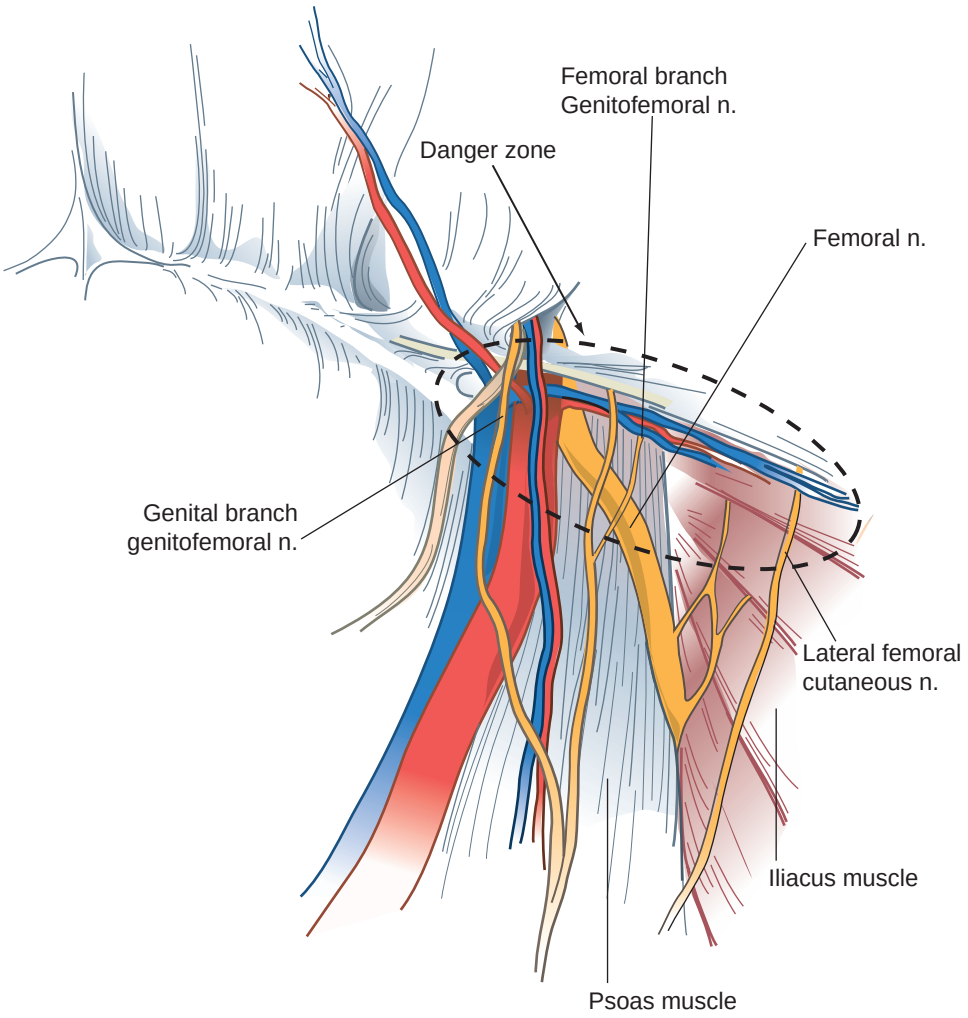

Figure 46–2. Important nerves and their relationship to inguinal structures (the right side is illustrated).

LAPAROSCOPIC OR CONVENTIONAL INGUINAL HERNIORRHAPHY

Over the past decade a number of randomized trials have been conducted to compare laparoscopic and conventional hernia repairs (Table 46–1). These trials, along with meta-analyses of pooled data, have indicated that patients undergoing laparoscopic hernia repair experience less pain in the early postoperative period, have lower analgesic and narcotic requirements and better cosmesis, and return to normal activities sooner.[26,27] These improvements are even more marked if we compare laparoscopic repairs with tissue-based/sutured conventional repairs (Table 46–2). Opinion about the laparoscopic approach leading to earlier return to work is divided. Social factors such as workers' compensation issues complicate objective evaluation.

The advantages attributed to the laparoscopic approach must be weighed against its potential disadvantages, which include complications related to laparoscopy such as major vascular injury or bowel injury, possible adhesion formation at trocar sites or where the prosthesis is placed, increased cost because of expensive equipment, increased operating room time, and the need for general anesthesia. Conversely, open/conventional inguinal herniorrhaphy can be performed under local anesthesia, with minimal risk for vascular or bowel injury. Many of the recent randomized trials show a recurrence rate with laparoscopic repair comparable to that of conventional tension-free repair. However, most have been conducted at single centers with a keen interest in laparoscopic surgery. A notable exception to these trials is a recently published multicenter trial conducted in the Veterans' Administration system in which laparoscopic preperitoneal hernia repair (mostly TEP) was compared with tension-free anterior (Lichtenstein) repair.[25] Recurrence was significantly more common after laparoscopic repair than after open repair of primary hernias (10.1% percent versus 4.0%), but rates of recurrence after repair of recurrent hernias were similar in the two groups. This particular study holds importance for surgeons practicing outside a specialty laparoscopic center and has caused many to suggest that the laparoscopic approach should be performed only at centers with a special interest. The early and delayed complication rates of the laparoscopic and conventional approaches are similar, but the seriousness of complications in the laparoscopic approach can be far greater.

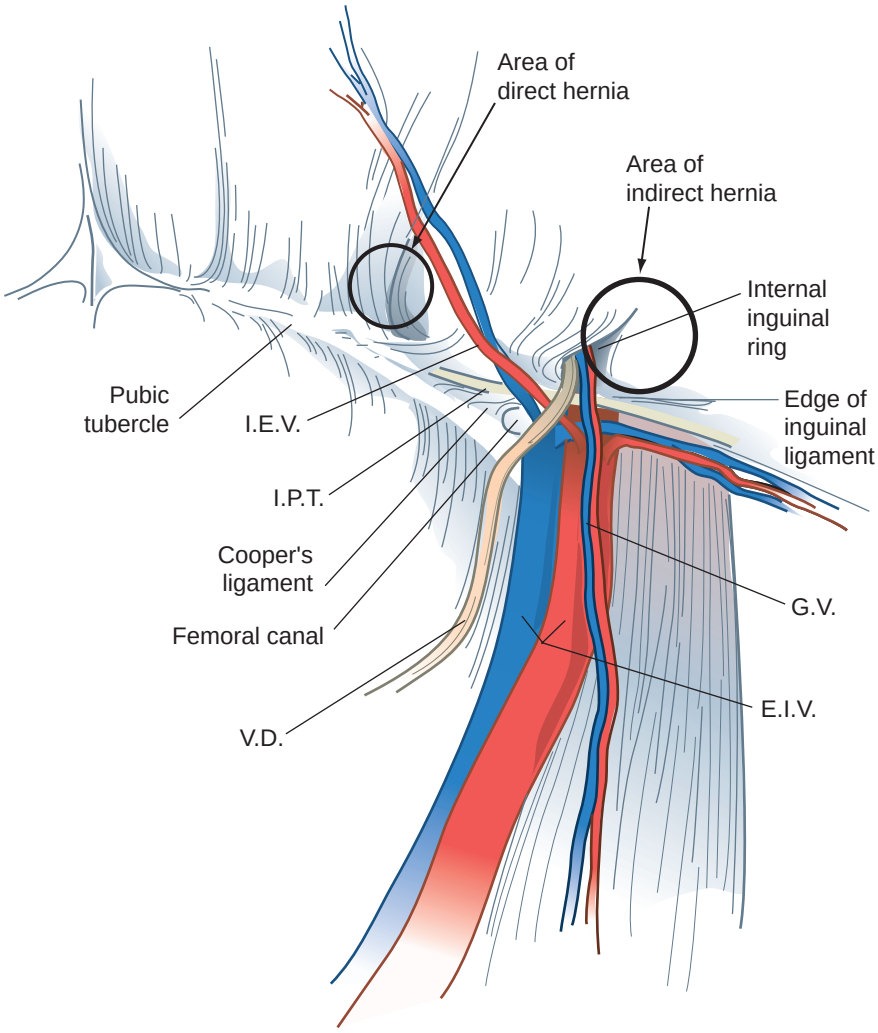

Figure 46–3. Anatomy of the important preperitoneal structures in the right inguinal iliopubic tract. EIV, external iliac vessels; GV, gonadal vessels; IEV, inferior epigastric vein; IPT, iliopubic tract; VD, vas deferens.

The hospital cost of laparoscopic repair is significantly higher than that of conventional repair, but it may be somewhat compensated by the higher productivity attributable to earlier return to work.

Patient Selection

Laparoscopic inguinal herniorrhaphy is technically more challenging than a tension-free anterior repair and thus has a steep learning curve. Consequently, patient selection for the procedure is heavily dependent on the surgeon's experience and skills. If laparoscopic and conventional repairs have equivalent complication and recurrence rates in the hands of a particular surgeon, any patient with an inguinal hernia who can undergo a general anesthetic is a candidate for laparoscopic repair. The laparoscopic approach is particularly useful for bilateral or recurrent hernias. Absolute contraindications include intra-abdominal infection and uncorrectable coagulopathy. Previous surgery in the retropubic space, intra-abdominal adhesions, and the presence of ascites are relative contraindications. Adhesions and suprapubic operations make retroperitoneal dissection difficult and can result in bladder injury or peritoneal tears leading to exposed mesh. An incarcerated inguinal-scrotal hernia is also a relative contraindication, especially when the colon is involved because of the risk for bowel injury during the dissection. Many laparoscopic herniorrhaphists find that sliding hernias, especially when reducible, are more effectively approached endoscopically than conventionally. However, in the absence of considerable experience, a conventional approach may be preferred.

Operative Strategies

The terminology used in the description of laparoscopic inguinal hernia repair can be confusing because terms such as *preperitoneal* have been used in conventional hernia repairs as well. For the purpose of this chapter, a laparoscopic hernia repair in which the peritoneal cavity is initially entered and the preperitoneal space is entered by another incision into the peritoneum from within the abdomen is called a *transabdominal preperitoneal,* or TAPP, repair. The next commonly used type of laparoscopic inguinal hernia repair is the *totally extraperitoneal,* or TEP,

Table 46–1 Comparative Trials of Laparoscopic and Open Inguinal Hernia Repair Using Mesh

Author	Hernias *(n)* LH vs. OH	Intervention	Recurrence Rate (%)	Salient Results
Horeyseck et al., 1996[4]	100 vs. 100	TAPP vs. Lichtenstein	8 vs. 0	Higher recurrence, higher cost
Zieren et al., 1996[5]	86 vs. 105	TAPP vs. PP	2.3 vs. 0	Higher recurrence, higher cost, similar complications
Sarli et al., 1997[6]	64 vs. 66	TAPP vs. Lichtenstein	0 vs. 0	Similar complications, missed contralateral hernias in OH group
Champault et al., 1997[7]	50 vs. 50	TAPP vs. Stoppa	6 vs. 2	Lower morbidity, higher patient comfort, higher recurrence rate
Khoury, 1998[8]	169 vs. 146	TAPP vs. MP	2.5 vs. 3	Similar recurrence rates, earlier return to normal activity, lower nerve complications
Paganini et al., 1998[9]	52 vs. 56	TAPP vs. Lichtenstein	2 vs. 0	Similar return to normal activity, higher cost
Aitola et al., 1998[10]	24 vs. 25	TAPP vs. Lichtenstein	13 vs. 8	Similar return to work, higher recurrence rates
Picchio et al., 1999[11]	53 vs. 52	TAPP vs. Lichtenstein	Not mentioned	Higher pain scores, similar recovery periods
Kumar et al., 1999[12]	25 vs. 25	TEP vs. Lichtenstein	4 vs. 8	*Nonrandomized,* lower pain score, fewer local complications
Johansson et al., 1999[13]	613 total	TAPP vs. preperitoneal mesh vs. conventional	2 vs. 5.5 vs. 2	Earlier resumption of normal activity and return to work, higher cost
MRC group, 1999[14]	468 vs. 460	TEP vs. mainly tension-free	1.9 vs. 0	Earlier resumption of normal activity, less long-term pain, higher recurrence rate
Beets et al., 1999 [15]	56 vs. 52	TAPP vs. Stoppa	12.5 vs. 1.9	Less pain, fewer early complications
Sarli et al., 2001[16]	40 vs. 46	TAPP vs. Licttenstein	0 vs. 4.3	Less pain, earlier return to work
Wright et al., 2002[17]	145 vs. 151	TEP vs. mostly Lichtenstein	2 vs. 2	Similar recurrences, similar missed contralateral hernias
Pikoulis et al., 2002[18]	309 vs. 234	TAPP vs. MP	1.9 vs. 0.4	*Nonrandomized,* higher cost, higher recurrence rate
Mahon et al., 2003[19]	60 vs. 60 (all bilateral or recurrent)	TAPP vs. Lichtenstein	6.7 vs. 1.7	Shorter operative time, less pain, earlier return to work
Andersson et al., 2003[20]	81 vs. 87	TEP vs. Lichtenstein	2.5 vs. 0	Similar complications, earlier return to work, less pain, higher recurrence rate
Douek et al., 2003[21]	122 vs. 120	TAPP vs. Lichtenstein	1.6 vs. 2.5	Less groin pain, less frequent paresthesias
Bringman et al., 2003[22]	Total $N = 298$	TEP vs. MP vs. Lichtenstein	1.3 vs. 1.3	Shorter sick leave period, less time to full recovery
Lal et al., 2003[23]	25 vs. 25	TEP vs. Lichtenstein	0 vs. 0	Earlier return to work better cosmesis, similar recurrence rate
Heikkinen et al., 2004[24]	62 vs. 61	TAPP vs, Lichtenstein	8 vs. 3.2	Similar recurrence rate, less long-term groin pain
Neumayer et al., 2004[25]	862 vs. 834	TAPP/TEP vs. Lichtenstein	10.1 vs. 4	Less pain, higher recurrence rate for primary hernias

IPOM, intraperitoneal onlay mesh repair; LH, laparoscopic hernia repair; MP, mesh plug repair; OH, open hernia repair; PP, patch plug repair; TAPP, transabdominal preperitoneal hernia repair; TEP, totally extraperitoneal repair.

Table 46–2 Comparative Trials of Laparoscopic and Open Tissue-Based Inguinal Hernia Repair

Author	Hernias (*n*) LH vs. OH	Intervention	Recurrence Rate (%)	Salient Results
Lawrence et al., 1995[28]	58 vs. 57	TAPP vs. Maloney darn	Not mentioned	Less pain, higher cost, similar return to work
Vogt et al., 1995[29]	30 vs. 32	IPOM vs. Bassini/McVay	3 vs. 6	Lower analgesic requirement, earlier return to normal activity
Liem et al., 1997[30]	487 vs. 507	TEP vs. mostly tissue repairs	3 vs. 6	Rapid recovery, shorter time to return to work, fewer recurrences
Dirksen et al., 1998[31]	114 vs. 103	TAPP vs. Bassini	6 vs. 21	Less pain, earlier resumption of normal activity, fewer recurrences
Tanphiphat et al., 1998[32]	60 vs. 60	TAPP vs. modified Bassini	1.5 vs. 0	Higher cost, less pain, earlier return to full activity, similar work leave
Zieren et al., 1998[33]	80 vs. 80 vs. 80	TAPP vs. MP vs. Shouldice	0 vs. 0 vs. 0	Less pain, less restriction of activity
Juul et al., 1999[34]	138 vs. 130	TAPP vs. Shouldice	2.9 vs. 2.3	Lower analgesic requirement, early return to work, similar recurrence rates
Leibl et al., 2000[35]	48 vs. 43	TAPP vs. Shouldice	2 vs. 5	Greater patient satisfaction, similar recurrence rates
Tschudi et al., 2001[36]	51 vs. 49	TAPP vs. Shouldice	3.9 vs. 10.2	Less pain, earlier return to full activity, fewer recurrences
Wennstrom et al., 2004[37]	131 vs. 130	Tep vs. Shouldice	Similar	Similar pain, hospital stay, complications, and recurrence rates

IPOM, intraperitoneal onlay mesh repair; LH, laparoscopic hernia repair; MP, mesh plug repair; OH, open hernia repair; TAPP, transabdominal preperitoneal hernia repair; TEP, totally extraperitoneal repair.

repair. Strictly speaking, the peritoneal cavity is not entered in this approach, and thus true laparoscopy is not performed; however, because a laparoscope and related instruments are used, it is appropriate to discuss this operation here. An inguinal hernia repair that is performed by placing mesh intraperitoneally over the defect via a laparoscopic approach is labeled an *intraperitoneal onlay mesh,* or IPOM, repair.

Transabdominal Preperitoneal Repair

The TAPP procedure is begun with placement of a Hasson cannula at the umbilicus under direct vision. Thorough diagnostic laparoscopy is performed to rule out any unrelated pathology, and both myopectineal orifices are inspected. Two additional 5-mm laparoscopic ports are placed on either side of the umbilical cannula just lateral to the rectus sheath (Fig. 46–4). This assumes the availability of a 5-mm fastening device. If a 10-mm instrument is to be used for this purpose, one of the lateral cannulas will need to be 10 mm. If the hernia is unilateral, a transverse incision of the peritoneum is begun on the lateral side of the medial umbilical ligament. The lateral leaf of the ligament is opened and the peritoneum is incised to a point medial to the anterior superior iliac spine while staying approximately 2 cm above the internal inguinal ring and the hernia defect. The medial umbilical ligament can be divided if needed and the remnant of the obliterated fetal umbilical artery

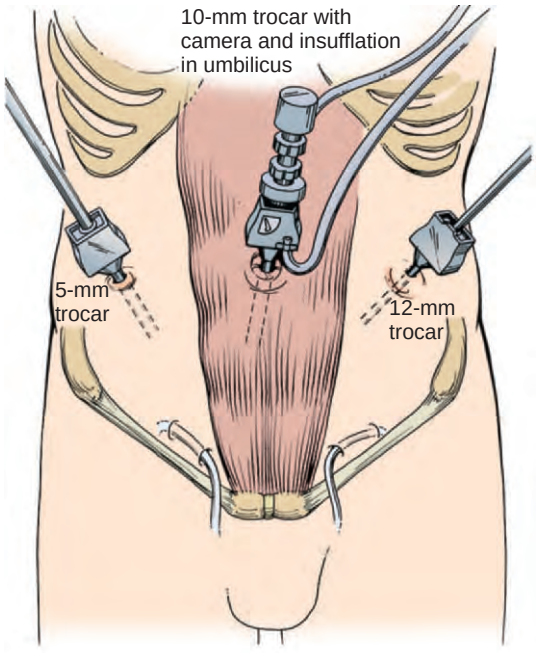

Figure 46–4. Trocar placement for a transabdominal preperitoneal laparoscopic hernia repair.

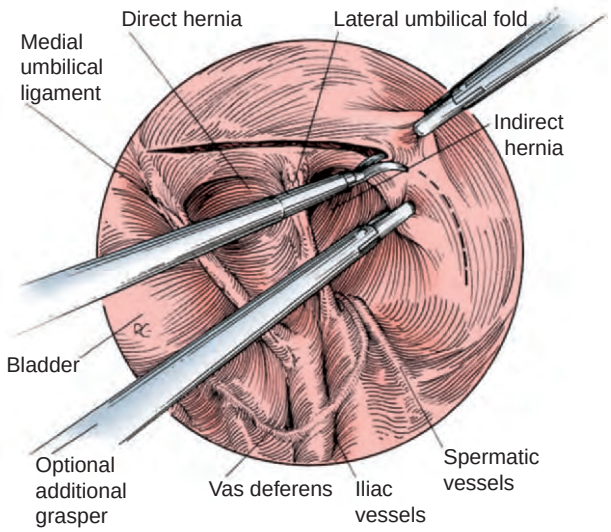

Figure 46–5. A transverse curvilinear peritoneal incision is made cephalad to the internal inguinal ring. The incision extends from the medial umbilical ligament to a point 2 to 3 cm lateral to the internal inguinal ring. The incision may be made in a medial-to-lateral or lateral-to-medial direction. Counteraction on the peritoneum inferior to the line facilitates dissection and reduces the risk of injury to underlying structures (e.g., inferior epigastric vessels). (From Eubanks S: Hernias. In Sabiston DC Jr, Lyerly HK [eds]: Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 15th ed. Philadelphia, WB Saunders, 1997, p 1226.)

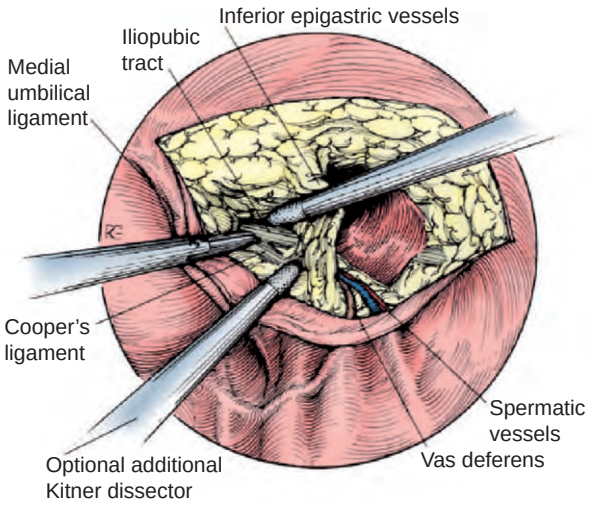

Figure 46–6. Blunt dissection of the inguinal floor. (From Eubanks S: Hernias. In Sabiston DC Jr, Lyerly HK [eds]: Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 15th ed. Philadelphia, WB Saunders, 1997, p 1226.)

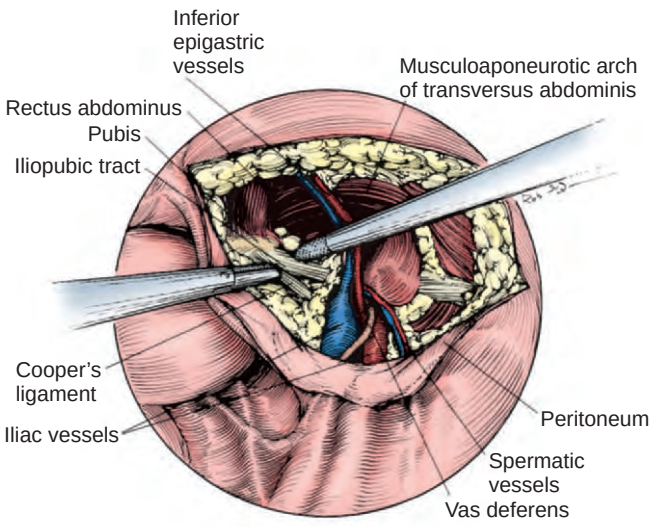

Figure 46–7. Completed dissection of the inguinal floor skeletonizes Cooper's ligament, the iliopubic tract, the lateral edge of the rectus abdominis, and the transversus abdominis aponeurotic arch. (From Eubanks S: Hernias. In Sabiston DC Jr, Lyerly HK [eds]: Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 15th ed. Philadelphia, WB Saunders, 1997, p 1226.)

controlled with electrocautery. Extensive, mostly blunt dissection is performed in the preperitoneal space. The use of electrocautery to prevent bleeding is especially helpful because bleeding interferes with adequate visualization by absorbing the light. It is important to dissect beyond the symphysis to the contralateral side to achieve sufficient overlap of all medial hernia openings. Both pubic tubercles, the inferior epigastric vessels, Cooper's ligament, and the iliopubic tract are identified (Figs. 46–5 to 46–8). The spermatic cord structures are mobilized and the peritoneal flap is dissected well proximal to the bifurcation of the vas deferens and the internal spermatic vessels. If the inferior peritoneal flap is not adequately mobilized, the mesh is prevented from laying flat or the inferior edge of the mesh will roll up when the peritoneum is closed. This has been identified as an important mechanism of recurrence with the TAPP procedure. A direct hernia sac is easily reduced during the preperitoneal dissection. A small indirect hernia sac can be dissected away from he cord structures and reduced. A larger sac needs to be divided at a suitable point distal to the deep inguinal ring, with only the proximal portion dissected away from the cord structures. No effort is made to disturb the distal part of the sac because it may lead to unnecessary vascular disruption, which can result in hematoma formation, ischemic orchitis, testicular atrophy, or any combination of these complications.

A large piece of prosthesis (at least 15 × 10 cm) is placed so that the entire myopectineal orifice is generously covered. At this point one must not forget about the femoral space. Slitting of the mesh laterally to create a new deep ring is optional. There is no conclusive evidence that such slitting confers any advantage over the technique of simply placing the unslit mesh over the internal ring. However, if the mesh is slit, it is important that it be adequately repaired around the cord structures because this step has been incriminated in recurrence.[38]

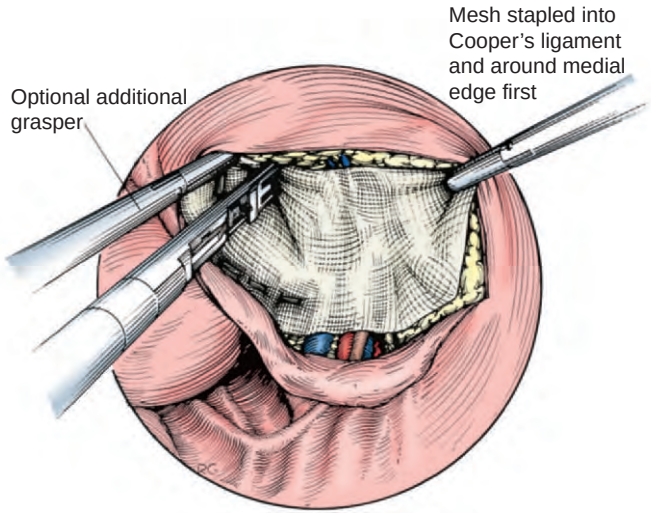

Figure 46–8. The mesh is secured to the anatomic frame with a hernia stapler. (From Eubanks S: Hernias. In Sabiston DC Jr, Lyerly HK [eds]: Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 15th ed. Philadelphia, WB Saunders, 1997, p 1226.)

The need for mesh fixation is another controversial subject. Most surgeons believe that the possibility of mesh shrinkage or migration mandates the use of staples, tacks, anchors, or biologic glue. Others think that if a large enough piece of mesh is used, fixation become unnecessary, thereby avoiding complications associated with trauma related to the fixation device.[39] If fixation is chosen, it is begun at the contralateral pubic tubercle and extended medially onto the anterior abdominal wall at least 2 cm superior to the hernia defect, to the anterior superior iliac spine laterally, and to the tissue just above Cooper's ligament inferiorly. Staples, tacks, or anchors should never be placed below the iliopubic tract when lateral to the internal spermatic vessels because of the possibility of nerve damage and neuralgias. For the superior border of the mesh, staples are placed in horizontal fashion to prevent trauma to the ilioinguinal and iliohypogastric nerves, which also run horizontally. Lateral staples are oriented vertically because the femoral branch of the genitofemoral nerve and the lateral cutaneous nerve of the thigh run in this direction. Meticulous peritoneal coverage of the prosthesis is essential, and hence lowering the pressure of the pneumoperitoneum and further undermining of the inferior peritoneal flap may be necessary. The goal is isolation of the prosthesis from the viscera, and if it is not possible to reapproximate the superior and inferior peritoneal flaps, the inferior flap should be tacked to the transversalis fascia after ensuring complete mesh coverage. If all else fails, omentum can be used to cover the exposed mesh.

For bilateral inguinal hernias, both preperitoneal spaces are dissected. The median umbilical ligament is left undisturbed to avoid the theoretical complication of dividing a patent urachus. However, because both preperitoneal spaces communicate with each other above the symphysis pubis, a single large piece of mesh (at least 30×10 cm) can be used to cover the entire lower portion of the pelvis. Some surgeons prefer two separate pieces of mesh for ease of handling, and there does not appear to be a significant increase in the recurrence rate.[40]

Totally Extraperitoneal Repair

A three-trocar approach for the TEP repair is also used. A 10-mm umbilical incision is deepened to either the ipsilateral or the contralateral anterior rectus sheath, depending on the preference of the surgeon. The rectus sheath is opened and the rectus muscle retracted laterally. The posterior sheath is visualized. Blunt dissection is now begun between the rectus muscle and the posterior rectus sheath with a blunt dissector or a finger while aiming toward the symphysis pubis. A blunt Hasson cannula with a laparoscope is introduced into the space between the rectus abdominis muscle and the posterior rectus sheath. It is aimed beyond the superior third of the distance between the umbilicus and the pubic symphysis. This allows the tip of the trocar to be placed inferior to the arcuate line. The cannula is now advanced at a 30-degree angle off the midline toward the side of the hernia. Gentle side-to-side movements of this assembly are used to dissect this preperitoneal space. Care must be taken to avoid aiming too far posteriorly because the bladder may be injured. Once adequate space has been created, two more ports are placed, one approximately 5 cm above the pubis symphysis and the other midway between the umbilicus and the pubis symphysis. Dissection of the preperitoneal space is now completed under direct vision. Popular technical variations include the use of a saline- or air-filled balloon to dissect the preperitoneal space and placement of the two accessory ports on either side of the midline as in the TAPP repair (Fig. 46–9). One of the advantages of the balloon device is that the preperitoneal space can be visualized through the transparent structure of the balloon. A disadvantage is a higher incidence of dissection in front of the inferior epigastric vessels, which causes them to be reduced with the peritoneal flap. This can complicate exposure. Once the preperitoneal space has been completely developed, treatment of the hernia sac and its contents, parietalization, and placement of the mesh proceed in an fashion identical to that for the TAPP repair.

Potential advantages of the TEP procedure are avoidance of complications associated with entering the peritoneal cavity, including visceral injury, intra-abdominal vascular injury, adhesion formation, and trocar site hernias. Perhaps most important, peritoneal closure does not have to be performed, which eliminates one of the more difficult aspects of the TAPP repair and greatly speeds up the operation. However, the operative space is limited and the anatomy is less easily understood than with the TAPP procedure, thus leading to a slower learning curve. Previous lower abdominal surgery can be a relative contraindication to the TEP repair. Studies comparing the TAPP and TEP repairs have not shown consistent superiority of one approach over the other. A comparison of recent studies of the various methods of

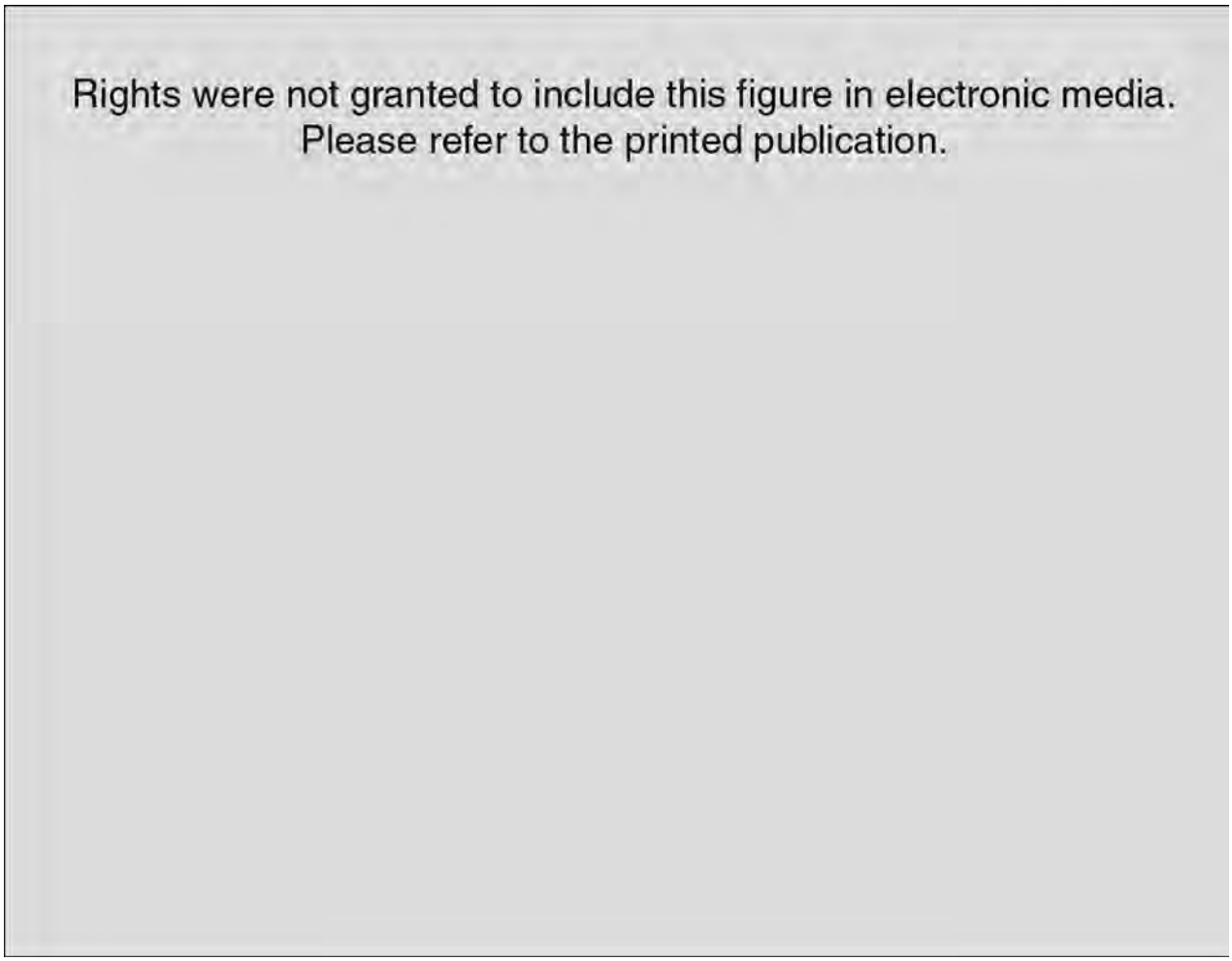

Figure 46–9. The totally extraperitoneal approach for laparoscopic hernia repair is demonstrated. Access to the posterior rectus sheath is gained in the periumbilical region. **A,** A balloon dissector is placed on the anterior surface. **B,** The balloon dissector is advanced to the posterior surface of the pubis in the preperitoneal space. **C,** The balloon is inflated, thereby creating an optical cavity. **D,** The optical cavity is insufflated with carbon dioxide, and the posterior surface of the inguinal floor is dissected. (From Shadduck PP, Schwartz LB, Eubanks WS: Laparoscopic inguinal herniorrhaphy. In Pappas TN, Schwartz LB, Eubanks WS [eds]: Atlas of Laparoscopic Surgery. Philadelphia, Current Medicine, 1996. Copyright © 1996 by Current Medicine. Reproduced by permission of the publisher.)

laparoscopic hernia repair is presented in Table 46–3. Surgeon expertise with a particular procedure may be the key to consistent good results.

Intraperitoneal Onlay Mesh Repair

Only a thin layer of peritoneum separates the abdominal cavity from the preperitoneal space. The rationale for the IPOM repair is to place a prosthesis directly onto the peritoneum so that radical preperitoneal dissection can be avoided. Initial laparoscopy, port placement, and landmark identification are the same as for the TAPP repair. A large prosthesis is introduced into the peritoneal cavity and secured in place with tacks, staples, or sutures. Some surgeons open the peritoneum over Cooper's ligament to ensure adequate fixation in this area.

This repair has been less popular than the TAPP and TEP approaches because of concern among surgeons about placing a prosthesis directly in contact with intraperitoneal structures. Many believe that it should be considered an experimental operation. In addition, the results in several series have not been as good as the results of other laparoscopic repairs, with a higher incidence of neuralgia and recurrence, but this may be more a reflection of experience than the operation itself.[45,49] The IPOM repair represents the only truly minimally invasive herniorrhaphy because radical dissection of the preperitoneal space is avoided. The development of a totally inert prosthesis might renew interest in the future.

Table 46–3 Comparative Trials of Different Types of Laparoscopic Inguinal Hernia Repair

Author	Hernias *(n)*	Intervention	Recurrence Rate (%)	Salient Results
Fitzgibbons et al., 1995[41]	Total 869	TAPP vs. IPOM vs. TEP	4.5 vs. 4.5 vs. 4.5	Similar complication and recurrence rates
Khoury, 1995[42]	60 vs. 60	TAPP vs. TEP		Longer hospital stay and higher analgesic requirement with TAPP
Ramshaw et al., 1996[43]	300 vs. 300	TAPP vs. TEP	2 vs. 0.3	Increased vascular injury and recurrence with TAPP
Kald et al., 1997[44]	393 vs. 98	TAPP vs. TEP	1.5 vs. 1	Higher major complications and recurrences with TAPP
Sarli et al., 1997[45]	59 vs. 56	TAPP vs. IPOM	0 vs. 11.1	Fewer neuralgias and recurrences with TAPP
Van Hee et al., 1998[46]	33 vs. 58	TAPP vs. TEP	2.7 vs. 2.8	Similar complication and recurrence rates
Cohen et al., 1998[47]	108 vs. 100	TAPP vs. TEP	1.9 vs. 0	Similar local complication and recurrence rates, TAPP technically easier
Lepere et al., 2000[48]	1290 vs. 682	TAPP vs. TEP	1 vs. 1	Similar local complication and recurrence rates

IPOM, intraperitoneal onlay mesh repair; TAPP, transabdominal preperitoneal hernia repair; TEP, totally extraperitoneal repair.

COMPLICATIONS OF LAPAROSCOPIC INGUINAL HERNIA REPAIR

The overall incidence of morbidity after laparoscopic inguinal hernia repair has been quite variable (Table 46–4). Complication rates vary from 3%[50] to 25%,[27] depending largely on the thresholds set for categorizing an event as a complication. Fortunately, serious complications are quite uncommon. One may classify these complications according to whether they are related to

Laparoscopy
Hernia repair
Prosthesis
Patient factors

It is also important to classify complications in relation to their timing: immediate (at the time of initial surgery), early (days to weeks), and delayed (months to years).

Complications Associated with the Laparoscopic Approach

Major Vascular Injury

The risk of major vascular injury requiring operative repair is 0.08%.[51] Many authors believe that this incidence is seriously underestimated because such injuries commonly go unreported. Access to the peritoneal cavity is the most crucial phase of laparoscopy, and over three quarters of major vascular injuries occur during insertion of the Veress needle or the trocars at the beginning of the procedure.[52] The vessels most frequently involved include the aorta, inferior vena cava, and the iliac artery and vein. Mesenteric and omental vessels, splenic vessels, and renal vessels have been injured occasionally. Epigastric vessels running in the rectus sheath may be injured during the placement of secondary trocars. The use of disposable trocars with safety shields, optical trocars, and blunt-tipped cannulas has not eliminated this dramatic complication. It has even been described during the open approach with the Hasson cannula used for initial access.

Knowledge of the anatomic relationships between the anterior abdominal wall and the retroperitoneum, careful introduction of the Veress needle, and avoidance of the Trendelenburg position during initial access have been reported to decrease the incidence of this complication. Major vascular injury is manifested as either hemoperitoneum or retroperitoneal hematoma. Mortality has been estimated to be as high as 36%. Expeditious laparotomy with repair of the vessel is usually required. Lacerations of the epigastric vessels can be controlled by applying pressure applied with a cannula. Occasionally, suture ligation is required, which is now possible with the use of an "exit device" for transfascial suture placement.

Bowel Injury

The incidence of bowel injury and bowel perforation in laparoscopic operations is about 0.13%.[53] Up to half of these injuries occur during the access phase of laparoscopy. The small bowel is the most frequently injured segment (56%). About two thirds of these injuries are detected intraoperatively. The injury can be repaired laparoscopically if the operator is experienced in intracorporeal suturing or the injury is amenable to a stapled repair without compromising luminal diameter. Patients with missed bowel injury typically manifest

Table 46–4 Complications of Laparoscopic Hernia Repair

Associated with Laparoscopy	Associated with the Patient	Associated with the Hernia Repair	Associated with the Prosthesis
Major vascular injury (I)	Ileus (E)	Recurrence (D)	Contraction (D)
Retroperitoneal	Urinary retention (E)	Trocar site problems	Erosion (D)
Intra-abdominal	DVT (E)	Hematoma (E)	Folding (E)
Abdominal wall	Cardiopulmonary complications (I, E)	Infection (E)	Infection (E, D)
Bowel injury (I, E)		Hernia (D)	Rejection (D)
Bladder injury (I, E)		Keloid (D)	Pain (E, D)
Gas embolism (I)		Seroma(E)	
Bowel obstruction (E, D)		Hematoma (I, E)	
Shoulder pain (E)		Groin	
Subcutaneous/preperitoneal emphysema (I, E)		Scrotal	
		Retroperitoneal	
Diaphragmatic dysfunction (E)		Hydrocele (E, D)	
Arrhythmias (I)		Orchitis (E)	
		Infertility (D)	
		Neurologic (D)	
		Groin pain	
		Anesthesia	
		Paresthesias	
		Dysejaculation (D)	

D, delayed manifestation (weeks to years); DVT, deep venous thrombosis; E, early manifestation (hours to days); I, immediate/intraoperative manifestation.

peritoneal signs and sepsis 1 day to 1 week after the index operation. The overall mortality rate with this complication is about 4%.[53]

Bladder Injury

Injury to the bladder may occur from suprapubic trocar placement or from dissection during the course of the operation. Bladder injury may be obvious when blood and gas collect in the drainage bag if a Foley catheter is in place. When there is any doubt about bladder injury, methylene blue dye may be instilled into the bladder to look for leakage.[54] Bladder injury recognized during laparoscopy should be repaired laparoscopically if the experience of the surgeon is sufficient, followed by bladder drainage for 7 to 10 days. Bladder injury may be manifested in delayed fashion as hematuria and lower abdominal discomfort. A retrograde cystogram generally confirms the diagnosis. Small defects may be managed with urinary drainage, whereas larger defects necessitate repair.

Gas Embolism

Gas embolism is a very rare, but potentially life-threatening complication. Carbon dioxide can be introduced into a large vein, most likely the result of inadvertant cannulation by the Veress needle, and trapped in the right ventricle, where it causes outflow obstruction into the pulmonary artery and sudden circulatory collapse. Careful insertion of the Veress needle and the usual confirmatory tests of its intraperitoneal position should keep the incidence of air embolism low.

Intestinal Obstruction

During the developmental years of laparoscopic inguinal hernia repair the importance of closing all fascial defects greater then 5 mm was not recognized. This resulted in the development of Richter's hernia with bowel obstruction in occasional patients.[55] Several devices that can be used to close fascial defects larger than 5 mm are now routinely available commercially. Inadequate peritoneal closure over the prosthesis after the TAPP repair may leave gaps that allow bowel to migrate into the preperitoneal space and thereby result in bowel obstruction. Operative strategies to minimize this complication have been described in the section on operative techniques. With the advent of the TEP repair it was hoped that bowel-related complications would be minimized or eliminated. However, frequently unrecognized peritoneal defects are common after the TEP repair, especially in patients with previous lower abdominal surgery, and intestinal obstruction has been reported.[56] Delayed adhesive small bowel obstruction is theoretically possible because of the intra-abdominal dissection. Fortunately, this complication is exceedingly rare.

Shoulder Pain

Shoulder pain is commonly seen after any laparoscopic procedure and can be quite troublesome to the patient.

It is commonly assumed that residual carbon dioxide in the peritoneal cavity is trapped under the diaphragm and causes diaphragmatic irritation and referred pain to the shoulder, but this has never been proved. Nevertheless, it is standard practice to completely deflate the pneumoperitoneum at the conclusion of laparoscopic inguinal herniorrhaphy with the patient still in the Trendelenburg position. A low-pressure pneumoperitoneum has also been recomended.[57]

Subcutaneous and Preperitoneal Emphysema

Subcutaneous emphysema is usually harmless and resolves spontaneously, aided by massaging the swollen anterior abdominal wall toward the nearest trocar site. Preperitoneal emphysema is due to a malpositioned Veress needle and can be frustrating to the surgeon. It can be avoided by using a Hasson cannula for primary access.

Diaphragmatic Dysfunction

Diaphragmatic dysfunction has been described after a variety of laparoscopic procedures. Its exact etiology is unclear, but the effects are transient and generally resolve spontaneously by 24 hours.

Cardiac Arrhythmia

Bradycardia may occasionally follow the creation of pneumoperitoneum. It is a reflex vagal response to peritoneal distention. It can usually be managed by stopping the inflow of carbon dioxide temporarily and administering an anticholinergic drug. Once the heart rate has recovered, pneumoperitoneum can be re-created gradually.

Complications Associated with the Patient

Ileus

Ileus is somewhat more common after a laparoscopic inguinal hernia repair than after a conventional repair. It is a self-limited problem but occasionally requires nasogastric decompression.

Urinary Retention

Older age, general anesthesia, aggressive hydration, narcotics for pain relief, and a history of prostatic symptoms predispose to urinary retention after hernia repair. Intermittent catheterization or temporary placement of an indwelling urinary catheter is usually adequate therapy. Prophylactic use of prazosin after herniorrhaphy may significantly reduce the incidence of urinary retention and catheterization.[58]

Deep Venous Thrombosis

The incidence of deep venous thrombosis after laparoscopic procedures is about 0.33%.[59] Thromboprophylaxis for laparoscopy should be the same as for conventional surgery, that is, tailored to individual risk and continued for a minimum of 7 to 10 days. Graduated compression stockings, sequential intermittent compression devices, maintenance of relatively low insufflation pressure, keeping use of the reverse Trendelenburg position to a minimum, and intermittent release of the pneumoperitoneum in longer procedures are other measures that can decrease the incidence of deep venous thrombosis.

Complications Associated with Hernia Repair

Recurrence

The often-quoted rate of recurrence after a laparoscopic repair is on the order of 3%.[27] Similar recurrence rates are also routinely seen after the open tension-free repair. Most of these data are from specialty centers, however, and the overall recurrence rate after laparoscopic herniorrhaphy may be closer to 10%.[25]

Hernia recurrences may be difficult to distinguish clinically from lipoma of the cord, a seroma, or a bulge in the internal oblique muscle and may require imaging with ultrasound, CT, or MRI. Definitive identification of recurrence is especially important to avoid unnecessary surgery in those with groin pain. It is logical to approach the recurrence through a previously undissected plane, and thus many surgeons prefer to perform an open anterior tension-free repair for a hernia previously repaired laparoscopically. Laparoscopic preperitoneal herniorrhaphy after a previous failed endoscopic herniorrhaphy is controversial. A strong argument can be made that this procedure should not be performed except in cases in which failure has occurred in both the conventional and the preperitoneal space. Nevertheless, surgeons are confronted with patients who request a laparoscopic repair regardless. This situation most commonly comes up when the patient has previously undergone conventional repair on the opposite side. In the hands of experienced laparoscopists, this would appear to be an acceptable approach. However, it is a technically demanding procedure with the potential for serious complications for the uninitiated, most notably bladder injury. Therefore, referral to a specialty center by the practicing surgeon should be considered in such cases. The TAPP procedure is the safest laparoscopic herniorrhaphy for these recurrent hernias inasmuch as a significant series using the TEP approach has not been reported.

Infertility

Injury to the vas deferens or the testes can cause infertility. The incidence of injury to the vas deferens during inguinal hernia repair is 0.3% in adults and up to 2% in children.[60] The vas deferens may be injured during dissection and mobilization or during fixation of the mesh. Traction injuries to muscular wall of the vas deferens sustained during mobilization may interfere with transfer of spermatozoa.[61] Unilateral injury to the cord can lead to exposure of spermatozoa to the immune system and the formation of antisperm antibodies, thus causing infertility.[62]

Ischemic Orchitis

Interruption of blood flow to the testis because of inguinal herniorrhaphy may result in ischemic orchitis and subsequent testicular atrophy. It is manifested 1 to 3 days after surgery as a painful, enlarged, firm testicle accompanied by low-grade fever. Its incidence in large series of TAPP repairs was 0.11%.[63] Complete excision of all indirect inguinal hernia sacs is thought to be an important cause secondary to trauma to the testicular blood supply, especially the delicate venous plexuses. Large indirect inguinal-scrotal hernia sacs should be divided just distal to the internal ring. The proximal portion of the sac is ligated and the distal part is opened on its anterior surface as far distally as convenient. Contrary to popular opinion in the urologic literature, this technique does not result in an excessive rate of postoperative hydrocele formation.[64] Treatment is largely supportive and consists of elevation and anti-inflammatory medication.

Groin Pain

Chronic groin pain is a major cause of morbidity after inguinal hernia surgery. Its incidence may be as high as 53% at 1 year of follow-up.[65] Evaluation of postherniorrhaphy groin pain involves ruling out a myriad of causes, including muscle injury, adductor strain, osteitis pubis, and lumbosacral disorders. The superior soft tissue resolution offered by MRI makes it the most useful diagnostic modality for evaluation of postherniorrhaphy groin pain. The etiology of this groin pain can be

Nociceptive—as a result of direct tissue damage
Somatic
Visceral
Neuropathic—as a result of nerve damage.

Nociceptive pain is further subdivided into (1) somatic, which is the most common and includes ongoing preoperative pathology that was the real cause of the patient's pain, usually related to ligament or muscle injury, new ligament or muscle injury caused by the operation, scar tissue, osteitis pubis, or a reaction to prosthetic material, and (2) visceral pain, which is pain related to a specific visceral function and includes urinary problems and the dysejaculation syndrome. Neuropathic pain is caused by damage to nerves or incorporation by staples or suture material during the repair. The nerves that may commonly be involved are the genital and femoral branches of the genitofemoral nerve and the lateral femoral cutaneous nerve. Treatment of all three types of pain is initially conservative and consists of reassurance, anti-inflammatory medications, cryotherapy, physical therapy, and local nerve blocks, except when sudden severe groin pain is present immediately after surgery, which suggests a stapled or sutured nerve. Such a patient can benefit from immediate reexploration. Otherwise, groin exploration should be reserved as a last resort because the results are often less than satisfactory. Our approach when groin exploration is the only option is to perform a combined laparoscopic and conventional groin exploration with fluoroscopic capability to maximize the chance of removing as much mesh and as many fastening devices as possible. Neurectomy, neuroma excision, and adhesiolysis are performed if indicated. The hernia is then repaired in the conventional space.

Wound Infection

Wound infection rates of up to 3% have been described with the laparoscopic approach,[66] but this problem is fortunately quite rare. Although antibiotic prophylaxis is quite commonly used for inguinal herniorrhaphy, its role in preventing infection is not clear.[67]

Seromas

Seromas are common and are almost entirely due to the use of prosthetic materials. Treatment is aspiration for symptomatic benefit, and one must weigh the risk of possibly introducing infection in a otherwise sterile collection.

Other Complications

Testicular descent is a complication related to complete division of the cremasteric fibers. The problem is sometimes described by patients as a "testicle dropping into the toilet." Avoiding complete transection of the cremaster prevents this problem. A hydrocele may occasionally develop, possibly related to a remnant of the hernia sac left in the scrotum, but this relationship has not been conclusively proved. Regardless, treatment is similar to that for a hydrocele unrelated to hernia surgery.

Mesh contraction by up to 20% has been described and may account for some of the recurrences after hernia repair.[68] The entity of mesh rejection is of doubtful significance and is probably a manifestation of prosthetic infection. Prosthetic erosion into cord structures or intra-abdominal viscera has been seen rarely.

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Chapter

47

Ventral Herniation in Adults

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A surgeon can do more for the community by operating on hernia cases and seeing that his recurrence rate is low than he can by operating on cases of malignant disease.

Sir Cecil Wakely
President, Royal College of Surgeons, 1948

Some of the first medical writings from thousands of years ago describe the anatomy and morbidity of hernias. Changes in their management have followed our understanding of their origins and, perhaps more importantly, our failures in their repair. Sutured repair continues to play a valuable role in herniorrhaphy, but suturing a defect under tension or using tissues of questionable strength results in a repair that is doomed to fail. Bridging a hernia with prosthetic mesh has established a valid position not only in the repair of large or recurrent hernias but also in small, primary repairs. The need for a strong prosthetic that is well tolerated by the human body is not a new thought or concept. In the mid-1800s, Bilroth stated, "If we could artificially produce tissue of the density and toughness of fascia and tendon, the secret of the radical cure of the hernia repair would be discovered." Nearly 150 years later we understand the importance of that statement. Industry also recognizes its worth, both in improving patient outcomes and in providing materials to a million-cases-a-year market. Research in the area of prosthetic mesh has soared over the last decade, with materials engineered for placement inside the abdomen and outside the abdomen, "nonstick" surfaces, mesh preformed for left- or right-sided laparoscopic inguinal hernias (in small, medium, or large sizes), umbrella-like "plugs," and other innovations. Natural material, such as that developed from cadaveric skin or porcine intestinal submucosa, has also seen a growth in interest. A perfect biomaterial is not currently available, but some very good and well-tolerated choices exist. There is little question that they have helped reduce rates of recurrence and morbidity in the most common operations performed by general surgeons.

DEFINITIONS

The term *ventral hernia* is used to describe any protrusion of abdominal viscera through the anterior abdominal wall. There are two categories of ventral hernia: spontaneous or primary hernias and incisional hernias. Ventral hernias can also be subdivided by location. Subxiphoid refers to the area just inferior to the xiphoid process. Epigastric hernias also overlap this area to some degree but include spontaneous hernias through the linea alba down to the umbilicus. Umbilical hernias are a special class of spontaneous or congenital ventral hernia that are located at the umbilicus. Hypogastric hernias are rare, spontaneous hernias inferior to the umbilicus. Suprapubic and parailiac hernias occur along the pelvic brim adjacent to their respective bony prominences. Spontaneous hernias along the semilunar line are termed spigelian; Adriaan van der Spiegel was a Belgian anatomist who first described the area. Traumatic hernias can occur almost anywhere in the anterior abdominal wall when fascial planes are disrupted after blunt or penetrating abdominal force.

Any hernia of the anterior abdominal wall that occurs through a previous surgical incision is naturally termed an incisional hernia. Two additional conditions apply to an anterior abdominal wall that appears to have a hernia but does not. Eventration of the anterior abdominal wall is a bulging that occurs from either paralysis of a portion of the abdominal musculature or congenital absence. There is no definable hernia sac or fascial defect; however, a bulge results from the lack of muscle tone. Similarly, diastasis recti is manifested as a midline bulge. The linea alba is broadened or stretched, which causes the medial margins of the rectus abdominis muscles to separate. Again, there is no hernia sac or fascial defect, and most are completely asymptomatic. If a diastasis results in significant symptoms, the abdominal wall can be reconstructed, but most often it is not a simple procedure. Incarceration describes the irreducible contents of a hernia sac. If not addressed, this process can compromise blood flow to the incarcer-

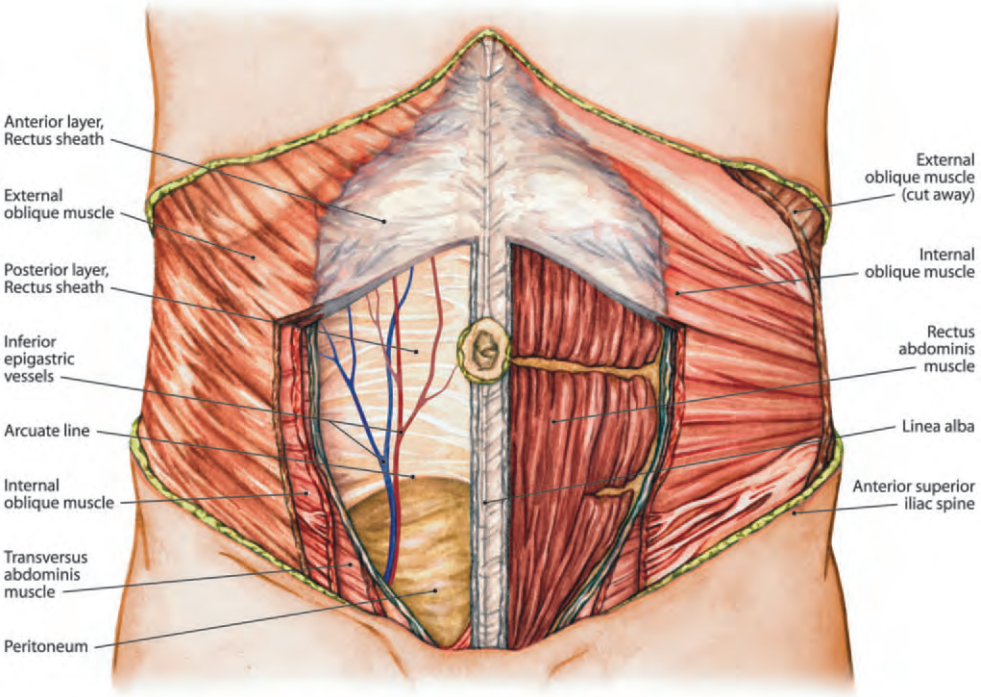


Figure 47–1. Layers of the abdominal wall.

ated hernial contents and potentially lead to necrosis or strangulation.

ANATOMY

The anterior abdominal wall is a complex layering of muscles, aponeuroses, and fascia (Fig. 47–1). The most obvious feature is the umbilicus, which represents the cicatricial remnants of the former umbilical cord and vessels. Typically, it lies at the midpoint between the xiphoid process and the pubis, depending on the amount of subcutaneous adipose tissue. The midline is further defined by the linea alba, which extends from the xiphoid to the symphysis pubis. It can be seen as a linear furrow in the anterior abdominal wall of muscular patients and is situated between the medial borders of the rectus abdominis muscles. The linea alba is composed of dense, crisscross fibrous bands from the blending aponeuroses of the external oblique, internal oblique, and transversalis muscles.[1] The linea alba is quite broad at the xiphoid, measuring 1 to 2.5 cm, as the rectus sheath fibers diverge to insert on the fifth, sixth, and seventh costal cartilages. Below the level of the umbilicus, the linea alba narrows to a fine line between the rectus muscles as it inserts on the pubis. Several tendinous intersections extend from the linea alba medially to the convex lateral rectus sheath border, the linea semilunaris, and firmly adhere the rectus muscles to the anterior rectus sheath.

The rectus sheath houses the rectus muscles and is a complex weaving of aponeuroses from the flat abdominal muscle. The anterior sheath is formed from fusion of the external oblique aponeurosis and the anterior lamina of the internal oblique aponeurosis. The posterior internal oblique lamina fuses with the transversus abdominis aponeurosis to generate the posterior sheath. Medially, these layers interlace to form the linea alba. Midway between the umbilicus and the pubis, the three aponeurotic layers fuse into one anterior sheath. The arcuate line marks the crescentic end of the posterior sheath.[2]

The spigelian fascia is a true aponeurosis formed by fusion of the internal oblique and transversus abdominis aponeurosis. It extends from the cartilage of the eighth rib to the pubis, lateral to the edge of the rectus muscle, and medial to the semilunar line. Below the umbilicus, the fibers of this aponeurosis run in parallel fashion, thus making it vulnerable to separation. At the level of the semicircular line of Douglas, the spigelian fascia is the weakest. The inferior epigastric vessels contribute to the weakness of that area by traversing the posterior aspect of the rectus abdominis. A spigelian hernia is a partial defect of the abdominal wall, with the preperitoneal fat or peritoneal sac protruding through the internal oblique but remaining posterior to the external oblique aponeurosis. Although it can occur anywhere along the semilunar line, 90% of hernias occur in the so-called spigelian belt, a 6-cm area of the aponeurosis extending cranially from the line between anterior superior iliac spines. This broad and weak region of the spigelian fascia is bounded by the semilunar line laterally, the inferior epigastric vessels medially, and the arcuate line superiorly (Fig. 47–2).

The lateral abdominal wall is composed of three layered flat muscles. The external oblique, the most superficial, courses inferior from its lower costal origins to its insertion on the iliac crest and medially to fuse

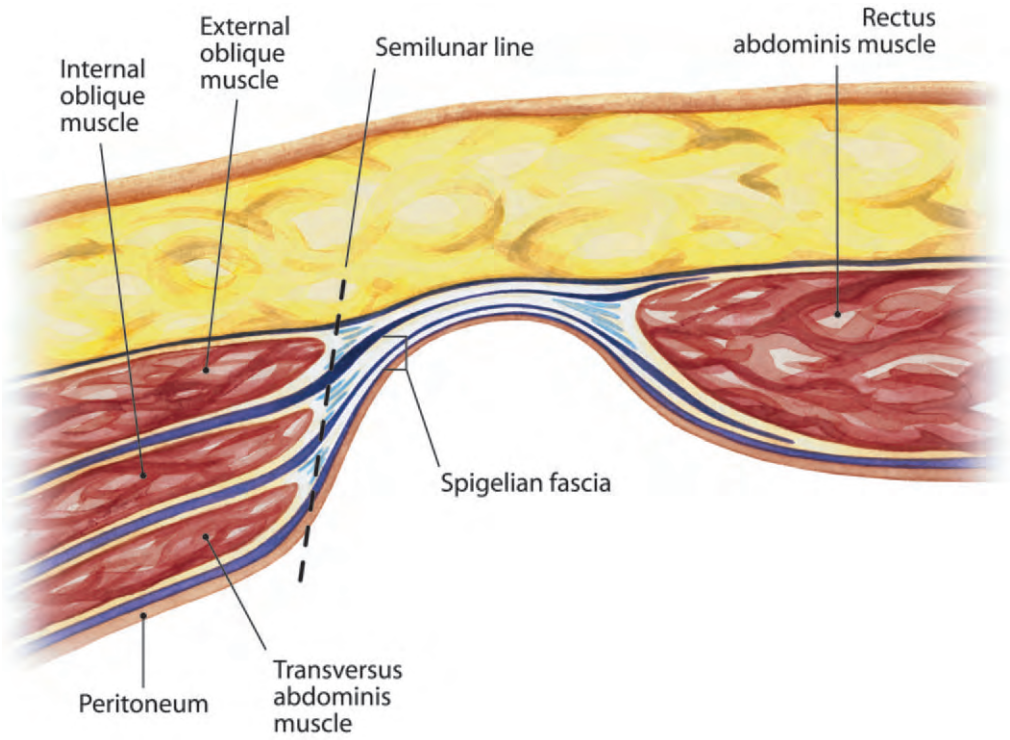


Figure 47–2. Spigelian fascia and location of hernias.

with the internal oblique. The intermediate abdominal muscle, the internal oblique, originates from the lateral half of the inguinal ligament and courses perpendicular to the external oblique superior and anteriorly. There is a significant contribution to the inguinal anatomy from this muscle layer. The innermost muscle layer, the transversus abdominis, courses horizontally and joins medially with the internal oblique aponeurosis. As with the internal oblique, many inferior fibers contribute to the inguinal region. The preperitoneal space separates the deep fascia layer from the peritoneum; this space often contains fat, which is more prominent in the lower part of the abdomen.

The blood supply to the anterior abdominal wall is derived from multiple sources. The upper part of the abdomen receives blood from the superior epigastric artery, the terminal branch of the internal thoracic artery, in combination with collateral branches of the lower intercostal arteries. The lower part of the abdomen is supplied by the inferior epigastric and deep circumflex iliac arteries, which are branches of the external iliac vessels. The superior and inferior epigastrics are continuous with each other deep to the rectus muscle. Nerves supply the anterior abdominal wall by running between the internal oblique and transversus abdominis muscles. The nerves then pierce superficially through the rectus sheath as anterior cutaneous nerves. Branches originate from the lower thoracic nerve roots (T7-T9) superior to the umbilicus, T10 innervates the periumbilical skin, and T11-L1 supplies the infraumbilical area. Several small blood vessels and nerves that penetrate the linea alba and umbilicus are occasional sites of spontaneous or acquired hernia.

ETIOLOGY

The formation of ventral hernias is a multifactorial and complex process. Three types of ventral hernias are recognized: spontaneous, congenital, and incisional hernias. Congenital hernias are just that, congenital, and are most often treated during the pediatric period of life. Spontaneous ventral hernias are most commonly found along the midline linea alba. Although they are typically supraumbilical in location, they can occur anywhere along this structure, and more than one hernia may be found. As previously described, the interlacing fibers of the aponeuroses in this portion of the linea alba are pierced by small blood vessels and nerves.[1] Through these openings, extraperitoneal areolar tissue may herniate and produce an epigastric (linea alba) hernia. The hernia opening is usually 1 cm in size or smaller. Extrusion of extraperitoneal fat may or may not be accompanied by a sac of the subjacent peritoneum. Though frequently referred to as lipomas, the fatty tissue is not a tumor; it is a mushroom-like mass of preperitoneal encapsulated fat with a feeding artery that usually comes through a tight, small defect. When a sac is present, it is generally small and barely protrudes through the opening in the fascia. This sac may not become apparent until the surrounding preperitoneal fat is removed. If the hernia contains only the preperitoneal fat of the falciform ligament, the hernia opening is almost always just to the right of midline. If the hernia does not contain fat from the falciform ligament, the opening is nearly always to the left, but occasionally in the midline. Small epigastric hernias increase in size slowly because the fascial ring through which they protrude is strong and

unyielding. If a larger sac is present, it may contain omentum, intestine, and other viscera.

Umbilical hernias are relatively common in the adult population and are another example of a spontaneous ventral hernia. Occasionally they can represent reappearance or persistence of a congenital umbilical hernia and are due to failure of the umbilical ring to close after umbilical cord ligation. In 90% of patients it is an acquired defect that is a direct result of increased abdominal pressure.[3] Causes of this increase in abdominal pressure include multiparous status, obesity, and cirrhosis with ascites.[4] Umbilical hernias are more common in females and often develop in the forth to fifth decade of life. The fascial ring that constitutes the neck of the hernia can be dense and is formed by gradual yielding of the cicatricial tissue closing the umbilical ring.[5] These hernias tend to enlarge with time and will not resolve spontaneously.

Numerous patient-related factors may lead to the formation of ventral hernias and include obesity,[6] older age,[7] male gender,[7] sleep apnea,[6] emphysema and other chronic lung conditions, prostatism,[8] abdominal distention, steroids,[8] and jaundice,[9,10] although some of these causes are controversial. Some evidence suggests that certain biochemical processes, including the metalloproteinases, may lead to both aneurysmal disease and hernia formation. These collagen defects have also been implicated in a higher rate of incisional hernia formation after aortic surgery.[11] The concept of "metastatic emphysema," that is, the same processes that break down pulmonary tissue disturb normal fascia, was introduced by Dr. Raymond Read and appears to be well founded.[12]

Every year, 4 to 5 million laparotomies are performed, with a hernia developing in 2% to 36% of these incisions.[13-15] This gives rise to well in excess of 150,000 ventral hernia repairs each year. Surgery-related factors may lead to subsequent incisional hernia formation. Wound infection, closure technique, suture material, and incision type have all been described as possible factors.[7] Primary closure of midline abdominal incisions has been the subject of numerous clinical trials. The two main variables compared are absorbable versus nonabsorbable suture and continuous versus interrupted closure technique. Ideally, the suture material used should retain high tensile strength until substantial wound healing has occurred and be a monofilament to prevent bacterial attachment among the fibers. Some additional evidence exists that absorbable suture eliminates the suture material as a nidus of infection,[9] although we have seen this regardless of the suture's permanence. A recent meta-analysis sought to answer the question of suture permanence.[16] In this study, the principal investigators divided suture material into rapidly absorbable, slowly absorbable, and nonabsorbable types. They included only prospective randomized controlled trials with at least 100 patients and follow-up of at least 1 year in their analysis. They identified 6566 patients from 15 studies. Closure of the midline abdominal incision by continuous, rapidly absorbable suture resulted in a statistically higher rate of incisional hernias than did closure by either continuous, slowly absorbable suture ($P < .009$) or nonabsorbable suture ($P = .001$). Although closure by continuous, slowly absorbable suture versus nonabsorbable suture was not statistically different ($P = .75$), patients with nonabsorbable suture had more suture sinuses ($P = .02$). No significant differences were noted when comparing continuous and interrupted closure techniques, except that continuous closure is more expeditious; again, there was no difference in hernia formation. These data led to a conclusion that a continuous, slowly absorbable fascial closure may lead to the lowest incidence of incisional hernia.[17] The ratio of suture length to wound length appears to be 4:1.[18] This allows a 2-cm purchase of fascia on each side of the incision followed by a 1-cm advance.

As laparoscopic techniques have become popular in nearly all aspects of abdominal surgery, it appears intuitive that the incidence of ventral hernias should decrease. Laparoscopic trocar site hernias are not rare and occur at a rate between 0.6% and 2.8%.[19] It appears that fascial defects larger than 5 mm should be closed in adults. However, there is debate, but little evidence, that dilating, noncutting trocar sites up to 10 mm do not need to be closed with suture. It is true that any size incision, given infection, poor tissue healing, increased abdominal pressure, and other factors, can give rise to a hernia. Additionally, closing only the anterior fascia can result in the rare Richter hernia or preperitoneal hernia, which can be difficult to diagnose without repeat laparoscopy or laparotomy.[20]

SYMPTOMS

Ventral hernias are often noted by the patient as an abdominal bulge. They can be exacerbated by any action that raises intra-abdominal pressure, such as coughing, performing a Valsalva maneuver, lifting weights, or elevating the head or legs. Rest or reduction of the incarcerated hernia may offer temporary relief. Smaller hernias are often asymptomatic or produce intermittent complaints. Discomfort or a ventral bulge is the most common initial symptom, but bowel obstruction can also be the first symptom that forces a patient to seek medical attention. Incarceration and strangulation are more common if the hernia neck defect is small.

INDICATIONS FOR SURGERY

Abdominal wall hernias in adults do not spontaneously heal or close, and nearly all enlarge with time. In most patients, if they are an appropriate surgical candidate, the presence of a hernia is an indication for repair, which allows the potentially dangerous sequelae of incarceration, obstruction, or strangulation to be avoided. As stated, hernias tend to enlarge over time; thus, delay can make repairing them more difficult.

PREPARATION

A standard patient evaluation consisting of a thorough history and physical examination should be undertaken. Pulmonary and cardiac comorbid conditions, diabetes,

and other medical problems need to be identified and addressed. The physical examination may be straightforward in patients who have hernias with well-defined fascial borders; however, a computed tomography scan can also be helpful when the presence of a hernia is questionable, such as in an obese patient, if it is located in an unusual location, or if there have been several failed attempts at repair. A cleansing bowel preparation is not often required, but it should be considered for patients at greater risk of enterotomy; such patients might include those with multiple previous surgeries and patients with recurrent hernias and intra-abdominal mesh. Questions concerning the hernia should include any symptoms of incarceration, such as pain, nausea, vomiting, and constipation. As much information as possible about the original or previous operations should be obtained, including the type of surgery, any postoperative wound complications, and if the patient has a recurrent hernia, the previous hernia size and location and the type and location of any prosthetic mesh. Obese patients have a higher risk for recurrence and should be considered for weight loss techniques or counseling before or around the time of hernia repair. The majority, however, will not be able to lose weight.

At the time of surgery, most patients should receive a first-generation cephalosporin, which should be dose-adjusted according to patient weight and repeated if the operation lasts longer than 2 hours. Compression stockings or another form of deep venous thrombosis prophylaxis is warranted. Placement of a gastric or bladder catheter should be considered, depending on the operative location, length of surgery, and extent of intestinal manipulation.

PROSTHETICS

Prosthetic mesh products have radically changed the repair of ventral hernias. The ideal characteristics of a prosthetic were popularized by Cumberland[21] and Scales.[22] These properties include chemical inertness, resistance to mechanical stress, pliability, lack of physical modification by the body's tissues, capability of being sterilized, no carcinogenic potential, no or limited inflammatory or foreign body reaction, and hypoallergenic nature. To date, no prosthetic has been able to attain all these properties. Early metallic prosthetics included tantalum gauze and stainless steel mesh. Numerous difficulties arose from their use, including lack of flexibility, fatigue fractures with subsequent herniation through these fractures or migrating fragments resulting in fistulas, loss of structural integrity, and need for abdominal wall resection if these materials became infected. These meshes never gained wide acceptance. In 1958, Usher et al. reported on the newly developed polypropylene mesh Marlex (C. R. Bard, Cranston, NJ).[23] The introduction of Marlex was a major change in available prosthetics (Fig. 47–3). Apart from it now being knitted instead of woven, the mesh used today has largely remained unchanged over the past 45 years. Several brands of heavyweight polypropylene mesh such as this are available and have become the standard mesh used in the United States. The large pores (600 nm) allow for ingrowth of native fibroblasts, but it does evoke an inflammatory reaction that can cause scarring and limit incorporation into the surrounding fascia or other tissues. It is flexible, but various manufacturing techniques give it various forms of rigidity. Because of the potential intestinal adhesions, ingrowth, and scarring around this mesh, it is not for use in an intra-abdominal location unless omentum or other tissue can be interposed between the mesh and the bowel. When placed against the intestine, the development of enterocutaneous fistulas is well documented and may eventually occur in more than 2% of patients.[24,25]

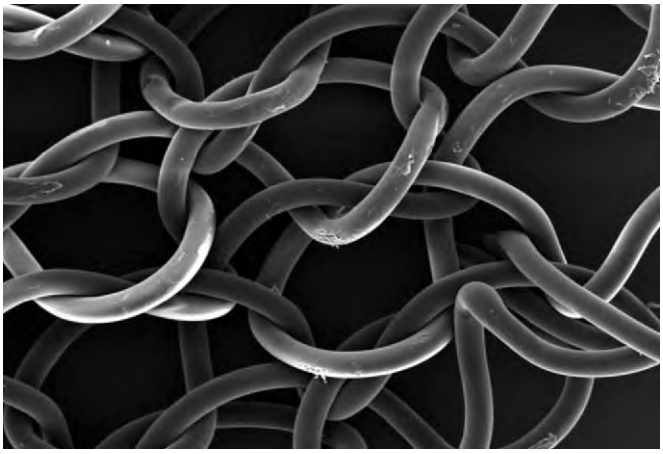


Figure 47–3. Scanning electron micrograph of Marlex mesh.

One concern regarding the long-term implantation of a heavy polypropylene mesh is the concept of decreased abdominal wall compliance. This prosthetic, though chemically inert, does generate an intense inflammatory reaction. The result is a rigid scar plate produced by pronounced perifilamentous fibrosis and deposition of collagen fibers.[26] Two observations are noted: the abdominal wall becomes stiff or exhibits decreased compliance, and the mesh prosthetic shrinks as much as 30% to 46%.[27,28] This decrease in compliance can lead to a sensation of stiffness and discomfort in many patients. Additionally, areas of the abdominal wall that have previous incisions but lack mesh coverage may experience an increase in herniation as the abdominal pressure is no longer distributed evenly. Ultrasound examination and three-dimensional stereography have been used to compare the effects of different concentrations of polypropylene mesh. As the amount of polypropylene decreases and the pore size increases, compliance of the abdominal wall appears to improve.[29] The curvature of the abdominal wall increased over time with the lighter weight meshes but not with the heavyweight polypropylene mesh.

The force required to burst the abdominal cavity is difficult to measure directly. In cadaveric models the maximum abdominal wall force has been calculated to be 16 N/cm.[30] When standard (heavyweight) polypropylene is tested, the bursting force is 40 to 100 N/cm.[31] In this same study, vertical distention of the abdominal wall

at the maximum of 16 N/cm is only 25% ± 7%. This measure of elasticity or compliance was severely reduced with the use of prosthetics; however, lightweight polypropylene biomaterials more closely resembled the natural distensibility of the abdominal wall at 21% to 31% relative distention.[32] This evidence suggests that the standard polypropylene mesh is "overengineered" and that a reduced-weight polypropylene material may offer several advantages without compromising the strength of the hernia repair. These findings have been confirmed in long-term animal studies.[27]

Lightweight polypropylene mesh products are now available. Reduced-mass polypropylene alone, however, can be so light and flexible that handling during surgery can be difficult. To correct this problem, the concept of adding an absorbable component to increase its initial stiffness has been adopted. Both Vicryl and Monocryl suture materials have been incorporated in this fashion. Vypro and Ultrapro (Ethicon, Somerville, NJ) are examples of this technology.

Polyester is a popular mesh choice in Europe, especially in France. This mesh is supple, has a grainy texture, and induces a rapid fibroblastic tissue response.[33] The supple handling properties of this mesh allow it to conform easily to curvatures in the abdominal wall. Infection rates with polyester mesh have been documented to be 12% or greater.[34] When placed in the intra-abdominal position, however, the fistula rate can exceed 15%.[24]

The first expanded polytetrafluoroethylene (ePTFE) hernia repair biomaterial was developed and introduced in 1983. This product now exists in several forms. There are perforated versions that are used for extraperitoneal and inguinal repairs and a solid version with two distinctly different sides that is intended for intra-abdominal use (DualMesh, W.L. Gore and Associates, Flagstaff, AZ) (Fig. 47–4). The mesh made for intra-abdominal use has a unique design; one side is smooth and microporous, resists tissue ingrowth, and as such, is ideal to face or touch the intestine. The opposite side is rough and has wide pores that allow intense tissue incorporation; this side is made for placement against the abdominal wall. This material conforms well to the abdominal wall and has minimal shrinkage and good long-term compliance. DualMesh Plus is the same ePTFE, but one side is impregnated with silver carbonate and chlorhexidine diacetate. These two agents act synergistically to inhibit bacterial colonization of the device for up to 10 days after implantation.[35]

Figure 47–4. Photograph of DualMesh.

Composite or combination mesh types have also increased in popularity. These products layer more than one type of material to form one mesh. By doing so, manufacturers attempt to take advantage of the different biomaterials. Most often, composite meshes are developed for intra-abdominal use, with a protective non–tissue ingrowth side facing the intestine and a tissue-incorporating mesh against the abdominal wall. One such product (Composix E/X, Bard, Cranston, NJ) layers polypropylene and ePTFE on top of one another. The ePTFE surface is positioned toward the abdominal contents and serves as a protective interface against the bowel. The polypropylene side faces the abdominal wall to be incorporated into the native peritoneum and fascial tissue. Other examples of these composite products add an absorbable "nonstick" layer to a standard polypropylene or polyester mesh. Such products include Proceed (Ethicon, Somerville, NJ) and Parietex Composite (Sofradim, Villfranche-sur-Saône, France), which apply a collagen-based material to inhibit intestinal adhesions. At present, no clinical data on the use of these products are available.

There have been several advances in tissue engineering that have introduced several new products into the market for hernia repair. The premise in all these products is a decellularization and protein stabilization process of human or porcine tissue to preserve the structural architecture of the tissue of origin but remove any cells that could precipitate a foreign body reaction. These products, essentially a collagen implant, allow remodeling by the host via native fibroblast migration with subsequent collagen deposition. In vitro studies demonstrate that fibroblasts grow rapidly through these meshes.[36] Surgisis Gold (Cook Biotech, West Lafayette, IN) is manufactured from porcine small intestinal submucosa, Permacol (Tissue Science Laboratories, Covington, GA) is porcine dermal collagen, and AlloDerm (LifeCell, Branchburg, NJ) is an acellular dermal matrix from cadaveric skin. FortaGen (Organogenesis, Canton, MA) is a highly purified type I collagen. All these products are considered biologic mesh prosthetics. They are extremely expensive, and long-term studies demonstrating the effectiveness of these products in hernia repair are currently not available. However, they appear to have advantages in abdominal closure involving complex or infected wounds. Early, short follow-up case series involving the use of these "tissue meshes" in contaminated wounds are encouraging.

PRINCIPLES OF SURGICAL HERNIA REPAIR

The Mayo repair, "vest over pants," was once thought to represent a major advance in the repair of incisional hernias. It involves overlapping layers of normal fascia and securing with a double row of mattress sutures (Fig. 47–5).[37] The operation is performed by incising the skin and dissecting the hernia sac free of surrounding tissue.

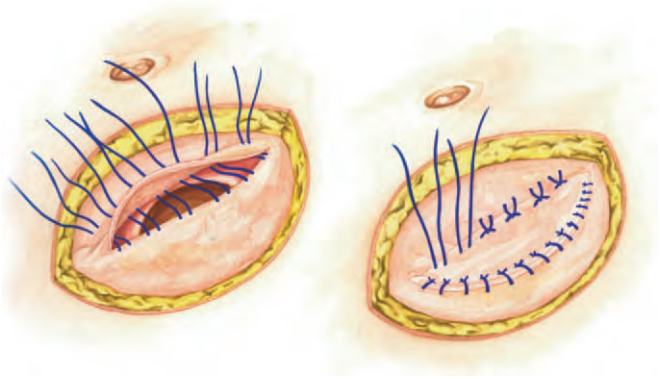


Figure 47–5. Mayo vest-over-pants technique.

The fascial edges are cleared of overlying tissue. Once free, the sac is opened carefully and the contents examined. Adhesions and scar to the sac are released if needed, and the hernia sac is resected. The classic description includes closing the peritoneum with absorbable suture. The fascia is then overlapped with a double row of nonabsorbable mattress sutures. Once completed, the skin is reapproximated. Relaxing incisions along the lateral rectus sheath reduce tension on the wound edges.[3] However, long-term studies have shown that this has not been an effective repair. Recurrence rates of up to 54% at 10 years have been reported and are similar to the rates of a standard, simple fascial reapproximation.[38] The inability to place strong fascia in apposition without tension in all hernias prevents this repair from attaining universal success. Other patient factors, as previously described, can significantly contribute to failure of hernia repair. Even relatively small defects repaired primarily had high recurrence rates in these series.

To determine the superior repair method, Luijendijk et al. performed a prospective randomized trial comparing suture repair with mesh repair for incisional hernias.[8] The 3-year cumulative rate of recurrence was 43% for suture repair and 24% for mesh repair ($P = .02$). One of the shortfalls in this study was that the mesh was essentially sewn to the edges of the fascia with little overlap, which possibly resulted in the higher than expected overall failure rate in the mesh group. A very important finding was discovered when smaller hernias were compared. When hernias less than 10 cm^2 were repaired with suture, their recurrence rate was greater than 40%; in contrast, the recurrence rate was only 6% when repaired with mesh. It is elementary that large hernias require mesh implantation for an adequate repair. However, it appears that the use of a prosthetic may be as important for small defects. The 10-year cumulative recurrence rate again confirms a 50% reduction in hernia recurrence if a prosthetic is used.[13]

The development of hernia prosthetics has led to a variety of techniques for placing the mesh. The onlay technique involves primary closure of the fascial defect and subsequent reinforcement by placing the mesh prosthetic on top of the fascial repair (Fig. 47–6A). Supporters of this technique promote the separation of

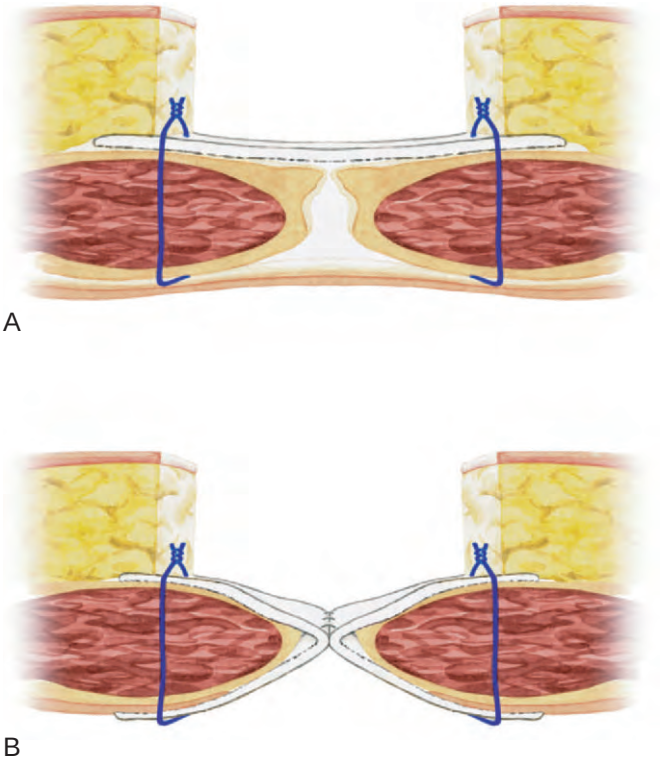
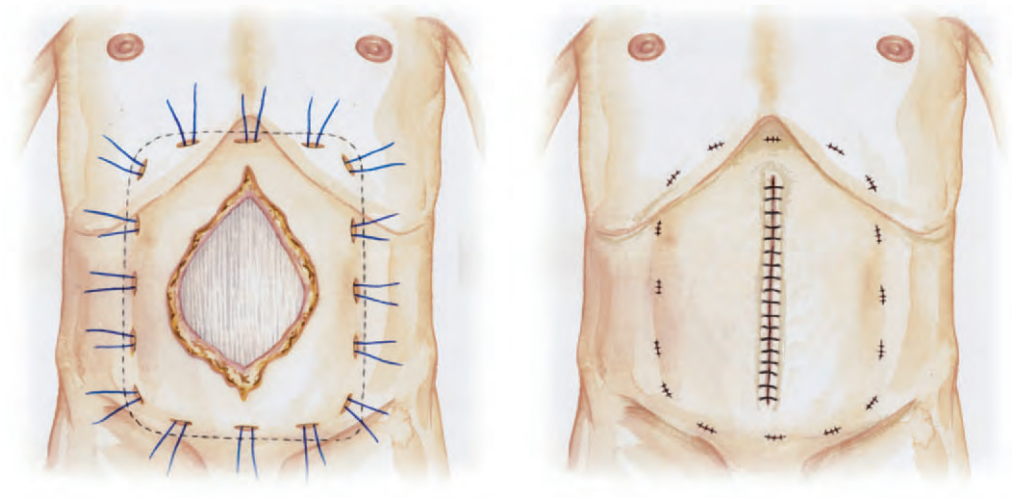


Figure 47–6. Mesh repair techniques. **A,** Onlay. **B,** Wrap-around.

the mesh from intra-abdominal contents as a major advantage in avoiding complications. The mesh is secured to the anterior rectus sheath with sutures or fascial staples. The onlay technique has several disadvantages. Significant subcutaneous dissection is needed to place the mesh, which can lead to devitalized tissue with seroma formation or infection. The superficial location of the mesh also puts it in danger of becoming infected if there is a superficial wound infection. The primary repair is often under tension, which can contribute to recurrence. Ideally, the transfascial sutures are placed before primary closure of the fascial defect to avoid the potential bowel injury that can occur if the sutures are placed blindly. Long-term studies are not available to accurately describe the recurrence rate with this technique, but retrospective review suggests a rate of 28%.[39]

Another variation of mesh placement is the wrap-around, or cuff, technique (see Fig. 47–6B). The mesh is wrapped around the anterior and posterior rectus sheath and secured with penetrating sutures. Unfortunately, these sutures can lead to underlying muscle necrosis and can be very painful if placed very tightly.[40] The prosthetic-reinforced edges of the fascia are then closed in the midline. Unfortunately, closure may not be possible without tension. In addition, the mesh on the underside of the abdominal wall is exposed to the intestines; if it is a macroporous mesh such as polypropylene or polyester, intestinal adhesion or possibly a fistula may result.

The French surgeons Rives and Stoppa revolutionized hernia repair by popularizing a retrorectus



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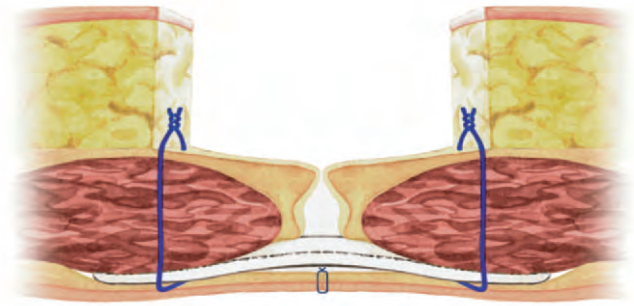


B

Figure 47–7. **A** and **B,** The Stoppa repair technique.

extraperitoneal repair with prosthetics.[34,41] This technique was additionally popularized in the United States by George Wantz.[33] The prosthetic is placed preperitoneally below the arcuate line or just superficial to the posterior rectus sheath above the umbilicus. The sutures ends are individually placed through the mesh and out through the abdominal wall with the knots buried in subcutaneous tissue.[33] In addition to a mesh repair the midline fascia is closed, which can restore the previously displaced abdominal muscle into a more anatomic and functional position (Fig. 47–7). Drains are placed above the prosthetic. This method has a documented recurrence rate of approximately 14%.[34] The advantages of a large mesh with significant overlap placed under the muscular abdominal wall can be explained by Pascal's principles of hydrostatics. The intra-abdominal cavity functions as a cylinder, and therefore the pressure is distributed uniformly to all aspects of the system. Consequently, the same forces that are attempting to push the mesh through hernia defects are also holding the mesh in place against the intact abdominal wall (Fig. 47–8). In this manner, the prosthetic is held firmly in place by intra-abdominal pressure. The mechanical strength of the prosthetic prevents protrusion of the peritoneal cavity through the hernia because the hernia sac is indistensible against the mesh. Over time, the prosthetic is incorporated into the fascia and unites the abdominal wall, now without an area of weakness. Lateral fixation sutures are again necessary to keep the mesh in position until fibrous ingrowth has occurred.

Laparoscopic Operative Method

The principles of retrorectus prosthetic reinforcement have been adapted for laparoscopic ventral hernia repair. Instead of applying the mesh in a preperitoneal position, an intraperitoneal onlay with wide coverage of the hernia defect is performed. The mesh is fixed in position with transfascial sutures and metallic staples or tacks. This wide overlap and combination fixation technique has been developed so that it mimics the open retrorectus or preperitoneal repair previously described. This technique also takes advantage of Pascal's principle of hydrostatics to provide a secure hernia repair.

Laparoscopic ventral hernia repair is usually performed with a 30- or 45-degree angled laparoscope. A minimal number of laparoscopic bowel graspers, dissectors, scissors, and blunt graspers are also necessary. Currently, 5-mm fixation devices (spiral tacks or anchors) are commonly used. A suture-passing device (W. L. Gore and Associates, Flagstaff, AZ) is used for full-thickness transabdominal wall sutures. This repair requires an intraperitoneal prosthetic to be in contact with the viscera. At this time, ePTFE is the best studied and most commonly used mesh for laparoscopic repair.

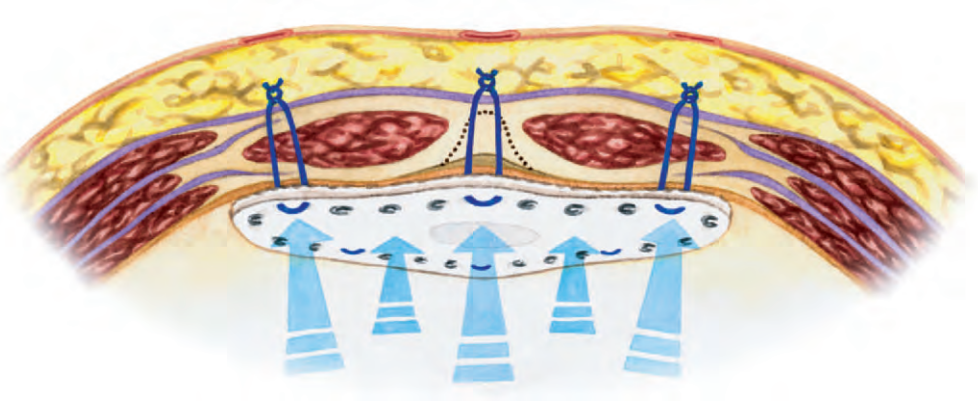


Figure 47–8. Intra-abdominal forces illustrating Pascal's principle of hydrostatics.

To establish pneumoperitoneum, an open abdominal access technique or Veress needle can be used safely. A window of access between the costal margin and the iliac crest on one side or the other is usually present, even in a multiply operated abdomen. After inserting the first trocar, the abdominal cavity is viewed, and under direct visualization, additional trocars are placed as far laterally as possible. Usually, three trocars are placed on the operative side for an in-line view and a two-handed technique for dissection, mesh deployment, and fixation. An additional trocar or two on the contralateral side is occasionally required.[42]

The most difficult and time-consuming portion of the procedure is adhesiolysis. Serious, albeit rare complications from this procedure are related to bowel injury; therefore, meticulous dissection technique must be used. Sharp dissection should be performed as much as possible to avoid thermal spread from electrothermal (cautery) and ultrasonic energy. The adhesions to the anterior abdominal wall surrounding the hernia and within the hernia sac are lysed, and the hernia contents are reduced. The peritoneal sac is left in situ.

To correctly size the mesh prosthesis, the hernia defect must be measured, which may be accomplished externally or internally. If the hernia margins are measured externally, the abdomen should be desufflated to more accurately delineate the actual size of the hernia; if not, a thick abdominal wall or large hernia can result in overestimation of the mesh needed to fix the hernia. Measuring the hernia internally is performed with a disposable plastic ruler that is brought through a trocar into the abdomen. The length and width of the hernia defect are determined inside the abdominal cavity. In this manner the size of the hernia can be very accurately measured. These measurements, whether obtained inside or outside the abdomen, are used to choose an appropriately sized prosthetic mesh that will overlap all margins of the defect by approximately 4 cm.

Four nonabsorbable, size 0 monofilament or ePTFE sutures (approximately 30 cm in length) are placed at the midpoint of each side (Fig. 47–9). Exit sites for the sutures are predetermined on the abdominal wall and marked 4 or more cm beyond the margin of the hernia. The mesh is rolled like a scroll from the superior and inferior ends and compressed and pulled or pushed into the peritoneal cavity through a 10-mm port site.[40]

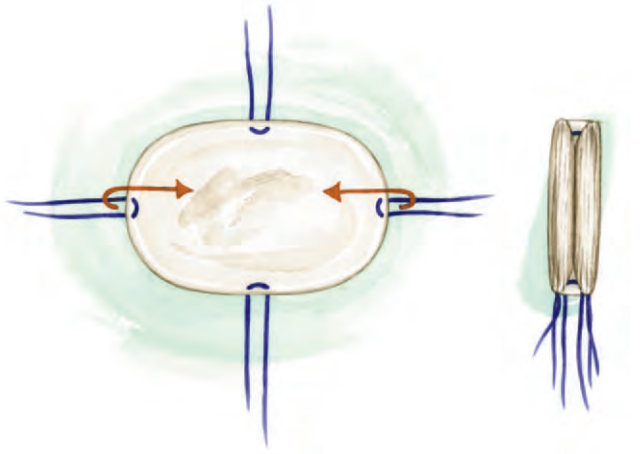


Figure 47–9. Orientation sutures for intra-abdominal mesh and rolling the mesh for insertion through the abdominal wall.

The mesh is unfurled within the abdomen. The sutures are individually pulled through the abdominal wall with a suture passer at the previously marked positions. The individual strands of each suture are brought out through separate fascial punctures but through the same skin incisions so that full-thickness abdominal wall "bites" are taken to fix the mesh in position (Fig. 47–10). The initial marked sites may need to be modified further radially to allow for taut placement of the mesh; it is important that the mesh be taut when the abdomen is insufflated. The sutures are individually tied with the knots left buried in subcutaneous tissue. The perimeter of the mesh is then secured with spiral tacks or staples placed 1 cm apart or so. The tacks are positioned close to the mesh edge to prevent infolding of the mesh and exposure of the rough, woven side to bowel (see Fig. 47–10). Additional full-thickness, nonabsorbable sutures are placed in the mesh every 4 to 7 cm circumferentially with the suture passer. The tacks ensure that bowel will not herniate between the sutures. They do add some security

Table 47–1 Comparison Studies of Laparoscopic and Open Ventral Hernia Repairs

Name	Year	No. of Patients		Morbidity (%)		Mesh Infection (%)		Infection (%)		Recurrence (%)	
		Lap	*Open*	*Lap*	*Open*	*Lap*	*Open*	*Lap*	*Open*	*Lap*	*Open*
McGreevy[48]	2003	65	71	8	21	3	0	0	10	—	—
Raftopoulos[49]	2003	50	22	28	45	2	0	2	5	2	18
Wright[50]	2002	90	90	17	34	1	1	1	9	1	6
Robbins[51]	2001	18	31	—	—	6	13	6	0	—	—
DeMaria[46]	2000	21	18	62	72	5	11	5	22	5	0
Carbajo[47]	1999	30	30	67	20	0	10	0	17	3	7
Ramshaw[52]	1999	79	174	19	26	1	3	8	1	3	21
Park[25]	1998	56	49	18	37	4	2	0	4	11	35
Holzman[53]	1997	21	16	24	31	0	6	5	0	10	13
Totals		430	501	23	30	2	4	3	6	4	16.5

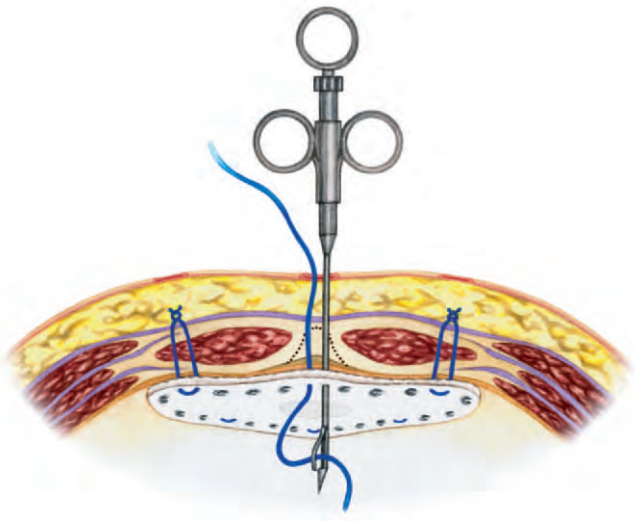


Figure 47–10. Full-thickness transfascial sutures placed with a suture passer device and tacks.

to the repair but do not provide enough strength to serve as the only points of fixation. Drains are not used.[43,44]

Minimally Invasive Versus Open Mesh Ventral Hernia Repair

The laparoscopic approach to ventral hernia repair has been the subject of numerous publications. The benefits of laparoscopy may include a reduction in postoperative pain, shorter length of stay, decreased morbidity and especially wound infections, and improvements in recurrence rates as compared with the open procedure.[42,45] Only two studies have been performed in a prospective, randomized fashion to compare laparoscopic and open ventral hernia repair. Carbajo et al. and DeMaria et al. published their trials in 1999 and 2000, respectively.[46,47] Carbajo et al. randomly assigned 60 patients to receive either laparoscopic ventral hernia repair or the open procedure. The two groups were matched for incisional hernia type, size of defect, age, and sex distribution. Postoperative hospital stay and operative time were significantly shorter in the laparoscopic ventral hernia repair group.[47] They also reported that the laparoscopic ventral hernia repair group had fewer complications and a reduced hernia recurrence rate (3% versus 6.7%) during their 27-month follow-up period.[47] DeMaria and associates similarly compared laparoscopic and open ventral hernia repair prospectively at a tertiary care, university setting. Thirty-nine consecutive patients were enrolled in their study. Ninety percent of the laparoscopic group was treated on an outpatient basis as compared with only 7% in the open group. The incidence of complications and the recurrence rate were not different between the two groups.[46] The laparoscopic repair was also statistically less expensive than the open repair. Retrospective studies appear to apply additional evidence to support the use of laparoscopic techniques to repair abdominal hernias.

Based on the data from the comparative studies (Table 47–1), postoperative complications are less frequent (23.2% versus 30.2%), wound and mesh infections are lower, and recurrence rates are reduced (4.0% versus 16.5%) in laparoscopic versus open repairs. Long-term follow-up data from the larger laparoscopic series continue to demonstrate potential advantages.[42,45] A randomized prospective trial with sufficient power is needed to truly answer the question of whether an open or laparoscopic repair is the safest and most durable.

Perioperative Considerations

Repair of smaller hernias may be performed on an outpatient basis, but larger repairs require inpatient stay. Feeding is advanced as tolerated and is frequently accom-

plished on the first postoperative day. In both open and laparoscopic surgery, early ambulation is encouraged and emphasized for resolution of atelectasis, reduction of venous stasis, bowel motility, and general recovery. The use of a first-generation cephalosporin perioperatively is recommended. Frequently, it is continued for the first 24 hours after surgery, but the effectiveness of this practice has not been verified. Routine deep venous thrombosis prophylaxis is started before surgery with sequential compression devices and continued in the postoperative period. Low-molecular-weight heparin can be used as an additional adjunct in patients with greater than average risk.

Extensive lysis of adhesions is commonly required during incisional ventral herniorrhaphy. Small bowel injuries during adhesiolysis can be catastrophic, especially if they are missed.[54] Nearly a fifth of open adhesiolysis operations may result in inadvertent enterotomy.[55] Enterotomy has been reported in an average of 1% of patients in all large series of laparoscopic ventral hernia repair.[42,45,56,57] Prompt recognition of a bowel injury is needed to avoid serious morbidity. Management of a recognized intraoperative enterotomy varies according to the type and extent of the injured intestine and the type of mesh available. Small lacerations in the small intestine or bladder without significant contamination may not be an absolute contraindication to mesh placement, either laparoscopically or by open means. In the event of fecal spillage, the bowel should be repaired and the adhesiolysis completed, and a delayed hernia repair is generally warranted if a prosthetic is required. The patient is usually placed on a regimen of antibiotics and returned to the operating room in 3 or 4 days for definitive repair if there are no signs of infection, or the procedure may be aborted all together. Primary repair of the hernia defect, with the anticipated higher recurrence rate, is another option. This may be a place for biologic or natural tissue, although the long-term durability of these repairs has not been established. Placement of standard mesh in the presence of significant contamination is contraindicated.

A patient-controlled analgesia device is often quite useful until the patient can be transitioned to oral analgesics. Postoperative pain when an open retrorectus or laparoscopic repair has been performed is frequently noted at sites of full-thickness transfascial sutures. Persistent suture site discomfort, lasting 2 to 4 weeks postoperatively, may be effectively treated by subfascial injection of a local anesthetic.[58] Its efficacy is perhaps due to the anesthetic's ability to block the affected nerve's afferent signal temporarily and allow the hypersensitivity to subside.[58] Few patients complain of this problem in the long term, and rates after laparoscopic repair vary from 2% to 4%. It appears that with the recent advent of minimal access techniques and heightened patient expectations, surgeons have paid greater attention to even minor incisional discomfort and ways to prevent and treat it.

Seromas develop in many patients undergoing ventral herniorrhaphy. Regardless of whether a laparoscopic or open approach is used, most hernia surgery results in a potential space that is filled with serous fluid in the postoperative period. Most often drains are recommended with open repairs. Nonetheless, seromas are common but rarely require any intervention. Seromas are ubiquitous in the early postoperative period after laparoscopic ventral herniorrhaphy. Expectant management is our preferred approach to all asymptomatic seromas. We reserve aspiration of fluid for patients with significant or persistent symptoms or if there is a question regarding infection. Long-term problems associated with seromas are rare.

Large abdominal incisions, wide tissue dissection with the creation of large flaps, and placement of a prosthetic (foreign body) result in a 12% to 18% rate of wound complications after open prosthetic repair.[24,34] The laparoscopic approach to incisional hernias has dramatically reduced wound-related morbidity. The consequences of any mesh infection are severe regardless of how the prosthetic was originally placed. Traditional surgical teaching has advocated removal of contaminated or exposed prosthetics, although the morbidity associated with resection is high. In addition, mesh removal almost always results in recurrence, an open wound, and a larger hernia that will require reoperation. Fortunately, mesh removal is not mandatory. Infected polypropylene, polyester, and ePTFE mesh is often capable of being salvaged with a combination of intravenous antibiotics, local wound débridement, vacuum-assisted closure, and subsequent soft tissue coverage of the granulated mesh.[59]

Special Considerations

Umbilical Hernia

Repair of an umbilical hernia as described by William Mayo's vertical fascial overlap technique was discussed previously.[37] This operation or simple fascial closure is still performed frequently today by many surgeons. These repairs are effective and may be the preferred technique for small umbilical hernias with no tension after fascial approximation, but larger hernias have been shown to have a recurrence rate of up to 28%.[60]

The introduction of mesh prosthetics has appropriately had an impact on umbilical hernia repair. These tension-free repairs, which have been popularized for other ventral hernias, may have a role in umbilical hernia repair. In 2001, Arroyo et al. published a randomized controlled trial comparing primary suture repair and mesh repair in 200 patients with umbilical hernias.[4] The two patient groups were comparable with regard to age, sex, hernia defect size, and American Society of Anesthesiologists class. Operative times and complications were not statistically different. The mean follow-up was 64 months. The major difference was the recurrence rate of 11% in the suture repair group versus 1% in the mesh repair group ($P = .0015$). Other studies using mesh implantation as a sublay or plug have also shown low recurrence rates.[61]

Laparoscopic techniques have recently been proposed for umbilical hernias as well. The technical aspects are essentially the same as applied to other ventral hernia defects. The laparoscopic approach took longer to

perform, tended to have fewer complications, and had no recurrences reported in a small retrospective group.[50] Criticism of the laparoscopic approach is the need for general anesthesia to establish pneumoperitoneum and the increased length of operating time. Conversely, placement of trocars around and not through the umbilicus has the potential to avoid the wound-related complications associated with an incision directly over the mesh.

There are many effective methods to repair umbilical hernias. Each patient must be evaluated individually, and one method of repair may not apply to all cases. Small primary umbilical defects in low-risk patients can probably be repaired with sutures alone and achieve good results. As the defect size increases, a mesh prosthetic should be considered. Whether the repair is better performed via an open or laparoscopic approach is controversial because prospective data are not available. Improvements in mesh prosthetics may continue to guide the ideal approach.

Spigelian Hernias

Adriaan van der Spiegel, a Belgian anatomist, was the first to describe the semilunar line as a concave region at the lateral border of the rectus muscle formed by the aponeurosis of the internal oblique. More than a hundred years later, in 1764, Klinkosh identified the "hernia of the Spigelian line" as a distinct entity.[62]

Although spigelian hernias are rare, accounting for 0.1% to 2% of all abdominal wall hernias, its diagnostic incidence has been rising because of improved imaging technology and incidental identification during laparoscopy. Spigelian hernias usually occur in the sixth and seventh decades and affect both sexes and sides equally. Most are acquired, and nearly 50% of patients with spigelian hernias have a history of previous laparotomy or laparoscopy.[63] Other factors that have been implicated in contributing to the development of these hernias are alterations in compliance of the abdominal wall as a result of morbid obesity, multiple pregnancies, prostatic enlargement, chronic pulmonary disease, and rapid weight loss in obese patients.[63]

A spigelian hernia is a challenge to diagnose and requires a high index of suspicion. Pain is the most common initial complaint. The fascial defect is masked by the intact overlying external oblique aponeurosis, thus complicating physical examination.[64] In addition, a palpable mass, when present, may mimic an abdominal wall lipoma or desmoid tumor. Although abdominal imaging may be helpful, the findings of unusual abdominal complaints in the proper anatomic location should alert one to the possibility of a spigelian hernia. Nevertheless, more than half of all spigelian hernias are diagnosed intraoperatively.[63]

Given the small neck of these hernias, 20% to 30% require emergency intervention.[63,64] Thus, even incidental spigelian hernias should be repaired electively to avoid incarceration. Surgical management of these hernias has typically been accomplished via a transverse incision and primary repair. Primary repairs have been associated with a low, but real recurrence rate of about 4%.[64] As expected, mesh repairs have been successfully applied to treat spigelian hernias. Few or no recurrences at long-term follow-up have been reported by several investigators.[62,64] More recently, laparoscopic repair of spigelian hernias has also been reported.[65,66] Evidence-based surgical recommendations are limited by the rarity of this condition, and a recommendation regarding suture- or mesh-based repair, either open or laparoscopic, is not clear at present for the treatment of spigelian hernias.

Components Separation

Large incisional hernias often occur in patients who have experienced traumatic injuries or intra-abdominal catastrophes and are at times left with an open abdomen. Damage control laparotomy and early recognition and treatment of abdominal compartment syndrome have improved survival, but at times patients are left with massive ventral hernias because the fascia is unable to be reapproximated. Subsequent skin closure alone or skin grafting directly to granulating abdominal viscera provides coverage. Over time, the musculature of the anterior abdominal wall, although anatomically present, retracts laterally and enlarges the hernia. The defects remaining after excision of the skin grafts are most often not amenable to primary closure, and prosthetic closure may be difficult as well. In addition, these cases have a high incidence of fistula formation and infection, which complicates the placement of prosthetics.

Native tissue transfer is a possibility for closure of these wounds. A vascularized and innervated muscle flap is ideal for maintaining support of the abdominal wall. Free flap tissue transfer has been used for this repair, but it may include the morbidity of a separate donor site in addition to potential vascular flow issues that can lead to flap necrosis. The flap is also denervated, and this leads to muscular atrophy and laxity in the new site, which are not ideal properties for abdominal hernia repair. Tissue expanders under the external oblique can be useful; however, they call for an additional surgical procedure, and the device requires a prolonged expansion phase and is associated with an inherent risk of infection, expander extrusion, and failure.[67] "Components separation techniques" have been developed to provide a tension-free and, most often, prosthetic-free repair of the abdominal wall.

The ideal timing of this procedure depends on the patient. The appropriate time is when complete healing of the abdomen has occurred and the overlying skin or graft is freely movable from the underlying viscera, which typically requires 6 to 12 months. Another benefit of delayed repair is to permit the most intense part of the inflammatory response to resolve and allow "softening" of the ubiquitous intra-abdominal adhesions. Aggressive nutritional support to achieve preinjury status is also essential.

The first goal in this technique is to acquire access to the abdominal cavity and lyse the necessary adhesions. Adhesions to the anterior abdominal wall skin or grafts should be cleared laterally to the anterior axillary line. Interloop adhesions need not be divided; however, any omentum that can be freed can be used later to protect

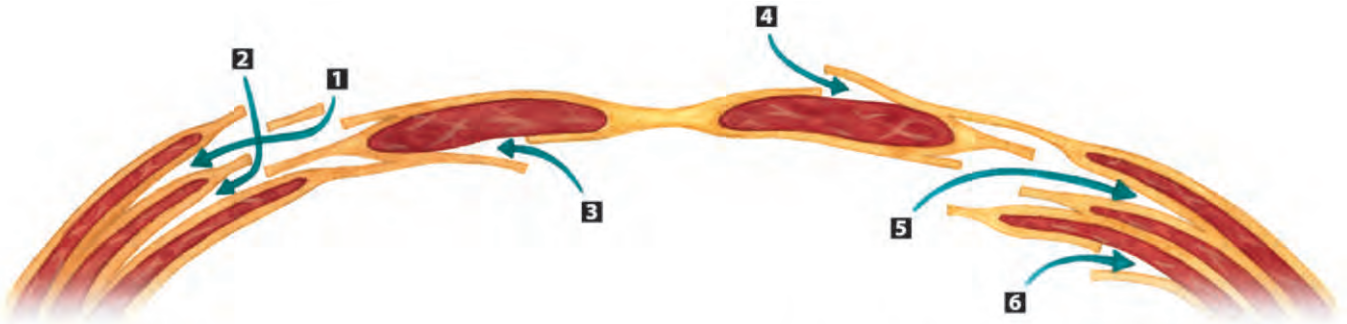
the bowel from a prosthetic if one is required.[68] If an abdominal skin graft is present, it is excised. This initial phase of the operation can be lengthy, depending on the density of the adhesions.

Once the adhesiolysis is complete, mobilization of the muscle or fascial flaps (or both) is started. The subcutaneous tissue is mobilized free of the superficial fascia and the dissection carried laterally to the anterior axillary line if needed. This in and of itself releases the muscular fascia somewhat and may provide enough additional length to close the fascial defect without tension. The dissection is typically stopped at the point when the fascia is approximated tension-free. If this first maneuver does not add sufficient medial mobilization to the fascia, component separation is performed. In the technique described by Ramirez et al., the external oblique fascia is incised lateral to the semilunar line from the costal margin to the pubis.[67] The plane between the external oblique muscle and the internal oblique fascia can be developed laterally to the anterior axillary line. The blood supply to the external oblique muscle enters between the posterior and anterior axillary line, so dissection medial to this point does not endanger the neurovascular bundle. After this maneuver has been completed, the posterior rectus fascia is incised just lateral to the linea alba. The muscle can then be freed from the posterior fascia while taking care to preserve the blood supply, which enters posteriorly near the central portion of the muscle. These techniques applied to both sides of the abdominal wall can yield up to 20 cm of combined medial mobilization of the fascia. Many other modifications of this procedure have been proposed, with similar results (Fig. 47–11).

An important aspect to be emphasized again is the necessity for a tension-free repair. If this cannot be achieved, a prosthetic material can be inserted. Peak inspiratory pressure can also be monitored during fascial closure to limit the pressure to less than 40 cm H_2O.[68] Because this procedure results in significant areas of dissection, a closed suction drain is placed to limit seroma formation. Hernia recurrence after this operation has been reported to be as high as 32%.[67,69] Wound complication rates also range from 5.7% to 33%.[69,70] The components separation technique offers ventral hernia repair to patients who have complicated courses and in whom prosthetics are often contraindicated. Although the presence of infection and fistula add morbidity to this patient population, many patients can undergo successful hernia repair.

Suprapubic Hernias

The abdominal oblique aponeurosis, rectus abdominis musculature, and rectus sheath insert on the symphysis pubis. Suprapubic hernias result from disruption of these musculotendinous elements of the lower abdominal wall and usually occur after blunt abdominal trauma or pelvic surgery. The origin of traumatic suprapubic hernias is often through a ruptured rectus muscle at or near its insertion to the pubic bone. In contrast, incisional suprapubic hernias develop as a result of apical pubic osteotomy or iatrogenic detachment of the rectus muscle from its pubic insertion to improve visualization during pelvic surgery. Inadequate tissue purchase inferiorly during closure may result in hernia formation, although infection and other patient factors may also play a role.



Technique	Author (Year)	Steps Involved
Components Separation Release	Ramirez (1990)	1 3
External Oblique Release	Shestak (2000)	1
External & Internal Oblique Release	Levine (2001)	1 2
"Sliding Door" Release	Kuzbari (1998)	1 3 4
External Oblique/Transversus Abdominis Release	Thomas (1993)	1 6
External Oblique/Anterior Rectus Release	Lucas (1998)	1 4
Anterior Rectus Fascia Release	Yeh (1996)	4
"Lateral" Release	Mathes (2000)	5
Modified Components Separation Release	Fabian (1994)	1 2 3

Figure 47–11. Components separation techniques.

Radical prostatectomy is the most common operative procedure that leads to the development of a suprapubic defect. Similar defects are also seen after operations involving the uterus, urinary bladder, and sigmoid colon.[71]

Suprapubic hernias may be manifested as vague lower abdominal discomfort, urinary symptoms such as frequency, or a palpable mass. The diagnosis of a suprapubic hernia may be missed because of the similarity of features with more common inguinal hernias. However, a thorough physical examination will demonstrate close proximity of the mass or defect, or both, to the pubis and not the external inguinal ring. Although suprapubic hernias may be a source of significant abdominal pain, bowel incarceration requiring emergency repair is extremely rare.

Primary repair of traumatic suprapubic hernias may be a viable alternative if the herniorrhaphy is undertaken without delay. With time, the rectus muscle retracts, which can lead to significant tension if primary repair is performed. Thus, a mesh repair is preferred for most traumatic and incisional suprapubic hernia repairs. Several approaches to mesh placement for suprapubic hernias have been described. An onlay repair involves placement of the mesh anterior to the defect and subsequent fixation to Cooper's ligament, the arcuate ligament, and the anterior abdominal wall fascia. Although this technique may require limited or no intra-abdominal dissection, it may impair visualization of the inferior aspect of the defect and lead to a high rate of hernia recurrence. On the other hand, the preperitoneal approach provides excellent delineation of the bladder and pubis and thus fixation of the inferior aspect of the mesh. The laparoscopic approach to suprapubic herniorrhaphy also allows for a definitive repair. This approach does require mobilization of the bladder, much like a transabdominal, preperitoneal inguinal hernia repair. In our series of 36 patients who underwent laparoscopic repair of a suprapubic hernia, the recurrence rate was 5.5% at nearly 2 years of follow-up; no major perioperative complications were documented, and there was one conversion to open surgery.[72] The dissection can be complex, whether open or laparoscopic, because of the close proximity of these hernias to bony, vascular, and nerve structures and the bladder (Fig. 47–12).

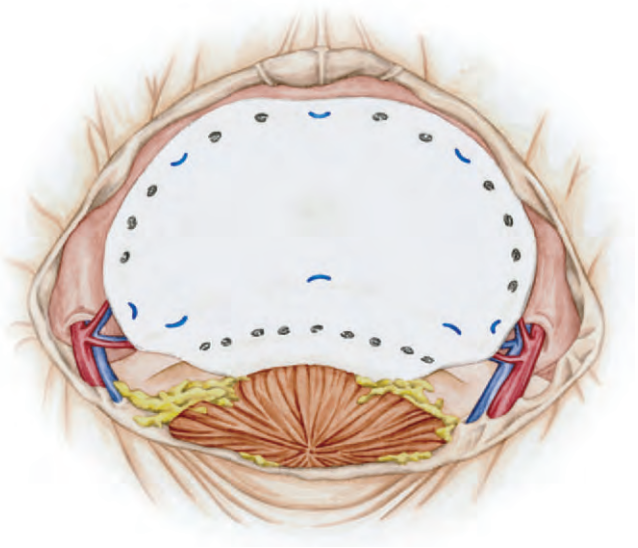


Figure 47–12. Suprapubic repair technique.

Ventral Hernia and Obesity

Obesity has long been considered a risk factor for the development of both primary and incisional ventral hernias. Medical comorbidity, increased intra-abdominal pressure, and technically difficult fascial closure are all likely contributors to the development of postoperative incisional hernias in overweight patients. The incidence of wound infections, perhaps the most important risk factor for the development of an incisional hernia, is also higher in the obese.[24,51,73-76] Sugerman et al. reported obesity to be the greatest risk factor for hernia recurrence.[6] Indeed, open ventral hernia repair in the obese has been marked by a recurrence rate of up to 50%.[15]

Weight loss may reduce the risk of hernia recurrence in obese patients. As a result, several alternative approaches combining ventral herniorrhaphy with bariatric or plastic surgery procedures have been proposed. Although several investigators reported low rates of hernia recurrence, the evidence remains inconclusive. At present, larger series with longer follow-up are still necessary to establish the long-term durability of herniorrhaphy combined with bariatric procedures and abdominoplasty.

The use of a laparoscopic approach to ventral hernia repair in obese patients has been shown to possibly reduce perioperative complications and improve failure rates. In a series of 167 obese and morbidly obese patients who underwent a laparoscopic ventral hernia repair, we found a 12.3% rate of perioperative morbidity and a low 5.5% recurrence rate at long-term follow-up.[77] These results were confirmed in a larger, multi-institutional trial.[42] In this study, obese patients had a significantly higher rate of recurrence than did patients of normal weight, but they also had larger and more frequently recurrent hernias. The results indicate the safety of the laparoscopic approach in the obese patients with complex hernias. A success rate of up to 94.5% may suggest improved outcomes with the minimally invasive technique when compared with historical open controls.[42]

CONCLUSION

Ventral hernia repair continues to evolve as new technologies and new techniques are developed. The past decade illustrates this point with the introduction of new prosthetics and new open and laparoscopic repair methods. The search for the ideal repair technique with low long-term recurrence rates is ongoing. Until ventral hernias can be prevented, surgical repair of

hernias will remain an important issue for the general surgeon.

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Chapter

48

Lumbar and Pelvic Hernias

Nir Wasserberg · Howard S. Kaufman

Lumbar and pelvic floor hernias, including obturator and sciatic hernias, present difficulties in diagnosis and treatment because of the deep position of the sac and the surrounding layers of muscle, fascia, and bone. Lumbar hernias have been described in children as well as adults and originate in an area of weakness in the parietal wall of the torso, namely, the superior triangle of Grynfeltt-Lesshaft and the inferior triangle of Petit. Obturator hernias are uncommon and occur most frequently in thin elderly women. In contrast, other pelvic floor hernias, such as those associated with advanced pelvic floor relaxation, occur more commonly in multiparous women. Obesity is a risk factor for hernias associated with pelvic relaxation. These hernias may be accompanied by entrapment of the rectum and symptoms of obstructed defecation, pelvic bulging, heaviness, pain, or any combination of these symptoms. Though more common, they may also produce diagnostic and therapeutic challenges.

Advances in both static and dynamic imaging techniques with computed tomography (CT), magnetic resonance imaging (MRI), and fluoroscopic pelvic floor imaging with cystocolpoproctography (with or without enteral or peritoneal contrast) have enhanced the clinician's ability to diagnose both lumbar and pelvic hernias. Moreover, laparoscopy has become a useful diagnostic tool, and many hernias may be approached and repaired via minimally invasive techniques. Overall, the low incidence of lumbar and pelvic hernias limits the opportunity to study different techniques of repair prospectively, and individual surgeon experience in their treatment is usually limited.

In the last edition of this text, DeMeester and Magnuson performed a comprehensive rewrite of this chapter.[1] Many of the historical and anatomic sections have not changed, and therefore we are grateful to them for their permission to reuse many of these sections. However, many advances in imaging, laparoscopic surgery, and graft materials have occurred in the past 5 years, and these areas will be highlighted.

As a general rule, the principle of tension-free repair should apply for most lumbar and pelvic floor hernias. However, discrete levator ani hernias may not be amenable to such an approach. A variety of synthetic and biologic materials are frequently used for hernia repairs, and a basic understanding of the biomechanical properties of synthetic and biologic grafts will aid the surgeon in choosing the best prosthesis for a given indication. Synthetic materials can be divided into absorbable and nonabsorbable, flat, single component, and combination. Types of mesh differ in pore size, weave variation, thickness, pliability, and weight. All are available in various sizes and can be cut and fashioned for a specific use. Biologic materials range from autologous tissues such as *tensor fascia lata* and allografts to xenografts. AlloDerm (LifeCell Corporation, Branchburg, NJ) is an acellular human dermal graft used for repair of a variety of soft tissue defects. Commonly used collagen/elastin xenograft materials include porcine submucosa (Surgisis, Cook Biotech Incorporated, West Lafayette, IN) and a variety of porcine dermal grafts (Pelvicol and PelviSoft, C.R. Bard, Inc, Covington, GA). Although most elective hernia repairs are clean cases, patients may have intestinal obstruction or compromised bowel and require concomitant intestinal resection. Though still debated, an increasing body of evidence supports the reasonably safe use of prosthetic materials in clean-contaminated and even contaminated cases.[2,3]

HISTORICAL BACKGROUND

The first description of a lumbar hernia is attributed to Barbette in 1672. Garangeot described the first incarcerated lumbar hernia, which was found at autopsy, and Ravanton was the first to perform surgical reduction of a lumbar hernia. Petit delineated the anatomic boundaries of the inferior lumbar triangle in 1783. Initially, all lumbar hernias were believed to arise from Petit's triangle. However, in 1866 Grynfeltt and Lesshaft independently described the anatomic landmarks of the superior lumbar triangle; therefore, a hernia at this region became known as a Grynfeltt-Lesshaft hernia.[4] The superior triangle was also described by Geiss and Saletta in

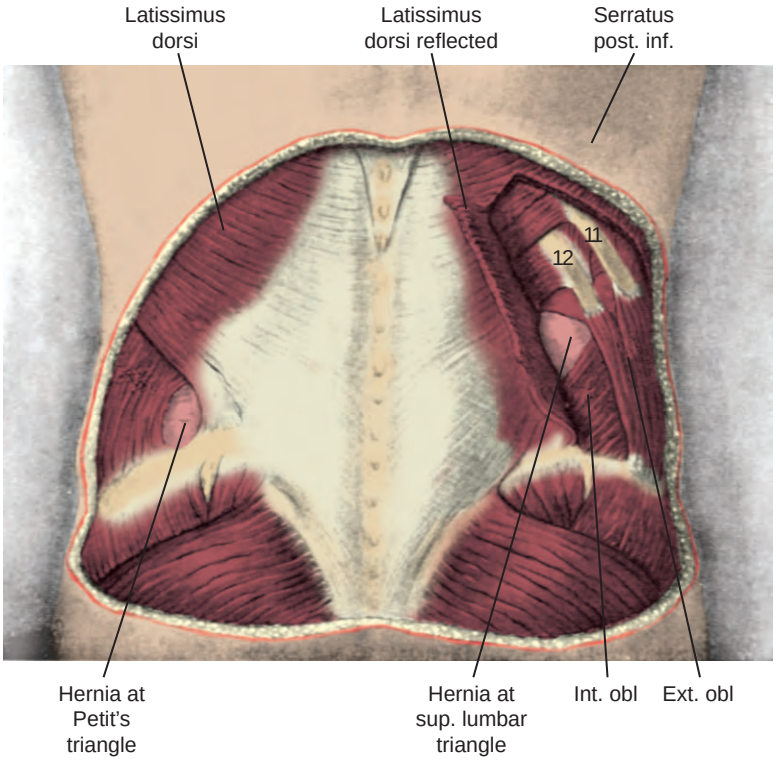


Figure 48–1. The anatomy of lumbar hernias, posterior view. On the *left* is Petit's triangle; on the *right* is the superior lumbar triangle of Grynfeltt-Lesshaft. (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

1869, who referred to a defect in this area as a hernia. Despite this long history of anatomic descriptions, only 300 cases have been reported in the literature.

Obturator and perineal hernias were originally described by the French physicians Rene Jacques Croissant de Garengeot and Roland Arnaud de Ronsil in the 1700s.[5] For this reason, an obturator hernia was for some time referred to as "the French hernia." Watson, in his classic text on hernias, claimed a sciatic hernia to be the rarest of all hernias, with only 35 documented reports in the literature though 1948.[6] He credited the original description of a sciatic hernia to both Verdier (1753) and Papen (1750).

LUMBAR HERNIAS

Anatomic Considerations of the Lumbar Region

The borders of the lumbar region are defined by the 12th rib superiorly, the crest of the iliac bone inferiorly, the erector spinae muscles medially, and the external oblique muscle laterally (Fig. 48–1). Although many areas of weakness may occur within the lumbar region, the two most commonly described areas are the superior lumbar triangle of Grynfeltt-Lesshaft and the inferior lumbar triangle of Petit. The superior lumbar triangle of Grynfeltt-Lesshaft is an inverted triangle bounded by the free border of the internal oblique muscles laterally, the erector spinae muscle group medially, and the inferior margin of the 12th rib superiorly. This triangle is larger and more constant in shape than the inferior triangle. The roof of this triangle is formed by the latissimus dorsi muscle, and the floor is formed by the transversalis fascia along with the aponeurosis of the transversus abdominis muscle. Collectively, these boundaries make up what is known as the lumbocostal abdominal space. The weakest aspect of this space is at its upper portion immediately below the 12th rib, where the 12th intercostal neurovascular bundle exists.

The inferior lumbar triangle described by Petit is upright in configuration and less constant in size and shape than the superior triangle is. Its base is formed by the crest of the iliac bone. The medial border is formed by the lateral border of the latissimus dorsi muscle, and the lateral border is the posterior free margin of the external oblique. The floor of the inferior triangle is formed by the lumbodorsal fascia, which is contiguous with the aponeurosis of the internal oblique and transversus abdominis muscles. Occasionally, the iliohypogastric or the ilioinguinal nerves pierce the lumbodorsal fascia and cause an additional weak area within the floor. In cadaveric studies, the inferior triangle ranges in size from nonexistent to up to 6 cm in width at the base and up to 8 cm in height.[7] Lesshaft, also studying cadavers, found the inferior triangle to be present in 77% of adults and 25% of children.[8]

Clinical Features and Diagnosis

Most lumbar hernias develop gradually, and there are no pathognomonic symptoms or signs. The patient often complains of a dragging sensation that disappears when supine. Occasionally, palpation of the hernia can result

in referred pain along the distribution of the sciatic nerve and to the testes or thigh. With time, the hernia defect grows and becomes more symptomatic, as well as cosmetically noticeable and displeasing to the patient. The most common manifestation is a unilateral bulge in the flank region discovered by the patient, which may be visible to the examiner only with the patient standing. Because the roof of the superior triangle prevents the protrusion of a discrete hernia mass, a more subtle bulge in the latissimus dorsi muscle bed may be palpable and tender. Pain may also be referred to the anterior aspect of the abdomen if viscera become entrapped in the hernia defect. On standing, the bulge may become more tense and large, and coughing produces an impulse over the hernia. The hernia may recede entirely if the patient is placed in the supine position. In children, a lumbar hernia gives rise to a large, soft mass that increases in size as the child cries. The hernia is usually reducible by palpation. On percussion, the hernia may be tympanitic.

Incarceration and strangulation of lumbar hernias are not common because of the large size of the hernia defect and the broad neck of the sac. In a review of 186 cases of lumbar hernia, Watson noted that strangulation was present in only 8% of all hernias.[6] Alternatively, strangulation occurred in 18% of cases of spontaneously acquired lumbar hernias. Goodman and Speese noted a 24% incidence of incarceration within a spontaneous lumbar hernia.[7] The most common cause of strangulation in this series was either the occurrence of volvulus within the sac or constriction at the neck of the sac.

The differential diagnosis of a flank bulge, with or without pain, includes lipoma; soft tissue tumor, including fibroma, rhabdomyoma, and sarcoma; hematoma; abscess; renal tumors; muscular hernia; pannicular lumbosacroiliac hernia (herniation of fascia but no true sac); and panniculitis. Indeed, most masses within the lumbar region do not prove to be a lumbar hernia.

The diagnosis of a lumbar hernia is easily made by CT of the abdomen and associated lumbar region (Fig. 48–2). The use of oral contrast may aid in the diagnosis. Barium enema, nuclear medicine testing (with tracer accumulating within the herniated bowel), and ultrasonography have also been used to diagnose a posterior abdominal wall hernia. MRI may assist in determining the cause of referred sciatic nerve pain or unexplained back pain in patients with a lumbar hernia.

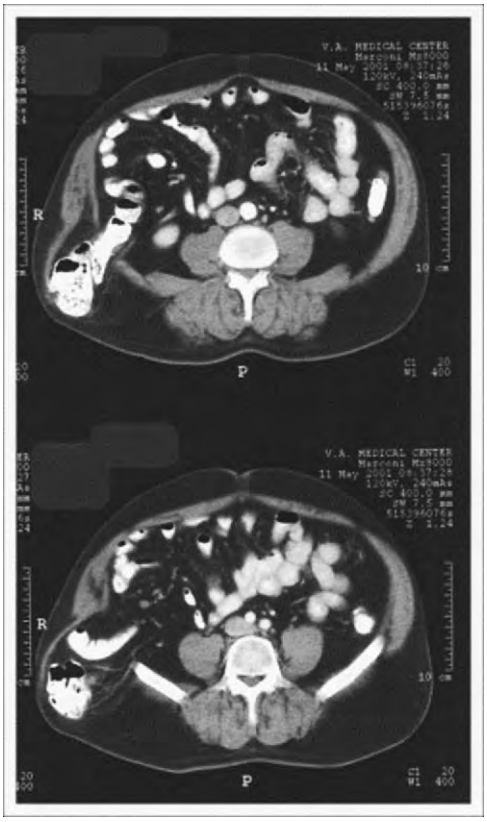


Figure 48–2. Intravenous and oral contrast-enhanced computed tomographic images of a right inferior lumbar hernia after iliac bone harvest. (From Patten LC, Awad SS, Berger DH, Fagan SP: A novel technique for the repair of lumbar hernias after iliac crest bone harvest. Am J Surg 188:85, 2004.)

Classification

Lumbar hernias have been classified according to their contents, cause, and site of protrusion. In general, the most accepted classification system, as proposed by Swartz,[9] is based on cause of the defect. In this classification system, all lumbar hernias that occur in infants and children with obvious musculoskeletal defects in the lumbar region are defined as *congenital* lumbar hernias, and all lumbar hernias not defined as congenital are termed *acquired*. With these simple criteria, about 20% of lumbar hernias are congenital and 80% are acquired. Acquired defects are further subdivided into *primary* and *secondary* hernias. Primary acquired lumbar hernias occur spontaneously and represent about 55% of reported cases. Factors contributing to the development of a spontaneously acquired lumbar hernia include older age, excessive weight loss, and pulmonary disease. Primary hernias are found mostly on the left side, more often on the upper triangle, and two thirds of them have been documented in men. In contrast, secondary hernias are usually associated with trauma, infection, or previous surgical intervention in this region. Approximately 25% of all lumbar hernias are considered secondary. Iliac crest bone harvesting has been associated with a 5% to 9% postoperative incidence of lumbar hernia formation.[10] Blunt trauma to the torso is another cause; however, only 66 cases have been reported in the English literature.[11] Most of these (70%) occurred in the inferior lumbar triangle. When the hernia defect encompasses both the superior and inferior triangle, it is termed a *diffuse* lumbar hernia. Common operative interventions in the lumbar region resulting in a postoperative hernia defect include iliac

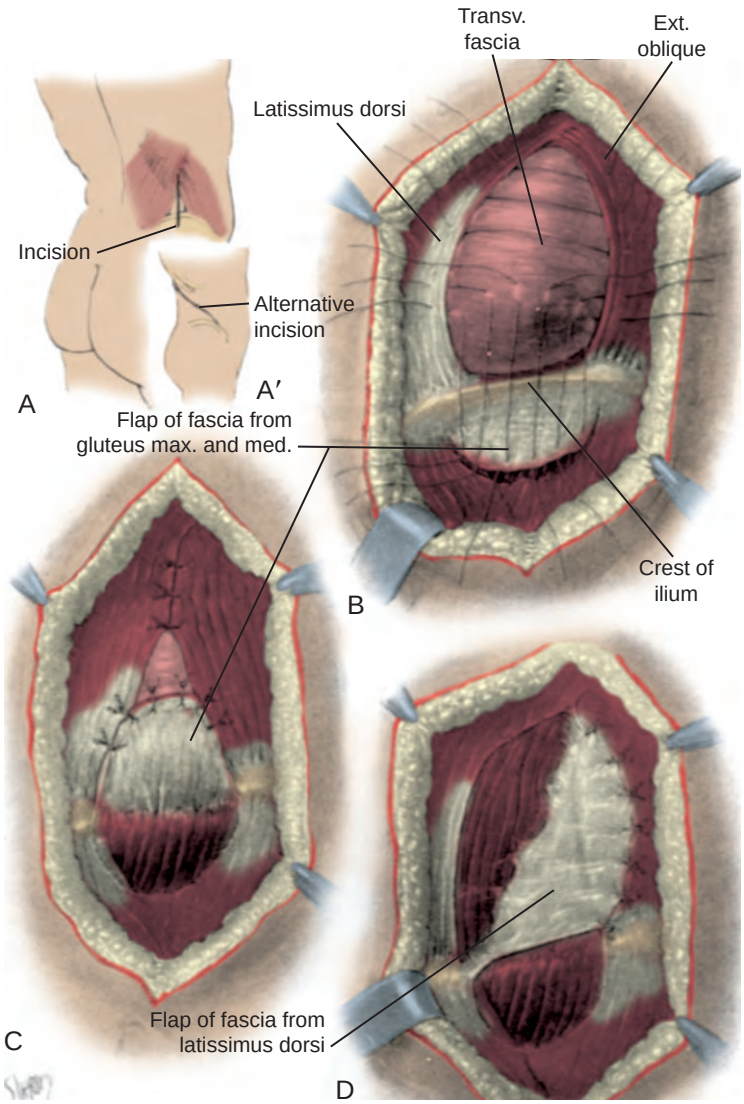


Figure 48–3. Dowd's operation for lumbar hernia. **A,** Line of incision. **B,** Turning up a flap of the fascia lata and aponeurosis of the gluteus maximus and medius muscles and suturing it to the lumbar fascia and external oblique and latissimus dorsi muscles. **C,** The flap sutured. **D,** Closing the remaining gap with a flap of fascia from the latissimus dorsi. (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

crest bone harvest, open nephrectomy, adrenalectomy, and renal biopsy.

Treatment

The prognosis of lumbar hernias is generally good, with or without surgery. However, as they enlarge, they become more difficult to repair. It is therefore recommended that all lumbar hernias be repaired early. The exception is newborns with a lumbar hernia, in whom repair should be delayed until the child reaches at least 6 months of age so that anatomic landmarks are easier to identify. Any suggestion of strangulation, including erythema and increasing pain, should lead to consideration of emergency operative intervention.

The preoperative preparation of a patient undergoing repair of a lumbar hernia defect should include an imaging study to demonstrate the position of the urogenital and gastrointestinal tracts in relation to the hernia defect. Contrast-enhanced CT or MRI should provide this information. If bowel contents are found within the hernia and the hernia defect is large, preoperative mechanical bowel preparation should be performed. Obese patients may be counseled to lose weight before undergoing repair.

A variety of surgical approaches and techniques for repair have been described. The patient should be placed in the lateral position, which provides the best access to all structures necessary for repair. The upper part of the leg is extended over the flexed lower part of the leg, the operating room table is flexed, and the kidney rest is elevated. Adequate padding and stabilization are essential in this position. These maneuvers increase the distance from the 12th rib to the iliac crest and therefore increase exposure. The operation is divided into two steps: exploration and repair.

Exploration and reconstruction are best accomplished through an oblique incision beginning posteriorly at the 12th rib and directed anteriorly toward the iliac crest (Fig. 48–3). During exploration, the hernia mass is carefully separated from the surrounding fatty tissue. If mesocolon is inadvertently mistaken for preperitoneum, injury to the colonic blood supply could result.

Small or moderately sized hernias in the superior or inferior triangles can be repaired securely by approximation of the transversalis fascia to the fascia of the transversus abdominis muscle. Repair of a defect in the superior lumbar triangle should include approximation of the transversalis fascia to the lumbocostal ligament and the periosteum along the undersurface of the 12th rib. In moderate-sized to large hernias, additional support is necessary for adequate repair. In 1907, Dowd popularized the use of a generous aponeurotic flap from the gluteus maximus muscle.[12] Ravdin subsequently popularized the use of free fascia lata grafts for the repair of large traumatic superior lumbar triangle hernias.[13] Given the availability of synthetic and biologic grafts, most of these techniques of autologous tissue transfer have been abandoned. Common to most of these procedures is an extraperitoneal approach with fixation of the prosthesis beyond the borders of the aponeurotic defect. When a pelvic iliac bony defect exists, the closure must be modified. The iliopsoas muscle has been used as a pedicle graft to replace lost soft tissue mass. However, more recently, corkscrew bone anchors have been used successfully to anchor mesh to the remnant of the iliac crest after harvest of bone grafts.[10] If extensive mobilization of flaps has occurred, a closed suction drainage system should be used.

Burick and Parascandola were the first to describe a laparoscopic approach for the repair of a traumatic lumbar hernia in 1996.[14] Arca and colleagues reported seven cases of laparoscopic lumbar hernia repair with mesh.[15] Complications included only one failed repair secondary to infection of the mesh. More recently, Moreno-Egea et al. published a nonrandomized prospective study of 16 patients who underwent laparoscopic ($n = 9$) versus open ($n = 7$) repair of secondary lumbar hernias.[16] Patients chosen for the laparoscopic approach had smaller hernias, but they also had a lower mean operating time, postoperative morbidity, length of stay, analgesic use, and time to return to normal activities. Hernias recurred in three patients in the open group, whereas there were no recurrences in the laparoscopic group between 1 and 4 years after surgery.

OBTURATOR HERNIA

An obturator hernia is an uncommon entity that represents less than 0.1% of all hernias. Because of the unyielding structures of the obturator foramen, these hernias have a high incidence of strangulation and may cause up to 0.4% of cases of small intestinal obstruction. Though initially reported by Le Maire in 1718, it was Pierre Roland Arnaud de Ronsil who published the first case report in 1724. The first successful repair has been attributed to Obre in 1851.[17] Through 2005, approximately 700 cases of obturator hernia have been described in the literature. The hernia results from the protrusion of a sac (often containing small intestine) through the obturator foramen and canal along the pathway of the obturator nerve and vessels. The classic example is a thin, frail, multiparous elderly woman with small bowel obstruction of unclear etiology.

Anatomy

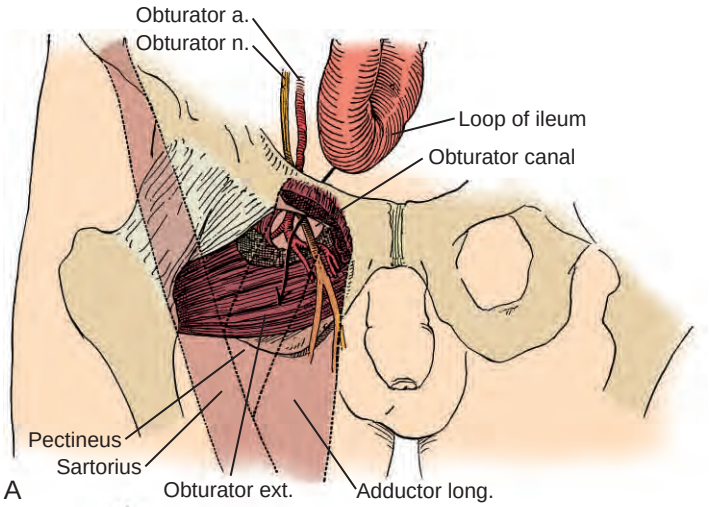
The obturator foramen is located within the anterolateral aspect of the pelvis. This is the largest foramen in the body, and it is usually larger in the female pelvis. The foramen is almost completely closed off by the obturator membrane, a fibrous covering that is an extension of the periosteum of the bony pelvis and tendinous attachments of the internal and external obturator muscles. Embryologically, the foramen and its membrane are an area of potential bone formation that has not been completed. The obturator canal is a 2- to 3-cm-long tunnel that begins in the pelvis, exits through the obturator foramen, and passes obliquely downward to end in the obturator region of the thigh (Figs. 48–4 and 48–5). The canal is bounded superiorly and laterally by the pubic bone and inferiorly by the obturator membrane and internal and external obturator muscles.

The obturator nerve, artery, and vein enter the canal through an opening in the anterosuperior aspect of the obturator membrane and pass through the canal, thereby creating a pathway for the protrusion of a hernia sac. The obturator nerve lies superior to the obturator artery within the canal and divides immediately on exiting the canal into anterior and posterior branches. The anterior branch of the obturator nerve emerges between the adductor longus and adductor brevis muscles and supplies sensory innervation to the medial aspect of the thigh, hip joint, and knee joint and motor innervation to the adductor longus, adductor brevis, gracilis, and pectineus muscles. The posterior division emerges between the adductor brevis and adductor magnus muscles to supply motor innervation to the obturator externus, adductor magnus, and occasionally the adductor brevis muscles.

Anatomically, there are three potential hernia pathways. The first and most common route is protrusion of the sac and contents through the external orifice of the obturator canal, accompanied by the anterior division of the obturator nerve. The sac lies in front of the obturator externus and underneath the pectineus. In the second type, the hernia emerges between the middle and superior fasciculi of the obturator externus along with the posterior division of the nerve. In this type the sac is posterior to the adductor brevis. In the third and most rare type, the sac emerges between the internal and external obturator muscles and membranes. Recognition of the three variants is important when repair is attempted through the thigh, but it has no bearing on emergency cases when the hernia is approached through the abdomen.

Clinical Features and Diagnosis

An obturator hernia is called "the skinny old lady hernia" because thin, elderly, multiparous and debilitated women are at greatest risk for the development of an obturator hernia. The female-to-male ratio for an obturator hernia is 6:1, and the female preponderance in this condition is thought to be secondary to the larger and more oblique incline of the obturator canal in the female pelvis. Though generally unilateral, bilateral obturator



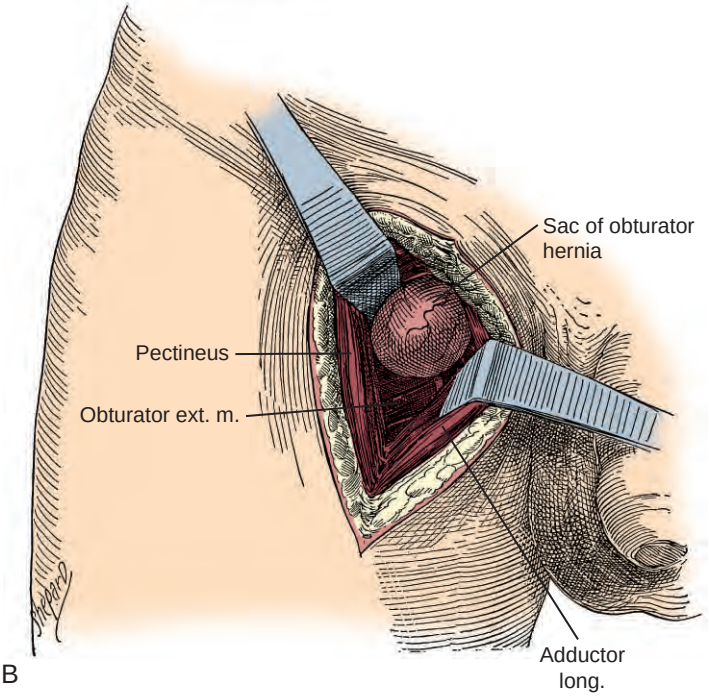


Figure 48–4. Anatomy of an obturator hernia. **A,** The structures passing through the obturator canal, in order of their superposition behind the hernial sac, are the obturator nerve, artery, and vein. **B,** Hernia in the obturator canal, the most common type of obturator hernia. The sac lies on the obturator externus muscle and is covered by the pectineus. The obturator nerve is seen directly behind the sac. (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

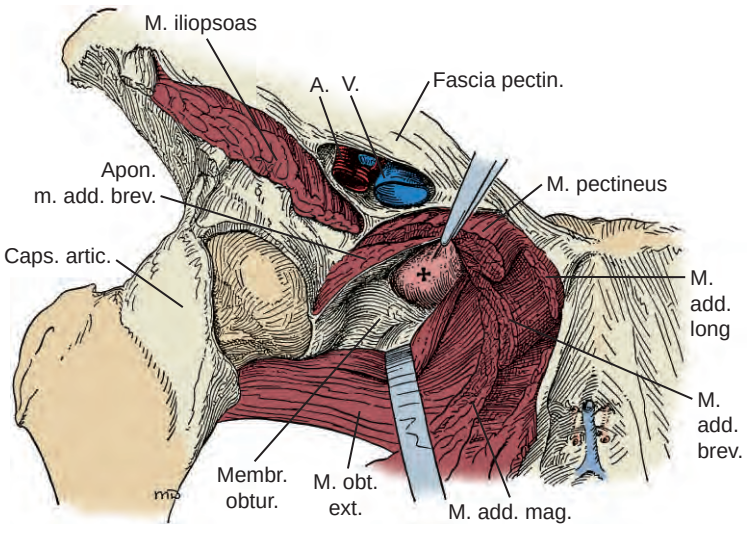


Figure 48–5. Obturator region: dissection carried to the level of the obturator membrane and obturator canal. The hernia sac can be seen protruding (marked by a *plus sign*). (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

hernias have been described in 6% of cases. Obturator hernias occur more frequently on the right side, which is thought to be due to the physical presence of the sigmoid colon overlying the obturator foramen in the left side of the pelvis. Predisposing factors include constipation, chronic obstructive pulmonary disease, multiparity, and ascites, all of which lead to increased intra-abdominal pressure and defects in collagen metabolism. Rapid weight loss with a decrease in fatty tissue surrounding the obturator foramen also predisposes to obturator hernia formation.

Formation of an obturator hernia consists of three stages: a prehernia stage, which involves preperitoneal fat, or "pilot tags"; a second stage, with formation of a true sac; and a third stage in which the hernia becomes clinically significant.[18] Diagnosis during the first two stages is uncommon. However, in the third or symptomatic stage, intestinal obstruction results from involvement of the jejunum or ileum within the hernia sac. Up to 90% of cases are initially seen because of obstruction, either intermittent or acute and complete.[19] Approximately 50% of patients have an incomplete obstruction secondary to a Richter-type hernia.

Three clinical signs are specific to incarceration of an obturator hernia. Obturator neuralgia is manifested as cramping or as hypoesthesia or hyperesthesia extending from the inguinal crease to the anteromedial aspect of the thigh. The *Howship-Romberg* sign is characterized by pain radiating down the medial aspect of the thigh to the knee and less often to the hip. The pain is a result of compression of the obturator nerve (anterior division) by the hernia sac within the canal and is relieved by flexion and external rotation of the thigh and exacerbated by extension, adduction, and medial rotation of the leg. The Howship-Romberg sign is considered pathognomonic for an incarcerated obturator hernia and is present in 25% to 50% of patients. The *Hannington-Kiff* sign is absence of the obturator reflex in the thigh, which is caused by compression on the obturator nerve. This reflex can usually be elicited by placing an extended index finger across the adductor muscle approximately 5 cm above the knee and percussing over the finger. Muscle contraction should be seen or felt with an intact reflex. If the patellar reflex of the ipsilateral side is present in the absence of an obturator reflex, it is highly likely that the obturator nerve is compressed. Occasionally, a mass may be palpated in the groin region. The optimal position for palpation of a mass is with the patient supine and the thigh flexed, abducted, and externally rotated. Transrectal or transvaginal palpation of the obturator canal may demonstrate a tender mass, which is indicative of possible strangulation.

A variety of modalities can assist in diagnosing an obturator hernia, including ultrasonography, CT, MRI, herniography, and laparoscopy.[19-23] Both CT and ultrasound (transvaginal or inner thigh views) (Fig. 48–6) have been shown to be useful in the diagnosis of obturator hernia in patients coming to the emergency room with bowel obstruction and predisposing risk factors. Kammori and colleagues recently reported improved diagnosis, treatment, morbidity, and mortality in the era of CT scanning for the diagnosis and treatment of

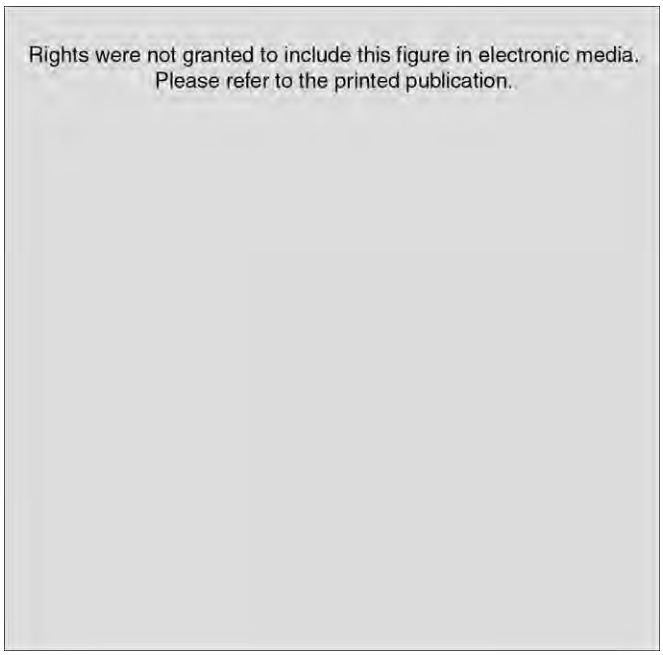


Figure 48–6. Pelvic computed tomographic scan showing bowel *(arrow)* protruding outside the right obturator foramen. (From Kim JJ, Jung H, Oh SJ, et al: Laparoscopic transabdominal preperitoneal hernioplasty of bilateral obturator hernia. Surg Laparosc Endosc Percutan Tech 15:106, 2005.)

obturator hernias.[24] MRI has been shown to be as good as but not superior to CT.[25] An abdominal radiograph obtained for the evaluation of a patient with suspected intestinal obstruction may show air in the obturator region (Fig. 48–7). Herniography, or the instillation of contrast material by infraumbilical injection into the peritoneal cavity, can be useful in the diagnosis of groin pain in adults with an inconclusive examination.[26] This method has no place in emergency diagnosis and is of questionable utility in the era of axial imaging. Laparoscopy may be used as a diagnostic tool, as well as a treatment modality.

Treatment

In more than half of suspected cases, an obturator hernia is found intraoperatively when the surgeon is performing a diagnostic laparoscopy or laparotomy. In patients with a preoperative diagnosis of obturator hernia, a variety of approaches for repair have been suggested, including abdominal, retropubic, obturator, inguinal, and laparoscopic. Historically, the preferred approach has been through a midline lower abdominal incision. With the patient in the Trendelenburg position, both obturator canals can easily be inspected, the diagnosis made quickly, and bowel resection performed if necessary. In the abdominal approach, both obturator foramina should be inspected and palpated to exclude bilateral herniation. If a dimple is found in the peritoneum of the obturator region and there is no defect palpable under

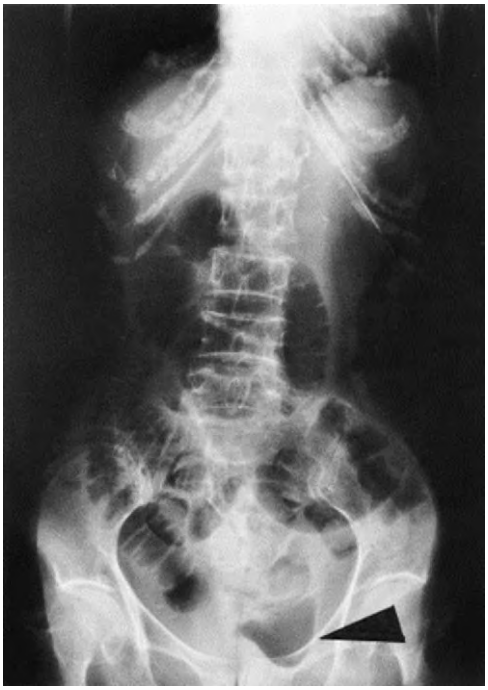


Figure 48–7. Abdominal radiograph in a patient with small bowel obstruction caused by an incarcerated obturator hernia. There is a gas shadow in the obturator foramen *(arrow).* (From Nishina M, Fujii C, Ogino R, et al: Preoperative diagnosis of obturator hernia by computed tomography in six patients. J Emerg Med 20:277, 2001.)

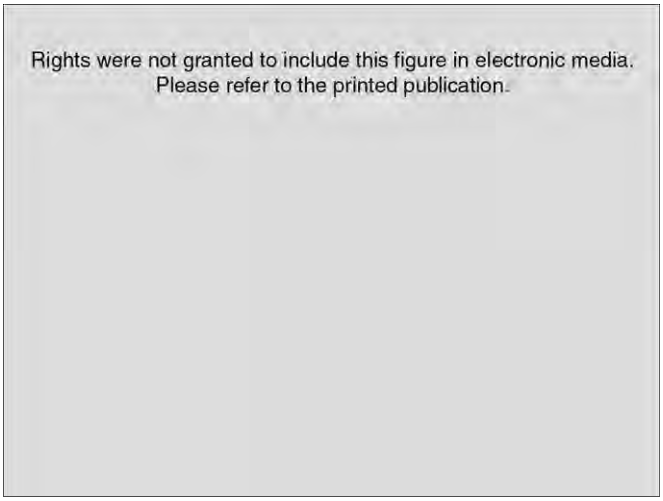


Figure 48–8. Laparoscopic view of a left obturator hernia with the sac reduced into the abdominopelvic cavity. (From Kim JJ, Jung H, Oh SJ, et al: Laparoscopic transabdominal preperitoneal hernioplasty of bilateral obturator hernia. Surg Laparosc Endosc Percutan Tech 15:106, 2005.)

the ischiopubic area, a decision must be made regarding whether to dissect the obturator region for possible herniation of preperitoneal fat. When incarcerated or strangulated bowel is present, the obturator ring can be gently stretched with the surgeon's fingers or incised inferiorly. Care should be taken with the obturator vessels, which although variable, usually lie lateral to the hernia sac.

Bowel reduction must be done carefully because necrotic bowel may rupture. Bowel resection is indicated in nearly half of all cases. The sac may contain omentum, uterus and adnexal organs, bladder, and appendix. Traditionally, simple opposition plus direct repair of a small defect has a low recurrence rate. The repair can be further reinforced with an autogenous fascial flap or by patching an adjacent structure with round ligament or uterus. Optimal repair generally involves the use of prosthetic mesh, or Teflon, with a final covering provided by closure of the peritoneum. Stoppa and Warlaumont[27] have championed the use of large prosthetic sheets of mesh for bilateral and recurrent inguinal hernias; such mesh may also be used to treat obturator hernias as well. Both totally extraperitoneal (TEP) and transabdominal preperitoneal polypropylene (TAPP) laparoscopic approaches were reported to be feasible and highly effective in the treatment of obturator hernia.[28] During laparoscopy, the sac may be easily identified (Fig. 48–8) and the defect repaired with a synthetic or biologic mesh. In the presence of frank peritonitis, the contralateral side must be routinely explored for an asymptomatic hernia that may cause problems in the future.

The retropubic, obturator, and inguinal approaches avoid the peritoneal cavity. These alternative approaches may be appropriate in a nonemergency setting when there is no evidence of strangulation and a palpable mass is felt in the obturator region. When an obturator or inguinal approach is used, a mass is palpable in the obturator region, and an incision is made just above this mass. The first structure encountered is fascia lata. On division of fascia lata, two muscles, the adductor longus and pectineus, are exposed. Drawing back these muscles allows visualization of the hernia sac (see Fig. 48–5). To strengthen the repair, the pectineus muscle is usually sutured to the periosteum of the ischium.

PERINEAL HERNIA

Classification of Perineal Hernias

The pelvic floor is a sling of muscles and connective tissue that connect the pubic and ischial bones to the greater sacrosciatic ligaments and the tip of the coccyx posteriorly and to the ischial tuberosities laterally. These tissues converge centrally on the perineal body and support the sphincter mechanisms, which allows for continence of urine and stool, and the paravaginal tissues, which allows for parturition. A perineal hernia is the protrusion of intra-abdominal or pelvic viscera or fat through a defect in the pelvic floor musculature and fascia.

Perineal or levator hernias are classified as either primary or secondary. A primary perineal hernia results from a congenital or acquired defect between the muscles and fascia that form the pelvic floor. Acquired

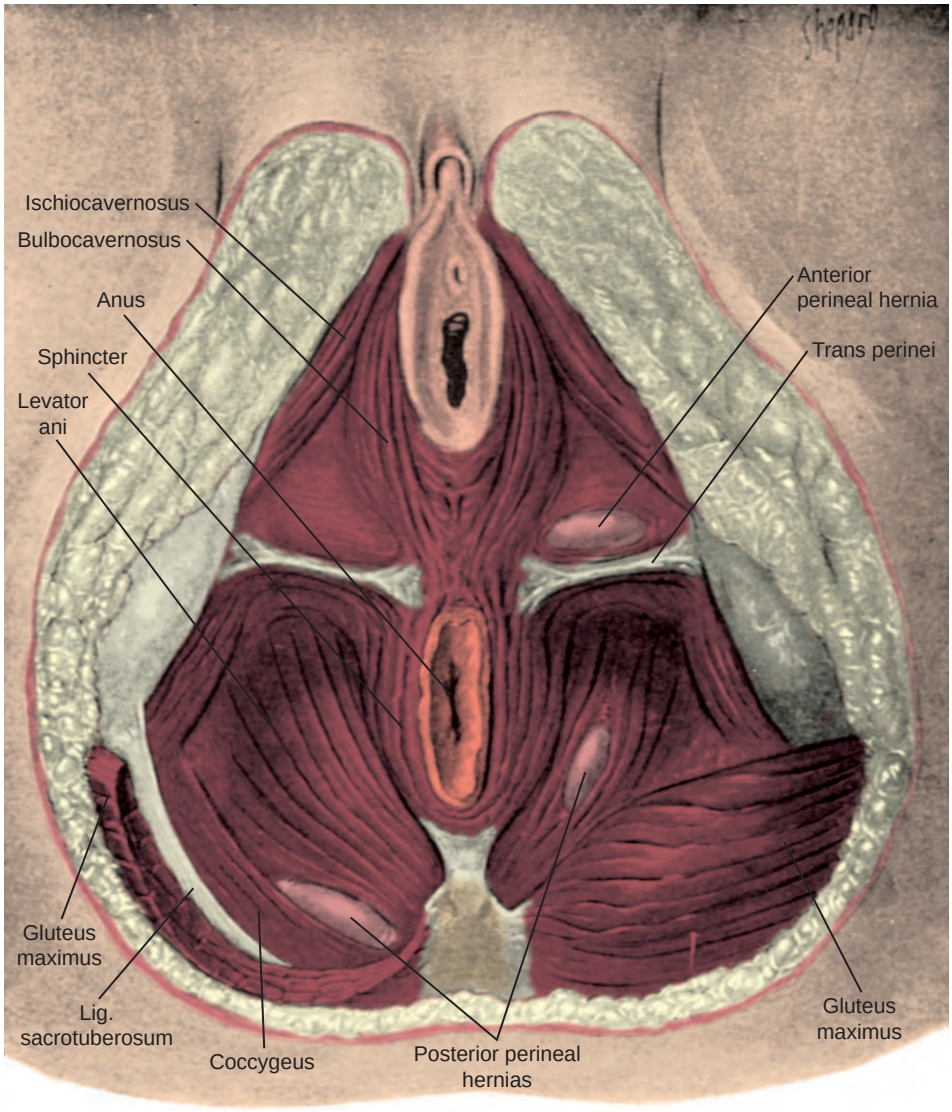


Figure 48–9. Anatomy of a perineal hernia in a woman with the points of exit of perineal hernias shown. (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

defects are much more common and often result from vaginal childbirth, aging, obesity, and chronic constipation with straining. Secondary perineal hernias are true incisional hernias that occur as a result of extensive perineal procedures, including abdominoperineal resection of the rectum, pelvic exenteration, parasacral–trans-sphincteric rectal resection, vaginal hysterectomy, and perineal prostatectomy.[29,30] Hernias of the perineum are further divided into two types, anterior and posterior. This classification is based on the position of the hernia in relation to the superficial perineal muscles (Fig. 48–9). In an anterior perineal hernia, the defect passes through the urogenital diaphragm and is bounded by the bulbocavernosus muscles medially, the ischiocavernosus muscles laterally, and the superficial perineal muscles posteriorly.

If the hernia is associated with a labial mass arising between the ischiopubic bone and the vagina, it is called a *pudendal* hernia (Fig. 48–10). Anterior perineal hernias are not believed to occur in men. Posterior perineal hernias protrude through the levator ani muscles or between the levator ani and coccygeus muscles in a plane posterior to the superficial transverse perineal muscles. A congenital anatomic defect that may lead to the development of a posterior perineal hernia is known as the *hiatus of Schwalbe,* which is a result of failure of the levator ani muscle to anchor to the obturator fascia. At times, a central perineal hernia may exist. Central defects are usually associated with detachment of the perineal body from the distal rectovaginal fascia or more extensive disruption of the perineal body. Fat, rectum, sigmoid colon, or small intestine may fill this distally dissecting hernia sac. Clinically, patients with a central perineal defect have symptoms associated with the syndrome of the descending perineum, including bothersome bulging accompanied by fecal or urinary incontinence or obstruction.

Perineal hernias may be associated with pelvic organ prolapse, a primary defect acquired as a consequence of relaxation of the supporting structures of the pelvic floor. Risk factors include multiparity, older age, obesity, connective tissue disease, and previous pelvic surgery. It is

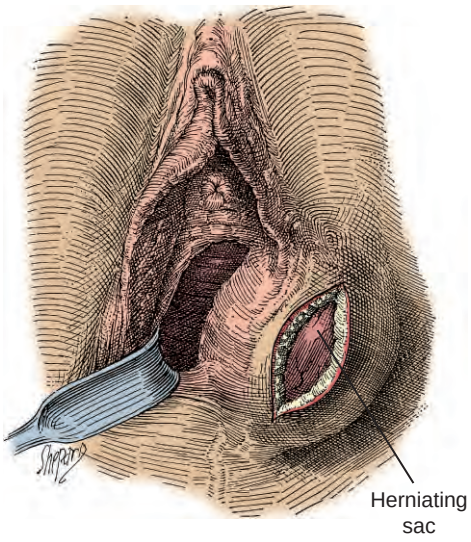


Figure 48–10. Anterior perineal hernia. When the hernia descends only into the posterior portion of the labium majus, it is known as a pudendal or vaginolabial hernia. (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

estimated that 50% of parous women have some degree of pelvic organ prolapse. Population-based data from the Kaiser group in Oregon suggest that a woman's lifetime risk of requiring surgery for prolapse or incontinence approaches 11% by the age of 80, with a reoperation rate of nearly 30% after primary repair.[31] This condition may involve any of the pelvic or abdominal viscera, including the small bowel (enterocele), vagina, urethra, bladder (cystocele), and anorectum (rectocele and rectal prolapse).

Although the topic of distal rectocele will be discussed, a complete discussion of all types of rectocele repair, as well as hernias that include the bladder, vagina, uterus, and cervix, is beyond the scope of this chapter. Rectal prolapse is discussed elsewhere.

Anatomy

The pelvic support anatomy is complex and includes a network of muscles and fascia (Fig. 48–11). Because most disorders of pelvic support occur in women, specific reference will be made to the female pelvic anatomy, although the muscles are similar in men. Grossly, the front of the pelvis is bounded by the internal surface of the pubic symphysis, whereas the sides are formed by the obturator internus muscles. The sacrum occupies a central position of the posterior pelvis, with the piriformis muscles bounding the posterior pelvis more laterally. The levator ani muscles form a sling within these boundaries. These muscles contain both slow- and fast-twitch fibers and are innervated by sacral efferents from S2-S4 on the pelvic side and by branches of the pudendal nerves on the perineal side. The slow-twitch fibers maintain resting tone of the pelvic floor, whereas the fast-twitch fibers contract during increases in intra-abdominal pressure.[32,33]

The levator ani muscle complex is composed of three muscle groups, the iliococcygeus, pubococcygeus, and puborectalis. A condensation of the parietal fascia overlying the obturator internus serves as the lateral origin of the iliococcygeus, which then inserts into the lateral aspect of the coccyx. The pubococcygeus arises from the superior ramus of the pubic bone and inserts onto the coccyx and anococcygeal raphe. The pubococcygeus muscle surrounds the lower third of the vagina. Most centrally, the puborectalis muscle arises from the superior and inferior pubic rami and forms a sling around the rectum. This muscle draws the anorectal junction anteriorly when contracted, thereby helping maintain fecal continence. When relaxed, the puborectalis allows for the formation of a more obtuse anorectal angle to facilitate defecation. A condensation of the parietal fascia of the levator ani complex, the arcus tendineus fasciae pelvis, stretches from the pubic arch to the ischial spine on each side. This important "white line" forms the basis for the lateral attachments of the pubocervical fascia and rectovaginal fascia.

The most distal and superficial supporting structure of the pelvic floor is the centrally located perineal body, which is located between the posterior aspect of the vaginal introitus and the anus. The perineal body is flat underneath the skin and extends in a pyramidal shape up into the distal portion of the rectovaginal septum, to which it attaches. The perineal body (and therefore pelvic floor support) is further stabilized through its connections via the rectovaginal fascia to the uterosacral ligaments and the sacrum. Other structures that condense and attach to the perineal body include the bulbocavernosus muscles, the superficial transverse perineal muscles, the distal central portion of the levator ani complex, and the external anal sphincter muscle complex.

Clinical Features and Diagnosis

Primary hernias occur most commonly in women older than 40 years. The female preponderance of perineal hernias is again related to the broader female pelvis and weakening of pelvic floor muscles during pregnancy and childbirth. Moreover, the growing epidemic of obesity is also associated with symptoms related to constant pressure on the muscles involved in pelvic floor support. A primary perineal hernia initially comes to medical attention because of the physical presence of a bulge or because of associated bowel or genitourinary dysfunction. Symptoms commonly associated with perineal hernias include obvious bulging, pain, heaviness, urinary or fecal incontinence, obstructed urination or defecation, constipation, and sexual dysfunction. Obstructed defecation may result from anterior or lateral rectocele formation with entrapment of the rectum through the levator defect (Fig. 48–12).

Patients should be examined both in the left lateral decubitus position and in the lithotomy position. The pelvic floor should be systematically palpated with the patient at rest and then with the patient attempting to expel the examiner's finger. This maneuver allows for the

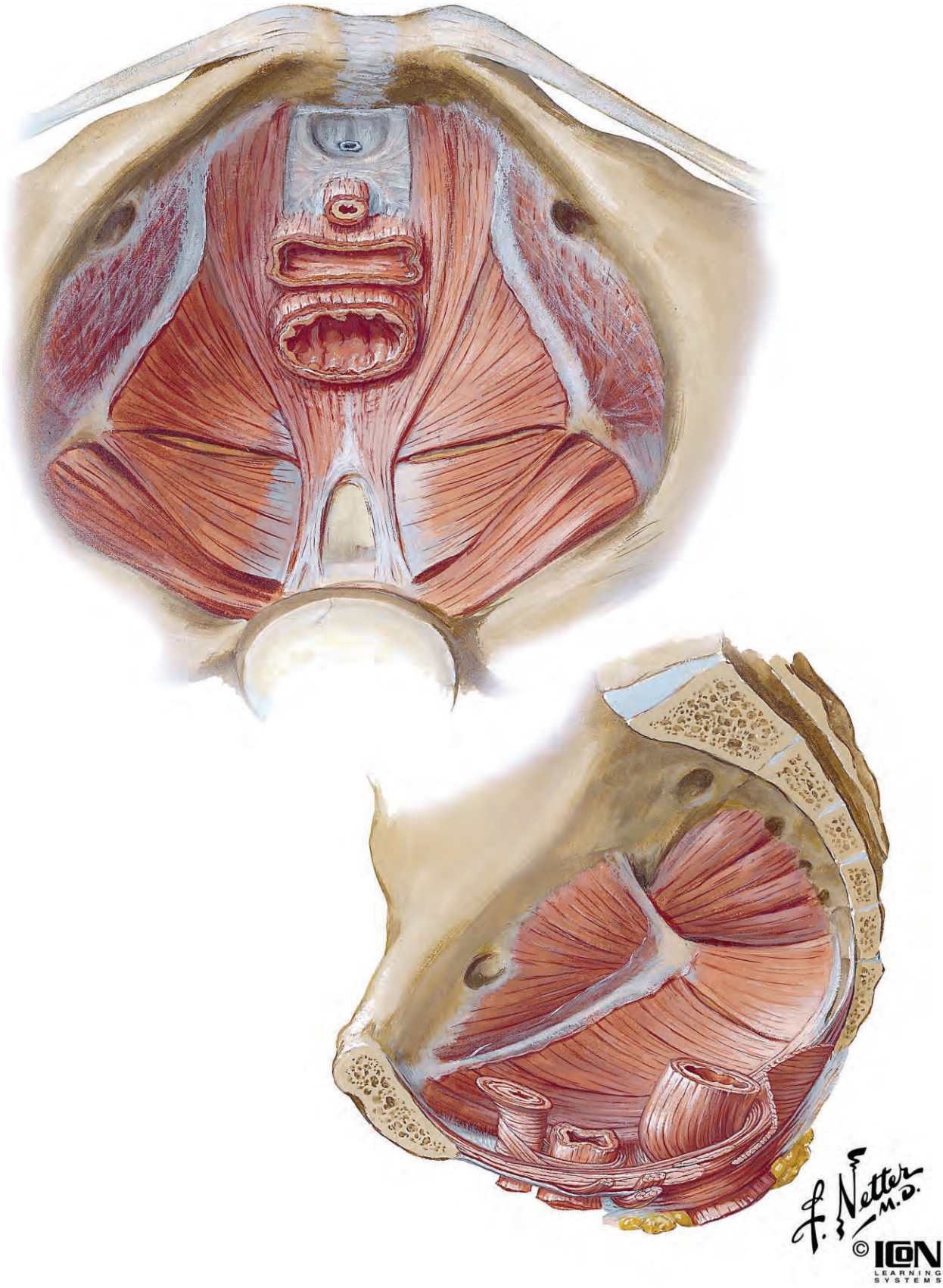


Figure 48–11. Muscles of the pelvis (female shown).

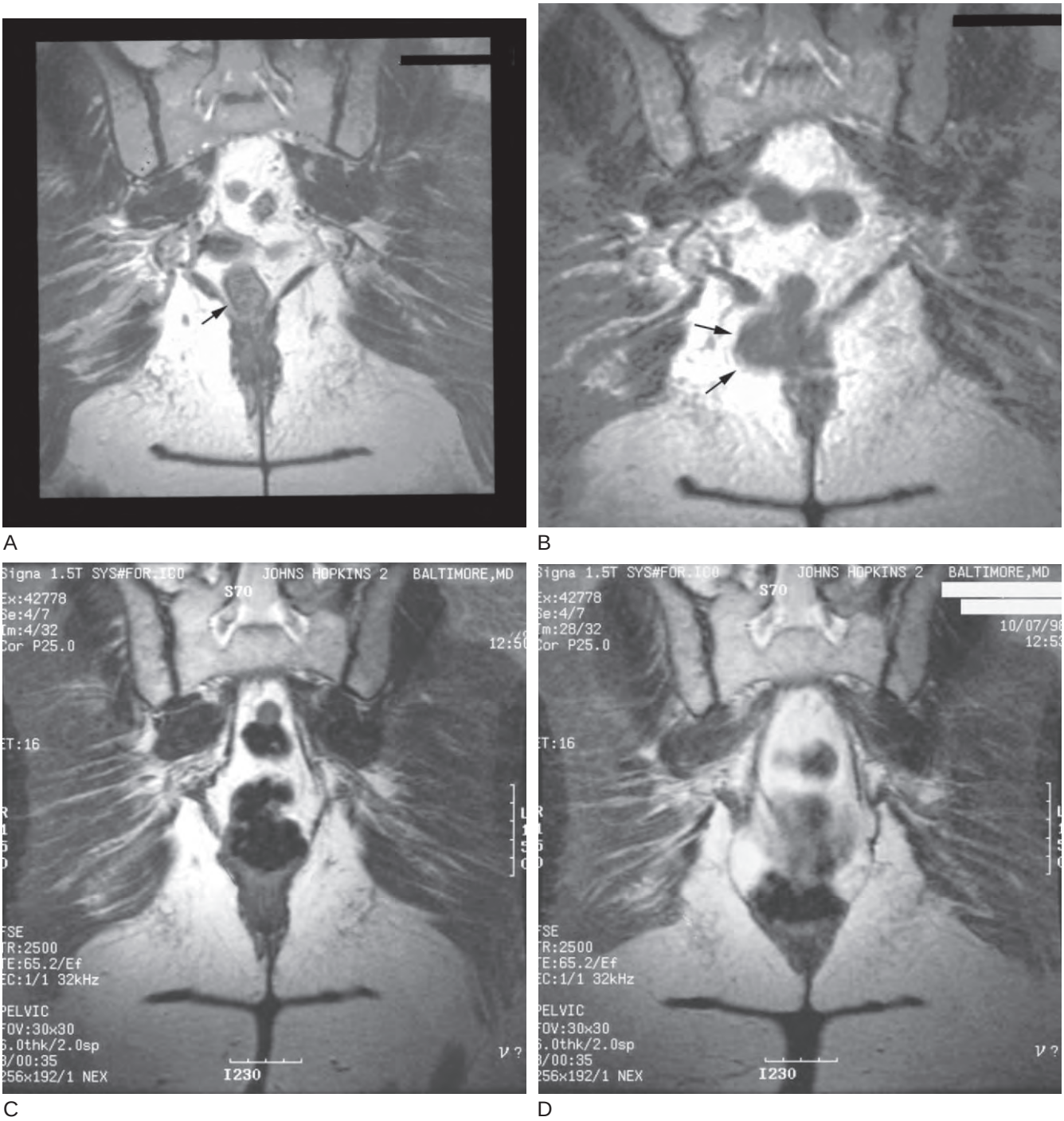


Figure 48–12. Coronal T2-weighted magnetic resonance images. **A,** Rest image showing a midline rectum *(arrow)* in patient with obstructed defecation. **B,** Strain image demonstrating the rectum *(arrows)* herniating through a defect in the right levator ani complex. **C,** Postoperative rest image after a combined abdominoperineal approach to simple levator hernia repair with no absorbable sutures. **D,** The rectum remains midline after hernia repair, and the patient's symptoms of obstructed defecation were resolved. (From Kaufman HS, Buller JL, Thompson JR, et al: Dynamic pelvic MR imaging and cystocolpoproctography alter surgical management of pelvic floor disorders. Dis Colon Rectum 44:1575, discussion 1584, 2001.)

detection of posterolateral levator defects, which become apparent with this bellowing of the pelvic floor. Moreover, paradoxical contraction of the puborectalis can be appreciated during this maneuver because an improperly functioning puborectalis will deflect the examiner's finger anteriorly. While the patient is in the lithotomy position, associated pelvic organ prolapse should be noted in relation to an anatomic landmark, such as the hymenal ring, at rest and during straining. It may be helpful to examine a woman while she is standing to rule

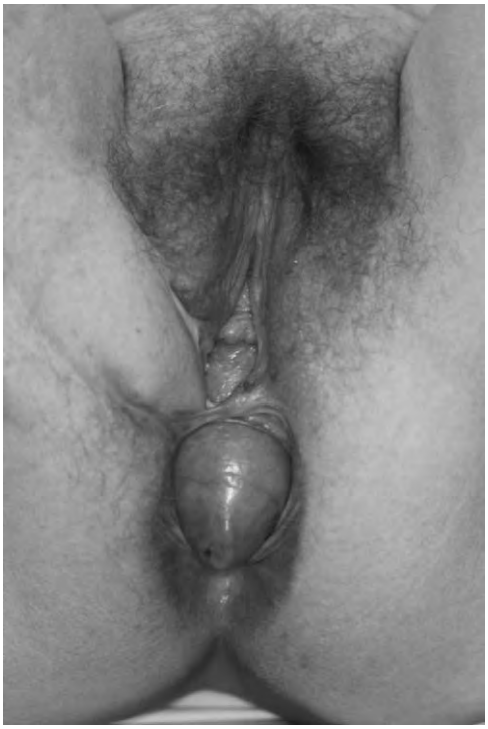


Figure 48–13. Perineal hernia after proctocolectomy for Crohn's disease. The patient has complete uterocervical procidentia. These skin bridges are seen attached to a previous harvest site of a gracilis flap.

out distal dissection of an enterocele, sigmoidocele, or rectocele high at the level of the cuff or more distally into the perineal body. Physical examination findings along with patient symptoms and complementary studies will help define the treatment modality.

Factors that may contribute to the formation of secondary perineal hernias include removal of the coccyx bone as part of an operative procedure, postoperative perineal infections, and complications of pelvic radiation therapy. A secondary perineal hernia is usually manifested as a palpable perineal mass that may cause the patient discomfort while sitting (Fig. 48–13). If the mesentery of the small bowel is long enough, the hernia defect may contain small bowel. Secondary perineal hernias most commonly develop within 1 year of an operation.[30]

Current imaging methods for evaluation of pelvic floor hernias include dynamic MRI, cystocolpoproctography, peritoneography, ultrasound, and CT. Additional anorectal physiologic and urodynamic testing may be required for associated symptoms of incontinence or obstruction (or both). Several investigations may be necessary to demonstrate pelvic floor abnormalities, especially in reoperative situations. Sentovich and colleagues described the use of dynamic proctography with peritoneography for pelvic floor disorders, and this imaging technique changed their operative plan in 85% of 13 women studied.[20] Dynamic MRI has been touted as a quick, noninvasive technique that demonstrates both pelvic visceral prolapse and the configuration of the pelvic floor musculature.[34] Kaufman et al. demonstrated that dynamic MRI and cystocolpoproctography were concordant with physical examination findings in only 41% of 22 patients with advanced pelvic floor disorders who underwent both tests.[35] Moreover, the use of these imaging studies changed operative management in 9 of the 22 patients (41%). Gearhart and colleagues[36] identified a total of 16 levator hernias (8 unilateral, 4 bilateral) in 12 of 80 patients (15%) evaluated at a tertiary center for advanced pelvic floor disorders. Levator hernias were not more frequent in women who had undergone previous pelvic surgery, nor was they associated with any specific symptoms. However, the finding of perineal descent on physical examination was associated with the presence of a levator hernia by dynamic MRI.

Treatment

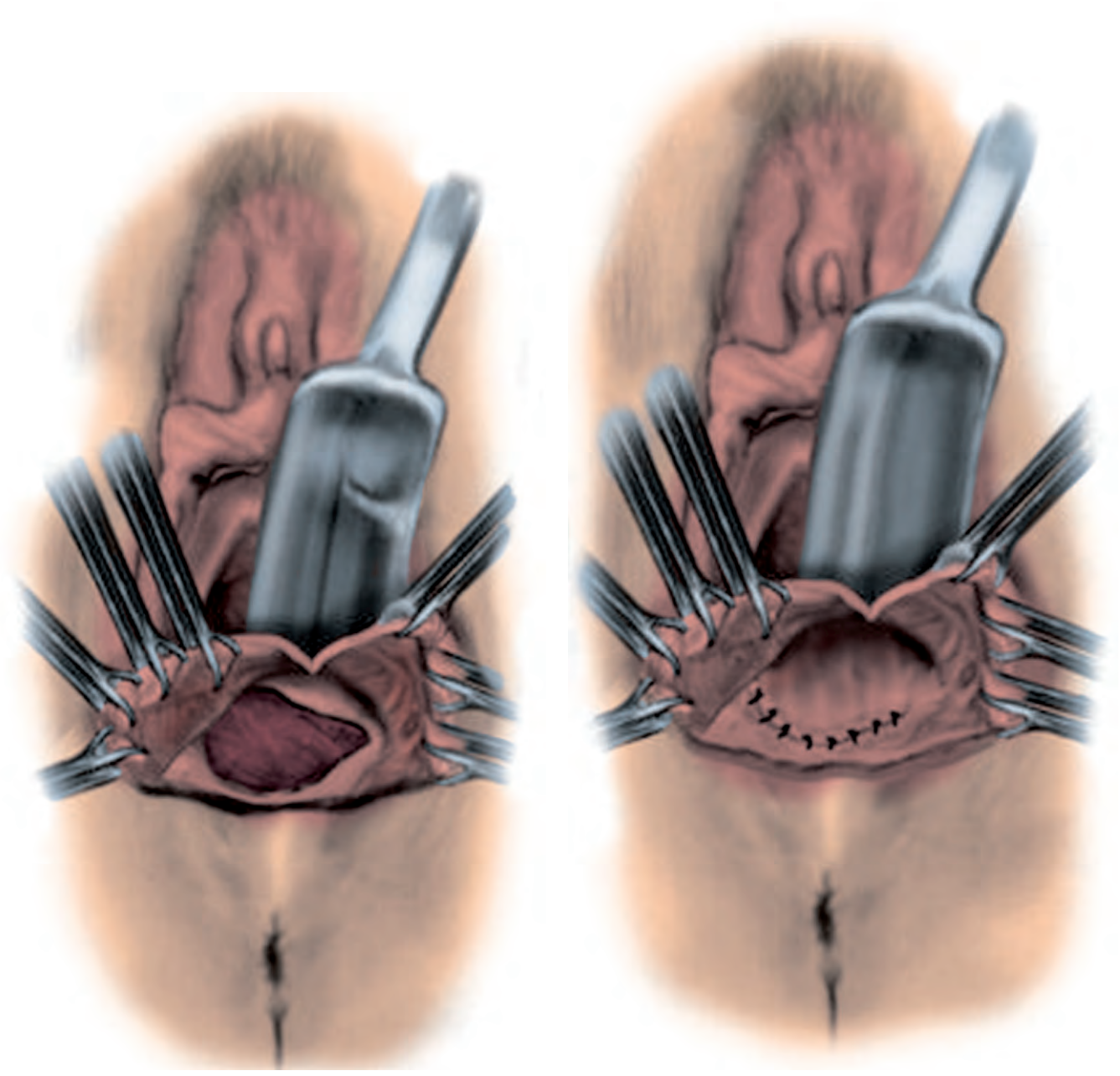
The natural history of a primary perineal hernia is not one of incarceration and strangulation but, rather, progressive enlargement and destruction of the pelvic floor. Compromise of the pelvic floor may lead to difficulty voiding and defecating, and formal evaluation of these functions should be considered. Breakdown of the perineum is rare but has also been an indication for surgery. Abdominal, perineal, and combined abdominoperineal approaches have been described for the repair of primary and secondary perineal hernias. The size of the defect, the contents of the sac, and the magnitude of the patient's symptoms usually dictate the approach for repair. Repair of secondary perineal hernias (see Fig. 48–13) often requires an abdominoperineal approach for reduction and support of herniated viscera and subsequent reinforcement of the pelvic floor.

If preoperative imaging does not suggest incarceration of a small levator hernia, an attempt may be made to repair it primarily through a perineal approach. Pudendal or vaginolabial hernias may also be approached in this manner. Similarly, most distal rectoceles that produce perineal bulging can be repaired via the discreet defect approach described by Richardson.[37] Debate continues in the urogynecologic and colorectal surgery literature about the preferred approach for rectocele repair.[38-40] Options include the aforementioned transvaginal discrete defect approach,[37,41,42] with or without an onlay graft (Fig. 48–14), the traditional transvaginal posterior colporrhaphy with midline levator plication,[38] and the transanal approach with rectal wall plication.[39] The presence of additional symptoms of pelvic relaxation should be investigated and ruled out before rectocele repair because more complex surgery to repair coexisting pelvic organ prolapse may be indicated. If the rectovaginal fascia is attenuated beyond repair, posterior fascial replacement with a biologic graft may be performed transvaginally (Fig. 48–15).[41] In addition, laparoscopic abdominal sacral colpoperineopexy has been used to attach a graft from the sacrum to the perineal body, which not only will fix the rectocele but will also primarily compensate for the central endopelvic fascial disruption associated with perineal descent (Fig. 48–16).[43]

The use of mesh or bioprostheses in pelvic floor surgery is frequently directed toward supporting pelvic viscera when the pelvic floor can no longer support these structures. Discrete hernias may not necessarily exist in the setting of global pelvic floor weakness (often with perineal descent). Sullivan et al. have described a total pelvic mesh repair with Marlex in these situations.[44] The procedure involves a strip of Marlex mesh secured between the perineal body and the sacrum; the strip may be partially wrapped around the rectum to treat rectal prolapse (Fig. 48–17). Two additional strips are tunneled laterally to support the vagina, bladder, and urethra. This procedure usually involves a multidisciplinary team of colorectal, urologic, and gynecologic surgeons. Sullivan and colleagues reported total mesh repair in 236 females with combined pelvic organ prolapse and a levator hernia. Satisfaction with correction of symptoms was achieved in 74% at greater than 6 years' follow-up. The main complication was mesh erosion to the vagina and bowel in 5% of patients.

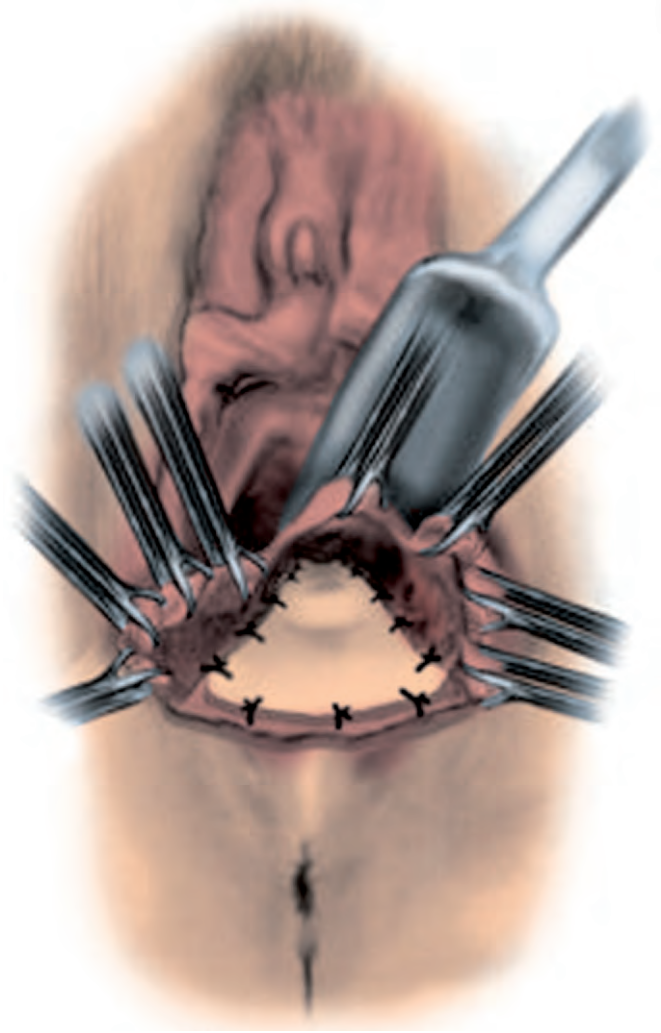
SCIATIC HERNIA

Sciatic hernias are rare, with fewer than 100 cases reported in the literature. A sciatic hernia is defined as



A B

Figure 48–14. Site-specific rectocele repair of a distal defect with separation of the rectovaginal fascia from the perineal body. **A,** Dissection of a discrete defect. **B,** Repair of the defect to the perineal body.



C

Figure 48–14, cont'd. **C,** Onlay dermal graft attached to the levators laterally, the rectovaginal fascia apically, and the perineal body distally. (From Kohli N, Miklos JR: Dermal graft–augmented rectocele repair. Int Urogynecol J 14:146, 2003.)

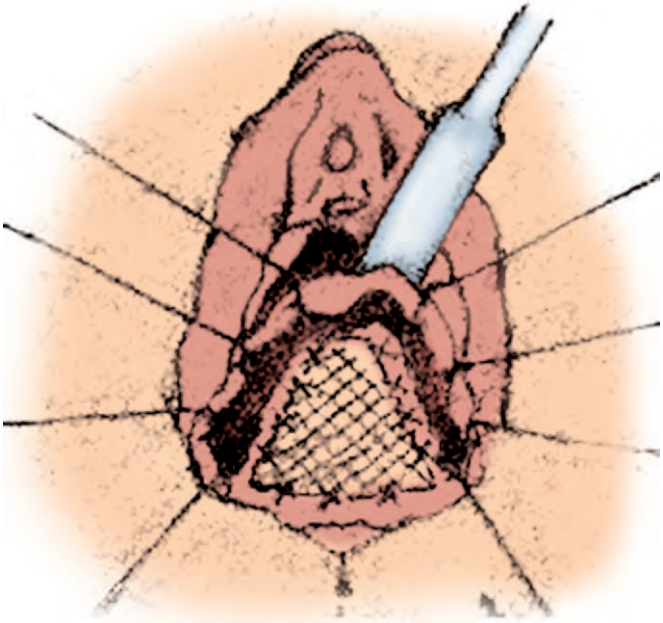


Figure 48–15. A meshed porcine dermal graft, PelviSoft (C.R. Bard, Inc, Covington, GA), replacing the posterior fascia for a large rectocele with inadequate host tissue for repair. (From Dell JR, O'Kelley KR: PelviSoft BioMesh augmentation of rectocele repair: The initial clinical experience in 35 patients. Int Urogynecol J 16:44, 2005.)

protrusion of a peritoneal sac and its contents through the greater or lesser sciatic foramen. They occur more frequently in women than in men, and the diagnosis should be considered in women with chronic pelvic pain. The development of a sciatic hernia is thought to be the direct result of piriform muscle atrophy, which allows the peritoneum to sag into the greater sciatic foramen. The sac may contain small bowel, ovary, fallopian tube, ureter, and occasionally bladder and colon. Classification of a sciatic hernia is based on anatomic relationships. Treatment consists of surgical repair.

Anatomy

Sciatic hernias have been classified according to the anatomic site of exit from the pelvis, either the greater or lesser sciatic foramen. The greater sciatic foramen is formed by a broad ligamentous band, the sacrotuberous ligament, which stretches across the greater sciatic notch on its way from the coccyx to the ischial tuberosity (Fig. 48–18). The lesser sciatic notch is converted to the lesser sciatic foramen by the bony attachments of the sacrospinous ligament. Greater sciatic hernias are further classified by their anatomic relationship to the piriformis muscle, either *suprapiriformis* or *infrapiriformis*. All vessels and nerves entering the gluteal region pass through the greater sciatic foramen. The course of the nerves and vessels entering the greater sciatic foramen is altered by the presence of the piriformis muscle. The superior gluteal artery, vein, and nerve can be found above the piriformis, whereas the inferior gluteal vessels and nerve and the internal pudendal vessels and nerve course below it. Importantly, the sciatic nerve also leaves the pelvis below the piriformis muscle near the ischial border of the greater sciatic notch.

Clinical Features and Diagnosis

Sciatic hernias are usually accompanied by varying degrees of pelvic, buttock, and posterior thigh pain. Because of the bulk of the gluteus muscles, there is rarely a palpable gluteal mass. The symptoms may be similar to those of classic sciatica with pain radiating down the back of the leg and aggravated by dorsiflexion, as well as the development of muscle weakness. A sciatic hernia may also cause pain as a result of incarceration or strangulation of bowel within the hernia sac. The patient

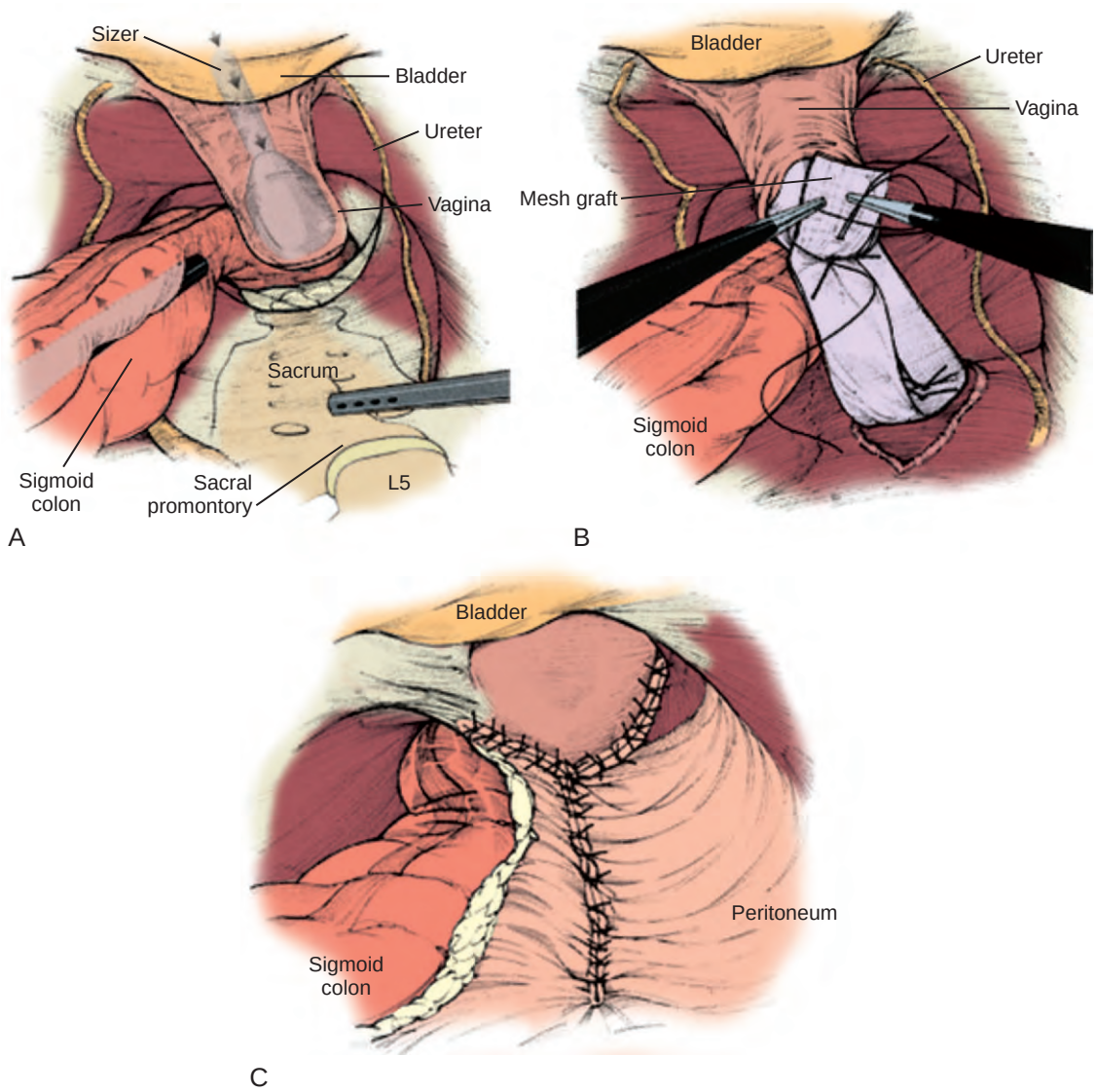


Figure 48–16. Laparoscopic sacral colpoperineopexy for vault prolapse and repair of perineal descent with mesh. **A,** Initial laparoscopic view with a sizer in the vagina showing the position of the vaginal apex and sacral promontory. **B,** Suturing graft material to the anterior aspect of the vagina. The posterior graft has been taken down to the perineal body. **C,** Completion with culdoplasty and exclusion of the graft from the peritoneal cavity. (From Link RE, Su LM, Bhayani SB, Wright EJ: Laparoscopic sacral colpoperineopexy for treatment of perineal body descent and vaginal vault prolapse. Urology 64:145, 2004.)

may have signs and symptoms of bowel or ureteral obstruction. On rare occasion, a gluteal mass may be palpable and appear more prominent with standing, straining, and coughing but diminished with lying down. If the gluteal mass is not reducible, however, one must entertain the diagnosis of a lipoma, cyst, abscess, aneurysm, or malignant tumor.

The presence of acute small bowel obstruction in the setting of a hernia warrants urgent or emergency surgery. The diagnosis may be made with ultrasound or CT (Fig. 48–19).[45] In more elective settings, especially in women with chronic pelvic pain, laparoscopy may allow both diagnosis and treatment. Miklos et al. have identified and repaired sciatic hernias laparoscopically in 20 of 1100 women with chronic pelvic pain over a 46-month period.[46]

Treatment

Definitive surgery should be performed soon after the diagnosis of a sciatic hernia has been made. There are two standard approaches: transabdominal and transgluteal. A transabdominal approach is mandatory in the presence of intestinal obstruction or evidence of strangulation. The transabdominal approach allows for easier identification of the important neurovascular structures that lie next to the hernia sac. When the diagnosis is certain and the hernia sac is reducible, a transgluteal approach may be used. Miklos et al. suggested that women with a history of chronic pelvic pain of more than 6 months' duration should be considered for diagnostic laparoscopy and, if a sciatic hernia is diagnosed, laparoscopic repair should be performed.[46] In 20 patients who

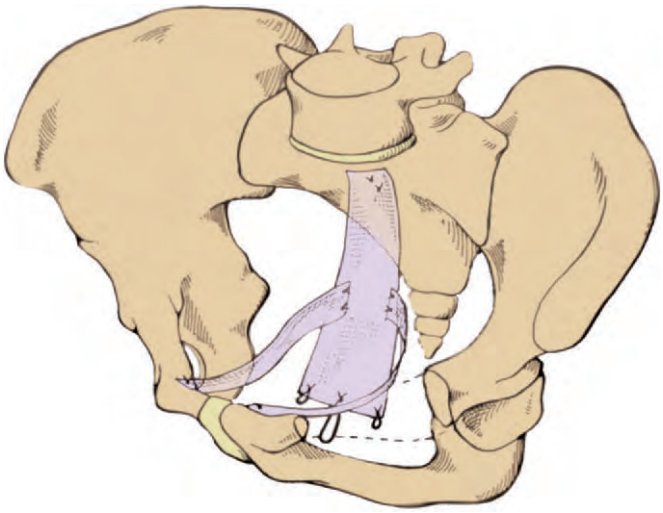


Figure 48–17. Total pelvic mesh repair as described by Sullivan et al. Mesh supports are used centrally from the upper part of the sacrum to the perineal body, and then two additional strips are tunneled laterally to support the vagina, bladder, and urethra. (From Sullivan ES, Longaker CJ, Lee PY: Total pelvic mesh repair: A ten-year experience. Dis Colon Rectum 44:857, 2001.)

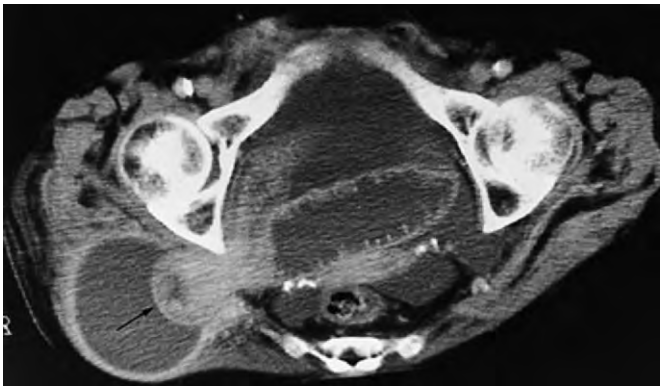


Figure 48–19. Computed tomographic scan showing incarcerated bowel *(arrow)* through the right sacral foramen and surrounding ascites in the right subgluteal region. (From Yu PC, Ko SF, Lee TY, et al: Small bowel obstruction due to incarcerated sciatic hernia: Ultrasound diagnosis. Br J Radiol 75:381, 2002.)

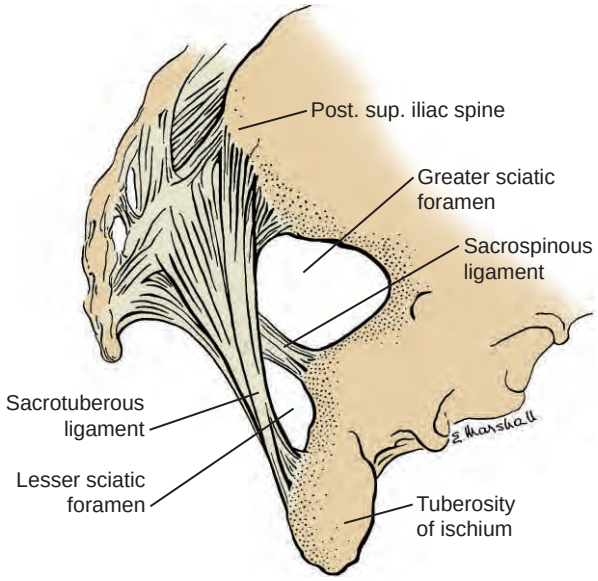


Figure 48–18. Posterolateral view of the pelvis showing the greater and lesser sciatic foramina and their ligamentous and osseous boundaries. (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

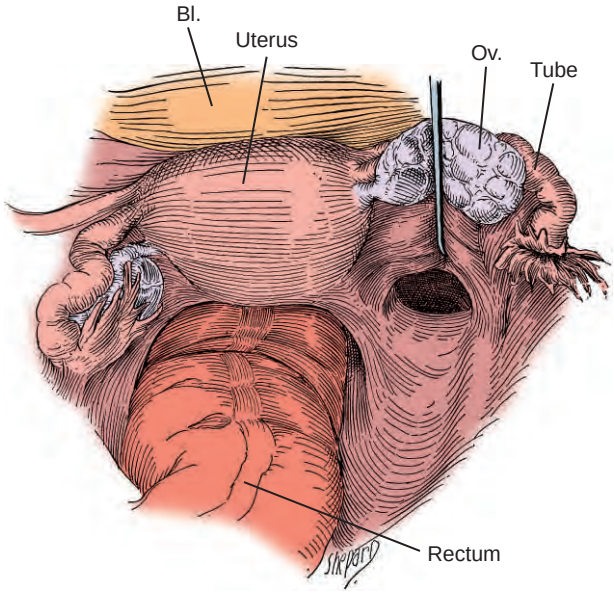


Figure 48–20. Anatomy of a sciatic hernia. In women, the sciatic opening is found behind the broad ligament. (From Watson LF: Hernia, 3rd ed. St Louis, CV Mosby, 1948.)

were found to have a sciatic hernia, the hernia was reduced laparoscopically, the peritoneum overlying the sciatic hernia was opened, and a polypropylene mesh plug was placed within the space created by the atrophic piriformis muscle. A second piece of mesh was secured as an onlay patch and the overlying peritoneum closed. All 20 women treated in this fashion were reported to have total relief or improvement of chronic pelvic pain at a median follow-up of 13 months (range, 3 to 36 months).

In an open transabdominal sciatic hernia repair, the patient is placed in the Trendelenburg position, and a lower midline incision is made. The abdomen is explored and the viscera inspected for evidence of incarceration or strangulation. In women, the internal opening of a sciatic hernia is posterior to the broad ligament and above the uterosacral ligament (Fig. 48–20). In men, the location of the internal opening is similar to that in women, in the lateral aspect of the pelvis between the bladder and rectum. If a ring is constricting the

hernia sac and thus precludes easy reduction, the ring can be manually dilated or sharply incised. With a suprapiriformis hernia, the most common type of sciatic hernia, the sac is usually lateral to the vessels. Therefore, the sac should be separated and excised in a posterior, lateral, and inferior direction. In the less common infrapiriformis sciatic hernia, the sac lies medial to the vessels and nerves and should therefore be separated and incised in a medial and superior direction.

For small hernia defects, repair may be performed by primary closure of the fascia of the piriformis muscle to the periosteum of the iliac bone. If the defect is larger or if the fascia of the piriformis muscle is weak, the hernia sac can be folded on itself and sutured to the piriformis muscle and the periosteum of the iliac bone. Greater durability can be achieved with the use of a synthetic mesh or biologic graft to close the defect.

In the transgluteal approach, the patient is placed in the prone position. This approach is best reserved for palpable masses and allows the surgeon to make an incision across the mass starting from the greater trochanter. The hernia sac is dissected free, opened, and inspected for any sign of strangulation. Once reduced, the hernia defect is closed by approximating the fascia of the piriformis muscle to the fascia of the gluteus maximus and medius. Alternatively and as in the transabdominal approach, synthetic mesh or biomaterials may be used to close the defect.

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Chapter

49

Hernias and Congenital Groin Problems in Infants and Children

Walter Pegoli, Jr.

Surgically significant problems involving the structures in the groin and scrotum are common in infants and children. The epicenter of this group of anomalies is geographically located in the area surrounding the ilioinguinal ligament. The problems most often encountered by general pediatric surgeons are inguinal hernia (direct and indirect), femoral hernia, and an undescended testis. An acute scrotum (most commonly the result of an incarcerated/strangulated inguinal hernia or testicular torsion), though rare, is a diagnostic challenge and requires real-time surgical decision making and intervention.

EMBRYOLOGY

The inguinal canal forms as the result of mesenchymal consolidation around the gubernaculum. The gubernaculum is then invaginated by an outpouching of peritoneum, the processus vaginalis.[1] At the start of the third trimester, the distal portion of the gubernaculum extends beyond the abdominal wall into the scrotum. The processus elongates proportionally within the gubernaculum to facilitate testicular descent.[2] Scrotal migration of the testicle begins during the seventh month of intrauterine life and is complete by 35 weeks' gestation. Persistent patency of the processus vaginalis is the principal factor required for the development of a hydrocele or indirect inguinal hernia. The difference between hernia and hydrocele is based on the size and content of the resultant sac. A hydrocele has a narrow sac neck and contains peritoneal fluid. Indirect inguinal hernias exhibit a wider neck and may contain intraperitoneal or retroperitoneal organs.

Normally, the processus vaginalis obliterates spontaneously from the internal ring to the testis. The distal end of the processus survives as the tunica vaginalis of the testis. Incomplete obliteration predisposes to the development of hydrocele or hernia. However, postnatal patency does not uniformly result in surgically significant disease. Postmortem studies in adults without clinical evidence of hernia have found patency of the processus vaginalis in 15% to 37% of groins examined.[3]

Any disruption in normal testicular descent can result in cryptorchidism. The location of the cryptorchid gonad is dependent on the timing of arrest along the natural path of testicular descent. Intra-abdominal testis are uncommon, being noted in only 5% to 10% of boys with undescended testes.[4] In most cases the testicle is located at the apex of the scrotum or slightly lateral to the external inguinal ring, within the superficial inguinal pouch. In such cases there is notable patency of the processus vaginalis 85% to 90% of the time.

A number of conditions have been identified as factors contributing to the development of indirect inguinal hernias. In infants with abdominal wall defects such as gastroschisis, omphalocele, and bladder exstrophy, congenital hernia or cryptorchidism, or both, may develop.[5] Patients with elevated peritoneal fluid volume as a consequence of ventriculoperitoneal shunting or peritoneal dialysis are at increased risk for the development of bilateral inguinal hernia.

INCIDENCE

The incidence of inguinal hernia in children ranges from 0.8% to 4.4% and is notably higher in infants.[6] It is highest during the first year of life, with a peak during the first months. The incidence is greatest in former premature infants, in whom it is reported to range from 16% to 25%.[7] Boys are affected six times more often than girls.[8] Right-sided hernias predominate. Rowe and Clatworthy reported that children manifest 60% of

hernias on the right, 30% on the left, and 10% on both sides.[9]

The incidence of undescended testes in infants has been reported to be approximately 4%.[10] Spontaneous descent has been documented for the first 3 months after birth but rarely beyond that time. A British study reported an incidence of 1.58% at 1 year of age.[11] The frequency of undescended testes is significantly higher in premature infants. However, these testes have been noted to descend postnatally, and if monitored over time as a function of postconceptual age, the incidence decreases to nearly normal.[12]

CLINICAL FEATURES OF INGUINAL HERNIAS AND HYDROCELES

Most commonly, inguinal hernias are manifested as a bulge in the groin that may extend down into the scrotum with increased intra-abdominal pressure. Congenital inguinal hernias contain an abdominal or retroperitoneal organ, whereas hydroceles contain only fluid. In communicating hydroceles, the processus vaginalis is in continuity with the peritoneal cavity. Noncommunicating hydroceles are walled off from the peritoneal cavity and therefore do not change in size with crying or straining.

Examination of the groin should take place in the supine and, if possible, the erect position. Struggling infants naturally increase their intra-abdominal pressure, which may result in spontaneous protrusion of abdominal contents into the hernia sac. Older, more cooperative children can perform the Valsalva maneuver and produce the hernia.

Palpation of a thickened spermatic cord as it exits the external inguinal ring and crosses the pubic tubercle may be a useful clinical finding. Rolling of the spermatic cord beneath the examining finger may mimic the sensation of rubbing two pieces of silk together (silk glove sign). The silk glove sign is a useful diagnostic aid when a hernia is suspected but not clinically evident.[13]

Scrotal swelling that historically changes over time, is not associated with a mass in the groin, and slowly evacuates with compression is suggestive of a communicating hydrocele. Scrotal swelling that has been present since birth, is static, and does not evacuate with compression is most likely a noncommunicating hydrocele. A nontender scrotal mass that transilluminates brightly is probably a hydrocele. Noncommunicating hydroceles that are evident shortly after birth and bilateral have a high likelihood of spontaneous resolution.[14]

An incarcerated hernia contains viscera that cannot be returned to the abdominal cavity. When the contents of the sac cannot be reduced and are ischemic or gangrenous, the hernia is strangulated. Early on, the contents of an incarcerated hernia are compressed by the rigid confines of the internal ring. Initially, compression leads to impaired lymphatic and venous return. Over time, pressure within the sac increases and arterial inflow is interrupted. If the herniated material is intestine, progressive ischemia results in gangrene and perforation. Concomitant testicular ischemia can result from compression of the spermatic cord by the strangulated hernia.[15]

The reported incidence of incarceration ranges between 12% and 17% in patients younger than 10 years.[16,17] The greatest risk for incarceration is in infancy, with reports ranging from 24% to 31% in children younger than 6 months.[18,19] Rates of incarceration have been noted to be lower in premature infants. Krieger et al. reported a 17% rate of incarceration in 52 premature infants.[20] The authors speculate that the reduced incidence in premature infants is due to an internal ring that is proportionately larger than in their full-term counterparts.

Irritability and vomiting, which may be bilious in nature, are typical in infants with incarcerated hernias. On examination, a firm, well-defined mass is present in the groin, and it often extends into the scrotum. If the mass has been present for some time, there is often edema and erythema of the overlying skin. Tenderness to palpation progresses over time.

The mass may transilluminate, but not brightly. Radiographs of the abdomen may show air-filled bowel in the scrotum. In addition, radiographic findings consistent with partial or complete bowel obstruction may be apparent. In a nonacute scrotum, ultrasound evaluation of the mass may differentiate hernia from hydrocele.

The initial management of an incarcerated but not strangulated indirect inguinal hernia is nonoperative.[21] More than 80% of incarcerated hernias are reducible without surgery.[22] An attempt at manual reduction of an incarcerated hernia in a crying infant is not usually successful. In an agitated infant, sedation and analgesia are often required. Relaxation reduces intra-abdominal pressure and decreases the extrinsic compression of the neck of the sac by the internal inguinal ring. Placement of the infant in the Trendelenburg position plus observation in a warm, dark, quiet room often results in spontaneous reduction. In the absence of spontaneous reduction, manual reduction should be attempted. Simultaneous pressure at the base of the hernia sac and the external ring applied over a period of several minutes produces the best clinical result. Isolated compression of the base of the sac causes the contents of the sac to ride over the external ring and markedly reduces the likelihood of a successful reduction. After reduction, definitive surgical intervention should be delayed 24 to 48 hours to allow for resolution of edema in the structures surrounding the hernia sac. When the hernia cannot be reduced, immediate surgical intervention is indicated to prevent further ischemic damage.

OPERATIVE MANAGEMENT OF AN INDIRECT INGUINAL HERNIA

The principle objective of repair of an indirect inguinal hernia in infants and children is high ligation of the sac at the internal inguinal ring. In most cases, the procedure requires general anesthesia. In infants, endotracheal anesthesia is preferred to secure the airway. In older children, in whom the airway is less problematic, facial or laryngeal mask anesthesia is adequate.

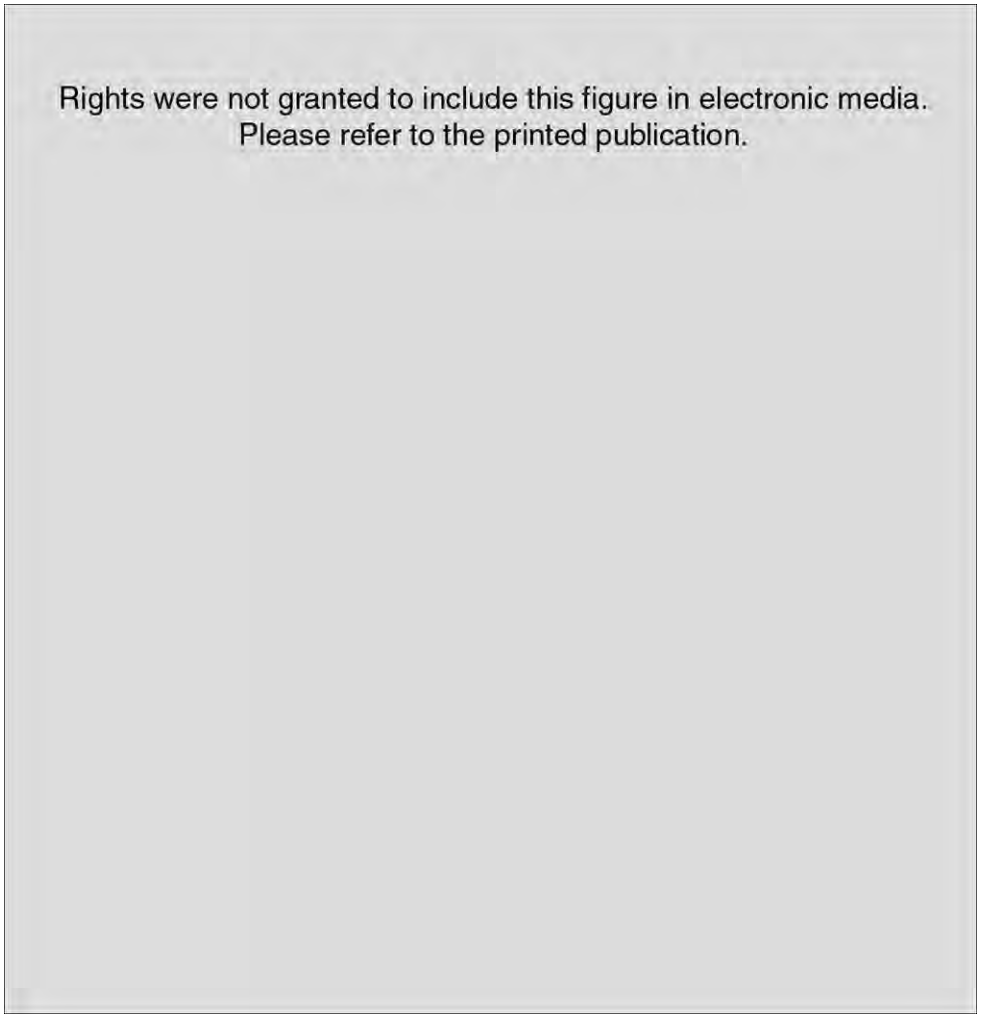

Figure 49–1. Indirect inguinal hernia repair. **A,** Skin incision in the groin crease. **B,** Incision in the external oblique aponeurosis. **C,** Dissection of the vas deferens and testicular vessels from the hernia sac. **D,** High ligation of the hernia sac. (From White JJ, Haller JA Jr: Groin hernia in infants and children. In Nyhus LM, Condon RE [eds]: Hernia, 2nd ed. Philadelphia, JB Lippincott, 1978, p 101.)

A transverse groin crease incision lateral to the pubic tubercle offers adequate exposure to the components of the inguinal canal (Fig. 49–1A). The length of the incision should be dictated by the size of the patient and the expected anatomic pathologic changes. In general, the incision should be long enough to provide adequate exposure to the spermatic cord and the totality of the inguinal canal. Scarpa's fascia is easily identified by gentile blunt separation of the subcutaneous fat. Visible vessels in the subcutaneum should be retracted aside, not transected, to prevent bleeding complications. Scarpa's fascia is then incised sharply to expose the external oblique aponeurosis. The external inguinal ring is identified just lateral to the pubic tubercle. The external oblique aponeurosis is then divided in the direction of its fibers to the external inguinal ring (see Fig. 49–1B). Care must be taken to not injure the underlying ilioinguinal nerve. In an infant, it may not be necessary to incise the external oblique aponeurosis to gain adequate access to the contents of the inguinal canal. In a newborn, the internal inguinal ring is almost directly subjacent to the external inguinal ring, thus allowing access to the cord structures at the level of the internal inguinal ring. With time, the inguinal canal elongates, and the inguinal rings become progressively farther apart.[23]

Dissection below the flaps of the incised external oblique aponeurosis exposes the spermatic cord. The spermatic cord is gently dissected free from the inguinal canal and elevated into the wound. The spermatic cord is stretched over fine forceps. Normally, the indirect inguinal hernia sac is found to lie anteromedial to the vas deferens and the testicular vessels.

Gentle separation of the cord structures from the hernia sac is accomplished by sweeping the vas deferens and testicular vessels laterally with nontoothed forceps (see Fig 49–1C).

The vas deferens should be carefully inspected. Failure to identify a vas deferens at surgery should prompt investigation for associated anomalies. The incidence of indirect inguinal hernia in patients with cystic fibrosis is reported to be 6% to 15%.[24] In cystic fibrosis, abnormalities range from atresia to complete absence of the vas deferens, and the anomalies are often bilateral. Absence of the vas deferens may be associated with ipsilateral renal agenesis and should prompt an investigation to rule out upper urinary tract abnormalities.

Once the distal sac is identified, it is elevated to expose the neck of the hernia sac. Traction on the sac aids in the dissection. With large sacs, hemisection aids in exposure. A short sac can be freed entirely to the internal ring.

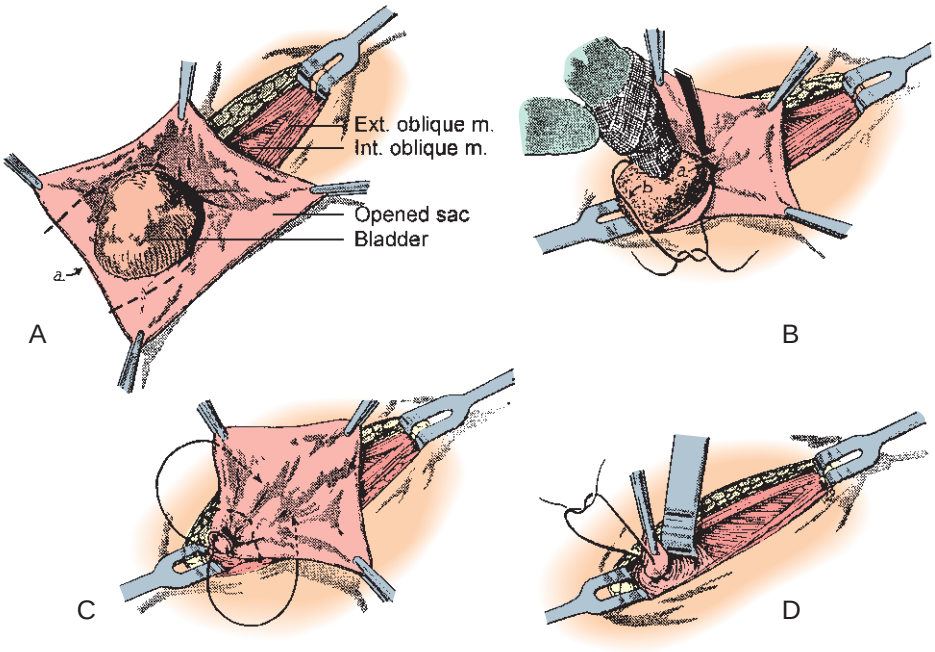

Figure 49–2. Sliding hernia repair. **A,** The bladder forms the medial wall of an open indirect inguinal hernia sac. **B,** Bladder turned down into the residual hernia sac. **C,** Purse-string suture of the sac at the internal ring. **D,** Invagination of the ligated residual sac. (From Golliday ES, White JJ: Hernias and congenital groin problems in infants and children. In Yeo CJ [ed]: Shackelford's Surgery of the Alimentary Tract, 5th ed. Philadelphia, Elsevier, 1996, p 196.)

The cord structures are dissected away to the level of the properitoneal fat. The sac is then inspected to confirm that it is empty. If the sac contains abdominal or retroperitoneal organs, reduction is accomplished by gentle compression of the base of the sac. When empty, the sac is twisted two to three times. This maneuver strengthens the sac to provide better purchase for transfixing sutures and narrows the internal inguinal ring. The sac is ligated high at the internal ring with one to two suture ligatures of absorbable material. Hernia sacs with large necks may require a purse-string suture technique to achieve satisfactory closure (see Fig. 49–1D).

Management of the distal segment of the hemisected hernia sac is controversial. Some pediatric surgeons cite the incidence of postsurgical scrotal hydrocele and recommend removal of the distal sac. Others are wary of increasing the risk of injury to the cord structures and the possibility of bleeding with the development of a scrotal hematoma. These surgeons recommend leaving the distal sac in situ.

After high ligation of the hernia sac the internal ring should be inspected. In infants with large indirect inguinal hernia sacs, the internal ring is often patulous and the floor of the inguinal canal attenuated. The internal ring may be plicated and the floor of the inguinal canal reconstructed by suturing the transversalis fascia to the shelving portion of the inguinal ligament. In infants, normal anatomy is best re-created by closing the floor over the spermatic cord. In children and adolescents, the floor is repaired under the spermatic cord.

The objective of surgical repair in girls is identical to that in boys: high ligation of the hernia sac. However, up to 20% of girls have a sliding component to the hernia sac.[25] On occasion, the fallopian tube, ovary, or uterus may make up a portion of the wall of the sac. The sac is routinely opened to evaluate for the presence of a sliding component. Empty sacs are ligated high. After high ligation, Bastionelli recommends securing the remaining sac to the undersurface of the conjoined tendon to maintain lateral uterine support.[26]

The surgical principles of sliding hernia repair are gender and organ neutral. Sliding hernias of the intestine, bladder, uterus, and fallopian tube are managed via similar surgical techniques (Fig. 49–2A). Redundant hernia sac is excised to the wall of the organ down to the level of the internal ring. The viscera and the remaining sac are invaginated through the internal ring (see Fig. 49–2B). At the level of the internal ring, the seromuscular segment of viscera and the inverted sac are secured with a purse-string suture (see Fig. 49–2C). The internal ring may be plicated to reinforce the repair (see Fig. 49–2D).[27]

At completion of the critical portion of the repair, gentle traction on the testis returns the testicle to the base of the scrotum and seats the spermatic cord within the inguinal canal. The external oblique aponeurosis and Scarpa's fascia are closed with several interrupted absorbable sutures. The skin is approximated with subcuticular absorbable suture and reinforced with adhesive strips or collodion.

Before closure of the superficial layers of the wound, administration of local anesthesia is highly recommended to aid in postoperative pain management. Local infiltration and ilioinguinal nerve blocks with 0.25% bupivacaine (maximum recommended dose of 1 ml/kg or 2 mg/kg) has been shown to significantly reduce postoperative pain after inguinal hernia repair.[28] Oral acetaminophen or nonsteroidal anti-inflammatory agents are excellent analgesics during the first few days of convalescence. Older children are encouraged to return to school after 2 or 3 days and may return to full, unrestricted activity in 3 to 4 weeks.

CONTRALATERAL INGUINAL EXPLORATION

The advantage of contralateral inguinal exploration is the diagnosis and repair of a patent processus vaginalis or indirect inguinal hernia that was not discernible at the time of physical examination. In the event of a patent processus vaginalis, it prevents the development of a future indirect inguinal hernia and the need for an additional general anesthetic for repair.

The major surgical risk involved in contralateral inguinal exploration is injury to the vas deferens or the testicular blood supply. The risk of proven injury to the vas deferens, based on finding a segment of the vas in the surgical specimen, has been reported to be 1.6%.[29] The risk of testicular atrophy after routine inguinal hernia repair, assumed to be the result of injury to the testicular vessels, is approximately 1%.[30] With an incarcerated inguinal hernia, the blood supply to the testis may be compromised by extrinsic compression at the internal inguinal ring. The incidence of testicular atrophy with incarceration ranges from 2.6% to 5%.[31,32]

In a review of published data, Rowe et al. concluded that in infants with a unilateral inguinal hernia, the processus vaginalis obliterates within the first 2 years of life in 40% of patients. Of note, a surgically significant contralateral indirect inguinal hernia eventually developed in half of these children. The remaining 20% were found to have a patent processus vaginalis that was clinically silent.[33] These data suggest that contralateral exploration will be negative in two of five infants and three of five children.

In a recent review of practicing pediatric surgeons, 40% limited contralateral exploration to infants younger than 1 year and 39% to children younger than 2 years.[34] Female gender was thought to increase the incidence of bilateral indirect inguinal hernias. However, the incidence of a positive contralateral exploration has been shown to be no different from that in boys.[35]

The risk of contralateral hernia developing after unilateral herniorrhaphy is low, and data suggest that the contralateral hernia rate is no higher than that of the general childhood population.[36] A growing number of practicing surgeons do not recommend routine contralateral exploration. However, there are exceptional circumstances that warrant contralateral exploration. Children who are at high anesthetic risk, such as those with cystic fibrosis, are candidates for contralateral exploration. In addition, children with conditions known to increase intra-abdominal pressure (ascites, ventriculoperitoneal shunts, peritoneal dialysis) should undergo contralateral exploration.

OPERATIVE MANAGEMENT OF UNDESCENDED TESTIS

Treatment of an undescended testis is based on the assumption that the best environment for testicular function is the base of the scrotum. Studies suggest that elevated temperature can result in testicular degeneration. The scrotal testis is 4° C cooler than core temperature, and this cooler temperature has been shown to be an essential requirement for normal testicular development.[37] Degeneration, which has been demonstrated at the electron microscopic level in the second year of life, has been shown to progress to gross atrophy in school-aged children.[38] As a result of the growing body of evidence that testicular degeneration begins in infancy, the recommended age for orchidopexy has decreased. Presently, the recommended age for orchiopexy ranges from 6 to 24 months.[39]

For an inguinal undescended testis, the initial steps in the operation mirror those of indirect inguinal hernia repair. An ipsilateral groin crease incision is made and carried down to the external oblique aponeurosis. The external ring is identified, and then the external oblique aponeurosis is divided to the level of the external ring to expose the inguinal canal and its contents.

A widely patent processus vaginalis, or an indirect inguinal hernia, has been reported in more than 70% of patients with canalicular undescended testes.[40] As described previously, the hernia sac most often lies anteromedial to the vas deferens and the testicular vessels (Fig. 49–3A). In a high undescended testis, the sac may contain the testicle, and the cord structures are intimately associated with the wall of the sac. The method of sac separation is similar to that used during indirect inguinal hernia repair. Separation of the critical cord structures from the sac proceeds to the level of the internal inguinal ring. At the internal inguinal ring the cord structures diverge from the vas deferens, with the cord structures coursing medially and the testicular vessels laterally. At this level, the sac is ligated and divided.

The most common impediment to reaching the scrotum is insufficient length of the testicular vessels. In most cases adequate length may be obtained by blunt dissection of the testicular vessels from the fibrous bands that fix the vessels within the retroperitoneum. If necessary, the dissection can be extended up the retroperitoneum to the inferior pole of the kidney. If an additional 1 to 2 cm of length is required, the cord can be translocated medially (see Fig. 49–3B). This maneuver requires ligation and division of the inferior epigastric vessels, along with incision of the transversalis fascia, which forms the posterior wall of the inguinal canal. The vas deferens is usually of sufficient length and reaches the scrotum without any special manipulation.

If after thorough dissection the testis cannot be made to reach the scrotum, a staged procedure should be performed. The testis is sutured to the pubis or the lowest portion of the scrotum that can be reached without undo tension. The second stage is performed 6 to 12 months later. Successful scrotal positioning via the two-stage procedure can be expected in 70% to 90% of children.[41]

When adequate length has been achieved, the testicle should be fixed in the scrotum. The most common technique anchors the testicle to the dartos fascia in a pouch located just below the scrotal skin.[42] A transverse skin incision is made at the base of the scrotum, and a subcutaneous pouch is developed between the skin and dartos fascia (see Fig. 49–3C). Once the pouch is large enough to accommodate the testicle, a small incision is made in the dartos fascia. A clamp is then passed

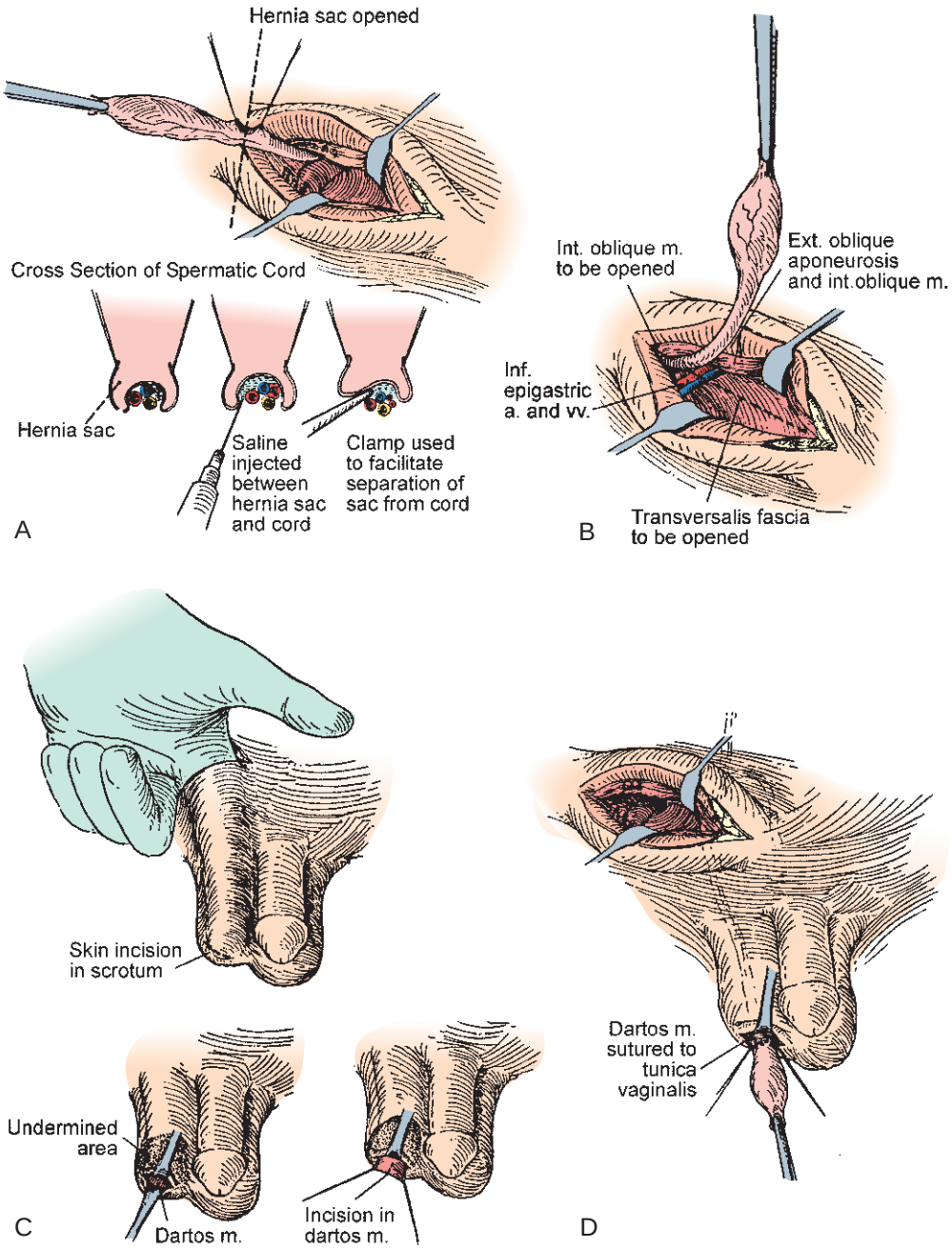

Figure 49–3. Dartos pouch orchidopexy. **A,** Hernia sac dissected free from the vas deferens and testicular vessels. **B,** Incision of the transversalis fascia to improve cord length. **C,** Tunnel to the scrotum created with the index finger and creation of the dartos pouch. **D,** Testicle brought through the defect created in the dartos fascia. The dartos fascia is sutured to the tunica to secure the testicle within the scrotum. (From Fonkalsrud EW: The undescended testis. In Ravitch MM, Benson CD, Mustard WT, et al [eds]: Current Problems in Surgery. Year Book, Chicago, 1978.)

retrograde from the scrotum into the inguinal canal, and the testicle is grasped and pulled into the scrotum. Care must be taken to avoid twisting the cord structures during this portion of the procedure. The testicle is secured in the scrotum by suturing the dartos fascia to the tunica albuginea with fine absorbable sutures (see Fig. 49–3D). The inguinal and scrotal incisions are closed in routine fashion.

Approximately 10% of undescended testes are not palpable.[43] An impalpable testicle may reside within the abdomen or may be absent. Intrauterine torsion of the spermatic cord can lead to testicular atrophy, or the "vanishing testis."[44] In such cases, the remaining testicle is grossly hypertrophic, which is a helpful physical sign and can be of use in determining the cause of the contralateral empty scrotum.[45]

Laparoscopy is a useful adjunct in the evaluation of an impalpable testis. The technique is highly effective in confirming the presence and location of the testicle. In addition, minimally invasive surgery can be used to remove or manipulate an abdominal or canalicular testis into the scrotum.

A laparoscope is inserted into the abdomen, and the anatomy on the side of the descended testicle is inspected to provide a reference. The testicular vessels and the vas deferens should converge at the internal ring. Normally, the internal ring should be closed and the peritoneum well coapted. On inspection of the involved side, if the testicular vessels and vas deferens end abruptly at the internal inguinal ring, the diagnosis of vanishing testis is made and the procedure terminated. In approximately 3% to 5% of children, a normal-appearing vas deferens and testicular vessels traverse the internal ring and a testis is probably present within the inguinal canal.[46] This finding mandates open inguinal exploration. In approximately half of these cases, the testicle is atrophic and should be removed because of the associated increase risk for malignancy. If the testicle is normal, orchidopexy should be performed.

An abdominal testicle visualized at laparoscopy may be approached via minimally invasive or open maneuvers. The Fowler-Stevens procedure offers the best opportunity to position a viable gonad in the scrotum.[47] The procedure requires the presence of a long, looping vas deferens to be successful. The testicular vessels are ligated and divided in the abdomen. The testicle is then brought down on the vas deferens supplied by collateral circulation derived from the inferior epigastric vessels and the gubernaculum.

The Fowler-Stevens operation is most often a two-stage procedure. In the first stage, the testicular vessels are ligated or clipped. Six months later, the testis is mobilized, with care taken to not disturb the collateral blood supply, through the inguinal canal into the scrotum. In long-term follow-up of the two-stage procedure, a 70% to 90% success rate has been reported.[48]

TORSION OF THE TESTIS

Twisting or torsion of the testis can produce occlusion of testicular blood flow and result in gonadal necrosis. The time frame for ischemic injury is variable. Loss of spermatogenesis occurs after 6 hours of torsion, loss of Leydig cells within 10 hours, and necrosis in as little as 2 hours, but mostly after 24 hours of ischemia.[49]

The most common form of torsion is intravaginal, and intravaginal torsion is predisposed by a high investment of the spermatic cord by the tunica vaginalis. The testis is pendulous and tends to lie horizontally within the scrotum. This position exposes the testicle to environmental conditions that can lead to twisting.

Extravaginal torsion is less common and confined to the newborn period. During testicular descent, the testis is loosely adherent to the surrounding structures. Inadequate fixation can allow the entire testis and spermatic cord to twist.

The incidence of testicular torsion is highest in infancy and adolescence. The peak incidence occurs in boys 13 to 16 years old. Patients complain of a sudden onset of pain in the scrotum, groin, or lower part of the abdomen. The pain may be associated with nausea or vomiting. On examination, the testis often lies horizontally within the scrotum and is extremely tender to palpation. The scrotum rapidly becomes edematous and erythematous. Over time the testis infarcts and the scrotum takes on a bluish discoloration.

Several clinical conditions can mimic the scrotal findings seen in testicular torsion. A child with torsion of the appendix testis has testicular pain that is of sudden onset. This condition occurs in younger adolescent boys, with a peak at age 11.[50] A blue dot may be seen at the upper pole of the testis. Palpation of this area results in severe pain, whereas the testicle itself is not tender.

Infectious conditions of the testis can produce significant inflammatory changes within the scrotum. Mumps virus has a predilection for the postpubertal testis. Epididymitis is usually the result of retrograde infection via the vas deferens in children with an *Escherichia coli* urinary tract infection. Children with underlying urinary tract anomalies or those who require intermittent catheterization are at increased risk.

Early diagnosis is the cornerstone of successful management of testicular torsion. Progressive ischemia mandates urgent clinical decision making. Doppler ultrasound and radioisotope scans have been used to determine whether there is blood flow to the testis in the acute scrotum.[51] In a small prepubescent testis, the volume of the gonad decreases accuracy and limits clinical utility. In older adolescents, a radioisotope scan can help differentiate between torsion and epididymo-orchitis. Blood flow is increased in infectious conditions, whereas it is markedly reduced in testicular torsion. Because of the time constraints imposed by progressive testicular ischemia, diagnostic delay and clinical indecision should not inhibit prompt surgical intervention.

Operative Management of Testicular Torsion

Treatment of testicular torsion is immediate scrotal exploration with a midline incision overlying the scrotal septum. The involved hemiscrotum is entered and the testicle is inspected. If the testis is twisted, it is untwisted and viability assessed. This maneuver usually results in the return of blood flow to the testis within several minutes. In some cases the testis appears congested or hemorrhagic, and it may be difficult to determine viability. A Doppler flow probe can prove helpful in determining the presence of testicular blood flow.

A viable testis should be fixed within the scrotum. The testis should be sutured to the septum with several nonabsorbable sutures. However, management of a testis of questionable viability remains a controversial issue. It has been shown that ischemia damages the blood-testis barrier and can expose the child to autoimmunization against his own sperm.[52] This risk is low in children younger than 10 years because there is no blood-testis barrier and spermatogenesis is dormant.[53] Thus, the current recommendation is to preserve a compromised testis in children younger than 10 years and proceed with

orchiectomy in older children. The contralateral scrotum should be explored because the defect in fixation is usually bilateral. Regardless of the clinical findings, the contralateral testis is also fixed within the scrotum to prevent future torsion.

FEMORAL HERNIA

Femoral hernias are rare in children. They are often clinically misdiagnosed as direct inguinal hernias or as recurrent indirect inguinal hernias. In a large review of patients with groin hernias, femoral hernias were found in only 0.2% of the patient population, with a girl-to-boy ratio of approximately 2:1.[54] The symptoms and signs associated with femoral hernias are nonspecific and may mimic those of inguinal hernia. The initial surgical exposure is also the same. A low inguinal crease incision is made and carried down to the inguinal ligament. In femoral hernias, a mass is identified in the femoral canal. The mass is reduced and the canal obliterated. The Cooper ligament repair closes the canal by suturing the inguinal ligament to the pectineal ligament and pectineal fascia. An alternative repair involves the use of a plug of prosthetic material sutured to the surrounding fascia to obliterate the orifice of the femoral canal.

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Chapter

50

Anatomy and Physiology of the Stomach

David W. Mercer · James W. Suliburk

ANATOMY

Divisions

The stomach originates as a dilatation in the tubular embryonic foregut during the fifth week of gestation. By the seventh week, it assumes its normal anatomic shape and position by descent, rotation, and further dilatation, along with disproportionate elongation of the greater curvature. After birth, the stomach is easily recognizable as the pear-shaped, most proximal abdominal organ of the alimentary tract. The stomach is divided into four anatomic regions, and although these divisions are useful to the surgeon when describing anatomic resections, they do not necessarily denote histologic or physiologic division of the organ (Fig. 50–1). The region of the stomach that attaches to the esophagus is called the cardia. Proximal to the cardia is the physiologically competent lower esophageal sphincter. The pylorus connects the distal stomach (antrum) to the proximal duodenum. Although the stomach is fixed at the gastroesophageal junction (GEJ) and the pylorus, the large midportion is mobile. The superior-most part of the stomach is the floppy, distensible fundus. It is bounded superiorly by the diaphragm and laterally by the spleen. The largest portion of the stomach is the body (corpus). The body contains the bulk of the gastric parietal cells and is bounded on the right by the relatively straight lesser curvature and on the left by the longer greater curvature. At the angularis incisura, the lesser curvature abruptly angles to the right. This point marks the end of the body and the beginning of the antrum, which extends to the pylorus. Another important anatomic angle (angle of His) is the one that the fundus forms with the left margin of the esophagus.

Anatomic Relationships

Most of the stomach is in the left upper quadrant of the abdomen (Fig. 50–2). The GEJ is normally about 2 to 3 cm below the diaphragmatic esophageal hiatus in the horizontal plane of the seventh chondrosternal articulation, a plane only slightly cephalad to that containing the pylorus. The left lateral segment of the liver usually covers a large portion of the stomach anteriorly. The remainder is bounded by the diaphragm, chest, and abdominal wall.

The relationship of the stomach to other intra-abdominal organs has important implications in disease. Adjacent organs include the pancreas and liver, which lie dorsal and ventral, as well as the spleen, which lies immediately to the left of the greater curvature. Inflammation of the pancreas may interfere with gastric emptying, whereas enlargement by neoplasm may cause an increased sensation of satiety or even obstruction of the gastric outlet. The transverse colon lies caudal and may interfere with function as a result of neoplastic invasion. The stomach itself may affect adjacent organs via perforation from peptic ulceration. Additionally, another closely related structure is the biliary tree, which runs posterior to the first portion of the duodenum, within centimeters of the gastric outlet, and can be injured during gastrectomy.

The stomach is anchored within the abdominal cavity to adjacent organs via a variety of flexible attachments known as ligaments. The gastrocolic ligament connects the greater curvature of the stomach and the transverse colon and runs along with the greater omentum, which hangs freely in the peritoneal cavity from the transverse colon. The lesser omentum is a double layer of peritoneum extending from the porta hepatis of the liver to the lesser curvature of the stomach and the first portion of the duodenum. The lesser omentum forms the anterior wall of the lesser sac and makes up the hepatogastric and hepatoduodenal ligaments; it contains the left and right gastric vessels, and its right free margin contains the hepatic artery, bile duct, and portal vein. The hepatogastric ligament attaches the stomach to the liver along the lesser curvature. The gastrosplenic ligament extends from the left portion of the greater curvature of

the stomach to the hilum of the spleen and contains the short gastric vessels and the left gastroepiploic vessels. Finally, the gastrophrenic ligament runs from the upper portion of the greater curvature to the diaphragm.

Blood Supply

The stomach derives the bulk of its blood supply (Fig. 50–3) from the celiac axis through four arteries: the left and right gastric arteries running along and supplying the lesser curvature and the left and right gastroepiploic arteries running along and supplying the greater curvature. A substantial quantity of blood may be supplied to the proximal part of the stomach by the inferior phrenic arteries and by the vasa brevia (short gastric arteries) from the spleen. The left gastric artery is the largest artery to the stomach. It originates from the celiac axis, generally courses cephalad and left, runs toward the gastric cardia, and gives off esophageal and hepatic branches before turning to the right and coursing along the lesser curvature of the stomach and the lesser omentum. It is also not uncommon (15% to 20%) for an aberrant left hepatic artery to originate from the left gastric artery. Occasionally, this vessel represents the only arterial flow to the left hepatic lobe. Proximal ligation of the left gastric artery, under these circumstances, could therefore result in acute left-sided hepatic ischemia. The right gastric artery arises from the hepatic artery but may occasionally come from the gastroduodenal artery. The right gastroepiploic artery provides blood supply to the wall of the greater curvature of the stomach, as well as the greater omentum, and originates from the gastroduodenal artery behind the pyloric channel. It usually runs along the greater curvature of the stomach and terminates in an anastomosis with the left gastroepiploic artery, which originates from the splenic artery. The anastomotic connection between these major vessels ensures that in most cases the stomach will survive if three of four arteries are ligated, provided that the arcades along the lesser and greater curvatures are not disturbed, an important surgical consideration in patients undergoing gastric resection. Generally, the veins of the stomach parallel the arteries. The left gastric (coronary) and right gastric veins usually drain to the portal vein. The right gastroepiploic vein drains into the superior mesenteric vein (a useful anatomic landmark), whereas the left gastroepiploic vein drains into the splenic vein.

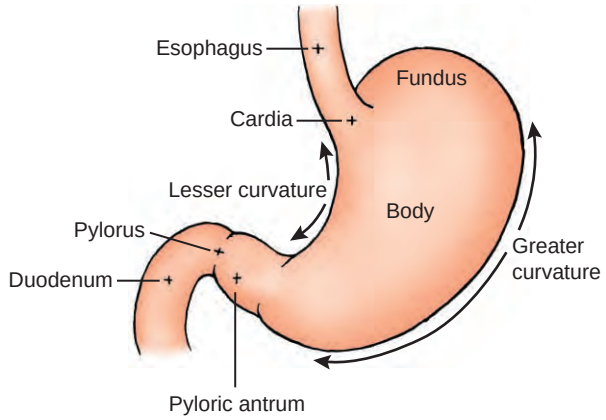

Figure 50–1. Divisions of the stomach.

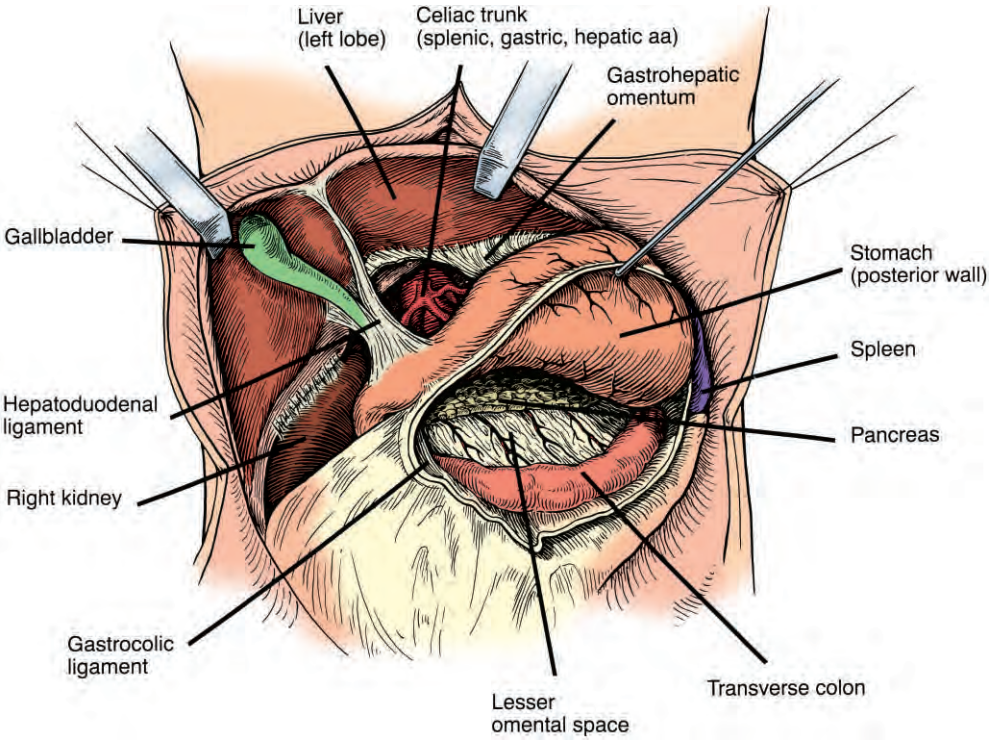

Figure 50–2. The stomach in relation to some of the deeper, adjacent structures.

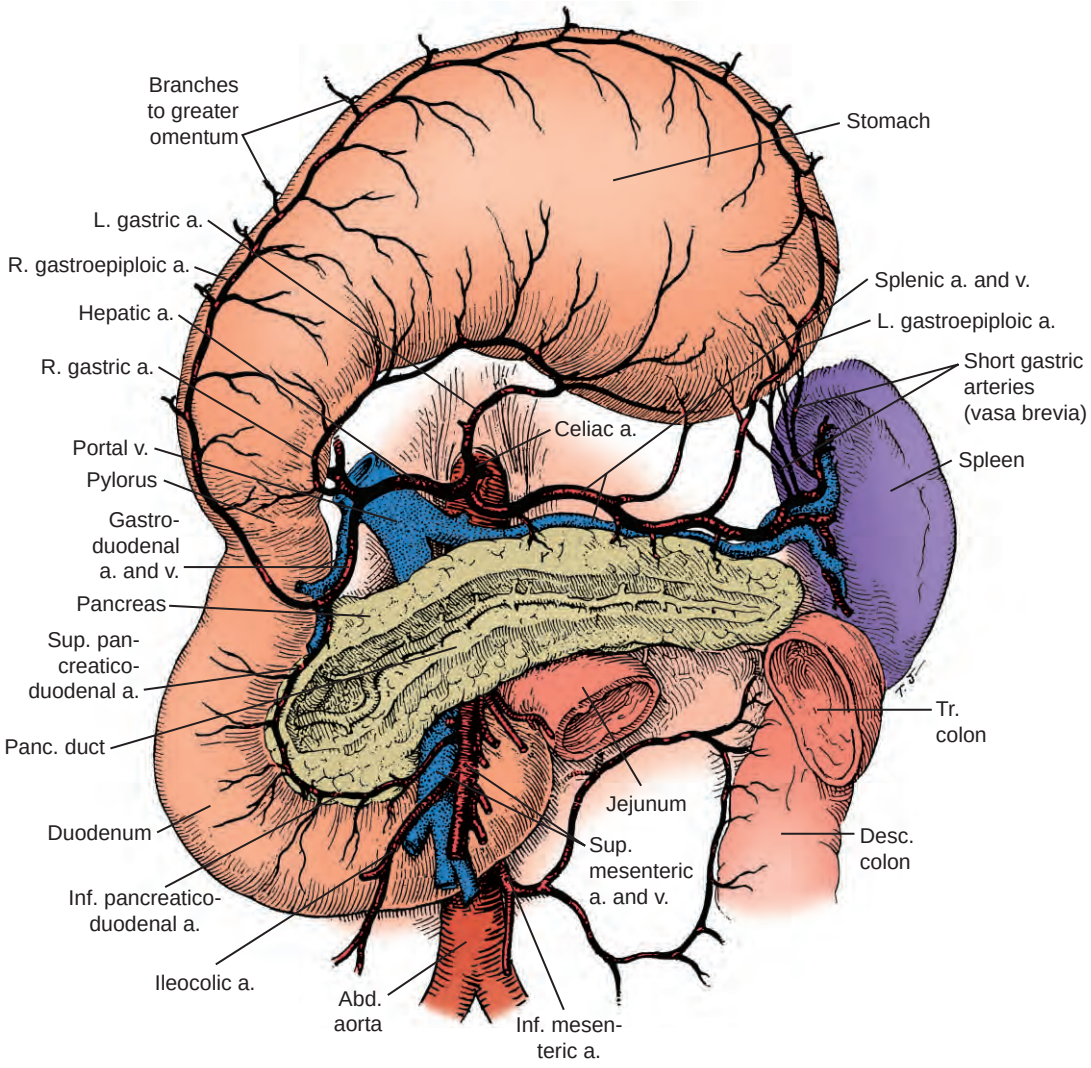

Figure 50–3. Blood supply of the stomach, duodenum, spleen, and pancreas. The stomach is shown reflected upward, and the pancreatic duct is exposed.

Lymphatic Drainage

The lymphatic drainage of the stomach usually parallels the vasculature. The cardia and medial half of the body drain to the left gastric nodes. The lesser curvature sides of the distal antrum and pylorus drain to the right gastric nodes. The greater curvature half of the distal 60% of the stomach drains into the right gastroepiploic nodal chain, whereas the proximal greater curvature drains into the left gastroepiploic chain. These four groups of nodes all drain to the celiac group, from which lymph drains into the thoracic duct. Although intraoperative and postmortem studies appear to corroborate this scheme of lymph drainage, it is widely recognized that a gastric cancer anywhere in the stomach may metastasize to any of the four nodal groups. The rich submucosal plexus of lymphatics accounts for the fact that there is often microscopic evidence of malignant cells several centimeters from the resection margin of gross disease. The anatomy of the lymph drainage of the stomach has received renewed interest as reports suggest that there may be improved survival with extended lymph node dissection in patients undergoing gastrectomy for primary gastric cancer, although this comes at a cost of increased morbidity with the more extensive procedure except when performed in high-volume centers.[1] Definitive randomized controlled trials are ongoing to determine the purported survival advantage.

Innervation

The extrinsic innervation of the stomach is both parasympathetic through the vagus and sympathetic through the celiac plexus (Fig. 50–4). From the vagal nucleus in the floor of the fourth ventricle, the vagus traverses the neck in the carotid sheath and enters the mediastinum, where it divides into several branches around the esophagus. These branches coalesce above the esophageal hiatus to form the left and right vagus nerves.

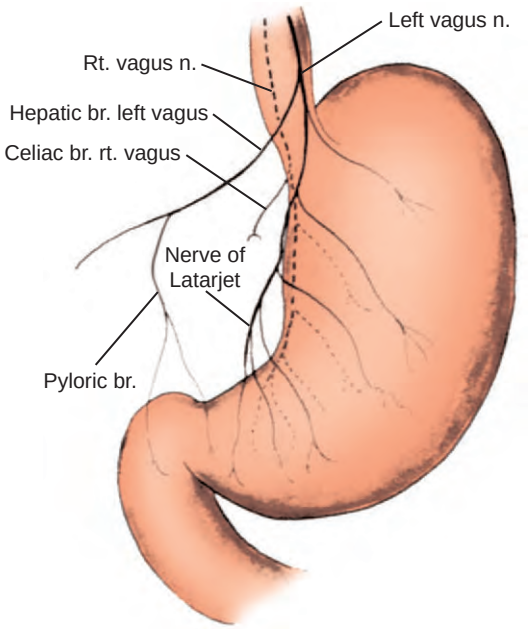

Figure 50–4. Diagram of vagal innervation of the human stomach. (From Menguy R: Surgery of Peptic Ulcer. Philadelphia, WB Saunders, 1976.)

Commonly, there are more than two vagal trunks at the distal end of the esophagus. At the GEJ the *l*eft vagus is *a*nterior, and the *r*ight vagus is *p*osterior (LARP mnemonic). Near the cardia, the left (anterior) vagus gives off a branch to the liver and then continues along the lesser curvature as the anterior nerve of Latarjet. The antral and pyloric portions of this nerve (crow's foot) must be preserved during a highly selective vagotomy so that gastric emptying is not compromised. The "criminal" nerve of Grassi is the first branch of the posterior vagus nerve. This branch has been recognized as a cause of recurrent ulcers when left undivided. The right (posterior) nerve also gives a branch off to the celiac plexus and then continues posteriorly along the lesser curvature. The majority of vagal fibers are afferent and carry stimuli from the gut to the brain. The vagal efferent fibers originate in the dorsal nucleus of the medulla and synapse with neurons in the myenteric and submucosal plexuses. These neurons use acetylcholine as their neurotransmitter and influence gastric motor function and gastric secretion. In comparison, the sympathetic nerve supply comes from T5-T10 and travels in the splanchnic nerve to the celiac ganglion. Postganglionic fibers then travel with the arterial system to innervate the stomach.

The intrinsic or enteric nervous system of the stomach consists of neurons in Auerbach's (myenteric plexus located between the longitudinal and circular muscle layers) and Meissner's (submucosal plexus located between the muscularis mucosa and circular muscle) autonomic plexuses. Cholinergic, serotonergic, and peptidergic neurons are present in addition to a newly identified system of neurons that use a nonadrenergic noncholinergic (NANC) pathway. There are probably more neurons in the intrinsic gastric nervous system than there are gastric vagal efferent fibers.[2] The function of these neurons is still poorly understood, although a number of neuropeptides have been demonstrated within these neurons. These neuropeptides include but are not limited to acetylcholine, serotonin, substance P, calcitonin gene–related peptide, bombesin, cholecystokinin (CCK), and somatostatin.

As just mentioned, there is a third and newly identified innervation of the stomach via an NANC pathway within the myenteric plexus. Signals in this pathway are mediated by gaseous messengers such as nitric oxide and carbon monoxide (NO and CO), in addition to other peptides such as vasoactive intestinal polypeptide (VIP). In this system, NO production occurs via activity of the nitric oxide synthase (NOS) enzyme system, of which there are two constitutive calcium-dependent isoforms, neuronal (n) and endothelial (e), as well as an inducible (i) calcium-independent isoform. CO is derived from the heme-oxygenase (HO) enzyme system, which itself has inducible (HO-1) and constitutive isoforms (HO-2 and HO-3). Research suggests that NO and CO expression may be regulated by vagal nerve nicotinic synapses and that they have important roles in modulating smooth muscle contractility in addition to the stomach's response to stress and injury.[3,4,5]

Thus, it is an oversimplification to think of the stomach as containing only parasympathetic (cholinergic input) and sympathetic (adrenergic input) supply. Moreover, the parasympathetic system contains adrenergic as well as cholinergic neurons, and the sympathetic system contains cholinergic as well as adrenergic neurons. In addition to these complex interactions, the exact mechanisms by which the NANC pathways are mediated continue to be the focus of ongoing research.

Gastric Morphology

The stomach is covered by peritoneum except for the exact lesser and greater curvatures and a small posterior area at the proximal cardia and distal pyloric antrum. The peritoneal coat forms the outer serosa. Below this is the thicker muscularis propria, or muscularis externa, which consists of three layers of smooth muscle (Fig. 50–5). The middle layer of smooth muscle is circular and is the only complete muscle layer of the stomach wall. This middle circular muscle layer becomes progressively thicker toward the pylorus, where it becomes impressively thick as a true anatomic sphincter. The outer muscle layer is longitudinal and continuous with the outer layer of longitudinal esophageal smooth muscle. Within the layers of the muscularis externa is Auerbach's myenteric plexus. Between the muscularis externa and the mucosa lies the submucosa, a collagen-rich layer of connective tissue that is the strongest layer of the gastric wall. The rich anastomotic network of blood vessels and lymphatics mentioned earlier lies in this layer, and it also contains Meissner's plexus.

The mucosa consists of surface epithelium, lamina propria, and muscularis mucosae. The latter is on the luminal side of the submucosa and is probably responsi-

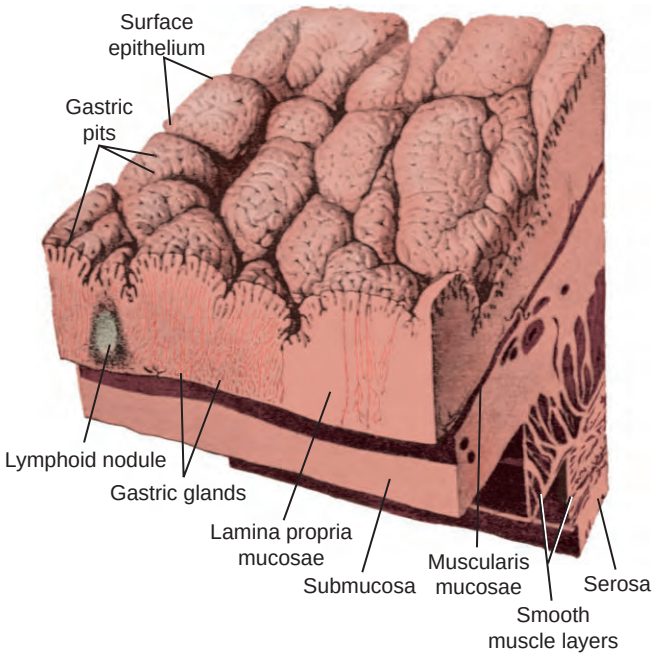

Figure 50–5. Surface of the gastric mucosa of a man (drawing based on a binocular microscope view). The cut surfaces are slightly diagrammatic. At the *left* is the normal distribution of gastric glands; to the *right,* only a few are indicated. Glands, *orange*; gastric pits, *black* (×17). (From Fawcett DW: Bloom and Fawcett's Textbook of Histology, 11th ed. Philadelphia, WB Saunders, 1986.)

ble for the rugae that greatly increase epithelial surface area. It also marks the microscopic boundary for invasive and noninvasive gastric carcinoma. The lamina propria is a small connective tissue layer that contains the capillaries, vessels, lymphatics, and nerves necessary to support the surface epithelium.

Gastric Glandular Organization

The gastric mucosa consists of columnar glandular epithelia. The functions of the glands and the types of cells lining them vary according to the region of the stomach in which they are found (Table 50–1). It should be noted that the endocrine cells, of which gastrin (G) cells and somatostatin (D) cells are best known, can be either open or closed. Open cells have microvilli on their apical membranes, which allows direct contact with the gastric contents. The microvilli probably possess chemical and pH sensors that signal the cell to secrete its prestored peptides. In contrast, closed cells do not have microvilli in contact with the gastric lumen. In the antrum, G cells and D cells are both of the open type, whereas in the fundus and body, the D cells are of the closed type and are in direct contact with the acid-secreting parietal cells. The glandular organization in the gastric mucosa differs, depending on the region of stomach examined. In the cardia, the mucosae are arranged in branched glands that secrete mostly mucus,

Table 50–1 Gastric Cell Types, Location, and Function

Cells	Location	Function
Parietal	Body	Secretion of acid, ghrelin, leptin, and intrinsic factor
Mucus	Body, antrum	Mucus
Chief	Body	Pepsin and leptin
Surface epithelial	Diffuse	Mucus, bicarbonate, and prostaglandins
ECL	Body	Histamine
G	Antrum	Gastrin
D	Body, antrum	Somatostatin
Gastric mucosal interneurons	Body, antrum	Gastrin-releasing peptide
Enteric neurons	Diffuse	CGRP, others

CGRP, calcitonin gene–related peptide; ECL, enterochromaffin-like.

and the pits are short. In the fundus and body, the glands are more tubular, and the pits are long. The fundus has an elaborate network of glands that arise from the base of the mucosa in groups of four or five and join together at the bottom of the gastric pit, or foveola. In the antrum, the glands are again more branched. The luminal ends of the gastric glands and pits are lined with mucus-secreting surface epithelial cells that extend down into the necks of the glands for variable distances. The glands at the cardia are predominantly mucus secreting. In the body, the glands are lined from the neck to the base mostly with parietal and chief cells (Fig. 50–6). There are a few parietal cells in the fundus and proximal antrum, but none are present in the cardia or prepyloric antrum. Stomach biopsy specimens have shown that parietal cells account for 13% of the epithelial cells, chief cells for 44%, mucous cells for 40%, and endocrine cells for 3%.

PHYSIOLOGY

Gastric Peptides

Gastrin

Synthesis and Action Gastrin is produced by G cells located in the gastric antrum. It is synthesized as a prepropeptide and undergoes post-translational processing to produce biologically active gastrin peptides. Several molecular forms of gastrin exist in the stomach. G-34 (big gastrin), G-17 (little gastrin), and G-14 (mini-gastrin) have all been identified. However, 90% of the antral gastrin produced is released as the 17–amino acid peptide, although G-34 predominates in the circulation because its metabolic half-life is longer than that of G-17.[6] The biologically active component of gastrin is the

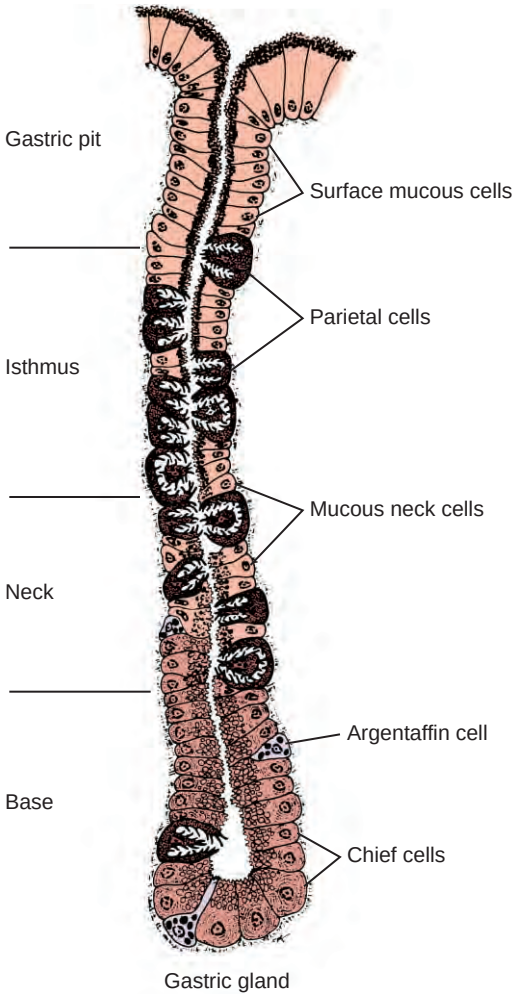

Figure 50–6. A gastric gland. (From Ito S, Winchester RJ: The fine structure of the gastric mucosa in the bat. J Cell Biol 16:541, 1963.)

pentapeptide sequence contained at its carboxyl terminus, which is identical to that found on another gut peptide, CCK. The two peptides differ in the location of tyrosine sulfation. A major stimulant for the release of gastrin is protein, as well as the digestion products of protein. Its release is inhibited by the presence of luminal acid. Somatostatin (see later) has paracrine actions on antral G cells and acts as a local inhibitor of gastrin release. In the antrum, somatostatin and gastrin release is functionally linked, and an inverse reciprocal relationship exists between these two peptides. Furthermore, somatostatin exerts a tonic inhibitory effect on gastrin release and probably mediates the inhibitory effects of luminal acid on gastrin release.

Gastrin is the major hormonal regulator of the gastric phase of acid secretion after a meal. Although parietal cells possess receptors to gastrin and exogenous gastrin elicits gastric acid secretion when given in physiologic doses, it is likely that histamine, released from enterochromaffin-like (ECL) cells, is the principal mediator of this action. Evidence supporting this concept is the finding that gastrin-stimulated gastric acid secretion is significantly blunted after the administration of H_2 receptor antagonists.[7] In addition to its acid secretory effects, gastrin has considerable trophic effects on parietal and gastric ECL cells. In fact, prolonged hypergastrinemia from any cause (e.g., gastrinoma, antisecretory drugs, atrophic gastritis) leads to mucosal hyperplasia, as well as an increase in the number of ECL cells; under some circumstances, it is associated with the development of gastric carcinoid tumors.[8] Finally, both exogenous gastrin and the release of endogenous gastrin have been shown to prevent the damaging effects of luminal irritants on gastric mucosa, thus suggesting that gastrin also plays a role in the intrinsic gastric mucosal defense system.[9]

Hypergastrinemia The hypergastrinemia that results from the administration of antisecretory agents is an appropriate response caused by a loss of feedback inhibition of gastrin release by luminal acid. Lack of acid causes a reduction in somatostatin release, which in turn causes increased release of gastrin from antral G cells. Hypergastrinemia also develops as a result of gastric atrophy, such as occurs with pernicious anemia or uremia, as well as after surgical procedures such as vagotomy or retained gastric antrum after gastrectomy. In contrast, gastrin levels increase inappropriately in patients with gastrinoma (Zollinger-Ellison syndrome). These gastrin-secreting tumors are typically located in the head of the pancreas, duodenal wall, or regional lymph nodes and secrete gastrin autonomously.

Somatostatin

Synthesis and Action Somatostatin is produced by D cells and exists endogenously as either a 14– or 28–amino acid peptide.[10] In the stomach, the predominant molecular form is somatostatin 14. Somatostatin is produced by diffuse neuroendocrine cells located in both the fundus and the antrum of the stomach. In these locations, their cytoplasmic extensions have direct contact with parietal cells and G cells, thus suggesting that somatostatin exerts its actions primarily through paracrine effects on acid secretion and gastrin release.[10] Somatostatin directly inhibits acid secretion by parietal cells but also inhibits gastrin release and down-regulates histamine release from ECL cells, which indirectly inhibits acid secretion. Antral acidification is the principal stimulus for somatostatin release, and acetylcholine from vagal fibers inhibits its release.

Effects of *Helicobacter pylori* on Somatostatin Basal and stimulated gastrin concentrations are significantly increased in patients infected with *H. pylori*. It has been proposed that *H. pylori* causes a decrease in antral D cells. The resultant decrease in somatostatin levels causes disinhibition of antral G cells and hence leads to increased gastrin in the antrum and serum.[11] Eradication of *H. pylori* restores the antral D-cell population, with a consequent increase in antral somatostatin and a decrease in gastrin levels.[11] Thus, it is tempting to speculate that infection with *H. pylori* decreases antral D cells and somatostatin levels, thereby increasing gastrin release

with a resultant increase in gastric acid secretion. However, although *H. pylori*–infected patients with duodenal ulcer disease usually have enhanced acid secretion, *H. pylori*–positive healthy volunteers with no peptic ulcer disease have either an increase of lesser magnitude or no increase at all when compared with *H. pylori*–negative volunteers. Nevertheless, cure of the infection in patients with duodenal ulcers has been demonstrated by some but not all investigators to diminish acid secretion.[11]

Gastrin-Releasing Peptide

Bombesin was isolated 20 years ago from an extract prepared from skin of the amphibian *Bombina bombina*. Its mammalian counterpart is gastrin-releasing peptide (GRP). GRP-staining immunoreactivity is particularly prominent in nerves ending in the acid-secreting and the gastrin-secreting portions of the stomach, as well as in the circular muscular layer.[12] In the antral mucosa, GRP stimulates gastrin and somatostatin release by binding to receptors located on G and D cells. GRP is rapidly cleared from the circulation by neutral endopeptidase and has a half-life of only 1.4 minutes.[12] Interestingly, exogenous GRP that is given peripherally stimulates gastric acid secretion, whereas central administration in the ventricles blunts gastric acid secretion induced by a variety of secretagogues.[12] The inhibitory pathway activated is not mediated by a humoral factor, is unaffected by vagotomy, and appears to involve the sympathetic nervous system. Research indicates that bombesin also possesses potent gastroprotective action mediated through an increase in gastric mucosal blood flow. This effect is most pronounced during times of stress and injury and acts to provide additional nutrients and remove toxins from the mucosa. This action is probably mediated via both NOS and COX (cyclooxygenase) enzyme systems.[12]

Histamine

Histamine plays a prominent role in parietal cell stimulation. H_2 receptor antagonists almost completely abolish gastrin-stimulated acid secretion and significantly blunt stimulated acid secretion induced by acetylcholine.[7] These findings suggest that histamine is a necessary intermediary of gastrin- and acetylcholine-stimulated acid secretion. Histamine is stored in the acidic granules of ECL cells, as well as in resident mast cells. ECL cells have been shown to possess receptors for gastrin, acetylcholine, and epinephrine, all of which stimulate histamine release. The ECL cell also has receptors for somatostatin, which inhibits gastrin-stimulated histamine release. Thus, the ECL cell plays a central role in parietal cell activation and possesses both stimulatory and feedback pathways that modulate the release of histamine and, consequently, acid secretion.

Ghrelin

Ghrelin is a recently discovered 28–amino acid acylated peptide secreted by oxyntic cells in the fundus of the stomach. Ghrelin is the first gut peptide found to have orexigenic (appetite stimulating) properties and appears to play a major role in energy homeostasis. Ghrelin levels have been shown to increase preprandially, coinciding with the development of feeling hungry, and then decrease postprandially after a satiating meal has been consumed.[13] Ghrelin appears to increase food intake through stimulation of ghrelin receptors located in the hypothalamic areas of the brain, such as the paraventricular nucleus and lateral hypothalamic area, as well as areas of the brainstem (all areas of major integration for the control of feeding behavior, energy expenditure, and gastrointestinal function) where neuropeptide Y (NPY)-expressing neurons and agouti-related protein (AgRP)-expressing neurons are localized.[14] This ghrelin-induced activation of NPY acts as a powerful orexigenic signal that results in increased food intake, decreased energy expenditure, and stimulation of peripheral glucocorticoid and insulin secretion, which favors the deposition of fat into adipose tissue.[15] Interestingly, gastrectomy and gastric bypass procedures significantly reduce plasma ghrelin levels, thus underscoring the importance of the stomach as an endocrine organ intimately involved in the maintenance of body weight and energy metabolism.[16] Additionally, it appears that the afferent vagus nerve fibers play an important role in transducing some of the effects of ghrelin inasmuch as vagotomy abolishes some of these effects.[17] Research further indicates that a complex signaling system involving the gut peptides leptin, CCK, pancreatic polypeptide, and peptide YY, along with ghrelin, works to control energy expenditure, although the exact interactions among these different peptides remain to be defined.[18]

Leptin

Leptin is a 14-kD protein discovered in 1994 that is also intimately involved in the regulation of metabolism and body weight.[19] Though mostly synthesized by adipocytes of white fat, another important source of leptin is the chief cells of the stomach because it is not found anywhere else in the gastrointestinal tract.[20] Like ghrelin, leptin exerts its influence on energy and appetite via stimulation of hypothalamic neurons expressing AgRP and NPY. When initially discovered, the elegant mechanism proposed indicated that levels of leptin rose in proportion to the amount of adipose tissue and signaled satiety to the hypothalamus with a resultant reduction in food intake. Thus, the actions of leptin seem to oppose those of ghrelin in that leptin acts as an antiobesity hormone that decreases appetite and increases metabolism by acting as a "satiety signal" as opposed to the "hunger signal" mediated by ghrelin. However, as the knowledge base has expanded, the effects of leptin have been found to be much more complex, and differential interactions among the pathways controlling both ghrelin and leptin probably play a major role in weight regulation. Additional data suggest that the vagus nerve may mediate gastric secretion of leptin and that short-term regulation of appetite may be due to differential alterations between systemic, plasma, and local gastric mucosal levels of leptin caused by the ingestion of enteral nutrients—again underscoring the important role of the stomach as an endocrine organ in the maintenance of body weight.[21,22]

Outside of its effects on appetite, leptin also has numerous other effects on the body. For example, leptin is a powerful gastroprotective agent against damage caused by luminal irritants and has effects on insulin sensitivity, inflammation and immune function, bone formation, and angiogenesis.[23-26] These additional actions of leptin outside its effects on energy balance are probably due to local rather than systemic effects and appear to be mediated via JAK-STAT phosphorylation protein kinases.[26]

Gastric Acid Secretion

In all vertebrates, gastric acid secretion by the parietal, or oxyntic, cell is regulated by three local stimuli: acetylcholine, gastrin, and histamine. These three stimuli account for basal and stimulated gastric acid secretion. Acetylcholine, released from the vagus and parasympathetic ganglion cells, is the principal neurotransmitter modulating acid secretion. In addition to innervating parietal cells, vagal fibers innervate G cells and ECL cells. Gastrin has hormonal (i.e., endocrine) effects on the parietal cell and causes release of histamine. Histamine, in turn, has paracrine-like effects on the parietal cell and is produced by ECL cells that receive additional endocrine (gastrin) and neural (acetylcholine) input. As shown in Figure 50–7, the ECL cell plays a central role in the regulation of acid secretion by the parietal cell. The model depicted also illustrates the inhibitory actions of somatostatin on gastric action secretion. The presence of intraluminal acid to a pH of 3 elicits the release of somatostatin from antral D cells, which inhibits gastrin release through paracrine effects and also modifies histamine release from ECL cells.[27] This negative feedback response is defective in some patients with peptic ulcer disease.[28] Thus, the precise state of acid secretion is dependent on the overall influence of these positive and negative stimuli.

Basal or Interprandial Acid Secretion

The secretory status of the parietal cell in the absence of food varies among species. Humans maintain a basal level of acid secretion that is roughly 10% of maximal acid output. Basal acid secretion also exhibits a circadian variation, with nighttime acid secretion being greater than daytime. Under basal conditions, 1 to 5 mmol of hydrochloric acid is secreted, and this amount is reduced by 75% to 90% after vagotomy or administration of atropine. These findings suggest that acetylcholine plays a significant role in basal secretion. However, H_2 receptor blockade also diminishes the magnitude of acid secretion by 90%, which suggests that histamine is also an important intermediary. Thus, it appears likely that basal acid secretion is the result of a combination of cholinergic and histaminergic input.

Stimulated Acid Secretion

The physiologic stimulus for acid secretion is ingestion of food. The acid secretory response that occurs after a meal has traditionally been described in three phases: cephalic, gastric, and intestinal. These three phases are interrelated and occur concurrently, not consecutively.

Cephalic Phase The vagal, or cephalic, phase originates with the sight, smell, thought, or taste of food, which excites neural centers in the cortex and hypothalamus. Although the exact mechanisms by which senses stimulate acid secretion remain to be fully elucidated, it is hypothesized that several sites are stimulated in the brain. Sensitive sites include the dorsal vagal complex, nucleus tract solitarius, and dorsal motor nucleus, with secretion of thyrotropin-releasing hormone possibly involved in stimulation. Signals are transmitted from these higher centers to the stomach by the vagus nerves via release of acetylcholine, which in turn activates muscarinic receptors located on target cells. Acetylcholine directly increases acid secretion by parietal cells and can both inhibit and stimulate gastrin release, the net effect being a slight increase in gastrin levels.[29] Vagal stimulation in humans by sham feeding (chew and spit) results in an increase in acid secretion to about 50% of the maximal acid response to exogenous gastrin or histamine. Although the intensity of the acid secretory response in the cephalic phase surpasses that of the other phases, because the duration of the cephalic phase is brief, it accounts for only 20% to 30% of the total volume of gastric acid produced in response to a meal in humans.

Gastric Phase The gastric phase of acid secretion begins when food enters the gastric lumen. Chemical components contained within the ingested food interact with the microvilli of antral G cells to stimulate gastrin release. Protein digests and amino acids are particularly effective at stimulating gastrin release, with the aromatic amino acids phenylalanine and tryptophan being the most potent. In addition, food stimulates acid secretion by causing mechanical distention of the stomach. Gastric distention activates stretch receptors in the stomach to elicit the long vagovagal reflex arc. It is abolished by proximal gastric vagotomy and is, at least in part, independent of changes in serum gastrin levels. However, antral distention does cause gastrin release in humans, and this reflex has been called the pyloro-oxyntic reflex.[30] It has been estimated from human studies that mechanical distention of the stomach results in about 30% to 40% of the maximal acid secretory response to a peptone meal, with the remainder being due to gastrin release. The entire gastric phase accounts for most (60% to 70%) of the meal-stimulated acid output because it lasts until the stomach is empty.

Intestinal Phase The intestinal phase of gastric secretion is still poorly understood but is initiated by entry of chyme into the small intestine. It occurs after gastric emptying and lasts as long as partially digested food components remain within the proximal part of the small bowel. It accounts for roughly 10% of the acid secretory response to a meal and does not appear to be mediated by serum gastrin levels. It is thought to be mediated by a distinct acid stimulatory peptide hormone (enteroxyntin) that is released from small bowel mucosa.

Cellular Basis of Acid Secretion

Parietal Cell Receptors

Gastrin Receptors CCK and gastrin initiate their biologic actions by activation of surface membrane receptors. These receptors are members of the classic G protein–coupled seven transmembrane–spanning receptor family and have been classified as either type A or type B CCK receptors. Type A CCK receptors have high affinity for sulfated CCK analogues and low affinity for gastrin.[9] Type B CCK receptors, on the other hand, have high affinity for both gastrin and CCK. The gastrin or CCK-B receptor has been cloned from a parietal cell library, and binding of ligand with receptor was found to be coupled to elevated intracellular calcium levels.[31]

Muscarinic Receptors The actions of acetylcholine on the parietal cell are mediated via the M_3 subtype of the muscarinic receptor family. This receptor is also coupled to increased levels of intracellular calcium, which is mediated by phospholipase-induced production of inositol triphosphate (IP_3).[31]

Histamine Receptors Histamine belongs to the same family of G protein–coupled seven transmembrane–spanning receptors. The receptor on the parietal cell is the H_2 subtype. Coupling with histamine causes activation of adenylate cyclase, which leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) levels.

Somatostatin Receptors At least five different types of somatostatin receptors have been cloned. These receptors are also members of the seven transmembrane–spanning receptors and are coupled to one or more inhibitory guanine nucleotide binding proteins. The different somatostatin receptors also appear to have divergent pharmacologic effects because one somatostatin receptor may associate with an inhibitory G protein whereas another may not.[10] In the stomach, parietal cell somatostatin receptors have been identified and appear to be a single subunit of glycoproteins with a molecular weight of 99 kD and equal affinity for somatostatin 14 and somatostatin 28.[10] Inhibition of parietal cell secretion by somatostatin occurs through both G protein–dependent and G protein–independent mechanisms. However, the ability of somatostatin to exert its inhibitory actions on cellular function is primarily thought to be mediated by inhibition of adenylate cyclase with a resultant reduction in cAMP levels.

Second Messengers Stimulation of acid secretion by parietal cells is primarily mediated by increased levels of intracellular cAMP and calcium. The production of these two second messengers in turn activates a variety of protein kinases. However, although these protein kinases become activated and result in the phosphorylation of parietal cell proteins within the cytosol, little is known about the precise phosphorylation pathways that result in activation of the proton pump, which is ultimately responsible for acid secretion. Nonetheless, the intracellular events following ligand binding to receptors on the parietal cell are demonstrated in Figure 50–8. As shown, histamine causes intracellular cAMP levels to increase, which activates protein kinases to initiate a cascade of phosphorylation events that culminate in the activation of H^+,K^+-adenosine triphosphatase (ATPase). In contrast, acetylcholine and gastrin stimulate phospholipase C, which converts membrane-bound phospholipids into IP_3 to mobilize calcium from intracellular stores. Increased intracellular calcium activates other protein kinases that ultimately activate H^+,K^+-ATPase to begin secretion of hydrochloric acid.

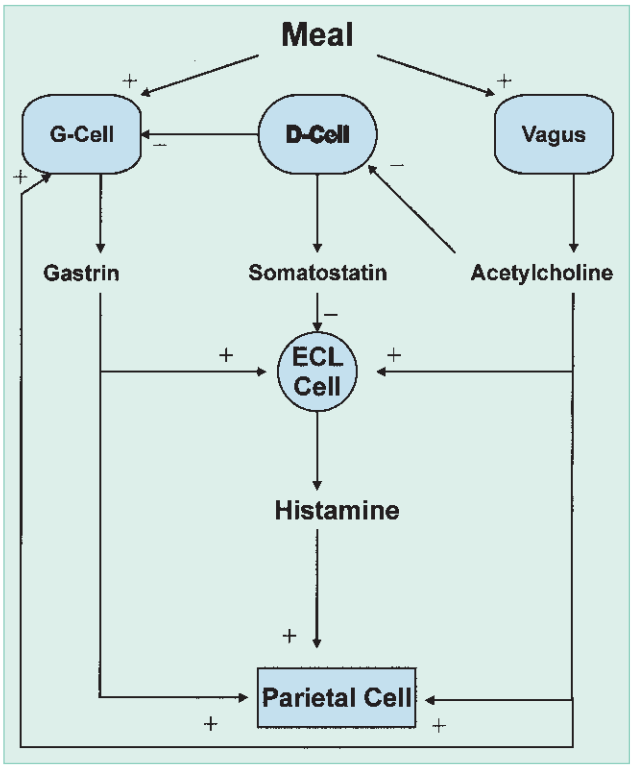

Figure 50–7. The central role of the enterochromaffin-like (ECL) cell in regulation of acid secretion by the parietal cell is depicted. As shown, after ingestion of a meal, vagal fibers are stimulated and release acetylcholine (cephalic phase). Acetylcholine binds to M_3 receptors located on the ECL cell, parietal cell, and G cell to cause the release of histamine, hydrochloric acid, and gastrin, respectively. Acetylcholine also interacts with M_3 receptors located on the D cell to inhibit somatostatin release. Food within the gastric lumen also stimulates the G cell to release gastrin, which in turn binds to type B cholecystokinin receptors located on the ECL cell and parietal cell and causes the release of histamine and hydrochloric acid, respectively (gastric phase). Somatostatin released from the D cell inhibits histamine release from the ECL cell and gastrin release from the G cell. Somatostatin also inhibits acid secretion by the parietal cell (not shown). The principal stimulus for activation of the D cell is antral luminal acidification (not shown).

Activation and Secretion by the Parietal Cell The final common pathway for gastric acid secretion by the

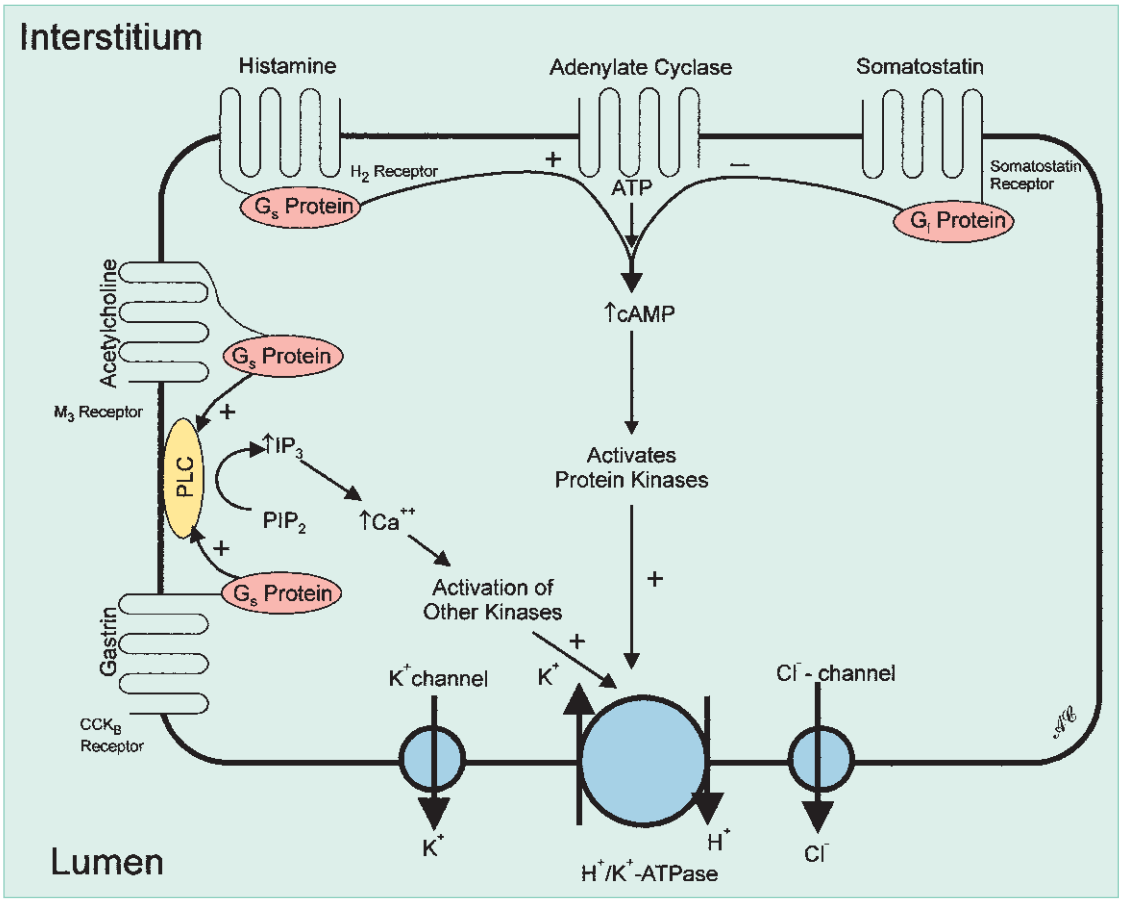

Figure 50–8. The intracellular events after ligand binding to the parietal cell are depicted. Gastrin binds to the type B cholecystokinin (CCK) receptor and acetylcholine binds to M_3 receptors to stimulate phospholipase C (PLC) through a G protein—linked mechanism. Activated phospholipase C converts membrane-bound phospholipids into inositol triphosphate (IP_3), which stimulates the release of intracellular calcium from intracellular calcium stores. The increase in intracellular calcium leads to the activation of protein kinases, which activate H^+,K^+-ATPase. Histamine binds to its H_2 receptor to stimulate adenylate cyclase, which also occurs through a G protein—linked mechanism. Activation of adenylate cyclase leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) levels, which activates protein kinases. Activated protein kinases stimulate a phosphorylation cascade that results in increased levels of phosphoproteins, which activate the proton pump. Activation of the proton pump leads to extrusion of cytosolic hydrogen in exchange for extracytoplasmic potassium. In addition, chloride is secreted through a chloride channel located at the luminal side of the membrane. ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; G_s, stimulatory guanine nucleotide protein; G_i, inhibitory guanine nucleotide protein; PIP_2, phosphatidylinositol 4,5-diphosphate.

parietal cell is H^+,K^+-ATPase. The enzyme is composed of a catalytic α (relative molecular weight [M_r], ≈100 kD) subunit and a glycoprotein β (M_r, ≈60 kD) subunit. During the resting or nonsecreting state, gastric parietal cells store H^+,K^+-ATPase within intracellular tubulovesicular elements. For acid secretion to increase in response to stimulatory factors, cellular relocation of the acid pump through cytoskeletal rearrangements must occur. Binding of secretagogues causes fusion of the tubulovesicles with the apical plasma membrane. This is an essential process, and research indicates that alkalinization of the gastric environment during critical illness may be due to failure of rearrangement of the cytoskeleton of the cell.[32] The subsequent insertion and heterodimer assembly of the H^+,K^+-ATPase subunits into the microvilli of the secretory canaliculus cause an increase in gastric acid secretion.[31] In addition, a potassium chloride (KCl) efflux pathway must exist to supply potassium to the extracytoplasmic side of the pump. H^+,K^+-ATPase secretes cytosolic hydrogen in exchange for extracytoplasmic potassium (see Fig. 50–8), which is an electroneutral exchange and therefore does not contribute to the transmembrane potential difference across the parietal cell. Chloride is secreted through a chloride channel that moves chloride from the cytoplasm to the gastric lumen. The secretion/exchange of hydrogen for potassium, however, does require energy in the form of ATP because hydrogen is being secreted against a gradient of more than 1 million–fold. Because of this large energy requirement, the parietal cell also has the largest mitochondrial

content of any mammalian cell, with the mitochondrial compartment representing 34% of its cell volume. In contrast to stimulated acid secretion, cessation of acid secretion requires endocytosis of H^+,K^+-ATPase with regeneration of cytoplasmic tubulovesicles containing the subunits, and this occurs through a tyrosine-based signal.[33] The tyrosine-containing sequence is located on the cytoplasmic tail of the β subunit and is highly homologous to the motif responsible for internalization of the transferrin receptor.

The normal human stomach contains more than 1 billion parietal cells that secrete about 20 mmol of hydrochloric acid per hour in response to a protein meal. Each individual parietal cell secretes 3.3 billion hydrogen ions per second, and there is a linear relationship between maximal acid output and parietal cell number. Gastric acid secretory rates are altered in patients with upper gastrointestinal diseases. For example, gastric acid is increased in patients with duodenal ulcer or gastrinoma, whereas it is decreased in patients with pernicious anemia, gastric atrophy, gastric ulcer, or gastric cancer. The lower secretory rates observed in patients with gastric ulcer are typically for proximal gastric ulcers, whereas distal, antral, or prepyloric ulcers are associated with acid secretory rates similar to those found in patients with duodenal ulcer.

Pharmacologic Regulation of Gastric Acid Secretion Gastric acid secretion can be blunted by the administration of site-specific receptor antagonists for histamine or gastrin, as well as by muscarinic receptor antagonists. These receptor antagonists inhibit gastric acid secretion by competitive inhibition of the receptor. The best known of the site-specific antagonists is the group collectively known as the H_2 or histamine receptor antagonists. The most potent of the H_2 receptor antagonists is famotidine, followed by ranitidine, nizatidine, and cimetidine. The half-life of famotidine is 3 hours, with an approximately 1.5-hour half-life for the others. All undergo hepatic metabolism, are excreted by the kidney, and do not differ much in bioavailability. The substituted benzimidazoles are another class of antisecretory agents, of which omeprazole, esomeprazole, rabeprazole, and lansoprazole are examples. These agents are more complete inhibitors of acid secretion because they act at the final step of gastric acid secretion to irreversibly inhibit the proton pump. The proton pump inhibitors are weak acids with a pK_a of 4.0 and therefore become selectively localized in the secretory canaliculus of the parietal cell, which is the only structure in the body with a pH lower than 4. After oral administration, these agents are absorbed into the bloodstream as prodrugs and then selectively concentrate in the secretory canaliculus. At low pH, they become ionized and then activated by the formation of an active sulfur group. For this reason, patients consuming substituted benzimidazoles should not take additional antisecretory agents because they will raise gastric pH and prevent activation of the benzimidazoles. Because the proton pump is located on the luminal surface, the transmembrane pump proteins are also exposed to acid or low pH. The cysteine residues on the α subunit form a covalent disulfate bond with activated benzimidazoles that irreversibly inhibits H^+,K^+-ATPase. Because of the covalent nature of this bond, omeprazole and agents like it exhibit more prolonged inhibition of gastric acid secretion than H_2 blockers do. It is quite likely that recovery of acid secretion after administration of these compounds requires the synthesis of new enzyme. Furthermore, the covalent bond causes a longer duration of action than the plasma half-life, with intragastric pH being maintained above 3 for 18 hours or more.

One side effect of the proton pump inhibitors is an elevation in serum gastrin levels, which also occurs in response to the other antisecretory agents. However, 24-hour plasma gastrin levels are greater with proton pump inhibitors than with H_2 receptor antagonists, and this effect is accompanied by hyperplasia of G cells and ECL cells when these agents are administered chronically. The effect is reversed after discontinuation of these agents, provided that gastric acidity returns to normal levels. Under long-term administration of omeprazole, it was also noted that ECL cell hyperplasia could progress to carcinoid tumors in rats.[8] These tumors were more common in females than in males and occurred only when the rats were at the end of their natural life span. This sequence of events was not specific for omeprazole and was reproduced by other agents that caused prolonged inhibition of acid secretion and resultant hypergastrinemia.

Functions of Gastric Acid

Gastric acid plays a critical role in the digestion of a meal. It is required to convert pepsinogen (see later) into pepsin, which is necessary for the hydrolysis of proteins into polypeptides. Gastric acid also elicits the release of secretin from the duodenum, which results in pancreatic bicarbonate secretion. Furthermore, gastric acid functions to limit colonization of the upper gastrointestinal tract by bacteria. Colonization of the stomach and duodenum is known to occur in patients with achlorhydria and those receiving antisecretory agents. In addition, there is evidence of causation between gastric colonization and the subsequent development of nosocomial pneumonia in the intensive care unit (ICU).[34] Gastric luminal alkalinization attenuates the natural bactericidal effect of gastric acid and thus creates an environment conducive to bacterial overgrowth. Interestingly, the pathogens involved in nosocomial pneumonia, the principal infection of patients with multiple organ failure in the ICU, are frequently found in gastric aspirates and appear to temporally colonize the stomach before the development of clinical pneumonia.[35] However, some studies challenge the importance of increased gastric colonization with bacterial pathogens in the subsequent development of nosocomial pneumonia.[36]

Other Gastric Secretory Products

Gastric Juice

Gastric juice is the result of secretions by parietal cells, chief cells, and mucous cells, in addition to swallowed

Table 50–2 Gastric Electrolyte Composition in the Human Whole Stomach

Parietal						
[H]	**[Na]**	**[K]**	**[All Cations]**	**[HCO_3]**	**[Cl]**	**[All Anions]**
148.9	—	16.9	165.8	—	166.3	166.3
Nonparietal						
[H]	**[Na]**	**[K]**	**[All Cations]**	**[HCO_3]**	**[Cl]**	**[All Anions]**
—	136.7	6.4	143.1	25.0	117.8	142.8

saliva and duodenal refluxate. The electrolyte composition of parietal and nonparietal gastric secretions (Table 50–2) varies with the rate of gastric secretion. Parietal cells secrete an electrolytic solution that is isotonic with plasma and contains 160 mmol/L. The pH of this solution is 0.8. The lowest intraluminal pH commonly measured in the stomach is 2 because of secretions that also contain sodium, potassium, and bicarbonate.

Intrinsic Factor

Intrinsic factor is a 60,000-dalton mucoprotein secreted by the parietal cell that is essential for the absorption of vitamin B_{12} in the terminal ileum. Intrinsic factor is secreted in amounts that far exceed what is necessary for vitamin B_{12} absorption. However, the gastric mucosa is the critical site of production for intrinsic factor, and thus patients undergoing gastrectomy or proximal stomach resection may require a monthly injection of vitamin B_{12}. Its secretion parallels that of gastric acid secretion, yet the secretory response is not necessarily linked to acid secretion. For example, proton pump inhibitors do not block secretion of intrinsic factor in humans, nor do they alter the absorption of labeled vitamin B_{12}. Deficiency of intrinsic factor can develop in the setting of pernicious anemia, and these patients also require vitamin B_{12} supplementation.

Pepsinogen

Pepsinogens are proteolytic proenzymes with a molecular weight of 42,500 that are secreted by the glands of the gastroduodenal mucosa. In general, two types of pepsinogens are secreted. Group 1 pepsinogens are secreted by chief cells and by mucous neck cells located in the glands of the acid-secreting portion of the stomach. In contrast, group 2 pepsinogens are produced by surface epithelial cells throughout the acid-secreting portion of the stomach, as well as the antrum and proximal duodenum. As a result, group 1 pepsinogens are secreted by the same glands that secrete acid, whereas group 2 pepsinogens are secreted by acid-secreting and gastrin-secreting mucosa. In the presence of acid, both forms of pepsinogen are converted to pepsin by removal of a short amino-terminal peptide. Pepsins become inactivated at a pH higher than 5, although group 2 pepsinogens are active over a wider range of pH values than the group 1 pepsinogens are.[37] Consequently, group 2 pepsinogens may be involved in peptic digestion in the setting of increased gastric pH, which commonly occurs with stress or in patients with gastric ulcer.

Mucus and Bicarbonate

Mucus and bicarbonate combine to neutralize gastric acid at the gastric mucosal surface. Both are secreted by surface mucous cells and by mucous neck cells located in the acid-secreting portion of the stomach and the antrum. Mucus is a viscoelastic gel that contains approximately 85% water and 15% glycoproteins and provides a mechanical barrier to injury by contributing to the unstirred layer of water found at the luminal surface of the gastric mucosa. It provides some impediment to ion movement from the lumen to the apical cell membrane and is relatively impermeable to pepsins. It is also in a constant state of flux because it is secreted continuously by mucosal cells on the one hand and solubilized by luminal pepsin on the other. Research suggests that both prostaglandins derived from the constitutive cyclooxygenase-1 enzyme and nitric oxide from the eNOS and nNOS systems are critical to maintenance of the protective mucous layer and may act as important molecular mediators of the protective mucous layer.[38] Vagal stimulation, cholinergic agonists, prostaglandins, and some bacterial toxins stimulate mucus production, whereas anticholinergic drugs and nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit its secretion. *H. pylori,* however, secretes various proteases and lipases that break down mucin, thereby impairing the protective function of the mucous layer.[39] Newer research techniques have shown that neither chief nor parietal cells have a significant amount of differential transcription expression in the presence of *H. pylori* whereas the mucous cell exhibits profound changes in its transcription patterns because of *H. pylori.* Furthermore, the genes that are differentially expressed upon infection are implicated in proinflammatory and mucosal defense responses, as well as modulation of angiogenesis, iron availability, and tumor suppression.[40]

In the acid-secreting portion of the stomach, bicarbonate secretion is an active process, whereas in the antrum, both active and passive secretion of bicarbonate occurs. It is noteworthy that the magnitude of bicarbonate secretion is considerably less than that of acid secretion, yet although the luminal pH is 2, the pH observed at the surface epithelial cell layer is usually 7. The pH gradient found at the epithelial surface is the result of the aforementioned unstirred layer of water contained within the mucous gel and the continuous secretion of bicarbonate by the surface epithelial cells. Gastric cell surface pH remains greater than 5 until the luminal pH is less than 1.4. However, luminal pH in patients with duodenal ulcer is frequently less than 1.4, so the cell surface is exposed to lower pH in these patients. This reduction in pH may reflect a decrease in gastric bicarbonate secretion, as well as decreased duodenal bicarbonate secretion, and may explain why some patients with duodenal ulcer have a higher relapse rate after treatment.[41]

Gastric Barrier Function and Peptic Ulcer Disease

Gastric barrier function depends on a number of physiologic and anatomic factors, including but not limited to cell membranes, tight junctions, cell renewal processes, mucus secretion, alkaline secretion, and gastric pH. Microvascular blood flow also plays a role in gastric mucosal defense by providing nutrients and delivering oxygen to ensure that the intracellular processes that underlie mucosal resistance to injury can proceed unabated. Decreased gastric mucosal blood flow has minimal effects on lesion production until it approaches 50% of normal. When blood flow is reduced by more than 75%, marked mucosal injury results and is exacerbated in the presence of luminal acid. Once damage occurs, injured surface epithelial cells are replaced rapidly by migration of surface mucous cells located along the basement membrane. This process is referred to as restitution or reconstitution.[42] It occurs within minutes and does not require cell division.

Exposure of the stomach to noxious agents causes a reduction in the potential difference across the gastric mucosa. In normal gastric mucosa, the potential difference across the mucosa is –30 to –50 mV and results from the active transport of chloride into the lumen and sodium into the blood whose gradients are maintained by the activity of Na^+/K^+-ATPase. Damage disrupts the tight junctions between mucosal cells and causes the epithelium to become leaky to ions (i.e., Na^+ and Cl^-), with a resultant loss of the high transepithelial electrical resistance normally found in gastric mucosa. In addition, damaging agents such as NSAIDs or aspirin possess carboxyl groups that are nonionized at low intragastric pH because they are weak acids. Consequently, they readily enter the cell membranes of gastric mucosal cells because they are now lipid soluble, whereas they will not penetrate the cell membranes at neutral pH because they are ionized. On entry into the neutral pH environment found within the cytosol, they become reionized, will not exit the cell membrane, and are toxic to the mucosal cells.

Duodenal ulcer disease is a disease of multiple causes. The only relatively absolute requirements are secretion of acid and pepsin in conjunction with *H. pylori* infection or ingestion of NSAIDs. Gastric acid secretory rates are usually increased in patients with duodenal ulcer disease. Both basal gastric acid output and peak pentagastrin-stimulated acid output are increased in duodenal ulcer patients when compared with controls, although there is extensive overlap between groups. Mean parietal cell numbers have also been shown to be increased in duodenal ulcer patients when compared with controls.[43] In contrast, the mean parietal cell number is not increased in patients with gastric ulcer disease, which is also not associated with excess gastric acid secretion. Pepsin secretion has likewise been found to be increased in duodenal ulcer patients and is associated with an increase in the peptic cell mass responsible for synthesizing pepsinogens. When compared with the level in control patients, serum pepsinogen 1, but not pepsinogen 2, was found to be increased in patients with duodenal ulcer.[44]

Gastric Motor Function

Gastric motility is regulated by extrinsic and intrinsic neural mechanisms, as well as by myogenic control. The extrinsic neural controls are mediated through parasympathetic (vagus) and sympathetic pathways, and the intrinsic controls involve the enteric nervous system already discussed in the "Anatomy" section. In contrast, myogenic control resides within the excitatory membranes of the gastric smooth muscle cells. When the cell membrane potential exceeds its threshold potential, an action potential is generated that results in muscle contraction. The resting potential changes in gradient from –48 mV in the gastric pacemaker interstitial cells of Cajal (ICCs), located in the proximal part of the stomach, to a resting gradient of –75 mV in the pylorus. This change in resting potential may be responsible in part for the reduced rate of contractions observed in the distal end of the stomach when compared with that in the proximal end. ICCs are critical for the generation of sequential contractions and probably receive input from a variety of mechanical as well as biochemical sources. Future research on ICCs will most likely yield important knowledge about the pathogenesis of gastric dysfunction.[45]

Fasting Gastric Motility

The electrical basis of gastric motility begins with depolarization of the pacemaker cells located in the midbody of the stomach along the greater curvature. Once initiated, slow waves travel at three cycles per minute in a circumferential and antegrade fashion toward the pylorus.[46] In addition to these slow waves, gastric smooth muscle cells are capable of producing action potentials, which are associated with larger changes in membrane potential than slow waves are. When compared with slow waves, which are not associated with gastric contractions, action

potentials are associated with actual muscle contractions. During fasting, the stomach goes through a cyclic pattern of electrical activity that has been termed the myoelectric migrating complex (MMC). Each MMC cycle lasts 90 to 120 minutes and is made up of four phases. Phase I of the MMC is the quiescent phase, in which slow waves are present without action potentials; this phase results in an increase in gastric tone but no gastric contraction. In phase II of the MMC, the motor spikes are associated with slow waves and occasional gastric contractions. During phase III, motor spike activity is associated with each slow wave, and forceful gastric contractions are produced every 15 to 20 seconds. The net effect of phase III MMC activity is clearance of large undigestible food substances contained within the stomach. Phase IV activity is characterized as a brief period of recovery before the next MMC cycle. The net effects of the MMC are frequent clearance of gastric contents during periods of fasting. The exact regulatory mechanisms of MMC activities are unknown, but these activities remain intact after vagal denervation.

Postprandial Gastric Motility

Ingestion of a meal results in a decrease in the resting tone of the proximal stomach and fundus, referred to as receptive relaxation and gastric accommodation. Because these reflexes are mediated by the vagus nerves, interruption of vagal innervation to the proximal part of the stomach, such as by truncal vagotomy or proximal gastric vagotomy, can eliminate these reflexes with resultant early satiety and rapid emptying of ingested liquids.[47] In addition to its storage function, the stomach is responsible for the mixing and grinding of ingested solid food particles. This activity involves repetitive forceful contractions of the midportion and antral portion of the stomach, which causes food particles to be propelled against a closed pylorus with subsequent retropulsion of solids and liquids. The net effect is a thorough mixing of solids and liquids and a sequential shearing of solid food particles to a size less than 1 mm.

The emptying of gastric contents is under the influence of well-coordinated neural and hormonal mediators. Systemic factors such as anxiety, fear, depression, and exercise can affect the rate of gastric motility and emptying. Additionally, the chemical properties, mechanical properties, and temperature of the intraluminal contents can influence the rate of gastric emptying. In general, liquids empty more rapidly than solids, and carbohydrates empty more readily than fats. Increases in the concentration or acidity of liquid meals cause a delay in gastric emptying. In addition, hot and cold liquids tend to empty at a slower rate than ambient-temperature fluids do. These responses to luminal stimuli are regulated by the enteric nervous system. Osmoreceptors and pH-sensitive receptors in the proximal part of the small bowel have also been shown to be involved in the activation of feedback inhibition of gastric emptying. Inhibitory peptides proposed to be active in this setting include CCK, glucagon, VIP, and gastric inhibitory polypeptide.

Abnormal Gastric Motility

Symptoms of abnormal gastric motility are nausea, fullness, early satiety, and abdominal pain and discomfort. Although mechanical obstruction can and should be ruled out with upper endoscopy or radiographic contrast studies (or both), objective evaluation of a patient with a suspected motility disorder can be accomplished with gamma scintigraphy, real-time ultrasound, and magnetic resonance imaging. The gastric motility disorders that are most commonly encountered in clinical practice are gastric dysmotility after vagotomy, delayed gastric emptying associated with diabetes mellitus, and gastric motility dysfunction related to *H. pylori* infection. Vagotomy results in the loss of receptive relaxation and gastric accommodation in response to meal ingestion, with resultant early satiety, postprandial bloating, accelerated emptying of liquids, and a delay in emptying of solids. Clinical manifestations of diabetic gastropathy can occur in insulin-dependent or insulin-independent patients and closely resemble the clinical picture of postvagotomy gastroparesis. Furthermore, structural changes have been identified in the vagus nerves of patients with diabetes, thus suggesting that diabetic autonomic neuropathy may be responsible. However, the metabolic effects of diabetes have also been implicated. Specifically, hyperglycemia has been shown to cause a decrease in contractility of the gastric antrum, an increase in pyloric contractility, and suppression of phase III activity of the MMC. Suppression of phase III MMC activity is thought to be responsible for the accumulation of gastric bezoars seen in some diabetics. In contrast, hyperinsulinemia, which is often associated with non–insulin-dependent diabetics, may play a role in the gastroparesis seen in non–insulin-dependent diabetics because it also leads to suppression of phase III MMC activity.[48]

Critically ill patients are also predisposed to gastric dysfunction. These patients frequently have impaired gastric emptying because of profound changes in their systemic physiology. Acidosis, sepsis, electrolyte derangements, and shock combine to impair the normal mechanisms that control emptying of the stomach. This impairment in emptying, when combined with an increase in reflux from the duodenum to the pylorus, results in increased gastric residual volumes. Additionally, these patients are frequently maintained nutritionally by enteral nasogastric tube feedings. The increased volume of gastric fluid combined with alkalinization of the gastric environment because of dysfunction of H^+,K^+-ATPase predisposes to bacterial colonization of the normal environment. Furthermore, aspiration of this increased gastric fluid, now colonized with pathogenic bacteria, may easily occur and result in the development of nosocomial pneumonia as previously mentioned.[34,35]

H. pylori–infected patients with non–ulcer-associated dyspepsia have also been demonstrated to have impaired gastric emptying that is accompanied by a reduction in gastric compliance.[49] In rats, lipopolysaccharide derived from *H. pylori* causes a delay in gastric emptying of a liquid meal for up to 12 hours by an unknown mechanism. Regardless of the cause of gastroparesis, treatment consists of prokinetic agents such as metoclopramide

and erythromycin. Both have been shown to have some benefit, although the evidence is more compelling in diabetics.[50]

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Chapter

51

Diagnostic and Therapeutic Endoscopy of the Stomach and Small Bowel

Jeffrey M. Marks ▪ Jeffrey L. Ponsky

Utilization of flexible endoscopic techniques for the diagnosis of gastrointestinal (GI) diseases of the stomach and small bowel has become the gold standard. Advances in instrumentation have also allowed for therapeutic interventions such that many problems previously requiring surgery are now managed in a less invasive fashion. In addition, newer technologies have facilitated further endoscopic diagnosis of small intestinal disease that had always been somewhat elusive to the flexible endoscope. Finally, further evolution of endoscopic procedures may eventually allow transvisceral access to the peritoneal cavity to perform appendectomy, organ removal, anastomoses, or treatment of gastroesophageal reflux disease, morbid obesity, and cancer.

DIAGNOSTIC ENDOSCOPY OF THE STOMACH

Indications

Common indications for diagnostic endoscopy include evaluation of pain that persists despite medical therapy, evaluation of symptoms in the postoperative stomach, assessment of hematemesis or GI bleeding from a suspected upper GI source, evaluation of an abnormal radiographic study, or follow-up for previously biopsied gastric ulcers. Other indications requiring upper endoscopy for evaluation of the esophagus include long-standing reflux disease, dysphagia, odynophagia, or work-up of identified cervical lymph node metastasis. Esophagoscopy is discussed in Chapter 6. Anatomic abnormalities of the stomach such as paraesophageal hernias, volvulus, or outlet obstruction can also be evaluated endoscopically. Finally, diagnostic esophagogastroduodenoscopy (EGD) may be used for sampling of gastric/jejunal tissue or fluid, surveillance of patients with familial adenomatous polyposis, or follow-up for symptoms of suspected organic disease and weight loss.

Indications for therapeutic endoscopy of the stomach include treatment of bleeding, dilation of gastric outlet obstruction, and resection of gastric tumors by either polypectomy or endoscopic mucosal resection. Laparoscopic-assisted therapeutic endoscopy has also been used for the management of GI stromal tumors. In addition, future technologies of transgastric intra-abdominal surgery are being developed for the management of appendicitis, cholecystitis, and alimentary tract obstruction.

EGD is not indicated in patients with chronic, non-progressive, and atypical symptoms without evidence of organic disease. It is also not indicated in patients with metastatic adenocarcinoma of an unknown primary when identification of the primary tumor will not result in alteration of management. EGD is contraindicated when the risk to the patient outweighs the most likely expected benefit of the procedure, when adequate patient cooperation cannot be achieved, or if a perforated viscus is already known or suspected.

Endoscopic Instrumentation and Patient Preparation

Flexible endoscopes initially contained fiberoptic bundles for transmission of light to the tip of the scope and return of a real image back to the endoscopist's eye. With advancement in video monitors and computer processors, flexible endoscopes now use fiberoptics only for transmission of light, and the image is transmitted via a CCD (charge-coupled device) computer chip at the tip of the endoscope. Similar to laparoscopy, multiple observers and assistants can observe a similar image, thereby permitting enhanced assistance when

performing advanced therapeutic procedures. It also provides better opportunities for education.

Flexible endoscopes with smaller outer diameters and larger biopsy channels have resulted in better patient tolerance and comfort and the performance of complex interventions. Double-channel endoscopes allow "two-handed techniques" such as mucosal resection and tissue approximation in the absence of more effective endoscopic suturing devices. Early prototypes of robotic arms placed on the outside of the endoscope have been used in an animal model and are hoped to some day solve the limitations of present instrumentation in performing advanced transgastric intra-abdominal procedures.

Preparation for diagnostic and therapeutic endoscopy of the stomach requires merely 6 to 8 hours of fasting before the procedure.[1] Patients with gastric outlet obstruction or profound gastroparesis require a longer period of fasting, and tube decompression before the procedure may be prudent. Fasting before the procedure may not be feasible in emergency situations such as GI bleeding, caustic ingestion, or foreign body removal. In these situations, one may consider the use of general anesthesia and endotracheal intubation to protect the airway and prevent aspiration. Otherwise, in the majority of cases, conscious sedation with the combination of a narcotic and a benzodiazepine delivered intravenously and titrated slowly is used to achieve acceptable patient sedation and comfort.

Delivery of conscious sedation requires adequate monitoring with pulse oximetry, blood pressure recordings, and regular documentation of respiration. In patients with extensive upper GI bleeding, placement of a large-bore orogastric tube is necessary for saline lavage to clear clots and old blood. Whether cold or warm water should be used has been debated, without identification of actual clinical benefit from one or the other. It should be noted that lavage of ice water may lead to hypothermia in patients with massive GI hemorrhage, possibly accentuating a coagulopathic state.

After delivery of conscious sedation and placement of the patient in the left lateral decubitus position, the endoscope is passed under direct visualization into the esophagus. Inspection of the vocal cords is important to rule out polyps or upper airway obstruction (Figs. 51–1 and 51–2). The endoscope is advanced posterior to the arytenoid processes, and with careful pressure and instillation of air, the endoscope is passed beyond the upper esophageal sphincter into the cervical esophagus under direct visualization. Asking the patient to swallow, as well as placing the head in a flexed position, may assist in this portion of the procedure. The endoscope is then advanced with direct view of the lumen at all times. The esophagus can be somewhat tortuous in older patients, and the endoscopist must be aware that anatomic changes such as cervical ribs or an esophageal diverticulum may increase the risk for complications such as perforation.

The squamous mucosa of the esophagus is somewhat shiny and whitish in coloration. Endoscopic findings in the esophagus and their management are discussed in Chapter 6. After advancement of the endoscope into the stomach, air is insufflated to distend the stomach. As the endoscope advances into the stomach, it assumes a "greater curve position," with the posterior wall at 3 o'clock, the greater curvature at 6 o'clock, the anterior wall at 9 o'clock, and the lesser curvature in the 12-o'clock position. When the scope is initially advanced into the stomach, rugal folds are identified in the fundus and body and are typically absent at the junction of the distal body and antrum (Figs. 51–3 and 51–4). As the scope is advanced further, the pylorus comes into view and appears round, but it may have different contours as a result of associated inflammatory diseases (Figs. 51–5 and 51–6). By continuing to look upward beyond the pylorus, a retroflex view will be obtained with visualization of the incisura and fundus of the stomach (Fig.

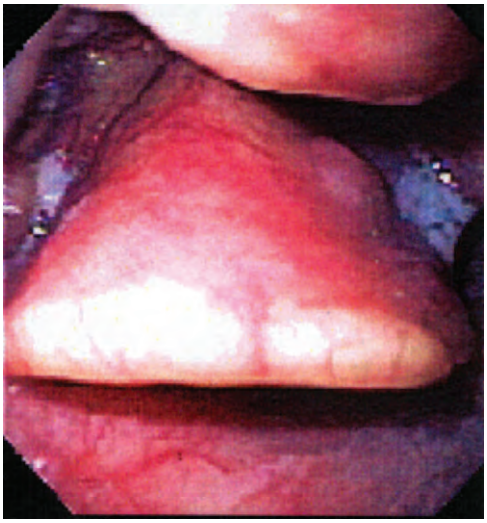

Figure 51–1. Initial view of the epiglottis before passage of the endoscope into posterior part of the pharynx.

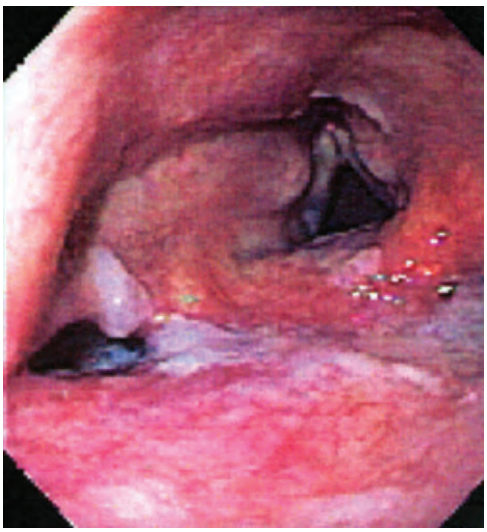

Figure 51–2. Visualization of normal vocal cords during esophagogastroduodenoscopy (EGD) is a vital part of a complete EGD.

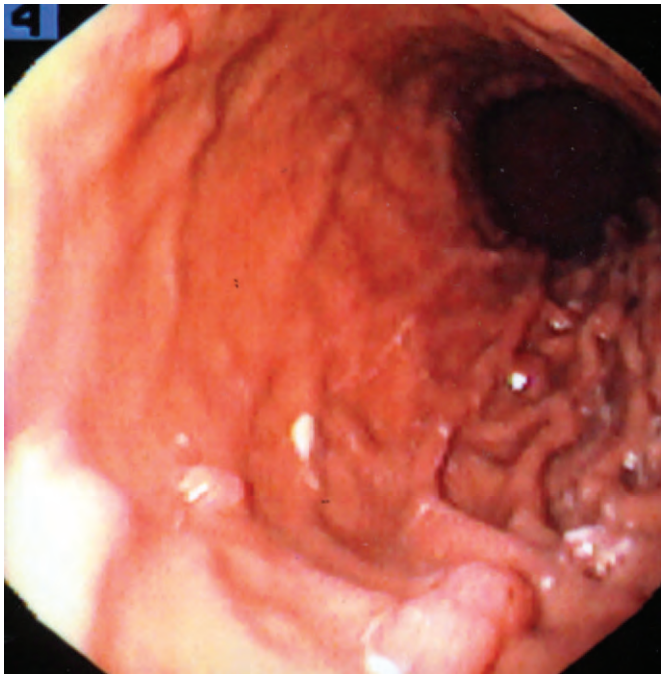

Figure 51–3. Appearance of the proximal part of the stomach with the presence of numerous rugal folds. Several small fundic gland polyps are also seen.

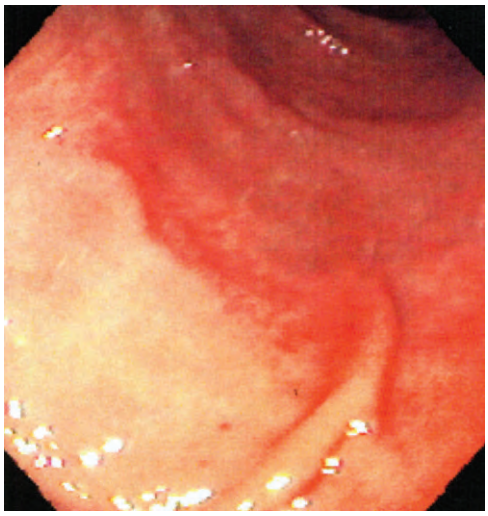

Figure 51–4. As the endoscope is advanced into the distal end of the stomach at the juncture of the body and antrum, the rugal folds become less pronounced.

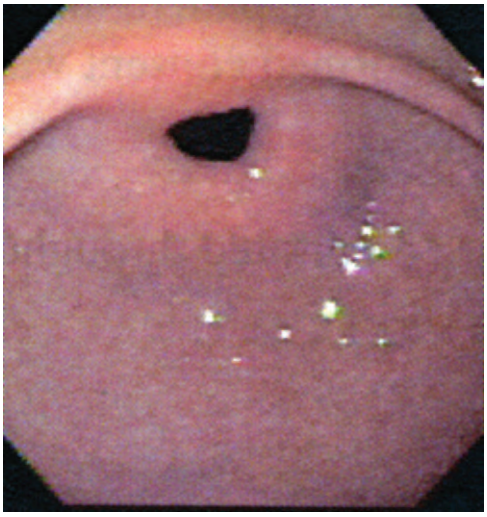

Figure 51–5. Normal-appearing distal antrum and pylorus.

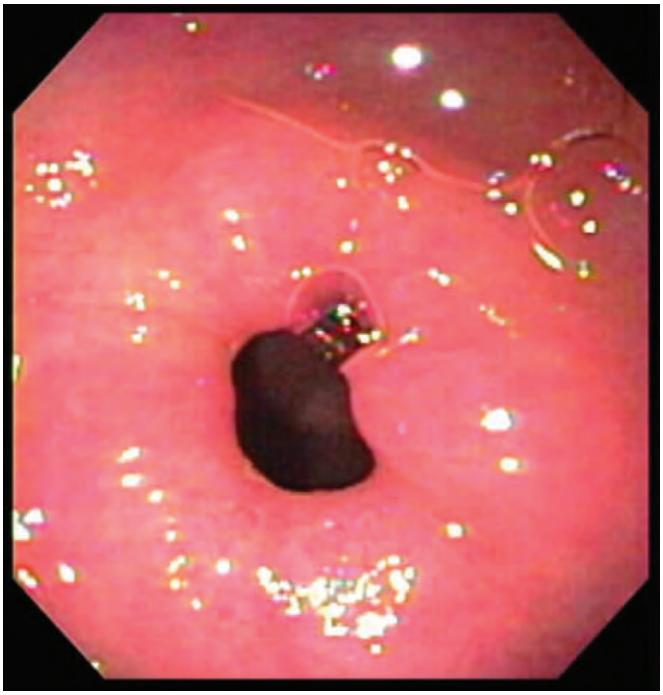

Figure 51–6. Notched pylorus secondary to a previous inflammatory process.

51–7). Withdrawing the endoscope at this time results in paradoxical movement and allows complete circumferential visualization of the fundus and cardia (Fig. 51–8). Full evaluation should be performed and the fundic pool should be aspirated to allow completion of this endoscopic evaluation. Evaluation of the angularis is important to rule out type I gastric ulcers.

The endoscope should then be advanced through the pylorus into the pyloric channel with assessment of all surfaces circumferentially to rule out duodenal ulcers (Fig. 51–9). Advancement of the scope into the second portion of the duodenum is possible by merely looking up and to the right and trolling back on the endoscope. This maneuver places the scope in what is called a "lesser curve" or "short" position and provides paradoxical advancement of the endoscope further down into the second and third portions of the duodenum (Fig. 51–10). With a forward-viewing scope, visualization of the ampullary complex may be somewhat difficult, but it may

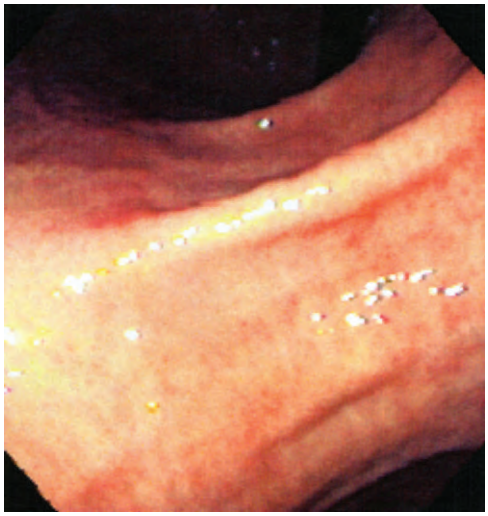

Figure 51–7. Retroflex view in the stomach showing the antrum and fundus simultaneously, separated by the angularis.

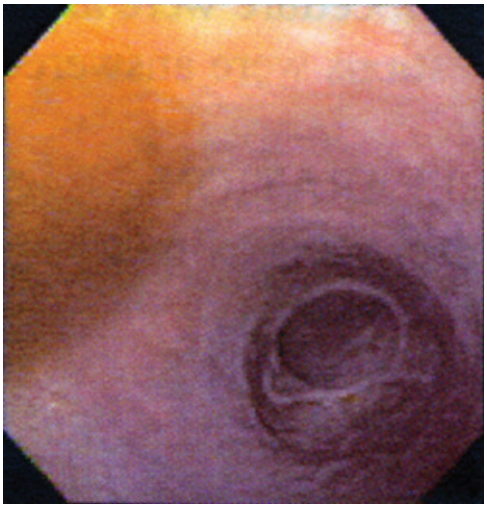

Figure 51–9. The smooth surfaces of the duodenal bulb are visualized after advancing through the pylorus. No valvulae conniventes (folds) are present in the bulb.

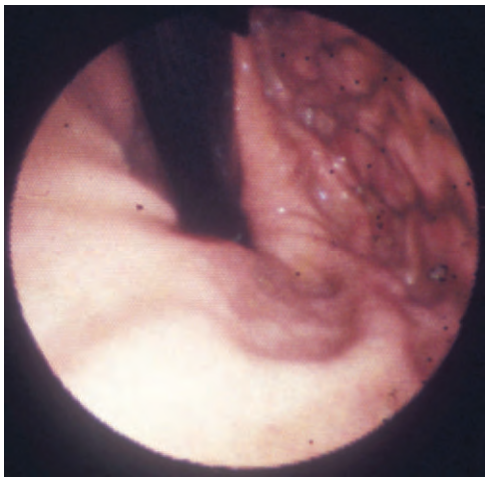

Figure 51–8. Full retroflex view showing the endoscope as it traverses the esophagogastric junction.

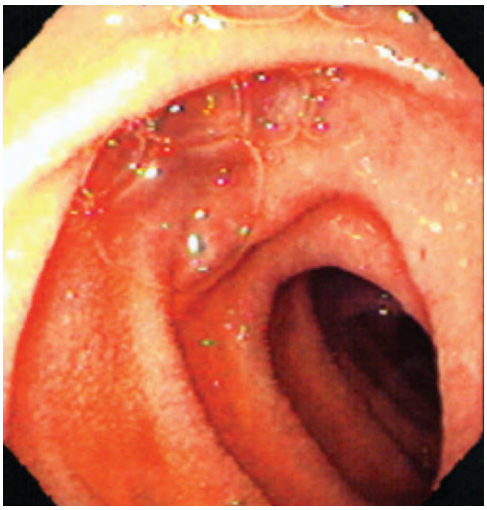

Figure 51–10. Normal-appearing view of the second portion of the duodenum. This view is obtained by trolling back (pulling out) the endoscope while looking up and to the right; the endoscope is left in a "short" or lesser curve position.

be seen at the 9-o'clock position. A side-viewing endoscope is necessary to obtain a full endoscopic view of this portion of the duodenum. The endoscope can then be withdrawn back into the stomach, and the luminal surfaces should again be reinspected for any abnormalities. The stomach is quite full at this juncture and should be evacuated of air before withdrawing the endoscope. If the vocal cords had not been inspected on intubation, they should be inspected during withdrawal of the endoscope. At completion of the procedure, patients are observed during resolution of the conscious sedation, and a clear liquid diet is started. Usually within 30 to 60 minutes patients should be stable for discharge from the endoscopy unit.

Gastric Pathology

The ability to differentiate normal from abnormal findings at the time of endoscopy is vital to ensure appropriate patient care. Normal variations, though possibly peculiar in appearance, may not require any intervention. Gastric lesions that can be identified at the time of endoscopy include inflammatory processes, benign and malignant neoplasia, vascular abnormalities, postoperative deformities, congenital lesions, and foreign bodies. Inflammatory changes of the gastric mucosa are the most common finding at the time of diagnostic endoscopy. Inflammatory changes in the stomach may be secondary

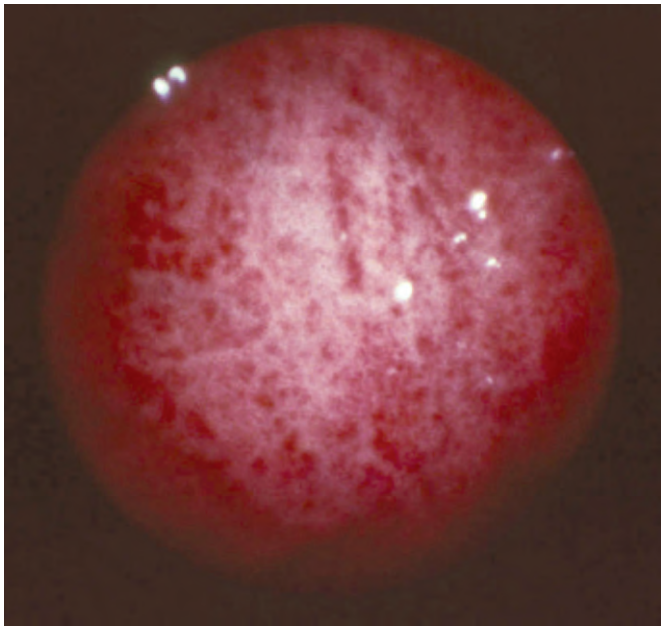

Figure 51–11. Diffuse gastritis in the body of the stomach. Testing for *Helicobacter pylori* must always be done in this situation.

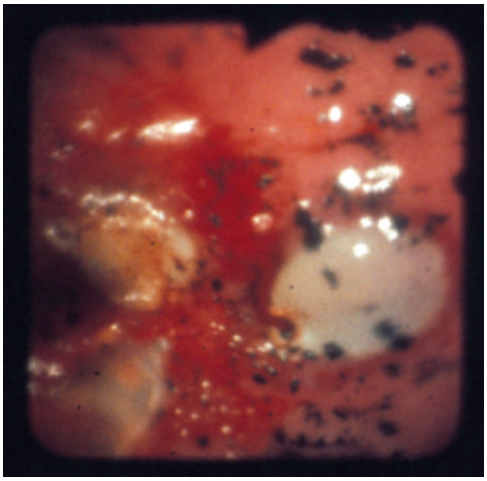

Figure 51–12. Coffee ground material secondary to bleeding seen in conjunction with multiple ulcerations in the distal part of the stomach.

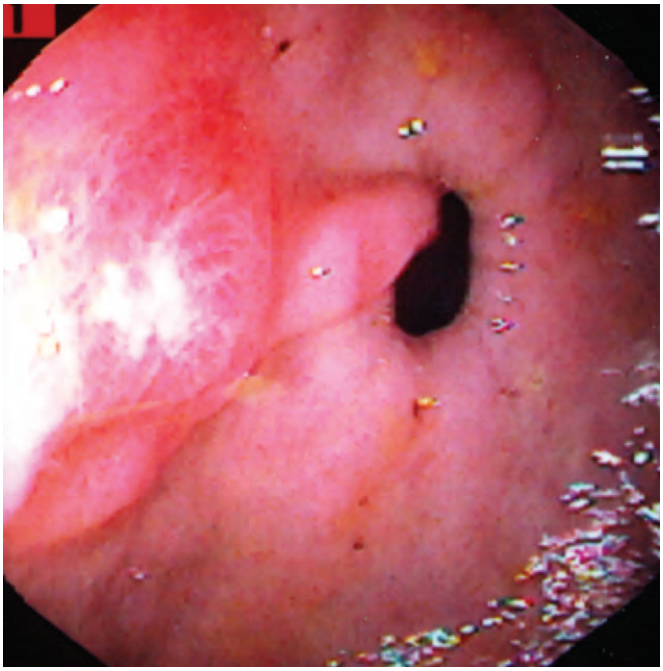

Figure 51–13. Prepyloric ulcer with surrounding induration of the gastric mucosa.

to medications, infections, caustic agents, postoperative changes in the upper digestive tract, or severe physiologic stress secondary to sepsis, hypoxia, or hypoperfusion (Fig. 51–11). A thorough physical examination and history are required, including identification of comorbid diseases, exogenous stress, previous surgery, and a social history of drugs, alcohol, and tobacco use.

Initial endoscopic evaluation must include documentation of the location and extent of the inflammatory process, associated anatomic changes, and intraluminal contents such as excessive bile, coffee ground material, undigested food, or blood (Fig. 51–12). Bleeding may be commonly associated with these conditions and may vary from minor occult bleeding with associated iron deficiency anemia all the way to severe active bleeding with hemodynamic compromise. Identification of the presence of *Helicobacter pylori* infection is also important for providing appropriate and complete treatment. Numerous tests are available for identification of *H. pylori,* including histology, urease testing (CLO test), serologic antibody testing, and the carbon-labeled urea breath test.[2] Eradication of *H. pylori* with antibiotic therapy is important when treating inflammatory lesions of the stomach. Antibiotic therapy minimizes the risk for recurrence in patients with *H. pylori*–associated inflammatory diseases of the stomach.[3]

Gastric ulcers may be identified in the prepyloric, body, and fundic portions of the stomach (Fig. 51–13). In addition, peptic ulcers may also hide on the angularis, and thus endoscopic evaluation of the entire stomach, including retroflex views, is important to discern these processes. Gastric ulcers found at the time of endoscopy require aggressive biopsy of all margins at the junction of the edges of the base and surrounding gastric mucosa (Fig. 51–14). Suspicion of malignancy may be supported by the presence of heaped edges, deeper ulcerated bases, or diffuse infiltrative processes. Follow-up endoscopy within 8 to 12 weeks is necessary for ulcers that are benign by initial biopsy but have an atypical appearance, are larger than 2 cm, appear suspicious pathologically, or are leading to persistent symptoms. Absence of healing at the time of second endoscopy may be an indication for surgical excision (Fig. 51–15).

Congenital lesions of the stomach are also frequently identified at the time of endoscopy. Hiatal hernias are

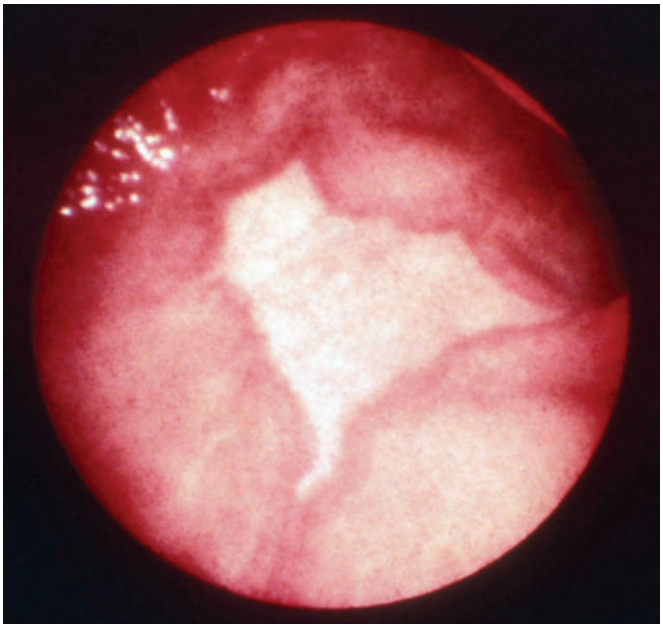

Figure 51–14. Large benign gastric ulcer seen on the greater curvature of the stomach.

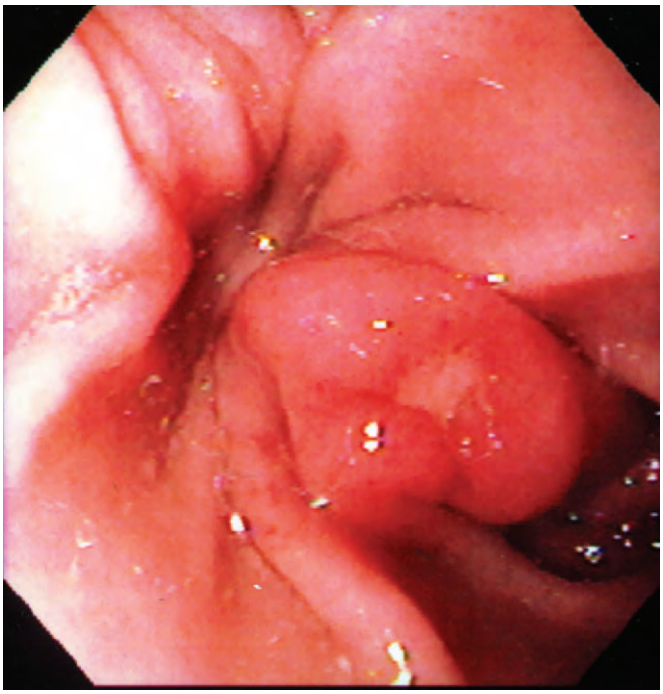

Figure 51–15. A chronic nonhealing gastric ulcer seen after 12 weeks of medical therapy. Multiple biopsy specimens of the periphery of the ulcer base are required again, and even with benign results on biopsy, surgical resection must be strongly considered.

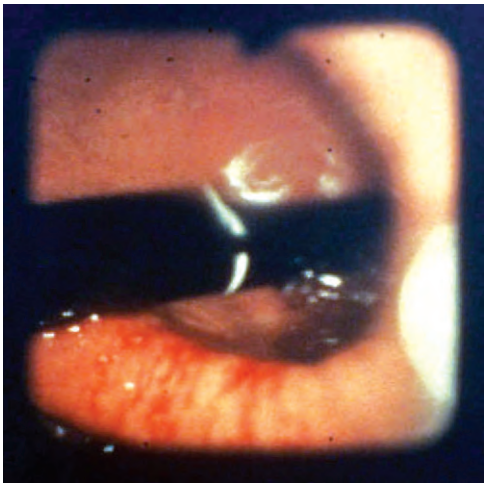

Figure 51–16. Type I sliding hiatal hernia seen on a retroflex view.

the most frequently encountered deformity of the stomach and may be identified during passage of the endoscope from the esophagus into the stomach or on the retroflex view (Fig. 51–16). These hernias may play no clinical role in a patient's symptoms but are commonly associated with reflux disease or dysphagia. Careful measurements from the incisors to the gastroesophageal junction, Z-line (squamous columnar junction), and diaphragmatic incursion on the stomach are important markers with implications for surgical intervention in this process. In patients with large paraesophageal hernias, entry into the stomach may be inhibited by incarceration of the stomach in an intrathoracic position. Commonly, paradoxical movement of the endoscope occurs when one tries to advance the endoscope into a gastric lumen complicated by a paraesophageal hernia. The endoscope will most likely not be able to be advanced into the body of the stomach, and the pylorus will not be visualized. Rarely, advancement of the endoscope may allow reduction of the stomach back into an intra-abdominal position, and temporary fixation can be provided at that time via percutaneous endoscopic gastrostomy.

Other congenital lesions identified may include antral webs or pyloric stenosis. Antral webs mimic the appearance of the pylorus but occur in the more proximal part of the antrum, and one may visualize the associated antral ring. Pyloric stenosis is more commonly seen in children, although it can be identified in adults. The diagnosis is made when the endoscope cannot be advanced beyond the pyloric channel and there is no associated inflammatory changes (Fig. 51–17). One final congenital lesion occasionally discovered, a pancreatic rest, is typically found in the antrum or duodenum and appears as a 5- to 10-mm raised donut-shaped lesion with a central punctate center (Fig. 51–18). These processes are benign, and biopsy will prove these rests to be of pancreatic origin.

Upper GI bleeding is quite common, and endoscopic identification of vascular abnormalities such as gastric

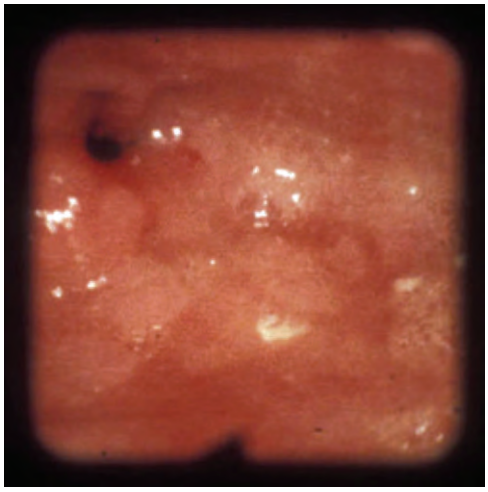

Figure 51–17. Pyloric stenosis.

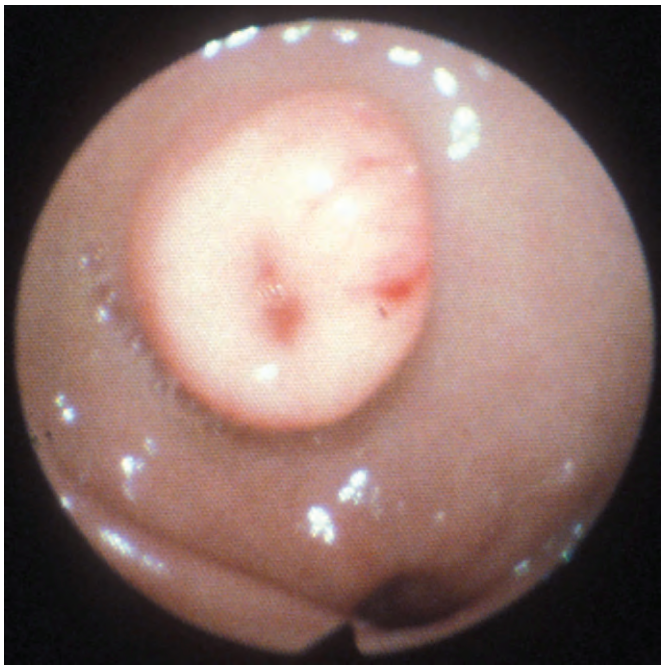

Figure 51–18. A pancreatic rest in the distal body of the stomach. No intervention is required for this benign congenital process.

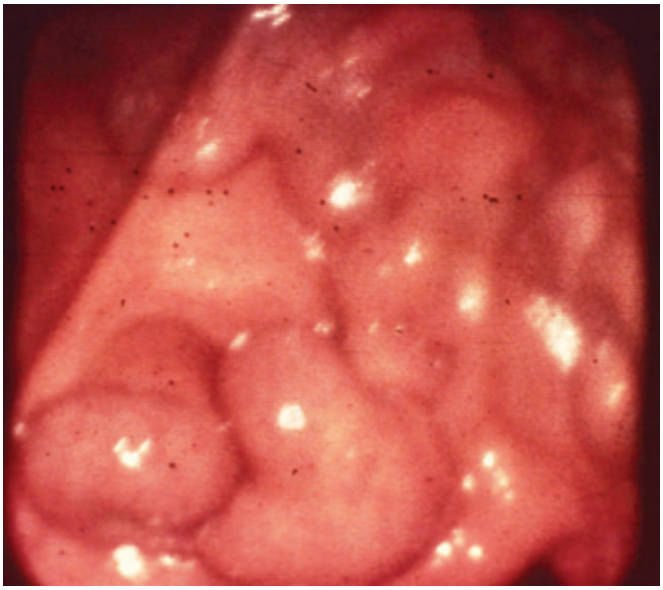

Figure 51–19. Gastric varices in the cardia of the stomach.

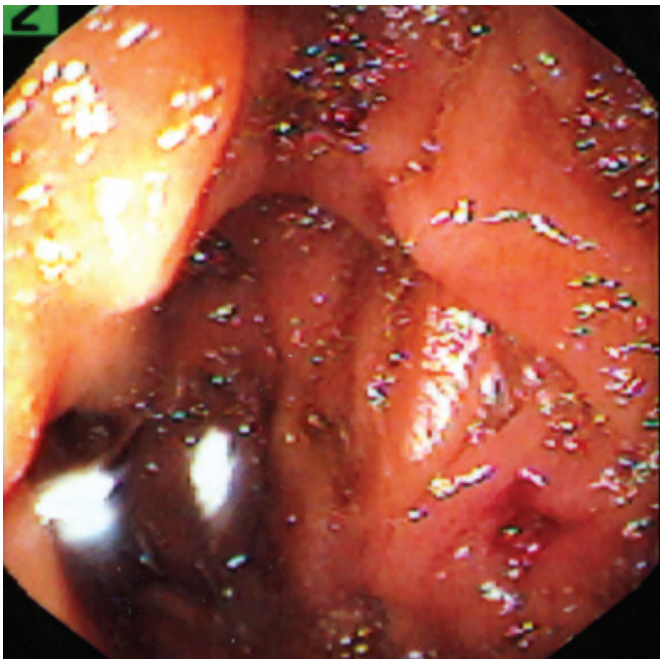

Figure 51–20. Arteriovenous malformation of the proximal part of the small bowel.

varices, angiodysplasia, and ulcerative lesions may require endoscopic therapy. Gastric varices are related to portal hypertension and are most commonly due to splenic vein thrombosis secondary to either pancreatitis or pancreatic neoplasms. Gastric varices may or may not be associated with esophageal varices and are most frequently found in the fundus (Fig. 51–19). Absence of esophageal varices is more pathognomonic of splenic vein than portal vein thrombosis. Gastric varices appear as serpentine folds crossing over the normally positioned gastric rugal folds. As opposed to rugal folds, varices are easily compressed when palpated with an endoscopic instrument. In addition, endoscopic ultrasound may be useful in the diagnosis of varices. Prophylactic therapy in patients without bleeding is debatable and may not alter overall survival. Angiodysplasia and arteriovenous malformations appear as red discolorations with tortuous feeding vessels at their base (Fig. 51–20). They may or may not have active bleeding at the time of endoscopy, and they are usually multicentric. A subset of angiodysplasia termed gastric antral vascular ectasia (GAVE)

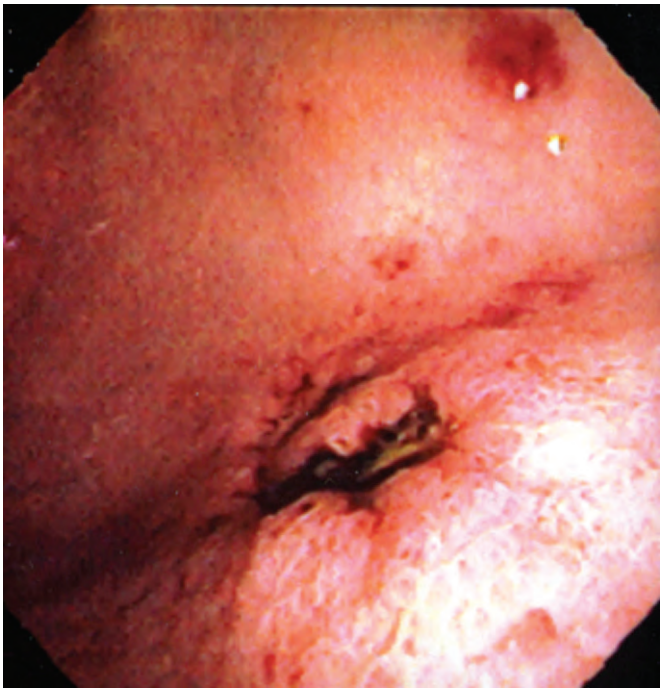

Figure 51–21. Dieulafoy's ulcer of the proximal part of the stomach.

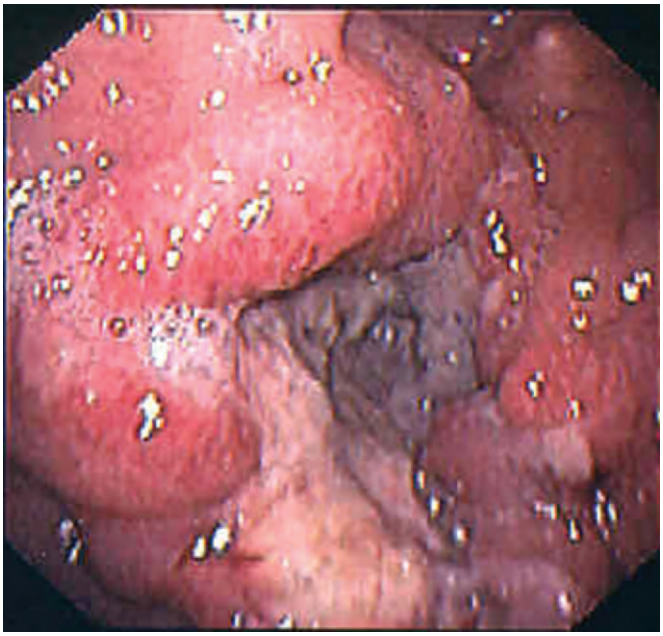

Figure 51–22. Diffuse gastric carcinoma of the distal end of the stomach.

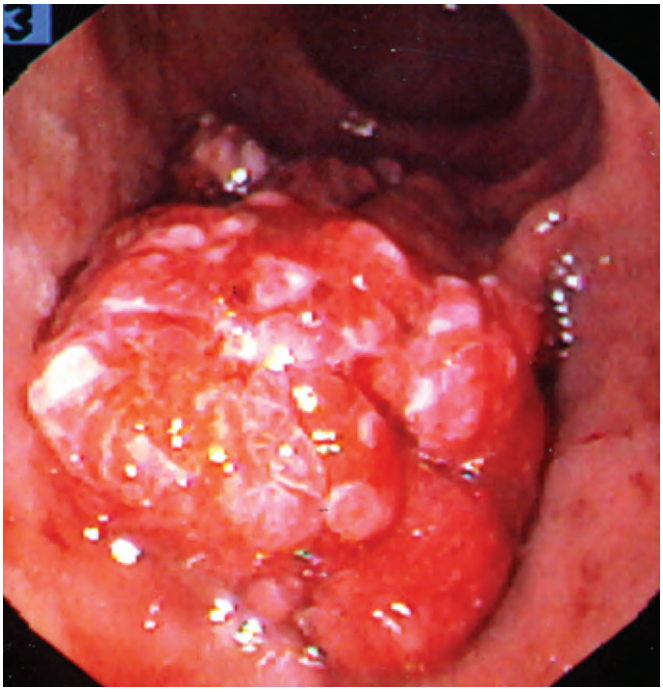

Figure 51–23. Inflammatory polyp with overlying mucosal irregularities.

refers to the presence of numerous vascular lesions throughout the antrum in a linear fashion and is also commonly referred to as watermelon stomach. GAVE was first identified by Jabbari et al. in 1984, and the term was used to describe the striped vascular lesions seen in watermelon stomach.[4] Argon plasma coagulation (APC) has been shown to be an effective therapy for watermelon stomach.[5-7]

Dieulafoy's lesions are superficial ulcerations with underlying exposed arterial structures that are commonly found in the upper portions of the stomach; they can be the source of massive upper GI bleeding (Fig. 51–21). If not actively bleeding, these lesions can be discriminated by endoscopic ultrasound or identified by visualizing bleeding stigmata of an exposed vessel in a small-caliber ulcer base. Gastric varices and GAVE syndrome are much less common than other sources of upper GI bleeding, such as gastritis and ulcers. It should be noted that most of these vascular lesions identified at the time of endoscopy can be managed with therapeutic maneuvers involving either thermal or nonthermal techniques.

Neoplasms of the stomach may be either benign or malignant. Cancer of the stomach has a wide variety of endoscopic appearances, including fungating, ulcerating, infiltrating, and exophytic (Fig. 51–22). Polypoid lesions may be inflammatory or adenomatous. Inflammatory polyps can be quite numerous, and although they may grow extremely large, they carry no malignant potential (Fig. 51–23). Fundic gland-type polyps are included in this category (Fig. 51–24). Adenomatous polyps of the stomach are also predominantly benign but should be removed because they have a small malignant potential similar to polyps in the colon. Other benign lesions include leiomyomas, lipomas, carcinoid, and pancreatic rests (Fig. 51–25). Leiomyomas, or gastrointestinal stromal tumors, are commonly found in the cardia of the stomach adjacent to the gastroesophageal junction (Fig. 51–26). They may lead to occult blood loss and have

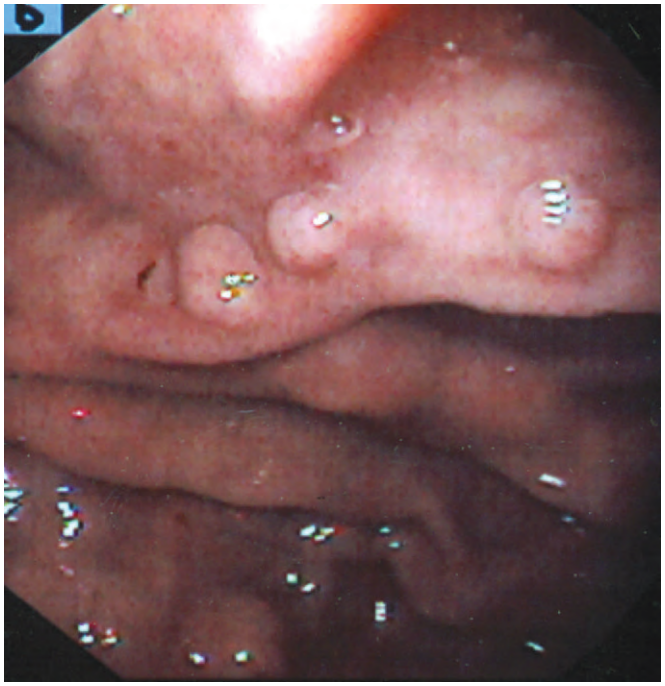

Figure 51–24. Multiple fundic gland polyps seen in the proximal part of the stomach. Random sampling is all that is required.

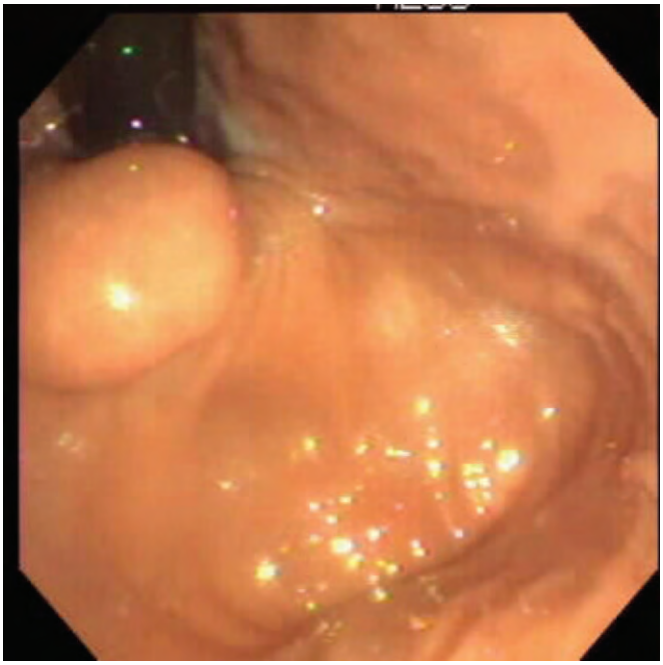

Figure 51–26. Gastrointestinal stromal tumor adjacent to the gastroesophageal junction.

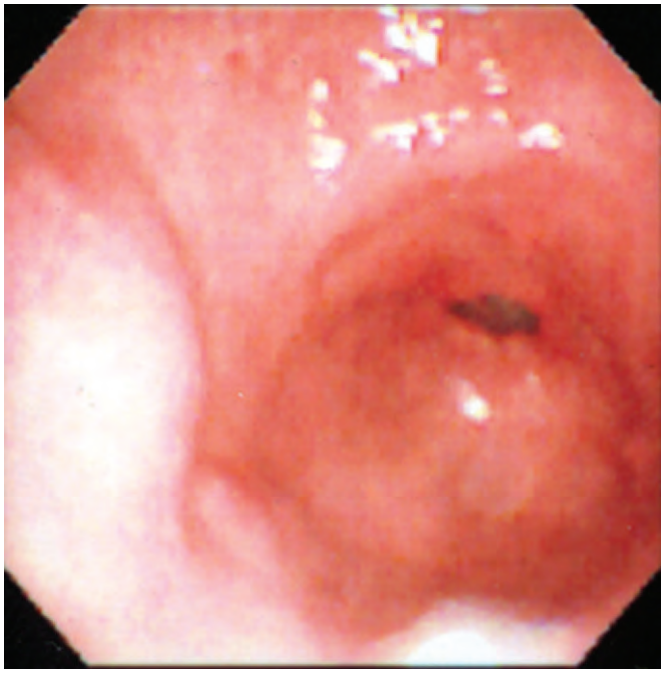

Figure 51–25. A submucosal mass identified in the distal end of the stomach eventually proved to be a gastrointestinal stromal tumor.

malignant potential based on size, mucosal invasion, and mitotic activity. Because of extension of leiomyomas through the entire gastric wall, endoscopic resection may result in full-thickness perforation or bleeding. A combined endoscopic and laparoscopic or intraluminal laparoscopic approach may be warranted. Benign submucosal lesions such as lipomas may require intervention before they lead to obstruction.

Standard endoscopic imaging can be enhanced with several techniques to improve visualization of obscure GI disease. Several staining solutions, including Lugol's solution, methylene blue, acetic acid, and indigo carmine, have been used to enhance discrimination of normal and abnormal tissue. Inflammatory tissue does not stain with Lugol's solution, and methylene blue is readily absorbed into absorptive epithelium such as intestinal metaplasia of the stomach or esophagus. Magnification endoscopy may also allow for more accurate identification of intestinal metaplasia and dysplasia, although it requires extended time for endoscopy and has quite variable sensitivity and specificity.[8]

Management of Bleeding

Endoscopic techniques for the management of bleeding can be divided into thermal and nonthermal modalities. Thermal modalities include bipolar and monopolar contact probes, APC, and laser therapy. Contact probes use direct tissue delivery of current and provide a deeper source of energy than APC does (Fig. 51–27). Hemostasis of an active bleeding site in the stomach may best be handled by initial injection sclerotherapy followed by delivery of thermal energy. Contact probes provide an

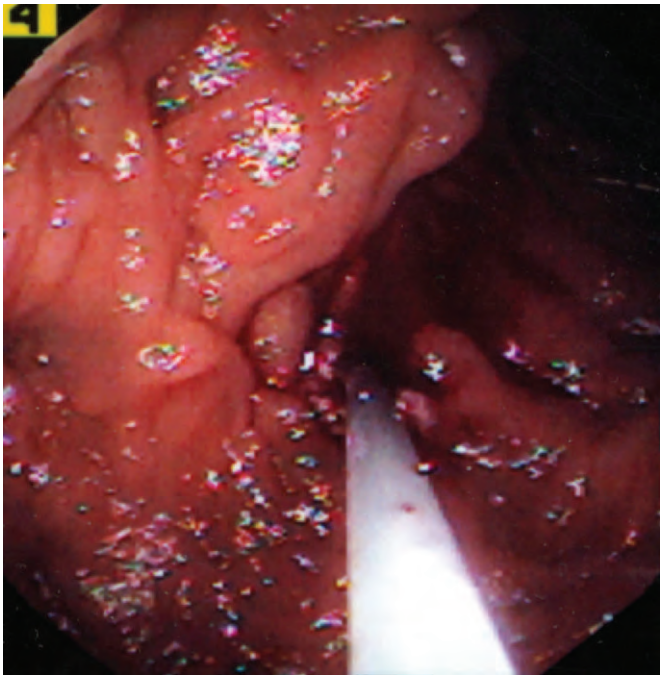

Figure 51–27. Cauterization of a small bowel arteriovenous malformation with an endoscopic contact probe.

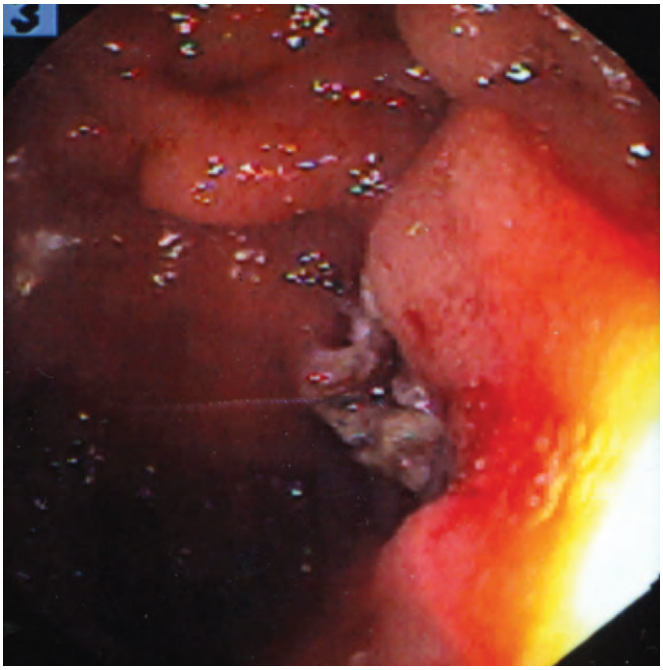

Figure 51–28. Appearance of mucosa after treatment of an arteriovenous malformation with contact probe therapy.

advantage in certain situations because of the ability to provide direct tamponade at the time of energy delivery (Fig. 51–28). APC provides a more superficial depth of penetration and may therefore be associated with a smaller risk of perforation than is the case with contact probes. In addition, APC can be applied over broader surface areas, similar to spray paint, as opposed to the single site of therapy provided by contact probes.[5-7]

Before any endoscopic management of gastric bleeding, adequate preparation of the stomach must be provided with gastric lavage via a large oral gastric tube (Fig. 51–29). Airway control with endotracheal intubation should be considered in patients with massive GI bleeding before initiating endoscopic treatment. Endoscopic management of gastric bleeding should be considered the first line of therapy, and reports have shown less morbidity and mortality than with initial surgical intervention when endoscopy has been used for both the initial episode of bleeding and the scenario of recurrent GI bleeding. Even if the patient requires surgical intervention, as long as endoscopy can be provided quickly and efficiently, the patient will benefit if the source of bleeding can be identified and slowed before an emergency surgical procedure. Flexible endoscopy will also guide the appropriate surgical therapy and is vital in differentiating the varied causes of gastric bleeding.

Nonthermal techniques for the management of gastric bleeding continue to be developed and improved. Injection sclerotherapy was probably the first nonthermal modality and is effective in achieving tissue hemostasis on the basis of several pathways. Injectable agents such as sodium morrhuate lead to vessel sclerosis, whereas vasoconstriction and local compression can be

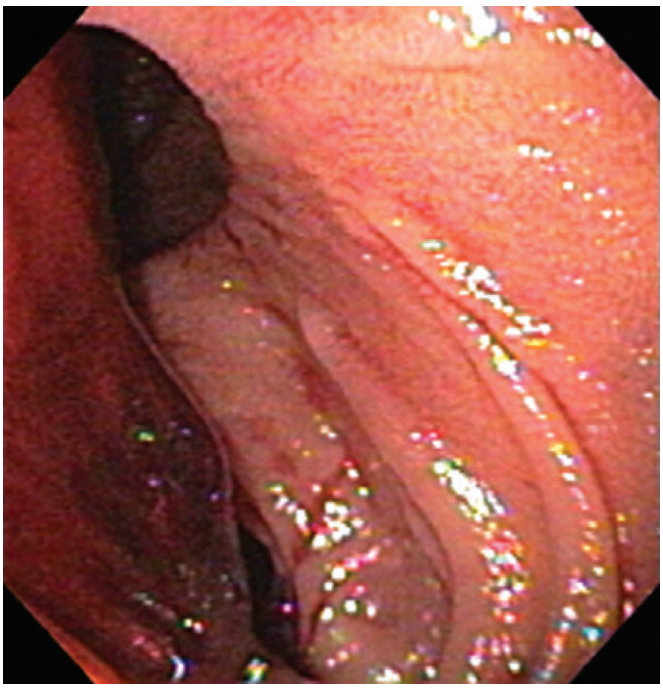

Figure 51–29. Extensive blood and clots in the stomach from a bleeding duodenal ulcer, which will limit the endoscopic examination and treatment if not adequately cleared with pre-endoscopic gastric lavage.

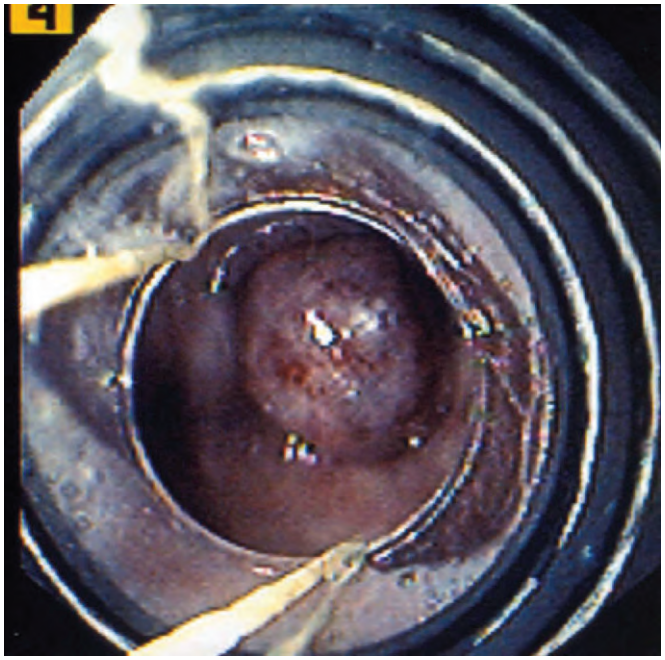

Figure 51–30. Image through the endoscopic band ligator after placement of a band.

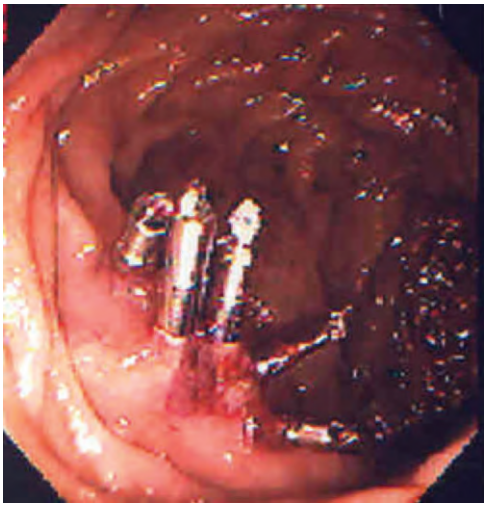

Figure 51–31. Endoscopic clips placed on a bleeding duodenal ulcer for hemostasis.

Figure 51–32. Self-expanding metal stent that can be used for palliation of an enteric stricture. These types of stents are considered unremovable and are predominantly used for malignant disease.

provided by other injected components such as saline, alcohol, or epinephrine. Injection therapy may be one of the best ways to provide initial hemostasis through the combination of these three factors, but one must be careful to avoid extensive tissue destruction because perforation may result. Perforation is more common in the thin-walled areas of the small bowel and colon, as opposed to the stomach. Combination contact probes and injection sclerotherapy needles are now available and provide efficient endoscopic management of GI bleeding without having to use numerous tools.

Other endoscopic nonthermal tools include clips, detachable loops, band ligators, and endoscopic suturing devices. A combination of thermal and nonthermal techniques may provide the best chance for resolution of GI bleeding. Detachable snares similar to laparoscopic Endoloops can be used to encircle structures and, after ligation, provide hemostasis. They are commonly used on stalks of pedunculated polyps that bleed after polypectomy. Endoscopic band ligation was first used for the management of esophageal varices, but it may also be used in the gastric lumen on gastric varices or Dieulafoy lesions (Fig. 51–30). Endoscopic clips provide mucosal approximation, as well as superficial vessel closure (Fig. 51–31). They usually fall off within 4 to 7 days. Novel endoscopic suturing devices are probably still too cumbersome to be used in patients with active GI bleeding, but they can be used to provide mucosal approximation over exposed submucosal surfaces after endoscopic resection. In the future, it is hoped that suturing technology will mimic that of open surgery.

Nonoperative management of alimentary tract obstruction has been performed since 1885 when Charter Simonds was able to relieve an esophageal obstruction with a short hollow wooden tube. Since that time, advancements in stent materials have allowed the development of smaller-diameter delivery systems (Fig. 51–32). In addition, the higher expansile force of these stents has led to increased patency. Endoscopic balloon dilation for benign alimentary tract strictures such as congenital pyloric stenosis or peptic ulcer–induced stenosis is now available. Balloon dilation via hydrostatic force can provide resolution, although complex strictures may require multiple serial dilations to achieve success. The risk for perforation is lower with hydrostatic balloons than with the pneumatic balloon dilators used previously. In patients with gastric emptying abnormalities, pyloric dilation may also be beneficial. Another endoscopic technique that has been investigated in small series for the treatment of gastroparesis or chronic gas/bloating syndromes is botulinum toxin treatment of the pylorus.[9] In a study by Bromer et al., more than 40% of patients had a short-term response.

Palliation of intrinsic and extrinsic lesions secondary to gastric, duodenal, or pancreatic cancer can be provided by endoscopic techniques, including laser debulking, dilation, or endoscopic stent placement. Self-expanding metallic stents have been shown to provide decreased complication rates (Figs. 51–33 and 51–34). In a multicenter study of palliation of patients with malignant gastric outlet obstruction, deployment of

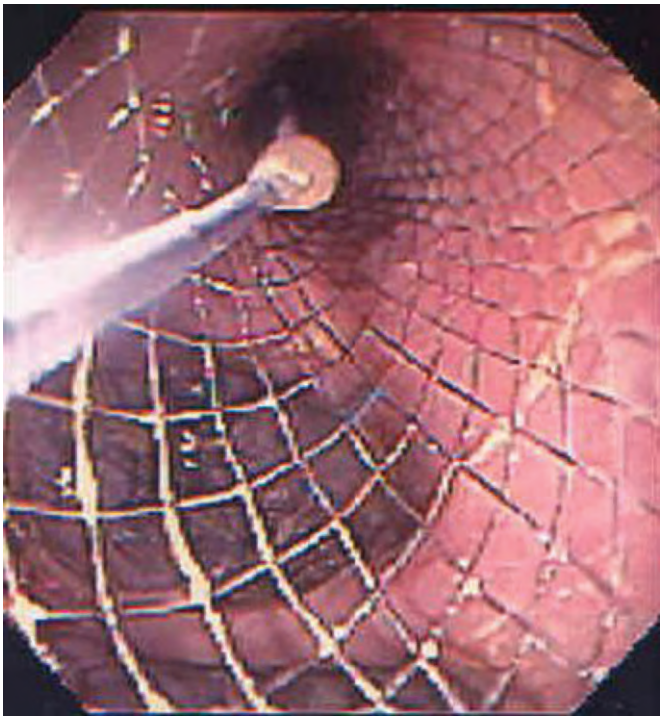

Figure 51–33. Endoscopic image after deployment of a self-expanding metal stent for malignant gastric outlet obstruction.

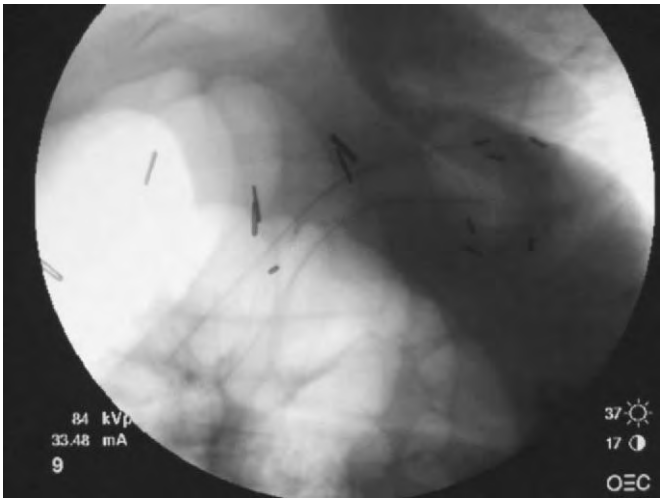

Figure 51–34. Fluoroscopic image of a self-expanding metal stent deployed across malignant gastric outlet obstruction.

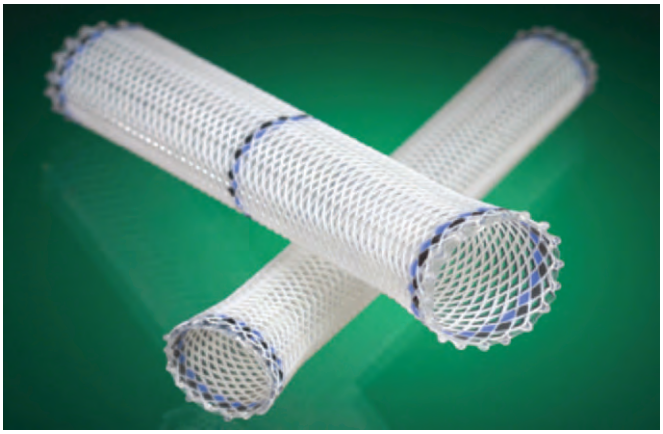

Figure 51–35. Covered self-expanding plastic stent that can be used for the treatment of strictures or fistulas. Unlike metal stents, these stents are to be removed after 2 to 3 months.

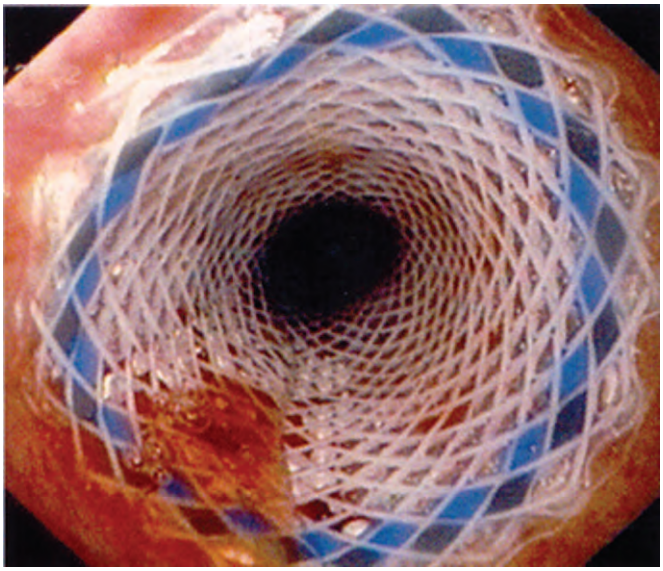

Figure 51–36. Endoluminal view after deployment of a self-expanding plastic stent.

self-expanding metallic stents was technically successful in 173 of 176 patients.[10] Eighty-four percent of patients resumed oral intake. It should be noted that expandable plastic stents that are removable have been used in small series for benign disease (Figs. 51–35 and 51–36). The longevity of relief of obstruction from stenting of benign gastric and duodenal strictures is not truly known, and dilation may be more beneficial. Overall, these patients may be better served by either resective therapy or operative gastroenteric bypass.

The role of endoscopy in the management of gastric neoplasia has advanced from a solely diagnostic use to a therapeutic technique over the past decade. Endoscopic mucosal resection techniques have allowed the removal of benign masses, as well as early gastric cancer. With the use of a double-lumen gastroscope, mucosal resection can be performed with a modified needle knife sphincterotome. Mucosal defects can then be reapproximated with endoscopic clips. Other techniques such as saline-lift or cap-assisted snare endoscopic mucosal resection also allow for larger segments of tissue to be removed safely. Submucosal masses such as GI stromal tumors and carcinoid tumors can likewise be removed with endoscopic resective techniques. A concern with this

approach, however, is the resultant full-thickness injury. One of the great limitations to fully endoscopic resective techniques is the ability to suture because endoscopic suturing techniques are still very primitive.

The combination of endoscopic and laparoscopic approaches for deeper tumors or those higher up on the cardia of the stomach can be beneficial. Laparoscopic evaluation at the time of endoscopic resection can identify the presence of a full-thickness defect, as well as provide access for repair. An alternative to the combined endoscopic and laparoscopic approach is intragastric laparoscopic techniques with ports placed in the gastric lumen.

Transgastric Endoscopic Surgery

Natural orifice transvisceral endoscopic surgery procedures have been investigated in animal models and performed in several small human series. Cholecystectomy, cholecystogastric anastomosis, gastroenteric anastomosis, appendectomy, and tubal ligation have all been attempted with transgastric techniques.[11-14] There are numerous inherent limitations in the use of transgastric techniques, including gastrotomy creation, reliable gastrotomy closure, abdominal insufflation, tissue retraction/exposure, tissue approximation, and difficulties with imaging. Other transvisceral techniques, or natural orifice surgeries, via the colon or vagina could possibly allow for a more direct avenue into the upper part of the abdomen. All these technologies need to be further investigated for efficacy and risk. One concern is intraperitoneal infectious complications related to visceral violation. These technologies may eventually require a combination of transvisceral and transabdominal laparoscopic techniques with an endoscope advanced via natural access in combination with microlaparoscopy devices for tissue manipulation or retraction. As endoscopic tools are improved, transvisceral techniques may find a role in the management of numerous intra-abdominal disease processes.

DIAGNOSTIC ENDOSCOPY OF THE SMALL BOWEL

Endoscopic evaluation plus treatment of lesions of the small bowel has always been very challenging. Transoral and transanal routes have been used and provide the ability to see the most proximal and most distal aspects of the small bowel, respectively. Push enteroscopy can be a valuable tool to identify mucosal abnormalities, as well as sources of bleeding in patients with an unidentified cause (Figs. 51–37 and 51–38). Push enteroscopy allows for biopsy and in some cases actual therapeutic interventions for bleeding. The use of an overtube permits advancement of the endoscope without the normal buckling of the scope in the greater curve position of the stomach. The overall diagnostic yield of push enteroscopy is about 30% in most series.[15-17]

Recently developed endoscopic modifications, as well as novel imaging devices, have allowed improved visualization of small bowel disease. Wireless capsule endoscopy has rapidly emerged as a safe and well-tolerated tool for assessment of small bowel lesions (Fig. 51–39). Capsule endoscopy can be used for the diagnosis of obscure GI bleeding, as well as inflammatory bowel

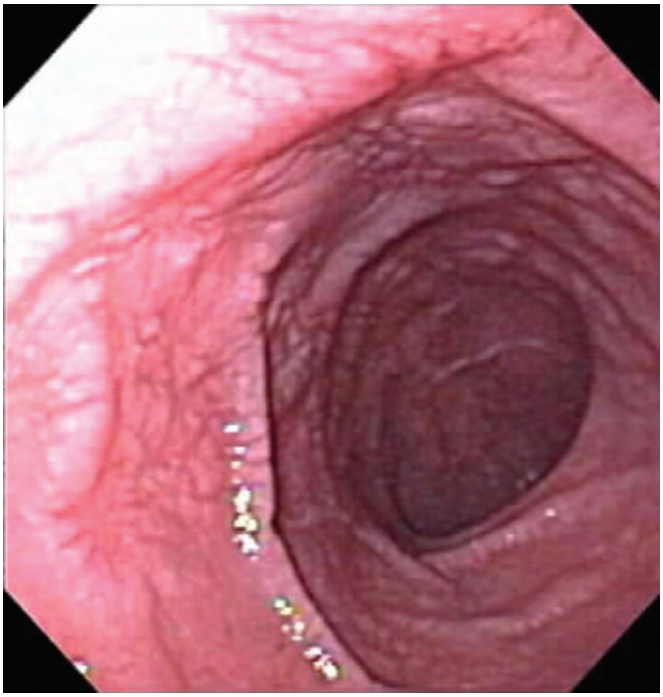

Figure 51–37. Small bowel sprue identified by push enteroscopy.

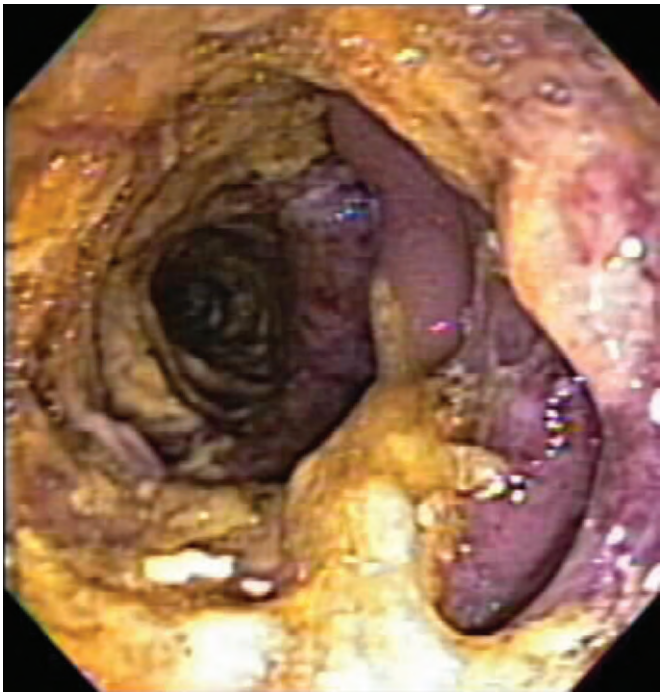

Figure 51–38. Ischemic enteritis seen on push enteroscopy.

Figure 51–39. Capsule used for wireless endoscopy.

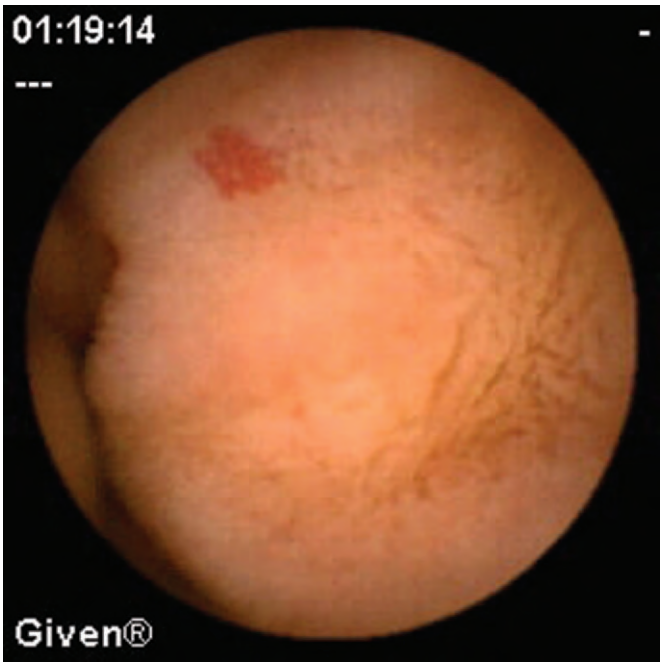

Figure 51–40. Wireless capsule endoscopic view of a small bowel arteriovenous malformation.

disease (Figs. 51–40 to 51–42).[18-29] Small bowel tumors have also been identified with capsule endoscopy (Fig. 51–43).[30] When compared with small bowel follow-through, capsule endoscopy identified 29% of patients with small bowel polyps as compared with 12% via small bowel follow-through. In another series comparing capsule endoscopy with push enteroscopy and enteroclysis, capsule endoscopy detected more lesions than the other two modalities did, and this led to a change in management in 70% of these patients.[31] Capsule endoscopy, however, is only a diagnostic tool and must be carefully used in patients with suspected small bowel obstruction or strictures.

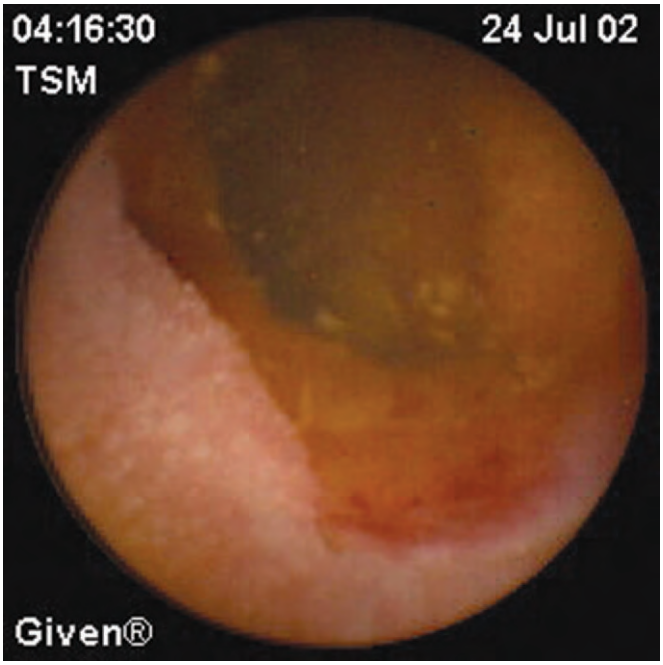

Figure 51–41. Arteriovenous malformation seen on capsule endoscopy.

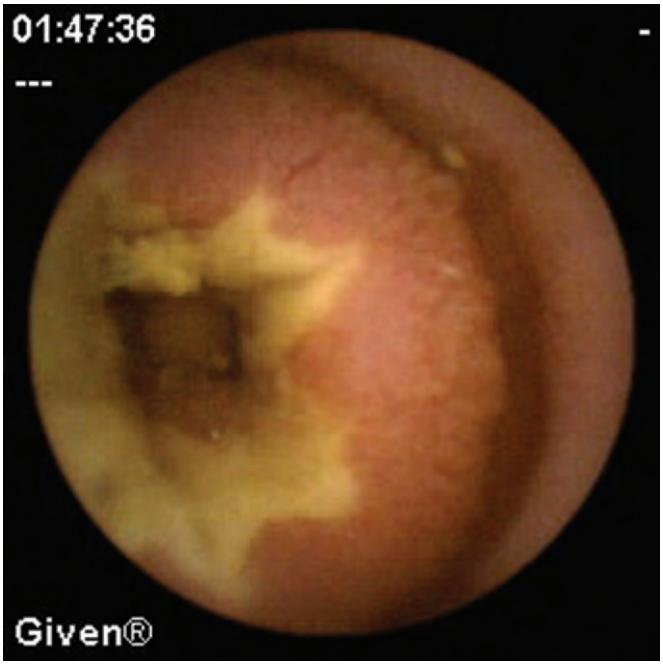

Figure 51–42. Wireless capsule endoscopic image revealing small bowel ulceration and stricture secondary to Crohn's disease.

The ability of intraoperative enteroscopy via enterotomy to identify occult small bowel sources of bleeding ranges from 70% to 100%.[32-39] Intraoperative enteroscopy, however, can be associated with a higher rate of complications, including wound infection,

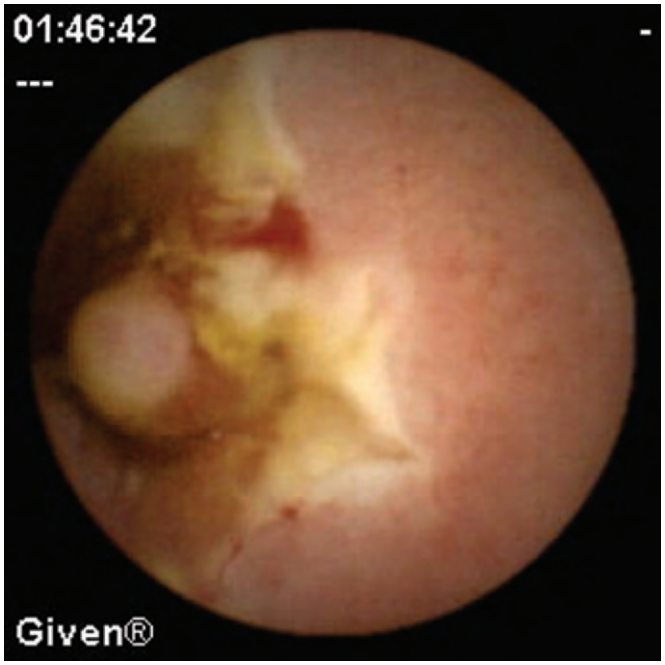

Figure 51–43. Polypoid mass in the small bowel seen on capsule endoscopy.

intestinal ischemia, mucosal laceration, and mesenteric hematoma. In one series comparing intraoperative enteroscopy as the gold standard with capsule endoscopy, capsule endoscopy had a sensitivity of 95% and a positive predictive value of 95%.[40]

Another novel technology being evaluated for the investigation of small bowel disease is double-balloon endoscopy. Peroral double-balloon enteroscopy has both diagnostic and therapeutic potential but is a time-consuming procedure requiring advanced endoscopic skills. In one case report, double-balloon endoscopy was used to identify a bleeding polyp in the distal end of the small bowel that was managed by a saline-lift polypectomy technique. At 8 months' follow-up, the patient had no evidence of recurrent bleeding.[41] Because these technologies are still in an evolutionary phase, therapeutic interventions for most small bowel lesions still commonly require a combination of endoscopic and surgical approaches with either intraoperative endoscopy and laparoscopy or endoscopic evaluation via enterotomy at the time of laparotomy.

CONCLUSION

Over the past several decades, flexible endoscopy has gained numerous therapeutic options that have now supplanted many surgical procedures for the management of GI disease. As these technologies continue to evolve in the future, it is imperative for GI surgeons to be skilled in these techniques, as well as maintain an understanding of the limitations, indications, and complications associated with these modalities.

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Chapter

52

Intubation of the Stomach and Small Intestine

Sean P. Harbison

Intubation of the gastrointestinal (GI) tract occurs frequently in the course of patient care for a variety of reasons. Enteral access, whether gastric or intestinal, nasal or percutaneous, is procured in the vast majority of instances for either decompression or nutrition. To a lesser extent, indications for intestinal intubation are both diagnostic and therapeutic for various disorders, such as upper GI bleeding. Despite the large number of devices and techniques for enteral intubation and the ubiquity of their use in modern medical and surgical practice, intestinal tubes are not always innocuous. Serious, even potentially fatal complications may result from placement or management complications of enteral tubes. Proper determination of the feasibility, timing, and route of access of intestinal tubes is essential for successful placement and use.

The treating surgeon must weigh the potential benefits of tube placement against possible morbidity. The time-honored practice of postoperative gastric decompression is being re-evaluated by evidence-based analysis. The conventional practice of postoperative gastric decompression via a nasogastric tube for patients undergoing laparotomy may not be required. The benefit of gastric decompression carries a concomitant risk of aspiration and sinusitis. Numerous studies, including a meta-analysis of more than 3000 postoperative patients, suggest that a selective approach to postoperative nasogastric decompression is more advantageous. Significantly more pulmonary complications occurred in patients with nasogastric tubes placed routinely, although there was no difference in wound-related complications when compared with selective placement of tubes for vomiting and gastric distention.[1]

Occasionally, patients undergoing laparotomy may not be able to tolerate intragastric feeding in the early postoperative period. Similar to GI intubation for decompression, the benefit of accessing the GI tract for feeding must be weighed against the potential risk associated with placement of a nasogastric or intraoperative feeding tube. The feasibility of placement, potential length of use, and route of enteral access are equally important considerations in determining the optimal intestinal intubation for nutrition. Gastric access for feeding may be of little value or even detrimental, such as in patients with a high risk for aspiration, impaired gastric emptying, or pancreatitis. It is imperative that the underlying medical and comorbid conditions, the anticipated length of time that enteral access will be required, and the setting in which it will occur be taken into account. Thoughtful consideration of these factors is needed to determine selection of the optimal device, route of access, and method of tube placement. Certain conditions create difficulty or completely preclude enteral intubation for decompression or nutrition. Obstruction of the nasopharynx, esophagus, or proximal part of the stomach is an absolute contraindication to nasoenteric intubation or endoscopically or fluoroscopically placed tubes. Coagulopathy, ascites, obesity, previous abdominal surgery, and esophagogastric varices are all relative contraindications to enteral tube placement by any method (Table 52–1).

Careful consideration of these factors and clear understanding of the risks and benefits of GI intubation lead to proper choice of materials and methods for appropriate enteral access.

NASOGASTRIC AND NASOENTERIC INTUBATION

GI intubation is a well-established diagnostic and therapeutic modality that has been in common use for centuries. The earliest descriptions of nasogastric tubes and intestinal intubation date from the 17th century.[2] Modern tubes are known eponymously for the individuals who introduced them into clinical practice. In 1921 Levin described a single-lumen catheter fenestrated at the distal end for decompression (low intermittent

Table 52–1 Enteral Access: Common Indications and Contraindications

Route	Indications	Contraindications
Nasogastric	Decompression, ileus, obstruction, upper gastrointestinal bleeding, toxic ingestion	Nasopharyngeal obstruction, varices, coagulopathy, thrombocytopenia, craniofacial injury
Nasoenteric	Short-term feeding, nutritional support, partial small bowel obstruction	Long term nutritional need >7-10 days, craniofacial injury
Gastric: percutaneous endoscopic gastrostomy	Malnutrition, head and neck cancer, cerebrovascular accident, trauma, prolonged intubation, respiratory failure	Gastroesophageal reflux disease, gastroparesis, gastric outlet obstruction, pancreatitis, recent foregut surgery
Gastric: open, Stamm	Inability to perform endoscopy, above indications	Above contraindications, recent foregut surgery
Intestinal: jejunal	Recent surgery, gastric outlet obstruction, gastroparesis, pancreatitis, fistula	Short-bowel syndrome, fistula, distal obstruction, inability to provide continuous infusion

suction or gravity drainage) or feeding.[3] A 1960s modification of the Levin tube is now widely used and known as a "Salem sump" tube (Fig. 52–1A). The Salem tube has a second lumen that allows air to be drawn into the stomach, or "sump," during suctioning, thereby avoiding adherence to the gastric mucosa. This tube is used most commonly today for GI decompression (e.g., ileus, partial small bowel obstruction) and is available in various sizes.

Long nasoenteric tubes designed for decompression are also available as single-lumen or multilumen tubes. Generally, long tubes have weighted or balloon-tipped ends and are intended to pass distally to provide intestinal rather than gastric decompression. Because of difficulty passing tubes through the pylorus, some authors espouse postpyloric endoscopic placement.[4] Others have shown little or no difference in the efficacy of long versus short decompressive tubes.[5] In 1934 Miller and Abbott first introduced a long, balloon-tipped intestinal tube designed to pass into the intestine via gentle advancement and peristalsis; subsequent modifications included percutaneous, weighted, multilumen, and silicone models (Baker, Cantor tubes) (see Fig. 52–1B and C).[6]

Nasoenteric tubes designed for feeding are similar to long tubes in that they are intended to pass distal to the pylorus, but in contradistinction to decompression tubes, they are generally of smaller caliber and made of softer plastic polymers than standard nasogastric or nasoenteric tubes are. These tubes often require a stiffening wire for passage and manipulation. The most familiar and widely used tube, introduced by Dobbie and Hoffmeister in the 1970s, is the now familiar Dobbhoff tube (see Fig. 52–1D).[7] The weighted, enlarged, radiopaque distal end purportedly facilitates spontaneous duodenal passage; however, evidence suggests that such is not usually the case.[8-10] Transpyloric passage may occur spontaneously in only limited instances. Silk and associates reported their experience with over 800 intubations and found that less than 4% spontaneously passed beyond the stomach.[10] Proper placement distal to the pylorus can be difficult and vexing and may require manipulation or endoscopic or radiologic maneuvers.

Indications

The most common indication for nasogastric and nasoenteric intubation is decompression of the stomach or intestine. It is used less frequently for diagnostic and therapeutic modalities such as gastric lavage and evacuation of gastric contents in the initial management of upper GI bleeding or toxic ingestion. Diagnostic uses are numerous and include aspiration to determine the presence of drugs or toxins; measurement of gastric secretion, volume, or pH; and procurement of specimens for culture of *Mycobacterium* or *Helicobacter pylori*. Decompression is by far the most common indication for nasointestinal intubation and includes decompression of air or enteric contents (or both) in the setting of ileus, partial or complete intestinal obstruction, gastric dilatation, perioperative gastric drainage, and reduction of the risk for aspiration. Routine postoperative nasogastric drainage after abdominal surgery is a time-honored practice, but the current literature and evidence-based medicine do not support such use. Studies suggest that selective use in patients for indications such as gastric distention, nausea, and vomiting is associated with fewer pulmonary complications than routine postoperative nasogastric tube decompression is.[11] Nasogastric and nasoenteric decompression is integral to the therapeutic and diagnostic management of intestinal obstruction. In terms of decompressive treatment of intestinal obstruction, placement of a nasogastric tube is often sufficient to relieve the obstruction. In the case of partial intestinal obstruction, decompression usually effects relief of the obstruction within 48 hours. If the obstruction is persistent, further diagnostic investigation and exploration should be considered. In patients with suspected

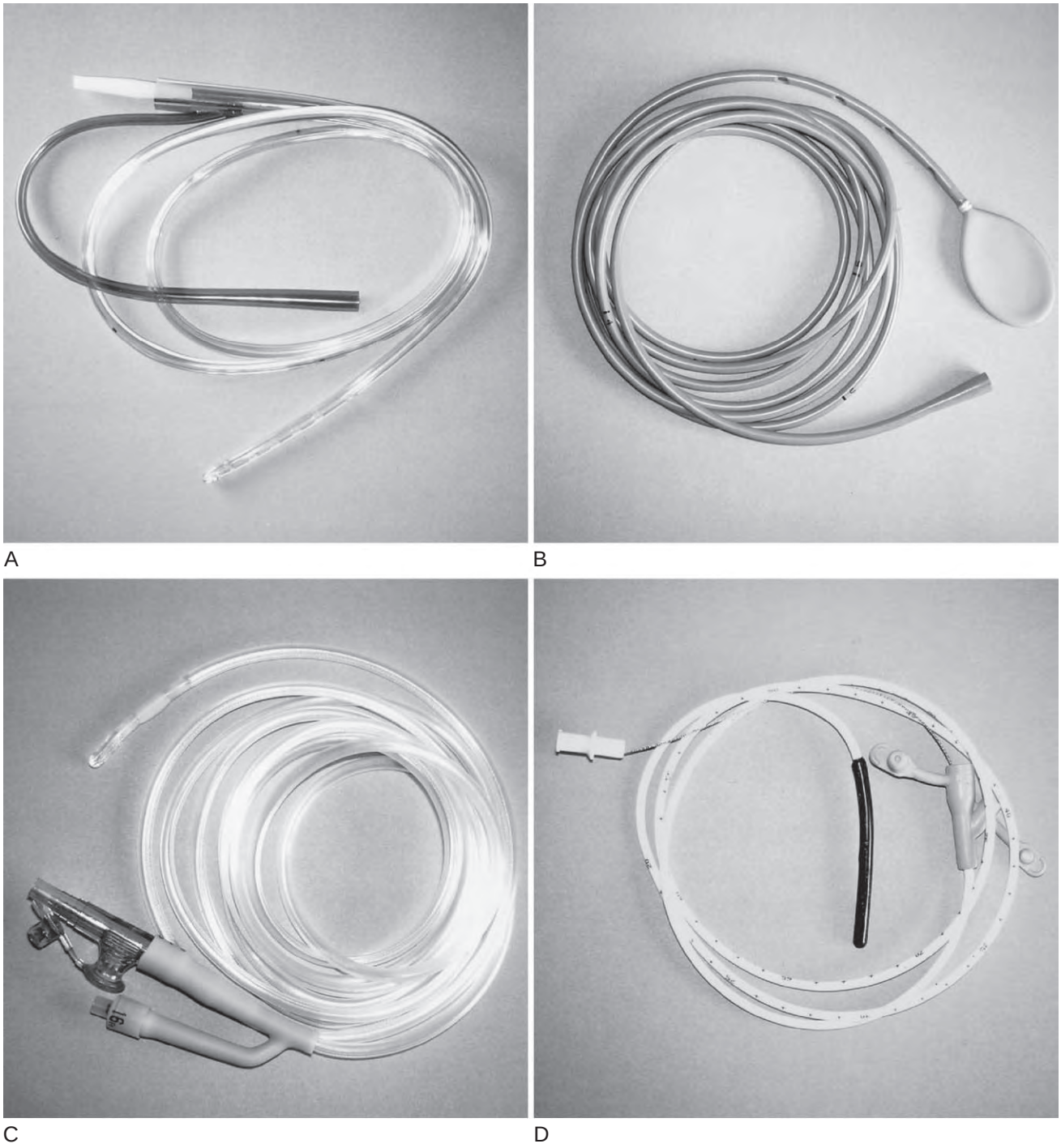

Figure 52–1. **A,** Salem sump tube. **B,** Cantor intestinal tube. **C,** Baker jejunostomy tube. **D,** Dobbhoff feeding tube.

complete intestinal obstruction, nasogastric intubation is important in the preoperative resuscitative period to decompress the stomach and minimize aspiration.

Long intestinal tubes (Miller-Abbott, Cantor, Baker) are available in numerous designs and sizes and are placed nasoenterically or operatively. The theoretical advantage of these tubes is that they decompress the small intestine distally at the site of obstruction. Long tubes use either an air-filled or weighted balloon to achieve transpyloric passage and rely on peristalsis for distal positioning. Long tubes are most effective and have been successful in the treatment of partial obstruction but have little, if any role in complete obstruction.[5] Limitations of long tubes and lack of clear superiority over nasogastric decompression have led to sparse use, mostly in specific clinical circumstances, such as in patients with significant operative comorbidity or malignant partial obstruction. Long tubes must be passed through the pylorus and then distally to the site of obstruction, both of which take time and may pose significant obstacles

requiring intervention. In addition, most long tubes do not have a gastric decompression port and therefore may allow emesis and aspiration from gastric dilatation. The superiority of long tubes has not been proved prospectively. Numerous authors have reported successful nonoperative treatment of partial small bowel obstruction with long tubes.[12] One randomized prospective study that compared nasogastric with long tube decompression for partial intestinal obstruction failed to demonstrate any significant difference in efficacy between the tubes.[5] In the management of partial intestinal obstruction, long tubes must still be considered a secondary treatment option to nasogastric decompression.

The aforementioned intestinal tubes are large bore (14 to 18 French) and designed to provide distal decompression; they are only occasionally used for gastric or jejunal feeding. Nasojejunal feeding tubes (e.g., Dobbhoff tubes) are smaller caliber (7 to 9 French) and softer and used exclusively for therapeutic purposes, such as feeding and drug administration in patients with functioning intestine who require nutrition but are unable to eat orally (see Fig. 52–1D). Distal enteral feeding through soft, small-bore tubes (Dobbhoff) positioned beyond the ligament of Treitz is thought to present a lower risk of aspiration than intragastric feeding does. Level 1 evidence does not exist to support this hypothesis. Some authors have shown that the risk for aspiration is not affected by the site of feeding. In critically ill patients maintained by either intragastric or jejunal feeding, there was no difference in the incidence of aspiration.[13-16]

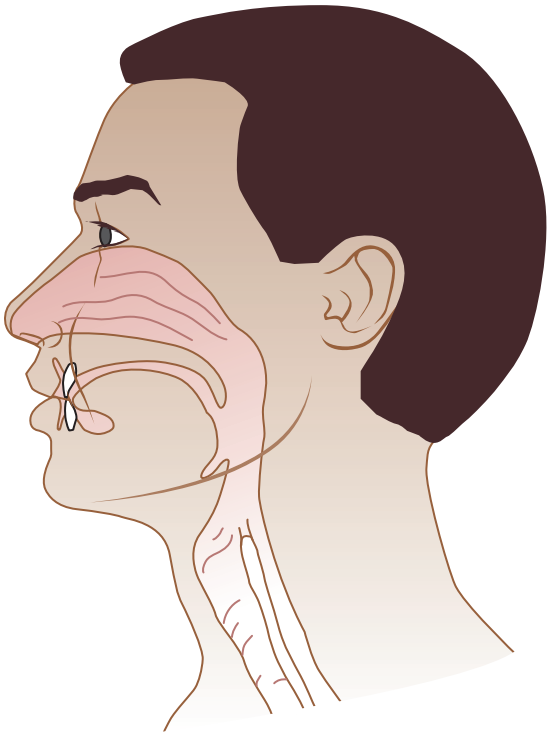

Figure 52–2. Sagittal section of the upper aerodigestive tract.

Contraindications

Strong contraindications to nasoenteric intubation include nasopharyngeal or esophageal obstruction, recent foregut surgery, and craniofacial injuries. Orogastric intubation is the preferred route of intubation in the presence of facial injuries or trauma, and it also temporarily facilitates stomach decompression when a patient is under anesthesia or in the event of toxic ingestion. Coagulopathy is a relative contraindication to nasogastric intubation and should lead to consideration of the orogastric route to avoid epistaxis. Patients with esophagogastric varices who require nasoenteric or oroenteric intubation should have tubes placed with caution and only for short periods to minimize the risk for variceal injury or erosion (see Fig. 52–1).

Methods of Intubation

Nasoenteric intubation is easily accomplished at the bedside and has several basic requirements for success, ease, and safety. As with many bedside procedures, the process can be divided into several phases, in this case three, to achieve the objectives of patient comfort, ease of placement, and minimal complications.[2,17] The insertion technique is identical for nasogastric and nasoenteric tubes. The steps are preparing the patient, passing the tube, and confirming position of the tube. If the patient is awake, explanation of the procedure pays dividends by alleviating anxiety and facilitating placement because patient cooperation simplifies the procedure.

Nasogastric intubation is easiest with the patient in the Fowler or upright sitting position with the neck flexed forward in the "sniffing" position. This position places the trachea anteriorly and provides a gentle curve for the tube to pass through the nasopharynx, often the most uncomfortable and problematic site through which the tube must be passed. Before placement, the length of tube that must be passed is gauged. Generally, tubes are placed approximately 50 cm from the nares so that they lie comfortably within the stomach. In the majority of adults the gastroesophageal junction is 40 cm from the incisors. Most tubes are marked to provide an approximation of proper placement. The length of insertion for blank tubes can be estimated by measuring from the patient's nares to the earlobe and then to the xiphoid (Fig. 52–2).

After consideration of the general contraindications to nasoenteric intubation (discussed in the previous section), each naris should be checked for obstruction. Both the nostril and the distal tip of the tube should be lubricated with water-soluble lubricant or, better yet, 2% viscous lidocaine. Topical anesthetic spray may also be used to anesthetize the posterior nasopharynx for improved patient comfort. The tube is inserted into the nostril aimed directly posterior toward the angle of the jaw or earlobe. A common mistake is to direct the tube in a cephalad direction, which may cause curling of the tube or trauma resulting in epistaxis. Placing the tip of the tube in ice for several minutes stiffens and may decrease curling of the tube, thereby facilitating passage. This practice is usually unnecessary, however, and can

easily cause discomfort or trauma. As the tube reaches the posterior nasopharynx and is redirected inferiorly, there is usually mild resistance. Gentle pressure is all that is required to turn the tube as it is redirected inferiorly and passes through the pharynx into the esophagus. Tubes should never be forced against resistance, which if encountered, is an indication to abandon the attempt and start anew. In awake and cooperative patients, a useful strategy is to enlist their involvement and have them sip water from a straw. Participation in the procedure helps alleviate anxiety, and sipping water closes the trachea and helps the patient swallow the tube. Placing the patient in the sniffing position helps direct the tube posteriorly and avoid tracheal intubation. Gagging, coughing, respiratory distress, or resistance should raise suspicion of tracheal intubation or misplacement and prompt immediate withdrawal of the tube.

Small-caliber (7 to 9 French) nasoenteric tubes used for feeding (Dobbhoff tubes) are softer and require a wire stylet for placement. Common wisdom holds that once removed, the stylet should never be replaced because it may result in perforation of the tube, mucosal damage, or both. Others, however, recommend routine reinsertion of the stylet as a means of transpyloric placement. With the tube successfully placed in the stomach, the stylet is removed and bent at a 30-degree angle several centimeters from its tip. The stylet is then reinserted and rotated; "corkscrewing" the tube while advancing it directs the tube toward and through the pylorus. Authors have reported this technique to be successful in more than 90% of insertions.[18-20]

Confirmation of proper tube placement should be accomplished before use for either aspiration or feeding. Placement is most often assessed by air insufflation into the tube during auscultation of the left upper quadrant. This routine method is certainly not foolproof; there are many reports of false-positive results.[2,21-23] Aspiration of enteric contents is helpful when large-bore, stiffer tubes are used, but again, this is not absolute proof of placement. Radiographic evidence of proper positioning of enteric tubes is most definitive. X-ray evidence of placement is prudent for all tubes placed with any degree of difficulty and should be considered necessary for all tubes before instituting feeding.

If the methods described fail, nasoenteric tubes can be successfully placed fluoroscopically or endoscopically into the duodenum in greater than 98% of cases.[24] Tubes should be anchored to the nose loosely after ascertaining placement to prevent inadvertent dislodgement and avoid undue pressure on the nasal ala.

Complications

Nasoenteric intubation is ubiquitous in the course of modern patient care but certainly is not always inconsequential. Complications associated with tubes and intubation have been reported in up to 15% of hospitalized patients undergoing nasoenteric intubation and range from minor to life-threatening.[17,21,25,26] The most serious complications occur in patients least able to compensate and protect themselves: those with impaired tracheopharyngeal defense mechanisms, impaired sensorium, or advanced age. Frequent complications associated with nasoenteric tubes include emesis, gagging, epistaxis, sinusitis, alar pressure necrosis, odynophagia, nasopharyngitis, and otitis. The litany of complications is more than merely annoying; apparently minor complications may easily progress or contribute to more serious conditions. Complications can be avoided by assiduous attention to proper placement and maintenance of tubes. Aspiration pneumonia is the most common serious complication associated with nasoenteric intubation. Malfunctioning tubes and simply the presence of a stent through the gastroesophageal junction are contributing factors. Some authors suggest that the incidence of tube-related aspiration approaches 50%.[27] Placing the patient's bed in the 30-degree head-up position and attention to proper function of the tube help prevent this potentially devastating complication. Less common, but equally serious complications include esophageal stricture or perforation, laryngeal injury, pulmonary complications, and insertion of the tube into the cranium through the cribriform plate. Proper insertion technique, assessment of placement, and management of the tube minimize complications. A common complication of small tubes is occlusion by solidified feeding matter or crushed drugs. Flushing solutions such as soda, cranberry juice, or enzyme solutions have met with only limited success.[28] Assiduous care of tubes, frequent flushing, limited aspiration, and use of pumps for feeding when indicated minimize occlusion. Replacement of the tube obviates the problem of occlusion and may be necessary but subjects the patient to discomfort and the risk of another procedure.

ENTERIC FEEDING

Feeding via the GI tract is preferable to nutrition via the parenteral route in patients who require nutritional support. Patients with functioning GI tracts who are nutritionally depleted or unable to swallow or who have inadequate food intake for their ongoing metabolic requirements benefit from enteral feeding.[29] Enteral nutrition is less expensive, easier to administer, safer, and more physiologic for the patient.[30] Animal evidence confirms that subjects maintained with parenteral nutrition succumb more easily to septic challenges than do those fed enterally.[31] Human studies confirm that enteral nutrition preserves the histologic structure and physiologic viability of the gut better than parenteral supplements do.[32] In contradistinction to total parenteral nutrition, enteral feeding is additionally beneficial to the patient because it helps maintain the immune system and the nutritional-metabolic axis.[33]

Intubation of the GI tract for nutritional support is frequent but not always innocuous. There are several considerations for optimal implementation and effect. The feasibility of enteral support depends on general patient considerations, the timing of tube placement, and the route of access. Any patient who is malnourished or expected to have inadequate oral intake for 5 to 7 days should be considered for enteral access for nutritional

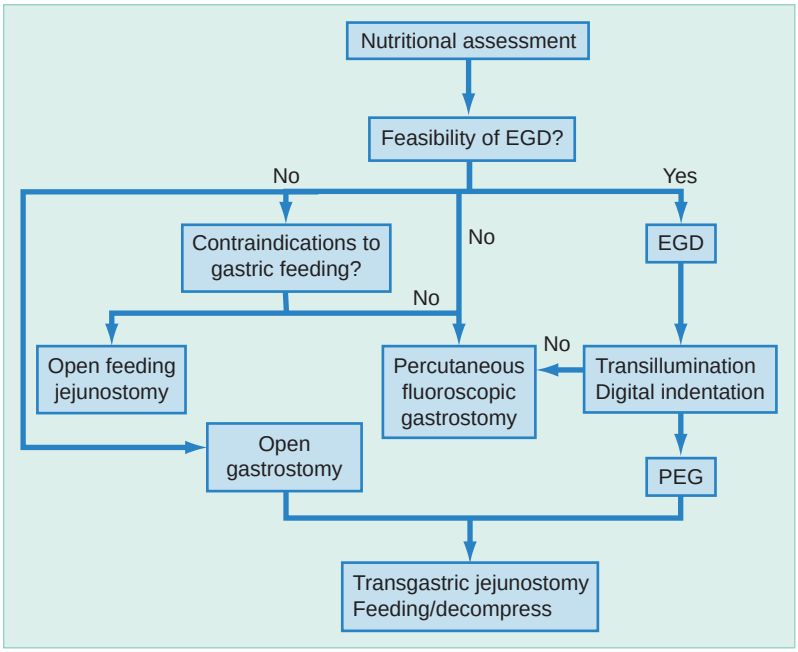

Figure 52–3. Algorithm for placement of tube enterostomies. EGD, esophagogastroduodenoscopy; PEG, percutaneous endoscopic gastrostomy.

support. Patients being considered for nutritional support within this very broad definition should subsequently undergo a clinical nutritional assessment, including a history, physical examination, and pertinent laboratory indices, to judge their nutritional status and anticipated needs. The route of nutritional support—enteral versus parenteral—should be part of the assessment. The GI tract should be used whenever possible. Patients with existing malnutrition, hypoalbuminemia (<3.3 g/dl), or recent significant weight loss (10% to 15% of pre-illness weight loss within 6 months) should be considered for immediate nutritional support. Nourished patients who have had insufficient intake for 5 to 7 days or are expected to have poor oral intake for 5 to 7 days subsequently should also be considered for nutritional support. Normally nourished or even mildly malnourished individuals requiring major operations do not usually require nutritional support if the procedure is prompt and the postoperative course is uncomplicated.[34] When a determination is made to provide nutritional support, initiation should be prompt. A small-bore nasoenteric (Dobbhoff) tube can easily and effectively provide short-term nutritional support and may temporize until a patient is capable of oral intake. If the GI tract is functional and longer-term nutritional support is required (>10 to 14 days), GI intubation via a gastrostomy (percutaneous or open) or jejunostomy should be considered. Moderately or severely malnourished patients undergoing open laparotomy should be considered for concomitant placement of gastrostomy or jejunostomy tubes at the time of surgery. Facilitated relatively easily during laparotomy, enteral access may pay dividends in the postoperative period if a patient is nutritionally depleted or requires ongoing support through postoperative recovery. Clinical judgment must be applied because placement of enteral access has its own risk-benefit balance. GI access should be prompt in patients requiring longer-term nutritional support without imminent surgery. Temporization with a soft small-bore nasoenteric tube (Dobbhoff) is an effective alternative until more effective access can be obtained. Soft, small-bore tubes are associated with difficult placement, frequent extubation, and a higher incidence of tube-related complications, which serve to impair or delay nutritional support. Feeding via nasogastric or nasoenteric tubes may be necessary but predisposes to aspiration. Authors have reported documented aspiration of enteric contents in up to 44% of critically ill patients receiving tube feeding regardless of whether it is delivered by the gastric or jejunal route.[13] Any candidate for nutrition via enteral access through any route should be evaluated the same as those requiring intestinal intubation for other indications. The patient's underlying medical and comorbid conditions, contraindications, and nutritional and ancillary needs, including the expected length of time that access will be required, are used to determine the method, route of placement, and choice of tube (Fig. 52–3).

Gastric Access for Nutrition

Currently, the most desirable—and common—route for enteral support is via a percutaneously placed gastrostomy. Authors have shown intragastric feeding to be more physiologic than parenteral nutritional support for several reasons.[35] The stomach provides a reservoir that allows cyclic bolus feeding, dilution of hyperosmolar solutions, and acidification of nutrients, which is bactericidal and improves the absorption of some nutrients. Cyclic feedings cause variations in insulin levels, thereby promoting lipolysis and anabolism. Other beneficial effects of feeding into the stomach include decreased gastric atony and bile stasis.

Gastric intubation is easier to accomplish than jejunal intubation because percutaneous gastrostomy does not require operative intervention and can be performed in sedated patients at the bedside. Technical, pathologic, and clinical impediments to gastric access may exist, however. Pharyngoesophageal obstruction, recent foregut surgery, or ascites may preclude gastric intubation by any method. Clinical conditions precluding use of the stomach include an inability to accommodate feeding, delayed gastric emptying, gastroesophageal reflux, ongoing pancreatitis, ileus, and intrinsic disease of the GI tract, including inflammatory bowel disease and radiation enteritis. These conditions should lead to abandonment of gastric intubation and consideration of jejunal or parenteral nutrition. If dictated by the clinical situation, combined gastric and jejunal tubes are available and can provide the advantage of postpyloric feeding and simultaneous gastric decompression. The only caveat is that combination tubes usually require placement by the open method and thus a small laparotomy.

TUBE ENTEROSTOMIES

Gastrostomy

Intubation of the stomach (exclusive of the nasogastric route) results in a planned gastrocutaneous fistula. Most commonly, simply placing the gastrostomy tube as a communicating stent from the gastric lumen to the exterior creates a temporary fistula with serosal lining. The anterior gastric wall and parietal peritoneum are held in direct contact by sutures or the tube itself. The Stamm or standard open gastrostomy, laparoscopic gastrostomy, and percutaneous endoscopic gastrostomy (PEG) are common examples of serosal gastrostomies and have the advantages of a low leak rate, ease of placement, and spontaneous closure when removed. One disadvantage is that inadvertent tube removal may result in rapid and premature loss of enteral access. These three methods—especially the PEG method—have been shown to be efficient and safe and represent the vast majority of gastrostomies placed today.[24,36] In unusual circumstances, a permanent gastrocutaneous fistula may be created in which part of the stomach wall is used to fashion a mucosa-lined tube between the lumen and exterior (Janeway-type gastrostomy).

Open Gastrostomy: Stamm Method

The Stamm, or open, gastrostomy is considered the gold standard for transabdominal gastric access and presents minimal risk. It requires a small laparotomy that can be performed under local anesthesia if necessary. The stomach is accessed via a small upper midline incision. The omentum or transverse colon is identified and retracted inferiorly. The appearance and arrangement of vessels along the greater curvature can identify the stomach. A relatively avascular site is chosen along the anterior wall of the stomach well away from the antrum and pylorus. The site should reach the planned abdominal wall exit site in the left upper quadrant to avoid undue tension on the tube and allow contact of the stomach serosa and parietal peritoneum of the abdominal wall.

The chosen tube, usually a large-bore (22 to 24 French) tube, often with a balloon or mushroom tip, is placed through the abdominal wall via a separate stab incision. One or two purse-string sutures are placed in the seromuscular layer of the anterior wall of the stomach at the prospective site. Creating a gastrotomy in the middle of the purse-string suture allows access for insertion of the tube several centimeters into the gastric lumen. If the tube is equipped with a distal balloon, it is inflated and the purse-string sutures tied securely. The anterior wall of the stomach is then affixed to the abdominal wall entry site with several sutures and the tube secured to the skin. The abdominal incision is closed in standard fashion (Fig. 52–4).

Laparoscopic Gastrostomy

Intragastric access is feasible with minimally invasive operative techniques. General anesthesia and pneumoperitoneum are required; open gastrostomy and PEG placement may actually be less invasive and therefore more attractive. Laparoscopic suturing may be used to replicate the open technique described in the previous section. Alternatively, approximation of the stomach to the abdominal wall is accomplished with T-fasteners placed percutaneously under laparoscopic visualization through the gastric wall into the lumen. Four T-fasteners placed around the prospective gastrostomy site are used to pull and maintain the anterior stomach wall in contact with the abdominal wall in the left upper quadrant. A gastrostomy tube is then placed percutaneously through the center of the T-fasteners into the gastric lumen. The stomach can be affixed to the abdominal wall via T-fasteners or sutures and further held in place with an intraluminal balloon. The need for general anesthesia and pneumoperitoneum and the technical requirements have rendered this method less often used than standard open (Stamm type) or percutaneous approaches.

Percutaneous Gastrostomy

Gastric access via a percutaneous endoscopic technique was developed and reported by Ponsky et al. in 1980.[37] The method allows safe, efficient transabdominal placement of a gastrostomy tube under local anesthesia at the bedside while avoiding laparotomy. Percutaneous gastrostomy has few absolute contraindications. Strong deterrents to PEG placement are recent upper abdominal surgery, especially on the foregut, and to a lesser extent any recent abdominal surgery. Two variations of this technique are used commonly and described in this section. Both techniques involve the use of esophagogastroduodenoscopy, air insufflation of the stomach, and transillumination of the anterior stomach wall through the abdominal wall. Transillumination and visualization of a probing finger indenting the stomach suggest that the transverse colon is displaced, the stomach is immediately adjacent to the abdominal wall,

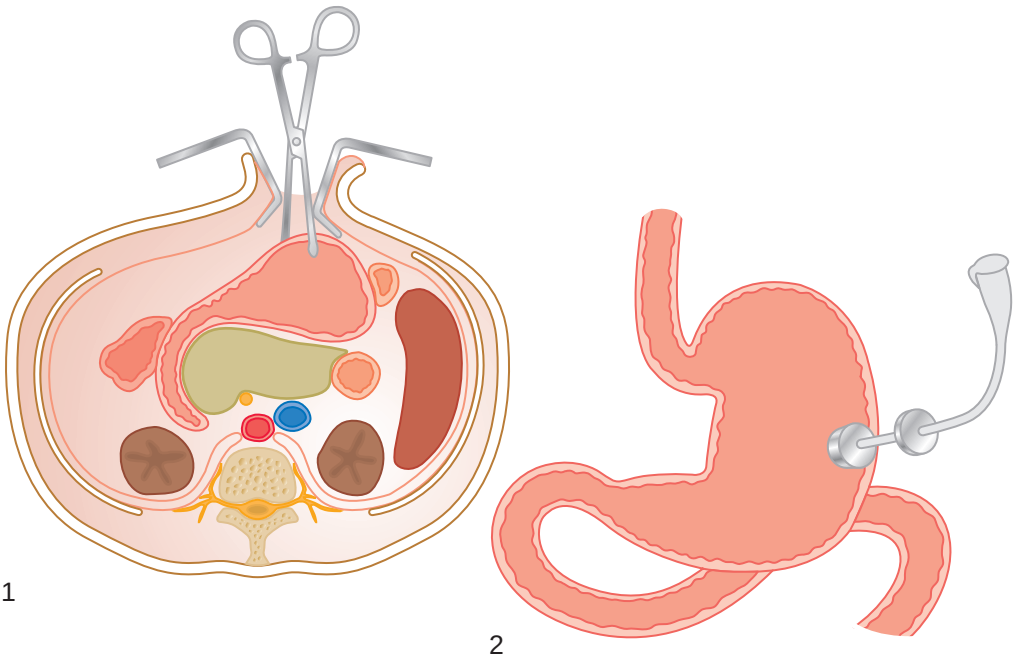

Figure 52–4. Open, or "Stamm," gastrostomy.

and percutaneous access is safe. A site should be chosen along the anterior aspect of the greater curvature within the stomach lumen well away from the pylorus. The skin site should be sufficiently distant from the costal margin in the left upper quadrant to minimize patient discomfort. The gastric lumen is accessed percutaneously with a small angiocatheter-type trocar under direct endoscopic vision. A guidewire is passed through the trocar into the gastric lumen and grasped with an endoscopic snare. The endoscope and wire are withdrawn through the esophagus, oropharynx, and mouth. Using the most common "pull" method originally described by Ponsky, the guidewire is pulled through the mouth and affixed to the gastrostomy tube. The abdominal end of the guidewire is then pulled to draw the gastrostomy tube through the mouth, pharynx, and esophagus so that it lies within the stomach. The preceding end of the tube is tapered to dilate the abdominal wall tract as the tube is passed. Tubes are equipped with a mushroom tip and gradations along the length. Initial placement can be estimated by determining the approximate thickness of the abdominal wall or the point where resistance is encountered. A second gastroscopy for ascertaining proper placement must be performed and can be facilitated by tightening the wire snare onto the "mushroom" end of the gastrostomy catheter.

The alternative "push" method, a variant of the Seldinger technique, is similar in all respects to the "pull method" except that the long tapered end of the gastrostomy tube is hollow and advanced over a guidewire while being pushed through the pharynx, esophagus, stomach, and abdominal wall. The tapered end of the tube effects dilatation of the abdominal wall tract. Direct visualization of the tube should be accomplished with either method to ascertain proper placement.

Procedure-related complications are divided into early (within 14 days) or late (after 14 days). Minor complications are generally tube related and include dislodged tubes, leaks, wound infections requiring wound care, mucosal obstruction or "buried bumper syndrome," and fever. Aspiration, bleeding, infection requiring antibiotic therapy, and abdominal emergencies (acute abdomen, peritonitis, gastric or colonic perforation) are major complications.[24] Percutaneous gastrostomy is well established and safe and can be done at the bedside with a minimum of anesthesia and complications.[38] Large clinical studies suggest that the technical success rate is greater than 99% with procedure-related mortality approaching 0%.[39] Barring contraindications, PEG is currently the method of choice for gastric intubation for nutritional support (Fig. 52–5).[40]

Combination Tubes

Multilumen tubes designed to provide postpyloric feeding and concomitant gastric decompression are a useful adjunct to standard gastric or jejunal tubes. Endoscopic, fluoroscopic, or open techniques have been used to place transgastric jejunal tubes. Transgastric jejunostomy tubes are more difficult to place, however, because the distal tube must pass through the pylorus and is thus usually placed operatively without endoscopy or fluoroscopy. Even with an initial open procedure, multiple procedures (endoscopy or fluoroscopy) may be required to successfully place the jejunal lumen of the tube in a postpyloric position. Care must be taken to avoid duodenal or jejunal perforation. Occasionally, clinical circumstances require conversion of a gastrostomy to a jejunostomy for more distal enteral feeding, such as in patients with gastric outlet obstruction or atony. Several options are available to accomplish conversion. Depending on the needs of the patient and the resources available, a percutaneous jejunostomy may be placed with a

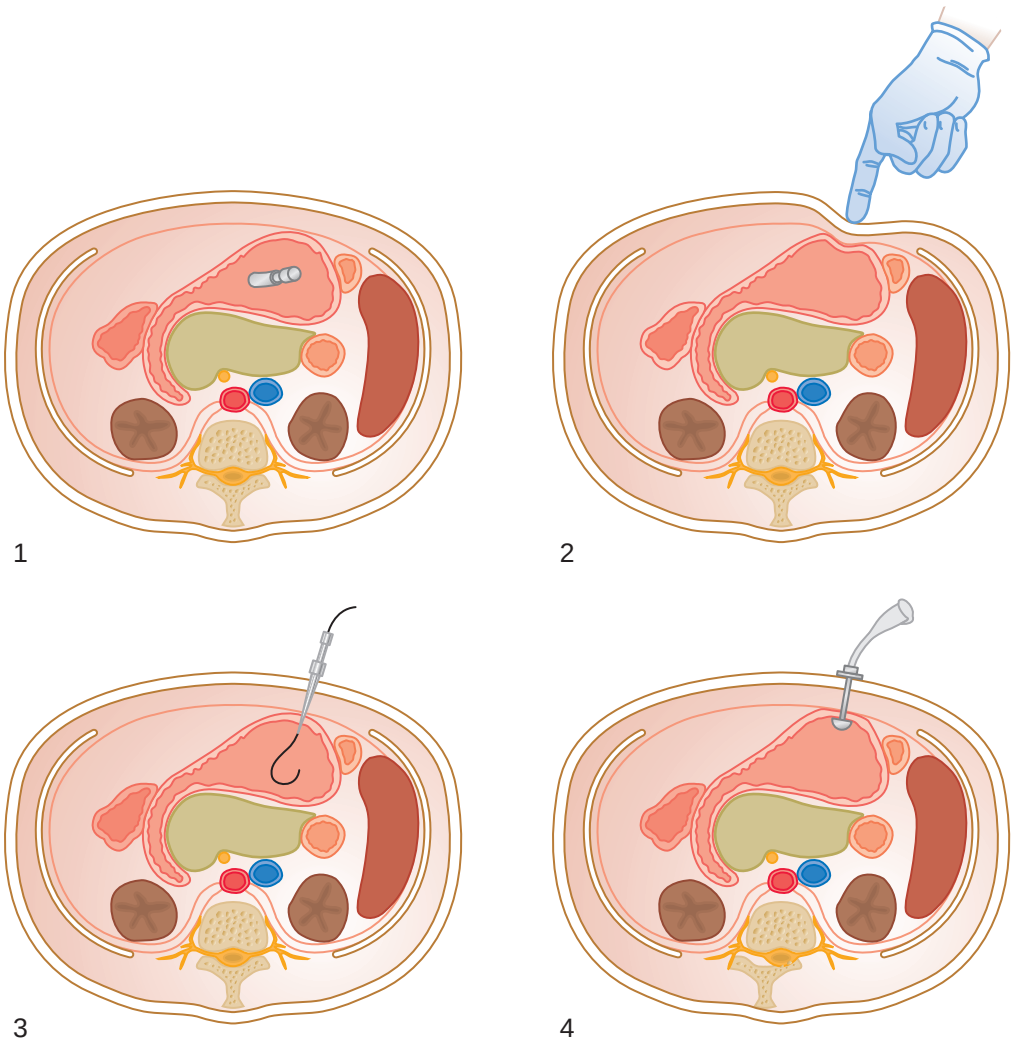

Figure 52–5. Schema of the percutaneous endoscopic gastrostomy procedure.

technique identical to the Ponsky PEG method after visualizing the proximal jejunum with an enteroscope. Other options include open or laparoscopic placement of a Witzel-type jejunostomy and endoscopic or fluoroscopic conversion of a gastrostomy to a transgastric jejunostomy tube.

Jejunostomy

Patients requiring enteral support in which gastric intubation or feeding is contraindicated for any reason may benefit from small intestinal access, or a jejunostomy. Enteral feeding distal to the ligament of Treitz is thought to decrease but does not eliminate the risk of aspiration.[14] Some authors hypothesize that distal feeding does not decrease aspiration and have shown similar documented aspiration rates in subsets of critically ill patients regardless of the route and site of feeding.[13] Witzel jejunostomy is the time-tested gold standard; the enteral access tube is incorporated in an oblique serosal or "Witzel" tunnel for several centimeters parallel to the small bowel lumen to prevent leakage of enteral contents. Placement of a Witzel-type jejunostomy requires laparotomy accomplished via a small upper midline incision. The site chosen for the jejunostomy is 15 to 20 cm distal to the ligament of Treitz. A purse-string suture is placed on the antimesenteric aspect of the jejunum. The chosen tube—usually a 14-French Silastic tube—is passed through an adjacent stab incision in the left upper quadrant. An enterotomy is created through the purse-string suture, and the tube is passed distally into the jejunal lumen. The purse-string suture is tightened, and a serosal tunnel is created proximally for approximately 3 to 5 cm by placing Lembert sutures over the tube along the antimesenteric border of the bowel. Care should be taken to avoid narrowing the jejunal lumen while creating the Witzel tunnel. Several sutures are used to affix the jejunum to the parietal peritoneum of the anterior abdominal wall at its exit site (Fig. 52–6).

Needle catheter jejunostomy, an alternative technique, is a method of access in which a large-bore needle is placed in the bowel lumen instead of a tube. The needle catheter is inserted identically to standard jejunostomy tubes via the Witzel method. The method has been used extensively in the critical care and trauma

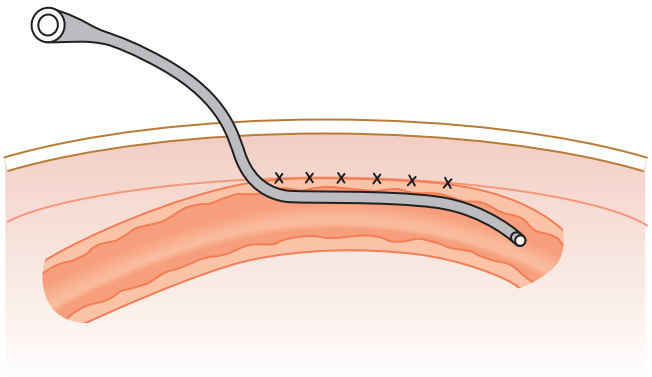

Figure 52–6. "Witzel" jejunostomy.

patient population. The small-bore catheter is easily removed when no longer needed but occludes easily.

Minimally invasive techniques similar to laparoscopic gastrostomy placement may easily be applied to jejunostomy tube placement. Identical technique using T-fasteners placed into the antimesenteric small bowel lumen under direct laparoscopic visualization allows fixation of the jejunum. An introducer with a peel-away sheath is placed through the abdominal wall and thence into the jejunum. The T-fasteners are cut at skin level 10 to 14 days later. Similar to laparoscopic gastrostomy, this technique is less often used because of technical requirements and tube-related complications. Alternatively, laparoscopic suturing expertise may allow the surgeon to mimic the open technique described earlier.

Enteral tubes may be placed by the same endoscopic techniques as used for PEG tubes, although it is substantially more difficult. Most often a PEG is placed first or a preexisting PEG is converted to a transgastric jejunal tube. Transpyloric placement of a guidewire is accomplished under direct endoscopic visualization. The jejunal tube is then advanced over the wire through the duodenum into the small bowel. This technique is fraught with difficulty and potential serious complications, such as perforation as a result of placing a relatively stiff tube through the curved duodenum. An alternative method of distal tube placement is to use fluoroscopic imaging to guide the tube through the pylorus.

MANAGEMENT AND COMPLICATIONS OF INTESTINAL TUBES FOR NUTRITION

There is great variability in the literature regarding when nutritional support can be initiated after GI intubation. The literature has suggested that early feeding, even within 2 to 3 hours, is feasible and does not result in an increased incidence of complications when compared with initiation of feeding at 24 hours.[10] Typically, with either gastric or jejunal tubes, feeding can be started safely within 24 hours of placement regardless of the method if certain criteria are met. Reasonable criteria for initiating enteral feeding include tube output or residual volume measured at less than 200 ml/8 hr and no abdominal distention, abdominal wall tube site leakage, or surrounding erythema. It is acceptable to begin full-strength feeding solutions at a low rate and progressively increase until the goal volume is reached.

Intestinal access tubes are placed and used almost without complications. In the relatively unusual circumstance that they occur, serious morbidity or even fatality may result, and thus they should be treated promptly. Postoperative and tube-related complications are similar for jejunal and gastric tubes. All tubes are subject to mechanical tube-related complications such as occlusion and tube displacement. Periodic flushing and proper use prevent catheter clogging. Assiduous attention to the tube itself minimizes dislodgement, although inadvertent extubation remains commonplace in the hospital setting.

Aspiration pneumonia has been documented in up to 44% of critically ill patients and is directly related to enteral feeding.[15] Measures to prevent aspiration should be instituted for all patients with intestinal intubation or those receiving enteral feeding regardless of the site. The literature has shown no difference in the rate of aspiration in critically ill patients fed into the stomach or small intestine.[13,23]

Dislodgement of gastrostomy or jejunostomy tubes is a common complication that is usually merely annoying but can be life-threatening. Tubes that are completely dislodged should be replaced with caution only if the transabdominal tract is well established (>14 days). A well-lubricated, small-bore tube or even a flexible guidewire may be used to access the intestinal lumen. A radiologic contrast study should be performed to confirm tube placement, especially before using a recently replaced tube.[41] In the absence of a well-established transabdominal tract, the more prudent course may be to leave the tube out and replace it formally at another setting because reinsertion risks inadvertent intraperitoneal placement.

Peritonitis from leakage of enteric contents or feeding formula, or both, may occur as a result of separation of the bowel from the abdominal wall with or without tube dislodgment. An acute abdomen or presumed peritonitis mandates prompt, urgent intervention. Bowel obstruction is a complication encountered both early and late after intestinal tube placement from various causes. Balloon-tipped catheters may cause obstruction by migration or simply lodge in a disadvantageous position. Jejunostomy catheters placed via the Witzel technique may become obstructed from a too tight Witzel tunnel or angulation of the jejunal loop as it apposes the abdominal wall. Additionally, tube or tube placement complications such as hematoma, contained leak, or abscess may cause either mechanical or functional obstruction. Volvulus or internal herniation of small intestine around a tube insertion site resulting in obstruction is a less frequent occurrence and may require operative repair. Regardless of the cause of obstruction, timely investigation and intervention are warranted.

SUMMARY

The two common broad indications for intestinal intubation—decompression and nutrition—are ubiquitous

in the course of care of surgical patients. Many options exist for establishing intestinal access. The practitioner must use clinical judgment and knowledge to choose the safest, most suitable method for the individual patient.

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Chapter

53

Injuries to the Stomach, Duodenum, and Small Bowel

Amy J. Goldberg · Mark Seamon · Abhijit S. Pathak

GASTRIC INJURIES

Historical

Throughout history, abdominal visceral wounds were generally considered fatal. It was not until the late 19th century, with improved surgical techniques and antisepsis, that intra-abdominal operations began to be performed on a widespread basis. By the early 20th century, laparotomy for abdominal penetration, including successful repair of gastric wounds, was being reported.[1] During World War I the role of surgery in penetrating abdominal trauma was further defined, and mandatory surgery for all penetrating abdominal wounds was an established principle by World War II.[2]

Anatomy and Physiology

The stomach is located in the superoanterior portion of the peritoneal cavity and is relatively well protected by its location and mobility. The inferior thoracic cage provides some protection laterally and anteriorly. Even though the stomach is tethered at the esophageal and duodenal junctions, it can descend into the lower part of the abdomen in an erect patient. The central location of the stomach in the upper part of the abdomen increases its risk for injury with thoracoabdominal penetration. Furthermore, if the esophagogastric junction and pylorus are constricted, the stomach, especially if distended or full, is at risk for rupture in blunt trauma.

Several upper abdominal viscera are in close relation to the stomach and can sustain an associated injury when blunt, penetrating, or corrosive injuries to the stomach occur. Both lobes of the liver overlap the stomach anteriorly, whereas posteriorly, the stomach is in close proximity to the pancreas, left kidney, and adrenal gland. Also in close proximity are the aorta, celiac trunk, and renal and splenic vessels. Most importantly, the stomach is in very close relation to the spleen posterolaterally and attached to it by the short gastric arteries. Superiorly, the left lobe of the liver overlaps the gastric fundus and is closely related to the left hemidiaphragm. During normal ventilation, the diaphragm rises and falls. In deep expiration, the left hemidiaphragm can rise as high as the fifth costal cartilage, thereby placing the stomach at risk for injury from thoracic penetration. Because the posterior gastric wall lies within the lesser sac, injuries to this region may not produce the usual signs of peritoneal irritation.

The stomach has a rich blood supply with extensive collateralization. The major vessels supplying the stomach include the left gastric artery, a branch of the celiac trunk; the right gastric and gastroepiploic arteries, which are branches of the hepatic artery; and the short gastric and left gastroepiploic arteries, which are distal branches of the splenic artery. Because of this extensive vascular supply, ligation of two major vessels and many times three vessels in young patients is well tolerated. In addition, the submucosa is highly vascular, and injuries that extend through this layer have the potential to cause life-threatening hemorrhage (Fig. 53–1).

The stomach has two major functions: storage of foodstuff and digestion. These important physiologic roles are also responsible for both its vulnerability to injury and the postinjury consequences. The stomach stores foodstuff and regulates passage of chyme into the duodenum. A distended, postprandial stomach is susceptible to both penetrating and blunt trauma. A rapid elevation in intragastric pressure when the lower esophageal sphincter and pylorus are contracted can lead to either partial- or full-thickness injury of the organ.

The stomach secretes HCl and the zymogen pepsinogen, which is converted to the proteolytic enzyme pepsin in the presence of acid. Pulmonary aspiration of acid-peptic contents can induce a florid chemical pneumonitis, a principal danger in trauma. Peritoneal spillage of gastric contents from a full-thickness injury can induce

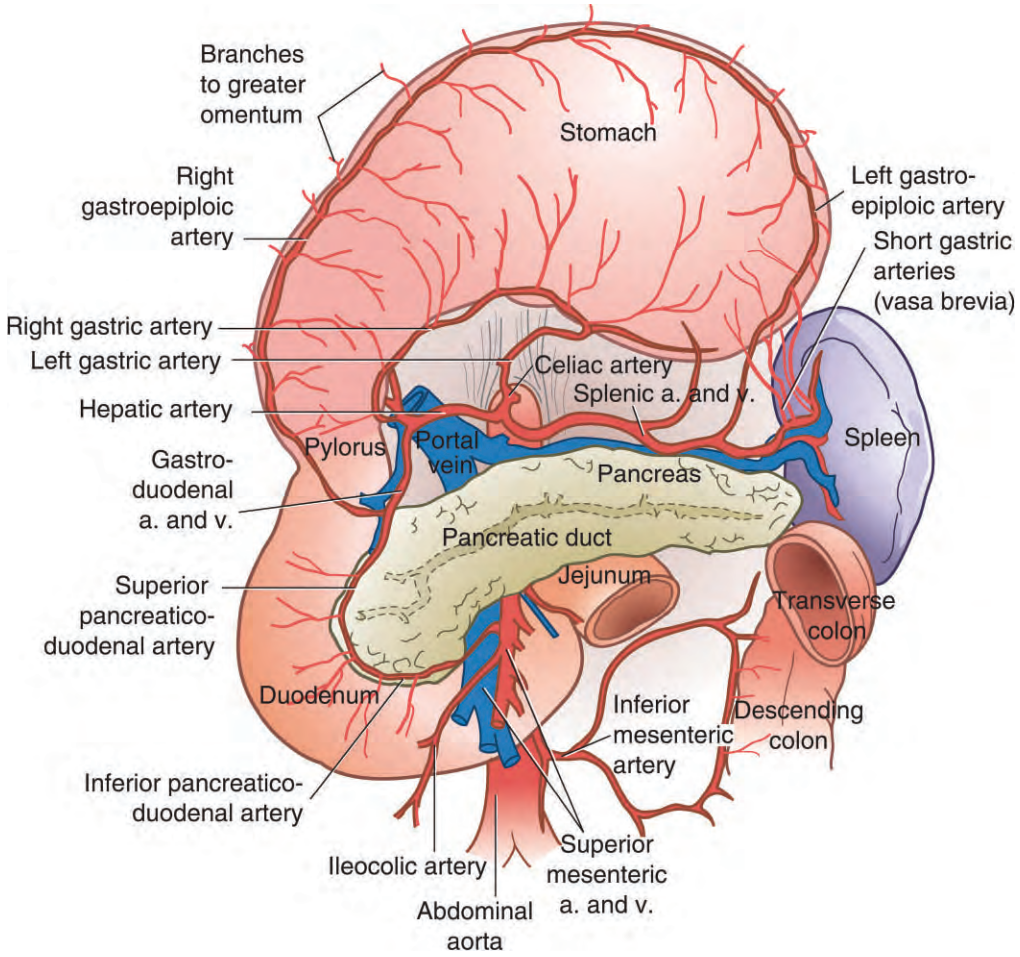

Figure 53–1. Anatomy of the stomach, duodenum, and pancreas. (From Zuidema G: Shackelford's Surgery of the Alimentary Tract, 4th ed. Philadelphia, WB Saunders, 1995.)

acute chemical peritonitis. If not immediately recognized, the subsequent inflammatory response leads to massive exudation of extracellular fluid into the peritoneal cavity. A delay in the diagnosis of gastric perforation will lead to intra-abdominal infection and sepsis. Even though the stomach has a low bacterial count, spillage of food particles enhances the virulence of these small numbers of bacteria.

Patterns of Injury

Penetrating Injuries

The incidence of gastric injury with penetrating abdominal trauma is anywhere from 5% to 20%.[3,4] As mentioned previously, its location and mobility, as well as its size, place the stomach at risk from penetrating injury. Missile injuries to the anterior abdominal, thoracoabdominal, or thoracic region can injure the stomach, depending on the trajectory. Stab wounds to the stomach are usually isolated injuries, whereas gunshot wounds generally have associated injuries. These associated injuries are mainly responsible for and strongly influence mortality because isolated gastric wounds are rarely fatal.[5,6]

Blunt Injuries

Blunt gastric injuries are fairly uncommon and have been reported in less than 1% of cases of blunt abdominal injury.[5,7] The pathophysiology of gastric rupture is related to constriction of the esophagogastric junction and pylorus with an increase in intragastric pressure and subsequent rupture, especially with a distended or full stomach. According to Laplace's law, gastric rupture would be predicted to occur along the greater curvature; however, this is not the general rule.[8] Blunt injuries usually occur as single lesions, with the most common site being the anterior wall (40%), followed by the greater curvature (23%), the lesser curvature (15%), and the posterior wall (15%).[9] Most blunt gastric injuries occur after rapid-deceleration motor vehicle collisions and are associated with significant concomitant injuries. Splenic and thoracic injuries are the two most commonly

associated with stomach injuries. Indeed, the multicenter hollow viscus injury study by the Eastern Association for Surgery in Trauma (EAST) demonstrated that the highest mortality rate was recorded for stomach injuries, 28.2%.[7] Furthermore, gastric injuries were associated with the highest injury severity scores, which is thought to be related to the significant amount of force required to cause gastric rupture.[7]

Besides rupture, blunt force may cause devascularization of the stomach and thereby lead to focal necrosis and delayed perforation.[10]

Caustic Injuries

Ingestion of caustic substances can lead to significant gastric injury. The most common corrosive agents fall into two major categories: alkali and acids.

Ingestion of alkaline agents such as lye (NaOH or KOH), which is found in household products such as drain cleaner, leads to injuries that are more severe than those caused by ingestion of acid because the mechanism of injury in alkali ingestion is liquefactive necrosis, which progresses over time and can result in transformation of the necrotic tissue to a liquid viscous mass. Ingestion of crystalline lye results in injury usually limited to the upper aerodigestive tract, such as the pharynx and esophagus. Ingestion of liquid lye can produce injury not only to the aforementioned structures but also to the esophagus and stomach. Severe gastric injury is unusual in the absence of significant esophageal injury. The duodenum and pancreas can be injured as well.

Gastric injury after acid ingestion is less common. Ingestion of acid leads to a coagulative necrosis that generally results in preservation of the general tissue architecture and is less severe than liquefactive necrosis. The stratified squamous epithelium of the pharynx and esophagus is relatively resistant to acid injury; however, the gastric columnar epithelium is not, and significant injury may occur. Transmural gastric necrosis is rare after acid ingestion, with the more common pattern of injury being mucosal ulceration and hemorrhage. Late sequelae of gastric acid injury may be manifested as gastric outlet obstruction from severe fibrosis.

Emetogenic Injuries

Emetogenic injuries of the stomach occur when there is a sudden increase in intragastric pressure that results in tearing of the mucosa or submucosa, usually near the esophagogastric junction. Also known as a Mallory-Weiss tear, these injuries can be a common cause of upper gastrointestinal (GI) bleeding.[11]

Iatrogenic Injuries

Iatrogenic gastric injuries can occur as a result of endoscopy or surgery or even after cardiopulmonary resuscitation or the Heimlich maneuver.[12-14] Delayed gastric necrosis has been reported after splenectomy and highly selective vagotomy, probably secondary to devascularization of the stomach.[15,16]

Diagnosis

Penetrating and Blunt Injuries

The mechanism of injury may help determine the potential for an intra-abdominal injury. In cases involving penetrating trauma, the external wound will draw attention to the body cavity most likely injured. In blunt trauma, the history as well as the mechanism of injury will suggest the presence of an intra-abdominal injury. Patterns of blunt abdominal trauma that may result in injury to a hollow viscus, such as the stomach, usually involve high energy transfer such as motor vehicle collisions and as a general rule are associated with other injuries as well.

Physical examination, especially in a multiply injured patient, can be unreliable, particularly in patients with neurologic injury, drug or alcohol ingestion, or significant distracting injury.[17] As mentioned previously, penetrating injuries tend to draw attention to the underlying body cavity most likely injured. Indeed, in patients with abdominal penetration, gastric injury is usually identified at the time of laparotomy.

Clinical findings that may suggest gastric injury include hematemesis, aspiration of blood from a gastric tube, or pneumoperitoneum on plain films. Routine laboratory analysis may be neither sensitive nor specific for diagnosing a gastric injury.[18] Other diagnostic studies available include computed tomography (CT), contrast-enhanced upper GI series, and diagnostic peritoneal lavage (DPL). Focused assessment of sonography in trauma (FAST) has gained wide acceptance as an adjunctive diagnostic modality in a blunt trauma victim. Its usefulness in blunt trauma is limited to identifying the presence or absence of free fluid within the peritoneal cavity, which in the majority of cases represents blood. It cannot distinguish between blood and other fluids and is therefore not specific in its ability to diagnose a hollow viscus injury.[19]

The role of CT scanning in trauma has emerged to the forefront in the past 15 to 20 years, especially for the evaluation of a hemodynamically stable blunt trauma patient and even for penetrating torso injuries.[20] CT scanning has proved to be useful in the diagnosis of blunt solid organ injury, thereby allowing subsequent nonoperative management of these injuries. The ability of CT to diagnose hollow viscus injuries is relatively limited. A delay in diagnosis of blunt hollow viscus injuries such as gastric injuries, though rare, can lead to increased morbidity and mortality.[7,21] The presence of free, low-density fluid without a solid organ injury should alert the surgeon that a hollow viscus injury may be present. Extravasation of oral contrast into the peritoneal cavity or pneumoperitoneum implies injury to a hollow viscus as well.

Water-soluble contrast studies of the upper GI tract can be used to detect gastric perforation, but their main use is for the diagnosis of gastric and duodenal hematoma. DPL is generally used for the evaluation of a hemodynamically unstable blunt trauma victim with equivocal or negative FAST results. Although it is a technique primarily for the diagnosis of intra-abdominal hemorrhage, DPL can provide evidence of hollow viscus

injury with high sensitivity. In particular, a white blood cell (WBC) count of greater than 500 WBCs/mm^3 in the lavage effluent or the presence of bile or food particles denotes a hollow viscus injury.

The role of laparoscopy in trauma has been mainly for evaluation of stable patients with penetrating torso wounds in whom absolute indications for exploration are not present and the work-up has not sufficiently eliminated peritoneal violation. Therefore, laparoscopy is frequently used to aid in the identification of diaphragmatic lacerations and peritoneal violation after penetrating wounds.[22] In particular, thoracoabdominal penetrating wounds and tangential gunshot wounds may be evaluated with this technique. Once identified, some injuries, such as diaphragm and gastric lacerations, have been repaired laparoscopically.[23] The drawback of laparoscopy for assessment of penetrating trauma has been its relatively low sensitivity for the identification of hollow viscus injuries and evaluation of the retroperitoneum.[22,24-26] Hence, its role as a therapeutic tool is still limited mainly to repair of anterior gastric and diaphragm injuries. It should be emphasized that caution should be exercised when using laparoscopy for identification and exclusion of hollow viscus injuries.

Caustic Ingestion

The most useful modality for the diagnosis of caustic injuries is endoscopy. After the ingestion of alkali, endoscopy is usually terminated at the point where deep, circumferential burns are identified because with second- or third-degree circumferential injury, further passage of the endoscope can produce additional injury.[27]

Treatment

Penetrating and Blunt Injuries

Initial care of a trauma patient centers on the standard advanced trauma life support (ATLS) principles. Once a gastric injury is suspected or confirmed, laparotomy is indicated. Patients should receive preoperative prophylactic antibiotics directed against GI flora. Preparation of the patient for surgery should include antisepsis and draping from the chin to the knees. A midline laparotomy incision from the xiphoid to the pubis is created and the abdominal cavity entered. After control of significant hemorrhage, contamination from the GI tract is addressed. Any hollow viscus perforations can initially be controlled with Babcock clamps.

Examination of the stomach must be thorough, and to do so, mobilization of the stomach is needed for visualization. A gastric tube should be placed for decompression and to facilitate exposure. It may be necessary to divide the left triangular ligament of the liver with medial retraction of the lateral segment of the left liver lobe to expose the gastroesophageal (GE) junction. The lesser sac and posterior surface of the stomach should be visualized by dividing the avascular portion of the gastrocolic omentum. A technique we find useful for evaluation of the posterior aspect of the stomach is to place a Deaver retractor along the posterior gastric wall after division of the gastrocolic omentum and apply posterior and caudal retraction on the pancreas with a sponge stick. The gastric retractor is directed cranially and the Deaver retractor is carefully withdrawn to allow visualization from the posterior GE junction proximally to the antrum distally. Any hematoma of the stomach wall should be evacuated and thoroughly explored. The presence of a single anterior wound should prompt a search for a second wound (especially posteriorly). A useful intraoperative adjunct for the diagnosis of small perforations or injuries in areas difficult to visualize is the intragastric instillation of methylene blue dye, which will stain the surrounding tissues.

Because of the stomach's large size and generous blood supply, most wounds are amenable to primary repair by either hand-sewn or stapling techniques. Narrowing the lumen is rarely a concern. Intramural hematomas are repaired with an interrupted Lembert suture technique after evacuation of the hematoma. Small lacerations can be repaired in two layers after adequate débridement. The inner layer should be a full-thickness hemostatic absorbable suture and the outer layer, an interrupted seromuscular suture. Alternatively, a TA stapler can be used to resect the gastric laceration.

Repair of wounds near the GE junction or pylorus may result in stenosis. A pyloric wound might require conversion to a pyloroplasty. Some wounds may be extensive and necessitate either proximal or distal gastrectomy. The standard principles of gastric resection are safely applied in these circumstances. If a vagus nerve injury is encountered, a drainage procedure should be performed.

Caustic Injuries

Laparotomy may be indicated in patients with severe gastric injury and suspected full-thickness necrosis. The entire stomach should be inspected and all areas of gastric necrosis resected, which may require subtotal or total gastrectomy. Reconstruction is based on the degree of resection: Billroth I or II for antrectomy and Roux-en-Y for total gastrectomy. Usually, if significant gastric injury is present, there may be an associated severe esophageal injury, especially with lye ingestion. In theses cases, total esophagectomy and gastrectomy with creation of a feeding jejunostomy may be needed.

Emetogenic Injuries

Bleeding from most emetogenic injuries is self-limited. Endoscopy generally identifies these injuries, which are located near the GE junction. Furthermore, gastroscopy is not only diagnostic but can also be therapeutic. Endoscopic treatment includes the injection of sclerosing agents and epinephrine, as well as electrocautery. Arteriography with the infusion of vasopressin or embolization of the left gastric artery can effectively provide hemostasis.

If surgery is indicated for refractory bleeding, a vertical gastrotomy on the anterior body of the stomach will

allow visualization of the injury. The injury is repaired and closed with running nonabsorbable suture.

Complications

As mentioned previously, isolated gastric injuries are rarely fatal. The associated injuries usually carry high morbidity and mortality. Specific complications relating to penetrating gastric wounds include postoperative bleeding, intra-abdominal abscess, sepsis, and gastric fistulas. A delay in the diagnosis of gastric wounds and extensive spillage of gastric contents at surgery increase the frequency of intra-abdominal infections and sepsis. Based on the current literature it seems reasonable that surgery should be performed within 8 hours of injury in patients with hollow viscus injuries to avoid the increase in morbidity.[21] Meticulous débridement of the gastric wound plus thorough cleansing of the peritoneal cavity of any spilled enteric contents is essential. When both diaphragm and gastric injuries are present, the incidence of empyema is increased. Therefore, if the pleural space has been contaminated by enteric contents, the pleural cavity should be irrigated through the diaphragmatic defect.[4] The presence of a gastric injury in addition to a colon injury has been shown to have a synergistic effect on the rate of postoperative infection.[28]

An intra-abdominal abscess may be manifested as postoperative fever, leukocytosis, ileus, and signs of sepsis. CT usually confirms the diagnosis, and most abscesses can be managed by percutaneous drainage and broad-spectrum antibiotics. Consideration of fungal elements such as *Candida* species should not be overlooked in patients who appear to be refractory to appropriate management. A leak from a repair or anastomosis, which is often the cause of the abscess, is usually of low output and can be managed with adequate drainage, antibiotics, and nutritional support.

Early postoperative bleeding after gastric repair is generally a technical error. Reoperation may be necessary if the bleeding continues despite adequate correction of any metabolic and coagulopathic abnormalities. Late (>7 days) bleeding is generally mild, self-limited, and caused by sloughing of the inner layer of the gastric repair.

DUODENAL INJURIES

History

Management of penetrating abdominal injuries was nonoperative until the late 19th century. Larrey probably provided the first description of a penetrating duodenal injury in 1811 when he reported a 17-year-old patient who was stabbed above the umbilicus.[29] He described eviscerated omentum, persistent hematemesis, and sepsis, but the patient was treated nonoperatively. Later, autopsy reports from the American Civil War described five soldiers with duodenal shot wounds.[30] All injuries were treated without surgery. It was not until 1896 that Herczel reported the first repair of a duodenal injury.[31] Sporadic reports and small series followed, but a nonoperative approach persisted until World War I, when surgeons began to use exploratory laparotomy to diagnose and treat penetrating abdominal injuries. Mortality remained substantial despite routine operative intervention for penetrating abdominal injuries in World War II. Cave et al. reported the first large military series (118 cases) of duodenal injuries after World War II and described a 55.9% mortality rate despite attempts at operative repair.[31] Since the mid-20th century, advances in operative technique, nutrition, antibiotics, and critical care have reduced the mortality associated with duodenal injuries.

Anatomy

The duodenum is the first portion of the small bowel and measures 25 to 30 cm in adults. The duodenum is divided into four portions. The first portion stretches from the pylorus to the gastroduodenal artery superiorly and the common bile duct inferiorly. The second, or descending, portion extends from the gastroduodenal artery and common bile duct to the ampulla of Vater. The third portion courses transversely and superiorly and extends from the ampulla to the superior mesenteric vessels. The final, or fourth, portion of the duodenum continues from the mesenteric vessels to the duodenojejunal flexure at the ligament of Treitz, located to the left of the second lumbar vertebra. Overall, the duodenum assumes a C shape and overlies the first three lumbar vertebrae (see Fig. 53–1). With the exception of the anterior half of the first portion, the duodenum is a retroperitoneal structure that lies in close proximity to numerous vital structures. In addition to the vertebral bodies, the posterior surface of the duodenum rests on the aorta, inferior vena cava, portal vein, right kidney, and psoas muscles. The common bile duct passes deep to the duodenum, between the first and second portions, and enters the posterior aspect of the pancreatic head in most patients. Anterior to the duodenum are the liver, gallbladder, hepatic flexure, transverse mesocolon, and stomach. The pancreas lies within the confines of the duodenal C loop. The mesenteric vessels protrude from the inferior aspect of the pancreas to lie atop the duodenum. Blood supply is shared between these two intimately associated organs. Arterial supply to the duodenum includes the gastroduodenal artery, superior and inferior pancreaticoduodenal arteries, supraduodenal artery, and retroduodenal artery. This close proximity to numerous organs and major vascular structures accounts for the high incidence of associated injuries, morbidity, and mortality common in patients with duodenal injuries.

Physiology

Each day, approximately 10 L of digestive fluids passes though the duodenum. It is here that the chyle, bile, and pancreatic secretions initially mix together. The duodenum is partially responsible for absorption of carbohydrates, protein, fats, water, ions, and vitamins. Although digestion of carbohydrates begins in the mouth, the majority of digestion occurs when chyle mixes with

pancreatic amylase in the duodenum. Further digestion by brush border enzymes in the small bowel takes place before carbohydrates are ultimately absorbed as monosaccharides. Protein digestion begins in the stomach through the enzymatic action of pepsin, but once again, the majority of digestion occurs in the upper portion of the small intestine. Once the duodenal brush border enzyme enterokinase comes in contact with chyle, trypsin is formed from inactive trypsinogen, and the remainder of pancreatic proteases (chymotrypsin, elastase, carboxypeptidase, etc.) are secreted into the duodenal lumen and activated. Most proteins are absorbed in the proximal part of the small bowel. Fats are emulsified through the action of bile salt– and lecithin-containing bile once excreted from the ampulla. Pancreatic lipase further digests triglycerides, which are ultimately absorbed in the proximal part of the small intestine. Whereas water is absorbed by simple diffusion, calcium and iron are absorbed by active processes in the duodenum. Importantly, this large volume of chyle and enzymatically active digestive secretions further contributes to the morbidity associated with failure of a duodenal repair—namely, a duodenal fistula.

Mechanisms

Deep in the retroperitoneum, the duodenum is protected from superficial injuries. Both blunt trauma and penetrating duodenal trauma are uncommon and account for just 3% to 5% of all abdominal injuries. Blunt injuries constitute roughly 22% of all duodenal injuries and are usually caused by motor vehicle collisions, assaults, or falls.[32] Motor vehicle collisions are responsible for 77% of blunt duodenal injuries, whereas assaults and falls each account for 10%.[32] The remaining 3% of blunt injuries are caused by various injury mechanisms. Overall, 78% of duodenal injuries are penetrating.[32] Of these penetrating injuries, 75% are inflicted by gunshots, 19% by stab wounds, and 6% by shotgun wounds.[32] Injuries may be further classified by anatomic location. Whereas penetrating injuries may be distributed more equally among the four duodenal segments, blunt mechanisms predominantly injure the second and third portions of the duodenum. When both blunt and penetrating mechanisms are considered, the second portion of the duodenum is the most commonly injured (33%), followed by third and fourth portions (19% each), first portion (15%), and multiple sites (14%).[32]

Penetrating mechanisms are responsible for the majority of duodenal injuries. Knife wounds are usually simple duodenal lacerations, but gunshot wounds are created by missiles that impart their kinetic energy on tissues and thereby create a pathway of tissue destruction. Associated injuries are commonplace. Asensio et al., in a review of 11 series, analyzed 1153 patients with duodenal injuries and found 86.9% to have associated injuries.[32] The liver was the most common organ to sustain associated injury, but injury to the pancreas, small bowel, major vascular structures, and colon was also common.

Blunt duodenal injuries are caused by a complex series of forces that may crush, burst, or shear the duodenum. Crush injuries are due to a blow to the anterior abdominal wall, which then crushes the duodenum against the underlying vertebral column. This injury pattern is commonly caused by a steering wheel in a head-on–type of collision. Simultaneous closure of the pylorus and contraction of the ligament of Treitz during a powerful blow to the abdomen can result in a bursting-type injury to the fluid- and air-filled duodenum. A shearing-type injury may also occur. Although the duodenum is anatomically fixed by the common bile duct and ligament of Treitz, the remainder of the duodenum remains highly mobile. Sudden changes in acceleration (e.g., falls) may shear the mobile segments of the duodenum from the fixed portions. Occasionally, these complex crushing or shearing forces rupture the small vessels within the submucosal layers and cause an intramural duodenal hematoma.

Diagnosis

The diagnosis of blunt duodenal injuries remains challenging. Information obtained from emergency medical service personnel present at the injury scene is essential to elucidate the injury mechanism and pattern of forces involved. Data should include the direction of collision, the use of restraints, airbag deployment, condition of the steering wheel, and whether extrication was necessary. However, less violent injury mechanisms such as falls and assaults may also injure the duodenum, but such injury is less often suspected. Given its retroperitoneal location, physical examination is often unimpressive despite frank duodenal perforation. The injured patient may have only vague or mild complaints. Peritonitis becomes evident later, only after retroperitoneal contents leak into the peritoneal cavity. Signs and symptoms of duodenal hematomas are even less convincing. Copious bilious vomiting may be observed in cases of nearly complete obstruction, but such symptoms are often late in onset. For these reasons, the diagnosis and treatment of blunt duodenal injuries are frequently delayed despite knowledgeable practitioners.

Laboratory data are of little diagnostic benefit. Although serum amylase is elevated in a majority of patients with pancreatic injuries, the level may be normal or only mildly elevated in those with duodenal injuries. Several reports have questioned the prognostic significance of a single serum amylase level, but work by Lucas and Ledgerwood found that serial amylase levels may improve the diagnostic yield.[33] Indeed, the presence of a normal amylase value does not preclude duodenal injury.

Plain films of the abdomen are equally unhelpful. Often described but present in less than a third of patients, evidence of duodenal injury on plain film includes air visualized around the right kidney, right psoas, or cecum; obliteration of the right psoas shadow; and scoliosis of the spine to the left. Free air is seen in less than 10% of patients with duodenal rupture.[33,34] An upper GI study with diatrizoate meglumine given either orally or via nasogastric tube improves the diagnostic yield. *A coiled spring* or *stacked coin* sign may indicate a duodenal intramural hematoma, whereas extraluminal

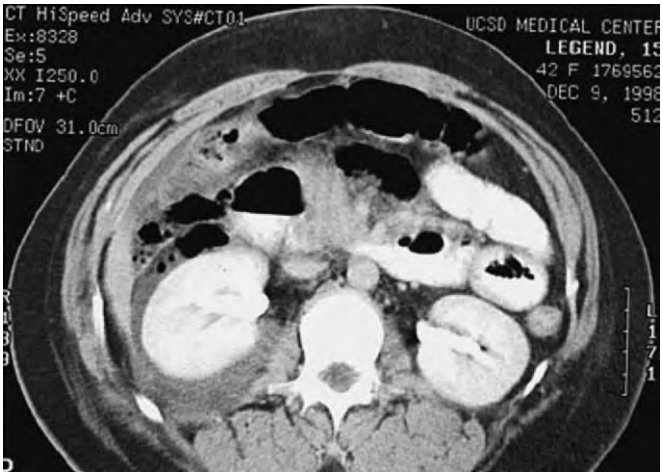

Figure 53–2. Computed tomography scan demonstrating retroperitoneal air and edema. (From Hoyt DB, Coimbra R, Potenza B: Management of acute trauma. In Townsend CM, Beauchamp RD, Evers BM, Mattox KL [eds]: Sabiston Textbook of Surgery, 17th ed. Philadelphia, WB Saunders, 2004, p 516.)

contrast or air indicates perforation. Both DPL and FAST are unreliable adjuncts for the diagnosis of duodenal injuries.

CT scanning with intravenous and intraluminal contrast is presently the diagnostic study of choice for hemodynamically stable patients with suspected retroperitoneal injury. CT has a unique ability to visualize the retroperitoneum, and findings consistent with blunt duodenal injury include bowel wall thickening or hematoma; extraluminal gas, fluid, or contrast medium; and retroperitoneal air or edema (Fig. 53–2). However, findings consistent with duodenal perforation (extravasation of contrast or the presence of retroperitoneal air) are infrequent, even in patients with documented full-thickness perforation. CT scans with subtle findings should be followed by an upper GI series. Patients with evidence of full-thickness duodenal perforations should undergo urgent operative exploration.

The diagnosis of penetrating duodenal injuries is usually made intraoperatively during laparotomy. All wound trajectories near the duodenum require full mobilization and visualization of the duodenum to ensure the absence of injury.

Management

Intramural hematomas are a rare subset of duodenal injuries with distinctly different management practices. Although operative intervention is the rule for most duodenal injuries, the majority of duodenal hematomas are managed nonoperatively. Hematomas generally resolve within a week with nasogastric decompression, bowel rest, and parenteral nutrition. Patients with prolonged complete obstruction or a deteriorating clinical condition may warrant laparotomy. A longitudinal seromuscular incision is made over the hematoma, and the contents are expressed. A careful search for occult perforations is then made, and complete hemostasis is achieved. The seromuscular wound is repaired with interrupted silk Lembert suture. However, most operations for duodenal injuries are performed to repair full-thickness perforations, not evacuate hematomas. Total exposure of the duodenum is essential before repair.

Exploratory laparotomy through a generous midline incision, from the xyphoid to the pubic symphysis, allows full inspection of the abdomen in cases of suspected duodenal injury. The abdomen is packed, and the zones of the retroperitoneum are quickly explored. Life-threatening hemorrhage and spillage of enteric contents are controlled. A methodical, organ-by-organ inspection then ensues. Evidence of paraduodenal injury such as hematoma, bilious staining, edema, or enteric contents mandates complete duodenal exposure. All duodenal hematomas must be thoroughly explored to exclude the possibility of an occult perforation.

Complete exposure of the duodenum is achieved with the aid of the Kocher and Cattell-Braasch maneuvers. The duodenum is kocherized by incising its lateral attachments while lifting the duodenum and pancreas medially until the superior mesenteric artery is approached. This procedure should completely expose the underside of the first, second, and third portions of the duodenum. The Cattell-Braasch maneuver consists of complete mobilization of the hepatic flexure, ascending colon, and small bowel from the right lower quadrant to the ligament of Treitz. With the bowel retracted cephalad, the entire third portion of the duodenum should now be visible (Fig. 53–3). Incision of the ligament of Treitz exposes the fourth portion of the duodenum (Fig. 53–4). All aspects of the duodenum must be fully inspected. Two options exist for patients with suspected injury but without evidence of obvious perforation. First, the abdomen may be filled with warm saline after a nasogastric tube is guided into the proximal part of the duodenum. Air is then instilled through the nasogastric tube as the surgeon watches for air bubbles arising from the duodenum. Methylene blue may also be instilled through the nasogastric tube after the duodenum is surrounded by clean lap sponges. Evidence of blue staining on the sponges indicates full-thickness perforation.

Before proceeding to duodenal repair, a careful assessment of the general condition of the patient should be made, with inspection for associated injuries to structures such as the pancreas, common bile duct, and ampulla. Diagnostic maneuvers such as cholangiography or pancreatography must be performed when a ductal injury is questioned. The presence of these high-grade injuries warrants more complex repairs and therefore may be more suitable for a subsequent operation in a hypothermic, coagulopathic, acidotic patient.

Still, the majority of duodenal wounds may be repaired by simple suture techniques.[32,35,36] Partial-thickness injuries may be either observed or buttressed with silk seromuscular Lembert sutures. Full-thickness wounds must be débrided back to healthy tissue. Adjacent wounds caused by a tangential trajectory are connected to create a single suture line. Wounds should be

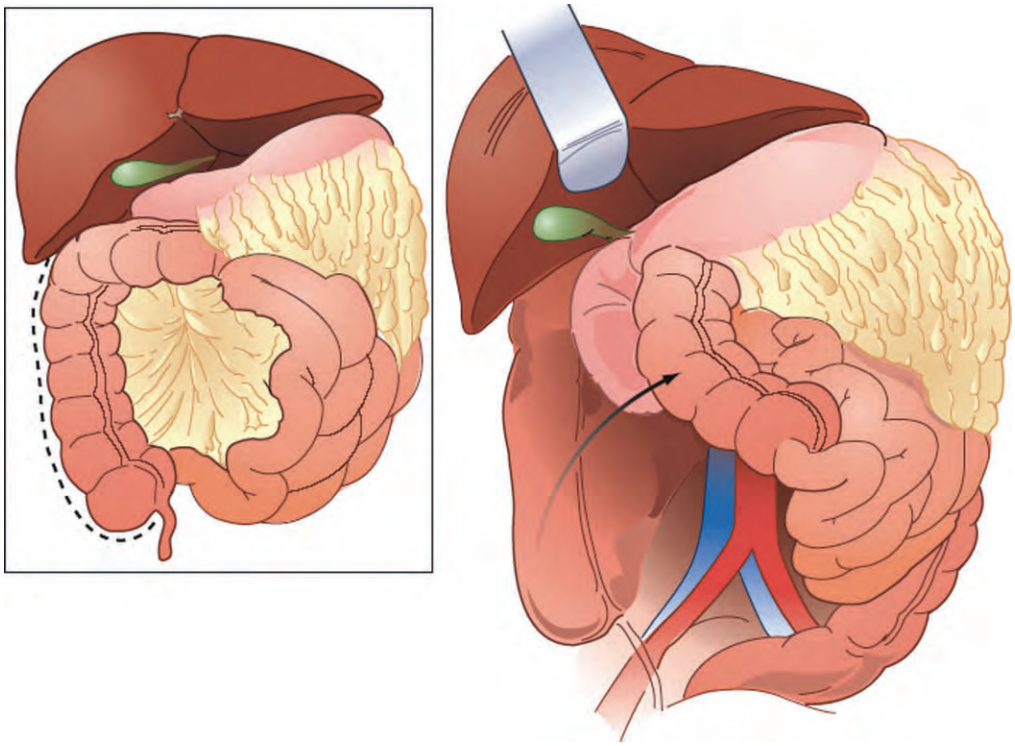

Figure 53–3. The Cattell-Braasch maneuver provides adequate exposure to the retroperitoneal structures. (From Hirshberg A, Mattox KL: Vascular trauma. In Townsend CM, Beauchamp RD, Evers BM, Mattox KL [eds]: Sabiston Textbook of Surgery, 17th ed. Philadelphia, WB Saunders, 2004, p 2041. Illustration by Jan Redden © Kenneth L. Mattox.)

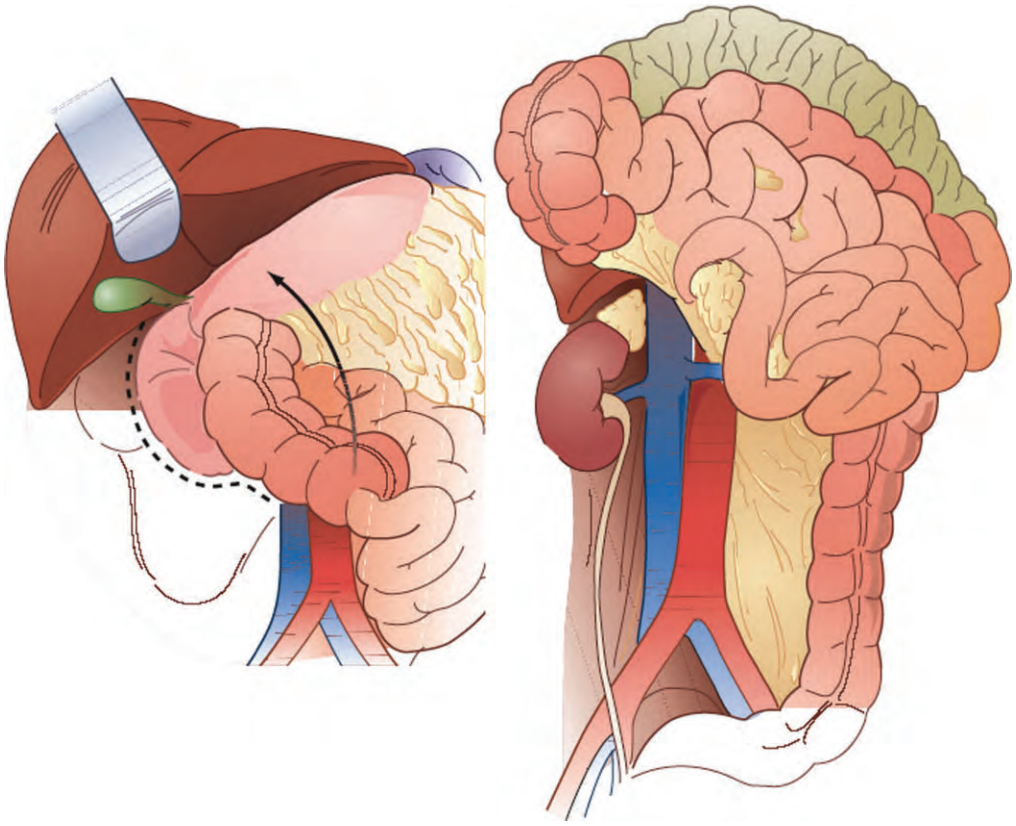

Figure 53–4. The Kocher maneuver provides adequate exposure and mobilization of the duodenum. (From Hirshberg A, Mattox KL: Vascular trauma. In Townsend CM, Beauchamp RD, Evers BM, Mattox KL [eds]: Sabiston Textbook of Surgery, 17th ed. Philadelphia, WB Saunders, 2004, p 2041. Illustration by Jan Redden © Kenneth L. Mattox.)

repaired transversely and may be one or two layered, interrupted or continuous, depending on surgeon preference. No study to date has conclusively shown the superiority of one technique over another.

Several repair options are available for larger wounds when simple repair may compromise the duodenal lumen. The first, third, and fourth portions of the duodenum are usually mobilized without difficulty. For destructive injuries to these portions, mobilization, resection, and primary end-to-end anastomosis may be performed. Because of tethering by the adjacent pancreas and several small vessels, mobilization of the second portion of the duodenum is more difficult, and as a result, resection with primary anastomosis is often impossible. In these cases, an end-to-side, Roux-en-Y duodenojejunostomy may be necessary. A jejunal Roux limb is brought up in retrocolic fashion if the patient's clinical condition permits, and a mucosa-to-mucosa anastomosis is performed. The duodenum requires only minimal mobilization, and the wound is repaired without tension. A serosal patch is another option for larger duodenal wounds. Originally described by Kobold and Thal, this method of repair involves overlaying the duodenal wound with a loop of jejunum.[37] The margins of the duodenal wound are sutured directly to the jejunal serosa to provide wound closure. All duodenal wound repairs should be externally drained. Closed-suction drains are placed adjacent to, but not touching repairs. In the unfortunate event of repair breakdown and duodenal fistula, adjacent closed-suction drains will better control the process and allow diagnostic imaging.

Duodenal fistulas are perhaps the most serious complication of duodenal injuries. Over the years, surgeons have developed several innovative procedures to prevent duodenal fistulas and convert them from a lateral to a more controllable end type of fistula. One adjunctive procedure to limit fistula formation is tube decompression. By preventing distention of the new repair, duodenostomy tubes may prevent fistula formation in severe injuries. Several methods of tube decompression have been described, the most simple of which is lateral tube duodenostomy. A small stab wound is made in the most dependent aspect of the third portion of the duodenum, through which a drainage catheter is placed. The catheter is then secured with a purse-string suture and brought out laterally along the retroperitoneum to exit the peritoneal cavity in the midaxillary line. This method, though efficient, unfortunately requires the addition of yet another wound to an already injured duodenum. Alternatively, a nasogastric tube may be fed under direct guidance to a postpyloric location, adjacent to the repair. Nasogastric tubes, however, are uncomfortable and are often removed by the patient before clinically indicated. Although tube decompression does not completely divert the digestive secretion stream, the suture line is protected and decompressed.

Perhaps the most protective form of tube decompression is the triple-tube ostomy described by Stone in 1966 and 1979.[34,34a] In their original work, the authors compared fistula rates in patients repaired without triple-tube drainage (44 patients) and those repaired with triple-tube drainage (237 patients). Eight duodenal fistulas were reported in the group repaired without triple-tube drainage, but only one duodenal fistula occurred in the tube decompression group. These encouraging results have never been duplicated, and reports since have been conflicting. Ivatury and Cogbill separately reported increases in both duodenal complications and mortality in patients treated by adjunctive triple-tube ostomy.[38,39]

The surgical technique of triple-tube drainage is straightforward. A standard gastrostomy tube is placed, after which two separate jejunal tubes are inserted. The proximal tube is threaded in retrograde fashion into the duodenum to decompress the suture line, whereas the distal tube is placed as for standard jejunal feeding access. This adjunctive procedure has several drawbacks. Three new perforations are required in the already injured GI tract. The decompressive tubes frequently do not drain as intended to protect the fresh duodenal repair. Finally, if the drainage tubes are inadvertently removed, the open perforation is a set up for a fistula—the very scenario that the surgeon had hoped to prevent. Although this method offers superior protection over single-tube decompression, procedures for complete diversion of the GI stream were soon developed.

Berne and Donovan first reported duodenal diverticulization in 1968.[40,41] As originally described, the procedure consists of vagotomy, antrectomy, oversewing of the duodenal stump, duodenostomy tube placement, T-tube biliary drainage, and gastrojejunostomy. Although the procedure completely diverts GI secretions away from the healing duodenal suture line, duodenal diverticulization is a fairly complex operation. In critically injured patients, this labor-intensive procedure is time-consuming. Diverticulization is seldom performed today and has largely been replaced by the pyloric exclusion technique. First described by Vaughan et al. in 1977, pyloric exclusion does not involve resection of normal, healthy tissue as is the case with duodenal diverticulization, but instead it consists of duodenal repair, oversewing the pylorus through a gastrotomy, and gastrojejunostomy.[42] The gastrotomy is made proximal to the pylorus, which is then grasped and closed with suture. Closure may be accomplished in a purse-string or running fashion, and use of a variety of suture materials has been described. The gastrotomy wound is then fashioned into a gastrojejunostomy (Fig. 53–5). Today, the pyloric exclusion technique is often performed by applying a noncutting stapler immediately distal to the pylorus. Stapled exclusion is quicker than the hand-sewn version and may be more permanent.

Despite its technical simplicity, pyloric exclusion with gastrojejunostomy permanently alters the GI tract in a predominantly young, healthy population. Although reports indicate that the pylorus reopens within 3 weeks in more than 90% of patients, pyloric exclusion remains an ulcerogenic operation.[42,43] Postoperative marginal ulceration rates range from 0% to 33%, with most studies indicating marginal ulcers in approximately 10% of patients who underwent surveillance.[43,44] Truncal vagotomy in addition to pyloric exclusion has been advocated by some but is not routinely performed in critically injured patients. With these problems in mind, several authors have attempted to define which

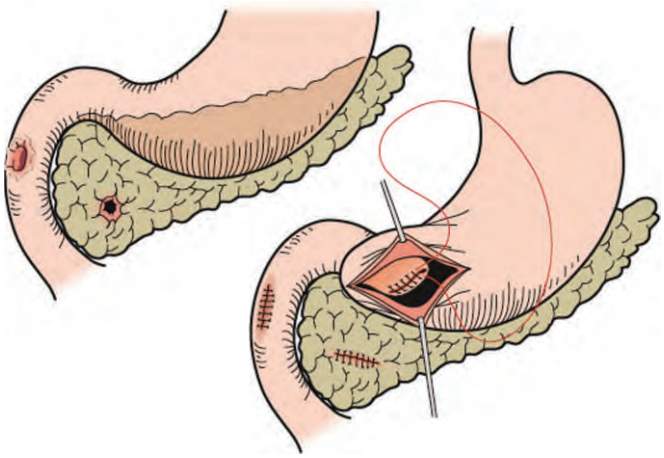

Figure 53–5. Pyloric exclusion. A gastrotomy is created and the pylorus is oversewn. The gastrotomy is then fashioned into a gastrojejunostomy. (From Steer ML: Exocrine pancreas. In Townsend CM, Beauchamp RD, Evers BM, Mattox KL [eds]: Sabiston Textbook of Surgery, 17th ed. Philadelphia, WB Saunders, 2004, p 1675.)

duodenal injuries may require these more sophisticated procedures.

Much time has been devoted to defining which duodenal injuries are in fact complex and which injuries may require the addition of these adjunctive procedures. Snyder and colleagues classified duodenal injuries as either mild or severe.[45] Severe injuries were characterized by one or more of the following criteria: missile injury, damage to greater than 75% of the duodenal wall circumference, involvement of the first or second portion of the duodenum, longer than 24 hours from injury to repair, and common bile duct injury. American Association for the Surgery of Trauma (AAST) grading may be used to classify duodenal injury severity, but it has not been a proven predictor of mortality.[46] Most authors consider grade III injuries (50% to 75% circumferential laceration) or greater to be severe, although there remains no clear consensus on the best operative treatment of these injuries. Timaran et al. showed that duodenal injury grade is not a risk factor predicting either duodenal fistula or mortality and that hypotension and shock are the most important predictors of outcome.[47] They concluded that even minor duodenal injuries compounded by hemorrhagic shock should be considered complex. Other authors consider a concomitant vascular or pancreatic injury an indication for a more sophisticated repair. Combined pancreaticoduodenal injuries deserve special mention.

Although injuries to the duodenum and body or tail of the pancreas may be managed separately, injuries to the duodenum and head of the pancreas require a unified approach. The first priority in these cases of combined pancreaticoduodenal injury is to fully examine the wound tract. Tracts in the vicinity of the common bile duct, main pancreatic duct, or ampulla are scrutinized and merit further diagnostic evaluation. Intraoperative cholangiography is required to completely examine the common bile duct. A cholangiocatheter is introduced into the cystic duct and contrast is injected. Dye is visualized throughout the common bile duct, into the main pancreatic duct, and into the duodenum. Cholecystectomy is then performed. Although the cholangiocatheter may be introduced into the common bile duct or gallbladder, these options are less appealing. Whereas complete visualization of the bile ducts is frequently achieved with cholangiography, the pancreatic duct is poorly visualized.

Several methods of pancreatography have been described, none of which are ideal. Thorough examination of the ampullary complex is imperative in all injuries involving the second portion of the duodenum. This inspection is accomplished through the duodenal wound. In patients with wound tracts adjacent to the ampulla, the ampulla should be thoroughly palpated and probed to ensure integrity of the structure. If the ampulla is visualized through the duodenal wound, a catheter may be introduced under direct vision for pancreatography. However, if the wound is not adjacent to the ampulla, a new duodenotomy may be created for placement of the catheter. Once again, this method involves further injury to an already wounded duodenum. Alternatively, the tail of the pancreas may be transected and pancreatography performed in retrograde fashion. This controversial maneuver has been widely criticized. After the healthy tissues in the pancreatic tail are transected, the duct is often exceedingly small and difficult to cannulate at this location. Perhaps the best option for complete visualization of the bile and pancreatic ducts is intraoperative endoscopic retrograde cholangiopancreatography (ERCP). At many centers, ERCP is either impractical or unavailable during afterhours. In the end, sound surgical judgment and wisdom are the tools that the surgeon often relies on to decide whether the main pancreatic duct is injured.

Unreconstructable ductal injury in the pancreatic head is one of the few possible indications for pancreaticoduodenectomy. Today, the trauma Whipple procedure is rarely performed. At our own institution, pancreaticoduodenectomy was performed for 1 of 54 duodenal injuries over the past 10 years.[48] Other institutions echo the same hesitation to perform this complex, time-consuming operation in critically ill patients—and with good reason. The value of pancreaticoduodenectomy for severe bleeding in the pancreatic head is questionable. The patient is probably better served by a so-called damage control laparotomy followed by a definitive procedure once the patient is warmed and resuscitated. Asensio et al. reviewed 52 series in the literature involving 172 patients who underwent pancreaticoduodenectomy and noted a 33% mortality rate.[32] Some small single series have revealed better mortality rates, but these same series used more liberal indications for pancreaticoduodenectomy, thus making interpretation difficult.

Currently, the trauma Whipple procedure is reserved for destructive, devascularizing, unreconstructable wounds

to the second portion of the duodenum and pancreatic head or for extensive injuries to the ampullary complex, distal common bile duct, and proximal main pancreatic duct that prevent reconstruction. As Walt once stated, "In the massively destructive lesions involving the pancreas, duodenum, and common bile duct, the decision to do a pancreaticoduodenectomy is unavoidable; and, in fact, much of the dissection may have been done by the wounding force" (p 641).[49]

Morbidity and Mortality

Complication rates remain significant for duodenal injuries despite improvements in perioperative care and operative technique. The morbidity and mortality related to duodenal injuries depend on the severity of injury, the presence of associated injuries, the general physiologic condition of the patient, the injury mechanism, and the elapsed interval between injury and repair. Several complications have been described, including duodenal fistula, abdominal abscess, pancreatitis, pancreatic fistula, duodenal or small bowel obstruction, and biliary fistula.

Perhaps the most serious and well described complication of duodenal repair is duodenal fistula. Asensio and colleagues reviewed 15 series involving 1408 patients and found an overall duodenal fistula rate of 6.6%.[32] The cornerstones of treatment of these fistulas remain drainage; nutritional support, ideally through a jejunostomy tube; skin protection; and antibiotics, if necessary. The somatostatin analogue octreotide may be used to decrease fistula output, but this agent has not yet been proved to promote spontaneous fistula closure. Unrelenting, high-output, lateral-type fistulas may require reoperation if spontaneous closure does not occur within a few weeks. At reoperation, the fistulous tract is resected, the duodenal repair is excluded from the GI stream, and feeding access is established. Nonoperative management of early postoperative duodenal and small bowel obstruction is the rule, but a gastrojejunostomy may be required for persistent duodenal obstruction.

In the extensive review by Asensio et al. involving 17 series in literature from 1968 to 1990, the overall mortality rate for duodenal injuries was 17%.[32] Roughly half of these deaths occurred early and were attributed to associated vascular injuries and exsanguination. When deaths caused by associated injuries are excluded, the mortality rate for duodenal injury remains an appreciable 6.5% to 12.5%.[32]

SMALL BOWEL INJURIES

History

Small bowel perforation from blunt abdominal trauma was first recognized by Aristotle.[50] Hippocrates was the first to report intestinal perforation from penetrating abdominal trauma. Before the late 19th century, the dismal results of surgical intervention for small bowel perforation led to the abandonment of laparotomy, even with obvious intestinal injury in war.[51] The routine use of exploratory laparotomy for suspected intestinal injury did not take place until late in World War I. Mortality rates associated with laparotomy for intestinal perforation dropped from 75% to 80% in World War I to 14% in World War II.[52] Further improvements in mortality occurred in the Korean and Vietnam wars.

Anatomy and Physiology

The small intestine includes the duodenum, jejunum, and ileum. This segment of the chapter focuses on the jejunum and ileum. The jejunum measures approximately 100 to 110 cm, whereas the ileum measures 150 to 160 cm. The major function of the small intestine is to serve as a surface for the absorption and digestion of proteins, carbohydrates, fat, water, and electrolytes. Proximal jejunal resections are better tolerated than distal ileal resections. A shorter length of small intestine is required for absorption if resection spares the ileocecal valve. Roughly 80 cm of small intestine is required to prevent short-bowel syndrome if the ileocecal valve is left in continuity. About 100 cm of small intestine is required to prevent short-bowel syndrome if the ileocecal valve has been resected.[53] The blood supply to the small intestine is the superior mesenteric artery and its branches. The superior mesenteric vein provides venous drainage into the portal system.

Mechanism

The small intestine is the most frequently injured organ after sustaining a penetrating injury. Stab wounds injure by direct contact, in contrast to gunshot wounds, which injure by both direct contact and transfer of energy from the bullet to the surrounding bowel.

After the spleen and liver, the small bowel is the third most common organ injured in blunt abdominal trauma. Approximately 5% to 20% of patients who require surgical exploration for blunt trauma have small bowel injuries.[54]

Blunt abdominal trauma can be due to motor vehicle crashes, falls, or assaults with blunt objects. Blunt injury to the small bowel can occur by one of three mechanisms. The small bowel can be crushed between the blunt object and the vertebral bodies. Sudden deceleration as a result of a fall from a height or a high-speed motor vehicle crash can lead to shearing of the small bowel at three fixed points: at the ligament of Treitz, at the ileocecal valve, and around the mesenteric artery. A bursting or blowout injury to the small bowel can occur secondary to an increase in intraluminal pressure in a functionally closed loop of bowel.

The presence of a seat belt sign on a patient who sustained a motor vehicle crash should lead the trauma surgeon to investigate for a Chance fracture of the lumbar vertebral body and subsequent small bowel injury.[55,56] In the EAST multi-institutional study, the seat belt sign was associated with a 4.7-fold increase in relative risk for small bowel perforation in patients after motor vehicle crashes.[57]

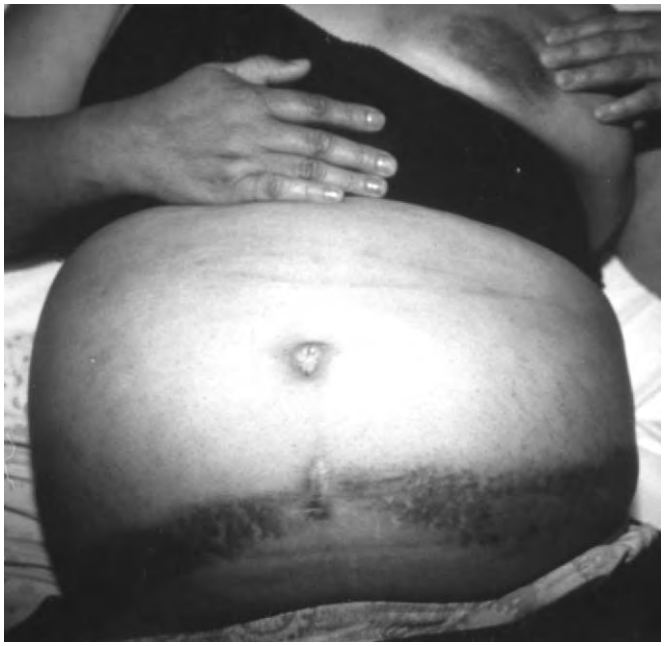

Figure 53–6. Abdominal wall ecchymoses secondary to seat belt deceleration.

Figure 53–7. Small bowel and mesenteric injury from seat belt trauma.

Iatrogenic perforation of the small bowel by cauterization or direct injury during laparoscopic procedures should be treated by immediate laparotomy and repair.

Diagnosis

The key to successful management of small bowel injuries is prompt recognition and treatment, which can be challenging with the increasing use of nonoperative management of blunt solid organ injuries. Delay in diagnosis of perforated small bowel injuries is associated with significantly increased mortality.[7,21]

The ability to arrive at a successful diagnosis of small bowel injury caused by either blunt or penetrating trauma begins with a thorough focused history. If the patient is evaluated after having sustained penetrating trauma, a description of the wounding instrument is obtained, as well as the handedness of the assailant. The time that the injury occurred is also critical. Rapid transit from the scene may lead to the patient arriving before peritoneal inflammation has time to develop. If the patient has sustained blunt trauma, a thorough description of the scene can be invaluable when provided by the emergency medical services staff.

A thorough physical examination should be performed. Examination begins with measurement of the vital signs: heart rate, blood pressure, and respiratory rate. Inspection for gunshot wounds and stab wounds is critical, and total exposure of the patient is required. Seat belt marks and abrasions are also noted on patients who have sustained blunt trauma. The presence of a seat belt sign should raise suspicion for enteric and mesenteric injuries (Fig. 53–6). In fact, in a published study by Velmahos et al., 23% of patients with a seat belt sign had intra-abdominal injuries.[58] Chandler et al. found that 21% of patients with abdominal seat belt signs had a small bowel perforation[59] (Fig. 53–7).

Loss of bowel sounds during auscultation could signify ileus secondary to injury to a hollow viscus. Tenderness to percussion and abdominal rigidity, guarding, and rebound suggest peritoneal irritation and warrant immediate exploration. Of special note, the abdominal examination may be compromised by alcohol or drug ingestion, as well as by head injury.

Radiographic work-up with an upright chest or abdominal radiograph may reveal free air; however, this sign can be rare.[60] Computed axial tomography (CAT) of the abdomen and pelvis with intravenous contrast only (oral contrast has recently been shown to offer no additional benefit, yet carries a risk for aspiration) can reveal findings suggestive of small bowel and mesenteric injury.[61,62] Such findings are free air, free fluid with no solid organ injury, small bowel wall thickening, mesenteric fat streaking, or mesenteric hematoma with extravasation of intravenous contrast.[63,64] (Fig. 53–8) Reports of the sensitivity and specificity of CAT scans in revealing small bowel injury have been quite varied. The experience of the Presley Regional Trauma Center with new-generation helical CAT scan evaluation for blunt bowel and mesenteric injuries indicates a sensitivity as high as 88.3%.[17] However, results from the EAST multi-institutional hollow viscus injury trial revealed that 13% of patients with a perforated small bowel found at the time of exploratory laparotomy had a normal preoperative abdominal CAT scan.[60]

The trauma surgeon must be cautious when the radiologist describes CAT scan findings in terms of general surgical diagnoses. The presence of mesenteric fat streaking and bowel wall thickening may be appropriate for a

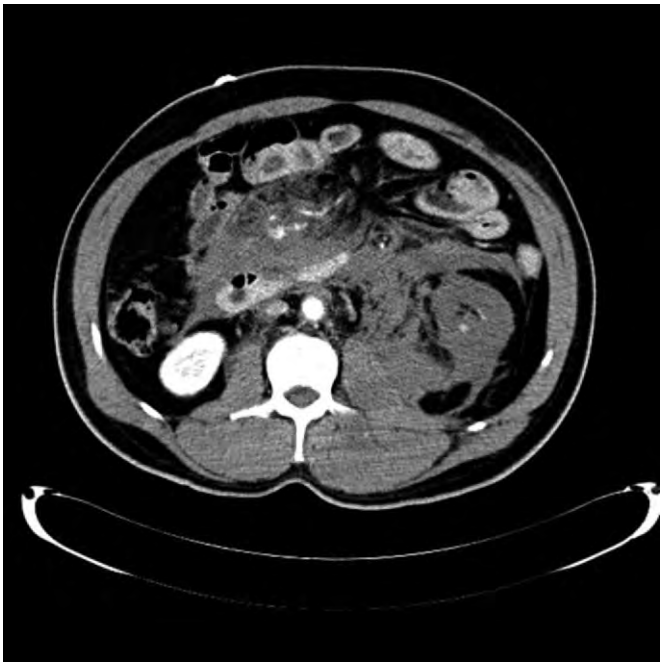

Figure 53–8. Computed axial tomographic scan of the abdomen and pelvis showing thickened loops of small bowel with extravasation of intravenous contrast into the mesentery.

patient with diverticulitis, but not for a patient who has sustained significant blunt abdominal trauma.

DPL has been replaced by FAST in the evaluation of unstable trauma patients. There is still a role for DPL in a blunt abdominal trauma patient who remains hypotensive after a repeat FAST examination fails to reveal free fluid. DPL would also be appropriate for a patient who sustains blunt abdominal trauma and is found to have free fluid on a CAT scan of the abdomen and pelvis with no solid organ injury. DPL revealing a WBC count of $500/mm^3$ or greater would mandate exploration to rule out small bowel injury. As an initial study, DPL may yield false-negative results when patients have been rapidly transported to the hospital and have had minimal time for leakage of enteric contents into the peritoneal cavity.

Diagnostic laparoscopy may be used as a diagnostic tool to determine peritoneal violation, as well as small bowel injury. However, the trauma surgeon must have the technical ability to evaluate the small bowel from the ligament of Treitz to the ileocecal valve. Once an injury is found, conversion to an open procedure would be recommended.

Operative Management

Exploration of the peritoneal cavity should be performed in a methodical, organized fashion. A midline incision is made, and all four quadrants of the peritoneal cavity should be packed. Control of hemorrhage is always the first priority. Once hemorrhage control is achieved, the next priority is to stop any ongoing enteric spillage.

The entire small bowel should be evaluated from the ligament of Treitz to the ileocecal valve. Attention should be particularly paid to both sides of the mesentery, as well as both sides of the bowel wall, mesenteric and antimesenteric. As injuries are discovered, control should be achieved with Babcock clamps. Hematomas of the bowel wall should be carefully unroofed and explored to assess for full-thickness injury. Hematomas of the mesentery should also be explored thoroughly as well. Any bleeding encountered should be controlled. Adequate evaluation of the small bowel to assess for viability should be performed, if necessary, with a Doppler probe. If there is any question about the viability of the small bowel, second-look laparotomy is always an option if the surgeon is not convinced of adequate blood supply or viability.

Grade I intramural hematomas may be repaired with inverted 3-0 silk seromuscular Lembert suture. Small wounds or wounds encompassing less than half the circumference of the small bowel can be managed by débridement if necessary and primary repair in two-layer fashion. Wounds involving more than half the circumference of the small bowel or multiple wounds of the small bowel should be managed by resection and primary anastomosis either in a two-layer hand-sewn manner or via stapled anastomosis.

In damage control situations, the bowel should be quickly repaired or resected. Definitive repair or primary anastomosis should not be performed until the patient returns to the operating room after all physiologic parameters have been corrected. Primary anastomosis can then be undertaken safely.

Adjacent through-and-through gunshot wounds or stab wounds to the small bowel may be joined, débrided, and closed primarily in the transverse direction. Use of the standard principles of a tension-free anastomosis with adequate blood supply will ensure proper healing.

Postoperative Management and Complications

The patient should receive 24 hours of antibiotics effective against gram-negative and anaerobic organisms. The first dose of antibiotics should be given as close to the time of injury as possible.

More commonly, complications are related to associated injuries and to delay in diagnosis and subsequent operative intervention of the small bowel injury. Postoperative complications can consist of wound infection, anastomotic leakage, intra-abdominal abscess formation, enteric fistula formation, and bowel obstruction. Anastomotic leakage requires return to the operating room if fever, tachycardia, an elevated WBC count, or peritonitis is found on physical examination. An intra-abdominal abscess can be treated by percutaneous drainage under CAT scan guidance.

If significant amounts of ileum have been resected, vitamin B_{12} deficiency may develop, as well as disruption of the enterohepatic recirculation of bile salts and subsequent fat malabsorption and hence fat-soluble vitamin deficiencies.

Short-bowel syndrome is usually seen after significant resections of the small bowel. Jejunal resections are better tolerated than ileal resections.

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Chapter

54

Small Intestinal Diverticula

Michael C. Stoner · Joanna C. Arcuni · John M. Kellum

Small intestinal diverticula are protrusions of various layers of the intestinal wall through the serosa and onto the mesenteric or peritoneal aspects of the bowel. In contrast to congenital diverticula, such as Meckel's diverticulum, which include all layers of the normal intestinal wall, the more common acquired diverticula, the pseudodiverticula, lack the muscularis propria. Although small intestinal diverticula are frequently asymptomatic, they can cause life-threatening complications. This chapter includes a discussion of duodenal, jejunoileal, and Meckel's diverticula.

In order of frequency, diverticula of the gastrointestinal tract occur in the colon, ileum (Meckel's diverticulum), duodenum, pharynx and esophagus, stomach, jejunum, appendix, and ileum (other than Meckel's).[1] Thus, for pseudodiverticula, the duodenum, after the colon, is the most common site, whereas the jejunum and ileum, excluding Meckel's diverticulum, are rarely the location of small intestinal diverticula.

DUODENAL DIVERTICULA

Small intestinal diverticula are difficult to demonstrate either radiographically or anatomically because of their frequent location in the mesentery. Consequently, their incidence is underestimated. The reported incidence of duodenal diverticula ranges from 0.2% to 7.1% based on radiologic contrast studies,[2,3] 9% to 20% by upper gastrointestinal endoscopy,[2] and 3% to 22% according to autopsies.[2] The lesion is most common in the fifth decade of life, with a 2:1 female preponderance.[3-5] Extraluminal duodenal diverticula are much more common than the intraluminal type. Most of the former are pseudodiverticula located on the pancreatic aspect (Fig. 54–1). Four percent to 12% of diverticula occur in the first portion of the duodenum, 56% to 80% in the second portion, and 4% to 36% in the third and fourth portions[4,6-9] (Fig. 54–2). Two thirds to three fourths of duodenal diverticula occur within 2 cm of the ampulla of Vater. Most patients with immediately juxtavaterian diverticula have ampullae entering the duodenum at the superior margin rather than through the diverticulum itself[3] (Fig. 54–3).

Although most duodenal diverticula occur on the medial aspect, 4% to 16% are on the lateral or anterior wall. Most of these latter lesions are true diverticula. Diverticula on the medial aspect of the duodenum may be embedded within the substance of the pancreas.[10] An autopsy study by Suda and colleagues[11] demonstrated that 18 of 27 diverticula in the second portion of the duodenum penetrated the pancreas.

Intraluminal diverticula are congenital webs that arise near the ampulla of Vater. They are caused by incomplete recanalization of the duodenum. As a result of stretching and peristalsis, they are transformed into diverticula. On contrast radiography, they give a typical *windsock* effect (Fig. 54–4). Only slightly more than 100 have been described in the world literature. Most attach to less than half the circumference of the duodenal lumen, but a few attach to the entire circumference. They all have an opening, usually located near the apex. Without an opening, they are manifested in neonatal life as duodenal obstruction.[12]

Pathogenesis

Because duodenal diverticula are often associated with colonic and jejunal diverticula, it is postulated that pulsion forces lead to herniation of mucosal or submucosal outpouchings through the muscularis of a weakened intestinal wall. Because most of these pseudodiverticula form on the concave (pancreatic) side of the duodenum, the pulsion theory postulates that diverticula occur at points of penetration of the duodenal wall by blood vessels or by the ampulla of Vater. As Roses and associates[13] noted, the pulsion theory is supported by the increasing incidence of diverticula with age and by the usual absence of muscularis in the wall of the diverticulum.

Horton and Mueller[1] noted that the pancreas often penetrates the longitudinal wall of the concave aspect of the duodenum, with only the circular muscle separating

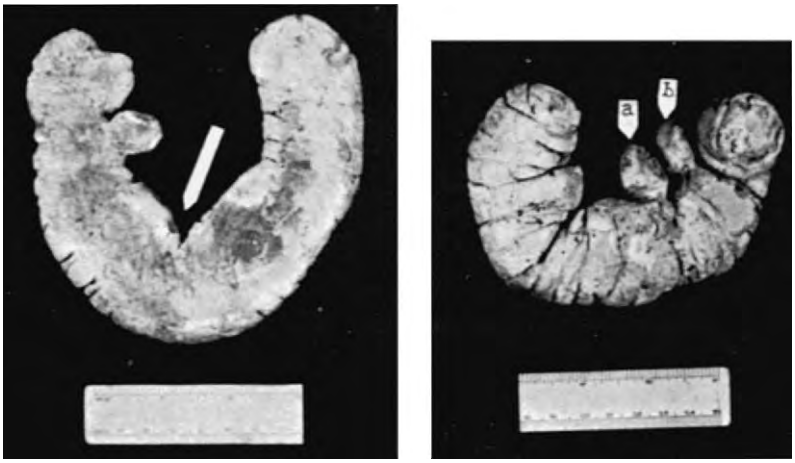


Figure 54–1. Plaster casts of diverticula in the second, third, and fourth portions of the duodenum. The *arrow* in the figure on the *left* marks the papilla of Vater. (From Ackerman W: Diverticula and variations of the duodenum. Ann Surg 117:403, 1943.)

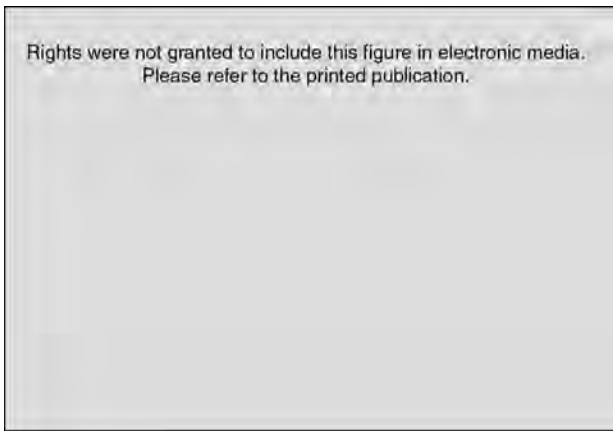


Figure 54–2. Distribution of duodenal diverticula within the four portions of the duodenum. (The *circled numbers* indicate how many cases were seen.) (From Townsend CM, Thompson JCT: Small intestine. In Schwartz SI [ed]: Principles of Surgery, vol 2, 6th ed. New York, McGraw-Hill, 1993, p 1178.)

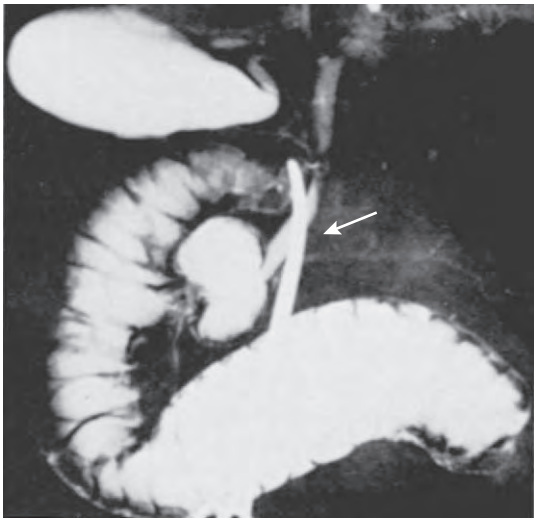


Figure 54–3. Air-contrast study of the small intestine demonstrating a diverticulum of the second part of the duodenum with the pancreatic duct and common bile duct entering directly into the diverticulum *(arrow).* (From Wolfson NS, Miller FB: Anatomic relationship of insertion of the common bile duct into primary duodenal diverticula. Surg Gynecol Obstet [now J Am Coll Surg] 146:628, 1978. By permission of *Surgery, Gynecology and Obstetrics.*)

it from the mucosa. Less commonly, pancreatic tissue penetrates both muscular layers and produces an intrinsically weak segment of duodenal wall. They postulated that either situation favored the development of diverticula.

An increased incidence of duodenal and jejunoileal diverticula has been reported in diseases associated with disorders of smooth muscle or the myenteric plexus and in systemic immunologic diseases. They have been reported as having a higher incidence in scleroderma, rheumatoid arthritis, ulcerative colitis, and myxedema after thyroiditis.[14,15]

Associated Disease

Duodenal diverticula have been associated with colonic diverticulosis (26% to 30%), gallbladder disease (18% to 22%), hiatal hernia (16% to 18%), and pancreatic disease (3%). Furthermore, duodenal diverticula frequently coexist with diverticula of the jejunum or ileum. It has been reported that jejunal and ileal diverticula are present in 6% to 13% of patients with duodenal diverticula whereas duodenal diverticula are noted in 22% to 44% of patients with jejunal diverticula.[16,17]

Uomo and colleagues[18] investigated the relationship of periampullary extraluminal duodenal diverticula and acute pancreatitis. They retrospectively reviewed 439 patients (58 with periampullary diverticula) who underwent successful endoscopic retrograde cholangiopancreatography (ERCP) over a 3-year period. When compared with the 375 control subjects (i.e., those without diverticula), the patients with periampullary diverticula were

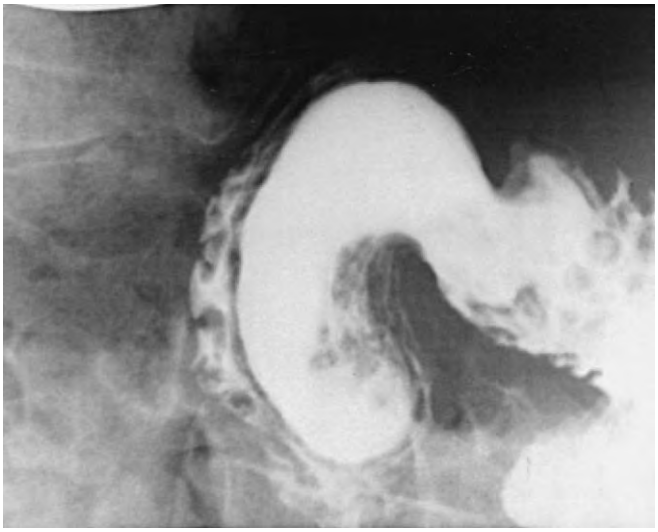


Figure 54–4. Demonstration of the windsock effect caused by an intraluminal duodenal diverticulum. (Courtesy of M. A. Turner, Medical College of Virginia.)

significantly older ($P < .0001$), had a significantly higher incidence of biliary lithiasis (65.5% versus 40.8%; $P < .0001$), and more frequently had a recent attack of acute pancreatitis as the indication for ERCP (62% versus 24.8%; $P < .0001$). On the other hand, they found that the prevalence of gallstone pancreatitis was not significantly different between the two groups. Noting a significantly ($P < .04$) higher incidence of idiopathic acute pancreatitis in the 58 patients, they postulated an autonomous etiologic role for periampullary duodenal diverticula in acute pancreatitis (see Fig. 54–3). We think it more likely that the periampullary diverticula, by disrupting the normal physiologic ampullary emptying mechanisms, contributed to both a higher incidence of biliary stasis and microlithiasis and, secondarily, a higher incidence of acute pancreatitis.

Another study in patients who had undergone cholecystectomy more than 2 years earlier noted a significantly increased incidence of recurrent biliary calculi in those with perivaterian diverticula as compared with those without. In our opinion, however, a causal relationship of duodenal diverticula to biliary tract stones has not been demonstrated.[3]

Miyazawa and associates[19] studied 115 patients with common duct stones. Most underwent simple choledochotomy with stone extraction and T-tube drainage. The 85 patients who still had their gallbladders also underwent cholecystectomy. Of the five in whom recurrent common duct stones developed, all had pigment stones and coexisting periampullary duodenal diverticula. We propose that end-to-side Roux-en-Y choledochojejunostomy be considered in patients with these two factors.

Symptoms

Neill and Thompson[20] reported that only 10% of people with small bowel diverticula have symptoms attributable to them. When symptoms do occur, they are usually secondary to obstruction of the diverticulum with subsequent stasis, bacterial overgrowth, pouch distention, and inflammation, or they result from compression of adjacent structures, such as the intestinal lumen or the pancreatic or bile duct. Jones and Merendino[17] and Chitambar[4] examined the frequency of symptoms in patients known to have duodenal diverticula. According to these authors, postprandial pain, usually epigastric or right upper quadrant in location, with radiation to the subscapular or costovertebral locations, occurred in half the patients referred to them. It will be obvious to the reader that these patients referred to clinicians were selected as having symptoms in the first place. The pain varied from mild abdominal distress to gnawing, crampy, sharp pain and generally occurred 2 to 4 hours after meals. In some cases, the pain was relieved by changing position and presumably draining the diverticulum. In addition, vague abdominal complaints such as bloating, belching, and flatulence have commonly been reported in this patient population. Nausea and vomiting, sometimes associated with weight loss, have been reported in 17% to 34% of patients. Christiansen and Thommesen[7] found a high incidence of gastroesophageal reflux and biliary calculi and recommended an evaluation for reflux and biliary disease in patients known to have duodenal diverticula with upper abdominal symptoms. Both diarrhea and constipation have been reported in these patients.

Duodenal diverticula can cause serious problems when complications such as ulceration with hemorrhage, obstruction of the neck, perforation into adjacent structures or the peritoneal cavity, or compression of adjacent structures occur. In these cases, the condition may mimic a perforated or bleeding duodenal ulcer or acute pancreatitis. Handelsman and co-workers[16] noted hematemesis, melena, or both in 32% of patients undergoing laparotomy for duodenal diverticula. Duodenocolic fistula secondary to rupture of a diverticulum into the transverse colon may cause malabsorption and diarrhea.[21,22]

Intraluminal, or congenital, duodenal diverticula are most often detected between the ages of 20 and 40 years. Twenty percent of these patients have had some upper abdominal discomfort since childhood. Two thirds have symptoms of duodenal obstruction, including postprandial epigastric or periumbilical crampy pain with or without bilious vomiting. Other manifestations include hemorrhage and pancreatitis. The latter, which is the initial symptom in as many as 20% of patients, is thought to arise from obstruction of the ampulla by the diverticulum. Many are discovered when the opening in the diverticulum is obstructed by food, gallstones, clots, ingested medications, or foreign bodies.[12,23-25]

Diagnosis

Duodenal diverticula are usually diagnosed by contrast-enhanced upper gastrointestinal radiographs or at laparotomy. They are occasionally difficult to demonstrate radiographically. Case[26] emphasized the importance

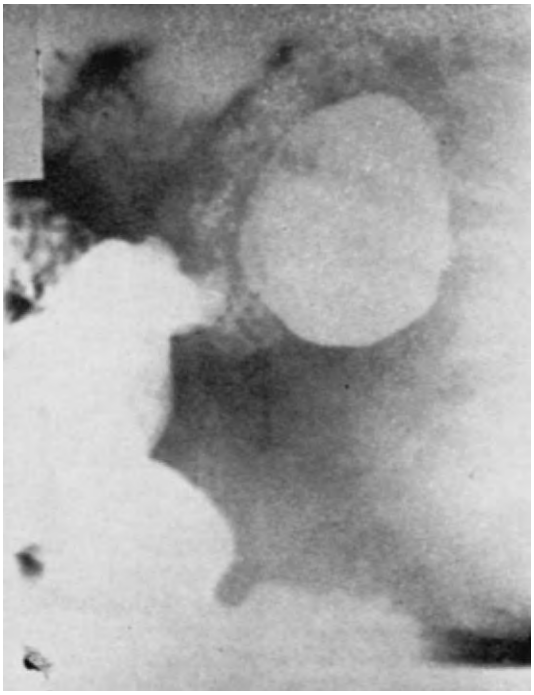


Figure 54–5. Large diverticulum arising from the second portion of the duodenum. (From Chitambar IA: Duodenal diverticula. Surgery 33:768, 1954.)

of manual palpation of the abdomen with pressure exerted over the pylorus and duodenojejunal junction to facilitate filling of the diverticula under fluoroscopy. Fluoroscopy is important because when the ostium is relatively large, duodenal diverticula often empty rapidly. When the ostium is narrow, the diverticulum fills poorly and can be missed as a result of rapid transit through the duodenal lumen. Hypotonic duodenography with the use of drugs that retard duodenal motility has also been advocated for the demonstration of diverticula not amenable to conventional techniques.[27]

During upper gastrointestinal contrast radiologic examination, duodenal diverticula appear as one or more collections of barium continuous with the duodenal lumen (Figs. 54–5 and 54–6). Residual barium after emptying may outline round, oval, or multiloculated radiolucencies corresponding to diverticula. Because emptying is often slow, delayed films are frequently recommended after 24 hours. Case[26] noted that retention extended 48 hours with some periampullary diverticula. Radiologic findings in patients with intraluminal duodenal diverticula include a collection of barium within the duodenal lumen surrounded by a narrow band of barium with a thin rim of radiolucency in between, the so-called windsock appearance[28] (see Fig. 53–4).

Stone and associates[29] examined computed tomography (CT) of the abdomen for evaluation of small intestinal diverticula. They noted that the presence of air with or without contrast was the most consistent finding. In cases of duodenal diverticula, the air-, contrast-, or fluid-filled mass was often in the region of the pancreas, mimicking a pseudocyst or abscess (Fig. 54–7).

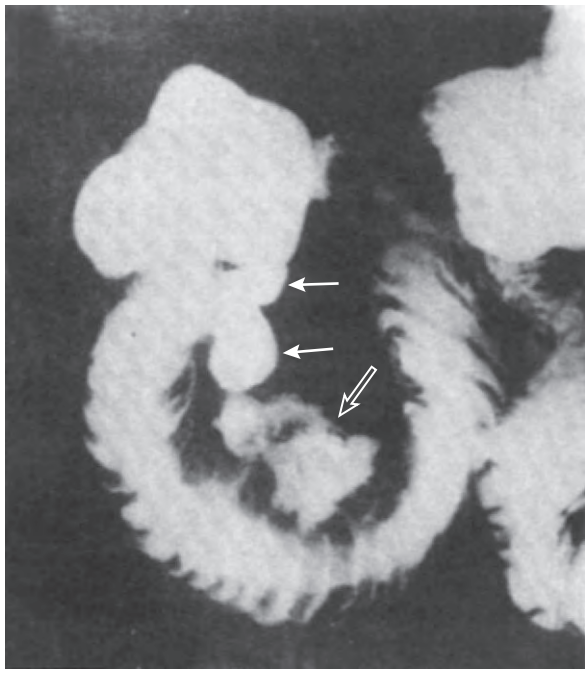


Figure 54–6. Upper gastrointestinal examination showing a lobulated periampullary diverticulum *(arrows)* and a large irregular collection of contrast material within an inflamed diverticulum *(open arrow).* It has a deformed lumen with ulcerated mucosa, and the adjacent duodenal folds are thickened because of peridiverticular inflammation. (From Gore RM, Ghahremani GG, Kirsch MD: Diverticulitis of the duodenum: Clinical and radiological manifestations of seven cases. Am J Gastroenterol 86:982, 1991.)

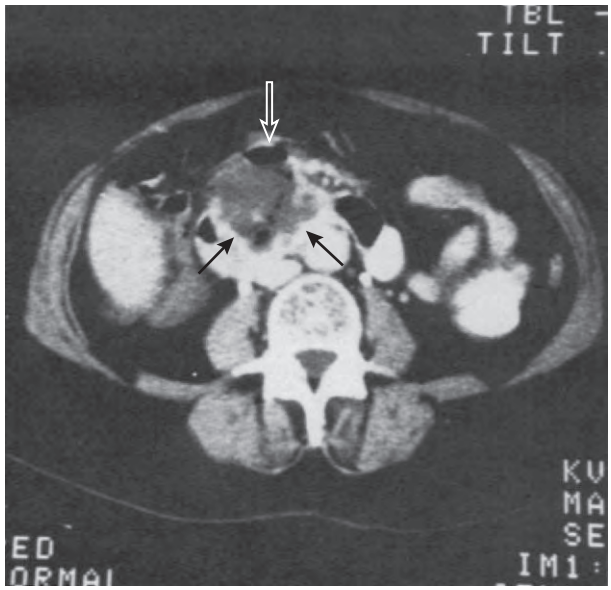


Figure 54–7. Computed tomography scan through the center of duodenal diverticulitis showing its markedly distorted margins *(arrows)* and a mixture of secretions, debris, and gas within its lumen *(open arrow).* (From Gore RM, Ghahremani GG, Kirsch MD: Diverticulitis of the duodenum: Clinical and radiological manifestations of seven cases. Am J Gastroenterol 86:982, 1991.)

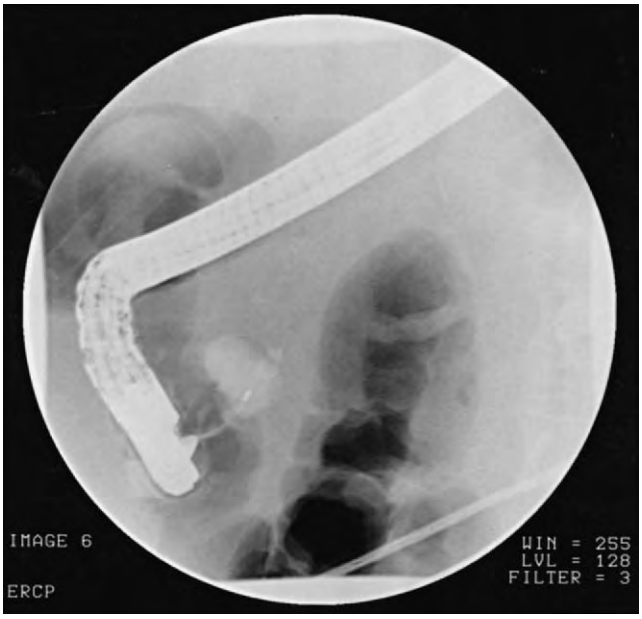


Figure 54–8. Endoscopic retrograde cholangiopancreatography demonstrating filling of a periampullary diverticulum with contrast. (Courtesy of M. A. Turner, Medical College of Virginia.)

Upper gastrointestinal endoscopy has become popular as a means of diagnosing and classifying duodenal diverticula. In many instances, intraluminal diverticula can be treated endoscopically by excision or by incision and widening of the ostium.[28] Endoscopy can also differentiate duodenal abnormalities noted on contrast radiography. After the diagnosis of a periampullary duodenal diverticulum, ERCP can be performed to delineate the relationship of the diverticulum to the pancreatic and common bile ducts in cases of pancreatitis or biliary sepsis[28,30] (Fig. 54–8).

Angiography may be indicated in cases of hemorrhage associated with diverticula. Tisnado and colleagues[31] reported the first angiographic demonstration of a bleeding jejunal diverticulum (Fig. 54–9). The same principles apply to duodenal diverticula, although they bleed less frequently than jejunal or ileal diverticula do. The characteristic feature is pooling of the material in a smooth-walled collection during the arterial and capillary phases, followed by spread of the contrast material into the lumen during the venous phase.

Complications

Serious complications occur in about 5% to 10% of patients with duodenal diverticula. Bleeding, perforation, and diverticulitis are all rare, but the morbidity and mortality are high because of delay in diagnosis as a result of lack of suspicion of the underlying condition. The diagnosis is seldom made preoperatively.[3]

A progressive inflammatory reaction within duodenal diverticula may lead to ulceration with associated duodenitis and pancreatitis. Perforation of an inflamed diverticulum may result in peritonitis, retroperitoneal abscess, or fistulization into the colon, adjacent segment of duodenum, or even the aorta. Stasis within a diverticulum may predispose to enterolith formation with subsequent obstruction of the diverticular neck and inflammation; stasis may also result in a blind-loop syndrome with resultant malabsorption. In addition, stasis can cause passive distention of diverticula with resultant obstruction of the intestinal lumen, common bile duct, or pancreatic duct.

Perforation

Perforation of duodenal diverticula is rare, with only slightly more than 100 cases reported in the world literature.[21] Perforation of a duodenal diverticulum is suggested when the surgeon observes retroperitoneal edema lateral to the duodenum, bile-stained phlegmon in the paraduodenal area, retroperitoneal crepitus or pus, or a right subhepatic abscess with no obvious primary source of infection. Only 13 of 101 cases of perforated duodenal diverticula were correctly diagnosed preoperatively.[21] The differential diagnosis includes perforated peptic ulcer, cholecystitis, pancreatitis, appendicitis, intestinal obstruction, and myocardial infarction. CT scanning has led to an increased frequency of correct preoperative diagnosis.[32]

Gross peritonitis is not characteristic of perforated duodenal diverticula. Because duodenal diverticula emanating from the concave aspect of the duodenum are partially supported by the pancreas, those arising from the lateral (convex) aspect are more likely to perforate, most commonly into the retroperitoneal space. Zeifer and Goersch[33] reported 23 cases of perforated duodenal diverticula. The mean patient age was 61 years, and men were affected twice as often as women. The second portion of the duodenum was the site of perforation in 19 of the patients. In 6 of the patients, the diagnosis was not made at surgery. The overall mortality rate was 48%. In a review of the world literature, Duarte and colleagues[21] defined the most common causes of duodenal diverticular perforation as being diverticulitis (57%), enterolithiasis (12%), ulceration (9%), and other rarer causes, including foreign bodies and trauma. Five cases of duodenocolic fistula have been reported as complications of perforated duodenal diverticula.[21,22]

Obstruction

Duodenal obstruction occurs primarily as a result of intraluminal duodenal diverticula, when the ostium of the diverticulum becomes obstructed by substances such as food and medication. The clinical picture is that of a high small intestinal obstruction with bilious vomiting; plain abdominal radiographs demonstrate dilation of the stomach and proximal duodenum but not the remaining small intestine. Upper endoscopy can usually confirm the diagnosis in such cases.

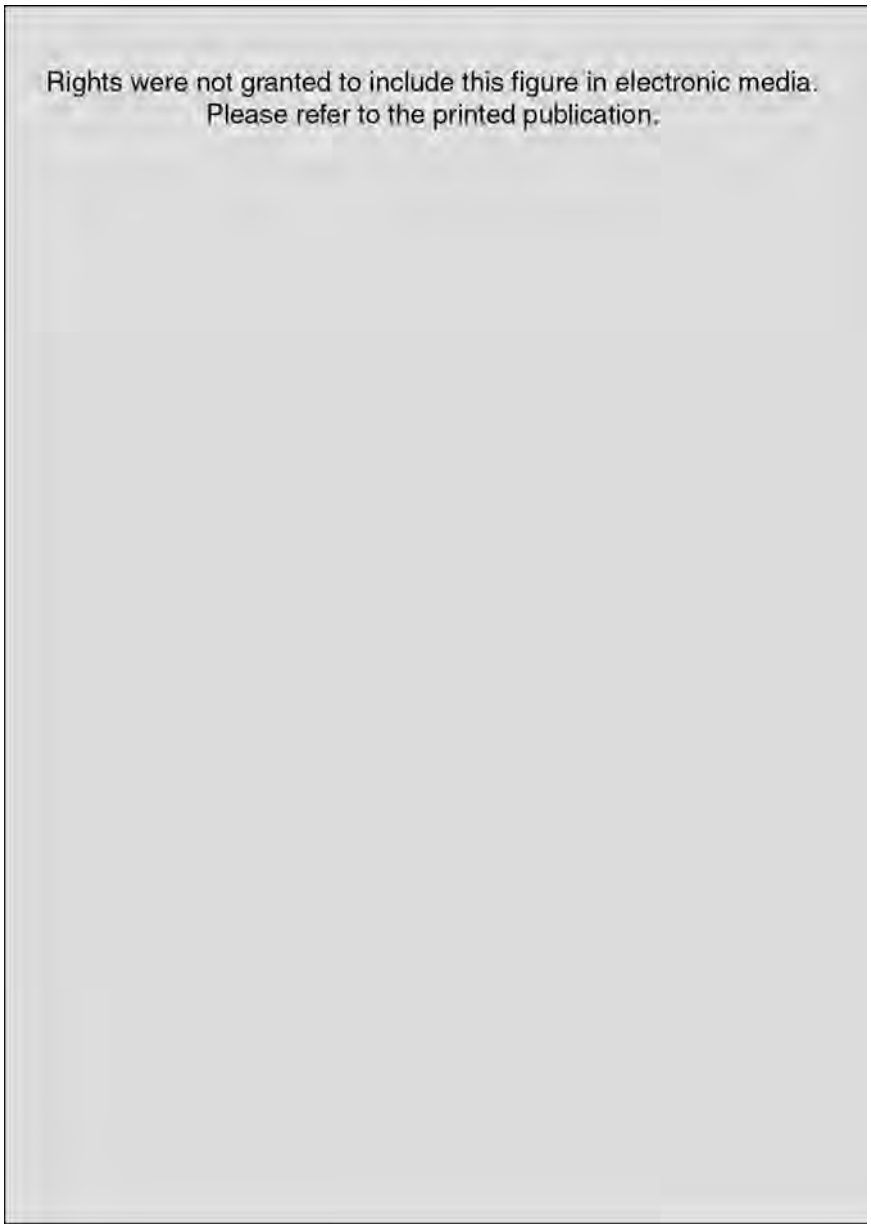


Figure 54–9. Angiographic study demonstrating a bleeding jejunal diverticulum. **A,** Arterial injection phase (2 seconds). **B,** Capillary phase showing a distinct smooth-walled lake of extravasation. **C,** Contrast medium filling the diverticulum and spreading into the lumen of the intestine *(arrow).* (From Tisnado J, Konerding KF, Beachley MC, et al: Angiographic diagnosis of a bleeding jejunal diverticulum. Gastrointest Radiol 4:291, 1979.)

Hemorrhage

When hemorrhage is a complication of duodenal diverticula, it may be manifested as hematemesis, melena, or both. Preoperative diagnosis can be made by upper endoscopy or arteriography (see Fig. 54–9). Bleeding has been described with ulceration,[34] cavernous hemangioma,[35] or angiodysplasia[36] within the diverticulum.

Biliary-Pancreatic Complications

Periampullary diverticula have been implicated in the pathogenesis of calculus formation and obstructive biliary tract disease. Stasis and inflammation within these periampullary diverticula may cause edema of the papilla of Vater and consequent insufficiency of the sphincter of Oddi with reflux of duodenal contents and bacterial colonization. Using endoscopic pull-through techniques with biliary manometry, Lotveit and co-workers[30] and Kubota and associates[37] showed that patients with juxtapapillary diverticula have dysfunction and insufficiency of the choledochal sphincter. Periampullary duodenal diverticula filled with debris and stones have been associated with biliary pancreatitis and obstructive jaundice.[38]

The incidence of biliary disease varies between 13% and 22% in patients with duodenal diverticula,[4,16,17,39] but it may rise as high as 50% if only juxtavaterian diverticula are considered.[5,40] These diverticula are over twice as likely to be associated with gallstones as diverticula more distal in the duodenum.[39] Furthermore, lending credence to the bacterial overgrowth theory, patients with juxtapapillary diverticula are more likely to have pigment stones, whereas those without diverticula are more apt to have cholesterol gallstones.[19,41] Recurrent stone disease or postcholecystectomy syndrome is more likely to develop after cholecystectomy. In addition, Lotveit and

co-workers[5,30] found diverticula in 17 of 75 patients with acute pancreatitis as compared with an incidence of 4.2% in a comparable control group.

Management

Nonoperative Treatment

Several approaches have been used for the nonoperative management of symptomatic duodenal diverticula. Cattell and Mudge[6] suggested that patients with presumed symptomatic duodenal diverticula be treated with trials of antacids, antispasmodics, a low-fat diet, and barbiturates. According to these authors, such a trial should last as long as 1 year. Most authors agree that medical treatment should be reserved for patients without complications of diverticula and those in whom other causes of the symptoms have been excluded by a thorough diagnostic evaluation.

Several nonsurgical approaches have been advocated for periampullary diverticula causing symptoms of biliary obstruction. Willcox and Costopoulous[42] reported on three patients treated endoscopically with common duct dilators. Urakami and colleagues[43] treated common duct stones associated with periampullary diverticula in 33 patients by endoscopic papillotomy. Endoscopic visualization and control of bleeding from duodenal diverticula have also been described.[44]

Operative Therapy

It is widely agreed that surgical treatment is indicated only for patients with serious complications of duodenal diverticula. These diverticula are difficult to treat surgically because of their frequent intimate association with the bile and pancreatic ducts. The mortality rate associated with surgical resection of uncomplicated diverticula has been reported to be 8% to 10%.[6,9,16] On the other hand, symptomatic improvement after surgical therapy has been disappointing, with 47% of the patients in Cattell and Mudge's series[6] having either fair or poor results.

Many intraluminal duodenal diverticula can be treated endoscopically by incision, excision, or dilation of the aperture. When ERCP cannot clearly delineate the biliary and pancreatic ducts, however, open duodenotomy with surgical excision remains the gold standard and offers better protection against ductal injury or iatrogenic pancreatitis.[45]

In cases of bleeding, duodenotomy with inversion and mucosal excision has been successful, but Slater reported a 28% mortality rate from this complication.[46] Excision is best reserved for patients in whom the diverticulum arises from the lateral aspect of the duodenum and the margins of the neck are clearly delineated. *In cases in which the diverticulum arises in the periampullary region, it is imperative that the ductal structures be protected whether excision or oversewing of a bleeding site is being performed.* In many cases, transduodenal sphincteroplasty should be performed, with fine suturing of the duodenal mucosa to the bile duct mucosa accomplished under direct vision (Figs. 54–10 and 54–11). The authors advocate a

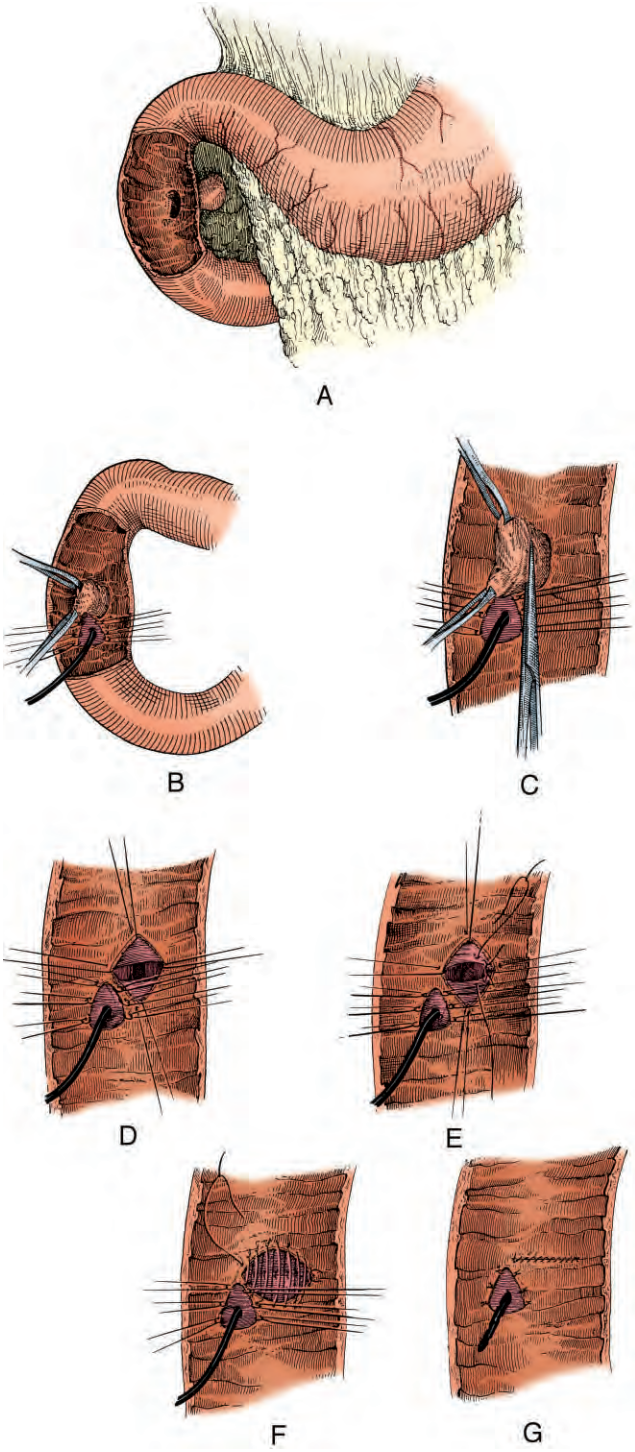


Figure 54–10. Technique for excising juxta-ampullary duodenal diverticula. **A,** Identification of a diverticulum through a duodenotomy. **B,** Eversion of the fundus of a diverticulum with Babcock forceps. **C,** Resection of the mucosa of the diverticulum. **D,** Stay sutures in the edges of the mucosa. **E,** Suture of the muscle layers. **F,** Transverse suture of the mucosa. **G,** Placing an intrapancreatic drain through the papilla. Observe the suture of the mucosal layer after diverticulectomy. (From Pinotti HW, Tacla M, Pontes JF, et al: Surgical procedures upon juxta-ampullar duodenal diverticula. Surg Gynecol Obstet [now J Am Coll Surg] 135:11, 1972. By permission of *Surgery, Gynecology and Obstetrics.*)

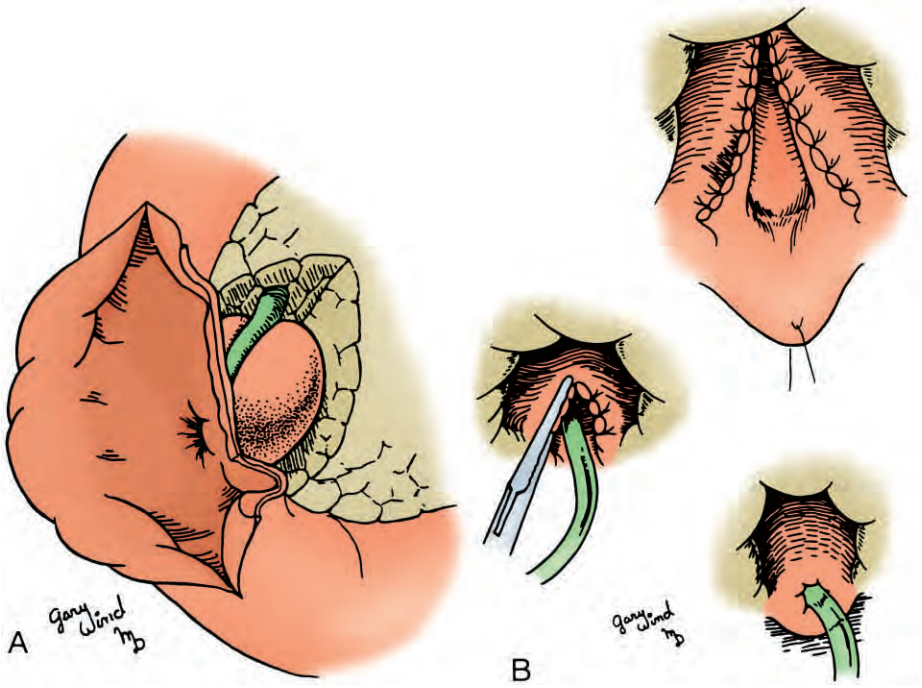
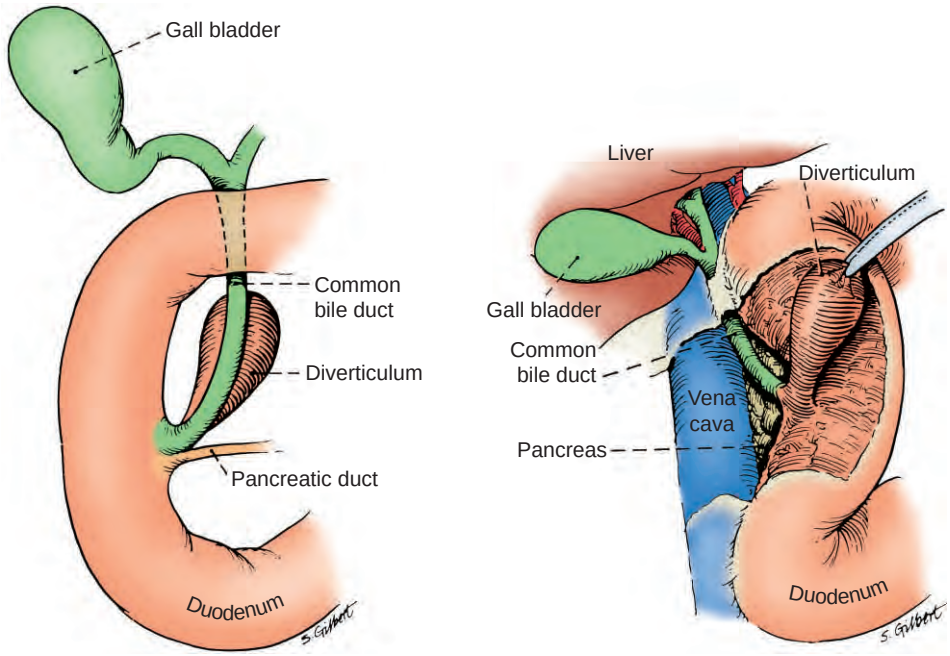


Figure 54–11. A, Anatomy of a juxtapapillary diverticulum. The relationship of the diverticulum to the pancreas makes transduodenal excision hazardous. **B,** When the wall between the diverticulum and the bile duct is divided, flow is established, thereby relieving stasis in both the duct and the diverticulum. (From Kaminsky HH, Thompson WR, Davis B: Extended sphincteroplasty for juxtapapillary duodenal diverticulum. Surg Gynecol Obstet [now J Am Coll Surg] 162:281, 1986. By permission of *Surgery, Gynecology and Obstetrics*.)



Anterior view

Duodenum retracted

Figure 54–12. Usefulness of the Kocher maneuver in demonstrating duodenal diverticula. (From Jones TW, Merendino KA: The perplexing duodenal diverticulum. Surgery 48:1068, 1960.)

generous Kocher maneuver to adequately visualize the relationship of the diverticulum to ductal structures (Fig. 54–12).

Handelsman and co-workers[16] emphasized the high morbidity and mortality associated with excision of juxtavaterian diverticula. This morbidity was primarily the result of the frequent occurrence of bile duct injury, duodenal fistula, or fulminant postoperative pancreatitis. These authors strongly advocated bypass procedures to avoid such potentially lethal complications.

Critchlow and colleagues[47] proposed Roux-en-Y duodenojejunostomy as treatment of pancreaticobiliary disease associated with perivaterian duodenal diverticula (Fig. 54–13). They note that this procedure has the advantage of removing the diverticulum from the food stream, thereby relieving stasis and stasis-induced problems such as cholangitis and pancreatitis. If the problem is that of recurrent choledochal stones after cholecystectomy or multiple choledochal pigment stones, even before cholecystectomy, end-to-side Roux-en-Y choledo-

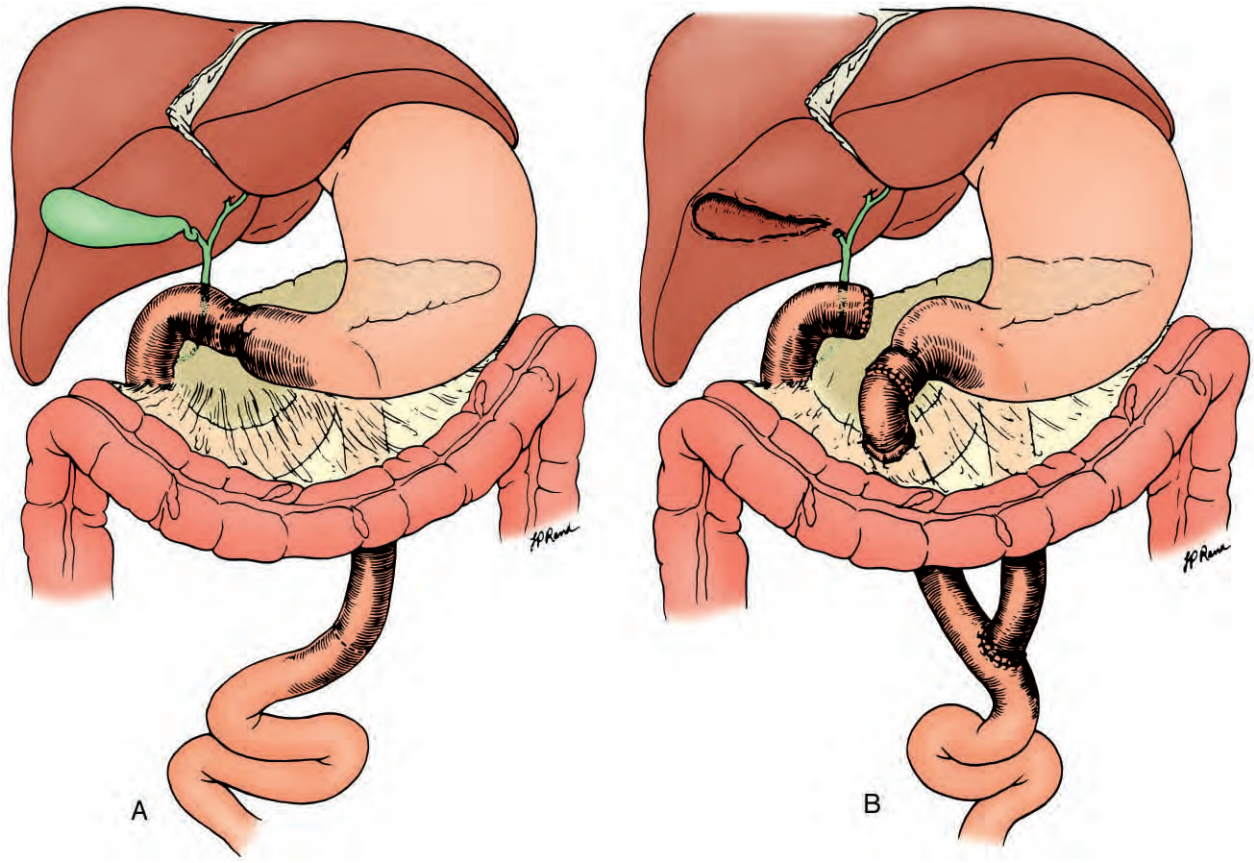


Figure 54–13. **A,** Anatomy before reconstruction. *Dashed lines* indicate proposed sites of division of the intestine. **B,** Anatomy after reconstruction. The gallbladder has been removed. The Roux limb has been brought through the mesocolon, the duodenojejunostomy has been completed, and the mesentery has been closed. (From Critchlow JF, Shapiro ME, Silen W: Duodenojejunostomy for the pancreaticobiliary complications of duodenal diverticulum. Ann Surg 202:56, 1985.)

chojejunostomy, as advocated by Miyazawa and colleagues,[19] is probably the preferred option because it more directly relieves biliary stasis (Fig. 54–14).

The authors of this chapter strongly concur that these bypass procedures are preferable to excision in patients with pancreaticobiliary complications of juxtavaterian duodenal diverticula. In addition, if excision, partial excision, or oversewing is necessary for such problems as ulceration, bleeding, or perforation, when possible, patients should be referred to experienced pancreaticobiliary surgeons.

JEJUNOILEAL DIVERTICULA

Incidence

By small bowel contrast-enhanced radiographic series, the incidence of jejunoileal diverticula in the general adult population ranges from 0.02% to 1.3%.[48] At autopsy, the incidence of jejunal diverticulosis has been cited to be as high as 7.1%.[49] Small bowel diverticula are difficult to demonstrate radiographically or anatomically, and therefore the incidence is probably much higher.

Associated Diseases

Jejunoileal diverticula are most commonly identified in the sixth and seventh decades of life and are more common in men than women. We previously alluded to the association of jejunoileal diverticulosis with other gastrointestinal diverticula. Concurrent diverticulosis of the colon and duodenum is particularly common.[50] Less commonly, urinary bladder and esophageal diverticula have been described as synchronous lesions.[51] Theories of this association with systemic disorders that affect muscle tone imply that diverticula can be a secondary manifestation of dysmotility.[15]

Pathogenesis

Jejunoileal diverticula, occasionally referred to as nonmeckelian diverticula, are generally considered to be acquired diverticula, although familial cases have been reported.[52] The familial distribution of diverticula may be related to a motility disorder or congenital weakness of the intestinal muscularis.[4] They are pseudodiverticula and lack a muscular wall. These lesions are pulsion-type

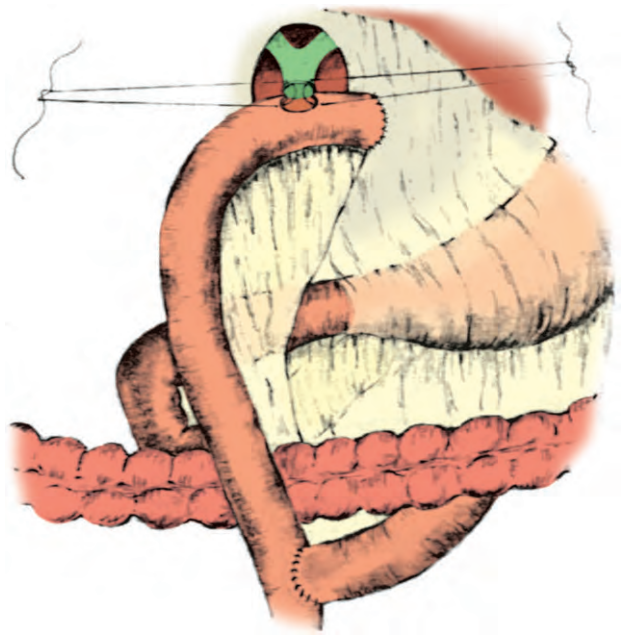


Figure 54–14. Roux-en-Y choledochojejunostomy to remove a diverticulum from the food stream and relieve biliary stasis. (From Schwartz SI: Current modalities in surgery. In Surgery: Excision of Extrapancreatic Bile Ducts and Hepaticojejunostomy. Marlton, NJ, Innovative Publishing, 1985, p 2.)

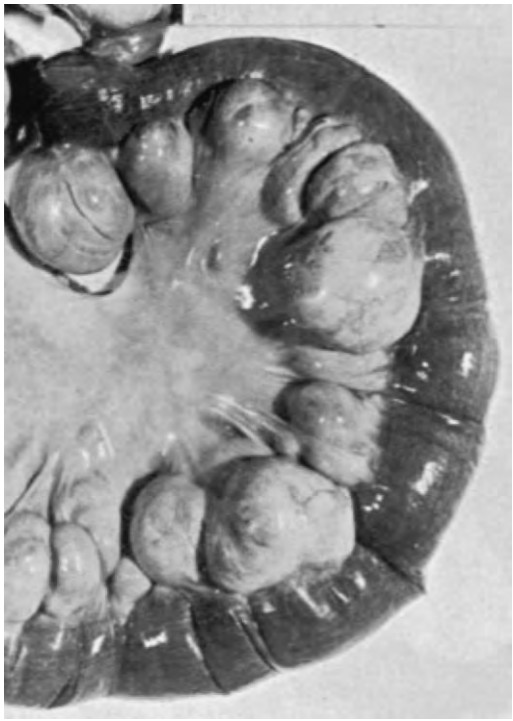


Figure 54–15. Formol-saline–preserved specimen demonstrating multiple jejunal diverticula. (From Badenoch J, Bedford P, Evans JR: Massive diverticulosis of the small intestine with steatorrhea and megaloblastic anemia. Q J Med 24:321, 1955.)

diverticula and are thought to result from a weakened intestinal wall.[13] An attenuated muscularis is associated with aging and with hereditary neuromuscular disorders. In addition, it has been postulated that local weakness exists at the points where the vasa recta penetrate the intestinal wall. This theory is supported by observations that small intestinal diverticula occur more commonly along the mesentery, with an increased frequency in the proximal jejunum and distal ileum, where the caliber of the blood vessels is greatest (Fig. 54–15).

Symptoms

Previously, it was thought that most cases remain asymptomatic throughout the patient's life. More recent studies have suggested that upward of 90% of patients with jejunoileal diverticula may manifest nonspecific symptoms.[53] This fact must be remembered when jejunoileal diverticula are incidentally found on diagnostic studies or at surgery. Because of the associated dysmotility, the most common symptoms of jejunoileal diverticulosis are nonspecific and include chronic abdominal pain, bloating, and early satiety. Diverticulitis is manifested as acute abdominal pain and may cause symptoms of a febrile illness, but this is rare. Obstructive symptoms, bleeding, and peritonitis occur at an incidence of 10% and are an indication that operative management is required.[54]

Diagnosis

Classically, the diagnosis of small bowel diverticula is made radiographically by small bowel contrast series or by an enteroclysis study (Fig. 54–16). A variety of techniques have been described to facilitate the diagnosis, but current consensus is that enteroclysis is the most accurate.[27,55] Preoperative diagnosis is unusual, however, because the symptoms overlap those of more common causes of acute abdominal pain. CT demonstrating extraluminal air within the small bowel mesentery should raise suspicion of a perforated diverticula.

Complications

Even though most patients with jejunoileal diverticula do not have symptoms and will never experience complications of their disease, there are potentially serious outcomes related to these lesions. The overall complication rate may be higher than the previously estimated 10% to 30%.[56]

Hemorrhage

Massive hemorrhage may be a sequela and can sometimes be fatal.[57,58] Hemorrhage is less common with jejunoileal diverticula than with other small bowel diverticula; it occurred in only 12% of patients according to a

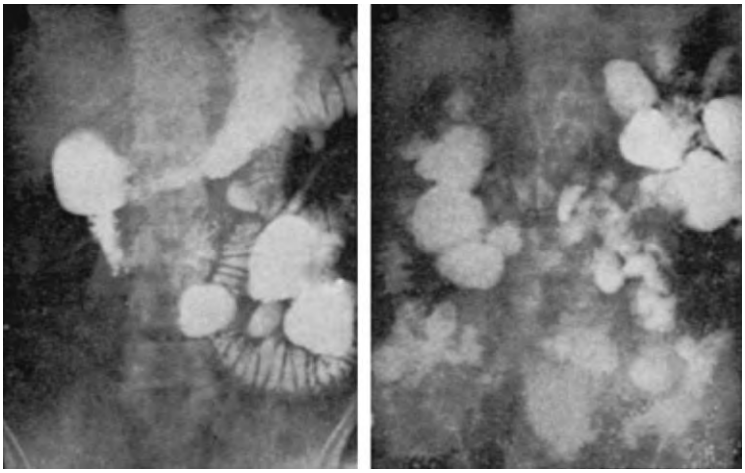


Figure 54–16. Multiple jejunal diverticula demonstrated on small intestine contrast examination. (From Altemeier WA, Bryant LR, Wulsin JH: The surgical significance of jejunal diverticulosis. Arch Surg 86:732, 1963. Copyright © 1963, American Medical Association.)

1996 series.[56] As a cause of gastrointestinal hemorrhage, a bleeding jejunoileal diverticulum is rare.[53] A radioscintigraphic bleeding scan or angiography may be useful in identifying the bleeding diverticulum in these patients. When angiography is performed, vital dyes can be introduced intraoperatively through angiographic catheters placed selectively in branches of the superior mesenteric artery that feed the involved segment and be used to guide the surgeon to the exact location of the bleeding lesion.[31]

Perforation

Perforation is a serious condition with a mortality rate that approaches 50% in some historical series. With modern perioperative care and intraoperative monitoring, this mortality rate should be much lower.[56] Perforation is the most common complication of jejunoileal diverticular disease and is a sequela of diverticulitis.[59] A perforated diverticulum can be difficult to identify at laparotomy because the peritonitis may be confined to the leaves of the mesentery. Astute intraoperative observation, often combined with a preoperative CT scan, is required if this potentially fatal complication is to be diagnosed correctly.[4] Signs of mesenteric inflammation with either retroperitoneal air or air within the mesentery should raise suspicion for this complication. Abscess formation is an obvious outcome of perforation in patients who do not succumb to sepsis.

Obstruction

Small bowel obstruction secondary to jejunoileal diverticula is well described and is identified at laparotomy.[54,60] Obstruction is typically cited as a less common complication, with an estimated incidence of 5% and only 27 cases described in the modern literature. This low incidence is a result of the liquid nature of the small bowel contents and the relatively large ostia of most intestinal diverticula. When obstruction does occur, it is usually due to enterolith formation. Nonmechanical obstruction, or pseudo-obstruction, may occur and is related to the dyskinesia associated with this condition.[61]

Malabsorption

Malabsorption is primarily reported to occur with jejunoileal diverticular disease.[53] Diverticular disease eventually leads to the physiologic equivalent of a blind-loop syndrome with ensuing bacterial overgrowth. Bacterial overgrowth within the diverticulum may then lead to symptoms associated with malabsorption and may contribute to cases of diverticulitis or perforation.

Management

Nonoperative Treatment

The role of antibiotics is agreed on for patients with bacterial overgrowth and is controversial for patients with evidence of perforation.[21] Metronidazole, tetracyclines, and ciprofloxacin are among the antibiotics recommended for bacterial overgrowth.[62] Isolated reports in the literature suggest that perforated diverticula can be managed with supportive measures. The combination of parenteral antibiotics, intravenous fluids, and close observation is acceptable treatment of isolated small bowel diverticulitis, although as stated previously, this diagnosis is difficult to make.

Nonoperative management of asymptomatic disease is based on increasing dietary fiber to decrease the intraluminal forces associated with peristalsis.[12] With the onset of symptoms, recommendations include small, frequent meals and rest in a supine position for 1 hour after each meal. Close observation is required to identify patients who may require surgical treatment.

Operative Therapy

Conservative management is the rule in the operative treatment of jejunoileal diverticular disease. Incidental, asymptomatic diverticula should be left alone. In patients

with hemorrhage or perforation, segmental resection of the affected bowel is indicated. Because of the mesenteric location of the diverticulum, simple diverticulectomy may impair blood flow and therefore lead to anastomotic breakdown or fistula formation.[63] In addition, local excision may be difficult because of inflammation.[64] Obstruction is best managed by resection as well, but in cases of enterolith impaction, simple enterotomy with stone extraction has been advocated in some reports.[54,65] Controversy persists regarding whether surgery should be performed for symptomatic, but uncomplicated lesions. Given the generally benign natural history of these acquired lesions, surgery should probably be reserved for complicated cases.

MECKEL'S DIVERTICULUM

Incidence

Meckel's diverticulum is the most commonly encountered congenital anomaly of the small intestine, with autopsy studies estimating the incidence to be 2%,[66,67] and it found with equal frequency in men and women.

Pathogenesis

Meckel's diverticulum is a true diverticulum; that is, it contains all layers of the bowel wall because it is derived from an intact embryologic vitelline duct (omphalomesenteric duct) that does not undergo normal obliteration during the fifth to ninth weeks of gestation.[68,69] Persistence of this duct results in (1) a fibrous cord between the umbilicus and the ileum, which represents an obliterated duct and its vessels; (2) an umbilical sinus when the umbilical side of the duct does not fully obliterate; (3) Meckel's diverticulum secondary to failure of the intestinal end to close; (4) a fistula between the umbilicus and the ileum when the entire duct remains patent; or (5) any combination of these abnormalities.[70,71]

Meckel's diverticulum usually arises from the antimesenteric border of the ileum, within 100 cm of the ileocecal valve, and derives its blood supply from persistent vitelline vessels that are present within a distinct mesentery.[72] The length and diameter vary from 1 to 12 cm. The embryologic cells lining the vitelline duct retain their pluripotential capability, and thus it is not uncommon to find heterotopic tissue within the diverticulum. Gastric mucosa is present in 30% to 50%,[73] and although Meckel's diverticula are usually benign incidental findings at laparotomy, 75% of patients with symptoms have gastric mucosa within their diverticula. The incidence of pancreatic tissue approximates 5%, and even though colonic mucosa, lipoma, leiomyoma, neurofibroma, angioma, and their malignant counterparts have been reported, these findings are uncommon.[74] Consideration must be given to these tumors, however, not only for their oncologic significance but also as lead points for intussusception.

Symptoms

About 4% of patients with Meckel's diverticulum have symptoms within their lifetime, and in more than half of these patients the symptoms occur before 2 years of age.[67] The average mortality rate in patients in whom symptoms develop is 6%,[67] and it is disproportionately high in elderly patients. Symptomatic manifestations are secondary to hemorrhage (23%), small bowel obstruction (31%), diverticulitis (14%), intussusception (14%), perforation (10%), and miscellaneous umbilical abnormalities and tumors (8%).[75]

Diagnosis

In patients who have ectopic gastric mucosa in Meckel's diverticulum, technetium scanning is a useful diagnostic aid. ^{99m}Tc-pertechnetate is taken up by gastric mucosa, and the uptake can be detected scintigraphically (Fig. 54–17). Pentagastrin given subcutaneously 20 minutes before the study has been shown to enhance uptake within the gastric mucosa.[73] Cimetidine, a histamine H_2 receptor blocker, has a similar effect and may enhance the intraluminal release of pertechnetate.[73] The sensitivity of this scan for detecting Meckel's diverticulum with ectopic gastric mucosa has been found to be 85%, with a specificity of 95% and an accuracy of 90% in surgically proven diagnoses.[73] A negative test excludes a diverticu-

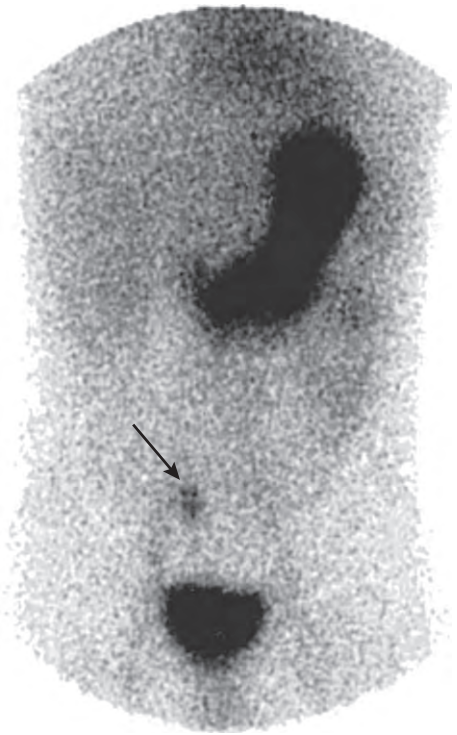


Figure 54–17. ^{99m}Tc-pertechnetate scintigraphy demonstrates ectopic gastric mucosa, indicative of Meckel's diverticulum *(arrow).* (Courtesy of P. R. Jolles, Medical College of Virginia.)

lum in more than 90% of patients who have none.[76,77] Meckel's diverticulum can also sometimes be detected by enteroclysis, in which a large volume of contrast medium is introduced through a fluoroscopically directed nasointestinal tube directly into the jejunum to induce distention, which makes morphologic abnormalities easier to visualize.[55] When the diverticulum itself is not visualized, a mass effect is sometimes noted and can lead to a correct diagnosis.[55] In some cases, the demonstration of intussusception is associated with an inverted Meckel's diverticulum as the lead point.

Complications

Hemorrhage

Hemorrhage is the most common symptom in children 2 years or younger with Meckel's diverticulum[73,78]; it is usually manifested as painless bright red blood from the rectum, with intermittent episodes persisting without treatment. The usual source of the bleeding is an ileal ulcer located adjacent to a Meckel diverticulum containing gastric mucosa. Diagnosis of a diverticulum containing gastric mucosa can be made via ^{99m}Tc-pertechnetate radioisotope scanning. The use of pentagastrin stimulation before the scan decreases false-negative results by enhancing uptake of the isotope by the gastric mucosa.[73] Although the diagnostic accuracy of this test approaches 90% because of a high index of suspicion in young children with painless rectal bleeding,[73] the scan is not as useful in adults, in whom enteroclysis has a high incidence of accurate diagnosis.[55]

Obstruction

Obstructive symptoms are common with Meckel's diverticulum and may be due to volvulus, intussusception, or incarceration of the diverticulum in an inguinal hernia (Littre's hernia). The most common of these causes is acute volvulus, in which the small bowel kinks around a fibrous band running from the tip of the diverticulum to the umbilicus.[70] Strangulation of the involved bowel may ensue if not suspected. Intussusception results from a broad-based diverticulum invaginating and being carried forward by peristalsis. The intussusception may be ileoileal or ileocolic[70] and is manifested as acute obstruction with early vomiting, an urge to defecate, and occasionally the classic currant-jelly stools. Reduction can be achieved with a barium enema; however, reduction is not as successful as in non-Meckel's intussusception (Fig. 54–18). Resection is indicated regardless of success with hydrostatic reduction.[74]

Diverticulitis

Diverticulitis accounts for 10% to 20% of symptomatic cases[70] and is more common in older patients (Fig. 54–19). It is the third most frequent complication in adults after obstruction and bleeding. Clinically indistinguishable from appendicitis, if not considered it may lead to perforation or peritonitis. If during exploration for appendicitis the appendix is found to be normal, inspection of the distal 100 cm of ileum for Meckel's diverticulum is crucial. The indications for resection in this clinical setting parallel those of appendectomy. Inflamed diverticula and diverticula found incidentally when other causes of the acute abdomen are not obvious should undergo resection.[72]

Umbilical Anomalies

Eight percent to 10% of patients with Meckel's diverticulum have umbilical abnormalities, including fistulas, cysts, sinuses, and fibrous bands.[75] Identification of such abnormalities is not usually difficult and may be signaled by the presence of intestinal mucosa at the skin level or a persistently draining fistula. Cannulation and injection of the enterocutaneous fistula draining at the umbilicus can delineate the fistula, after which elective surgical exploration and resection can be performed.[75] If a fibrous band is found at laparotomy, it is generally recommended that the diverticulum be resected because of the risk for internal herniation and volvulus.[67] Should a situation arise in which resection is not safe, simple division of the band is sufficient.

Management

Operative Therapy

Management of Meckel's diverticulum discovered incidentally at laparotomy for another condition is controversial. Supporters of incidental diverticulectomy state that minimal postoperative complications occur with removal.[66,79] It is generally agreed that diverticula that appear to have heterotopic mucosa on physical examination should be resected, given their higher risk for subsequent complications.[72,80] Age younger than 40 years, diverticula longer than 2 cm,[72] and fibrous bands to the umbilicus or mesentery are risk factors for complications and relative indications for resection. Resection of asymptomatic diverticula in children at laparotomy is also generally recommended.

In 1976, Soltero and Bill[67] estimated a 4.2% lifetime risk for complications from Meckel's diverticulum with the use of population-based life-table analysis. They used previously published mortality rates after resection of symptomatic and asymptomatic diverticula and estimated that 800 asymptomatic diverticula would need to be resected to save the life of one patient with an asymptomatic Meckel's diverticulum. Assuming Von Hendenberg's morbidity rate of 9% after incidental removal,[81] these authors opposed prophylactic diverticulectomy. Cullen and colleagues,[66] however, reported an epidemiologic, population-based study of 145 patients undergoing resection of Meckel's diverticulum in which 87 were incidentally found; they calculated a 6.4% lifetime risk for complications of Meckel's diverticulum. These authors reported an operative morbidity rate of 2% after resection of diverticula found incidentally and, in contrast to Soltero and Bill[67] and others[80] who demonstrated a greater complication rate occurring in patients of

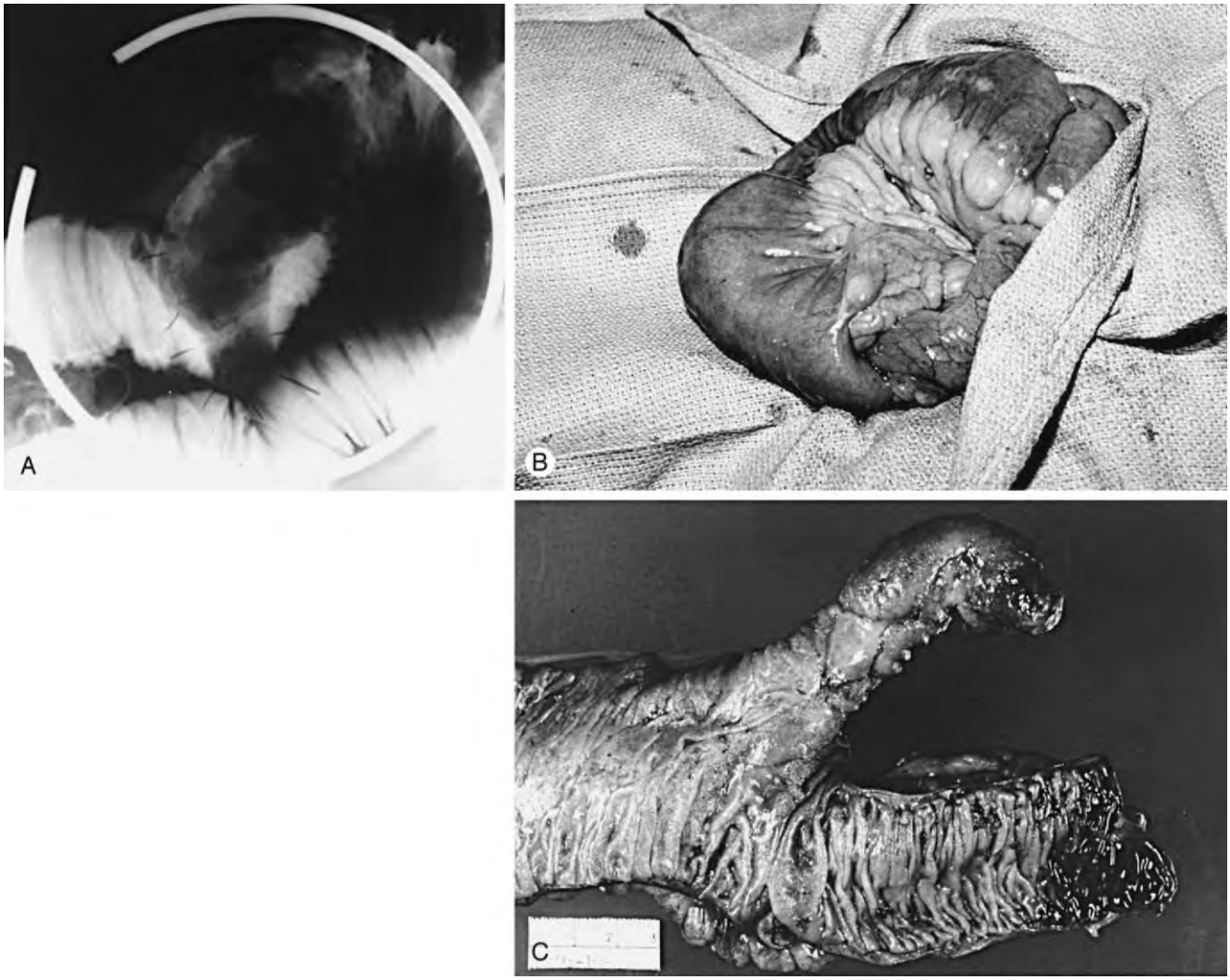


Figure 54–18. A case of small bowel obstruction secondary to intussusception of Meckel's diverticulum. A preoperative barium study **(A)** demonstrates a diverticulum. An intraoperative view **(B)** and specimen **(C)** show the relationship of the diverticulum to the small bowel. (Courtesy of J. M. Kellum, Medical College of Virginia.)

younger age, showed no trend consistent with age. The risk for long-term complications included a 2% risk for adhesive small bowel disease as compared with a 7% risk in patients undergoing resection of complicated diverticular disease. The authors of this study concluded that incidentally discovered diverticula should be resected in the absence of peritonitis or other conditions precluding the safe performance of this operation.[66] In summary, the standard of care in recent decades has been selective resection of incidentally discovered diverticula based on estimated risks for future complications. Studies conducted since the advent of laparoscopy demonstrate that performance of prophylactic diverticulectomy under appropriate operative conditions is safe and may be beneficial.

Patients experiencing a complication of Meckel's diverticulum should be treated by diverticulectomy. Resection in this setting is associated with a 5% to 10% mortality rate. A simple diverticulectomy can be performed in which the diverticulum is divided at its junction with the small intestine and the defect in the small intestine is closed with sutures or staples; alternatively, wedge excision of a portion of the ileal wall with the diverticulum can be performed. Finally, some patients require excision of the segment of ileum containing the diverticulum with an enteroenteric anastomosis.

The choice of operation depends, in part, on the condition of the diverticulum and the adjacent ileum. In general, the worse the condition, the more extensive the resection. In patients with hemorrhage from adjacent ileal ulcers, simple diverticulectomy does not remove the ulcer, and postoperative bleeding may recur. Segmental resection is also advocated in small children who have broad-based diverticula, in whom postoperative ileal

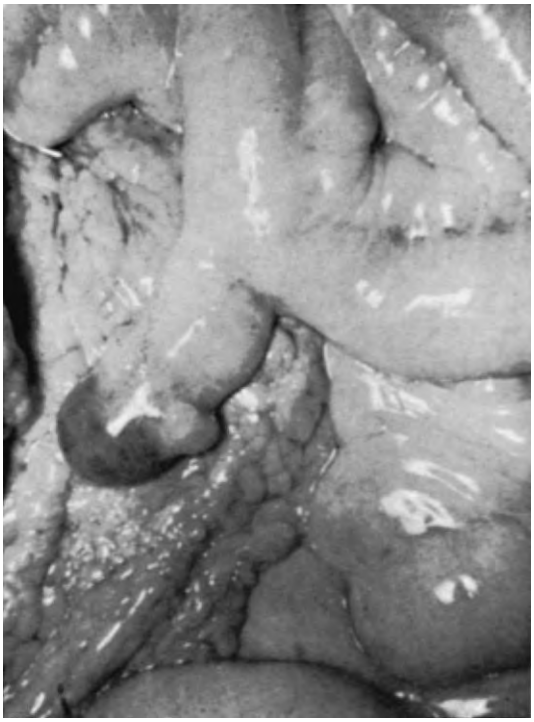


Figure 54–19. Meckel's diverticulitis. The tip of the diverticulum is reddened because of peptic ulceration secondary to a rest of gastric epithelium. (From Robbins SL, Cotran RS, Kumar V: Pathologic Basis of Disease, 3rd ed. Philadelphia, WB Saunders, 1984.)

stenosis is a risk. Recent reports demonstrate the feasibility of laparoscopic removal[78,82,83]; however, long-term results of these techniques are not available. With increasing use of diagnostic laparoscopy, further controversy regarding the management of asymptomatic diverticula is inevitable.

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Chapter

55

Operations for Peptic Ulcer

Ali Tavakkolizadeh · Stanley W. Ashley

Gastroduodenal peptic ulcer disease (PUD) is a common problem, with an estimated 2% of the U.S. population having a symptomatic ulcer at any given time. A recent review of Medicare records estimates nearly 900,000 peptic ulcer–related hospital admissions per year, with an annual cost of $4.8 billion and an overall ulcer-related mortality rate of 4.5%.[1] With the identification of *Helicobacter pylori (H. pylori)* and recognition of nonsteroidal anti-inflammatory drugs (NSAIDs) as etiologic factors, our understanding of the disease has improved significantly, which has lead to the introduction of more potent and successful therapeutic regimens. Before the introduction of histamine H_2 receptor antagonists and proton-pump inhibitors (PPIs), operations for chronic intractable PUD were common. With the advent of successful medical therapy, the role of elective surgery in this field has diminished. Based on a population study from Finland, the number of elective peptic ulcer procedures fell from 11.9 to 1.3 per 100,000 population between 1987 and 1999, an 89% reduction.[2] This reduction has also been confirmed by large epidemiologic studies from Iceland and the United Kingdom.[3,4]

Complications of ulcer disease will develop in 10% to 20% of people during the course of their disease, and operative intervention is often required when such complications occur. Although the new drug regimens have reduced the number of elective operations for PUD, the number of admissions and surgical interventions for complications of this disease has remained unchanged.[5] In fact, epidemiologic data from the United Kingdom suggest that the incidence of duodenal ulcer bleeding and perforation has increased in older age groups. Interestingly, this increase has been documented during a period when there has been a 50-fold increase in the prescription of PPIs and a lower prevalence of *H. pylori* infection in the cohort.[3] This finding has led to the conclusion that the increased prevalence of PUD complications is due to the wider use of ulcerogenic drugs such as NSAIDs, low-dose aspirin, and selective serotonin reuptake inhibitors. The mortality rate for those undergoing surgery has also remained unchanged, which in part reflects the population that is undergoing surgery: the sickest and eldest individuals, in whom such problems eventually develop.

Current indications for surgical intervention are

1. Bleeding—most common complication of PUD, with an incidence of approximately 100 per 100,000 population
2. Perforation—with an annual incidence of 11 operations per 100,000 population
3. Obstruction—occurs as a result of scarring of prepyloric and duodenal ulcers
4. Failed medical therapy—in the era of PPIs, an uncommon indication for surgery
5. Risk for malignancy—of particular importance with regard to large gastric ulcers

The goals of surgical procedures are to

1. Permit ulcer healing
2. Prevent or treat ulcer complications
3. Address the underlying ulcer etiology
4. Minimize postoperative digestive consequences

No single procedure satisfies all these objectives. To choose the best operation, the surgeon must consider the characteristics of the ulcer (location, chronicity, type of complication), the probable cause (acid hypersecretion, drug induced, possible role of *H. pylori*), the patient (age, nutrition, comorbid illness, condition at initial evaluation), and the operation (mortality rate, side effects). In some respects, all ulcer operations represent a compromise: the morbidity of ulcer disease is replaced by the morbidity of the operation. Finally, surgeon experience must play a role in the choice of operation; today, most surgical residents complete their training with significantly less experience in more complex procedures, which undoubtedly influences their choices for both elective and emergency operations.

In this chapter we first discuss elective surgery for intractable peptic ulcers before discussing emergency procedures to deal with complications of ulcer disease.

ELECTIVE SURGERY FOR PEPTIC ULCER DISEASE

Elective Surgery for Intractable Duodenal Ulcer Disease

With the identification of *H. pylori,* the recognition that greater than 95% of duodenal ulcers are associated with this organism, and the fact that eradication of the pathogen results in cure rates in excess of 95% without the need for chronic acid suppression, medical therapy for duodenal ulcer has shifted away from an antisecretory/antacid approach to an antimicrobial strategy. This change has resulted in a dramatic reduction in the number of elective procedures performed for intractable, noncomplicated disease. However, when operative intervention is being considered, the strategy continues to be based on reduction of acid secretion. Acid secretion by the parietal cells is normally stimulated by acetylcholine from the vagus nerve and release of gastrin from the antrum. Surgeons attempt to reduce this acid secretion by sectioning the vagus (vagotomy) and eliminating hormonal stimulation from the antrum (antrectomy). Each of these maneuvers has effects on acid secretion and consequences in terms of the normal physiology of the upper gastrointestinal tract that tend to be amplified when procedures are combined (e.g., vagotomy and antrectomy). In the past, the choice of operation involved weighing rates of recurrent ulceration with the risk for postoperative complications and long-term sequelae (postgastrectomy syndromes). This decision dilemma prompted a large number of trials comparing the procedures in the surgical literature. Recently, improvements in medical therapy, particularly treatment of *H. pylori,* have markedly reduced the risk for ulcer recurrence, thus rendering much of these data obsolete. Consequently, surgical decision making has become confusing, with few quality data available from the post–*H. pylori* era. The choices of surgical intervention for intractable duodenal ulcer disease, however, have remained unchanged:

1. A form of vagotomy
2. ± A drainage procedure
3. ± Gastric resection/anterectomy

Here we discuss the choices available within each category.

Vagotomy

Technically speaking, the term *vagotomy* implies transection of the vagus nerve and thus interruption of sensory, secretory, and motor impulses to the stomach and other gastrointestinal organs. In common practice, a 1- to 2-cm section of each nerve is actually resected and sent to the pathologist, who confirms that it is nerve tissue. Although the proper term for the resection should be *vagectomy, vagotomy* is the much more commonly used term. The rationale for vagotomy is the elimination of direct cholinergic stimulation of acid secretion. In the stomach, vagal fibers innervate the mucosa and play a major role in the cephalic phase of gastric acid secretion by releasing acetylcholine; once released, acetylcholine stimulates acid secretion via a specific receptor on the parietal cell. The distal portions of the anterior and posterior trunks send branches to the antrum and pylorus that serve primarily a motor function. The celiac branch of the posterior vagus stimulates small intestinal motility. Gastric motility is affected not just by the antral and pyloric branches of the vagus, which stimulate peristaltic activity of the antrum and relaxation of the pylorus; the vagus also stimulates receptive relaxation of the fundus, which results in accommodating intake without a corresponding increase in pressure.

Vagotomy results in a variety of physiologic alterations in the stomach. Acid secretion is drastically reduced because of diminished cholinergic stimulation of parietal cells, and the cephalic phase of gastric secretion is essentially eliminated. There is a 75% decrease in basal acid secretion and a 50% decrease in maximum acid output. After vagotomy, the parietal cells are less responsive to histamine and gastrin, with a resultant increase in serum gastrin levels and gastrin cell hyperplasia. Because of loss of reflex relaxation of the gastric fundus, increased gastric volume after eating is accompanied by an increase in pressure, which results in rapid emptying of liquids. Similarly, vagotomy adversely affects distal stomach motility and thereby results in difficulty emptying solids. As a result of the latter alterations, gastric atony develops in approximately 20% of patients and leads to stasis, chronic abdominal pain, and distention. For that reason, it is recommended that after truncal vagotomy patients undergo a drainage procedure to counteract the nonrelaxing pylorus, which acts as an obstruction. The various drainage procedures available are discussed later. Four types of vagotomy have been described in the surgical literature: *truncal, selective, highly selective,* and *supradiaphragmatic.* Truncal and highly selective vagotomy are commonly used to treat PUD, whereas selective and supradiaphragmatic vagotomies are used infrequently.

Truncal Vagotomy Truncal vagotomy involves division of the anterior and posterior vagal trunks after they emerge below the diaphragm (Fig. 55–1). As part of truncal vagotomy, all branches of the two trunks that lie on the esophagus, between the diaphragm and gastroesophageal junction, should be sought and transected as well. This procedure not only completely denervates the stomach but also eliminates vagal innervation to the pancreas, small intestine, proximal part of the colon, and hepatobiliary tree. Although truncal vagotomy significantly reduces acid secretion, it also markedly alters gastric motility by impairing both receptive relaxation of the stomach and the process of antral grinding and pyloric sphincter coordination, which permits gastric emptying. As discussed earlier, some form of gastric-emptying procedure should be performed. This procedure is often combined with antrectomy, but in the event of an emergency, pyloroplasty or gastroenterostomy is performed.

Selective Vagotomy Selective vagotomy was developed in an attempt to decrease the incidence of postvagotomy diarrhea and ameliorate the increased incidence of gallbladder stasis, which leads to increased gallstone forma-

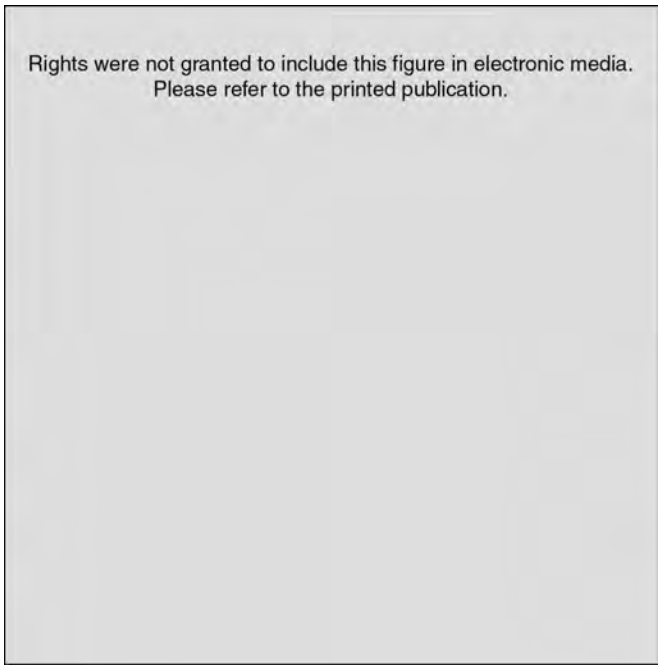

Figure 55–1. Truncal vagotomy involves resecting a 2- to 3-cm section of the anterior and posterior nerve trunks between the gastroesophageal junction and diaphragm. (From Zollinger RM: Atlas of Surgical Operations. New York, Macmillan, 1975.)

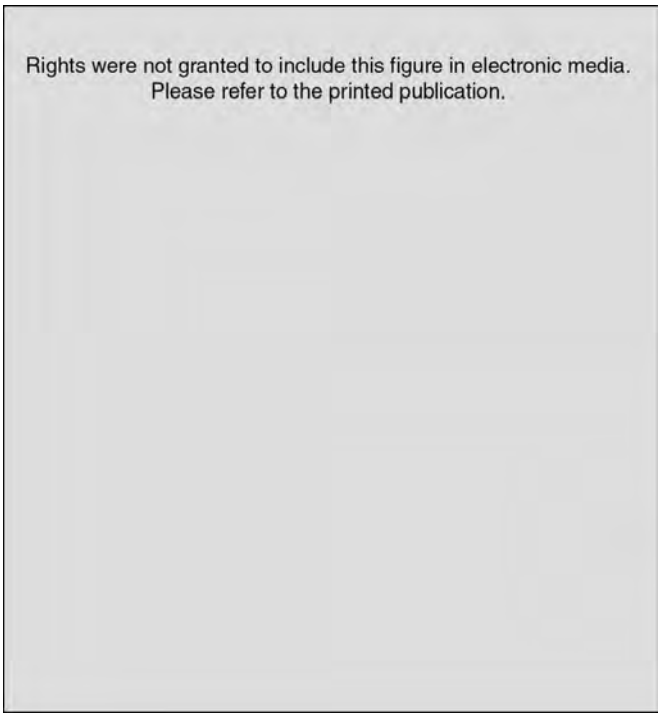

Figure 55–2. Selective vagotomy involves a bilateral vagotomy distal to the takeoff of the hepatic and celiac vagal brunches. (From Zollinger RM: Atlas of Surgical Operations. New York, Macmillan, 1975.)

tion and cholecystitis. The vagal fibers are divided distal to the takeoff of the hepatic branches (from the anterior vagus) and the celiac branches (from the posterior vagus) (Fig. 55–2). This procedure is technically more demanding than truncal vagotomy and requires more careful and meticulous dissection. The effectiveness of this procedure, when performed carefully, is borne out by reported ulcer recurrence rates as low as 2%. This low recurrence rate is in part due to the meticulous periesophageal dissection that is performed. This technique spares vagal innervation to the gallbladder and intestine while completely denervating the stomach. Because vagal pyloric innervation is also eliminated, a drainage procedure is still required. The drainage procedure could take the form of a pyloroplasty, or the procedure may be combined with antrectomy. Unlike truncal vagotomy, after which antrectomy is recommended, trials have shown that selective vagotomy, when performed in conjunction with pyloroplasty or antrectomy, results in similar recurrence rates. The main reason for the evolution of this technique, however, was its presumed lower side effect profile. Nonetheless, a prospective randomized study failed to show substantial benefit for selective vagotomy over truncal vagotomy. Although the incidence of diarrhea after selective vagotomy appeared to be lower, it did not reach statistical significance.

The introduction of highly selective vagotomy (HSV) with a lower side effect profile and the need for a drainage procedure with selective vagotomy resulted in limited use of selective vagotomy as a therapeutic option.

Highly Selective Vagotomy HSV is also known as *parietal cell vagotomy* and *proximal gastric vagotomy*. The rationale for HSV is to eliminate vagal stimulation to the acid-secreting portion of the stomach without interrupting motor innervation to the antrum and pylorus. The operation involves severing all branches of the vagus nerve along the lesser curvature that innervate the corpus and fundus of the stomach while preserving the hepatic and celiac branches, as well as the distal vagal branches extending to the antrum and pylorus (Fig. 55–3). The end result of this technically demanding and somewhat tedious procedure is the same reduction in acid secretion that occurs after truncal vagotomy (basal and stimulated acid secretion is reduced by more than 75% and 50%, respectively), but without the troublesome stasis and gastric atony. Because the distal motor nerves are preserved, emptying of solids is normal; however, the nerves affecting receptive relaxation are divided, and thus some rapid emptying of liquids may occur. The alteration in liquid emptying is usually minimal. This procedure is associated with the lowest morbidity rate of all vagotomy procedures and became the operation of choice in many centers despite an ulcer recurrence rate of 5% to 20%. A meta-analysis of 12 trials has confirmed that HSV has a higher recurrence rate than truncal vagotomy with pyloroplasty, but fewer long-term side effects.[6] HSV has also been compared with truncal vagotomy in a randomized trial, in which it was shown to have a lower incidence of dumping syndrome and weight loss. Although ulcer recurrence rates were higher with HSV,

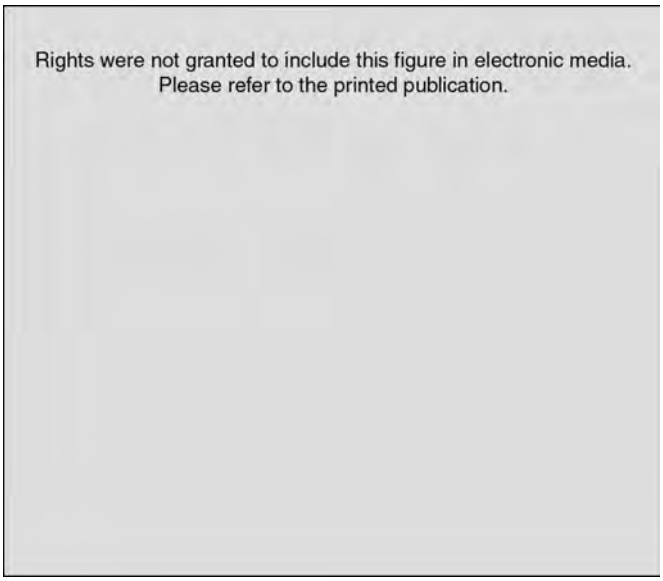

Figure 55–3. Highly selective vagotomy involves dividing the vagal branches to the fundus and corpus of the stomach while preserving the motor branches to the antrum and pylorus. (From Zollinger RM: Atlas of Surgical Operations. New York, Macmillan, 1975.)

this was not significant when prepyloric ulcers (for which HSV is now known to be an inadequate operation) were excluded.[7]

Both truncal vagotomy with antrectomy and selective vagotomy with antrectomy are more effective than HSV in curing PUD and would have been regarded as the gold standard were it not for their higher incidence of side effects.

It was assumed that when duodenal scarring is present and pyloroplasty or gastroenterostomy is needed, HSV is unlikely to offer any benefit and the procedure was abandoned in favor of the simpler truncal vagotomy. Several studies have, however, shown that this simplified thinking is incorrect and that HSV offers symptomatic advantages over vagotomy even when performed with a drainage procedure. Preservation of antral innervation is thought to preserve antral motility and prevent bile accumulation in the stomach, as well as minimize early dumping in patients.[8]

HSV is a complex and lengthy procedure, and to help simplify the procedure, several variations have been described. They usually consist of a posterior truncal vagotomy and a more selective ablation of the anterior vagal fibers to the gastric fundus and body. Hill and Baker performed posterior truncal vagotomy with anterior HSV (Hill-Baker procedure). Taylor combined posterior truncal vagotomy with anterior lesser curve seromyotomy (Taylor procedure). Randomized studies have confirmed superiority of the Taylor procedure over truncal vagotomy[9] and have documented outcomes equal to those of HSV with a shorter operative time.[10] With the decreased incidence of elective ulcer surgery, these operations are not commonly performed. However, such approaches have proved popular for laparoscopic treatment of ulcer disease (see Laparoscopic Surgery, later).

Supradiaphragmatic Vagotomy This type of vagotomy is performed primarily in patients for whom attempts at complete vagotomy via an abdominal approach have failed; it is thought that further attempts to find the missed trunks in a reoperated abdomen may be difficult and thus a thoracic approach is advised. This operation involves performing a thoracotomy or thoracoscopy, identifying the two large nerve trunks, and then performing truncal vagotomy.

The surgical technique for various vagotomies is covered in Chapter 56.

Drainage Procedures

In Dragstedt's initial series of truncal vagotomy for the treatment of duodenal ulcer disease without drainage, nearly a third of his patients experienced postoperative nausea, vomiting, and distention. Further investigations revealed that truncal vagotomy denervated the antrum and pylorus, which resulted in loss of the antral pump mechanism and failure of the pylorus to reflexively relax and allow emptying into the duodenum. The end result was a functional gastric outlet obstruction. It became apparent that a drainage procedure was necessary to avoid the symptoms of gastric stasis. Accordingly, any patient being treated by truncal, selective, or supradiaphragmatic vagotomy should undergo a drainage procedure to facilitate gastric emptying. Drainage procedures fall into two categories—pyloroplasty and gastrojejunostomy. Pyloroplasty is the preferred approach because it perpetuates the original anatomy, is a simple procedure, and is associated with less bile reflux than gastrojejunostomy. More than 90% of all drainage procedures performed today are variations of pyloroplasty.

Pyloroplasty In children with pyloric hyperplasia, a pyloromyotomy is performed to divide the pylorus muscle and relax the pyloric sphincter while leaving the mucosa intact. Such an approach in adults is often unsuccessful because the duodenal mucosa is adherent to the muscle layer and the intestinal lumen is often entered during the myotomy. Thus, a pyloroplasty is performed. Three different types of pyloroplasty have been described (Fig. 55–4).

Heineke-Mikulicz This procedure was described independently by two surgeons, Heineke and Mikulicz, in 1888, years before it found routine application as the most commonly performed drainage procedure. The technique is popular because it is simple, applicable to many clinical ulcer scenarios, and associated with few complications. The procedure may be performed with single- or double-layer closure, with the latter being more commonly used. The Heineke-Mikulicz pyloroplasty entails making a longitudinal incision through the pylorus (thus interrupting the circular muscle) and reconstructing the duodenotomy in a transverse fashion. It is the most

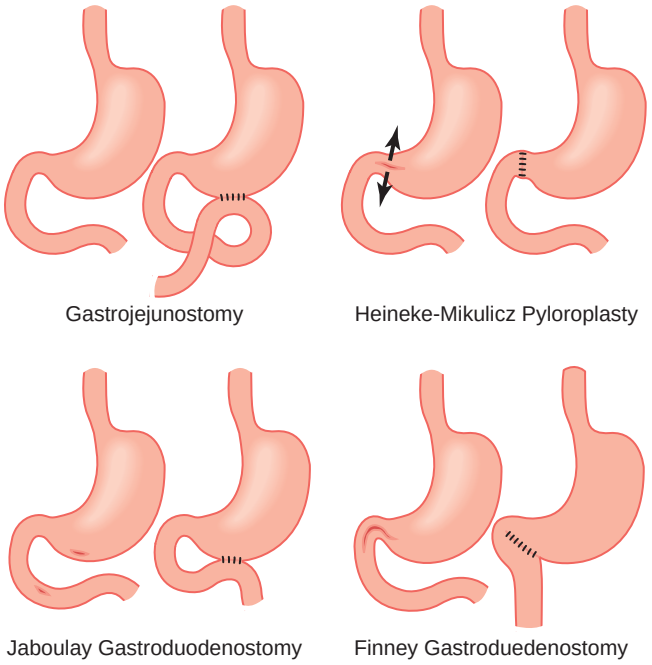

Figure 55–4. Drainage procedures used with truncal or selective vagotomy. (From Matthews JB, Silen W: Operations for peptic ulcer disease and early operative complications. In Sleisenger MH, Fordtran JS [eds]: Gastrointestinal Disease. Philadelphia, WB Saunders, 1993.)

commonly performed drainage procedure, and when conducted carefully and in a technically sound fashion, obstruction is rare. Candidates for this procedure include patients who have a mobile, uninvolved anterior pylorus and those who have no evidence of a severely distorted or edematous pylorus. A variety of postgastrectomy complications may occur after pyloroplasty, including dumping, diarrhea, alkaline reflux gastritis, anemia, and marginal ulceration. Such complications may be seen on a temporary basis in up to 50% of patients after surgery, but they resolve within 6 to 8 months in most, and only 5% to 7% of patients have a persistent, symptomatic postoperative complication such as dumping.

Finney This uncommonly used pyloroplasty is indicated primarily for patients with a J-shaped stomach or extensive scarring and narrowing of a significant portion of the duodenal bulb, thus making Heineke-Mikulicz pyloroplasty untenable. Use of this drainage procedure makes a larger lumen possible and involves a fairly long incision from the stomach, through the pylorus, and well into the duodenal bulb, with closure of the inferior duodenum to the inferior stomach and the superior duodenum to the superior stomach (see Fig. 55–4). It is a much more complicated procedure than the Heineke-Mikulicz technique, involves a great deal more suturing, and has more potential for complications.

Jaboulay Gastroduodenostomy This drainage procedure is the only one of the three described here that does not transect the pyloric muscle. As the name implies, the procedure involves anastomosis of the distal part of the stomach to the first and second portions of the duodenum, thus bypassing the pylorus (see Fig. 55–4). The procedure is rarely used and is indicated primarily for a severely scarred or deformed pylorus or duodenal bulb that would be too treacherous to operate on. Use of the Jaboulay procedure may also be associated with increased bile reflux because the anastomosis is close to the ampulla of Vater.

Gastrojejunostomy This procedure was first performed alone in 1881 and was plagued by two problems: ulcers (because no vagotomy was performed) and vomiting, which was thought to be due to kinking with excessive length of the afferent limb of jejunum. The two problems have been overcome with the addition of vagotomy and construction of a shorter afferent jejunal segment (see Fig. 55–4). Gastrojejunostomy is most commonly indicated as a drainage procedure when there is duodenal obstruction and the duodenal bulb is so scarred, inflamed, and edematous that pyloroplasty would not be safe or would be technically demanding. A vagotomy should always be performed when using gastrojejunostomy as a drainage procedure for the treatment of PUD. Older patients with achlorhydria and atrophic gastritis secrete little acid, and thus a vagotomy may not be necessary, especially in the setting of malignant obstruction. A decision that has to be made when creating a gastrojejunostomy is whether the anastomosis will be antecolic or retrocolic. In most circumstances, it is desirable to perform the anastomosis in a retrocolic manner because there is likely to be less tension and less interference with gastric emptying when the colon becomes distended. The antecolic approach is generally used when there are no well-defined mesenteric windows and the blood supply to the colon might be compromised by attempts to create a window. In addition, many prefer this approach when bypassing a malignant obstruction, which might invade a more posterior retrocolic limb.

The surgical technique for various drainage procedures is detailed in Chapter 56.

Gastric Resection Procedures

Although subtotal gastrectomy was used for the treatment of duodenal ulcer disease in the past, today it is most commonly performed for gastric ulcer and distal gastric malignancies. A more common gastric resection performed for intractable duodenal ulcer is antrectomy (35% distal gastrectomy), combined with truncal or selective vagotomy. The simultaneous effects of vagotomy and antrectomy remove both the cholinergic and the gastrin stimulus to acid secretion. Basal acid secretion is virtually abolished, and stimulated secretion is reduced by nearly 80%. After antrectomy, gastrointestinal continuity must be restored by some form of reconstruction. The remnant is anastomosed either to the duodenum (Billroth I) or, after closing the duodenal stump, to the jejunum distal to the ligament of Treitz (Billroth II)

(Fig. 55–5). Billroth I reconstruction has several theoretical advantages:

1. Restores normal gastrointestinal continuity
2. Leaves specialized duodenal mucosa next to the gastric mucosa
3. Avoids problems with an afferent and efferent limb
4. Allows easier performance of endoscopic retrograde cholangiopancreatography and endoscopic examination of the bowel
5. Is associated with a reduced incidence of gastric cancer in the remnant stomach[11]

Despite the theoretical physiologic advantages, no important functional differences have ever been demonstrated between these reconstructions. Although studies have shown larger fecal fat loss after a Billroth II procedure, this is unlikely to be of any significance. The difference in cancer risk is real, but significant only after a long follow-up period (>15 years). Typically, the choice is based on the degree of scarring of the duodenum and the ease with which the duodenum and gastric remnant can be brought together. Several variations of the Billroth I and Billroth II operations have been described and are summarized in Figures 55–6 and 55–7.

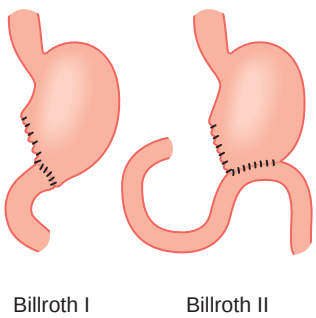

Figure 55–5. Reconstruction techniques after partial gastrectomy: Billroth I gastroduodenostomy and Billroth II gastrojejunostomy. (From Matthews JB, Silen W: Operations for peptic ulcer disease and early operative complications. In Sleisenger MH, Fordtran JS [eds]: Gastrointestinal Disease. Philadelphia, WB Saunders, 1993.)

The Billroth reconstructions can lead to bile reflux, which can result in disabling symptoms. To avoid such complications, some favor a Roux-en-Y reconstruction. Unfortunately, Roux-en-Y reconstruction can be plagued by Roux stasis syndrome. Studies have shown that the Braun variation of Billroth II (see Fig. 55–7) is associated with a lower incidence of bile reflux[12] and therefore has been recommended as the standard reconstruction technique by some authors. Others, however, promote the uncut Roux-en-Y reconstruction (Fig. 55–8), but this technique has not gained widespread use because of reports of staple line dehiscence leading to severe alkaline reflux.

The surgical techniques for the various gastrectomies and reconstructions are described in detail in Chapter 57.

Choice of Operation for Intractable Duodenal Ulcer

As can be seen from the foregoing descriptions, a variety of surgical operations are available for patients with intractable duodenal ulcers. Reliable data on the results of the various procedures for duodenal ulcer were generated by a series of trials during the latter half of the 20th century. Published series in general used different criteria for patient selection and for estimating the incidence of side effects. Table 55–1 summarizes the data on the three most commonly performed procedures: vagotomy and antrectomy, vagotomy and drainage, and HSV. Mortality and early morbidity were highest for the resection procedures and lowest for HSV, which avoids opening the gastrointestinal tract. Recurrence rates were significantly lower for vagotomy with antrectomy. Truncal vagotomy plus pyloroplasty is virtually never indicated as an elective procedure because it has the disadvantages of both a high incidence of postgastrectomy complications and a high ulcer recurrence rate (10% to 15%).

Historically, an important factor when considering the choice of surgery would have been the ulcer recurrence rate. However, with identification of *H. pylori,* it is believed that recurrences are for the most part

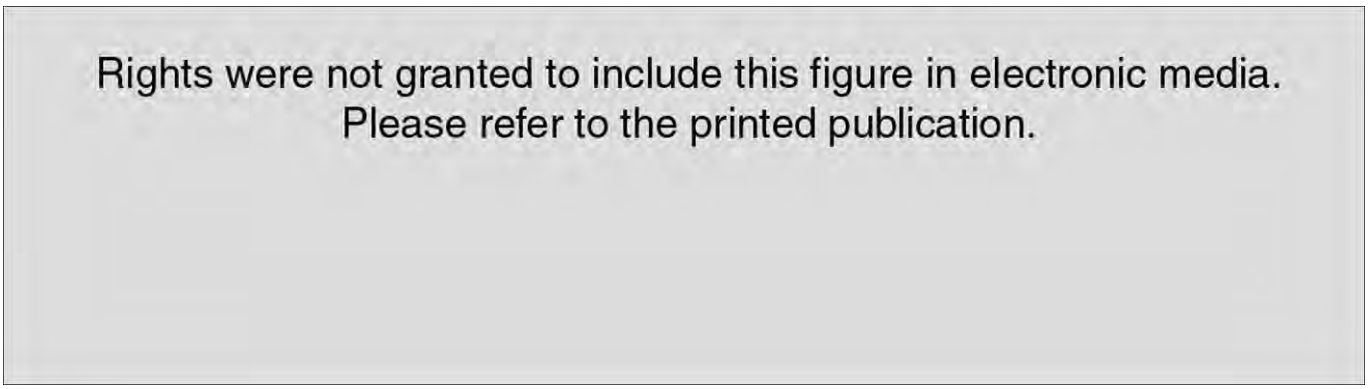

Figure 55–6. Variations of Billroth I reconstructions. (From Siewert JR, Bumm R: Billroth I gastrectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery. Philadelphia, Lippincott, Williams & Wilkins, 2001.)

Figure 55–7. Variations of Billroth II reconstruction. (From Wastell C, Davis PA: Billroth II gastrectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery. Philadelphia, Lippincott, Williams & Wilkins, 2001.)

eliminated, although no data in this setting have yet been generated. Consequently, HSV, which is associated with fewer postoperative sequelae, is the preferred acid-reducing procedure in patients with intractable ulcer symptoms. One trial randomized 248 patients with stable PUD to truncal vagotomy and drainage, selective vagotomy and drainage, or HSV. At 11 to 15 years after surgery, HSV was associated with a reduction in the incidence of severe postvagotomy symptoms such as dumping, diarrhea, and dyspepsia. Interestingly, this study did not show a significant difference in ulcer recurrence rates between the three groups.[13] Although this would more strongly favor HSV, today's experience with this more complex procedure is limited. In a review of the experience of surgical chief residents in the United States, the average number of vagotomies performed by each resident has decreased dramatically during the 1990s.[14] In addition, most patients undergoing operation now are elderly and debilitated, conditions favoring the most expeditious procedure, usually truncal vagotomy and antrectomy.

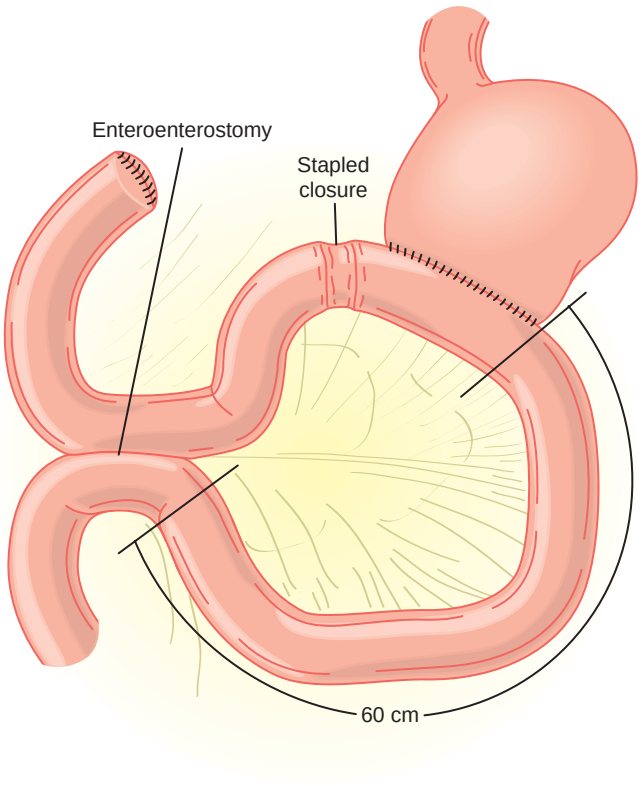

Figure 55–8. "Uncut" Roux-en-Y reconstruction after partial gastrectomy. A jejunoduodenostomy with a 60-cm efferent limb is constructed. The afferent limb is occluded with a staple line. (From van Stiegmann G, Goff, JS: An alternative to Roux-en-Y for treatment of bile reflux gastritis. Surg Gynecol Obstet [now J Am Coll Surg] 166:69, 1988.)

Table 55–1 Ulcer Recurrence Rates for the Three Common Acid-Reducing Procedures

Surgical Procedure	Ulcer Recurrence Rate	Risk for Side Effects
Truncal vagotomy and drainage	15%	Highest
Truncal vagotomy and antrectomy	2%	High
Highly selective vagotomy	15%	Low

Figure 55–9 summarizes the recommended surgical approach to a patient with a chronic duodenal ulcer.

Recurrent Peptic Ulcer Disease

Supradiaphragmatic vagotomy is used almost exclusively for the treatment of ulcer recurrence after previous acid-reducing surgery that included vagotomy. The most common cause of ulcer recurrence after an acid-reducing procedure is a missed vagus. If attempts to find the missed nerve are unsuccessful through the densely scarred upper abdomen, thoracic truncal vagotomy may be used successfully. The procedure can now be performed with minimally invasive techniques that include the use of a thoracoscope.

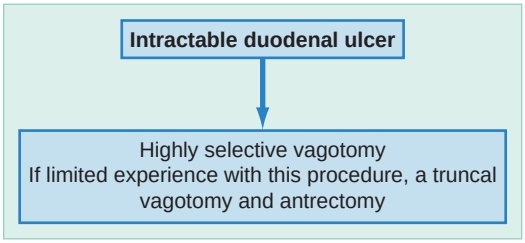

Figure 55–9. Treatment algorithm for intractable duodenal ulcer.

Laparoscopic Surgery

An increasing number of reports indicate the feasibility of laparoscopic approaches to operations for duodenal ulcer disease. Although most open procedures have been attempted laparoscopically, including the more difficult HSV, the Taylor procedure (anterior seromyotomy with posterior truncal vagotomy) seems to be the simplest option. The Taylor procedure was reported in 1982 as an open procedure. Although the open approach is not widely performed, the technique is very suitable for a laparoscopic approach. This procedure begins with a posterior truncal vagotomy followed by a seromyotomy that should start approximately 6 cm from the pylorus. The circular muscle is incised 1.5 cm from the lesser curve and the muscle fibers divided with a hook coagulator. The dissection is continued caudally as far as the gastroesophageal junction. All the circular muscle fibers along the length of the myotomy are divided, but it is not necessary to divide the deeper thin layer of the oblique muscle. Air is injected through a nasogastric tube to ensure that no leaks are present. The seromyotomy is then closed with overlapping running suture. The serosal myotomy can be performed as a stapled anterior linear gastrotomy, which helps expedite the procedure[15] (Fig. 55–10). Other groups have used the Hill-Baker procedure with good results.[16]

Elective Surgery for Intractable Gastric Ulcer Disease

Although both gastric and duodenal ulcers are peptic lesions, fundamental differences between these entities affect surgical strategy. The most important is that a gastric ulcer may harbor malignancy and must therefore be excised or generous biopsy specimens taken. Acid hypersecretion, which is important in pathogenesis of duodenal ulcers, does not have a role in the pathogenesis of many gastric ulcers. A classification system

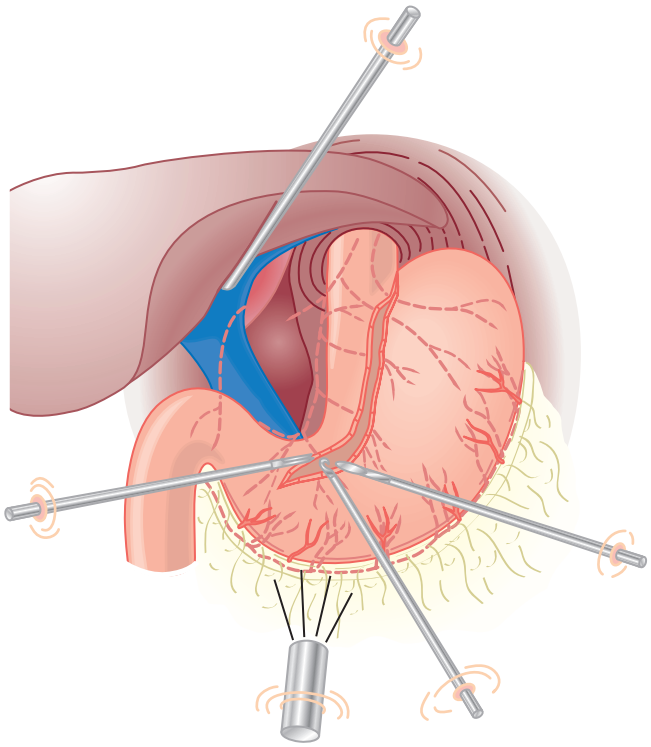

Figure 55–10. Laparoscopic anterior seromyotomy as part of the Taylor procedure. (From Dubois F: New surgical strategy for gastroduodenal ulcer: Laparoscopic approach. World J Surg 24:270, 2000.)

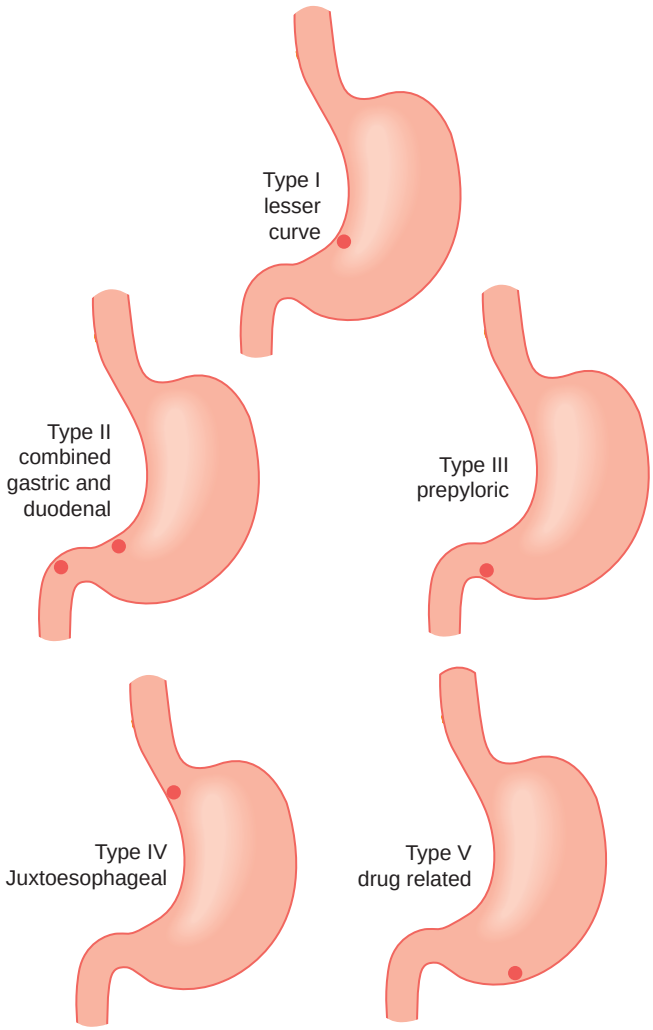

Figure 55–11. Classification of gastric ulcer based on anatomic location. (From Matthews JB, Silen W: Operations for peptic ulcer disease and early operative complications. In Sleisenger MH, Fordtran JS [eds]: Gastrointestinal Disease. Philadelphia, WB Saunders, 1993.)

Table 55–2 Modified Johnson Classification of Gastric Ulcers

Type	Location	Acid Secretion
I	Lesser curvature	Low
II	Body of the stomach and duodenum	High
III	Prepyloric (within 2-3 cm of the pylorus)	High
IV	High on the lesser curve, near the gastroesophageal junction	Low
V	Anywhere, induced by medication	Low

developed by Johnson that is based on anatomic location and acid secretory potential provides a useful basis for considering operative treatment of gastric ulcer (Table 55–2) (Fig. 55–11).

Type I Gastric Ulcer

Type I ulcers are the most common form. They occur along the lesser curvature at the junction of fundic and antral mucosa and develop in the setting of acid hyposecretion. Distal gastrectomy with Billroth I or II reconstruction is recommended for most patients because this approach removes the ulcer and the diseased antrum. Partial gastrectomy also eliminates the risk of missing a malignancy, which can occur with biopsy, and reduces the acid secretory potential. Earlier recommendations of performing a biopsy of the ulcer combined with vagotomy and drainage have now become outdated because of high ulcer recurrence rates.[17] Low recurrence rates (5%) and excellent symptomatic relief are usually achieved with a distal gastrectomy alone. Experience from the Cleveland Clinic has shown that the addition of truncal vagotomy to gastric resection offers no additional benefit to the patient.[18] Reported mortality rates for elective surgery have generally been less than 5%; however, because formal gastric resection can add to the morbidity and mortality of the operation, some have tried less disruptive surgical procedures for type I gastric ulcers, including ulcer excision combined with HSV. The value

of HSV in treating gastric ulcer may derive from its ability to decrease acid secretion while maintaining adequate gastric emptying and minimizing postoperative duodenogastric reflux. The procedure is performed with the addition of a gastrotomy to excise or biopsy the ulcer bed. In one series of 48 patients, HSV combined with mucosal ulcerectomy produced an excellent clinical outcome in most patients with a recurrence rate of 6.5% and few side effects.[19] A Swedish randomized study in which gastrectomy with Billroth I reconstruction was compared with ulcer excision and HSV has shown equal outcomes in terms of complications and ulcer recurrence.[20] Ulcer size and location may make this operative approach untenable for some patients in whom ulcer-induced inflammation, edema, or scarring may obscure accurate dissection.

Type II Gastric Ulcer

Type II gastric ulcers occur synchronously with scarring or ulceration in the duodenum or pyloric channel. They tend to be large, deep ulcers with poorly defined margins. They frequently occur in younger men and are associated with increased acid secretion. Preoperative endoscopic examination of such ulcers must include biopsy of the lesion to rule out an underlying malignancy. Treatment is similar to that for duodenal ulcer, with vagotomy plus antrectomy or HSV being the preferred approach.

Type III Gastric Ulcer

Type III ulcers are prepyloric, although no precise anatomic definition exists. They occur in the setting of increased acid secretion and are approached in a manner similar to that for duodenal ulcer and type II gastric ulcer. Curiously, HSV (as well as medical therapy with H_2 receptor antagonists) has been associated with poor results in type III gastric ulcer, with recurrence rates ranging from 16% to 44% in various series.[6] This finding plus the observation that these lesions may harbor gastric malignancy makes vagotomy and antrectomy the most prudent approach. Early consideration of surgical referral is advisable for resistant ulcers or those causing obstructive symptoms.

Type IV Gastric Ulcer

Type IV gastric ulcer is distinguished by its anatomic location high along the lesser curvature, close to the gastroesophageal junction. Antral mucosa may extend to within 1 to 2 cm of the gastroesophageal junction; thus, type IV ulcers may simply represent a subset of type I gastric ulcer. Type IV ulcers are associated with gastric hyposecretion and come to attention early as a result of dysphagia and reflux. Large ulcer size, the degree of surrounding inflammation, and proximity to the gastroesophageal junction render operative management difficult and potentially dangerous. If the integrity of the distal end of the esophagus can be ensured, subtotal gastric resection (including the ulcer bed) is considered optimal. Lesions close to the cardia, however, pose a particular challenge, and to help avoid total gastrectomy and an esophageal anastomosis, other surgical approaches have been described. Such alternatives include the Schoemaker procedure (a modification of Billroth I resection with tube-shaped resection of high gastric ulcers and anastomosis of the duodenum to the greater curvature side of the stomach; see Fig. 55–6), Pauchet's procedure[21] (a modification of the Schoemaker procedure that involves a lower gastrectomy and freehand resection of the ulcer with scissors), or nonresective procedures in which the ulcer itself is not excised. The latter includes procedures such as the Kelly-Madlener procedure (a distal gastrectomy is performed but the ulcer is left in place, after biopsy, to avoid compromise of the gastroesophageal junction) and vagotomy plus pyloroplasty, which has a high ulcer recurrence rate. The risk for malignant transformation or missed malignancy (despite biopsies) is small but real, and thus nonresective procedures should not be used routinely.

Although there is no consensus in the literature, some have suggested that for ulcers 5 cm below the cardia, Pauchet's procedure should be used, whereas for lesions within 2 cm of the cardia, the Kelly-Madlener procedure (nonresective) or the Csendes procedure should be attempted[22] (Fig. 55–12). The Csendes procedure involves a near-total gastrectomy and an esophagogastrojejunostomy for reconstruction. The principle of this operation is to remove the high gastric ulcer such that the circumference of the esophageal mucosa remains intact. The reconstruction involves a Roux-en-Y loop 30 cm distal to the ligament of Treitz. The end of the loop is closed and a terminolateral esophagogastrojejunostomy is created. The reconstruction is completed by forming a jejunojejunostomy 40 cm distal to the gastric anastomosis.

Type V Gastric Ulcer

These lesions can occur anywhere in the stomach and are induced by the use of medications such as NSAIDs. A definitive antisecretary operation is recommended for these ulcers, especially if treatment with the offending medications cannot be stopped.

Figure 55–13 summarizes the recommended approach to chronic intractable gastric ulcers. The surgical technique for various gastrectomies and reconstructions is described in detail in Chapter 57.

EMERGENCY SURGERY FOR COMPLICATED PEPTIC ULCER DISEASE

Such operations are most often performed in the elderly and the sick. Patients may have bleeding, perforation, or obstruction. The objectives of surgery in these cases follow:

1. Deal with the complication that necessitated surgical intervention.
2. Reduce the risk for future ulcer recurrence.
3. Perform a safe, quick, and effective operation.

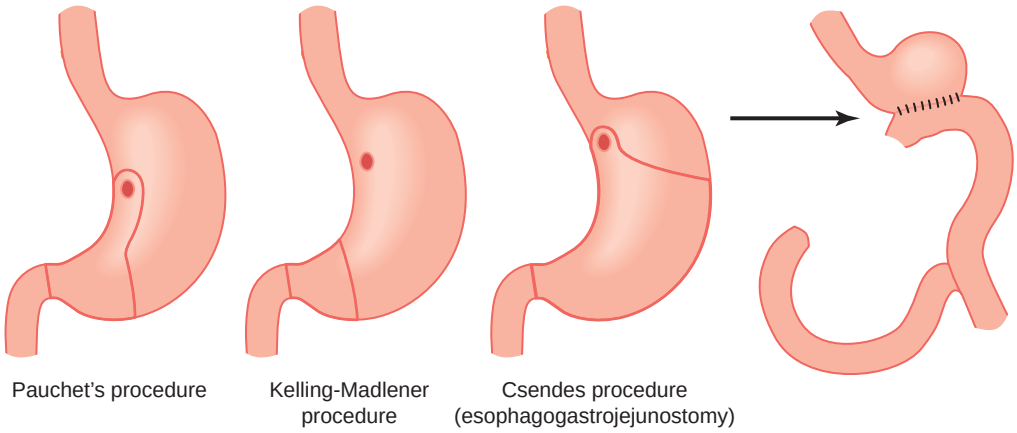

Figure 55–12. Operations for a type IV gastric ulcer. (Modified from Seymour NE: Operations for peptic ulcer and their complications. In Feldman M, Scharschmidt BF, Sleisenger MH [eds]: Gastrointestinal Disease. Philadelphia, WB Saunders, 1998.)

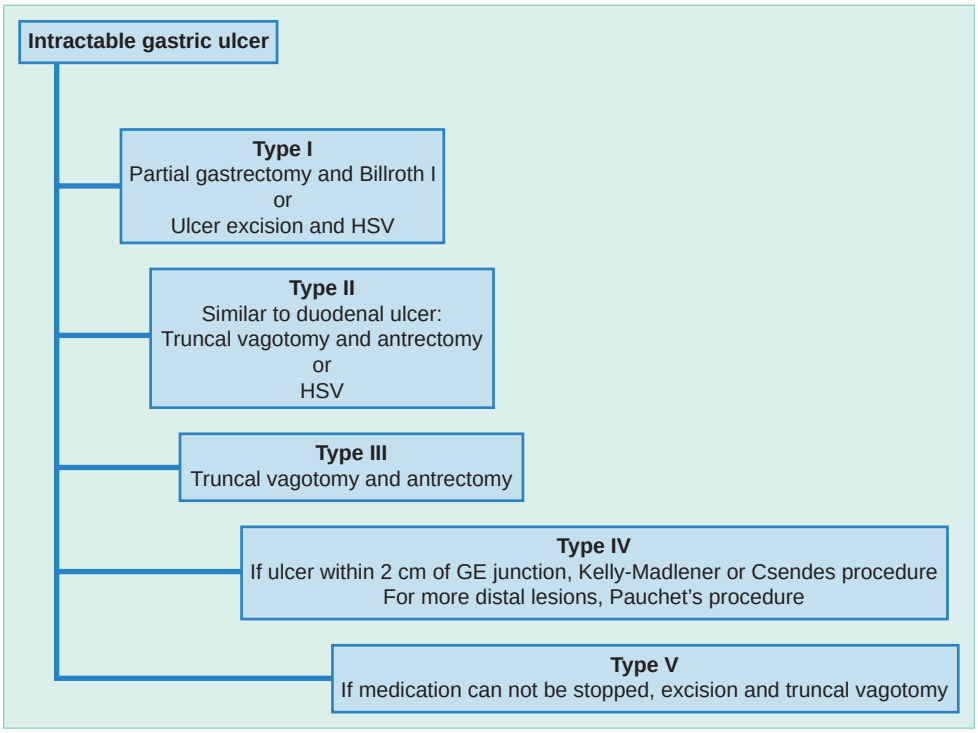

Figure 55–13. Algorithm for the surgical treatment of intractable gastric ulcers. GE, gastroesophageal; HSV, highly selective vagotomy.

4. Minimize long-term effects on the gastrointestinal tract
5. Establish the *H. pylori* status of the patient

Usually, the biggest intraoperative dilemma is whether to proceed with a definitive antiulcer operation (to reduce the risk for recurrence), in addition to addressing the specific ulcer complication. This issue has received considerable attention over the past several decades but remains unsettled. Shifting ulcer epidemiology, recognition of the role of *H. pylori,* and improvements in medical therapy have confused this issue considerably, and the decision must be individualized. Omission of an acid-reducing ulcer procedure carries a risk for recurrent ulcer symptoms and complications; this risk is variable in the literature, but not negligible. Recent evidence would suggest that this risk may be considerably reduced by treatment of *H. pylori* postoperatively, but obviously only if the patient is *H. pylori* positive. Unfortunately, there is no reliable, rapid test for *H. pylori* status at the time of surgery to help guide this decision making. A definitive procedure is always more appropriate in the setting of NSAIDs, especially if the patient is unlikely to be able to stop the treatment because of an underlying medical condition. On the other hand, inclusion of an acid-reducing ulcer procedure may result in

serious gastrointestinal sequelae in patients who may not have required the intervention. Definitive surgery is generally avoided during emergency procedures in patients with major underlying medical illness or intraoperative hemodynamic instability.

Bleeding

Most patients with a bleeding upper gastrointestinal lesion undergo an endoscopic examination of the stomach and the first and second portions of the duodenum. This procedure enables identification of the site of bleeding and allows therapeutic attempts at stopping the bleeding. An estimated 10% to 20% of patients admitted with bleeding peptic ulcers, however, fail medical therapy and require emergency surgical intervention. Despite endoscopic advances, the mortality rate has remained stable at 5% to 10%. In fact, recent epidemiologic data suggest that the incidence and mortality rate of bleeding duodenal ulcers may be increasing in older women.[3] The ability to predict the risk for rebleeding is important to the endoscopist and the surgeon because it permits closer monitoring of high-risk patients and early involvement of the surgical team in their management. High recurrent bleeding rates have been associated with a spurting vessel, a visible arterial vessel in the ulcer bed, adherent clot, or a large ulcer bed. The Forrest classification was developed in an attempt to assess the risk for rebleeding based on endoscopic findings (Table 55–3).

In those who have recurrent bleeding, it has been shown that a second endoscopic attempt at control of bleeding will fail in 25% of patients, who will then require emergency surgery. This has stimulated some debate regarding the timing of surgery for a bleeding peptic ulcer and the role of a second attempt at endoscopic therapy. Randomized prospective studies have, however, shown no increase in mortality rate in patients who undergo a second therapeutic endoscopic procedure versus surgery after the first failed endoscopy. Therefore, most clinicians would encourage a second attempt at endoscopic control.[23]

Current indications for surgery for peptic ulcer hemorrhage include the following:

1. Hemodynamic instability despite vigorous resuscitation (transfusion of >3 units)
2. Failure of endoscopic techniques to arrest hemorrhage
3. Recurrent hemorrhage after initial stabilization (with up to two attempts at obtaining endoscopic hemostasis)
4. Shock associated with recurrent hemorrhage
5. Continued slow bleeding with a transfusion requirement exceeding 3 U/day

Secondary or relative indications include a rare blood type or difficult crossmatch, refusal of transfusion, shock on initial evaluation, advanced age, severe comorbid disease, and a bleeding chronic gastric ulcer. These criteria also apply to elderly patients, in whom prolonged resuscitation, large-volume transfusion, and periods of hypotension are poorly tolerated.

Table 55–3 The Forrest Classification for Endoscopic Findings and Rebleeding Risk

Classification	Description	Rebleeding Risk
Grade Ia	Active, pulsatile bleeding	High
Grade Ib	Oozing, nonpulsatile bleeding	Low/ Intermediate
Grade IIa	Nonbleeding visible vessel	High
Grade IIb	Adherent clot	Low/ Intermediate
Grade IIc	Black dot	Low
Grade III	No signs of recent bleeding	Low

Surgery for Bleeding Duodenal Ulcer

The first priority during emergency surgery for a bleeding duodenal ulcer is control of the bleeding site. If esophagogastroduodenoscopy has failed to precisely identify the source of hemorrhage, pyloroduodenotomy may be necessary to inspect the duodenal bulb and gastric antrum. The gastroduodenal artery is the usual source of bleeding, and it should be controlled by placement of suture ligatures. Once the bleeding has been addressed, a definitive acid-reducing operation may be performed. With the identification of *H. pylori,* the utility of vagotomy has been questioned. The data, however, suggest that even in the era of *H. pylori* and our ability to eradicate it, truncal vagotomy should be performed in those with a bleeding duodenal ulcer. There are several reasons for this recommendation:

1. Only 40% to 70% of patients with a bleeding duodenal ulcers are positive for *H. pylori.*
2. *H. pylori* testing in the setting of acute bleeding is less reliable, with the CLO (*Campylobacter*-like organism) test having a false-negative rate of 18% versus 1% in those not actively bleeding.[24]
3. If an acid-reducing procedure is not performed, up to 50% of patients are at risk for recurrent bleeding.

Our inability to determine the *H. pylori* status in the case of acute bleeding and a lower prevalence of *H. pylori* infection for patients with bleeding reinforce the need to perform an acid-reducing operation at the time of initial surgery. In contrast to other situations, the argument for performing a less aggressive operation in the face of massive bleeding exposes the patient to a high rebleeding risk after surgery.

Because it is simple to open the pylorus in longitudinal fashion, truncal vagotomy with pyloroplasty is the

most frequently used operation for a bleeding duodenal ulcer.

The procedure starts with a midline laparotomy to enter the peritoneal cavity. A Kocher maneuver is then performed to mobilize the duodenum. This will give better exposure and relieves any tension on the subsequent suture line. Careful palpation reveals the firm, rubbery pylorus at the junction between the stomach and duodenum. The pyloric vein of Mayo is virtually always present on the anterior surface of the inferior pylorus. Two 3-0 silk traction sutures are placed astride the anterior pylorus and parallel to each other. While lifting up on the traction sutures, a longitudinal incision is made through the pyloric muscles and extended 2 to 3 cm proximally into stomach and distally into duodenum. The duodenal mucosa is inspected for any evidence of active bleeding, ulceration, or induration. If active bleeding is encountered, it is controlled by digital pressure, which in addition to controlling the bleeding, gives time for fluid resuscitation of the patient. The bleeding vessel is then ligated. This vessel is often the gastroduodenal artery, which at the level of the posterior duodenal wall has a three-vessel junction. It is important to suture-ligate the gastroduodenal artery superiorly and inferiorly, followed by ligation of the medial transverse pancreatic branches with a U-stitch (Fig. 55–14). Care should be taken to avoid injury to the common bile duct during suture placement. If no bleeding is encountered on opening the lumen, the mucosa should be carefully inspected for an ulcer. If identified, the ulcer base should be cleaned to help identify a visible vessel, which if seen should be ligated. In situations in which no active bleeding is seen, it is important to carry out a careful inspection of the mucosa to look for other potential bleeding ulcers, even if a nonbleeding ulcer is identified. This inspection can be done by manual palpation of the lumen with a finger. In cases in which preoperative endoscopy has failed to identify a specific location, it is reasonable to start with a duodenotomy, which can be extended proximally or distally to allow further exploration. On occasion, a second gastrostomy near the esophageal junction is needed to inspect the proximal part of the stomach.

After gaining control of the bleeding, a pyloroplasty is performed, most often a Heineke-Mikulicz pyloroplasty. The traction sutures initially placed are used as superior and inferior edges of the closure, with the longitudinal opening converted to a horizontal one. If the duodenum is soft, pliable, and minimally deformed, running closure of the inside layer is performed with absorbable suture in an inverting fashion. Either a baseball stitch or whip stitch (inside-out, outside-in) works well. It is imperative that tension be kept on the suture while closing this layer and that adequate purchase of the duodenal side be obtained. An outside Lembert layer of 4-0 silk suture in interrupted fashion completes the procedure. Care is needed to not turn in too much serosa in the Lembert layer because an obstruction could result; however, such obstruction rarely occurs. Some prefer single-layer closure because of the potential risk for obstruction associated with a two-layer closure. The single-layer closure (Weinberg variation) could be done as a single layer of inverting 3-0 silk suture (Gambee stitch) (Fig. 55–15). The procedure is then completed by performing truncal vagotomy as described in Chapter 56.

Figure 55–14. Technique of suture control of a bleeding duodenal ulcer. After making a longitudinal pyloric incision and identifying the bleeding vessel, figure-of-eight sutures are placed at the cephalic and caudal aspects of the ulcer deep enough to occlude the gastroduodenal artery. An additional U-stitch is placed to control small transverse pancreatic branches from the main vessel. (From Debas HT, Mulvihill SJ: Complications of peptic ulcer. In Zinner MJ, Schwartz SJ, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lang, 1997.)

In experienced hands, HSV may be the best therapy for a bleeding duodenal ulcer. Several reports have shown that even in the setting of acute bleeding, HSV can be performed safely with good long-term results.[25,26] However, because endoscopic hemostatic techniques have reduced the total number of surgical referrals and because many patients who do require surgery are bleeding so massively that they are unstable or have refractory hemorrhage after multiple attempts at endoscopic control, undertaking a procedure that takes longer to perform is not recommended unless the surgeon has significant experience with the operation. As a result, more traditional expedient operations with proven efficacy, such as truncal vagotomy with pyloroplasty, are recommended over HSV. A recent survey of surgeons in the United Kingdom, however, has shown that although they were more likely to perform a vagotomy for a bleeding ulcer than for a perforated duodenal ulcer, 40% of those surveyed would refrain from performing a vagotomy in the acute setting.[27] This highlights the issue of shrinking clinical experience with vagotomy and the reluctance of

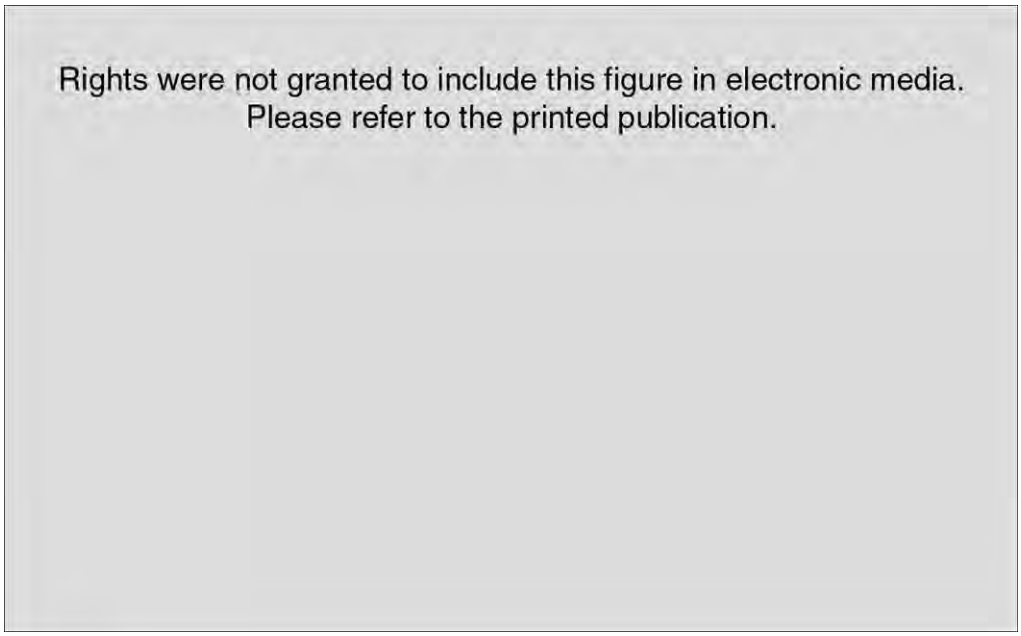

Figure 55–15. Heineke-Mikulicz closure with a single-layer technique using the Gambee stitch. (From Schirmer BD, Kouretas PC: Bleeding duodenal ulcer. In Baker RJ, Fischer JE [eds]: Mastery of Surgery. Philadelphia, Lippincott, Williams & Wilkins, 2001.)

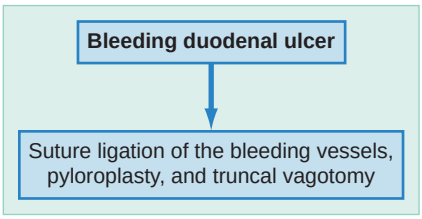

Figure 55–16. Recommended surgical procedures for bleeding duodenal ulcer.

many to perform it in an acute setting. Figure 55–16 summarizes the recommended surgical therapy for a bleeding duodenal ulcer.

Bleeding Gastric Ulcer

For bleeding gastric ulcers, distal gastrectomy with Billroth I or II reconstruction is preferred. This approach permits excision and histologic evaluation of the ulcer to rule out malignancy. In high-risk patients or those with ulcers that are high, excision of the ulcer and vagotomy plus pyloroplasty may be considered.

Perforation

Smoking and NSAIDs are important etiologic factors for ulcer perforation, and recent epidemiologic studies have documented an increasing rate of perforation, particularly in older women. The outcome of patients with a perforated ulcer depends on the following:

1. Delay from initial evaluation to treatment: recent data suggest increasing delay until surgical treatment, in part because of more extensive diagnostic work-up.
2. Site of perforation: gastric perforations are associated with a poorer prognosis.
3. Patient's age: elderly patients, who often have associated comorbid conditions, have a worse outcome.
4. Presence of hypotension at initial evaluation (systolic blood pressure <100 mm Hg).

Recent studies have shown that in carefully selected groups of patients, perforation can be treated conservatively with nasogastric decompression and antibiotics. Such treatment should, however, be used only if a water-soluble contrast study has confirmed that the ulcer is sealed with no extravasation of contrast into the peritoneal cavity. These patients should be monitored closely with regular physical examination and, if their abdominal examination or laboratory findings indicate progressive sepsis, undergo surgery. This approach is generally used for individuals who have had a perforated ulcer for 24 hours or longer, and are stable. It should be noted that although this approach is often used for elderly patients with comorbid conditions, studies have shown that the risk for failure of conservative treatment is highest in the elderly, and thus close observation of such patients is recommended. Because perforated gastric ulcers have a higher rate of reperforation and complications, conservative therapy in situations in which the source of the perforation is known to be gastric is not recommended.

Perforated Duodenal Ulcer

An acute perforation is estimated to occur in 2% to 10% of patients with a duodenal ulcer. Surgeons have traditionally performed either simple patch closure or truncal vagotomy with pyloroplasty (incorporating the perforation). The natural history of those treated by simple repair has been documented in a paper that followed the course of 122 such patients over a 25-year period. In total, 48% of the original study population required additional ulcer treatment in the form of prolonged medical therapy or further surgery.[28] Therefore, truncal vagotomy with pyloroplasty had been recommended as the minimal therapy required. A recent study reported the outcomes of 159 patients who were monitored more than 10 years after vagotomy and pyloroplasty for perforated duodenal ulcer.[29] Perioperative mortality was 5.5%, ulcers recurred in 8.8%, and postoperative digestive sequelae, notably diarrhea and dumping, developed in 16%. Nevertheless, the overall results were good to excellent in almost 90% of cases. HSV with patch closure does at least as well. Boey et al., in a prospective study of 101 patients randomized to simple closure, truncal vagotomy and pyloroplasty, or HSV, reported 39-month recurrence rates of 63.3%, 11.8%, and 3.8%, respectively. Operative time was significantly longer for HSV, but no deaths occurred in any of the groups. The study, however, excluded the elderly (>70 years) and patients with preoperative shock, which may account for the low mortality rates.[30] Another randomized study by the same group in which HSV was compared with simple closure documented recurrence rates of 10.6% and 36.6% (half requiring surgical intervention) at 3 years. Again, there was a sample bias in the group because unstable and elderly patients were excluded.[31] Another report of 107 patients with perforated pyloroduodenal ulcers documented minimal morbidity, low mortality, and excellent patient satisfaction for omental patching and HSV, with a recurrence rate of 3.7% for duodenal ulcer; the recurrence rate for pyloric and prepyloric ulcer was substantially higher at 16%.[32] Chronic pyloroduodenal scarring is considered a relative contraindication to the use of HSV in this setting because it may be associated with delayed gastric emptying after surgery.

With the identification of *H. pylori,* the ideal surgical approach has once again been questioned. A recent study has shown that 81% of patients with a perforated duodenal ulcer are *H. pylori* positive. In this study all patients underwent simple closure of the perforation. The *H. pylori*–positive patients were then randomized postoperatively to a 4-week course of PPIs alone versus *H. pylori* eradication therapy. The ulcer recurrence rate at 1 year was 5% in the *H. pylori*–eradicated group versus 38% in the PPI-treated group, as determined by repeat endoscopy. Notably, the 5% recurrence rate is equivalent to the recurrence rate in those who undergo a definitive antiulcer procedure.[33] These data have provided good evidence for the practice of simple closure of perforated duodenal ulcers in the acute setting. However, at the time of surgery, the *H. pylori* status of the patient is often unknown, and in the absence of a reliable intraoperative test, the merits of a definitive antisecretary procedure have to be considered. This may be particularly important in patients with a previous history of peptic ulcer surgery, *H. pylori* eradication, or chronic ulcer symptoms despite the use of PPIs or in those taking NSAIDs in whom this therapy cannot be discontinued. In general, simple patch closure is appropriate for patients with the following:

1. Acute NSAID-related perforation (provided that use of the drugs can be discontinued postoperatively) and for patients who have never been treated for PUD and can be treated with PPIs and *H. pylori* eradication
2. Perforation in the setting of ongoing shock, delayed evaluation, considerable comorbid disease, or marked peritoneal contamination

Figure 55–17 summarizes the recommended approach to a perforated duodenal ulcer.

To perform the patch procedure, a midline laparotomy is carried out and the intra-abdominal organs inspected. The presence of bilious fluid in the peritoneal cavity suggests an upper gastrointestinal perforation. Once a duodenal perforation has been confirmed, pads are placed around the perforation to contain any further spillage, and 3-0 silk or PDS sutures are placed across the perforation. Usually, three to four sutures are needed. It is important to take bites of appropriate width (0.5 to 1 cm) to prevent the sutures from cutting through the inflamed duodenal tissue. To ensure bites that are full thickness, it is recommended that one pass the needle through the wall of the duodenum on one side of the ulcer, retrieve the needle through the perforation, and then pass it through the wall on the other side of the perforation (Fig. 55–18). These sutures should not be tied to approximate the ulcer; rather, the adjacent omentum should be mobilized on an intact vascular pedicle and brought up. Sutures are tied over this omental pedicle to secure the omentum in place. These sutures should not be tied too tightly to avoid strangulation of the omental patch (Fig. 55–19). Sewing the ulcer closed before placing the omental pedicle over the perforation is discouraged because it reduces surface contact of the omentum with the duodenal mucosa (Fig. 55–20).

After closure of the ulcer, irrigation of the peritoneal cavity with warm saline solution should be carried out. There is no evidence to suggest that the use of antibiotic or iodine solutions helps in any way. The abdomen is then closed in standard fashion. Drains are not needed and their use is discouraged.

There is a growing body of literature on laparoscopic suture patch repair, as well as laparoscopic sutureless techniques with fibrin glue to repair a perforated ulcer. These studies have demonstrated the feasibility of minimally invasive approaches. The first randomized study on this issue showed that laparoscopic suture and sutureless repair of perforated ulcers is equal to open repair of perforated ulcers in terms of hospital stay and time to resume normal diet, with less postoperative analgesia being required.[34] A subsequent randomized trial has documented a shorter operative time, shorter hospital stay, and fewer pulmonary complications with the laparoscopic approach.[35] Conversion rates for such laparoscopic procedures have been between 15% and 20%.

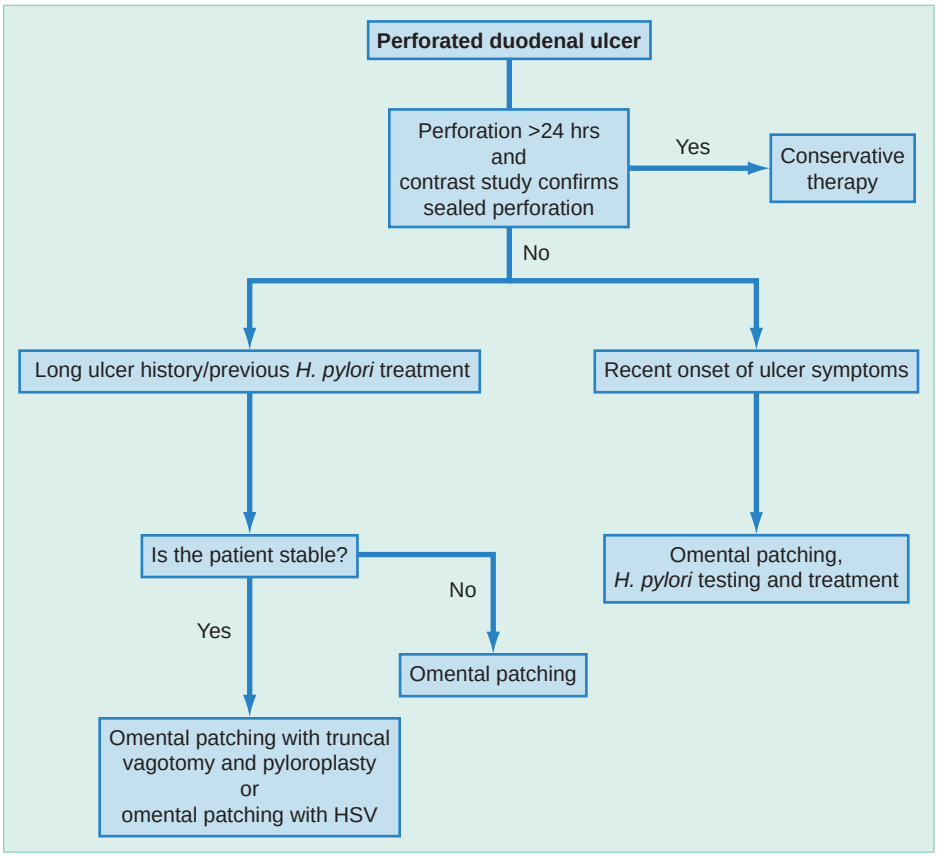

Figure 55–17. Treatment algorithm for surgical treatment of perforated duodenal ulcers. HSV, highly selective vagotomy.

Perforated Gastric Ulcer

A perforated gastric ulcer is associated with greater overall mortality that may range from 10% to 40% and increases significantly with age (>65 years).[36] There has been debate in cases of perforated type I and IV gastric ulcers over whether to perform partial gastrectomy or proceed with simple patching of the perforation. Partial gastrectomy is the preferred approach unless the patient is at unacceptably high risk because of advanced age, comorbid disease, intraoperative instability, or severe peritoneal soilage.[37] Even in this high-risk group who may initially be in shock, there is increasing evidence that definitive surgery can be tolerated as well as the simpler and quicker patching technique.[38,39] It is therefore recommended that a patient with a perforated type I gastric ulcer undergoes partial gastrectomy unless the patient is unstable with significant comorbid conditions. Biopsy and patch closure may be an appropriate approach for the treatment of a high type IV ulcer, where more extensive resection may lead to total gastrectomy in a critically ill patient. If closure techniques are to be used, patch closure is favored over simple suturing and closure of the ulcer, which has a reported mortality of greater than 60%.[40] Because the pathophysiology of such ulcers does not involve acid hypersecretion, an antacid procedure is not required. It is important to perform an adequate four-quadrant biopsy of ulcers that are not excised.

For type II ulcers the treatment algorithm should be similar to that for perforated duodenal ulcers because the pathophysiology of the disease is very similar. This means that the ulcers should be patched, the *H. pylori* status of the patient determined by intraoperative biopsy, and the patient treated appropriately. For such ulcers, it is important to obtain an intraoperative biopsy to rule out malignancy, which can be associated with these gastric ulcers. Similar to a perforated duodenal ulcer, an acid-reducing procedure is not required unless the patient has a history of recurrent ulcer disease and has been previously treated for *H. pylori*. In circumstances in which a definitive antiulcer procedure is deemed appropriate because of the chronicity of symptoms and lack of response to PPIs, HSV or truncal vagotomy and antrectomy should be considered.

Type III ulcers are thought to have a pathogenesis similar to that of duodenal ulcers; however, their treatment in the event of acute perforation deserves particular attention. Patch repair of such prepyloric ulcers is associated with a high incidence of gastric outlet obstruction,[40] and HSV has been shown to be associated with a high recurrence rate for these ulcers. Therefore, antrectomy and vagotomy may be the best surgical approach.

Figure 55–21 summarizes the proposed surgical approaches to a perforated gastric ulcer.

Gastric Outlet Obstruction

This problem accounts for 5% to 8% of ulcer-related complications and results in an estimated 2000

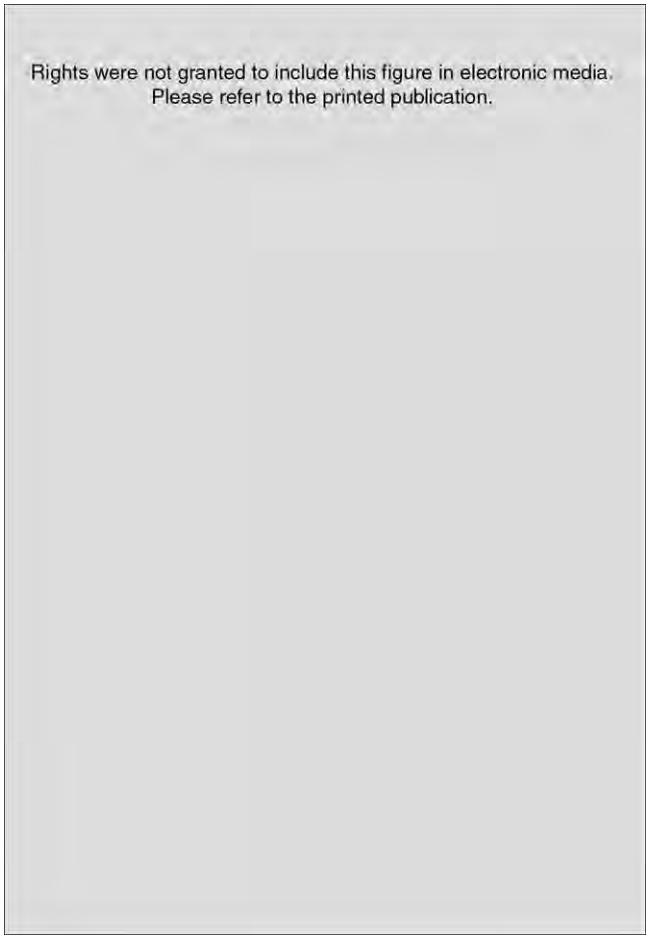

Figure 55–18. **A** to **C,** Perforated duodenal ulcers. Repair is begun by placing sutures through the full thickness of the bowel wall in two steps. This allows the use of smaller tapered needles and reduces the risk for inadvertent penetration of the posterior duodenal wall. (From Baker RJ: Perforated duodenal ulcer. In Baker RJ, Fischer JE [eds]: Mastery of Surgery. Philadelphia, Lippincott, Williams & Wilkins, 2001.)

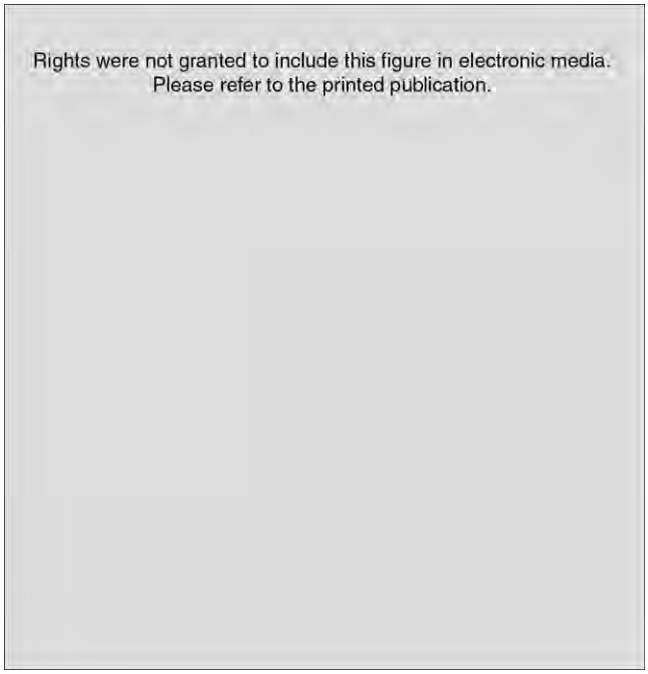

Figure 55–19. The omentum, which has been mobilized on a vascular pedicle, is secured in place with sutures tied loosely enough to prevent tissue strangulation. This technique allows effective closure of the perforation without narrowing the duodenal lumen. (From Baker RJ: Perforated duodenal ulcer. In Baker RJ, Fischer JE [eds]: Mastery of Surgery. Philadelphia, Lippincott, Williams & Wilkins, 2001.)

operations per year in the United States.[41] Patients with gastric outlet (pyloric) obstruction as a result of a duodenal ulcer typically have symptoms of gastric retention, including early satiety, bloating, indigestion, anorexia, nausea, vomiting, epigastric pain, and weight loss. They are frequently malnourished and dehydrated and have a metabolic alkalosis, factors that increase operative risk. Nevertheless, surgery is generally indicated if the obstruction fails to resolve despite 48 to 72 hours of adequate intravenous fluid replenishment, antisecretory therapy, and nasogastric tube decompression. In less acute settings, where the obstruction is not complete, balloon dilatation of the scarred pylorus has been attempted, with an unacceptably high recurrence rate over the short term and a morbidity rate of 0% to 6%. The most serious complication is perforation. If balloon dilatation is being attempted, it is important to rule out

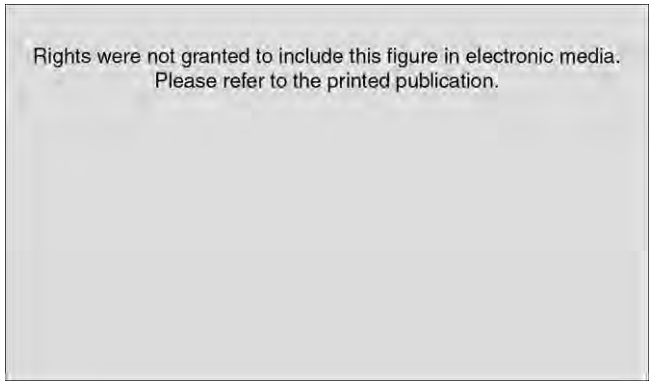

Figure 55–20. When the sutures are initially tied to approximate the edges of the ulcer and the omentum is placed above these knots **(A),** there is less intimate apposition of the duodenal serosa to the omentum. By performing the procedure as described, the omentum plugs the hole **(B)** and is closely applied to the serosa, thereby ensuring a watertight closure. (From Baker RJ: Perforated duodenal ulcer. In Baker RJ, Fischer JE [eds]: Mastery of Surgery. Philadelphia, Lippincott, Williams & Wilkins, 2001.)

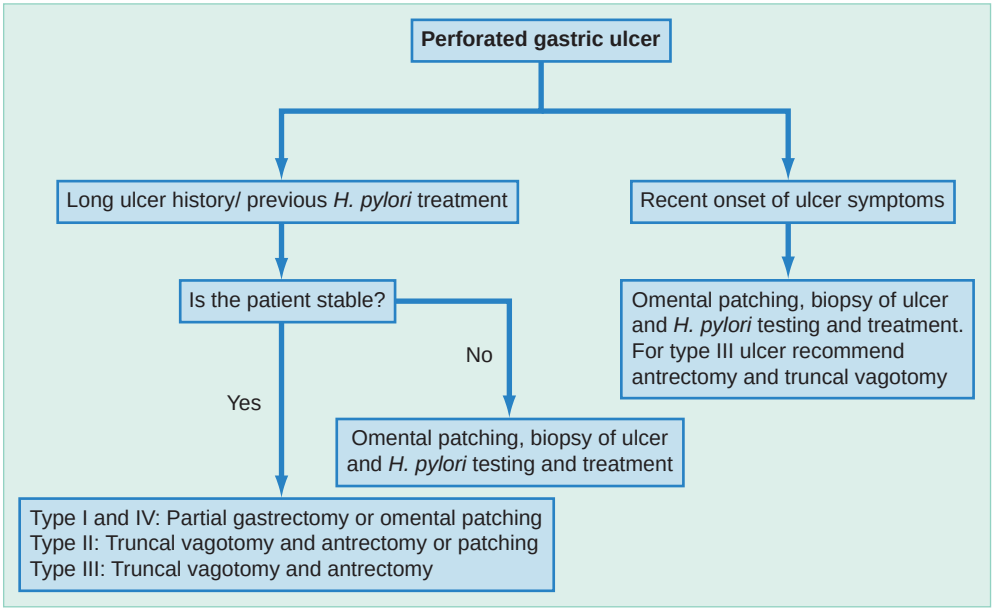

Figure 55–21. Recommended treatment algorithm for the surgical management of perforated gastric ulcers.

an underlying malignancy because cancer has been identified in more than 50% of patients who have gastric outlet obstruction.[24]

Truncal vagotomy and antrectomy is the ideal procedure for this condition. Placement of a feeding jejunostomy tube at the time of surgery is usually recommended, both because of preoperative malnutrition and because the chronic gastric outlet obstruction predisposes to delayed postoperative gastric emptying. The inflammation and scarring at the duodenal bulb may at times prevent safe performance of an antrectomy. In this setting, truncal vagotomy with drainage is the preferred approach. Again, in such a procedure in which the ulcer is not being excised, biopsy of the lesion to rule out an underlying malignancy is important.

Debate persists regarding the optimal drainage procedure. The Jaboulay side-to-side duodenoplasty has gained popularity as a result of its technical simplicity and because the anastomosis is performed in healthy tissue, distinct from the ulcer bed. In one report of 19 patients treated with this procedure combined with HSV, there was a high degree of patient satisfaction (100% modified Visick grade I or II), universal weight gain, and no operative mortality or ulcer recurrence at mean follow-up of 31 months.[42] However, these benefits have not been noted in all reports. One trial randomized 90 consecutive patients with gastric outlet obstruction secondary to duodenal ulcer to HSV with gastrojejunostomy, HSV with Jabouley duodenoplasty, or selective vagotomy with antrectomy. There were no differences in the postoperative course or reduction in gastric acid secretion; however, both HSV with gastrojejunostomy and selective vagotomy with antrectomy produced clinical results superior to those of HSV with Jaboulay pyloroplasty.[43]

As already mentioned, HSV with drainage has been used in the setting of obstructing ulcer. Although the need for pyloric reconstruction or bypass would theoretically negate several advantages of HSV over other options, maintenance of antropyloric innervation may preserve controlled gastric emptying and minimize bile reflux.[8]

With the identification of *H. pylori,* its role in the pathogenesis of gastric outlet obstruction has been evaluated. Studies have shown that the incidence of *H. pylori* infection in this population is low (33% to 57%).[41] In those infected with the organism, however, eradication therapy and balloon dilatation may result in long-term symptomatic relief and alleviate the need for surgery. In general, surgery should be the standard of therapy in this group (in particular, *H. pylori*–negative patients) until further studies define the role of conservative therapy in *H. pylori*–positive patients.

COMPLICATIONS OF ULCER OPERATIONS

Postgastrectomy Syndromes

After operations on the stomach, a variety of chronic undesirable sequelae may develop. Although some of these conditions are related more to vagotomy than to resection, they have been referred to collectively as postgastrectomy syndromes. Virtually all patients note a change in their digestive habits postoperatively, and about 20% are significantly affected. Most are able to adapt with time; lifelong symptoms develop in only 5%, and 1% are significantly debilitated by these syndromes. The following is a summary of the main issues with regard to postgastrectomy syndromes, and a more detailed discussion is provided in Chapter 59.

Early Satiety Early satiety may develop as a result of postsurgical atony, gastric stasis secondary to denervation, or the small gastric remnant related to resection. Symptoms consist of epigastric fullness with meals, often followed

by emesis. Atony can be identified with a solid food–emptying test and may respond to prokinetic agents such as metoclopramide and erythromycin. If these measures fail, although there is some anecdotal evidence that gastric pacing may prove useful, completion gastrectomy is the procedure of choice for atony. The small gastric remnant syndrome will usually improve with small frequent feedings and time.

Postvagotomy Diarrhea After truncal vagotomy, postvagotomy diarrhea develops in approximately 30% of patients. Its pathogenesis is unclear, but it may be related to the rapid passage of unconjugated bile salts from the denervated biliary tree into the colon, where they stimulate secretion. Most cases are self-limited; oral cholestyramine, which binds bile salts, can be effective in persistent cases.

Dumping Syndrome Dumping syndrome is a constellation of postprandial symptoms that occurs in about 20% of patients after gastrectomy or vagotomy and drainage. Although the exact mechanism has eluded definition, it appears to be related to rapid emptying of hyperosmolar chyme, particularly carbohydrate, into the intestine. The symptoms may occur within 30 minutes of eating, referred to as *early dumping*, or 2 to 3 hours after the meal, referred to as *late dumping*. The symptoms vary in intensity, and the syndrome varies from a mild nuisance to disabling.

Early Dumping Rapid introduction of hyperosmolar chyme into the bowel lumen draws fluid into the intestine and probably releases one or more vasoactive hormones such as serotonin and vasoactive intestinal polypeptide. This is associated with epigastric distention, cramps, nausea, vomiting, dizziness, flushing, and palpitations. In most patients, the symptoms tend to resolve as they learn to avoid foods that aggravate the problem. Frequent small meals low in carbohydrate may eliminate the problem. In the most refractory cases, octreotide may be of benefit.

Late Dumping This condition is a reactive hypoglycemia that occurs 2 to 3 hours after the meal in response to excess insulin release. Symptoms of late dumping are relieved by the administration of sugar.

Alkaline Reflux Gastritis After operations that eliminate the pyloric sphincter, reflux of bile into the stomach is common. Alkaline reflux gastritis, a syndrome of persistent burning epigastric pain and chronic nausea that is aggravated by meals, develops in about 2% of patients. The diagnosis is one of exclusion, although endoscopy may reveal gastritis and a technetium biliary scan can demonstrate increased reflux of bile into the stomach. A variety of medical therapies have been reported, but none has proved particularly effective, although there is enthusiasm for the use of ursodeoxycholic acid (Actigall). In debilitating cases, conversion of the original drainage procedure to a Roux-en-Y anastomosis, in which bile is diverted 45 to 60 cm from the gastric remnant, has proved effective in selected patients.

Afferent and Efferent Loop Syndromes These syndromes develop after Billroth II reconstruction or gastroenterostomy. They are related to mechanical obstruction of the limbs by kinking, anastomotic narrowing, or adhesions. Afferent loop syndrome is typically associated with postprandial epigastric pain and nonbilious vomiting, which is then relieved by projectile bilious vomiting. Detection of a distended afferent loop on computed tomography is diagnostic. Conversion to a Roux-en-Y anastomosis is necessary to treat this problem. Several different surgical reconstructions have been proposed to help reduce the incidence of afferent loop syndrome after a Billroth II reconstruction, including the Braun variation of Billroth II and the uncut Roux-en-Y reconstruction.

Efferent loop syndrome is associated with epigastric pain, distention, and bilious vomiting; surgery to relieve the obstruction is the treatment of choice.

Roux Stasis Syndrome Roux stasis syndrome occurs after a Roux-en-Y reconstruction. It consists of chronic abdominal pain, nausea, and intermittent vomiting. The etiology of this syndrome is unknown, and treatment is often difficult. The uncut Roux-en-Y reconstruction previously mentioned has been shown to reduce the incidence of Roux stasis syndrome and may be a better reconstruction technique.[44]

Gastric Cancer In patients who have undergone gastric resection for gastric but not duodenal ulcers, an increased risk for gastric cancer has been documented. This risk is twofold at 15 years and increases with time after partial gastrectomy.[45] The risk for development of gastric cancer is higher after a Billroth II than after a Billroth I reconstruction.[11]

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Chapter

56

Vagotomy and Drainage

Timothy J. Broderick · Jeffrey B. Matthews

VAGOTOMY AND DRAINAGE IN THE MODERN ERA

Recognition of the roles that *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs) play in peptic ulcer disease has revolutionized the care of patients who suffer from gastroduodenal ulcer. Research over the last decade confirmed that *H. pylori* infection and NSAID use are highly associated with peptic ulcer disease.[1-4] Recent data suggest that less than 1% of all duodenal ulcers and 4% of all gastric ulcers are *not* associated with either *H. pylori* infection or NSAID use.[5] Medical therapy has become significantly more effective with targeted treatment of *H. pylori,* improved antisecretory medications (histamine H_2 receptor antagonists and, subsequently, proton pump inhibitors), and the introduction of NSAIDs that have less effect on mucosal integrity. Endoscopic diagnosis and therapy have also improved in the past decade.

Classically, complications of peptic ulcer disease requiring surgery included intractability, obstruction, perforation, and hemorrhage. With more effective medical therapy, intractable peptic ulcer and peptic gastric outlet obstruction have become an uncommon indication for elective surgery,[6-9] but perforated or bleeding peptic ulcers have remained a relatively common indication for urgent surgery.[6-8] Recent data confirm that surgical treatment of peptic ulcer disease has evolved from elective surgery for medically refractory ulcer disease to urgent surgery for the treatment of perforation or hemorrhage.[6-8,10]

Although *H. pylori* eradication has significantly decreased the need for elective surgery, it has also changed the selection of which procedures are commonly performed in the treatment of ulcer complications. Local procedures such as suture duodenorrhaphy and gastrorrhaphy were used in 25% of operations for peptic ulcer disease in 1987 and in 90% of such operations in 1999 in Finland.[7,8] Additional studies from the United Kingdom demonstrated that most surgeons in the United Kingdom no longer perform vagotomy for peptic ulcer complications.[11,12] A recent study from the United States suggests that surgical treatment of peptic ulcer disease has similarly evolved.[13] The indication for and selection of operations for peptic ulcer disease have evolved, and the majority of surgeons now choose the simplest and quickest operation that will address the ulcer complication while minimizing postoperative gastrointestinal side effects. The decrease in ulcer recurrence provided by definitive acid reduction surgery has been replaced by *H. pylori* eradication, tailored NSAID therapy, and proton pump inhibitor therapy.[8,11,12,14]

Traditional operations such as vagotomy and drainage remain effective in addressing complications of peptic ulcer disease. However, modern medical therapy that effectively treats the underlying ulcer diathesis and the occasional patient who is crippled by the unpleasant digestive side effects of vagotomy and drainage argue for limited use of this procedure in modern treatment of peptic ulcer. The historical, anatomic, and physiologic basis for the recommendation of limited application of vagotomy and drainage in the treatment of select patients suffering from complications of peptic ulcer is discussed in the remainder of this chapter. Additional investigation is needed to determine the optimal combination of medical, endoscopic, and surgical therapy in the treatment of peptic ulcer disease in the modern era.

PATHOGENESIS OF PEPTIC ULCER DISEASE

Surgical treatment of peptic ulcer has been based on the assumed central role of acid and pepsin in its pathogenesis. The notion of autodigestion of the stomach as the cause of ulceration dates back at least as far as John Hunter in 1772.[15] The epidemiologic evidence supporting a role for acid and pepsin in the pathogenesis of duodenal ulcer is abundant. Elevated basal, nocturnal, induced, and maximal levels of gastric acid output have been demonstrated in duodenal ulcer patients in comparison to the normal population,[16,17] and this increased capacity to secrete HCl has been correlated with

increased parietal cell mass.[18] The oxyntic cells of duodenal ulcer patients appear to be more sensitive to stimulation because the dose of pentagastrin necessary to induce a maximal secretory response is reduced in ulcer patients as compared with controls.[19]

Consequently, the development of surgical procedures for the treatment of duodenal ulcer had its foundation in the reduction of acid-peptic aggression. The works of Pavlov, Brodie, Jabouley, and Bircher in identifying the vagus as the anatomic effector of the cephalic phase of acid secretion provided the foundation for surgical vagotomy in the treatment of ulcer disease. Dragstedt and Edkins established that the gastric phase of acid secretion is derived from the gastrin-producing antrum, and this concept supported the use of distal gastrectomy to achieve a greater reduction in secretory capacity. The importance of acid and pepsin in mucosal injury is illustrated convincingly by the therapeutic efficacy of antacids, H_2 receptor antagonists, and proton pump inhibitors and supports the use of vagotomy and other forms of acid reduction surgery in surgical therapy.

Impaired mucosal defense mechanisms may also contribute to ulcerogenesis. Normal mucosal defense systems against acid-peptic aggression are dynamic, multifactorial, and multilayered. Pre-epithelial factors include the intrinsic surface hydrophobicity of mucosal surfaces and the physiochemical ability of mucus to retard acid diffusion. The epithelial cell itself confers a degree of resistance against the harmful effects of luminal acid by secreting mucus and bicarbonate ions and precisely regulating its intracellular pH. Moreover, the apical membrane and intracellular junctions have limited permeability to protons. Subepithelial defenses include bicarbonate production, which balances parietal cell proton secretion and provides a rich source of neutralizing base to the surface epithelium. Furthermore, rapid epithelial restitution allows repair of the superficial damage incurred from daily chemical and physical surface trauma.

The pathogenesis of chronic gastric ulceration is even less well understood than duodenal ulcer disease, but "impaired mucosal defenses" are often cited as an etiologic factor,[20-22] although this notion is rather vague and hence unhelpful. Gastric ulcer affects older patients without a sex predilection and occurs in the setting of atrophic gastritis. It is associated with normal or decreased acid secretory capacity and pepsin levels, and this epidemiologic factor has led some to suggest that gastric ulcer represents a fundamentally different disease process. Despite this concept, surgical procedures for the treatment of gastric ulcer to a large degree resemble procedures used for duodenal ulcer to reduce acid-peptic aggression. Yet in the absence of a coherent theory of gastric ulcerogenesis, it is difficult to account for their efficacy. It has been reasoned that the gastric mucosa of patients in whom ulcers develop in the setting of normal or decreased secretion must have inherently increased sensitivity to autodigestion. This concept has provided justification for distal gastrectomy with the removal of susceptible mucosa in the surgical treatment of gastric ulceration.

The paradigm for modern medical therapy has tended to shift away from combating acid-peptic aggression toward enhancing mucosal defenses. Maintenance of adequate gastroduodenal blood flows appears to be important in preventing mucosal damage in experimental injury,[23] and new data suggest a possible therapeutic role for growth factors and angiogenesis factors in accelerating the reparative processes crucial for ulcer healing. Medical efforts to bolster defenses by using so-called cytoprotective agents have met with mixed results. For example, synthetic prostaglandin analogues, which enhance mucosal self-protective mechanisms at a number of levels (e.g., production of mucus, bicarbonate secretion, and mucosal blood flow[24]), have been shown to prevent or reverse mucosal injury associated with NSAID use but have been effective in duodenal ulcer disease only when given at antisecretory doses. Altered gastrointestinal motility has been implicated in ulcer genesis in that rapid emptying of acidic gastric contents has been hypothesized to overwhelm duodenal neutralization capacity[25] and duodenogastric reflux of bile salts is thought to promote mucosal injury.[26]

No discovery has so profoundly altered the fundamental concepts of ulcerogenesis and dramatically altered approaches to therapy as the isolation of *H. pylori* by Warren and Marshall in 1983.[27] A causal relationship between *H. pylori* infection and chronic gastritis is well established,[28] but the mechanistic basis for the association of *H. pylori* infection with duodenal ulcer disease has proved more difficult to elucidate. In some cohorts, greater than 95% of patients with duodenal ulcer and 75% with gastric ulcer harbor *H. pylori*.[29,30] Duodenal ulcers develop far more frequently in the setting of established infection than they do de novo,[31,32] and eradication of the pathogen markedly reduces the ulcer recurrence rate, in some series from 60% to less than 15%.[33-35] Furthermore, a modest acceleration in ulcer healing has been observed when *H. pylori* treatment is combined with standard antisecretory therapy.[28] Although much of the evidence suggesting a pathogenic role for *H. pylori* is circumstantial, it is also quite compelling. A recent National Institutes of Health consensus conference concluded that ulcer patients with demonstrated infection should be treated with antisecretory drugs and adjuvant antimicrobial agents, even in the setting of NSAID-induced ulceration.[28] It must be noted that only a small proportion of patients transition from antral gastritis to the development of gastric or duodenal ulceration and that infection or colonization is frequently asymptomatic.[36] Furthermore, primary healing of ulcers in the setting of active *H. pylori* infection is achieved in a majority of patients with drug regimens that do not include antimicrobials.

VAGAL ANATOMY

The vagus nerve originates in the medulla oblongata, and most of its fibers are involved in forming the parasympathetic division of the autonomic nervous system. The vagus nerve is the longest of the cranial nerves, and it has an extended distribution with branches

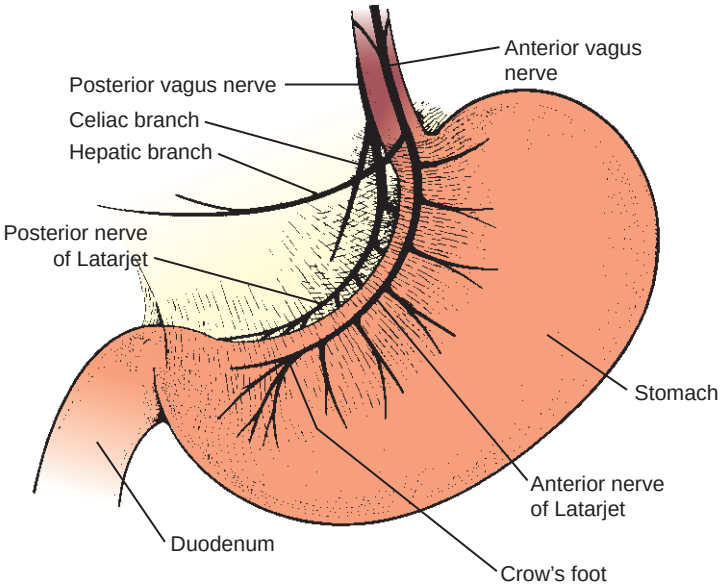

Figure 56–1. Anatomy of the vagus nerve on the lower part of the esophagus and stomach. (From Lawrence PF: Essentials of General Surgery. Philadelphia, Lippincott, Williams, & Wilkins, 2000.)

to the cervical, thoracic, and abdominal regions. Multiple branches extend to both thoracic (esophagus, heart, lungs, and bronchi) and abdominal (stomach, gallbladder, small intestine, colon, and other viscera) structures. After leaving the plexus surrounding the hilum of the lung, the vagal fibers reunite in two large lateral bundles on the left and right sides of the esophagus.

A clockwise rotation of the nerves as they course inferiorly results in the left vagus nerve appearing anteriorly and the right appearing posteriorly as the trunks enter the abdominal cavity. Gastric branches run from both the anterior and posterior trunks as they course parallel and superior to the lesser curvature of the stomach and finally extend to the pylorus (Fig. 56–1). Additional branches given off in the abdomen include hepatic branches from the anterior vagus and celiac branches from the posterior vagus. There may be substantial variation in vagus nerve distribution around the esophagus as the trunks pass beyond the diaphragm into the abdomen (Fig. 56–2). Although the great majority of individuals (80%) have a single large anterior and posterior trunk, other variations include multiple branches, fusing of branches, tangential branches, and plexiform branches. Awareness of these variations should result in a careful circumferential search of the mobilized esophagus for any additional branches after presumed complete truncal vagotomy.

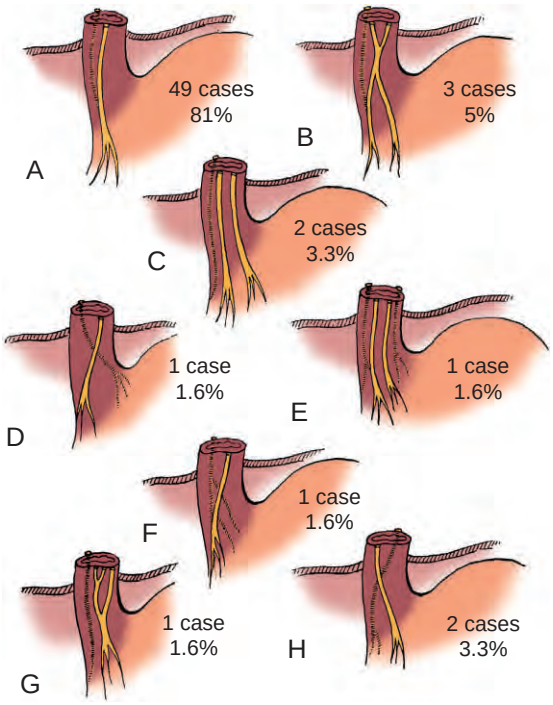

Figure 56–2. Illustrations of the high degree of variability in vagus nerve distribution along the lower part of the esophagus. (From Dragstedt LR, Fournier HJ, Woodward ER, et al: Transabdominal gastric vagotomy. A study of the anatomy of the vagus nerves at the lower portion of the esophagus. Surg Gynecol Obstet [now J Am Coll Surg] 85:461, 1947.)

VAGAL PHYSIOLOGY

The pioneering work of Pavlov, Brodie, and Latarjet elucidated the role of the vagus nerve in gastric acid secretion. The vagus nerves provide somatic and visceral afferent fibers that innervate the mucosa of the stomach and play a major role in the cephalic phase of gastric acid secretion by releasing acetylcholine. Release of acetylcholine stimulates acid secretion via a specific receptor on the parietal cell. Vagotomy diminishes direct cholinergic stimulation of the parietal cell and eliminates vagally mediated release of gastrin.[37] The parietal cell becomes generally less responsive to gastrin stimulation.[19,38,39] As a result, basal acid secretion is reduced by up to 85% and stimulated secretion by 50%.[40] Vagotomy also reduces pepsin secretion by the chief cell.[41]

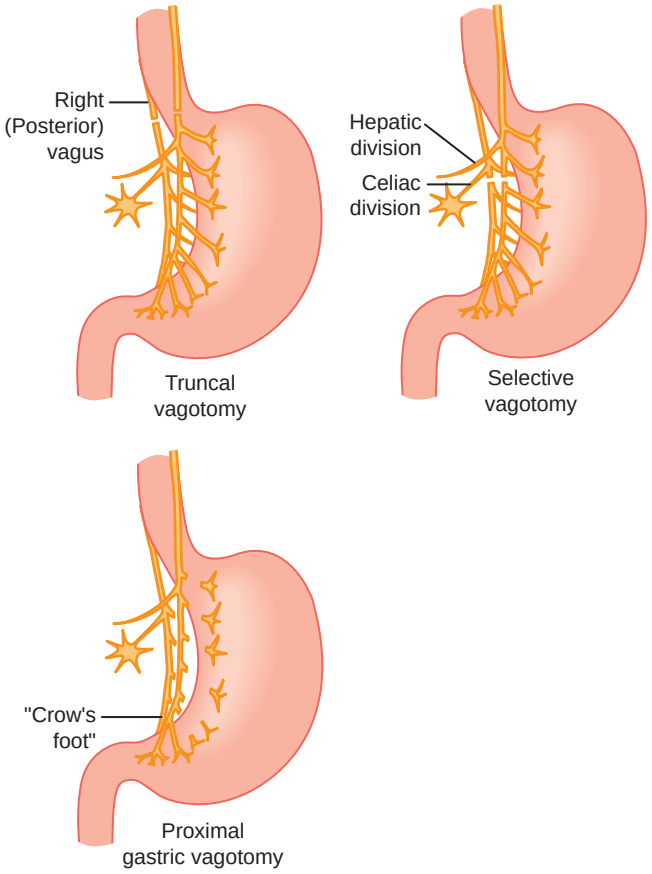

Figure 56–3. Schematic representation of the three standard forms of vagotomy. (From Sleisenger MH, Fordtran JS: Operations for peptic ulcer disease and early postoperative complications. In Sleisenger MH, Fordtran JS: Gastrointestinal Disease, 5th ed. Philadelphia, WB Saunders, 1993.)

The distal portions of the anterior and posterior trunks send branches to the antrum and pylorus that serve primarily a motor function. The celiac branch of the posterior vagus stimulates small intestinal motility. Gastric motility is affected by the antral and pyloric branches of the vagus, which stimulate peristaltic activity of the antrum and relaxation of the pylorus; in addition, the vagus stimulates receptive relaxation of the fundus, which results in accommodating liquid intake without a corresponding increase in pressure. The impaired gastric emptying seen after truncal vagotomy reflects not only impaired relaxation of the pyloric sphincter[42] but also disturbances in antral grinding and propulsive function,[43] as well as loss of fundic receptive relaxation.[44]

VAGOTOMY

Vagotomy is defined as transection of the vagus nerve or its branches, thus interrupting sensory, secretory, and motor impulses to the stomach and other gastrointestinal organs. The most commonly used vagotomies have been truncal, selective, and proximal gastric vagotomy. The various types of vagotomies are illustrated in Figure 56–3.

Dragstedt and Owens introduced transthoracic truncal vagotomy as treatment of duodenal ulcer in 1943.[45] Although two main vagal trunks in the chest make transthoracic vagotomy easy to perform, the postoperative gastric retention and ulceration that occurred in approximately a third of patients necessitated a transabdominal approach to add a concomitant procedure for improvement of gastric drainage.[46] In modern practice, transthoracic vagotomy may be performed thoracoscopically, but this approach is generally reserved for rare refractory cases of recurrent ulceration in which incomplete previous vagotomy has been demonstrated.

Transabdominal truncal vagotomy requires division of the two main vagal trunks, as well as division of the multiple small vagal branches that are often present at the distal esophageal level. The procedure is begun with a high midline incision and division of the triangular ligament of the left lateral hepatic segment. The hiatus is exposed and the nasogastric tube is palpated within the abdominal esophagus. The peritoneum overlying the distal esophagus is incised, and the index finger is used to begin gentle blunt dissection around the esophagus until it meets the thumb on the other side. A Penrose drain is then placed around the distal esophagus for anterior and inferior retraction. The distal end of the esophagus is dissected free from surrounding connective tissue to delineate the anterior (left) and posterior (right) vagi. Sharp dissection is used to free the vagal trunks, and a 3-cm segment of the nerves is excised. Some surgeons recommend placement of metal clips to mark the superior and inferior vagal remnants, as well as confirmation of nerve division via pathologic evaluation. The posterior (right) vagus is more difficult to find, and the surgeon must be particularly attentive in this dissection. A careful search of the distal esophagus excludes any additional branches, which must be resected if encountered. It must be emphasized that multiple small branches of both the anterior and posterior trunks are generally found at this level; if only the main anterior and posterior trunks are severed, the vagotomy will almost certainly be incomplete. In cases of recurrent ulcer after vagotomy, histologic review of the number of vagal nerve specimens from the original procedure is advisable.

Truncal vagotomy sacrifices the vagal innervation of not only the entire stomach but also the hepatobiliary system, pancreas, small intestine, and proximal part of the colon. A number of the adverse sequelae of ulcer operations have been blamed on vagotomy, particularly diarrhea and cholelithiasis.[47] Truncal vagotomy cures the majority of patients of their duodenal ulcer diathesis but does not entirely eliminate the problem of recurrent ulceration. Moreover, to obviate the problem of postoperative gastric retention, the pyloric sphincter must be bypassed (gastroduodenostomy or gastrojejunostomy), destroyed (pyloroplasty), or resected (antrectomy). The evolution, description, and indications for the use of "drainage" procedures are discussed in detail in a subsequent section.

In an effort to decrease the incidence of these postoperative side effects, selective vagotomy (with preservation of the hepatic and celiac divisions of the anterior

and posterior vagus nerves) was introduced in 1948.[48,49] In selective gastric vagotomy, the anterior and posterior nerves of Latarjet are divided distal to the branching of the hepatic and celiac divisions. This procedure denervates the antropyloric region of the stomach, and gastric reservoir function and gastric emptying are impaired to the same extent as with truncal vagotomy. In a comparison of truncal and selective vagotomy, controlled studies have demonstrated a similar incidence of postoperative diarrhea,[50,51] postoperative dumping symptoms,[52] and recurrent ulceration with the use of selective or truncal vagotomy. Because selective gastric vagotomy offers little advantage over truncal vagotomy and is technically more difficult to perform, there remain few advocates of this procedure. Selective vagotomy will not be discussed further in this chapter.

Proximal gastric vagotomy has been called by a variety of names: highly selective vagotomy, superselective vagotomy, and parietal cell vagotomy. We prefer proximal gastric vagotomy and will use that term throughout the remainder of this chapter. Based on the anatomic studies of Griffith and Harkins,[53] proximal gastric vagotomy was introduced in the late 1960s by groups from Great Britain, Germany, and Scandinavia[54-56] as a method of vagotomy that limits the field of denervation to the fundus of the stomach and preserves vagal innervation of the antrum and pylorus. By preserving the antropyloric motor apparatus, proximal gastric vagotomy avoids the need for concomitant drainage or resection. For the most part, the details of the technique of proximal gastric vagotomy are well established. The nerves of Latarjet course along the lesser curvature of the stomach within the anterior and posterior leaves of the gastrohepatic (lesser) omentum. Starting from the incisura angularis, these fibers are divided systematically at their attachment to the stomach wall. The dissection is carried proximally to the gastroesophageal junction, and the distal 4 to 7 cm of esophagus is meticulously cleared of all vagal fibers. Small branches of the vagus nerve extend to the gastric cardia in this region and are easily overlooked.[57] The distal antral branches of the nerves of Latarjet (the "crow's foot"), as well as the hepatic and celiac divisions of the main vagal trunks, are preserved, and as a result, antropyloroduodenal innervation remains intact and gastric stasis and biliary reflux are minimized. To minimize the risk for the unusual, but life-threatening complication of lesser curvature necrosis, the lesser curvature should be imbricated.

Anterior lesser curve seromyotomy along with posterior truncal vagotomy was introduced by Taylor et al.[58] as a means of decreasing the technical difficulty of proximal gastric vagotomy. In this procedure, a seromyotomy along the anterior aspect of the lesser curve divides the branches of the anterior nerve of Latarjet that course through the superficial seromuscular layer of the stomach before penetrating the gastric wall to innervate the parietal cell mass. Posterior truncal vagotomy is performed to denervate the entire posterior gastric wall. Despite such denervation, normal antral motility seems to be preserved[59] because neural impulses appear to be adequately transmitted from the distal antral branches of the anterior branch of the nerve of Latarjet to the posterior wall via intramural arcs.[60] There does not appear to be an increased incidence of postoperative diarrhea and dumping symptoms after this procedure despite the loss of vagal innervation to the pancreas and proximal portion of the small bowel,[61,62] again attesting to the central role that emptying procedures appear to play in the development of diarrhea.

Minimally invasive versions of vagotomy have been reported in recent years and include truncal vagotomy and pyloric stretch, truncal vagotomy and pyloromyotomy, posterior truncal vagotomy and anterior seromyotomy, and posterior truncal vagotomy with anterior highly selective vagotomy. Enthusiasm for these approaches should continue to be tempered with skepticism. Laparoscopic proximal gastric vagotomy has met with some promising results, although is unlikely to find wide application because of its technical demands.[63] The minimally invasive version of the Taylor procedure may prove to be a better alternative. Anecdotal results with this approach have been reported,[63] but until long-term follow-up becomes available, the role of minimally invasive vagotomy in the treatment of duodenal ulcer disease remains to be established. As previously mentioned, thoracoscopic truncal vagotomy has been reported[65] and may be useful in the setting of recurrent ulceration secondary to incomplete truncal vagotomy.

DRAINAGE PROCEDURES

In Dragstedt's initial series of truncal vagotomy for the treatment of duodenal ulcer disease, nearly a third of his patients experienced postoperative nausea, vomiting, and distention. As described earlier, further investigations revealed that truncal vagotomy denervated the antrum and pylorus and thereby resulted in a functional gastric outlet obstruction. Gastrojejunostomy was the drainage procedure originally explored but was later supplanted by pyloroplasty[66] and then by antrectomy.[67]

Gastrojejunostomy remains a useful and effective option for providing gastric drainage in the setting of an extensive scarred or acutely inflamed pylorus, particularly in patients with obstruction. First performed in 1881, gastrojejunostomy was originally plagued by two problems: marginal ulcers and vomiting. The two problems were subsequently overcome with the addition of vagotomy and construction of a shorter afferent jejunal limb. Gastrojejunostomy is currently most commonly performed for the treatment of benign and malignant duodenal obstruction. In peptic ulcer disease, gastrojejunostomy is performed for duodenal obstruction when the duodenal bulb is so scarred, inflamed, and edematous that pyloroplasty would not be safe or would be excessively technically demanding. A vagotomy should be performed when using gastrojejunostomy as a drainage procedure for the treatment of peptic ulcer disease. Obstruction as a result of pancreatic cancer is another common indication for palliative gastrojejunostomy. In many cases, the pancreatic cancer patient is elderly, secretes little hydrochloric acid, and does not require a vagotomy to accompany the bypass.

Gastrojejunostomy begins with taking down the greater omentum of the transverse colon to open the lesser sac and access the posterior aspect of the stomach. A site in the distal part of the stomach that is posterior and close to the greater curve is selected for the anastomosis to ensure dependent drainage of the stomach. A decision is then made with regard to whether the anastomosis will be antecolic or retrocolic. In the setting of peptic obstruction, many surgeons perform the anastomosis in a retrocolic manner. The antecolic approach is preferred when bypassing a malignant obstruction to avoid possible invasion of the more posterior retrocolic limb. A site approximately 15 to 20 cm from the ligament of Treitz is selected on the jejunum, a generous window is made in the mesocolon, and the stomach is pushed through the window until it lies next to the selected jejunal site (Fig. 56–4A).

The afferent limb of the proximal jejunum at the site should be attached to the lesser curve of the distal stomach. A posterior row of interrupted silk sutures is then placed to attach the serosa of the jejunum to the serosa of the stomach. A gastrotomy and enterotomy of equal size (4 to 5 cm) are then made 5 to 6 cm lateral to the Lembert layer. Running absorbable suture is used to close the inside layer while making certain that full-thickness tissue bites are procured. A final layer of interrupted Lembert silk sutures completes the anterior outside layer (see Fig. 56–4B). So that no torsion occurs, it is usually wise to fix the jejunal limb in one additional place to either the stomach or the liver capsule with a single suture. The defect in the mesocolon is then closed with absorbable suture to obviate internal hernia. A stapled anastomosis may also be performed, but it is unwise to use the stapler in extremely edematous or scarred tissue.

Pyloroplasty is used for approximately 90% of all drainage procedures. Pyloroplasty is the most popular drainage procedure for peptic ulcer disease because it is simple to perform and is associated with less bile reflux than gastrojejunostomy is. A number of methods for performing pyloroplasty have been described, the sheer variety attesting to a general unspoken dissatisfaction with the procedure.[68] The Heineke-Mikulicz pyloroplasty is the most widely practiced,[69] although no firm data support its superiority over other methods.

Heineke-Mikulicz Pyloroplasty

This procedure was described independently by two surgeons, Heineke and Mikulicz, in 1888, years before it found routine application as the most commonly performed drainage procedure. The technique is popular because it is technically straightforward, applicable to many clinical ulcer scenarios, and associated with few complications if performed correctly. The procedure may be performed with a single- or a double-layer closure, with the latter being performed more commonly. Careful palpation reveals the firm, rubbery pylorus at the junction between the stomach and duodenum. The pyloric vein of Mayo is virtually always present on the anterior surface of the inferior pylorus. If helpful, a Kocher maneuver to mobilize the duodenum may be performed, but it is usually not necessary. Two silk traction sutures are placed astride the anterior pylorus and parallel to each other. While lifting up on the traction sutures, a longitudinal incision is made through the pyloric muscles and extended 2 to 3 cm proximally into the stomach and distally into the duodenum (Fig. 56–5, part 1). With the incision open, careful palpation with the index finger in the lumen of the stomach and duodenum rules out obstruction, tumor, active bleeding, or additional ulcers.

After careful inspection, the inside layer of the closure is initiated by selecting the midpoint of the longitudinal incision and pulling it laterally to convert the longitudinal opening into a horizontal one (thus opening up the pyloric muscle). If the duodenum is soft, pliable, and minimally deformed, a running closure of the inside layer is begun with absorbable suture in an inverting fashion (see Fig. 56–5, part 2). An outside layer of Lembert silk sutures in an interrupted fashion completes the procedure (see Fig. 56–5, part 3). Caution must be exercised to not turn in too much serosa while placing the Lembert layer to avoid the rare complication of obstruction. With scarring, edema, or deformation of the pylorus and duodenal bulb, the running technique on the inside layer described earlier may not be possible. When these conditions are present, an interrupted, simple layer of absorbable suture may be placed while making certain that adequate purchase of both the stomach and duodenum is obtained. A final, interrupted Lembert layer can then be completed if the tissue is sufficiently pliable. Many surgeons prefer a single layer of interrupted suture to close the pyloroplasty, and this technique is likely to be sufficient in the vast majority of cases. To make certain that the outlet is of adequate size, the initial longitudinal incision should be approximately 5 to 7 cm in length. Some surgeons recommend extension of the gastric portion of the incision approximately 1 cm longer than the duodenal portion.

Finney Pyloroplasty

This uncommonly used pyloroplasty is primarily performed in patients with a J-shaped stomach or extensive scarring and narrowing of a significant portion of the duodenal bulb, thus making a Heineke-Mikulicz pyloroplasty untenable. Use of this drainage procedure makes a larger lumen possible and involves a fairly long incision from the stomach, through the pylorus, and well into the duodenal bulb with closure of the inferior duodenum to the inferior stomach and superior duodenum to the superior stomach. It is a more complicated undertaking than the Heineke-Mikulicz procedure and has more potential for complications.

The procedure is begun by identifying the pylorus and performing a duodenum-mobilizing Kocher maneuver. After placement of silk traction sutures through the pylorus on the anterior duodenum, an incision is made through the pylorus and extended 5 to 7 cm onto the stomach and 5 to 7 cm onto the duodenum. After the careful exploration previously described, closure is initiated by using absorbable suture to begin a running

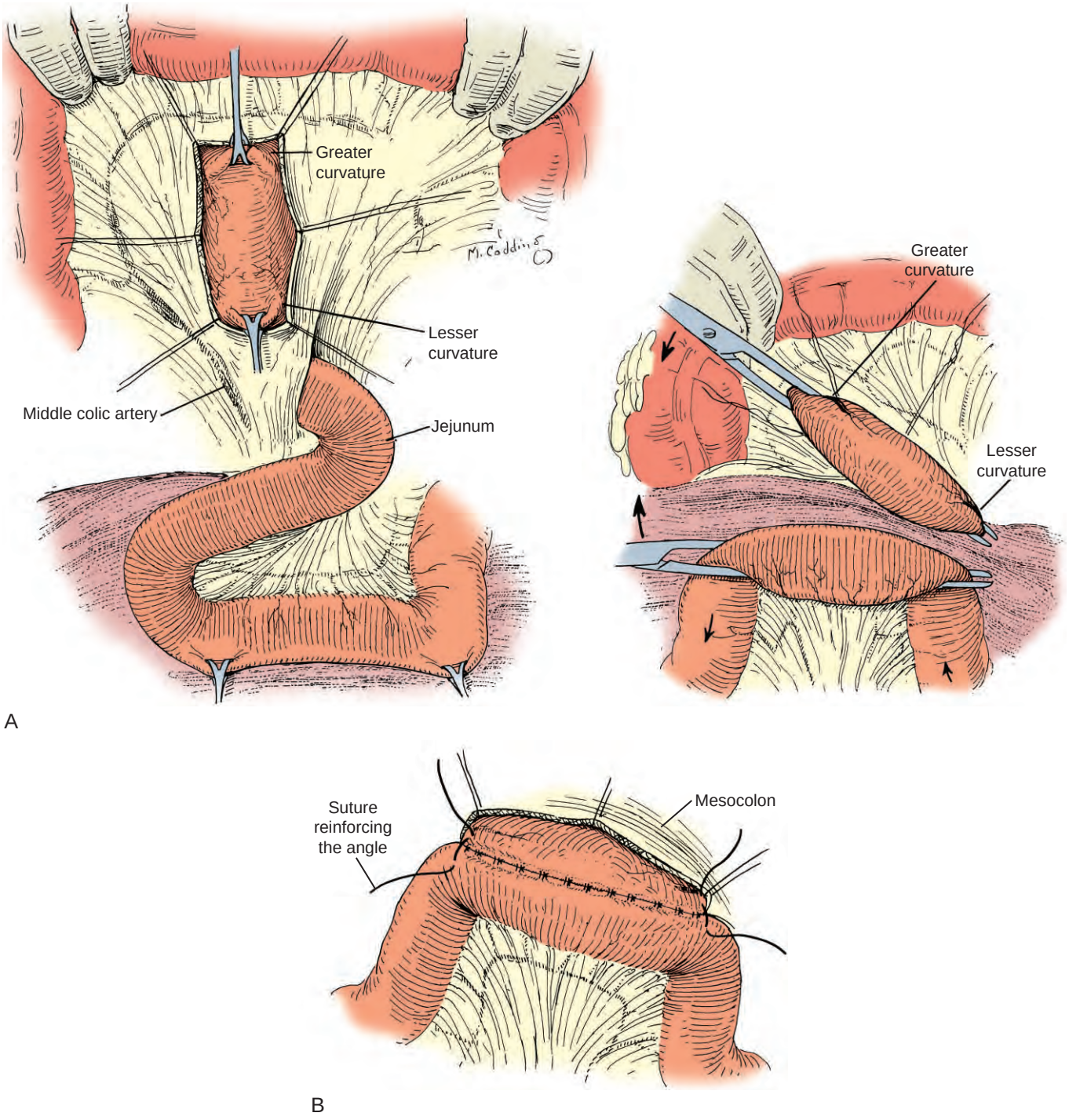

Figure 56–4. Schematic representation of a gastrojejunostomy. A site approximately 15 to 20 cm from the ligament of Treitz is selected on the jejunum, a generous window is made in the mesocolon, and the selected jejunal site is pushed through the window until it lies next to the selected gastric site **(A).** A final layer of interrupted Lembert silk sutures completes the anterior outside layer **(B).** (From Zollinger RM: Atlas of Surgical Operations. New York, Macmillan, 1975.)

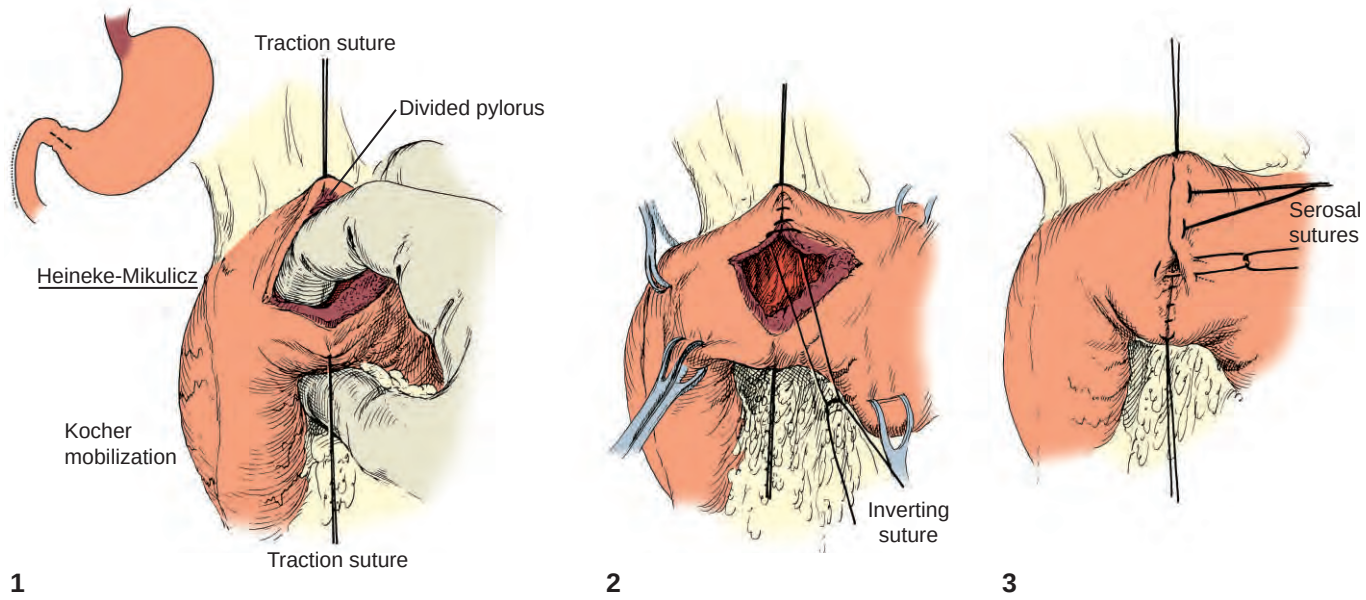

Figure 56–5. Schematic representation of Heineke-Mikulicz pyloroplasty. While lifting up on the traction sutures, a longitudinal incision is made through the pyloric muscles and extended 2 to 3 cm proximally into the stomach and distally into the duodenum *(part 1).* If the duodenum is soft, pliable, and minimally deformed, a running closure of the inside layer is begun with absorbable suture in an inverting fashion *(part 2).* An outside layer of Lembert silk sutures in an interrupted fashion completes the procedure *(part 3)* (From Zollinger RM: Atlas of Surgical Operations. New York, Macmillan, 1975.)

closure (Fig. 56–6, part 4). The repair begins at the pylorus with suture being used to sew the inferior duodenum to the inferior stomach and, as the closure moves superiorly, the superior duodenum to the superior stomach. A final, interrupted row of silk sutures is then placed in Lembert fashion to complete the pyloroplasty (see Fig. 56–6, Part 5).

Jaboulay Gastroduodenostomy

The Jaboulay gastroduodenostomy is infrequently used in modern practice. This drainage procedure does not transect the pyloric muscle but instead involves an anastomosis of the distal end of the stomach to the first and second portions of the duodenum. The procedure is rarely performed, but when used, it is indicated primarily for a severely scarred or deformed pylorus or duodenal bulb. The procedure begins with adequate duodenal mobilization through a Kocher maneuver. The first and second portions of the duodenum are then folded back on the distal end of the stomach, and a posterior row of interrupted Lembert silk sutures is used to attach the duodenum to the distal stomach. Equal-size incisions approximately 4 to 5 cm in length are then made in the distal stomach and proximal duodenum (Fig. 56–7, part 6). An inside posterior running absorbable suture is placed to approximate the inferior duodenum to the inferior stomach. As the closure moves inferiorly, the superior duodenum is sewn to the superior stomach. A final anterior, outside layer of interrupted Lembert silk sutures is then placed to complete the gastroduodenostomy (see Fig. 56–7, part 7).

A variety of gastrointestinal complications may occur after gastric drainage, including dumping, diarrhea, bezoar formation, alkaline reflux gastritis, anemia, and marginal ulcers. These complications may develop in up to 50% of patients after surgery, but they resolve within 6 to 8 months in most patients. Five percent to 7% of patients have a persistent, symptomatic postoperative complication such as dumping. Should ulcers recur and a distal gastrectomy become necessary, the Finney and Jaboulay drainage procedures make reoperation more difficult. The choice of operation for the treatment of recurrent postoperative peptic ulcer is described in detail later in this chapter. Use of the Jaboulay procedure may also be associated with increased bile reflux because the anastomosis is close to the ampulla of Vater.

SURGICAL TREATMENT OF PEPTIC ULCER DISEASE

The fundamental goals of surgical treatment of peptic ulcer are to treat ulcer complications, address the ulcer diathesis, and minimize physiologic disturbances. No single procedure satisfies all the stated goals or is universally applicable to all surgical candidates. In choosing the most appropriate procedures, the surgeon must consider the characteristics of the ulcer (location, chronicity, presence of complications), the characteristics of the patient (age, nutritional status, comorbid illness, condition at initial evaluation), and the characteristics of the procedure itself (mortality rates and potential postoperative sequelae). This choice is heavily influenced by the surgeon's training, personal experience, and biases.

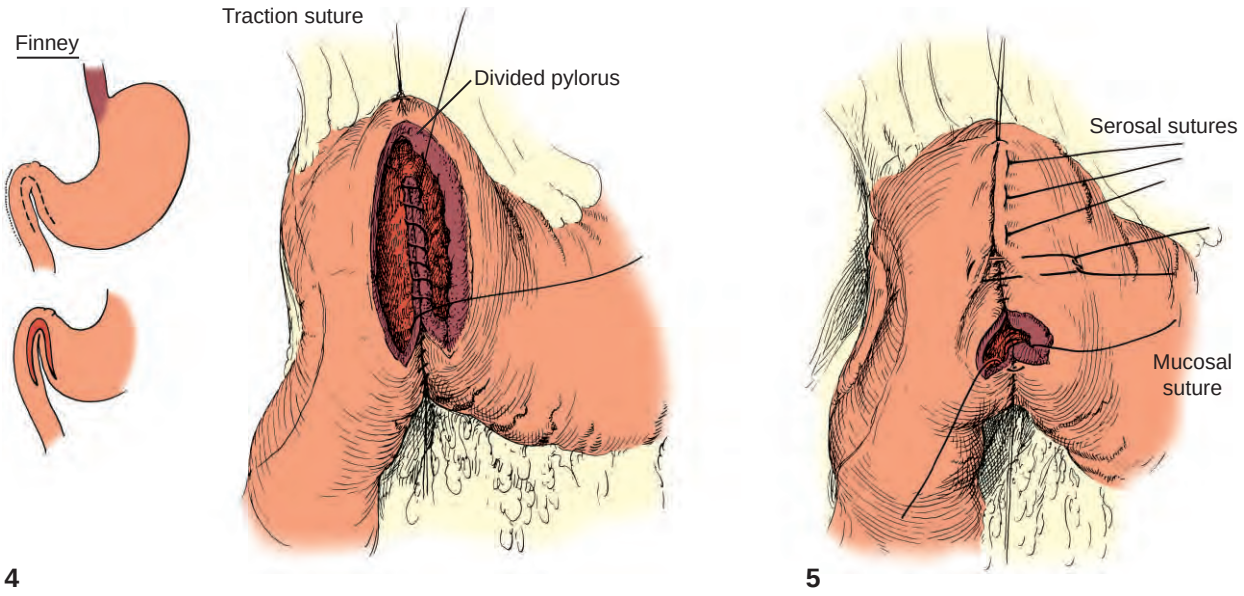

Figure 56–6. Schematic representation of the Finney pyloroplasty. After the careful exploration previously described in Figure 55–5, closure is initiated by using absorbable suture to begin a running closure *(part 4).* A final, interrupted row of silk sutures is then placed in Lembert fashion to complete the pyloroplasty *(part 5).* (From Zollinger RM: Atlas of Surgical Operations. New York, Macmillan, 1975.)

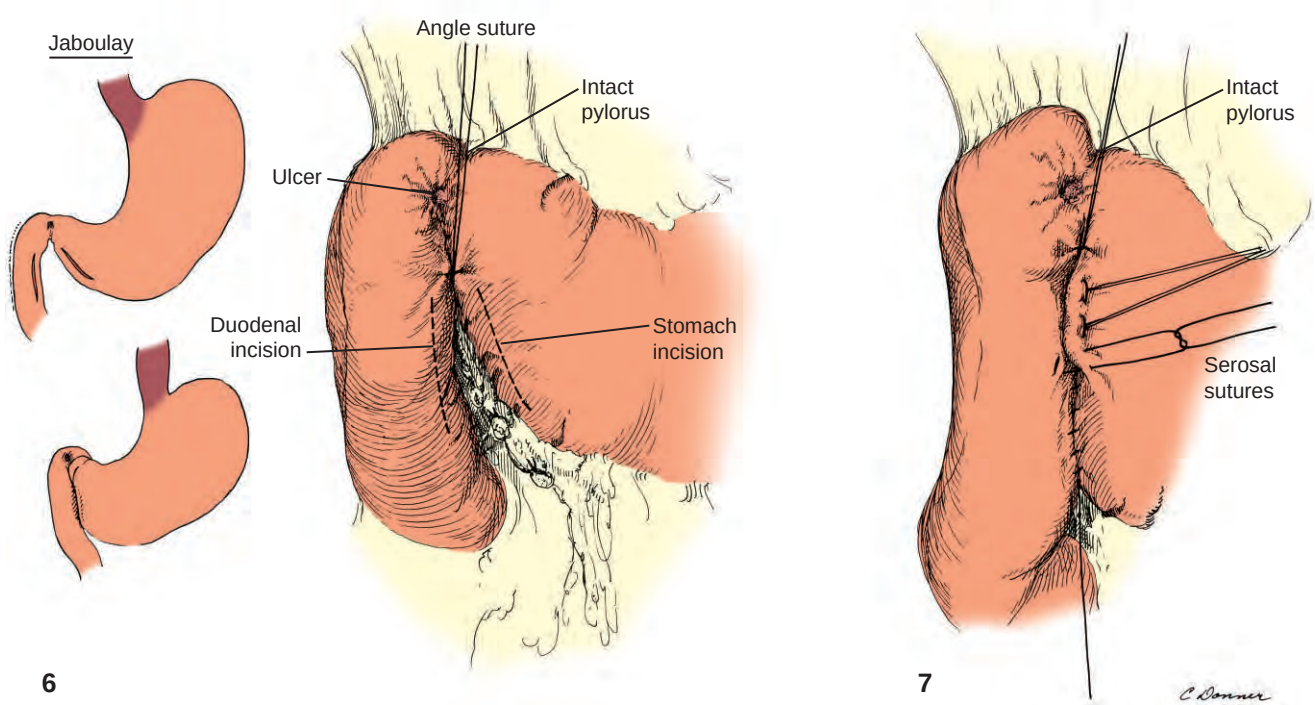

Figure 56–7. Schematic representation of the Jaboulay gastroduodenostomy. Equal-size incisions are made in the distal stomach and proximal duodenum approximately 4 to 5 cm in length *(part 6).* A final anterior, outside layer of interrupted Lembert silk sutures is then placed to complete the gastroduodenostomy *(part 7).* (From Zollinger RM: Atlas of Surgical Operations. New York, Macmillan, 1975.)

Gastric Ulcer

It is useful to consider a classification system modified after Johnson,[70] one based on anatomic location and acid secretory potential, when discussing operative therapy for gastric ulcer. This classification system is illustrated in Figure 56–8. Of importance, it may be impossible to distinguish between benign and malignant gastric ulcers purely on clinical or radiographic grounds, and 5% of ostensibly benign ulcers are found to harbor foci of malignancy.[71] A type I gastric ulcer is typically located along the lesser curvature of the stomach, usually at the antral-fundic junction, and is associated with acid hyposecretion. A type II ulcer is also found on the lesser curvature, but it occurs in younger patients in conjunction with active or healed duodenal ulcer disease. A type III gastric ulcer occurs in the prepyloric region. Both type II and type III ulcers are associated with high acid secretory capacity. A type IV ulcer encroaches on the gastroesophageal junction along the lesser curvature. A type V gastric ulcer is the result of chronic aspirin or NSAID use and may occur anywhere in the stomach.

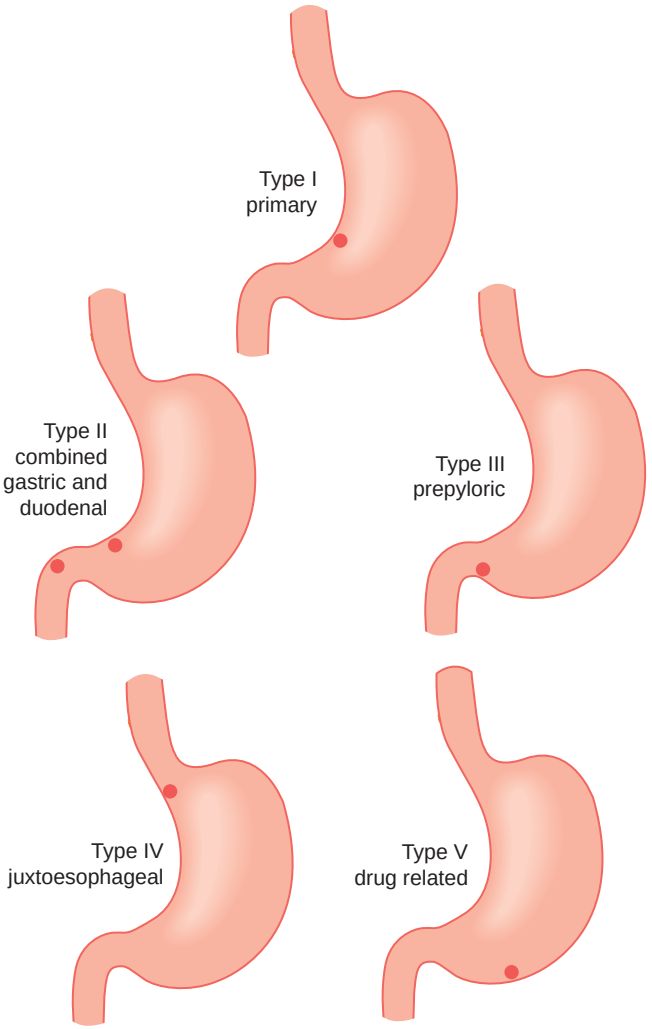

Figure 56–8. Five types of chronic gastric ulcer. (From Sleisenger MH, Fordtran JS: Operations for peptic ulcer disease and early postoperative complications. In Sleisenger MH, Fordtran JS: Gastrointestinal Disease, 5th ed. Philadelphia, WB Saunders, 1993.)

Type I ulcers account for up to 60% of all gastric ulcers and occur in the setting of acid hyposecretion. Primary gastric ulceration occurs at the junction of the fundic and antral mucosa, often at or near the incisura, and almost always on the lesser curvature. The standard approach to these ulcers is a distal gastrectomy that encompasses the ulcer itself, followed by Billroth I or II reconstruction. Recurrence rates are very low,[72-74] and excellent symptomatic relief is usually achieved.[73,75] In general, closure of the duodenal stump is almost never a problem in the setting of a type I ulcer because the duodenal bulb is usually normal. Distal gastrectomy removes not only the ulcer itself but also much of the remaining susceptible mucosa, excises the diseased antrum, reduces acid secretory potential, and speeds gastric drainage. Distal gastrectomy also removes a major mucosal colonization site for *H. pylori*.

Because acid hypersecretion is not a major pathogenetic factor in gastric ulcer disease, it is unnecessary to add vagotomy to distal gastrectomy for a type I ulcer, which serves to only increase postoperative sequelae. Truncal vagotomy with drainage, when compared with distal gastrectomy in prospective series, carries greater morbidity, as well as higher recurrence and reoperation rates for gastric ulcer.[76-78] Furthermore, because the ulcer is left in situ, extensive biopsy is necessary to exclude malignancy. Consequently, vagotomy with pyloroplasty has a limited role in the treatment of this disease and should be reserved for high-risk patients requiring an expedient operation.[76]

Type II ulcers occur synchronously with duodenal ulcer disease or diathesis and account for up to 25% of all gastric ulcers. They exhibit pathologic derangements associated with duodenal rather than gastric ulcers, such as acid and pepsin hypersecretion, and the principles of treatment are analogous to those for duodenal ulcer. Vagotomy plus antrectomy is frequently preferred because it reliably addresses the duodenal ulcer, removes the gastric ulcer, and excises susceptible antral mucosa. There are advocates for truncal vagotomy and drainage in conjunction with ulcer excision, but no consensus exists in the literature. The use of proximal gastric vagotomy for type II ulcers has not been adequately assessed, but the data of Jordan[70] would appear to advise against its use in this setting.

A type III gastric ulcer refers to lesions situated in the prepyloric region of the stomach, although no precise anatomic definition exists. Accounting for 20% of all gastric ulcers, they also occur in the setting of increased acid and pepsin secretion and should be approached in a manner similar to duodenal ulcer. Truncal vagotomy plus antrectomy is probably superior to truncal vagotomy, drainage, and ulcer excision for these lesions. Proximal gastric vagotomy in this setting has been associated with excessively high recurrence rates approaching 35% and is therefore not recommended.[79-81]

Type IV ulcers are high-lying ulcers located within 1 to 2 cm of the gastroesophageal junction. Pathophysiologically, type IV ulcers are associated with gastric hypose-

cretion and represent a subset of primary gastric ulcers that occur in antral mucosa and extend high along the lesser curvature. The technical difficulty involved in their surgical treatment accounts for their separate categorization. If distal esophageal integrity can be ensured, subtotal gastric resection, including the ulcer bed, is considered optimal.[69] A variety of techniques have been proposed to address ulcers whose proximity to the gastroesophageal junction makes standard resection problematic. A Roux-en-Y jejunal segment (Csende procedure) may be useful for reconstruction. Other alternatives include the Pauchet procedure (a distal gastrectomy that is extended along the lesser curve to include the ulcer) and the Kelling-Madlener procedure (in which a distal gastrectomy is performed with the ulcer left in situ after biopsy). Safe management of type IV ulcers requires mature surgical judgment.

Drug-associated type V gastric ulcer lesions are best treated by withdrawal of the offending agent and only in rare circumstances come to surgery in the absence of severe complications.

As previously mentioned, chronic postoperative morbidity inevitably affects a significant minority of patients. The most common adverse digestive side effects of ulcer operations are epigastric fullness and episodic diarrhea, each occurring in about 20% to 35% of patients after classic ulcer operations. Many patients also experience nausea, heartburn, and intermittent vomiting of bile or food. "Dumping" symptoms (postprandial faintness, sweating, and other vasomotor symptoms) occur in approximately 10%. The incidence and severity of these postoperative sequelae must be considered when comparing various surgical options and should be discussed in detail with patients during the planning stages of elective surgery.

Historically, the functional outcome after antiulcer surgery has been assessed by a four-grade system introduced by Visick in 1948[82] and subsequently modified by Goligher et al.[83] Patients are categorized as "excellent" (grade 1, asymptomatic), "good" (grade 2, mild symptoms but no disability), "satisfactory" (grade 3, moderate symptoms not easily controlled and producing some disability), or "unsatisfactory" (grade 4, severe postoperative symptoms with considerable disability). The Visick system has a number of obvious shortcomings, most notably the fact that it relies heavily on subjective evaluation by both the patient and surgeon. Moreover, all cases of recurrent ulceration are classified as grade 4 regardless of whether the ulcer is symptomatic or easily treated by medication. Rates of postoperative ulcer recurrence vary widely and depend on not only the surgical technique but also the vigilance with which recurrence is sought. Many series report only symptomatic recurrences despite the fact that endoscopic surveillance indicates that as many as half of recurrences are asymptomatic.[84] Most would agree that trials of ulcer surgery performed in the pre-endoscopy era greatly underestimate the true incidence of recurrence.

Since the introduction of truncal vagotomy with antrectomy as an alternative to gastrojejunostomy or pyloroplasty by Smithwick in 1945,[67] surgeons have repeatedly argued about the indications for use of vagotomy and drainage. Although proponents of truncal vagotomy with pyloroplasty have maintained that the incidence of postoperative sequelae is greater with resection than with drainage, this has not been demonstrated. In fact, a number of trials were performed in the 1960s that compared the results of subtotal gastrectomy, truncal vagotomy with drainage, and truncal vagotomy with resection. The several series reported from the Leeds-York group,[66,83,85] as well as prospective studies by Price et al.[86] and by Jordan and Condon,[87] uniformly demonstrate that the resectional procedures yielded the lowest recurrence rates (1% to 2% versus up to 10% with drainage procedures) without a clear difference among these procedures in the incidence of postoperative functional disturbances. Operative mortality was generally somewhat higher with resection than with drainage procedures, and even ardent supporters of antrectomy tend to avoid gastric resection in high-risk or elderly patients.[88] Because of concern of leakage from the duodenal suture line, antrectomy is also avoided in the presence of extensive duodenal inflammation.

When compared with truncal vagotomy and drainage, proximal gastric vagotomy preserves the antropyloric motor apparatus, avoids the need for concomitant drainage or resection, and minimizes the complications of dumping, diarrhea, malnutrition, anemia, bile gastritis, and weight loss.[84,88-96] Because the stomach is not entered during the course of the procedure and no suture lines are created, infectious complications are few and problems of afferent or efferent loop obstruction (by definition) do not occur. Mortality from proximal gastric vagotomy has been estimated to be less than 0.3%.[97]

Proximal gastric vagotomy was initially slow to gain popularity in the United States, largely because of fears that preservation of an innervated antrum would result in hypergastrinemia and continued nonvagal stimulation of the parietal cell mass. Additionally, concern was raised over the adequacy of gastric emptying after the procedure. That these additional procedures are unnecessary was established in a prospective study reported by Holle.[56] In practice, these concerns have not been realized. Postoperative gastrin levels are comparable to those measured after total vagotomy,[98] and meal-stimulated acid secretion approximates that of selective vagotomy.[99] Gastric emptying approaches normal. In fact, the degree of postoperative digestive disturbances with this procedure is quite minimal. The percentage of patients who are categorized as Visick grade I after this procedure is nearly indistinguishable from normal control populations after exclusion of patients with ulcer recurrence.[100,101] The symptoms of postoperative diarrhea and dumping are vanishingly small. The fact that these sequelae are commonly seen after selective gastric vagotomy but not after proximal gastric vagotomy strongly suggests that it is the emptying procedure and not the vagotomy that is responsible for the postvagotomy diarrhea and dumping.

The greatest concern with proximal gastric vagotomy is the high rate of recurrent ulceration. Long-term follow-up data from prospective studies have reported recurrence rates approaching 40% with this procedure.[51] Part of this may be due to the close scrutiny that this

procedure has received and the vigilance with which recurrences (many of them minimally symptomatic or silent) have been sought, particularly since the beginning of the modern endoscopic era. Technical familiarity and expertise with this procedure are clearly important,[57,102] the major problem being inadequate denervation of the acid-secreting regions. Some investigators, notably Jordan,[103] also attribute the high rate of recurrence to the inclusion of patients with pyloric channel or prepyloric ulcers. Although these patients, as a population, are acid hypersecretors and should benefit from vagotomy, the incidence of recurrent ulceration is particularly high in this subset. This high rate of recurrence may be due to a degree of gastric outlet obstruction associated with the presence of a local inflammatory reaction in the region of the pylorus. Based on these data, proximal gastric vagotomy is probably best avoided in patients with prepyloric or channel ulcers.

Laparoscopic proximal gastric vagotomy has met with some promising results, although it is unlikely to find wide application because of its technical demands.[63] The minimally invasive version of the Taylor procedure may prove to be a better alternative. Anecdotal results with the use of this approach have been reported.[64] Most surgeons agree that the trade-off between ulcer recurrence and postoperative digestive sequelae tends to weigh in favor of proximal gastric vagotomy for the few patients who require elective ulcer surgery. Recurrences after proximal gastric vagotomy are frequently mild and generally easily managed medically, particularly when antisecretory agents can be combined with antimicrobials in the setting of *H. pylori* infection. Numerous clinical series, including several prospective randomized trials, have demonstrated its superiority to other acid-reducing operations in terms of postoperative morbidity.[79,91,94,96,100,102,104-106]

The results of Taylor's anterior lesser curve seromyotomy and posterior truncal vagotomy are comparable to those of proximal gastric vagotomy with regard to reduction in acid secretion and ulcer recurrence. The great advantage of this procedure is its relative technical simplicity in comparison to proximal gastric vagotomy. Siriwardena and Gunn[107] reported an experience involving 241 patients in which they observed a 14% recurrence rate in 5 years. Eighty-one percent of their patients were classified as Visick grade I or II, and only 10% experienced significant postoperative symptoms (heartburn, distention, or flatulence). There were no instances of dumping or significant diarrhea. Taylor and colleagues performed a prospective randomized trial comparing this procedure with truncal vagotomy plus pyloroplasty.[108] Both procedures produced similar reductions in the acid secretory response to provocative insulin challenge (Hollander test). As with proximal gastric vagotomy, anterior lesser curve seromyotomy with posterior truncal vagotomy was associated with more recurrences but substantially fewer undesired postoperative effects. Ulcer recurrence rates appear to be equivalent to the results of proximal gastric vagotomy. A small subset of patients have experienced delayed gastric emptying that has required reoperation for a drainage procedure.[63]

CURRENT INDICATIONS FOR VAGOTOMY AND DRAINAGE

Although truncal vagotomy plus pyloroplasty is infrequently performed in the elective treatment of intractable peptic ulcer, it is useful in select patients suffering from perforated and especially bleeding duodenal and type II and III gastric ulcers. Vagotomy with drainage (pyloroplasty and gastrojejunostomy) also remains useful in the treatment of select patients with peptic gastric outlet obstruction. These recommendations are explained in detail in the following section.

Peptic Ulcer Intractability

Few patients have peptic ulcers that are absolutely refractory to optimal medical management. The duration and severity of symptoms, a history of patient noncompliance, or the frequency of recurrences may render elective surgery an excellent therapeutic alternative in some patients. Most patients who require surgery for duodenal ulcer are seen in the context of ulcer complications (hemorrhage, perforation, or obstruction), either as surgical emergencies or semi-electively after nonoperative management of a severe complication. Occasionally, patients who have suffered frequent recurrences, have chronic blood loss, or are at high risk for ulcer complications (e.g., renal transplant patients) will become appropriate candidates for elective surgical treatment. Elective surgery is indicated for many patients with giant gastric ulcers, which are more difficult to heal with medical therapy and carry a greater risk for complications and malignancy. Finally, patients who cannot tolerate the side effects of antiulcer drug regimens, particularly those used for the treatment of *H. pylori* infection, should be considered for elective ulcer surgery.

In the absence of concomitant complications, vagotomy plus drainage is not recommended for the treatment of intractable peptic ulcer. We recommend proximal gastric vagotomy as the procedure of choice in the elective treatment of intractable duodenal and type II and III gastric ulcers. Intractable type I and IV gastric ulcers are best treated by resection without concomitant vagotomy. The results of a prospective randomized controlled trial conducted by Gear[109] are interesting in the context of patient selection for elective surgery. Patients with endoscopically proven severe duodenal ulcers were treated by either proximal gastric vagotomy or H_2 receptor antagonists and underwent yearly endoscopic evaluation. After 1 to 4 years (which included maintenance H_2 receptor antagonist therapy for patients on the medical arm), 90% of the surgically treated patients versus 46% of the medically treated patients were found to be Visick grade I or II. The ulcer recurrence rate for vagotomy was 10% as compared with 54% for maintenance medical therapy. Based on this experience, it is reasonable to suggest that for severely symptomatic ulcer patients, surgery offers efficient and arguably more effective primary therapy.

Although the effect of long-term H_2 blockade on the incidence of ulcer complications remains undetermined

because studies of maintenance medical therapy have had limited follow-up or insufficient sample size,[110] it has been demonstrated that within the first 6 weeks of medical therapy for a newly diagnosed ulcer, complications of hemorrhage, perforation, or obstruction develop in 3% to 6% of patients.[111] Indeed, since the introduction of H_2 receptor antagonists there has been a somewhat paradoxical increase in the complications and mortality attributable to peptic ulcer disease.[112] In contrast, in a 14- to 18-year follow-up of patients treated by proximal gastric vagotomy,[91] despite a troubling 30% ulcer recurrence rate, there were no instances of bleeding or perforation, even though 30% of the patients initially had hemorrhage as the indication for surgery. In a study of 779 patients with surgically treated peptic ulcer disease and a minimum follow-up of 15 years, none of the 360 deaths were related to ulcer disease.[113] These findings suggest that surgical therapy offers excellent protection against life-threatening complications of ulcer disease.

A similar line of reasoning has led Taylor[112] to suggest that surgical therapy should have a more prominent role early in the management of patients who exhibit the strongest ulcer diathesis and are at the greatest risk for morbid complications. He has defined candidate patients as those who frequently relapse on maintenance therapy with H_2 receptor antagonists, those who relapse early after two or more 2-month courses of medical therapy, or those who have relapsed after three or more courses of treatment at or about the age of 50.

Peptic Ulcer Perforation

In general, the incidence rates of emergency surgery, hospital admissions, and mortality for perforated peptic ulcer have remained stable throughout the last 2 decades. In older patients, admission rates for duodenal ulcer perforation increased and gastric ulcer perforation decreased in the last decade. Duodenal perforation currently accounts for approximately 75% of peptic perforations. Of note, the mortality rate for perforated ulcer is higher in the elderly and higher after gastric than after duodenal perforation. A recent study reported a 19% postoperative mortality rate in patients with perforated peptic ulcer but 41% in the elderly.[114] Factors such as concomitant diseases, shock on admission, delayed surgery (greater than 24 hours), resectional surgery, and postoperative abdominal and wound infections have been associated with increased morbidity and mortality in patients with perforated ulcer.[115-118] For decades, delay in operative treatment has remained a primary determinant of morbidity, mortality, and cost.

The mean prevalence of *H. pylori* infection in patients with perforated peptic ulcer is approximately 60%, as opposed to the 90% to 100% figure reported for uncomplicated ulcer disease. However, if NSAID use is excluded, the prevalence of infection is similar to that found in patients with nonperforating ulcer disease—approximately 90%.[119] In addition to *H. pylori* infection and NSAID use, smoking and alcohol consumption are also associated with perforated peptic ulcer.

In patients who do not have generalized peritonitis, hemodynamic instability, or free peritoneal perforation on a diatrizoate meglumine (Gastrografin) upper gastrointestinal study, nonoperative management can be considered. Retrospective and prospective randomized studies suggest that conservative management is effective in properly selected patients.[120-124]

Over the last decade, much has been published regarding the minimally invasive approach to peptic ulcer disease. Although essentially all of the procedures used to treat peptic ulcer disease have been performed laparoscopically, the more complicated procedures are challenging laparoscopic procedures even in the elective setting. Fortunately, open management of peptic ulcer disease has evolved such that most surgeons currently perform simple closure for perforated duodenal ulcer and do not routinely add complex acid reduction procedures. Simple closure translates well from the open to the laparoscopic approach for surgeons with advanced laparoscopic skills.

In the *H. pylori* era, a perforated duodenal ulcer is routinely closed with interrupted suture. The point of perforation is usually easily recognized in the proximal anterior aspect of the duodenum. If not apparent, exploration of the remainder of the duodenum, the anterior and posterior gastric walls, and the jejunum is undertaken. Omentum is laid over the closure and secured with the ends of the previously placed sutures. Additional sutures can be placed as necessary to plicate the omentum about the closure. When combined with postoperative *H. pylori* eradication, morbidity, mortality, and ulcer recurrence after closure and omental onlay have been shown to be acceptably low.[125-127]

Most surgeons agree that a laparoscopic diagnosis of perforated ulcer is readily apparent in the majority of cases. Laparoscopic surgery has not been as widely used as expected for perforated ulcer because of concern regarding the technical challenge of two-handed manipulation and intracorporeal suturing of indurated and friable tissue. Recent studies have confirmed the appropriateness of the laparoscopic approach for treating perforated peptic ulcer in appropriately selected patients.[128-135] Laparoscopic duodenal ulcer closure with an omental patch combined with postoperative *H. pylori* eradication and proton pump inhibitor therapy has been shown to be technically feasible and associated with low morbidity and mortality and appropriately low ulcer recurrence.

Laparoscopic closure of perforated duodenal ulcer has also been shown to be a simple and safe procedure. Although initial reports of laparoscopic closure of perforated duodenal ulcer demonstrated little difference in comparison to open duodenal ulcer closure, recent data demonstrate that the laparoscopic approach is safe and maintains the benefits of the minimally invasive approach.[128,130-135] Specifically, laparoscopic closure of perforated duodenal ulcer has been associated with shorter operating time, less postoperative pain, a shorter postoperative hospital stay, and earlier return to normal daily activities than the conventional open repair has. Patients in shock, with delayed evaluation, or with a high Acute Physiology and Chronic Health Evaluation

(APACHE) II score are better served by expeditious open closure of the ulcer.[129]

Postoperatively, patients should be treated with antisecretory medications and antibiotics to eradicate *H. pylori*. A number of regimens are effective in eradicating *H. pylori*.[136,137] Treatment should be started during the immediate postoperative period, and eradication should be confirmed at the conclusion of therapy. Eradication of *H. pylori* after ulcer closure has been shown to significantly decrease ulcer recurrence in patients with *H. pylori*–associated perforated ulcers.[125] Current practice contrasts with the previous recommendation to add a concomitant acid reduction procedure to ulcer closure. Because there is no significant alteration in gastrointestinal anatomy with ulcer closure, patients suffer no postvagotomy or postgastrectomy side effects after this procedure.

Ulcer closure without a concomitant acid reduction procedure is especially indicated in patients with generalized peritonitis, shock, perforation for longer than 24 hours, or no significant symptoms for 3 months before perforation. However, in patients with perforated duodenal ulcers, truncal vagotomy and drainage could be of value in the unusual situation in which an unclear diagnosis mandates gastroduodenotomy for intraluminal exploration, a concomitant complication such as obstruction mandates drainage, or the patient has a chronic ulcer refractory to medical therapy. It should be reiterated that the benefit of definitive acid reduction surgery over closure and antibiotic therapy has not been demonstrated, and vagotomy plus drainage is not routinely used in treatment of perforated duodenal ulcer.

In patients with gastric ulcer perforation, the clinical condition and comorbid disease dictate which surgical procedure should be chosen. Truncal vagotomy with drainage is not routinely used in the treatment of perforated gastric ulcer. Commonly used procedures include simple closure with biopsy, excision and closure, and resection. Most perforated gastric ulcers are prepyloric. Prepyloric and pyloric ulcers are best treated with distal gastric resection because this technique avoids the 15% incidence of postoperative gastric obstruction seen with simple closure and also allows histologic assessment.[138] If a gastric ulcer is difficult to include in a resection, generous biopsy samples should be taken to exclude malignancy, and the ulcer is primarily closed or patched with omentum.

Peptic Ulcer Bleeding

Bleeding ulcers not associated with *H. pylori* or NSAIDs are uncommon. Recent data demonstrate that a negative biopsy urease test is unreliable for exclusion of *H. pylori* infection during the acute phase of ulcer bleeding and that bleeding peptic ulcers are not associated with *H. pylori* or NSAIDs in approximately 4% of patients.[139] Approximately half of patients with peptic ulcer bleeding use NSAIDs.

The incidence of peptic ulcer hemorrhage has decreased over the past decade. For example, in the Netherlands the incidence was 62 per 100,000 persons in 1993 and 48 per 100,000 in 2000.[140] Interestingly, despite changing treatment patterns during the 1990s, mortality rates from gastrointestinal bleeding have been relatively stable.[140,141] The incidence remained stable for both duodenal and gastric ulcer bleeding, but it was higher in patients of more advanced age. Bleeding from peptic ulcer disease most often occurs in the sixth decade of life. Epidemiologic data suggest that the incidence of emergency surgery has not changed over the last decade despite major improvements in endoscopic treatment.[142] Similarly, rebleeding (15% to 22%) and mortality (14% to 15%) in the modern endoscopic era remain unchanged.[140]

Ulcer bleeding is still a frequent cause of upper gastrointestinal bleeding and has been estimated at approximately 40% to 46%.[140] However, a recent study from the United States suggests that the percentage of patients with peptic ulcer as the source of upper gastrointestinal bleeding is decreasing.[143] A review of endoscopic data from 7822 patients with upper gastrointestinal bleeding from December 1999 until April 2001 in the national Clinical Outcome Research Initiative database demonstrated that peptic ulcer was the source of upper gastrointestinal bleeding in 20% of patients and a nonbleeding visible vessel was present in only 7% of the ulcers.

Increasing age, the presence of shock on initial evaluation, severe comorbidity, and rebleeding are associated with higher mortality in patients with bleeding ulcers.[140] The cause of death is usually multiple-system organ failure and not exsanguinating hemorrhage. Elderly patients with a hemorrhagic gastric ulcer have a high incidence of severe ulcer disease and concomitant medical problems.[144,145] Although initial endoscopic diagnosis and therapy for hemorrhagic peptic ulcer disease in the elderly are agreed on, debate exists regarding the advisability of early surgical intervention in elderly patients who have stopped bleeding.[142,146-150]

The optimal surgical management of patients with a bleeding peptic ulcer is debated. Most surgeons agree that patients with a profusely bleeding peptic ulcer associated with hemodynamic instability require aggressive resuscitation, endotracheal intubation to protect their airway, and emergency exploration to control the hemorrhage. However, the necessity and timing of surgical intervention to prevent or treat recurrent bleeding are less clear.[142,148] Some surgeons offer elderly patients with comorbid disease and an ulcer with stigmata worrisome for recurrent bleeding a semi-elective surgical procedure as soon as the initial bleeding spontaneously stops or is endoscopically controlled.[147,149,150] The role of angiographic embolization in the control of recurrent or intractable hemorrhage remains unclear. Further investigation is required to delineate the optimal medical, endoscopic, and surgical treatment of acute peptic ulcer bleeding.

A bleeding duodenal ulcer is approached through an upper midline incision. A longitudinal duodenotomy is performed to locate the ulcer, which is usually situated in the posterior duodenal bulb. As necessary, the duodenotomy is extended proximally across the pylorus or

Figure 56–9. Technique of suture control of a bleeding duodenal ulcer. Through a longitudinal pyloric incision, figure-of-eight sutures are placed at the cephalad and caudad aspect of the ulcer deep enough to occlude the gastroduodenal artery. An additional U stitch is placed to control small transverse pancreatic branches of the gastroduodenal artery. (From Zinner M: Maingot's Abdominal Operations, 10th ed. New York, McGraw-Hill, 1997.)

distally beyond the first portion of the duodenum to find the ulcer. The bleeding is controlled with digital pressure and suture ligation. Figure-of-eight sutures are applied at the cephalad and caudad margins of the ulcer to ligate the gastroduodenal artery. A U stitch is placed in the ulcer base to occlude pancreatic branches of the gastroduodenal artery. The technique suggested for suture control of ulcer bleeding is illustrated in Figure 56–9. After hemostasis is obtained, the duodenal bulb and prepyloric stomach are examined for additional ulcers. As necessary, the duodenotomy is extended to control bleeding from additional ulcers. A small duodenotomy is closed primarily and longer duodenotomies are closed via a Heineke-Mikulicz or a Finney pyloroplasty.[151]

In the past, the addition of a truncal vagotomy has been recommended to decrease recurrent bleeding. As described earlier, surgeons are less likely to add vagotomy to pyloroplasty in the *H. pylori* era. Although a vagotomy is not recommended, further study of bleeding duodenal ulcer is required to validate this recommendation. In the past, many surgeons favored the aggressive addition of a truncal vagotomy and antrectomy to duodenal ulcer oversewing in the hope of further decreasing the incidence of recurrent bleeding and ulceration. Studies of vagotomy and antrectomy without *H. pylori* treatment suggest that the morbidity and mortality of antrectomy for a bleeding duodenal ulcer are equal to that of pyloroplasty and that antrectomy decreases the incidence of recurrent bleeding.[152] Regardless of which procedure is performed, patients with a bleeding duodenal ulcer will probably have a lower rebleeding rate if *H. pylori* is eradicated than if they are treated by surgery alone. NSAID use should also be limited.

Surgical treatment of a bleeding gastric ulcer is determined by the clinical status of the patient, as well as the gastric ulcer type. In general, the recommended surgical treatment of a bleeding gastric ulcer mirrors the surgical treatment previously described for intractable gastric ulcers. In type I ulcers, the pathogenesis is not clearly understood and surgical recommendations include excision of the ulcer. At this point on the lesser curve, wedge excision is difficult and a partial gastrectomy is recommended unless the patient is unstable. If the patient is unstable, the ulcer should be excised and closed. In extreme instability, the ulcer is biopsied and oversewn and the gastrotomy is closed. Vagotomy plus pyloroplasty has previously been recommended in high-risk patients requiring urgent operations for bleeding type I gastric ulcers. However, the functional outcome of vagotomy and pyloroplasty is worse than that of vagotomy and distal gastrectomy. In addition, the lesser curve ulcer should be excised, and this makes vagotomy and pyloroplasty less attractive. Because the duodenal dissection is usually easy in patients who do not have duodenal ulceration, distal gastrectomy is recommended over vagotomy and pyloroplasty.

There is no consensus regarding surgical treatment of type II and type III bleeding ulcers. Because of concern for malignancy in gastric ulcers, excision of these gastric ulcers is recommended. The anatomy, inflammation, and patient condition at surgery dictate selection of the procedure. Excision with primary closure is acceptable when technically feasible. When simple closure would narrow the gastric outlet or multiple ulcers are present, distal gastrectomy is recommended. If significant duodenal inflammation would make distal gastrectomy technically challenging, gastric ulcer excision with vagotomy and pyloroplasty is performed. When combined with gastric ulcer excision, proximal gastric vagotomy is less appealing and has been associated with a high recurrence rate. Postoperatively, patients should have *H. pylori* infection eradicated and avoid the use of NSAIDs.

Peptic Ulcer Obstruction

In peptic ulcer disease, gastric outlet obstruction is less common than perforation or bleeding. Obstruction from a duodenal ulcer is the most common cause of peptic outlet obstruction and occurs in approximately 2% of patients with chronic duodenal ulcer. Although prepyloric, pyloric, and duodenal ulcers previously caused up to 80% of gastric outlet obstructions, it is likely that the percentage of outlet obstructions caused by ulcer disease has significantly decreased. This putative decrease has not been confirmed, however. Malignancy and chronic pancreatitis continue to cause gastric outlet obstruction and must be considered in all patients with a clinical picture suggestive of gastric outlet obstruction.

Risk factors for the development of peptic gastric outlet obstruction are similar to those for other complications of peptic ulcer disease and include NSAID use and *H. pylori* infection. Therefore, in patients with peptic gastric outlet obstruction, *H. pylori* should be eradicated and NSAID use should be limited as much as possible. Fortunately, experience has shown that many cases of gastric outlet obstruction will resolve with such treatment. Although recurrent gastric outlet obstruction has been a significant problem in the past, anecdotal clinical experience suggests that improved medical treatment of peptic ulcer disease has decreased recurrent peptic gastric outlet obstruction. However, in a number of cases, obstruction is associated with significant irreversible cicatrix formation, and nonoperative management will not provide lasting resolution of obstruction.

The recommended operation is vagotomy and antrectomy with insertion of a feeding jejunostomy tube to provide postoperative enteral nutritional support. In cases of severe inflammation that precludes safe resection of the duodenum, vagotomy plus gastrojejunostomy is recommended. A prolonged preoperative period of obstruction suggests that a gastrostomy tube could help decompress the stomach and avoid the need for prolonged use of a nasogastric tube in the postoperative period. Recent data suggest that the morbidity and mortality of elective surgical treatment of intractable gastric outlet obstruction have decreased. Interestingly, in one small series, *H. pylori* infection was present in a minority of patients with peptic gastric outlet obstruction who required surgical intervention. Endoscopic balloon dilation was used in a number of these patients without success. Operative morbidity was low and mortality was zero. Importantly, patient satisfaction was positive by the Visick scale.[153] Further investigation is required to determine the optimal combination and timing of medical, endoscopic, and surgical treatment in patients with peptic gastric outlet obstruction.

RECURRENT POSTOPERATIVE PEPTIC ULCER AFTER VAGOTOMY AND DRAINAGE

Recurrent postoperative ulceration after peptic ulcer surgery has become an increasingly uncommon problem in the last decade. Primary treatment of peptic ulcer disease with *H. pylori* eradication, NSAIDs with fewer gastrointestinal side effects, and proton pump inhibitors have decreased the incidence of peptic surgery, as well as the use of acid reduction procedures such as vagotomy and drainage. Despite less aggressive surgical procedures, postoperative recurrence rates are low because of improved medical treatment in the postoperative period. The contribution of incomplete vagotomy and gastrinoma to the development of recurrent ulcer disease requires further study in the *H. pylori* era. Because the incidence of acid reduction surgery has decreased and the incidence of gastrinoma has remained stable, it is likely that the percentage of postoperative patients with gastrinoma will increase from the 2% previously described.

Evaluation of recurrent ulceration after vagotomy and drainage begins with a thorough history and physical examination. The patient should be asked and the medical record should be reviewed regarding the initial operative indication and the procedure performed. Furthermore, past treatment of *H. pylori*, use of NSAIDs, use of antisecretory agents, smoking, alcohol consumption, and a family history of multiple endocrine neoplasia should be explored. Surreptitious use of aspirin or other NSAIDs is probably the most common cause of recurrent ulceration. The previous operative report and pathology specimens should be reviewed to seek evidence of incomplete vagotomy.

Laboratory evaluation includes a complete blood count to detect anemia, comprehensive metabolic profile to detect dehydration, a coagulation profile to detect coagulopathy in the presence of bleeding, and a gastrin level. Gastrin levels greater than 1000 pg/ml are diagnostic of a gastrinoma, and normal levels below 100 pg/ml exclude gastrinoma.[154] Moderate hypergastrinemia should be further evaluated with a secretin stimulation test. An increase in gastrin secretion greater than 100 pg/ml with secretin administration suggests gastrinoma. Previous vagotomy and G-cell hyperplasia are not associated with a significant increase in gastrin levels with secretin administration. Protein meal–stimulated gastrin levels greater than 300 pg/ml suggest G-cell hyperplasia or retained gastric antrum in patients who have previously undergone gastrectomy. Measurement of postoperative acid secretory function and sham feeding to evaluate the completeness of vagotomy are infrequently necessary and have little clinical relevance in the modern era.

Upper gastrointestinal barium study and upper endoscopy are useful in the evaluation of recurrent postoperative ulcer. Upper endoscopy can help make the diagnosis of recurrent ulcer disease, as well as localize the ulcer. Biopsy specimens are taken to assess for the presence of *H. pylori* and malignancy. Malignant ulceration is more common in gastric ulcers and is surprisingly uncommon in duodenal or jejunal ulcers. Barium studies help delineate the postoperative anatomy and functional abnormalities. However, barium studies are less sensitive and specific for recurrent ulcer disease than endoscopy is.[155,156]

Management of patients with recurrent ulcer disease after vagotomy and drainage consists of antibiotics directed at *H. pylori* if present, limitation of NSAID use, treatment with an antisecretory medication, smoking cessation, and limitation of alcohol intake. Ulcer disease refractory to such treatment is unusual. If the ulcer persists for longer than 3 months despite eradication of *H. pylori*, or maintenance antisecretory therapy for the ulcer is associated with perforation, bleeding, or obstruction, surgery is indicated. Although few data exist regarding therapeutic endoscopy for the treatment of a complicated postoperative recurrent ulcer, endoscopic control of bleeding and dilatation of the obstruction are routinely applied in a manner similar to the preoperative setting.

The choice of surgery for a recurrent ulcer after vagotomy and drainage depends on the indication for the

initial operation, the original operation performed, the cause of the recurrence, and patient comorbidity.[157] Because these ulcers have recurred despite previous peptic ulcer disease surgery and maximal medical therapy, surgery should be appropriately aggressive. Persistent ulcers are worrisome for malignant disease and should be resected. After previous vagotomy and drainage, reoperation should include repeat vagotomy and antrectomy. Of note, the functional results after reoperative peptic surgery are not as good as those after primary surgery, with good to excellent results achieved in only 60% to 70% of patients.[158-160] Fortunately, even in the pre–*H. pylori* era, second recurrences were unusual and developed in less than 10% of patients managed by gastric resection.[160]

SUMMARY

The fundamental goals of surgical treatment of peptic ulcer are to treat ulcer complications, address the ulcer diathesis, and minimize physiologic disturbances. No single procedure satisfies all the stated goals or is universally applicable to all surgical candidates. In choosing the most appropriate procedures, the surgeon must consider the characteristics of the ulcer, the patient, and the procedure, as well as previous surgical training. Vagotomy plus drainage is infrequently performed in the modern era, but it remains a valuable procedure in the surgical armamentarium. Although vagotomy plus pyloroplasty is not routinely performed for the treatment of intractable peptic ulcer, it is useful in select patients suffering from perforated and especially bleeding duodenal and type II and III gastric ulcers. Vagotomy with drainage (pyloroplasty and gastrojejunostomy) also remains useful in the treatment of select patients with peptic gastric outlet obstruction.

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Chapter

57

Gastric Resection and Reconstruction

Douglas J. Turner · Michael W. Mulholland

PREOPERATIVE PREPARATION

A first- or second-generation cephalosporin is adequate coverage for the majority of gastric operations, with a broader-spectrum antibiotic used in patients with achlorhydria or gastric outlet obstruction. The intravenous delivery is completed before skin incision. Pneumatic compression boots are worn for prophylaxis of deep vein thrombosis.

A bowel preparation is useful only in complicated cases and will both aid exposure through decompression and lessen the bacterial load if an intestinal bypass is required. In this instance, oral erythromycin and neomycin are administered in 1-g preparations at 1 PM, 2 PM, and 11 PM for a morning surgery planned for the next day. Polyethylene glycol solutions are administered to mechanically cleanse the bowel.

After a general anesthetic agent is administered, the patient is placed in the supine position, with the operating surgeon on the right side of the patient. Some degree of reverse Trendelenburg positioning will also facilitate exposure. A midline incision from the xiphoid to the umbilicus is adequate for most gastric operations and can easily be extended bidirectionally in obese patients and those for whom better exposure is mandated.

On entering the abdomen, the surgeon should perform a routine exploration of the abdominal cavity. A nasogastric tube for decompression of the stomach should be placed by the anesthetist, if not already in place, to allow orientation within the abdomen. Although it is often maintained postoperatively, routine nasogastric decompression has not been shown to affect outcomes in postgastrectomy patients in several reports.

PROCEDURES

Truncal Vagotomy

The steps involved in truncal vagotomy include the following sequence: exposure of the esophagogastric junction (Figs. 57–1 to 57–4), exposure of the anterior vagus nerve (Fig. 57–5), ligation of the nerve trunk (Fig. 57–6), exposure and isolation of the posterior vagus nerve (Fig. 57–7), and ligation of the nerve trunk (Fig. 57–8).

Proximal Gastric Vagotomy

The steps involved in proximal gastric vagotomy include the following sequence: interior anterior dissection (Figs. 57–9 and 57–10), neurovascular ligation (Fig. 57–11), periesophageal and posterior dissection (Figs. 57–11 and 57–12), and esophageal skeletonization (Figs. 57–13 and 57–14).

Highly Selective Vagotomy

The steps involved in highly selective vagotomy include the following sequence: port placement (Fig. 57–15), exposure of the gastroesophageal junction (Fig. 57–16), division of the gastrohepatic omentum (Fig. 57–17), isolation of the posterior trunk (Fig. 57–18), division of the posterior trunk (Fig. 57–19), identification of the anterior trunk (Fig. 57–20), and division of the vagal branches (Fig. 57–21).

Pyloroplasty

The steps involved in pyloroplasty include the following sequence: (1) incision (Figs. 57–22 and 57–23) and closure (Figs. 57–24 and 57–25) for the Heineke-Mikulicz pyloroplasty; (2) incision (Fig. 57–26), posterior closure (Fig. 57–27), and anterior closure for the Finney pyloroplasty (Figs. 57–28 and 57–29); and (3) incision (Figs. 57–30 and 57–31) and closure (Fig. 57–32) for the Jaboulay pyloroplasty.

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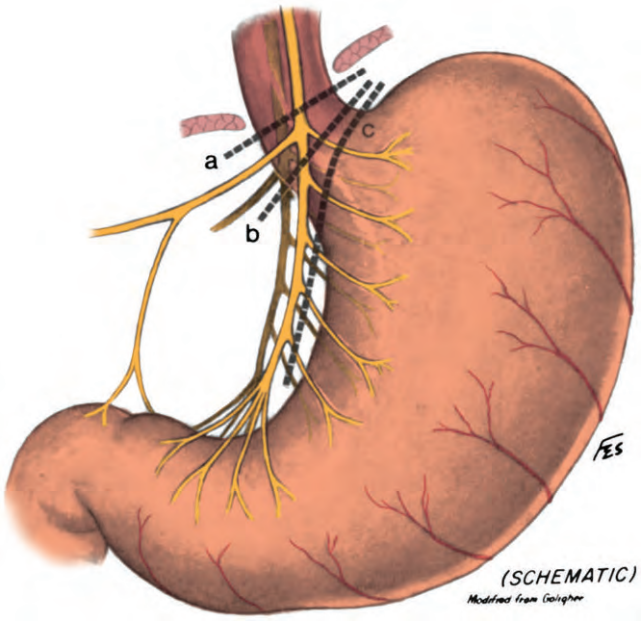

Figure 57–1. Depiction of normal vagal anatomy and the traditional incision sites for standard vagotomies. Truncal vagotomy, shown as the incision at level *a,* involves transection of the nerves as they traverse the diaphragmatic hiatus. Selective vagotomy *(b)* severs the vagal trunks after the takeoff of the hepatic and celiac branches. Proximal gastric vagotomy (also highly selective vagotomy and parietal cell vagotomy) *(c)* incises the esophagogastric vagal branches at the level of the stomach while preserving the hepatic and celiac branches, as well as innervation to the antrum and pylorus (the "crow's foot" of the nerves of Latarjet). (From Braasch JW: Truncal vagotomy and Heineke-Mikulicz pyloroplasty including selective vagotomy. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 48.)

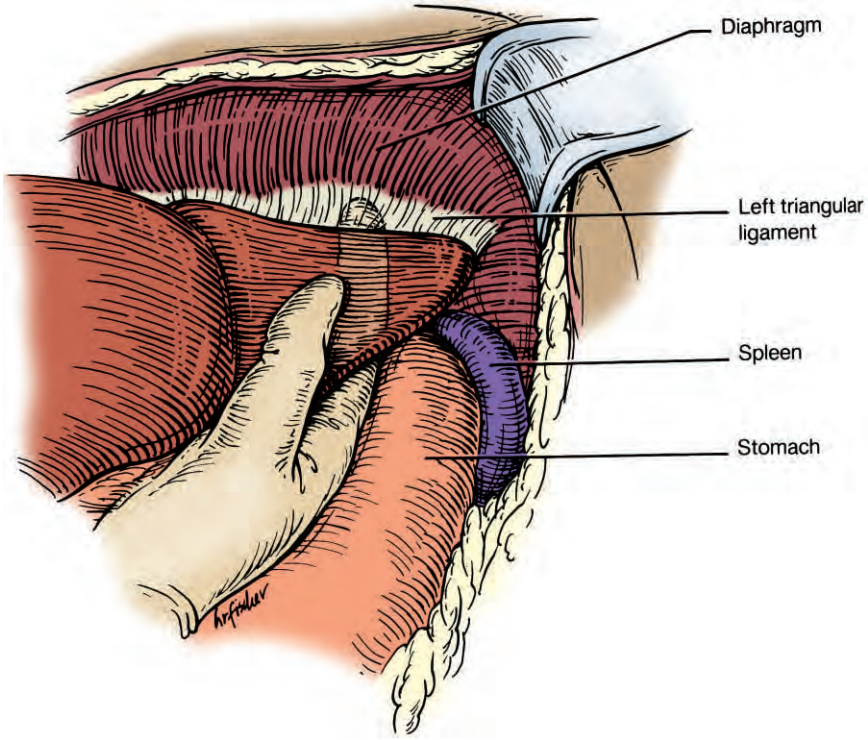

Figure 57–2. The left lateral segment of the liver should be mobilized to allow full exposure of the gastroesophageal junction. The surgeon's right hand retracts the left lateral segment inferiorly to expose the left triangular ligament, which is thin and translucent. This ligament can be divided by electrocautery; mobilization need proceed only to the midline for adequate exposure. Care should be taken to avoid the inferior phrenic vein as the midline is approached. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 306.)

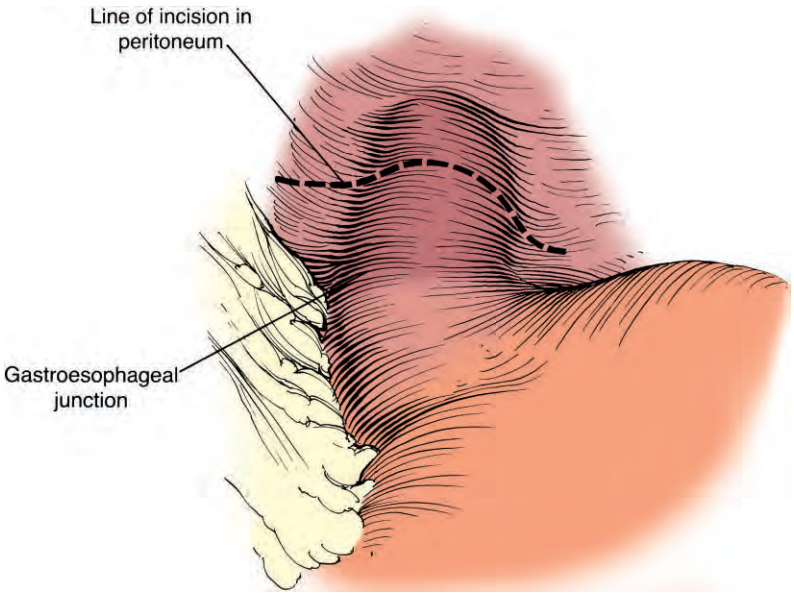

Figure 57–3. Line for incision of the peritoneum to expose the distal esophagus and gastroesophageal junction. Palpation of the preoperatively placed nasogastric tube ensures that this location is correct. (From Pappas TN: Truncal vagotomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia WB Saunders, 1994, p 330.)

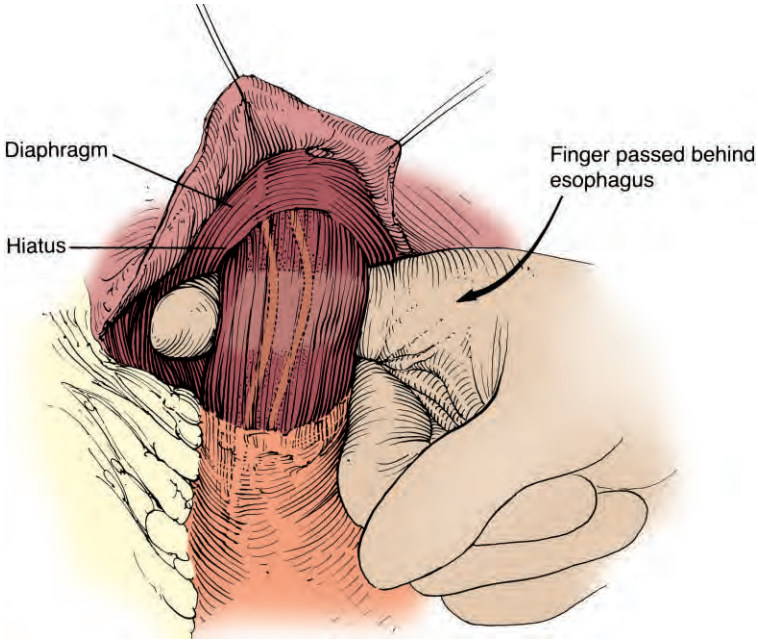

Figure 57–4. Blunt, gentle encirclement of the esophageal hiatus after exposure should be attempted as cephalad as possible to capture the posterior vagus in the encirclement. Palpation of the nasogastric tube before this maneuver will help avoid errors. A Penrose drain or umbilical tape is then placed around the esophagus to aid in retraction. (From Pappas TN: Truncal vagotomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 330.)

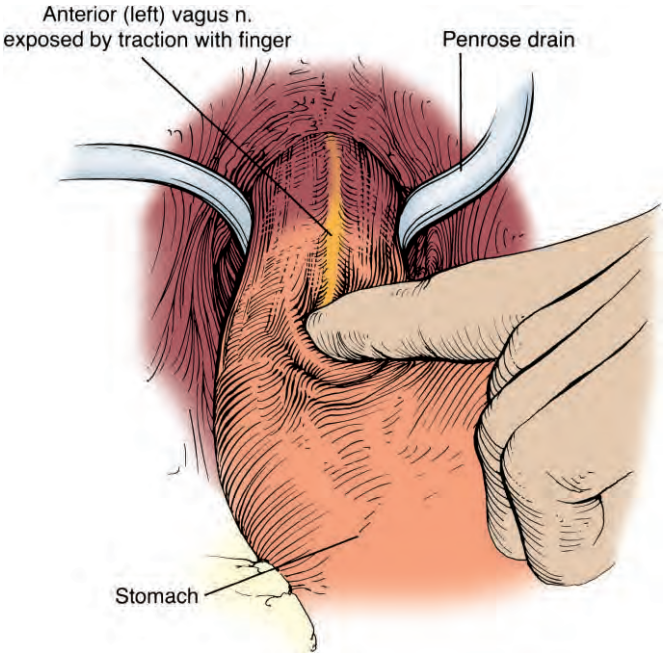

Figure 57–5. Exposure of the anterior vagus nerve. This structure is often likened to a bowstring and is palpated by passing a finger across the distal end of the esophagus. If the anterior vagus is not palpable, it usually becomes more prominent, as shown here, with gentle downward traction on the stomach. If the nerve cannot be found with these maneuvers, gentle downward traction can be placed on the hepatic branch of the anterior vagus nerve, which will expose the anterior trunk. The hepatic branch is usually visible within the gastrohepatic ligament. (From Pappas TN: Truncal vagotomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 331.)

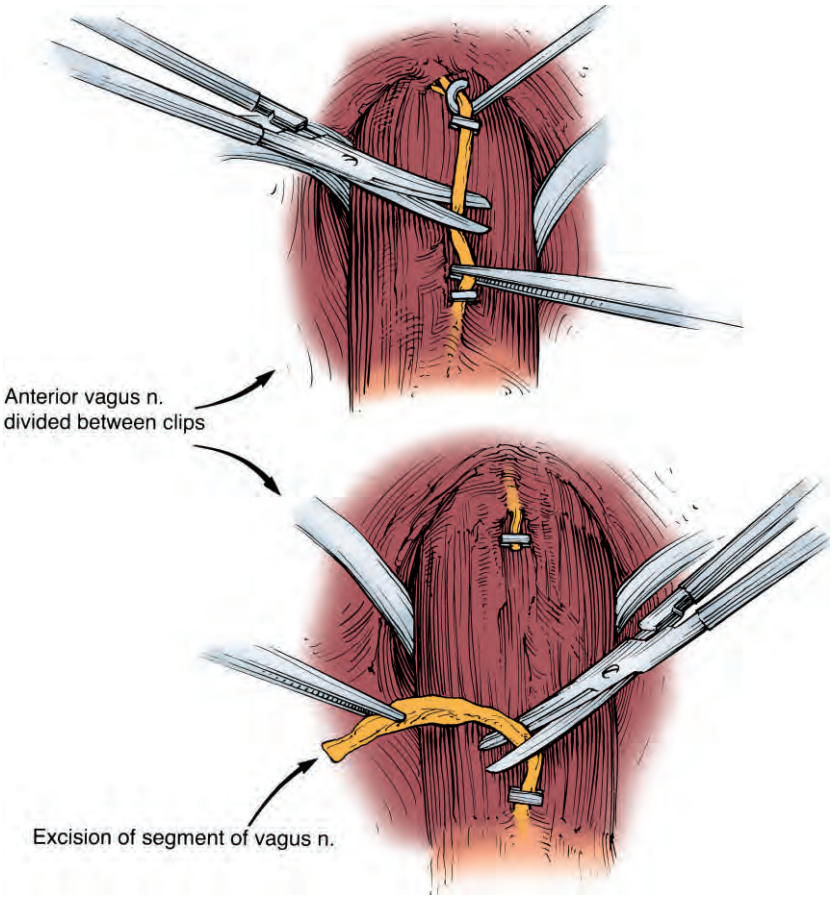

Figure 57–6. Ligation and excision of the anterior vagus nerve. A 2-cm length of nerve is excised and sent to the pathology laboratory for histologic confirmation. (From Pappas TN: Truncal vagotomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 331.)

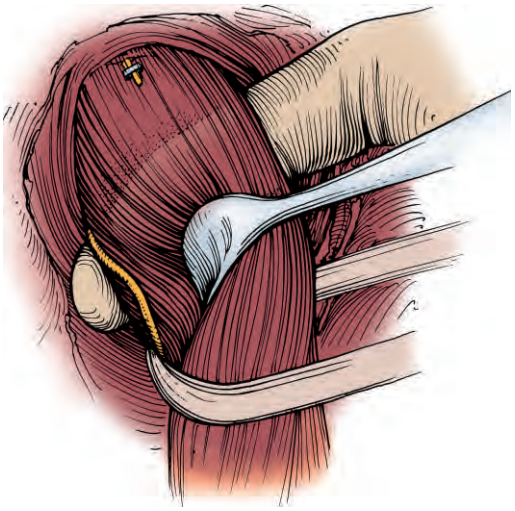

Figure 57–7. Exposure of the posterior vagus nerve, which usually lies between the esophagus and the right crus of the diaphragm. The esophagus is retracted to the left and anteriorly to expose the right crus. The Penrose drain should contain the posterior vagus nerve if the blunt encirclement was performed at or above the level of the diaphragm. With slight rotation of the esophagus, the nerve is identified by the surgeon's finger and delivered into view. If the vagus cannot be found, palpation of the esophagus should be performed to locate the nerve before separating it from the esophagus. Alternatively, one could retract the celiac division of the posterior vagus if it is easily seen. (From Pappas TN: Truncal vagotomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 332.)

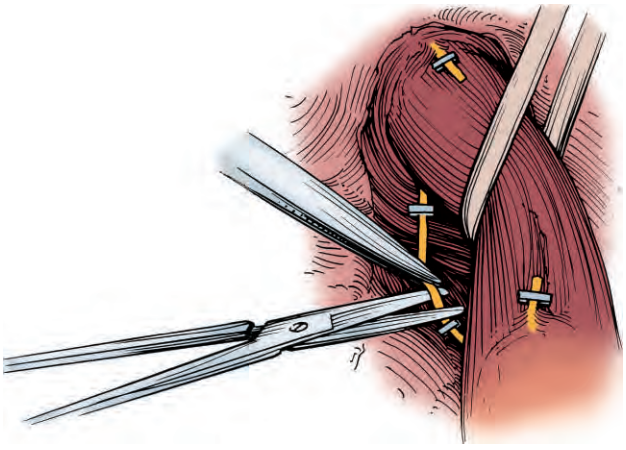

Figure 57–8. Ligation of the posterior vagus, with excision of a 2-cm portion that is sent to the pathology laboratory. (From Pappas TN: Truncal vagotomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 332.)

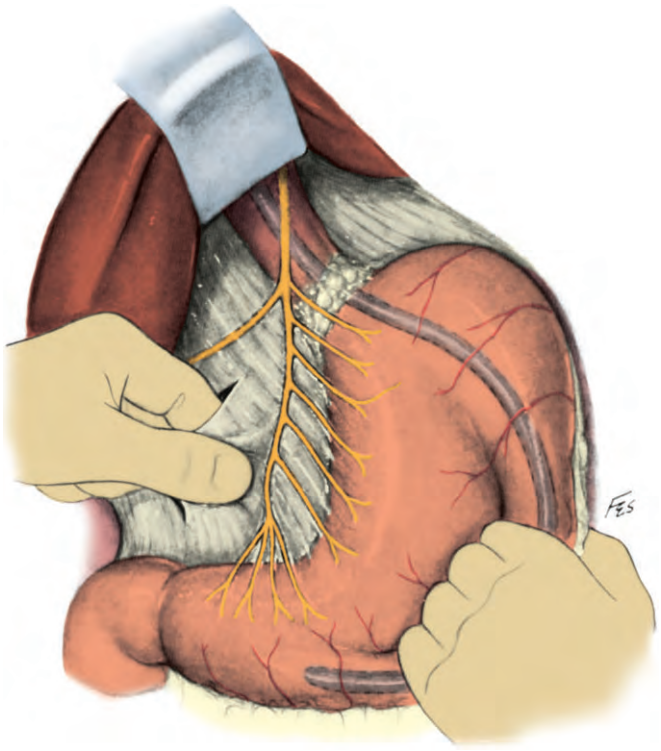

Figure 57–9. Initial exposure for proximal gastric vagotomy. The gastrohepatic ligament is opened after confirmation of the absence of a replaced left hepatic artery. The anterior nerve of Latarjet is tented to expose its gastric branches. The hepatic branch is identified and preserved. The first assistant stabilizes the stomach to prevent avulsion of the short gastric vessels and consequent splenic injury. (From Rossi RL: Parietal cell vagotomy [highly selective vagotomy]. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 56.)

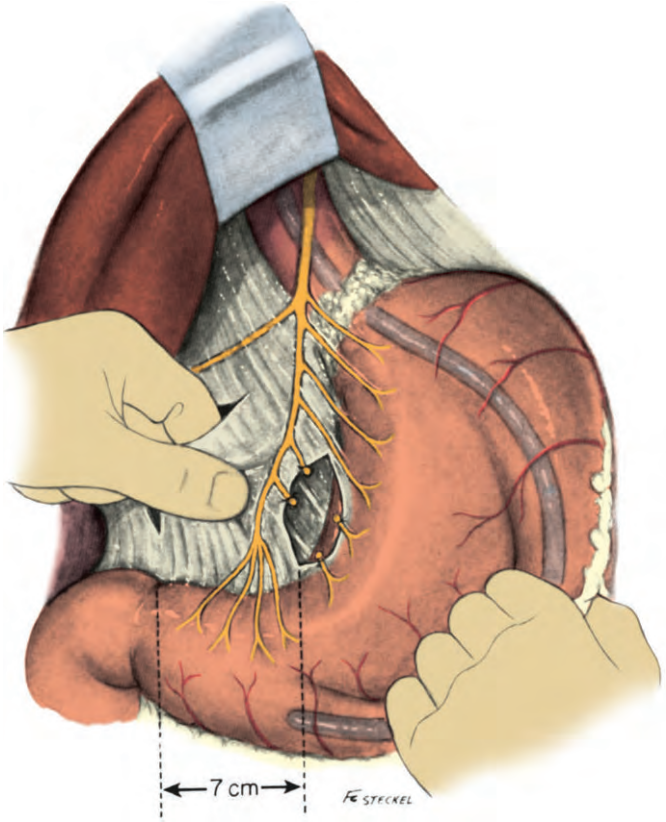

Figure 57–10. Dissection is initiated 7 cm proximal to the pylorus, which will allow preservation of the anterior nerve of Latarjet and maintain antral and pyloric innervation. (From Rossi RL: Parietal cell vagotomy [highly selective vagotomy]. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 57.)

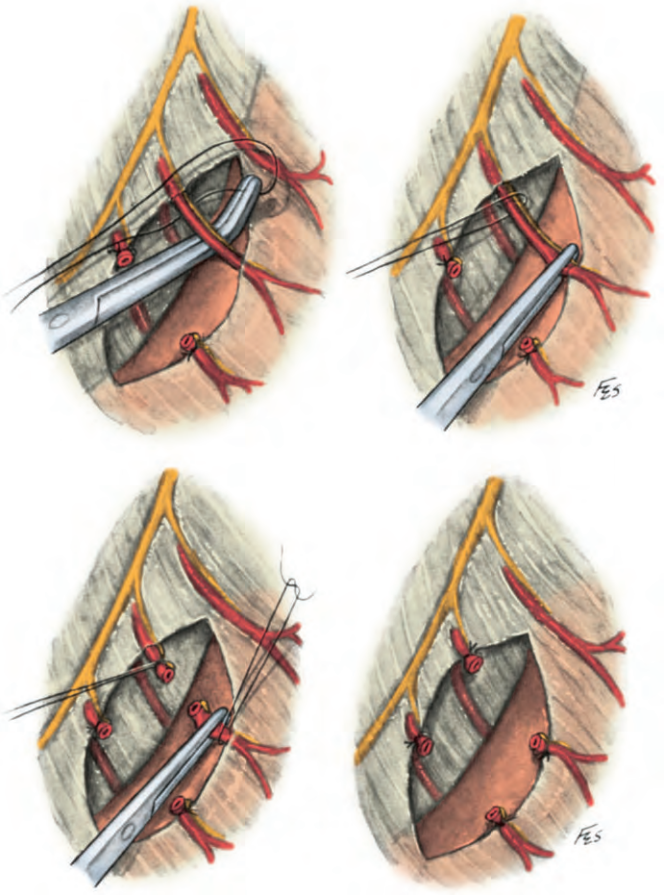

Figure 57–11. Ligation of the neurovascular bundles, which proceeds cephalad toward the gastroesophageal junction and continues completely over the esophagus toward the angle of His to completely skeletonize the stomach body and fundus. (From Rossi RL: Parietal cell vagotomy [highly selective vagotomy]. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 56.)

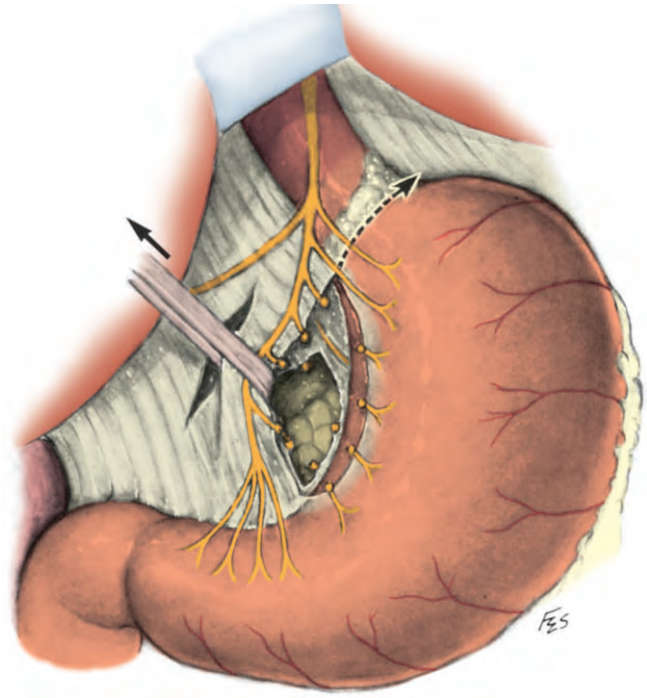

Figure 57–12. The posterior leaf of the gastrohepatic ligament is dissected in a similar manner through the window created by the anterior dissection. The dissection proceeds cephalad toward the esophagogastric junction and continues across the peritoneum overlying the anterior surface of the esophagus toward the angle of His. (From Rossi RL: Parietal cell vagotomy [highly selective vagotomy]. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 58.)

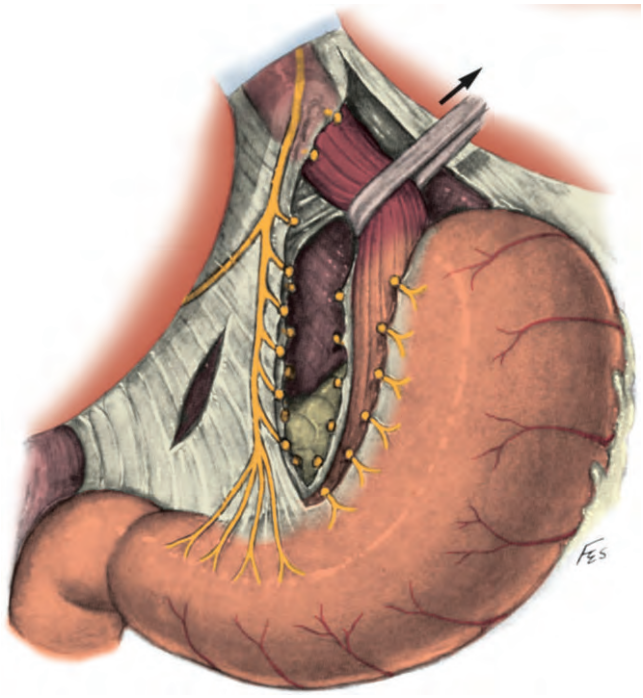

Figure 57–13. Fibers from the anterior vagus are gently swept off the anterior surface of the esophagus and divided. The distal end of the esophagus is skeletonized for 6 to 8 cm to completely divide the vagal efferents, some of which travel intramurally to innervate the proximal part of the stomach. Special attention should be directed toward division of the "criminal" nerves of Grassi, which loop off the posterior vagus and travel posteriorly to innervate the superior fundus. (From Rossi RL: Parietal cell vagotomy [highly selective vagotomy]. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 59.)

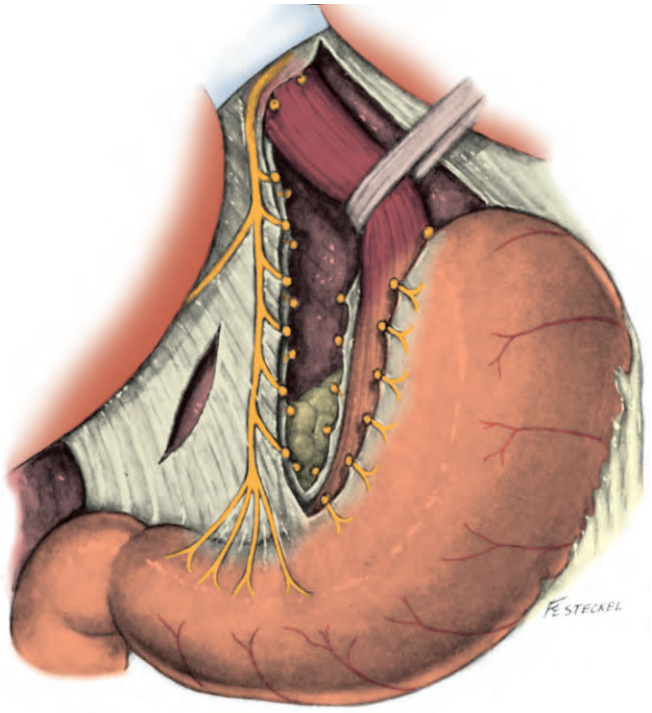

Figure 57–14. Completed dissection demonstrating sparing of the anterior and posterior trunks, as well as innervation to the antrum. (From Rossi RL: Parietal cell vagotomy [highly selective vagotomy]. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 59.)

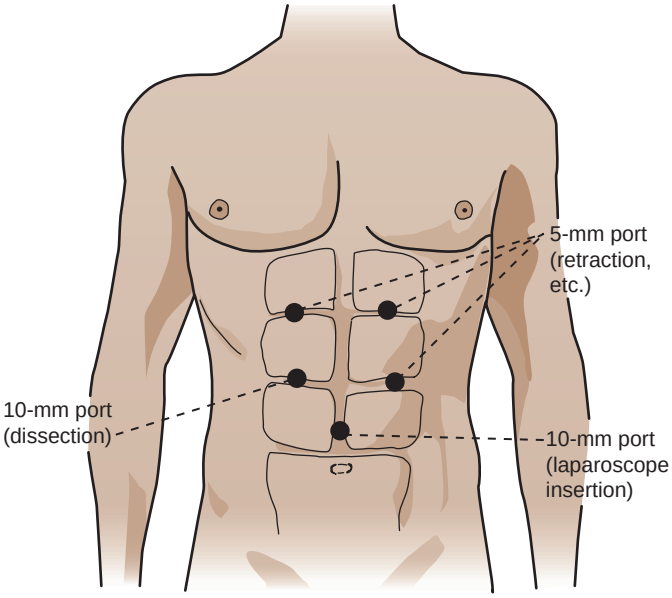

Figure 57–15. Sites of port placement for laparoscopic highly selective vagotomy. Pneumoperitoneum is established in standard fashion. The camera is introduced through the umbilical port, retractors for the liver and the stomach are placed through the two superior ports, and the remaining ports are used for the dissection. Reverse Trendelenburg positioning is used to aid in exposure.

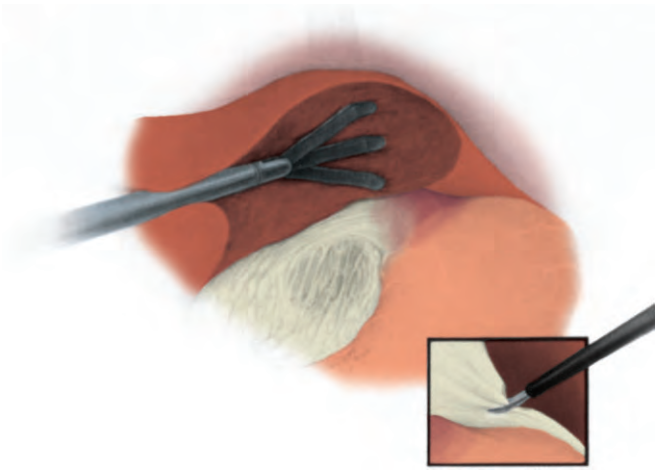

Figure 57–16. A fan-type retractor is used to retract the left lateral segment of the liver away from the gastroesophageal junction. Partial division of the left triangular ligament *(inset)* allows for optimal retraction. (From Bailey RW, Zucker KA, Flowers JL: Vagotomy. In Ballantyne GA, Leahy PF, Modlin IM [eds]: Laparoscopic Surgery. Philadelphia, WB Saunders, 1994, p 409.)

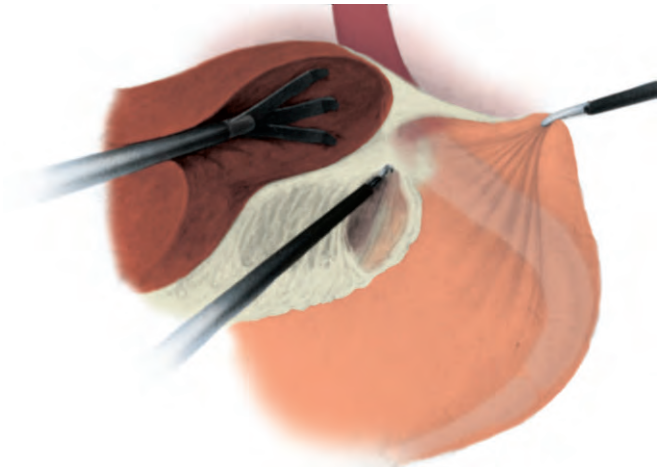

Figure 57–17. A window is created in the avascular portion of the gastrohepatic ligament along the lesser curvature to approach the posterior aspect of the gastroesophageal junction. The stomach is retracted toward the left to aid in this dissection. (From Bailey RW, Zucker KA, Flowers JL: Vagotomy. In Ballantyne GA, Leahy PF, Modlin IM [eds]: Laparoscopic Surgery. Philadelphia, WB Saunders, 1994, p 409.)

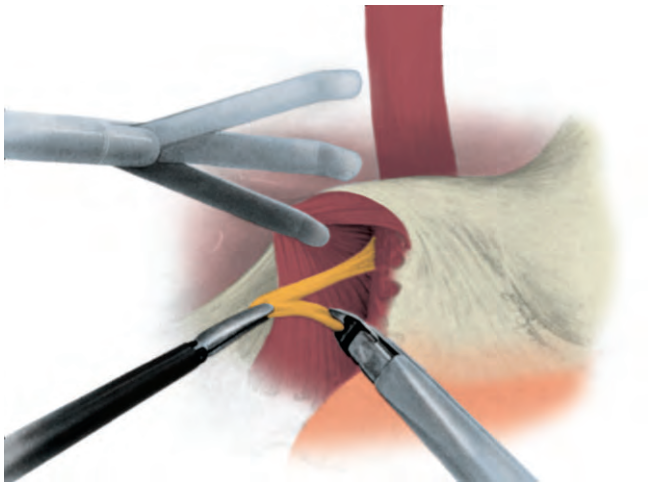

Figure 57–18. The right crus of the diaphragm is retracted to the patient's right to allow identification of the posterior vagal trunk behind the esophagus. The nerve is isolated and exposed for ligation. (From Bailey RW, Zucker KA, Flowers JL: Vagotomy. In Ballantyne GA, Leahy PF, Modlin IM [eds]: Laparoscopic Surgery. Philadelphia, WB Saunders, 1994, p 411.)

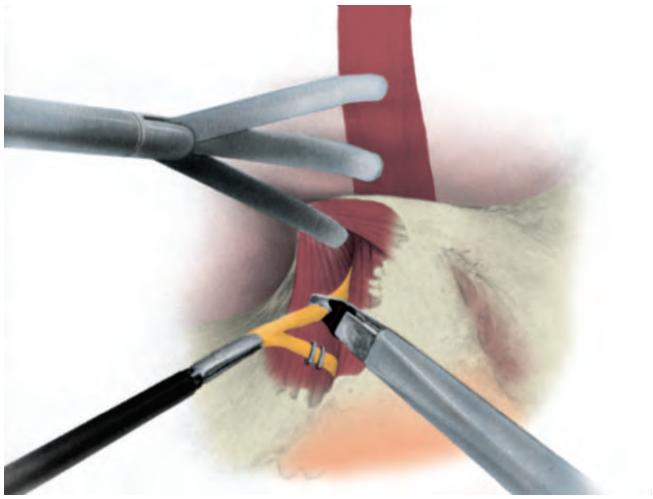

Figure 57–19. The main trunk of the posterior vagus is clipped and ligated; the proximal extent of ligation should be as close as possible to the esophageal hiatus. (From Bailey RW, Zucker KA, Flowers JL: Vagotomy. In Ballantyne GA, Leahy PF, Modlin IM [eds]: Laparoscopic Surgery. Philadelphia, WB Saunders, 1994, p 411.)

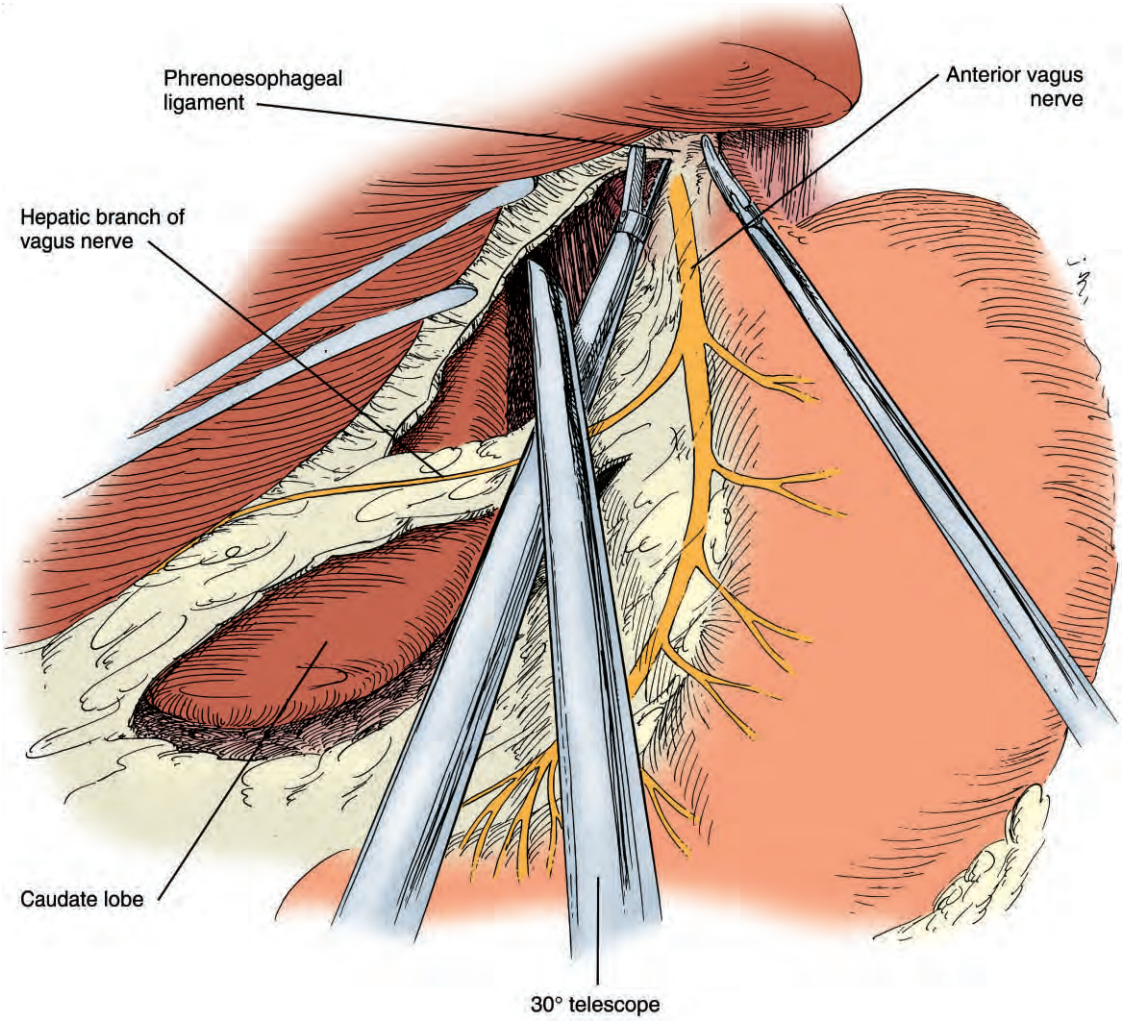

Figure 57–20. The anterior vagal trunk is located in the peritoneum on the anterior surface of the esophagus and then gently elevated to provide optimal exposure. (From Ballantyne GH: Atlas of Laparoscopic Surgery. Philadelphia, WB Saunders, 2000, p 167.)

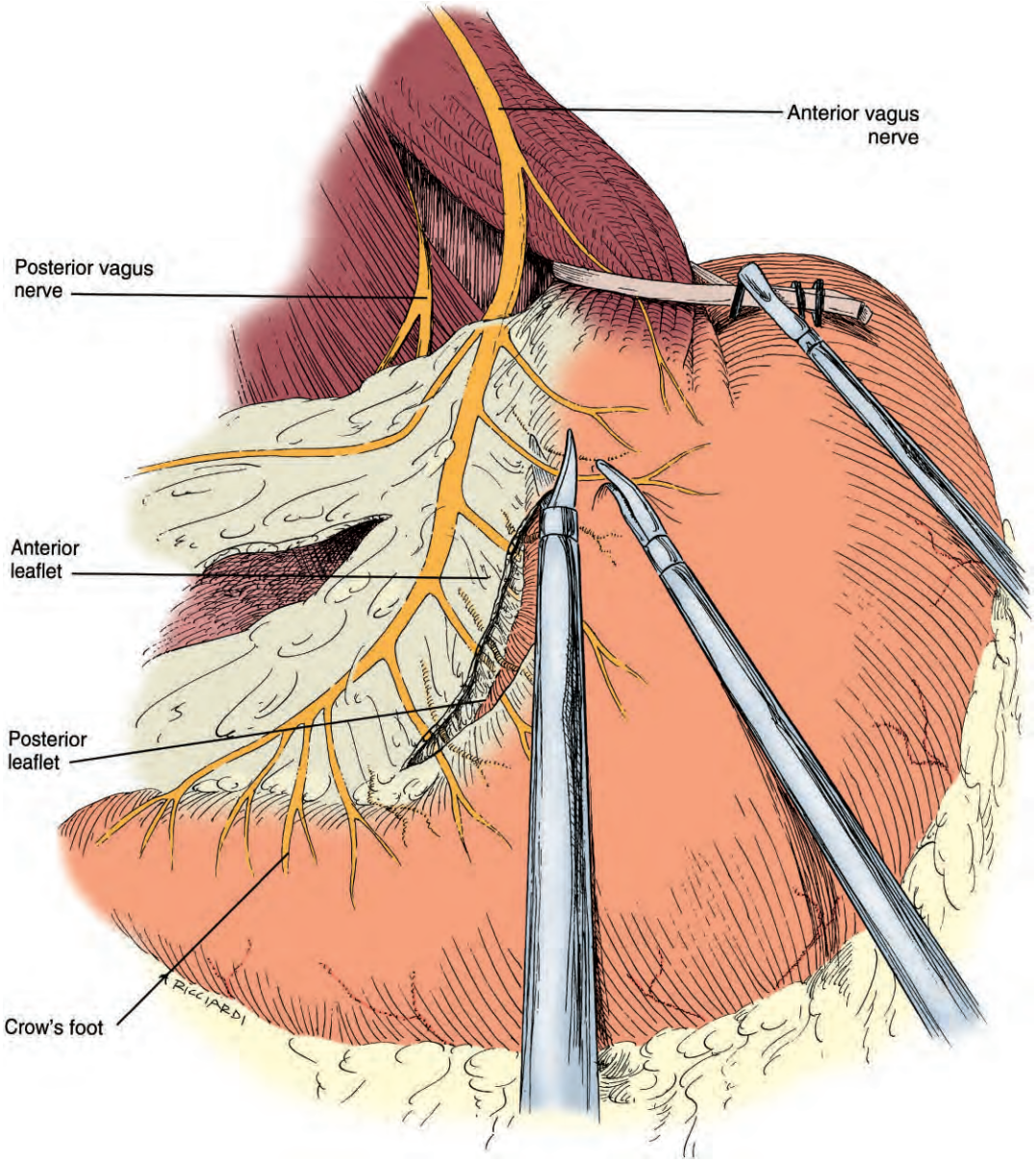

Figure 57–21. Anterior vagal branches to the distal end of the esophagus and stomach are clipped and ligated. This continues caudally but spares the anterior nerve of Latarjet, which innervates the distal 7 cm of stomach proximal to the pylorus. (From Ballantyne GH: Atlas of Laparoscopic Surgery. Philadelphia, WB Saunders, 2000, p 171.)

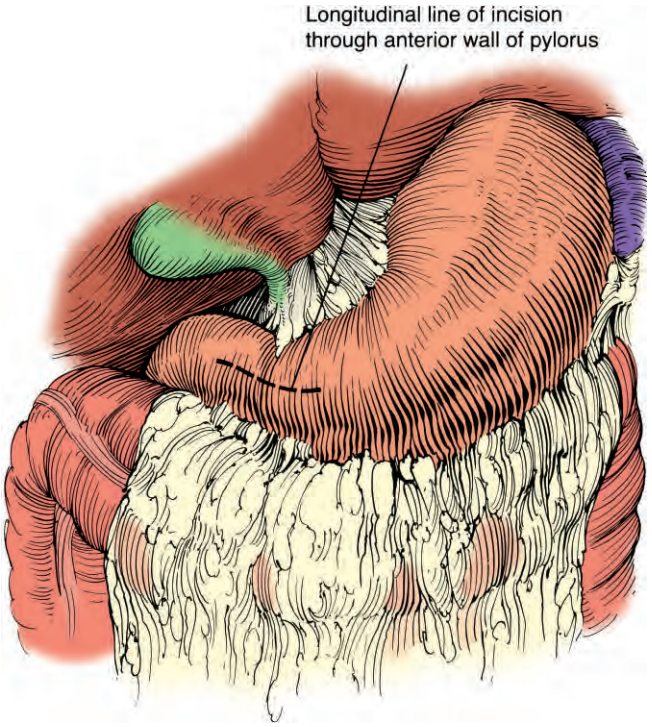

Figure 57–22. The Heineke-Mikulicz procedure is the most widely used pyloroplasty. In a strict sense, a Heineke-Mikulicz pyloroplasty is a two-layer closure, whereas most surgeons actually perform the one-layer modification: the Weinberg pyloroplasty. This procedure is acceptable if there is minimal scarring at the pylorus and no foreshortening of the proximal end of the duodenum. After kocherization of the duodenum, a longitudinal incision is centered over the anterior pylorus and extends 2 to 3 cm proximally and distally. (From Meyers WC: Heineke-Mikulicz pyloroplasty. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 251.)

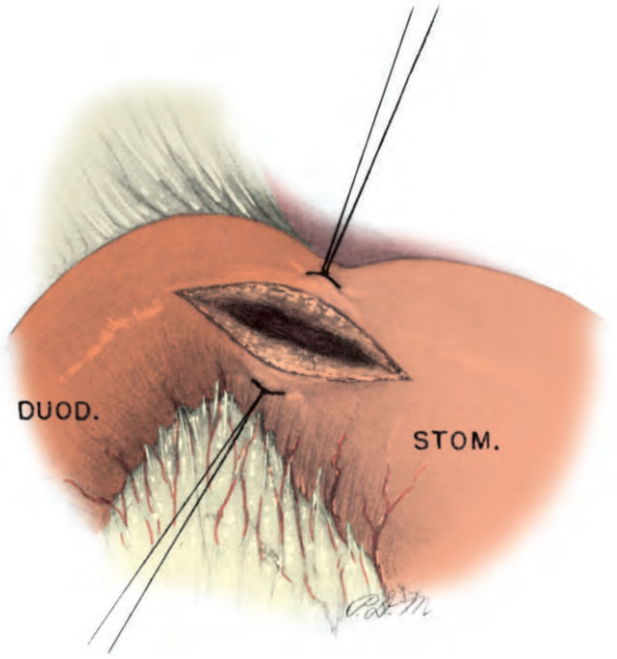

Figure 57–23. After the incision, silk sutures are placed superiorly and inferiorly at the pylorus for traction and orientation. (From Braasch JW: Truncal vagotomy and Heineke-Mikulicz pyloroplasty including selective vagotomy. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 51.)

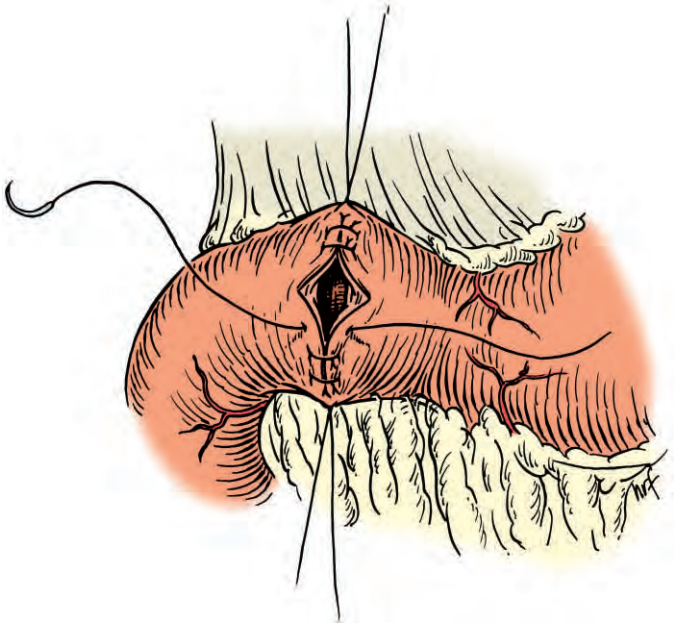

Figure 57–24. The longitudinal incision is closed transversely, which widens the pyloric channel. The closure is usually performed with a single layer of interrupted nonabsorbable sutures, each placed as shown. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 316.)

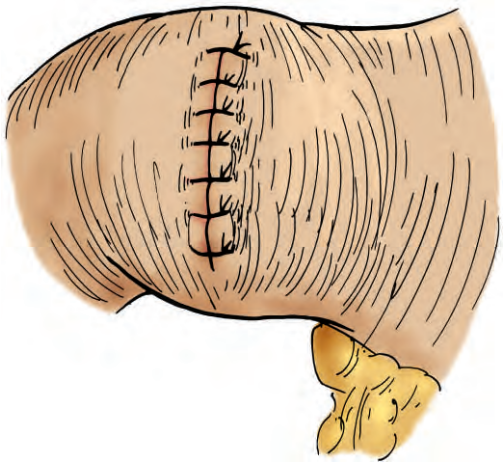

Figure 57–25. Completed Heineke-Mikulicz pyloroplasty. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1095.)

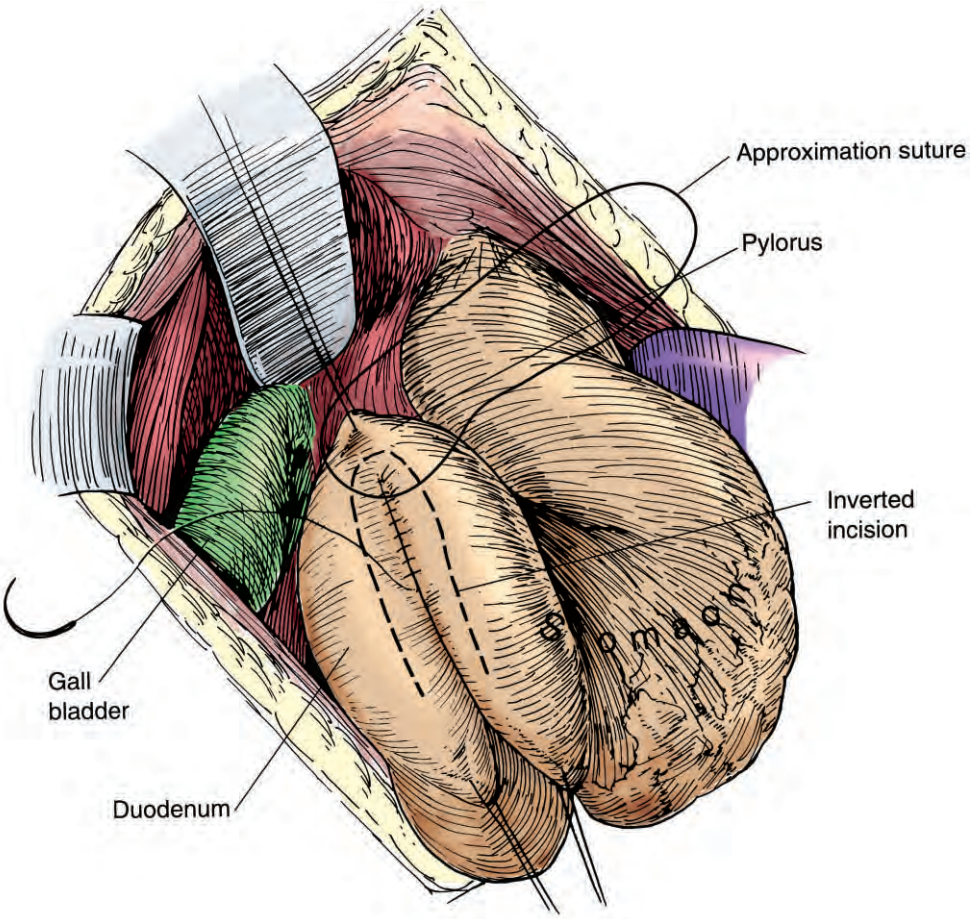

Figure 57–26. Orientation for a Finney pyloroplasty. After kocherization of the duodenum, a single stay stitch is placed superiorly for traction. A posterior row of sutures is used to appose the duodenum to the distal antrum with 3-0 silk sutures. An inverted U-shaped incision is made between the aligned duodenum and stomach. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1096.)

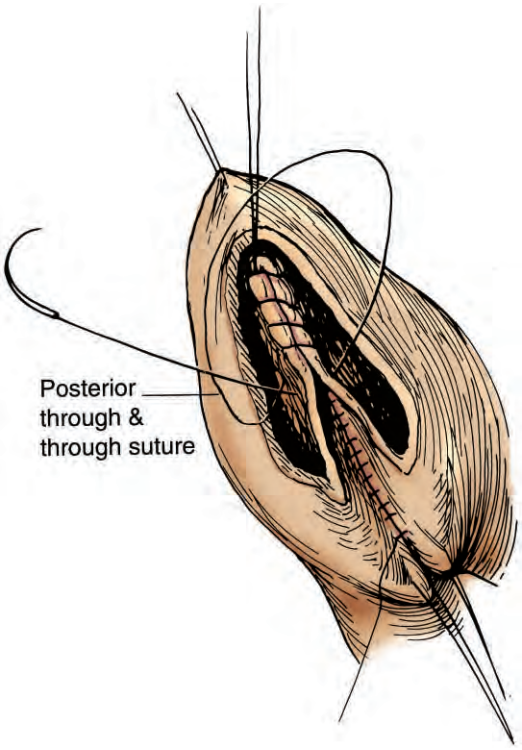

Figure 57–27. Absorbable suture is used to anastomose the mucosa of the stomach to that of the duodenum. This suture line starts posteriorly and continues anteriorly. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1096.)

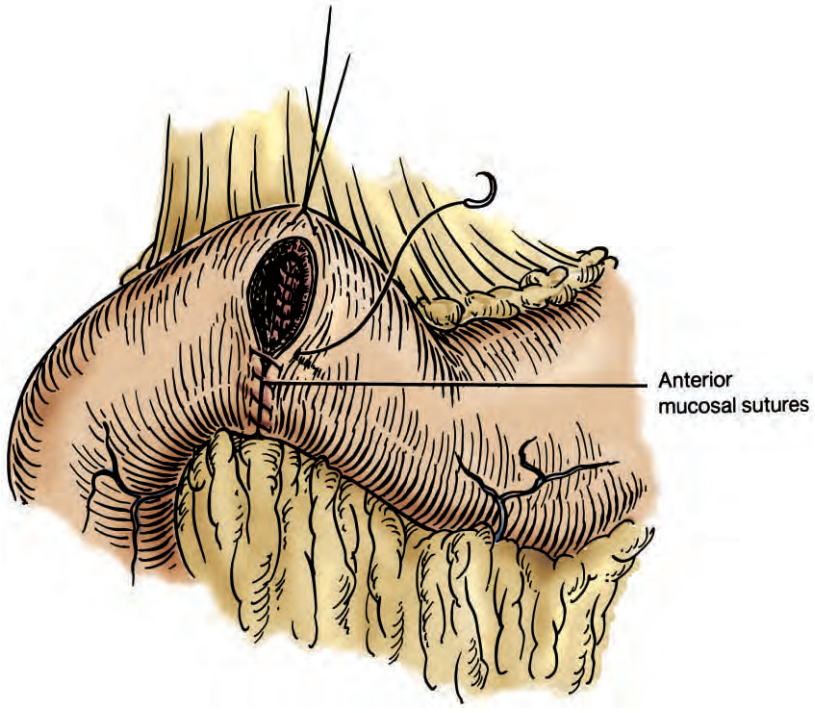

Figure 57–28. The mucosal stitch is continued anteriorly to complete the anastomosis. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 318.)

Figure 57–29. Nonabsorbable sutures are placed in Lembert fashion over the closure to complete the anastomosis. (From Sawyers JL: Selective vagotomy and pyloroplasty. In Nyhus LM, Baker RJ, Fischer JE [eds]: Mastery of Surgery. Boston, Little, Brown, 1997, p 888.)

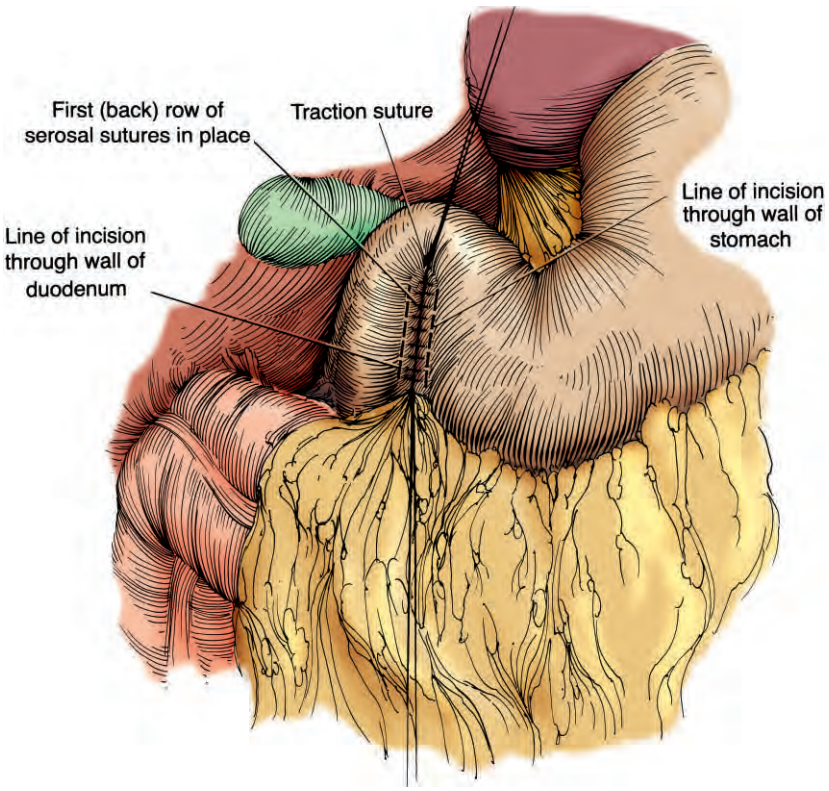

Figure 57–30. A Jaboulay pyloroplasty is used when pylorus is too scarred to attempt to manipulate it. In actuality, a Jaboulay pyloroplasty is a gastroduodenostomy that does not traverse the pylorus. After a Kocher maneuver to mobilize the duodenum, traction sutures are placed to allow the normal duodenum distal to the scarring to be apposed to the distal antrum. Interrupted silk sutures are placed posteriorly before matching incisions are made. (From Meyers WC: Jaboulay pyloroplasty. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 259.)

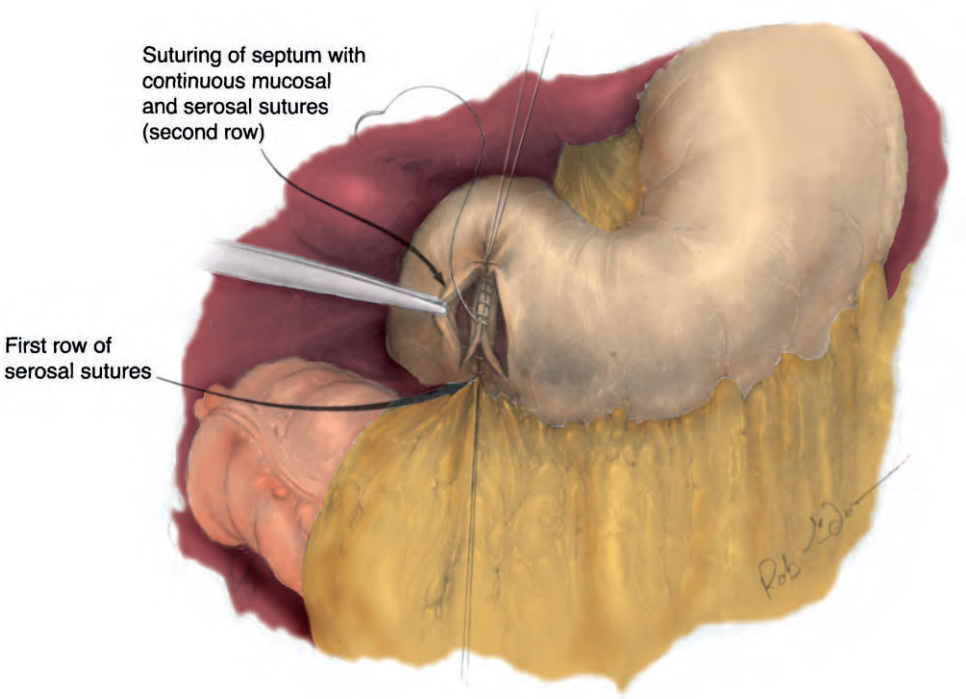

Figure 57–31. Parallel incisions are made in the duodenum and stomach and closed in two layers with mucosal absorbable suture and outer nonabsorbable suture. The pylorus is not incised or dilated. (From Meyers WC: Jaboulay pyloroplasty. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 260.)

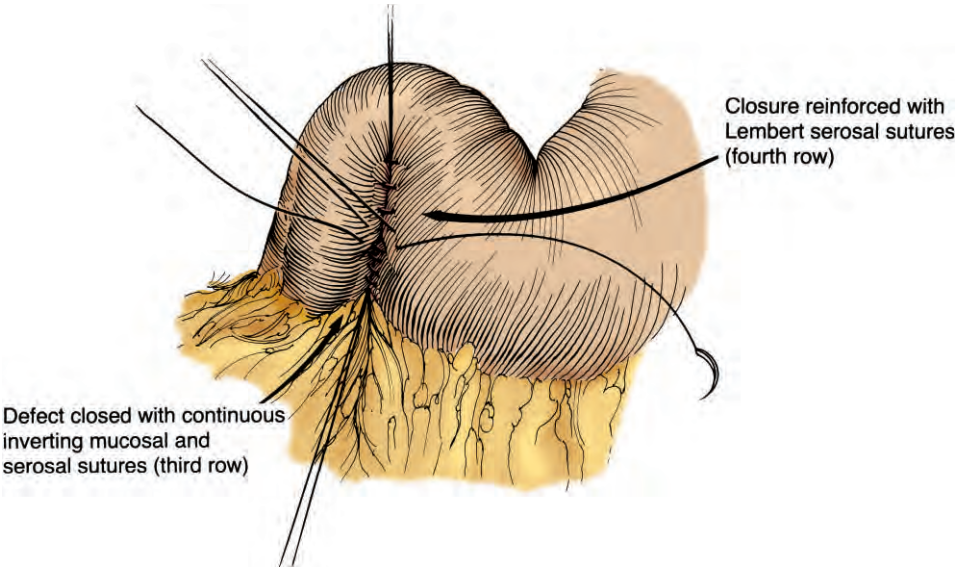

Figure 57–32. Lembert serosal sutures complete the anastomosis. (From Meyers WC: Jaboulay pyloroplasty. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 260.)

Gastrojejunostomy

The steps involved in gastrojejunostomy include the following sequence: creation of a transverse mesenteric window (Fig. 57–33), selection of the site for anastomosis (Figs. 57–34 and 57–35), completion of a two-layer anastomosis (Figs. 57–35 to 57–39), and closure of the mesenteric defect.

Distal Gastrectomy

The steps involved in distal gastrectomy include the following sequence: division of the gastrocolic omentum (Fig. 57–40); division of the gastroepiploic vessels (Fig. 57–41); ligation of the right gastric vessels and dissection of the lesser curvature (Fig. 57–42); division of the duodenum (Fig. 57–43); division of the proximal end of the stomach (Fig. 57–44); reconstruction by gastrojejunostomy, sutured technique (Figs. 57–45 to 57–48) and stapled technique (Figs. 57–49 and 57–50); and reconstruction via gastroduodenoscopy, sutured technique (Figs. 57–51 to 57–54) and stapled technique (Figs. 57–55 to 57–57).

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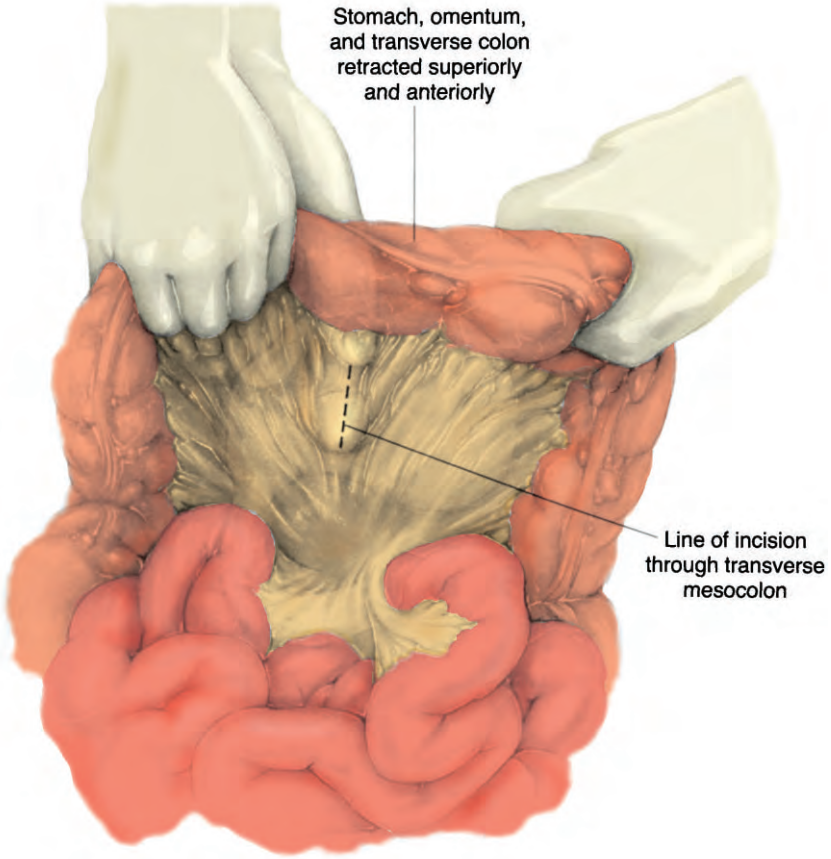


Figure 57–33. Selection of the site in the transverse mesentery to create a window for the gastrojejunostomy. The transverse colon is retracted upward to allow inspection for identification of an avascular area to the left of the middle colic vessels. A vertical incision is created to allow delivery of the distal end of the stomach. (From Peete WPJ: Gastrojejunostomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 348.)

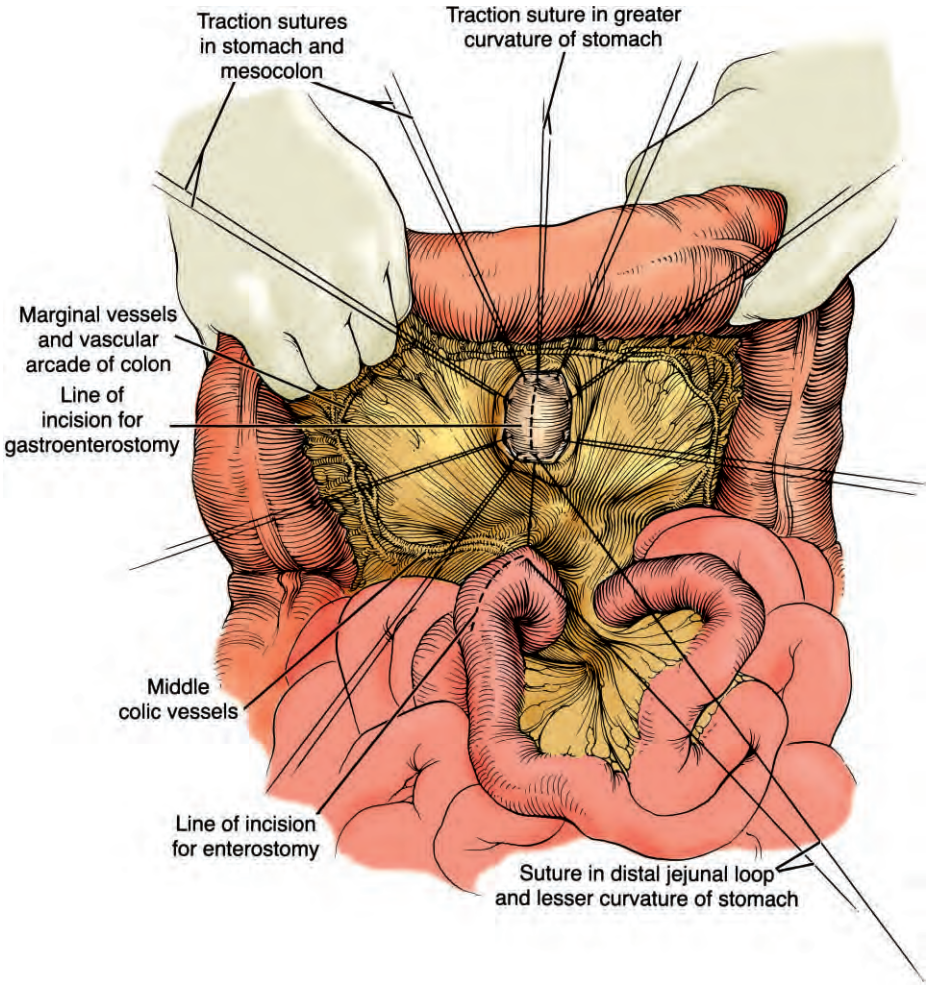


Figure 57–34. The gastric site that is chosen for anastomosis should be in the distal antrum for optimal drainage, be of normal tissue, and be free of large vessels. The stomach is delivered through the mesenteric defect and secured in place with interrupted sutures between the transverse mesocolon and the antrum. These sutures also close the mesenteric defect. The most proximal portion of jejunum that reaches the antrum without tension is placed in apposition to the stomach. (From Peete WPJ: Gastrojejunostomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 349.)

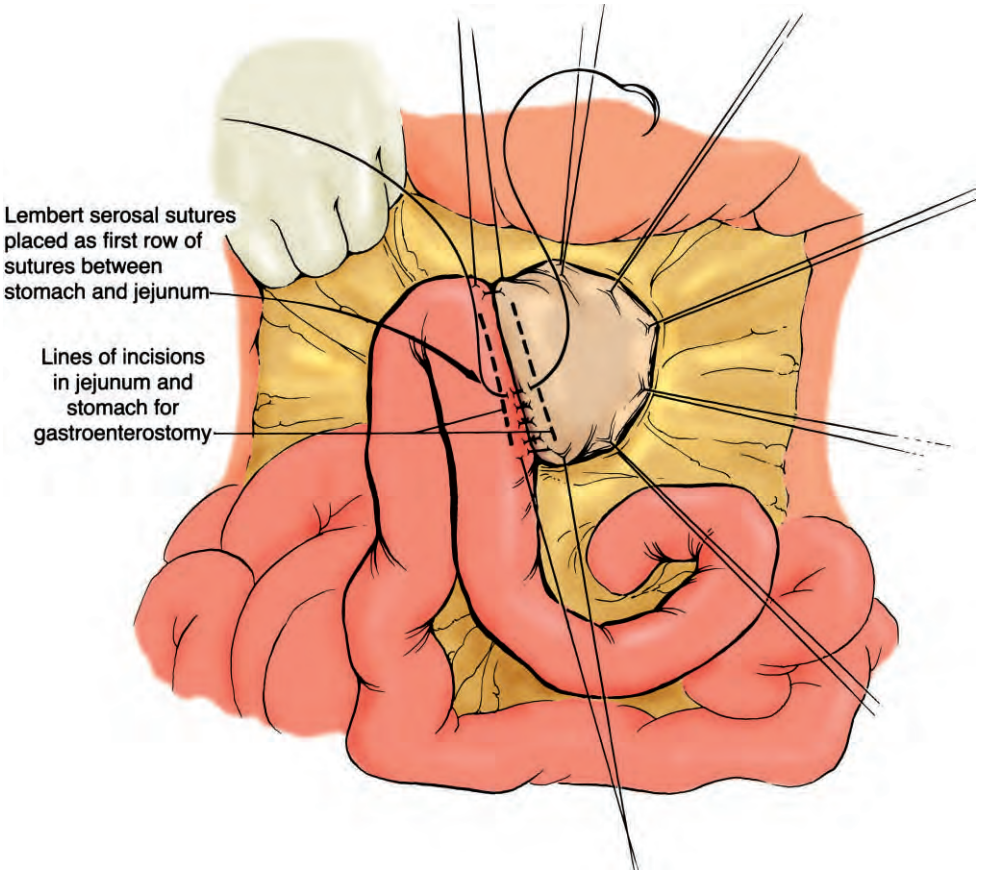


Figure 57–35. The jejunum is fixed in position with traction sutures. Interrupted nonabsorbable sutures are then placed in seromuscular fashion from the inferior gastric wall to the antimesenteric border of the jejunum. (From Peete WPJ: Gastrojejunostomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 350.)

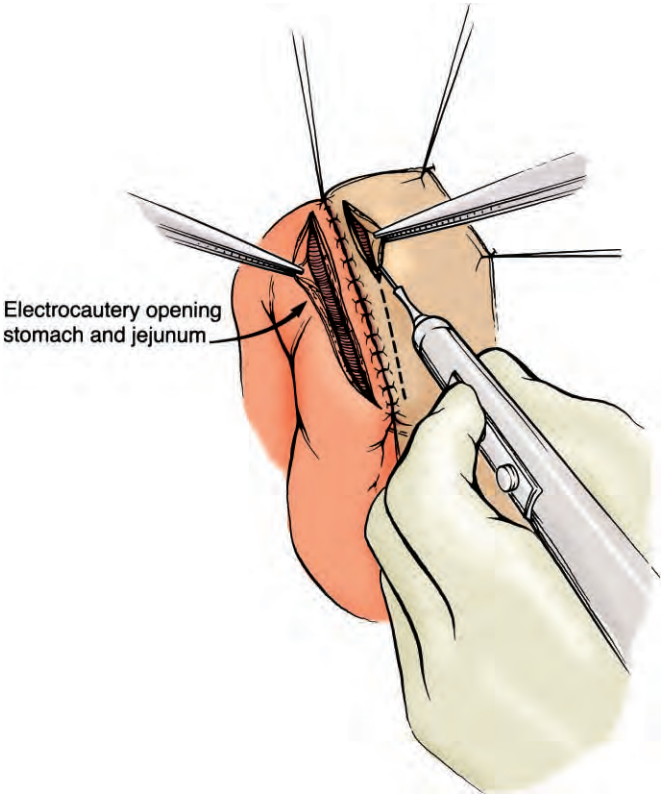


Figure 57–36. Matching incisions in the stomach and jejunum are created with electrocautery. (From Peete WPJ: Gastrojejunostomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 351.)

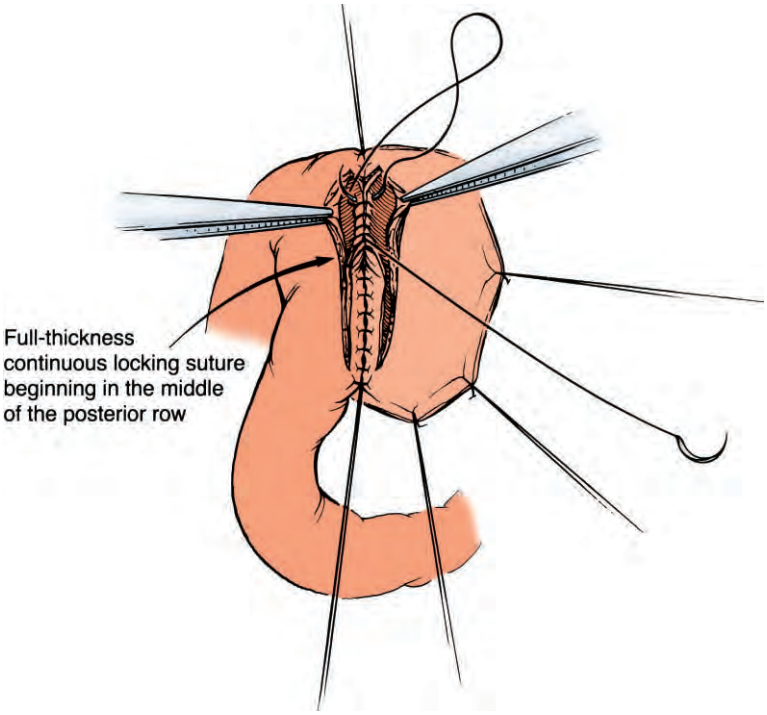


Figure 57–37. A continuous mucosal suture with 3-0 absorbable material is placed. The suture starts posteriorly and is performed most easily with a double-armed stitch. (From Peete WPJ: Gastrojejunostomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 351.)

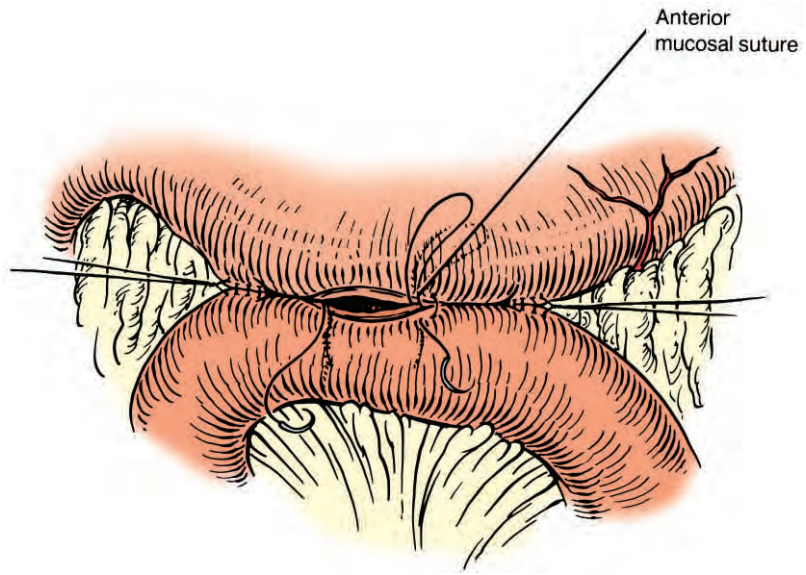


Figure 57–38. The anastomosis continues anteriorly. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 325.)

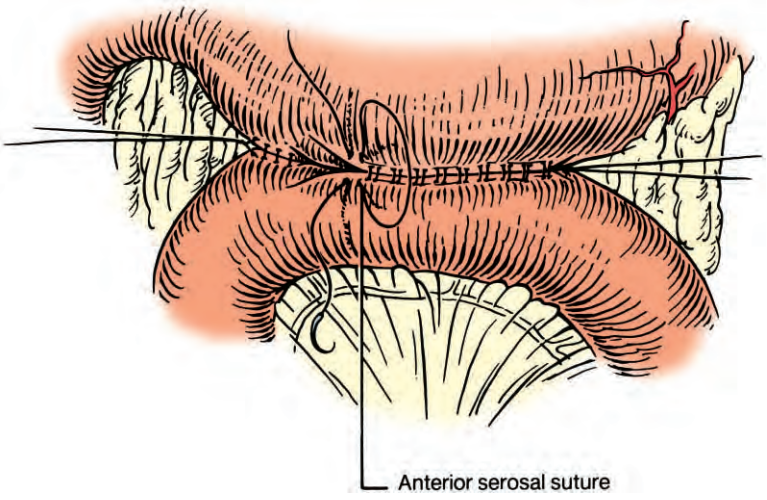


Figure 57–39. The double-layer anastomosis is completed with an anterior seromuscular layer of interrupted silk 3-0 sutures. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 326.)

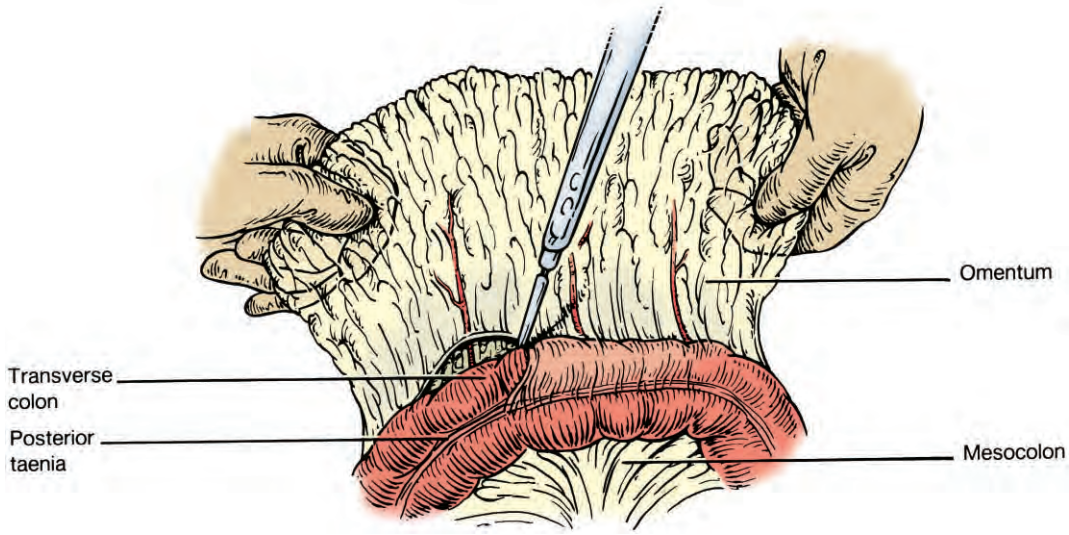
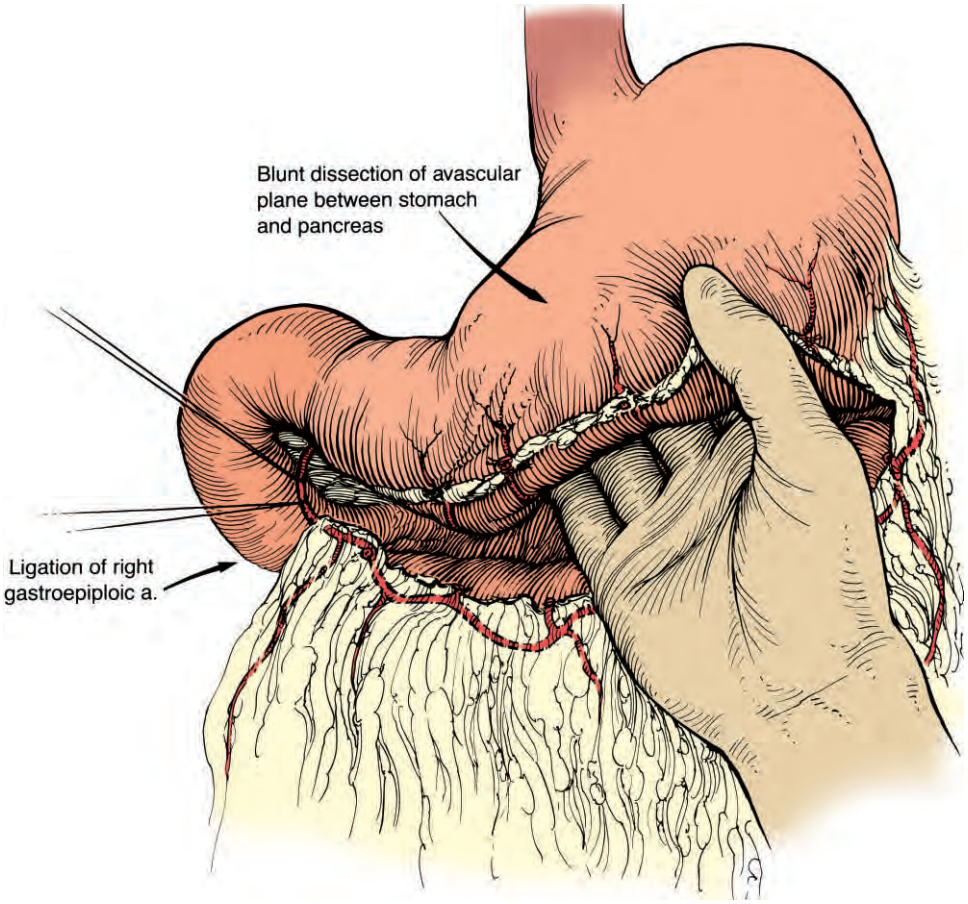


Figure 57–40. Partial gastrectomy is initiated with a full Kocher maneuver that mobilizes the duodenum. The next goal is entry into the lesser sac to allow early evaluation of the posterior surface of the stomach and to aid in division of the greater omentum. With cephalad retraction of the greater omentum, an avascular plane above the transverse colon can be entered. The maneuver is performed left of midline to avoid encroachment on the middle colic vessels. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 342.)

Figure 57–41. The gastrocolic omentum is then dissected from the stomach. The dissection begins at the pylorus with ligation of the right gastroepiploic artery and proceeds cephalad along the greater curvature. The gastroepiploic vessels may be preserved with benign disease. For a 50% gastric resection, the dissection ends halfway between the pylorus and the esophagogastric junction and spares the left gastroepiploic vessels and the short gastric vessels. For subtotal gastrectomy, the left gastroepiploic vessels are divided, as well as a portion of the short gastric vessels. The posterior antrum is then separated from the anterior pancreas and base of the transverse mesocolon by division of fine connective tissue attachments. (From Jones RS: Gastric resection: Billroth I anastomosis. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 263.)



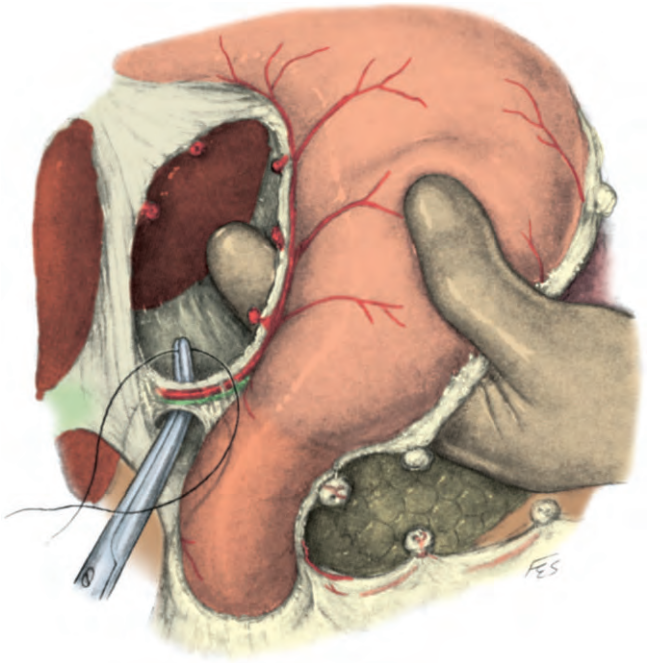


Figure 57–42. The gastrohepatic ligament is incised, and the lesser curvature is dissected. The right gastric vessels are ligated close to the stomach. In patients with pyloric inflammation, care must be taken to avoid injury to both the hepatic artery and the common bile duct. (From Sedgewick C: Gastrectomy. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 37.)

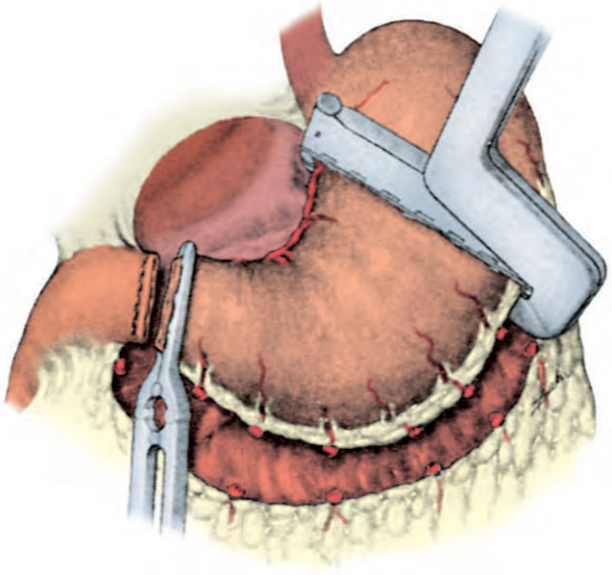


Figure 57–44. The proximal end of the stomach is divided with a TA-90 stapling device. Gastric resection can also be accomplished with two applications of a GIA stapling device. (From Stapling Techniques in General Surgery. Norwalk, CT, United States Surgical Corporation, 1988, p 59. Trademark of United States Surgical. Copyright © 1974, 1980, 1988, 2001 United States Surgical. Reprinted with permission of United States Surgical, a Division of Healthcare Group LP.)

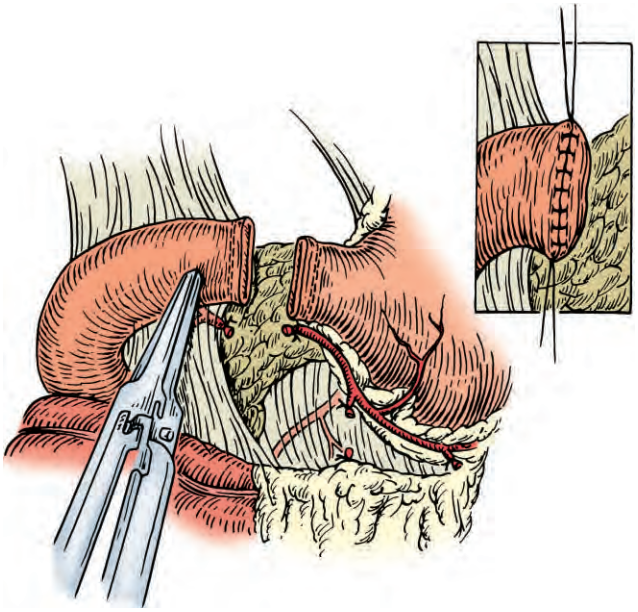


Figure 57–43. The proximal duodenum is divided with care to avoid injury to the common bile duct. The closure is reinforced with interrupted 3-0 silk sutures at the discretion of the surgeon. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 348.)

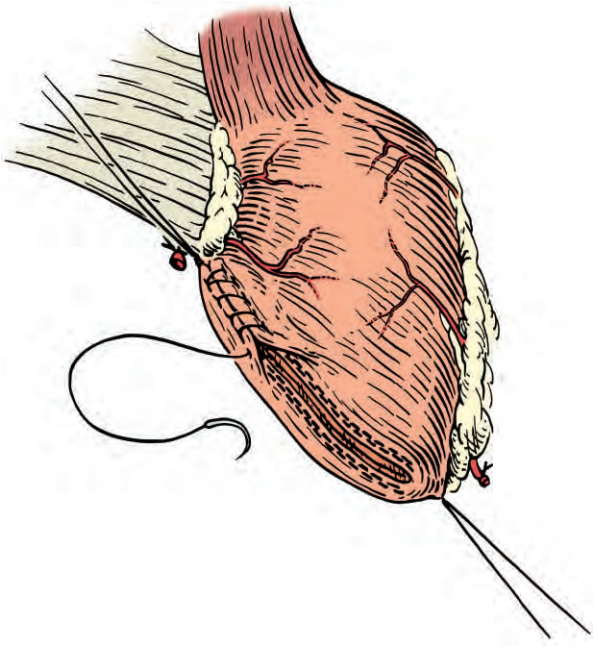


Figure 57–45. The gastric staple line is oversewn superiorly with either continuous or running suture. Traction sutures are useful to steady the remnant within the operative field. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 350.)

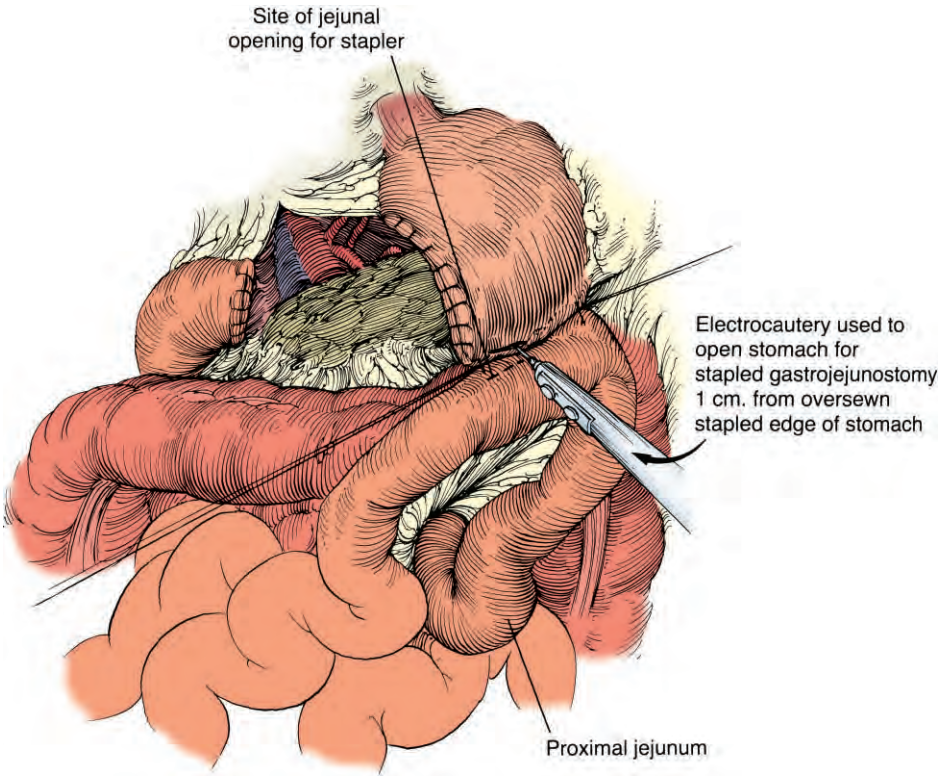


Figure 57–46. A proximal loop of jejunum is apposed to the stomach. The jejunum can be delivered through an incision in the transverse mesocolon or anterior to the transverse colon. Interrupted sutures are placed in seromuscular fashion between the posterior gastric wall and the antimesenteric border of the jejunum. (From Jones RS: Gastric resection: Billroth II. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 284.)

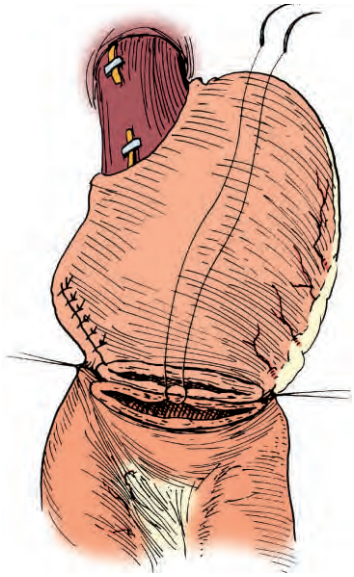


Figure 57–47. Matching incisions are made with electrocautery in the jejunum and stomach, with the latter involving partial excision of the stapled gastric closure. The posterior mucosal closure is initiated with a continuous suture of absorbable material on a double arm. Corner stitches include the anterior gastric wall, the posterior gastric wall, and the jejunum. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1112.)

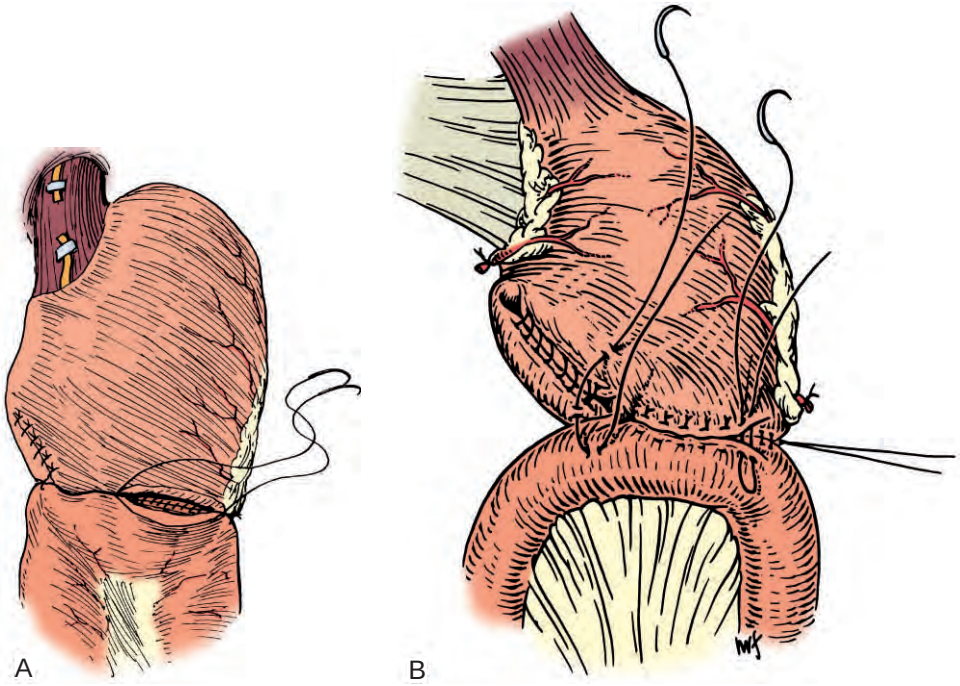


Figure 57–48. **A,** The mucosal suture is continued along the length of the anterior aspect of the anastomosis. **B,** An anterior layer of interrupted silk sutures completes the anastomosis. (**A** from Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1112; **B** from Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 352.)

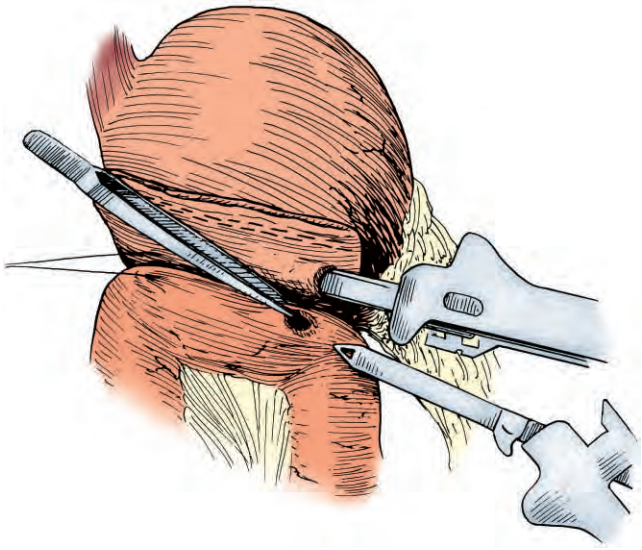


Figure 57–49. A stapled gastrojejunostomy can be created with a GIA stapling device. The posterior gastric wall is apposed to the antimesenteric surface of the jejunum with traction sutures. The site on the posterior gastric wall is usually 2 to 3 cm proximal from the stapled closure. Matching gastrotomy/enterotomy incisions are made with electrocautery to allow insertion of the GIA limbs. After the stapler is fired, the device is withdrawn and the staple line inspected for hemostasis. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1131.)

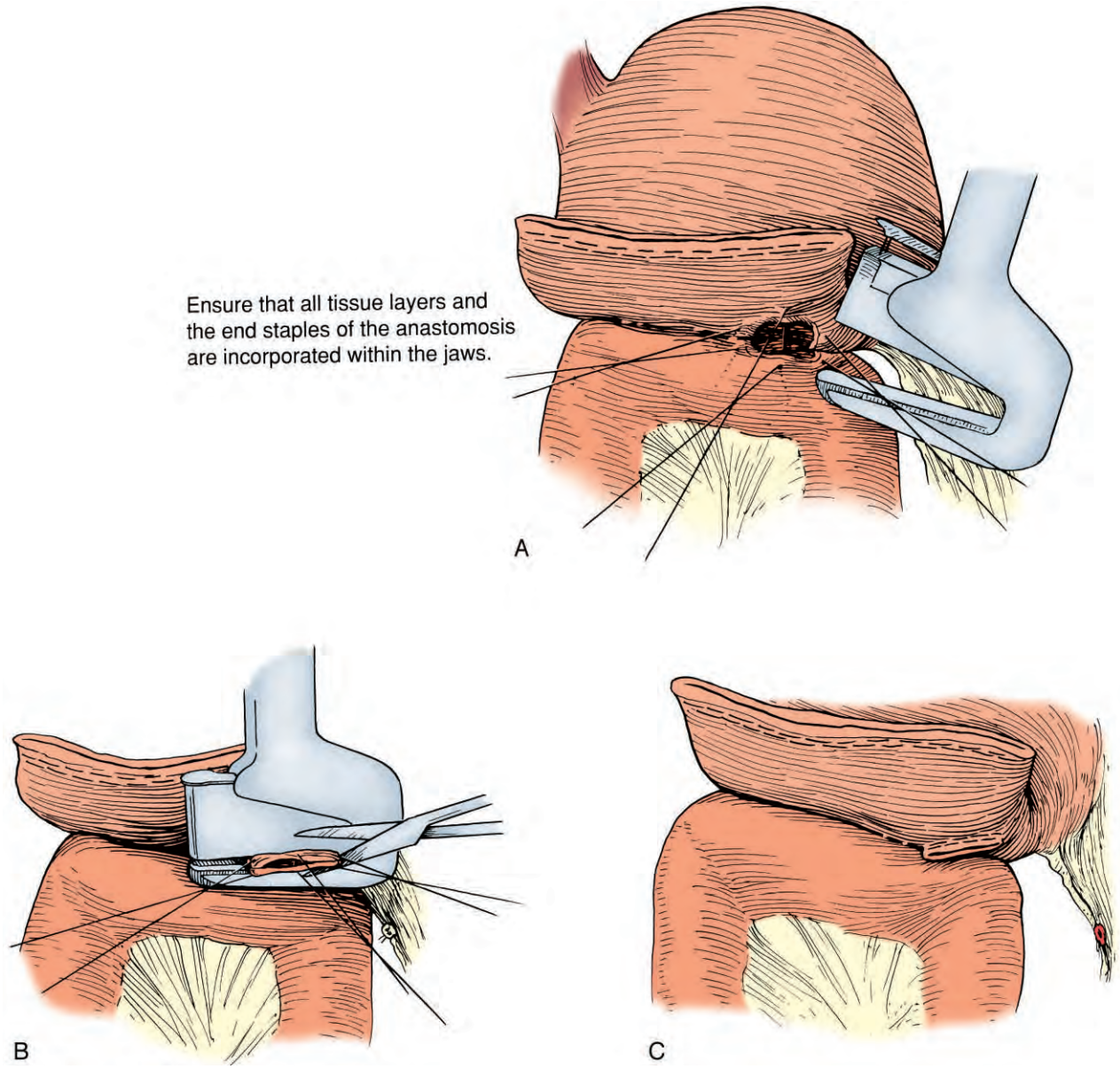


Figure 57–50. The GIA defect is closed with the application of a TA stapler. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1114.)

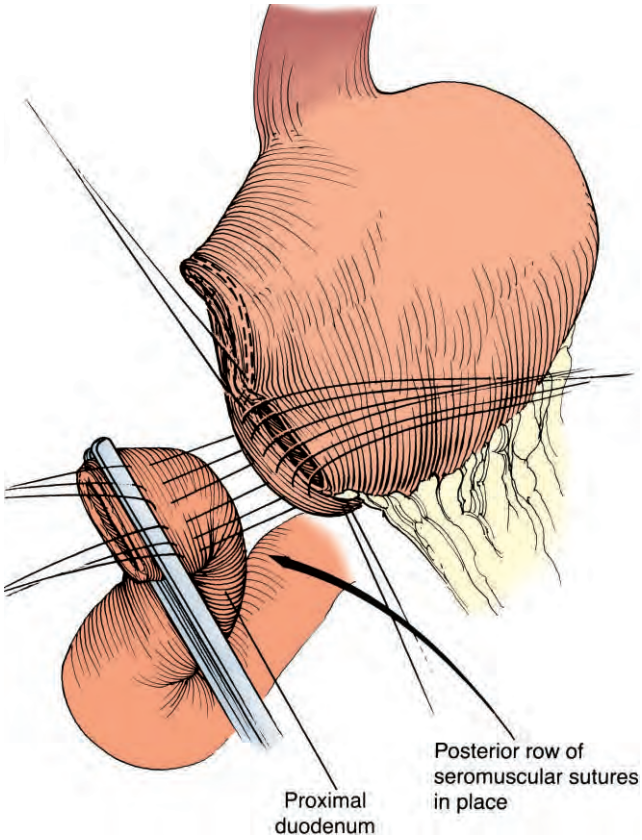


Figure 57–51. For gastroduodenostomy reconstruction, the duodenum and the inferior gastric staple line are apposed through the placement of a posterior serosal layer of interrupted silk sutures. (From Jones RS: Gastric resection: Billroth I. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 267.)

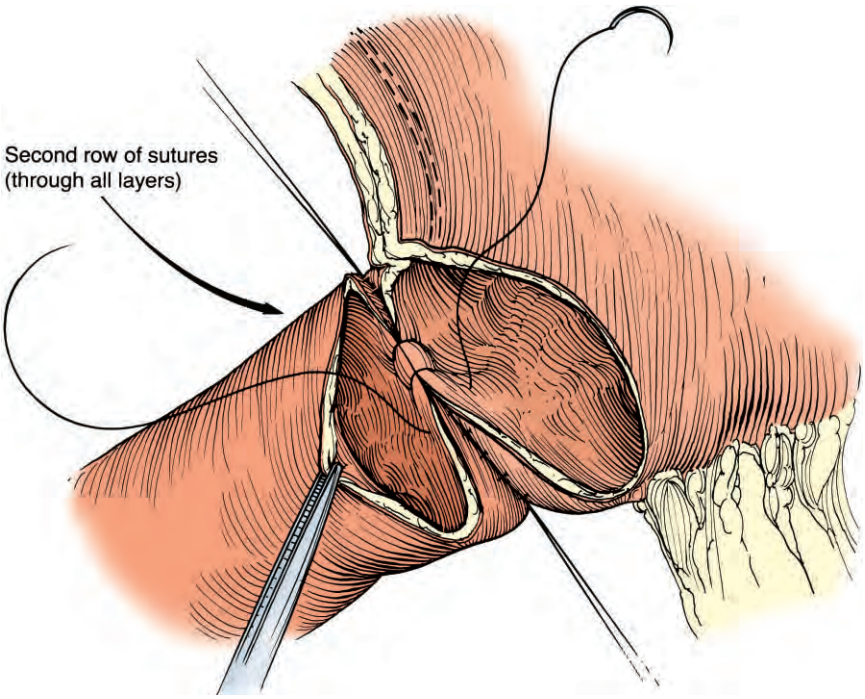


Figure 57–52. An inner mucosal closure is initiated with a continuous absorbable suture. (From Jones RS: Gastric resection: Billroth I. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 268.)

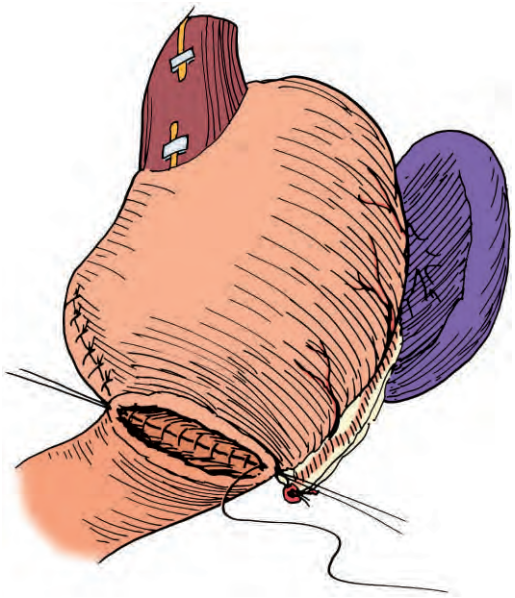


Figure 57–53. The mucosal suture continues anteriorly. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1105.)

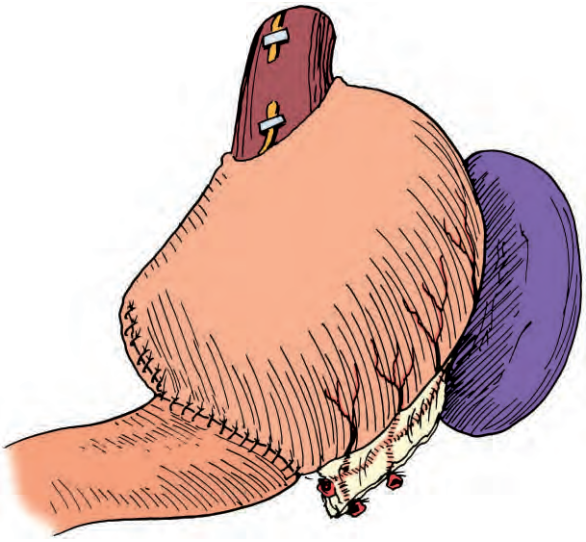


Figure 57–54. An anterior serosal layer is placed with interrupted silk seromuscular sutures. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1105.)

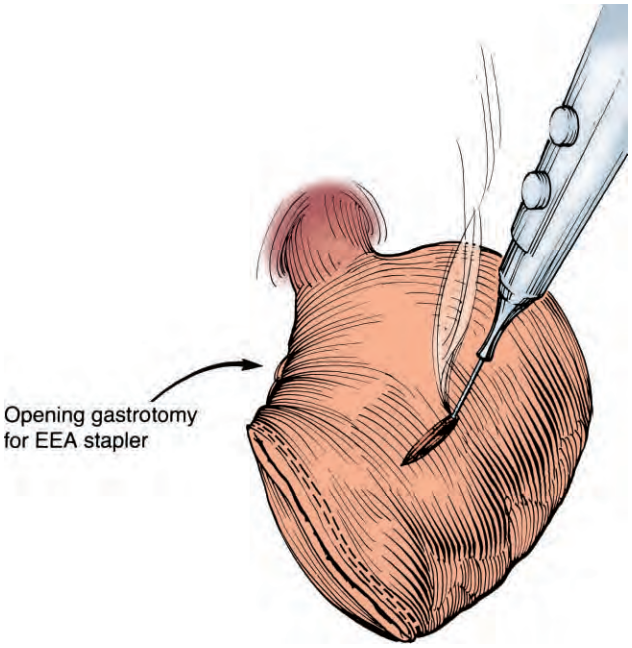


Figure 57–55. For a stapled gastroduodenostomy, a gastrotomy is created with electrocautery on the anterior surface of the stomach at least 3 cm proximal to the staple closure. (From Siegler HF: Gastric resection: Billroth I anastomosis [stapler]. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 274.)

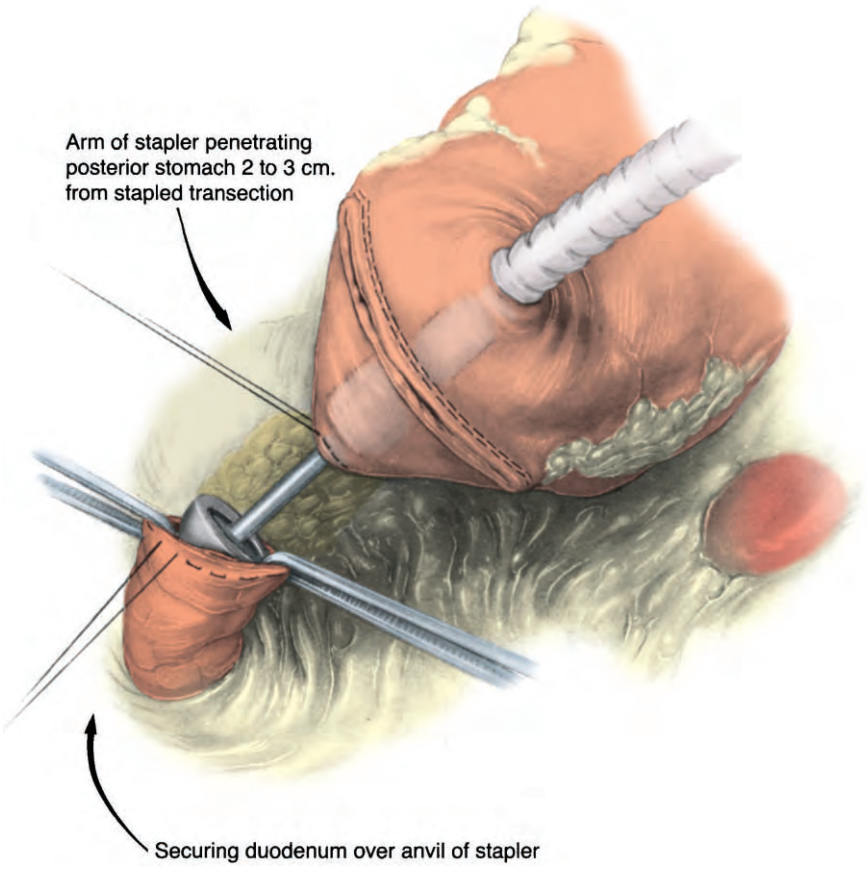


Figure 57–56. The end-to-end stapling device, without the anvil, is passed into the anterior gastrotomy with the rod advancing through the posterior gastric wall, again 3 cm proximal to the stapled edge. The anvil is introduced into the duodenum after placement of a purse-string suture with an automatic device. The EEA is closed, fired, and withdrawn. (From Siegler HF: Gastric resection: Billroth I anastomosis [stapler]. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 275.)

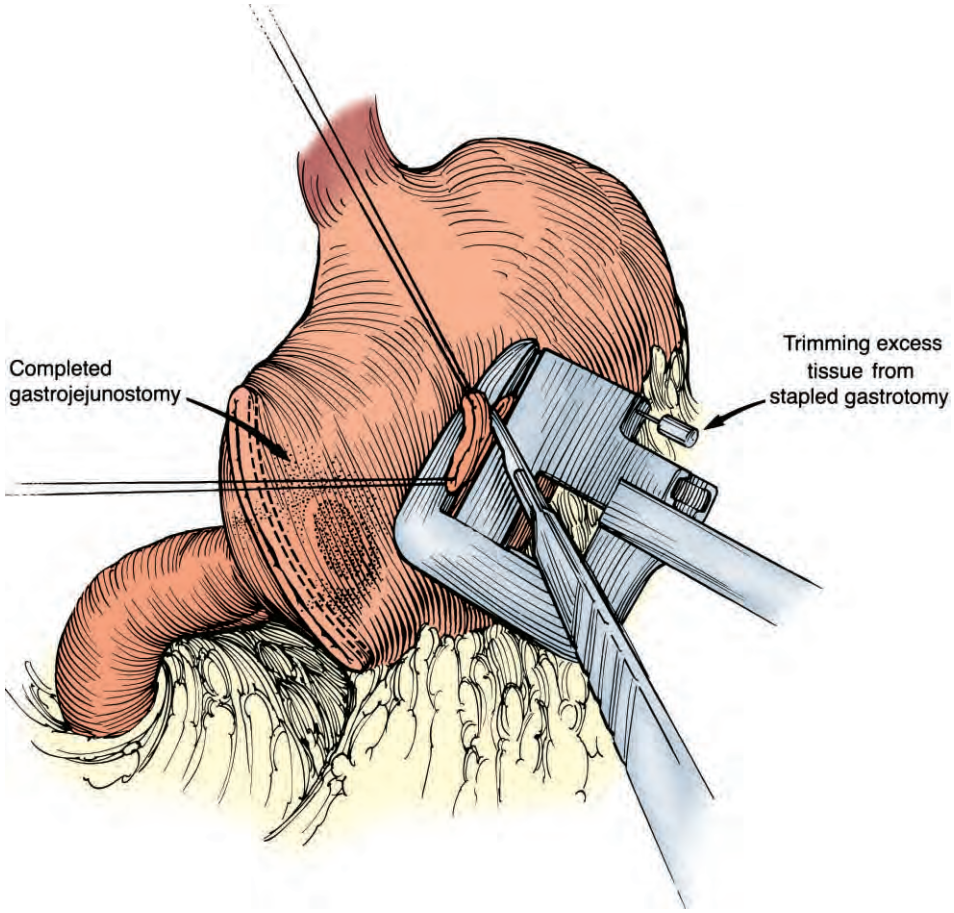


Figure 57–57. The anastomosis is inspected to ensure adequate hemostasis. The anvil is then removed and checked to ensure that tissue doughnuts from both the duodenum and the stomach are present. The gastrotomy is closed by the application of a TA stapling device. (From Siegler HF: Gastric resection: Billroth I anastomosis [stapler]. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 276.)

Total Gastrectomy

The steps involved in total gastrectomy include the following sequence: division of the short and left gastric vessels (Figs. 57–58 to 57–60), purse-string suture and division of the esophagus (Fig. 57–61), creation of a Roux-en-Y limb (Fig. 57–62), use of the EEA stapling device (Figs. 57–63 and 57–64), completion of the anastomosis (Fig. 57–65), and enteroenterostomy.

Stamm Gastrostomy

The steps involved in the Stamm gastrostomy include the following sequence: placement of purse-string sutures (Fig. 57–66), insertion of a Foley catheter (Fig. 57–67), and placement of anchoring sutures (Fig. 57–68).

POSTOPERATIVE MANAGEMENT

Postoperative patients will often experience ileus and should undergo nasogastric decompression until bowel function returns. At this time, a diet can be initiated as well.

The incision will be closed unless a contamination event has occurred intraoperatively. Perioperative antibiotics should continue for 24 hours unless there are indications to lengthen this period.

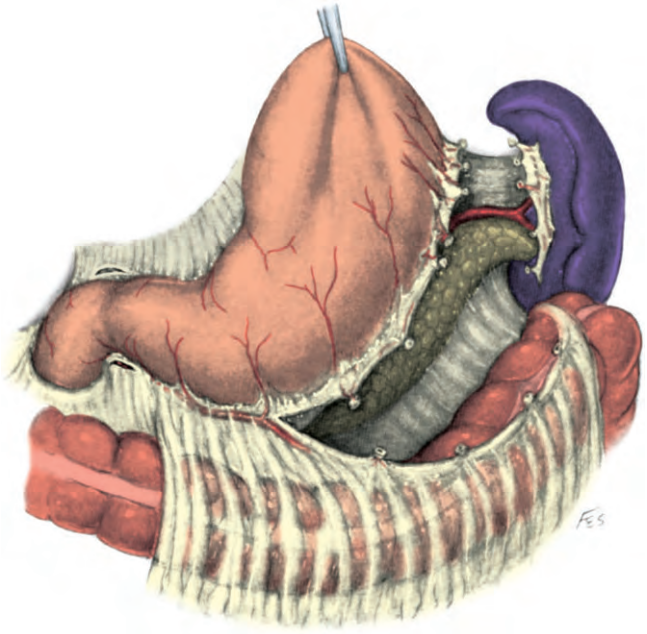


Figure 57–58. The initial steps in total gastrectomy are similar to those of distal gastrectomy. Total gastrectomy mandates a complete omentectomy. In total gastrectomy, the dissection continues cephalad to include division of the left gastroepiploic artery, as well as the short gastric vessels. (From Sedgewick C: Gastrectomy. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 36.)

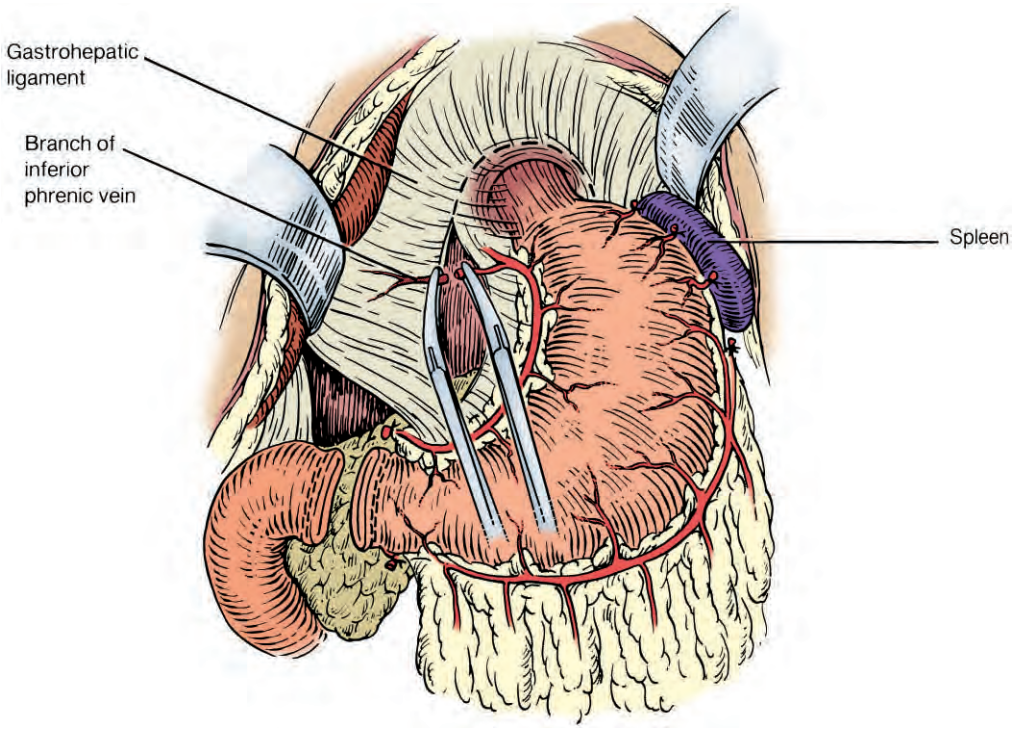


Figure 57–59. The gastrohepatic ligament is entered as in a distal gastrectomy, with ligation of the right gastric artery. The inferior phrenic vein is ligated if encountered within the gastrohepatic ligament. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 360.)

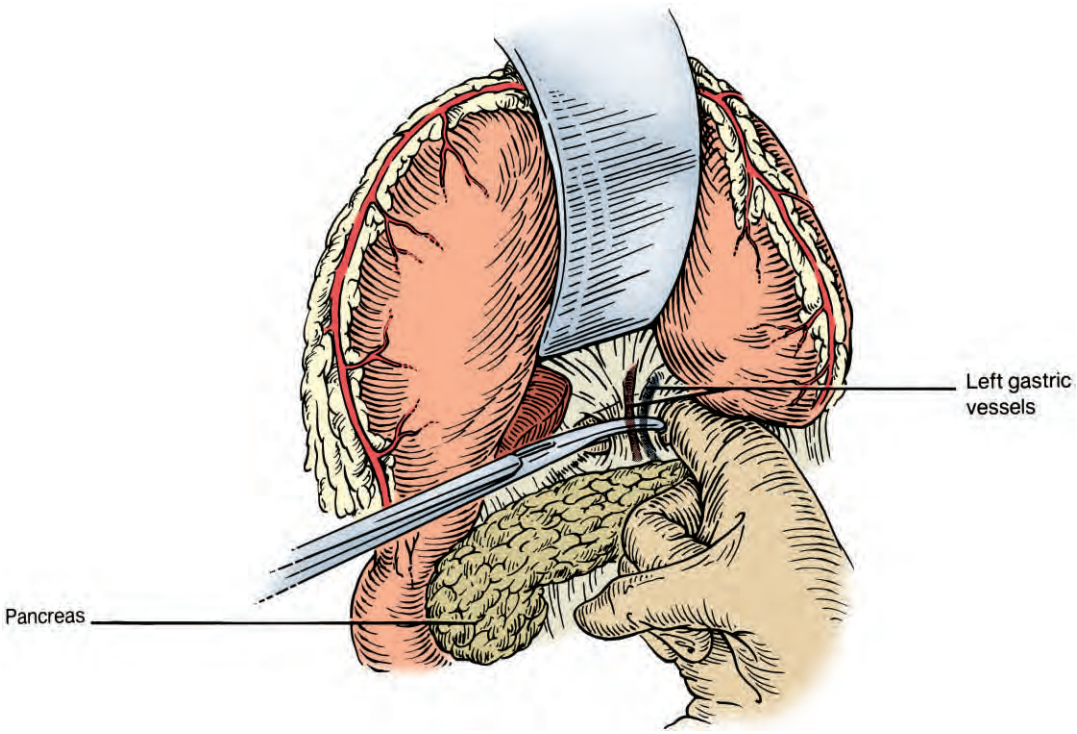


Figure 57–60. Identification and ligation of the left gastric artery is best accomplished with cephalad retraction of the stomach. (From Mulholland MW: Atlas of gastric surgery. In Bell RH Jr, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery. Philadelphia, Lippincott-Raven, 1996, p 361.)

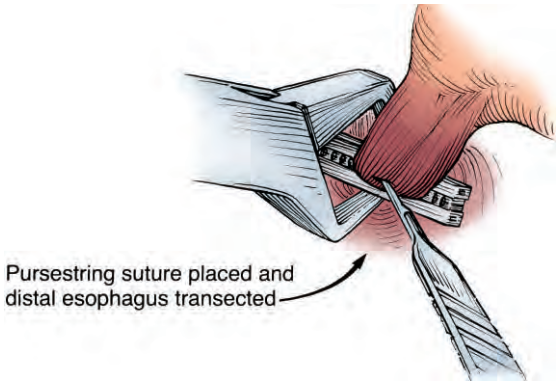


Figure 57–61. A purse-string device is placed on the distal end of the esophagus. The esophagus is divided, and the gastric specimen is removed. (From Siegler HF: Total gastrectomy [stapler]. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia WB Saunders, 1994, p 309.)

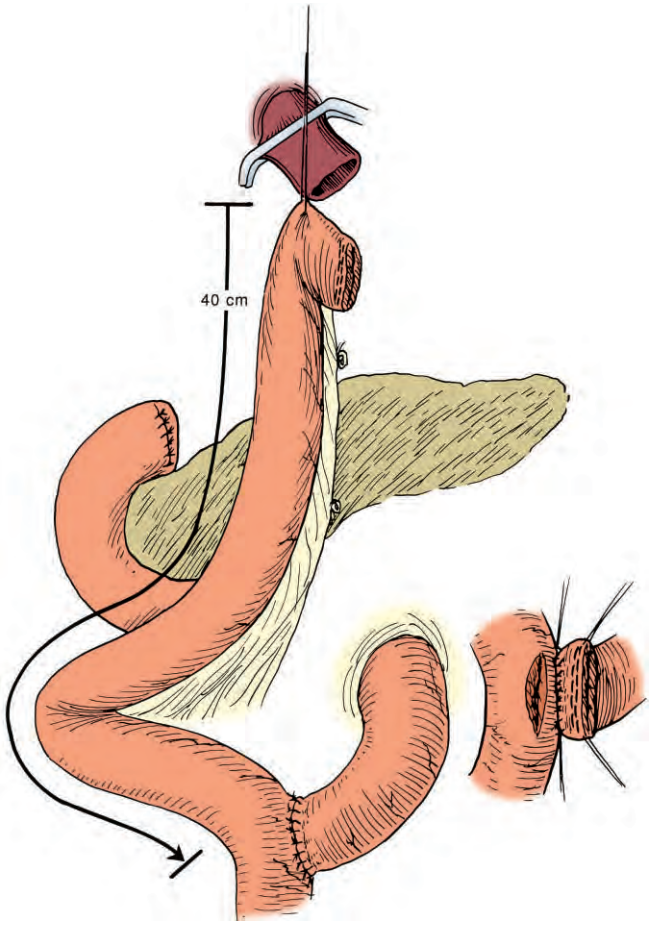


Figure 57–62. The proximal end of the jejunum is divided 10 to 20 cm distal to the ligament of Treitz. A Roux limb is delivered to the distal end of the esophagus and is 40 cm long. An end-to-side enteroenterostomy (*inset*) is performed to complete the Roux-en-Y. (From Soybel DI, Zinner MJ: Stomach and duodenum: Operative procedures. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stamford, CT, Appleton & Lange, 1997, p 1121.)

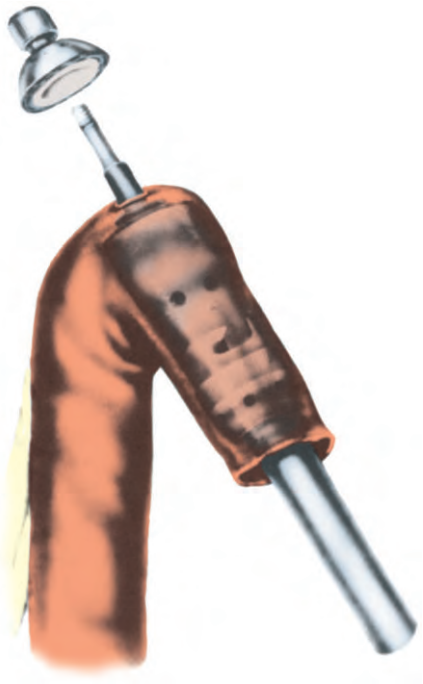


Figure 57–63. An EEA stapling device is introduced through the open end of the Roux-en-Y limb, and the rod exits 3 cm proximally along the antimesenteric border of the jejunum. The EEA device can be properly sized before the gastric resection by introducing the sizing instruments through a proximal gastrotomy just before removing the specimen. (From Ravitch MM, Steichen FM: Principles and Practice of Surgical Stapling. Chicago, Year Book, 1987, p 229.)

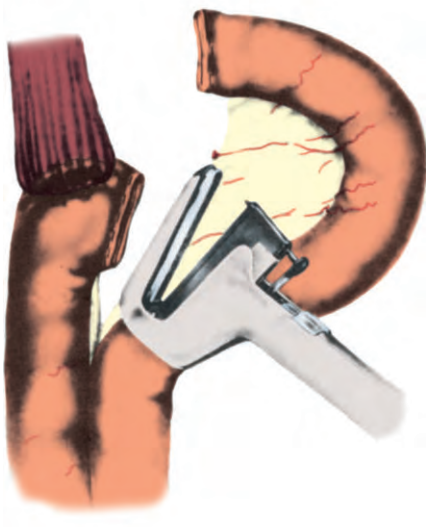


Figure 57–64. After EEA device placement, the anvil is positioned through the purse string and into the distal end of the esophagus. After the purse string is secured, the EEA is fired to create an end-to-side esophagojejunostomy. The EEA is carefully removed and inspected for tissue doughnuts from the esophagus and the jejunum. The anastomosis is inspected to ensure adequate hemostasis, and the open end of the jejunum is closed with a TA stapler. The nasoenteric tube is gently guided through the anastomosis. Anastomotic integrity is tested by insufflating air via the nasogastric tube after the operative field is filled with saline. The absence of bubbling from the anastomosis suggests an intact anastomosis. (From Ravitch MM, Steichen FM: Principles and Practice of Surgical Stapling. Chicago, Year Book, 1987, p 230.)

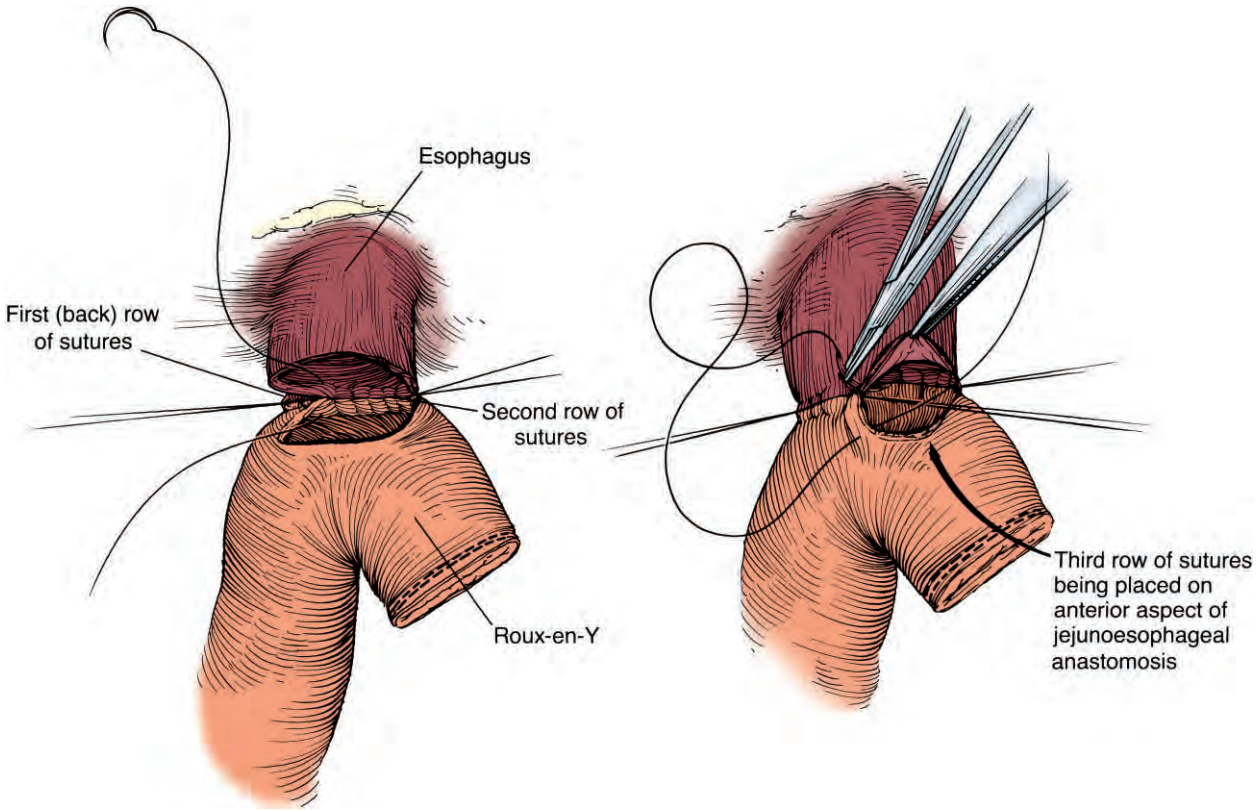


Figure 57–65. Alternatively, hand-sewn esophagojejunostomy can be performed. This is typically performed with two layers of 3-0 silk in interrupted fashion. (From Meyers WC: Total gastrectomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 304.)

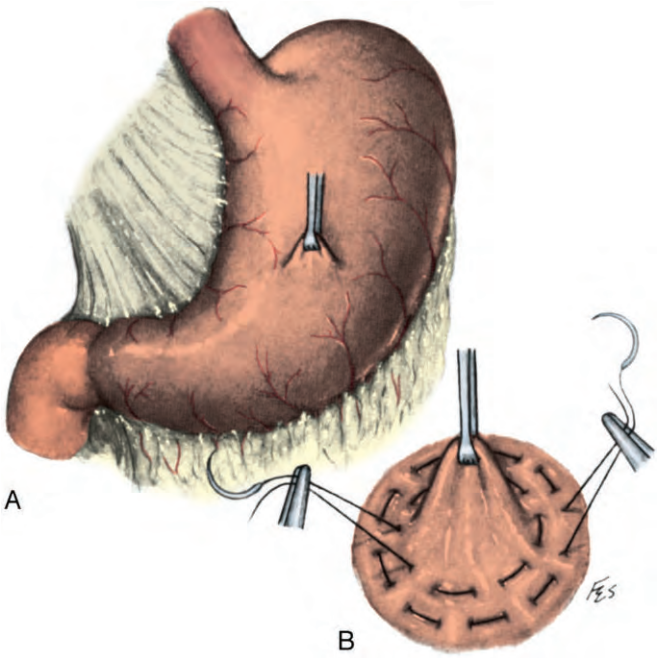


Figure 57–66. Open gastrostomy is performed either primarily or as an adjunct to a separate abdominal procedure **(A).** The selected site on the anterior gastric wall is grasped with an Allis clamp, and two concentric purse-string sutures are placed with nonabsorbable material **(B).** Electrocautery is used to create the gastrotomy within the purse strings. (From Sedgewick C: Gastrectomy. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 26.)

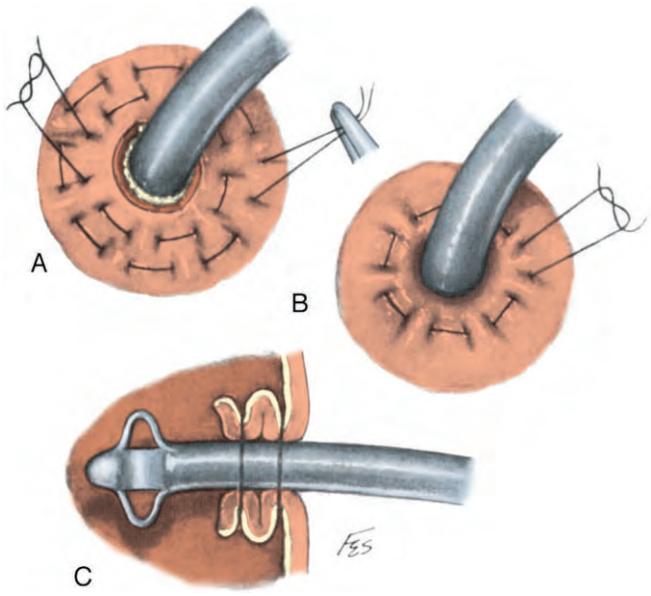


Figure 57–67. A large mushroom-tipped or Foley catheter is placed, and the purse strings are tied. (From Sedgewick C: Gastrectomy. In Braasch JW, Sedgewick CE, Veidenheimer MC, Ellis FH Jr [eds]: Atlas of Abdominal Surgery. Philadelphia, WB Saunders, 1991, p 27.)

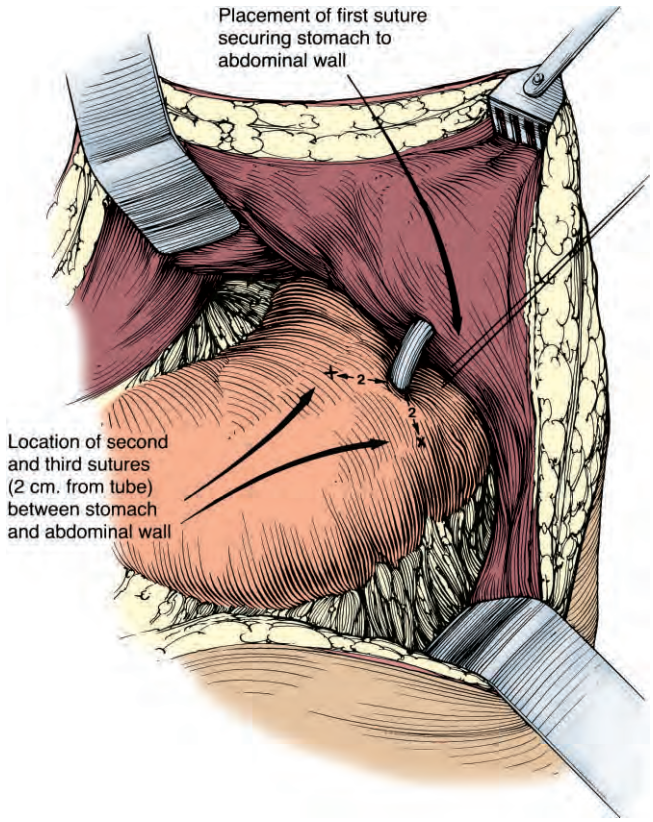


Figure 57–68. The tube is brought out through the abdominal wall at a site where the stomach will reach without tension. Three or four tacking sutures are placed through the abdominal wall and the seromuscular surface of the stomach. The sutures are tied to secure the stomach to the abdominal wall around the tube. (From Grant JP: Stamm gastrostomy. In Sabiston DC Jr [ed]: Atlas of General Surgery. Philadelphia, WB Saunders, 1994, p 232.)

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Chapter

58

Zollinger-Ellison Syndrome

James P. Dolan · Jeffrey A. Norton

In 1955, Zollinger and Ellison[1] first reported the occurrence of unusual, severe jejunal peptic ulcer disease associated with gastric acid hypersecretion and islet cell tumors of the pancreas. After vagotomy, antrectomy, and hemigastrectomy, recurrent peptic ulceration still developed and required total gastrectomy for control of symptoms. In consideration of the patients' complex clinical course, they postulated that the pancreatic tumor was the cause of the peptic ulcer diathesis. Subsequently, in 1972 Oberhelman and others noted that the syndrome did not require a pancreatic neuroendocrine tumor and described duodenal gastrinoma as a cause of Zollinger-Ellison syndrome (ZES).[2] We now know that ZES is caused by both pancreatic and duodenal tumors, but the most common causative tumor is a duodenal neuroendocrine tumor that elaborates excessive and unregulated amounts of the hormone gastrin.

ZES is one of many functional duodenal or pancreatic neuroendocrine syndromes. It occurs in both sporadic (80% of cases) and familial or inherited (20% of cases) forms. The familial form is associated with multiple endocrine neoplasia type I (MEN-I) syndrome, which consists of primary hyperparathyroidism and pituitary tumors in association with duodenal or pancreatic neuroendocrine tumors, of which most functional tumors are gastrinomas.[3] Although the precise incidence is unknown, it is estimated that gastrinomas develop in 1 to 3 persons per 1 million each year.[4] Furthermore, gastrinomas are the underlying cause of peptic ulcer disease in approximately 0.1% to 1% of patients.[5]

Although slow growing, more than 60% of gastrinomas are malignant, with patients having lymph node, liver, or distant metastatic disease at laparotomy.[6] In 25% of cases the tumor pursues an aggressive course.[7,8] As screening of patients with peptic ulcer disease for hypergastrinemia has become more common, a larger proportion of localized, nonmetastatic tumors are being discovered and treated.

SYMPTOMS AND SIGNS

The mean age at diagnosis of ZES is 50 years, although children as young as 7 years and adults as old as 90 years have been identified. There is a male preponderance, with a male-to-female ratio of approximately 2:1. In patients with MEN-I syndrome, ZES is usually diagnosed at the age of 20 to 30 years, whereas in the sporadic form it occurs at approximately 50 years of age.[3,6,8] The clinical manifestations are related to excessive secretion of gastric acid; the most common symptoms are epigastric pain, diarrhea, heartburn, and dysphagia (Table 58–1). The majority of patients with ZES (80% to 90%) are found to have peptic ulceration, and the proximal duodenum is the most common site of ulcer. Moreover, some patients still have multiple peptic ulcers or ulcers in unusual locations, such as the distal duodenum (14%) and jejunum (11%), or even recurrent ulceration after surgery.[9] In 7% to 10% of patients, a perforated peptic ulcer is the initial sign of ZES.[9] Gastric acid hypersecretion also leads to secretory diarrhea, which occurs in up to 40% of patients with ZES and may be the sole initial complaint in 20% of individuals.[9] In patients with diarrhea, malabsorption may be manifested as weight loss and malnutrition. Approximately 10% of patients with ZES have signs and symptoms of gastroesophageal reflux disease (GERD). Endoscopy shows evidence of lower esophageal inflammation, ulceration, and even stricture if the reflux symptoms are long-standing. As a large primary tumor burden develops or metastases occur, symptoms such as bleeding or obstruction may be related to the tumor itself.

DIAGNOSIS

Evidence suggests that in most cases there is a delay in diagnosis of ZES, with a mean period of 6 years from initial symptoms to diagnosis.[4] This delay occurs for a

Table 58–1 Usual Symptoms and Signs of Zollinger-Ellison Syndrome

Symptom or Sign	Patients (%)
Dyspepsia	80
Gastroesophageal reflux disease	60
Dysphagia	30
Diarrhea	40
Duodenal ulceration	80-90

Box 58–1 Differential Diagnosis of Hypergastrinemia

With excessive gastric acid formation (ulcerogenic)
- Zollinger-Ellison syndrome
- Gastric outlet obstruction
- Retained gastric antrum (after Billroth II reconstruction)
- G-cell hyperplasia

Without excessive gastric acid formation (nonulcerogenic)
- Pernicious anemia
- Atrophic gastritis
- Renal failure
- Postvagotomy status
- Short-gut syndrome (after significant intestinal resection)

Box 58–2 Situations in Which the Diagnosis of Zollinger-Ellison Syndrome Should Be Considered

- When standard antiulcer and *Helicobacter pylori* treatments fail and surgery is being considered
- Secretory diarrhea
- Peptic ulcer disease in conjunction with diarrhea
- Recurrent peptic ulceration after acid reduction surgery
- Ulcers in unusual locations
- Gastric rugal hypertrophy
- Multiple ulcers
- Peptic ulceration and reflux esophagitis
- Reflux esophagitis with stricture
- Peptic ulceration at a young age
- Perforation or bleeding from peptic ulceration
- Family history of peptic ulceration or endocrine tumors
- Ulcers and primary hyperparathyroidism

number of reasons. First, although excessive gastrin secretion is the hallmark of the ZES, hypergastrinemia may also occur as a consequence of other diseases or conditions, most of which do not lead to excessive gastric acid secretion and ulcer formation (Box 58–1). Second, because ZES is uncommon, there may be resistance or failure to consider the diagnosis of ZES in the face of clinical, endoscopic, radiologic, and biochemical findings suggestive of it. In this regard, ZES should be considered in all patients with one or more symptoms referable to the upper gastrointestinal tract or in those with primary hyperparathyroidism and nephrolithiasis or a family history suspicious for MEN (Box 58–2).

In general, ZES can be accurately diagnosed in all patients by measurement of an elevated fasting serum level of gastrin in association with an increase in basal acid output (BAO). The diagnosis can be confirmed by the addition of a secretin stimulation test. Measurement of the fasting serum level of gastrin is the initial study to diagnose ZES. Of patients with ZES, virtually 100% will have a fasting serum gastrin level greater than 100 pg/ml. Patients should not be taking antisecretory medications for 3 to 7 days before the determination because medications that reduce gastric acid secretion (e.g., H_2 blockers or omeprazole) cause an elevation in serum gastrin levels. It should be noted that fasting serum gastrin levels in individuals with renal failure, pernicious anemia, or atrophic gastritis may exceed 300 pg/ml, and therefore concomitant measurement of BAO is necessary to confirm the diagnosis of ZES. In this case, a BAO greater than 15 mEq/hr in most patients and greater than 5 mEq/hr in patients with previous surgery to decrease gastric acid secretion unequivocally confirms the diagnosis. Alternatively, a gastric pH less than 2 is also consistent with ZES. With a working diagnosis of ZES, confirmatory provocative testing with secretin should be undertaken. The *secretin stimulation test* is the test of choice because it has a sensitivity of 85% or greater.[10] With this test, a 2-U/kg bolus of secretin is administered intravenously, and fasting serum levels of gastrin are measured before and 2, 5, 10, and 15 minutes after administration. An increase of 200 pg/ml in the gastrin level after secretin administration is consistent with a diagnosis of ZES (Fig. 58–1). However, in our experience the secretin test is positive in only 80% of ZES patients, so it is not absolutely required for diagnosis.[11]

TUMOR CHARACTERISTICS

Because of the small size of the tumor, even the most sensitive preoperative localization study for gastrinoma may prove falsely negative. Gastrinomas may be single, multiple, or metastatic and range in size from less than 1 cm to more than 3 cm. When associated with MEN-I, gastrinomas are usually multiple and commonly found within the duodenum.[12,13] Although it has been suggested that

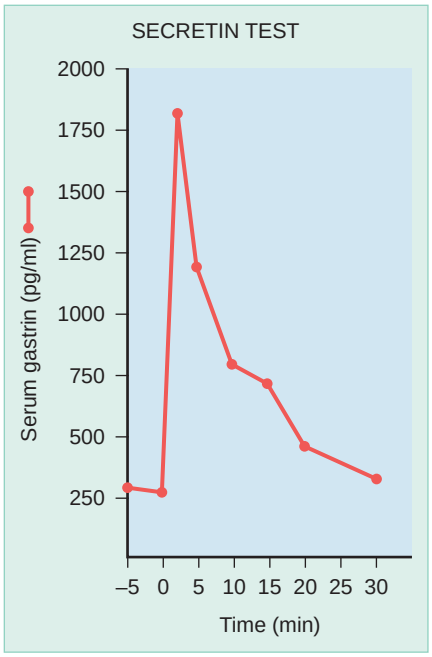

Figure 58–1. Secretin test for the diagnosis of Zollinger-Ellison syndrome (ZES). The patient had an elevated basal fasting serum level of gastrin, 260 pg/ml (normal, <100 pg/ml). After he received 2 U/kg intravenous secretin at time 0, serum gastrin levels increased to 1800 pg/ml at 5 minutes. This increment in serum gastrin level with secretin administration (>200 pg/ml) is diagnostic of ZES. However, these clearly abnormal results occur only in approximately 80% of patients with ZES.

the tumors found in patients with MEN-I have a lower potential for metastasis, they appear to metastasize with a frequency similar to that of regional lymph nodes, thus necessitating careful dissection of periduodenal and pancreatic lymph nodes. Furthermore, some tumors in patients with MEN-I may still act aggressively and be malignant.[8]

Approximately 80% of gastrinomas are found within the *gastrinoma triangle*, an area that includes the first, second, and third portions of the duodenum and the head of the pancreas.[14] In addition to the duodenum and pancreas, primary gastrinomas have been found in the jejunum, stomach, liver, spleen, mesentery, ovary, and heart.[15,16] A particularly confusing tumor is one that is found to be both extrapancreatic and extraintestinal within a lymph node. Though uncommon, it is now clear that some patients have been biochemically cured of ZES after excision of solitary gastrinomas that appear to have arisen within a lymph node. Patients have remained disease-free for more than 10 years. This strongly supports the possibility that there is a *lymph node primary gastrinoma*.[17] Gastrinomas of the duodenum and pancreas appear to have a similar incidence of metastases; however, pancreatic gastrinomas have a higher incidence of liver metastases than duodenal tumors do, and duodenal tumors have a higher incidence of lymph node metastases than pancreatic tumors do. Liver metastases are the rate-limiting step in long-term survival in that patients in whom liver metastases develop generally die of tumor whereas lymph node metastases do not adversely affect survival. This leads to decreased long-term survival in patients with primary pancreatic gastrinomas.[7]

LOCALIZATION PROCEDURES

Preoperative localization of tumor in patients with ZES continues to be imprecise. No solitary imaging or localization study can clearly identify the total extent of tumor. In general, preoperative imaging includes multiphasic computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor scintigraphy (Octreoscan), and endoscopic ultrasound (EUS). More invasive localization studies, including portal venous sampling for gastrin levels or intra-arterial injection of secretin with hepatic venous sampling for gastrin levels, provide functional localization to a region of the pancreas. However, because most occult gastrinomas are in the gastrinoma triangle,[14] these invasive regional localization studies are seldom indicated.

The accuracy of *CT scanning* is dependent on the size of the gastrinoma. Tumors smaller than 1 cm are seldom visualized. With current advanced helical multiphasic CT sequences, most tumors between 2 and 3 cm are seen. CT can detect primary and metastatic tumors larger than 3 cm. Overall, CT imaging can identify approximately 80% of pancreatic and 35% of extrahepatic gastrinomas.[18] *MRI* may be useful in identifying small lesions and, in particular, liver metastases. It is also useful in distinguishing metastatic liver neuroendocrine tumors from benign hemangiomas. However, MRI images only about 25% of primary gastrinomas.[19]

Somatostatin receptor scintigraphy (Fig. 58–2) with ^{111}In-labeled diethylenetriamine pentaacetic acid (DPTA)-D-Phe^{1}-octreotide was first evaluated in 1993.[20] It is the imaging test of choice for localizing both primary and metastatic gastrinomas, although it may not image small duodenal gastrinomas. The radiolabeled somatostatin analogue has high affinity for the type 2 somatostatin receptor, which is expressed in more than 90% of gastrinomas. Ninety percent of tumors can be imaged with this modality, with a specificity approaching 100%.[21,22] In the setting of ZES, when clinical suspicion of gastrinoma is high, it has a positive predictive value of 100% and can have a sensitivity exceeding that of all other imaging studies combined.[20] However, it may still miss some small duodenal tumors (<1 cm).

EUS is an observer-dependent method of localizing neuroendocrine tumors, including gastrinomas. It is invasive because an endoscope is positioned in the duodenum or stomach to image tumors with a high-frequency ultrasonic transducer. EUS has achieved its best results in imaging small intrapancreatic islet cell tumors such as insulinomas.[23] Tumors appear sonolucent, as opposed to the more echo-dense pancreas. The procedure has had difficulty in reliably identifying small duodenal tumors, possibly because of the mixed echogenicity of the duodenum, which contains both

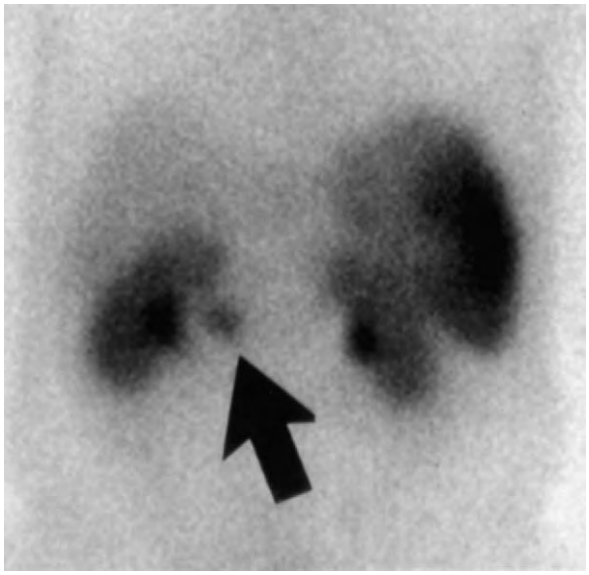

Figure 58–2. Somatostatin receptor scintigraphy showing a lesion that is consistent with a gastrinoma *(arrow)* within the area of the gastrinoma triangle. On exploration, the lesion was found in the medial wall of the duodenum.

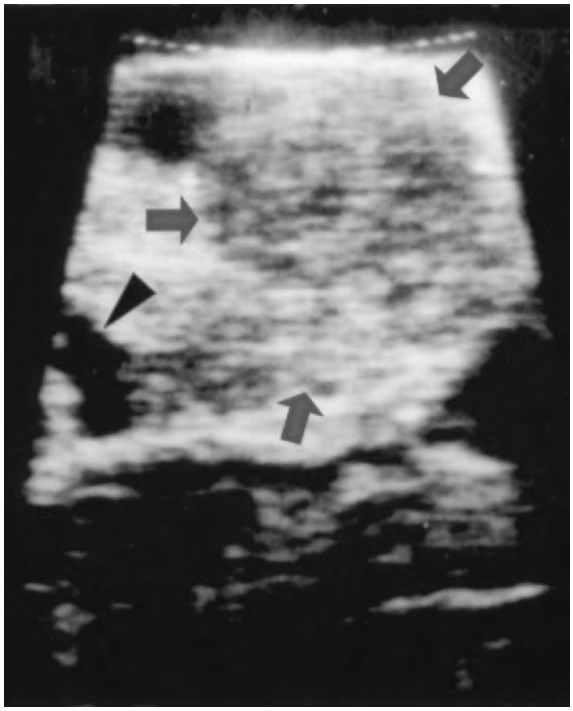

Figure 58–3. Intraoperative ultrasound showing the echogenic characteristics of a gastrinoma within the head of the pancreas *(arrows).* The mass itself is about 2 cm in diameter. The pancreatic duct is seen in the lower left of the screen *(arrowhead).*

liquid and gas within a thin solid wall. In addition, EUS may have difficulty differentiating normal lymph nodes from those containing tumor because the sonographic appearance is similar. One study found the sensitivity of EUS to be 50% to 75% for duodenal, 75% for pancreatic, and 63% for lymph node gastrinomas.[24]

Because noninvasive studies may fail to image the gastrinoma, regional localization studies have also been used. The *selective infusion of secretin was combined with angiography* in an attempt to identify the region of the pancreas that contained the gastrinoma. This approach became popular because it obviated the need for transhepatic portal venous sampling. In this study, secretin is selectively and sequentially injected into arteries that supply specific regions of the pancreas and liver. Gastrin levels are then measured in the hepatic vein. A substantial increase in hepatic vein gastrin levels localizes the gastrinoma to the area supplied by the injected artery.[25] However, this study seldom identifies tumors outside the gastrinoma triangle and appears to add little new information.[14] One advantage is that it can be used to identify patients who would probably be cured by Whipple pancreaticoduodenectomy.[26]

Intraoperative methods have been used to localize tumors not imaged preoperatively and to confirm preoperative findings. In this regard, *intraoperative ultrasound (IOUS)* has proved to be most useful for pancreatic neuroendocrine tumors.[27] It images gastrinomas within the pancreas as sonolucent masses (Fig. 58–3) and facilitates the removal of these tumors by showing the relationship of the tumor to the pancreatic duct and other structures. IOUS has not been effective in imaging duodenal gastrinomas, so *opening the duodenum (duodenotomy)* was developed (Fig. 58–4).[28] With duodenotomy, duodenal wall tumors appear as firm nodules within the wall of the duodenum that dimple the mucosa. Opening the duodenum has been able to identify more duodenal gastrinomas than any other method. It has resulted in an increased cure rate and prolonged survival.[29] The tumor is removed with a small rim of normal duodenum to allow complete resection.

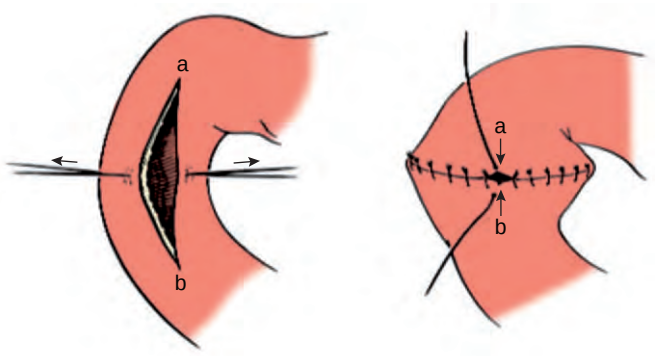

Figure 58–4. Duodenotomy for intraoperative localization of duodenal gastrinomas. The duodenum is opened longitudinally *(left panel),* and the wall is palpated and the mucosa examined. Gastrinomas feel like firm nodules within the wall, and they dimple the mucosa. The duodenum is closed transversely *(right panel)* so that the lumen is not narrowed.

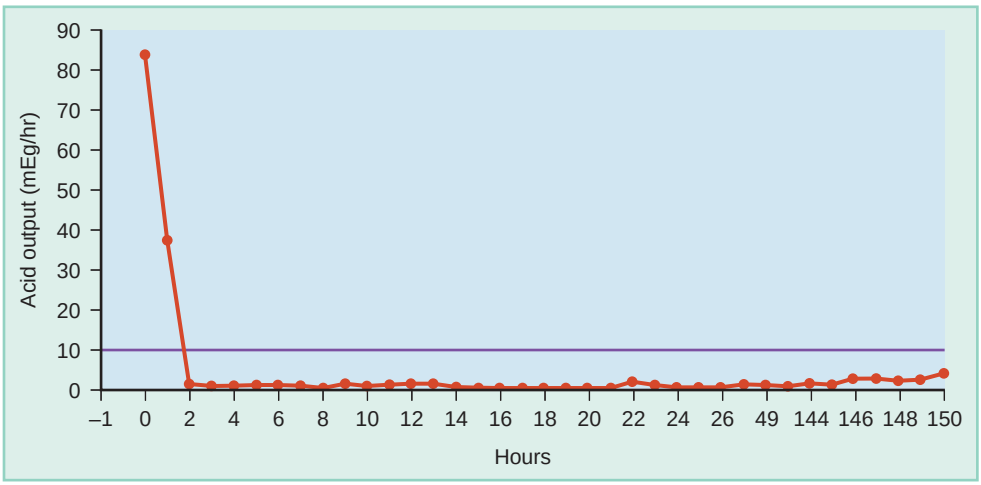

Figure 58–5. Intravenous pantoprazole to control gastric acid hypersecretion in a patient with Zollinger-Ellison syndrome (ZES). Gastric acid output needs to be kept below 10 mEq/hr at all times *(solid purple line)*. The patient's basal acid output is 85 mEq/hr, which is markedly elevated (normal, <15 mEq/hr), consistent with ZES. After being administered 80 mg of pantoprazole intravenously, his acid output drops to 2 mEq/hr within 2 hours and remains less than 10 mEq/hr for more than 24 hours. Therefore, to control the gastric acid hypersecretion of this patient with ZES, he needs 80 mg of pantoprazole intravenously every 24 hours. The oral dose is equally effective.

MEDICAL MANAGEMENT

Gastric acid hypersecretion can be effectively controlled with medications in all patients with ZES. Originally, total gastrectomy was the procedure of choice for the control of gastric acid hypersecretion, but it is no longer indicated. With the advent of proton pump inhibitors, all patients can experience control of acid hypersecretion and complete relief of symptoms. Omeprazole and pantoprazole are two members of the class of antisecretory drugs that inhibit gastric acid secretion by inhibiting parietal cell apical H^+,K^+-adenosine triphosphatase (ATPase). The usual dosage is 20 to 40 mg twice a day, and patients with ZES may require dosages in the 80-mg/day range.[30] Pantoprazole is a new intravenous proton pump inhibitor that has been shown to be effective in control of gastric acid secretion in ZES patients. It is especially useful during surgery or acute hospitalization. The usual dose is 40 to 80 mg intravenously every 12 hours (Fig. 58–5).[30]

Measurement of BAO is necessary to adjust the dose of proton pump inhibitor for effective medical treatment of individual cases. Furthermore, relief of symptoms is not a reliable indicator of overall medical control of ZES. To allow healing of ulceration and to prevent recurrences, gastric acid secretion should be maintained below 10 mEq/hr before the next dose of medication and should be kept below 5 mEq/hr if previous ulcer surgery has been performed or in patients with GERD and esophageal stricture. Even with long-term medical control of ZES, there are the associated risks of sustained achlorhydria. In particular, diffuse malignant gastric carcinoid tumors have developed in some patients with MEN-I after prolonged treatment with omeprazole.[31] It is therefore necessary to perform periodic gastric surveillance endoscopy on patients with MEN-I who are treated with proton pump inhibitors for long periods.

SURGICAL MANAGEMENT

Medical control of symptoms allows time for localization and nonemergency surgical treatment of gastrinoma. It also obviates the need for total gastrectomy. With the results of a number of long-term studies, it is evident that the malignant potential of the tumor itself becomes the main determinant of survival (Fig. 58–6).[32] Therefore, all patients with sporadic (nonfamilial) gastrinoma should be considered candidates for tumor localization and exploratory laparotomy for cure of ZES.[11] Management of patients with MEN-I and ZES is controversial and more complex. In patients with MEN-I and primary hyperparathyroidism, the usual parathyroid pathology is multigland disease or hyperplasia. It has been shown that successful neck exploration for resection of parathyroid hyperplasia can significantly ameliorate the end-organ effects of hypergastrinemia (Fig. 58–7). In patients with MEN-I, ZES, and primary hyperparathyroidism, neck exploration should be performed before resection of gastrinoma.[33] Removal of pancreatic and duodenal tumors seldom cures MEN-I patients of ZES.[11,34] It has been shown that resection of primary gastrinomas in all patients decreases the likelihood of liver metastases[35]; however, surgical resection of localized gastrinoma has not been demonstrated to prolong survival of patients with ZES.[35] The goals of surgical management, therefore, are resection of the primary tumor for potential cure and prevention of malignant progression. This latter goal is desired whether the patient has a sporadic gastrinoma or one in the setting of MEN-I syndrome. Operative

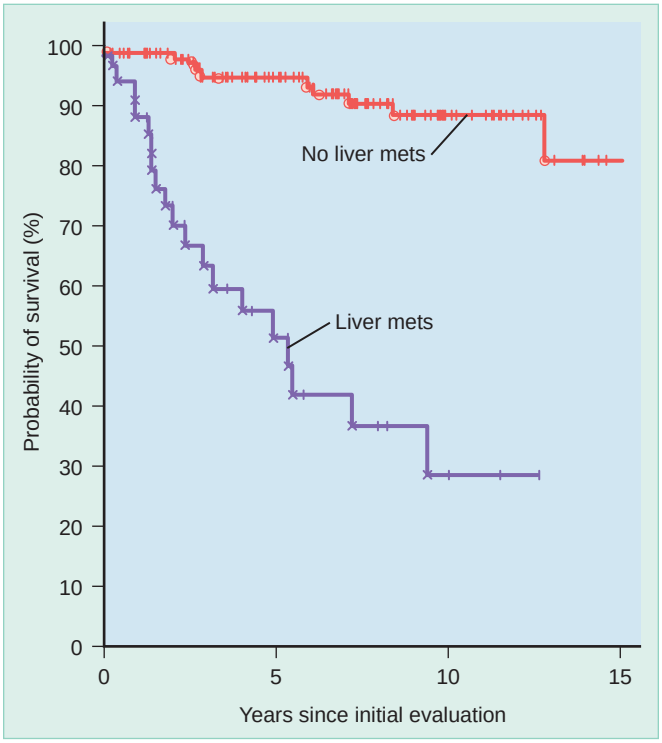

Figure 58–6. Kaplan-Meier survival curve for patients with gastrinoma in the presence or absence of liver metastasis (mets). Data are derived from follow-up of a cohort of patients who were evaluated and treated at the National Institutes of Health.

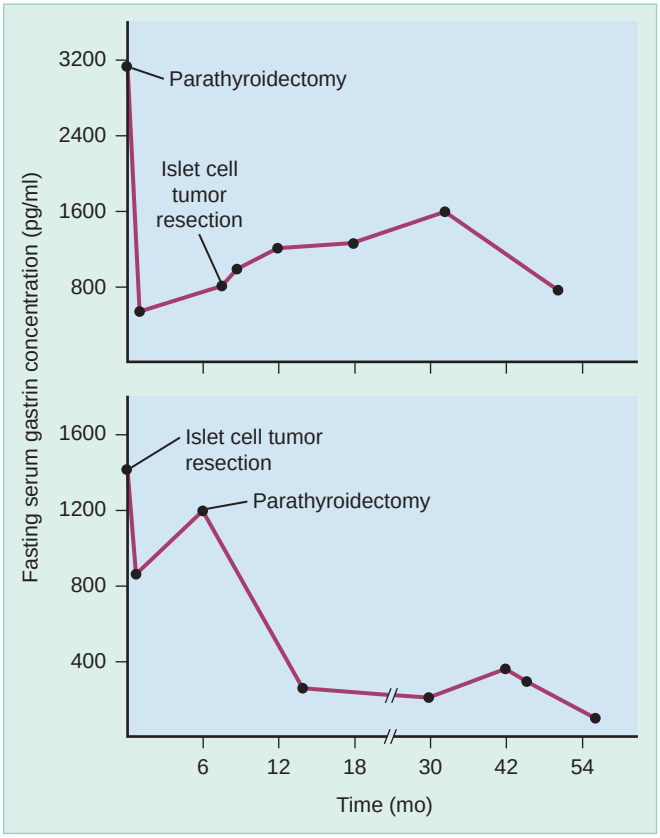

Figure 58–7. Effect of parathyroidectomy on the fasting serum levels of gastrin in two patients with multiple endocrine neoplasia type I. In each case, resection of parathyroid disease significantly reduced serum gastrin levels regardless of the timing of islet cell tumor resection.

management of patients with MEN-I and gastrinoma is complicated by the fact that within this setting the tumors tend to be multiple and small (4 to 6 mm), usually involve the duodenum,[13] and spread early to lymph nodes. In these patients the controversy centers on the fact that surgery is seldom curative,[11,34] yet it may be effective in treating the potential malignant disease and preventing liver metastases.[36]

Recommendations for management of MEN-I ZES patients have ranged from medical management to aggressive surgery, without a clear consensus for a single ideal therapy.[3,36] We have operated on patients with MEN-I when the primary tumor is imaged at 3 cm or larger.[34] This decision is based on the fact that the presence of liver metastases correlates with primary tumor size: liver metastases develop in 4% of patients with primary gastrinomas smaller than 1 cm as compared with 28% of patients with tumors between 1 and 3 cm and 61% with tumors larger than 3 cm.[7] After a review of current data, it seems more prudent to operate on patients with MEN-I who have smaller, but clearly identifiable pancreatic and duodenal gastrinomas (2 cm in size) because this should decrease the probability of hepatic metastases considerably.[36]

Approximately 95% of patients with sporadic ZES will have gastrinomas found at surgery, and 60% to 68% will be cured.[11,29] Importantly, duodenotomy has increased the tumor detection and cure rate (see Fig. 58–4).[29]

Surgery is also effective treatment of localized metastatic liver gastrinoma because it appears to prolong survival and cure some patients.[37,38] In patients with MEN-I and gastrinoma, identification of all tumor foci is problematic, and surgery results in a much lower cure rate.[11,34] Paradoxically, although patients with gastrinoma associated with MEN-I may be identified at a younger age, have multiple small duodenal tumors, and undergo abdominal exploration without surgical cure, liver metastases develop at a lower rate than in their sporadic counterparts, and they have excellent survival.[3] However, recent studies have shown that in some (25%) the activity of pancreatic neuroendocrine tumors is significant and survival is dependent on the aggressive behavior of the pancreatic tumor.[8]

In general, in MEN-I patients with ZES, if 2-cm tumors are clearly imaged on preoperative studies, surgery is indicated to remove these tumors, which may be malignant.[36] In patients with sporadic ZES who have no clear imageable tumor[11] or localized primary or metastatic[37,38] tumor, laparotomy is also indicated because duodenotomy will find duodenal tumors and imageable tumors (even when metastatic) can usually be completely resected. Surgery for gastrinoma requires careful dissection of the regional lymph nodes that may contain

metastases. Furthermore, primary lymph node gastrinomas have been described, resection of which can result in cure of ZES.[17] Enucleation of pancreatic head tumors is generally sufficient, whereas distal pancreatectomy with splenectomy is indicated for tumors of the body and tail. In all patients with ZES, duodenotomy is critical.[29] Whipple resection has been advocated by some; however, it is indicated only for localized large (>3 cm) tumors in the duodenum or pancreatic head, with or without extensive nodal metastases.[39] It has also been used in MEN-I patients with locally advanced tumor confined to the gastrinoma triangle.[40]

Performance of the standard operation for gastrinoma relies on careful exploration of the entire abdomen, as previously described.[11] It is important to explore and palpate the liver, stomach, small bowel, mesentery, pancreas, and pelvis, including the ovaries in female patients. An extended Kocher maneuver should be performed to mobilize the duodenum and gain access to the pancreatic head. The pancreatic body and tail is examined by dividing the gastrocolic ligament. IOUS is used to image the pancreas and liver. A 7.5- to 10-mHz near-field transducer is necessary to examine the pancreas, whereas a 2.5- to 5-mHz wide-angle transducer is best for the liver. Tumors appear sonolucent (see Fig. 58–3) and should be imaged in two dimensions. The duodenum can then be palpated between the thumb and forefinger for the presence of a tumor mass. Duodenal gastrinomas feel like sharply defined, small firm nodules within the wall. A longitudinal duodenotomy is indicated in all cases (see Fig. 58–4) because it permits visualization, as well as more careful palpation of the entire duodenal wall, particularly its medial portion. Suspicious nodules on the medial wall should not be excised until after clear identification of the nodule and its relationship to the ampulla of Vater and pancreatic duct. The duodenum is preferably closed transversely in two layers to minimize the risk for leakage or obstruction (see Fig. 58–4). If a long duodenotomy is necessary, longitudinal closure may be necessary. The peripancreatic, porta hepatis, and celiac lymph nodes are also sampled and excised for pathologic review. Reoperation for recurrent localized gastrinoma is indicated if the tumor can be clearly imaged, and it results in complete resection of all tumor in nearly every patient and complete remission in 30%.[41]

METASTATIC DISEASE

With successful control of gastric acid hypersecretion and the indolent growth pattern of the gastrinoma, distant metastatic disease is the most important determinant of survival (see Fig. 58–6).[7] A histologic diagnosis of cancer is impossible to make pathologically, and malignancy is diagnosed by identifying lymph node and distant visceral metastases. Previously, about 60% of patients had metastatic disease at diagnosis. However, with more widespread availability of biochemical testing and earlier diagnosis, that percentage has decreased to 25%.[6] The long-term survival rate for patients with distant metastatic disease is approximately 20%, and chemotherapy has not been helpful.[7,42] In patients with completely resected localized liver metastases, the 5-year survival rate is 80%.[38] In contrast, patients with unresectable hepatic disease have a 5-year survival rate of 20% to 38%.[32] Most recently, lesser surgical procedures than open resection have been used to effectively deal with liver metastases from neuroendocrine tumors. Laparoscopic radiofrequency ablation (RFA) of liver metastases from pancreatic neuroendocrine tumors is associated with a liver tumor control rate of 90%.[43] Because of the indolent nature of these tumors and the lack of other effective treatments, surgical resection has been the main treatment of recurrent or metastatic gastrinoma (or both), and the results have been encouraging. Furthermore, growth of tumor can be suppressed by somatostatin analogues.[44] If a tumor is imaged by Octreoscan and expresses somatostatin receptors, we combine surgical resection or RFA with long-term high-dose somatostatin analogues (Sandostatin LAR, 30 mg intramuscularly every 3 weeks). This regimen has provided excellent results in terms of symptom-free survival.

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Chapter

59

Postgastrectomy Syndromes

Thomas A. Miller · Jeannie F. Savas

Before the late 1970s, surgical management of acid-peptic diseases of the stomach and duodenum was relatively commonplace. Depending on the site of the ulcer, its chronicity, and what role acid hypersecretion was thought to play in its pathogenesis, surgical options varied from vagotomy and gastric drainage with some form of pyloroplasty to more radical procedures in which substantial portions of the distal part of the stomach were removed. The derangements in gastric function induced by these various operations were not infrequently associated with a variety of postoperative sequelae that have collectively been called the "postgastrectomy syndromes."

With the commercial introduction of cimetidine (Tagamet) in 1977, management of peptic ulcer disease radically changed. For the first time, effective treatment of the ulcer diathesis was now possible with a pharmacologic agent. Shortly after the introduction of this H_2 receptor blocker, several other similar blockers appeared on the market. In addition, by the late 1980s, proton pump inhibitors were also released and made inhibition of acid secretion even more effective than had previously been observed with the H_2 receptor blockers. Such pharmacologic manipulation resulted in most forms of acid-peptic disease being effectively managed nonoperatively. Concomitant with these developments was the further observation that a bacterium known as *Helicobacter pylori* was probably responsible for most forms of duodenal ulcer disease and a significant proportion of gastric ulceration. Surprisingly, it now became possible to actually eradicate peptic ulceration with antibiotic therapy in a large majority of patients. Thus, as we entered the 21st century, peptic ulcer disease has become a predominantly medical disease that can be effectively managed in most patients with nonsurgical interventions. Only when complications occur that are resistant to medical therapy, such as perforation, uncontrolled hemorrhage, and gastric outlet obstruction, is the surgeon called on to offer expertise in the management of peptic ulceration.

Along with these advances in peptic ulcer therapy has been a steady decline in the incidence of gastric cancer in the United States and most areas of Western Europe. Thus, the radical surgical procedures that were previously used to manage this malignancy have likewise become less radical. In fact, with early surveillance by upper endoscopy, gastric cancer is now being diagnosed in many patients at much earlier stages of development, and less radical procedures are required for cure.

All these advances have resulted in a major decrease in patients with postgastrectomy problems, and many surgeons have actually had minimal experience managing them. Because a sufficient number of patients with refractory ulcer disease and more advanced gastric cancer still require ablative procedures for effective management, the small, but consistent number of patients who will still be subject to postgastrectomy problems require that the surgeon of the early 21st century be cognizant of their management until other treatment modalities evolve that make gastric operations a relative thing of the past. This chapter highlights the major postgastrectomy syndromes that still occur and demand thoughtful management by the treating surgeon. Three types of causes have been identified: gastric reservoir dysfunction, vagal denervation, and aberrations in surgical reconstruction. Discussion of their pathogenesis and management forms the basis of this chapter.

GASTRIC RESERVOIR DYSFUNCTION

Dumping Syndrome

The human stomach possesses a remarkable capability of adapting to large volumes of orally administered liquids and solids through a process known as receptive relaxation.[1] These intragastric contents are then acted on by secreted acid and pepsin along with muscular churning to prepare an isosmotic gastric chyme that is then slowly discharged into the upper part of the gut for subsequent processing so that effective digestion and absorption can occur throughout the small bowel. If a portion of the stomach has been previously removed or the normal pyloric sphincter mechanism has been deranged, the

ingested meal is not as effectively processed by the stomach and is prematurely discharged into the upper intestine. Depending on the speed of this discharge and the osmolarity of the contents being discharged, a variety of symptoms may result that have been referred to as the *dumping syndrome*. Both an early and late form of this disorder have been identified.

The early form of dumping syndrome is by far the more common and usually occurs within 10 to 30 minutes after the ingestion of a meal. A constellation of postprandial symptoms have been described that range in severity from annoying to disabling. The classic gastrointestinal (GI) symptoms include nausea and vomiting, epigastric fullness, eructations, abdominal cramping, and occasionally, explosive diarrhea. Cardiovascular symptoms are often associated with these GI complaints and include tachycardia, palpitations, diaphoresis, and a feeling of lightheadedness and flushing that may be accompanied by blurred vision. This symptom complex may occur while the patient is still seated at the table eating; more commonly, however, it occurs shortly after completing the meal. The precise mechanism or mechanisms responsible for early dumping are still being debated, but most investigators are in general agreement that rapid passage of food of high osmolarity from the stomach into the small intestine is the basic cause.[2,3] Thus, the previous gastric resection or interrupted pyloric sphincter mechanism no longer enables the intact stomach to prepare its contents and deliver them into the proximal part of the bowel in the form of small particles in isosmotic solution. The rapid discharge of this hyperosmotic chyme then induces a rapid shift of extracellular fluid into the intestinal lumen so that the newly received gastric chyme is brought to a state of isotonicity. Accordingly, the gut distention and autonomic responses induced by the changes in plasma volume are thought to be responsible for the underlying symptomatology.

A variety of clinical conditions may give rise to early dumping. As many as 5% to 10% of patients experience dumping symptoms after operations involving the pyloric sphincter, such as pyloroplasty or pyloromyotomy, or after varying degrees of distal gastric resection.[4,5] The type of GI reconstruction after distal gastrectomy also appears to play a role because dumping after partial gastrectomy with a Billroth II reconstruction is especially common, as opposed to a Billroth I gastrectomy, in which this condition is less frequently observed.[6] The role that various neuroendocrine responses may play in its pathogenesis remains to be defined. A variety of hormonal abnormalities have been observed in early dumping, including aberrations in serotonin, vasoactive intestinal peptide, cholecystokinin, neurotensin, peptide YY, enteroglucagon, renin-angiotensin-aldosterone, and atrial natriuretic peptide.[7-12]

In contrast to early dumping, which usually occurs within 30 minutes of eating, late dumping is delayed until 2 to 3 hours after the ingestion of a meal. It is also much less common than its early counterpart. The basic pathophysiology appears to be the same, namely, rapid discharge of hypertonic chyme from the stomach into the upper part of the gut. This form of dumping, however, seems to be specifically related to carbohydrates such as monosaccharides and disaccharides. After rapid delivery of these sugars into the small intestine, hyperglycemia results from their relatively quick absorption. The pancreas is subsequently triggered to release insulin to control the elevated blood sugar and, in the process of doing so, actually "overshoots" so that marked hypoglycemia is induced. This insulin shock condition then activates the adrenal gland to release catecholamines, which cause a constellation of symptoms, among which are tachycardia, tachypnea, diaphoresis, and lightheadedness. Why late dumping develops in some patients whereas the majority have an early expression of this syndrome remains unknown.

In most patients in whom dumping develops after gastric surgery, medical management is usually successful. The simple dictum of limiting the amount of liquids ingested during a meal has greatly improved symptoms in many patients. Certainly, hyperosmolar substances such as ice cream or liquids such as milkshakes should be cautiously avoided because these substances may prove to be particularly troublesome. Sometimes, measures as simple as avoiding certain foods, eating small meals more frequently, separating liquids from solids, or lying down when symptoms start to occur may be all that is necessary to control or significantly alleviate the symptomatology. In some instances, carbohydrate gelling agents such as pectin, when taken with a meal, have proved to be successful.[13] The α-glucosidase inhibitor acarbose has proved to be particularly helpful in ameliorating the symptoms of late dumping.[14,15] If dumping continues after instituting these various measures, octreotide has proved useful in many patients.[16,17] Administered subcutaneously in a 100-μg dose twice daily, this somatostatin inhibitor has been shown to ameliorate many of the hormonal abnormalities seen in patients with dumping syndrome, as well as restore a fasting motility pattern in the small intestine known as the migratory motor complex. If this low dose is not successful, it can be increased to as high as 500 μg twice daily.

Fortunately, the majority of patients with dumping symptoms will respond to these conservative measures. In only 1% or less of patients will operative intervention be required. Great care should be taken in selecting patients who might benefit from surgery. Every effort should be made to define the severity of the patient's symptoms, whether disciplined nonoperative measures have been used to alleviate the symptoms, and whether some associated stressful situation (such as divorce or financial problems) is contributing to the symptomatology and would very likely not be altered by operative intervention. If surgery has been judged to be the best alternative for management, the type of procedure previously performed and the amount of gastric reservoir that still exists will influence the operative approach. If no stomach has been previously resected and the dumping has resulted primarily from pyloric dysfunction, pyloric reconstruction can often be performed in these patients. The advantage of this technique is that it is quite safe and does not require irreversible maneuvers such as gastric resection or vagotomy. Cheadle and associates[18] performed pyloric reconstruction in a

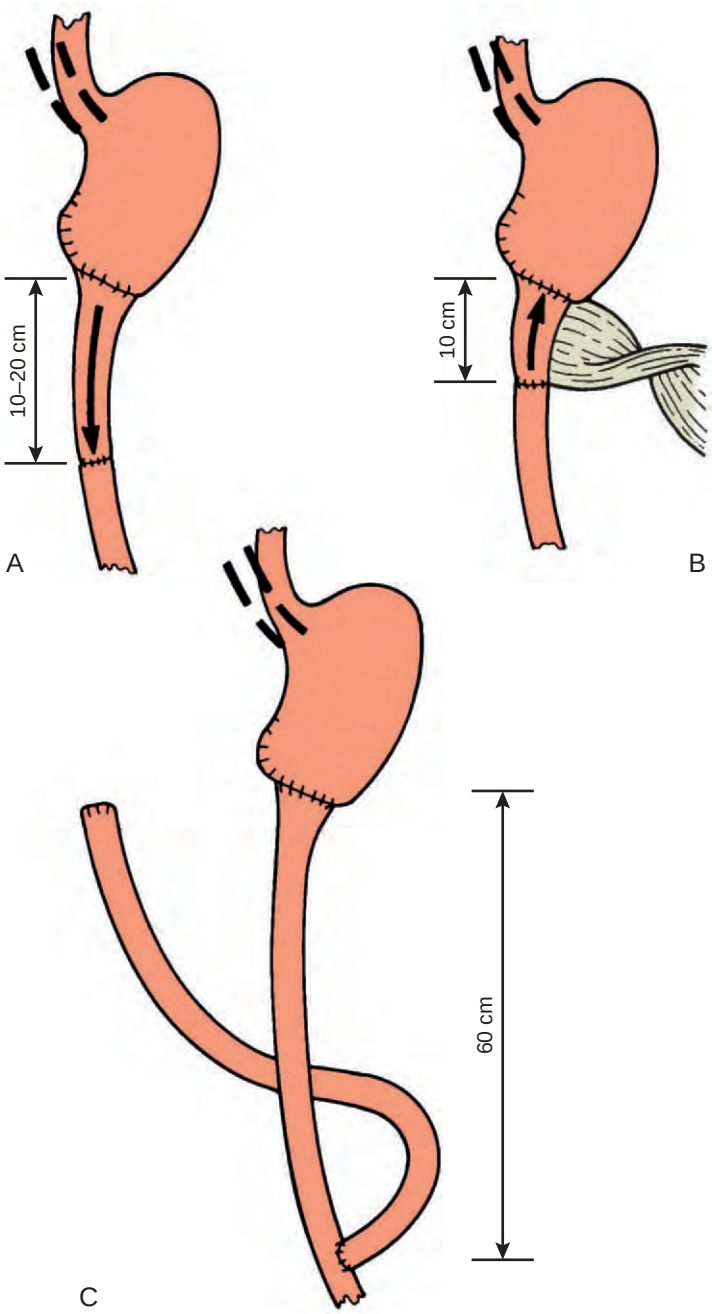

Figure 59–1. Surgical approaches to treat dumping syndrome. **A,** A 10- to 20-cm loop of jejunum is interposed between the stomach and small intestine in an isoperistaltic fashion. **B,** A 10-cm loop of jejunum is twisted on its mesentery so that its distal end is anastomosed to the stomach and its proximal end to the small intestine in an antiperistaltic fashion. **C,** Long-limb Roux-en-Y anastomosis in which the jejunojejunostomy is fashioned approximately 60 cm from the gastrojejunostomy. (From Miller TA, Mercer DW: Derangements in gastric function secondary to previous surgery. In Miller TA [ed]: Modern Surgical Care: Physiologic Foundations and Clinical Applications, 2nd ed. St Louis, Quality Medical, 1998, p 400.)

number of patients with severe dumping after vagotomy and pyloroplasty (Visick 4 score) and were able to demonstrate considerable symptomatic improvement so that their new scores were reduced to 2 or 3. Although Frederiksen and associates had similar results in a small series with disabling diarrhea or dumping after vagotomy and pyloroplasty,[19] other experienced gastric surgeons have not been as successful.[20] If a previous gastric resection and Billroth II reconstruction gave rise to the dumping, simple takedown of this anastomosis and converting it to a Billroth I reconstruction may be all that is needed.[21]

Two other options have also been used to surgically treat dumping syndrome (Fig. 59–1). The first has involved the use of isoperistaltic or antiperistaltic jejunal segments interposed between the stomach and small intestine. The rationale behind these procedures is that the 10- or 20-cm loop of jejunum used for interposition slows down gastric emptying. Although early results with both procedures suggested considerable benefit, amelioration of severe dumping has not been consistently demonstrated in the long term.[20] Furthermore, such interposition operations have often led to obstruction, thereby necessitating a reoperation.[20]

The most durable procedure has been the Roux-en-Y-gastrojejunostomy (see Fig. 59–1). This procedure delays gastric emptying, probably on the basis of disordered motility in the Roux limb as shown by Cullen and Kelly[22]

in a study in which electrical and mechanical activity in the Roux limb was found to advance toward the stomach rather than in an aborad direction. In a series of 22 patients treated over a period of 13 years, Vogel and colleagues showed that this operative approach successfully managed the dumping syndrome, with complete resolution of symptoms in 19 of these individuals.[20]

Metabolic Aberrations

Three metabolic disturbances may occur after gastric surgery, including anemia, bone disease, and weight loss. Although any type of gastric procedure can induce such problems, gastric resection is more commonly associated with them than vagotomy is, and the incidence after gastrectomy with a Billroth II reconstruction is greater than that encountered with a Billroth I approach.[23]

Of the causes of anemia, a deficiency in iron is clearly the most commonly encountered. As many as 30% to 50% of patients experience this type of anemia after gastrectomy. Although iron absorption takes place primarily in the proximal portion of the gut, it requires an acidic environment for this action to maximally occur. Thus, any gastric procedure that alters acidity can contribute to this problem. Vagotomy is known to decrease both fasting and stimulated acid production, and antrectomy removes an important source of the hormone gastrin, which physiologically contributes to gastric acid production. If a larger portion of stomach is resected than the antrum, not only is the gastrin source removed, but some of the parietal cell mass is also absent. If iron deficiency develops, the problem is easily corrected by the addition of iron supplements to the patient's diet.

The other common anemia is related to a deficiency of vitamin B_{12}. Because intrinsic factor, which is made by the parietal cells of the stomach, is essential for the enteric absorption of vitamin B_{12}, any gastric procedure that alters parietal cell mass can contribute to this problem.[23] Furthermore, vitamin B_{12} bioavailability is also facilitated by an acidic environment. Thus, any patient who has undergone vagotomy or gastrectomy (even if only partial) should be periodically monitored by hematocrit, red cell indices, iron, transferrin, and vitamin B_{12} to be sure that an incipient anemia is not developing. Although folate deficiency can also occur after gastric resection, it is quite uncommon in comparison to the other types described. It is usually related to inadequate oral intake rather than a defect in absorption, as occurs with iron and vitamin B_{12} deficiencies. Finally, it needs to be emphasized that in all patients who have undergone total gastrectomy, vitamin B_{12} deficiency will invariably develop, and thus they must be given an intramuscular injection of cyanocobalamin every 3 to 4 months for the rest of their lives because oral administration is not a reliable route for absorption.

Calcium and vitamin D metabolism may also be perturbed by previous gastric surgery. Fat malabsorption is not uncommon after gastric resection with a Billroth II reconstruction as a result of the inefficient mixing of food, bile, and pancreatic enzymes. Because vitamin D is a fat-soluble vitamin, this circumstance can significantly affect its absorption.[24] Of equal importance, calcium absorption, which predominantly occurs in the duodenum, can also be adversely affected by gastrectomy and Billroth II reconstruction.[23,24] The metabolic bone disease that can occur in patients under these circumstances is usually insidious and may require many years to manifest itself. Unexplained aches and pains in the back or bones may be the initial symptomatology. Occasionally, a spontaneous fracture indicates the presence of bone disease. Patients suspected of having this problem should undergo a bone density study. Skeletal monitoring of patients at risk (i.e., elderly men and women, postmenopausal women) may prove useful in identifying skeletal deterioration, which may be arrested with appropriate treatment. In selected patients, dietary supplementation of calcium and vitamin D appears to be useful in preventing these complications.

Weight loss is a frequent finding after surgical procedures on the stomach. Often, it is temporary, and once the patient adjusts to the dietary aberrations evoked by the operation, sufficient protein/calorie nutrition commonly results so that no clinically significant problem develops. In patients who have had either all or substantial portions of their stomach removed, considerable malnutrition may occur, particularly in thin women. Thus, great care should be taken to avoid a gastric procedure for benign disease in a woman who is marginally normal in terms of weight. In a patient who has lost weight after gastric surgery, it is important to determine whether it is related to an alteration in dietary intake or is a consequence of malabsorption. If a stool stain for fecal fat is negative, decreased caloric intake is the probable cause. Usually, an improvement in nutritional balance can be accomplished by changing one's diet to multiple small feedings if dumping-like symptomatology occurs with regular feeding. If intractable problems with weight loss become chronic, a surgical procedure to delay gastric emptying or enhance the gastric reservoir effect, as discussed under "Dumping Syndrome," may become the most prudent means of management.

VAGAL DENERVATION

Diarrhea

At least 30% of patients who undergo gastric surgery will complain of diarrhea postoperatively if carefully questioned.[5] As already indicated in the section on dumping syndrome, diarrhea is frequently a component of this entity. Regardless of cause, for most patients the diarrhea is not severe and often abates within several months of the operation. Even in patients with dumping syndrome, the diarrhea usually improves as patients adjust their diet to modify intake of food that may trigger this response. Distinct from other causes of diarrhea, vagotomy by itself may induce changes in postoperative bowel function that may range from a simple increase in stool frequency to frank, explosive bowel movements that could result in soiling of clothing if the patient does not find a toilet in time. Fortunately, clinically significant postvagotomy diarrhea occurs in only 5% to 10% of

patients, and over time this problem also corrects itself in the majority of individuals.

Despite scores of studies by multiple investigators, the precise mechanisms responsible for postvagotomy diarrhea have not been elucidated. It was originally thought that this problem occurred only in patients with truncal vagotomy and that maintaining vagal innervation of the small bowel with more selective vagotomy approaches would obviate this problem. Long-term follow-up of this latter group of patients has not borne out this contention, so intestinal dysmotility and accelerated transit secondary to vagal denervation are only partially responsible for the diarrhea, if at all.[25,26] Other proposed mechanisms include bile acid malabsorption, rapid gastric emptying, and bacterial overgrowth.[26-29] The latter problem is known to be facilitated by the decreased gastric acid secretion after vagotomy; furthermore, bacterial overgrowth can be confirmed in many postvagotomy diarrhea patients, and anecdotal reports indicate that the diarrhea has abated or markedly decreased after antibiotic therapy. Whether this proves a cause-and-effect relationship can be debated. Interestingly, a subset of patients with postvagotomy diarrhea have been shown to respond to cholestyramine.[30] This anionic exchange resin absorbs bile salts and renders them inactive. Moreover, it has been shown experimentally that the total bile acid content in the stools of patients with postvagotomy diarrhea, though not significantly greater than in those without this problem, has more than twice the amount of chenodeoxycholic acid.[29] Such findings lend support to the hypothesis that bile acid malabsorption may contribute to postvagotomy diarrhea in some patients.

Fortunately, no more than 1% of all patients undergoing vagotomy will experience a sustained problem with diarrhea. Over time, the problem seems to abate. In patients not responsive to cholestyramine, codeine or loperamide may prove useful. In patients who have incapacitating diarrhea for at least a year after the initial operation that is unresponsive to medical management, remedial surgery is an appropriate treatment option. The operation of choice is to interpose a 10-cm segment of reversed jejunum placed in continuity 70 to 100 cm from the ligament of Treitz (Fig. 59–2). In patients requiring operative intervention, this approach has been associated with sustained relief from the diarrheal problem.[21]

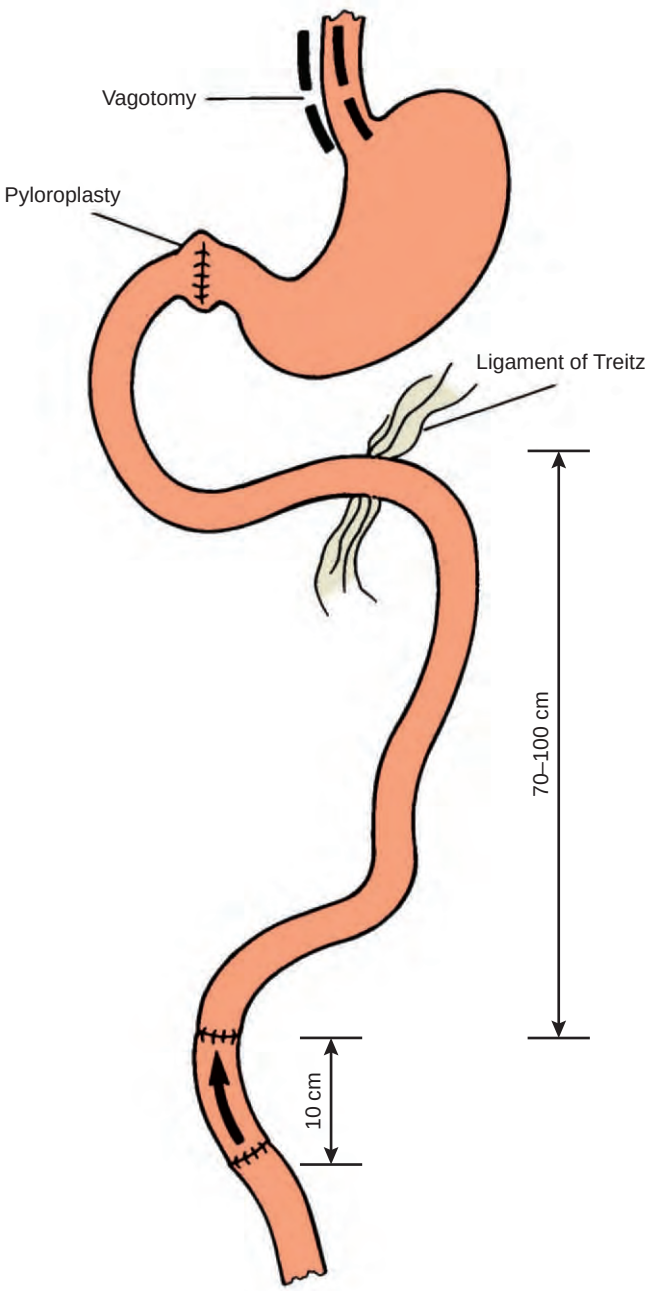

Figure 59–2. Surgical management of postvagotomy diarrhea. (From Miller TA, Mercer DW: Derangements in gastric function secondary to previous surgery. In Miller TA [ed]: Modern Surgical Care: Physiologic Foundations and Clinical Applications, 2nd ed. St Louis, Quality Medical, 1998, p 407.)

Gastric Stasis

It is not unusual for some degree of delayed gastric emptying to occur after vagotomy, particularly if the major vagal trunks were transected (i.e., both truncal and selective vagotomy). This circumstance is not surprising because the nerves of Latarjet are denervated in both these procedures, thus disrupting the normal function of the vagus nerve in adjusting gastric tone to changes in gastric volume so that normal peristalsis and emptying are coordinated properly.[22] The atonic stomach that results from these procedures is not a problem with parietal cell vagotomy because this approach to vagal transection does not disrupt antral innervation and accordingly allows propulsive activity of the distal part of the stomach to be maintained.

In patients subjected to truncal or selective vagotomy and in whom gastric stasis occurs, treatment is determined by the degree of symptomatology. Often, the only significant symptom is a feeling of fullness in the epigastric region, which at worst is simply a nuisance. Fortunately, this problem usually abates within several weeks after vagotomy as the patient resumes more normal

alimentation. In other individuals, marked abdominal pain may occur, and in rare individuals a functional gastric outlet obstruction may develop.

In evaluating a patient with presumed postvagotomy gastroparesis, other causes of delayed gastric emptying must be excluded. Medical causes include diabetes mellitus, electrolyte imbalance, toxicity to drugs, and neuromuscular diseases. Mechanical causes include postoperative adhesions, anastomotic stricture, afferent or efferent loop obstruction, and internal adhesions if a gastroenterostomy or a concomitant gastric resection and Billroth II reconstruction were done in conjunction with the vagotomy. At the very least, evaluation should include esophagogastroduodenoscopy and some type of gastric emptying study with either barium or a scintigraphic agent.[31] In most individuals, gastric emptying is best quantified clinically with scintigraphic techniques that give half-lives for liquid and solid emptying. If the underlying problem responsible for gastric stasis is thought to be a disorder of intrinsic motor function, additional techniques such as electrogastrography and GI manometry may prove helpful.[32]

Assuming that mechanical obstruction has been excluded, short-term treatment with various pharmacologic agents has proved successful in most cases of motor dysfunction. Such treatment includes a combination of dietary modification and various pharmacotherapeutic agents that enhance promotility. One of several gastrokinetic agents, such as metoclopramide, domperidone, and erythromycin, will generally prove efficacious in a given patient. Metoclopramide is a dopamine antagonist that works on the stomach by facilitating acetylcholine release from enteric cholinergic neurons.[33] Domperidone works on both the stomach and the intestine by facilitating acetylcholine release from the mesenteric plexus of the gut.[34] Erythromycin is a motilin agonist that works on both the stomach and intestine by binding to motilin receptors on GI smooth muscle.[35] One of the agents mentioned is usually sufficient to enhance gastric tone so that improved gastric emptying results. Unfortunately, cisapride, a very effective prokinetic agent that works similar to domperidone, was taken off the market by the Food and Drug Administration because of associated cardiac problems in a small subset of patients with underlying heart disease.

In the rare patient recovering from gastric surgery, persistent nausea and vomiting prevent removal of the nasogastric tube. If one is patient, even such individuals can usually be nursed through this turbulent experience. If the nasogastric tube cannot be removed within a period of 7 to 10 days after surgery, a gastrostomy may be placed either laparoscopically or endoscopically. Alimentation can then be given via a J-tube extension placed during one of these techniques. If the gastric remnant is not of sufficient size to accommodate these approaches, a decompressing gastric tube can often be passed retrograde through the efferent limb and exited through the skin via a Witzel technique. Distal to this placement, another tube may be placed antegrade as a Witzel feeding jejunostomy. In patients in whom these enteral approaches to alimentation are not possible, total parenteral nutrition is still an alternative. In any event, reoperative surgery should generally be delayed for at least 3 months because the majority of patients will regain satisfactory GI function. Only after this period should re-exploration be considered.

Gallstones

The role of vagal denervation in causing gallstone formation has been debated for more than 30 years. The argument in favor of this contention is that division of the hepatic branches of the anterior vagal trunk (as occurs during truncal vagotomy and is frequently done during antireflux and bariatric operations) increases gallstone formation by the creation of gallbladder dysmotility.[36] Both experimental and clinical evidence can be provided that support and challenge this hypothesis. For most forms of gastric surgery in which concomitant vagotomy is anticipated, prophylactic cholecystectomy is not justified. It should be seriously considered only if the gallbladder appears abnormal and if subsequent cholecystectomy is likely to be difficult, as would occur in a patient undergoing gastric bypass for morbid obesity. Obviously, if preoperative evaluation reveals sludge or gallstones in a patient scheduled for gastric surgery and no other complicating problems are anticipated, concomitant cholecystectomy should probably be performed.

ABERRATIONS IN RECONSTRUCTION

A variety of disorders may occur after gastric resection that are greatly influenced by the type of reconstruction performed to re-establish GI continuity. By far, the majority of problems develop in patients who have previously undergone a Billroth II gastrectomy.

Bile Reflux Gastritis

Bile reflux commonly occurs after gastric surgery regardless of the procedure performed. Bile in the stomach on endoscopic examination is often seen when the pyloric sphincter has been ablated or resected; it is even more commonly encountered if a portion of the distal part of the stomach has been resected, regardless of whether a Billroth I or Billroth II reconstruction has been fashioned. Because most patients have no symptoms that can be definitely linked to bile reflux, the attribution of symptomatology to this event has been challenged by many clinicians. Nonetheless, it is generally accepted that in a small subset of patients such reflux is associated with marked, unrelenting epigastric pain, nausea, bilious vomiting, and quantitative evidence of excessive enterogastric reflux.[37,38] For reasons that are not clear, these symptoms may be delayed for months or years after the initial operation. Interestingly, the bilious vomiting may occur anytime during the day or night and not infrequently awakens a patient who is sleeping comfortably. In patients in whom this condition develops, endoscopic examination of the stomach demonstrates a beefy red and friable mucosa with diffuse, superficial erosions that may involve the entire stomach with extension into the

distal end of the esophagus. The parietal and gastrin cell mass may be greatly decreased, and hemorrhage, atrophy, and intestinalization of the epithelial surface are often demonstrable microscopically. In some patients achlorhydria may be present, which is indicative of a profound effect on parietal cell mass. Depending on the chronicity of this problem, weight loss is often a part of the initial symptomatology, as is iron deficiency anemia.

Although bile reflux (also called alkaline reflux) gastritis has been reported in patients after undergoing a Billroth I gastrectomy or gastroenterostomy as a drainage procedure following vagotomy, the large majority of patients have previously undergone gastric resection with restoration of GI continuity via a Billroth II approach.[37,38] For reasons that are unclear, asymptomatic patients may demonstrate the same histologic and endoscopic changes in the gastric epithelium as those with bile reflux gastritis. Furthermore, a clear correlation between the volume of bile reflux, the type of bile acid components in this reflux, and which of these components is more likely to induce alkaline gastritis remains to be delineated. Thus, great care must be exercised in attributing symptomatology to reflux when other problems may be at fault, such as afferent or efferent loop obstruction, gastric stasis, or small bowel obstruction from adhesion formation. If radiologic or endoscopic evaluation excludes these other possibilities, a diagnosis of bile reflux as the cause of the symptomatology is on much firmer ground.

Quantification of bile reflux by gastric analysis or scintigraphy (bile reflux scan) is essential for diagnosis.[39] Marked abnormalities in either or both of these studies strengthen the diagnosis. Medical treatment, including acid secretory inhibitors, anticholinergic drugs, and cholestyramine, has been used in an attempt to attenuate the symptoms but unfortunately has not consistently demonstrated any substantial benefit.[37,38] Accordingly, patients with unrelenting or intractable symptoms are best managed with surgery. The physiologic principle underlying surgical intervention should be to divert the bile and pancreatic secretions away from the stomach. Several procedures have been recommended, each with its proponents.[37,40-43] These procedures include Roux-en-Y gastrojejunostomy (Fig. 59–3), interposition of a 40-cm

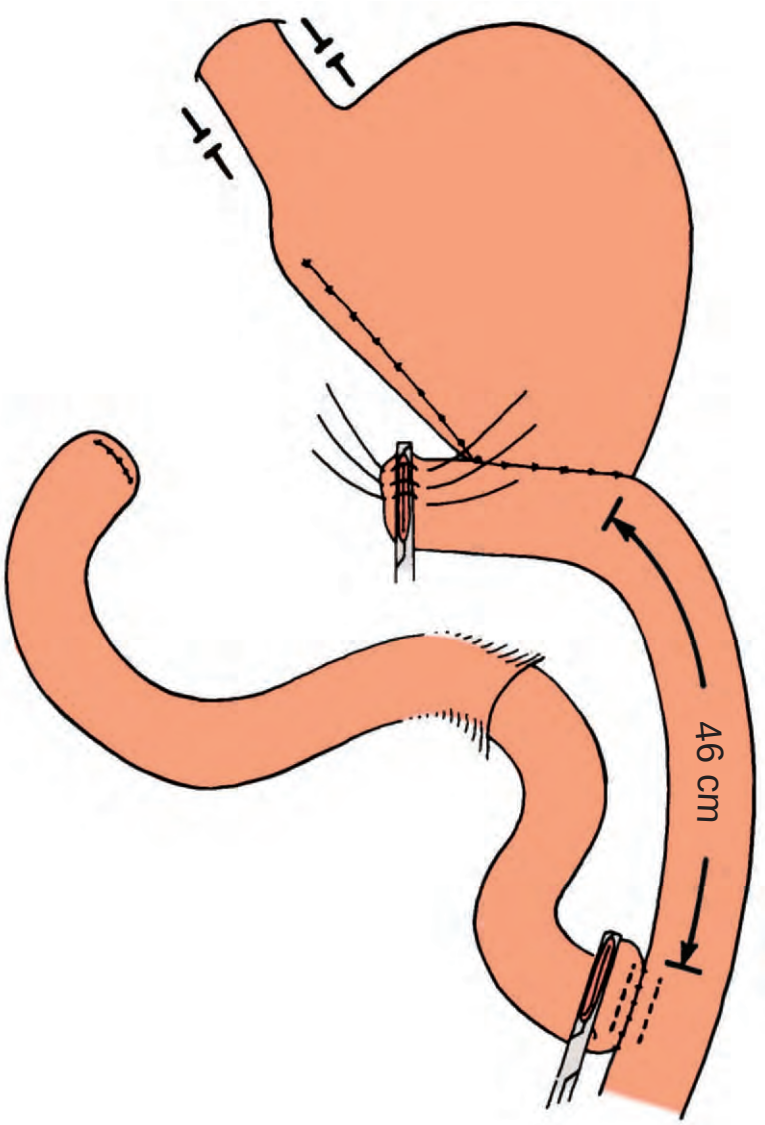

Figure 59–3. Roux-en-Y gastrojejunostomy for the treatment of alkaline reflux gastritis. Note the generous distal gastrectomy and truncal vagotomy. Adequate Roux length minimizes bile reflux. (From Fromm D: Ulceration of the stomach and duodenum. In Fromm D, ed: Gastrointestinal Surgery. New York, Churchill Livingstone, 1985.)

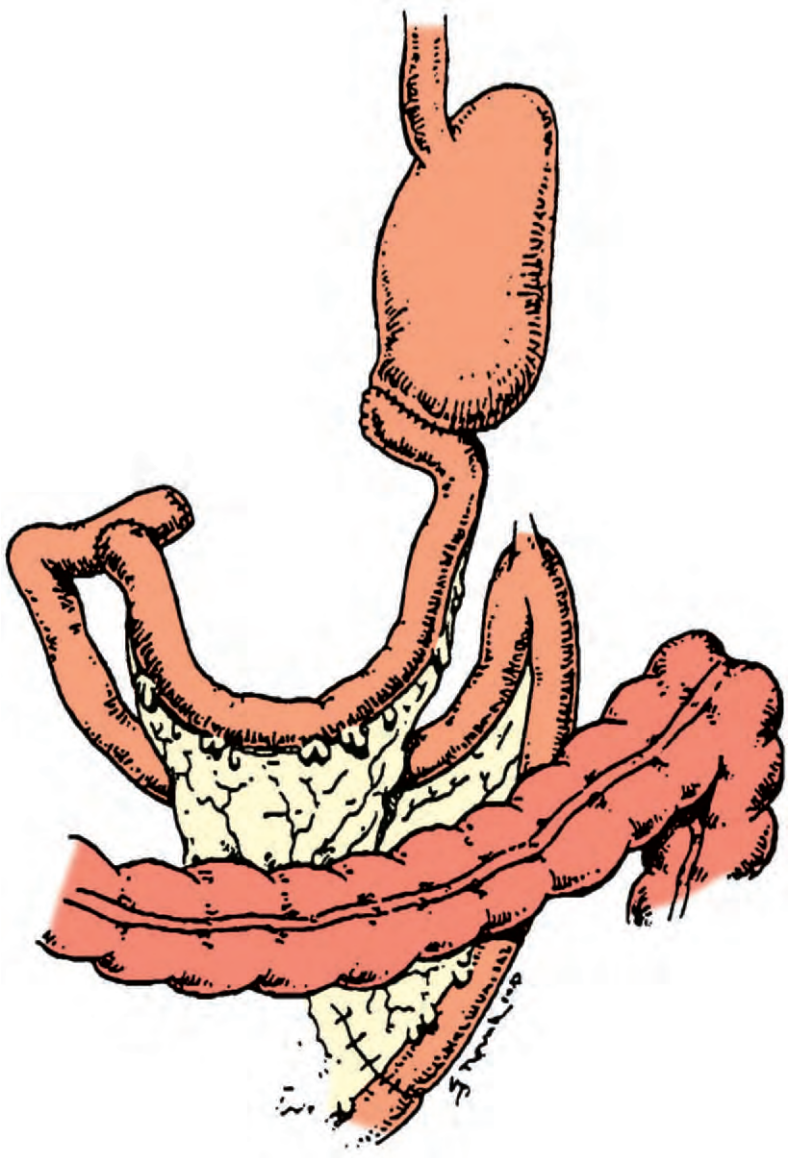

Figure 59–4. Interposition of a 40-cm isoperistaltic jejunal segment between the stomach and duodenum to treat alkaline reflux gastritis. (From Aronow JS, Matthews JB, Garcia-Aquilar J, et al: Isoperistaltic jejunal interposition for intractable postgastrectomy alkaline reflux gastritis. J Am Coll Surg 180:648, 1995.)

isoperistaltic jejunal loop between the gastric remnant and the duodenum (Henley loop) (Fig. 59–4), and revision of a Billroth II gastrojejunostomy, if previously performed, with a Braun enteroenterostomy (anastomosis between the afferent and efferent limbs) (Fig. 59–5). All of these procedures have proved successful to varying degrees. It is our belief that a Roux-en-Y gastrojejunostomy in which the Roux limb is at least 45 cm in length is the most consistent in relieving symptoms, promoting weight gain, and reversing the findings associated with bile gastritis.

Afferent and Efferent Loop Obstruction

Afferent loop obstruction, known as the *afferent loop syndrome,* is a mechanical problem resulting from the inability of this loop to empty its contents. A variety of causes can give rise to this syndrome, all resulting in partial obstruction of the afferent limb, as shown in Figure 59–6. The afferent limb is nearly always greater than 30 to 40 cm in length for such obstruction to occur; the longer the afferent limb, the more likely obstruction will occur.

Although both acute and chronic forms of afferent loop syndrome have been described, chronic, intermittent obstruction is by far the more common clinical manifestation.[44,45] Typically, increasingly severe epigastric pain develops secondary to the presence of food in the gastric remnant and efferent loop; this food elicits various neurohumoral mechanisms that induce bile secretion and pancreatic enzyme secretion involved in the normal digestive process. As these secretions become more and more pronounced, the obstructed duodenum and proximal jejunum become more distended, and approximately 30 to 60 minutes after eating, copious, often projectile bilious vomiting occurs and provides dramatic relief of pain as the intraluminal pressure in the afferent limb overcomes the obstruction and shoots bile into the gastric remnant. The reason that the vomitus is

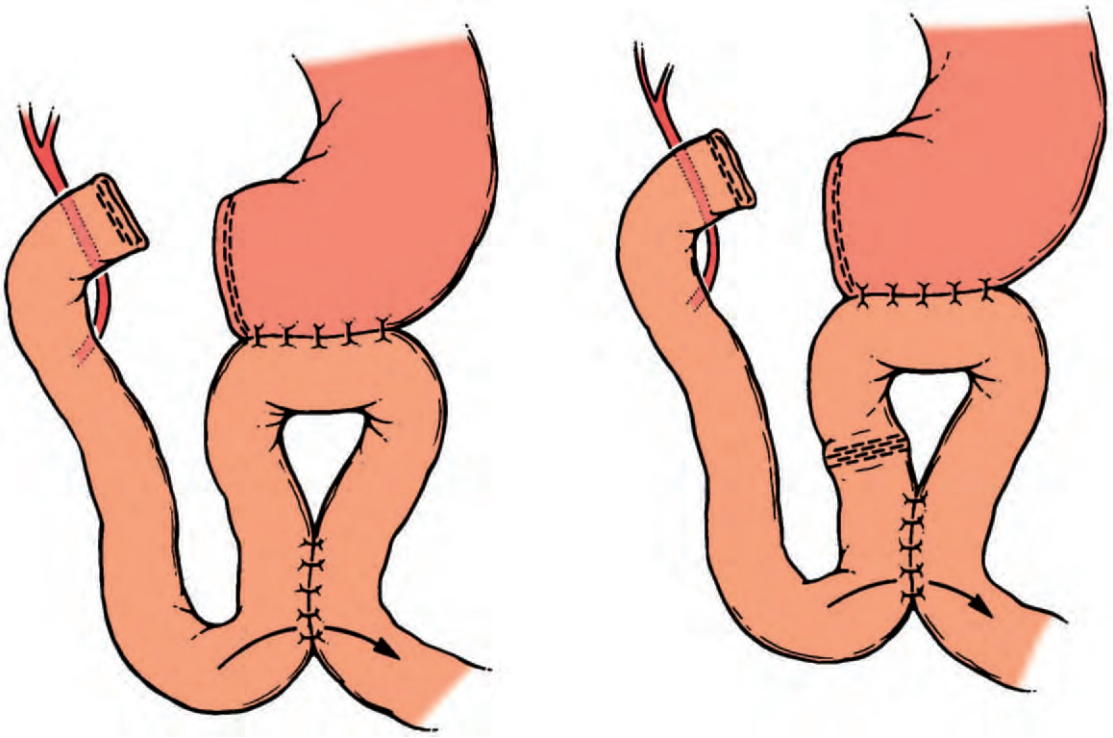

Figure 59–5. The Braun procedure is one of the oldest attempts at bile diversion. The figure on the *left* shows the original procedure with gastrojejunostomy and "downstream" enteroenterostomy to divert bile distally. A recent modification (on the *right*) adds a staple line distal to the enteroenterostomy in an effort to further divert the duodenal contents distally. It has been designated the uncut Roux-en-Y. (From Madura JA: Postgastrectomy problems: Remedial operations and therapy. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. St Louis, CV Mosby, 2001.)

bilious in nature is because the food has already passed into the efferent limb. If the obstruction is severe enough, the distended afferent loop may not be able to sufficiently discharge its contents, and a clinical picture of "closed loop obstruction" manifested as an acute abdomen will result. If this condition is not recognized in its early stages, the afferent loop may actually perforate and result in peritonitis. Obviously, urgent surgery is necessary to correct this problem.

Occasionally, diarrhea may be part of the symptomatology associated with an obstructed afferent limb. It occurs because of bacterial overgrowth, which ultimately binds with vitamin B_{12} and deconjugates the bile acids. The net result of this process is a systemic deficiency of vitamin B_{12}, development of megaloblastic anemia, inefficient micelle formation necessary for fat digestion, and ultimately, steatorrhea if not corrected. This situation can be an especially complex problem if a long afferent loop was created in a more distal segment of the small intestine. Gastroileostomy is the extreme example of this problem. Not only are the aforementioned abnormalities present, but any acid produced by the gastric remnant is also less buffered when it enters distally in the small bowel, thereby leading to a potentially high incidence of marginal ulceration with the long afferent loop.

In contrast to the relatively stereotypical manifestation of afferent loop obstruction, efferent loop obstruction generally mimics proximal small bowel obstruction. It can be caused by intra-abdominal adhesions, like most small bowel obstruction, or can result from herniation of the limb behind the gastrojejunostomy anastomosis, usually in a right-to-left direction. Such herniation occurs because a space generally exists posterior to the anastomosis regardless of whether the initial procedure was antecolic or retrocolic.[46] Because the gastrojejunostomy is usually positioned to the left of the main mass of the small intestine, it is mechanically easier for herniation to occur in a right-to-left direction.

In diagnosing afferent or efferent loop obstruction, it is of utmost importance to remember that obstruction can occur in any patient who previously underwent a Billroth II gastrectomy, no matter how experienced the operating surgeon might have been. In any patient with bilious vomiting, especially if projectile and associated with eating, the possibility of an afferent loop syndrome must be considered. Helpful diagnostic tests include esophagogastroduodenoscopy, computed tomography (CT), upper GI series, and a hepato-iminodiacetic acid (HIDA) scan (not necessarily in that order). Furthermore, if it is known that the afferent loop is long and the Billroth II anastomosis was performed in an anticolic

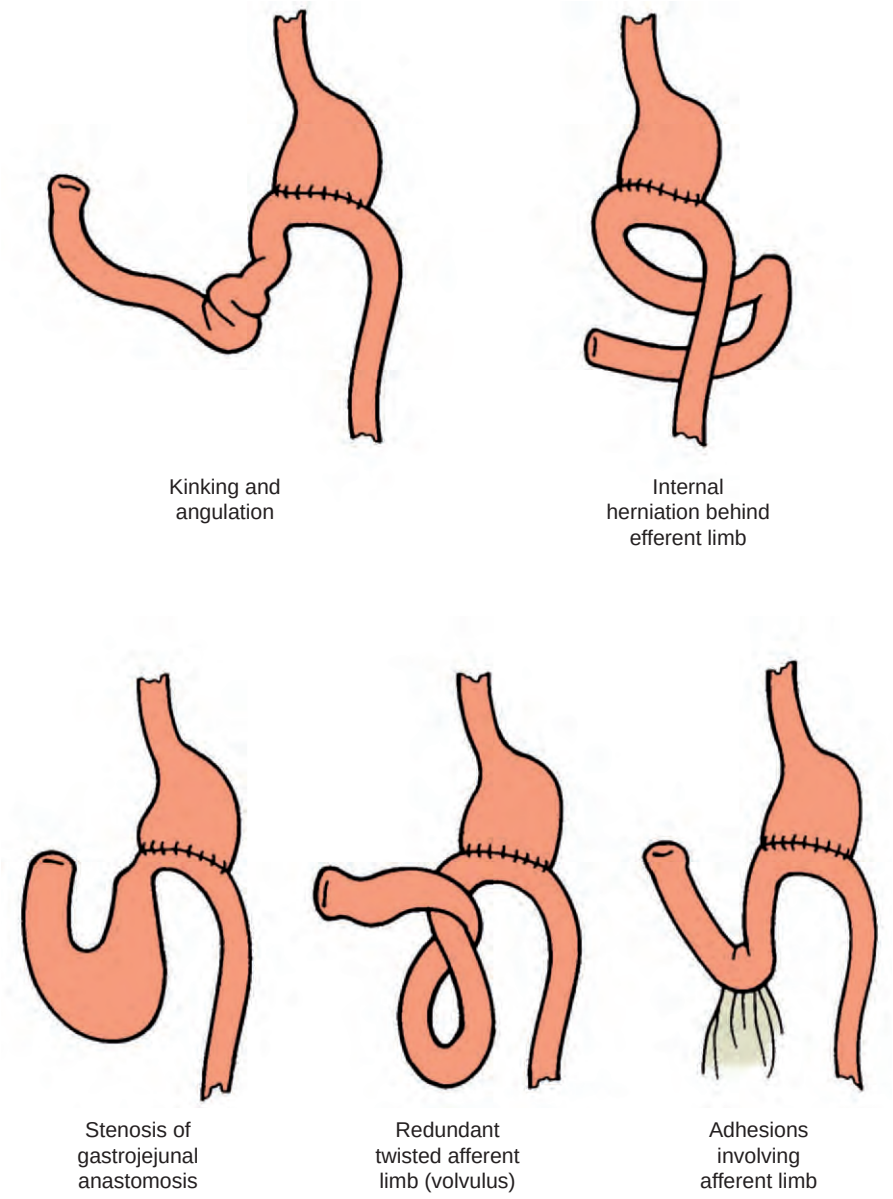

Figure 59–6. Causes of afferent loop syndrome. (From Miller TA, Mercer DW: Derangements in gastric function secondary to previous surgery. In Miller TA [ed]: Modern Surgical Care: Physiologic Foundations and Clinical Applications, 2nd ed. St Louis, Quality Medical, 1998, p 402.)

fashion, the diagnostic possibility of an obstructed afferent loop is strengthened, especially if the clinical picture supports this diagnosis. Because there is no medical means of managing this problem, a reoperation will always be needed. The underlying reason for the obstruction will dictate the surgical procedure performed. Possible approaches to management are illustrated in Figure 59–7. If an efferent limb obstruction is the cause of the patient's problem, simple lysis of adhesions may be all that is necessary. If herniation of the limb behind the gastrojejunostomy is responsible for the obstruction, suture closure of the retroanastomotic space may be effective therapy. An alternative approach is to anastomose the two limbs (i.e., afferent and efferent) together to create an enteroenterostomy so that a retroanastomotic hernia would be less likely to occur from a mechanical standpoint. Finally, the Billroth II anastomosis may be converted to a Billroth I.

Jejunogastric Intussusception

Jejunogastric intussusception is a rare complication of gastrojejunostomy. It may occur after a Billroth II gastrectomy but has most commonly been seen after simple gastroenterostomy. In the majority of cases, the efferent limb becomes intussuscepted into the stomach. The clinical manifestation is acute upper abdominal pain and vomiting. Not infrequently, fresh or old blood is identified in the vomitus. The patient is often acutely ill, and a palpable mass may be present in the upper part of the abdomen. Even though both acute and chronic forms of this condition have been described, the possibility that the intussusceptum may incarcerate and eventually strangulate makes it a true surgical emergency more commonly than not. Although the diagnosis is often difficult to make, it should be considered in any patient with a gastrojejunal anastomosis who has severe abdominal

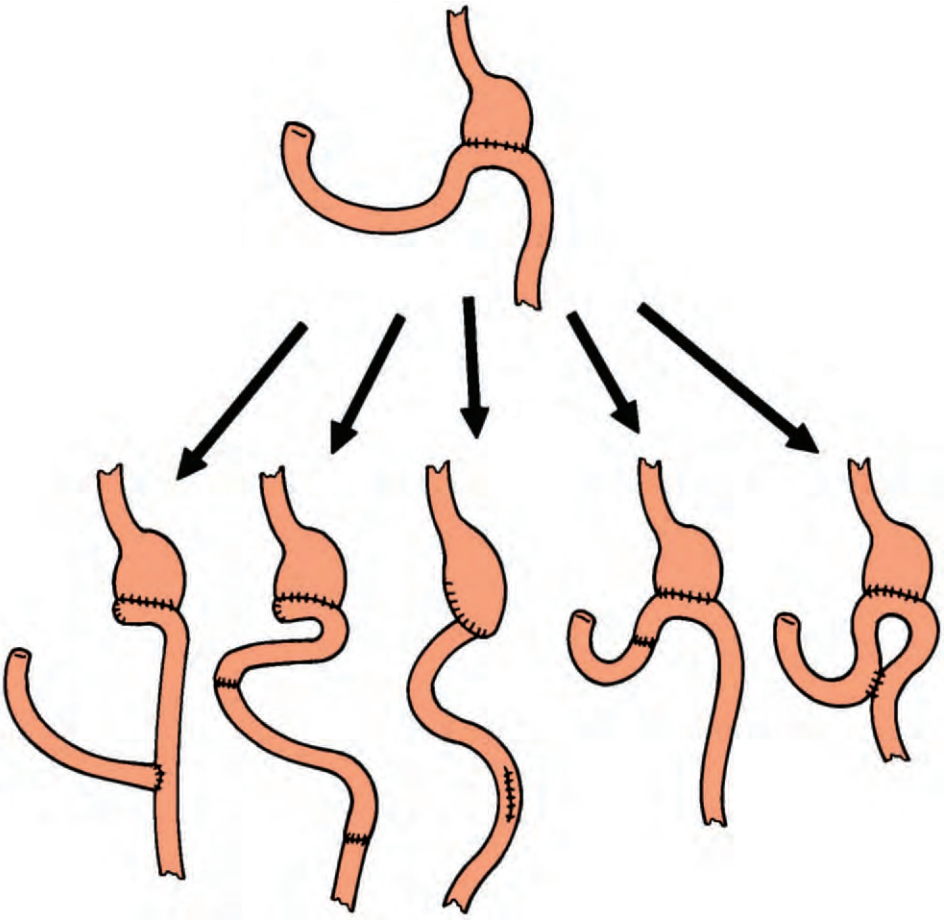

Figure 59–7. Surgical management of afferent loop syndrome. (From Miller TA, Mercer DW: Derangements in gastric function secondary to previous surgery. In Miller TA [ed]: Modern Surgical Care: Physiologic Foundations and Clinical Applications, 2nd ed. St Louis, Quality Medical, 1998, p 404.)

pain, persistent vomiting (especially if bloody), a palpable upper abdominal mass, and tenderness over the epigastrium.[47] The operation of choice is resection of the intussuscepting small bowel if there is any question regarding strangulation. If the intussuscepted intestine is viable, the afferent and efferent limbs of jejunum may be fixed to adjacent tissue such as the mesocolon, colon, or stomach to prevent recurrence. An alternative operative approach is to convert the Billroth II anastomosis to a Billroth I.

The Roux Syndrome

Occasionally, a patient who has undergone distal gastrectomy with a Roux-en-Y reconstruction will have difficulty with gastric emptying along with symptoms such as gastric vomiting, epigastric pain, and weight loss. Endoscopically, the gastric remnant may be dilated as well as the Roux limb, but no evidence of mechanical obstruction can be identified on CT or upper GI series. The only significant finding with this latter study is a delay in gastric emptying. This constellation of clinical findings has been called the *Roux syndrome*.[48]

The cause of this syndrome appears to be an abnormality in motility.[22,49] Key findings include abnormal propulsive activity in the Roux limb that proceeds toward the stomach rather than away from it; in some patients gastric motility is also perturbed. This disordered motility appears to occur in all patients after this procedure, but why the Roux syndrome develops in only a small subset remains unknown. Furthermore, it seems to be more common in patients with a large gastric remnant and in those who have previously undergone truncal vagotomy.

Some patients benefit with promotility agents. Many, however, require surgical intervention. If gastric motility appears to be a major contributing factor, the gastric remnant should be pared down; in some patients 95% gastrectomy has been performed.[50] If the Roux limb is unusually dilated or flaccid, it too should be resected. Various approaches to re-establishing GI continuity include another Roux limb, a Billroth II anastomosis with an enteroenterostomy between the afferent and efferent limbs, or an isoperistaltic jejunal interposition between the stomach and the duodenum.[42] Because this syndrome is relatively rare, data supporting one surgical approach in preference to another are limited, and selection of the approach has often been dictated by surgeon preference.

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Chapter

60

Miscellaneous Benign Lesions and Conditions of the Stomach, Duodenum, and Small Intestine

Emil L. Popa† ▪ Daniel T. Dempsey

STOMACH

The gastrointestinal tract accounts for more neoplastic disease than any other organ system in the human body. A variety of pathologic lesions can occur in the stomach (Table 60–1), many of them polyps, but like in other segments of the digestive tract, adenoma is the only lesion that is truly neoplastic and carries a threat for the development of cancer. The risk is related most closely to the histologic type, size, and number of polyps. Variations in these three factors account for the wide range in reported risk associated with gastric polyps. Other benign lesions found in the stomach are also discussed.

Benign Mucosal (Epithelial) Hypertrophy and Hyperplasia

Benign Focal Mucosal Hypertrophy and Hyperplasia

The principal causes of focal or multifocal thickening of the gastric mucosa are polyps, the presence of heterotopic tissue, and the localized effects of inflammation and repair (Table 60–2).

Benign Polyps The term *polyp* (from the Greek πολυπους, or "morbid excrescence") refers to a macroscopic nodular lesion that protrudes above the mucosal surface of a hollow organ into its lumen. Benign gastric polyps may be neoplastic or non-neoplastic, and their nature can be determined only by histologic examination. The first report of a gastric polyp is believed to have probably been made in 1557. In 1761, Morgagni described a pedunculated polyp near the pylorus, and in 1835, Cruveilhier mentioned the possibility of a polyp causing obstruction or becoming malignant.[1] In 1888, Ménétrier described and illustrated in detail the formation process and malignant transformation of gastric polyps and classified them for the first time.

One of today's classifications is based on the location of the bulk of the lesion in relation to the wall of the stomach: intraluminal or intramural. Such a distinction is clinically relevant. Intraluminal polyps are usually mucosal lesions, which may bleed if their surface is eroded or obstruct if their location is near the orifices of the stomach and their size is large. Intramural polyps are generally submucosal and asymptomatic if small, but if large, the covering mucosa may become ulcerated and bleed as well; a large intramural mass may also become obstructive, depending on its location.

Gastric polyps are not common, with an incidence varying between 0.4% in autopsy series[2] and 3% to 5% in endoscopy series.[3-5] Polyps account for 3.1% of all gastric tumors,[6] and their frequency increases to almost 90% of benign tumors in patients who have undergone upper endoscopy with biopsy, thus making them at present the most common benign tumor of the stomach.

Non-neoplastic Benign Polyps Non-neoplastic benign polyps represent localized expansions of the mucosa and are usually composed of hyperplastic epithelial elements, mainly surface-foveolar mucous cells and pyloric glands,

†Deceased.

Table 60–1 Incidence of Benign Lesions of the Stomach

Type of Lesion	%	Tissue of Origin
Epithelial polyps	41	Epithelium
Leiomyomas (GIST)	37	Smooth muscle
Inflammatory polyps	<5	Inflammatory
Heterotopic tissues	<5	Pancreas
Lipomas	<4	Fat tissue
Neurogenic tumors (GIST)	3	Neural elements
Vascular tumors	2	Vascular tissue
Eosinophilic granulomas	2	Lymphoid tissue
Fibromas	1.5	Connective tissue
Miscellaneous lesions	1	Other

GIST, gastrointestinal stromal tumor.
Modified from Ming SC, Goldman H: Pathology of the Gastrointestinal Tract, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 1998.

together with varying amounts of edema, inflammatory cells, and proliferating stromal cells of the lamina propria.[7,8]

Hyperplastic or Regenerative Polyps The most common gastric polyps are hyperplastic or regenerative polyps, which occur in 0.5% to 1% of the general population and account for 70% to 80% of all gastric polyps in most series. Regenerative polyps frequently occur in the setting of gastritis and have low (<1%), if any malignant potential. Hyperplastic polyps contain an overgrowth of histologically normal-appearing gastric epithelium. Atypia is rare. Size of the polyp does not appear to be an important factor. Because *Helicobacter pylori* is a major cause of gastritis, its relationship with hyperplastic polyps has been studied: in a report by Varis et al., *H. pylori* was present in 81% of stomachs with inflammatory polyps and in 45% to 48% of stomachs with hyperplastic polyps or foveolar hyperplasia, respectively.[9] A well-developed hyperplastic polyp is a distinct oval lesion. The polyps are usually single but can be multiple and exceptionally confluent in their appearance. The incidence of hyperplastic polyps is particularly high in the gastric remnant after partial gastrectomy. Enterogastric reflux is common in

Table 60–2 Benign Focal Mucosal Hypertrophy of the Stomach

Type of Benign Hypertrophy	%	Tissue of origin
Non-neoplastic benign polyps		Epithelium
Hyperplastic/regenerative	70-90	Foveolae and pyloric-type glands
Focal polypoid hyperplasia		
Hyperplastic regenerative polyp		
Hyperplastic adenomatous polyp		
Inflammatory	20-33	Inflammatory, pauciepithelial
Inflammatory pseudopolyp		
Inflammatory/retention polyp		
Inflammatory fibroid polyp	3	
Eosinophilic granulomas	2	Lymphoid tissue
Hamartomatous		Epithelium and mesenchyme
Peutz-Jeghers polyp		
Juvenile polyp		
Gardner's polyp		
Familial adenomatous polyposis coli		
Fundic gland polyp	1	Epithelial cells, lymphoid tissue
Heterotopic/ectopic polyp	2-4	
Ectopic pancreatic (±biliary) tissue		Acinary pancreas ± bile ducts
Brunner's gland hyperplasia	1	Duodenal exocrine glands
Adenomyoma		Ductal cells and smooth muscle
Nodular mucosal remnants		
Neoplastic benign polyps = adenomatous	10-15	Adenomatous epithelium
Flat/tubular adenomas		
Papillary/villous adenomas		
Benign inflammatory lesions		Inflammatory
Edema		
Regeneration		

Modified from Ming SC, Goldman H: Pathology of the Gastrointestinal Tract, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 1998.

these patients, but its role in polyp formation is not certain. Polyps were present in 20% to 66% of gastric stumps 20 years after gastrectomy.[10,11] Finally, hyperplastic polyps may enlarge, shrink, or disappear, but in most cases they remain stationary.

Most people with hyperplastic polyps are asymptomatic. Dyspepsia and vague epigastric discomfort are the most common complaints, although coexistent gastroduodenal disease is also frequently identified. Complications are unusual and gastric hemorrhage occurs in less than 20%.

Inflammatory Polyps Inflammatory polyps are heterogeneous and encompass several entities. They account for a fifth to a third of gastric polyps.[4] A polyp made of inflammatory tissue can be properly called an *inflammatory pseudopolyp* because glandular tissue is either lost or absent. A special form of inflammatory polyp known as *inflammatory fibroid polyp* occurs most commonly in the stomach, mainly the distal region and the pylorus, and constitutes 3% of gastric polyps. It is the name given collectively to group expansile, mainly submucosal lesions that contain a mixture of spindle cells, small vessels, and inflammatory cells.[12]

An inflammatory polyp with prominent cystic glands may be called a *retention polyp* because of the dilated glands that are filled with retained mucus; such polyps are rare in the stomach. Polyps associated with Cronkhite-Canada syndrome (CCS) are of retention type. This syndrome is characterized by diffuse gastrointestinal polyposis associated with ectodermal changes. Polyps are common in the stomach of patients with CCS; they are 0.5 to 1.5 cm in diameter and either are long and finger-like or resemble a hydatid mole.[13,14] In CCS, the lesions first appear late in adult life, with 80% of patients being in their sixth decade. The male-to-female ratio is close to 1:1.

Hamartomatous Polyps Hamartomatous polyps are tumor-like nodules composed of tissue present in the location, but in a disorganized arrangement. Because the stomach consists of many different types of cells, the composition of hamartomatous polyps is not uniform. They are encountered most commonly in association with hereditary gastrointestinal polyposis syndromes, including generalized juvenile polyposis (15% of patients), Peutz-Jeghers syndrome (25% to 50% of patients), familial adenomatous polyposis coli (FAP), and the related Gardner syndrome.[15-18] In these syndromes the polyps are located more commonly in the intestine than in the stomach, so they will be discussed more extensively in that segment. It is noteworthy that gastric and intestinal polyps in the same disease may be of different types. For instance, whereas intestinal polyps in Gardener's syndrome and FAP are mostly adenomas, the most common form of gastric polyp in these syndromes is hamartomatous, and it involves mainly the fundic mucosa. Although the polyps in both Peutz-Jeghers syndrome and juvenile polyposis are hamartomatous, they have different histologic characteristics. Finally, hamartomatous polyps may be seen in patients without other characteristics of these syndromes.

Fundic Gland Polyps Also known as fundic gland hyperplasia or glandular cysts, the less common fundic gland polyps occur in the oxyntic mucosa of the stomach.[19,20] These lesions are composed of fundic pits, or glands lined with increasing numbers of normal-appearing parietal and chief cells with prominent cystically dilated, tortuous changes, and benign lymphoid polyps, or localized areas of marked lymphoid hyperplasia.[21] Fundic gland polyps have been found in patients with Gardner's syndrome, as well as in FAP patients.[22,23] Histologically, the constituent cells of the polyp appear normal and the polyp may regress and disappear, thus suggesting that these lesions may not be hamartomatous.

Heterotopic Pancreatic Polyps More commonly, heterotopic polyps are made of tissue from the neighboring pancreas and duodenum. Ectopic foci of mature pancreatic tissue may be observed in the stomach, more often in the distal, prepyloric portion.[24-27] The gastric implants consist of pancreatic elements alone—exocrine glands and ducts—or occur in combination with varying amounts of biliary elements (bile ducts epithelia, smooth muscle). The lesions are usually small and primarily confined to the gastric submucosa, but they may enlarge and extend into the mucosal region.

Endoscopic examination reveals slightly raised, umbilicated, or nipple-like nodules. The umbilication represents the outlet of the exocrine duct. Biopsy samples are generally too superficial to detect the heterotopic glandular tissue. The lesions are asymptomatic, with no malignant potential, but if they are large, ulceration and bleeding are common manifestations. In children, pancreatic heterotopia can be manifested as peptic ulcer or intermittent pyloric obstruction.

Brunner's Gland Polyps Brunner's gland hyperplasia has been called *adenoma* because of the tightly packed glands, whereas in reality, only hyperplasia is present and the glands are normal. Some categorize it as a hamartoma because of its stationary appearance. The lesion accounts for only about 1% of gastric polyps,[28] and it always occurs in the prepyloric region.[29,30] Brunner's glands, normally found in the duodenal submucosa, secrete an alkaline, bicarbonate-rich fluid and mucus that serves to neutralize acidified luminal contents arriving from the stomach.

Because of its presence in the prepyloric region, obstruction is the common manifestation.

Adenomyomas A rare benign gastric lesion related to heterotopic tissue is adenomyoma or adenomyosis, which is composed of a mixture of ducts lined by columnar cells and bundles of smooth muscle in a haphazard arrangement. Pancreatic tissue or Brunner's glands, or both, may also be present. Most of the lesions are smaller than 2 cm, but some are as large as 5 cm in diameter.[31]

Inflammatory, hamartomatous, and heterotopic polyps have negligible malignant potential.

Adenomatous or Neoplastic Polyps Neoplastic or adenomatous polyps constitute about 10% to 15% of gastric polyps and are composed of immature and dysplastic

cells. On the basis of their architectural pattern and the cytologic appearance of cells, adenomas are subdivided into a flat (tubular) type and a papillary (villous and tubulovillous) type. Rarely, dysplastic or adenomatous lesions are present in hyperplastic polyps. Among patients with FAP, gastric polyps are common in 33% to 60%, whereas gastric adenoma occurs in 15%.[32,33] Affected individuals are usually in the seventh decade of life. The incidence of gastric adenoma increases with age, from only 0.1% in the third decade to 3.7% in the ninth decade. Men are affected more often then women (2:1 to 3:1). The adenomas are generally solitary lesions. They may arise anywhere in the stomach, with about 50% at the lesser curvature and only 5% in the upper third of the stomach; the preferred location is the distal portion of the stomach, particularly the antrum.[34] In gastric adenomas, mucosal atypia is frequent and mitotic figures are more common than in hyperplastic polyps. Gastric adenomas may undergo malignant transformation, similar to adenomas in the other segments of the gastrointestinal tract. The frequency of malignant transformation ranges from 5% to 75% in different series,[35,36] with an average of 10% to 20%, and is greatest for polyps larger than 2 cm in diameter. Multiple adenomatous polyps increase the risk for cancer. The presence of an adenomatous polyp is also a marker indicating an increased threat for the development of cancer in the remainder of the gastric mucosa. Gastric flat adenomas have a lower incidence of malignant changes; the incidence increases with the grade of dysplasia, the papillary pattern, and the size of the lesion.[34]

Flat Adenomas Flat adenomas are the most common form of adenoma in the stomach, especially in Japan.[37] Their gross appearance resembles that of early gastric carcinoma. Most flat adenomas are slightly elevated lesions with an irregular, but flat surface, or they show varying degrees of nodularity. Some adenomas, however, have a smooth surface that is even with the surface of the surrounding mucosa. The histologic features of gastric flat adenomas are unique; whereas the atypical cells in other adenomas extend through the entire thickness of the mucosa, in gastric adenomas they occupy only the upper third to half of the gastric mucosa and maintain a two-layer structure. Depressed adenomas, however, usually occupy the entire thickness of the mucosa. The two-layer architecture and relative indolence of the immature epithelial cells are hallmarks distinguishing flat adenomas from papillary adenomas. The possibility that flat adenomas are earlier forms of papillary adenoma has not been confirmed; most flat adenomas appear stationary. Despite the lack of growth, flat adenomas are clearly neoplastic, as evidenced by cellular atypism and a relatively high incidence (10%) of malignant change within the lesion. As a neoplasm, a flat adenoma is a sharply delimited lesion that spreads horizontally within the confines of the epithelium, thereby resulting in a demarcation between the lesion and the neighboring non-neoplastic epithelium.

Symptoms are similar to those for non-neoplastic polyps.

Papillary Adenomas Papillary adenomas of the stomach are sessile or broad-based nodular lesions with a lobulated contour and deep crevices. The average size of papillary adenomas is 4 cm, although lesions as large as 15 cm have been reported.[38] Gastric papillary adenomas are located mostly in the antrum. Fixation to deep tissue indicates carcinomatous changes with invasion. In contrast to the relative uniformity of cells in gastric flat adenomas, pleomorphism and mitosis are common in papillary adenomas. The neoplastic cells end abruptly at the junction with the neighboring epithelium. Adenomas with malignant change are positive for carcinoembryonic antigen.[39]

On endoscopy, the lesions are soft and freely mobile and have a velvety appearance. On radiologic examination, barium trapped in the crevices gives a pathognomonic finding of a "soap bubble" or "paint brush" appearance because of rounded radiolucent areas intermixed with a meshwork of radiopaque material. Esophagogastroduodenoscopy (EGD) with biopsy is appropriate after a positive result on a radiologic study.

All types of the aforementioned polyps that are symptomatic, larger than 2 cm, or adenomatous should be resected, usually by endoscopic snare polypectomy. Consideration should also be given to removing hyperplastic polyps for histologic examination, especially if large, and such treatment should be sufficient. Endoscopic resection is adequate for the pedunculated adenomatous type if the polyp is completely removed and shows no evidence of invasive cancer on histologic examination. Larger or sessile lesions should be removed by laparoscopic wedge resection when present on the anterior gastric wall or by a laparoscopic intragastric approach for lesions present in other areas (posterior wall, lesser curvature, gastroesophageal junction). Polyps with biopsy-proven invasive carcinoma, if not amenable to laparoscopic resection, may need open surgical removal. Repeat EGD for surveillance of the gastric mucosa should be done after removal of adenomatous polyps and perhaps after removal of hyperplastic polyps as well.

Benign Inflammatory Lesions These lesions are most often observed adjacent to ulcers and appear as uniform elevations of the mucosa or as deformed folds. Mucosal biopsy is frequently performed to confirm the inflammatory nature of such areas and to exclude other more significant lesions such as neoplasms.

Benign Diffuse Mucosal Hypertrophy and Hyperplasia

Rugae are limited to the gastric fundus and corpus region and are composed of both mucosal and submucosal tissue. Enlargement of rugae can be readily appreciated by radiographic and gross endoscopic examination, and the diagnosis of a normal variation depends on noting that the rugae are simply enlarged, not deformed in any way, and excluding any associated inflammation or hypersecretory state. More significant causes of diffuse mucosal hypertrophy in the stomach include Zollinger-Ellison syndrome (hyperplasia of the parietal cells), Ménétrier's disease (hyperplasia of the

surface-foveolar mucous cells), or some sort of combination. The disorders must be distinguished from a variety of inflammatory (tuberculosis, syphilis, sarcoidosis, allergic gastroenteritis, etc.) and neoplastic (lymphoma) conditions that can also infiltrate and expand the mucosal region.

Ménétrier's Disease (Hypertrophic Gastropathy) Ménétrier's disease, originally described in 1888, is a rare clinical syndrome characterized by diffuse epithelial hyperplasia leading to giant cerebriform enlargement of the rugal folds in the proximal part of the stomach, usually with sparing of the antrum. The etiology and pathogenesis are unclear, although a frequent association with previous respiratory infections has been noted in cases in children.[40] The disorder is characteristically associated with protein-losing gastropathy resulting in hypoalbuminemia and with hypochlorhydria. Mucosal biopsy shows diffuse hyperplasia of the surface mucus-secreting cells with accompanying glandular atrophy. The reduction in gastric acid may be related to dilution by mucous secretions or to loss of parietal cells secondary to expansion of foveolar cells—this issue has not been decided yet. There is also a hyperplastic hypersecretory variant of Ménétrier's disease characterized by normal or increased acid secretion and no protein loss. There may be an increased risk for gastric cancer, although the present literature suggests that the risk for cancer in patients with Ménétrier's disease may have been exaggerated in the past because of confusion with other cases of chronic gastritis. The tendency has been to consider all cases with giant folds in the proximal part of the stomach, with the exception of Zollinger-Ellison syndrome, as potential examples of Ménétrier's disease, without further consideration of their histologic and functional features.

Symptoms and Diagnosis Most patients with Ménétrier's disease are men (M/F = 3:1) 30 to 60 years of age with complaints of epigastric discomfort or pain, weight loss, diarrhea, and hypoalbuminemia/hypoproteinemia with possible peripheral edema. Familial cases have been recorded rarely.[41] Bleeding related to superficial rugal erosions can also be an initial sign. In some cases the disease regresses spontaneously.[42,43]

Definitive diagnosis of Ménétrier's disease requires documentation of foveolar hyperplasia without significant inflammation, lack of increased acid production, and the presence of protein loss from the mucosa.

Treatment Medical treatment is limited mainly to albumin replacement and maintenance of adequate nutrition. Gastric resection may be indicated for bleeding, severe hypoproteinemia, or cancer in some patients with this rare problem.

Childhood Cases of Ménétrier's Disease Although many children have an antecedent history of a respiratory infection and peripheral blood eosinophilia, the exact etiology and pathogenesis have not been established. When compared with the clinical course in adults, Ménétrier's disease in children is self-limited and regresses spontaneously after several weeks. This disease neither recurs nor is associated with carcinoma.

Symptoms and Diagnosis The major differential diagnosis is allergic gastroenteritis, manifestations of which include enlarged gastric folds and protein loss.[44] In the allergic condition, however, the lesions are typically located in the gastric antrum, blood loss and anemia are often evident, and an increased number of eosinophils is noted in biopsy tissue.

Treatment Because the condition is self-limited and regresses spontaneously after several weeks, surgical excision is not required.

Benign Mesenchymal (Nonepithelial) Lesions

Vascular Lesions

"Watermelon Stomach" (Gastric Antral Vascular Ectasia) Gastric antral vascular ectasia is a rare entity characterized by the presence of both inflammatory and vascular components in the mucosa. Gross endoscopic examination reveals prominent longitudinal folds with parallel striking red stripes atop the mucosal folds of the distal part of the stomach, much like the rind of a watermelon. Histologically, the disorder is distinguished by dilated mucosal blood vessels in the lamina propria, often containing thrombi, with no evidence of vascular malformation on angiographic and morphologic examination. Mucosal fibromuscular hyperplasia and hyalinization are often present. The histologic appearance can resemble portal gastropathy, but "watermelon stomach" predominantly affects the distal portion of the stomach, whereas the former usually affects the proximal portion. Patients with gastric antral vascular ectasia are generally elderly women with chronic bleeding. Most have an associated autoimmune connective tissue disorder, and at least 25% have chronic liver disease.

Symptoms and Diagnosis Patients typically have iron deficiency anemia and chronic gastrointestinal blood loss requiring transfusions. The diagnosis of gastric antral vascular ectasia is based on the typical endoscopic and biopsy appearance of the mucosa, together with angiographic findings and a compatible clinical history.

Treatment The lesions are treated by endoscopic cautery. Antrectomy is not ordinarily necessary but may be required to control blood loss. In patients with portal hypertension, a transvenous intrahepatic portosystemic shunt (TIPS) should be considered first.

Dieulafoy's Disease (Gastric Congenital Arteriovenous Malformation) Dieulafoy's disease is a rare condition characterized by an unusually large (1 to 3 mm in diameter) tortuous artery that courses through the submucosa of the proximal part of the stomach for a variable distance.[45] Erosion of the gastric mucosa overlying the vessel results in necrosis of the arterial wall and brisk hemorrhage. The mucosal defect is usually small (2 to 5 mm) and without evidence of chronic inflammation. This

condition typically occurs in middle-aged (sixth decade of life) and elderly men, although younger men and women can be affected.[46] The lesion occurs twice as frequently in men as in women. No significant association has been found with alcohol abuse or antecedent symptoms.[46]

Symptoms and Diagnosis Recurrent painless hematemesis and melena are the typical symptoms at initial evaluation. Recurrent bleeding with spontaneous cessation is likewise common.[46] Massive gastric hemorrhage can also occur.[47]

The diagnosis is most frequently made endoscopically by demonstrating arterial bleeding from a pinpoint mucosal defect. Occasionally, a small arterial vessel may be seen protruding from the gastric mucosa. Characteristically, the lesions are located within 6 cm of the gastroesophageal junction along the lesser curvature, although they may occur at other sites. When a relatively small ulcer is noted together with a single large bleeding artery during endoscopy for upper gastrointestinal hemorrhage, the possibility of a Dieulafoy vascular malformation of the stomach should be considered.

Treatment Most patients can be managed by endoscopic electrocoagulation of the bleeding vessel.[48] If operative excision is required, a combined endoscopic and surgical approach may be useful.[49]

Angiodysplasia Angiodysplastic lesions may occur throughout the gastrointestinal tract, but they are found most commonly in the stomach and duodenum. The lesions are frequently multiple rather than single. They appear as minute flat or slightly raised red lesions with round or stellate shapes. The margins are characteristically sharp with a pale mucosal halo surrounding the lesion. They are all arteriovenous malformations, microscopically visible as dilated, distorted, thin-walled vessels (small arteries, capillaries, and veins). The etiology of angiodysplasia is unknown, but the lesions are considered degenerative lesions.[50]

Symptoms and Diagnosis These lesions may be diagnosed by endoscopy, although their minute size and sessile nature complicate detection. Because the lesions are mostly submucosal, endoscopic mucosal biopsy is often not diagnostic. The lesions may be mistaken for submucosal hemorrhage associated with acute gastritis or trauma artifacts from a nasogastric tube or endoscope. The mainstay of diagnosis of angiodysplastic lesions is selective arteriography, which often features an early filling vein, a densely opacified and slowly emptying, dilated, tortuous vein, and a vascular tuft.[49]

Treatment Endoscopic injection of sclerosants, electrocoagulation, and laser photocoagulation have all been used to treat gastroduodenal angiodysplasia with good results. The multiplicity of lesions often necessitates several courses of therapy to eliminate recurring hemorrhage. Surgical resection of the gastric wall containing the lesion and oversewing of the bleeding lesion have been reported to control hemorrhage successfully.

Telangiectasia Telangiectasia is a localized dilation of arterioles, capillaries, and venules. Multiple congenital lesions may occur in the gastrointestinal tract in Osler-Weber-Rendu syndrome and Turner's syndrome. As acquired lesions, they occur in the CRST syndrome (calcinosis cutis, Raynaud's phenomenon, sclerodactyly, telangiectasia).

Congenital Telangiectasia Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia) is inherited as an autosomal dominant disorder. Telangiectases arise from simple dilation of normal vascular structures because of congenital thinning of the muscular layer and elastic fibers in the arteriolar wall. Telangiectases occur in many places, including the skin, mucous membranes, and internal organs, and result in recurrent hemorrhage. Gastrointestinal bleeding is present in about 15% of patients. The vascular lesions may be stellate or nodular; they are punctate, red to purple noncompressible lesions that vary in diameter from 1 to 4 mm. The mucocutaneous lesions usually become clinically apparent in the second and third decades of life and are later manifested as chronic bleeding, usually in the fourth decade. It should be noted that vascular anomalies also occur in other organs: the meninges, spinal cord, eyes, liver, and genitourinary tract.

Turner's syndrome (ovarian dysgenesis) is associated with hemorrhage from telangiectases present mostly lower in the gastrointestinal tract and is discussed later.

Acquired Telangiectasia Telangiectases are also present in patients with systemic sclerosis, especially the CRST syndrome. Gastrointestinal hemorrhage may result from lesions in the stomach, as well as lesions in the rectum and colon.[51] Most frequently, the lesions are found on the hands, lips, face, and tongue.

Treatment Frequently, endoscopy with electrocoagulation, a heater probe, or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser can adequately treat these lesions.

Hemangiomas Whether gastrointestinal hemangiomas are true neoplasms or represent hamartomas continues to be a subject of controversy and debate. Gastric hemangiomas are very infrequent and not hereditary, whereas hemangiomas in the small intestine account for about 10% of all benign small bowel tumors. Because of these aspects, the subject is discussed more extensively under the duodenum and small intestinal segment.

Diffuse gastrointestinal hemangiomatosis is an entity in which as many as 100 lesions involving the stomach, small bowel, and colon are encountered. Bleeding or anemia in childhood usually leads to diagnosis of this condition.

Lymphangiomas Lymphangiomas of the gastrointestinal tract are extremely rare. They have been reported beside the stomach and in the small intestine (mostly jejunum) and esophagus, as well as in the colon.[52] They are usually soft, submucosal polypoid lesions with a broad base, and cystically dilated lymph vessels are seen on microscopic examination.

Glomus Tumors These benign neoplasms are composed of uniform round cells that ultrastructurally are mature smooth muscle cells. In the gastrointestinal tract, glomus tumors occur almost exclusively within the stomach, especially the antral region, where they appear grossly as intramural circumscribed masses.[12] A few have been described in the esophagus and even fewer in the small intestine. Most tumors are about 2 to 2.5 cm in size, but they may grow to 4 cm in diameter. The bigger lesions are likely to ulcerate. Microscopically, glomus tumors lie mostly within the muscularis propria; the mucosa is never infiltrated. The monotonous cells are arranged in sheets, cords, or clusters, usually intimately applied to the walls of capillaries.

The major differential diagnosis for such a small intramural round cell tumor is an epithelioid cell stromal tumor.

Leiomyomas

In recent years, what used to be called leiomyoma is now termed gastrointestinal stromal tumor (GIST) because it has been recognized that these tumors may arise not just from smooth muscle but from other components of the wall as well.[53] GIST may arise from pluripotential mesenchymal cells within the muscular wall of the gastrointestinal tract, most commonly those supposed to become smooth muscle or neural cells. Gastric leiomyomas are well-differentiated benign GISTs arising from the smooth muscle in the stomach wall. The typical leiomyoma is submucosal and firm.

Symptoms and Diagnosis Lesions smaller than 2 cm are usually asymptomatic and benign. Larger lesions have greater malignant potential and a greater likelihood of causing symptoms such as bleeding, obstruction, or pain. If ulcerated, they have an umbilicated appearance and may bleed.

Treatment Asymptomatic lesions smaller than 2 cm may be observed. Larger lesions and symptomatic lesions should be removed by wedge resection—often possible laparoscopically or by a laparoscopic intragastric approach. When these lesions are observed rather than resected, the patient should be made aware of their presence and the small possibility for malignancy.

Neurogenic Benign Tumors

Neurogenic tumors are too rare in the stomach to be of concern, and they account for less than 3% of all gastric neoplasms. Patients with von Recklinghausen's multiple neurofibromatosis commonly have gastric and intestinal involvement, sometimes taking the form of neurofibromas with a plexiform pattern. Less commonly, diffuse neurofibromas extend from the submucosa across the muscularis mucosae into the mucosa, where they expand and distort the crypts and produce a picture resembling the mucosa of patients with incipient juvenile polyps. The occurrence of a typical neurofibroma of the stomach in the absence of von Recklinghausen's disease is too rare to discuss. It is important to remember that GISTs of the typical or usual type may also occur in patients with von Recklinghausen's multiple neurofibromatosis.[54]

Neurilemomas originating from nerve sheaths and ganglioneuromas arising from components of the sympathetic nervous system are other tumors originating from neural tissue. These tumors can also be associated with von Recklinghausen's disease. When these proliferations are confined to the mucosa, they result in the formation of polyps or plaques. The Schwann cells also present distort them, and such distortions again resemble those encountered in juvenile polyps.

Symptoms and Diagnosis Pain, intestinal bleeding, and obstruction occur as the initial complaint with equal frequency.

Treatment Symptomatic lesions are treated by local excision.

Lipomas

These circumscribed intramural yellow masses attenuate the overlying mucosa. In the case of larger lesions, the mucosa can become ulcerated with secondary fibrotic and hemorrhagic changes at the ulcer base. The bigger the tumors, the more likely they are to produce bleeding, pain, or obstruction. Microscopically, these submucosal masses of rather uniform adipose cells compress the muscularis mucosae and often cause thinning of the overlying mucosa.

Symptoms and Diagnosis Descriptions of gastrointestinal lipomas are especially prevalent in the radiologic literature because of a set of fairly characteristic features, including pliability, which allows for changing shape of the tumor, and their low density, as noted on computed tomography (CT).

Treatment Many gastric lipomas are discovered as incidental findings during endoscopic procedures and can be amputated completely at that time if they are large or pedunculated. Otherwise, small tumors less than 2 cm can be safely observed. Excision is necessary in symptomatic patients with bleeding or obstruction, and treatment is by local excision. Resection can be accomplished by either open or laparoscopic techniques. Larger or growing lesions should be resected to rule out malignant liposarcoma.

Fibromas

Fibromas are large, well-circumscribed tumors consistent with dense collagen bundles and a variable number of mature fibroblasts. They occur in the submucosa, muscularis, or serosa of the stomach. Fibromas are difficult to distinguish from scar tissue. They usually occur in adults 50 to 60 years of age.

Symptoms and Diagnosis Most tumors are asymptomatic and discovered at exploratory laparotomy performed for other reasons or at autopsy.

Treatment Small tumors can be safely observed. Local excision provides satisfactory treatment of symptomatic lesions.

Congenital Lesions

Duplication Cysts Gastric duplication cysts are tubular or cystic lesions surrounded by smooth muscle that is continuous with the muscle of the stomach.[55,56] The underlying mechanism of formation that has been suggested is adherence or fusion (or both) of proliferating gastric longitudinal folds during fetal development.[57] The lining of duplication cysts most frequently represents a mixture of gastric epithelia, with possible pancreatic heterotopia. Sometimes the lining can be destroyed by inflammation. These lesions occur most often along the greater curvature in children, typically infants, and can be detected incidentally. Most of the cystic lesions range in size from 3 cm to less than 12 cm, whereas the tubular forms communicate with the stomach. True congenital gastric diverticula with full muscular walls that are manifested in childhood may be considered gastric duplication cysts that have incompletely separated. Associated malformations include other foregut complete duplications or malformations, vertebral anomalies, but most frequently, esophageal duplication.

Symptoms and Diagnosis These lesions can be detected incidentally or be manifested as bleeding with extrinsic compression and obstruction of the stomach and vomiting. They can also cause symptoms as a result of perforation or fistulization into other adjacent organs.

Treatment Although isolated duplication cysts can be removed surgically, even when extensive, complex malformations are harder to manage and can be fatal.

DUODENUM AND SMALL INTESTINE

Even though the small intestine constitutes 70% to 80% of the total length of the gastrointestinal tract and more than 90% of its inner mucosal surface area, it is the site of only 5% to 7% of neoplasms that arise. This discrepancy is thought to be due to the rarity of non-neuroendocrine epithelial tumors in the small bowel.[58] Moreover, little consensus has been reached regarding the relative incidence rates of small bowel tumors in the United States or worldwide. Noticeably, geographic variations are found around the world. Given the rarity of small intestinal tumors and the wide variety of histologic types, the actual reported numbers are small even in the largest series, so reliable comparisons are difficult and incidence rates are impossible to confirm. Primary small bowel tumors are 40 to 60 times less common than colonic neoplasms, and they are found in 0.2% to 0.3% of autopsies, which is 15 times higher than the operative incidence. The frequency of benign small bowel tumors generally increases from the duodenum to the ileum. However, per unit area, the proximal 20 cm of intestine has the greatest number. Therefore, the duodenum, which constitutes less than 10% of the small intestine, contributes a disproportionately higher percentage of tumors.

Benign neoplasms of the small bowel can occur at any age, but the average age at diagnosis is 62 years. The incidence of small intestinal neoplasms is about equal in men and women.

Benign neoplasms can arise from all constituent tissues of the small intestine. The most frequently encountered benign tumors of the small intestine are leiomyomas (25% to 50% in different series) and adenomas (11% to 35% in different series), followed by lipomas (15% to 25%), lymphangiomas (2% to 12%), hemangiomas (<10%), fibromas (<6%), and others that occur less commonly (Table 60–3).[59-61] Hamartomas usually occur as part of Peutz-Jeghers syndrome, whereas schwannomas of the small intestine occur most frequently in the clinical setting of von Recklinghausen's disease. Hemangiomas and telangiectasia are often associated with Osler-Weber-Rendu syndrome and, to a lesser extent, Turner's syndrome.

Symptoms and Diagnosis

Tumors of the small intestine, besides being uncommon, are also insidious in manifestation and frequently represent a diagnostic challenge.[62] Benign tumors generally cause vague, nonspecific symptoms, but about half are asymptomatic (Table 60–4). They are often encountered as incidental findings at laparotomy or autopsy. Therefore, the relative distribution of benign tumors of the small intestine is affected by whether the reported series is based on clinical or autopsy findings. Thus, in clinical series, two thirds of small bowel tumors reported are malignant. The converse is true in autopsy series, in which benign tumors account for more than three fourths of all tumors.

When symptomatic, benign tumors of the small intestine are usually associated with either abdominal pain or symptoms of iron deficiency anemia secondary to occult gastrointestinal hemorrhage. Indeed, small bowel tumors are the second most common cause of obscure gastrointestinal bleeding and account for 5% to 10% of all cases of chronic blood loss; in patients younger than 50 years, small bowel tumors are the single most common lesion with occult digestive bleeding.[58] The abdominal pain is usually due to episodes of intermittent obstruction secondary to transient intussusception of the small bowel, with the tumor serving as the lead point.[63] Finally, benign periampullary duodenal neoplasms may initially be manifested as obstructive jaundice.

The diagnosis of small bowel tumors requires a high index of suspicion. Bowel obstruction in a patient without previous abdominal surgery should raise suspicion for a neoplasm. An accurate preoperative diagnosis is made in only about a third of patients. The history and physical examination, though essential, are usually nonspecific and unrevealing. In a minority of patients laboratory data may reveal iron deficiency anemia that is due to intestinal bleeding.

Evaluation of patients with gastrointestinal bleeding thought to be secondary to a small bowel neoplasm can be particularly difficult. Diagnostic methods for small bowel tumors include enteroclysis, visceral arteriography, CT scanning, magnetic resonance imaging, and enteroscopy.

Table 60–3 Incidence of Benign Tumors of the Small Intestine

Type of Lesion	%	Tissue of Origin
Leiomyomas (GIST)	25-50	Smooth muscle
Adenomas	11-35	Epithelium
Tubular		
Villous	<1	
Lipomas	15-25	Fat tissue
Hemangiomas	7-10	Vascular tissue
Neurogenic tumors (GIST)	<5-10	Neural elements
Schwannomas		Peripheral neural elements
Neurilemomas		Nerve sheath
Ganglioneuromas		Sympathetic nervous system
Fibromas	0-6	Connective tissue
Hamartomas	0-6	Various elements
Lymphangiomas	2-3	Lymphoid tissue
Ectopic tissue	Rare	
Pancreatic tissue		Pancreas
Endometriosis		Endometrium
Dermoid cysts	Rare	
Eosinophilic "granulomas"	Rare	Nonspecific inflammation with eosinophils
Angiodysplasia	Rare	Vascular
Hyperplastic polyps	Rare	Mucosal crypts

GIST, gastrointestinal stromal tumor.
Modified from Greenfield LJ, Mulholland MW, Oldham KT, et al: Surgery, Scientific Principles and Practice, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2001.

Table 60–4 Clinical Findings in Patients with Benign Tumors of the Small Intestine

Symptom	%
Asymptomatic	47-60
Abdominal pain	24-50
Acute gastrointestinal bleeding	29-44
Anemia	28-58
Intermittent obstruction	12-28
Jaundice	<2
Nausea and/or vomiting	Rare
Abdominal mass	Rare
Perforation	—
Weight loss	—

Modified from Greenfield LJ, Mulholland MW, Oldham KT, et al: Surgery, Scientific Principles and Practice, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2001.

Radiologic studies are the cornerstone of diagnosis for small bowel neoplasms. Plain abdominal radiographs indicating obstruction are not specific in terms of the cause. CT scanning of the abdomen with oral administration of contrast is a valuable technique for both demonstrating the primary lesion and defining any extraluminal extension. In patients with partial obstruction or those undergoing elective evaluation, barium contrast examination of the small bowel is the diagnostic procedure of choice. Enteroclysis study or small bowel enema with direct instillation of contrast material into the small bowel is preferred over standard upper gastrointestinal series with small bowel follow-through.[64] In the enteroclysis study, air-contrast techniques and fluoroscopic observation of the flow of contrast through the bowel improve the sensitivity for detection of subtle mucosal lesions. However, this technique can sometimes produce false-positive results.

Standard contrast-enhanced radiologic studies are useful in detecting tumors only if they are of substantial size. Tagged red blood cell radionuclide scans may localize the bleeding site to the small intestine but generally lack sensitivity. Visceral angiography can be useful in diagnosing and localizing the site of bleeding, but only in situations in which the hemorrhage is rapid (>0.5 ml/min).

Upper endoscopic examination or *total colonoscopy with ileal intubation* is useful in patients with duodenal or terminal ileal neoplasms. Direct visualization of tumors and endoscopic biopsy can often be obtained. *Endoscopic ultrasound examination* may be useful in the staging of periampullary duodenal tumors. *Push enteroscopy* can identify tumors in the jejunum with high effectiveness and efficiency. Nevertheless, the fact that exploration is restricted to the jejunum is a limitation of the method. In some patients, laparotomy with intraoperative push endoscopy may be required. Experience using enteroscopy and push endoscopy to visualize the entire small bowel is limited. *Sonde enteroscopy* can potentially identify tumors throughout the small intestine. Although encouraging results have been reported in small series, these techniques are not widely available.[65,66]

Benign Mucosal (Epithelial) Lesions

Non-neoplastic Benign Polyps

Non-neoplastic benign polyps of the small intestine include Peutz-Jeghers polyps, juvenile polyps, lymphoid polyps, and inflammatory fibroid polyps. Peutz-Jeghers polyps are discussed later, under the section on polyposis and small intestinal hamartomas, juvenile polyps under juvenile polyposis of the small bowel segment, and lymphoid polyps under intestinal lymphoid polyposis.

Inflammatory Fibroid Polyps

Inflammatory fibroid polyps are benign tumor masses that occur in the stomach and the small and large intestine. These uncommon lesions occur at all ages and have a worldwide distribution.[67] Their cause is unknown and they are not associated with any known syndromes; however, they have been reported in ileal pouches or the terminal ileum in patients with ulcerative colitis[68] and Crohn's disease.[69] They are also named eosinophilic granulomas, submucosal fibromas, hemangiopericytomas, inflammatory pseudotumors, and fibromas. Inflammatory fibroid polyps can occur at any age from 3 to 80 years. They range in size from 1.5 to 13 cm. These lesions must be distinguished from malignant mesenchymal tumors. Inflammatory fibroid polyps may penetrate the bowel wall with a pattern of dissection between the muscle fibers that causes splitting of the muscle layer; in contrast, mesenchymal neoplasms infiltrate and push the muscle layers aside.[67]

Symptoms and Diagnosis In decreasing order of incidence, symptoms include episodic abdominal pain, vomiting, melena or hematochezia, diarrhea, constipation, abdominal distention, and weight loss. Inflammatory fibroid polyps can also cause intussusception. The vast majority of these lesions are found in the small intestine, mainly in the ileum, but they can occur less commonly in the colon.

Treatment Inflammatory fibroid polyps are benign, and surgical resection is curative.

Adenomas or Neoplastic Polyps

Adenomas are the most common benign tumors of the small bowel with malignant potential and account for up to 35% of all benign small intestinal tumors. The most frequent location is the duodenum, and they typically occur in the periampullary region; however, each type has a characteristic pattern of occurrence. They vary in size from a few millimeters to several centimeters in diameter and can be sessile or pedunculated. The villous or tubulovillous architecture is prevalent in the small bowel, perhaps in relation to the normal villous anatomy of the mucosa in this segment. The premalignant potential of small intestinal adenomas is reliably attested, and histologic evidence indicates malignant transformation of adenomatous tissue.[70]

Even though all adenocarcinomas of the intestinal tract arise in adenomatous polyps, not all polyps evolve into carcinoma. The malignant potential of adenomas is related to polyp size and histologic characteristics. From the point of view of histologic characteristics, the malignant potential of an adenomatous polyp correlates with its degree of villous architecture. These features are interdependent, however, because large polyps tend to be villous and dysplastic. Diminutive polyps that measure 5 mm or less in diameter are most often tubular adenomas and are not likely (<0.5%) to contain high-grade dysplasia or invasive carcinoma. Only 1% to 2% of adenomatous polyps smaller than 1 cm contain carcinoma. Adenomas larger than 2 cm should be considered worrisome for malignancy; autopsy studies suggest that 40% of adenomas larger than 2 cm contain cancer.

Adenomas may occur in association with polyposis syndromes (FAP, Gardner's syndrome) or sporadically. In FAP, duodenal adenomas are extremely common. It is still uncertain whether patients with duodenal adenomas without FAP are at greater risk for colorectal neoplasia than the general population is.

Tubular Adenomas Tubular adenomas can occur anywhere in the small intestine but are found most frequently in the ileum, followed by the duodenum and jejunum. They may be solitary or multiple and are usually pedunculated. There is an increased incidence of adenomatous polyps in the small intestine in patients with familial polyposis syndromes. Tubular adenomas are characterized by a complex network of branching adenomatous glands.

Symptoms and Diagnosis Although most tubular adenomas are asymptomatic, they may be the source of gastrointestinal bleeding. The blood loss tends to be chronic and results in iron deficiency anemia rather than major acute hemorrhage. If the polyps become particularly large, episodes of intestinal obstruction can occur, generally with the polyp serving as the lead point for intussusception.

Treatment Duodenal adenomas can often be removed by endoscopic snare polypectomy. Side-viewing endoscopic examination may be necessary for the diagnosis of ampullary adenomas. Most adenomas of the duodenal papillae without intraductal extension can also be fully resected by snare papillectomy. Today, endoscopic therapy appears to be a reasonable alternative to surgery for the management of these papillary tumors because it is relatively safe and easily performed. However, adenomas recur in about a third of patients (32% to 42%) by 3 years after index polypectomy, so longer follow-up is needed. The 3-year recurrence rate in patients with a known history of adenomas was higher (42%). In the case of adenomas with intraductal expansion, however, the traditional approach with surgical excision should be considered.[70]

Tumors present in the jejunum or ileum require laparotomy or laparoscopy with either enterotomy and local excision or limited segmental sleeve resection. Endoscopic resection and submucosal excision via

operative enterotomy may be appropriate, depending on the size and location of the lesion. Intraoperative examination of the small bowel with careful palpation and the use of enteroscopy to evaluate suspected abnormalities is essential to rule out synchronous lesions. If intussusception is found at laparotomy for intestinal obstruction, the involved segment should be reduced to determine its viability. If compromised, this segment should be resected.

Villous Adenomas Villous adenomas occur predominantly in the periampullary duodenum and account for less than 1% of all small intestinal tumors. They are almost always sessile and may attain quite large size before becoming symptomatic. Malignant degeneration is common and occurs in roughly 25% to almost half of these tumors. Villous adenomas contain glands that extend straight down from the surface to the base of the polyp. Frequently, both histologic types, adenomatous and villous, coexist in a mixed tubulovillous adenoma. The malignant potential of an adenomatous polyp correlates with its degree of villous architecture.

Symptoms and Diagnosis Most villous adenomas cause chronic gastrointestinal bleeding, but tumors in the periampullary area may also be associated with obstructive jaundice secondary to biliary obstruction. The diagnosis of duodenal villous adenomas can be suggested by upper gastrointestinal series and confirmed by upper gastrointestinal endoscopy with biopsy. On radiologic examination, as in the case of gastric lesions, the "soap bubble" or "paint brush" appearance is pathognomonic. CT may be helpful to differentiate adenoma from carcinoma because an adenoma is not associated with thickening of the bowel wall. EGD with biopsy is appropriate after a positive result on a radiologic study. The accuracy of endoscopic biopsy is limited by sampling error, and a malignant neoplasm may be missed in up to 60% of cases.[71] Endoscopic ultrasound examination has recently proved to be particularly useful in determining the level of invasion, the presence of lymphadenopathy, and prediction of malignant versus benign tumors.

Treatment Regardless of the preoperative diagnosis, complete excision of the entire lesion and thorough histologic evaluation are necessary. Endoscopic polypectomy with transduodenal excision of sessile lesions is adequate treatment if complete resection can be accomplished.[72] The entire lesion should be submitted for careful histologic examination for invasive carcinoma, which may be present in up to 50% of larger tumors.[73,74] If invasive carcinoma is found, major resection is indicated. A recent retrospective review demonstrated local recurrence rates of 40% at 10 years, with 25% of the recurrences being malignant. Based on these data, periampullary lesions usually require pancreaticoduodenectomy (Whipple procedure), whereas a pancreas-sparing duodenal resection can be performed for more distal lesions.[75] Patients who undergo local excision require annual surveillance with endoscopy.[76]

Brunner's Gland Adenomas Brunner's gland adenomas are rare tumors that represent hyperplasia of the exocrine glands of the first portion of the duodenum. Brunner's glands, normally found in the duodenal submucosa, secrete alkaline mucus that aids in the neutralization of acidified luminal contents arriving from the stomach. These adenomas are usually solitary, always benign, and proximal to the ampulla. They have minimal, if any malignant potential.

Symptoms and Diagnosis Brunner's gland adenomas are generally asymptomatic and detected incidentally at endoscopic examination. The tumors may rarely bleed, and tumors of large size can cause duodenal obstruction.

Treatment Endoscopic resection is adequate treatment of most Brunner's gland adenomas. Surgical management is indicated for larger tumors with local excision of a portion of the duodenal wall. If the lesion is so large that local resection is not technically possible, gastroenterostomy after histologic confirmation is appropriate treatment of the duodenal obstruction.

Ectopic Tissue Polyps Ectopic gastric, pancreatic, and endometrial tissue usually involves the duodenum, but it can be seen in the subserosa of the small intestine in cases of trisomy, in intestinal duplication cysts, and in Meckel's diverticulum. In the small bowel, ectopic tissue can be manifested as a neoplasm.

Ectopic pancreatic tissue is generally found in the duodenum and jejunum and is asymptomatic, with no malignant potential.

Gastric heterotopia is a relatively common condition characterized by the presence of mature gastric fundic-corpus–type mucosa in ectopic locations throughout the gastrointestinal tract.[77] The proximal duodenum is the second most common place, after the esophagus and before the rectum. Nodules have also been noted in the jejunum, in Meckel's diverticulum, and in enteric and colonic duplication cysts, whereas they are rarely seen in the normal distal ileum and proximal part of the colon. The lesions are thought to arise from congenital rests. Such heterotopia in the intestine must be distinguished from the more common process of gastric metaplasia, which typically consists of the appearance of gastric pyloric glands or the surface-foveolar type of mucous cells and develops as a consequence of chronic inflammatory disorders such as peptic duodenitis, celiac disease, and Crohn's disease. Gastric heterotopia of the small intestine may be seen in either gender and occurs in all age groups.

Symptoms and Diagnosis Most cases are asymptomatic and detected as incidental findings during endoscopic examination of the duodenum or as part of a pathologic study of excised diverticula or cysts, or both. Symptomatic cases appear to be more common in children. The specialized glandular cells are functional and secrete acid and proteolytic enzymes, but the occurrence of peptic injury is mainly related to the location of the lesions. Thus, ulceration of the adjacent unprotected mucosa is often observed when the gastric heterotopia involves relatively stagnant areas such as congenital diverticula and duplication cysts. Peptic injury is rarely seen

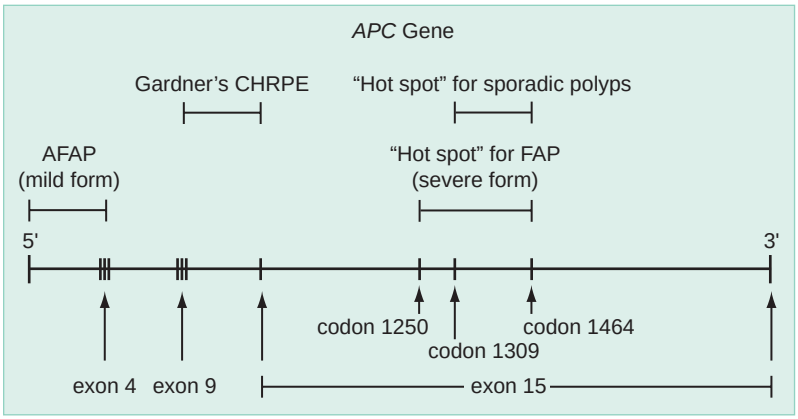

Figure 60–1. Schematic representation of the *APC* gene and its most important genotypic points of mutation with the corresponding phenotype expressions. AFAP, attenuated familial adenomatous polyposis; FAP, familial adenomatous polyposis; CHRPE, congenital hypertrophy of the retinal pigment epithelium. (Modified from Greenfield LJ, Mulholland MW, Oldham KT, et al: Surgery, Scientific Principles and Practice, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2001.)

in cases affecting the duodenum, possibly because of prompt dilution of the acid by biliary secretions in this area. The gastric tissue in Meckel's diverticulum may show changes of reflux gastritis because of action of the adjacent intestinal secretions, similar to what is noted in the stomach after reflux of duodenal contents.

Treatment Segmental intestinal excision is usually the best surgical treatment of perforation or recurrent bleeding. Meckel's diverticulectomy is indicated for incidental findings, with segmental resection if a peptic ulcer is found.

Endometriosis Endometriosis can also occur on the surface of the small intestine and can cause either partial or complete bowel obstruction. Gastrointestinal involvement is noted in about 33% of cases of endometriosis. There are two major theories regarding the development of endometriosis. One suggests that endometrial tissue may extrude through the fallopian tubes at the time of normal menstruation, which would explain the concentration of lesions in pelvic tissues and on the peritoneal surfaces. Alternatively, it is known that the coelomic epithelium is capable of pluripotential differentiation and is the probable source of endometriosis in all regions, including those that are remote from the uterus. In either situation, the ectopic endometrial tissue can respond to the cyclic hormonal stimulation.

Symptoms and Diagnosis In endometriosis, obstruction may be secondary to kinking, stenosis, fibrosis, volvulus, or intussusception. The diagnosis may be suggested by either barium enema or small bowel contrast study and is strongly suggested in a patient with known pelvic endometriosis.

Treatment Segmental excision is usually the best surgical treatment, but hormonal therapy may also be helpful.

Intestinal Polyposis Syndromes

Familial Adenomatous Polyposis

FAP (Table 60–5) is a hereditary autosomal dominant disorder in which the large intestine and rectum are carpeted with multiple adenomas ranging from hundreds to thousands. No true case of FAP has fewer than 100 adenomas, and if less than 100, we are talking about attenuated FAP (see later).

The genetic defect is due to the chromosome allele loss 5q21, called the adenomatous polyposis coli *(APC)* gene (Fig. 60–1). The *APC* gene encodes 2844 codons, 1 for each amino acid, and is broken into 15 translated exons. *APC* is a tumor suppressor gene that encodes a large protein (311 kD) that binds to β-catenin and causes its degradation. The structure of the *APC* gene is unique in that the 15th exon makes up about 75% of the coding sequences of the gene. Because of its unusual length, the open reading frame is an easy target for the types of mutations that result in premature stop codons.[78] The portion of the *APC* gene that binds to β-catenin is represented in this 15th exon. The most common defects in *APC* are point mutations and microdeletions leading to truncated protein. Normal APC protein is localized in the cytoplasm and modulates extracellular signals that are transmitted to the nucleus through the cytoskeletal protein β-catenin, whereas mutant or truncated protein could disrupt this normal process. Mutations in a "hot spot" immediately downstream from the β-catenin binding site (see Fig. 60–1) result in a more virulent, profuse form of FAP. Abnormalities in the *APC* gene may also lead to disruption of normal cell-to-cell adhesions through interactions with the cellular adhesion molecule E-cadherin.

The lesions in FAP are adenomas and are histologically similar to those seen in patients without FAP, with flat/depressed adenomas representing 30% of the lesions. Originally described in association with FAP, *APC* gene mutations are found in more than 60% of sporadic adenomas.[79] Besides having colonic polyps, most patients with FAP also have upper gastrointestinal polyps: adenomatous changes in the duodenum in 60% to 90% of cases and fundic gland polyps or adenomas in the stomach. They are relatively rare in the bulb, whereas they are more frequent in the second and third portions of the duodenum,[80] where numerous sessile polyps are found, generally small in size but sometimes a few centimeters in diameter. There is a tendency for adenomas to involve the periampullary region, with 50% to 85% of patients having adenomatous alterations of the papilla of

Table 60–5 Polyposis Syndromes with Gastrointestinal Lesions

Polyposis Syndrome	Type	Gene	Locus	Polyp Type
Familial adenomatous polyposis (FAP)	AD	*APC*	5q21	Adenomas Lymphoid polyps Fundic gland polyps Hamartomas
Gardner's syndrome	AD	*APC*	5q21	Adenomas Lymphoid polyps Fundic gland polyps Hamartomas
Turcot's syndrome	AD	*APC, hPMS2, hMLH1*	5q21, 7p22, 3p21-23	Adenomas
Attenuated familial adenomatous polyposis (AFAP)	AD	*APC*	5q21	Hamartomas Adenomas
Hereditary flat adenoma syndrome (HFAS)			5q21-22	Flat adenomas Fundic gland polyps
Muir-Torre syndrome	AD	?	?	Adenomas
Juvenile polyposis syndrome	AD	*SMAD4, PTEN*	10q22-24, 18q21	Villous/papillary polyps Hyperplastic polyps Fundic gland polyps
Bannayan-Zonana (Bannayan-Ruvalcaba-Riley) syndrome	AD	*PTEN*		Hamartomas
Cowden's disease	AD	*PTEN/MMAC1*	10q22-23	Hamartomas Inflammatory polyps Ganglioneuromas Lipomas
Peutz-Jeghers syndrome	AD	*STK11/LKB1*	19p13	Hamartomas
Cronkhite-Canada syndrome (CCS)	NH			Juvenile polyps–like inflammatory polyps
Intestinal ganglioneuromatosis syndrome				Ganglioneuromas
Lymphoid polyposis syndrome				Lymphoid polyps
Hereditary mixed polyposis syndromes	AD	?	6q	Tubular adenomas Villous adenomas Flat adenomas Hyperplastic polyps Atypical juvenile polyp

AD, autosomal dominant; NH, nonhereditary.
Modified from Ming SC, Goldman H: Pathology of the Gastrointestinal Tract, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 1998; and Greenfield LJ, Mulholland MW, Oldham KT, et al: Surgery, Scientific Principles and Practice, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2001.

Vater.[81,82] Staging of duodenal polyposis uses the Spigelman classification, with severity based on architectural parameters—villous status, grade of dysplasia, and number and size of polyps. Stage I indicates minimal duodenal disease, whereas stage IV represents advanced disease. The severity of duodenal polyposis increases with age, but progression may be especially rapid in patients at advanced stages of disease.[83] About 11% of patients have stage IV lesions; thus, it is not surprising that the risk for duodenal cancer in patients with FAP is about 100 times higher than in the general population.[84,85] Based on data from the John Hopkins Polyposis Registry,[85] it appears that the relative risk for adenocarcinoma of the duodenum developing in a patient with FAP is 331, whereas the relative risk for the development of periampullary adenocarcinoma is 124. These neoplasms are thus the most important cause of mortality in patients already subjected to prophylactic colectomy, and they involve about 5% of cases.[86]

Finally, one should be aware of reports that patients with FAP may have benign lymphoid polyps of the terminal ileum.[87] Otherwise, little is known concerning the true prevalence of either polyps or cancer in the postduodenal small intestine in FAP patients. Reports on the prevalence of polyps in the jejunum-ileum derive from the use of intraoperative enteroscopy.

Symptoms and Diagnosis The incidence of FAP has been estimated to be 1 in 8000 births, 20% of which are a new mutation in a family. The average age at detection

in patients with symptoms is 36.5 years. In contrast, in patients who are examined because of a family history of FAP, the average age at detection is only 23.8 years. Adenomas do not usually appear before the age of 10. Adenocarcinoma will develop in all patients who are left untreated. The average age at diagnosis of adenocarcinoma in the FAP group is 39 years, which is at least 25 years younger than the average age at diagnosis of adenocarcinoma in the general population.

A clinical diagnosis of FAP is not generally difficult. When FAP is known to run in a family, relatives at risk should undergo surveillance sigmoidoscopy on an annual basis beginning in their mid-teenage years. Sigmoidoscopy is sufficient to detect carriers of the abnormal gene because the entire colon is at risk. If a single adenoma appears in a teenager at risk, the disease is strongly suspected. The lesion must be biopsied to confirm that it is an adenoma. In a family with FAP, each first-degree relative of an affected patient has a 50% likelihood of inheriting the mutated gene. With each passing year, negative sigmoidoscopy further reduces the probability that a patient carries the gene.

Endoscopic ultrasound and ultrasound miniprobe technology may increase the accuracy of duodenal staging, thus adding a further parameter to the decision-making process in advanced cases when surgery is not clearly indicated.

Treatment Because untreated FAP inevitably leads to colorectal adenocarcinoma, prophylactic colectomy is indicated. The clinical decision involves selection and timing of the operation because a delay of 20 years or more from appearance of the first adenoma to the development of cancer is typical. The safest surgical procedure is total proctocolectomy with ileoanal anastomosis. Any residual rectal mucosa that is left behind is at risk for the development of neoplasia and rectal carcinoma. Intraoperative enteroscopy in FAP patients should be carried out during surgical colectomy. Endoscopic screening of the upper gastrointestinal tract in FAP patients aims to identify high-risk individuals and to diagnose cancer at an early stage. The St. Mark's Hospital group[85] recommends beginning checkups at age 20. Subsequently, endoscopy should be repeated every 2 to 3 years for polyposis at Spigelman stages 0 to II. For stages III and IV, checkups should be performed every 12 months, mostly after the age of 30. Even if most duodenal adenomas appear to not change for considerable periods, it is prudent to remove most polyps and, above all, large ones or those showing rapid growth via routine upper endoscopy.

For periampullary surveillance, a side-viewing duodenoscope must be used. Biopsy samples must also be taken from the papilla of Vater, even if it has normal morphology. Various alternative therapies have been used for periampullary adenomas. Transduodenal submucosal excision with sphincteroplasty is beneficial only in the short term because of the high recurrence rate. On the other hand, snare ampullectomy and the Nd:YAG laser involve a risk for perforation. Highly selective thermal ablation via bipolar coagulation after sphincterotomy can be safer and may be preferable.[88,89] For patients at Spigelman stage IV, endoscopic laser photodynamic therapy appears to be promising,[90] but large case studies are not yet available.

If endoscopic snare polypectomy is appropriate for small or pedunculated lesions, as previously mentioned, pancreaticoduodenectomy may be required for adequate treatment of larger villous adenomas in the periampullary region.

Medical therapy with a nonsteroidal drug (sulindac) has been described.[91,92] Although colorectal adenomas have been found to regress in patients with FAP in response to sulindac, similar effectiveness was not found in the management of upper gastrointestinal tract neoplasia.

Gardner's Syndrome Polyposis

Gardener's syndrome (see Table 60–5) is presently thought to be a variant of FAP characterized by the triad of intestinal polyps, soft tissue abnormalities, and abnormalities of bones.[93] Also noted is congenital hypertrophy of the retinal pigment epithelium (CHRPE), which consists of single or multiple pigmented ovoid lesions occurring unilaterally or bilaterally. The retinal lesions occur when the mutations are between exons 9 and 15 on the *APC* gene (see Fig. 60–1). Traditionally, patients with signs and symptoms of FAP together with extraintestinal manifestations were historically considered to have Gardner's syndrome. It is now appreciated that no distinction can be made between families with Gardner's syndrome and those with FAP because extraintestinal manifestations have also been found in families with FAP. The genetic defect is identical to that for FAP. Similar to FAP, patients with Gardener's syndrome have upper gastrointestinal polyps,[93] and also as in FAP, the intestinal polyps are adenomas. This syndrome represents the variable expression of germline mutations in the *APC* gene. Benign lymphoid polyposis of the ileum has been associated with this syndrome.[94] At times, the soft tissue abnormalities, including epidermal cysts, fibromas, lipomas, and desmoid tumors, may precede the intestinal manifestations by years. The bony lesions are osteomas and cortical thickening of the long bones and ribs. In addition, dental abnormalities such as impacted teeth, supernumerary teeth, and dental cysts have been reported. There is an increased incidence of adenocarcinomas of the pancreaticoduodenal region, the thyroid gland, the adrenal gland, and the brain (particularly medulloblastomas). Malignant tumors of the colon are considered to be nearly inevitable.

Symptoms and Diagnosis CHRPE lesions may be seen in the general population but are small and usually single. Multiple, bilateral, and large CHRPE lesions are essentially diagnostic of FAP. The intestinal manifestations, number of adenomas, incidence of intestinal cancer, and methods of diagnosis have been described earlier under FAP syndrome.

Turcot's Syndrome Polyposis

Turcot's syndrome (see Table 60–5) is presently thought to also be a rare variant of FAP. The syndrome was

originally described in 1959 in two siblings with polyposis coli in whom malignant brain tumors developed.[95] Traditionally, the occurrence of a malignant brain tumor in conjunction with intestinal polyposis was referred as Turcot's syndrome. Interestingly, one of the index families initially reported by Turcot did not have FAP but rather had hereditary nonpolyposis colorectal cancer (HNPCC), which is characterized by an excess of astrocytomas (glioblastoma multiforme). To date, evidence suggests that all of the aforementioned can result from two distinctive types of germline defects: the association with the *APC* gene mutation is a variant of FAP, whereas the association with mutation of a mismatch repair gene *(hPMS2, hMLH1)* is a variant of HNPCC. The lesions are adenomas and the malignant potential may be the same as for FAP. However, the true frequency of Turcot's syndrome may be difficult to assess because central nervous system tumors are associated with high mortality and may precede the detection of intestinal polyps or the onset of intestinal carcinoma. Like Gardner's syndrome, this syndrome represents variable expression of germline mutations in the *APC* gene.

Attenuated Familial Adenomatous Polyposis

Attenuated FAP (see Table 60–5) is a less severe form of polyposis with a lower number of adenomatous polyps, usually less than 100, but patients still have a high risk for intestinal cancer. The cancers usually develop 15 years later than in classic FAP patients, but 10 years earlier than in the sporadic cancer group.[79] Linkage to the *APC* gene has been found; the genetic defect is similar to that of FAP, linked to 5q21.[96,97] Four distinct mutations have been identified and described in a few families with attenuated FAP. These mutations predict truncated proteins; however, they differ from the situation in patients with classic *APC* base substitutions or small deletions in that the four mutated sites are very close to each other and to the 5′ end of the *APC* gene.

Hereditary Flat Adenoma Syndrome Polyposis

Hereditary flat adenoma syndrome (see Table 60–5) is presently thought to also be a variant of FAP with the genetic defect linked to 5q21-22. In contrast to FAP, the majority of adenomas are of the flat type. Signs of hereditary flat adenoma syndrome in patients consist of the following:

1. Multiple colorectal adenomas are present, but usually fewer than 100.
2. The adenomatous polyps tend to occur at a later age than in classic FAP.
3. The adenomatous polyps tend to show a more proximal location, so patients have adenomas and cancers of the stomach and duodenum.
4. Fundic gland polyps of the stomach are also noted, and in some patients they may be present in the absence of colorectal adenomas.[98,99]
5. The onset of intestinal cancer is later than with HNPCC and FAP.

Muir-Torre Syndrome Polyposis

Muir-Torre syndrome (see Table 60–5) is a rare autosomal dominant disorder with fewer than 100 adenomas that is typically present in the proximal part of the colon. Originally, Muir-Torre syndrome was subclassified as a form of FAP, but today it is believed that the syndrome is an HNPCC in which the intestinal adenomas are associated with skin lesions such as basal cell carcinoma, sebaceous carcinoma, and squamous cell carcinoma.

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (see Table 60–5) is a heterogeneous and complex group of disorders, with some patients expressing polyps limited to the colon, whereas others have polyps that also involve the stomach and small intestine; some cases are familial, whereas others are not; and some patients have coexisting separate adenomas, whereas others have juvenile polyps with adenomatous changes. Three different syndromic manifestations have been reported, but it is not known whether these are truly distinctive syndromes. They may consist of familial juvenile polyposis limited to the colon, familial juvenile polyposis limited to the stomach, and familial juvenile polyposis distributed throughout the gastrointestinal tract. To date, a unifying definition of juvenile polyposis syndrome considers juvenile polyps throughout the entire gastrointestinal tract, any number of juvenile polyps in a patient with a family history, or any patient with 3 or more, 5 or more, or 10 or more juvenile polyps. In general, 20% to 50% of patients have a familial or genetic history that indicates autosomal dominant inheritance. The genetic basis of this syndrome is not understood, but germline mutations in the *SMAD4* gene located on chromosome 18q21, which encodes an intracellular mediator in the transforming growth factor-β signaling pathway, have been identified in some affected patients. The *PTEN* gene located on chromosome 10q22-24 has also been linked to some cases. In juvenile polyposis the number of polyps ranges from dozens to hundreds; however, they are not as numerous as in FAP. Frequently, the polyps appear as pedunculated, cherry-red, edematous growths with a smooth surface and contour. From the literature, the reported distribution of juvenile polyps throughout the gastrointestinal tract shows 98% in the colorectum, 13.6% in the stomach, 2.3% in the duodenum, and 6.5% through the jejunum and ileum.[100] Extraintestinal congenital anomalies have been reported in 11% to 20% of both familial and nonfamilial cases.[100] Juvenile polyposis syndrome is diagnosed in infancy in most cases (75% occur in children younger than 10 years), with only 15% being detected initially in adults. Although juvenile polyps individually are not in themselves neoplastic, there is an increased risk for intestinal cancer ranging from 15% to 21% in patients with juvenile polyposis. The various anomalies associated with the syndrome and reported in the literature are gut malrotation, mesenteric lymphangioma, hypertelorism, amyotonia congenita, hydrocephalus, tetralogy of Fallot, coarctation of the aorta,

thyroglossal duct cyst, and idiopathic hypertrophic subaortic stenosis.

There is a rare form of juvenile polyposis syndrome of infancy that consists of diarrhea, bleeding, protein-losing enteropathy, alopecia, and clubbing of the fingers and toes; it is often fatal and clinically mimics adult CCS.

Histologically, the lesions in juvenile polyposis syndrome are typical and atypical polyps. The typical ones are grossly round and smooth and are similar to solitary juvenile polyps. The atypical polyps often adopt a villous or papillary configuration. Separate hyperplastic polyps can also be seen.

Symptoms and Diagnosis Gastrointestinal bleeding, because these lesions are highly vascular, intussusception, and obstruction are typical manifestations of the disease. The passage of autoamputated lesions has been mentioned. Total colonoscopy, EGD, and small bowel enteroclysis are indicated for surveillance of these patients.

Treatment When surgery is necessary, careful examination of the entire small bowel with intraoperative enteroscopy should be performed, and larger polyps should be removed either endoscopically or surgically to prevent future intussusception, obstruction, or bleeding. It is important that the pathologist examine the lesions carefully for the presence of adenomatous tissue in the polyps because it indicates which lesions are premalignant. When mixed lesions are found, patients in these families should be subjected to colonoscopic surveillance, perhaps as often as every 2 years. In children with life-threatening protein-losing enteropathy, surgical resection of the affected segment of intestine is required.

Bannayan-Zonana (Bannayan-Ruvalcaba-Riley) Syndrome Polyposis

Bannayan-Zonana (Bannayan-Ruvalcaba-Riley) syndrome (see Table 60–5) is an inherited autosomal dominant disorder characterized by ileal and colonic hamartomatous polyps and lingual lesions. Other characteristics include ocular abnormalities, delayed motor development, lipid storage myopathy, and Hashimoto's disease. This disease is also linked to germline mutations in the *PTEN* gene and appears to be a variant of familial juvenile polyposis.

Cowden's Disease Polyposis

Cowden's disease (see Table 60–5) is an uncommon autosomal dominant disorder. This disease is discussed under the small bowel polyposis syndromes because of the presence of numerous colonic and small intestinal polyps. The disease is associated with facial trichilemmomas, acral keratosis, and oral mucosal papillomas, as well as with breast and thyroid cancer. Glycogenic acanthosis of the esophagus may also occur. Based on different authors, the lesions have been described as hamartomatous[101] or inflammatory or as lipomas or ganglioneuromas.[102] There is no increased risk for gastrointestinal cancer in this disorder. It is of interest that a germline mutation in the *PTEN* gene on chromosome 10q22-23 has been identified in most families with Cowden's syndrome, the same locus affecting some families with juvenile polyposis.

Symptoms and Diagnosis The diagnosis of Cowden's syndrome should be considered in patients with multiple trichilemmomas. Gastrointestinal polyps are usually asymptomatic.

Treatment No specific therapy need be directed toward the gastrointestinal tract.

Peutz-Jeghers Syndrome Polyposis

Peutz-Jeghers syndrome (see Table 60–5) is a rare autosomal dominant inherited disorder associated with mutation in the *STK11/LKB1* gene and deregulation of mTOR. The gene responsible for the disease was mapped to chromosome 19p13 and encodes a serine/threonine kinase. Peutz first reported the syndrome in 1921, and Jeghers and colleagues described it anew in 1949. Multiple gastrointestinal polyps scattered throughout the entire gastrointestinal tract, but occurring primarily in the jejunum and ileum, and mucocutaneous melanotic pigmentation on the lips, oral mucosa, face, genitalia, and palmar surfaces characterize the disease. The number of polyps is usually counted in the dozens rather than in the hundreds as in FAP. In most patients the disorder is diagnosed in the twenties, and the male-to-female ratio is 1:1. On histologic examination these polyps are hamartomas and range from only few millimeters to several centimeters in diameter, but most often these lesions are less than 1 cm in diameter and are rarely large enough to cause symptoms. They are histologically distinct from juvenile polyps and show no inflammatory cell infiltrate. They may be found in the stomach, in the large bowel, and more frequently in the small intestine. Although the hamartomas are not premalignant, carriers of the *STK11* gene are at significant risk for the early onset of other malignant neoplasms, mainly pancreas, breast, lung, ovary, uterus, and sex cord tumors. In a series reported by Spigelman and associates,[103] another neoplasm developed in 23% of patients, 56% of which were gastrointestinal in origin. It is thought that neoplasia may arise from foci of adenomatous epithelium found in some Peutz-Jeghers polyps.

Symptoms and Diagnosis Peutz-Jeghers syndrome is manifested early and the diagnosis is made in the first 3 decades of life, with the clinical symptoms varying according to the location of the polyps. The larger hamartomas can cause obstruction as a result of intussusception and, less frequently, intestinal hemorrhage; obstruction and abdominal pain are also associated with small intestinal polyps because of its narrower diameter. Whereas surveillance of the upper and lower gastrointestinal tract is easily achieved through EGD and total colonoscopy with terminal ileoscopy, the small intestine is still an important and challenging problem. Enteroclysis can identify polyps and define the map of their distribution.

Treatment The aim of management of these patients is to identify and remove the polyps endoscopically or surgically before they can cause complications. With EGD and total colonoscopy, the stomach, most of duodenum, and the entire large intestine can be kept free of polyps. Push enteroscopy allows only limited exploration of the jejunum but does permit operative procedures to be carried out further in the small bowel. Because the lesions are extensive in distribution, resection should be limited to the segment responsible for the symptoms. Since they have no malignant potential, no internal organ is at sufficient risk for cancer that a specific screening regimen is indicated, and prophylactic surgery or extensive resection of hamartomas is not justified. However, when surgery is necessary, careful examination of the entire small bowel with intraoperative enteroscopy should be performed and larger polyps removed either endoscopically or surgically to prevent future obstruction or intussusception. Most patients require several surgical intestinal resections during their lifetime and sometimes emergency operations at brief intervals, which may cause short-bowel syndrome. That is why some authors consider it necessary to schedule periodic radiologic and endoscopic checkups at intervals of 3 to 5 years or decide on a case-by-case basis. The clinician should be also aware of the extradigestive malignancy risk and should be particularly alert for the development of gonadal tumors.

Cronkhite-Canada Syndrome Polyposis

CCS (see Table 60–5) is an acquired, nonhereditary, nonfamilial gastrointestinal polyposis disorder associated with skin pigmentary changes, hair loss, and nail atrophy (onychodystrophy).[104,105] CCS is found worldwide and is characterized by the initial appearance of intestinal lesions in late adult life, with approximately 80% of patients being 50 years or older at onset. The male-to-female ratio is close to 1:1. The polyps in CCS are found in the stomach, small intestine, colon, and rectum and may be sessile or pedunculated. Histologically, the polyps are identical to juvenile polyps. There have been reports of adenomatous changes in these polyps.[106]

Symptoms and Diagnosis The clinical symptoms (in decreasing order of frequency) are diarrhea, weight loss, abdominal pain, anorexia, weakness, and hematochezia. The physical findings, as already mentioned, are onycholysis, alopecia, and hyperpigmentation. The hair loss has been noted in all parts of the body, and hair regrowth has been mentioned during spontaneous remission and after therapy. Approximately 50% of cases are fatal, usually secondary to cachexia and anemia.

Treatment Supportive therapy for CCS may provide long-term remission; it has been reported that polyps may decrease in size or number.[105] Primary attention should be drawn to treatment of the diarrhea and maintenance of nutritional status. In a number of cases, treatment of the bacterial overgrowth with antibiotics and maintenance of nutritional status have resulted in complete resolution of the cutaneous features. At present, surgery is recommended only for complications such as prolapse, bowel obstruction, or malignancy. Present data on CCS indicate that the potential risk for development of intestinal cancer is not great enough to indicate colectomy, although there have been reported cases of colorectal malignancy in correlation with CCS.[106]

Intestinal Ganglioneuromatosis Syndrome Polyposis

The intestinal ganglioneuromatosis syndrome (see Table 60–5) is a familial disorder that has been associated with multiple endocrine neoplasia type IIB and with von Recklinghausen's disease.[107] There may be a diffuse proliferation of ganglioneuromatous elements that at times may be polypoid. In some instances, the syndrome has been found in association with juvenile polyposis.[107] See also the later discussion under "Neurogenic Benign Tumors."

Lymphoid Polyposis Syndrome

Benign lymphoid polyposis syndrome (see Table 60–5) occurs most often in children. The lesions are entirely benign and in some cases have been reported to disappear spontaneously. Histologically similar to solitary lymphoid polyps, lymphoid polyposis consists of prominent active lymphoid nodules in the mucosa and submucosa. In patients with a family history of polyps, it is essential to determine the exact histologic nature of the lesions so that unnecessary surgery is not performed.

As previously mentioned, benign lymphoid polyposis of the terminal ileum has been reported in patients with FAP and Gardner's syndrome.[94]

Hereditary Mixed Polyposis Syndrome

Hereditary mixed polyposis syndrome (see Table 60–5) is an autosomal dominant disorder that has been mapped to chromosome 6q. Five types of polyps have been described in the literature in individuals with this disorder: tubular adenomas, villous adenomas, flat adenomas, hyperplastic polyps, and atypical juvenile polyps. This disorder might be a variant of juvenile polyposis; however, in juvenile polyposis, only 2% of the polyps are adenomas, whereas in hereditary mixed polyposis, the majority of polyps are adenomas. In addition, in hereditary mixed polyposis the number of polyps is lower than seen in the juvenile syndrome, and hereditary mixed polyposis usually occurs 1 decade later than juvenile polyposis does.

Benign Mesenchymal (Nonepithelial) Lesions

Vascular Lesions

Angiodysplasia The general aspects, symptoms and diagnosis, and treatment of angiodysplasia were described in detail earlier in the section on gastric angiodysplasia.

Telangiectasia Telangiectases arise from simple dilation of normal vascular structures as a result of congenital

thinning of the muscular layer and elastic fibers in the arteriolar wall. Multiple congenital lesions may occur in the gastrointestinal tract in Osler-Weber-Rendu syndrome and Turner's syndrome. Turner's syndrome (XO) is associated with gastrointestinal hemorrhage from telangiectases that may be found throughout the small and large bowel and mesentery, but it occurs most frequently in the small intestine.

Symptoms and Diagnosis Gastrointestinal bleeding is present in less than 15% of patients.

Treatment In Turner's syndrome, these vascular lesions tend to regress spontaneously; therefore, a conservative approach is generally warranted.[51] When necessary, intraoperative push enteroscopy with electrocoagulation or a heater probe can adequately treat these lesions.

Hemangiomas Hemangiomas are rare congenital lesions of the small intestine and account for about 7% to 10% of all benign small bowel tumors; they affect predominantly the jejunum and ileum. Arising from the submucosal vascular plexuses, hemangiomas are classified as capillary, cavernous, or mixed, depending on the size of the vessels primarily affected. Intestinal hemangiomas are usually solitary or, more rarely, multiple, and malignant degeneration is exceedingly rare. The appearance of the lesions may be quite varied, from bluish-colored areas to swollen bluish-colored polypoid lesions with a nodular surface and soft, elastic consistency.

Hemangiomas of the small bowel may also be associated with cutaneous lesions such as cavernous skin hemangiomas in the blue rubber bleb nevus syndrome or with capillary skin hemangiomas (port-wine stain) and soft tissue and bony hypertrophy in the Klippel-Trénaunay-Weber syndrome. In Peutz-Jeghers syndrome, intestinal hemangiomas without the presence of intestinal polyps has been reported. These cases are thought to represent incomplete penetrance of the gene responsible for the syndrome.[108]

Symptoms and Diagnosis Intestinal hemangiomas grow slowly, typically coming to medical attention in the third decade of life because of acute or chronic blood loss. Preoperative diagnosis may be achieved through angiography, but is usually difficult. Push enteroscopy and intraoperative enteroscopy have been used to diagnose hemangiomas of the small bowel.[58,109]

Treatment Depending on their size, hemangiomas may be locally excised or resected via limited small bowel resection. Efforts to manage intestinal hemangiomas with endoscopic or operative sclerotherapy or coagulation and operative or angiographic interruption of their arterial supply have been minimally successful.

Diffuse Gastrointestinal Hemangiomatosis As many as 100 lesions involving the stomach, small bowel, and colon can be encountered in patients with diffuse gastrointestinal hemangiomatosis. Bleeding or anemia in childhood usually leads to the diagnosis of this condition.

Symptoms and Diagnosis Patients often have hemangiomas of the skin and soft tissue of the head and neck. The gastrointestinal hemangiomas may be large enough to cause intussusception. In diffuse neonatal hemangiomatosis, angiography is probably the most reliable means of detecting the lesions.

Lymphangiomas Lymphangiomas are rare and account for less than 2% to 3% of benign small bowel neoplastic tumors. They are developmental lymphatic malformations and on microscopic examination consist of dilated submucosal lymphatic vessels. They are usually solitary, lobulated, and intramural and appear as circumscribed polypoid masses of soft consistency with an irregular surface and micronodules.

Symptoms and Diagnosis Almost all lymphangiomas are asymptomatic and discovered either incidentally or at autopsy. When symptomatic, they cause abdominal pain, obstruction, and more rarely, occult gastrointestinal bleeding. Cases of small bowel lymphangiomas responsible for bleeding have been reported, and their diagnosis was made with push enteroscopy[110] or sonde enteroscopy.[111]

Treatment Symptomatic lesions should be treated by segmental resection.

Leiomyomas

Leiomyoma is either the first or the second most common benign tumor of the small intestine, with some authors considering adenoma to be the most common.[40,112] It is the most frequent tumor of the postduodenal small intestine and occurs equally in the jejunum and in the ileum. Leiomyomas are the second most common small bowel neoplasms manifested by occult bleeding. As already mentioned under gastric leiomyomas, intestinal leiomyomas are well-differentiated benign GISTs that arise from smooth muscle in the small bowel wall. The GIST label is more appropriate in that the previous terminology—leiomyoma versus leiomyosarcoma—implied a clear definition between benign and malignant tumors. The distinction is often not clear at the time of original diagnosis and histologic examination. The incidence is equal in males and females. The peak incidence in both men and women is between the ages of 50 and 59 years. A relatively recent large review of the world's literature identified 2763 GISTs of the small bowel.[113] In this review approximately 40% were classified as benign and 60% as malignant, with the jejunum being the most frequent site of origin. Interestingly, a disproportionately high number of GISTs are located in Meckel's diverticulum.

The most frequent growth pattern is extraluminal (65%), whereas the form with intraluminal or intramural development is less frequent.[114] In gross appearance, leiomyomas are wide-based submucosal formations that are firm, gray, lobulated, and nonmobile on the underlying plane. Although well circumscribed, they are not encapsulated and frequently demonstrate cystic

degeneration. Their biologic behavior is best correlated with the degree of mitotic activity and tumor size.[115-117]

Symptoms and Diagnosis As with gastric leiomyomas, most are asymptomatic, but many are associated with either bleeding or obstruction. Occasionally, the onset may consist of massive bleeding. Larger leiomyomas may outgrow their blood supply, thereby leading to central necrosis, ulceration, and intraluminal bleeding. Small bowel obstruction can occur either from luminal compression or more commonly from intussusception. Finally, patients may have an asymptomatic, yet palpable abdominal mass. The diagnosis can be made by contrast radiology, which shows a space-occupying lesion creating a smooth eccentric filling defect with intact small bowel mucosa. CT scanning is currently the most specific diagnostic study and often distinguishes a GIST with central necrosis from a lipoma, which would be of consistent fat density.

Treatment Because it is virtually impossible to differentiate benign from malignant lesions at laparotomy, even by frozen section, treatment of a small intestinal GIST should include segmental intestinal resection. Extensive lymph node dissection is not necessary because lymph node metastases are rare. Even if a tumor is asymptomatic, it should be resected because malignant behavior cannot be accurately predicted.

Neurogenic Benign Tumors

Neurogenic tumors are rare and account for less than 5% to 10% of all small intestinal neoplasms. They are GISTs with neural differentiation rather than being derived from smooth muscle like leiomyomas, leiomyosarcomas, or leiomyoblastomas. **Schwannomas** arise from peripheral neural elements, can be either solitary or multiple, and can occur at any age. Von Recklinghausen's disease is present in 15% of patients with schwannoma and is usually associated with multiple tumors.[118] Solitary tumors generally occur in the ileum. They appear as nodules of hard, elastic consistency, are mobile on the underlying plane, and are covered with smooth mucosa. Some nodules may demonstrate ulceration, which is responsible for the bleeding. **Neurilemomas** originating from nerve sheaths and **ganglioneuromas** arising from components of the sympathetic nervous system are other tumors originating from neural tissue. These tumors can also be associated with von Recklinghausen's disease.

Symptoms and Diagnosis Of patients with intestinal neurogenic tumors, symptoms will develop in approximately 70%.[119] Pain, intestinal bleeding, and obstruction occur as the initial complaint with equal frequency.

Endoscopic biopsy is not justified because it is not diagnostic. The diagnosis should be suspected in patients with von Recklinghausen's disease.

Treatment Symptomatic lesions are treated by local excision or segmental resection.

Lipomas

Lipomas, the third most common benign neoplasm of the small intestine, are submucosal fatty tumors and represent 15% to 25% of small intestinal benign tumors. Lipomas occur primarily in the distal portion of the small intestine: 60% are located in the ileum, with 20% present in the duodenum and 20% in the jejunum. They are most commonly found in older patients and in men. Occasional lipomas are pedunculated, and because they are also compressible, they may cause intussusception and obstruction. Lipomas may be multiple and are occasionally present diffusely throughout the small intestine. These rare cases of extremely numerous lesions have been termed *lipomatosis*. Microscopically, these submucosal masses of rather uniform adipose cells compress the muscularis mucosae and often cause thinning of the overlying mucosa. The bigger the tumors, the more likely they are to produce bleeding, pain, or obstruction.

Symptoms and Diagnosis Small intestinal lipomas are typically asymptomatic. In almost two thirds of patients, clinical symptoms are caused by intestinal obstruction; the most common point of obstruction is the ileocecal valve. Lipomas, which are usually asymptomatic, can be found incidentally on upper gastrointestinal series or EGD. The diagnosis can occasionally be made by barium enema with reflux into the terminal ileum or by a small intestinal contrast study. Contrast studies reveal a smooth, well-circumscribed, eccentric filling defect and intact mucosa. CT is particularly useful in the diagnosis of small intestinal lipomas because of the low density of the tumor as noted on studies. Endoscopically, they have a characteristic appearance, and there is also a distinctive appearance on endoscopic ultrasound.

Treatment Small tumors under 2 cm can be safely observed. Excision is unnecessary unless the patient is symptomatic. For lesions associated with bleeding or obstruction, treatment is by local excision, but segmental resection is usually necessary for larger tumors. Resection can be accomplished by either open or laparoscopic techniques. Larger or growing lesions should be resected to rule out malignant liposarcoma.

Lipohyperplasia (Lipomatous Hypertrophy) of the Ileocecal Valve In this condition, both sides of the ileocecal valve submucosa (ileal mucosal side and colonic mucosal side) contain adipose tissue in excess and produce a large, protruding valve that grossly resembles a uterine cervix.[120,121] The patients are more commonly middle-aged women; obesity does not provide an explanation.

Symptoms and Diagnosis Because the big valve protrudes in the cecal lumen, it can produce a dramatic radiographic filling defect resembling a neoplasm—cecal carcinoma. The condition is easily identified at colonoscopy and demonstrates adipose tissue covered by normal mucosa. Patients may have nonspecific clinical problems, such as constipation or abdominal pain, presumably the reasons for performing the radiographic or

colonoscopic studies. In most cases the hypertrophic valves are found incidentally. Intestinal obstruction and bleeding from an ulcerated valve have been reported, but these cases are truly unusual.

Fibromas

Fibromas are large, well-circumscribed tumors consisting of dense collagen bundles and a variable number of mature fibroblasts. They occur in the submucosa, muscularis, or serosa. Fibromas are difficult to distinguish from scar tissue. They typically occur in adults 50 to 60 years of age and represent about 0% to 6% of all benign small intestinal tumors.

Symptoms and Diagnosis Most tumors are asymptomatic and are discovered at exploratory laparotomy performed for other reasons or at autopsy.

Treatment Local excision provides satisfactory treatment of symptomatic lesions.

Congenital Lesions

Duplication Cysts Intestinal duplication cysts may be closed ovoid or spherical cystic structures that range in size from a few millimeters to 10 to 15 cm in diameter. As in the case of gastric duplication cysts, intestinal cysts may also appear as communicating tubular, elongated structures. Duplications are lined by functioning intestinal mucosa with a wall composed of smooth muscle. They are always dorsal to the intestine, usually within the mesentery between the spinal cords and the small bowel and sometimes intramural. Almost 50% of cases affect the terminal ileum and are generally single; however, they may be associated with multiple abdominal and thoracic duplications. Pathogenetically, they are thought to originate secondary to abnormal recanalization of the intestinal lumen obliterated by epithelial proliferation. Another likelihood is persistence of the outpouchings of the intestine that have been observed during embryogenesis and intrauterine intestinal ischemia. Their frequent association with vertebral clefts and rib anomalies suggests another possible explanation, such as failure of complete separation of the foregut and notochord. They occasionally communicate with the lumen of the bowel. Tubular duplication cysts generally lie parallel to the small bowel and share the muscular layer; they often communicate with the lumen of the intestine in their distal portion. Cases of extension along the entire small bowel have been reported.[122] Most duplications are manifested in the newborn period or early childhood, much less frequently in adult life. Gastrointestinal hemorrhage may be cause by peptic ulceration or by intestinal ischemia secondary to an altered blood supply by a mass effect or intussusception. The wall of a duplication cyst is thick and muscular and contains from one to three layers of smooth muscle with identifiable Auerbach's plexuses. The mucosal lining of the duplication may be gastric, intestinal, or pseudostratified ciliated columnar mucosa with occasional heterotopic pancreatic tissue. Peptic ulcers may occur within the duplication, usually at the gastrointestinal mucosal junction or at its communication with normal bowel. Small intestine duplication cysts occur at a 22:10 female-to-male ratio.

Duplication cysts of the duodenum are rare. They are usually submucosal, generally noncommunicating, and separated by only a thin muscularis layer. They bulge into the lumen of the adjoining duodenum.

Symptoms and Diagnosis When distended by mucous accumulations, cystic or tubular duplications may cause extrinsic compression of normal adjacent bowel and secondary intestinal obstruction or provoke intussusception (mostly seen with small intramural cysts) or volvulus. Small intestine duplication cysts may be palpable, and because they may be partially calcified, they are radiographically detectable as curvilinear densities on abdominal radiographs of children with associated intermittent pain, melena, or intussusception.

Treatment Although isolated duplication cysts can be removed surgically, even when extensive, complex malformations are harder to manage and can be fatal.

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Chapter

61

Adenocarcinoma of the Stomach, Duodenum, and Small Intestine

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GASTRIC ADENOCARCINOMA

Approximately 90% of all tumors of the stomach are malignant, the vast majority of which are gastric adenocarcinoma. Gastric cancer has been one of the leading causes of cancer-related mortality in the world for the past century and is currently the second most common cancer worldwide after lung cancer. Though still common in many parts of the world, particularly in the Eastern Hemisphere, the incidence has shown a dramatic decline in many parts of the Western world, including the United States. The incidence of proximal gastric cancers, however, is increasing. Surgical resection remains the only curative option, but the majority of patients in the United States are initially found to have unresectable disease. Advances in adjuvant therapies, including chemotherapy and radiotherapy, have improved survival rates in patients with resectable disease but remain palliative in patients who are not candidates for resection.

Epidemiology

In 2005 there will be an estimated 21,800 new cases of gastric cancer in the United States and approximately 13,000 deaths, which makes it the 14th most common malignancy and cause of cancer death in the United States.[1] Worldwide, gastric cancer remains the second or third most common malignancy (nearly 900,000 new cases annually) and the second most common cause of death (approximately 650,000 deaths).[2] The incidence of gastric cancer has significant geographic variation, with the highest incidence (75 to 100 per 100,000 men) occurring in Japan, Korea, and parts of South America and Eastern Europe and the lowest incidence (as low as 5 per 100,000 men) occurring in the United States and Western Europe.[3,4] In the United States, gastric cancer is more prevalent in men than women (2:1) and is also more common in African Americans, Hispanics, and Native Americans.[3,4] The incidence also increases with age starting in the fourth decade of life and generally peaks in the seventh decade.[5]

The incidence of gastric cancer in the United States has dropped approximately 75% since the 1930s, when it was the leading cause of cancer-related death in men.[4] The mortality rate has also decreased significantly from approximately 31 per 100,000 in the 1930s to 7.8 per 100,000 by the mid-1980s.[3] Part of this decrease in mortality is due to an increase in the overall incidence, however. The decrease in incidence of gastric cancer from 1930 to 1976 was largely due to a decrease in distal gastric cancers. Interestingly, however, since 1976, the incidence of proximal (i.e., cardia and gastroesophageal [GE] junction) adenocarcinomas in the United States and Europe has increased at a rate exceeding that of any other malignancy, and it currently accounts for nearly half of all gastric cancers.[6-8] This trend is particularly concerning because proximal gastric cancers and distal esophageal cancers are generally more difficult to treat and are also associated with higher overall mortality than distal gastric cancers are. The reasons for this shift from distal to proximal cancers are unclear, but it has been suggested that factors such as increased body mass index, increased caloric intake, and GE reflux may play a role.[6-8]

The overall 5-year survival rate for all stages of gastric cancer in the United States from 1995 to 2000 was approximately 23%, with a range of 58% in patients with localized disease to below 5% in patients with distant metastases, thus making it one of the more lethal cancers.[9] In the United States, nearly two thirds of patients are initially seen at an advanced stage, and more than 80% have lymph node metastases. The overall

5-year survival rate has improved significantly, however, from only 15% in 1976 to 23% by 2000,[10] probably because of earlier and more accurate diagnosis and staging, improvements in surgical resectional technique, and significant improvements in adjuvant therapy regimens. In contrast, however, the overall 5-year gastric cancer survival rate in Japan and the Far East is about 50%, where earlier-stage disease is diagnosed in a far greater percentage of patients.[3,4]

Pathology

Adenocarcinomas constitute 95% of all gastric cancers in the United States, with gastric lymphoma, carcinoid, gastrointestinal (GI) stromal tumors, and squamous cell carcinomas making up the remaining 5%.[4] Several pathologic classifications have been devised to describe gastric adenocarcinoma. The Borrmann classification scheme categorizes gastric cancer into five types by its macroscopic appearance.[2,11] Type I consists of polypoid or fungating cancers, type II includes tumors that are fungating and ulcerated and surrounded by elevated borders, type III includes ulcerated lesions infiltrating the gastric wall, type IV cancers infiltrate diffusely, and type V consists of those that are unable to be classified.[12]

The Lauren classification is the most commonly used classification scheme and divides gastric cancers into two distinct types—intestinal and diffuse[3,13] (Box 61–1). The intestinal variant arises from the gastric mucosa and is glandular in origin. Intestinal-type tumors often arise from precancerous lesions similar to other cancers of the GI tract. They are more common in men, in older patients, and in the distal part of the stomach. The intestinal variant is associated with *Helicobacter pylori* infection, chronic atrophic gastritis, intestinal metaplasia, and dietary factors (discussed in the next section).[5,11] In contrast, the diffuse-type pathology appears to arise from the lamina propria, is associated with an invasive growth pattern, and is less related to environmental factors.[5,11] Diffuse-type tumors are more common in younger patients and in the proximal part of the stomach. These tumors are characterized by noncohesive malignant cells diffusely infiltrating the stomach with minimal to no gland formation. They tend to spread rapidly in the submucosa, as well as by transmural extension and lymphatic invasion. Peritoneal metastases are also more common with diffuse-type gastric cancers. These cancers have increased in incidence and are associated with a worse prognosis than the intestinal variants are.[5,11]

The World Health Organization has further characterized gastric adenocarcinoma into five categories, depending on the degree of intestinal metaplasia. The classification includes adenocarcinoma (intestinal and diffuse), signet cell, mucinous, tubular, and papillary.[2,11]

Traditionally, most gastric cancers were found in the antrum; however, in the 1980s and 1990s, antral cancers declined and the proportion of proximal tumors and those of the cardia have increased.[4,14] In general, cancer of the lesser curve is more common than cancer of the greater curve. In almost 10% of cancers, the tumor can involve the entire stomach with malignant cells infiltrating beyond the apparent mass, a condition termed *linitis plastica*. This entity portends an especially poor prognosis, with 5-year survival being very unusual.[4,14]

Early gastric cancer is an entity characterized by tumor confined to the gastric mucosa or submucosa. In Japan, where extensive screening programs exist, early gastric cancer accounts for nearly 50% of all gastric cancers, whereas in the United States it is much less common (<10%).[4,15]

Box 61–1 Risk Factors and Protective Factors Involved in the Pathogenesis of Gastric Cancer

Intestinal Variant

- Arises from precancerous areas (gastric atrophy, metaplasia)
- 5:1 Male-to-female ratio
- Older population
- Dominant histology in areas where stomach cancer is epidemic (environmental cause)
- Declining in incidence

Diffuse Variant

- Does not typically arise from a precancerous area
- Women >> men
- Younger patients
- Higher association in familial occurrence (genetic cause)
- Major histologic type in endemic areas
- Worse overall prognosis

Risk Factors

Because there is such a pronounced difference in the incidence of gastric cancer in different areas of the world, many consider ethnic origin as a potential risk factor for the development of gastric cancer. In fact, the National Cancer Institute has categorized ethnic groups in three risk categories. Japanese, Koreans, Vietnamese, Native Americans, and Hawaiians are at the highest risk; Latino, Chinese, and blacks are at intermediate risk; and Filipinos and whites are at the lowest risk.[2] In addition, immigrants from high-risk to low-risk countries remain at high risk, but subsequent generations have a risk that is native to their new environment, thus suggesting that environmental factors may play a more important role.[5]

Several dietary factors have been found to be associated with an increased risk for gastric cancer (Box 61–2), including diets high in salt, cured and smoked foods, nitrates, and nitrites.[5,16] In contrast, diets high in fruits, vegetables, and antioxidants, as well as vitamins A and C

Box 61–2 Characteristics of Intestinal and Diffuse Variants of Gastric Adenocarcinoma

Acquired Factors
- High-salt diet
- High-nitrate diet
- Smoked/cured food
- Low vitamin A and C
- Well water
- Cigarette smoking
- *Helicobacter pylori*
- Epstein-Barr virus
- Radiation exposure
- Previous gastric surgery
- Coal workers
- Rubber workers

Genetic Factors
- Type A blood
- Pernicious anemia
- Family history
- Hereditary nonpolyposis colorectal cancer
- Li-Fraumeni syndrome

Precursors
- Adenoma
- Atrophic gastritis
- Dysplasia
- Intestinal metaplasia
- Ménétrier's disease

Protective Factors
- Raw vegetables
- Citrus fruits
- Antioxidants—vitamins A and C
- Selenium, zinc, iron
- Green tea

and calcium, have been associated with a decreased risk for gastric cancer.[5,17] Smoking also appears to be a risk factor, but the role of alcohol is less clear.[17,18] In the United States, male gender, African American race, and low socioeconomic status, as well as occupational hazards in the metal-working, mining, and rubber-working industries, are all associated with a higher risk for gastric cancer.[3,4]

Infection with *H. pylori* has also been associated with an increased risk for the development of gastric cancer. In a study by Parsonnet and colleagues, infection with *H. pylori* increased the risk for gastric cancer 3.6-fold as compared with noninfected patients. This increase in risk was present for the development of both intestinal- and diffuse-type cancers, but interestingly, there was no associated increase in risk for the development of GE junction tumors.[19] Similarly, a recent prospective cohort study from Japan showed a statistically significant increase in risk for gastric cancer in those infected with *H. pylori* as compared with controls. This risk was even higher in patients with severe atrophic gastritis, corpus-predominant gastritis, or intestinal metaplasia.[20] Epstein-Barr virus and medical conditions such as pernicious anemia, chronic atrophic gastritis, intestinal metaplasia, gastric villous adenoma, and obesity are also associated with an increased risk for gastric cancer.[3,4] Patients who have undergone partial gastrectomy for benign gastric ulcer disease are likewise at increased risk for gastric cancer in the stomach remnant. This risk for cancer also has a long latency period of about 15 years.[21,22]

Although most gastric cancers occur sporadically, approximately 10% have an inherited component.[23] Patients with hereditary nonpolyposis colon cancer syndrome and polyposis syndromes such as Peutz-Jeghers and familial adenomatous polyposis have an increased risk for the development of gastric cancer.[2] Gastric cancer can also develop in patients with germline mutations in p53 and *BRCA2*.[2] Finally, mutations in the cell adhesion protein E-cadherin lead to an increased risk for hereditary diffuse gastric cancer, and it has been recommended by some that prophylactic gastrectomy be considered in affected kindreds.[24]

Clinical Features

Early gastric cancer seldom produces symptoms, and when it does, they are usually nonspecific. Consequently, nearly 80% to 90% of patients are initially seen with locally advanced or metastatic disease. When early evaluation does take place, most patients complain of weight loss, anorexia, and abdominal pain. Anemia secondary to chronic blood loss is also common, but overt GI bleeding is not unless the tumors are large and ulcerated.[2,4] Dysphagia occurs predominantly in patients with proximal cancers, whereas nausea, vomiting, and symptoms of gastric outlet obstruction are more common with distal tumors that obstruct the lumen. Early satiety is especially prominent in patients with *linitis plastica* because of the nondistensibility of the stomach.[2,4,5]

Patients with early gastric cancer seldom have significant physical findings. Patients with more advanced disease may have a palpable abdominal mass, as well as ascites and cachexia.[2,4,5] Patients with metastatic disease may exhibit Blumer's shelf nodules or Krukenberg tumors (on rectal or pelvic examination), periumbilical lymphadenopathy or peritoneal metastases (Sister Mary Joseph's node), and palpable supraclavicular adenopathy (Virchow's node).[2,4,5]

Diagnosis

Although mass screening, usually by upper endoscopy or double-contrast barium studies, for the detection of gastric cancer is recommended in endemic areas such as Japan, routine screening in Western countries such as the United States is not practical because of the low incidence. Once diagnosed, the National Comprehensive Cancer Network has developed consensus guidelines for the evaluation and staging of patients with suspected gastric cancer.[25] Patients with newly diagnosed gastric cancer should undergo a complete history and physical examination; laboratory studies, including a complete blood count, platelets, and chemistry profile; chest radiography; computed tomography (CT) of the abdomen (and the chest with proximal tumors); CT/ultrasonography of the pelvis in females; and upper endoscopy and biopsy with the goal of a tissue diagnosis and anatomic localization of the tumor.[25] Although double-contrast barium esophagography can still be very helpful in the detection and localization of gastric cancers,[26] it has largely been supplanted by esophagogastroduodenoscopy (EGD) and CT as a *routine* diagnostic modality.[3,27] Serum tumor markers, including carcinoembryonic antigen (CEA), CA 19-9, CA-125, CA 72-4, and β-human chorionic gonadotropin (β-HCG), can be elevated in patients with gastric cancer, although the individual sensitivities are generally low—in the 40% to 50% range.[28-30] The sensitivity of these tumor markers is significantly improved, however, when several are elevated.[31] Furthermore, in patients with known gastric cancer, markedly elevated tumor markers may also signify aggressive disease or tumor burden.

This work-up will usually allow one to classify patients into one of two groups—those with locoregional disease (stage I to III or M0) and those with systemic metastases (stage IV or M1). Patients with locoregional disease are further stratified according to resectability, functional status, and comorbid conditions, with further evaluation often including laparoscopy and endoscopic ultrasound (EUS). Patients with metastatic disease are considered for palliative therapy, depending on their symptoms and functional status.[25]

Upper GI endoscopy (EGD) with biopsy remains the modality of choice for the diagnosis of gastric cancer.[4] Tumor location and the size and extent of mucosal involvement are readily ascertained, provided that the gastric lumen is not obstructed by the tumor. In more than 95% of patients, four to six tissue biopsy specimens and brushings are sufficient to establish the diagnosis, although this can often be difficult in patients with linitis plastica.[27,32] In advanced disease, EGD can be a means to provide palliative therapy, including laser ablation, dilatation, and stenting, although the precise role of these modalities is still evolving.[3,4]

EUS has also become a valuable staging tool for patients with locoregional disease. In experienced hands, EUS can often accurately determine the depth of invasion and nodal status in patients with gastric cancer. The overall accuracy of EUS in staging is about 75% to 80%, but it is significantly operator and institution dependent. Staging of T1 (80%) and T3 (90%) lesions is quite accurate, but EUS is limited in accurately staging T2 lesions (35% to 40%).[32,33] Nodal staging is also less accurate with EUS, but newer techniques have increased its accuracy 50% to 85%.[32,33] EUS-guided fine-needle aspiration for additional tissue diagnosis has also been performed, but experience with this technique is limited and usually confined to large referral centers.

CT of the abdomen and pelvis is also very useful and commonly used in the preoperative work-up of patients with gastric cancer. Contrast-enhanced CT can detect metastases to the liver and peritoneum, local invasion into adjacent structures, and regional and distal lymphadenopathy, as well as ascites suggesting peritoneal disease. The overall accuracy in assessing tumor stage is 66% to 77%, but its accuracy in correctly staging nodal disease is much more variable, from 25% to 86%. CT is also limited in detecting early gastric tumors or small (<5 mm) peritoneal or hepatic metastases.[34,35]

Magnetic resonance imaging (MRI) has also been shown to be as accurate as CT in the staging and detection of gastric cancer. Though expensive and associated with motion artifact, several studies have reported MRI as being slightly superior to CT in the T staging of tumors, with overall T staging accuracy between 73% and 88%.[36] Although MRI may also be superior to CT in N staging (73% versus 65%), both techniques suffer from under-staging. MRI has also been shown to be superior to CT in the detection of liver, bone, and peritoneal metastases.[37,38] Nevertheless, the continued improvement in CT scanning equipment and technique, combined with the expense and relative less availability of routine MRI, continues to result in CT being the preferred staging modality for gastric cancer at most institutions.

Positron emission tomography (PET) with [^{18}F]-fluorodeoxyglucose (FDG) is increasingly being used in the preoperative staging of GI cancers. Though fairly well established in the work-up of colorectal cancer and more recently esophageal cancer, experience with PET scanning in patients with gastric cancer is limited. Preliminary data suggest that PET may be very useful in identifying the primary gastric cancer (90% to 95% sensitivity) and perhaps in monitoring treatment response. Its usefulness in determining N stage is more variable, however (35% to 60% sensitivity), and in general, PET is more accurate in detecting N2- and N3-level nodes because they are further away from the primary tumor.[39,40] Nevertheless, additional studies are needed before PET scanning can be recommended as a *routine* diagnostic and staging tool for gastric cancer.

Diagnostic laparoscopy remains a popular diagnostic modality for the staging of gastric cancer and is especially helpful in detecting small-volume peritoneal and liver metastases. It has been demonstrated in several studies that the sensitivity of laparoscopy in detecting liver metastases is as high as 85% to 96%, though somewhat lower in detecting peritoneal disease. In general, between 23% and 37% of patients with gastric cancer are up-staged by the use of staging laparoscopy and therefore potentially spared a laparotomy.[41-45]

Laparoscopic ultrasound (LUS) has also been used in hope of further improving the capability of laparoscopic exploration.[46] The specific benefit of LUS over high-

quality CT scanning and laparoscopy is unclear, however, and the use of LUS in the staging of gastric cancer remains limited.

Cytologic analysis of peritoneal washings may identify patients with occult carcinomatosis, and many institutions have adopted cytologic analysis of peritoneal washings obtained at laparoscopic staging or even during laparotomy as part of the diagnostic algorithm. Patients with positive findings on peritoneal cytology have a prognosis similar to those with occult visceral metastatic disease.[47,48] Cytologic analysis may result in false-positive results, however, and because some reports fail to confirm the prognostic significance of positive cytologic findings, it has not been universally adapted. At our institution, we use peritoneal cytology as an indication for systemic therapy, but not as an absolute contraindication to resection.

Staging

The most widely used staging system is the American Joint Commission for Cancer TNM system (Box 61–3), which involves standard evaluation of the tumor (T), regional lymph nodes (N), and the presence of metastatic disease (M). The T stage is divided into four levels, depending on the depth of invasion, with recent subdivision of the T2 level into T2a (invasion of the muscularis propria) and T2b (invasion of the subserosa). The N status reflects the number of lymph nodes involved, with the requirement that at least 15 lymph nodes be removed for the patient to be properly staged. Of note, N3 cancers (>15 metastatic lymph nodes) are considered stage IV. Studies from both the United States and Japan have validated the prognostic value of the number of lymph nodes involved in the TNM staging system. The Japanese staging system defines nodal stage by anatomic location and proximity to the tumor. This system is based on 16 nodal stations and is complicated and difficult to use, particularly in institutions where gastrectomies are rarely performed. However, because the TNM staging system has shown prognostic value and is simpler to use, it has largely supplanted the Japanese staging system for gastric cancer in the United States.[4]

Box 61–3 AJCC Staging of Gastric Cancer

Tumor

T1	Tumor invades the lamina propria or submucosa
T2	Tumor invades the muscularis propria (a) or submucosa (b)
T3	Tumor invades through the serosa without invading adjacent structures
T4	Tumor directly invades adjacent structures

Lymph Nodes

N0	0 lymph nodes
N1	1 to 6 positive lymph nodes
N2	7 to 15 positive lymph nodes
N3	>15 positive lymph nodes

Distant Metastases

M0	No distant metastases
M1	Distant metastases

TNM Grouping

Stage IA	T1, N0, M0
Stage IB	T1, N1, M0
	T2a, N0, M0
	T2b, N0, M0
Stage II	T1, N2, M0
	T2a, N1, M0
	T2b, N1, M0
	T3, N0, M0
Stage IIIA	T2a, N2, M0
	T2b, N2, M0
	T3, N1, M0
	T4, N0, M0
Stage IIIB	T3, N2, M0
Stage IV	Any T4 + any N1
	Any N3 or M1

Adapted from American Joint Commission for Cancer Staging Manual, 6th ed. New York, Springer, 2002, pp 114-115.

Surgical Treatment

In the absence of metastatic spread, surgical resection remains the gold standard for the treatment of gastric cancer and the only chance for cure. The types of resection options vary according to the location, stage, and pattern of spread of the tumor, but in general they involve a wide enough resection to achieve negative microscopic margins (R0 resection), as well as en bloc resection of surrounding lymph nodes and any adherent organ or organs if required. In a study by Papachristou and associates, it was found that patients with a 2-cm gross margin had a 30% positive microscopic margin, those with a 4- to 6-cm gross margin had a 10% positive microscopic margin, and no patients with a 6-cm or larger gross margin had a positive microscopic margin.[49] Typically, a gross margin of 5 to 6 cm for intestinal and up to 8 to 10 cm for diffuse-type cancers is recommended, if possible, to ensure adequate negative margins by final histologic analysis.[50,51] Both positive microscopic (R1) and gross (R2) margins are associated with an increased recurrence rate and subsequent decrease in overall survival.[4]

Proximal Tumors

Proximal tumors and tumors of the GE junction represent 35% to 50% of all gastric cancers and require different considerations for resection and reconstruction. In general, these tumors are more advanced at initial evaluation, and therefore curative resection is often

more difficult. The three types of GE junction tumors according to the Siewert classification include type I, or cancer associated with Barrett's esophagus or true esophageal carcinoma growing down to the GE junction; type II, or tumor at the true junction (within 2 cm of the squamocolumnar junction); and type III, or tumors of the subcardial region.[14,52] Patients with type I tumors are best considered for either a gastric pull-up to the neck or an Ivor-Lewis esophagogastrectomy.[4,14,52] Type II or III tumors can be resected by either total gastrectomy or proximal subtotal gastrectomy.[4,14,52] Total gastrectomy has been the traditional procedure of choice and may offer an advantage in that patients are unlikely to have reflux esophagitis after total gastrectomy and Roux-en-Y reconstruction.[53-55] In addition, the lymph nodes along the lesser curve, which is a common site of disease spread, may be more difficult to completely remove by proximal subtotal resection than by total gastrectomy.

An advantage of proximal subtotal gastrectomy is the presence of a gastric reservoir, and it has been reported to have similar mortality rates, hospital stay, and recurrence and survival rates as total gastrectomy in a retrospective study of nearly 100 patients with proximal gastric cancers from Memorial Sloan Kettering Cancer Center.[56] Nevertheless, other series have reported an increase in postoperative morbidity and mortality, as well as a poorer functional outcome and quality of life, in patients undergoing proximal versus total gastrectomy.[53-55] Although it is difficult to make definitive conclusions in the absence of a prospective randomized trial, it does appear that total gastrectomy is associated with a better functional outcome and fewer complications.

Midbody Tumors

Midstomach tumors account for 15% to 30% of all gastric cancers. Unless the tumor is very small, it is very difficult to achieve negative margins and leave enough residual stomach for adequate function. Total gastrectomy is therefore usually required.

Distal Tumors

For tumors of the distal part of the stomach, which represent about 35% of gastric cancers, there remains some controversy regarding the preferred approach, particularly for diffuse-type cancers, but in general, subtotal gastrectomy is performed when possible. A few prospective randomized studies have compared total versus subtotal gastrectomy for distal gastric cancers. A study from France involving 169 patients with antral cancer revealed a higher mortality rate (3.2% versus 1.3%) in patients undergoing total gastrectomy, but similar overall complication rates (34% versus 32%). There was no difference in overall 5-year survival between the two groups.[57] A prospective randomized trial by the Italian Gastrointestinal Tumor Study Group reported similar results. In a study of more than 600 patients with middle and distal cancers randomized to subtotal or total gastrectomy, 5-year survival rates were 65% and 62%, respectively. Patients who underwent subtotal gastrectomy had fewer complications, better nutritional status and overall quality of life, and a shorter hospital stay.[58] Finally, a trial from Hong Kong in which subtotal gastrectomy with D1 lymphadenectomy (see later) was compared with total gastrectomy and D3 resection found no difference in overall survival.[59]

Numerous other studies have also reported higher mortality and morbidity rates for total gastrectomy, along with poorer functional results and quality of life.[60-62] Therefore, for distal and some midbody cancers, distal subtotal gastrectomy with at least a 5- to 6-cm gross margin and adequate remnant stomach should be performed whenever feasible.

Endoscopic Mucosal Resection

If diagnosed at an early stage, it may be possible to obtain a margin-negative resection (R0) without gastrectomy. Analogous to endoscopic polypectomy for colon adenomas, endoscopic mucosal resection (EMR) has been used, particularly in Japan, where nearly 50% of patients have early gastric cancer as a result of extensive screening programs.[3,4,14] Because nodal resection is not performed, this technique is appropriate for cancers with a low likelihood of nodal involvement, including well-differentiated tumors confined entirely to the mucosa, ultrasound T1 and Borrmann's type I (polypoid or fungating cancers), and type IIa and IIb (ulcerated lesions surrounded by elevated borders, but not infiltrating the gastric wall).[63,64] If EMR is performed, the specimen must be carefully examined with serial sectioning to evaluate for invasion of the submucosa. If the submucosa is involved, the chance of nodal involvement is higher and therefore gastric resection should be performed. Though used in Japan, experience in the United States is limited, but in experienced hands, EMR is certainly a suitable alternative for the small subset of patients with very early gastric cancer.

Extent of Lymphadenectomy

The extent of lymph node dissection in surgical resection of gastric cancer remains a very controversial issue despite the existence of several randomized clinical trials. The Japanese Research Society for Gastric Cancer, as well as other Asian counterparts, has advocated radical lymph node dissection, the so-called D2 lymphadenectomy, for the treatment of gastric cancer. Retrospective studies involving thousands of patients from Japan suggest that extended lymphadenectomy can improve survival, particularly in patients with stage II or III disease, with overall reported 5-year survival rates of greater than 60% as compared with 20% in most Western series.[65-68] The prevailing feeling among some Western surgeons, however, is that the presence of lymph node metastases represents a marker for systemic metastases and that radical lymphadenectomy will rarely improve the overall outcome but may instead be associated with a significant increase in morbidity and mortality. Lymphadenectomy is therefore viewed as a staging procedure rather than as part of a curative resection.

The incidence of lymph node involvement varies with the stage of the primary tumor. For tumors limited to the

mucosa, the chance of lymph node involvement is less than 5%; for those involving the submucosa, it is up to 25%; and for stage III and IV, lymph nodes are involved in nearly 90%.[5,65-68] The extent of lymph node dissection is designated by "D." D1 dissection includes only the perigastric lymph nodes, usually within 3 cm of the stomach. D2 dissection also includes nodes along the hepatic, left gastric, celiac, and splenic arteries, as well as those in the splenic hilum, in addition to perigastric nodes farther than 3 cm from the primary tumor, along with omentectomy. D3 lymphadenectomy also includes nodes along the porta hepatis and hepatoduodenal ligament, retropancreatic nodes, and nodes along the base of the mesentery and periaortic regions (Fig. 61–1). For an absolute curative resection, it is often recommended that the level of lymph node resection be one level greater than the highest level of involved lymph nodes.[4,14] For grossly uninvolved nodes, Japanese surgeons typically advocate a standard D2 resection for most gastric cancers and have reported mortality rates of less than 2%, as well as improved stage-for-stage overall survival when retrospectively compared with lesser resections.[65-68]

Four prospective randomized trials have been conducted in an attempt to clarify the extent of lymphadenectomy most appropriate for gastric cancer (Table 61–1). In a small study from South Africa, only 43 of 400 evaluated patients were eligible for randomization. There was no benefit in overall survival, whereas operative time, blood loss, and hospital stay were all increased in the D2 group.[69] In a large trial started in 1989 by the Medical Research Council (MRC) in the United Kingdom, 400 patients (out of 737 who registered) were randomized to D1 versus D2 resection at the time of laparotomy. Perioperative mortality (13% versus 6.5%, $P < .04$) and morbidity (46% versus 28%, $P < .001$) were both significantly higher in the D2 group, whereas overall 5-year survival rates were similar (33% versus 35%).[70] Much of the increase in mortality and morbidity in this trial was associated with the routine use of distal pancreatectomy and splenectomy in the D2 group, and it is unclear how a D2 resection without distal pancreatectomy/splenectomy would compare with a D1 resection. Furthermore, the average number of nodes resected was 13 in the D1 group and 17 in the D2 group, although the Japanese advocate the removal of at least 26 nodes for an adequate D2 resection.

Similarly, in the Dutch Gastric Cancer Group Study, approximately 1000 patients were randomized to D1 versus D2 resection.[71] In an attempt to monitor the quality of surgery, Professor Sasako from the National Cancer Center in Tokyo trained a group of Dutch surgeons, who subsequently supervised the resection techniques at the 80 participating centers. An R0 resection was achieved in 711 patients (380 in D1; 331 in D2), who

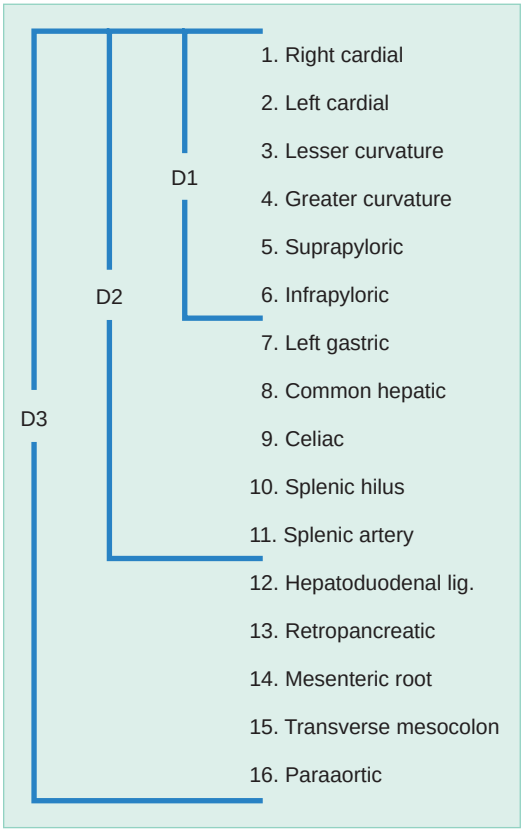

Figure 61–1. Lymph nodes removed in D1 versus D2 versus D3 lymphadenectomy during resection of gastric cancer.

Table 61–1 Prospective Randomized Trials of D1 Versus D2 Gastric Resection

	D1				D2			
Study	***N***	**Morbidity**	**Mortality**	**5-yr Survival**	***N***	**Morbidity**	**Mortality**	**5-yr Survival**
Dent, 1988[69]	22	22%	0%	69%	21	43%	0%	67%
Robertson, 1994[59]	25	0%	0%	1511 days	30	59%*	3%	922 days
Cuschieri, 1999 (MRC)[70]	200	28%	6.5%	35%	200	46%*	13%*	33%
Bonenkamp, 1999 (Dutch)[71]	380	25%	4%	42%	331	43%*	10%*	47%

*$P < .05$ versus the D1 group.
MRC, Medical Research Council.

were therefore eligible for analysis in this trial. Similar to the British trial, perioperative morbidity and mortality were significantly higher in the D2 group (43% and 10% versus 25% and 4%, respectively, $P = .004$ for mortality, $P < .001$ for morbidity).[71,72] Moreover, there was no difference in overall 5-year survival (47% for D2, 42% for D1).[71] Several subsequent analyses and comments have been published regarding this trial. Perhaps most significant, despite having supervision, noncompliance (failure to remove the required number of lymph nodes) occurred in 51% of patients in the D2 group and 36% of patients in the D1 group. Similarly, contamination (removing additional unnecessary lymph nodes) occurred in 6% of the D1 group and 7% of the D2 group.[14,73] Because over half the patients in the D2 resection group did not undergo an adequate D2 resection, it is very difficult to make definite conclusions from this trial. Nevertheless, subsequent subset analysis of this trial revealed that patients with stage II and IIIA did appear to have a significant survival advantage. In addition, there was a significant decrease in local recurrence (41% versus 29%, $P = 0.02$) in the D2 group.[71]

In a report from Hong Kong, 55 patients were randomized to a D1 resection with subtotal gastrectomy or a D3 resection with total gastrectomy, distal pancreatectomy, and splenectomy. Operative time and hospital stay were longer in the D3 group, whereas median survival was significantly less. There was one death, which occurred in the D3 group.[59] The Japanese Cooperative Oncology Group, however, recently reported preliminary results of the JCOG 9501 trial in which D2 versus D3 resection was compared. More than 500 patients were randomized, and there was no difference in major complications between the groups. Overall mortality was less than 1% (two patients in each group).[74] Although recurrence and survival data are forthcoming, this study suggested that radical gastric resection, including extended lymphadenectomy, can be performed safely in experienced hands.

Several nonrandomized prospective trials in the United States and Europe from specialized centers have suggested an increase in survival with a D2 resection that approximates the results in Japan, particularly for stage II and III disease.[75-79] When the pancreas and spleen are preserved, the overall morbidity and mortality approach that of a more limited dissection.[75-79] One of the main problems with many of these studies is the continued noncompliance with D2 resection guidelines. Analysis of the INT-0116 adjuvant chemotherapy trial[80] (see later) in which a D2 resection was recommended but not required showed that only 10% of the patients actually underwent a true D2 resection, 36% underwent a D1 resection, and 54% underwent a D0 resection, as defined by Japanese staging criteria.[80] Although this may be the fault of surgical technique, the quality of pathologic evaluation of the specimen and lymph nodes is another potential concern.

In summary, although randomized prospective data on the extent of lymphadenectomy exist, controversy persists. Based on the available data, gastrectomy with a D2 resection, but without routine splenectomy/pancreatectomy, should be performed whenever possible, particularly for patients with stage II or III disease. Furthermore, in view of the morbidity and mortality data, these resections should also be performed at specialized centers whenever possible.

Reconstruction After Gastrectomy

After distal subtotal gastrectomy, several options exist for reconstruction, including Billroth I gastroduodenostomy, Billroth II gastrojejunostomy (either antecolic or retrocolic), and Roux-en-Y gastrojejunostomy (also either antecolic or retrocolic). All three methods have their advantages and disadvantages, and there is support in the literature for all of them.[54,81-89] A Billroth I reconstruction is often difficult to perform without creating undue tension on the anastomosis. A Billroth II reconstruction, with or without a Braun enteroenterostomy, is another option, particularly when a large remnant of stomach remains. In general, however, Roux-en-Y gastrojejunostomy is simpler and useful with a small stomach remnant and probably better in controlling dumping and bile reflux gastritis. In the absence of definite prospective randomized data, surgeon preference often dictates the reconstruction.

After total gastrectomy, options for reconstruction include a standard Roux-en-Y esophagojejunostomy, construction of a pouch, and jejunal interposition. Again, although there is no clear consensus on the preferred method of reconstruction,[54,81-89] Roux-en-Y esophagojejunostomy has the advantage of being simpler to construct and is usually associated with the least morbidity while providing generally equivalent functional outcome. The anastomosis is typically performed in an end of esophagus–to–side of jejunum manner. It can be done in a stapled fashion (usually circular, although linear has also been described) or hand sewn in one or two layers. Although leak rates are generally equivalent, there may be a higher rate of strictures and more difficulty in dilating strictures with a circular stapled technique.[4,14]

When constructing an esophagojejunostomy, one may use a jejunal pouch to provide for a neostomach reservoir. The pouch is constructed similar to an ileal J-pouch, with a linear stapler used to fashion the pouch. In addition, many surgeons prefer to leave a lip of undivided intestine at the end of the linear staple line to optimize blood supply to the esophageal anastomosis. The esophagojejunostomy is performed at the antimesenteric bend of the pouch with either the staple or hand-sewn technique. When constructing the pouch it is important that it not be longer than 15 cm to prevent stasis and ineffective clearing.[4,14]

Prognostic Factors and Patterns of Failure

The ability to achieve resection with a negative margin (R0) is the most important prognostic factor and determinant of survival, as has been shown in multiple studies throughout the world.[10,12,79,90,91] The pathologic stage also has valuable prognostic implications inasmuch as a higher T stage or N stage is associated with a higher chance of relapse and poorer overall survival.[12,79,92] As

discussed earlier, location of the tumor is also related to prognosis, with proximal gastric cancers more likely to recur than distal cancers.

In patients who undergo curative resection, between 25% and 80% of cancers will recur locoregionally.[65,92,93] This large disagreement in the literature suggests that there are many factors governing recurrence, such as the adequacy of surgical and lymph node resection and tumor characteristics, including location, stage, and aggressiveness.

Adjuvant Therapy

Survival rates after resection for localized, node-negative gastric cancer approach 75% to 80% with surgery alone.[10,92,94] Unfortunately, however, most patients in the United States have node-positive disease, and survival rates drop to 10% to 30% with high local and distant recurrence rates.[10,92,94] This has generated great interest in developing effective adjuvant strategies to help decrease recurrence rates and provide long-term survival. Though initially somewhat disappointing and conflicting, recent studies using combined-modality therapy have shown significant improvement in survival rates in patients with gastric cancer. A continued problem with many studies is the inconsistent population groups and stages of gastric cancer, as well as the different surgical techniques, particularly the extent of lymph node dissection, as discussed earlier.

Adjuvant Chemotherapy

Numerous systemic chemotherapy trials have been published over the past few decades, with overall disappointing results and conclusions. Most of these trials were underpowered or poorly designed and have resulted in nonreproducible findings. Large meta-analyses of adjuvant chemotherapy trials have suggested only minimal benefit and in particular just in subgroups of node-positive or Asian patients.[95,96] Most single agents have response rates in the 15% to 20% range, and although some small trials have shown a survival benefit, it has not been reproducible.[14,92] Combination chemotherapy with agents such as 5-fluorouracil (5-FU), epirubicin, mitomycin, and methyl-CCNU have been associated with somewhat better response rates; however, in larger prospective trials, a clear benefit of combination chemotherapy has not been reproduced.[14,92] Several meta-analyses of the randomized clinical trials of adjuvant chemotherapy have also been published, and even though some have suggested a small survival benefit,[95,97,98] several others, as well as the majority of individual studies, failed to show a significant survival advantage.[2,14,92] In light of these nonconclusive results, routine adjuvant chemotherapy should be used only as part of a clinical trial.

Adjuvant Chemoradiotherapy

The combination of chemotherapy and radiotherapy has been extensively studied in the treatment of many GI cancers, including gastric cancer. Although early trials primarily using 5-FU and radiotherapy showed a small benefit,[99-101] it was very difficult to draw definitive conclusions because of their small patient numbers, lack of standardization of surgical technique, and heterogeneous populations. The largest gastric cancer adjuvant trial ever conducted in North America was recently published and updated. The Gastrointestinal Cancer Intergroup Trial (INT-0116)[80] randomized 556 eligible patients with stage IB to IV (M0) gastric cancer, who underwent margin-negative (R0) resection, to surgery alone or to surgery followed by bolus 5-FU/leucovorin (LV), followed by 45 Gy radiotherapy, followed by additional 5-FU/LV. Overall, 85% of patients were node positive and two thirds had T3 or T4 lesions. With more than 6 years of median follow-up, median disease-free survival was significantly improved in the adjuvant chemoradiotherapy group (30 versus 19 months, $P < .001$).[102] Overall median survival was also significantly improved in the adjuvant chemoradiotherapy group (35 versus 28 months, $P = .01$).[102] Given these results, postoperative chemoradiotherapy with this regimen has essentially become the standard of care for patients who have undergone curative resection for gastric cancer in the United States. Nevertheless, critics of the Intergroup trial point out that although a D2 resection was recommended, only 10% of patients underwent a D2 resection whereas 36% underwent a D1 resection and an alarming 54% underwent a *D0* resection.[80,92] Therefore, some believe that adjuvant therapy may have made up only for poor and inadequate surgical resection. For example, a randomized trial from Japan of 252 patients who underwent D2 or greater resection versus resection plus adjuvant mitomycin, 5-FU, and cytarabine failed to show any significant survival advantage for chemotherapy.[103] In this study it was noted that 98% of the patients underwent D2 or greater resection.[103]

In addition, the chemotherapy used in the Intergroup trial was bolus 5-FU, which was standard in the late 1980s when the trial was designed. Bolus 5-FU as a single agent has low response rates in gastric cancer, however, and newer agents and combinations, including the epirubicin, cisplatin, and 5-FU (ECF) regimen as discussed later,[104] have shown higher response rates and will need to be further studied in the adjuvant setting.

Adjuvant Intraperitoneal Therapy

Because a significant proportion of postoperative recurrences in patients who undergo resection for gastric cancer occur in the peritoneal cavity, intraperitoneal (IP) therapy has been an attractive option. An initial randomized trial from Japan comparing IP mitomycin C with no postoperative therapy showed a significant survival advantage of IP treatment.[14] Subsequent studies, both retrospective and randomized, failed to show a survival benefit of IP mitomycin C, however, and actually suggested a significant increase in postoperative complications and mortality.[105] A study from Korea randomized 248 patients to IP mitomycin and 5-FU versus observation. Morbidity and mortality were higher in the IP group, and although overall survival was not different, subset analysis did show a benefit for stage II and III

disease.[106] Another randomized trial used IP cisplatin in both the adjuvant setting and patients with peritoneal carcinomatosis but failed to show a survival advantage.[3,14]

Similarly, continuous hyperthermic peritoneal perfusion (CHPP) has been used in patients with gastric cancer in both the adjuvant and palliative setting. This method relies on the synergistic effect of cytotoxic chemotherapy and hyperthermia. Several studies have reported on CHPP with mitomycin C after resection of gastric cancer. Although many of these trials are small, some of them have shown a survival advantage of CHPP versus surgery alone.[3,14]

Nearly all of these studies have compared IP or CHPP therapy with surgery alone rather than standard adjuvant therapy as discussed earlier. Future studies and newer agents will need to be compared against these systemic regimens before definitive conclusions can be made.

Neoadjuvant Therapy

Neoadjuvant or preoperative therapy has several theoretical advantages and has increasingly been used for the treatment of a variety of GI cancers. These advantages include improved patient tolerance, more effective delivery (increased oxygenation in the tumor bed), removal of treated tissue, early initiation of systemic therapy (in the case of preoperative chemotherapy), potential down-sizing of the primary tumor, ability to achieve better margins at resection, and evaluation of response to therapy, thereby adding to prognostic information and assisting in the planning of future therapy.

Neoadjuvant Radiotherapy

Though seldom used without systemic chemotherapy, preoperative radiotherapy has shown promise in a few reports. A large randomized trial from China reported on 360 patients who underwent preoperative radiotherapy versus surgical resection alone. The radiotherapy group had a higher overall resection rate (89% versus 79%, $P < .01$) and 10-year survival rate (20% versus 13%, $P = .009$).[107] Tumor down-sizing and nodal down-staging were also noted, and there was no increase in operative mortality with the use of preoperative radiotherapy.[107] A smaller trial randomized 78 patients to preoperative radiotherapy, surgery and intraoperative radiotherapy, or surgery alone.[108] Patients with node-positive disease and T4 lesions had a significant survival advantage with the radiotherapy regimen, and again there was no increase in perioperative mortality or morbidity.[108]

Neoadjuvant Chemotherapy

Several phase II studies investigating systemic chemotherapy in the neoadjuvant setting have been reported and in general have suggested that preoperative chemotherapy can be given with acceptable toxicity and no increase in operative complications or mortality.[3,14,92] Furthermore, overall survival in these trials was generally improved when compared with historical controls. In addition, it has been suggested in several trials that the response to chemotherapy was a significant predictor of survival.[3,14,92]

The preliminary results of a small randomized trial of 107 patients randomized to receive neoadjuvant etoposide, cisplatin, and 5-FU or surgery alone were reported in 1996.[109] No significant differences in resectability rate or overall survival were noted.[109] More recently, preliminary results of the MAGIC trial from the United Kingdom were reported.[104] In this randomized controlled trial, 503 patients with adenocarcinoma of the stomach or lower esophagus were randomized to preoperative ECF, followed by surgery and postoperative ECF, versus surgery alone. No recommendation was given regarding the extent of lymphadenectomy because the results of the MRC and Dutch trials were unavailable at the start of this trial. The primary outcome was overall survival, and secondary outcomes were progression-free survival, surgical resectability, and quality of life. Patients in both groups were well matched in age, gender, performance status, site, and pretreatment size of tumor. Operative complications, mortality, and length of hospital stay were similar in both groups. A higher proportion of patients in the chemotherapy group underwent curative resection (79% versus 69%, $P = .018$) and were noted to have significantly smaller tumors at surgery, as well as significantly lower T and N stages.[104] Progression-free survival at 2 years was significantly improved in the ECF group (45% versus 30%, $P = .002$), but the improvement in overall survival did not quite reach statistical significance (48% versus 40%, $P = .063$; hazard ratio, 0.80; 95% confidence interval, 0.63 to 1.01).[104] Although these results are preliminary and a longer follow-up period is needed, they strongly suggest a benefit of perioperative chemotherapy with the ECF regimen in patients with operable gastric cancer.

Neoadjuvant Chemoradiotherapy

On the basis of the results of neoadjuvant chemoradiotherapy in the treatment of other cancers, including esophageal and rectal carcinoma, multimodality regimens involving preoperative chemotherapy and radiotherapy are currently under study. In a pilot phase II study at the M.D. Anderson Cancer Center, 24 patients were treated with 45 Gy of external beam radiotherapy with concurrent infusions of 5-FU.[110] Surgery was carried out 4 to 6 weeks later in 19 (79%) of the patients and consisted of D2 lymphadenectomy and intraoperative radiotherapy (10 Gy). Two (11%) patients had a complete pathologic response and 12 (63%) were noted to have a major treatment effect.[110] Another trial from M.D. Anderson involved 34 patients who were treated with 5-FU, folinic acid, and cisplatin, followed by 5-FU–potentiated radiotherapy (45 Gy).[111] Surgical resection after this preoperative regimen was safe, with a complete pathologic response in 30% and a partial pathologic response in 24%.[111] A phase II trial by the Radiation Therapy Oncology Group (RTOG 9904) investigated induction chemotherapy with cisplatin, 5-FU, and folinic acid, followed by radiotherapy with concomitant 5-FU in

the preoperative setting and then surgical resection.[92] The trial is now closed, but the results are pending at this time. Because many of these trials are small and nonrandomized in nature, however, it is difficult to make definitive recommendations until larger prospective randomized trials are performed, and thus patients with resectable disease should receive preoperative chemoradiation only as part of a clinical trial. Nevertheless, in view of these promising preliminary results, patients with locally advanced gastric cancer should also be considered for preoperative chemoradiotherapy in an attempt to down-size the tumor—although this remains unproved.

Management of Advanced Disease

More than 50% of patients with gastric cancer have unresectable or metastatic disease at initial evaluation, and therefore appropriate use of palliative techniques is important. Surgical palliation may include resection alone or in combination with endoscopic, percutaneous, or radiotherapeutic interventions. Other options for palliation include chemotherapy and radiotherapy. In the absence of prospective trials, the optimal choice for palliation is largely patient dependent.

Surgery for Palliation

Because survival in patients with advanced gastric cancer is so short, any attempt at palliative resection should not only provide symptomatic relief but also be associated with minimal morbidity and mortality. Although no randomized trials have been performed, several retrospective studies have been published. A study by Ekbom and Gleysteen compared palliative resection with intestinal bypass in 75 patients with advanced gastric cancer.[112] Operative mortality was similar, and 80% of patients had relief of their symptoms for a mean of 6 months in the bypass group, whereas 88% of patients experienced relief of symptoms for a mean of 14.6 months in the resection group.[112] Although patients with palliative resection appeared to have a longer duration of relief, this was not a randomized trial and selection bias may have accounted for the differences. In a similar report of 51 patients with advanced gastric cancer, palliative resection resulted in a higher percentage of patients having relief of symptoms and for a longer duration than with palliative bypass.[113] In a large review of nearly 250 patients from Italy who underwent exploratory laparotomy alone, GI bypass, or palliative resection, resection was associated with longer survival in patients with both local (8 versus 4.4 months) and distant (8 versus 3 months) spread of disease.[114]

Although these data are retrospective, they do suggest that for select patients with symptomatic advanced gastric cancer, palliative resection may offer relief of symptoms for a majority of patients with acceptable morbidity and mortality. The treatment options may also largely depend on the extent of resection required for adequate palliation; for example, total gastrectomy with possible resection of adjacent organs is not usually indicated for palliation of unresectable disease.

Endoscopic Palliation

In patients who are not good candidates for palliative resection but have symptoms of obstruction, endoscopic palliative techniques may be useful, including placement of metal expandable stents and laser recanalization. Although very limited prospective randomized data comparing endoscopic techniques and surgical bypass or resection are available, several studies suggest that both techniques are safe and can lead to some relief in many patients.[115,116] Endoscopic stenting may result in similar short-term relief of obstruction as surgical bypass and is certainly a less invasive option.[115] Long-term data, however, are unavailable. Laser therapy can also be used as a complement to stenting and has been shown to provide short-term relief of obstruction in some patients.[116,117] Although none of these techniques would be expected to improve survival, they are good alternatives in patients who are not candidates for palliative surgery but are suffering from signs of obstruction. After relief of obstruction, many of these patients can later receive palliative chemotherapy. Generally speaking, patients with peritoneal disease, hepatic or nodal metastases, or other poor prognostic factors will probably benefit most from endoscopic palliation, including laser recanalization, dilatation, and stent placement. For patients with a better prognosis and excellent performance status, consideration can be given to surgical resection if it can be accomplished with minimal morbidity.

Palliative Chemotherapy

Similar to the results of adjuvant therapy for resected gastric cancer, systemic chemotherapy for advanced gastric cancer has been demonstrated to be beneficial. Several randomized trials, albeit small, have shown that patients receiving systemic chemotherapy have a longer median survival (9 to 11 months versus 3 to 5 months) and better 1- and 2-year survival rates (35% to 40% versus 10% and 6% to 10% versus 0%, respectively) than with best supportive care alone.[3,14] More recently, combination chemotherapy with agents such as cisplatin, paclitaxel, and irinotecan have shown similar response rates and median survival times in several phase II studies.[118-121] Certainly, multiagent chemotherapy should be offered to all patients with advanced disease who have reasonable performance status.

Palliative Radiotherapy

Experience with radiotherapy in patients with advanced gastric cancer is much more limited. Although its use seems to be fairly effective in controlling symptoms such as bleeding and pain, most patients have diffuse metastatic disease, and the use of radiotherapy alone would not be expected to provide much increase in overall survival.[3,14] Nevertheless, in patients with advanced local disease precluding resection but with no distant metastases, radiotherapy in combination with chemotherapy could be considered, preferably as part of a clinical trial.

Summary

Although gastric cancer is decreasing overall worldwide, patterns have shifted toward more aggressive variants of the disease, including cancers of the proximal part of the stomach and GE junction. Aggressive surgical resection, including adjacent organs and extended lymphadenectomy, can lead to prolonged survival and is safe in experienced hands. Most patients in the United States, however, have advanced disease at initial evaluation. The use of adjuvant and neoadjuvant chemotherapy and chemoradiotherapy regimens has resulted in significant prolongation of survival in resected patients and has essentially become the standard of care in the United States, although continued prospective trials are needed in light of newer promising agents. For patients with advanced disease, control of symptoms is paramount, and options include surgical and endoscopic therapy, as well as a host of palliative chemotherapy and chemoradiotherapy regimens, again often as part of a clinical trial.

ADENOCARCINOMA OF THE DUODENUM AND SMALL INTESTINE

Small intestinal tumors are rare, and although the small bowel accounts for 80% of intestinal length, they make up only about 10% of GI tumors.[122,123] It is estimated that approximately 5000 cases of small bowel carcinoma are diagnosed per year in the United States.[124] Approximately two thirds of small bowel tumors are malignant (less than 5% of all GI malignancies), and nearly half of these are adenocarcinomas, the rest being carcinoid and GI stromal tumors and lymphomas.[123,125,126] Of the adenocarcinomas, approximately 40% occur in the duodenum, including the periampullary region, and the rest are distributed throughout the rest of the small intestine.[123,127-129] There is a slight male preponderance, and even though the incidence is low, there is a steady increase after the age of 30 years.[129]

Pathogenesis and Risk Factors

In general, small bowel malignancies are about 40 to 60 times less common than malignancies of the large intestine despite the increased length and absorptive capacity.[123,124] Several theories and hypotheses have been proposed to explain why such may be the case. The bacterial flora and count in the small bowel are significantly less active than in the colon,[130] transit time is faster, and the volume of enteric contents is much greater.[123] In addition, the small bowel contains many digestive enzymes, particularly in the proximal portion, which may help degrade potential carcinogens.[131,132] The presence of lymphatic tissue, especially Peyer's patches in the distal ileum, may also help provide immune surveillance against potential tumorigenesis.[123,125]

Because of overall duodenal length, adenocarcinoma of the duodenum, particularly the periampullary region, is much more common than that of the remaining small intestine. This may be due to increased susceptibility of the duodenal or ampullary mucosa to malignant transformation or be secondary to increased exposure to biliary and pancreatic secretions or ingested carcinogens and toxins, similar to pancreatic cancer.[125,133,134]

A few studies have reported some potential risk factors for the development of small bowel adenocarcinoma. One study reported on 430 patients with small bowel cancer and more than 900 patients who had died of other causes and found that increased consumption of red meat and salt-cured smoked foods was associated with an increased incidence, similar to other GI cancers.[135] Interestingly, however, smoking and alcohol use were not. Similarly, increased consumption of fat has also been reported as a risk factor, similar to colon cancer.[136] Small bowel cancers are also more likely (seven to nine times more likely) in patients with a history of colon cancer, and the converse is also true—patients with a history of small bowel carcinoma are at a higher risk for colon cancer.[137]

Small bowel adenocarcinomas are also thought to follow the adenoma-carcinoma sequence as in other GI organs. Studies have shown that adenomatous epithelium exists in many specimens of small bowel cancer. In addition, patients with Crohn's disease, celiac sprue, familial adenomatous polyposis, and cystic fibrosis are also at increased risk for the development of small bowel adenocarcinoma.[126,137,138]

Duodenal Adenocarcinoma

Approximately 50% of all small bowel adenocarcinomas occur in the duodenum, with 15% in the proximal, 40% in the middle, and 45% in the distal duodenum.[125,139,140] The most common initial symptoms include abdominal pain, nausea, and vomiting related to duodenal obstruction[125,140]; anemia from bleeding tumors; and biliary obstruction with ampullary lesions.[125,139,141] The diagnosis is usually made by upper endoscopy with biopsy or an upper GI study.[123,125]

Treatment of duodenal carcinoma is surgical resection, the details of which depend on the site of the tumor. In general, however, resectability rates for duodenal carcinoma are significantly higher than those for other upper GI cancers such as pancreatic, biliary, gastric, and esophageal cancer.[125,126] The overall 5-year survival rate is generally in the 25% to 60% range, also much better than that of other upper GI cancers.[125,126] For patients with cancer of the first or second portion of the duodenum, pancreaticoduodenectomy or a Whipple procedure is usually necessary to completely resect the cancer. For patients with tumors in the third or fourth portions of the duodenum, segmental duodenal resection with primary anastomosis is often possible, provided that negative proximal margins can be obtained. In either case, regional lymphadenectomy is recommended because up to 70% of patients may have nodal involvement and many of these patients survive 5 years.[125,139-141]

Adjuvant therapy after resection for duodenal cancer has not been well studied, although many patients are treated with 5-FU–based therapy, which is the standard

for most GI cancers. Nevertheless, there is no clear evidence that chemotherapy prolongs survival,[126] and investigational therapies and participation in clinical trials using novel agents are often recommended. For patients with unresectable disease, palliative chemotherapy does appear to provide some survival advantage over best supportive care, and radiation therapy may help decrease ongoing blood loss.[125,126] Many patients with advanced cancer of the duodenum will become obstructed and therefore require palliative GI bypass or endoscopically placed stents.

Jejunal and Ileal Carcinoma

Jejunal and ileal carcinomas usually cause symptoms of obstruction or occult GI bleeding.[126,142,143] Because these lesions are located beyond the reach of a standard upper endoscopy scope, CT scanning and a small bowel series are usually the modes of diagnosis, but neither examination is very specific.[123,126] Many are found on exploration for obstruction or other GI symptoms. A majority (70% to 100%) of distal small bowel cancers are resectable,[126,143,144] although regional lymph nodes are usually involved.[126,145] The resection strategy is similar to that for colon cancer, specifically, obtaining negative proximal and distal margins and resection of the involved mesentery and corresponding lymph nodes.

Survival after resection largely depends on the histologic grade and stage of the disease, particularly lymph node status. Patients with a margin-negative resection and no nodal involvement have 5-year survival rates as high as 50% to 70%, whereas patients with nodal involvement have 5-year survival rates in the 10% to 15% range.[142,144] Most patients unfortunately have advanced disease at initial evaluation, and survival rates are generally in the 20% to 30% range.[126,142] Experience with adjuvant therapy is even more limited for jejunal and ileal cancers than for duodenal cancers, although 5-FU–based regimens are generally used. Radiation therapy, however, is not usually feasible because of the mobile nature of the small bowel.

For patients with metastatic disease, surgical resection or bypass is often required to relieve symptoms of obstruction and to provide enteral feeding if possible.

Summary

Cancers of the small bowel are rare, though more common in the duodenum. Although the diagnosis of duodenal cancer is usually made by EGD, diagnosis of more distal small bowel cancer is often more difficult. Surgical resection with negative margins plus resection of adjacent lymph nodes remains the only curative option and may also provide relief from symptoms, including bleeding and obstruction. Experience with adjuvant chemotherapy and chemoradiotherapy is very limited, although they are usually administered to appropriate patients.

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Chapter

62

Motility Disorders of the Stomach and Small Intestine

John E. Meilahn

GASTRIC MOTILITY

Normal gastric emptying reflects a coordinated function of the gastric fundus, corpus, antrum, pylorus, and duodenum. Proper gastric emptying thus involves a sequence of events involving all of these structures. Eating a meal causes receptive relaxation of the fundus for gastric storage. Subsequent fundic contraction is important for emptying liquids from the stomach. The gastric pacemaker is located in the body along the greater curvature and stimulates filling and mixing of food in the corpus and antrum. Food is sequentially mixed to and fro in the antrum against pyloric resistance in the process of trituration until food particles are ground down. Subsequent antral peristalsis, at the rate of three per minute, with associated pyloric relaxation allows small particles and liquids to pass to the duodenum. Therefore, the stomach may be thought of as three regions of motility that must act in a coordinated fashion to produce acceptable emptying of the stomach: the fundus, with relaxation and subsequent contraction; the body, with filling and mixing; and the antropyloroduodenal complex, with trituration and emptying into the duodenum as the pyloric sphincter opens.

Symptoms of abnormal gastric motility are nonspecific and generally include nausea, vomiting, epigastric fullness, postprandial bloating, and heartburn. The list of differential diagnoses includes gastroparesis, rapid gastric emptying as in dumping syndrome, functional dyspepsia with impaired fundic distention, ulcer, cancer, gastroesophageal reflux disease, rumination syndrome, cyclic vomiting syndrome, bulimia, and superior mesenteric artery (SMA) syndrome. Organic causes may be diagnosed with a combination of upper endoscopy, enteroscopy and enteroclysis, upper gastrointestinal (GI) series, or upper GI series with small bowel follow-through. If these studies are inconclusive, further testing along with gastroenterologic consultation is necessary to differentiate between nonorganic causes.

Gastroparesis

Gastroparesis is delayed gastric emptying in the absence of specific organic causes, such as stricture, ulcer, tumor, SMA syndrome, or mechanical obstruction, or of nonorganic causes, such as functional dyspepsia, rumination syndrome, cyclic vomiting syndrome, or bulimia/anorexia nervosa. Abnormal peristaltic contractile activity and abnormal electrical slow waves are usually present. Females are most often affected (about 80% female, 20% male), with the average age at onset of symptoms being about 34 years. Causes are evenly divided between diabetes and idiopathic (about 28% each), with other causes including postviral, postsurgical (especially with intended or inadvertent vagotomy), Parkinson's disease, scleroderma, and pseudo-obstruction. The predominant symptoms are nausea and vomiting with abdominal bloating and early satiety. Epigastric abdominal pain may be present in about half the patients, and some of them have become dependent on narcotics. Abdominal pain, in general, is not well treated by gastric electrical stimulation or by prokinetic drugs.[1]

The diagnosis of gastroparesis is usually made by the gastroenterologist after extensive testing to rule out other causes. Evaluation of gastric emptying by scintigraphy may be diagnostic of gastroparesis, with more than 50% of a solid meal being retained 2 hours after ingestion or more than 10% of a solid meal being retained at 4 hours. Liquid emptying, although quantifiable, is less accurate in the diagnosis of gastroparesis because liquids may empty normally even with an abnormal solid emptying scan. Either a ^{99m}Tc–sulfur colloid–labeled egg sandwich or an Eggbeaters meal is used as a test meal for the solid emptying scan. Though not commonly used in clinical settings, breath testing for gastroparesis can be performed with ^{13}C-labeled octanoate in a solid meal, which is absorbed in the small bowel after gastric emptying, metabolized there to $^{13}CO_2$, and then removed by respiration.[1]

General principles for the treatment of gastroparesis are to correct fluid and electrolyte abnormalities, as well as nutritional deficiencies, identify and treat any underlying causes, and suppress or eliminate symptoms such as nausea or vomiting. Diets may be changed toward softer solid foods and more toward liquid supplements, with smaller, more frequent meals. Total parenteral nutrition (TPN) may be necessary to provide the daily caloric intake for maintenance of body weight. In a diabetic patient, tight glucose control should be achieved because hyperglycemia may worsen gastroparetic symptoms. Hyperglycemia can impair both antral contractions and antropyloric coordination. The mainstay of medical treatment is the use of both antiemetic and prokinetic medications.[1]

Antiemetic agents useful in treating gastroparesis include prokinetic agents with antiemetic properties, such as metoclopramide (Reglan) or domperidone (Motilium). Phenothiazine derivatives, which antagonize dopamine receptors in the area postrema, include prochlorperazine (Compazine) and trimethobenzamide (Tigan). Antihistamines with H_1–receptor antagonist properties include diphenhydramine (Benadryl), promethazine, and meclizine (Antivert). Antiserotoninergics, which antagonize 5-hydroxytryptamine ($5\text{-}HT_3$) receptors, include ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet). Other agents include scopolamine, an anticholinergic, and aprepitant (Emend), a substance P/neurokinin-1 receptor antagonist.[1]

Not many effective prokinetic agents are currently available. Metoclopramide (Reglan) is the only Food and Drug Administration (FDA)-approved agent for gastroparesis, but it produces central nervous system side effects in 10% to 20% of patients. Cisapride (Propulsid) was approved only for the treatment of heartburn and was taken off the market in 2000 because of prolongation of the QT interval. Although domperidone (Motilium) has both prokinetic and antiemetic properties, it has not been approved by the FDA and is available only outside the United States. Erythromycin is useful as a motilin agonist, but it may have GI side effects of nausea, vomiting, and abdominal pain and is known to have decreasing effect as a result of tachyphylaxis.

Botulinum Toxin Injection

Because pyloric sphincter opening is the final step in gastric emptying, pyloric relaxation via injection of botulinum toxin A (Botox) into the pyloric sphincter may improve symptoms in those with idiopathic or diabetic gastroparesis. Botulinum toxin inhibits cholinergic neuromuscular transmission and has been used in multiple areas of the GI tract, including the lower esophageal sphincter to treat achalasia[2] and the anal sphincter to treat anal fissures. Multiple injections of botulinum toxin are placed circumferentially at endoscopy into the prepyloric area (within 2 cm of the pyloric channel). If there is a beneficial effect from injection, the process may be repeated at several-month intervals.

In a retrospective study at Temple University Hospital, 63 patients (53 females and 10 males with a mean age of 42 years) with gastroparesis were injected with botulinum toxin A.[3] Major symptoms were vomiting, nausea, and abdominal pain. Less than 10% had early satiety, decreased appetite, bloating, or weight loss as their major symptoms. None had a previous injection, and all had at least a 4-week follow-up after treatment (mean length of 9.3 months with a range of 1 to 37 months). Treatment consisted of five circumferential injections into the prepyloric area with a total of 100 to 200 U of botulinum toxin. There were no complications from endoscopy or the injection of toxin. Antiemetic and prokinetic agents were generally continued after injection, but gastric emptying studies were not usually performed. A positive symptomatic response was observed in 27 (42.9%) of the 63 patients, with a mean duration of response of 4.0 ± 2.7 months. Nine of the 27 responders had improvement for more than 6 months, all of whom were female. Fourteen of the 27 responders experienced complete resolution of all of their symptoms, with a duration of response of 5.1 ± 2.8 months. Females and patients older than 50 years had a better response rate than males and younger patients did.

Gastric Electrical Stimulation

Several different approaches have been used in gastric electrical stimulation in an effort to improve either gastric emptying or symptoms of gastroparesis. Because the intrinsic gastric pacemaker located along the greater curvature produces antral stimulation at 3 cycles per minute (cpm), low-frequency stimulation was used in an attempt to entrain and pace the gastric slow waves at 3.3 cpm to accelerate gastric emptying through possible activation of motor efferent nerves. Although the concept seems promising and has been reported in a small series of nine patients,[4] with improvement in both gastric emptying and symptoms of gastroparesis, this approach is not currently being used. *Sequential circumferential muscle stimulation* involves the use of bursts of suprahigh-frequency electrical stimulation to produce propagated antral contractions and to accelerate gastric emptying; however, this technology has not made the transition to actual clinical practice. In contrast, high-frequency stimulation is now being used in clinical practice for the treatment of both idiopathic and diabetic gastroparesis. With electrical stimulation at 12 cpm, symptoms improve in up to 60% of patients. It is thought that such stimulation activates sensory afferent nerves rather than increasing antral contractions. In addition, gastric emptying studies after stimulation may show little change in actual gastric emptying even though the gastroparetic symptoms may have improved.[5]

Medtronic (Enterra) Gastric Electric Stimulation Using high-frequency, low-energy, short-pulse electrical stimulation at 12 cpm, the Enterra stimulator with two electrical leads has been approved by the FDA for the treatment of patients with chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic origin. Ideally placed in patients who have previously undergone gastric surgery, the stimulator has also been used in those with an existing

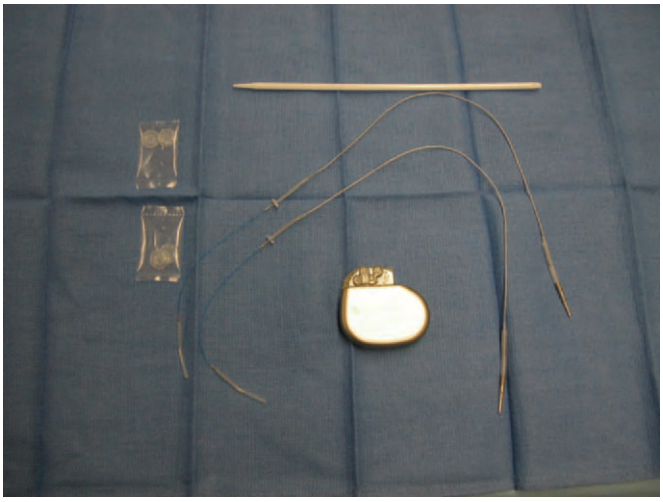

Figure 62–1. Enterra gastric electric stimulator system, with two Enterra leads, an introducer rod, plastic disks, and Enterra stimulator.

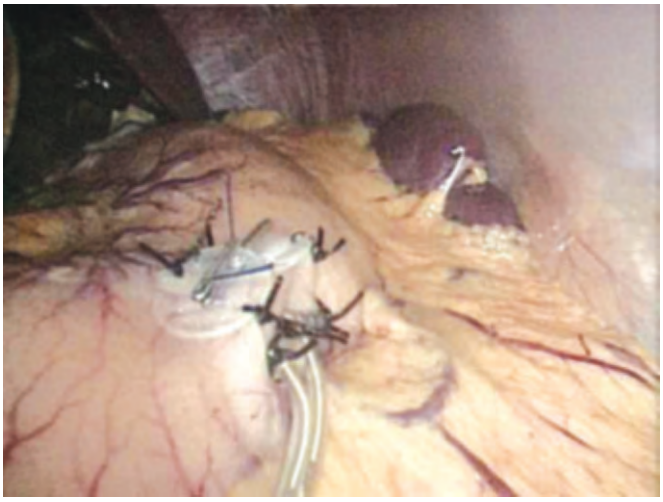

Figure 62–2. The Enterra leads are placed in the gastric wall 10 and 11 cm proximal to the pylorus and secured with plastic disks.

venting gastrostomy and feeding jejunostomy tubes. The beneficial effect of the stimulator may not be clinically apparent for several months, although some patients do report early improvement in well-being.

The stimulator package consists of a Medtronic Enterra stimulator (sized much like a cardiac pacemaker) and two insulated wire electrodes with an uninsulated metal tip connected to a monofilament suture with a straightened needle (Fig. 62–1). The two electrodes are positioned along the anterior greater curvature of the stomach, separated by about 1 cm. The most distal electrode is located about 10 cm proximal to the pylorus.[5] Both electrodes are placed parallel to each other, with partial-thickness penetration into the muscularis. The attached plastic flange of each electrode is sutured to the serosa to prevent dislodgement. Electrode placement may be done laparoscopically,[6] although needle and electrode passage in partial-thickness fashion is more difficult laparoscopically than with an open procedure, which can be performed through a small upper midline incision. In either case, upper endoscopy is recommended at the time of electrode placement to exclude full-thickness gastric wall penetration. If noted, the electrode can be repositioned and sutured (Fig. 62–2).

The stimulator itself is placed in a subcutaneous pocket on the abdominal wall in a location consistent with the patient's wishes, previous surgical procedures, and the potential need for future feeding tubes. The right side of the abdomen is preferred over the left for at least two reasons. First, space may need to be preserved for placement of a future venting gastrostomy tube or a feeding jejunostomy tube in the event that the stimulator does not reduce nausea, vomiting, or malnutrition. Second, if there are current venting/feeding tubes on the left, positioning the stimulator also on the left may increase the risk for contiguous spread of infection to the

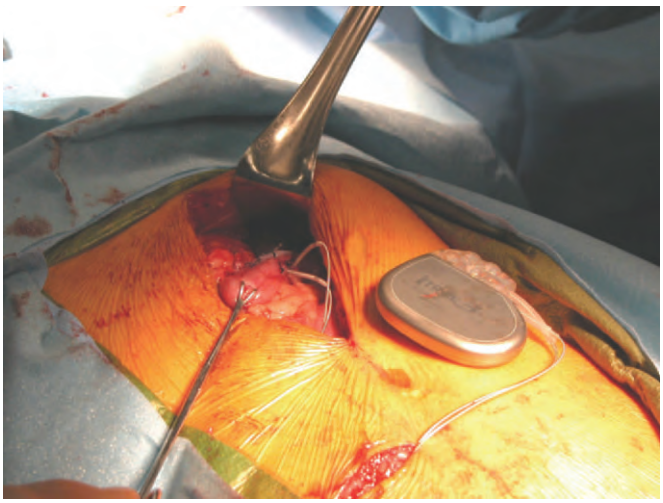

Figure 62–3. Open placement of the Enterra stimulator in a right lower quadrant pocket. Leads may be placed laparoscopically as well.

stimulator pocket if an infection or cellulitis develops at the tube site. A right upper quadrant location is easily facilitated unless the patient is short and thin, in which case the device may impinge on the costal margin when sitting. If a lower abdominal location is chosen, the stimulator should not be placed so low that it is forced upward when the patient sits. Both electrodes are brought through the abdominal wall with a trocar or provided tunneler and then connected to the stimulator (Fig. 62–3).

Next, the electrical resistance of the circuit through the gastric wall is determined before closure of the incisions. Transcutaneous interrogation of the stimulator

is performed with a sterile plastic drape–wrapped transducer connected to the Enterra computer. A typical impedance value of less than 800 ohms is satisfactory. If the impedance is greater, the electrodes could be too far apart and may need to be positioned more closely together. After closure of the incisions, the stimulator may be left in the *off* position for the first day. Nausea and vomiting are common after surgery and anesthesia, and because the stimulator is unlikely to diminish these early symptoms, it may be psychologically better to delay activation for a day until the immediate postoperative symptoms subside.

Risks associated with the gastric electrical stimulator include full-thickness penetration of the gastric wall at the time of placement or erosion into the gastric lumen with subsequent infection or abscess. Dislodgement of the leads from the stomach is possible in the early postoperative period if the plastic flanges have been inadequately sutured. Moderate fibrosis subsequently covers the lead implant sites on the stomach, thus making dislodgement a remote possibility. The presence of two looping wire electrodes within the abdomen can lead to small bowel obstruction. This possibility is quite small with the omentum in its normal configuration because the electrodes are positioned in the upper part of the abdomen and on top of the omentum. However, previous major abdominal surgery such as colectomy or partial small bowel resection may predispose to small bowel obstruction unless the electrodes are sutured loosely to the upper abdominal wall at the time of placement. It is unusual for the electrodes to become adherent to the abdominal viscera, but if it does occur, subsequent dissection of the electrodes from surrounding attachments does risk cutting the insulating layer and negating the effect of the stimulator. Hematoma may develop in the subcutaneous pocket for the stimulator in the postoperative period, either from vessels within the pocket or from the abdominal wall as a result of passage of an electrode through it. Subsequent infection or abscess at the stimulator site mandates removal of it. Erosion of the stimulator through the skin, even without cellulitis, is also treated by removal. Placement of the stimulator in the lower portion of the abdomen is sometimes complicated by local pain when sitting, either from displacement of the stimulator upward in the sitting position or from pressure on local nerves. This problem is treated by relocation of the stimulator to a more cephalad position, with care taken to not position it under a skin fold of the abdomen. Magnetic resonance imaging (MRI) is not possible after stimulator placement. If there has been no therapeutic effect from placement of the stimulator and MRI is needed to evaluate another body area, the electrodes and stimulator are removed. Laparoscopy allows evaluation and dissection of the electrodes up to the gastric wall; traction alone usually allows removal of the leads with mechanical cutting of the wires at the stomach if necessary.

At Temple University Hospital, 28 patients with a mean age of 40 years underwent Enterra implantation over an 18-month study period, with an average follow-up of 148 days.[7] Of these 28 patients, 14 felt improved, 8 remained the same, and 6 worsened according to the validated Gastroparesis Cardinal Symptom Index (GCSI) questionnaire scoring. The overall GCSI score significantly decreased by 12% ± 7%, with improvement in nausea and vomiting but no improvement in bloating or abdominal pain. The decrease in GCSI score was greater for the 12 diabetic patients (18% ± 11%; $P < .05$) than for the 16 idiopathic patients (7% ± 9%; P = NS). The subgroup of 22 patients with a chief complaint of nausea/vomiting had greater improvement (16% ± 9%; $P < .05$) than did the 6 patients with a chief complaint of abdominal pain (3% ± 11%; P = NS). The 13 patients taking narcotic analgesics at the time of Enterra implantation had a poorer GSCI response (increasing by 9% ± 10%; P = NS) than did the 15 who were not. As a result, three clinical parameters associated with a favorable clinical response to implantation were identified: diabetic rather than idiopathic gastroparesis, nausea/vomiting rather than abdominal pain as the primary symptom, and independence from narcotic analgesics before stimulator implantation.

Gastric Electrical Stimulation for Postsurgical Gastroparesis Gastric electrical stimulation is most commonly used on an intact stomach, without previous resection or surgery, except for prior gastrostomy tube placement. Postsurgical gastroparesis may develop in up to 10% of patients who have undergone vagotomy, in the absence of mechanical obstruction, and in up to 50% of those with chronic gastric outlet obstruction before surgery. Gastroparesis has been associated with partial gastrectomy, fundoplication, esophagectomy with colon interposition, and pylorus-preserving Whipple procedures. Gastric electrical stimulation is not usually thought to be suitable in these cases. However, McCallum et al. reported the application of electrical stimulation for postsurgical gastroparesis, including gastroparesis after Nissen fundoplication, vagotomy and pyloroplasty, Billroth I and vagotomy, Billroth II and vagotomy, spinal surgery, esophagectomy with colonic interposition, and cholecystectomy.[8] Sixteen patients (15 female, 1 male) with a diagnosis of gastroparesis for more than 1 year and refractoriness to antiemetics and prokinetics underwent implantation of the Enterra stimulator. In cases of antrectomy, the two electrodes were positioned within the muscularis propria 2 and 3 cm proximal to the gastric anastomosis. In those with an intact stomach, the electrodes were positioned in the usual manner at 10 and 11 cm proximal to the pylorus. Gastrostomy tubes were removed; however, feeding jejunostomy tubes were placed in 7 patients because of existing malnutrition. All patients were then monitored for at least 12 months. At 6 months after implantation, the severity and frequency of upper GI symptoms (vomiting, nausea, early satiety, bloating, postprandial fullness, and epigastric pain) were significantly reduced, and the improvement over the initial baseline state was sustained at 12 months ($P < .05$). Hospitalization for gastroparesis symptoms, which averaged 31 ± 13 days for the year preceding stimulator implantation, was reduced to 6 ± 2 days ($P < .05$) during the first year after implantation.

Gastric electrical stimulation in an intact stomach is not thought to generally improve symptoms by improve-

ment in gastric emptying, verifiable by scintigraphy. However, some patients may demonstrate improvement or normalization of gastric emptying rates by scintigraphy.[6] Retrograde stimulation of the vagal nerves has been thought to be a possible mode of symptom improvement, and therefore it may be questioned whether improvement should be expected after placement of a stimulator in those in whom vagotomy or inadvertent vagal injury has already occurred. Although vagal nerve damage or disruption was thought to be part of the underlying pathophysiology of these 16 postsurgical patients, electrical stimulation was still effective in improving symptoms. Moreover, our experience at Temple is that in an intact stomach (with no divided vagus nerves), diabetic patients improve more than idiopathic gastroparetic patients. Some neuropathy is characteristic of diabetes, which implies that vagal dysfunction was present before stimulator implantation; it also implies that gastric electrical stimulation can be effective without normal vagal function.

Surgical Procedures

When prokinetic and antiemetic medications alone are not sufficient to maintain body weight, venting and feeding tubes are used. A percutaneous gastrostomy tube alone may reduce the incidence of vomiting through intermittent venting or by setting the tube at continuous external drainage. Previous upper abdominal surgical procedures may indicate the need for laparoscopic or open gastrostomy tube placement instead of the endoscopic approach. A combination transgastric gastrojejunal tube can vent the stomach and also provide proximal jejunal tube feeding. Although the concept is attractive, it is more difficult to place the tube properly and maintain correct placement in the proximal jejunum. In addition, this combination tube design is subject to proximal displacement of the jejunal tube, with repeated bouts of emesis. The jejunal end of the tube may be forced back into the duodenum or even back into the stomach with repeated vomiting.

Placement of a feeding jejunostomy tube allows the provision of both adequate nutrition and fluids and can help reduce the need for hospitalization for intravenous repletion of fluids. Placement of both a gastrostomy tube for gastric venting and a jejunostomy tube for fluids and nutrition allows many patients with gastroparesis to manage their symptoms and improve their quality of life. Enteral feeding is preferred over parenteral nutrition because of lower overall cost and avoidance of more severe complications from central intravenous access. Enteral feeding via the jejunostomy tube may be maintained for months or years. Potential complications of a feeding jejunostomy include tube dislodgement with closure of the opening, infection and cellulitis at the site, and leakage from the site if the tract enlarges, which would require the insertion of a larger-diameter feeding tube. If small bowel dysmotility accompanies the gastroparesis, tube feed rates may need to be limited because of the nausea, pain, or bloating that may occur with normal rates of feeding. If ongoing weight loss then occurs, TPN is mandated via a PICC (percutaneous indwelling central venous catheter) line or tunneled central venous catheter. More aggressive surgical procedures have not been found to reliably reduce gastroparetic symptoms. Such procedures include pyloroplasty, gastrojejunostomy, and partial gastric resection. If gastric resection is chosen, a near-total gastrectomy with creation of a small proximal gastric pouch via a vertical staple line, as performed for a gastric bypass procedure, should be considered if blood supply is adequate. Additionally, a Roux gastrojejunostomy with at least a 15-mm opening, a short Roux limb, and a feeding jejunostomy should be performed.

Postsurgical Gastroparesis

After previous gastric procedures, complete evaluation of the gastric remnant and any anastomosis should be performed. An upper GI series will evaluate the overall morphology and may help assess for possible partial obstruction. Gastric emptying studies may be performed to evaluate the existing stomach if obstruction is not noted on the upper GI study. Endoscopic examination should be performed to examine the stomach for gastritis, the presence of *Helicobacter pylori,* ulcers, and the diameter and state of the anastomosis, as well as the possible presence of a marginal ulcer. If ulceration or friability is noted, medical treatment with proton pump inhibitors and sucralfate suspension and avoidance of nonsteroidal anti-inflammatory drugs may permit healing. A stricture may be balloon-dilated endoscopically if it is not overly fibrotic and if active inflammation is not present.[9] A perforation may occur if the dilation is overly aggressive, so limited dilation at one setting is advised. The dilation may be repeated one or more times for sequential enlargement of the anastomosis, up to 15 to 20 mm in diameter with current balloons. A wire-guided balloon catheter is safer for an initial dilation if the gastroscope cannot be passed through the anastomosis because the wire guide helps prevent perforation of the nonvisualized bowel distal to the stricture when the balloon is inflated. A gastroscope with a large working channel will be necessary if a wire-guided balloon is used.

If persistent marginal ulceration remains at the anastomosis after medical therapy (including treatment of *H. pylori* if present) or if an anastomotic stricture cannot be suitably dilated, surgical revision of the anastomosis should be considered. Revision should include completion vagotomy if there is a persistent ulcer, along with additional gastric resection. Before performing a larger operation, thoracoscopic truncal vagotomy should always be considered. If vagotomy and antrectomy have previously been performed, consider a subtotal (75%) gastrectomy. If subtotal gastrectomy has previously been performed, consider a near-total gastrectomy. If a recurrent ulcer is present after previous Roux gastroenterostomy, consider re-resection to a 95% gastrectomy with Roux gastrojejunostomy.[9,10]

In those with chronic postvagotomy, postgastrectomy gastric stasis, even aggressive resection with Roux recon-

struction may not produce satisfactory outcomes. The results of near-total completion gastrectomy for severe postvagotomy gastric stasis in 62 patients (51 female, 11 male) at the Mayo Clinic were followed for more than 5 years.[11] In these patients the gastric remnant was largely resected, with a 1- to 2-cm remnant of gastric cardia left for the gastrojejunostomy. Despite a median of four previous gastric operations and symptoms of nausea, vomiting, postprandial pain, chronic abdominal pain, and chronic narcotic use, all or most symptoms were relieved in 43% of those operated on (Visick grade I or II). However, the rest remained in Visick grade III or IV. Although nausea, vomiting, and postprandial pain were improved, chronic pain, diarrhea, and dumping syndrome were not significantly improved.

Roux Stasis Syndrome

Roux stasis syndrome is a term that has been applied to symptoms of early satiety, vomiting, and postprandial pain occurring after distal gastrectomy with Roux gastrojejunostomy; it affects up to 30% to 50% of such patients.[9] It was postulated that ectopic pacemakers occur in the Roux limb and cause orally directed Roux limb contractions, as well as aboral contractions, thereby resulting in functional obstruction to gastric emptying. Most of these patients underwent vagotomy as part of their initial surgical procedure. Although Roux limb motility may be affected by division of its mesentery, it is also likely that gastric stasis plays a significant role in producing symptoms. Endoscopy may show gastric bezoar formation or dilation of the gastric remnant, as well as possible dilation of the Roux limb. Improvement after near-total gastrectomy in patients with previous vagotomy suggests that the gastric stasis component was more significant than the effect in the Roux limb itself.[9] Moreover, current experience with Roux gastric bypass procedures for morbid obesity tends to support this concept. In most gastric bypasses, vagotomy is not performed and a small gastric pouch not based on the fundus is retained. Postprandial pain and vomiting do not usually occur in these patients. Early satiety seems to be a function of the small pouch and the controlled size of the gastrojejunostomy. In patients with a dilated gastrojejunostomy in which food more rapidly enters the Roux limb from the pouch, early satiety and vomiting do not generally occur. Instead, more food can be ingested, and feelings of hunger usually return more quickly as a result. The Roux syndrome is therefore more likely to primarily be postoperative gastric atony.

INTESTINAL MOTILITY

In the fasting state, small intestinal motility is controlled by the migrating motor complex (MMC), which exhibits three phases. Phase I is a quiescent period and represents 20% to 30% of the total cycle length. Phase II accounts for 40% to 60% of the total cycle length and is characterized by intermittent and irregular contractions. In phase III, intense, rhythmic contractions develop and propagate from the proximal to the distal portion of the intestine over a 5- to 10-minute period. The MMC cycle occurs about every 90 minutes during the interdigestive period. However, after a meal, this fasting pattern of intestinal motility is changed to a postprandial pattern, with intermittent phasic contractions of irregular amplitude that are similar to the phase II contractions of the MMC.[12] Peristalsis occurs when a segment of circular muscle contracts as a result of excitatory motor neurons while the intestinal segment aboral to the contracted segment is simultaneously relaxed by inhibitory neurons.[13]

The interstitial cells of Cajal (ICCs) are known to be essential regulators of GI motility and seem to serve as pacemaker cells in the GI tract and mediators of neural regulation in GI motility. They lie in close proximity to smooth muscle cells and elements of the enteric nervous system. The generation of slow waves occurs within Auerbach's plexus and is an intrinsic property of ICCs; both circumferential intestinal contractions and longitudinal contractions are produced.[13] ICC abnormalities are increasingly being recognized in a number of GI tract disorders, such as chronic intestinal pseudo-obstruction, with findings of decreased ICCs or an abnormal ICC network.[14,15] Surgical procedures involving the small intestine produce disruption of ICC networks at the level of the myenteric and deep muscular plexuses, with resultant loss of slow waves and phasic contractions. This loss of intestinal motility, however, partially recovers within 24 hours after surgery.[16]

Because intestinal motility is controlled by interactions between smooth muscle, enteric nerves, extrinsic nerves, and humoral factors, abnormalities in each of these areas may result in intestinal dysmotility. Small intestinal dysmotility symptoms include abdominal bloating, distention, pain, nausea, and vomiting. Primary disorders of small intestinal dysmotility include inherited familial visceral myopathies, characterized by smooth muscle degeneration, and familial visceral neuropathies, characterized by the degeneration of enteric nerves. Secondary causes of small intestinal dysmotility include myopathic processes (scleroderma, muscular dystrophies, amyloidosis), neurologic diseases (Parkinson's disease, neurofibromatosis, Chagas' disease), endocrine disorders (diabetes mellitus, hyperthyroidism, hypothyroidism, hypoparathyroidism), celiac disease, and pharmacologic agents (anti-Parkinson medications, phenothiazines, tricyclic antidepressants, narcotics).[17]

Smooth muscle disease such as scleroderma frequently affects the GI tract, and small intestinal dysmotility develops in about 40% of such patients. Proximal involvement leads to megaduodenum or wide-mouth diverticula of the small bowel, with delayed transit, bacterial overgrowth, and malabsorption. Octreotide has been useful in treating stasis and the resultant bacterial overgrowth. Muscular dystrophies affect motility of the entire gut; although barium studies may be normal, small intestinal manometry may reveal a myopathic pattern. Amyloidosis produces infiltration of both smooth muscle and the autonomic nerves and affects the motility of the entire GI tract.[17]

Neurologic disease is most commonly seen with Parkinson's disease, with degeneration of the enteric nervous system and inhibition of intestinal motility by anti-Parkinson medications. Neurofibromatosis may produce dysmotility as a result of mechanical obstruction with GI tract tumor formation, but it is also associated with neuronal dysplasia of the enteric nervous system. Chagas' disease (infection with *Trypanosoma cruzi*) results in neuronal injury and is manifested as megaduodenum, megajejunum, or pseudo-obstruction.[17] Hirschsprung's disease or its allied disorders hypoganglionosis and intestinal neuronal dysplasia may produce small intestinal dysmotility.[18]

Endocrine disorders may give rise to intestinal dysmotility that may be treated. Hypothyroidism produces delayed transit, constipation, and pseudo-obstruction, which is reversible with thyroid hormone replacement. Hypoparathyroidism may be associated with small intestinal dysmotility and pseudo-obstruction, which improve with calcium repletion. Small intestinal complications of diabetes with autonomic neuropathy include delayed transit with bacterial overgrowth and diarrhea. Celiac sprue produces abdominal pain, distention, and malabsorption, with delayed intestinal transit, bacterial overgrowth, and pseudo-obstruction.[19] Both villous damage and small intestinal dysmotility improve with a gluten-free diet.[17]

GI motility is enhanced by the stimulation of distinct serotonin (5-HT) receptors on intestinal sensory nerves. 5-HT is released from mucosal enterochromaffin cells in response to mechanical and chemical stimuli within the intestine. 5-HT activates 5-HT_4 receptors on nerves synapsing in the myenteric plexus, which then results in motor responses and increased peristalsis and intestinal transit.[16] Tegaserod, a selective 5-HT_4 partial agonist, has been shown to significantly accelerate small bowel transit time, as well as gastric emptying.[20]

Diagnosis of Intestinal Dysmotility

After the history, physical examination, and conventional radiographic studies suggest the possibility of intestinal dysmotility, an upper GI study with small bowel follow-through should be performed. This study should suggest the possibility of obstructing lesions such as tumor, stricture, diverticula, or adhesions and, in their absence, may identify general small bowel dysmotility. Evaluation of small intestinal transit may be then done by small bowel scintigraphy, with imaging up to 6 hours after ingestion of a radiolabeled meal. Scintigraphy has a specificity of up to 75% for the diagnosis of dysmotility, but it does not differentiate between myopathic and neuropathic causes.

Small bowel manometry is then performed if abnormal small bowel transit is found to be present. In the interdigestive period the MMC is monitored to examine the cycle duration (interval between phase III events), the duration of each phase, including the amplitude and propagation velocity of phase III, and the rate of contraction of phase III. A motility disorder is present with abnormal bursts of phasic activity, low-amplitude contractions, poorly coordinated activity, or absent, incomplete, or retrograde phase III activity. With eating, a change to typical postprandial activity is expected, with irregular, phasic contractions of variable amplitude as the intestinal contents are mixed and propelled distally. This postprandial period lasts for about 4 hours, and then a return to the interdigestive pattern should be noted. Whereas short-duration (2-hour) manometry studies may diagnose abnormalities while a patient is in the fed or postprandial state, longer study periods facilitate study in the interdigestive period as well. This concept has been extended to ambulatory study systems in an attempt to improve diagnostic accuracy. Manometry may also help distinguish myopathic causes of dysmotility from neuropathic causes.

Pharmacologic Treatment

Octreotide has been used to treat the chronic pseudo-obstruction and bacterial overgrowth seen with dysmotility from connective tissue diseases such as scleroderma. It induces phase III–like activity in the small intestine; however, it also decreases antral activity.[17] The addition of erythromycin, a motilin agonist, stimulates gastric emptying and also intestinal contractions at low doses. Tegaserod, a 5-HT_4 partial agonist, has been shown to accelerate small bowel transit time, as well as increase both gastric emptying and colonic transit.[17,20]

Surgical Treatment

Surgical options for the treatment of nonmechanical small intestinal dysmotility are limited. Mechanical causes of slow bowel transit, abdominal pain, or small intestinal dilation should first be investigated. The differential diagnosis includes luminal webs, polyps, carcinoid, duplication, internal hernias, intussusception, adhesions, malrotation, SMA syndrome, chronic gut ischemia, inflammatory bowel disease, radiation enteritis, and neoplasm. Radiographic modalities available for evaluation include upper GI series with small bowel follow-through and computed tomography with both oral and intravenous contrast. Transit studies with radiopaque markers may assess small intestinal motility. Upper endoscopy with enteroscopy allows evaluation of the proximal jejunum and also permits mucosal biopsy. Small intestinal manometry allows assessment of the MMC.

If radiologic and gastroenterologic studies have not enabled a diagnosis to be made, the surgeon may be requested to perform diagnostic laparoscopy. In a patient without extensive previous surgery, laparoscopy affords an adequate examination of the small intestine from the ligament of Treitz to the terminal ileum. Conversion to exploratory laparotomy may be indicated with previous surgery or with questionable findings at laparoscopy. If requested, a feeding jejunostomy tube may be placed and a full-thickness jejunal biopsy performed to evaluate for visceral myopathy or neurogenic causes of small bowel dysmotility and chronic intestinal pseudo-obstruction.[21]

Small bowel resection is uncommonly performed, although localized findings may justify segmental resection. Isolated megaduodenum (type I familial visceral myopathy) has been treated by either drainage or subtotal duodenal resection, with the posterior biliopancreatic duodenal wall left intact and the proximal jejunum used as an onlay patch.[17,22] Primary amyloidosis confined to the small intestine has been reported in the setting of persistent pseudo-obstruction and has been treated by partial jejunectomy.[23]

Chronic intestinal pseudo-obstruction in the pediatric population may occur as a result of short-gut syndrome after resection for intestinal aganglionosis or as a result of neuropathic or myopathic causes. When intestinal failure leads to permanent dependence on parenteral nutrition, patients are at risk for liver failure, eventual loss of central venous access, and catheter sepsis.[24] Small bowel transplantation with immunosuppressive treatment may be indicated for a subset of these patients and has resulted in improved outcomes. Early referral for transplantation should be considered once permanent TPN has become necessary. Multivisceral transplantation in children has also been reported, with 88.9% and 77.8% survival rates at 1 and 2 years, respectively, and all long-term survivors tolerating enteral feeding and off parenteral nutrition.[25] Intestinal and multivisceral (stomach, duodenum, pancreas, and intestine, with or without liver) transplantation has been extended to the adult population as well for short-bowel syndrome caused by intestinal infarction and for intestinal failure caused by chronic intestinal pseudo-obstruction.[26] With a mean age of 34.8 years and a mean TPN duration of 5.8 years, the 1-year graft survival rate was 88.4% for an isolated small bowel transplant and 42.8% for multivisceral transplants; the overall mortality rate was 18.5%.

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Chapter

63

Operations for Morbid Obesity

Robert E. Brolin ▪ Christopher Kowalski

THE OBESITY EPIDEMIC

Prevalence

The term *epidemic* has frequently been used to describe the dramatic increase in the prevalence of both overweight and obesity in the United States. It was recently estimated that approximately two thirds of adults in the United States are overweight, with a body mass index (BMI) greater than 25 kg/m^2, and that nearly half are obese, with a BMI greater than 30 kg/m^2.[1] Other reports suggest that the most rapid increases in prevalence are seen in the most severely obese subgroups.[2] It is estimated that nearly 24 million Americans are severely obese, with a BMI greater than 35 kg/m^2, and that more than 8 million are morbidly obese, with a BMI greater than 40 kg/m^2.[3] The rate of obesity is increasing even more rapidly in children. It was recently estimated that more than 25% of children 17 years or younger are obese.[4] This percentage had more than doubled during the past decade. The prevalence of morbid obesity, a BMI greater than 40 kg/m^2, may be increasing at a more rapid rate. There are a number of recent reports of severe obesity-related comorbid conditions in children, including type 2 diabetes, hypertension, hyperlipidemia, and sleep apnea syndrome.

Health Risk, Mortality

Entering the new millennium, it was estimated that obesity is the second leading cause of preventable deaths in the United States and that it accounts for approximately 300,000 deaths annually.[5] Moreover, it was projected that because of rapidly increasing prevalence, obesity would soon overtake cigarette smoking as the foremost cause of preventable deaths. The prevalence of complications related to severe obesity increases sharply at a level corresponding to approximately 60% above desirable weight. At that level there is a twofold increase in morbidity and mortality. However, the slope of the "risk curve" rises almost exponentially above the 60% overweight level such that the complication rate corresponding to 100% above ideal weight is in the range of 13 to 14 times normal. Unfortunately, there is a paucity of actuarial statistics for adults who are more than 45 kg overweight. These data are particularly lacking in women, who are the most frequent subjects of obesity operations.

The mortality rate associated with *morbid* obesity, or a BMI greater than 40 kg/mg^2, has not been accurately estimated. Until recently, only one study was focused on mortality differences between morbidly obese subjects and normal-weight individuals of similar age and gender. In 1980, Drenick et al. reported a markedly increased mortality rate in morbidly obese males versus age-matched normal-weight men (Fig. 63–1).[6] The most common causes of death in the overweight men in this study were myocardial infarction and stroke. More recently, there have been three published reports in which mortality was compared in surgically treated, morbidly obese patients and a similar age/gender group who did not have surgery. In 1997, MacDonald et al. reported a greater than sixfold increase in mortality among morbidly obese diabetics who for a variety of reasons did not undergo gastric bypass surgery after preoperative evaluation versus a similar age/gender mix of patients who underwent Roux-en-Y gastric bypass (RYGB).[7] In 2004, Flum and Dellinger reported a 1.5 times higher mortality rate over a 15-year period in 62,781 subjects who did not have surgery versus 3328 who had surgical treatment in Washington State.[8] The 1.9% operative mortality rate in the Washington report is at least twice as high as in most published series of bariatric surgical patients.[7,9,10] During the same year, Christou et al. reported 0.68% mortality in surgical patients versus

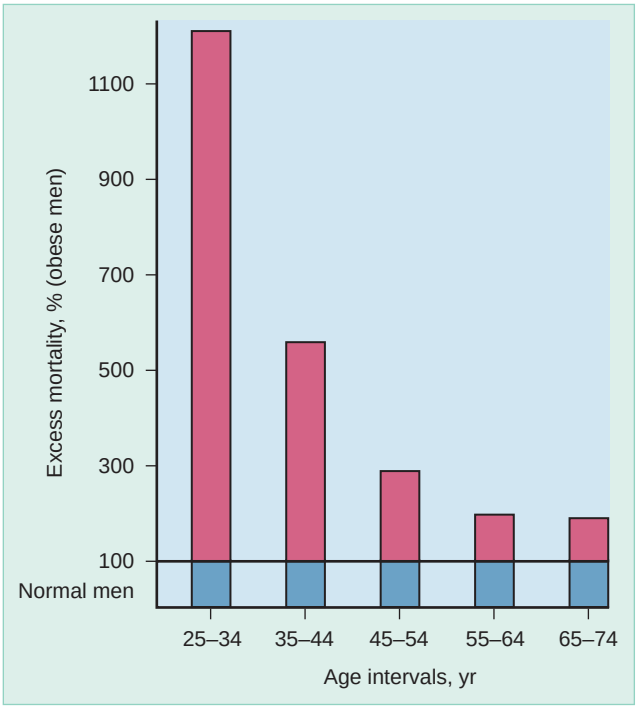


Figure 63–1. Comparison of excess mortality in men with morbid obesity *(red bars)* versus normal-weight men *(blue bars)* by age interval. (From Drenick EJ, Bale GS, Seltzer F, Johnson DG: Excessive mortality and causes of death in morbidly obese men. JAMA 243:443-335, 1980.)

Table 63–1 Diseases Associated with Severe Obesity

Comorbidity	Incidence (%)
Hypertension	20-55
Obesity-hypoventilation/sleep apnea syndrome	20-50
Cholelithiasis	25-45
Degenerative osteoarthritis	20-50
Psychological depression	15-35
Hyperlipidemia	15-25
Diabetes mellitus	10-25
Asthmatic bronchitis	10-15
Coronary artery disease	5-15
Heart failure (right sided and/or left sided)	5-15
Stasis ulcers/venous insufficiency	5-15
Gastroesophageal reflux	5-15
Stress overflow urinary incontinence	5-15
Pseudomotor cerebri	1-2
Sexual hormone imbalance/infertility	—*
Malignancy (uterine, colon, gallbladder)	—*
Pulmonary embolism/thrombophlebitis	—*
Necrotizing subcutaneous infections	—*

Comorbid conditions are listed in the approximate order of reported frequency.
*Lack of specific numerical data in diseases known to be more common in obese patients.

a 6.17% death rate in a similar mix of nonoperative subjects monitored over a 16.5-year period, which represents a greater than 80% reduction in mortality risk in the surgical group.[11]

The health risk associated with severe obesity is intimately related to obesity-related illnesses. Table 63–1 shows a list of diseases associated with severe obesity. Although cardiovascular disease is reported as the leading cause of death in obese patients, the prevalence of cardiovascular symptoms in bariatric surgical cohorts is relatively low. Many obesity-related comorbid condition, such as degenerative arthritis, sleep apnea, and venous stasis, have a profoundly negative impact on *quality of life.*

Obesity-Related Cost

In 2000, the combined estimated direct and indirect costs associated with treatment of obesity and related comorbid conditions approached $117 billion.[1] At the same time, the annual expenditure in weight loss–related endeavors in the United States was conservatively estimated at $30 billion. Medicare is currently re-evaluating its policy on reimbursement for treatment of obesity because of the rapidly rising cost of obesity-related disability and medications used for the treatment of various comorbid diseases.

INDICATIONS FOR SURGERY

The primary premise as well as justification for surgical treatment of morbid obesity has been the compelling evidence that severe obesity is associated with a shortened life span and a variety of other serious medical problems. Severe obesity has been notoriously refractory to virtually every method of nonoperative treatment. The 2-year failure rate of diet and behavior modification in the morbidly obese approaches 100%. Many morbidly obese patients gain substantial weight after unsuccessful attempts at dieting. This so-called yo-yo syndrome is characterized by transient weight loss, followed by greater weight gain, and probably contributes to the refractoriness of nonsurgical treatment of severe obesity. A prospective randomized trial that compared a low-calorie diet with a now discarded method of stapled gastroplasty showed significantly better weight maintenance in the surgically treated group 2 years after intervention.[12] These results suggest that involuntary gastric restriction of oral intake is necessary for long-term weight control in morbidly obese patients.

In 1992 the National Institutes of Health Consensus Development Panel on gastrointestinal surgery for severe obesity recommended criteria for consideration of surgical treatment.[13] The panel recommended that surgical treatment be considered for any patient with a BMI of 40 kg/m^2 or higher who had failed serious attempts at nonsurgical treatment. The panel also recommended

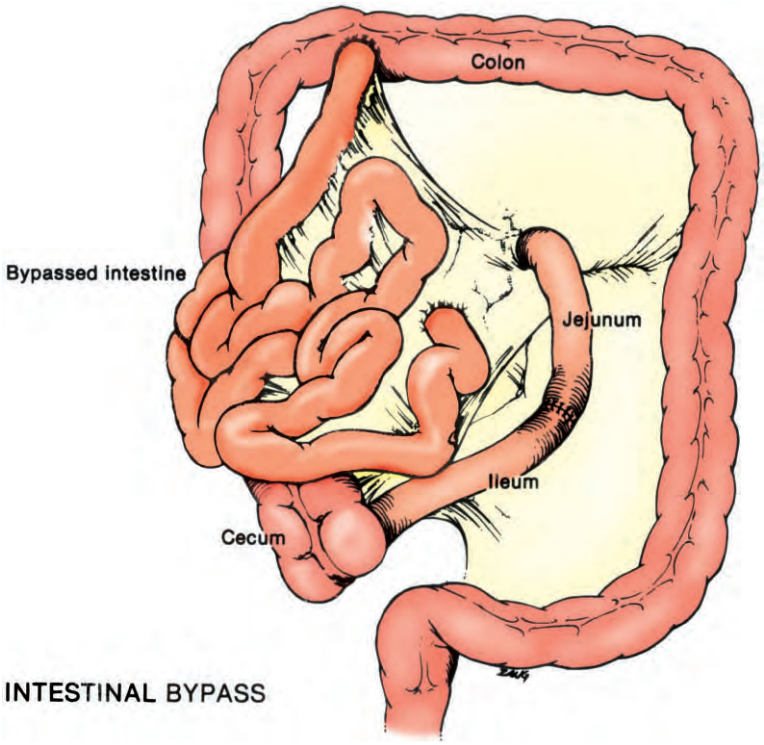


Figure 63–2. Jejunoileal bypass in which a 12-inch segment of jejunum is anastomosed end to end to 6 inches of terminal ileum. The remainder of the small bowel *(dark shaded)* is totally excluded from digestive continuity. The distal end of the excluded bowel is anastomosed to the transverse colon. (From Miller TA [ed]: Modern Surgical Care: Physiologic Foundations and Clinical Applications, 2nd ed. Chapter 68. St. Louis, Quality Medical Publishing, 1998.)

that surgery be considered for patients with a BMI of 35 kg/m^2 or greater who have serious coexisting medical problems such as diabetes, hypertension, hyperlipidemia, or sleep apnea.

Psychological stability should be assessed in some reliable manner before the operation, although standardized psychological tests and interviews with psychologists or psychiatrists have not reliably predicted postoperative outcome after obesity operations. However, many insurance carriers now require a formal psychological evaluation of prospective patients. Patients should also be carefully queried regarding the abuse of addictive drugs and alcohol before having surgery. All patients who undergo surgical treatment of obesity should be admonished that sustained long-term weight loss is not guaranteed merely by having an operation. This understanding is particularly important for patients who undergo gastric restrictive operations, which can be defeated by consuming large quantities of high-calorie liquids and soft junk food.

EARLY BARIATRIC OPERATIONS

Jejunoileal Bypass

The concept of surgery for morbid obesity was introduced by Kremen et al. in 1954 in the form of malabsorption-induced weight loss.[14] After experimenting with various lengths of jejunum and ileum, satisfactory weight loss was reported in patients in whom 30 to 35 cm of jejunum was anastomosed to 10 to 15 cm of terminal ileum (Fig. 63–2). During the 1960s and 1970s, thousands of intestinal bypasses were performed for the treatment of morbid obesity. However, by the mid-1970s, reports of serious late complications appeared in the literature, including hepatic failure, urinary calculi, arthritis, and major nutritional deficiencies. Bacterial overgrowth of the distal bypassed bowel was suspected as the cause of the bypass enteritis syndrome, which was characterized by intermittent episodes of abdominal pain, bloating, arthralgia, rash, and diarrhea. The first public repudiation of jejunoileal bypass was delivered in 1979. Within less than 2 years jejunoileal bypass fell into a status of disrepute. Jejunoileal bypass is no longer recommended for the treatment of morbid obesity.[15]

Gastric Restrictive Operations

The concept of gastric restriction as treatment of morbid obesity was introduced by Mason and Ito in 1967.[16] All the current gastric operations are designed to restrict intake of solid food. Conversely, intake of liquids is not limited by these operations. In 1977, Mason et al. defined the anatomic parameters of restriction that were considered necessary for adequate weight loss with the gastric bypass operation, including a calibrated 1.2-cm-diameter gastrojejunostomy stoma and a small 50-ml-capacity upper gastric pouch.[17] Complication rates with gastric bypass decreased after introduction of the concept of stapling the stomach in continuity rather than dividing it. Use of the Roux-en-Y technique eliminated the problems with bile reflux esophagitis that were common after loop gastric bypass.

Stapled gastric partitioning was introduced in 1979. However, an unacceptably high incidence of early staple line failure led to a proliferation of modifications of gastric stapling in the hope of finding a more reliable technique. Gastroplasty techniques have evolved in favor of stapling in a vertical direction along the lesser curvature of the stomach. Stapling along the lesser curvature has also facilitated reinforcement of the outlet with prosthetic

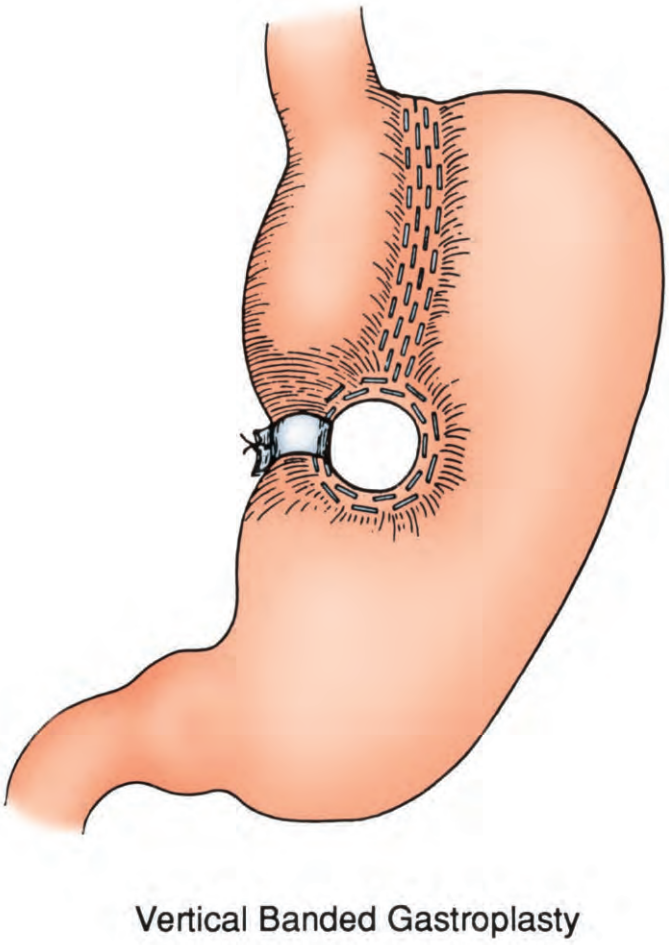


Figure 63–3. Vertical banded gastroplasty in which an upper gastric pouch with a capacity of 15 to 20 ml empties into the remainder of the stomach through a calibrated stoma 5.0 cm in circumference. The stoma is reinforced with a strip of polypropylene (Marlex) mesh. The mesh is placed around the stoma through a "window" created by firing a circular stapling instrument alongside a 32-French bougie. (From Miller TA [ed]: Modern Surgical Care: Physiologic Foundations and Clinical Applications, 2nd ed. Chapter 68. St. Louis, Quality Medical Publishing, 1998.)

materials to prevent progressive stomal dilatation. Horizontal gastroplasty techniques have now been abandoned because of an unacceptably high incidence of staple line disruption, stomal dilation, and pouch dilation.

In 1982 Mason introduced vertical banded gastroplasty (VBG), as shown in Figure 63–3.[18] In VBG the stoma is reinforced with a strip of polypropylene (Marlex) mesh measuring 5.0 cm in circumference to create a stoma with an internal diameter of 1.0 to 1.2 cm. The mesh is placed around the stoma through a hole or window created by firing a circular stapling instrument alongside a 32-gauge-diameter bougie. The mesh is sutured to itself rather than the stomach, a modification that has greatly reduced the incidence of outlet stricture and leaks.

Morbidity and mortality rates with VBG have been low. An overall morbidity rate of less than 10% and a mortality rate of 0.25% were reported in a series of more than 1200 VBGs.[19] Early weight loss results have generally been acceptable. MacLean et al. reported a mean 60% excess weight loss in 57 patients monitored for 5 years after VBG.[10] However, a substantial number of patients in this series required surgical revision for either complications or inadequate weight loss during the study period. There are remarkably few reports of long-term weight loss results after VBG. Weight loss maintenance after VBG has been somewhat problematic in that many patients regain at least 20% of their lost weight between 3 and 5 years postoperatively, perhaps in part because of increased intake of liquid or soft high-calorie foods that easily pass through the banded stoma.

CURRENT OPERATIONS

Roux-en-Y Gastric Bypass

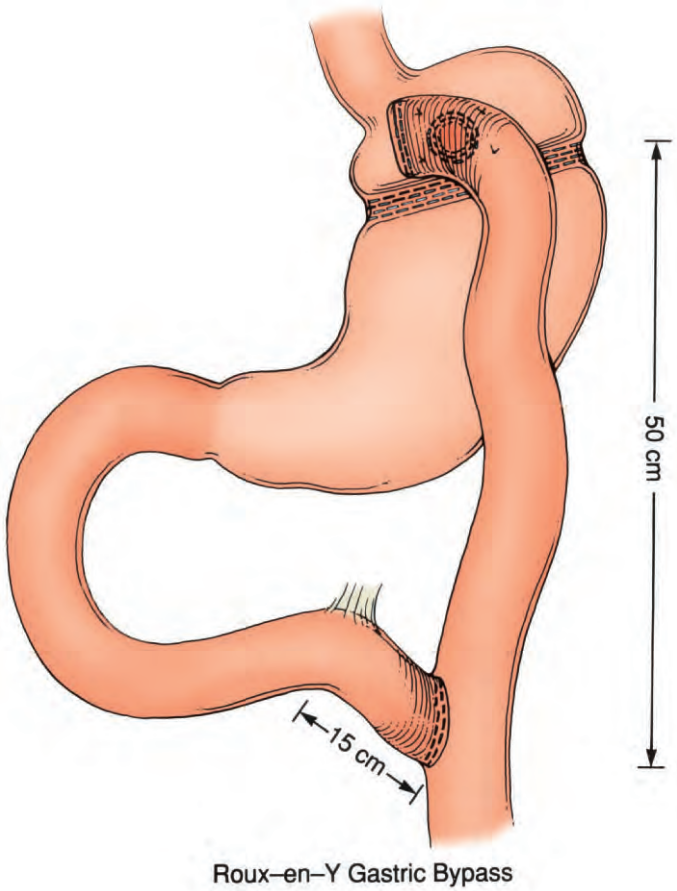
RYGB is illustrated in Figure 63–4. Gastric bypass combines gastric restriction with a small amount of malabsorption. Many surgeons consider RYGB to be the "gold standard" bariatric operation because it has produced durable weight loss for most patients with an acceptable incidence of postoperative complications. Weight loss is in the range of 70% to 80% of the excess weight at 2 years with maintenance in the range of 50% to 60% after 5 years.[7,10] The East Carolina group showed maintenance of approximately 50% of the excess weight loss 14 years after RYGB.[7] No difference in weight loss has been found between the open and laparoscopic approach. There have been several large prospective randomized comparisons of RYGB with different gastric restrictive operations, each of which showed significantly better weight loss after gastric bypass and similar early morbidity rates.[9,20,21]

Currently, laparoscopic RYGB is the most commonly performed bariatric operation in the United States. RYGB was first performed via laparoscopy by Wittgrove and Clark in 1994.[22] Although the physiology and weight loss outcome of open and laparoscopic RYGB are essentially the same, there are considerable differences between the open and laparoscopic approach with respect to the required instrumentation and surgical skill set. Laparoscopic RYGB is a technically demanding procedure with a considerably longer learning curve than for the open approach.

Five distinct technical components are involved in performing laparoscopic RYGB: (1) abdominal access/trocar placement, (2) creation of the gastric pouch, (3) mobilization and positioning of the Roux limb, and (4) performance of the gastrojejunostomy and (5) jejunojejunostomy.

Most surgeons place five or six access ports in the upper part of the abdomen. The location of individual ports is influenced by the type of staplers to be used. Access is achieved with either a Veress needle or a 12-mm visualization port placed just below the left costal margin in the midclavicular line. After the abdomen is entered, CO_2 is insufflated at a pressure of 15 mm Hg. A 30-degree laparoscope is then inserted. The remaining ports are placed sequentially under direct visualization.

Creation of the upper gastric pouch begins by dividing the phrenoesophageal ligament at the angle of His with ultrasonic shears. The angle of His defines the end



A

B

Figure 63–4. Roux-en-Y gastric bypass (RYGB). **A,** The upper part of the stomach is stapled closed in continuity, which was typical of procedures performed in the 1980s and 1990s. An upper pouch with a capacity of 30 ml is created with exclusion of more than 95% of the stomach, all of the duodenum, and approximately 15 cm of proximal jejunum from digestive continuity. The Roux limb between the upper gastric pouch and jejunojejunostomy measures 50 cm in length. (From Brolin RE, Kenler HA, Gorman RC, Cody RP: The dilemma of outcome assessment after operations for morbid obesity. Surgery 105:337-346, 1989.) **B,** Transected retrocolic, antegastric RYGB typical of current laparoscopic techniques. (Courtesy of Inamed Health, Santa Barbara, CA.)

point of the gastric transection. Sliding-type hiatal hernias should be reduced before transection to prevent the creation of a large pouch. The lesser sac is then entered by dividing the vasa brevia along the lesser curvature of the stomach, starting 3 to 4 cm below the gastroesophageal junction. The stomach is then stapled horizontally with a 45-mm linear stapler. Subsequent stapling is directed vertically toward the angle of His until the stomach is completely transected. Usually, four or five firings of the 45-mm stapler are required to create a gastric pouch with a capacity of 15 to 30 ml.

The gastrojejunostomy can be performed with either a linear or a circular stapling device. In the circular approach, the anvil of the 21 mm or 25 mm EEA stapler is introduced into the gastric pouch either transorally attached to a percutaneous endoscopic gastrostomy (PEG)-type tube or with an endoscope or directly through a laparoscopic port site. In the transabdominal approach, a gastrotomy is required to place the EEA anvil into the gastric pouch before the stomach is completely transected. The gastrotomy site is then stapled shut after the anvil is properly positioned within the pouch. Integrity of the gastrojejunostomy can be evaluated by several methods. Some surgeons pass an orogastric tube into the gastric pouch and instill 10 to 30 ml of a methylene blue dye/saline mixture. Others perform intraoperative upper endoscopy and air insufflation with the pouch submerged in normal saline. Anastomotic defects should be repaired immediately, after which a second test for integrity is performed.

The intestinal portion of the procedure begins with identification of the ligament of Treitz at the base of the transverse mesocolon. The jejunum is measured for a distance of 20 to 50 cm and divided with a 45-mm linear stapler. The Roux limb is then positioned in either an antecolic or retrocolic location before anastomosis to the gastric pouch. At this point the surgeon must avoid twisting the mesentery of the Roux limb. Division of the greater omentum is usually required when the antecolic route is chosen so that tension on the Roux limb is minimized. The circular stapler is placed in the abdomen via the left upper quadrant port site and inserted into the

Table 63–2 Complications After Open and Laparoscopic Gastric Bypass

Complication	No. (%) of Patients		
	Open GBP	Laparoscopic GBP	*P* Value
Intraoperative			
Iatrogenic splenectomy	5/1218 (0.41)	Not reported	
Perioperative			
Anastomotic leak	42/2497 (1.68)	71/3464 (2.05)	.31
Bowel obstruction	Not reported	10/577 (1.73)	
Gastrointestinal tract hemorrhage	8/1334 (0.60)	11/570 (1.93)	.008
Pulmonary embolus	20/2577 (0.78)	11/2651 (0.41)	.09
Wound infection	34/513 (6.63)	97/3258 (2.98)	<.001
Pneumonia	5/1504 (0.33)	3/2075 (0.14)	.24
Death	24/2771 (0.87)	8/3464 (0.23)	.001
Late			
Bowel obstruction	53/2507 (2.11)	91/2887 (3.15)	.02
Incisional hernia	128/1492 (8.58)	14/2958 (0.47)	<.001
Stomal stenosis	12/2233 (0.67)	164/3464 (4.73)	<.001

Comparison of postoperative complications between open and laparoscopic gastric bypass (GPB).
Data from Podnos YD, Jimenez JC, Wilson SF, et al: Complications after laparoscopic gastric bypass. A review of 3464 cases. Arch Surg 138:957-961, 2003.

proximal end of the Roux limb. The spike of the circular stapler is advanced through the antimesenteric border of the Roux limb and engaged with the anvil protruding from the pouch. The stapler is fired and removed. The redundant open end of the Roux limb is then resected flush with the gastrojejunostomy with a linear stapler to avoid a long afferent limb, which can increase reservoir capacity.

Creation of the jejunojejunostomy begins by measuring the Roux limb distally for a distance of 75 to 150 cm from the gastrojejunostomy. Most surgeons perform a side-to-side, stapled anastomosis with a linear stapler. Several techniques can be used to close the enterotomies that remain after side-to-side stapling, including stapling in a perpendicular orientation to the previous stapling and laparoscopic suture closure. Alignment after stapled closure of the enterotomy defects must be precise to avoid kinking and obstruction. Several so-called antiobstruction stitches should be placed between the distal Roux limb and the biliopancreatic limb to prevent kinking at the anastomosis. Many surgeons are fastidious in closing mesenteric defects at the jejunojejunostomy site, including mesocolic defects (in the retrocolic technique) and Petersen's space. Closure of mesenteric defects should be performed with a nonabsorbable suture.

Postoperative morbidity and mortality rates observed with current techniques of RYGB are in the range of 10% and 1%, respectively. Table 63–2 shows a comparison of postoperative complications during open and laparoscopic RYGB.[23] The incidence of incisional hernia and wound infection is significantly lower with laparoscopic RYGB than with the open approach. Conversely, the incidence of bowel obstruction from internal hernia is significantly higher after the laparoscopic approach and ranges from 2% to 8%.[23] The majority of internal hernias occur in mesenteric defects at the jejunojejunostomy or at Petersen's space. Internal herniation can be manifested as mild intermittent distention with crampy abdominal pain or as complete bowel obstruction with or without bowel infarction. Symptoms may be intermittent. The single most useful radiologic test in evaluating the possibility of internal hernia, small bowel obstruction, or both in patients after RYGB is probably computed tomography (CT) with oral contrast. Prompt passage of oral contrast into the colon and absence of distention in the bypassed stomach and duodenum are reassuring signs that an internal hernia with obstruction is unlikely. Although radiographic imaging aids in diagnosis, persistent symptoms in the face of equivocal radiographs should prompt exploration.

Typical mortality statistics of large published series of bariatric surgical patients were challenged in an article by Flum et al., which showed 30-day and 1-year death rates of 2.0% and 4.6%, respectively, in a series of 16,155 Medicare patients who underwent bariatric operations between 1996 and 2002.[24] The 30-day and 1-year mortality rates in the age 65 and over Medicare patients were an astounding 4.8% and 11.1%, respectively. Mortality rates were significantly less for high-volume surgeons versus low-volume (≤35 procedures annually) surgeons. Two findings in this important study warrant emphasis:

1. The mortality rate of bariatric operations (and likely other complex surgical procedures) is lowest in the hands of the most experienced surgeons.
2. The mortality rate of bariatric operations published in peer-reviewed journals is considerably better than that of the community at large.

Gastric bypass is occasionally associated with symptoms of "dumping syndrome," including nausea, bloating, diarrhea, and colic. These symptoms are thought to be due to rapid emptying of the small gastric pouch directly into the small bowel. Vasomotor symptoms of dumping are associated with hypoglycemia and include lightheadedness, palpitations, and sweating. These symptoms occur in a smaller percentage of patients. The severity of dumping after gastric bypass is variable, with some patients reporting no symptoms, others having symptoms associated with eating specific foods such as milk products or sweets, and a few patients reporting troublesome symptoms after almost every meal.

Several metabolic complications are inherent in gastric bypass surgery, including iron, folate, and vitamin B_{12} deficiencies, each of which may result in anemia. Because of the relatively high incidence of these micronutrient deficiencies, prophylactic multivitamin/mineral supplements are routinely given to all patients who undergo gastric bypass. However, the efficacy of multivitamin supplements in prevention of both iron and calcium deficiency is problematic. In our experience, a daily multivitamin supplement does not consistently prevent the development of iron deficiency and anemia in women who have undergone gastric bypass. Additional supplements of specific vitamins or minerals in addition to multivitamins are frequently necessary to correct these deficiencies. Fortunately, the vast majority of vitamin and mineral deficiencies after gastric bypass are subclinical and easily corrected with oral supplements of the deficient micronutrients. Injection therapy is rarely required in patients who are willing to take oral supplements. Hospitalization for treatment of these vitamin and mineral deficiencies is rare.

Malabsorption of protein, carbohydrate, and fat has not been documented after conventional gastric bypass.

Gastric Banding

Gastric banding is the most commonly performed bariatric operation in Europe and Australia. Early techniques of gastric banding incorporated a premeasured strip of prosthetic material to restrict oral intake. However, these techniques lacked precision in measuring the volume of stomach above the band. The circumference of the band was generally in the range of 5.0 cm, similar to the measurements used for VBG. The band is sutured to both itself and the stomach to prevent "slipping." Complication rates with nonadjustable techniques of gastric banding were relatively high, with morbidity and mortality rates in the range of 30% and 3%, respectively.[25] Band erosion occurred in 10% to 15% of cases. Erosion occasionally resulted in leaks and obstruction that frequently required reoperation. The concept of an inflatable silicone band was introduced by Kuzmak in 1988.[26] The diameter of the inflatable band is adjusted by infusion of saline through a subcutaneous reservoir. The reported weight loss results and the complication rate with inflatable bands are better than those observed after nonadjustable banding techniques in which strips of polypropylene or Teflon were used.

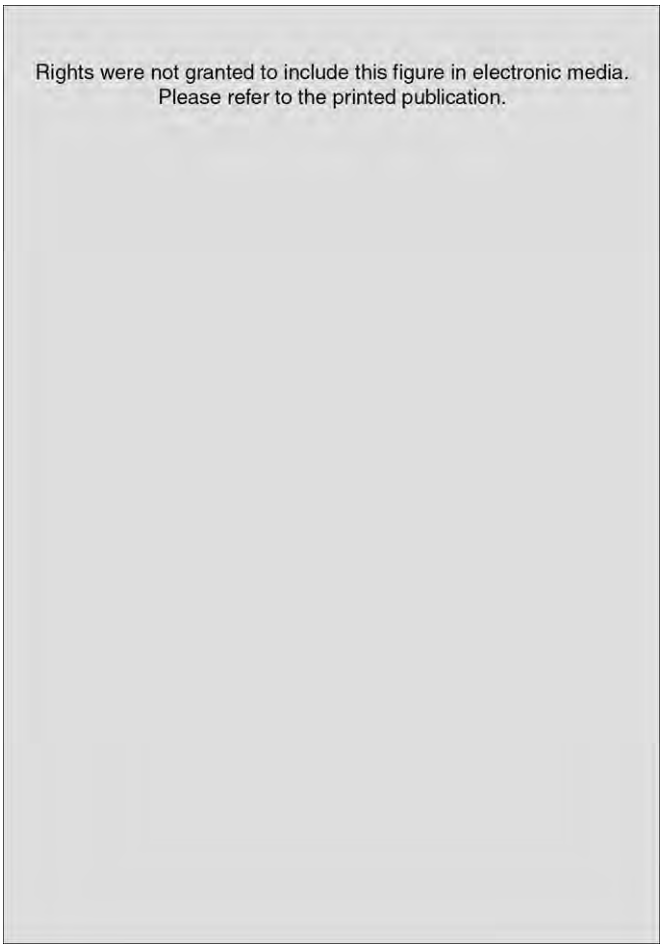
Kuzmak's concept of adjustability was incorporated into laparoscopic approaches. Currently, there are two major brands of laparoscopic adjustable gastric bands: the Lap-Band (Inamed Health, Santa Barbara, California) and the Swedish adjustable gastric band (Obtech Medical, Baar, Switzerland). The Food and Drug Administration approved the Lap-Band device for use in the United States in June 2001. This device is illustrated in Figure 63–5. Adjustable gastric bands are placed laparoscopically via five or six access ports. The original technique used to position the adjustable gastric band involved perigastric dissection high along the lesser curvature of the stomach and entering the omenta bursalis. The band is passed around the upper part of the stomach through this space. Because the perigastric approach was associated with an excessive rate of pouch enlargement and prolapse, the pars flaccida technique was introduced.[27] Dissection with this technique begins at the angle of His, where the phrenoesophageal ligament is opened. The pars flaccida along the lesser curvature of the stomach is then incised to expose the anterior border of the right diaphragmatic crus. A grasper is advanced behind the upper part of the stomach toward the angle of His.

The adjustable band is then inserted into the abdomen. One end of the band is grasped at the angle of His, pulled behind the stomach, and locked anteriorly to create a small proximal gastric pouch. Several nonabsorbable stitches are then placed in the stomach to secure the band as shown in Figure 63–5. The tubing is pulled from the band through the subcutaneous tissue and connected to the access port. The port is secured to the abdominal wall fascia with four nonabsorbable sutures placed through the eyelets on the port. The presence of a hiatal hernia makes band placement more difficult because the normal anatomic landmarks are distorted. Some surgeons consider hiatal hernia an absolute contraindication to banding. Others recommend repair of the crus concomitant with band placement. The gastric band gradually forms a fibrous membrane that fixes its position around the stomach.

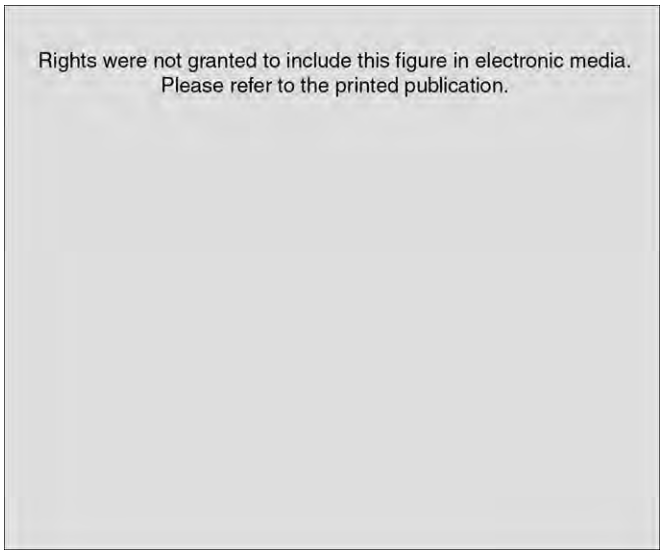
Adjustments begin approximately 6 to 8 weeks after placement and fixation of the band. These adjustments are essential for weight loss and regulate the amount of solid food that can be consumed at one sitting. Usually, four to six adjustments are required during the first year after placement.

Perioperative complications are rare after adjustable gastric banding, with the most common being infection at the access port, which occurs in about 1% of cases and usually requires removal of the port.[27,28] Occasionally, the tubing and band can be spared from port site infection by capping the tubing and reducing it intraperitoneally while the wound heals. After the infection has cleared, the tubing can be reconnected to a new port.

Late complications after adjustable laparoscopic banding are more common and include difficulty with accessing the subcutaneous port, tubing problems, gastric prolapse or "slip," band erosion, esophageal obstruction/dilatation, and dilatation of the gastric pouch. Tubing breaks and problems with access to the



A



B

Figure 63–5. **A,** Lap-Band (Inamed, Santa Barbara, California) in situ just below the gastroesophageal junction. The *inset* shows imbricating sutures that fix the band to the stomach. **B,** Entire Lap-Band device, including tubing and access port. (Courtesy of Inamed Health, Santa Barbara, California.)

subcutaneous port for adjustments occur in 1% to 5% of patients.[28,29] The fixation sutures may occasionally become separated from the fascia and result in angling of the port away from the skin. Although fluoroscopy can facilitate access in these cases, some malrotated ports require repositioning or replacement.

"Slippage" of the band encompasses a spectrum of problems, including gastric pouch dilatation because of placement of the band too low on the stomach and prolapse of the distal part of the stomach beneath the band. Herniation of the distal fundus through the band with resulting necrosis is a rare life-threatening complication. Prolapse may occur on either the anterior or posterior aspect of the stomach. Causes of band prolapse include excessive perigastric dissection, the presence of a sliding hiatal hernia, and protracted, forcible vomiting. Another cause of gastric pouch dilatation is overinflation of the band. It is important to distinguish prolapse from gastric pouch dilatation because prolapse requires operative treatment. Conversely, deflation of the band frequently resolves simple dilatation. Widespread adoption of the pars flaccida technique has reduced the incidence of pouch enlargement and prolapse to approximately 1% and 3% of cases, respectively.[28-30]

Erosion or intragastric migration of adjustable gastric bands occurs in 1% to 3% of patients.[28,30] Possible causes include gradual pressure necrosis and subclinical injury to the stomach adjacent to the band. Band erosion requires operative removal of the band and repair of the residual defect. These procedures may be difficult because of intense inflammatory scarring.

Esophageal dilatation may occur either in the perioperative period or, more commonly, months to years after surgery. Acute esophageal obstruction is rare, whereas late dilatation of the esophagus may be relatively common.[31] The clinical significance of this problem is disputed because most cases are easily remedied by deflation of the band. Conversely, cases associated with dysphagia and complete esophageal obstruction have been reported. Band erosion should be ruled out as the cause of obstruction in these cases.

Weight loss with most techniques of gastric banding has been less consistent than weight loss reported after banded gastroplasty and RYGB. Weight loss after gastric banding is slower (3- to 5-lb weight loss per month) than after other bariatric procedures, but it tends to be protracted over a longer time frame (3 to 4 years).[28,30] Weight loss with the laparoscopic adjustable gastric band is better at international centers than in the United States. International series report mean percent excess weight loss ranging from 40% to 70% with a follow-up of 3 to 8 years.[28-30,32] Results in the United States have been mixed and range between 32% and 58% excess weight loss with a follow-up of 4 years.[31,32]

Biliopancreatic Diversion

Biliopancreatic diversion combines a modest amount of gastric restriction with substantial malabsorption. The concept of biliopancreatic diversion was introduced by Scopinaro during the late 1970s.[33] The technique includes performance of subtotal gastrectomy, with an approximately 400-ml-capacity gastric remnant anastomosed to the proximal ileum. All of the jejunum is excluded from digestive continuity and is anastomosed end to side to a "common channel" of ileum 50 cm proximal to the ileocecal junction. Because this degree of malabsorption predisposes to cholelithiasis, cholecystectomy is also routinely performed. In 1987 DeMeester introduced the duodenal switch procedure for treatment of refractory bile reflux gastritis.[34] Hess, Marceau, and colleagues independently modified this technique of biliopancreatic diversion for bariatric patients.[35,36] A conventional modification of the duodenal switch is illustrated in Figure 63–6. This procedure preserves enough parietal cells that vitamin B_{12} deficiency and marginal ulcers are unusual late complications.

Early postoperative complications are reported in 30% of patients who undergo biliopancreatic diversion, with a 1.3% mortality rate. However, the incidence of metabolic complications within the first postoperative year has been high, including a 30% incidence of anemia, an 8% to 10% incidence of marginal ulcers, and a 20% incidence of hospitalization for treatment of protein-calorie malnutrition.[33] Deaths from hepatic failure have been reported in patients who underwent biliopancreatic diversion. Weight loss results with biliopancreatic bypass have been almost uniformly good. A mean loss of 70% of preoperative weight was reported in a series of 57 patients monitored for more than 18 years, with excellent weight maintenance after stabilization.[37] Other surgeons have reported an average weight gain of only 5% from the point of maximum weight loss at 5 years after biliopancreatic diversion.[35]

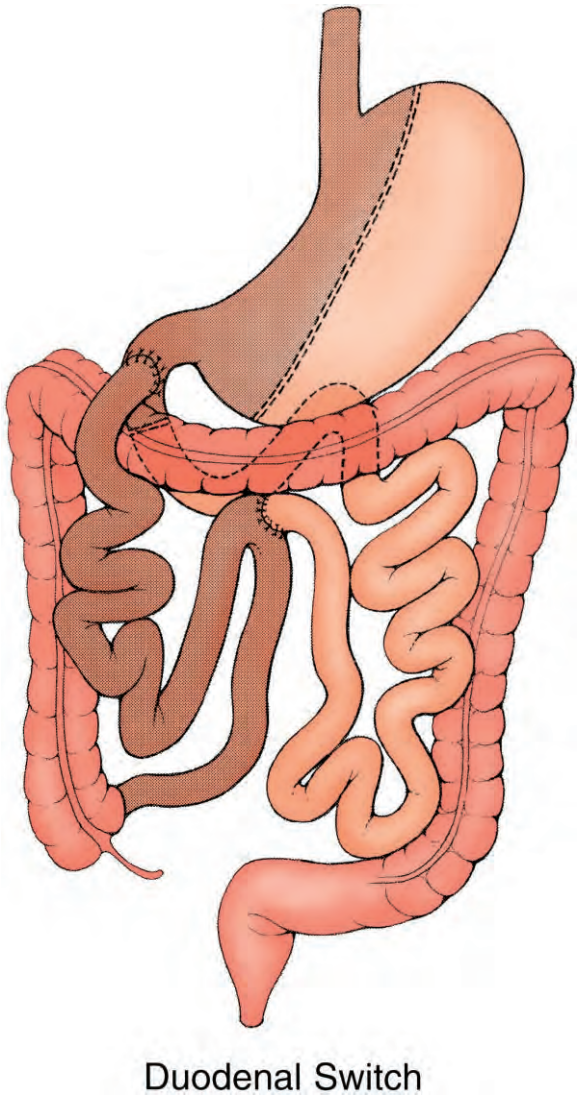


Figure 63–6. Biliopancreatic diversion with duodenal switch. Two thirds of the stomach is excised along the greater curvature with linear staplers. The duodenum is dissected from the head of the pancreas for a distance of 5 cm beyond the pylorus and transected. The ileum is then transected at a point 250 cm proximal to the ileocecal junction. The distal end of the transected ileum *(shaded)* is anastomosed to the proximal duodenum. The remainder of the small bowel *(unshaded portion)* is diverted from the digestive stream. The distal end of the bypassed segment is reanastomosed to the ileum 100 to 150 cm proximal to the ileocecal junction to create the common channel. (From Miller TA [ed]: Modern Surgical Care: Physiologic Foundations and Clinical Applications, 2nd ed. Chapter 68. St. Louis, Quality Medical Publishing, 1998.)

REVISION OPERATIONS

Occasionally, bariatric operations require revision for either inadequate weight loss or late complications. The incidence of major postoperative complications after revision of bariatric procedures is high, with reports ranging from 15% to 60% and a mortality rate ranging from 0% to 15%. The reoperating surgeon must be aware of a persistent gastrogastric fistula and ischemic or undrained gastric remnants (or both). Patients who undergo revision operations for complications frequently have lost a sufficient amount of weight after their initial procedure. These patients should generally be offered a gastric restrictive rather than a malabsorptive procedure. Patients who require takedown of an intestinal bypass for metabolic complications and are no longer overweight are best managed by conversion to a banded gastroplasty for weight maintenance. Conversely, intestinal or biliopancreatic bypass patients who remain substantially overweight are best converted to RYGB in the hope of providing further weight loss through the added gastric restriction. Gastroplasty patients with stomal stenosis and an intact staple line may undergo stomal dilatation by upper endoscopy. Endoscopic dilatation is usually performed with balloon-tip dilators. Unfortunately, less than 50% of patients with stomal stenosis obtain permanent relief with dilatation. Patients who do not respond to dilatation require operative revision, which is best accomplished by conversion to RYGB.

Reversal of bariatric operations without conversion to another weight reduction procedure is invariably associated with prompt regaining of previously lost weight. Gastroplasty patients with unsatisfactory weight loss are best converted to RYGB or, in some cases, biliopancreatic diversion. Gastroplasty or RYGB patients with staple line disruption require transection of the stomach between staple lines. There is a high incidence of subsequent staple line disruption in patients who undergo restapling in continuity. Gastric bypass patients with anatomically intact operations and unsatisfactory weight loss have almost certainly "outeaten" the operation. These patients may be converted to a biliopancreatic diversion procedure with anticipation of further weight loss. A small number of morbidly obese patients will "outeat" any bariatric operation or die trying. Whenever a patient has failed a second technically sound and intact operation, surgeons should approach the prospect of further revision with considerable caution and skepticism. Rejection of such patients for another operation is frequently a prudent decision.

PERIOPERATIVE CARE

All candidates for obesity operations should be interviewed in an outpatient setting before being considered for surgery. During the screening interview, the surgeon should provide prospective patients with a clear understanding of the risks and goals of the operation and explain the mechanism by which the proposed procedure produces weight loss. At the same time, the surgeon should obtain a complete medical history and make a preliminary assessment of the patient's operative risk. Psychological stability should also be evaluated, particularly in terms of the patient's willingness to adjust to the permanent postoperative side effects of gastric restriction and malabsorption. At the conclusion of the interview, the patient should have obtained sufficient information to give informed consent.

Routine preadmission tests include a complete blood count, Chem-21 screen, urinalysis, chest radiograph, electrocardiogram, testing for *Helicobacter pylori* antigen, and ultrasound of the gallbladder. *H. pylori* testing is performed to rule out a treatable cause of postoperative peptic ulcer disease. Patients with a positive test are treated with a combination of antibiotic and proton pump inhibitor therapy. Patients who have symptoms of gastroesophageal reflux disease or peptic ulcer disease should undergo upper endoscopy. An active peptic ulcer is a contraindication to bariatric surgery. The reported incidence of biliary tract disease in the morbidly obese ranges from 25% to 45%, which is three to four times higher than that in the normal-weight population. Hence, preoperative or intraoperative screening for gallstones is recommended in all bariatric surgical patients who have not undergone cholecystectomy. Ultrasonography is the most popular method of evaluation. The reported incidence of symptomatic cholelithiasis after obesity operations ranges from 3% to more than 50%, depending on the type of operation performed. Because symptomatic gallstones developed in more than 50% of patients after Scopinaro's biliopancreatic bypass, it has been recommended that routine cholecystectomy be included as an integral part of that operation. The incidence of gallbladder disease after gastric restrictive operations varies from 3% to greater than 30%. Most surgeons do not perform prophylactic cholecystectomy during gastric restrictive operations, even though the risk of adding cholecystectomy to these procedures is negligible. Ultrasound of the gallbladder is performed to rule out unsuspected gallstones. Patients scheduled to have gastric or biliopancreatic bypass operations should also undergo testing for serum iron, iron-binding capacity, and vitamin B_{12}. Levels of fat-soluble vitamins should be obtained in patients before biliopancreatic diversion. All patients scheduled to undergo revision of a failed bariatric procedure should have blood cross-matched for possible transfusion because blood transfusion is often necessary in patients who undergo revision of failed gastric restrictive operations. All patients should be given intravenous (IV) prophylactic antibiotics during the perioperative period.

Although bariatric surgical patients do not require admission to the intensive care unit (ICU) postoperatively, all patients with sleep apnea, congestive heart failure, or severe asthmatic bronchitis should be considered for admission to the ICU for close monitoring of their cardiopulmonary status. Occasionally, patients who undergo open operations require overnight intubation. Conversely, virtually all patients who undergo laparoscopic operations are extubated within the first several hours postoperatively.

Because obesity is considered a risk factor for postoperative pulmonary embolism, a variety of methods of prophylaxis have been used in an attempt to prevent this feared complication, including subcutaneous low-dose heparin or enoxaparin (Lovenox), pneumatic compression stockings, IV low-molecular-weight dextran, and use of the Trendelenburg position intraoperatively. However, none of these methods have been proved to decrease the incidence of postoperative venous thromboembolism in bariatric surgical patients. Early postoperative ambulation is strongly encouraged and almost certainly contributes to the low incidence of postoperative venous thromboembolism reported in laparoscopic patients. All patients should get out of bed on the night of their operation and walk on the first postoperative day. Prophylactic superior vena cava filters should be considered in patients with a history of deep venous thrombosis or pulmonary embolism.

We routinely use IV patient-controlled analgesia (PCA) in postoperative bariatric patients. PCA provides more consistent pain relief than do intermittent intramuscular injections of narcotic analgesics. Oral narcotics are usually begun on the second or third postoperative day after administration of IV fluids has been stopped. All pills and tablets are crushed and administered as a slurry with a liquid beverage. Patients are instructed to not swallow whole pills during the first 4 weeks postoperatively.

A limited upper gastrointestinal contrast study is routinely performed on the first or second day to examine the integrity of the staple line and outlet stoma, although some experts have questioned the utility of this

approach. If the contrast study is unremarkable, a clear liquid diet is begun. IV fluids are discontinued after clear liquids are tolerated without difficulty. A maximum 1000-calorie full-liquid diet is started on the next day, followed by a pureed diet shortly thereafter. Patients are usually discharged on the second or third postoperative day. Hospitalization for more than 4 days is unusual in the absence of major complications.

Severe distention of the bypassed stomach is an unusual, but serious complication that can be managed by percutaneous decompression or Stamm gastrostomy.

FOLLOW-UP AND DIETARY MANAGEMENT

Postoperative follow-up is extremely important in bariatric surgical patients. During the first year postoperatively, visits are scheduled at 1 week, at 4 weeks, and then at 3-month intervals thereafter. Two follow-up visits are scheduled at 6-month intervals during the second year, with subsequent annual visits. All patients should have easy access to both the operating surgeon and a clinical nutritionist.

Postoperative dietary counseling is essential to the long-term success of bariatric operations. Patients are instructed to follow a full liquid pureed diet for 4 weeks after discharge. A liquid or chewable multivitamin supplement is taken during this phase of the diet. The purpose of the pureed liquid diet is to (1) allow time for patients to adjust to their tremendously restricted stomach capacity by consuming foods that are relatively easy to chew and swallow and (2) minimize the likelihood of vomiting during the early postoperative period. Repeated episodes of vomiting during the early postoperative period have been associated with staple line disruption and leaks. Patients are started on a soft solid diet at the 4-week visit and then gradually progress to a normal diet. Patients can resume swallowing whole pills and tablets after solid food is well tolerated.

Patients who undergo gastric bypass or biliopancreatic diversion require periodic blood tests to check for possible nutritional deficiencies. These patients should take a multivitamin supplement with minerals daily for the rest of their lives. Menstruating women who have undergone gastric or biliopancreatic bypass should also take additional prophylactic iron supplements. Oral calcium supplementation of at least 1 g daily should be taken by all bypass patients. After biliopancreatic diversion, many patients require additional protein and other nutritional supplements, particularly fat-soluble vitamins.

AMELIORATION OF OBESITY-RELATED DISEASES

Amelioration of obesity-related medical problems is a primary goal of all bariatric operations. The incidence of type 2 diabetes mellitus in the morbidly obese ranges from 10% to 20%. Improvement or resolution of morbid obesity–associated diabetes, including a significant decrease in insulin resistance after weight reduction surgery, has been reported by many investigators. Postoperative changes in glucose metabolism in morbidly obese diabetic patients have been studied extensively. Pories, Schauer, and colleagues independently reported that nearly 85% of patients with either overt diabetes or impaired glucose tolerance become euglycemic after open and laparoscopic RYGB.[38,39] Fasting insulin and glycosylated hemoglobin concentrations were also reduced to normal levels, whereas insulin release, insulin resistance, and utilization of glucose were substantially improved.

There is relatively little information about the effects of weight reduction surgery on obesity-related cardiovascular dysfunction. Echocardiography was used to measure a number of parameters of ventricular function in 63 morbidly obese patients. Surgically induced weight loss was associated with significant improvement in left ventricular ejection fraction and smaller, but measurable improvements in mean blood pressure, cardiac chamber size, and ventricular wall thickness.[40] Two groups have independently reported the response of blood pressure to weight loss in hypertensive patients after RYGB. Although each group noted improvement or resolution of high blood pressure in approximately 70% of patients after weight stabilization, there were conflicting results relative to the magnitude of the weight loss. One group found a significant correlation between improved blood pressure and proximity to ideal weight.[41] The other reported a correlation between improved blood pressure and the absolute quantity of weight lost.[42]

The ameliorative effects of weight reduction surgery on obesity-related hyperlipidemia have been documented by a number of investigators. Independent reports have demonstrated significant decreases in both total cholesterol and triglyceride levels after both gastroplasty and gastric bypass. Several investigators reported high-density lipoprotein/low-density lipoprotein ratios after gastric bypass and suggested that the risk for atherosclerosis may be decreased by surgically induced weight loss.[43] Our group and others have shown that these lipid reductions persist for as long as weight loss is satisfactorily maintained.[44] Occasionally, patients who regain a substantial portion of their lost weight are able to maintain the salutary changes in lipid profile.

Obesity-hypoventilation syndrome probably poses the greatest immediate risk to life of any of the obesity-related comorbid conditions. There have been a number of independent reports of complete resolution of sleep apnea symptoms and significant improvement in both arterial blood gas parameters and lung volumes after gastric restrictive operations. Significant reductions in mean pulmonary artery pressure have also been reported in patients with obesity-hypoventilation syndrome after RYGB.[45] Many patients in these reports were incapacitated by their condition preoperatively but, after losing weight, were able to lead normal lives.

Morbidly obese women of childbearing age are known to have a high incidence of infertility, as well as other menstrual and hormonal problems. Perioperative abnormalities have been reported in sex hormone–binding globulin (SHBG) in infertile morbidly obese women who were attempting pregnancy. However, after gastroplasty-induced weight loss, there were significant improvements

in SHBG levels and a significantly decreased incidence of irregular menses.[46] A number of previously infertile women became pregnant and delivered normal babies after surgically induced weight loss. Similar results were reported by another group after gastric bypass. Despite restricted intake, both the mother and the developing fetus maintained adequate nutritional status. Pregnancy is not recommended during the period of active postoperative weight loss (the first 18 months postoperatively).

Although the proliferation in numbers of bariatric surgical procedures has slowed during the past 2 years, it appears that a need for surgical treatment will continue to exist in the absence of an effective alternative treatment. The current gastric restrictive operations appear to be safe and effective enough to justify their continued use. At present, surgery offers the only realistic hope for successful weight loss in the morbidly obese.

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Chapter

64

Foreign Bodies and Bezoars of the Stomach and Small Intestine

Karen A. Chojnacki

FOREIGN BODIES

Foreign bodies in the stomach and duodenum are relatively common, and nearly 80% of cases of foreign body ingestion occur in the pediatric population.[1] Such ingestion is usually inadvertent and a result of the natural oral curiosity of an infant or child. In several series, coins are the most commonly ingested objects by infants and children.[2-7] Other foreign bodies frequently found in this population are listed in Table 64–1. The foreign bodies most commonly ingested by adults are listed in Table 64–2. Several adult populations are at risk for foreign bodies in the gastrointestinal (GI) tract. The elderly, demented, and intoxicated have an increased risk for accidental foreign body ingestion. Denture wearers have decreased tactile sensation of the palate and are also at risk for accidental foreign body ingestion.[8,9] Psychiatric patients and prisoners are more apt to intentionally swallow foreign bodies for secondary gain. This population often swallows multiple objects on multiple occasions.[10]

Eighty percent to 90% of ingested foreign bodies pass through the GI tract spontaneously without injury,[11] 10% to 20% require endoscopic removal, and 1% require surgery.[11,12] Perforation, obstruction, and failure of an object to progress though the GI tract are all complications of foreign bodies that require surgical or endoscopic intervention. Obstruction and perforation can occur at any point along the GI tract. Obstruction is most likely to take place at the pylorus, the duodenal sweep, the ligament of Treitz, and the ileocecal valve. Objects greater than 5 cm in length or 2 cm in diameter are unlikely to pass through the pylorus.[13] Patients with a history of pyloric stenosis, previous pyloric surgery, or ulcer disease are at increased risk for obstruction.[14]

One percent of foreign body ingestions result in perforation of the GI tract. Perforation by a foreign body is often secondary to accidental ingestion of a sharp or pointed object such as a fish or chicken bone or a toothpick. The duodenal sweep is at increased risk for perforation from long or pointed objects (or both) because of its C shape.[4] In cases of perforation, the diagnosis of foreign body ingestion is often made intraoperatively because the patient is rarely aware of the ingestion.

Interestingly, once foreign bodies travel beyond the ligament of Treitz, complications are rare. In the small bowel lumen, objects are subject to axial flow and reflex relaxation of the muscle wall. This tends to orient objects with the blunt end leading and the sharp end trailing, thus decreasing the risk for bowel injury.[15] Within the colon, objects become centered in stool, which further protects the bowel wall and allows the objects to safely exit the GI tract.[16]

Diagnosis

The diagnosis of foreign bodies within the stomach and small intestine is established by patient history, radiology studies, or endoscopy (or any combination). Most communicative adults will be able to provide an accurate history of how, what, and when an object was ingested. Symptoms most commonly occur when the ingested object is in the esophagus and include dysphonia, dysphagia, and odynophagia. Retrosternal pain, pharyngeal discomfort, and respiratory compromise are also symptoms of a foreign body lodged in the esophagus. Patients will be able to localize an object when lodged at the cricopharyngeal muscle, but localization becomes less accurate as the object moves distally. Patients are able to accurately localize ingested foreign bodies in the esophagus in 30% to 40% of cases but are rarely able to localize objects when in the stomach.[17] Sudden resolution of symptoms often indicates that the object has passed to

Table 64–1 Foreign Bodies Found in Children Aged 3 Months to 10 Years

Coins	33
Bones	4
Pins	4
Jacks/jackstones	2
Battery	1
Toy bell	1
Button	1
Marble	1
Meat	1
Metal clip	1
Tack	1
Total	50

From Pfau PR, Ginsberg GG: Foreign bodies and bezoars. In Feldman M, Friedman LS, Sleisenger MH, et al (eds): Gastrointestinal and Liver Disease. Philadelphia, WB Saunders, 2002: 386-398.

Table 64–2 Foreign Bodies Found in Older Children and Adults Aged 11 to 91 Years

Meat	115
Bones	35
Fiber	13
Pills	6
Coins	5
Dental hardware	3
Batteries	2
Brush bristle	2
Brazil nut	1
Guitar pick	1
Herb	1
Miller-Abbott tube	1
Pencil	1
Popcorn husk	1
Potato	1
Razor blade	1
Splinter	1
Spoon	1
Wrapper	1
Total	192

From Pfau PR, Ginsberg GG: Foreign bodies and bezoars. In Feldman M, Friedman LS, Sleisenger MH, et al (eds): Gastrointestinal and Liver Disease. Philadelphia, WB Saunders, 2002: 386-398.

the stomach. Once a foreign body has reached the stomach, patients are usually asymptomatic unless perforation or obstruction develops.

The history and symptoms are less reliable with children and psychiatric patients. Most often the ingestion is a witnessed event or suspected by a caregiver. Recurrent foreign body ingestion is reported in 3.3% to 10% of psychiatric patients and prisoners.[4,18] Symptoms of foreign body ingestion in these patient populations include choking, vomiting, blood-stained saliva, respiratory distress, and stridor. Children may also fail to thrive or refuse to eat.[19] Thirty-three percent of children and infants may be asymptomatic after foreign body ingestion, but the true percentage may even be higher.[20]

All patients with suspected foreign body ingestion should have anteroposterior and lateral radiographs of the chest and abdomen taken to aid in determining the presence, type, and location of the foreign body. Plain films may also identify signs of perforation such as pneumoperitoneum, pleural effusion, or subcutaneous air.[4,21] Lateral films help distinguish between objects in the tracheobronchial tree versus the esophagus. Some objects, such as glass, bone, aluminum, plastic, and wood, are radiolucent and can be difficult to detect on plain radiography. If ingestion of one of these objects is suspected, flexible endoscopy is recommended to confirm and treat the ingestion.[4] In patients with a contraindication to endoscopy, a thin barium contrast study can be used to evaluate the upper GI system.[11] Barium esophagograms should not be performed if there is concern of perforation or obstruction.

Patients who remain symptomatic with normal imaging studies should undergo flexible endoscopy because it provides safe and effective management of foreign bodies in the upper GI tract. Multiple series report success rates for endoscopic management of foreign bodies in excess of 95%.[4,5,22,23]

Management

Once a foreign body has reached the stomach, the risk for complications diminishes greatly. Nearly 90% of objects in the stomach will progress through the GI tract without complication. Most patients can be managed conservatively. Patients who have ingested small or blunt objects, such as coins, can be observed with daily or weekly radiographs to document progression of the foreign body. Endoscopic removal of certain objects is recommended before passage from the stomach, as discussed in the next section. Surgery is indicated if signs or symptoms of perforation, hemorrhage, fistula formation, or obstruction of the small or large bowel develop. Failure of a sharp or pointed object in the small intestine to progress after 3 days is also an indication for surgery.[10] Several authors have reported success with laparoscopic removal of ingested foreign bodies.[24-26]

Certain foreign bodies deserve special consideration.

Sharp/Pointed or Long Foreign Bodies

Toothpicks, nails, needles, bones, razor blades, safety pins, and dental prostheses are the most commonly ingested sharp foreign bodies. Surgical intervention is most often required for bones and toothpicks.[21,27] The terminal ileum is the most frequent site of perforation by a sharp foreign body. Because 15% to 35% of these sharp foreign bodies will cause perforation, they should

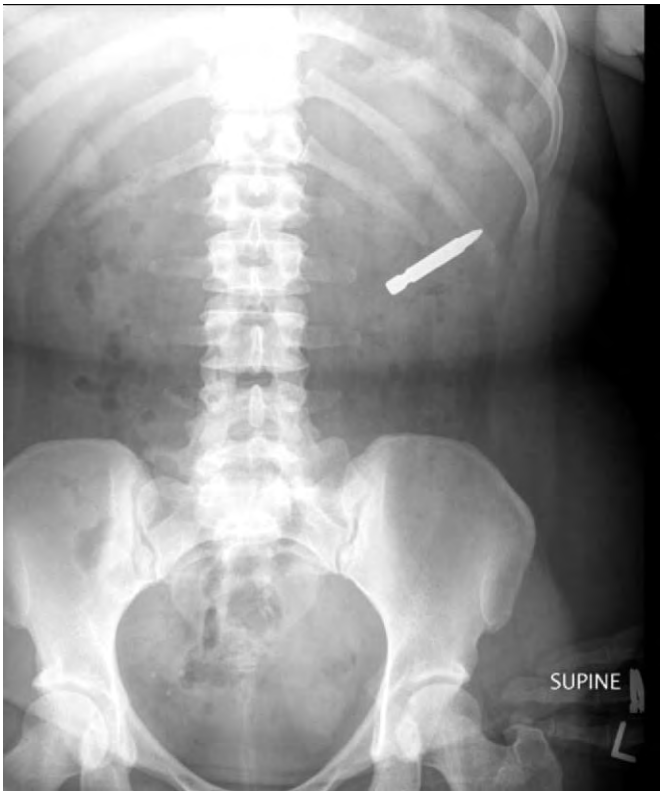

Figure 64–1. A 36-year-old woman ingested a drill bit while working on home repairs. By the time that she arrived at the emergency department and this radiograph was taken, the bit had passed through the stomach into the small bowel.

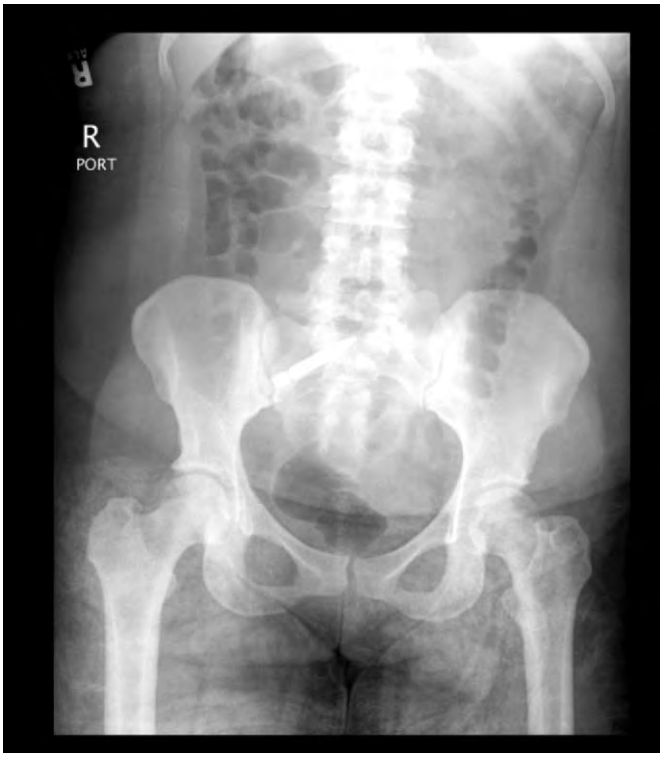

Figure 64–2. After 24 hours, the drill bit had progressed to the terminal ileum. Here it lies in the right lower quadrant with the blunt end leading.

be removed by flexible endoscopy while still in the stomach. Objects longer than 5 cm are unlikely to pass through the duodenum and should also be removed.[13] Sharp or pointed objects that do pass through the duodenum into the small intestine can be treated conservatively unless symptoms of perforation or obstruction develop (Figs. 64–1 and 64–2). If the foreign body fails to reach the colon within 3 days, it should be surgically removed. When removing a sharp object with the endoscope, the foreign body should be positioned so that the sharp end trails distal to the endoscope.[10] This follows Jackson's axiom: "Advancing points puncture, trailing points do not" (Fig. 64–3).[28]

Button Batteries

Several common devices, such as hearing aids, calculators, cameras, computers, watches, and electronic games, are powered by small, often coin-like "button batteries." Ingestion of these batteries is widely reported.[29-33] Ten percent of ingested button batteries will become symptomatic. Batteries larger than 21 mm are more likely to cause problems. The most common battery systems contain an alkaline electrolyte solution that is a 26% to 45% solution of potassium or sodium hydroxide. This

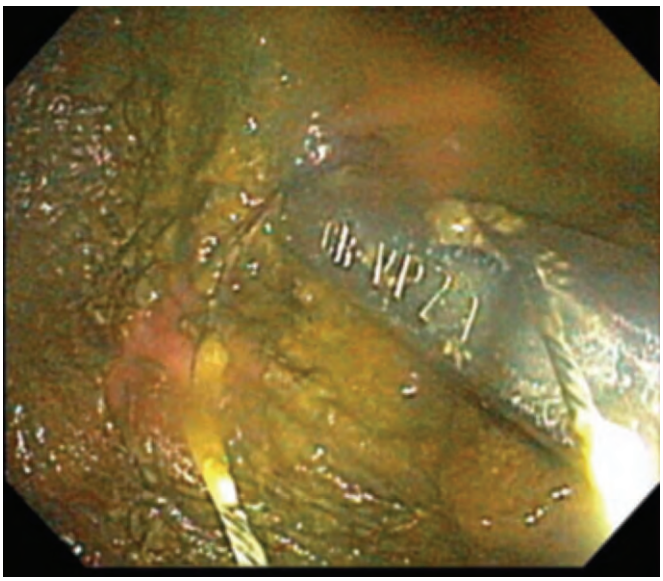

Figure 64–3. The drill bit failed to progress into the colon over the next 3 days. It was removed by colonoscopy from the terminal ileum with a snare.

alkaline electrolyte can cause rapid liquefaction necrosis of tissues if it leaks into the GI tract. Batteries can also cause tissue damage by low-voltage burns and pressure necrosis.[31,34]

Button batteries lodged within the esophagus should be removed by endoscopy as soon as the diagnosis is established to prevent burn, perforation, or stricture of the esophagus. Once a battery has reached the stomach, it will usually pass without difficulty. Daily radiographs should be obtained. If the battery has not progressed beyond the pylorus by 36 to 48 hours, it should be retrieved by endoscopy. Emesis should not be induced to avoid aspiration of the battery into the trachea.[29,32,35] If symptoms of epigastric pain, fever, or peritonitis develop, the patient should be considered for surgical exploration.

Once in the small intestine, complications from an ingested button battery are quite rare. Only one complication has been reported in nearly 100 cases involving the intestine. In this case, the battery lodged in Meckel's diverticulum and caused perforation.[36] Most batteries will pass through the entire GI tract in 72 hours, with a range of 12 hours to 14 days.[29] After the battery has passed the pylorus, radiographs are obtained every 3 to 4 days. Surgery is warranted if the battery fails to progress or symptoms of perforation or obstruction develop.

Double AA and triple AAA alkaline batteries will usually pass from the stomach to the anus without complications.[4]

Illicit Drugs

Because of the ongoing popularity and profitability of heroin and cocaine, these drugs continue to be smuggled into the United States by "body packers" or "mules." Body packers ingest multiple small packages containing heroin or cocaine. The packets are usually condoms stuffed with 3 to 5 g of an illicit drug.[37] The packets are then swallowed so that they are concealed in the GI tract. Body packers often take high doses of anticholinergic drugs to postpone passage of the packets through the GI tract. Cocaine is lethal at a dose of 1 to 3 g; therefore, rupture of only one packet can be fatal.[38]

Body packers can have a variety of symptoms; however, they are often asymptomatic and are brought to medical attention by drug enforcement officials. These patients may also have signs and symptoms of bowel obstruction.[39] Plain radiographs will demonstrate the drug packets in 70% to 90% of cases (Fig. 64–4).[40] Patients may also have symptoms of toxicity from the carried drug, indicative of packet rupture. Patients with toxicity or obstruction, or both, should be stabilized and undergo urgent surgical evaluation. Gastrostomy, multiple enterotomies, or colotomies (or any combination) may be required to remove all drug packets.[41] Endoscopic retrieval is contraindicated because of the risk for perforation of the packet.[37] If a patient comes to medical attention within 24 hours of packet ingestion and is stable, conservative management can be attempted. These patients require close observation, whole-gut lavage, and serial radiographs to document evacuation of all packets.[42]

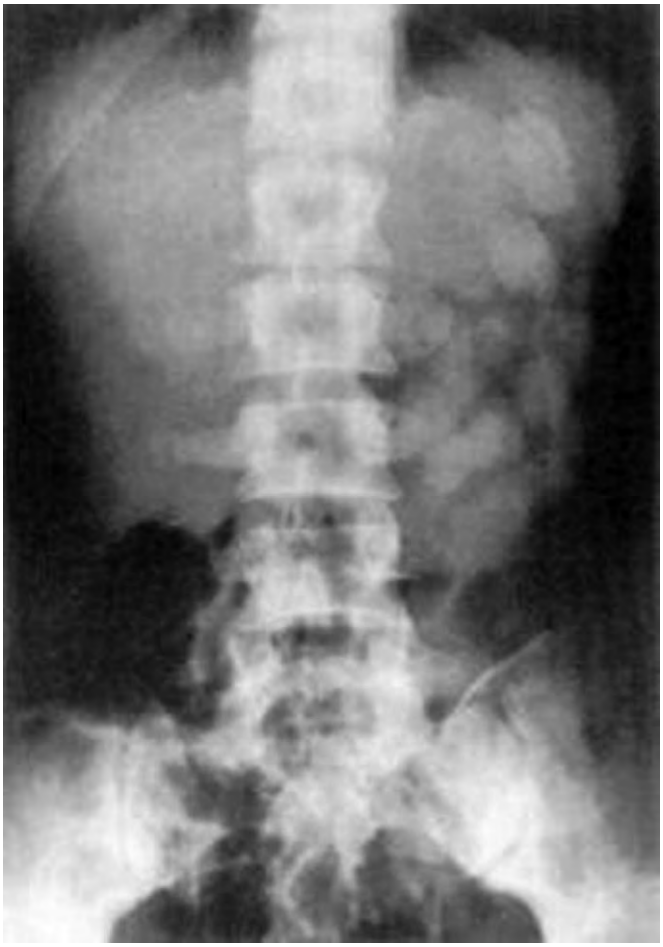

Figure 64–4. Plain abdominal radiograph showing multiple drug-containing packets within the bowel lumen. This patient is a "body packer" or "mule" attempting to smuggle drugs. (From Miller JS, Hendren SK, Liscum KR: Giant gastric ulcer in a body packer. J Trauma 45:617, 1998.)

BEZOARS

Bezoars are retained collections of indigestible foreign material that accumulate in the GI tract. Most bezoars are located in the stomach, but they may be encountered in the esophagus, small intestine, and rectum.[43] Altered gastric physiology with impaired gastric emptying and decreased acid production is often the cause of bezoar formation. These changes are usually consequences of previous gastric surgery, which is present in 70% to 94% of patients with bezoar formation.[44] Vagotomy with pyloroplasty or antrectomy is a predisposing factor for bezoar formation.[45] Patients with gastroparesis, diabetes, end-stage renal disease, and prolonged mechanical ventilation are at increased risk for bezoars.[46] In some patients, ingestion of large amounts of indigestible material is the only risk factor for bezoar formation.

There are four types of bezoars: phytobezoars, trichobezoars, pharmacobezoars, and lactobezoars. Phytobezoars are the most frequent type of bezoar and occur most commonly with the foods listed in Table 64–3.

Table 64–3 Contents of Various Bezoars

Phytobezoar	Trichobezoar	Pharmacobezoar
Celery	Hair	Nifedipine
Pumpkin	Carpet fibers	Procainamide
Grape skins	String	Verapamil
Prunes	Clothing	Theophylline
Raisins		Cholestyramine
Leeks		Meprobamate
Beets		Sucralfate
Persimmons		Kayexalate resin
		Guar gum
		Enteral feeding formulas
		Vitamin C tablets
		Vitamin B_{12}
		Lecithin
		Ferrous sulfate

From Pfau PR, Ginsberg GG: Foreign bodies and bezoars. In Feldman M, Friedman LS, Sleisenger MH, et al (eds): Gastrointestinal and Liver Disease. Philadelphia, WB Saunders, 2002:386-398.

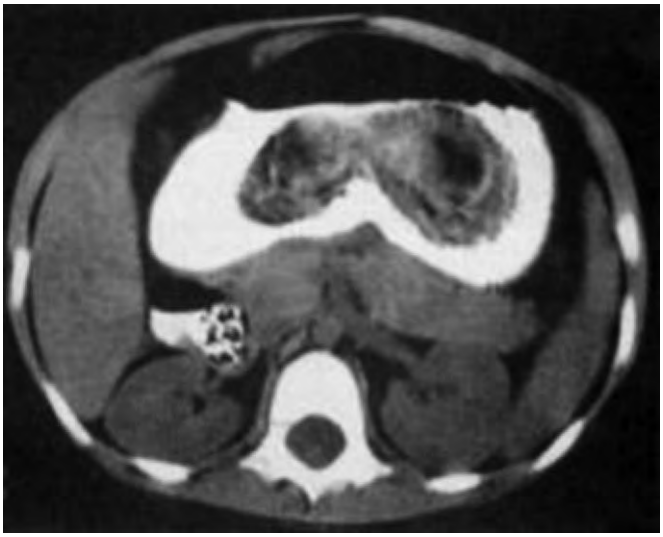

Figure 64–5. Computed tomography scan revealing a dilated stomach with an intraluminal mass consistent with a trichobezoar. (From Phillips MR, Zaheer S, Drugas GT: Mayo Clin Proc 73:653-656, 1998.)

These foods are composed of large amounts of nondigestible fiber such as cellulose, lignin, and fruit tannin.[47] A high concentration of tannins, exposed to gastric acid, can form a coagulum leading to bezoar formation.[48] Phytobezoars are typically dark brown, black, or green when visualized by endoscopy.

Trichobezoars are composed of hair or hair-like fibers (see Table 64–3). They are observed most commonly in children and women younger than 30 years.[49] Frequently, these patients have underlying mental retardation or psychiatric disorders. Trichotillomania is an impulse control disorder characterized by the repeated urge to pull out scalp and body hair. Trichophagia is the compulsion to eat or chew on hair. These behavioral disorders are associated with trichobezoar formation. Hair and fibers in the stomach become trapped in gastric folds. Trichobezoars are typically black regardless of the color of the hair ingested because of enzymatic oxidation of gastric acid on the hair fibers. Some gastric trichobezoars have a long extension of hair that trails into the duodenum, a condition known as the Rapunzel syndrome.[50] It has been reported to cause jaundice and pancreatitis as a result of obstruction of the ampulla of Vater by hair.[51,52]

Pharmacobezoars are composed of medications or vitamins (see Table 64–3). Resin-coated, extended-release products or other products designed to resist digestion are most often the nidus for this type of bezoar formation.[46] Pharmacobezoars can result in reduced medication efficacy because the active agent is trapped in the bezoar and cannot be absorbed. Alternatively, toxicity can result when the previously bound active agent is released in excessive amounts. Fatality secondary to pharmacobezoars has been reported. At autopsy the patient was found to have a serum theophylline concentration of 190.1 mg/ml (normal, 10 to 20 mg/ml). A 318-g pharmacobezoar containing 29 g of theophylline in sustained-release tablets was found within the stomach.[53]

Lactobezoars are a compact mass of undigested milk concretions located within the GI tract of infants and toddlers. These rare bezoars have been linked to nearly every commercially available infant formula and breast and cow milk.[54]

Symptoms and Signs of Bezoars

The most common symptom present in 80% of patients with bezoars is vague epigastric discomfort. Other symptoms include nausea, vomiting, anorexia, early satiety, and weight loss. If a bezoar reaches a large size and is present for a prolonged period, it may cause pressure necrosis and ulcers. Ulceration can lead to bleeding or obstruction. Once in the small bowel, bezoars most commonly result in obstruction.[55]

Physical examination is often unrevealing. Occasionally, a palpable mass may be present. Patients with trichotillomania and trichobezoars may have patchy baldness.[56]

Diagnosis

Bezoars can be demonstrated on plain films and computed tomography scans (Fig. 64–5). Barium studies will reveal a gastric filling defect (Fig. 64–6).[47] Up to 75% of bezoars may be missed on radiography. Endoscopy is the gold standard for the diagnosis of bezoars. The endoscopic appearance of phytobezoars consists of an amorphous mass of brown, green, or black material (Fig. 64–7). Trichobezoars are black, hard, and concrete-like. Pharmacobezoars contain whole pills or pill frag-

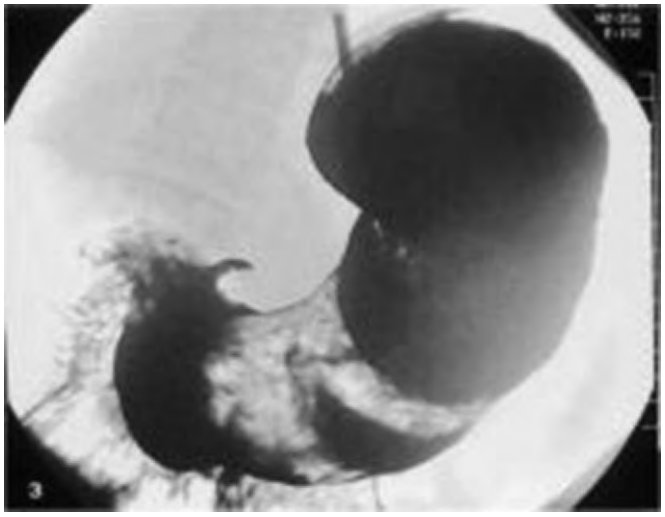

Figure 64–6. Barium study outlining a large gastric mass consistent with a bezoar. (From Zamir D, Goldblum C, Linova L, et al: J Clin Gastroenterol 38:873-876, 2004.)

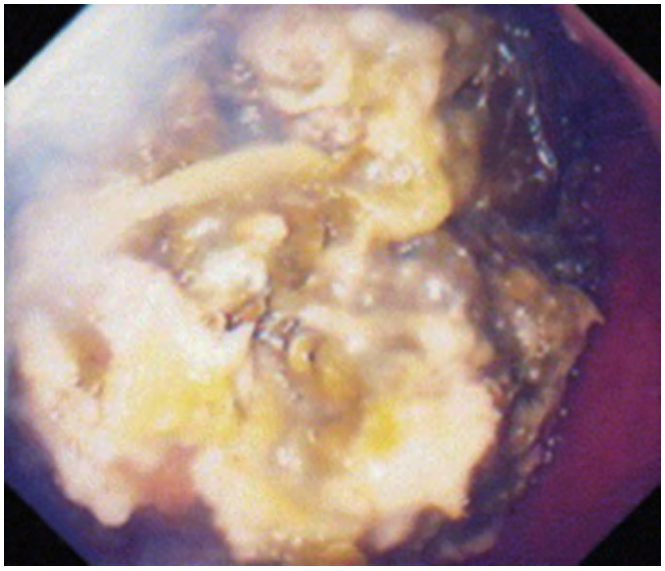

Figure 64–7. Endoscopic appearance of a phytobezoar. (From Sechopoulos P, Robotis JF, Rokkas T: Gastric bezoar treated endoscopically with a carbonated beverage: case report. Gastrointest Endosc 60:662-664, 2004.)

ments.[47,56] Lactobezoars are most commonly identified on contrast-enhanced upper GI series or ultrasound.[54]

Treatment

Treatment of bezoars involves removal of the mass and prevention of recurrence. Some small bezoars can be managed medically. Once a diagnosis is established by endoscopy, institution of a clear liquid diet and a prokinetic agent may clear the bezoar. Nasogastric lavage may be useful for these small bezoars.[57]

Most bezoars require endoscopic therapy. Using biopsy forceps or polypectomy snares, a bezoar can be fragmented and the pieces removed with multiple passes of the endoscope. The reported success rate of this technique is 85% to 90%. In addition to endoscopic fragmentation, success has been reported with the use of electrohydraulic lithotripsy, pulsed water jets, Nd:YAG laser, and needle-knife bezotome.[58-60] Enzymatic dissolution of bezoars has also been described with cellulose, papain (meat tenderizer), *N*-acetylcysteine, and Coca-Cola.[61-63]

Surgical intervention is required if endoscopic therapy fails or complications of bleeding, obstruction, or perforation occur. Trichobezoars are the most likely to require surgical management and can be removed by open or laparoscopic gastrostomy.[57,64] During surgery, the small bowel should be examined for a concomitant bezoar, which should be removed by enterostomy or milked into the cecum for passage through the large bowel.

In addition to removal of the bezoar, attempts must be made to prevent recurrence. Avoidance of foods causing a phytobezoar is necessary. Prophylactic treatment with cellulose can be considered. Patients with a motility disorder may benefit from prokinetic agents such as metoclopramide.[57] Patients with an underlying psychiatric disorder require specific therapy, which may include selective serotonin uptake inhibitors, hypnosis, or play therapy (children) to avoid recurrence.[65]

Lactobezoars are treated by withholding oral feedings and instituting intravenous hydration.[66] Gentle gastric lavage may decrease treatment time.[67] Although some recommend switching these infants to elemental formula, this may be unnecessary because recurrence has never been reported.[54]

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Chapter

65

Surgical Diseases of the Stomach and Duodenum in Infants and Children

Harsh Grewal ▪ William H. Weintraub

Surgical diseases of the stomach and duodenum in infants and children are often the result of developmental anomalies. This chapter reviews congenital and acquired diseases of the stomach and duodenum in infants and children that a surgeon may encounter.

EMBRYOLOGIC DEVELOPMENT

At the beginning of the fourth week of development, the primordial gut forms from lateral and craniocaudal folding of the embryo. The distal part of the foregut dilates to form the stomach around the fourth to fifth week of development. During the 6th to 10th week, as the stomach enlarges, it also rotates 90 degrees in a clockwise direction. These differential rates of growth and subsequent rotation result in the stomach assuming its final position: the cranial part (gastric fundus) on the left and the caudal part (pylorus) on the right of the midline, the lesser curvature facing cranially and to the right, and the greater curvature located caudally.

The transition from foregut to midgut occurs at the second portion of the duodenum, just distal to the entry of the bile duct. The celiac arterial trunk supplies this part of the stomach and duodenum, whereas the superior mesenteric artery supplies the midgut (the bowel distal to the entry of the bile duct). The proximal duodenum moves superiorly and to the right as the distal duodenum rotates down and to the left, thereby resulting in the "C-loop" configuration of the duodenum around the 6th to 10th week of development. Elongation of the midgut around the fifth to sixth week causes herniation of the midgut into the umbilical cord (physiologic umbilical herniation). The midgut then rotates nearly 270 degrees counterclockwise around an axis formed by the superior mesenteric artery, which results in fixation of the fourth portion of the duodenum to the left of the aorta. At the 10th to 12th week, the extraembryologic coelomic gut returns to the abdominal cavity. Subsequent shortening of the duodenal mesenteric base plus fusion with the parietal peritoneum fixes the duodenum in its retroperitoneal location at the ligament of Treitz to the left of the midline. The ampulla of Vater, in the second part of the duodenum, is medial and is the site where the common bile duct and often the pancreatic ducts enter into the duodenum.[1]

During this period of development, the proximal duodenum undergoes epithelial proliferation, and a transitional solid cord is created that obliterates the lumen. Around the eighth week, this transitional solid phase undergoes vacuolization with resultant recanalization. Vascular accidents or aborted recanalization can result in congenital duodenal obstruction. The pancreas develops from the rotation and fusion of paired buds arising from the dorsal and ventral duodenal entodermal epithelium, so abnormalities in development can result in an annular pancreas and in heterotopic pancreatic rests in the proximal duodenum or pylorus.[1]

INTESTINAL OBSTRUCTION IN THE NEWBORN

Because congenital and acquired diseases of the stomach and duodenum in the newborn may cause proximal intestinal obstruction, a brief review of the signs and symptoms and a diagnostic approach are presented in this section. Neonatal intestinal obstruction is often accompanied by bilious vomiting and alterations in the passage of meconium. Bilious vomiting in a newborn or infant should be presumed to be secondary to malrota-

tion with midgut volvulus, and this condition should always be ruled out with an upper gastrointestinal (GI) study because untreated midgut volvulus can rapidly lead to intestinal ischemia and gangrene with loss of intestine and possibly death. The differential diagnosis of neonatal intestinal obstruction, especially with bilious vomiting, covers both proximal and distal obstructive lesions, including congenital gastric or duodenal obstruction, proximal and distal small intestinal atresia, meconium ileus secondary to cystic fibrosis, GI duplications, Hirschsprung's disease, colonic atresia, meconium plug syndrome, small neonatal left colon syndrome, and imperforate anus. Spontaneous gastric perforation and necrotizing enterocolitis may also be manifested as feeding intolerance and bilious vomiting. Clinically, neonatal sepsis with ileus may suggest intestinal obstruction.

Clinical Features and Diagnosis Proximal intestinal obstruction is usually accompanied by vomiting and a nondistended abdomen, whereas abdominal distention characterizes a distal intestinal obstruction; however, localized upper abdominal distention can suggest duodenal atresia or gastric outlet obstruction. Abdominal wall discoloration plus peritonitis may be associated with intestinal necrosis or perforation and indicates the need for immediate laparotomy. Plain abdominal radiography, followed by an upper GI series, is the usual sequence of studies in the evaluation of proximal intestinal obstruction. A plain film revealing pneumatosis suggests necrotizing enterocolitis. The "double bubble" from a distended stomach and duodenal bulb, with a gasless lower abdomen on a plain radiograph in a neonate, is suggestive of duodenal atresia. The presence of distal gas with a "double bubble" suggests malrotation with midgut volvulus. Distention of the small and large intestine is difficult to distinguish on plain radiographs in a newborn; therefore, differentiation of distal from proximal obstruction relies on the number of distended air-filled loops because with proximal obstruction there will be fewer air-filled loops. A prone cross-table lateral radiograph to determine the presence of gas in the distal end of the rectum may also help identify the level of obstruction.

Suspicion of a proximal obstruction will then suggest the need for an upper GI study, and distal obstruction, a lower GI study. In the absence of an acute abdomen on examination, an infant or newborn with bilious vomiting should have an upper GI study performed urgently to rule out malrotation with possible volvulus (Fig. 65–1A and B). The study should demonstrate the ligament of Treitz in its normal location to the left of the spine and at or above the level of the duodenal bulb to exclude malrotation. An upper GI study may also demonstrate malrotation without volvulus (see Fig. 65–1C), atresia, or stenosis, although in the absence of suspicion for midgut volvulus, it may not be necessary to perform this study urgently.

The following discussion of surgical diseases of the stomach and duodenum in infants and children is separated into congenital and acquired conditions.

CONGENITAL CONDITIONS

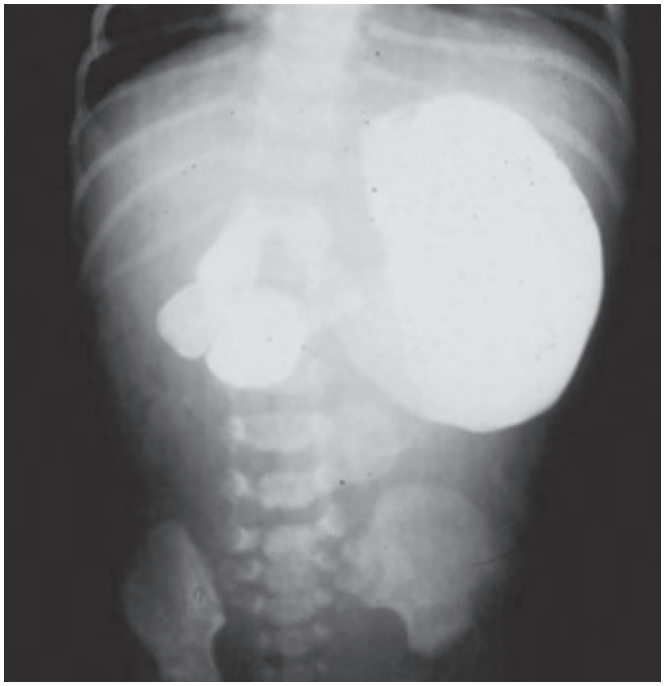
Gastric Duplications

Incidence and Etiology Duplications in the stomach and duodenum are uncommon and constitute less than 15% of all GI duplications. There are a number of theories on the embryogenesis of duplications, including the "split notochord" and "partial twinning" theory; additionally, duplications may be related to disordered recanalization of the solid-cord transitional embryonic phase. Duplications are usually found along the mesenteric border and share the blood supply of the adjacent functional stomach or intestine.[2,3]

Clinical Features In neonates or infants, gastric and duodenal duplications may be associated with signs and symptoms of gastric outlet obstruction. Less acute manifestations include a palpable mass or a mass detected on imaging (including fetal ultrasound), failure to thrive, abdominal discomfort, or GI bleeding. Duplications occasionally first come to attention as an emergency because of either a perforation or bleeding secondary to peptic ulceration. Gastric duplications are typically cystic, usually appear along the greater curve, and rarely communicate with the gastric lumen. Tubular duplications, which communicate with the gastric lumen and are also found along the greater curve, are less common. Communications between gastric duplications and intrathoracic esophageal duplications have been reported, and these patients may have respiratory symptoms such as effusions and occasionally vertebral anomalies.[2,4,5] Communications between a gastric duplication and the pancreatic ductal system have been reported and are associated with pancreatitis.[6] Duodenal duplications occur along the posterior aspect of the first or second part of the duodenum. Besides proximal intestinal obstruction and bleeding, duplications can obstruct the biliary and pancreatic ductal system and result in jaundice or pancreatitis. Malignant degeneration of the cyst lining to an adenocarcinoma or carcinoid tumor has been rarely reported in adults.[7,8]

Diagnosis Ultrasound, computed tomography (CT), or an upper GI study can define the duplication, which is usually cystic (Fig. 65–2A). Antenatal ultrasound may detect gastric duplication in a fetus. Technetium 99m imaging will identify duplications that contain ectopic gastric mucosa, which is more prone to bleeding; all histologic types of GI epithelia can be present ectopically in GI duplications.[2,3]

Management Resection of the cyst may be preferable (see Fig. 65–2B), but stripping of the mucosal lining and internal drainage into the duodenal lumen may be a safer alternative to avoid damage to the biliary and pancreatic ductal systems. Duodenal duplications may be drained into a Roux-en-Y jejunal limb. Recently, laparoscopic resection has been described for managing duplications in newborns and infants.[9]



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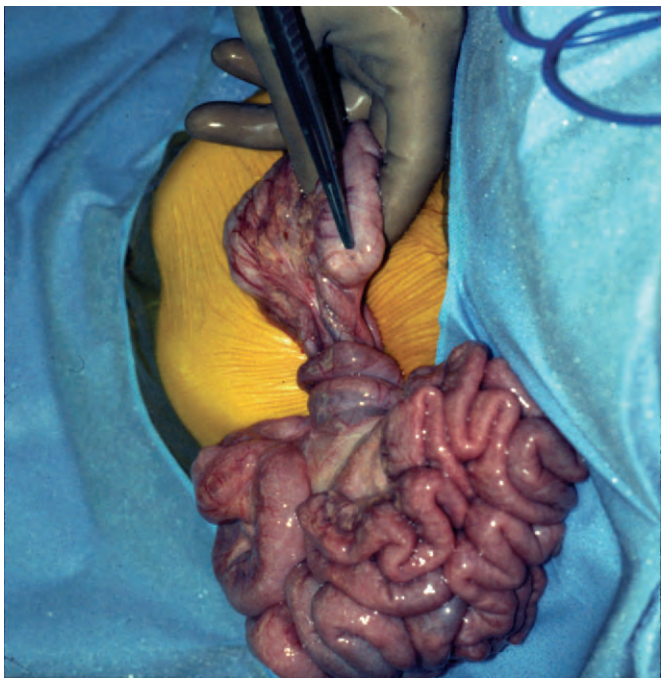

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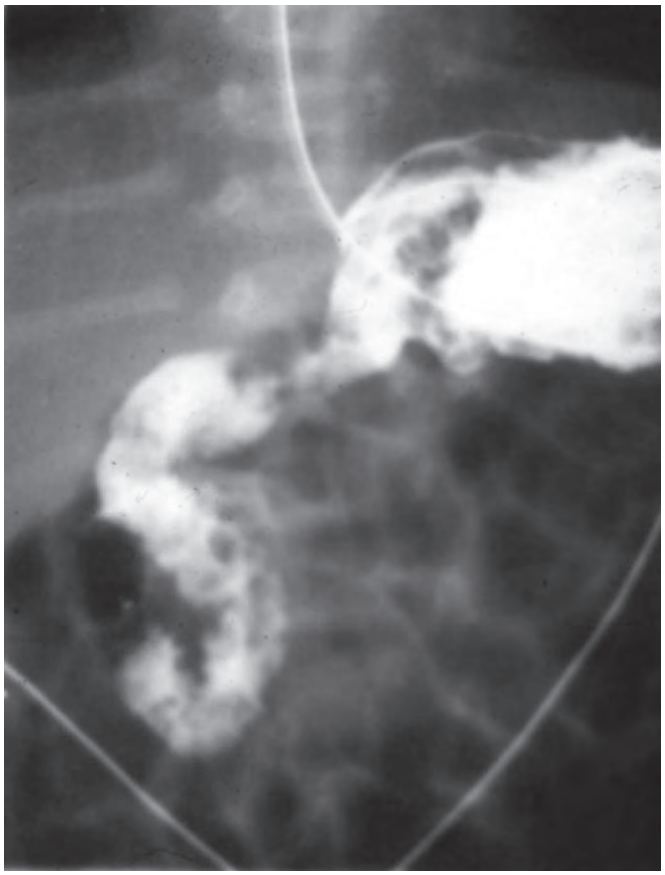
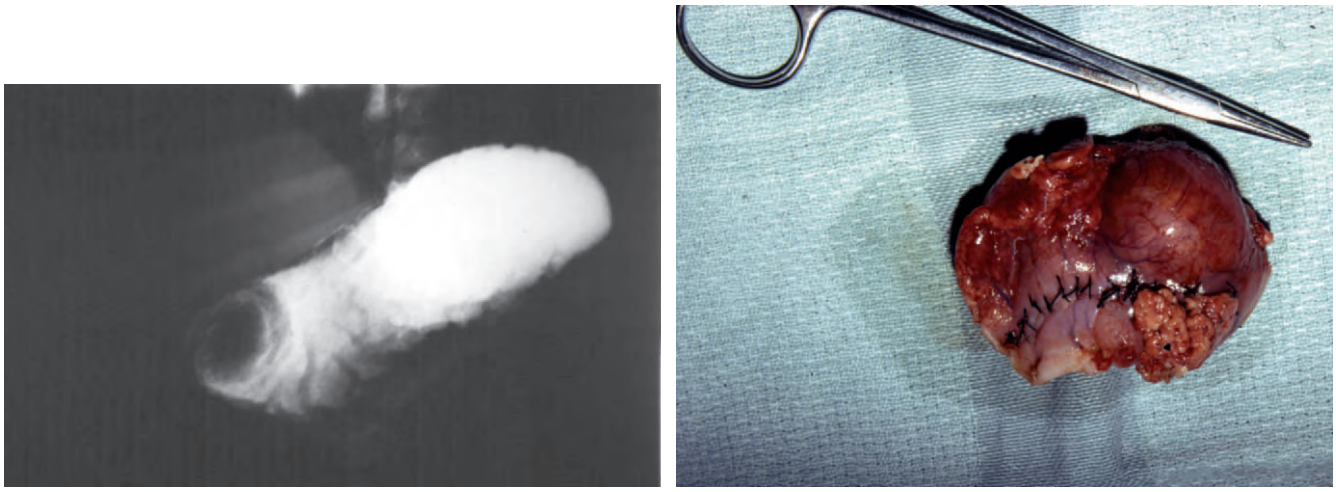


C

Figure 65–1. **A,** Upper gastrointestinal (UGI) study showing malrotation with midgut volvulus. **B,** Operative photograph showing midgut volvulus secondary to malrotation; the intestine is viable in this child. **C,** UGI study showing malrotation, with the ligament of Treitz to the right of the midline and no evidence of volvulus.



A B

Figure 65–2. **A,** Upper gastrointestinal (UGI) study showing a gastric duplication in the antral region of the stomach. **B,** Resected specimen of a gastric duplication from the antral region of the stomach as seen on the UGI study.

Gastric Volvulus

Incidence and Etiology Gastric volvulus is a rare condition in childhood. It occurs more commonly as a chronic condition, but acute gastric volvulus can be a surgical emergency.[10-12] Anomalies in rotation and fixation of the stomach are responsible for most cases of childhood gastric volvulus; the presence of a wandering spleen or asplenia may be a predisposing factor.[12,13] The multiple ligamentous attachments of the stomach probably account for its rarity. The peritoneal attachments and the gastrophrenic, gastrosplenic, and gastrohepatic ligaments along with the retroperitoneal position of the duodenum stabilize its position in both the longitudinal and transverse axes. In organo-axial volvulus, the stomach remains fixed at the gastroesophageal junction and the duodenum, which allows it to twist along its longitudinal axis. Mesenterico-axial volvulus is a more common cause of acute gastric volvulus in children, with rotation around the transverse axis of the stomach through the greater and lesser curvatures.[11]

Clinical Features and Diagnosis Typical symptoms range from an acute proximal intestinal obstruction and gastric necrosis to a chronic picture of postprandial pain with intermittent volvulus. Plain radiographs and an upper GI study are used to make the diagnosis of gastric volvulus.

Management In acute gastric volvulus, hydration, correction of electrolyte abnormalities, and gastric decompression with nasogastric suction are essential; if not possible, emergency surgery is indicated. Derotation and anterior gastropexy along with crural repair may be sufficient if the stomach has no evidence of necrosis. If possible, gastric perforations are typically closed around a tube gastrostomy to fix the stomach to the anterior abdominal wall and create an anterior gastropexy. Management of chronic gastric volvulus is controversial, and some patients with intermittent primary volvulus may respond to nonoperative therapy.[10] There are recent case reports in which laparoscopic-guided gastropexy has been used for the management of gastric volvulus.[14,15]

Microgastria

Congenital microgastria is another rare condition of the distal foregut that results in a disproportionately small stomach. The infant initially has failure to thrive or gastroesophageal reflux (GER), or microgastria is observed at surgery performed for another intra-abdominal problem. The diagnosis is confirmed with an upper GI study, which demonstrates a dilated esophagus and a transverse lie of a small tubular stomach. Initial management includes multiple small feedings through a feeding tube and medical management of GER. If unsuccessful, surgery is indicated to provide adequate nutrition, but the size of the stomach limits the ability to perform an antireflux procedure and gastrostomy at the initial surgery. A feeding jejunostomy followed by creation of a jejunal reservoir (Hunt-Lawrence pouch) may be required.[16,17] Most of these children have multiple anomalies, including malrotation, situs inversus, megaesophagus, and asplenia, as well as cardiovascular, renal, and skeletal abnormalities.[18,19]

Gastric Outlet Obstruction

Incidence and Etiology Congenital gastric outlet obstruction, which may be caused by antral and pyloric webs, diaphragms, and atresia, is another uncommon cause of newborn obstruction. The embryologic cause of antral and pyloric atresia is not well understood.

Clinical Features Antral webs or partial diaphragms cause prepyloric obstruction and have varied clinical manifestations, depending on the severity or completeness of the obstruction. Pyloric atresia is usually ac-

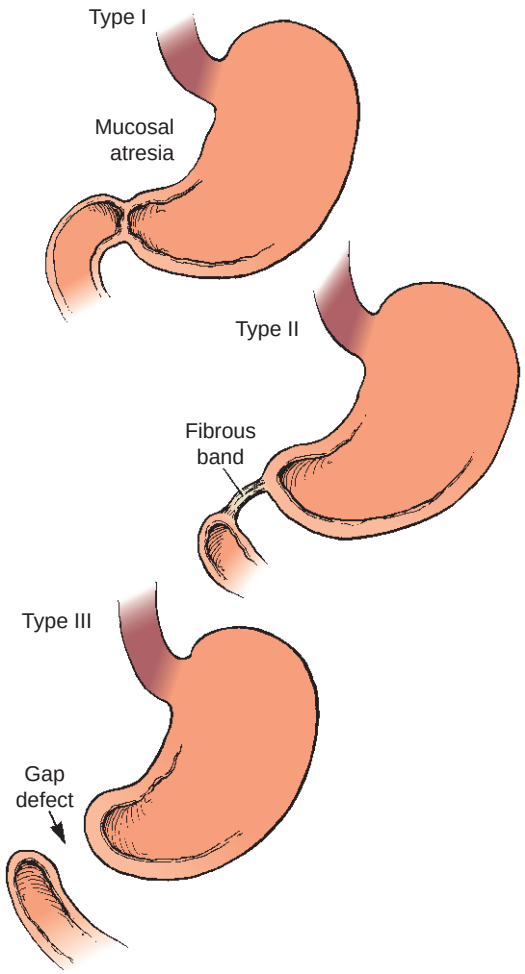


Figure 65–3. Illustration showing the different types of congenital pyloric atresia. (From O'Neil JA Jr [ed]: Principles of Pediatric Surgery, 2nd ed. St Louis, CV Mosby, 2003, p 486.)

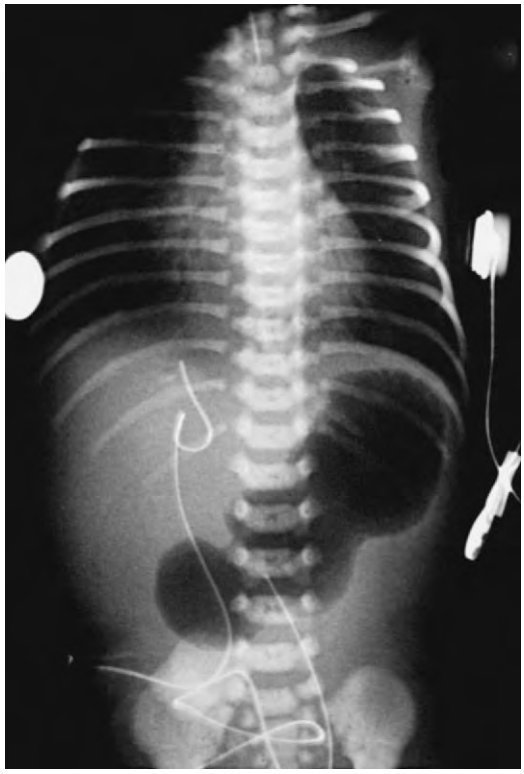


Figure 65–4. Classic plain film radiograph showing gastric outlet obstruction.

companied by nonbilious vomiting and gastric distention consistent with complete obstruction. If the diagnosis is delayed, a complete gastric outlet obstruction can become a surgical emergency with gastric perforation occurring within the first few days of life.[20] An incomplete web or diaphragm causes partial gastric outlet obstruction and may be associated with insidious findings of epigastric pain, failure to thrive, halitosis, and postprandial nonbilious vomiting; the diagnosis of an incomplete web may be delayed into adulthood.[21] The association of other anomalies, including epidermolysis bullosa with pyloric atresia, should be evaluated before surgery.[22,23]

Types Congenital pyloric anomalies are more frequent than antral anomalies. Pyloric webs are more common than atresia. The following three varieties of pyloric atresia have been described: type I, the most common type, is an intraluminal pyloric membrane or web; in type II, the pyloric channel is a solid cord; and in type III, there is a gap between the stomach and duodenum (Fig. 65–3).

Diagnosis The diagnosis may be indicated prenatally on ultrasound examination by the presence of polyhydramnios, a dilated stomach, and a narrowed gastric outlet. Postnatally, plain radiographs may show a large gastric bubble (Fig. 65–4); gastric outlet obstruction or the presence of a web may be seen on an upper GI study. Endoscopy is useful in the diagnosis of an incomplete web, especially if the results of radiographic studies are equivocal.

Management Nasogastric decompression and preoperative fluid and electrolyte resuscitation are indicated to correct the electrolyte abnormalities associated with gastric outlet obstruction. The type of congenital obstruction will dictate the surgical procedure.[20] Type I pyloric atresia requires a longitudinal gastrotomy to identify the web, followed by extension into the pylorus, excision of the web, and transverse closure of the pylorus as a pyloroplasty. Before closure, a catheter should be passed distally to ensure that no additional atresias are present. If there is difficulty in performing a transverse closure, a serosal or omental patch may be considered. Type II or III atresia is repaired by performing a gastroduodenal anastomosis or a pyloric reconstruction. Postoperatively, the stomach should be decompressed with a nasogastric tube; in patients with associated anomalies, a gastrostomy with a transanastomotic gastrojejunal feeding tube may be needed. Prepyloric membranes can become redundant and act as a "windsock" that produces an obstruction distal to the actual origin of the web; in

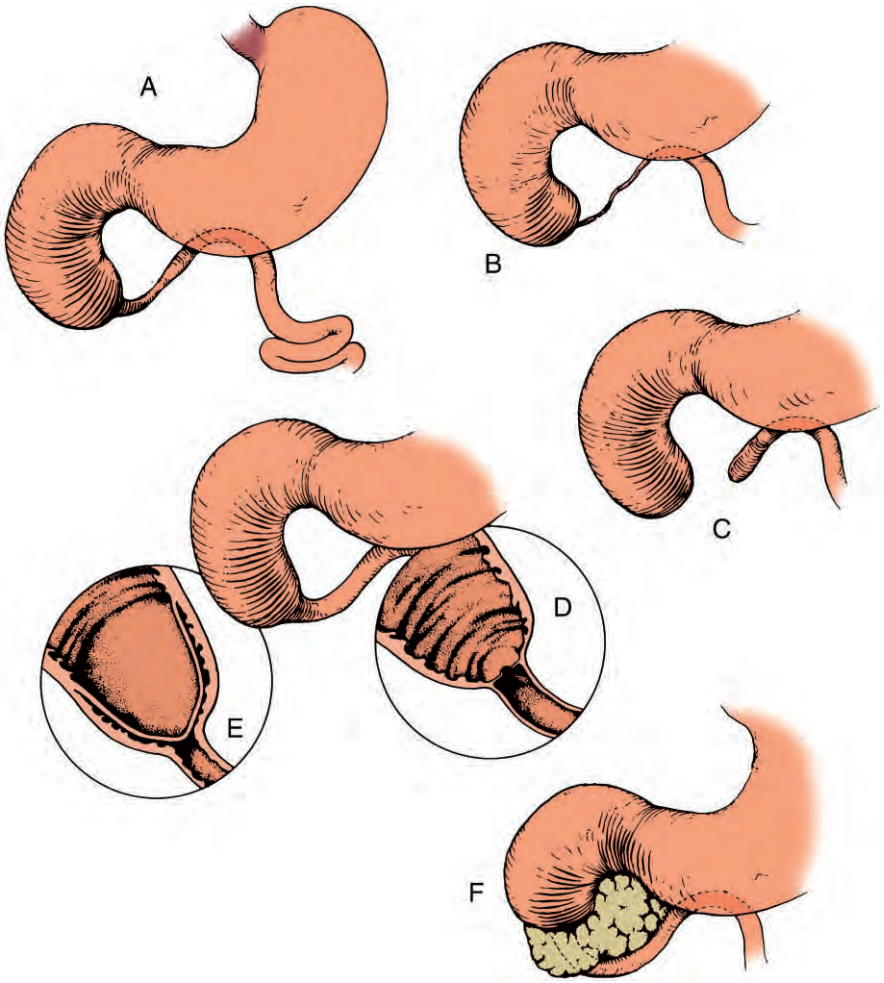


Figure 65–5. Classification of anomalies causing duodenal obstruction. **A,** Type I atresia with intact membrane producing marked discrepancy in size between proximal and distal segments. **B,** Blind ends (type II) of duodenum connected by a fibrous cord. **C,** Blind ends (type III) are separated, and the mesentery is absent at the separation. **D,** Intraluminal membrane with a perforation. **E,** Windsock anomaly. An incision in the distal portion of the dilated segment is still beyond the obstruction. **F,** Annular pancreas. (From O'Neil JA Jr [ed]: Principles of Pediatric Surgery, 2nd ed. St Louis, CV Mosby, 2003, p 472.)

such instances the surgeon can mistakenly think that the obstruction is more distal. Longitudinal enterotomy, partial web excision, and transverse closure are sufficient. Incidentally noted ectopic pancreatic tissue or hamartomas in the pylorus should be excised.

The survival of infants and children with isolated congenital gastric outlet obstruction is excellent. In neonates with multiple anomalies, however, survival is lower. The presence of epidermolysis bullosa is associated with higher mortality and morbidity.[23]

Duodenal Obstruction

Incidence and Epidemiology The overall incidence of congenital duodenal obstruction is approximately 1 in 5000 to 10,000 live births; it appears to be more common in males. The most common causes of congenital duodenal obstruction are atresia and stenosis. Duodenal atresia is associated with trisomy 21 in up to 30% of cases.[24-27] A rare familial duodenal atresia has been described as part of the "Feingold syndrome," which has associated microcephaly, limb anomalies, and tracheoesophageal anomalies; it appears to be autosomal dominant.

Embryology and Etiology The embryonic duodenum is formed by the terminal part of the foregut and the cephalic portion of the midgut. Simultaneously, epithelial proliferation and recanalization occur in the duodenum. Vacuolization of the solid cord of proliferating epithelium results in recanalization. Abnormalities in recanalization or vascular accidents result in congenital duodenal anomalies, which may be associated with coexistent pancreatic and biliary anomalies. Around the third to fourth week the paired dorsal and ventral pancreatic buds originate from the duodenal entodermal epithelium and migrate to form the pancreas. The dorsal bud forms the body and tail; the ventral bud rotates 180 degrees and joins the dorsal gland to form the uncinate process. Abnormalities in rotation and fusion of the paired ventral buds around the pancreas result in an "annular" pancreas, which can cause extrinsic obstruction and may coexist with duodenal atresia.

Types Duodenal obstruction can result from an intrinsic obstruction secondary to congenital atresia, stenosis, or a web, or it can result from an extrinsic obstruction secondary to GI duplications, compression by Ladd's bands, or an annular pancreas. The three morphologic types of intrinsic congenital duodenal obstruction are the following: type I, in which the duodenal wall is intact but there is an intraluminal membrane or web (Fig. 65–5A); type II, in which the atretic proximal and distal ends are connected by a fibrous cord (see Fig. 65–5B); and type

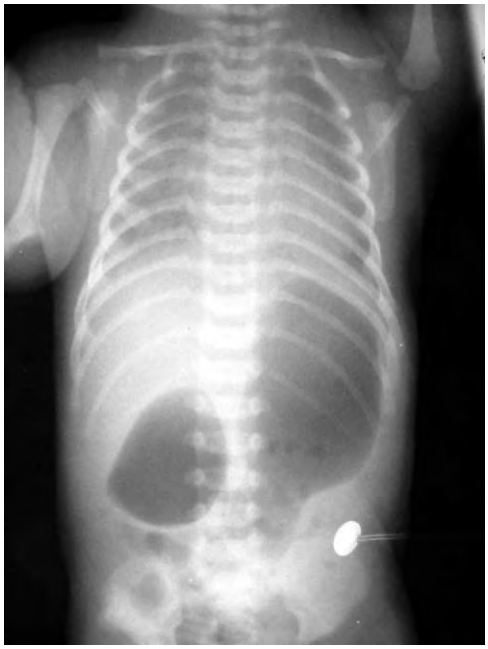


Figure 65–6. Classic plain film radiograph showing the "double bubble" in a patient with duodenal atresia. (Courtesy of Dr. Polly Kochan.)

III, in which there is a gap between the atretic ends, as well as a mesenteric defect (see Fig. 65–5C).

Clinical Features and Diagnosis Upper abdominal fullness with a flat or scaphoid lower abdomen is usual; feeding intolerance and bilious vomiting are classic signs. Congenital duodenal obstruction is associated with other congenital anomalies and trisomy 21, with more than 50% of patients having anomalies of the cardiac, renal, tracheoesophageal, anal, skeletal, and central nervous systems.[25-27] In addition, up to a third of these neonates may have an associated annular pancreas (see Fig. 65–5F) or malrotation. The diagnosis may be made prenatally by maternal ultrasound, which may also demonstrate polyhydramnios. Most often the diagnosis is made by the classic plain film radiographic image of a "double bubble" secondary to a distended stomach and duodenum (Fig. 65–6). Complete duodenal obstruction is associated with a gasless distal bowel. The presence of distal luminal air may indicate an incomplete membrane, a partially obstructing lesion, and most worrisome, a possible midgut volvulus causing the duodenal obstruction. In a neonate with a "double bubble" and distal air or one in whom it is uncertain whether the obstruction is related to a midgut volvulus, an urgent upper GI study needs to be performed because volvulus requires an immediate operation.

In the absence of any suspicion of volvulus, surgery can be performed less urgently. Patients with type I atresia can have a redundant intraluminal web that extends for a distance, thereby resulting in a windsock morphology (similar to antral or pyloric webs) (see Fig. 65–5E). Stenosis is usually secondary to an incomplete diaphragm (Fig. 65–7A and B) or mucosal web with a central opening (see Fig. 65–5D). If the web has a larger opening, clinical detection may be delayed. Atresias usually cause postampullary obstruction, although up to 10% of cases can be preampullary.[24]

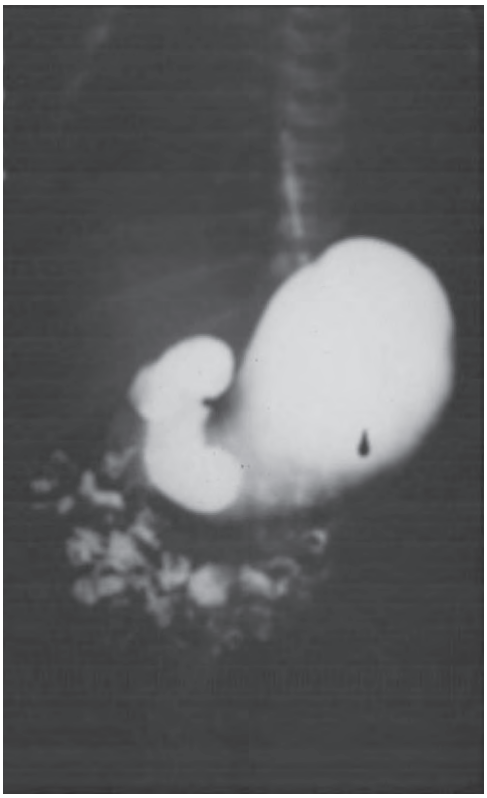
Management The stomach should be decompressed with an orogastric tube and all fluid and electrolyte abnormalities corrected. Associated anomalies should be investigated expeditiously before surgical repair. Chromosomal analysis for possible trisomy and a preoperative cardiology evaluation should be performed. A supraumbilical, right upper quadrant transverse incision is the usual surgical approach. Intestinal rotation is first inspected, and if malrotation is present, a "Ladd" procedure is performed before repair; if normal rotation is present, an extended "Kocher" maneuver is performed to expose the duodenum, pancreas, and root of the mesentery. The duodenum and distal bowel should be inspected to evaluate for additional coexisting distal atresia, which can occur in up to 5% of patients.

Type I atresias with a web and possible "windsock" should have the origin of the web confirmed by passage of an orogastric tube (Fig. 65–8A) or a balloon catheter into the duodenum or through a gastrotomy and withdrawal with the balloon inflated. A longitudinal duodenotomy is performed over the origin of the web (see Fig. 65–7B), and the location of the ampulla of Vater is identified; the web is then excised while taking care to avoid injury to the ampulla. The duodenotomy is closed transversely with interrupted sutures. The presence of distal atresia is excluded by passage of a balloon catheter distally through the duodenotomy.

Type II and III atresias may be repaired by a number of techniques, including side-to-side duodenoduodenostomy (see Fig. 65–8, *C1*), an end-to-side "diamond-shaped" duodenoduodenostomy (see Fig. 65–8, *C2*) and duodenojejunostomy (see Fig. 65–8B). The diamond-shaped duodenoduodenostomy appears to be the technique of choice and requires a transverse incision in the proximal duodenum with a longitudinal incision in the distal duodenum and an end-to-side duodenoduodenostomy (Fig. 65–8, *C2*). This technique results in a wider anastomosis that functions earlier and has reduced stasis from a blind loop or stenosis.[28] The side-to-side duodenoduodenostomy is often associated with delayed anastomotic transit times and megaduodenum.[29]

An annular pancreas causes duodenal obstruction in infancy and early childhood, although it is less frequent than intrinsic duodenal obstruction (see Fig. 65–5F).[26,30] A recent review of six case series since 1954 revealed a total of 66 reported cases of annular pancreas.[30] Such children are more likely to initially be seen in the neonatal period with nonbilious vomiting; they often have trisomy 21 and tracheoesophageal anomalies. Management is similar to that for type II and III duodenal atresia, with the diamond-shaped duodenoduodenostomy being the technique of choice to bypass the obstruction.[26,30] In the absence of significant comorbidity, the outcome is excellent.

Although we prefer using parenteral nutrition, enteral feeding after repair may be achieved early via a transanas-



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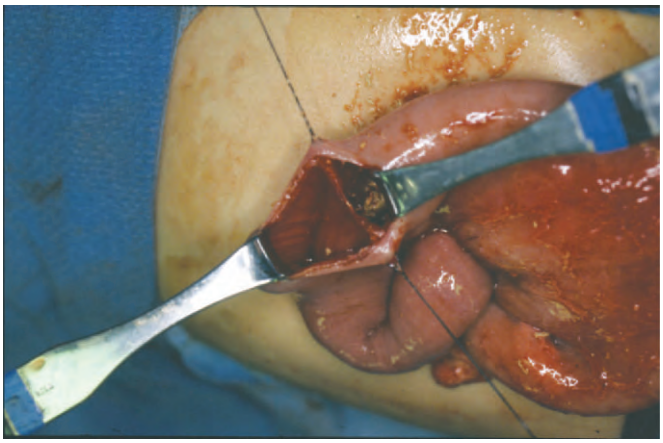

B

Figure 65–7. **A,** Upper gastrointestinal study demonstrating a congenital type I duodenal web with incomplete obstruction of the duodenum. **B,** Operative photograph demonstrating a congenital type I duodenal web with incomplete obstruction of the duodenum visualized through the duodenotomy.

tomotic feeding tube because duodenal emptying is often delayed. Normal peristalsis is slow because of the dilated proximal duodenum, and in selected cases in which the proximal duodenum is markedly dilated, a tapering duodenoplasty is useful. A feeding gastrostomy is sometimes helpful in a complicated duodenal repair. The outcome depends on the associated comorbid conditions, such as congenital cardiac defects and chromosomal abnormalities.[25] Long-term follow-up studies have shown delayed morbidity in 12% and delayed mortality in 6% of patients undergoing repair of congenital duodenal anomalies.[29] GER disease and megaduodenum with upper GI motility disorders were the most common delayed morbidities identified in these studies. It appears that the dilated proximal duodenum is associated with disturbed transit.[31] Plication or a tapering duodenoplasty is recommended for the management of these delayed complications.[29,31]

ACQUIRED CONDITIONS

Hypertrophic Pyloric Stenosis

Incidence and Epidemiology Hypertrophic pyloric stenosis (HPS) is one of the most common disorders of the stomach and duodenum in infants that requires surgical correction. The reported incidence is 1 to 2 per 1000 live births.[32-34] It is more common in males at a 4 : 1 to 5 : 1 ratio and more common in white and Hispanic infants than in Asian and black infants. First-degree relatives have an almost fivefold increase in risk for HPS.[35]

Etiology and Pathogenesis Hypertrophy of the pyloric muscle obstructs the passage of gastric contents through the pyloric canal. The pathogenesis has not been fully understood despite the frequency of its occurrence. A lack of nitric oxide synthase in pyloric muscle causes pylorospasm, and the loss of nitric oxide–mediated relaxation of smooth muscle may result in the hypertrophied and contracted pyloric muscle.[36] Abnormalities in peptide-containing nerve fibers, including a loss of peptide immunoreactivity in nerve fibers in the circular muscle, have also been described in the hypertrophied muscle.[37] Possible changes in hormonal control of pyloric sphincter function have been implicated, including abnormalities in gastrin and prostaglandins. Defects of the intestinal pacemaker (interstitial cells of Cajal), as well as abnormalities in extracellular matrix proteins and growth factors, are being reported as possible etiologic factors in the development of HPS.[38,39]

Clinical Features Typically, infants are 3 to 6 weeks old when they are initially evaluated for vomiting. They may start vomiting, however, as early as 2 weeks, or it may be delayed up to 12 weeks. The vomiting is usually nonbilious, postprandial, projectile, and progressive. HPS is most commonly seen in otherwise normal infants, but it occurs more frequently, at a 1% to 10% incidence, in patients who have undergone correction of esophageal

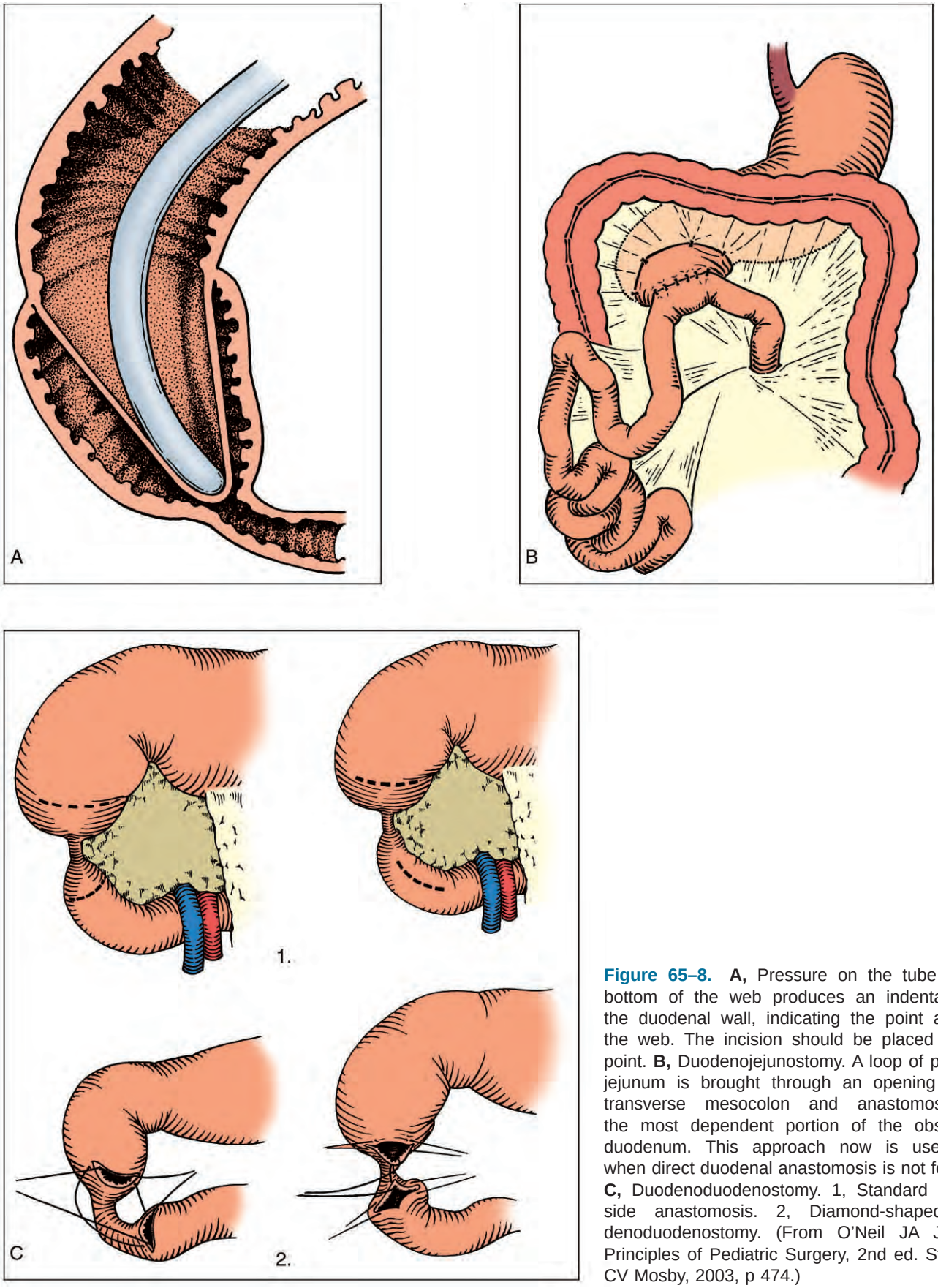

Figure 65–8. **A,** Pressure on the tube at the bottom of the web produces an indentation in the duodenal wall, indicating the point apex of the web. The incision should be placed at that point. **B,** Duodenojejunostomy. A loop of proximal jejunum is brought through an opening in the transverse mesocolon and anastomosed to the most dependent portion of the obstructed duodenum. This approach now is used only when direct duodenal anastomosis is not feasible. **C,** Duodenoduodenostomy. 1, Standard side-to-side anastomosis. 2, Diamond-shaped duodenoduodenostomy. (From O'Neil JA Jr [ed]: Principles of Pediatric Surgery, 2nd ed. St Louis, CV Mosby, 2003, p 474.)

atresia.[32,40] Intestinal malrotation and obstruction of the urinary tract also occur more frequently in association with this disorder.[32] A transient self-limited unconjugated hyperbilirubinemia secondary to a glucuronyl transferase deficiency similar to Gilbert's syndrome is seen in 1% to 2% of infants.[41] The differential diagnosis of nonbilious vomiting should include GER and overfeeding, gastroparesis, pylorospasm, other congenital gastric outlet obstruction (as discussed earlier in the chapter), and peptic ulcer disease.

Diagnosis An infant with a typical history and a palpable hypertrophic pylorus does not need additional diagnostic testing. The ability to successfully palpate a hypertrophic pylorus is variable, and this clinical ability appears to be decreasing with the increased reliance on imaging studies.[42] In a study of infants with HPS, for example, the pyloric mass was palpated in 87% during 1974 to 1977, as compared with 49% during 1988 to 1991.[43] In a more recent report (2000 to 2002), only 32% had a palpable "olive."[44] To successfully palpate the pyloric "olive," the infant needs to be quiet with a relaxed abdominal wall. One technique is to allow the infant to suck a pacifier, and while standing on the infant's left side and holding the legs flexed at the hips in the left hand, the fingertips of the right hand are gently swept from the liver edge toward the umbilicus. Increased serum bicarbonate and decreased serum chloride levels favor a diagnosis of HPS.[45]

In the absence of a palpable "olive," either an upper GI study or an ultrasonogram may be performed. An upper GI study is approximately 95% sensitive, although error rates of up to 11% have been reported.[46] On an upper GI study, a "string" sign indicating a narrowed elongated pyloric canal that does not relax is seen; a "shoulder" sign caused by the hypertrophied muscle indenting the antrum and a "double-track" sign caused by the redundant mucosa may be observed.[46,47] Real-time ultrasonography, however, appears to be the most reliable diagnostic test; it is almost 100% accurate in the hands of an experienced operator, it does not involve radiation exposure, and the examiner does not have to wait for the stomach to empty.[46,47] Sonographic measurements that are reported to be diagnostic include a pyloric wall thickness of at least 4 mm and a channel length of at least 17 mm.[48] The actual measurements may not be as important as evaluation of the overall morphology of the antrum and pylorus and evaluation of gastric emptying.[46] Measurement of the volume of gastric aspirate in a vomiting (nonbilious) infant can help determine whether an upper GI study or ultrasonography should be performed, and this has been suggested as a more cost-effective approach in deciding the appropriate imaging study.[49]

Management In an infant with normal fluid and electrolyte status, surgical correction with general anesthesia as soon as logistically feasible is appropriate. Some infants will need correction of their fluids and electrolytes, and about 10% to 15% will be significantly dehydrated and have a hyponatremic, hypochloremic, hypokalemic metabolic alkalosis.[42] In a severely dehydrated infant, initial resuscitation is begun with a 10- to 20-ml/kg bolus of normal saline. Correction of both electrolyte losses and intravascular depletion is essential before surgery because pyloric stenosis is not a surgical emergency. Once adequate hydration and normal urine output are achieved, potassium is added to the intravenous fluids. The metabolic alkalosis is chloride responsive; further fluids (5% dextrose with 0.45% saline and 20 mEq of potassium chloride per liter) are given at 150% of the maintenance requirement. A serum bicarbonate level of 28 mEq/L or lesser is usually the target for correction before surgical repair. Keeping the stomach empty before the repair by using a gastric tube may help limit further vomiting.

The procedure of choice is a Ramstedt-Fredet extramucosal pyloromyotomy performed with the infant under general anesthesia. A number of incisions to perform the pyloromyotomy have been described, including a transverse right upper quadrant incision, vertical midline incision, and circumumbilical incision (Fig. 65–9A-D),[50,51] as well as three-port laparoscopic approaches. There does not seem to be a significant difference in outcome between the laparoscopic and open approaches, although more complications may occur in the laparoscopic group.[52-54] In the open approach, after the peritoneum is opened and the hypertrophied pylorus is delivered to the surface, a seromuscular incision is made into the pyloric muscle. The pyloromyotomy incision extends from just proximal to the duodenum (pyloric vein) onto the antrum of the stomach. The initial myotomy is deepened bluntly with the back of a scalpel handle or a Benson pyloric spreader. Protrusion of the gastric submucosa and mucosa into the myotomy site indicates that the obstruction has been relieved (see Fig. 65–9D). If an inadvertent duodenal perforation occurs, the enterotomy can be managed by mucosal closure with fine absorbable suture and reinforced with omentum (Fig. 65–10A). An alternative approach is to perform a two-layer closure of the pylorus, followed by a second myotomy at a site rotated 90 to 180 degrees from the repair (see Fig. 65–10B). In an uncomplicated pyloromyotomy, feeding is resumed within 4 to 6 hours. A number of different feeding protocols that include incremental advances from sugar water to increased amounts of formula volume and osmolarity every 2 to 3 hours have been used. The type of feeding protocol may influence postoperative vomiting but does not appear to affect the time to full feeding or discharge.[55,56] Regardless of whether a feeding schedule or early ad libitum feeding is used, most infants will reach their feeding goal within 24 hours postoperatively. In an infant with a duodenal perforation that is repaired, a period of gastric decompression and antibiotics may be prudent. If there is persistent vomiting and clinical deterioration, an upper GI study to rule out a leak is appropriate. Complications include persistent emesis in up to 10%, mucosal perforation in less than 5%, and wound infection in up to 10% of infants.[42,56,57] Incomplete myotomy is a rare complication that may be suspected in an infant with persistent vomiting beyond the second week after pyloromyotomy. An upper GI study is helpful in showing the vomiting to be secondary to GER, which is a more likely diagnosis in this situation.

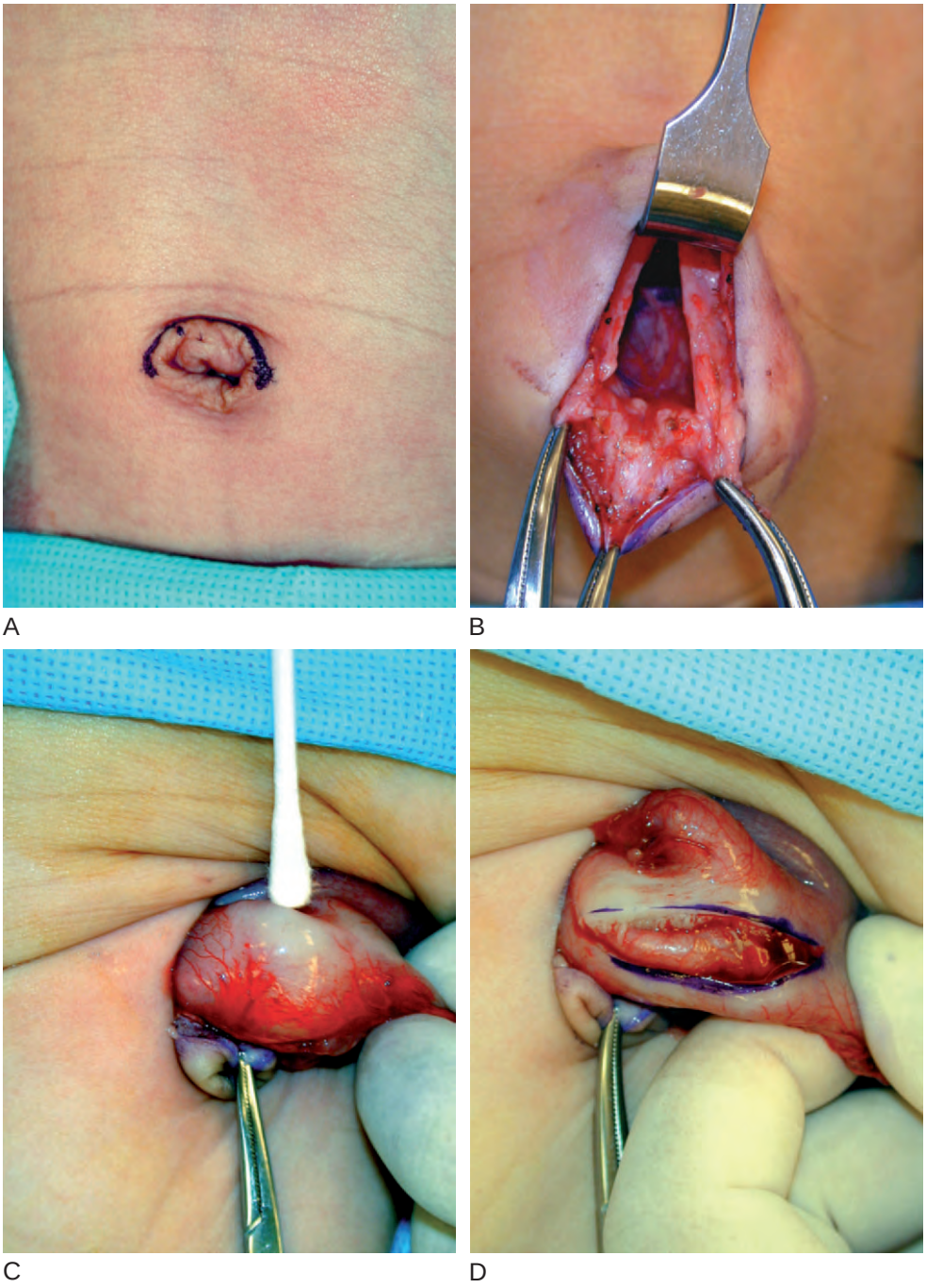

Figure 65–9. **A** to **D,** Operative photographs showing pyloromyotomy through a circumumbilical incision.

Neonatal Gastric Perforation

Incidence Gastric perforations are uncommon in neonates, but they may be seen in both term and preterm newborns and usually occur in the first week of life.[58-61] Perforations often occur in newborns who have undergone neonatal resuscitation.

Etiology There is no consensus regarding the cause of neonatal gastric perforation, and even whether these perforations are "spontaneous" or secondary to other factors is controversial.[58,59] "Mechanical" causes secondary to gastric dilatation from resuscitation and mechanical ventilation, as well as "low-flow" or "ischemic" causes from hypoxia and prematurity, have been postulated.[59,61] The cause is probably multifactorial; possibly, the cause of perforation in a preterm newborn may be a low-flow state, whereas in a term newborn it may be a mechanical cause.[59-61]

Clinical Features and Diagnosis Gastric perforation may be manifested as feeding intolerance, abdominal distention, upper GI bleeding, respiratory distress, or a picture of "sepsis." The diagnosis of perforation is almost always evident on plain film radiographs with massive pneumoperitoneum. A cross-table lateral or decubitus film

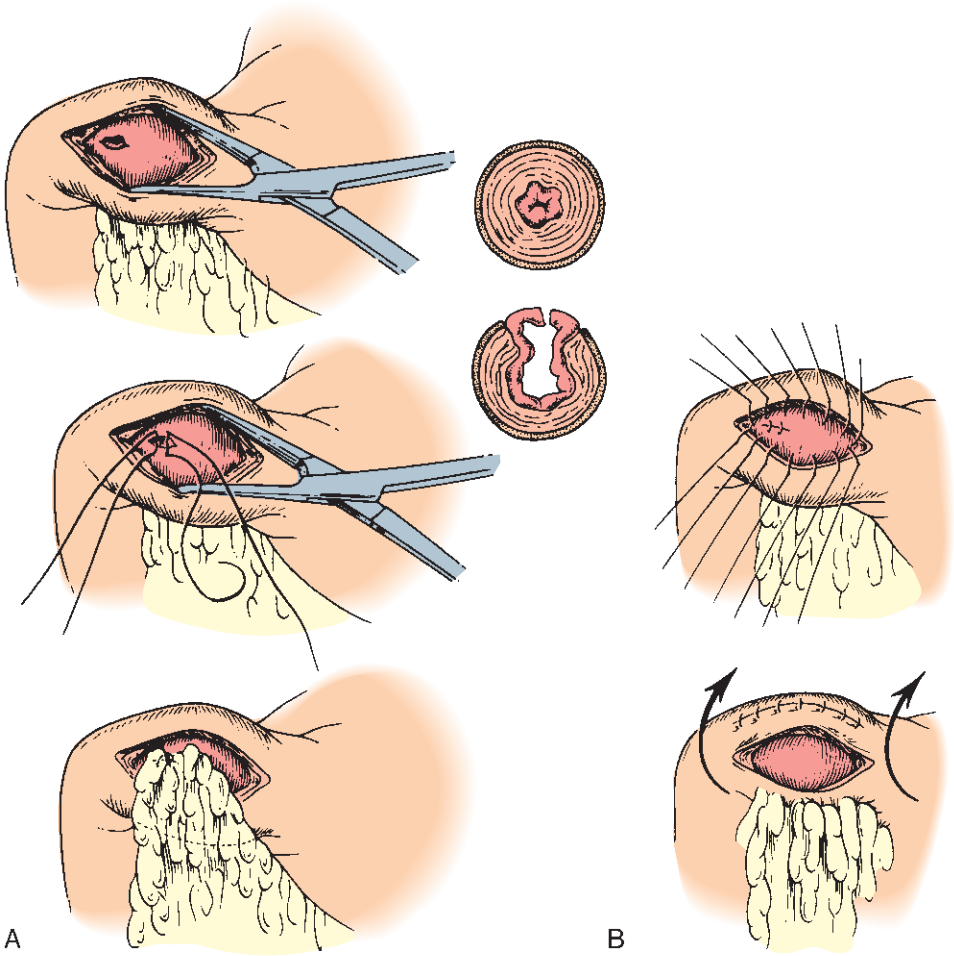

Figure 65–10. **A** and **B,** Alternative techniques for closure of an inadvertent enterotomy.

may clarify the presence of pneumoperitoneum. In neonates with rapid deterioration and ventilation difficulty because of significant abdominal distention, decompressive peritoneocentesis may relieve the acute respiratory distress. There is usually a single perforation on the anterolateral aspect of the greater curvature near the fundus, although the perforation may be seen along the lesser curvature and rarely posteriorly near the gastroesophageal junction.[58-61] The differential diagnosis includes perforation from necrotizing enterocolitis, pyloric atresia, colonic atresia, and Hirschsprung's disease.

Management Early surgical exploration is lifesaving, and the usual surgical approach is a transverse right supraumbilical incision. The posterior aspect of the stomach and the gastroesophageal junction should always be inspected by opening the lesser sac. Most isolated gastric perforations can be repaired primarily in one or two layers without major resection of the stomach. The addition of a gastrostomy or drain depends on individual preference. Cases of significant gastric necrosis from necrotizing gastritis may require subtotal gastrectomy. In up to 20% of infants with possible neonatal gastric perforation based on the clinical picture and radiographs, a perforation may not be identified at surgery and presumably a small perforation has sealed itself by the time that surgery is performed.[61] In preterm newborns maintained on ventilator support, air leaks can track from the lungs into the peritoneal cavity.[62] These newborns will usually have an obvious pneumomediastinum and pulmonary interstitial emphysema and do not show signs of sepsis from intestinal perforation. Despite the presence of perforation and peritonitis, most of these neonates have a good surgical outcome.

Gastric Tumors

Incidence Gastric tumors are rare in infants and children.[63] A 10-year review of 1403 reports of gastric disease at a single institution revealed only three pediatric gastric tumors.[64] Another review of 39 children with gastrointestinal tumors over a 20-year period revealed one leiomyosarcoma of the stomach.[65]

Clinical Features and Diagnosis Although rare, the most common gastric tumors are teratomas. They usually occur in males and are marked by a mass, abdominal distention, vomiting, and rarely, upper GI bleeding or perforation.[63,66] The diagnosis can be made with a combination of imaging modalities; usually, ultrasonog-

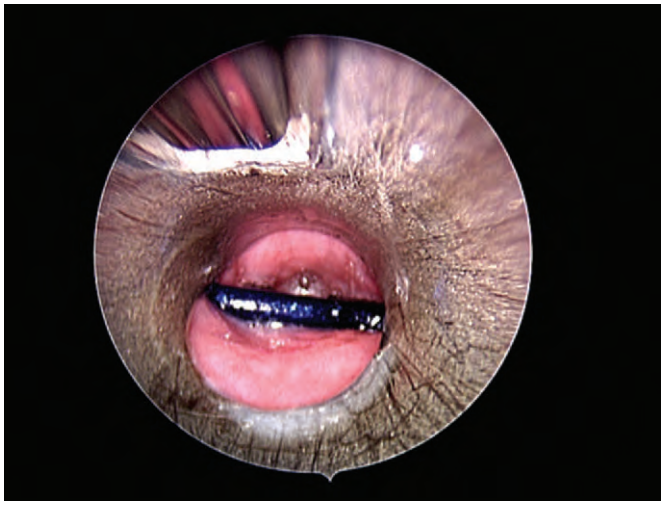

Figure 65–11. Endoscopic view of an impacted foreign body in the esophagus before removal. (Courtesy of Dr. Glenn Isaacson.)

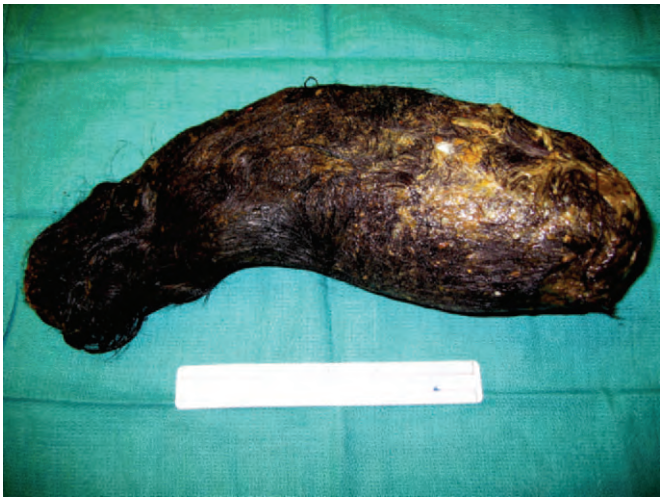

Figure 65–12. A large trichobezoar that caused gastric obstruction removed surgically.

raphy and CT will identify the characteristic cystic and solid areas with densities of soft tissue, fat, and calcium or bone.[63,66] Most gastric teratomas are benign, with less than a dozen reported immature teratomas in children.[66]

Management Treatment of gastric teratoma is complete surgical excision with reconstruction of the remaining stomach. In an immature gastric teratoma, a strategy of monitoring the α-fetoprotein level after resection seems prudent rather than giving these children chemotherapy.[66] After complete excision the prognosis for these benign tumors is excellent.

Foreign Bodies

Incidence Children swallow foreign bodies as a result of their exploration of the environment. The peak incidence is between 6 months and 3 years of age. Coins are the most commonly ingested objects. Most foreign bodies in the GI tract are asymptomatic and probably pass spontaneously in stool.

Clinical Features and Diagnosis Swallowed foreign bodies are diagnosed when plain radiographs are obtained for symptoms related to the airway or the esophagus. Transient coughing or choking, pain in the pharynx or retrosternal region, and excessive salivation, drooling, or retching are the common symptoms in a child with a foreign body in the esophagus. A plain radiograph, including a lateral view, can differentiate an esophageal from a tracheal foreign body; the lateral view demonstrates the foreign body's posterior relationship to the tracheal air column.

Management All esophageal foreign bodies confirmed by plain radiography should be removed by flexible or rigid esophagoscopy (Fig. 65–11).[67] If the foreign body passes into the stomach, extraction can usually be avoided because most of these foreign bodies will pass spontaneously. Expectant management is appropriate for smaller rounded objects, with occasional serial radiographs taken after several weeks; exceptions include sharp objects and button batteries. If symptoms occur that are suggestive of obstruction or perforation or if the object remains lodged in the stomach for more than 4 weeks, endoscopic retrieval is recommended. Sharp objects, such as needles and safety pins, should be extracted if they are localized in the stomach because of the risk for perforation.[68] Button batteries are a special case, especially if they are larger than 15 mm, because of the risk of corrosive damage if lodged in the esophagus or the stomach.[69] Removal of an esophageal button battery as soon it is detected is recommended. Although most foreign bodies usually pass through the GI tract once they enter the stomach, button batteries should be extracted to avoid gastric perforation.[67]

Bezoars

Definition and Types Bezoars are foreign bodies in the lumen of the stomach or rarely the intestine that increase in size over time because of continued deposition of ingested food or fibers. There are principally three types: trichobezoars, composed of hair, are the most common; phytobezoars are composed of vegetable matter; and lactobezoars are derived from milk precipitates.

Clinical Features and Diagnosis Bezoars are an uncommon cause of gastric outlet obstruction and are associated with early satiety, abdominal pain, vomiting, and abdominal distention. They can usually be diagnosed by CT, upper GI study, or endoscopy.[70]

Management Although endoscopic and laparoscopic removal has been described, surgical removal is generally required because of their large size (Fig. 65–12).[71,72] Trichobezoars are often associated with trichotillomania,

a psychiatric disorder associated with pulling and ingestion of hair, and psychiatric management is recommended to avoid recurrence. Phytobezoars can be digested with enzymes such as papain or fragmented endoscopically. Lactobezoars are often seen in newborns receiving formula feedings and usually respond to nasogastric lavage and decompression.

Gastrostomy

Short-term enteral access can be obtained in infants and children with a nasogastric tube; however, they occlude easily and can contribute to airway obstruction in an infant, who is an obligate nasal breather.

Indications The primary indication for a gastrostomy tube is the need for long-term enteral access for fluids and nutrition. Other indications include the need for gastric decompression in a neurologically impaired infant with a fundoplication, after repair of atresia, or the need for urgent gastric decompression in a newborn with a congenital tracheoesophageal fistula and ventilatory difficulty. A rare indication is for the management of gastric volvulus. A gastrostomy may be contraindicated in those with uncontrolled ascites and coagulopathy, and a relative contraindication is a terminal condition in an infant or child.

Types of Gastrostomy

Open Gastrostomy The Stamm gastrostomy, the most commonly used surgical gastrostomy, has the advantage of not requiring a surgical procedure for closure if the need for the gastrostomy is temporary. An upper midline or left paramedian muscle-splitting incision is used. A site on the anterior wall of the stomach at the junction of the body and antrum is chosen, not too close to the pylorus because the tube could act as an obstruction. Two concentric purse-string sutures are placed to invert the seromuscular layer of the anterior gastric wall around the tube, thus creating a tunnel. The exit site on the abdominal wall should be chosen so that it avoids tension between the stomach and abdominal wall; a separate stab incision is made for the exit site, or it may exit from the incision, and four-quadrant sutures secure stomach to the abdominal wall (see Chapter 52 for a detailed description). Usually, feeding can be started within 24 hours of gastrostomy placement. Any child who may need an esophageal replacement, such as those with long-gap esophageal atresia or a corrosive esophageal injury, should have the gastrostomy placed closer to the lesser curvature of the stomach to avoid injury to the gastroepiploic vessels because these vessels would be the blood supply for a potential gastric tube.

The Witzel gastrostomy is a modification of the Stamm gastrostomy that consists of imbrication of an additional anterior seromuscular layer of stomach over the tube to make a longer tunnel (see Chapter 52 for a detailed description).

The Janeway gastrostomy, the least common type of gastrostomy, is a permanent gastrostomy fashioned from a gastric flap that is tubularized (see Chapter 52 for a detailed description).

Percutaneous Endoscopic Gastrostomy A percutaneous, endoscopically assisted gastrostomy (PEG) was introduced by Gauderer et al. to allow placement of a feeding gastrostomy without laparotomy (see Chapter 52 for details).[73]

Once gastric access is obtained, the gastrostomy tube can be replaced by a gastrostomy button after 6 weeks (to ensure a mature gastrocutaneous tract). The gastrostomy button is a low-profile skin-level device with a valve that can also be placed primarily at the initial surgery.

Laparoscopic-Assisted Gastrostomy This technique involves percutaneously accessing the stomach for placement of a gastrostomy under visual control with the laparoscope. Sutures passed through the abdominal wall or "T-fasteners" are used to stabilize the anterior wall of the stomach while the tube is inserted. This technique is useful if the child is already undergoing a laparoscopic procedure; it may also be a safer alternative to PEG if there is concern regarding the anatomy of the colon.[74]

Percutaneous Image-Guided Gastrostomy There are a number of image-guided gastrostomy placement techniques. The retrograde percutaneous fluoroscopic technique is commonly used and involves fluoroscopic visualization of a needle puncture of the stomach followed by the creation of a tract over a guidewire.[75] A "pull" technique similar to PEG can also be used for image-guided gastrostomy.

Complications Gastrostomies have a number of reported complications. Major complications include dislodgement of the tube with peritonitis, inadvertent enteric perforation, gastrocolic fistula, GI bleeding, and peritonitis. Leakage around the gastrostomy occurs if the stomach separates from the abdominal wall. Placement close to the pylorus or inadvertent advancement of the tube toward the pylorus can cause gastric outlet obstruction. Local erythema, cellulitis, and tissue necrosis can occur if there is excess tension at the exit site. Surrounding tissue necrosis can result in an enlarging gastrostomy stoma with peristomal leakage. Granulation tissue often develops around the stoma and needs to be cauterized with silver nitrate. A review of PEG in children reported an overall 27% complication rate, including infection, abscess, vomiting, malposition of the gastrostomy, and one death.[76] A review of 208 children with image-guided gastrostomy or gastrojejunostomy tubes revealed a major complication rate of 5% and a minor complication rate of 73% after the insertion of gastrostomy and gastrojejunal tubes by the image-guided retrograde percutaneous route. Major complications included peritonitis, septicemia, abscess, GI bleeding, and death. Minor complications included tube dislodgement, leakage, skin infection, tube migration, and obstruction.[77]

There are reports of worsening GER after gastrostomy, which can be prevented by placing the gastrostomy closer to the lesser curve.[78] In neurologically impaired patients, an upper GI study and pH probe monitoring should be done, and in the absence of significant GER, a gastrostomy without a protective antireflux procedure is adequate. If GER is significant, some recommend

that a fundoplication be performed along with the gastrostomy.[79]

The gastrocutaneous tract matures during a 3- to 6-week period. Removal of a Stamm-type gastrostomy can result in closure of the tract within 24 hours; therefore, immobilization of the tube at the exit site is important to avoid dislodgement. Inadvertent removal of the tube before a mature tract has formed warrants placement of a small catheter through the tract and confirmation of tube position by fluoroscopy and a water-soluble contrast study. If the tract cannot be safely accessed in the office, the tube should be replaced under fluoroscopic guidance.

Peptic Ulcer Disease

Definition and Types Clinically significant peptic ulcer disease is an uncommon condition in infancy and childhood, and with improved diagnosis and medical management, there are few indications for surgical therapy. The pediatric surgeon is usually consulted for complications of peptic ulcer disease, such as persistent life-threatening upper GI bleeding, acquired gastric outlet obstruction from chronic ulceration and scarring, and perforation.[80,81]

Peptic ulcers in infants and children are usually classified as primary or secondary ulcers. A primary ulcer occurs in the absence of any predisposing illnesses or factors and is often associated with gastric acid hypersecretion. A secondary ulcer is generally associated with increased stress from illness, trauma, burns, or medications such as steroids and nonsteroidal anti-inflammatory drugs (NSAIDs).

Etiology Primary ulcers may have a genetic basis and occur more frequently in association with blood group O. They are located in the duodenum and pyloric channel and are rarely seen in the stomach. Although increased or excessive acid secretion is important in the pathophysiology of primary peptic ulcer disease, no direct relationship has been established between consistently elevated levels of acidity in children with primary ulcer disease. There appears to be increasing evidence that the chronic relapsing ulcer disease characteristic of a primary peptic ulcer is linked to coexisting, chronic, active antral gastritis secondary to *Helicobacter pylori* infection.[82,83]

H. pylori is a gram-negative spiral-shaped organism that has been associated with the presence of chronic gastritis. *H. pylori* infection appears to be very common in developing countries, but it may also be seen in about 10% of children in the United States by the time that they are 10 years old.[82-84] It appears that up to 10% of cases of *H. pylori* gastritis will result in duodenal ulcers, especially in children older than 10 years.[83,84] In addition, it is a significant risk factor for the development of gastric cancer in adults. Eradication of *H. pylori* reduces the recurrence of ulcers to less than 5%.[86] Children with *H. pylori* infection and peptic ulcer disease should be treated with a 10- to 14-day triple-therapy regimen.[82,85,86]

Zollinger-Ellison syndrome, which results from a functional gastrinoma, G-cell hyperplasia, or G-cell hyperfunction, is a rare condition associated with acid hypersecretion. The increased gastrin levels lead to increased gastric acid output, which in turn results in diarrhea and multiple or recurrent peptic ulcers. These ulcers may also involve the proximal jejunum (see Chapter 58 for a discussion on Zollinger-Ellison syndrome).

Secondary peptic ulcers are more common in infants and children than primary ulcers are. They are also called "stress" ulcers because they occur with stresses that increase acid secretion or reduce mucosal defense mechanisms, or both. Drugs such as aspirin and NSAIDs decrease mucosal blood flow by inhibiting prostaglandin synthesis and stimulating inflammatory mediators. In addition, protective mucosal secretions can be inhibited by pharmacologic agents. Ulcers associated with head trauma are characterized by increased gastric acid secretion ("Cushing ulcer"); however, ulcers associated with thermal injury have normal gastric acid secretion (Curling's ulcer). Other stresses, such as sepsis, cardiac insufficiency, surgical trauma, and hypoxia, may result in ulcer disease. Secondary ulcers are usually located in the stomach, although they can occur in the duodenum as well. Secondary ulcers do not usually recur if they are treated and the associated factors are controlled.

Clinical Features Primary peptic ulcer disease in an older child is usually manifested as abdominal pain and vomiting and rarely as significant GI bleeding. In addition, iron deficiency anemia from occult blood loss may be an initial sign. Gastric outlet obstruction and perforation from peptic ulcer disease are rare in children. Stress ulcers are seen in critically ill infants and children, most often with GI bleeding from diffuse erosive mucosal lesions of the stomach. Perforation from stress ulceration is an unusual event, although more common than a perforated primary peptic ulcer in a child.

Diagnosis The diagnosis of peptic ulcer disease is based on endoscopic examination of the gastric and duodenal mucosa. Although an upper GI contrast study can be helpful in defining gastric outlet obstruction, it is inadequate for the diagnosis of mucosal ulceration. Antral and duodenal biopsy with the rapid urease test plus histopathologic examination is the current diagnostic standard for *H. pylori*.

Management The initial treatment of peptic ulcer disease is medical therapy. The goal is to heal the ulcer, prevent recurrence, and avoid the complications of bleeding, perforation, and obstruction. Secondary ulcers are treated by eliminating the stressful event; those related to NSAIDs are treated by discontinuing their use. Additionally, treatment involves the use of acid suppression and mucosal protection with antacids, H_2 blockers, proton pump inhibitors, or mucosal coating agents, alone or in combination. Secondary ulcers can be prevented by H_2 blockers or mucosal coating agents. In children with a diagnosis of *H. pylori* and documented peptic ulcer, it is essential to initiate a 7- to 14-day triple-therapy regimen. The traditional indications for surgical treatment include perforation, uncontrolled bleeding,

gastric outlet obstruction, and intractable pain. Children with peptic ulcer disease may have complications requiring surgery in adulthood. Although the incidence of surgery has declined over time, the incidence of obstruction as an indication for surgery appears to be unchanged.[81] In a child with a refractory primary ulcer or multiple recurrences, or both, Zollinger-Ellison syndrome should be ruled out by evaluation of gastrin levels both at baseline and after secretin challenge. If a benign gastrinoma is suspected, localization and excision will result in cure.

Initial treatment of a bleeding peptic ulcer is medical and includes resuscitation, pharmacologic therapy, and diagnostic endoscopy. Endoscopic sclerotherapy or treatment with a heater probe is initiated by the gastroenterologist. Persistent bleeding after failed medical and endoscopic therapy, as indicated by the loss of half a blood volume in 8 hours or one blood volume in 24 hours, is an indication for surgery. The surgical approach is dictated by the location and the hemodynamic status and age of the patient. In a younger child with bleeding gastric ulcers, oversewing the ulcer along with intensive pharmacologic medical therapy is usually adequate. In an older child with a bleeding duodenal ulcer, management is similar to that for an adult: oversewing the bleeding ulcer and vagotomy with pyloroplasty or selective vagotomy. Perforations are treated by plication and an omental patch followed by intensive medical therapy; an acid reduction procedure is not usually needed in a child. Children with gastric outlet obstruction generally require vagotomy with a drainage procedure or vagotomy and antrectomy. Because of the lack of large series of children who have undergone these procedures, adult surgical recommendations are often extrapolated to these patients. A detailed description of the management of ulcer disease and vagotomy and drainage procedures may be found in Chapters 55 and 56.

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Chapter

66

Anatomy and Physiology of the Duodenum

John M. Kellum · Roberto C. Iglesias · Jarrod Day

GROSS ANATOMY

The duodenum is so named because its length is approximately 12 fingerbreadths, or 20 to 30 cm. This first portion of the intestine begins at the end of the gastric pylorus, at the right of the spine, in the plane of the first lumbar vertebra. The duodenum then extends in a C-shaped curve around the head of the pancreas and connects with the jejunum to the left of the second lumbar vertebra. It is the most proximal portion of the intestine and the widest, shortest, and least mobile segment. The duodenum is divided into four parts: the first (or superior) portion, also known as the duodenal bulb or cap; the second, or the vertical or descending portion; the third, or the horizontal or transverse portion; and the fourth, or the oblique or ascending portion (Fig. 66–1).

The duodenal cap is freely mobile in the peritoneal cavity, and it is the area where 90% of duodenal ulcers occur. It has longitudinal mucosal folds, whereas the remainder of the duodenum displays prominent transverse folds. The anterior and posterior layers of the peritoneum join over the duodenal cap's upper aspect to form the hepatoduodenal ligament, which contains the portal triad (common bile duct, hepatic artery, and portal vein). The anterior border of the foramen of Winslow is formed by the free margin of this ligament (Fig. 66–2). Immediately above the duodenal cap are the gallbladder and the quadrate lobe of the liver. Below and behind the cap is the head of the pancreas. Also behind the bulb lies the gastroduodenal artery; thus, by eroding into this vessel, peptic ulcers can cause bleeding.

The mobility and circumferential serosal coating of the duodenal bulb facilitate operations on the pylorus and duodenum. Pyloroplasties and gastroduodenal resections are performed with greater ease when the pylorus and the adjoining second portion of the duodenum are mobilized forward into the abdominal cavity by Kocher's maneuver (Fig. 66–3). The proximity of the superior duodenum to the gallbladder explains the sometimes spontaneous passage of gallstones into the duodenum via a cholecystoduodenal fistula. The peritoneum covers the distal 2.5 cm of the first portion of the duodenum only ventrally. Its range of movement depends on the peritoneal coat. The posterior wall of the first portion of the duodenum is often intimately opposed to the structures of the hepatoduodenal ligament.

The second portion of the duodenum is retroperitoneal and fixed in position through fusion of its lateral visceral peritoneum to the parietal peritoneum of the lateral abdominal wall. By dividing the peritoneum at the right lateral edge of the segment (Kocher's maneuver), one mobilizes the descending duodenum to render the retroduodenal and intrapancreatic bile ducts surgically accessible. The right kidney and its hilar structures, the adrenal gland, and the vena cava lie posterior to the second portion of the duodenum (Fig. 66–4). Horizontally across the descending midpoint of the duodenum, folds of peritoneum come together from above and below to form the mesocolon. At the superior duodenal flexure, the descending second portion of the duodenum forms an acute angle with the first portion and descends about 7 to 8 cm to the inferior duodenal flexure. The transverse colon crosses it anteriorly and may or may not possess a mesocolon at this point. One must reflect the hepatic flexure of the colon anteromedially to fully mobilize the duodenum. About halfway down the posteromedial wall of the second portion of the duodenum is the papilla of Vater (see Fig. 66–1), which contains the opening of the common bile duct and the main pancreatic duct of Wirsung. The opening of the accessory pancreatic duct (of Santorini) is more proximal and may inadvertently be injured during gastrectomy for ulcer or distal gastric cancer. The superior pancreaticoduodenal branch of the gastroduodenal

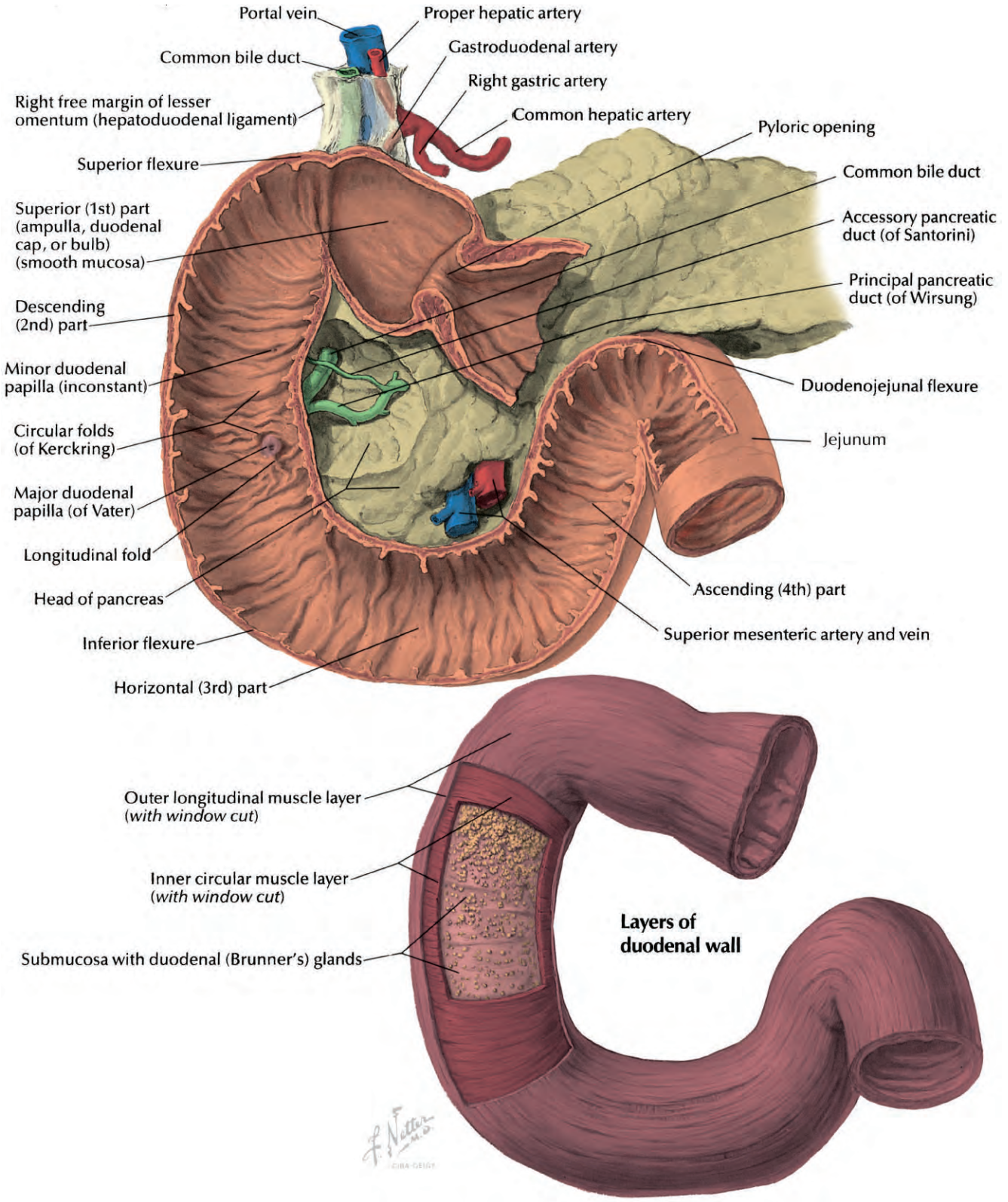


Figure 66–1. The duodenum, the four portions, and their relationship to the bile duct and pancreas identified. (From Netter FH: Atlas of Human Anatomy. East Hanover, NJ, Ciba-Geigy, 1989, plate 262. Copyright, 1999. Icon Learning Systems, LLC, a subsidiary of Havas MediMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H Netter, MD. All rights reserved.)

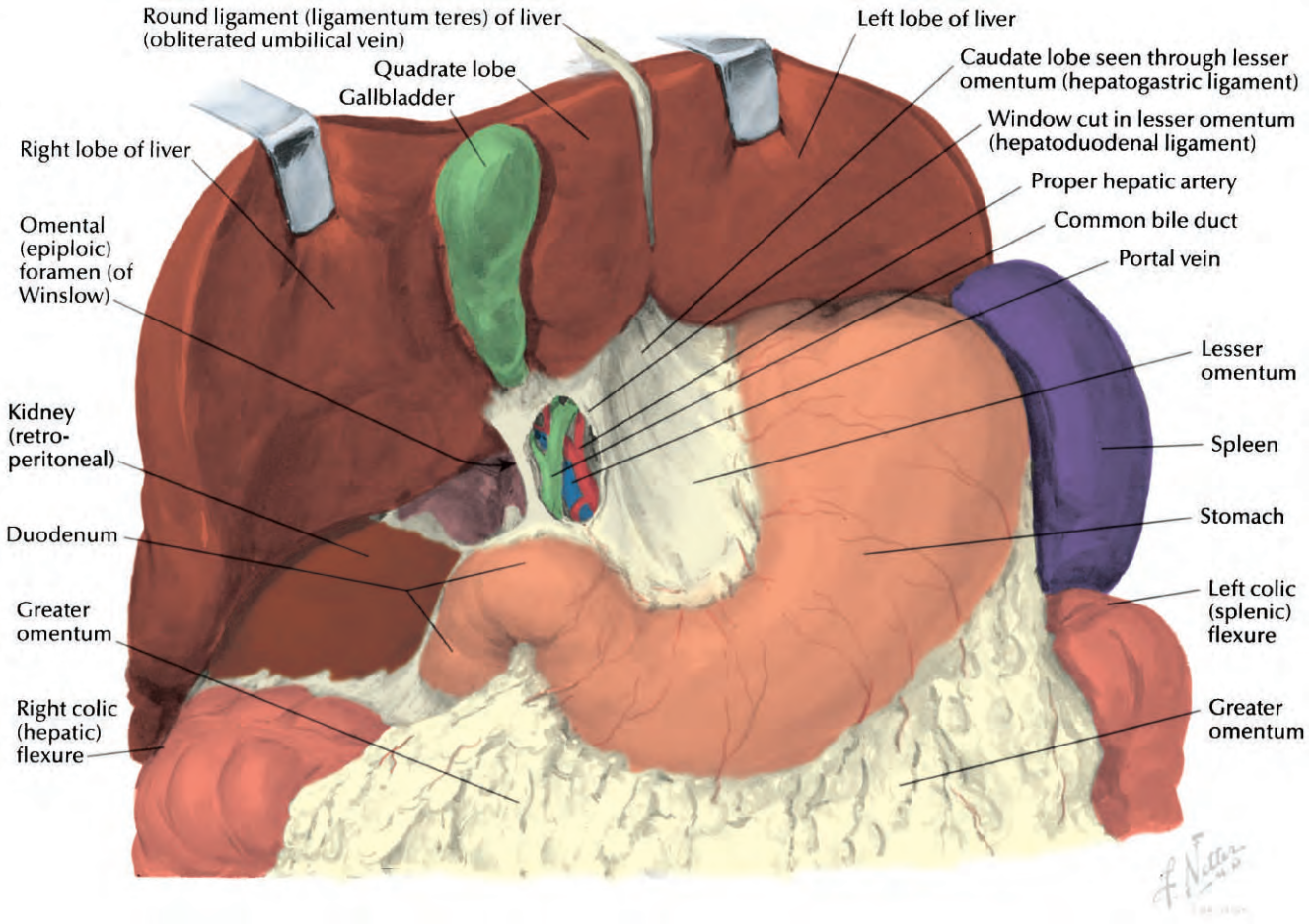
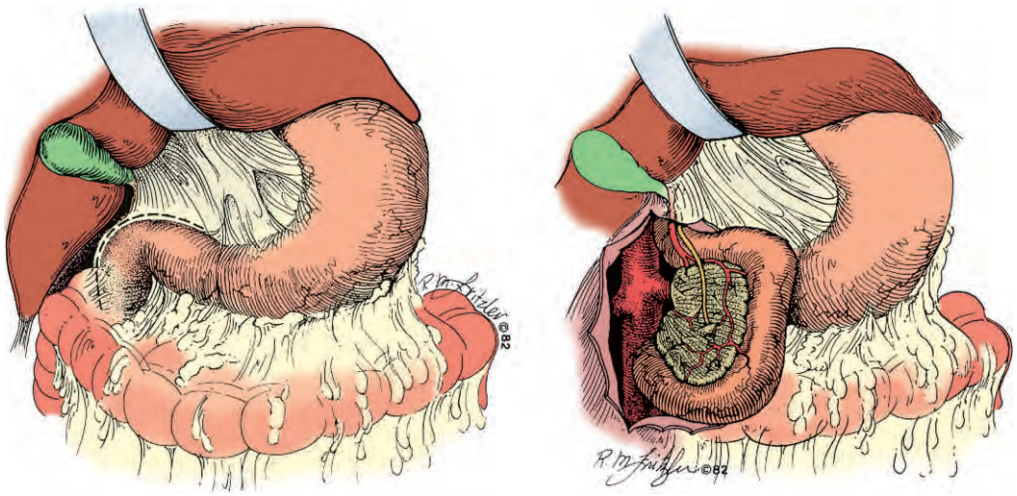


Figure 66–2. The duodenum and its relationship to the foramen of Winslow and the hepatoduodenal ligament containing the portal triad. (From Netter FH: Atlas of Human Anatomy. East Hanover, NJ, Ciba-Geigy, 1989, plate 271. Copyright, 1999. Icon Learning Systems, LLC, a subsidiary of Havas MediMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H Netter, MD. All rights reserved.)



A B

Figure 66–3. **A,** Kocher's maneuver begins by incising the peritoneum lateral to the first and second portions of the duodenum. **B,** By mobilizing the duodenum and head of pancreas medially, the posterior aspect of the head can be inspected. (From Nyhus LM, Baker RJ: Reparative procedures for the injured pancreas. In Mastery of Surgery, vol 2, 2nd ed. Boston, Little, Brown, 1992.)

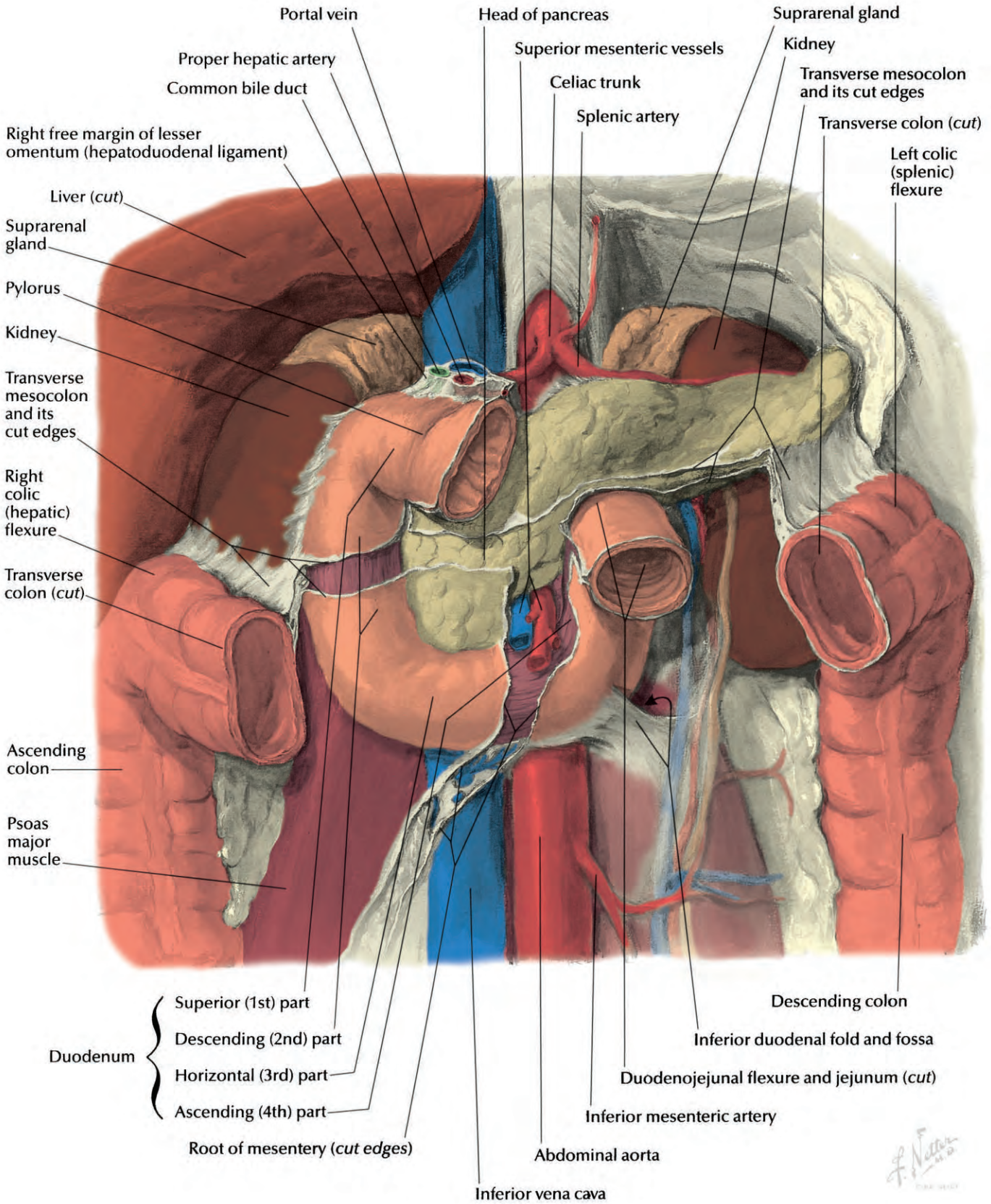


Figure 66–4. The abdominal contents as seen after removal of the stomach, jejunum, and ileum. The branches of the superior and inferior mesenteric arteries are shown. (From Netter FH: Atlas of Human Anatomy. East Hanover, NJ, Ciba-Geigy, 1989, plate 261. Copyright, 1999. Icon Learning Systems, LLC, a subsidiary of Havas MediMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H Netter, MD. All rights reserved.)

artery runs in the groove between the head of the pancreas and the descending duodenum; this intimate association of the duodenum with the pancreatic head generally mandates excision of the pancreatic head with attempted duodenum resection.

The third portion of the duodenum is about 12 to 13 cm in length; runs horizontally to the left in front of the aorta, inferior vena cava, lumbar column, and ureter; and ends at the left of the third lumbar vertebra. The root of the jejunoileum mesentery crosses it near its termination. The superior mesenteric artery runs downward over the anterior surface of the transverse duodenum to enter the root of the mesentery (Fig. 66–5). The inferior pancreaticoduodenal artery separates the pancreas from the upper border of this segment.

The fourth part of the duodenum runs upward and slightly to the left for 2 to 3 cm along the left side of the spine to the duodenojejunal angle at the root of the transverse mesocolon. At the left of the second lumbar vertebra, the terminal portion of the duodenum bends sharply downward, forward, and leftward to form the duodenojejunal flexure. At this point the suspensory ligament of the duodenum (ligament of Treitz) attaches (Fig. 66–6). This ligament is a small, triangular band of muscular and fibrous tissue that extends retroperitoneally, behind the pancreas and splenic vein, in front of the left renal vein, from the left or right crus of the diaphragm, to attach retroperitoneally to the upper margin of the terminal duodenum and sometimes to the adjacent jejunum. The ligament of Treitz is usually tenuous and is not invariably present. The duodenojejunal flexure is a readily recognized landmark that can be used to guide the search for obstruction in the small bowel and to locate a loop of upper jejunum for gastrojejunostomy. At laparotomy, it is found by passing the hand backward to the posterior abdominal wall below the transverse mesocolon and palpating upward along the left of the spine until the flexure is identified by its fixation. The bend is in contact with the inferior margin of the pancreas through the root of the transverse mesocolon.

Fusion of the pancreaticoduodenal visceral peritoneum with the primitive posterior parietal peritoneum anchors the entire duodenum, except part of the first portion. Variation in fusion of the duodenum to the posterior abdominal wall accounts for variation in mobility. The right colic flexure, the fixed portion of the transverse mesocolon, and vascular and ampullary connections anchor the duodenum still more firmly. In its deep position, the duodenum appears to be well protected from injury, yet it is sometimes crushed and even torn against the spine with severe blunt abdominal trauma, in part because of its comparatively unyielding peritoneal fixation.

Arterial Supply

The arterial supply of the duodenum is derived from the anterior and posterior pancreaticoduodenal arcades, which form a major arterial anastomosis between the celiac and superior mesenteric arterial circulations. The duodenum shares its blood supply with the proximal portion of the pancreas, thus making resection of either the duodenum or the pancreas alone usually impossible and always hazardous. The superior pancreaticoduodenal artery is a branch of the gastroduodenal artery, and the inferior pancreaticoduodenal is a branch of the superior mesenteric artery. These two arteries split and run in posterior and anterior grooves between the descending and transverse portions of the duodenum and the head of the pancreas, where they anastomose to form continuous anterior and posterior arcades (Fig. 66–7; see also Fig. 66–5). This rich periduodenal anastomotic network of arteries often frustrates attempts to control bleeding secondary to posterior duodenal ulcers.

Venous Supply

The veins that parallel the pancreaticoduodenal arteries are arranged in anterior and posterior pancreaticoduodenal arcades that accompany the arteries (Fig. 66–8). The posterior arcade ends in the portal vein above and the superior mesenteric vein (SMV) below. The posterosuperior pancreaticoduodenal vein may follow its companion artery anterior to the bile duct, or it may run behind the duct. The vein terminates inferiorly on the left border of the SMV. Here, it may be joined by a jejunal vein or by the anterior inferior pancreaticoduodenal vein. The gastrocolic trunk (Henle's trunk) drains most of the anterior arcade.[1] Several small branches drain the duodenal bulb and empty into the pancreaticoduodenal, right gastroepiploic, or portal vein; a key landmark for the pylorus is the prepyloric vein.

During pancreaticoduodenectomy, the SMV may be located by following the middle colic vein to its junction with the SMV just inferior to the neck of the pancreas. Sometimes, incision of the avascular peritoneum along the lower border of the gland to the left of the SMV facilitates identification. Superior to the pancreas, division of the common bile duct and gastroduodenal artery readily exposes the portal vein. Occasionally, a tortuous hepatic artery may be mistaken for the gastroduodenal artery; therefore, before ligation of the gastroduodenal artery, it should be transiently occluded with a vascular clamp or the surgeon's fingers while the hepatic artery pulse is palpated in the hilum of the liver.

Lymphatic Drainage

The lymphatic drainage of the duodenum generally parallels the vasculature. Lymph passes through several levels of lymph nodes that are located adjacent to the bowel wall, adjacent to the mesenteric arcades, and along the superior mesenteric and celiac arteries. Primary duodenal carcinomas may invade the pancreas via direct extension or lymphatic infiltration, but they usually first spread to the periduodenal lymph nodes and liver. Nodes at the superior duodenal flexure and retroduodenal nodes are commonly involved in metastatic pancreatic carcinoma.

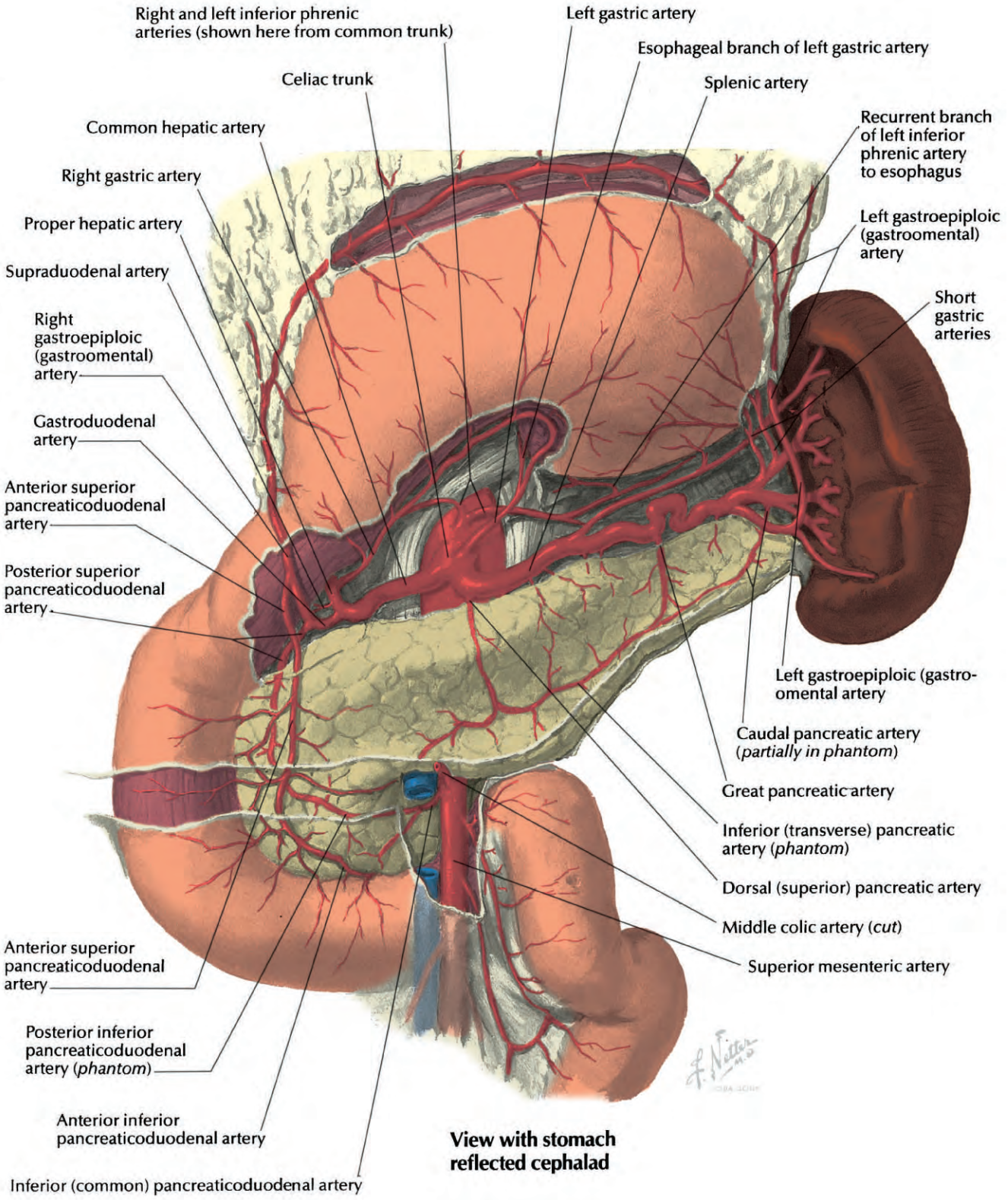


Figure 66–5. View of the arteries of the duodenum and pancreas, with the stomach reflected cephalad. (From Netter FH: Atlas of Human Anatomy. East Hanover, NJ, Ciba-Geigy, 1989, plate 283. Copyright, 1999. Icon Learning Systems, LLC, a subsidiary of Havas MediMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H Netter, MD. All rights reserved.)

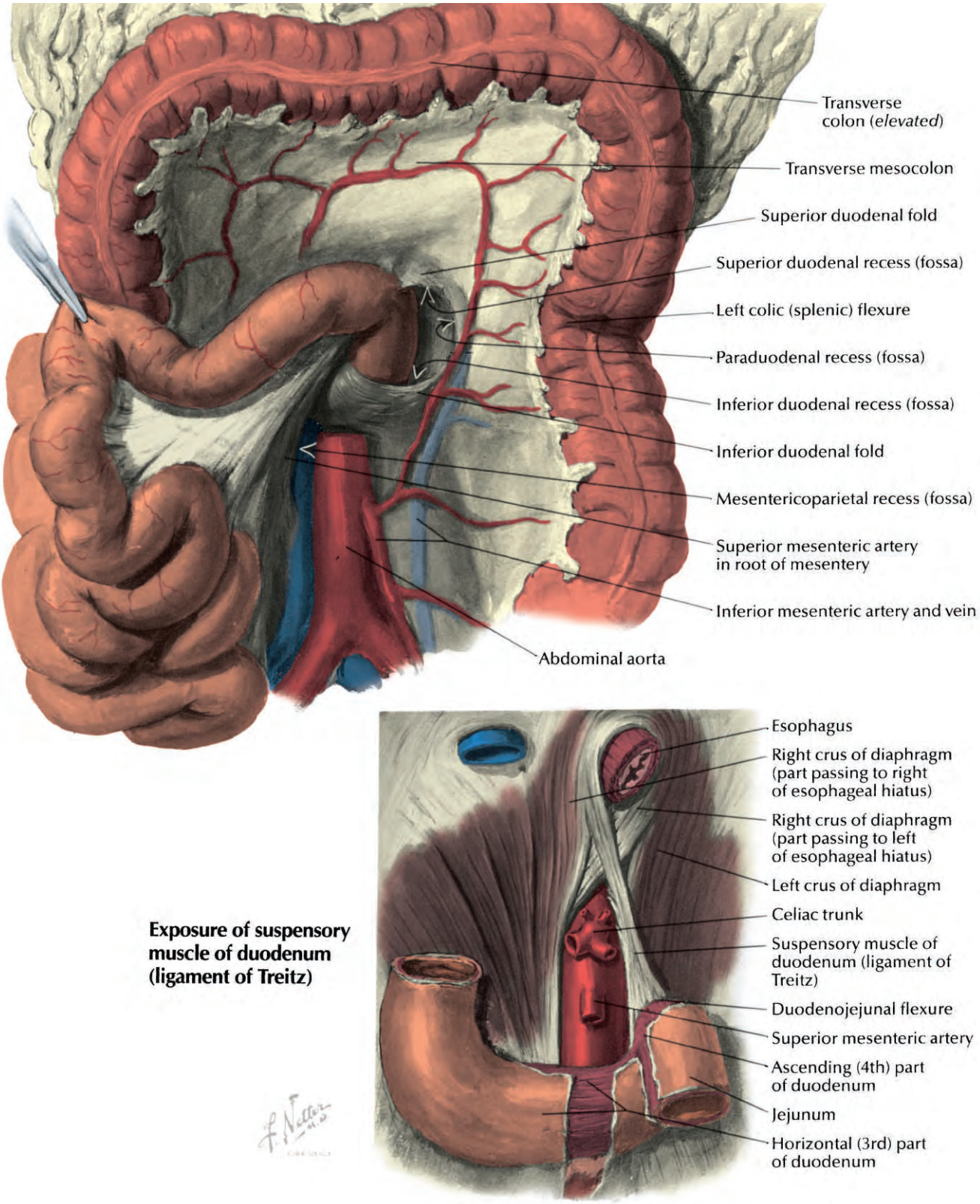


Figure 66–6. The duodenojejunal junction showing exposure of the suspensory ligament of Treitz. (From Netter FH: Atlas of Human Anatomy. East Hanover, NJ, Ciba-Geigy, 1989, plate 53. Copyright, 1999. Icon Learning Systems, LLC, a subsidiary of Havas MediMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H Netter, MD. All rights reserved.)

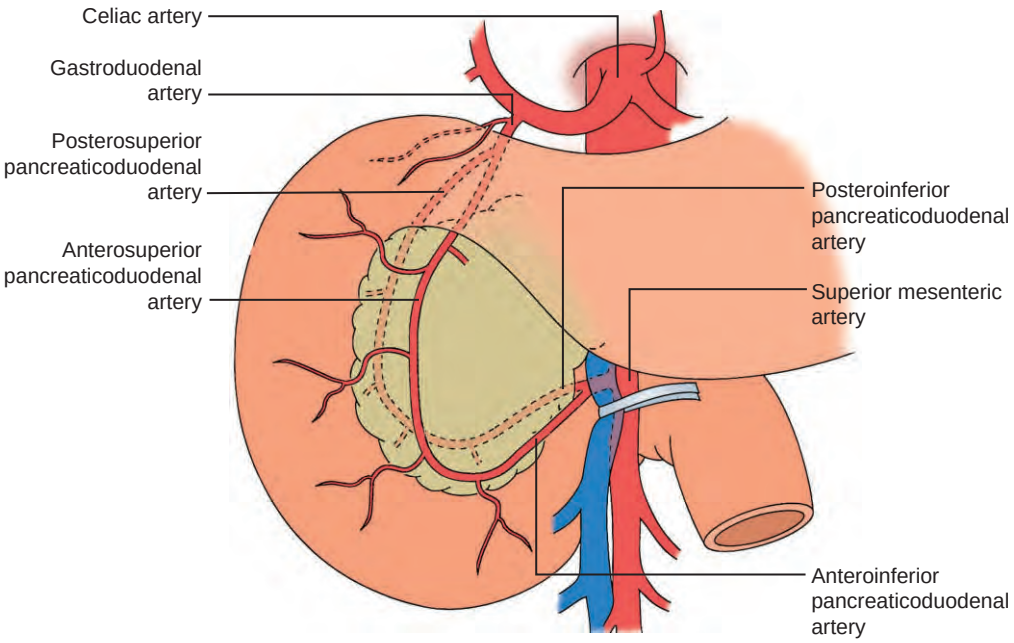


Figure 66–7. Arterial supply to the duodenum. (From Anatomy and physiology of the small intestine. In Greenfield LJ, Mulholland WM, Oldham KT, et al [eds]: Surgery: Scientific Principles and Practice, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2001, p 788.)

Histology of the Duodenum

The wall of the duodenum is made up of four layers: an outer peritoneal coat, the serosa; a muscular coat made up of longitudinal and circular fibers, the muscularis; the submucosa; and the mucosa, which forms its inner lining (Fig. 66–9). Portions of the posterior and lateral walls of the duodenum are retroperitoneal and therefore lack the peritoneal or serosal coat. The serosa is an extension of the peritoneum. It consists of a single layer of flattened mesothelial cells overlying loose connective tissue.

Two layers of smooth muscle make up the muscularis, an outer or longitudinal layer and an inner or circular layer. The myenteric plexus of Auerbach lies between these two layers. Meissner's plexus is found in the submucosa along with a network of loose connective tissue rich in lymphatics and small blood vessels. Here, in the submucosa, are found the characteristic histologic features of the mammalian duodenum: the glands of Brunner, which empty into the crypts of Lieberkühn through small secretory ducts (Fig. 66–10). Brunner's gland secretion is viscous, alkaline (pH 8.2 to 9.3), and clear. These mucoid, viscous, alkaline secretions probably contribute to protection of the duodenal mucosa against the corrosive action of gastric juice.

The intestinal mucosa is thrown into numerous finger-like projections, or villi, that greatly increase the mucosal surface area. The columnar cell–lined epithelium contains both mucus and HCO_3^--secreting surface cells and absorptive cells. The mucosa can be divided into three layers: the deepest is the muscularis mucosae, the middle layer is the lamina propria, and the inner layer consists of a continuous sheet of a single layer of columnar epithelial cells lining both the crypts and the villi.

The main known functions of the crypt epithelium include (1) cell renewal; (2) exocrine, endocrine, water, and ion secretion; and (3) absorption of salt, water, and specific nutrients. The crypt epithelium is composed of at least four distinct cell types: Paneth, goblet, undifferentiated, and endocrine cells.

Innervation of the Duodenum

The gastrointestinal (GI) tract is innervated by the autonomic nervous system, which may be divided into extrinsic and intrinsic or enteric nervous systems. The extrinsic innervation of the duodenum is parasympathetic from the vagus nerves (anterior and celiac branches) and sympathetic from the splanchnic nerves of the celiac ganglion. Intrinsic innervation is from Auerbach's myenteric plexus and Meissner's submucosal plexus. Processes from these neurons innervate target cells such as smooth muscle, secretory, and absorptive cells, but they also connect to sensory receptors and interdigitate with processes from other neurons located both inside and outside the plexus. Thus, pathways within the enteric nervous system can be multisynaptic, and integration of activities can take place entirely within the enteric nervous system (Fig. 66–11).

Adult Anatomic Abnormalities That May Require Surgery

The main anatomic abnormalities of the duodenum that the surgeon may be asked to treat in adult patients are duodenal diverticula, vascular anomalies, and

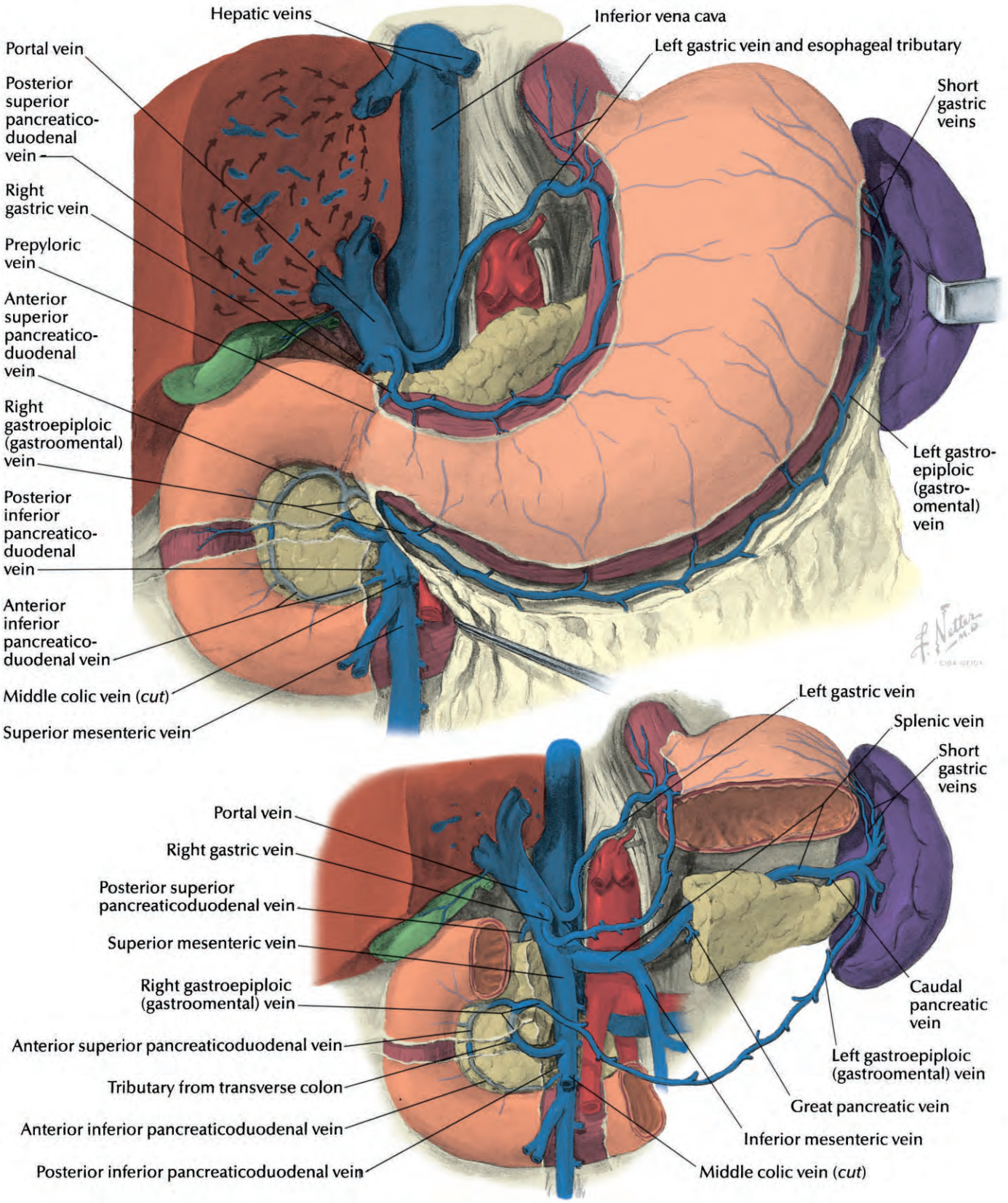


Figure 66–8. View of the veins of the duodenum and pancreas, with the stomach removed. (From Netter FH: Atlas of Human Anatomy. East Hanover, NJ, Ciba-Geigy, 1989, plate 294. Copyright, 1999. Icon Learning Systems, LLC, a subsidiary of Havas MediMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H Netter, MD. All rights reserved.)

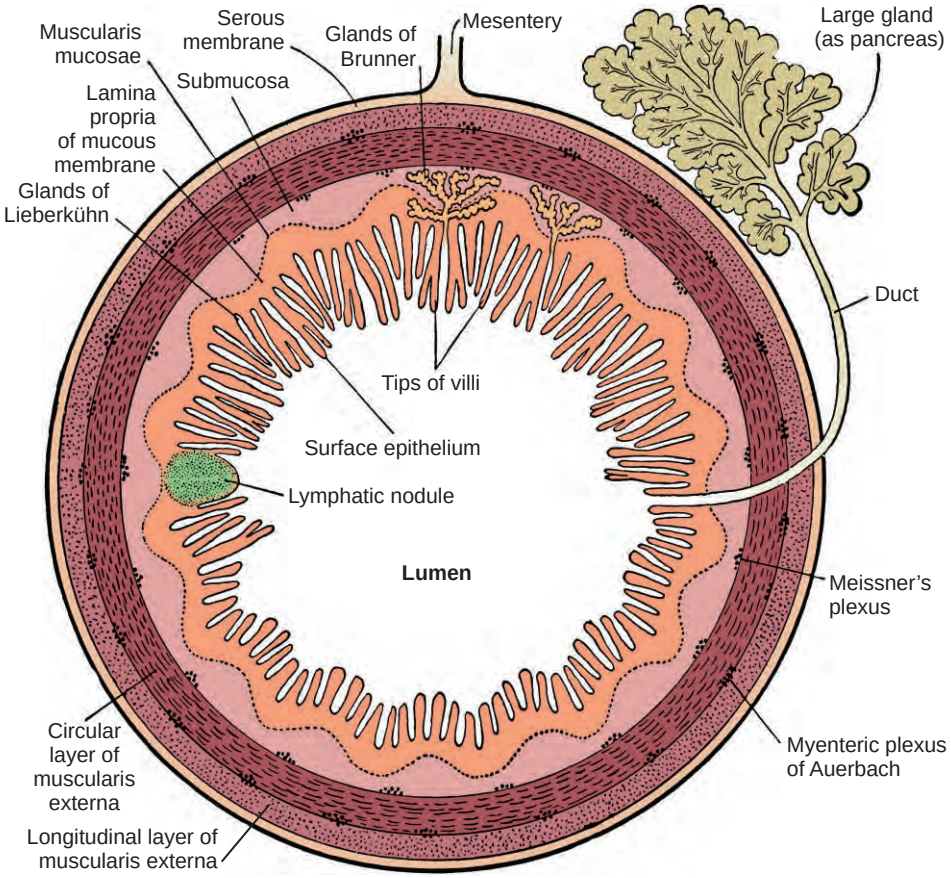


Figure 66–9. Schematic diagram of a cross section of the intestinal tract. (From Bloom WN, Fawcett DW: A Textbook of Histology. Philadelphia, WB Saunders, 1968.)

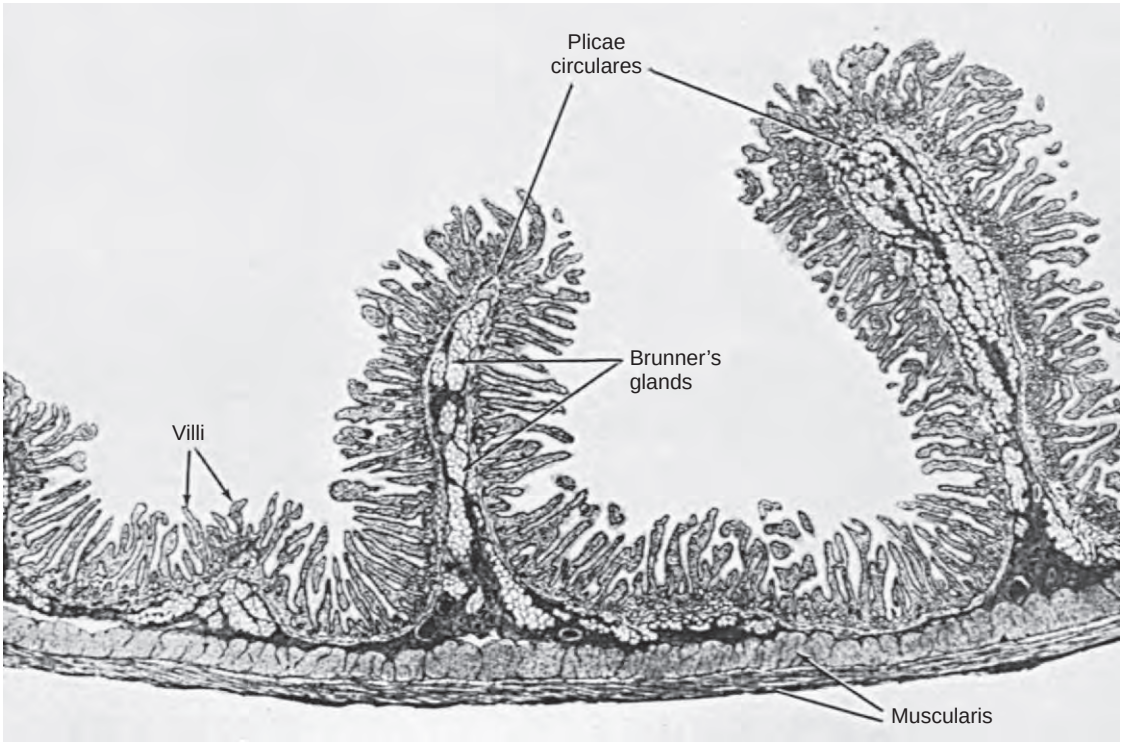


Figure 66–10. Drawing of a longitudinal section through the wall of the duodenum of an adult human showing the plicae circularis (valves of Kerckring), the villi, and the submucosal glands of Brunner. (From Bargmann W: Histologie und Mikroskopische Anatomie des Menschen, 6th ed. Stuttgart, Germany, Georg-Thieme Verlag, 1962.)

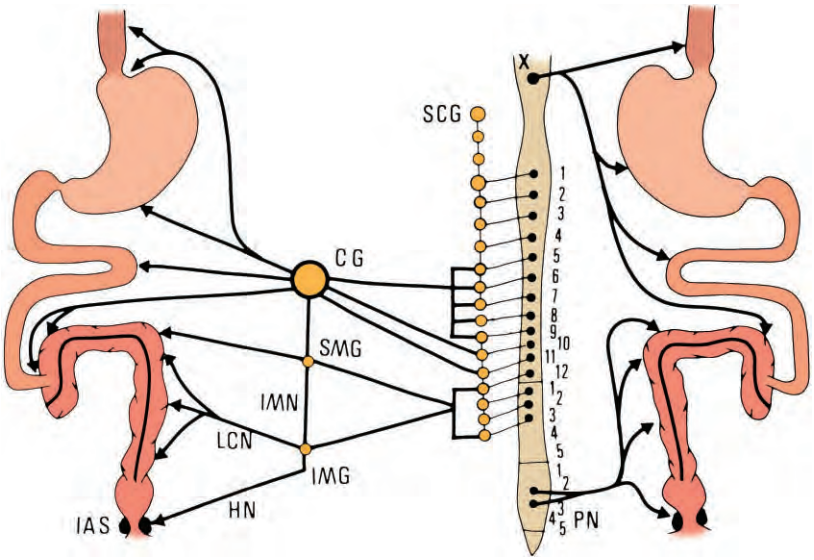


Figure 66–11. Schema of the extrinsic efferent innervation of the gut showing the sympathetic innervation *(left)* and the parasympathetic innervation *(right).* This representation is a synthesis of various data and may present variations according to different species. CG, celiac ganglion; HN, hypogastric nerves; IAS, internal anal sphincter; IMG, inferior mesenteric ganglion; IMN, intermesenteric nerve; LCN, lumbar colonic nerves; PN, pelvic nerves; SCG, superior cervical ganglion; SMG, superior mesenteric ganglion; X, vagus dorsal motor nucleus and vagus nerve. (From Roman C, Gonella J: Extrinsic control of digestive tract motility. In Johnson LR [ed]: Physiology of the Gastrointestinal Tract, 2nd ed. New York, Raven Press, 1987, p 507.)

paraduodenal hernias. Although duodenal atresia or stenosis, malrotation, and annular pancreas are sometimes found in adults, they are more commonly seen in pediatric surgical patients and are discussed elsewhere.

Preduodenal Portal Vein

A rare, but important venous anomaly of which the duodenal surgeon should be aware is the preduodenal portal vein. In this congenital anomaly the portal vein passes anterior to the duodenum rather than lying in its normal posterior position. The anomaly is due to abnormal development of the vitelline veins, as described by Bower and Ternberg (Fig. 66–12).[2] The majority of cases reported in the literature involve infants or children, and there is a very high association with additional congenital anomalies such as (in decreasing order) malrotation, situs inversus, and cardiac lesions.[3] Most patients have acute or chronic high intestinal obstruction or symptoms of gastric outlet obstruction. The diagnosis is rarely made preoperatively.

At surgery, when the duodenum is found to be obstructed and a preduodenal portal vein is present, it is important to accurately determine whether the obstruction is caused by the anomalous vein, by associated anomalies, or by both. If the preduodenal portal vein is not causing obstruction, it is left undisturbed, and associated abnormalities are treated. If the anomalous vein is causing obstruction, relief can be obtained via one of two surgical procedures: (1) transection of the proximal duodenum with end-to-end duodenoduodenostomy anterior to the portal vein[2] or (2) duodenojejunostomy or gastrojejunostomy.[3] Both procedures have been used successfully.

Superior Mesenteric Artery Syndrome

Rokitansky first described compression and obstruction of the third portion of the duodenum by the superior mesenteric artery more than 100 years ago. Synonyms include Wilkie's syndrome, cast syndrome, and arteriomesenteric duodenal ileus or compression.[4] Despite intermittent waves of enthusiasm for this diagnosis, surgeons are generally reluctant to ascribe upper GI symptoms to this relatively rare abnormality (0.2% of 6000 upper GI examinations).[5] It is generally thought that for vascular compression to cause duodenal obstruction, some combination of three mechanical factors must be present: (1) an abnormally narrow aortomesenteric angle, (2) an abnormally highly fixed transverse duodenum, and (3) an abnormal course of the mesenteric

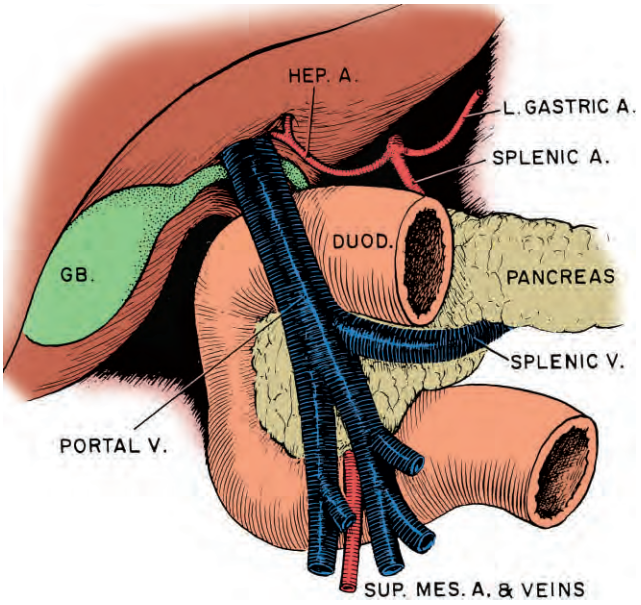


Figure 66–12. Anomalous preduodenal portal vein. GB, gallbladder. (From Edwards EA, Malone PD, MacArthur JD: Operative Anatomy of Abdomen and Pelvis. Philadelphia, Lea & Febiger, 1975.)

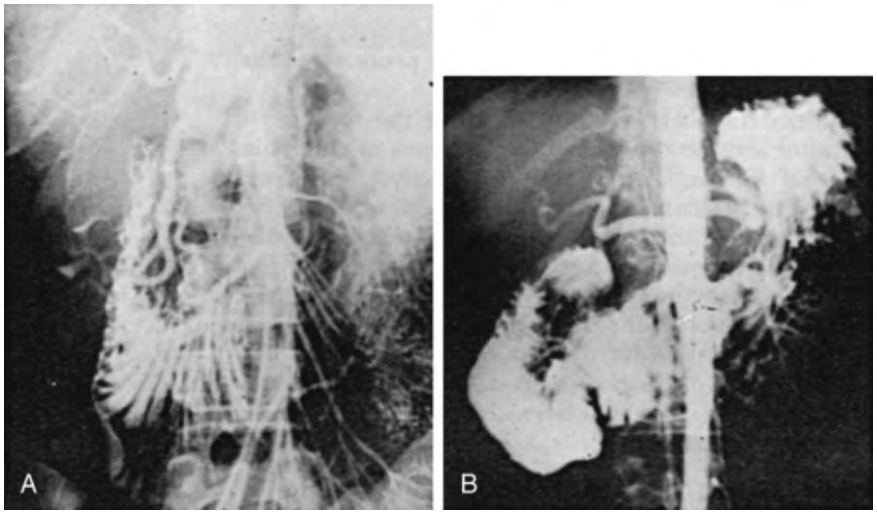


Figure 66–13. Combined gastrointestinal barium and aortography study revealing the point of compression and the abnormal course of the superior mesenteric artery. **A,** Narrow superior mesenteric-aortic angle. **B,** Aberrant course of the superior mesenteric artery. (From Mansberger AR: Vascular compression of the duodenum. In Sabiston DC [ed]: Textbook of Surgery, 13th ed. Philadelphia, WB Saunders, 1986, p 877.)

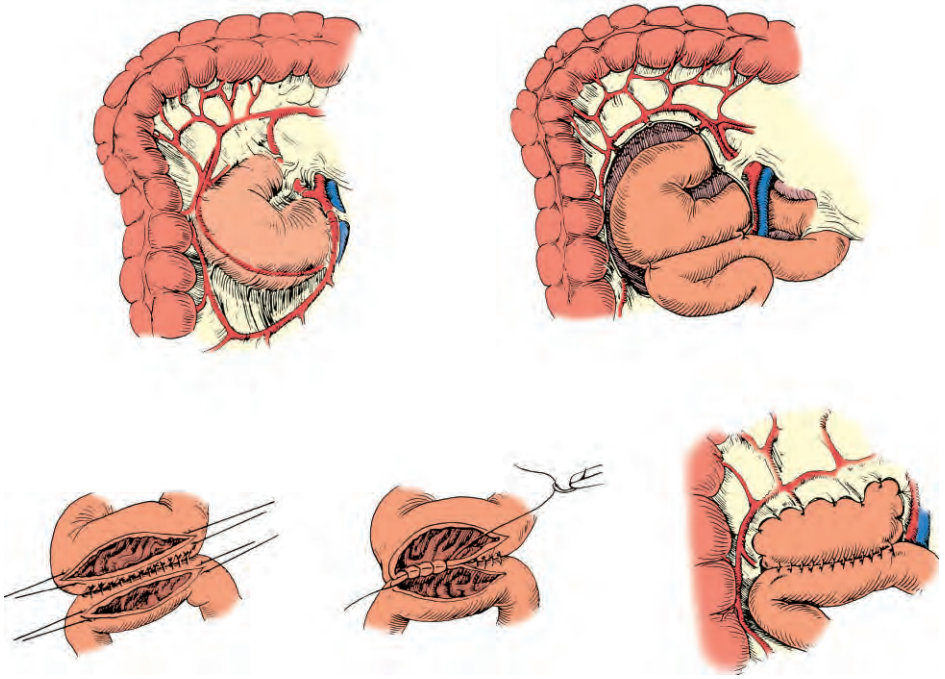


Figure 66–14. Duodenojejunostomy for vascular compression of the duodenum. (From Mansberger AR: Vascular compression of the duodenum. In Sabiston DC [ed]: Textbook of Surgery, 13th ed. Philadelphia, WB Saunders, 1986, p 877.)

artery continuing inferiorly, anterior to the unyielding vertebral column (Fig. 66–13). Hyperextension of the spine (as may occur after the application of a body cast or skeletal traction) and weight loss (associated with depletion of retroperitoneal fat) further narrow the aortomesenteric angle and are associated with progressive symptoms of distal duodenal obstruction in patients with this diagnosis. This syndrome has also been described in patients with severe scoliosis after so-called spine-straightening surgery.

The preferred method of surgical treatment is duodenojejunostomy, which can be performed in side-to-side fashion between the dilated proximal jejunum after the mesocolon of the hepatic flexure has been opened (Fig. 66–14). Gastrojejunostomy is a poor second choice because it relies on retrograde decompression of the duodenum through the pylorus. A third option is extensive mobilization of the ligament of Treitz after mobilization of the hepatic flexure of the colon. After this maneuver, the distal duodenum and small bowel are passed under the mesenteric vessels, and the C loop of the duodenum is straightened out (Fig. 66–15). Although this third option does not involve opening the GI tract, it does require division of some small vessels to the distal duodenum. Segmental ischemia apparently has not been a problem.

Paraduodenal Hernia

Paraduodenal (or mesocolic) hernias and hernias of the foramen of Winslow are the two most frequent types of congenital internal hernia.[6] They most commonly cause

symptoms of acute small bowel obstruction, and frequently plain radiographs of the abdomen are suggestive of the diagnosis. Some patients have symptoms of chronic intermittent obstruction for years before a definitive diagnosis is made. Bowel strangulation is commonly found at surgery for these disorders.

The most common paraduodenal hernia is the so-called left paraduodenal hernia (Fig. 66–16).[7] In this condition, variable amounts of small intestine herniate through the so-called vascular arch of Treitz formed by the inferior mesenteric vein and the left colic artery. The herniated small bowel is therefore posterior to the mesocolon. The cecum and terminal ileum are in their normal anatomic configuration. Operative treatment of a left paraduodenal hernia involves opening the retroperitoneum just to the right of the inferior mesenteric vein and artery. The bowel can be reduced to its normal anatomic position, and the root of the mesentery of the left colon can be joined to the peritoneum anterior to the aorta to obliterate the arch of Treitz.

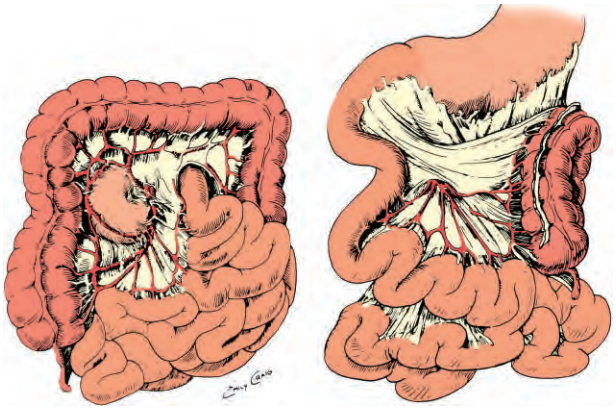


Figure 66–15. Operation to straighten the duodenum and return it to its prerotation position. (From Sabiston DC [ed]: Textbook of Surgery, 13th ed. Philadelphia, WB Saunders, 1986, p 877.)

The more unusual right paraduodenal hernia is due to an abnormality in embryonic intestinal rotation.[8] The cecum is usually in the right upper quadrant, and Ladd's bands are apparent. In this hernia, the small bowel is trapped in a hernia sac, the anterior wall of which is formed by the mesentery of the small bowel. It is as though the herniated bowel has rotated under the superior mesenteric artery and is trapped in the right upper quadrant. The hernia is best approached by incising the attachments of the right colon rather than attempting to open the hernia sac from the medial side because this might involve the division of critical mesenteric arteries.

The least common paraduodenal hernia is a hernia of the foramen of Winslow.[9] It is almost always associated with an unusually patulous foramen of Winslow, which allows the bowel or right colon to herniate through the foramen into the lesser peritoneal sac (Fig. 66–17). The radiographic diagnosis is usually made in retrospect. Operative treatment involves gentle traction on the herniated bowel in an attempt at reduction. If reduction cannot be achieved, the lesser sac should be opened by incising the gastrocolic omentum, and the hernia can be reduced by both pulsion and traction. Rarely, strangulated bowel within the lesser peritoneal sac must be resected before reduction of the remaining contents. Once reduction has been completed, the patulous foramen of Winslow should be closed with interrupted sutures.

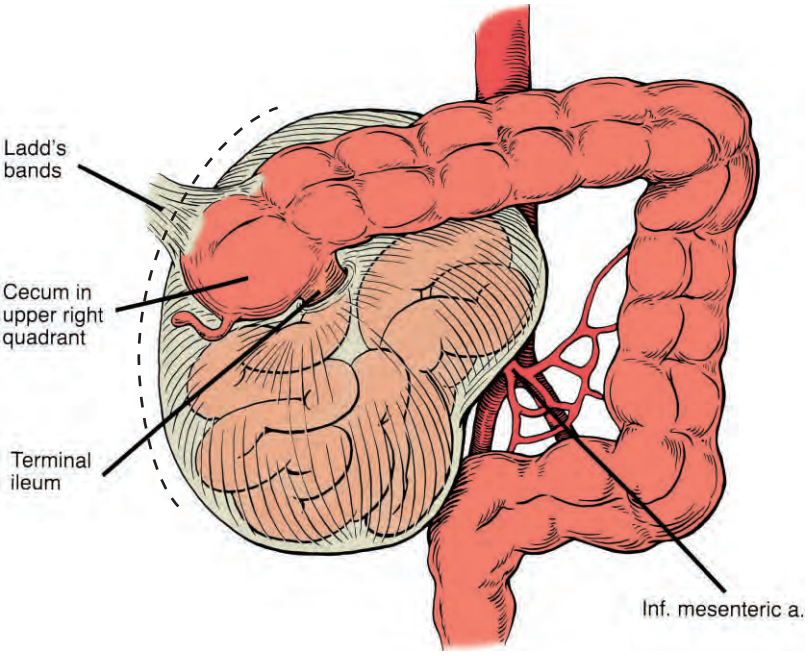


Figure 66–16. Right mesocolic hernia. The prearterial segment *did not* rotate during the second stage. The postarterial segment *did* rotate and has trapped most of the small bowel behind the ascending mesocolon containing the ileocolic, right colic, and middle colic vessels. The *dashed line* shows the incision for release of the hernia. (From Nyhus LM, Harkins HN (eds): Hernia. Philadelphia, JB Lippincott, 1978, p 493.)

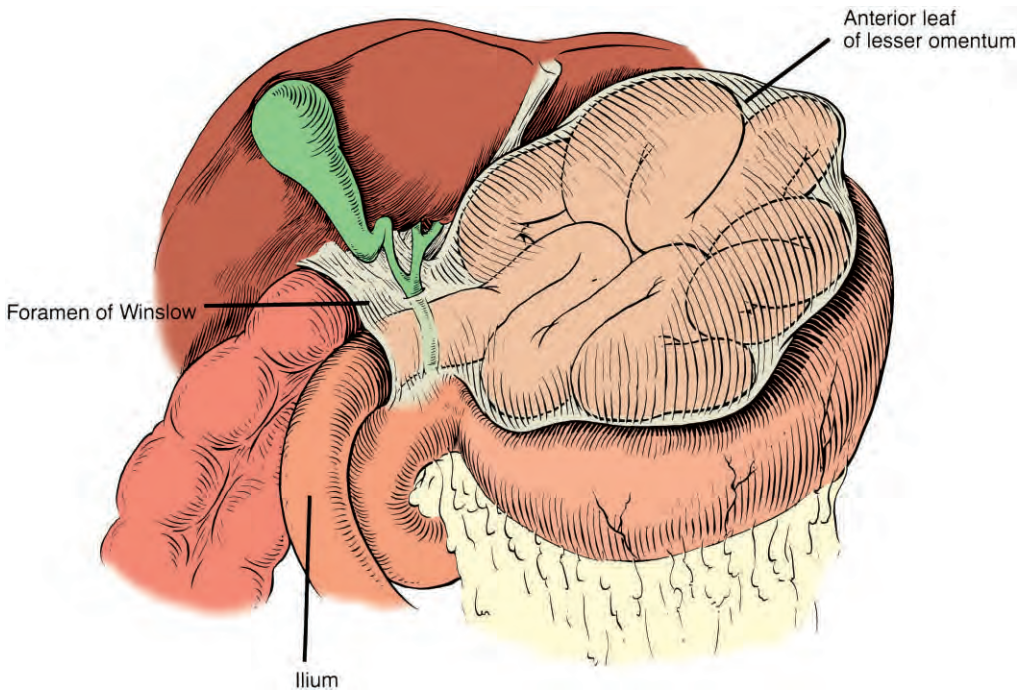


Figure 66–17. Diagrammatic illustration of a hernia into the lesser sac through the foramen of Winslow. (From Nyhus LM, Harkins HN [eds]: Hernia. Philadelphia, JB Lippincott, 1964, p 598.)

Duodenal Diverticula

Most duodenal diverticula are asymptomatic and come to the attention of the clinician during routine barium examination. They may be acquired or congenital, and up to 15% of the adult population is affected. Duodenal diverticula are probably true diverticula because the few resected specimens appear to have a complete, though attenuated, muscularis propria. The vast majority of patients with GI symptoms and duodenal diverticula have other causes for these symptoms, which is why excision should be undertaken with a great deal of circumspection. Another reason for caution is that most duodenal diverticula are located along the posteromedial surface of the second portion of the duodenum, where they are intimately related to the pancreatic head and occasionally contain the ampulla of Vater. About 20% occur in the third portion and 10% occur in the fourth portion of the duodenum.

Although usually asymptomatic, duodenal diverticula occasionally require emergency surgery because of perforation or association with massive hemorrhage.[10] Peri-Vaterian diverticula have been implicated in the pathogenesis of primary choledocholithiasis and pancreatitis. Elective surgery is occasionally undertaken because of chronic abdominal pain or symptoms of bacterial overgrowth. Bleeding is treated by excision and duodenal closure, although duodenal diverticularization, or duodenostomy, should be considered and peritoneal drainage of the paraduodenal space should always be performed.

DUODENAL PHYSIOLOGY

The duodenum is a complex organ with a unique set of structural and physiologic properties that differentiate it from the stomach and the remainder of the small intestine. It is here that the process of digestion and absorption truly begins, where meal contents are alkalinized and mixed with digestive enzymes and bile. The main functions of the duodenum are to (1) alkalinize acidic chyme from the stomach, (2) serve as a reservoir for pancreaticobiliary secretions, (3) be the main site of calcium and iron absorption, (4) further the breakdown of food products, and (5) exert neuroendocrine control of upper GI motility. Thus, duodenectomy can disrupt the relationship between cycles of both interdigestive GI motility and insulin secretion and can lead to anemia, secondary hyperparathyroidism, and other diseases caused by malabsorption.[11,12]

Exocrine Physiology

The duodenum is unique in that there are no tight junctions that provide inherent protection as in the stomach. Instead, it has a leaky epithelium between duodenocytes, and as a result, it must use alternative defense mechanisms against concentrated gastric acid and other irritants discharged by the stomach. Many compounds have been implicated in stimulating bicarbonate secretion after duodenocyte exposure to acid, including vagally produced acetylcholine; prostaglandins (especially

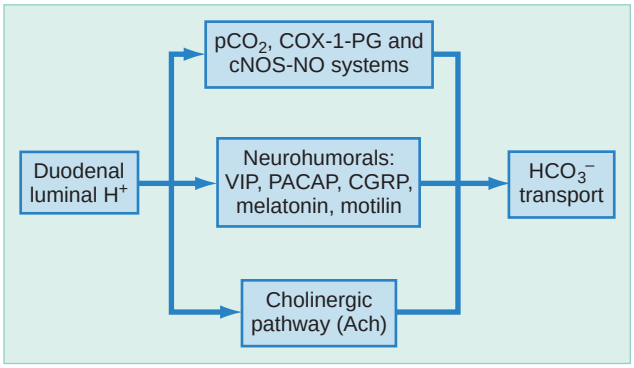


Figure 66–18. The mechanism of duodenal HCO_3^- secretion in response to gastric H^+ involves a variety of neurotransmitters, P_{CO_2}, cyclooxygenase-1–prostaglandin (COX-1–PG), and the constitutive nitric oxide synthase–nitric oxide (cNOS-NO) system. (From Konturek PC, Konturek SJ, Hahn EG: Duodenal alkaline secretion: Its mechanisms and role in mucosal protection against gastric acid. Dig Liver Dis 36:505-512, 2004.)

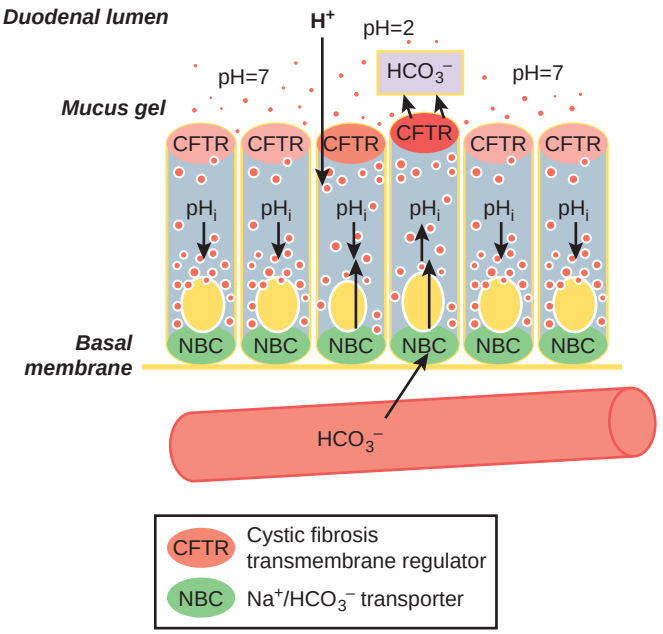


Figure 66–19. In the duodenocyte membrane transport system, HCO_3^- is exchanged for Cl^- at the apical cell membrane. This bicarbonate then neutralizes gastric acid entering the proximal duodenum. (From Konturek PC, Konturek SJ, Hahn EG: Duodenal alkaline secretion: Its mechanisms and role in mucosal protection against gastric acid. Dig Liver Dis 36:505-512, 2004.)

PGE)[13]; vasoactive intestinal polypeptide (VIP) and its analogue PACAP (pituitary adenylate cyclase activating polypeptide); melatonin[14,15]; motilin; and P_{CO_2}, prostaglandin, and nitric oxide (NO) (Fig. 66–18).[16]

One defensive barrier lies in the bicarbonate secreted by the pancreas and liver in response to duodenal acidification and release of duodenal secretin; however, the majority of protection is inherent within the duodenal bulb, which coordinates a complex array of titrating mediators that ultimately produce neutralizing bicarbonate.

The duodenocyte membrane transport system is believed to be coordinated with phase II/III of the migrating motor complex (MMC) and functions as follows (Fig. 66–19)[16]:

1. Luminal H^+ diffuses into duodenocytes through their apical membrane and reduces their intracellular pH.
2. The acidification of duodenocytes promotes movement of extracellular bicarbonate into the cell through basolateral Na^+/HCO_3^- transporter (NBC) channels.
3. This base loading causes apical cystic fibrosis transmembrane conductance regulator (CFTR)-related HCO_3^-/Cl^- exchangers to transport bicarbonate into the duodenal lumen and thus further buffer the acid load.

Another alkaline-secreting mechanism relies on H^+ activation of capsaicin-sensitive afferent nerves within the axon-reflex pathway that stimulate the release of sensory neuropeptides such as enteroglucagon and calcitonin gene–related peptide (CGRP), which in turn activate the release of NO and cyclooxygenase-prostaglandin (COX-PG).[16] In addition, this system is self-perpetuating; as HCO_3^- is hydrolyzed to increase the partial pressure of CO_2 (P_{CO_2}), duodenocytes further increase HCO_3^- secretion. The cumulative sum of these factors leads to the following (Fig. 66–20):

1. Stimulation of goblet cells and Brunner's glands to increase the thickness of the mucus gel layer
2. Stabilization of the pH gradient and prevention of acid from entering epithelial cells
3. NO-mediated mucosal vasodilation leading to hyperemia and increased blood flow

In support of this capsaicin–CGRP mechanism, COX inhibitors abolish this response and patients with duodenal ulcers have been shown to have decreased bicarbonate secretion as a result of *Helicobacter pylori* production of the NO inhibitor, asymmetric dimethylarginine (ADMA).[17] Finally, the last mechanism for maintaining cell integrity is repair from injury.

Absorption and Digestion

The duodenum receives largely undigested food particles from the stomach; it is the function of a duodenocyte's brush border to begin the process of nutrient absorption via a variety of complex transport systems. This process is aided by pancreaticobiliary secretion and a host of hormones that make the food content more manageable. The main nutrients absorbed are discussed.

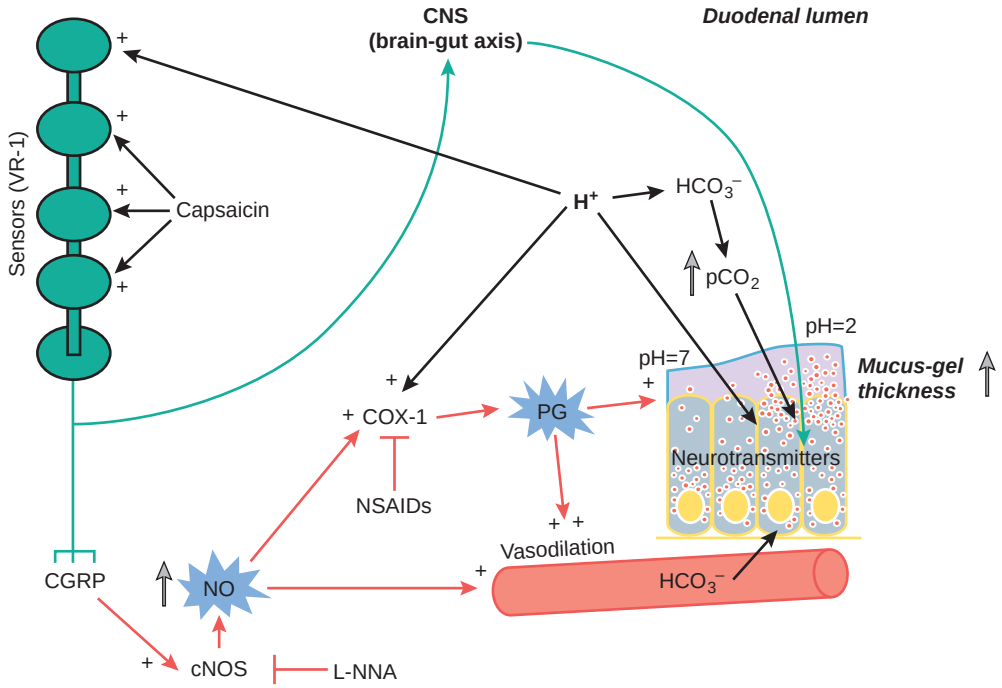


Figure 66–20. Involvement of capsaicin-sensitive nerves, calcitonin gene–related peptide (CGRP), nitric oxide (NO), prostaglandin (PG), and an increase in P_{CO_2} in the stimulation of mucus HCO_3^- secretion by duodenal mucosa in response to acidification. cNOS, constitutive nitric oxide synthase; CNS, central nervous system; COX-1, cyclooxygenase-1; L-NNA, *N*(ω)-nitro-L-arginine; NSAIDs, nonsteroidal anti-inflammatory drugs. (From Konturek PC, Konturek SJ, Hahn EG: Duodenal alkaline secretion: Its mechanisms and role in mucosal protection against gastric acid. Dig Liver Dis 36:505-512, 2004.)

Calcium

The duodenum plays a major role in calcium absorption, especially when oral dietary calcium is low, at which time as much as 80% to 100% is absorbed through an active transport–dependent transcellular system that upregulates and thus increases calcium absorption through three steps[18,19]: entry through the brush border, diffusion into the cytosol via the calcium binding protein calbindin D9k, and extrusion into blood through basal membrane Ca^{2+}-ATPase and Na^+/Ca^{2+} exchangers. This mechanism is confined to the duodenum and proximal jejunum and is dependent on vitamin D, which is essential for the biosynthesis of calbindin and possibly for increasing the number of extrusion pumps.[19]

Although calcium can also be absorbed through paracellular regulation throughout the small intestine, this mechanism is not as efficient because it absorbs only 20% to 60% and is time and concentration gradient dependent and thus most effective with high levels of dietary calcium intake or slow transient time.[18] The existence of this paracellular system ensures calcium absorption in the absence of vitamin D, as may be the case with northern winters, malabsorption, or inadequate oral intake.

The importance of this transcellular regulation mechanism is highlighted in patients in whom metabolic bone diseases develop after Roux-en-Y gastric bypass (RYGBP). Through bypassing the duodenum, this weight loss operation forces the body to become strictly dependent on paracellular regulation, which when not appropriately supported with a high-calcium diet, can result in calcium deficiency. In addition, the procedure can cause poor mixing of bile salts with fats and thus lead to malabsorption of fat-soluble vitamin D and, as a result, secondary hyperparathyroidism, osteoporosis, and osteomalacia.[20] Although the incidence of secondary hyperparathyroidism after RYGBP is unknown, Rhode and MacLean[21] reported elevated parathyroid hormone (PTH) in 14% and Amaral and colleagues[22] observed an increase in alkaline phosphatase in 34% of patients. Johnson et al.[23] found that elevated PTH was common after RYGBP and correlated with low vitamin D levels. The deficiency was progressive over time.

Iron

Another important function of duodenocytes is to serve as the main check point for iron homeostasis. Iron is an essential constituent of many important metabolic processes, including oxygen transport as a component of hemoglobin; however, too much iron can lead to free radical formation and thus toxic states such as hemochromatosis.

The mechanism by which duodenocytes regulate iron is a subject of debate. Whereas older theories support the programming of immature crypt cells to absorb more or less iron, depending on body stores,[24] more recent studies support the action of a number of molecules responsible for iron transport by mature enterocytes.[25]

The components of the current intestinal iron absorption pathway stem from direct action of the iron circulating inhibitor hepcidin on mature villus enterocytes; the process involves the following steps[25] (Fig. 66–21):

1. Dietary iron in the gut lumen is mainly in the Fe^{3+} form.
2. In the lumen, Fe^{3+} is reduced to Fe^{2+} by the ferrireductase Dcytb.
3. Fe^{2+} is transported intracellularly across the brush border membrane (BBM) by the divalent metal transporter DMT1.
4. Fe^{2+} is then transferred to the basolateral membrane (BLM) by the ferroxidase hephaestin.
5. Finally, Fe^{2+} is transferred across the BLM into the body by Ireg1.

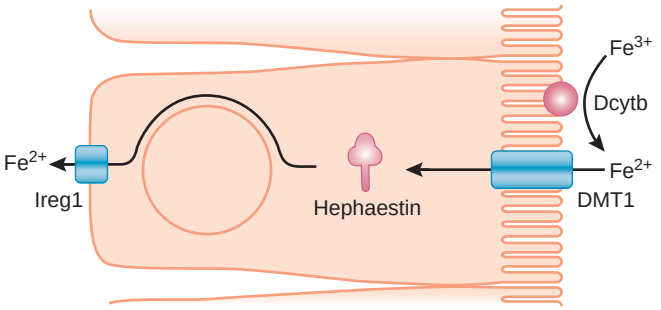


Figure 66–21. Components of the intestinal iron absorption pathway. (1) Luminal Fe^{3+} is reduced to Fe^{2+} by Dcytb. (2) Fe^{2+} is transported intracellularly across the brush border membrane (BBM) by the divalent metal transporter DMT1. (3) Fe^{2+} is transferred to the basolateral membrane (BLM) by hephaestin. (4) Fe^{2+} is transferred across the BLM into the body by Ireg1. (From Frazer DM, Anderson GJ: The orchestration of body iron intake: How and where do enterocytes receive their cues? Blood Cells Mol Dis 30:288-297, 2003.)

The complexity of this system is beyond the scope of this chapter; however, it is a negative feedback system dependent on continuous monitoring of transferrin levels by the liver, and it ultimately produces the so-called humoral factor hepcidin, which regulates Ireg1 expression. When iron stores are high, the liver increases hepcidin production and thus decreases Ireg1 expression, which in turn leads to decreased iron absorption.

The importance of the duodenum in iron absorption is highlighted in patients whose duodenum is bypassed during RYGBP, and the incidence of iron deficiency in such patients is at least 14% to 16% and up to 49% to 52%.[26,27] This deficiency is usually corrected by oral supplementation with multivitamins, but additional iron supplementation is frequently required, especially in menstruating females.

Macronutrients

Luminal macronutrients are absorbed via the BBM by a variety of transport systems.

Carbohydrates The duodenum plays a crucial role in the process of starch hydrolysis because pancreatic amylase is required, so by the time that the carbohydrate load reaches the proximal jejunum, this process is almost complete. After hydrolysis into simpler compounds, the monosaccharide fructose is passively absorbed through a GLUT5 transporter, whereas glucose and galactose are actively absorbed via the BBM sodium-glucose cotransporter SGLT-1.[28] Absorption occurs mostly in the early and midportion of the small intestine by mature enterocytes on the upper third of the villi.[29]

Protein Although protein digestion begins in the stomach by the action of pepsin, most proteolysis occurs in the proximal part of the small intestine. The duodenocyte brush border enzyme enteropeptidase (enterokinase) plays a key role in initiating proteolytic digestion by converting trypsinogen into trypsin, which in turn activates all other pancreatic zymogens.[30] Furthermore, the majority of protein digestion occurs through dipeptide and tripeptide proton-coupled cotransporters, or PepT1, which are found mostly in the duodenum and jejunum.[31] As much as 50% of the protein ingested is digested and absorbed in the duodenum.

Lipids Most dietary fat is absorbed in the duodenum and upper jejunum. Entry of fat into the duodenum stimulates secretion of cholecystokinin (CCK) from the duodenal mucosa, which in turn promotes the release of pancreatic lipase. Duodenal hydrolysis of dietary lipids and biliary phospholipids and cholesterol is carried out by pancreatic lipase, colipase, phospholipase A_2, and cholesterol esterase. Bile acid solubilization starts in the duodenum and results in mixed micelles and liposomes, which are delivered to the brush border for passive diffusion of their lipid contents via fatty acid transport proteins.

Endocrine Physiology

The duodenum produces a diverse group of hormones that are crucial for initiating and coordinating digestion and absorption throughout the small intestine. Ingested nutrients stimulate the secretion of GI hormones that are necessary for the coordinated processes of digestion and absorption of food. The most clinically relevant are reviewed (Table 66–1).

Secretin

Bayliss and Starling[32] discovered secretin in 1902. Secretin is a helical peptide that shares structural similarities with pancreatic glucagons and VIP. It is released from S cells in the duodenal mucosa in response to fat, protein, and bile acids, but the most important is intraluminal acid, especially with a pH less than 3.0.[33] Release is neurally mediated by secretin-releasing peptide (SRP).[34,35]

Secretin is known as nature's antacid because it stimulates large volumes of alkaline pancreatic secretions. Other functions include (1) synergy with CCK in stimulating the exocrine pancreas; (2) stimulation of biliary bicarbonate, chloride, and water secretion; (3) decreasing the bile salt concentration; (4) stimulation of pepsin release; (5) antagonism of gastrin and thus acid production; (6) inhibition of gastric emptying, lower esophageal sphincter tone, and colonic contraction; and (7) increasing mucus production by gut mucosa.

Clinically, secretin paradoxically elevates gastrin levels in patients with Zollinger-Ellison syndrome and is thus often used as a diagnostic tool; it is also used to dilate the pancreatic duct for improved ductal evaluation during endoscopic retrograde cholangiopancreatography.

Cholecystokinin

CCK was discovered and named by Ivy and Oldberg,[36] who found that lipid infusion into the proximal part of

Table 66–1 Physiologic Functions of Gastrointestinal Hormones

CCK	Stimulates gallbladder contraction
	Stimulates exocrine pancreas secretion
	Growth of the pancreas
	Satiety
	Sphincter of Oddi relaxation
	Inhibits gastric emptying
GIP	Glucose-dependent insulin release
	Inhibits gastric secretion
Motilin	Initiation of the migrating motor complex
	Stimulates gastric emptying
	Stimulates pepsin secretion
NO	Smooth muscle relaxation
	Stimulates intestinal secretion
Secretin	Stimulates exocrine pancreaticobiliary function
	Growth of the pancreas
	Stimulates gastric pepsin secretion
	Stimulates colonic mucin
	Inhibits gastric acid secretion
	Inhibits gastrointestinal motility
Serotonin	Gastric relaxation
	Stimulates intestinal secretion
	Stimulates intestinal motility
Somatostatin	Inhibits gastric acid and biliary secretions
	Inhibits pancreatic secretions
	Inhibits gastrointestinal secretion/motility
	Inhibits gallbladder contraction
	Inhibits cell growth
Gastrin	Stimulates gastric acid secretion
	Gastric trophic factor
Ghrelin	Growth hormone secretagogue
	Stimulates appetite
GRP	Stimulates gastrin release
Melatonin	Stimulates bicarbonate secretion
	Antioxidant
Neurotensin	Stimulates pancreas secretion
	Inhibits gastrointestinal motility
NPY	Inhibits intestinal motility
	Inhibits intestinal fluid/electrolyte absorption
	Vasoconstrictor
Opioids	Inhibit gastrointestinal motility
	Stimulate bicarbonate production
PP	Stimulates GI and pancreaticobiliary secretion
	Causes satiety
	Stimulates UGI motility
PYY	Causes satiety
	Inhibits gastrointestinal motility
Substance P	Stimulates GI motility
	Smooth muscle contractility
	Immune activity
	Simulates GI secretion
	Stimulates CCK release
	Gastric protection
VIP	Stimulates water and electrolyte secretion
	Smooth muscle relaxation
	Inhibits intestinal absorption
	Immunomodulator

CCK, cholecystokinin; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GRP, gastrin-releasing peptide; NO, nitric oxide; NPY, neuropeptide Y; PP, pancreatic polypeptide; UGI, upper gastrointestinal; VIP, vasoactive intestinal polypeptide.

the small intestine resulted in gallbladder contraction. In 1943, Harper and Raper[37] found that the same physiologic stimulus resulted in pancreatic enzyme release and named it *pancreozymin*. It was not until 25 years later that Jorpes[38] sequenced these peptides and found that they were the same.

In a highly coordinated manner CCK regulates the ingestion, digestion, and absorption of nutrients. This hormone is a dipeptide produced by I cells and is present throughout the small intestine but concentrated in the duodenum and secreted into blood after the ingestion of proteins and fats. There are reports that acidification of the intestine can also release CCK. The physiologic actions of CCK include (1) stimulation of pancreatic enzyme secretion, (2) acetylcholine-mediated gallbladder contraction, (3) VIP/NO-mediated sphincter of Oddi relaxation, (4) potentiation of the pancreatic exocrine stimulatory effects of secretin, and (5) induction of satiety.[39]

Other less well known functions have been attributed to CCK, including relaxation of the lower esophageal sphincter, VIP-mediated regulation of gastric emptying, and slowing of intestinal transit, which have been attributed to CCK-mediated interruption of the MMC. CCK may also function to decrease gastric acid release, stimulate insulin release, and stimulate pancreatic growth, and it has been found to be a central nervous system neurotransmitter responsible for panic and anxiety conditions.

Clinically, CCK has limited uses, but it has been suggested to reduce the incidence of acalculous cholecystitis and is being investigated as an anxiolytic. It can also be used during biliary imaging to stimulate gallbladder contraction.

Gastric Inhibitory Polypeptide (Glucose-Dependent Insulinotropic Peptide)

Gastric inhibitory polypeptide (GIP) was first purified and sequenced by Brown and Dryburgh in 1971,[40] who found it to have remarkable homology to secretin. GIP, along with glucagon-like peptide-1 (GLP-1), an

enteroglucagon, is an incretin hormone, or a hormone responsible for endocrine enhancement of insulin secretion. Incretins, secreted from endocrine cells located in the intestinal mucosa, act to enhance meal-induced insulin secretion by the endocrine pancreas and are believed to inhibit meal-stimulated gastric secretion. They are stimulated by the presence of glucose and fat in the intestinal lumen. Direct contact of glucose and fat with these open-type K cells (GIP) and L cells (GLP-1) releases these hormones, although GIP release is postulated to be more dependent on the rate of absorption. K cells are found primarily in the duodenum but can be found throughout the small intestine; in contrast, L cells are found throughout the small intestine but predominately in the distal ileum.

Though not fully delineated, suggested mechanisms for neural modulation of incretin release include muscarinic, β-adrenergic, hormonal, and peptidergic (gastrin-releasing peptide [GRP]) fibers, and secretion is restrained by α-adrenergic stimulation, glucagon, insulin, peptide YY (PYY), and somatostatin.[41]

The importance of incretin hormones lies in their possible contribution to the early pathogenesis of type 2 diabetes in that it is believed that the incretin effect is greatly impaired in such patients. Thus, these hormones are being evaluated as potential treatment targets.[42]

Somatostatin

Somatostatin has been identified in nerves and cell bodies in the central and peripheral nervous system, including the intramural enteric nervous system and endocrine-like D cells of the stomach and small intestine.[43,44] It is a hormone present throughout the mammalian organism and has paracrine, endocrine, and neurocrine activity. Over two thirds of the circulating concentration of somatostatin is derived from the GI system, especially the distal part of the stomach, duodenum, jejunum, and pancreas. Although the mechanism of somatostatin secretion remains poorly understood, it has been shown that a significant increase occurs in response to the ingestion of a meal, more specifically, the presence of fat, protein, and to a lesser extent, carbohydrate in the distal portion of the stomach and duodenum. CGRP and catecholamines are also stimulants for somatostatin release. Release of acetylcholine from cholinergic neurons inhibits somatostatin release. Plasma somatostatin fluctuations are found during the interdigestive period and are controlled by a complex interplay between cholinergic and adrenergic neural input, prostaglandins, and circadian rhythms. Additional hormones affect circulating concentrations, including the stimulants gastrin, CCK, secretin, GIP, and bombesin.

A wide spectrum of GI actions has been attributed to somatostatin. In the stomach, somatostatin inhibits gastric acid and pepsin secretion by reducing the response to gastrin in addition to attenuating gastrin release. This effect is believed to be due to a paracrine effect of the hormone. Furthermore, it inhibits the absorption of amino acids in the duodenum and attenuates glucagon-induced jejunal water and electrolyte secretion. In the pancreas, somatostatin inhibits enzymatic, but not bicarbonate secretion and blocks the response to CCK and secretin. Somatostatin reduces the frequency of the MMC of the stomach and small intestine, which may be due to direct inhibition of acetylcholine release from peripheral neurons. Because of its role as a universal inhibitor of GI activity, much research has been invested in the production of somatostatin analogues for the treatment of many GI diseases.

Motilin

Motilin is a regulatory polypeptide of 22 amino acid residues that originates in nonargentaffin endocrine cells, which are scattered in the absorptive epithelial cells covering the villi of the duodenum and upper jejunum.[45] It is released into the general circulation at about 100-minute intervals during the interdigestive state and is an important factor in initiation of phase III contractions in the stomach, also known as the MMC. Additionally, motilin has a stimulatory effect on gastric pepsin secretion and pancreatic exocrine secretion[46-48] while causing gallbladder contraction, including the sphincter of Oddi.[49,50] Previously, it was believed that changes in duodenal pH were stimulatory for motilin release (i.e., duodenal acidification). However, more recent data have refuted this theory.[51] Nevertheless, it is clear that the presence of nutrients in the duodenum, especially fat, is strongly inhibitory for motilin release.[52] Although the mechanism of action of motilin remains a mystery, it has generally been accepted that it exerts its effect on gastric smooth muscle by a vagal-dependent and vagal-independent pathway. Motilin has been shown to increase serum concentrations of insulin and pancreatic polypeptide (PP). Clinical application of motilin as a prokinetic agent has become possible since erythromycin and its derivatives were proved to be nonpeptide motilin receptor agonists.

Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) is a nonpeptide hormone important in intestinal secretion and motility. Although it is now recognized to be localized throughout the enteric neuronal system, over 90% of total-body serotonin is contained in the enterochromaffin (EC) cells lining the mucosa of the intestine, including the duodenum.[53] It is widely accepted that in the GI tract serotonin acts as both a neurotransmitter and a mucosal signaling molecule. As a neurotransmitter, serotonin is involved in gastric relaxation through vagally induced activation of an inhibitory neural circuit containing serotoninergic neurons.[54] 5-HT also has a role in induction of the slow excitatory postsynaptic potentials in enteric neurons. As a mucosal signaling agent, the EC cell is purported to be a signal transducer such that mucosal distention or the presence of intraluminal nutrients (e.g., glucose, fat), or both, stimulates these cells to release 5-HT into the bowel wall, which initiates a cascade of physiologic events.[55-57] Included in these events are increased intestinal secretions via enhanced electrolyte transport and increased intestinal motility. The multitude of responses initiated by serotonin is attributed to

the various serotonin receptor subtypes identified throughout the enteric smooth muscle, mucosal, and neuronal milieu. In fact, pharmacologic manipulation has become an area of intense investigation in the treatment of both constipation-prone and diarrhea-prone irritable bowel syndrome (IBD) inasmuch as serotonin is thought to be intricately involved in such pathologic phenomena. Serotonin is also a product of carcinoid tumors and is implicated in most of the symptoms seen in carcinoid syndrome.

Nitric Oxide

The inhibitory mechanism of nonadrenergic, noncholinergic (NANC) neurotransmission in the GI tract was discovered to be primarily mediated by NO.[58-60] First known as endothelium-derived relaxing factor, NO is an inorganic gas important in the neural and hormonal regulation of intestinal physiology. It is produced from the conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS), an enzyme that exists as inducible and constitutive isoforms, the latter being present in neurons and the endothelium.[61] NO was first shown to be an inhibitory NANC neurotransmitter in isolated superperfused segments of canine intestine, in which it caused smooth muscle relaxation that was inhibited by NOS inhibitors. In the stomach, NO release is important in vagally mediated receptive relaxation and gastric distention–induced pyloric relaxation. NO is also an inhibitory neurotransmitter in duodenal and jejunal smooth muscle in the neuronal regulation of intestinal transit. In addition, it causes relaxation of the sphincter of Oddi, the pyloric sphincter, and the gallbladder smooth muscle. Moreover, NO has a role in intestinal secretion. It has been shown that the addition of NO donors to isolated rat gastric cells in suspension causes secretion.[62] Furthermore, in rat distal colon, NO has been suggested to be a secretomotor neurotransmitter responsible for increasing electrolyte transport initiated by serotonin.[63] Not only may NO be important in gastric acid secretion but also it has been implicated in pancreatic exocrine and endocrine function. In addition, it may serve to protect gastric mucosal integrity against various noxious intraluminal contents through inhibition of endothelial smooth muscle, thus increasing gastrin blood flow in times of stress.

Other Hormones

Other hormones are secreted by the duodenum but are not necessarily predominant in that region; such hormones include the following: VIP, neurotensin (NT), substance P (SP), GRP, ghrelin, enkephalins and endorphins, peptide tyrosine tyrosine (PYY), PP, neuropeptide Y (NPY), melatonin, and gastrin. Their relationships to the duodenal control of gastric and intestinal function remains poorly understood.

Vasoactive Intestinal Peptide VIP is a gut neuropeptide with similar structure to secretin and glucagon. It is released by intraduodenal hydrochloric acid, ethanol, fat, and vagal stimulation. VIP is a smooth muscle relaxant of blood vessels and sphincters, although it is best known for increasing intestinal secretion of water and electrolytes via stimulation of adenylate cyclase. Excess secretion of VIP into the blood by secretory tumors, which are most commonly localized in the pancreas, leads to the watery diarrhea hypokalemia achlorhydria (WDHA) syndrome, also known as a VIPoma or the Vernor-Morrison or *pancreatic cholera* syndrome. In addition, VIP is also known to inhibit intestinal absorption, increase bile flow, induce gallbladder relaxation, and inhibit acid and pepsin secretion, and it has a small glycogenolytic effect in the liver.[64] Recently, VIP has been recognized as an immunomodulator and possibly as a cytokine-like molecule[65]; a decrease in this function in the lamina propria and submucosa has been implicated in the pathophysiology of IBD.[66]

Neurotensin NT is most abundant in the ileum, with a lesser amount in the jejunum and duodenum; this tridecapeptide is also found in the brain to a lesser degree, where it has been linked to clinical disorders hypothesized to involve dopamine circuits, such as schizophrenia, Parkinson's disease, and drug abuse.[67] NT is present in the endocrine cells labeled N cells,[68] which are of the open type. NT is also present in nerves of the myenteric plexus, in the muscular layer, and in the submucosa of the stomach and duodenum. Release of NT is stimulated by intraluminal fat, and it functions to stimulate pancreatic secretion and inhibition of gastric and small bowel motility.

NT has been implicated in facilitating fatty acid translocation and stimulating the growth of various GI tissues, including cancer cells. It also stimulates colonic contraction and defecation; its release is accelerated in patients with dumping syndrome. The NT gene is developmentally regulated in the gut of both rats and humans in a distinctive temporally and spatially specific pattern[69]; therefore, this gene is an excellent model for defining differentiation pathways leading to gut development, maturation, and neoplasia. Some of the effects of NT are inhibited by COX inhibitors, thus suggesting prostaglandin-mediated release.

Substance P The first brain-gut peptide discovered, SP belongs to a group of neuropeptides called tachykinins, and it plays an important role as a neurotransmitter in the central and peripheral nervous system. In response to intraluminal food, SP leads to excitatory action on GI motor activity, which is seen virtually at all levels and in all layers of the mammalian gut, with the highest concentrations in the duodenum and jejunum. SP regulates smooth muscle contractility, epithelial ion transport, vascular permeability, and immune function in the GI tract.[70] It appears to increase the contraction of intestinal and gallbladder smooth muscle, reduce bile flow, and increase pancreatic juice outflow. This neurotransmitter has been suggested to play a role in the pathophysiology of inflammatory diseases such as arthritis, colitis, and intestinal inflammation. Elevated levels of SP have been reported in the rectum and colon of patients with IBD and correlate with disease activity. Preventing the proinflammatory effects of SP with tachykinin receptor

antagonists may have therapeutic potential in inflammatory diseases such as asthma, sarcoidosis, chronic bronchitis, IBD, and rheumatoid arthritis. In gut-associated lymphoid tissue (GALT), the high concentrations of SP in intestinal nerve endings and expression of a specific SP receptor on T and B cells in murine Peyer's patches suggest that SP may act as a trophic factor, a homing factor, or a differentiation factor for IgA-secreting plasma cells.[71]

Gastrin-Releasing Peptide Bombesin was discovered in 1970 in extracts taken from the skin of amphibians.[72] It was later noted to have a mammalian counterpart that was named GRP, which has been detected throughout the digestive tract but is particularly prominent in both the acid- and gastrin-secreting portions of the stomach. It is known to modulate acid and gut peptide secretion, and it stimulates CCK release from the GI tract. Secretion of GRP causes the release of endogenous gastrin, which activates sensory neurons, and it is modified by somatostatin. Studies have shown that activation of sensory neurons causes increased production of NO through activation of constitutive NOS, thereby leading to increased gastric mucosal blood flow and thus protection from damage by irritants.[73] In addition to activation of capsaicin-sensitive sensory neurons, GRP requires endogenous prostaglandins to fully exert its gastroprotective actions.[74] This process is reminiscent of that described in protecting the duodenal mucosa. Clinically, GRP has been shown to improve maintenance of gut mucosal integrity after severe burns by decreasing burn-induced gut mucosal atrophy and epithelial cell apotosis.[75]

Ghrelin *Ghrelin* is a recently identified peptide important in the peripheral regulation of energy balance. Endocrine cells of the gastric oxyntic mucosa are the primary site of production; they are responsible for over 70% of the circulating ghrelin concentration.[76] Through ultrastructural analysis these ghrelin cells are distinct from the histamine-producing enterochromaffin-like (ECL) cell, the somatostatin-producing D cell, and the serotonin-producing EC cell. Ghrelin cells have also been discovered in the small intestine and pancreas.[77] Ghrelin dose-dependently stimulates release of growth hormone from pituitary cells and is in fact the most potent growth hormone secretogogue discovered. Although the exact mechanism of action is not clearly defined, its orexigenic effect is well documented, and it increases appetite in a circadian fashion.[78] These findings suggest a role for ghrelin as a humoral signal from the stomach for meal initiation. This increase in appetite is associated with an increase in body weight via increased adipogenesis and reduced lipid metabolism.[79] It has been postulated that ghrelin may be a signal to the central nervous system regarding acute and chronic changes in food intake, metabolism, or body fat mass, thereby initiating efferent responses that regulate energy homeostasis.[80] Circulating levels of ghrelin are inversely related to body mass index, adipose tissue mass, and insulin plasma levels such that dysregulation of ghrelin gene expression may explain the impaired regulation of body weight in obesity.[81] Moreover, ghrelin has a motilin-like effect on gastric motility and stimulates the release of somatostatin and PP by increasing glucose and decreasing insulin levels.[80]

Endorphins and Enkephalins Endorphins and enkephalins are opioid peptides found in a variety of tissues. Though present in lower concentration in the gut than in the central nervous system, the proximal portion of the intestine has a particularly high concentration of enkephalins. Both are present in enteric nerves, especially in the myenteric plexus. Enkephalins are found in the intrinsic nerves of the stomach and innervate the pyloric sphincter; in contrast, endorphins have been found in pyloric antral G cells and in the submucosal plexus of the duodenum and ileum.[82]

Although their specific effects on the GI system are unknown, opioid peptides have been associated with several functions, including motility, acid secretion, and intestinal electrolyte and fluid transport. They have also been implicated in stimulating duodenocyte HCO_3^- production in response to duodenal acid. The antimotility effects of opioid drugs arise from changes in both motility and secretion caused by activation of opioid receptors located in the gut wall,[83] which leads to interruption of the enteric nerve pathways governing acetylcholine and other excitatory transmitters that stimulate muscle contraction. Allescher et al.,[84] in a naloxone-sensitive system, demonstrated that opioid-active drugs modify the peristaltic reflex by reducing the efficacy of the reflex response and modulating the timing of the ascending excitatory and descending inhibitory reflex pathway. Clinically, exogenous opioids, including morphine, have been well known to cause constipation, and other medications that interact with opioid receptors have been used for antidiarrheal therapy.

Peptide YY and Pancreatic Polypeptide PYY and PP belong to the NPY family, which contain several tyrosine residues within their homologous sequences. These peptides activate G protein–coupled Y receptors.

PP is restricted to endocrine cells mainly in the duodenal portion of the pancreas, but it is also found throughout the GI tract. It is released into blood in response to a meal rich in protein and especially fats. PP is known to stimulate gastric, pancreaticobiliary, and intestinal secretion, and it stimulates motility of the upper GI system. PP, along with PYY, has been implicated as an anorexigenic peptide promoting satiety.[85]

NPY is a neuropeptide widely distributed in the central and peripheral nervous system; its nerve fibers are widely located through the intestinal tract, with the largest numbers in the duodenum and upper part of the small intestine. Functionally, NPY is known to regulate large and small intestinal motility, vasoconstriction of surrounding vessels, and inhibition of small intestinal fluid and electrolyte secretion.

PYY is secreted in response to intraluminal carbohydrates and lipids, and it is expressed in both endocrine cells and enteric neurons throughout the gut. L cells that secrete GLP-1 also secrete PYY.[86] These cells predominate in the ileum, colon, and especially the rectum; however,

enteric nerve fibers that innervate myenteric plexus smooth muscle are found in highest number in the stomach and duodenum.[87] The dual localization of PYY in endocrine cells and intestinal nerves suggests that it is important in several gut functions similar to NPY, including motility and secretion. Furthermore, its presence during early fetal development suggests that it may play a role in promoting development and maturation of the digestive tract.

Melatonin A product of intestinal EC cells and the pineal gland, melatonin is a potent stimulant of duodenal mucosal HCO_3^- secretion in the rat. Melatonin receptors are distributed throughout the GI tract. The effects of melatonin are mediated by specific high-affinity membrane-associated melatonin receptors that belong to the superfamily of G protein–coupled receptors. On the basis of pharmacologic evidence, three subtypes are reported. The total amount of melatonin in the alimentary tract is much higher (400-fold) than that in the central nervous system, but the role of melatonin in GI function has been largely unknown.[88] Melatonin may also exert a potent anti-inflammatory effect that may be useful in the treatment of IBD. These effects are attributed partly to its antioxidant property, which stems from eliminating NO in the inflamed colon.[89]

Gastrin A peptide hormone produced by G cells in the gastric antrum and duodenum, gastrin is induced by the presence of protein or calcium in the gastric lumen or by antral/duodenal distention. Gastrin stimulates gastric acid secretion by parietal cells in the stomach. Zollinger-Ellison syndrome is caused by a gastrinoma, or a gastrin-secretin tumor, which is usually localized in the pancreas or duodenum. Gastrin has also been documented to have trophic action and may contribute to the growth of gastric and colorectal carcinoma.[90] *H. pylori*–associated antrum gastritis produces hypergastrinemia by disinhibition of gastrin release and thereby contributes to hypersecretion of acid in *H. pylori*–associated gastritis and duodenal ulcer disease.[91] Pentagastrin, a gastrin analogue, is used clinically to measure maximal gastric secretion.

DUODENAL MOTILITY

Intrinsic Control

The intrinsic rhythm of small intestinal contractions probably originates from the MMC of the distal part of the stomach. It has been demonstrated that slow-wave and spike activities take place in preparations of neuron-free intestinal smooth muscle. The low-resistance junctions that exist between adjacent smooth muscle cells allow rapid propagation of electrical activity.[92] This intrinsic activity is modified by neural input and by hormones working in an endocrine, paracrine, or neurocrine pattern. Baseline duodenal peristalsis generally occurs at higher frequency (10 to 12/min) than in the jejunum or ileum. The electrical activity of duodenal smooth muscle is such that longitudinal waves of contraction continue for some distance down the small bowel, possibly resulting in a strong propulsive forward movement of duodenal contents.

Extrinsic Control

Extrinsic control of duodenal motility is primarily regulated by the autonomic nervous system.[93] Afferent and efferent vagal fibers innervate the entire small intestine, including the duodenum. The sympathetic innervation consists of preganglionic neuronal processes originating from T9 and T10. These run in the splanchnic nerves and synapse with the celiac ganglia. Thus, the duodenum derives its sympathetic innervation from both celiac (proximal duodenum) and superior mesenteric (distal duodenum) ganglia. These fibers consist of both cholinergic and noradrenergic neurons; however, the sympathetic innervation of the stomach and duodenum is largely inhibitory.

The preganglionic vagal efferent neurons have cholinergic excitatory and inhibitory interneuronal connections before intestinal innervation. Therefore, the vagus nerve can elicit several responses in the stomach and duodenum, and there is a delicate interplay between stimulatory and inhibitory effects in the net response to vagal activity. In the stomach, vagal stimulation causes gastric acid secretion, and it has been shown that truncal vagotomy causes incoordination of antral contractions and loss of receptive relaxation and gastric emptying. In the duodenum, vagal stimulation has been linked to inhibition of duodenal motility. In addition, a large number of receptors have been identified on smooth muscle cells that are important in the initiation of contraction,[94] including receptors for CCK, gastrin, SP, bombesin, and acetylcholine. Other agents have been identified as smooth muscle relaxants, such as VIP and adenosine triphosphate. This is a testament to the complex interplay of local and extrinsic hormonal and neural input in the regulation of intestinal motility.

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Chapter

67

Small Intestine

Mary F. Otterson · David Binion · Seth J. Karp · David I. Soybel · Edward C. Mun · Jeffrey B. Matthews

ANATOMY

The duodenum, jejunum, and ileum make up the small intestine. The duodenum is anatomically distinct, but the jejunum (proximal two fifths) and ileum (distal three fifths) have no true anatomic border between them.

The duodenum is divided into four parts: the first portion or the bulb, the second or descending portion, the third or transverse portion, and the fourth or ascending portion. The first portion begins at the pylorus and sweeps to the right; it is anchored by the hepatoduodenal ligament and is referred to as the bulb of the duodenum. Just beyond the bulb, Kerckring's folds begin. These circular folds of mucosa and submucosa extend for the length of the small bowel. Radiographically, Kerckring's folds are referred to as the *valvulae conniventes*. Posterior to the bulb of the duodenum are the gastroduodenal artery and the pancreas. Blood supply is from the supraduodenal and gastroduodenal arteries; both arise from the hepatic artery. The second portion of the duodenum travels posteriorly and caudad to the level of the first lumbar vertebra, where it is retroperitoneal and attached to the head of the pancreas. Posterior is Gerota's fascia and the kidney, anterior is the hepatic flexure of the colon, and medial lies the inferior vena cava. The arterial supply is from the celiac axis through the gastroduodenal artery to the anterosuperior and posterosuperior pancreaticoduodenal arteries and from the superior mesenteric artery (SMA) through the anteroinferior and posteroinferior pancreaticoduodenal arteries. The common bile duct and the main pancreatic duct enter in the middle of the second portion of the duodenum, about 10 cm distal to the pylorus at the ampulla of Vater. The sphincter of Oddi surrounds and controls the ampulla of Vater. When an accessory pancreatic duct is present (6% of normal patients), it usually enters about 2 cm proximal to the ampulla.[1] The third portion begins as the duodenum sweeps to the left at the level of the third lumbar vertebra and ends at the aorta. It is associated with the uncinate process of the pancreas and is dorsal to the superior mesenteric artery. Subtle anatomic anomalies can result from a high ligament of Treitz, prolonged immobilization, spinal surgery, rapid height gain, or scoliosis and can cause compression of the duodenum by the SMA and result in obstruction (variously called *SMA syndrome, cast syndrome, Wilkie's syndrome, duodenal ileus,* or *duodenal compression syndrome*).[2] The fourth portion of the duodenum begins at the aorta, extends to the left, and passes ventral to the left psoas. It emerges into the peritoneum at the duodenojejunal flexure, which is fixed to the posterior abdominal wall at the ligament of Treitz, striated fibromuscular tissue that arises from the right crus of the diaphragm. Defects in the mesentery of the flexure may give rise to internal hernias. Venous drainage from the duodenum is through the splenic, superior mesenteric, and portal veins.

The jejunum and ileum are suspended from the posterior aspect of the peritoneal cavity by mesentery that travels obliquely from the left upper quadrant to the right lower quadrant of the abdomen (Fig. 67–1). The mesentery begins at the ligament of Treitz, where a double fold of peritoneum is pulled up as the bowel exits the retroperitoneum. From a base of about 15 cm, this mesentery fans out to connect to the entire 2.5 m of small intestine. The intestinal blood supply, as well as fat and lymphatic tissue, resides within the mesentery. The blood supply of the jejunum and ileum derives from the SMA, which has an extensive anastomotic network (the vasa recta) near the mesenteric border of the bowel called the *marginal artery*. This artery runs along the length of the small bowel. At the ileal branch of the ileocolic artery, the marginal artery breaks up as the anastomotic network of the vasa recta increases in complexity. Venous drainage follows the course of the arteries.

Although there is no true anatomic distinction between the jejunum and ileum, a number of anatomic features progress in an orderly fashion over the course of the intestine and help distinguish the two portions of

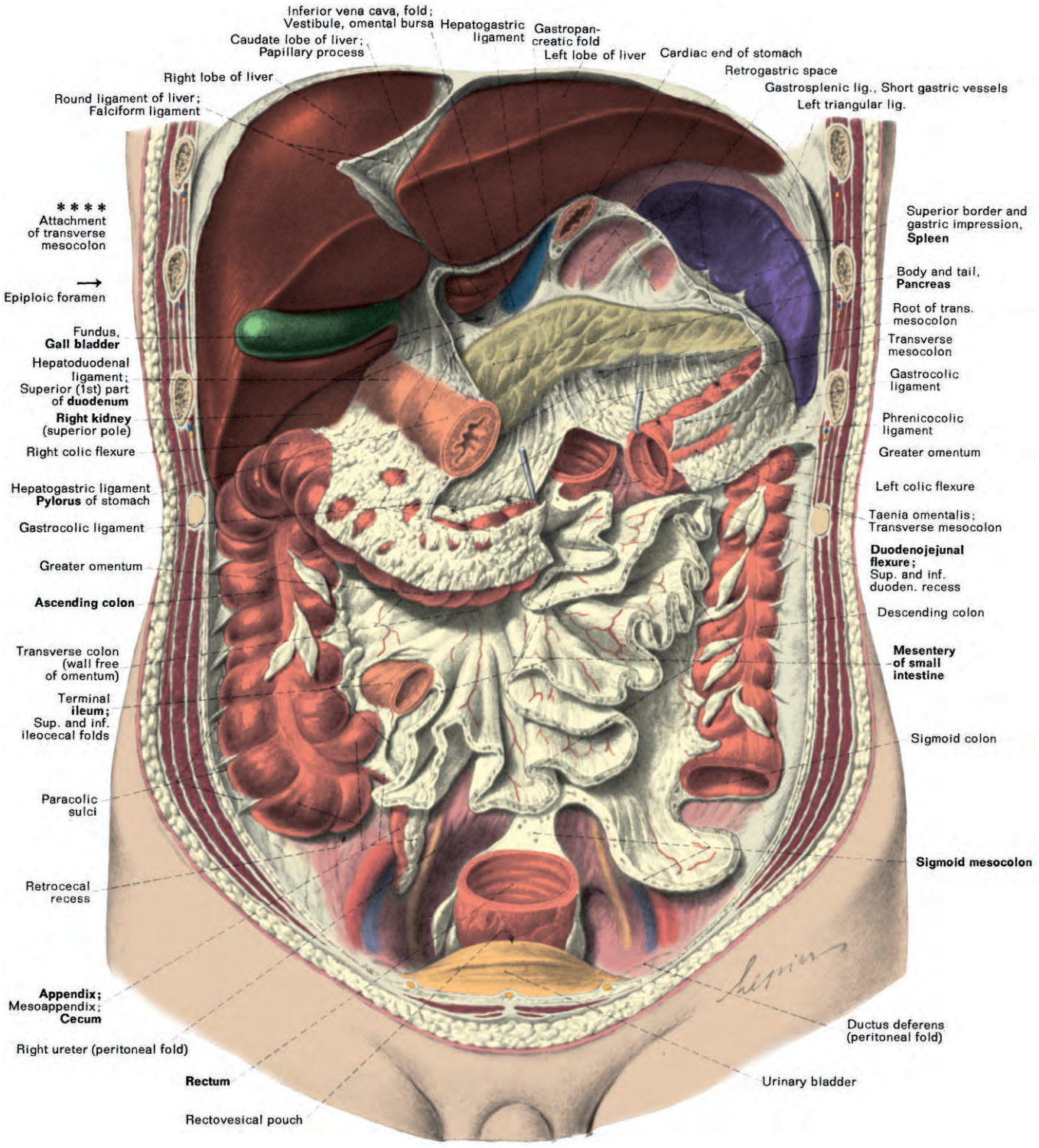

Figure 67–1. View of the mesentery and attachments of the small intestine. The small intestine has been removed, as has the sigmoid colon. (From Clemente CD: Anatomy: A Regional Atlas of the Human Body. Philadelphia, Lea & Febiger, 1975, plate 305.)

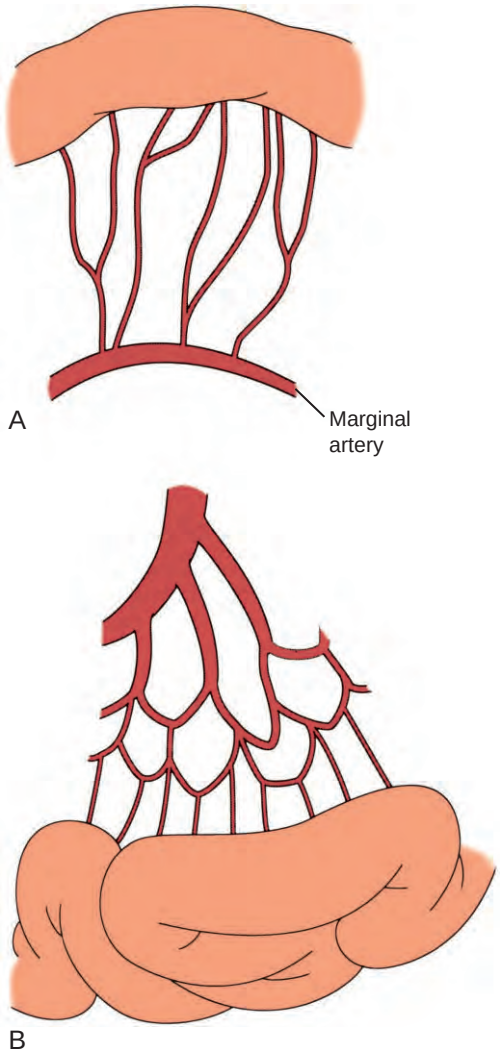

Figure 67–2. Schematic of the arterial network to different regions of the small intestine. **A,** Typical jejunal pattern. **B,** Typical ileal pattern. (From Greenfield LT, Mulholland MW [eds]: Surgery: Scientific Principles and Practice. Philadelphia, Lippincott-Raven, 1997, p 2036.)

bowel. The jejunum tends to have a single marginal artery from which arise long, relatively straight branches of the vasa recta (Fig. 67–2A). This pattern gradually blends into arcades that travel close to the mesenteric edge of the bowel and give rise to short branches in the ileum (see Fig. 67–2B). The amount of fat along the mesenteric border tends to increase distally, at times encroaching on the bowel in the distal aspects. The intestine tends to become thinner and paler distally, along with a decrease in diameter. Lymphatic tissues unique to the small intestine and called *Peyer's patches* are most numerous in the distal ileum, whereas plicae circulares are more prominent in the proximal jejunum. Small intestinal lymphatic drainage courses through a hierarchy of mesenteric nodes following the vascular arcades: through the wall of the small intestine into the mesenteric arcade and then to a lymphatic trunk around the SMA. The lymph ultimately drains into the *cisterna chyli*. In addition to its usual reticuloendothelial function, the small intestinal lymphatic drainage serves as a major transport route into the circulation for absorbed lipid.

HISTOLOGY

The intestine has four distinct functional layers. The innermost is the mucosa, followed by the submucosa, muscularis, and serosa (Fig. 67–3). The mucosa is subdivided into three layers. Innermost is an epithelial layer, the middle layer is a lamina propria, and the outer layer is the muscularis mucosae. The epithelial layer consists of a single thickness of columnar cells supported by a basement membrane. The lamina propria consists of connective tissue, and the muscularis mucosae is a true muscular layer. Morphologically, the mucosa is arranged into finger-like projections called *villi* that serve to increase the surface area for absorption. Villi are covered with columnar cells and goblet cells. The former are responsible for absorption, and the latter secrete mucus. At the base of the villi, mucosal invaginations form crypts that contain secretory Paneth cells. The submucosa is the next layer radially outward and contains blood vessels, lymphatics, and nerves, including the parasympathetic ganglion, which make up Meissner's plexus. Continuing outward, the muscularis consists of an inner layer of circular muscle and an outer layer of longitudinal muscle. Between these muscular layers is the myenteric or Auerbach plexus. Finally, the serosa is an extension of the peritoneum and consists of a single layer of mesothelial cells and loose connective tissue.

The duodenum is distinguished histologically by the presence of Brunner's glands. These glands are spiral tubes that form an interconnected network beginning in the submucosa—below the lamina propria—and opening into the crypts between the villi. They secrete a thin, alkaline mucus that protects the duodenum and aids in acid neutralization. Additional features that mark the duodenum as a small intestinal structure include circular folds of mucosa and submucosa called *plicae circulares* or *Kerckring's valves*. Crypts in the small intestine termed *Lieberkühn's crypts* secrete bactericidal and digestive enzymes.

INNERVATION

Innervation to the small intestine is through the autonomic nervous system and includes sympathetic, parasympathetic, and enteric divisions. Sympathetic fibers arising from thoracic segments of the spinal cord synapse in the celiac ganglion before sending axons to the intestine. Parasympathetic fibers arise from the vagus nerve and synapse in the submucosal (Meissner's) and myenteric (Auerbach's) plexus. The myenteric plexus is responsible for basal electrical activity of the gut. Stimulation of the parasympathetic neurons in general prepares the intestine for activity by increasing blood flow, contractility, and secretion. These functions are antagonized by the sympathetic system.

The enteric nervous system is an integrative system distinct from the central nervous system (CNS) that

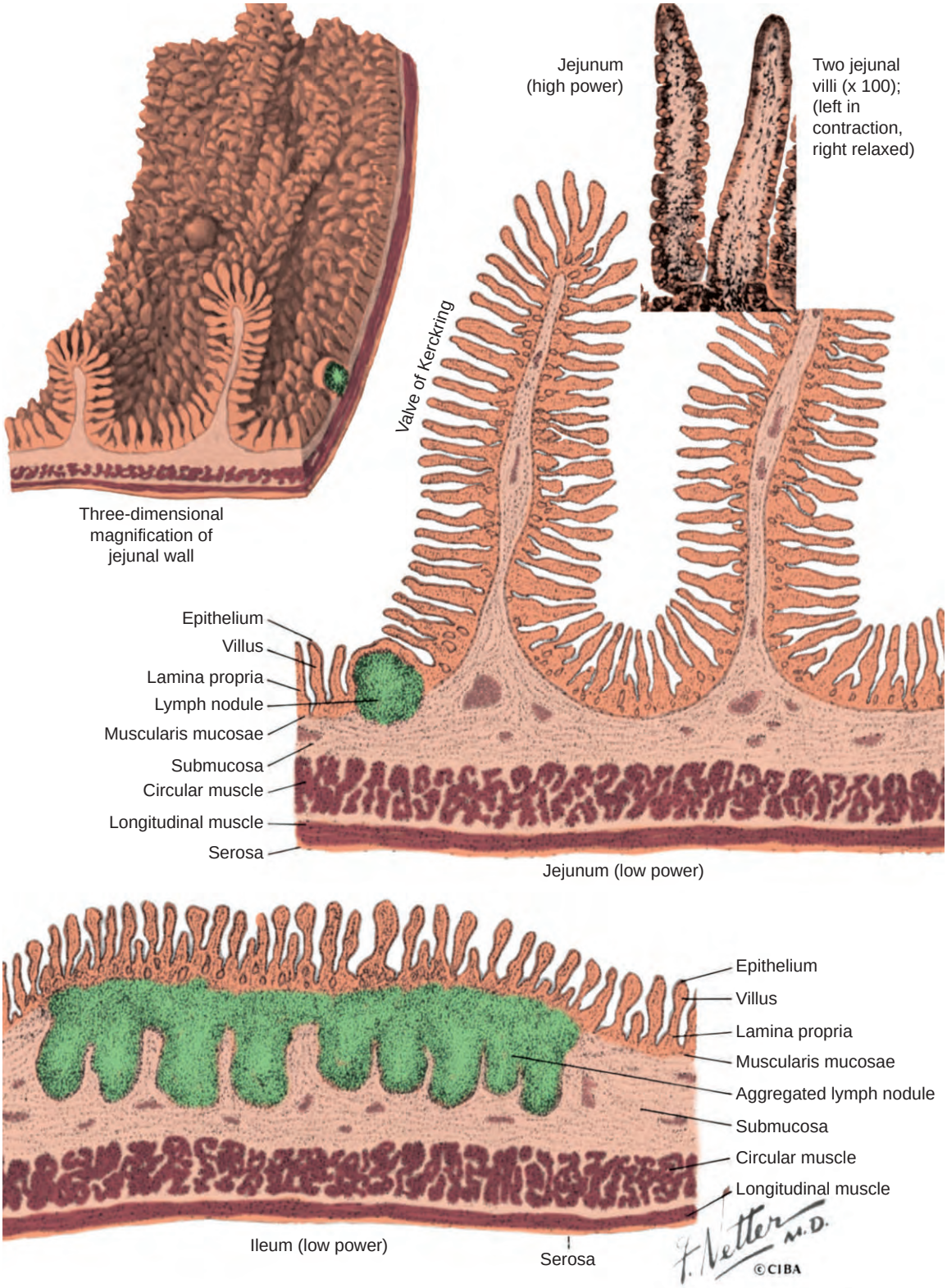

Figure 67–3. Schematic views of the histology of the jejunum and ileum. (Copyright, 1997. Icon Learning Systems, LLC, a subsidiary of Havas MultiMedia USA Inc. Reprinted with permission from ICON Learning Systems, LLC, illustrated by Frank H. Netter, MD. All rights reserved.)

ramifies throughout the submucosal and myenteric plexus of the gut. It senses the composition and characteristics of the luminal contents and integrates digestive functions that require motor or epithelial cell response. In particular, it regulates gut function by integrating smooth muscle tone and endocrine and exocrine secretion via input from afferent neurons sensitive to mechanical, chemical, osmotic, and thermal stimuli. Neurons of this system synthesize and secrete peptides that can act as neurotransmitters, paracrine factors, or endocrine factors.[3]

Pain from the small intestine is divided into visceral and somatic components. The clinical manifestations of each type of pain can be attributed to the type of innervation. Visceral pain occurs as a result of irritation of the visceral peritoneum, contraction of a tube against resistance, or distention of a tube and is carried by the autonomic nerves. Representation for these fibers is bilateral, and the pain tends to occur in the midline at the corresponding sensory level, which for the small bowel is in the epigastrium or periumbilical region. In general, this pain tends to be dull and deep in character. In contrast, parietal pain occurs as a result of irritation of the peritoneum lining the abdominal wall and is carried by somatic (spinal) nerves. This pain tends to be well localized, severe, and sharp.

LYMPHOID FUNCTIONS AND ARCHITECTURE

The intestine is protected from its tremendous bacterial load by mucosal defense mechanisms and a network of lymphatic tissue. At the mucosal level, three populations of lymphoid tissue form the first barrier to infection. Peyer's patches lie in the mucosa and submucosa and sample antigens to begin specific host responses. The lamina propria contains a separate collection of lymphoid cells consisting of T cells, B cells, and plasma cells. Intraepithelial lymphocytes form the final level of mucosal host defense. Three sets of nodes drain the small intestine. The first set lies in proximity to the mesenteric border, the second set is at the level of the arcades, and the third set is along the SMA.

MICROVASCULATURE

The vascular supply to the small intestine arises from the left side of the SMA.[4] The arterial branches derived from the SMA pass through the two layers of the mesentery into the gut at the mesenteric margin of the small bowel. Within the mesentery, the SMA branches into arcades that enter the gut wall via the vasa recta. In the jejunum, the arcades are comprised of long vasa recta (3 to 5 cm), whereas in the distal ileum the arcades are elongated and the vasa recta are relatively short. Venous drainage from the intestine parallels the arterial supply, with the superior mesenteric vein being the major venous collecting system; it also lies within the mesentery to the right of the SMA.

The vasa recta entering the bowel wall reach intramural distributive vessels located within the submucosa. These vessels in the submucosa extend to the antimesenteric border of the intestine and form plexuses that are interconnected throughout the length and circumference of the small intestine. Blood supply to the outer muscle layers of the intestine is largely derived from this submucosal plexus, as is the venous drainage, although smaller direct branches from the vasa recta can also be demonstrated. Despite housing the submucosal vascular plexus, the submucosa itself is sparsely vascularized. This is in marked contrast to the mucosa, which contains a rich microvascular network. The extensive vascularization of the mucosa is arranged in microvascular capillary and venular arcades that form a subepithelial network within the small bowel villi.

The mucosal microvasculature in the small bowel differs from other vascular beds in the body by its high rate of blood flow, oxygen utilization, and transcapillary exchange of fluid and solutes. This distinct mucosal vascular physiology is thought to result from the high metabolic demand required by the epithelial layers, which receive up to 80% of intestinal blood flow during resting conditions.[5] The highly vascularized mucosal anatomy also accommodates the physiologic need demonstrated during nutritive function, when significant portions of cardiac output are shunted into the gut. Intestinal perfusion via the SMA ranges from a low of 29 to 70 ml/min/100 g intestinal tissue, whereas in the fed state, splanchnic hyperemia increases perfusion 28% to 132%. Resistance arterioles located in the submucosa beneath the muscularis mucosae play a major role in the regulation of intestinal perfusion. The molecular physiology underlying human intestinal microvascular function was assessed directly by Hatoum et al., who characterized vasodilator responses in isolated gut resistance arterioles 50 to 150 μm in diameter by measuring in vitro vasodilatory capacity in response to acetylcholine.[6] Normal intestinal microvessels vasodilate in response to acetylcholine via predominantly nitric oxide– and cyclooxygenase-dependent mechanisms. Interestingly, microvessels from patients with chronically inflamed inflammatory bowel disease (Crohn's disease, ulcerative colitis) and radiation enteritis demonstrated a significantly diminished vasodilator capacity in comparison to control microvessels.[6,7] These findings suggest that impaired vasodilator capacity is linked to an ischemic contribution found in both classic chronic inflammation (i.e., inflammatory bowel disease) and stricture formation (i.e., long-term complication of radiation enteritis).

EMBRYOLOGY

Gastrulation

Shortly after gastrulation specifies the three embryonic germ layers, the endoderm undergoes rapid elongation. At the rostral end of the embryo, invagination of the head fold results in formation of the foregut tube. In similar fashion, the hindgut is formed by invagination of the caudal aspect of the embryo. The midportion of the tube remains in broad communication with the yolk sac and is called the *midgut* (Fig. 67–4).[8] At 18 days'

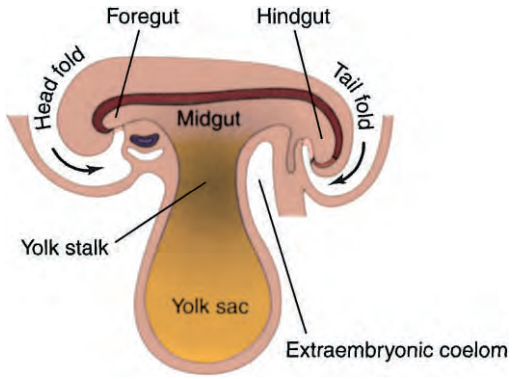

Figure 67–4. Schematic view of a 16-day-old human embryo showing the derivation of the foregut, midgut, and hindgut regions from endoderm. (From Moore KL, Persaud TVN: The Developing Human, 6th ed. Philadelphia, WB Saunders, 1998, p 84.)

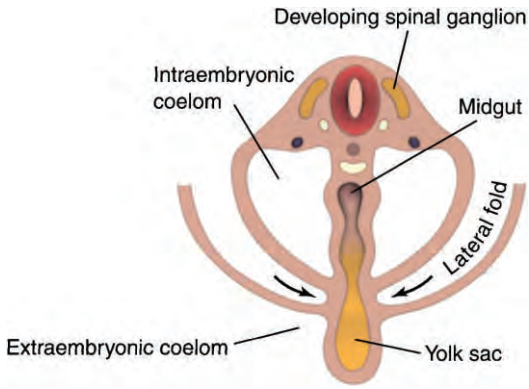

Figure 67–5. Schematic view of an 18-day-old embryo showing the derivation of the mesentery. (From Moore KL, Persaud TVN: The Developing Human, 6th ed. Philadelphia, WB Saunders, 1998, p 84.)

gestation, bilateral body folds ingress below the embryo and begin to separate it from the yolk sac. This causes splanchnic mesoderm to envelop the gut and defines the dorsal and ventral mesentery (Fig. 67–5).[8] The resulting increased distance between the neural tube and the gut may be important in preventing congenital gut duplications or diverticula, which occur at this time.[9] This separation may be necessary to remove the gut from the influence of secreted signaling molecules produced in the notochord. Consistent with this hypothesis, partial gut duplications can be induced in transgenic mice that overexpress one of these notochord-derived factors in the pancreatic region.[9]

At 28 days' gestation, continued elongation of the endoderm converts the open midgut into a tube with its midportion still connected to the yolk sac through the yolk stalk. The liver forms within the ventral mesentery, whereas the leaves of mesentery become the falciform ligament; the dorsal mesentery gives rise to the adult mesentery and within it the blood supply to the gut.

At 35 days' gestation, the foregut, midgut, and hindgut all have a distinct blood supply, which serves to distinguish them throughout adult life. The foregut is supplied by the precursor of the celiac trunk and consists of the alimentary canal proximal to the ampulla of Vater. The midgut is supplied by the precursor of the SMA and consists of the small bowel distal to the ampulla and the proximal two thirds of the transverse colon. The hindgut consists of the distal third of the transverse, descending, and sigmoid colon and is supplied by the precursor of the inferior mesenteric artery. At this time, the yolk stalk separates from the intestine and the vitelline duct is obliterated. Failure of this process can result in diverticula (Meckel's diverticulum), cysts, cords, or combinations of these abnormalities.

At 42 days' gestation, the differentiated smooth muscle envelops the gut. This process is probably regulated by members of the "hedgehog" family of proteins secreted by the endoderm, which act as inductive signals on the mesoderm.[10] Mesodermal factors important in this process include members of the transforming growth factor-β family. There is evidence that these molecules initiate preprogrammed expression of *Hox* genes, which serve to establish the regional identity of the foregut, midgut, and hindgut.[10] At this point, elongation of the midgut is so rapid that the midgut can no longer be contained in the abdominal wall previously defined by the body folds and thus herniates out. The cecum is visible as a dilation of the midgut distal to the axis of the SMA. This location of the cecum distal to the SMA is important for understanding subsequent rotation. At about this time, innervation of the gut is under way, a process that is increasingly being appreciated as essential for normal gut development.

At 60 days' gestation, the herniated gut rotates counterclockwise 180 degrees around the axis of the SMA (Fig. 67–6). This rotation causes the cecal swelling to lie superior to the more proximal small bowel. If such rotation does not occur, the small bowel will lie on the right, with the cecum in the middle and the colon on the left.

At 10 weeks' gestation, the intestines return to the abdomen in a proximal-to-distal progression, with the proximal bowel being located in the dorsal aspect of the abdominal cavity and the cecum passing ventral to the small bowel. Failure of this return causes omphalocele. At this point a final additional 90 degrees of counterclockwise rotation sets the cecum in its final location in the right lower quadrant, with the transverse colon being ventral to the small bowel (see Fig. 67–6). Failure of this final rotation leads to a variety of anatomic anomalies.

At 12 weeks' gestation, the intestines become fixed in permanent position. The mesocolon of the ascending colon fuses with the parietal peritoneum to fix the ascending colon in a retroperitoneal position. In similar fashion, the left side of the mesocolon of the descending colon fuses with the parietal peritoneum of the dorsal body wall to fix the descending colon in a retroperitoneal location. Failure of this process can lead to spaces into which herniations can occur.

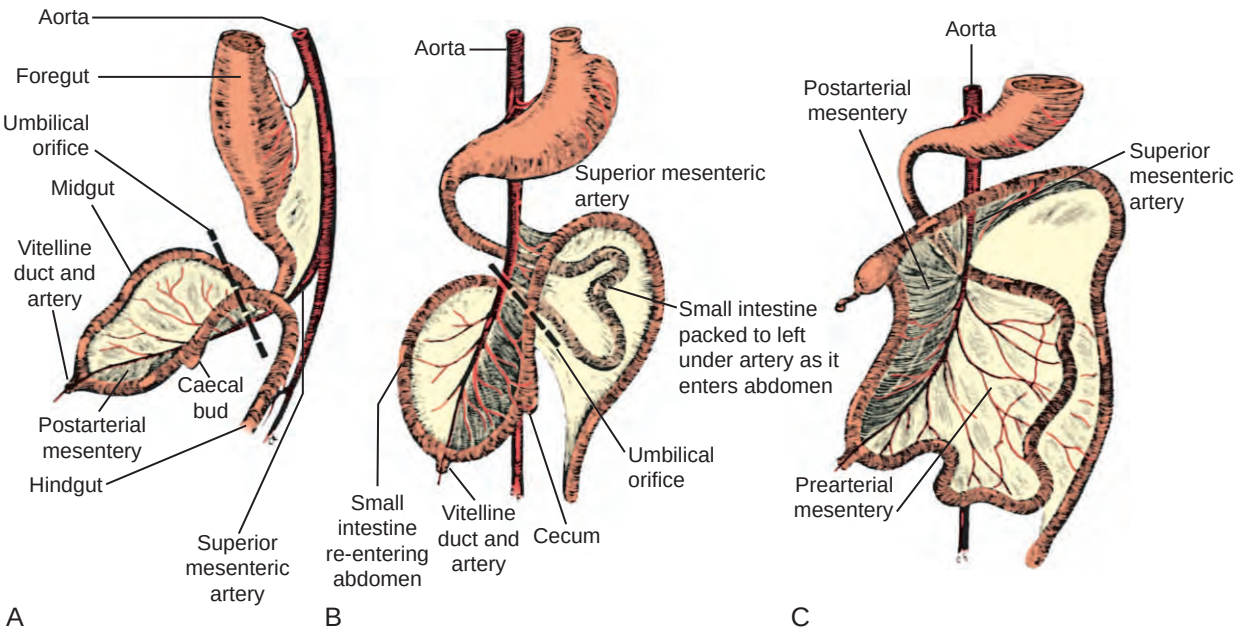

Figure 67–6. Rotation of the midgut. **A,** First stage: the loop has rotated 90 degrees counterclockwise. **B,** Second stage: the physiologic umbilical hernia is reducing; the small gut is reentering the abdomen on the right side of the superior mesenteric vessels and passing to the left side of the abdomen behind the vessels. The cecum still lies outside the umbilicus. **C,** Completion of the second stage: the cecum is in contact with the posterior abdominal wall in the right pelvis; the midgut loop has rotated 270 degrees counterclockwise. (From Louw JH: Embryology and developmental abnormalities of the small and large intestines. In Bockus HL [ed]: Gastroenterology, vol 2. Philadelphia, WB Saunders, 1978, p 8.)

CLINICAL ASPECTS OF DEVELOPMENTAL ANOMALIES

Duplications

Duplications occur early during development as described previously. The duplication may communicate with the normal gut lumen and share its blood supply. Management of duodenal duplications can be particularly difficult because of the involvement of surrounding structures, including the biliary tree, pancreatic duct, and pancreas.[9] Small bowel duplications may serve as a lead point for intussusception or create a fixed axis for the development of volvulus. Enlargement of the duplication may cause compression of adjacent structures. These abnormalities frequently contain ectopic gastric mucosa whose acid secretion can cause bleeding, pain, or perforation.

Vitelline Duct Abnormalities (Meckel's Diverticulum and Others)

The vitelline duct connects the midgut to the yolk sac during development. Any portion of this duct can remain as either a tube or a fibrous cord (Fig. 67–7). Persistence of the entire duct results in an enterocutaneous fistula. If the intestinal portion does not obliterate, Meckel's diverticulum results, the most common gut malformation. It occurs on the antimesenteric border of the intestine and is present in about 2% of the population. The diverticulum can be attached (25%) or unattached (75%) to the anterior abdominal wall by a remnant of the vitelline duct.[2] This abnormality generally occurs within 2 ft of the ileocecal valve and is always on the antimesenteric border of the intestine. Meckel's diverticulum is most commonly manifested as bleeding, usually resulting from acid-secreting ectopic gastric mucosa that causes ulceration of the nearby intestine. This abnormality also increases the risk for intussusception, with the diverticulum serving as the lead point. If the yolk sac side of the vitelline duct does not obliterate, an umbilical sinus results. Occasionally, a fibrous band with or without a cystic component (omphalomesenteric cyst) remains and can serve as an attachment point around which the bowel can rotate and lead to volvulus.

Omphalocele and Ventral Hernias

Failure of the intestine to return to the abdominal cavity can result in abdominal wall defects and omphalocele or gastroschisis. Omphalocele occurs when the intestines herniate through the anterior abdominal wall with only a peritoneal covering (Fig. 67–8). Most cases occur in association with other abnormalities, including those of the cardiac, neurologic, skeletal, or genitourinary system.[11] Gastroschisis occurs when an entire portion of the anterior abdominal wall is absent and abdominal viscera herniate without a peritoneal covering. Associated defects are much less common than with

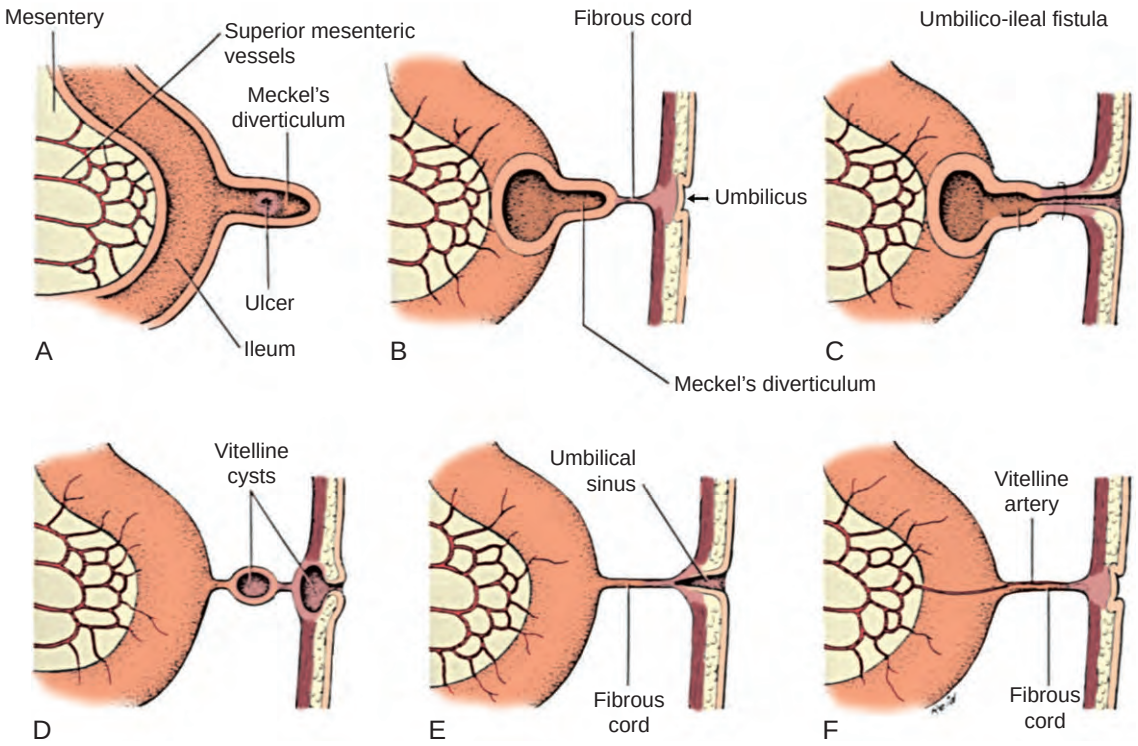

Figure 67–7. Meckel's diverticulum and other remnants of the yolk stalk. **A,** Section of the ileum and Meckel's diverticulum with an ulcer. **B,** Meckel's diverticulum connected to the umbilicus by a fibrous cord. **C,** Umbilicoileal fistula resulting from persistence of the entire intra-abdominal portion of the yolk stalk. **D,** Vitelline cysts at the umbilicus and in a fibrous remnant of the yolk stalk. **E,** Umbilical sinus resulting from persistence of the yolk stalk near the umbilicus. The sinus is not always connected to the ileum by a fibrous cord as illustrated. **F,** The yolk stalk has persisted as a fibrous cord connecting the ileum with the umbilicus. A persistent vitelline artery extends along the fibrous cord to the umbilicus. (From Moore K: The Developing Human: Clinically Oriented Embryology. Philadelphia, WB Saunders, 1982, p 245.)

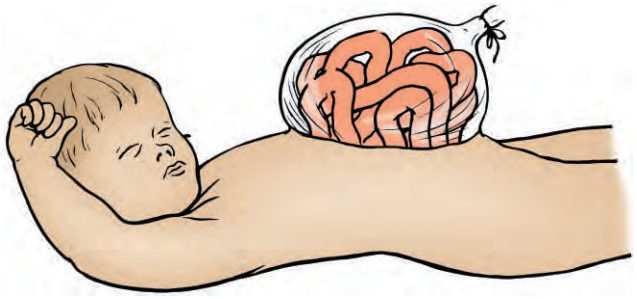

Figure 67–8. Exomphalos (omphalocele). The intestines fail to return to the abdomen in the first stage of intestinal rotation and fixation. (From Gray SW, Skandalakis JE: Embryology for Surgeons: Embryological Basis for Treatment of Congenital Defects. Philadelphia, WB Saunders, 1972, p 136.)

omphalocele and include intestinal abnormalities such as stenosis and atresia.[11]

Rotational Abnormalities

Midgut malrotation may occur in as many as 0.2% of live births.[12] These abnormalities are associated with a variety of other anomalies, including abdominal wall or diaphragmatic hernias, intestinal atresia, imperforate anus, and cardiac defects.[2] Down's syndrome is not as common with malrotation as with other anomalies, such as duodenal atresia.[2]

Rotational abnormalities of the small bowel can be divided into mixed rotation, nonrotation, and reversed rotation (Fig. 67–9).[2] In mixed rotation, partial failure of rotation may result in an abnormally high cecum or a duodenum that does not pass dorsal to the SMA. Such cases are often associated with adhesive bands (Ladd's bands) that course from the ligament of Treitz to the ileocecal junction. These bands may traverse the duodenum and can result in duodenal obstruction. This problem is associated with duodenal, pancreatic, and biliary abnormalities.

Nonrotation occurs when failure of rotation results in return of the bowel in a distal-to-proximal fashion; the small intestine is located on the right side of the abdomen with the cecum in the middle and the colon on the left. The mesentery is usually short, and fibrous bands are common. These bands may result in obstruction or volvulus.

Reversed rotation occurs when the initial counterclockwise rotation is only 90 degrees and subsequent rotation is 180 degrees clockwise. This results in a

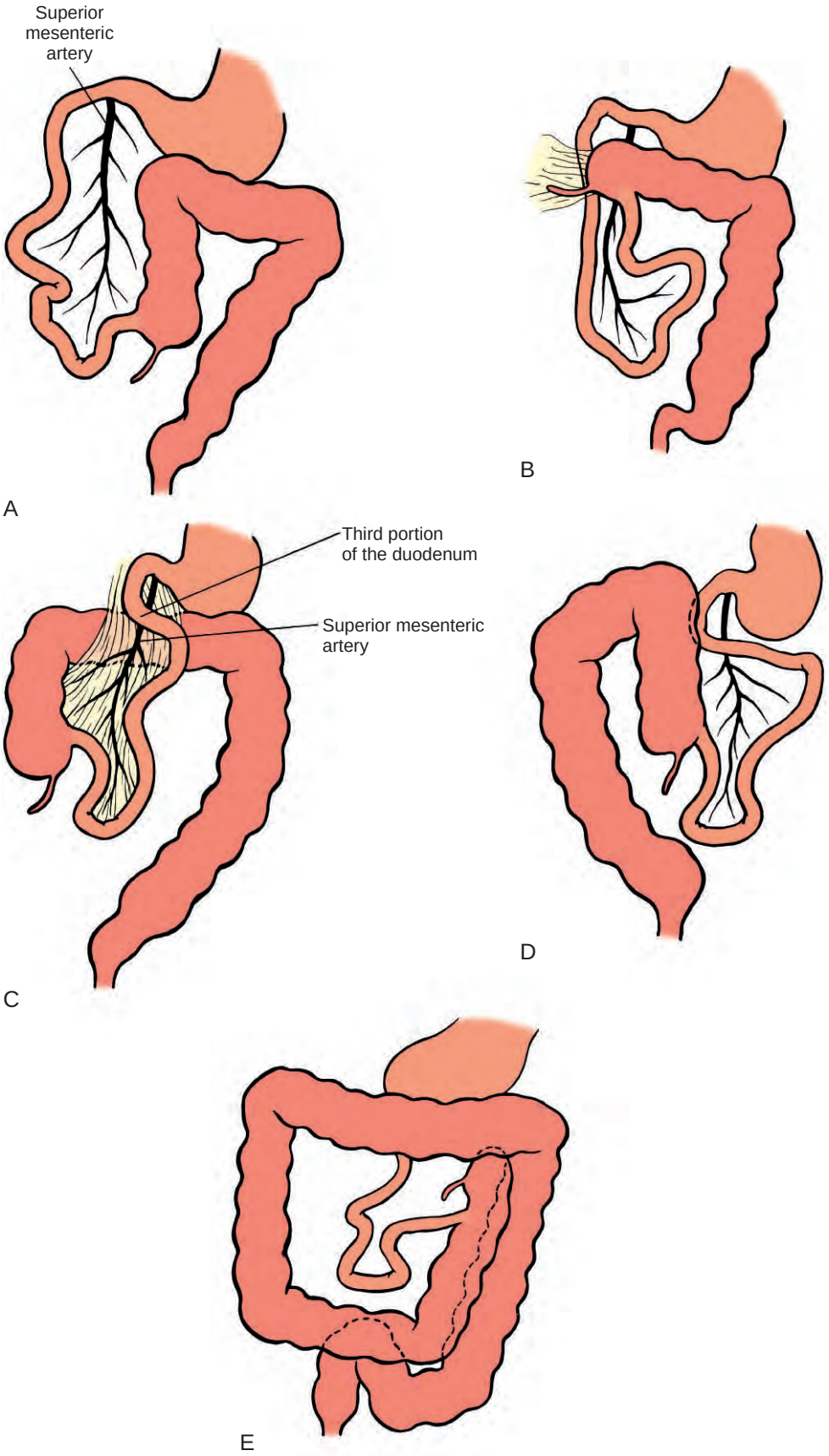

Figure 67–9. Different rotational abnormalities of the small intestine. **A,** *Nonrotation.* Return of the postarterial segment leaves the whole colon on the left and the small intestine on the right. **B,** *Mixed rotation.* The prearterial segment has failed to rotate, so the cecum is fixed to the abdominal wall and now lies anterior to the second portion of the duodenum. **C,** *Reversed rotation.* The third portion of the duodenum is anterior to the superior mesenteric artery, which in turn is anterior to the transverse mesocolon; the postarterial segment has entered the abdomen ahead of the prearterial segment. **D,** *Reversed rotation.* The colon occupies the right half of the abdomen, and the small intestine occupies the left half. **E,** *Hyperrotation.* The colon is longer than normal and the cecum has reached the splenic flexure. (From Gray SW, Skandalakis JE: Embryology for Surgeons: Embryological Basis for Treatment of Congenital Defects. Philadelphia, WB Saunders, 1972, p 178.)

transverse colon that passes dorsal to the duodenum and the SMA. Obstruction may result from various fibrous bands that may fix the colon.

Atresia and Stenosis

Atresias are divided into four types (Fig. 67–10).[2] Type I occurs when a membrane of mucosa and submucosa obstructs the bowel lumen. Type II is characterized by a fibrous band that replaces a portion of the intestine. In type III, the bowel is discontinuous, with proximal and distal blind ends. Type IV occurs when multiple areas of the intestine become fibrous bands. Duodenal atresia is probably due to failure of recanalization, whereas jejunal and ileal atresia is thought to occur as a result of intestinal ischemia. Patients with duodenal atresia have Down's syndrome in 30% of cases.[13] This abnormality is also associated with esophageal atresia, midgut malrotation, annular pancreas, imperforate anus, congenital anomalies of the heart, and intrauterine growth retardation.[13]

Internal Hernias

A variety of congenital hernias may result from abnormal rotation or fixation of the bowel on the abdominal wall. By far the most common type is a paraduodenal hernia, which results from abnormal fixation of the ascending or descending colon.

PHYSIOLOGY

The small intestine absorbs water, electrolytes, and nutrients. The process of digestion involves mechanical grinding of food, as well as chemical enzymatic digestion. For adequate absorption to occur, regulated fluid secretion and proper peristalsis must take place in concert to facilitate luminal surface hydration and mixing of food. The small intestine performs a number of other functions in addition to digestion. It is an important endocrine organ from which a host of gut-associated hormones are released. The epithelial barrier function of the small intestine protects the internal milieu against noxious luminal substances, such as bacteria and ingested toxins. The small intestine is also a major lymphoid organ where foreign antigens initially encounter the body's immune cells. The importance of the mucosal immune system is increasingly being appreciated as its involvement in the pathogenesis of intestinal disorders is elucidated.

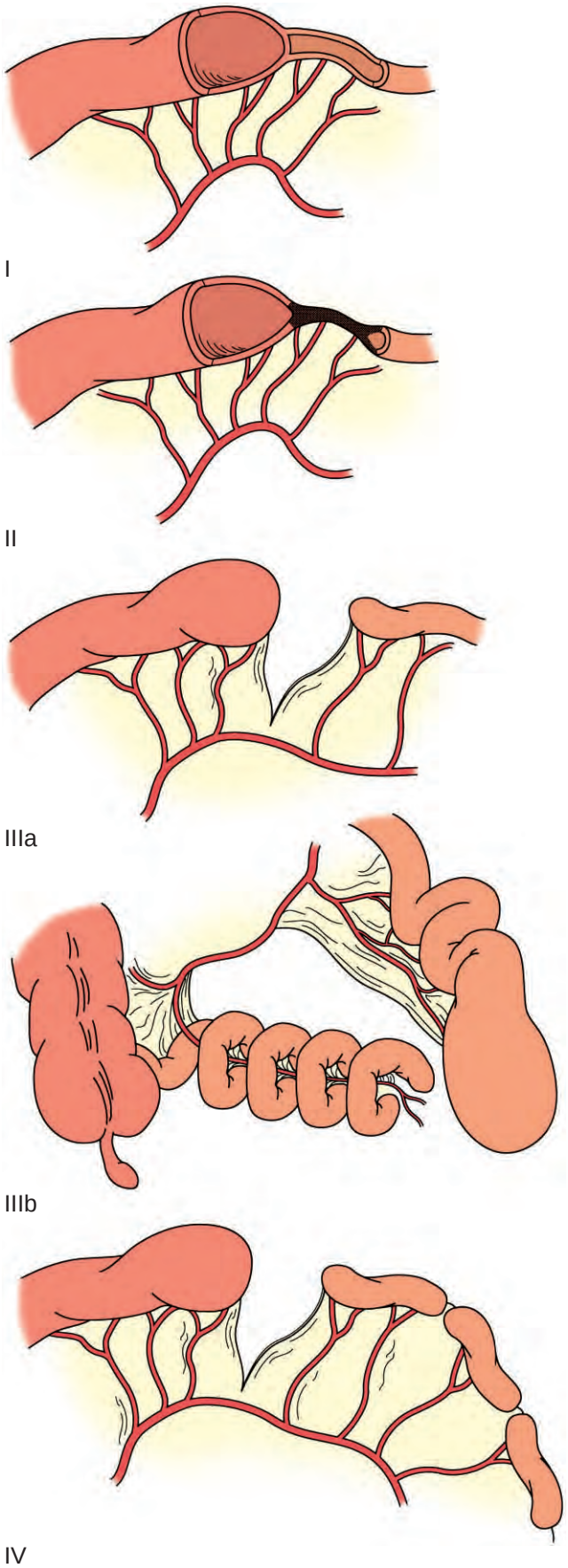

Figure 67–10. Different types of intestinal atresia. **Type I,** Continuity of mesentery and bowel with an incomplete web. **Type II,** The mesentery is intact, but the bowel has reduced to a fibrous cord. **Type IIIa,** The bowel and mesentery are focally disconnected. **Type IIIb,** The mesentery and bowel are completely separated, a so-called apple peel or Christmas tree deformity. **Type IV,** Multiple atresias (can be seen in combinations of type IIIa and IIIb). (From Welch KJ, Randolph JG, Ravitch MM, et al [eds]: Pediatric Surgery, 4th ed. Chicago, Year Book Medical Publishers, 1986.)

Layers of the Bowel Wall

The small bowel wall consists of the innermost *mucosa,* followed by the *submucosa, muscularis propria,* and the outermost *serosa.* The serosa is contiguous with the peritoneal lining and is absent in the posterior aspect of the duodenum because of its retroperitoneal location. The smooth muscle cells of the muscularis provide the motor activity necessary for intestinal peristalsis, and this smooth muscle consists of a thick inner circular layer and a thinner outer longitudinal layer. Gap junctions found on the plasma membrane of intestinal smooth muscle cells permit efficient propagation of peristaltic signal by allowing electrical coupling between adjacent cells. Ganglion cells and neural fibers form an extensive plexus throughout the layers of small intestine. The myenteric (Auerbach's) plexus is located between the circular and longitudinal layers of the muscularis.

The submucosa is a strong connective tissue layer that contains rich networks of vessels, nerves, and lymphoid tissue. The mucosa of the small intestine is structurally characterized by finger-like projections called *villi* and consists of three microscopic layers: the epithelium, the lamina propria, and the muscularis mucosae. The innermost epithelium is lined by a single layer of columnar epithelial cells of various types. The apical surface of these cells is covered by brush-border microvilli that project into the lumen of the intestine. The architectural arrangements of the villi and microvilli further contribute to the vast surface area of the small intestine. The lamina propria is located between the intestinal epithelium and the muscularis mucosae and consists of various connective tissue cell types and a rich microvascular network between artery and vein that enables efficient secretion and absorption of water, electrolytes, and nutrients. In addition, a central lymphatic vessel called a *lacteal* facilitates transport of fats and immunologic substances. The muscularis mucosae consists of a thin layer of smooth muscle cells between the mucosa and submucosa.

INTESTINAL EPITHELIUM AND ITS FUNCTIONS

Intestinal epithelial cells form a layer that separates the internal milieu from an external environment full of potentially harmful entities, such as luminal bacteria, toxins, digestive enzymes, xenobiotics, and ingested chemicals. The intestinal epithelium plays a central role in digestion and absorption of nutrients, as well as transport of water and electrolytes. Additionally, the epithelium is a major participant in intestinal immune function. These complexly regulated and multiple functions of the epithelium are accomplished by heterogeneous populations of specialized epithelial cells.

Architecture

The mucosal surface of the intestine is characterized by two structural features: villi and the crypts of Lieberkühn (Fig. 67–11). A single layer of simple columnar epithelial cells rests on a thin basement membrane overlying the lamina propria (Fig. 67–12). The lamina propria of the villus core contains numerous connective tissue cells, including fibroblasts, lymphocytes, plasma cells, eosinophils, smooth muscle cells, and nerve fibers. The function of the overlying epithelial cells is closely influenced by humoral factors released by cells in the lamina propria and by the matrix components of the basement membrane.

The intestinal epithelium is renewed continually, with an enterocyte life span of 3 to 7 days. Pluripotent stem cells located near the base of the crypt migrate along the so-called crypt-villus axis while differentiating into one of the four major cell types: absorptive enterocytes, enteroendocrine cells, goblet cells, and Paneth cells. Frequent mitoses are observed in the crypt zone as these cells differentiate into mature absorptive cells during their migration toward the villus tips. Villus enterocytes then undergo apoptosis and are subsequently shed from the epithelium. The spontaneous rate of apoptosis is lower in colonic epithelium than in the small intestine. The difference may reflect altered expression of the anti-apoptotic survival gene *bcl-2* and may be one of many factors that contribute to the lower incidence of cancer in the small intestine.[14]

Several distinct cell types are found in the crypts. Enterochromaffin cells, also known as *enteroendocrine cells,* do not maintain direct contact with the intestinal lumen. The contents of their secretory granules are released into blood in response to regulatory stimuli. Paneth cells reside at the base of the crypts and are the only cell type to undergo downward migration from the proliferative zone. They resemble pancreatic or parotid acinar cells morphologically and may contribute to mucosal immunity by secreting antimicrobial peptides, including α-defensins.[15] Goblet cells are seen in both the villi and crypts and secrete a protective mucous layer onto the mucosal surface. Villus columnar epithelial cells are primarily responsible for the absorption of fluid and electrolytes, whereas secretion occurs mostly in the crypts, although recent observations suggest that villi and crypts can both absorb and secrete to some extent.[16,17] Microscopically, the luminal border of the villus cells has a fuzzy appearance (brush border) because of the presence of microvilli in the apical plasma membrane. In addition to increasing absorptive surface area, microvilli directly enhance digestion through the presence of high concentrations of membrane-associated digestive enzymes.

Barrier Function

One of the most distinctive functions of epithelial cells is the ability to establish a barrier or a seal at the interface between the external and internal environments of the tissue. In the intestine, the barrier function of the epithelium protects the internal milieu from the permeation of potentially harmful luminal substances. This function is attributed to several morphologically distinct components of the intercellular junctional complex, a structure that circumferentially seals adjacent epithelial cells.[18,19]

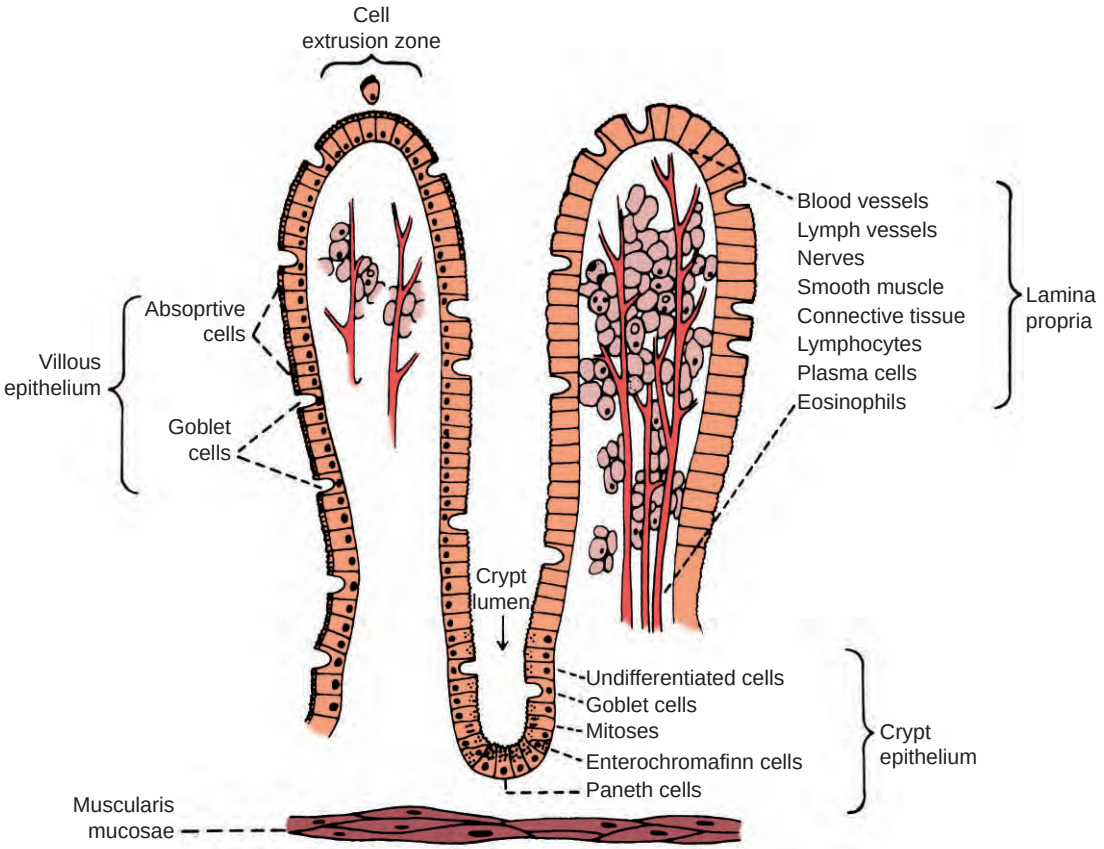

Figure 67–11. Schematic diagram of two sectioned villi and a crypt of the small intestinal mucosa. (From Trier JS, Winter HS: Anatomy, embryology, and developmental abnormalities of the small intestine and colon. In Sleisenger MH, Fordtran JS [eds]: Gastrointestinal Disease: Pathophysiology, Diagnosis, Management, 5th ed. Philadelphia, WB Saunders, 1993, p 796.)

The tight junction, or zonula occludens, forms a continuous contact at the apical-most aspect of the lateral membrane border between enterocytes (Fig. 67–13). The intercellular barrier is formed in part by the homotypic interactions of occludin between adjacent cells. *Occludin* is a transmembrane protein whose cytoplasmic tail is bound to a complex of cytoplasmic plaque proteins, including ZO-1 and ZO-2. A novel family of tight junction–associated transmembrane proteins known as *claudins* may account for the permselectivity characteristics of the intercellular junctional complex.[20] Adjacent and deep to the tight junction is the intermediate or adherens junction (zonula adherens), which also forms continuous contact by similar homotypic interaction of the transmembrane protein E-cadherin between adjacent cells. Intracellularly, E-cadherin associates directly with the cytoplasmic proteins α-, β- and γ-catenin and thereby with a contractile ring of actin and myosin that may regulate junctional permeability. Thick bands of perijunctional actin connect the adherens junction to the cytoplasmic plaque proteins of the tight junction. The tight junctions and adherens junctions are closely arranged spatially and behave as an integrated functional unit. Regulatory proteins of various tyrosine and serine-threonine kinase–based signaling pathways are localized in the vicinity of this apical junctional complex, thus reflecting the potential for regulatory control of junctional permeability by multiple cellular signaling mechanisms. Beneath the zonula occludens and zonula adherens are the desmosomes and gap junctions, which form focal contacts between neighboring cells.

The epithelial intercellular junctional complex does not present a static barrier. Solute permeability characteristics vary widely across different epithelia. The small intestine is classified as a "leaky" epithelium in comparison to the colon or urinary bladder. The influence of various humoral factors and other mediators on paracellular permeability is tissue and cell specific.[21,22] Tight junctions in absorptive cells become dilated by luminal glucose.[23-25] Physiologic regulation of junctional integrity can also occur in response to activation of Na^+-coupled transporters in the apical plasma membrane.[26] Intestinal barrier function is altered in many pathologic conditions. Bacterial toxins such as those elaborated by *Clostridium difficile* directly perturb intestinal barrier function by disrupting the interaction between junctions and the actin cytoskeleton.[27] ZO toxin from *Vibrio cholerae* has also been shown to disrupt actin and junctional integrity in a protein kinase C–dependent manner.[28] Translocation of bacteria and bacterial products as a result of increased intestinal paracellular permeability (associated with junctional disruption) in critically ill patients has

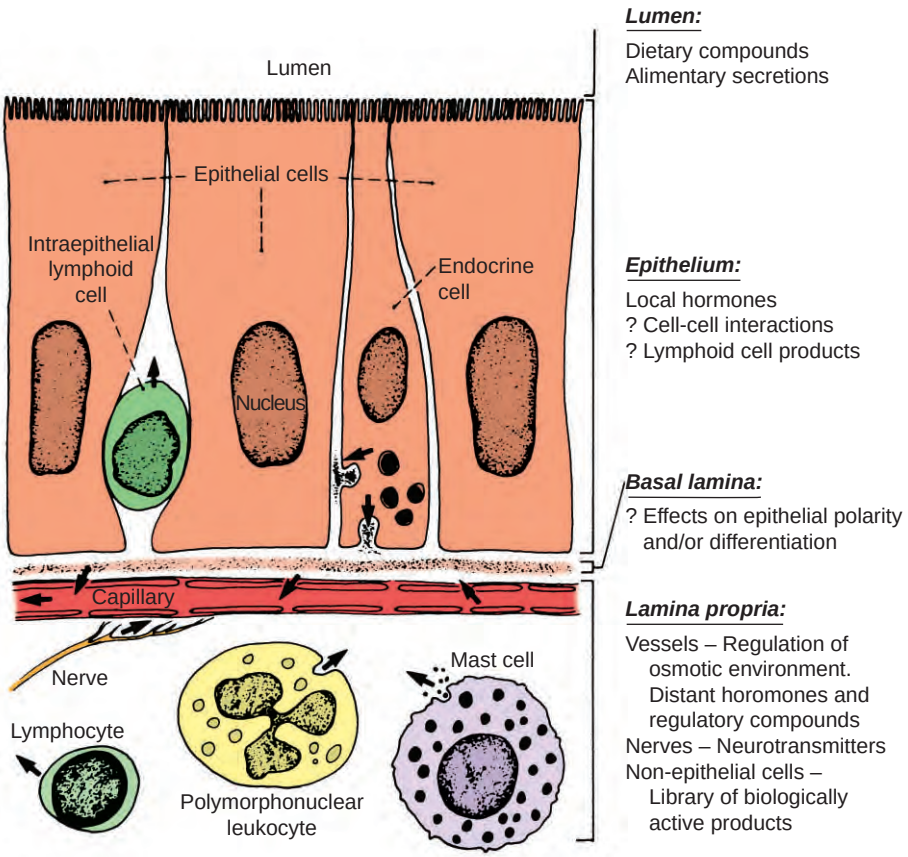

Figure 67–12. Schematic illustration of some factors in the microenvironment of intestinal epithelial cells that may influence their function. With the exception of extravascular polymorphonuclear leukocytes, all elements are normally present at this site. (From Madara JL: Functional morphology of epithelium of the small intestine. In Handbook of Physiology: The Gastrointestinal System. Bethesda, MD, American Physiological Society, 1991, p 85.)

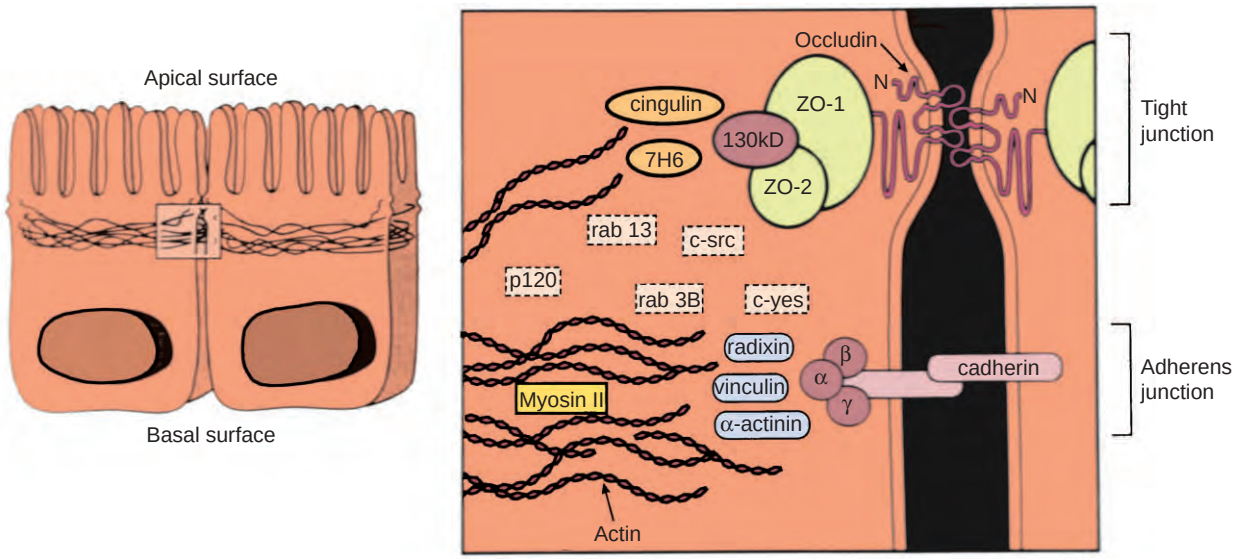

Figure 67–13. **Left,** Tight junctions are positioned as continuous contacts at the apical-lateral membrane borders between enterocytes. The *boxed region* is enlarged at the right. **Right,** Hypothetical model of protein interactions at the tight junction and adherens junction of two simple columnar epithelial cells. The intercellular barrier at the tight junction is formed by homotypic contacts of the transmembrane protein occludin, which is bound on the cytoplasmic surface directly to ZO-1. The ZO-1/ZO-2 heterodimer binds an uncharacterized 130-kD protein. Binding interactions of cingulin and the transmembrane protein cadherin are shown; they associate directly with the cytoplasmic proteins α-, β-, and γ-catenin. A thick band of perijunctional actin is positioned under the adherens junction with connections to tight junction plaques. (From Anderson JM, Van Itallie CM: Tight junctions and the molecular basis for regulation of paracellular permeability. Am J Physiol 269:G468, 1995.)

Table 67–1 Water and Electrolytes

Nutrient	Receptor	Comment	References
Water	Aquaporins (AQP) Transcellular route for water transport	First described in the kidney AQP3: colon, small intestine AQP4: colon AQP5: salivary glands AQP7: small intestine AQP8: small intestine	33-40
Na^+/K^+	Na^+,K^+-ATPase	Absorption of Na^+ coupled to organic solutes (glucose, amino acids) Na^+ entry into the cell is dependent on the concentration gradient Cl^- entry is passive Co-entry of Na^+Cl^- through the Na^+/H^+ $Cl^-/HCO3^-$ exchanger operates in parallel. This accounts for Na^+ absorption between meals and is disrupted during diarrheal diseases	41
Na^+/K^+	Apical Na^+/H^+ exchangers (NHE)	NHE2: small intestine NHE3: small intestine (major functional brush-border isoform) NHE1: basolateral (important in intracellular pH homeostasis)	42-44

been postulated to underlie the development of a sepsis-like state in multiorgan failure. However, direct evidence in support of this hypothesis has been difficult to establish. Various cytokines have been shown to alter junctional permeability, including interferon-γ and tumor necrosis factor-α.[29,30]

Digestion and Absorption

The vast total surface area of the small intestine enables it to absorb large quantities of water, electrolytes, and nutrients. The small intestine receives 8 to 10 L of fluid daily, including 1 to 1.5 L of ingested fluid. The remainder consists of salivary, gastric, pancreaticobiliary, and small intestinal secretions. Most of this fluid load is absorbed by the small intestine before reaching the ileocecal valve. Absorption of specific luminal components is accomplished by complex mechanisms that consist, to varying degrees, of intraluminal processing, epithelial uptake, and transport into the portal or lymphatic circulation. These processes display distinct patterns of expression along the longitudinal axis of the gut.

Water

The absorptive capability of the small intestine is estimated to be 12 L/day. Water movement across the epithelial layer is driven by the active transport of Na^+ and Cl^- and by the absorption of small molecules such as glucose and amino acids. The principal energy for many of these transport processes derives from the Na^+ gradient generated by the action of a basolateral Na^+,K^+-ATPase pump. The low intracellular Na^+ concentration maintained by this pump allows uptake of Na^+ and other solutes through coupled ion exchangers (Na^+/H^+ and Cl^-/HCO_3^-) and Na^+-coupled nutrient transporters. The precise route of water movement across an epithelium (transcellular, paracellular, or both) is controversial. The paracellular route (across the intercellular junctional complex) was previously thought to be the dominant pathway. However, this concept has been questioned on the basis of a number of recent observations, including attempts to directly measure water flow through junctions.[31] It is now recognized that water movement across plasma membranes can be greatly facilitated by members of a specialized family of proteins known as aquaporins (Table 67–1), which function as water channels.[32]

Another possible mechanism of bulk water transport has been proposed on the basis of observations that water may move in substantial quantities through the solute pocket of Na^+-coupled transporters. For example, water movement through the Na^+-glucose cotransporter SGLT1 appears to occur with a fixed stoichiometry of 2 Na^+, 1 glucose, and 210 H_2O in human SGLT1.[45] The physiologic relevance and relative contributions of these nonclassic routes of water transport in the intestine are not yet clear (see Table 67–1).

Sodium

Sodium absorption is driven by active transcellular uptake. Passive transport through the paracellular pathway also contributes to overall Na^+ absorption to a varying degree along the length of the gastrointestinal tract. A sizable, if not the major fraction of Na^+ and water

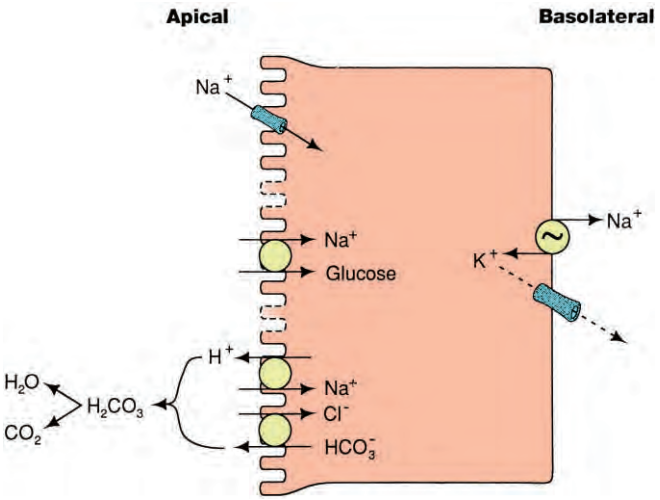

Figure 67–14. Apical sodium transporters. Luminal sodium enters the absorptive epithelial cell down an electrochemical gradient. Mechanisms for this transport include an ion-specific channel sensitive to amiloride, a carrier that couples the movement of sodium and nutrients (i.e., glucose), or a carrier that allows electroneutral entry of sodium in exchange for intracellular hydrogen (antiport). The common exit pathway across the basolateral membrane is the sodium pump. (From Sellin JH: Intestinal electrolyte absorption and secretion. In Sleisenger MH, Fordtran JS [eds]: Gastrointestinal Disease: Pathophysiology, Diagnosis, Management, 5th ed. Philadelphia, WB Saunders, 1993, p 960.)

absorption in the proximal part of the small intestine occurs paracellularly across the relatively leaky and nonselective intercellular junctions. The junctions become "tighter" and more cation selective distally in the ileum and colon, which enables active transport mechanisms to absorb Na^+ against a large osmotic gradient.

The engine driving active transcellular Na^+ absorption is the Na^+,K^+-ATPase pump, which generates electric and chemical gradients by extruding Na^+ in exchange for K^+ in a 3:2 stoichiometry across the basolateral cell membrane (Fig. 67–14). This energy-dependent pump action establishes a transmembrane potential difference with the cell interior of about −35 mV and maintains a low intracellular Na^+ concentration and a high intracellular K^+ concentration. Na^+ and Cl^- absorption across the apical membrane from the intestinal lumen involves three different mechanisms.

The apical Na^+/H^+ exchangers (NHEs) are members of the mammalian Na^+/H^+ exchanger gene family.[42,43] Among these exchangers, NHE2 and NHE3 are present in the apical membrane of human small intestinal epithelia, more specifically, the ileum.[44] NHE3 appears to be the major functional brush-border isoform in mammalian intestine, whereas the role of NHE2 is less clear (see Table 67–1).

Carbohydrates

Carbohydrates provide a major portion of adult dietary energy requirements. Human intestine is incapable of digesting and processing certain complex carbohydrates, such as cellulose-containing β-linked glucose molecules. Unlike the α bond found in starch, the β bond 1-4 is resistant to the digestive activity of amylase, although cellulose can be converted to absorbable fatty acids to some extent by colonic bacteria. Dietary fiber from "unavailable carbohydrates" also comes from pectins, gums, alginates, and lignins and helps reduce constipation by retaining water and increasing fecal bulk. Major dietary digestible carbohydrates include, in order of abundance, starch, sucrose, and lactose. Starch consists of amylose and the more abundant amylopectin. Sucrose is a disaccharide of glucose and fructose and is commonly found in fruit and sugar cane. The major source of lactose, a disaccharide consisting of glucose and galactose, is milk products.

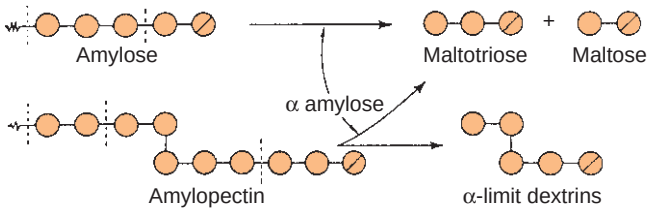

Figure 67–15. Action of α-amylase on amylose and amylopectin molecules. Because the a 1-6 link in the latter is resistant to amylase, the products include α-limit dextrin. (From Gray GM: Carbohydrate absorption and malabsorption. In Johnson LR [ed]: Physiology of the Gastrointestinal Tract. New York, Raven Press, 1981, p 1064.)

Digestion of carbohydrates begins in the mouth, where salivary amylase is active. Ingested starch is broken down into smaller oligosaccharides by the action of amylase. The resulting digestive products therefore include maltose, maltotriose, short oligosaccharides, and α-dextrins, as well as short-branched oligosaccharides from amylopectin (Fig. 67–15). Because salivary amylase is promptly inactivated at low gastric pH, pancreatic amylase in the duodenum is thought to be the major enzyme for starch digestion. The resultant short-chain oligosaccharides from amylase digestion, along with ingested sucrose and lactose, are further digested into basic monosaccharides in the small intestine before absorption into enterocytes. The brush-border membrane of villus enterocytes contains three hydrolase activities: lactase, sucrase, and isomaltase. The final products of carbohydrate digestion consist primarily of three major diet-derived hexoses: glucose, galactose, and fructose.

Absorption of these major monosaccharides into enterocytes can occur by several different transport mechanisms. Glucose transporters are categorized into two broad categories: Na^+ dependent (SGLT) and Na^+ independent (GLUT, Table 67–2) (Fig. 67–16).[71]

Proteins

Although ingested dietary proteins constitute the main source of amino acids, a significant amount of the

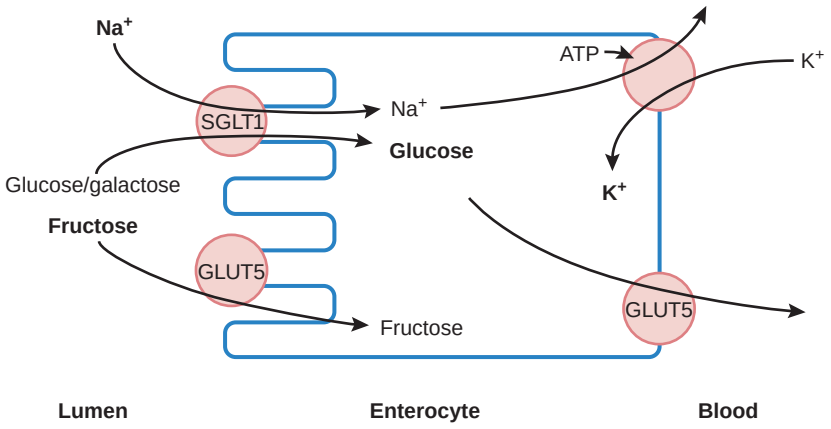

Figure 67–16. Schematic diagram for sugar transport across the enterocyte showing the brush-border SGLT1 and GLUT5 transporters and the basolateral Na^+-K^+ pumps and sugar transporter GLUT2. ATP, adenosine triphosphate. (From Wright EM: Genetic disorders of membrane transport. I. Glucose galactose malabsorption. Am J Physiol 275:G880, 1998.)

Table 67–2 Carbohydrates, Proteins, and Lipids

Nutrient	Receptor	Comment	References
Carbohydrates			
		The α bond (found in starch) is disrupted by amylase The β bond (found in cellulose) is resistant to human digestive activity and contributes to dietary fiber	
Glucose	SGLT (Na^+ dependent)	SGLT1 actively absorbs glucose and galactose against a concentration gradient	
	GLUT (Na^+ independent)	GLUT2 is the major transporter for intestinal absorption (moves in the direction of the glucose concentration) GLUT5 absorbs fructose (fructose is also absorbed paracellularly through glucose-activated solution drag)	46-48
Proteins			
Single amino acids (neutral, acidic and basic)	Na^+-dependent active transport		49
Oligopeptides	Pep T-1	Transports dipeptides and tripeptides through H^+-coupled active transport (very sensitive to luminal and intracellular pH; absorbed peptides are hydrolyzed by cytoplasmic peptidases)	50-62
Lipids			
Short- and medium-chain fatty acids		Diffusion into the cell	63, 64
Long-chain fatty acids	Fatty acid transport proteins (FATPs)	FATP4: apical membrane of mature enterocytes	65-67
	Fatty acid binding proteins (FABPs)	Promote the intracellular transport of fatty acids by decreasing the amount of fatty acids that my otherwise bind to immobile membranes	68-70

protein content in the intestinal lumen is derived from endogenous sources such as salivary, gastric, and pancreaticobiliary secretions, as well as desquamated epithelial cells. Digestion of proteins starts in the stomach by the action of pepsins, which are specialized proteolytic enzymes. Their precursor pepsinogens, released from chief cells, are converted into active enzyme pepsins with the truncation of a small peptide by low gastric pH.[72] When in the duodenum, pepsins are irreversibly inactivated by the alkaline pH. Further digestion of luminal proteins is facilitated by the action of pancreatic proteases in the small intestine. Unlike amylase and lipase, which are secreted in their active forms, all pancreatic proteases are released as proenzymes that require proteolytic digestion for activation. Initiation of the activation cascade requires conversion of trypsinogen to trypsin by

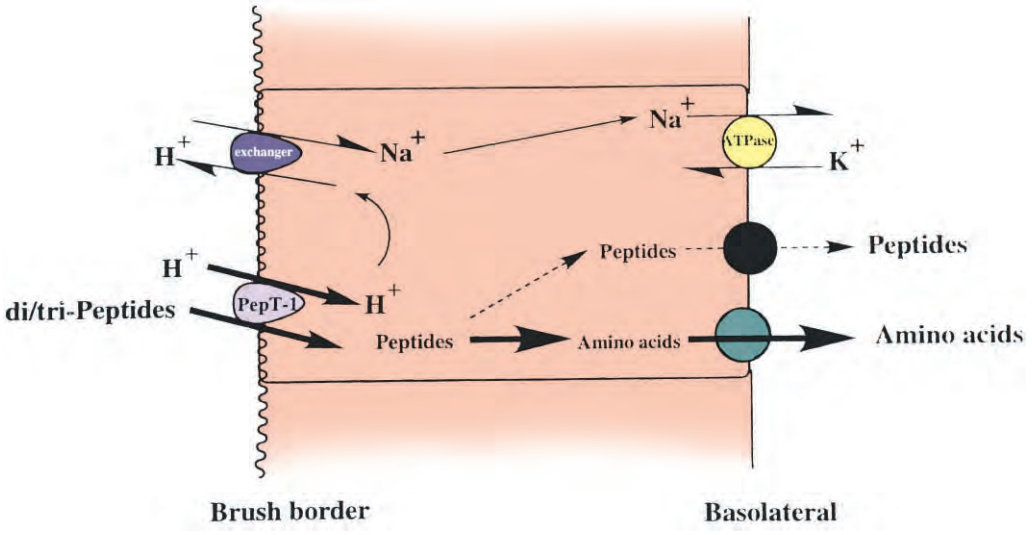

Figure 67–17. Cellular processes that are involved for optimal function of the intestinal oligopeptide transporter (Pep T-1). (From Adibi SA: The oligopeptide transporter [PepT-1] in human intestine: Biology and function. Gastroenterology 113:336, 1997.)

brush-border enterokinase (enteropeptidase), which involves removal of a six–amino acid peptide from the proenzyme. Trypsin in turn activates other proteolytic enzyme precursors. Activated proteases are classified into two groups according to their relative site of action: endopeptidases and exopeptidases. Endopeptidases such as trypsin, chymotrypsin, and elastases display digestive activity against peptide bonds adjacent to specific amino acids within a polypeptide chain. Exopeptidases include carboxypeptidase A and B and release a single amino acid from the carboxyl terminal end. The digestive activities of these proteases in the small intestine result in the release of luminal amino nitrogen in the form of 30% single amino acids and 70% oligopeptides.[73]

Transport of luminal amino nitrogen involves the uptake of both single amino acids and oligopeptides. Multiple transport mechanisms exist for the 20 single amino acids, including carrier-mediated active transport, facilitated diffusion, and simple diffusion.[74] Separate Na^+-dependent active transport processes have been characterized for neutral, acidic, and basic amino acids. Since cloning of the first γ-aminobutyric acid and cationic amino acid transporters, the cDNA of more than 20 mammalian amino acid transporters has been isolated.[49] Facilitated diffusion may play a role, though a minor one, in the absorption of charged amino acids. Exit of absorbed intracellular amino acids through the basolateral membrane involves similar transport mechanisms.

The significance of the transport of oligopeptides in protein absorption has been demonstrated in several kinetic studies when it was shown to be more efficient than the absorption of single amino acids.[50-53] This oligopeptide transporter (Pep T-1) has recently been cloned as a 708–amino acid membrane protein[54] that transports only dipeptides and tripeptides through H^+-coupled active transport and thus is very sensitive to luminal and intracellular pH (Fig. 67–17, see Table 67–2).[55] In patients requiring enteral nutrition, Pep T-1 provides enhanced absorption of total protein in the form of dipeptides and tripeptides (1) through superior oligopeptide absorption over that of single amino acids, (2) by facilitating an alternative route of delivery of unstable glutamine and poorly soluble tyrosine, and (3) by decreasing the hypertonicity of elemental diets.[56] The clinical importance of Pep T-1 is further displayed by its ability to transport orally administered β-lactam antibiotics, whose structure resembles that of tripeptides.[57,58] Enterocytes consume about 10% of absorbed amino acids when glutamine appears to be a major source of energy.

Lipids and Cholesterol

Dietary fat, made up primarily of triglycerides, is an efficient source of energy that is derived from both animal and vegetable fat. A triglyceride consists of a glycerol backbone with three attached fatty acid chains of various length. Most dietary triglycerides consist of both saturated and unsaturated fatty acids of 16 and 18 carbons and include palmitic (C16:0), oleic (C18:1), stearic (C18:0), and linoleic (C18:2) fatty acids. About 10% of triglycerides consist of medium-chain (6 to 12 carbons) and short-chain (4 carbons) fatty acids. Phospholipids such as lecithin exist in smaller amounts.

Digestion of dietary fat begins in the stomach by acid hydrolysis and gastric lipase. Because of the insoluble nature of fat in water, however, digestion and absorption of lipids predominantly occur in the small intestine by emulsification. Optimal emulsion requires bile salts and phospholipids (either ingested or lecithin) and results in stable small emulsion droplets with a large surface area (Fig. 67–18). Triglycerides in this stable emulsion are then exposed to pancreatic lipase for hydrolysis in the duodenum. Binding of lipase to triglyceride, a prerequisite for hydrolysis, is inhibited by luminal bile salts. Colipase, secreted by the pancreas as an inactive proenzyme,

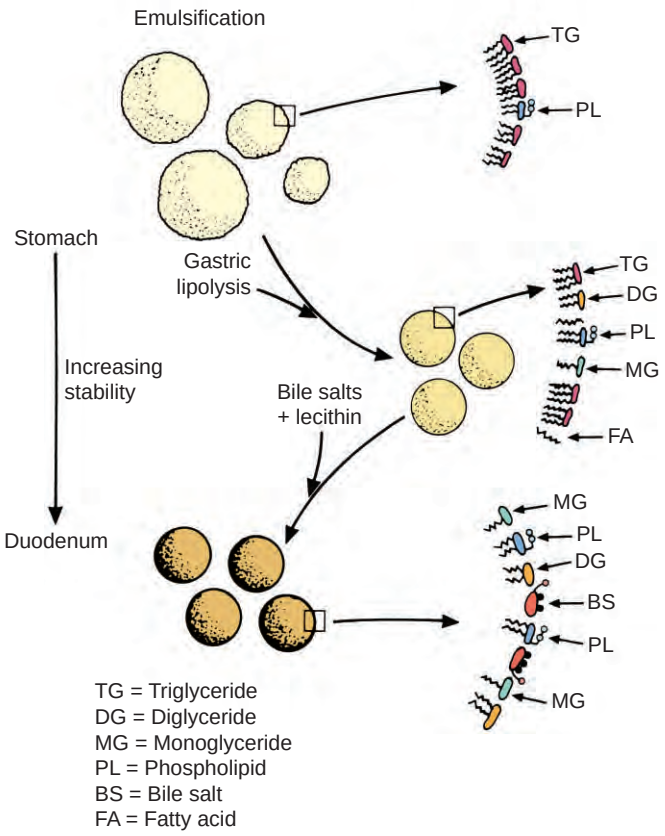

Figure 67–18. Diagram of steps leading to an increasingly stable emulsion. Gastric lipolysis yields fatty acids and diglyceride, which enhance emulsification, and this is further enhanced in the duodenum by bile salts and phospholipid. (From Tumberg LA, Riley SA: Digestion and absorption of nutrients and vitamins. In Sleisenger MH, Fordtran JS [eds]: Gastrointestinal Disease: Pathophysiology, Diagnosis, Management, 5th ed. Philadelphia, WB Saunders, 1993, p 984.)

is activated by luminal trypsin and facilitates exposure of the lipolytic site after binding to lipase in the presence of bile.[75] Sequential hydrolysis of the two outer ester bonds of the triglyceride molecule by the lipase-colipase complex yields two molecules of free fatty acid and a 2-monoglyceride molecule. Lipase helps present the products of hydrolysis to the mucosal absorptive surface by binding to the brush-border membrane. A specific lipase inhibitor, orlistat (tetrahydrolipstatin), is currently used clinically as a treatment of obesity. Ingested phospholipids are digested by pancreatic phospholipase A_2. Cholesterol is liberated from its esterified form by pancreatic cholesterol esterase.

For the products of lipolysis to be absorbed optimally, they must form micelles with bile salts because of their poor solubility in water. The amphipathic nature of bile salts allows solubilization of free fatty acids, monoglycerides, and cholesterol (but not triglyceride) within the lipophilic area of the micelles.[76] Micelles, shaped like disks, are much smaller (50 to 80 nm in diameter) than emulsion droplets and can form only when the bile salts are above a critical concentration. Alternatively, droplets containing the products of lipolysis may form smaller spherical lipid droplets from their surface in the absence of an adequate bile salt concentration.[77,78] This nonmicellar lipid transport to the mucosal surface, though a minor mechanism, may account for significant triglyceride absorption when bile salts are absent.

At the brush border the lipid contents of the micelle pass into the enterocytes, whereas bile salts remain within the intestinal lumen. Liberation of fatty acids and glycerides at the surface of the brush border may in part be explained by the presence of an "unstirred water layer."[63] This layer is thin (about 40 µm[64]) and is thought to maintain an acidic microenvironment by the action of surface NHE. A low luminal pH in this layer decreases the solubility of the fatty acids in micelles and thus may enhance their liberation. Additionally, fatty acids are uncharged when protonated at an acidic pH and may thereby diffuse across lipid membrane more easily. Once inside cytoplasm, the near-neutral pH may trap them in their ionized form. Uptake of short-chain and medium-chain fatty acids across the brush-border membrane occurs predominantly by simple diffusion. Long-chain fatty acids (LCFAs), however, are transported into enterocytes by a saturable and specific uptake mechanism. Recently, a family of homologous fatty acid transport proteins (FATPs, see Table 67–2) has been identified and cloned, and these proteins were demonstrated to transport LCFAs across the plasma membrane.[65,66] Overexpression of FATP4 in nonenterocytes can facilitate uptake of LCFAs with the same specificity as enterocytes, whereas reduction of FATP4 expression in primary enterocytes inhibits fatty acid uptake significantly,[67] thus making such reduction a potential target for novel antiobesity therapy.

Once within the cell, fatty acids are transferred to the endoplasmic reticulum for re-esterification back to triglyceride. Intracellular movement of free fatty acids is facilitated through codiffusion with fatty acid binding proteins (FABPs, see Table 67–2), a group of low-molecular-weight cytosolic proteins capable of binding hydrophobic molecules.[68] In the endoplasmic reticulum, resynthesis of triglyceride can occur by two processes. The more predominant monoglyceride pathway involves sequential esterification to diglyceride and triglyceride by acetylcoenzyme A derived from activated fatty acids. The minor pathway involves acylation of α-glycerophosphate by glycerol and fatty acids and may become important during fasting.

After they are synthesized, triglycerides, along with cholesterol and phospholipids, coalesce with apoprotein to form a large lipoprotein complex called a *chylomicron.* During fasting, instead of chylomicrons, very-low-density lipoproteins with different apoproteins and fatty acids are mainly formed. Packaged vesicles containing chylomicrons from the Golgi apparatus then migrate to the basolateral membrane to be released by exocytosis (Fig. 67–19). Chylomicrons subsequently enter the lacteals and pass through the lymphatics into the system's venous circulation. Medium-chain fatty acids and polyunsaturated fatty acids are capable of passing directly into the portal circulation.

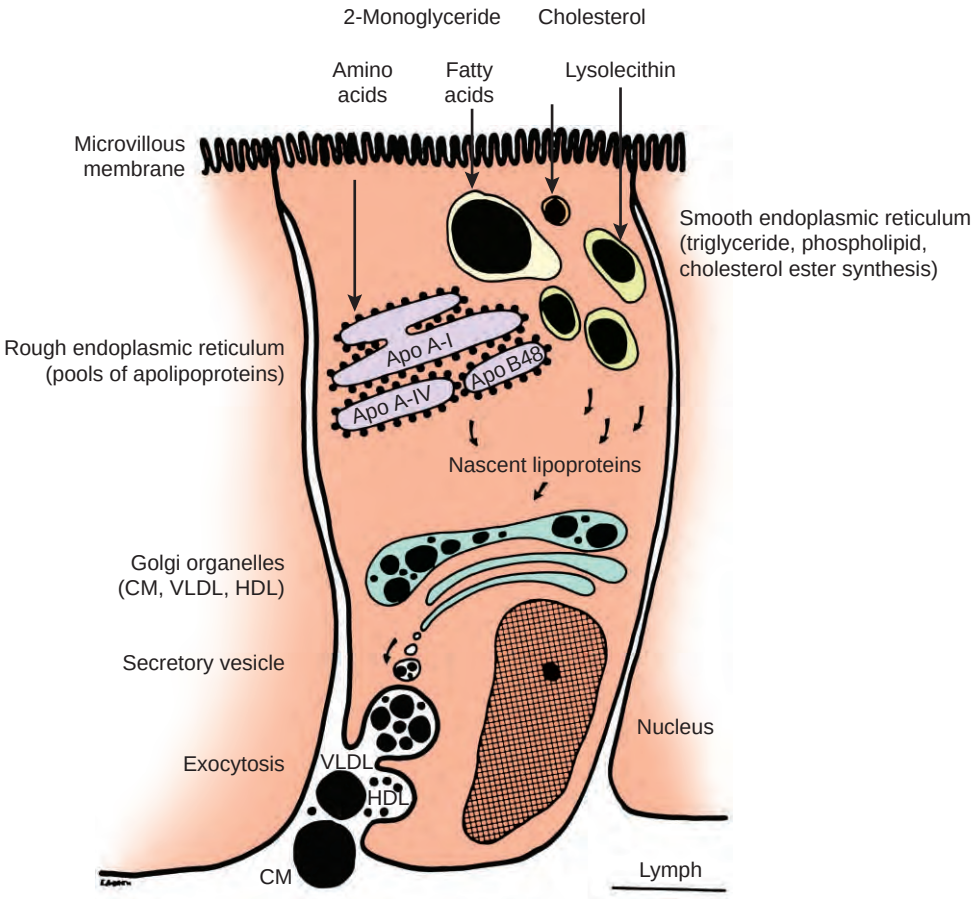

Figure 67–19. Enterocyte lipoprotein assembly. Lipid and amino acid products of digestion are absorbed from the intestinal lumen across the microvillous membrane, where they serve as substrates for the resynthesis of protein and lipid in the rough and smooth endoplasmic reticulum. Apolipoproteins are mobilized from the intracellular pool of protein to form nascent lipoproteins. Lipoproteins are progressively modified within Golgi organelles and secretory vesicles and then secreted into the intracellular space. Apo A-I, A-IV, and B_{48}, apolipoproteins A-I, A-IV, and B_{48}, respectively; CM, chylomicron; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein. (From Davidson NO, Magun AM, Glickman RM: Enterocyte lipid absorption and secretion. In Handbook of Physiology: The Gastrointestinal System. Bethesda, MD, American Physiological Society, 1991, p 516.)

Intestinal cholesterol absorption is dependent on luminal bile salts and follows steps similar to those for triglyceride absorption. Free cholesterol, derived from the hydrolysis of esterified cholesterol by pancreatic cholesterol esterase, is transported to the brush-border surface in micelles. After entering the cells by simple diffusion, cholesterol is re-esterified, mainly with oleic acid, and then incorporated into chylomicrons for subsequent lymphatic release. De novo cholesterol synthesis, particularly in the liver, increases when intestinal cholesterol absorption is reduced. Although cholesterol absorption is not significantly enhanced by increased intake of dietary cholesterol, certain dietary fats, such as saturated fats and short-chain fatty acids, may increase cholesterol absorption in the intestine.

Vitamins

Water-soluble vitamins were previously thought to be absorbed by simple passive diffusion; however, it is now clear that specific carrier-mediated mechanisms are involved. Additionally, some of these vitamins undergo hydrolysis before absorption because of attached conjugates or coenzymes.

Primates are incapable of synthesizing ascorbic acid (vitamin C) and thus require dietary supplementation.[75] In the small intestine, an active Na^+-dependent process transports vitamin C in the form of sodium ascorbate (Table 67–3).[80]

Folic (pteroylglutamic) acid is present in the diet in the form of polyglutamates and requires hydrolysis by a brush-border hydrolase (carboxypeptidase, see Table 67–3).[81] Ethanol inhibits the hydrolysis (but not uptake) of polyglutamates and may account for the folate deficiency seen in alcoholics.[82,83]

Vitamin B_{12} (cobalamin; see Table 67–3) is derived almost entirely from animal sources and has a multistep process for absorption. Vitamin B_{12} deficiency can therefore arise from multiple sources: loss of intrinsic factor (gastric resection), defective pancreatic proteolysis of cobalamin from R protein (pancreatic insufficiency or biliary obstruction), or loss of ileal receptors (distal ileal disease or resection).

Other water-soluble vitamins, such as thiamine, riboflavin, biotin, and pantothenic acid, also use specific Na^+-dependent active transport processes for their absorption.[74] After absorption into an enterocyte, thiamine exits through the basolateral membrane into the portal circulation. Ethanol decreases thiamine absorption by inhibiting this exit step, an effect that may account for thiamine deficiency in alcoholics.

Fat-soluble vitamins include vitamins A, D, E, and K, and they are primarily absorbed from the small intestine through passive diffusion, with absorption being dependent on their structure and hydrophobicity.[87] After they are absorbed, these vitamins enter the intestinal lymphatic system in chylomicrons and join the systemic venous circulation through the thoracic duct. Vitamin A

Table 67–3 Vitamins and Minerals

Nutrient	Receptor	Comment	References
Vitamins			
Ascorbic acid (vitamin C)		Na^+-dependent active absorption	79, 80
Folic acid (pteroylglutamic acid)		Hydrolysis by carboxypeptidase at the brush border (inhibited by ethanol)	81-83
		Hydrolysis is also inhibited in celiac sprue; subsequent uptake is carrier mediated and Na^+ dependent	
Cyanocobalamin (vitamin B_{12})	R protein Intrinsic factor	Bound to salivary binding protein (R protein) in the stomach until freed by hydrolysis in the duodenum Binds to intrinsic factor (secreted by the parietal cells of the stomach) to protect B_{12} from proteolytic digestion In the terminal ileum, specific brush-border receptors bind the cobalamin–intrinsic factor complex	83a, 83b
Thiamine	Na^+-dependent active transport	Exits through the basolateral membrane into the portal circulation (inhibited by ethanol)	74
Riboflavin	Na^+-dependent active transport		74
Biotin	Na^+-dependent active transport		74
Pantothenic acid	Na^+-dependent active transport		74
Vitamin A	Passive diffusion		87
Vitamin D	Passive diffusion		
Vitamin E	Passive diffusion		
Vitamin K	Passive diffusion		
Minerals			
Calcium	Passive paracellular process (throughout the small intestine)	Enhanced by vitamin D and luminal-associated increases in junctional permeability	
	Active, transcellular process (duodenum)	Occurs down its electrochemical gradient Binds to calbindin and transported out of the cell across the basolateral membrane by calcium-dependent ATPase Calbindin is up-regulated in villus enterocytes by vitamin D	84, 85
Magnesium	Passive diffusion, carrier-mediated process	Occurs primarily in the ileum	86
Iron	Non–transferrin receptor–mediated process	Modulated by the degree of transferrin receptor saturation	88, 89
Iron	Divalent cation transporter (DCT-1)		
Bile salts	Apical Na^+-dependent carrier transporter (ASBT)	Located on the luminal surface of ileal epithelial cells (ileal specific)	90, 91
	Liver Na taurocholate cotransporting polypeptide (NTCP)	Expressed on the basolateral membrane of hepatocytes	92

(retinol) is derived from dietary carotenoids, of which β-carotene is a principal form. β-Carotene undergoes hydrolysis by a brush-border oxygenase into two retinol molecules. Absorbed vitamin A is then released into the lymphatics in the form of retinyl palmitate. Two physiologically significant vitamin D sterols, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol), are converted from their precursor sterols by ultraviolet irradiation in skin. Vitamin E consists of several related tocopherols, of which the α-isomer is the most potent species. Dietary vitamin D and vitamin E are absorbed in the small intestine by simple diffusion and pass into the lymphatics largely unchanged. Vitamin K consists of two forms: plant-derived K_1 (phytomenadione) and colonic

bacteria-produced K_2 (prenyl menaquinones). Absorption of vitamin K_1 occurs through a carrier-mediated process in the small intestine and is facilitated by luminal bile salts[93]; vitamin K_2 is passively absorbed in the ileum and colon.[94]

Minerals

Several essential divalent cations, such as calcium, magnesium, phosphorus, and iron, must be absorbed by the intestine; only trace amounts of other minerals are needed, such as zinc, copper, and selenium.

Intestinal absorption of calcium is mediated by two processes: an active, transcellular transport process occurring predominantly in the duodenum and passive, paracellular diffusion throughout the small intestine (see Table 67–3).[95] Magnesium, unlike calcium, is absorbed predominantly in the ileum, and its absorption involves both passive diffusion and a carrier-mediated process.[96]

Iron is an essential constituent of myoglobin and hemoglobin because of its flexible redox potential. Because excessive amounts of iron are toxic, sophisticated mechanisms exist for transport regulation and detoxification. Circulating iron in serum is tightly bound by transferrin, an 80-kD glycoprotein that can bind two molecules of ferric iron.[88] Because of the abundance of serum transferrin, full saturation of transferrin is seen only in pathologic conditions such as hereditary hemochromatosis and transfusion-related iron overload. Diferric transferrins bind to the transferrin receptor, a specific cell membrane protein ubiquitously present on cellular membranes. The receptor-ligand complex, along with bound iron, is then internalized by receptor-mediated endocytosis, a process regulated by post-transcriptional modulation of transferrin receptor mRNA expression.[89] The bulk of iron absorption from the intestine, however, appears to involve a non–transferrin receptor–mediated mechanism, although it is modulated through an unknown mechanism by the degree of transferrin receptor saturation.

Although mammalian divalent cation export systems have previously been characterized for zinc and copper,[97,98] only recently has a mammalian uptake system been identified. Divalent cation transporter 1 (DCT-1), an H^+-coupled divalent cation and metal ion transporter, has recently been characterized as the major iron transport protein in the intestine.[99-101] DCT-1 is a 561–amino acid transmembrane protein expressed highly in the proximal part of the duodenum and has a broad substrate specificity for many divalent metal ions, including Fe^{2+}, Zn^{2+}, Mn^{2+}, Co^{2+}, Cd^{2+}, Cu^{2+}, Ni^{2+}, and Pb^{2+}. In the intestine, dietary ferric (Fe^{3+}) iron is reduced to ferrous (Fe^{2+}) iron by ferrireductase or ascorbic acid and transported by DCT-1 into enterocytes of the villus tip.[102] Similar to regulation of transferrin receptor expression, iron levels appear to modulate the expression of DCT-1 mRNA.

The hemochromatosis *(HFE)* gene, which encodes a novel major histocompatibility complex class I–like protein, has also been cloned recently.[103] HFE protein interacts with transferrin receptor with high affinity at the plasma membrane and modulates the binding of diferric transferrin to the transferrin receptor.[103] HFE is prominently expressed in the crypt cells of the duodenum, where most iron absorption occurs. HFE protein in the duodenal crypts is thought to modulate the uptake of transferrin-bound iron, where these cells may act as sensors of the level of body iron stores (Fig. 67–20). In patients with a defect in the *HFE* gene, transferrin receptor–mediated iron uptake into crypt cells appears to be inappropriately modulated by HFE such that a false signal is sent that serum iron stores are low. Consequently, expression of DCT-1 and intestinal iron absorption are subsequently up-regulated, thereby leading to iron overload in these patients.

Bile Salts

Bile is synthesized from cholesterol in the liver as two primary bile salts: cholate and chenodeoxycholate. They are secreted into the small intestine conjugated with taurine or glycine. Bile salts in the intestinal lumen mix with ingested lipids and form micelles, thus facilitating their digestion. Reabsorption of bile acids from the lumen involves both passive and active reuptake, with active reabsorption in the ileum accounting for most of the total enterohepatic circulation. Absorbed bile salts return to the liver through the portal circulation and are resecreted into bile, thus completing the cycle of enterohepatic circulation. Active uptake of bile acids is mediated by an Na^+-dependent carrier transporter (apical Na^+-dependent bile acid transporter [ASBT]) located on the luminal surface of ileal epithelial cells.[90,91] A related, but distinct bile salt transporter (liver Na^+-taurocholate cotransporting polypeptide [NTCP]) is expressed on the basolateral membrane of hepatocytes.[92] Substrate (bile salt) specificity for ASBT is much narrower than that for NTCP, which suggests that in the lumen of the ileum, efficient recovery of bile acids accompanies elimination of non–bile acid metabolites and xenobiotics, whereas the multispecific transporter in the liver facilitates hepatic clearance of organic anion metabolites.[90] ASBT expression is ileal specific; this transporter is not induced in more proximal gut segments after resection.

Secretion

Intestinal fluid secretion is thought to derive primarily from cells lining the crypts and is dependent on the secondary active transcellular transport of Cl^-. This process facilitates the mixing of luminal nutrients for enhanced absorption and may be important in mucosal defense by diluting or "flushing" harmful toxins and organisms away from the epithelial surface. The driving force for epithelial secretion comes from Na^+,K^+-ATPase, which establishes a low intracellular Na^+ concentration (Fig. 67–21). Na^+ then enters the cell along this gradient coupled to the movement of K^+ and Cl^- through a basolateral Na^+-K^+-$2Cl^-$ cotransporter (NKCC1). Intracellular Cl^- is then extruded across the apical membrane through Cl^- channels, including the cystic fibrosis conductance regulator (CFTR). Na^+ and possibly water

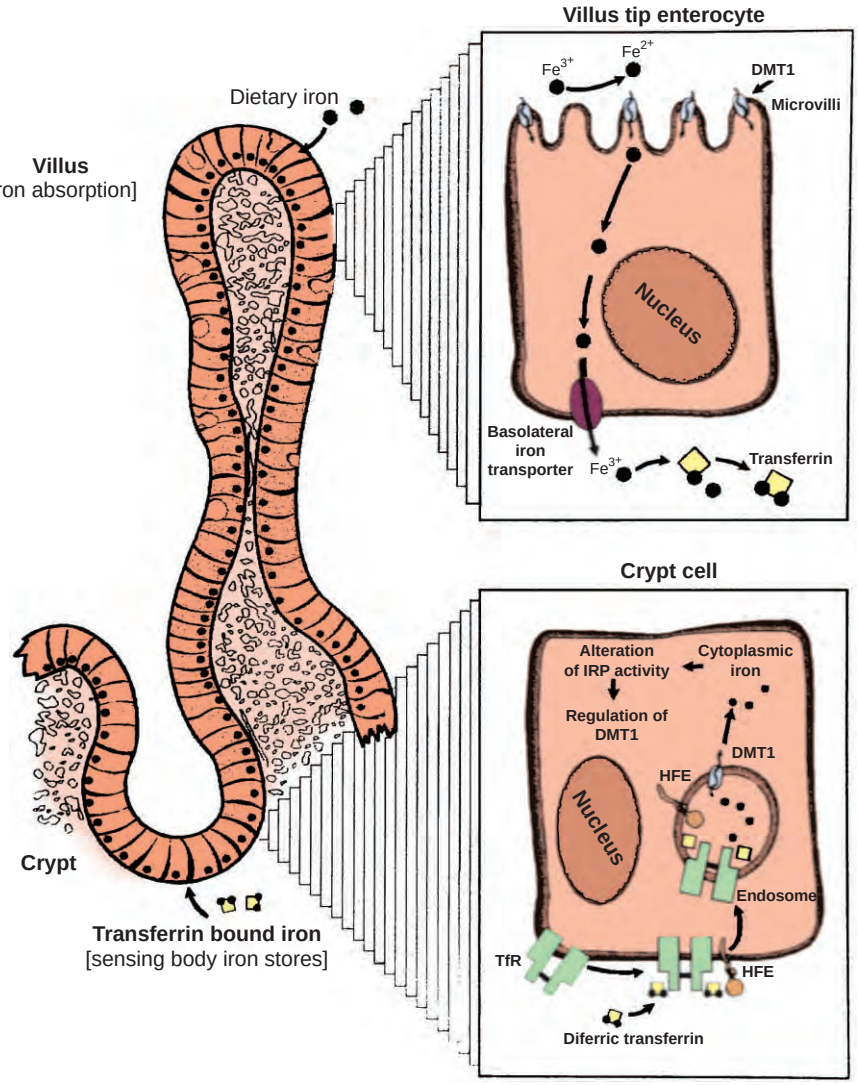

Figure 67–20. Hypothesis of the regulation of iron absorption by the hemochromatosis gene *(HFE).* An intestinal villus is shown with *insert* enlargements of an enterocyte on the villus tip (where iron is absorbed from the intestine) and a deep crypt cell (where the body iron stores are sensed by means of transferrin-mediated and HFE-modulated iron transport). Ferric iron is reduced in the intestine to ferrous iron and absorbed through the divalent metal transporter (DMT-1, also known as DCT-1) into the enterocyte on the villus tip. In the enterocyte, iron is oxidized to ferric iron and transported through an unidentified basolateral iron transporter into the circulation. In the deep crypt, HFE bound to the transferrin receptor (TfR) modulates the uptake of diferric transferrin. The level of cytoplasmic iron then acts through the binding of iron regulatory proteins (IRPs) to iron response elements (IREs) on the production of DMT-1 transporter mRNA. Mutations in *HFE* cause lack of cell surface expression of HFE, dysregulation of TfR-mediated iron uptake, and consequent alterations in DMT-1 production. (From Bacon BR, Powell LW, Adams PC, et al: Molecular medicine and hemochromatosis: At the crossroads. Gastroenterology 116:197, 1999.)

(see earlier) follow passively through the paracellular space into the lumen.

At least three major signal transduction pathways activate Cl^- secretion, including cyclic nucleotides (cyclic adenosine monophosphate [cAMP] and cyclic guanosine monophosphate [cGMP]), as well as intracellular calcium.[104] Vasoactive intestinal peptide (VIP), adenosine, prostaglandins, and certain bacterial enterotoxins elevate intracellular cyclic nucleotides, which leads to protein kinase A–dependent CFTR phosphorylation and subsequently to an increase in apical membrane permeability to Cl^-. Secretory responses depend on the extent of the increase in cAMP and the duration of the stimulus. Calcium-dependent agonists such as histamine and acetylcholine, on the other hand, activate Cl^- secretion primarily through the opening of Ca^{2+}-activated K^+ channels in the basolateral membrane. Ca^{2+}-mediated secretory responses, in contrast to that activated by cyclic nucleotides, are transient in duration despite the continued presence of agonist and sustained elevation of intracellular Ca^{2+}.[104-106] Cyclic nucleotides and Ca^{2+} regulatory pathways are synergistic for secretion.[107,108] Overall secretory capacity may be largely determined by the activity of basolateral NKCC1, which may be affected at the level of gene transcription by multiple proinflammatory and anti-inflammatory factors.[109]

INTESTINAL IMMUNE SYSTEM

The human intestinal tract is the single largest organ of the immune system. The immune apparatus in the intestine has a dual role of modulating both local and systemic immune responses. Locally, the lymphoid tissue in the intestine plays an important role in defense against various toxic and pathogenic agents from the intestinal lumen. Both the epithelial cells per se and the various lymphoid cells in the lamina propria participate in the delicate balancing of mucosal defense with potential overstimulation of the immune system by the considerable foreign antigen load presented to the intestine daily.

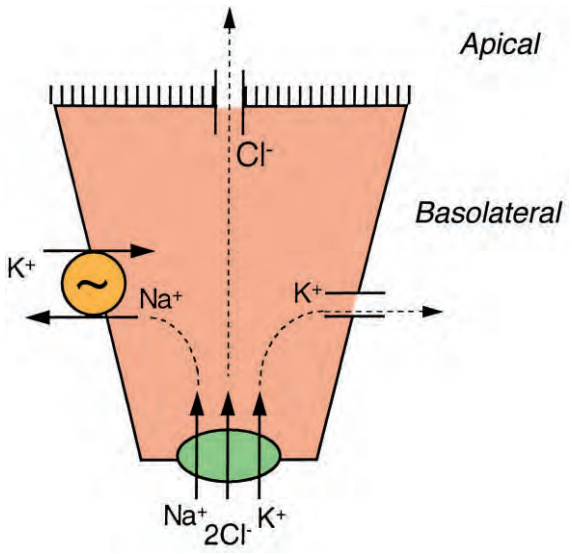

Figure 67–21. Chloride secretion. Na^+,K^+-ATPase generates the driving force for epithelial Cl^- secretion by establishing a low intracellular Na^+ concentration. The Cl^- entry step through the basolateral membrane Na^+-K^+-$2Cl^-$ (NKCC1) cotransporter involves the movement of sodium, potassium, and chloride in a 1:1:2 stoichiometry. Accumulated Cl^- above its electrochemical equilibrium exits the cell across the apical membrane through a Cl^- channel. Recycling of intracellular Na^+ and K^+ is facilitated by the sodium pump and a basolateral potassium channel, respectively.

Secretory Immunoglobulin A and Epithelial Immune Function

Immunoglobulins are synthesized and secreted by B lymphocytes. In the gut, immunoglobulin A (IgA) and IgM play a protective role of neutralizing luminal antigens. IgG antibodies in intestinal secretions are derived mainly from the serum, fix complement, and play an important role in inflammatory reactions and tissue injury. IgE appears to mediate the inflammatory response to antigens that penetrate the intestinal mucosa, as seen in bacterial invasion of the intestinal tract. The most abundant immunoglobulin secreted in the intestine is IgA, with IgM being secreted to a lesser extent. Their secretion into the lumen involves binding to the polymeric immunoglobulin receptor present on the basolateral membrane of the epithelial cells (Fig. 67–22). IgA interaction with microbial antigens prevents them from penetrating the epithelial layer. Although not lymphoid cells per se, intestinal epithelial cells (IECs) clearly participate to some degree in the immune function of the gut. These cells express major histocompatibility class I and II molecules on their surface, possess antigen-presenting activity for T cells,[110] produce cytokines to regulate the proliferation of mononuclear cells in the lamina propria,[111] and express functional receptors for several T-cell–derived cytokines and chemokines.[112] Thus, the epithelial cell layer may transmit important immune regulatory information to the underlying lymphocytes.

M Cells and Gut-Associated Lymphoid Tissue

The major route of passage of luminal antigens to resident lymphoid follicles occurs by means of specialized cells overlying Peyer's patches called *M cells*.[113] These cells rapidly internalize foreign antigens by the endosomal pathway through specialized apical membrane invaginations (Fig. 67–23). Lymphocytes and macrophages in these compartments then process the antigens from the delivered luminal substance. Antigen can also be taken up directly across the enterocytes by either transcellular or paracellular pathways. When the information from these antigen-processing cells reaches the underlying follicle, antigen-specific B-cell proliferation and subsequent IgA production occur. Antigen-specific B cells migrate from Peyer's patches to regional lymph nodes into the systemic circulation, from which they migrate back to the intestine to populate the mucosa diffusely within the lamina propria (Fig. 67–24). In Peyer's patches, B cells are segregated in the germinal centers from the T cells occupying the interfollicular area. Intraepithelial lymphocytes (IELs), however, are predominantly T lymphocytes. They are specialized T cells found in the paracellular space between absorptive enterocytes and are thought to mediate crosstalk between epithelial cells and the underlying immune cells of the lamina propria. Lamina propria lymphoid tissue contains numerous immune cell types, including plasma cells, mast cells, lymphocytes, and macrophages. These cells produce cytokines, chemokines, and immunoglobulins. In addition to these local actions, IgA-producing lymphocytes of Peyer's patches migrate to regional lymph nodes and into the systemic circulation.

Regulation of Gut Immune Activity

A remarkable feature of the mucosal immune system is its overall "hypoactive" or immunosuppressed tone. Despite the enormous antigenic load that passes through the gastrointestinal tract each day, spontaneous inflammatory responses are rare except in pathologic conditions such as inflammatory bowel diseases. This is partly explained by the production of secretory IgA, which unlike other immunoglobulins, does not participate in the proinflammatory response, fix complement, or serve as opsonizing antibody. Additionally, IELs appear to contribute to the overall tone of immunosuppression. Most IELs express the γδ-receptor instead of the αβ-receptor expressed in the more abundant T cells found in most peripheral lymphoid sites. Activation of the immune system by IECs that are capable of presenting antigen and triggering the immune response is also attenuated. The level of uptake and processing of antigens by IECs is quite low[114] because of the absence or minimal expression of appropriate processing enzymes (cathepsins) in the endosomal compartments. Even when the enzymes are present within normal epithelial cells, they are there in reduced amounts.[115] Thus, these cells may have only a limited ability to process intact protein antigens and elicit potent immune responses.

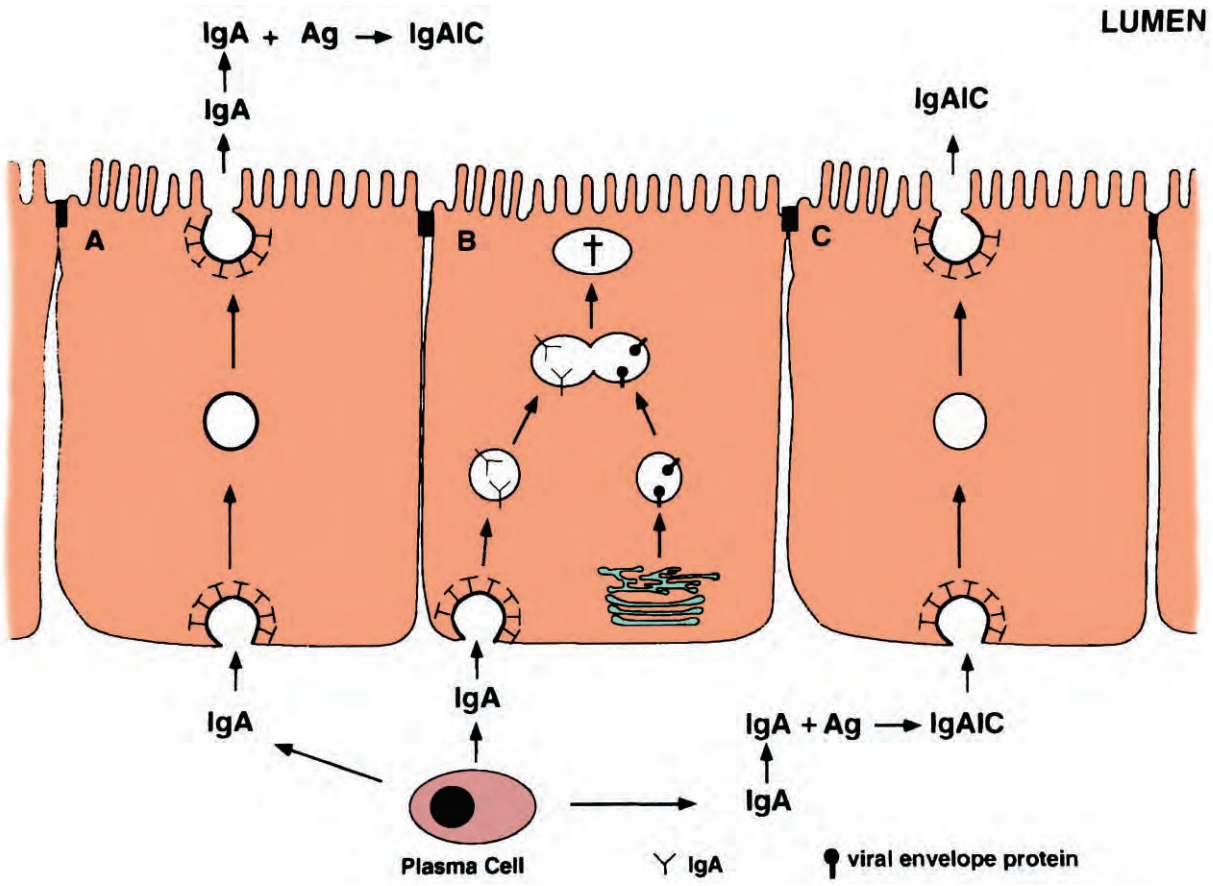

Figure 67–22. Compartments where immunoglobulin A (IgA) can potentially function in relation to mucosal epithelium. The lumen is above the layer of epithelial cells, which are interconnected by apical tight junctions. The lamina propria is below. Plasma cells (not drawn to scale) in the lamina propria secrete polymeric IgA. *Cell A* shows that polymeric IgA can be endocytosed at the basolateral surface (by pIgR), transcytosed, and secreted into the lumen, where it can combine with antigen (Ag) to form immune complexes (IgAIC). In *cell B,* which has been infected by a virus, it is suggested that a transcytotic vesicle containing IgA antibody to viral envelope protein can fuse with a post-Golgi vesicle containing newly synthesized envelope protein, which provides an opportunity for the antibody to disrupt the production of new virus. In the lamina propria below *cell C,* IgA antibody combines with antigen. The immune complex is endocytosed (by pIgR) and transported intact across the cell and into the lumen. (From Lamm ME: Current concepts in mucosal immunity. IV. How epithelial transport of IgA antibodies relates to host defense. Am J Physiol 274:G615, 1998.)

Immune Regulation of Gut Function

Intestinal epithelial function is also influenced by the gut immune system. Evidence for immune regulation of gastrointestinal water and electrolyte transport has recently accumulated. Mast cells play an important role in gut immune effector function and are distributed throughout the intestine but are most abundant in the small intestine. Mast cells secrete various mediators and cytokines upon degranulation after stimulation (e.g., IgE-mediated type I hypersensitivity reaction). Some of these mediators are preformed and stored in vesicles (e.g., histamine); others are newly synthesized as needed (e.g., prostaglandins, leukotrienes, interleukins). In the intestine, these mediators can affect smooth muscle function, vascular permeability, and the epithelial transport of electrolytes, water, acid, and mucin. Histamine activates H_1 receptors on the intestinal epithelial cell surface and stimulates chloride secretion. Histamine also synergistically enhances secretory responses to cAMP-dependent secretagogues such as adenosine, also a mast cell product. Important roles of mast cells in gut function are demonstrated by experimental manipulations of knockout animals. In genetically mast cell–deficient (W/W^v) mice, the intestinal secretory response associated with anaphylaxis is diminished.[116] They also exhibit reduced colonic mucin secretion from goblet cells and prostaglandin E_2 release in response to stress.[117] In addition, histamine-mediated intestinal epithelial chloride secretion plays an important role in parasitic nematode infections, in which mast cell hyperplasia is a predominant feature.

Immune regulation of intestinal epithelial water and electrolyte transport is manifested by the increased

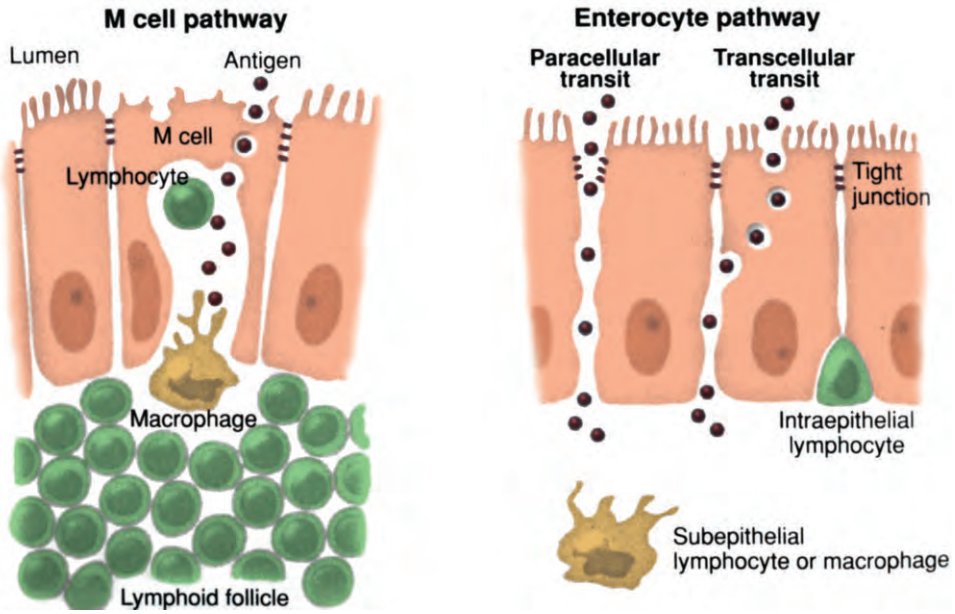

Figure 67–23. Paths across the lining of the gut. Antigen can enter the body from the gut through rare M cells *(left)* specialized to deliver antigen directly to underlying immune cells or through the more common enterocytes *(right),* the epithelial cells that line the gut. (From Madara JL: The chameleon within: Improving antigen delivery. Science 277:910, 1997.)

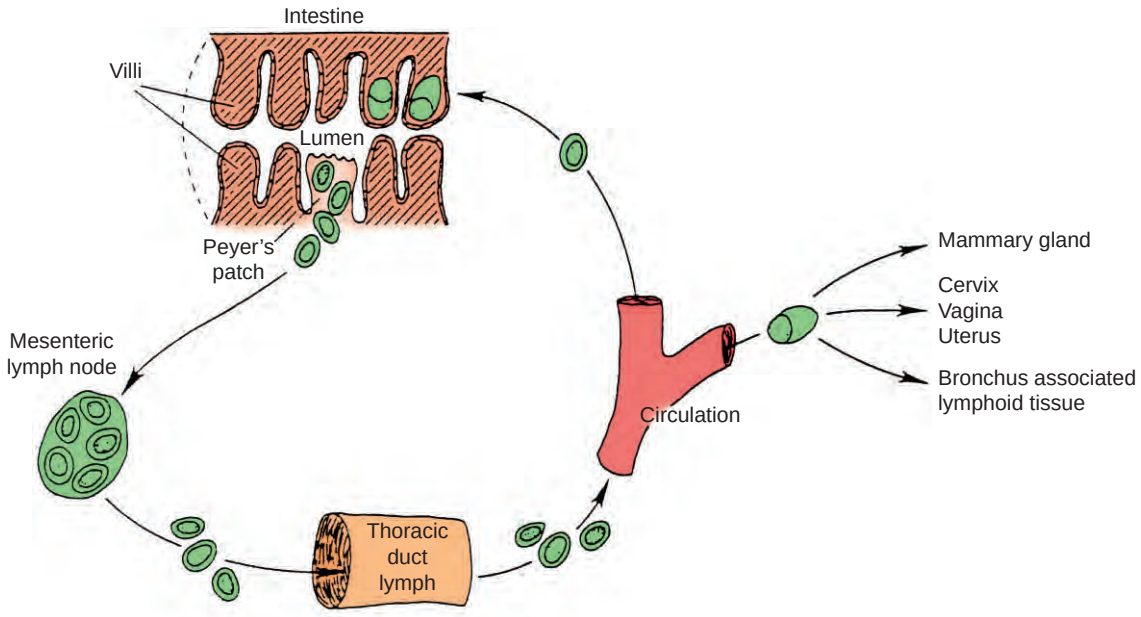

Figure 67–24. Migration of lymphoid cells from Peyer's patches. Lymphocytes travel from the mesenteric lymph nodes through the thoracic duct to the systemic circulation. These cells can disseminate to the lamina propria of the intestine or to extraintestinal sites, such as the mammary gland, female genital tract, and bronchus-associated lymphoid tissue. (From Kagnoff MF: Immunology of the digestive system. In Johnson LR [ed]: Physiology of the Gastrointestinal Tract. New York, Raven Press, 1981, p 1344.)

gastrointestinal fluid secretion and diarrhea seen in patients with food allergies, inflammatory bowel diseases, and various enteric infections.

MOTILITY OF SMALL INTESTINE

The primary goal of the small intestine, digestion, is facilitated by the contractile movements of the smooth muscle layers, which provide antegrade propulsion of the luminal contents combined with mixing action through segmentation. Organized periodic motor activity is present in the absence of luminal nutrients. Regulation of these motor activities in the intestine is complex and involves an autonomous intrinsic neural network that not only senses and responds to local mechanical and chemical signals but also communicates with central neurons in the spinal cord and brain.

Intestinal Smooth Muscle Cells

Smooth muscle cells form the outer longitudinal and inner circular muscle layers of the intestinal wall and the muscularis mucosae layer. Smooth muscle cells of the intestine derive their contractile force from the interaction between actin and myosin filaments. The actin content relative to myosin is much higher in smooth muscle cells than in skeletal muscle. Additionally, smooth muscle can maintain contractile tension at a lower rate of ATP hydrolysis. Smooth muscle cells of the small intestine display spontaneous electrical depolarizations and are able to propagate this signal to neighboring smooth muscle cells through gap junctions, thus resulting in a coordinated muscle contraction as a syncytium. The dominant intestinal pacemaker that initiates cyclic electrical impulses and contractions is localized in the proximal portion of the duodenum. Recently, the interstitial cell of Cajal (ICC) has been identified as the cell type responsible for the generation of pacemaker currents.[118,119] ICCs and smooth muscle cells originate from common mesenchymal precursor cells.[120-122] ICCs are found within the circular muscle layer of the intestinal wall and are interconnected by long processes containing gap junctions (Fig. 67–25).

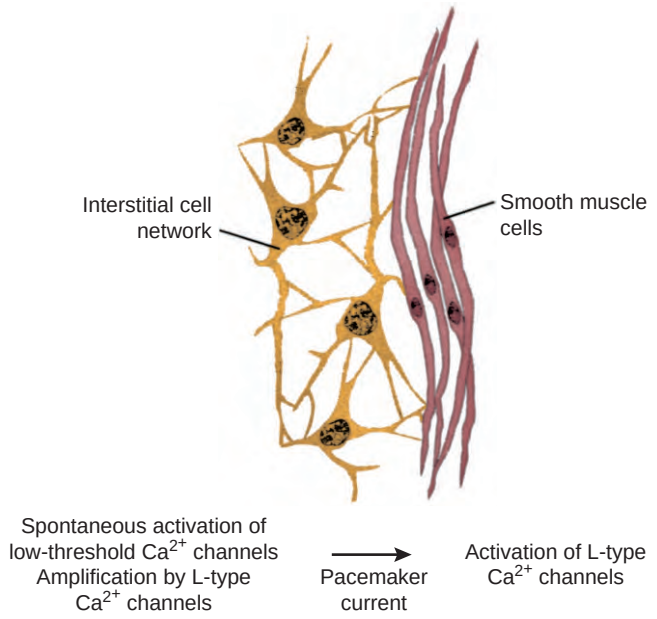

Figure 67–25. Model for initiation of pacemaker activity. Pacemaker activity appears to originate in the interstitial cell of Cajal. Spontaneous activation of low-threshold Ca^{2+} channels occurs near the resting potentials of these cells. As depolarization proceeds, L-type Ca^{2+} channels are also activated and amplify the current. The pacemaker current spreads to smooth muscle cells that are coupled through occasional gap junctions. In smooth muscle cells, L-type Ca^{2+} channels are activated, thus coupling the electrical activity to contraction. (From Sanders KM: A case for interstitial cells of Cajal as pacemakers and mediators of neurotransmission in the gastrointestinal tract. Gastroenterology 111:503, 1996.)

Patterns of Contractions

The small bowel accomplishes the absorption of ingested nutrients by using specific spatial and temporal patterns of contractile activity or motility. The contractions mix and propel ingested food at a rate that facilitates digestion; keep the intestinal tract clear of debris, secretions, and bacteria between meals; and in special situations, propel the intestinal contents rapidly over great distances. The contractile activity of the small intestine is under a variety of control mechanisms, including myogenic, neural, and chemical control.

Myogenic Control

Myogenic control refers to the electrical activity generated by the smooth muscle of the gut. Electrical control activity (ECA; slow waves, basic electrical rhythm, pacesetter potential)[123-126] is the omnipresent rhythmic depolarization of the cell membranes of the smooth muscle of the small intestine. This electrical activity may be recorded with either intracellular or extracellular electrodes. In humans, periodic depolarizations in membrane potential occur 11 to 13 times per minute in the proximal part of the small intestine and decrease to 8 to 10 times per minute in the ileum. With neural or chemical stimulation, membrane depolarization exceeds an excitation threshold and a contraction results. The electrical correlate of a contraction is called *electrical response activity* (ERA; spike burst, action potentials).[123-126] These ERA bursts have a 1:1 relationship with contractions. Because ERA occurs only during the depolarization phase of the ECA cycle, the frequency of contractions is limited to and determined by the frequency of ECA. Neural and chemical stimulation may not be present during each depolarization of ECA, and thus contractions then do not occur at the maximum possible frequency.

The spatial coordination of contractions along the small intestine is coordinated by ECA. Adjoining cells interact, and when electrical coupling is greater, ECA is phase locked such that oscillation of ECA between cells will occur with a fixed time lag. Cells with higher intrinsic frequency drive those with lower intrinsic frequency.

ECA frequency decreases as one progresses from the duodenum to the terminal ileum. There appears to be a *pacemaker region* in the proximal duodenum, similar to the pacemaker region of the stomach, that has an intrinsic ECA frequency that drives or paces the distal part of the small intestine.[127] In the duodenum and proximal jejunum, the electrical coupling is so strong that all the cells oscillate at the same frequency.[124,128] In the more distal portion of the small intestine, the electrical coupling between cells is not strong enough to entrain surrounding cells, and these cells have greater intrinsic frequency variation than do cells of the duodenum. Because individual contractions of the distal variable-frequency region[124,128] are not as coordinated and do not propagate over great distances in the proximal part of the gut, the transit time in the distal portion of the small intestine is longer than that of the proximal portion.[129]

Although both spatial and temporal patterns of contractile activity are ultimately under myogenic control, whether a contraction will occur at any given site depends on local neurochemical stimulation.

Neural Control

Small intestinal smooth muscle contractile activity is influenced by both extrinsic autonomic (parasympathetic and sympathetic) neural activity from the CNS and the intrinsic neurons of the enteric nervous system.

Extrinsic Neural Control The small intestine derives its parasympathetic innervation through the vagus nerve. The vagus nerve contains both afferent and efferent fibers. Efferent motor fibers arise from the dorsal motor nucleus in the region of the fourth ventricle. Relative to the intrinsic enteric neurons, the efferent potion of the vagus is really quite small; however, each vagal efferent fiber may influence about 2000 enteric neurons.[130,131]

In contrast, the sensory component of the vagus nerve is much greater. Sensory fibers account for 80% of all vagal fibers[132] and have their cell bodies primarily in the nodose ganglia. Vagal afferents detect both mechanical and chemical stimulation of the small intestine and relay this information centrally for processing.

Sympathetic innervation of the small intestine arises from the thoracic and lumbar spinal nerves (generally T5 through L3). These nerves pass through the paravertebral ganglia and form the splanchnic nerves, which go to the prevertebral ganglia—the celiac, superior mesenteric, and inferior mesenteric. Within these ganglia, cell bodies receive synaptic input from interganglionic mesenteric neurons. These ganglia intercommunicate and relay sensory information from the gut to the CNS, thereby allowing interactions between different areas of the gut. Stimulation of vagus fibers produces contractile activity within the upper part of the small intestine.[130,131] Electrical stimulation of the mesenteric sympathetic nerves releases norepinephrine and other neuroregulatory substances that inhibit small intestinal contractions.[133]

The enteric nervous system, or the "little brain" of the gut,[134] consists of an intricately coordinated network composed of all neurons having their cell bodies within the bowel wall. Though less well studied than the CNS, the enteric nervous system is quite complicated in that it contains nearly as many neurons as the CNS does.[135]

The enteric nervous system is made up of interconnected neural plexuses and ganglia, which contain the nerve cell bodies. The subserous plexus lies between the serosal and the external muscle of the small intestine. The longitudinal muscle plexus is made of fine nerve bundles that run parallel to the muscle cells and provide innervation to the longitudinal muscle. The myenteric (Auerbach's) plexus is located between the longitudinal and circular muscle layers. The myenteric plexus integrates sensory, extrinsic, and enteric neural information. As in the longitudinal muscle layer, the circular muscle layer has a plexus running parallel to the muscle fibers. This layer communicates with both the myenteric and the deep muscular plexus.[135,136] The deep muscular plexus is located in the inner aspect of the circular muscle layer and separates a thin layer of muscle cells from the bulk of the circular muscle. The fibers of this plexus originate with the myenteric ganglia. The submucosal (Meissner's) plexus also contains ganglia. The muscularis mucosae is a fine layer of smooth muscle just deep to the mucosa that contains a plexus of delicate nerve fibers. Finally, the mucosal plexus intertwines amid the lamina propria of the intestinal crypts and villi.

The majority of neurons controlling contractile activity in the small intestine have their cell bodies in the myenteric plexus.[137,138] Two classes of postsynaptic neurons innervate small intestinal smooth muscles: cholinergic excitatory and nonadrenergic noncholinergic (NANC) inhibitory neurons. Acetylcholine is the excitatory neurotransmitter, but NANC inhibitory neurotransmission is accomplished by nitric oxide,[139-144] ATP, and VIP.[145-148]

The enteric nervous system interfaces directly with the intestinal smooth muscle and provides moment-to-moment control of contractile activity. Neural isolation from the CNS has only a minor effect on the orderly propulsion of chyme within the small intestine.[149] Intrinsic neural pathways may extend 100 to 150 cm proximal and distal to any given point in the small intestine.[1501]

The *peristaltic* or *myenteric reflex* is a classic enteroenteric reflex. Bayliss and Starling[151] described excitation orad and relaxation aborad to the site of mechanical stimulation or chemostimulation. This reflex implies that chyme is propelled in an aborad direction. Although the precise significance of this reflex in normal postprandial contractile activity is uncertain, it reflects the coordinated neurocircuitry within the enteric nervous system.[152] Descending inhibition and ascending excitation are not seen with individual phasic contractions. However, in special situation such as giant migrating contractions (GMCs), both ascending and descending inhibition can be demonstrated.[153] It may be that the greater strength and duration of this special-situation contraction are needed to elicit the peristaltic reflex.

Chemical Control

Chemical control involves the stimulation or inhibition of smooth muscle contractile activity by humoral substances[124] that may act through either a neurocrine, paracrine, or endocrine mode. Examples of these regulatory substances include serotonin, histamine, opioids, cholecystokinin (CCK), motilin, somatostatin, VIP, and substance P. These and many other putative neuroregulatory substances administered exogenously can modulate contractile activity within the small intestine.

There is an intimate relationship between the immune system of the gut and the enteric nervous system that may extend to the motor activity of the small intestine. The best-recognized immune modulator is histamine, which is found within the mast cells of the gut. When mast cells degranulate in response to antigenic stimulation, the enteric nervous system is activated and specific patterns of contractile activity may be initiated.[154-157] Although the precise mechanism by which inflammatory cells and inflammatory mediators affect

Box 67–1 Types of Contractions in the Small Intestine

Individual phasic contractions
Organized groups of contractions
  Migrating motor complexes
  Migrating clustered contractions
Special propulsive contractions
  Retrograde giant contractions
  Giant migrating contractions

small intestinal motility is unknown, it is clear that an interaction exists.

Organization of Contractile Activity

Contractions of the small intestine may be divided into individual phasic contractions, organized groups of contractions, and special propulsive contractions (Box 67–1). The specific characteristics of these contractions or groups of contractions and how they relate to the previously described control mechanisms are explored in the following sections.

Individual Phasic Contractions

Individual phasic contractions are the basic contractile activity of the small intestine. They occur in both the fasted and the fed state. In the proximal portion of the small intestine, contractions occur more regularly and propagate caudally over a variable distance that tends to be greater than what occurs in the distal portion of the small intestine. Contractions in the distal part of the small intestine are much less coordinated, and consequently, the rate of propulsion in the distal part of the small bowel is less than that in the proximal part.

Oscillations of ECA directly determine the maximum frequency and duration of individual phasic contractions. When neurochemical stimulation is superimposed, a contraction occurs. Phasic contractile activity does occur without recordable ECA from extracellular electrodes. In this unique situation after drug administration and during some enteric infections, ECA gradually decreases in amplitude and becomes progressively unstable in the distal portion of the small intestine.[155,158] Rapidly migrating contractions may then occur without the tethering influence of ECA. These contractions are similar in amplitude and duration to individual phasic contractions, but they migrate at a velocity as great as 30 cm/sec over distances of up to 200 cm within the proximal part of the small intestine; these rapidly migrating contractions do not occur in the distal portion. Under these conditions, the absence of ECA has been called *amyogenesia*. This electrical and contractile pattern can be disrupted by an event such as feeding, and a special-situation contraction called a *GMC* frequently occurs.

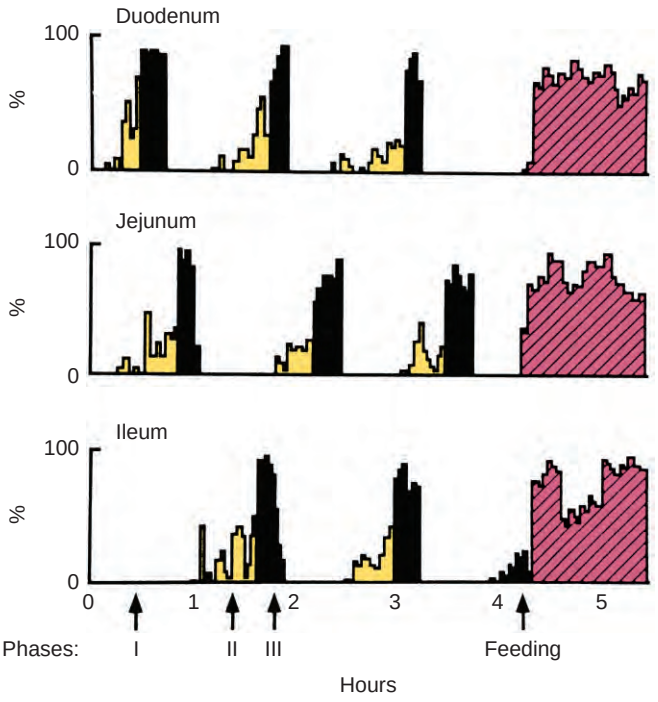

Figure 67–26. The migrating motor complex. *Bars* are used to show the level of intensity in phases II *(open bars)* and III *(solid bars).* The periodicity of activity in fasting *(left)* is interrupted by feeding, when activity rises to a more constant level *(hatched bars).* (From Christensen J: Motility of the intestine. In Sleisenger MH, Fordtran JS [eds]: Gastrointestinal Disease: Pathophysiology, Diagnosis, Management, 5th ed. Philadelphia, WB Saunders, 1993, p 829.)

Organized Groups of Contractions

Migrating Motor Complex The migrating motor complex (MMC) is a cyclic pattern of phasic contractile activity that occurs in the interdigestive state. The MMC originates in the proximal portion of the small intestine and migrates to the distal ileum, with cycling every 90 to 120 minutes (Fig. 67–26).[125,159] The MMC cycle is divided into four distinct phases. Phase I is an interval of contractile quiescence; phase II consists of intermittent contractions that eventuate into phase III, which consists of regular phasic contractions of large amplitude that occur at maximum frequency for approximately 6 to 8 minutes. Phase IV of the MMC consists of a short transition of intermittent contractions. In humans, the MMC occurs only during the fasted state (Fig. 67–27). Its purported function is to cleanse the small intestine of residual food, desquamated cells, and enteric secretions and keep bacterial growth to a minimum.[161] Many people refer to phase III of the MMC as "the MMC."

These patterns of small intestinal motor activity develop as the fetus matures.[161,162] Early in gestation, motor activity is irregular and disorganized, but as the fetus develops, the MMC pattern appears.[162] This maturation may occur postnatally in preterm infants.[161] MMCs are preserved in the small intestine throughout the process of aging.[163]

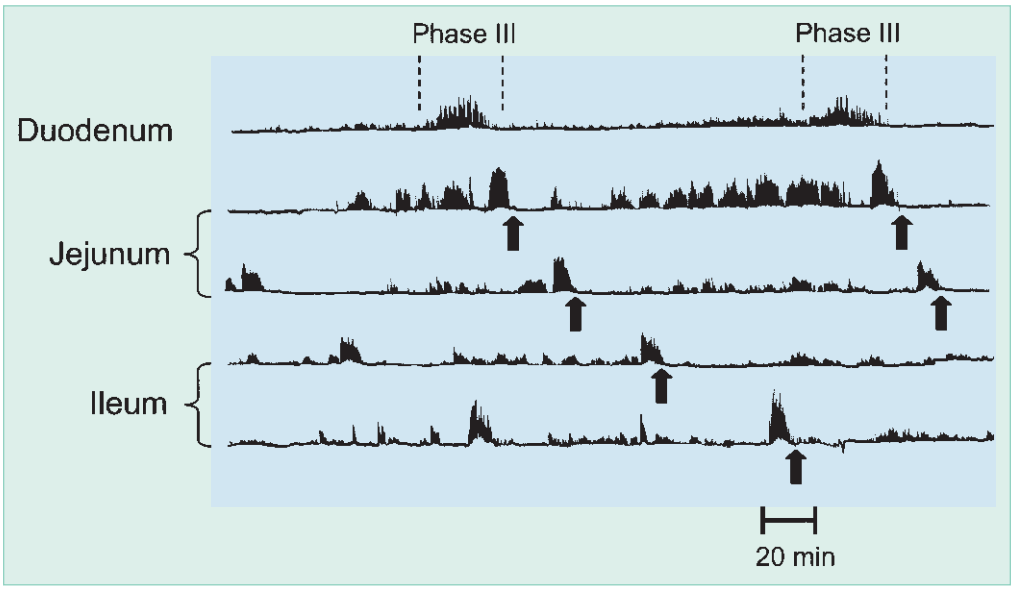

Figure 67–27. Migrating motor complex (MMC). The MMC migrates along the length of the small intestine from the duodenum to the terminal ileum. During the most intense period of contractile activity (phase III), contractions are occurring at their maximum frequency.

The MMC is not under direct CNS control. Truncal vagotomy,[126,164,165] superior and inferior mesenteric ganglionectomy,[166] sympathectomy,[135,167] and even total extrinsic denervation[149] do not abolish MMC cycling. It is likely, however, that the CNS modulates the MMC cycle, particularly during periods of stress.[168,169] Cyclic alterations of circulating regulatory peptides, in particular, motilin, appear to have an influence on the MMC.[170-172] When exogenous motilin is administered, a premature MMC cycle is initiated.[173] During spontaneous cycling of the MMC, plasma motilin concentrations are in their nadir during phase I, increase during phase II, and peak a few minutes after phase II in the duodenum.[174,175] Phase I of the MMC may be produced by ascending inhibition caused by the distally migrating phase III activity. This ascending inhibition may compete with other factors that stimulate contractile activity.

Overall control of the MMC appears to reside in periodic activation of the enteric nervous system, which initiates the cyclic contractile activity we recognized as the MMC. If a segment of the small intestine is isolated as in a loop of small intestine, MMCs cycle above and below as well as within the loop independent of one another.[176,177] Simple transection of the small intestine will disrupt normal migration of the MMC along its flanks.

Migrating Clustered Contractions Migrating or discrete clustered contractions last 1 to 3 minutes, and aborad migration over distances of 10 to 30 cm have been documented to occur.[178-181] Because they do not occur as regularly and predictably as MMCs, the mechanisms of initiation of propagation of the contractions have been less well studied. These migrating clustered contractions are highly effective at propulsion.[182] They usually occur during phase II of the MMC.

Special Propulsive Contractions

The small intestine usually propels chyme slowly in the aborad direction. In special situations, it is advantageous to the organism to expel ingested material rapidly. The small intestine is capable of generating special propulsive contractions to achieve rapid movement of chyme. If aborad propulsion is necessary, retrograde giant contractions (RGCs) occur. These small intestinal contractions immediately precede vomiting. When rapid aborad evacuation of the small bowel is necessary, GMCs rapidly propel chyme into the colon.

Retrograde Giant Contractions An RGC is a large-amplitude, long-duration contraction that originates in the midportion of the small bowel and rapidly propels the intestinal contents in the stomach for subsequent expulsion. It is one of the gastrointestinal motor correlates of vomiting. An RGC travels at a rapid velocity of 8 to 10 cm/sec.[183] By contrast, the MMC migrates at 2 to 8 cm/min.[125,159] RGCs have been extensively studied in the canine model.[183] RGCs also occur in primates but have not yet been documented in the human gastrointestinal tract. The powerful and rapid nature of this contraction may preclude recording with the manometric or solid-state methods currently used in human studies.

RGCs precede spontaneous or drug-induced emetic episodes but may also occur without subsequent vomiting.[183] This appears to be a dose-dependent response. For example, with low doses of an emetic agent, an RGC is initiated; higher doses generate an RGC followed by vomitus expulsion.

An RCG is associated with a series of unique electrical and contractile changes in the small intestine. The first to occur is the obliteration or disorganization of ECA.[183] This change inhibits normal phasic contractions of the

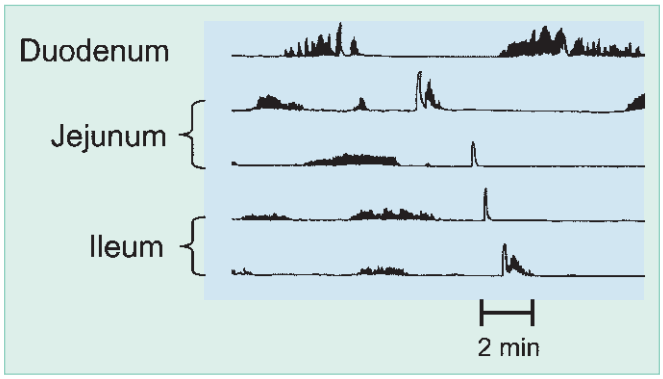

Figure 67–28. Giant migrating contraction. This giant migrating contraction begins in the proximal part of the small intestine and rapidly propels intestinal contents into the colon. In healthy humans, these contractions occur very infrequently and are limited to the distal end of the small intestine. In disease states, they may originate more proximally and are associated with the sensation of abdominal cramping.

small intestine, thus enhancing the propulsive efficiency of the subsequent RGC. An RGC then occurs and may or may not be followed by the somatomotor response of vomitus expulsion. The myoelectric correlate of an RCG is a large potential change, sometimes with a superimposed brief ERA burst.[183] RCGs are followed by a group of phasic contractions throughout the small intestine that last longer distally than proximally.[183] These contractions may propel distal intestinal contents into the colon just as the RGC propels proximal enteric contents into the stomach. Although an RGC itself is not controlled by ECA, the post-RGC phasic contractions are under myogenic control.

Spontaneous RGCs or those initiated by apomorphine or mucosal irritants are abolished by vagotomy.[183] Postvagotomy studies suggest that an RGC requires vagal involvement, but the actual mechanism for the initiation or propagation of an RGC exists within the intestinal wall, and they may be activated by high doses of the hormone CCK-8.[184] Atropine blocks the occurrence of RGCs, which suggests that the final neurotransmitter involved in the contraction is acetylcholine. Interestingly, atropine does not disrupt the ECA slowing and post-RGC phasic contractions, thus suggesting that other neurochemical transmitters may be involved.

Giant Migrating Contractions GMCs, also called *prolonged propagated contractions* (Fig. 67–28), are large-amplitude, long-duration contractions that propagate rapidly in an aborad direction. Their amplitude is approximately 1.5 times that of the phasic contractions of the MMC.[180,185] Once initiated, these contractions usually propagate uninterruptedly to the ileocolonic junction. GMCs are even more propulsive than the MMC.[182] In the normal, healthy state, these contractions occur intermittently in the distal part of the small intestine and are never seen postprandially. In pathologic states or after the administration of certain drugs, GMCs are more frequent and originate more proximally in the small intestine.[153,155,157,185-187] In patients with irritable bowel syndrome, GMCs are associated with the sensation of abdominal cramping.[188] These powerful contractions may generate abdominal pain because they stimulate nociceptive receptors within the bowel wall above their threshold level and hence produce discomfort. Another theory is that effective propulsion of intestinal chyme by GMCs distends the distal intestinal wall and thereby produces pain.

A function of small intestinal GMCs may be to return fecal contents refluxed from the ileum into the colon.[186] In pathologic states, frequent GMCs may contribute to diarrhea by propelling bile and intestinal secretions rapidly through the gastrointestinal tract without allowing sufficient time for reabsorption.[155,187] Postprandial GMCs that propel undigested food into the colon would contribute to diarrhea[187]; partially digested food exposed to bacterial degradation in the colon would result in gas production and increase the colonic osmotic load.

The myoelectric correlate of the GMC is a brief burst of ERA at the beginning of the contraction. Sometimes the GMC has phasic contractions superimposed on the down-stroke of the contraction. When this occurs, the electrical recording is followed by one or two ERA bursts during the down-stroke.[185] The velocity of GMCs is not bound by the normal constraints of ECA. These contractions require the enteric nervous system for propagation and for generation of the descending inhibition associated with them. Interestingly, ascending inhibition associated with GMCs requires neural input extrinsic to the bowel wall.[153]

The small intestine produces a large number of different contractions in various spatial and temporal patterns that promote efficient digestion, absorption, and propulsion of ingested material. The small intestine also serves a protective role through the use of special-situation contractions that rapidly propel enteric contents into the stomach or colon, from which they may be expelled. Contractile activity of the small intestine is coordinated by the interplay of myogenic, neural, and chemical control.

INTESTINAL NEUROENDOCRINE FUNCTION

The small intestine is a major source of peptides that regulate various aspects of gut function and influence events in the body as a whole. Since the discovery of secretin by Bayliss and Starling in 1902,[189] an increasing number of regulatory peptides have been identified from the gut. These substances are released by local, luminal, or neural stimuli and elicit biologic actions by binding to membrane receptor proteins. Some of the peptides act locally in a paracrine fashion, whereas others work at distant sites in an endocrine fashion as circulating hormones. Many of the receptors for these peptides belong to the superfamily of G protein–coupled receptors. Examples include receptors for secretin, VIP, and pituitary adenylate cyclase activating peptide (PACAP).[190] Some

Box 67–2 Human Gastrointestinal Peptides

Gastrin-Cholecystokinin Family

- Gastrin
- Cholecystokinin (CCK)

Secretin-Glucagon-VIP Family

- Secretin
- Glucagon
- Gastric inhibitory peptide (GIP)
- Vasoactive intestinal peptide (VIP)
- Glucagon-like peptide 1 (GLP1)
- Glucagon-like peptide 2 (GLP2)
- Pituitary adenylate cyclase activating peptide (PACAP)

Tachykinin-Bombesin Family

- Substance P (SP)
- Gastrin-releasing peptide (GRP)

Insulin Family

- Insulin
- Insulin-like growth factor 1

Somatostatin Family

- Somatostatin

Other Peptides

- Motilin
- Neurotensin

representative gastrointestinal peptides are categorized in Box 67–2.

Secretin and Related Peptides

Secretin is a 27–amino acid peptide released from the enteroendocrine cells of duodenal mucosa in response to luminal acid, bile salts, and fat. Its main function is to facilitate digestion by stimulating pancreatic and biliary bicarbonate and water secretion and, to a certain extent, pancreatic exocrine enzyme secretion.[191] At high concentrations, secretin inhibits gastrin release, gastric acid secretion, and postprandial gastric emptying and stimulates secretion of bicarbonate and epidermal growth factor from Brunner's glands.[192,193] Intravenous infusion of secretin stimulates rather than inhibits gastrin release in patients with Zollinger-Ellison syndrome and forms the basis of the diagnostic test for this condition.[194]

VIP is one of the major inhibitory neurotransmitters in the gut and induces relaxation of smooth muscle. Its receptor, a G protein–coupled receptor, elevates intracellular cAMP by means of adenylate cyclase. It is localized, along with PACAP, to the nerve terminals in humans[195] and is released as a neurotransmitter to act on smooth muscle cells to regenerate nitric oxide.[196] It relaxes many sphincter muscles, including the sphincter of Oddi, and mediates relaxation of the peristaltic reflex.[197] VIP also stimulates intestinal epithelial chloride secretion, as well as pancreatic bicarbonate, water, and enzyme secretion.[198-200] More recently, VIP has been shown to affect normal and neoplastic cell growth. It stimulates the growth of astrocytes and certain non–small cell lung cancer cells and inhibits the growth of colonic adenocarcinoma cell lines, probably by virtue of elevated intracellular cAMP.[201]

PACAP was isolated from bovine hypothalamus[202] and shares 68% sequence homology with VIP. PACAP activates both exocrine and endocrine pancreatic secretion in mammals.[203,204] More recently, PACAP activation of pancreatic fluid, bicarbonate, and protein secretion in rats was shown to involve release of secretin and CCK independent of cholinergic stimulation.[205]

Other members of the secretin family, including glucagon, gastric inhibitory polypeptide (GIP), glucagon-like peptide 1 (GLP1), and enteroglucagon, share substantial sequence homology and bind similar G protein–coupled receptors.[206-208] GIP is a 43–amino acid polypeptide released primarily from enterochromaffin cells of the jejunum when stimulated postprandially by carbohydrates and fat, and it subsequently elevates the serum insulin level. Enteroglucagon is primarily released in the distal portion of the small intestine on stimulation by carbohydrate and LCFA and inhibits intestinal motility. GLP1 may be the major hormonal factor responsible for gut adaptation and glucose homeostasis.[209]

Cholecystokinin

CCK is a 33–amino acid polypeptide released by specialized small intestinal mucosal cells in response to luminal amino acids and medium-chain to long-chain fatty acids, and its release is inhibited by intraluminal trypsin and bile salts.[210] The C-terminal tetrapeptides of CCK and gastrin are identical and possess the activity of both hormones. CCK enhances emptying of the gallbladder and bile flow by stimulating simultaneous contraction of the gallbladder and relaxation of the sphincter of Oddi, thus facilitating digestion by luminal mixing of bile with ingested food.[211] Additionally, CCK stimulates pancreatic enzyme secretion, intestinal mucosal cell growth, insulin release, and gut motility. The prostimulatory effect of CCK on gallbladder contraction is clinically used as a provocative test in patients with suspected acalculous biliary disease.[212,213]

Somatostatin

Somatostatin is a cyclic peptide consisting of 14 amino acids[214] and is released in various tissues, including the

brain and gut. In the gastrointestinal tract and pancreas, somatostatin, released by specialized enteroendocrine and nerve cells, acts locally in an autocrine, paracrine, or neuronal regulatory manner to perform a wide variety of inhibitory functions.[215,216] It inhibits neurotransmission, smooth muscle contraction, intestinal and pancreaticobiliary secretion, the function of activated immune cells, and cell growth.[215-218] Synthetic analogues of somatostatin, such as octreotide, are used clinically in patients with enterocutaneous and pancreatic fistulas, as well as various hormone-secreting tumors.[218]

Motilin

Motilin, a peptide containing 22 amino acid residues, is released in the small intestine, primarily in the jejunum. Its major actions include local enhancement of smooth muscle contraction and acceleration of gastric emptying.[212] Its prokinetic activity is used clinically in the form of macrolide antibiotics such as erythromycin, a motilin receptor agonist. Erythromycin improves not only emptying of the stomach and gallbladder but also colonic motility.[219-221]

Guanylin and Uroguanylin

Guanylin and uroguanylin, peptides secreted in the intestine, are endogenous ligands for guanylate cyclase, the membrane receptor for the cGMP signaling pathway. Guanylin contains 15 amino acid residues, whereas bioactive uroguanylin exists as 13-, 14-, and 15-residue peptides.[222,223] Both guanylins are highly expressed in the small and large intestines as inactive propeptides that require enzymatic digestion to yield active peptides.[224,225] Heat-stable enterotoxin (Sta) from *Escherichia coli* causes traveler's diarrhea by means of the cGMP signaling pathway by binding the same guanylate cyclase receptor on the intestinal luminal surface.[222,226] Activation of guanylate cyclase by these ligands leads to stimulation of transepithelial secretion of Cl^- and HCO_3^- through the intracellular accumulation of cGMP and thereby results in enhanced fluid secretion and modulation of intraluminal pH.[222,227,228] In particular, uroguanylin, highly expressed in the proximal duodenum, appears to play an important role in neutralizing luminal acid by enhanced anion secretion at low pH.[227]

Other Peptides

Peptide YY is a 36–amino acid polypeptide released in the distal part of the small intestine. Its functions in the gastrointestinal tract are most inhibitory: it inhibits gastric acid secretion and decreases intestinal motility, pancreatic secretion, and release of various intestinal hormones.[229,230] Neurotensin is released from the ileum and enteric nerves and is thought to affect various gastrointestinal functions, such as gastric acid secretion, gastric emptying, and intestinal motility and secretion. Some of the peptides are released from enteric nerves and function primarily as neurotransmitters; such peptides include galanin, bombesin, neuropeptide Y, and substance P, among many others.[231,232] Although efforts to understand their precise physiologic roles are ongoing, these substances appear to influence multiple aspects of gut physiology, such as motility, local blood flow, and epithelial and exocrine secretion.

SUMMARY

The small intestine provides the largest interface with the outside world, provides immune integrity, allows the absorption of most nutrients required by our bodies, and functions largely independently of our perception. Our understanding of the complex mechanisms that allow these functions to occur is expanding.

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Chapter

68

Small Bowel Obstruction

Soo Y. Kim · Jon B. Morris

Small bowel obstruction (SBO) is one of the most common admitting diagnoses in surgery, and yet these patients may be the most difficult to manage. They account for 12% to 16% of surgical admissions for acute abdominal complaints. Manifestations of SBO can range from a fairly good appearance with only slight abdominal discomfort and distention to a state of hypovolemic or septic shock (or both) requiring an emergency operation. The process of determining appropriate management can at times be extremely difficult. Despite our advances in the technology of diagnostic procedures, the decision to treat operatively or nonoperatively is still dependent on the surgeon's clinical experience and acumen. There has been some improvement in patient outcome over the years, however, with mortality from SBO declining from 50% in 1900 to less than 3% today. This reduced mortality may be due to multiple factors, including improved imaging techniques that prompt earlier operative intervention versus appropriate conservative management, as well as more advanced methods of resuscitation and intensive care in more severe cases.

CLASSIFICATION

Obstruction can be classified according to its mechanism. For instance, *mechanical* obstruction is the inability of contents to pass through an area because of physical blockage. It can be further divided into extrinsic or extraluminal (e.g., adhesions), intrinsic or mural (e.g., duodenal hematoma), and intraluminal (e.g., gallstone or intussusception) causes. Neoplastic processes may cause any of these mechanical obstructions by way of extrinsic compression of carcinomatosis, mural compression as a result of lymphoma or smooth muscle tumor, or mucosal tumor (Table 68–1).

In contrast, *functional* obstruction is caused by dysmotility of bowel without a physical obstacle to luminal flow. Neurogenic disturbances may contribute to this dysfunction of normal gut motility and peristalsis. Examples include ileus and pseudo-obstruction (Ogilvie's syndrome).

Obstruction can also be categorized as *partial* or *complete*. Partial obstruction may allow gas or liquid stool, or both, to pass the point of narrowing, whereas complete obstruction would not allow the passage of any substance at all. Similarly, obstruction may be labeled *low grade* or *high grade* to indicate the severity of obstruction as interpreted from radiology studies. This category is not to be confused with the designation *high* and *low* obstruction, which is used to stratify the location of pathology within the small bowel, that is, proximal versus distal.

MOTILITY

In the fasted state, migrating myoelectric complexes start in the duodenum and progress to the distal ileum. They occur every 90 to 150 minutes and normally last 90 minutes during their course through the small intestine.

In the case of early obstruction, these propulsive forces work aggressively to pass through the point of blockage and subsequently increase as intraluminal pressure increases. They subside and then recur episodically, alternating with quiescent periods. When the site of obstruction is high, or proximal, the duration of quiescence is shorter. In contrast, when the site is low, or distal, the duration is much longer. Bowel proximal to the site of obstruction becomes increasingly distended, and the distal bowel becomes increasingly inhibited.

In the case of partial obstruction, some intraluminal contents are able to pass through, whereas with complete obstruction, retrograde propulsion develops after bowel contents have accumulated.

PATHOPHYSIOLOGY OF OBSTRUCTION AND STRANGULATION

The clinical course of SBO is variable, depending on the site and severity of the obstruction, and it is even unpredictable. However, a common entity is volume depletion or *third spacing*. One method of fluid loss is net secretion into the lumen of the bowel. The small bowel secretes

Table 68–1 Classification of Small Bowel Obstruction

Extrinsic	Intrinsic	Intraluminal
Adhesions	Tumors of the bowel wall	Intussusception
Hernias	Carcinoid	Gallstones
External	Lymphoma	Bezoars
Inguinal	Leiomyosarcoma	Foreign body
Femoral	Inflammation	Mucosal tumors
Incisional	Crohn's disease	
Obturator	Tuberculosis	
Internal	Hematoma	
Paraduodenal	Endometriosis	
Epiploic foramen		
Diaphragmatic		
Transmesenteric		
Tumors		
Peritoneal metastasis		
Desmoid		
Abscess		
Diverticulitis		
Pelvic inflammatory disease		
Crohn's disease		

8.5 L of fluid daily, most of which is reabsorbed in the small intestine. The net flux of fluid in cases of SBO, however, results in fluid secretion into the lumen. The process is believed to be due to prostaglandin release as a response to bowel distention. It may be manifested in varying degrees of severity, from symptoms of thirst and dry mucous membranes to systemic consequences of renal failure and shock.[1]

Another route of fluid loss is into the wall of the bowel secondary to venous congestion and edema. This loss then results in ascites as the serosal layer of the bowel wall secretes fluid into the peritoneal cavity. The degree of wall edema corresponds to the duration of the obstruction process. In addition, bowel obstruction causes nausea and vomiting, which further contributes to the volume-depleted state of patients with SBO. Furthermore, if a nasogastric tube is placed to suction drainage, copious amounts of fluid, as well as electrolytes, may be lost via this route, and aggressive intravenous replacement may be required.

Early in the obstructive state, a patient is found to have isotonic volume depletion secondary to vomiting or nasogastric tube decompression, as well as third spacing of fluid. As the obstruction persists, hypokalemia occurs as a result of emesis, as well as hyperaldosteronism, which is a response to hypovolemia. In addition, bicarbonate is lost as it is expelled within pancreatic and enteric fluid.[2]

As more air and fluid accumulate within the obstructed bowel, the normal absorptive capabilities of the gut deteriorate and the distention is further exacerbated. In addition, bacterial colonization increases with protracted stasis of the bowel. As a result, more gas is produced by the bacteria, thereby worsening the luminal distention.[3] The risk for bacteremia, peritonitis, and subsequent bacterial translocation is also increased as more bacteria accumulate. If the obstruction is unresolved and the bowel lumen continues to enlarge, vascular compromise becomes more likely. As a result, strangulation occurs, with the later development of necrosis and, ultimately, perforation.[4] Examples include volvulus and mesenteric torsion, which may progress to strangulation, ischemia, and infarction. In these cases, fluid accumulation occurs as well as derangement of bowel motility. In addition, venous obstruction caused by strangulation results in bloody ascites and release of toxins from the bowel wall. Subsequently, toxic metabolic effects may lead to septic conditions and, ultimately, even circulatory collapse.

Closed-Loop Obstruction

Closed-loop obstruction is caused by obstruction of both the afferent and efferent limbs of the involved loop of bowel (Fig. 68–1). Such patients may not have the usual distended abdomen on physical examination because only a limited loop of bowel is usually affected and therefore dilated. Progression to strangulation may occur much sooner than with other forms of obstruction because of an inability to decompress proximally or distally, with subsequent vascular compromise. Causes of closed-loop SBO include mesenteric torsion, adhesive bands, and internal as well as abdominal and inguinal hernias. In the colon, any obstructing lesion may

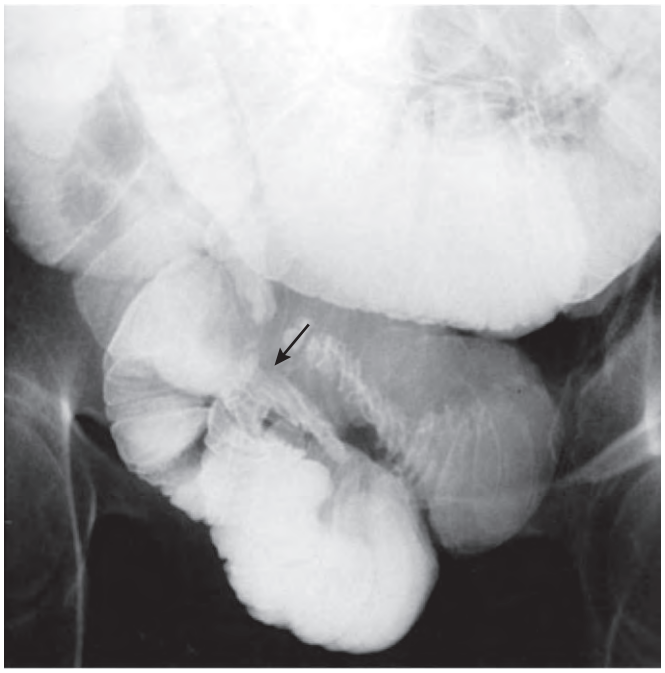

Figure 68–1. Enteroclysis film showing closed-loop obstruction. Apposition of the entering and exiting limbs at the point of constriction is caused by an adhesive band *(arrow).*

cause a closed-loop phenomenon if the ileocecal valve is competent.

ETIOLOGY

The most common cause of SBO is peritoneal adhesions postoperatively, which constitutes about 75% of all cases of SBO.[5] Pelvic or lower abdominal procedures are blamed for adhesion formation more commonly than upper abdominal procedures are, although any abdominal operation can be responsible.

Hernias, particularly inguinal hernias, are considered the next most common cause of SBO (25%).[4] However, femoral hernias are thought to be more likely to cause incarceration and, possibly, strangulation. Internal hernias can also occur, such as obturator and paraduodenal hernias, as well as hernias through the foramen of Winslow.

Inflammatory processes may likewise cause obstruction by way of secondary angulation of bowel, such as diverticulitis and appendicitis. The remaining causes include Crohn's disease, ischemia, radiation, intussusception, volvulus, and mass lesions such as neoplasms, gallstones, and bezoars.[1]

Adhesions account for the majority of early postoperative obstructions that develop after violation of the peritoneum, reportedly occurring in up to 92% of patients requiring surgical treatment.[6] They result in an inflammatory cascade involving the activation of complement and coagulation. Fibrinogen is produced during this response and is converted to fibrin by thrombin. If fibrin persists, it adheres to injured surfaces and initiates the formation of a matrix of collagen and fibroblasts, thereby forming *fibrous* adhesions from *fibrinous* adhesions. Fibrin degradation should then occur and allow the fibrinous adhesions to disintegrate and mesothelial regeneration to occur. An abdominal operation causing peritoneal injury dramatically inhibits this process of fibrin degradation by increasing levels of plasminogen activator inhibitors[7] and decreasing levels of tissue plasminogen activator.[8] Thereafter, adhesions are permitted to form and can be potential causes of bowel obstruction.

Another cause of postoperative SBO is internal herniation through defects created at the time of surgery. This category includes mesenteric or omental defects that occur after partial bowel resection. In addition, peritoneal defects that arise around a colostomy or enterostomy, as well as those that occur in the pelvic floor after abdominoperineal resection, can be sites of obstruction. In general, large defects do not seem to pose as much a threat as small defects do.[9] Therefore, controversy still exists regarding whether to close or leave mesenteric defects open after bowel resection or peritoneal defects after abdominoperineal resection.

Inflammatory processes can also cause bowel obstruction early in the postoperative period. Examples are abscesses after bowel surgery, which may form adhesions to nearby loops of bowel and thereby cause partial obstruction. Because of the time frame in which this situation may occur, differentiation between actual obstruction and postoperative ileus may be difficult.

Other consequences of bowel surgery include intramural bleeding with hematoma formation and intussusception. Postoperative anticoagulation can result in hemorrhage within the bowel wall or in the mesentery. Intussusception may occur with or without a lead point, particularly in pediatric patients. A well-described cause in this patient population is an inverted appendicular stump after appendectomy.[10] Another cause in adults is obstruction after retrocolic gastrojejunostomy for gastric bypass without concomitant gastrectomy when the jejunal limb intussuscepts into the gastric lumen.[11]

RISK FOR SMALL BOWEL OBSTRUCTION AFTER LAPAROSCOPY

With the advent of more and more laparoscopic procedures, surgeons are gaining increasing knowledge and experience with associated complications, as well as benefits. Less adhesion formation is one potential benefit of laparoscopy over laparotomy.

Theoretical advantages ensue from less abdominal wall injury as a result of smaller incisions, less use of foreign body materials (talc, gauze, lint from drapes), less tissue desiccation, and less tissue trauma and hemorrhage. However, because of the lack of uniform classification of adhesions in clinical and experimental studies, only suggestions rather than conclusions can be made.

Recent studies have compared adhesion formation after laparoscopy and laparotomy at various sites. With

regard to adhesion formation at the operative site, more studies favored laparoscopy over laparotomy. As for adhesions at the incision site, studies consistently supported laparoscopy as causing less adhesion formation. Finally, there are few data assessing the adhesive effects of laparoscopy versus laparotomy at distant sites, such as within abdominal viscera or interenteric surfaces. Experimental studies, however, again favor laparoscopy over laparotomy.[12]

CLINICAL FINDINGS

The most common symptoms of SBO are nausea, vomiting, crampy abdominal pain, distention, and obstipation. Mechanical obstruction usually causes pain before the onset of nausea and emesis, whereas nonmechanical obstruction causes earlier emesis, perhaps followed by subsequent pain. In addition, the site of obstruction may be discernible by the pattern and type of symptoms. Proximal obstruction tends to cause early and more frequent nausea and vomiting, whereas distal obstruction causes crampy pain and obstipation with delayed nausea and vomiting.

Early in the process, the vomitus will represent partially digested food and light-colored liquid. However, later in the process, the vomitus becomes bilious and even feculent. As the luminal contents persist and conglomeration of intestinal bacteria takes place, the emesis becomes malodorous and more consistent with feces.

Abdominal distention develops as the bowel loops proximal to the site of obstruction accumulate gas and fluid. This is less likely in very proximal obstructions, such as those in the duodenum, and occurs more frequently in midgut obstructions. Because up to 10 L can be secreted and reabsorbed by the small intestine in normal situations, the bowel may become quite distended in the setting of obstruction in which routine absorption is hampered (Table 68–2).

Symptoms of obstipation may not be apparent initially because residual gas and stool in the bowel distal to the obstruction may continue to evacuate. In partial obstruction, patients may continue to pass flatus and feces, in conjunction with the other symptoms. However, in complete obstruction, nothing is able to traverse the problem area.

Symptoms of postoperative ileus are often confused with those of bowel obstruction, particularly after abdominal surgery. Extended hospital stay and associated complications, including nosocomial infections, arise as a result. Therefore, many clinicians have investigated various methods of preventing or diminishing the extent of postoperative ileus. One technique that has been published by various centers is gum chewing as an adjunct to postoperative care in which gastrointestinal motility is stimulated via *sham feeding*. This technique has been studied after laparoscopic colon surgery in the hope of further decreasing hospital stay in these patients. Interestingly, when patients were randomly assigned to gum chewing, earlier passage of flatus and feces than in the control group was reported by some authors.[13]

PHYSICAL EXAMINATION

Symptoms may range from minimal discomfort with few physical abnormalities to toxicity and sepsis. Patients may show signs and degrees of dehydration from poor skin turgor and dry mucous membranes to tachycardia, hypotension, oliguria, and mental status changes.

Abdominal examination may reveal distention of varying severity. Auscultation may reveal rushing or tinkling high-pitched bowel sounds or absent bowel sounds in more advanced stages.[14] The abdomen may be tympanitic to percussion if bowel loops are filled with gas, but it may be dull if filled with fluid. Palpation may elicit tenderness if strangulation is present or impending. Signs of guarding and peritonitis would also indicate strangulation and perhaps ischemia or perforation, and they are usually sufficient evidence for exploration. In addition, as part of the abdominal examination, previous surgical scars should be noted because they can be used to predict the location and degree of adhesions likely to be encountered at the time of exploration. When examining a patient with SBO, abdominal and inguinal hernias should always be sought as possible causes of the condition.

Table 68–2 Clinical Findings in Small Bowel Obstruction

Features	Proximal/High Obstruction	Distal/Low Obstruction
Onset of symptoms	Sudden	Gradual
Pain	Epigastric, intense, colicky, usually relieved by vomiting	Periumbilical, colicky
Vomiting	Early, bilious, voluminous, frequent	Later, infrequent, feculent
Tenderness	Epigastric or periumbilical, usually mild unless strangulated	Diffuse and progressive
Distention	Absent	Diffuse and progressive
Obstipation	Absent or mild	Mild or moderate
Radiologic findings	Distended proximal small bowel loops or gasless	Diffusely distended small bowel loops, air-fluid levels

Rectal examination should always be performed in these patients to search for rectal masses that could be obstructing. The finding of hematochezia is a possible indication of a more proximal mass, inflammation, or strangulation and infarction of bowel. Fecal impaction is not an uncommon finding in older patients and often mimics bowel obstruction. As an extension of the rectal examination, proctoscopy and sigmoidoscopy are helpful in the diagnosis and treatment of distal colonic volvulus.

LABORATORY TESTS

Patients with early or partial SBO who are initially seen soon after symptoms have started may have completely normal laboratory studies. However, evidence of dehydration may be evident in the form of abnormal electrolytes and elevated blood urea nitrogen, creatinine, and hematocrit levels. Hyponatremia and hypokalemia are also common abnormalities. Metabolic acidosis occurs as a result dehydration, starvation, ketosis, and loss of alkaline fluid by way of secretion. In the setting of severe vomiting, metabolic alkalosis can occasionally be seen secondary to vomiting of acidic juices.

Mild elevation in the white blood cell count can occur in patients with bowel obstruction, but severe leukocytosis and the presence of many immature polymorphonuclear cells suggest strangulation with possible ischemia. In the case of ischemia, hyperkalemia, lactic acidosis, and elevated amylase levels may be present. It is important, however, to keep in mind that bowel ischemia may be present despite normal laboratory studies and that clinical suspicion should prompt expeditious surgical intervention.

RADIOLOGIC INVESTIGATIONS

Plain Radiographs

Although the diagnosis of SBO may be made with only a thorough history and careful physical examination, diagnostic imaging is often used to verify, locate, and assess the severity. Plain radiographs in the form of an obstruction series, otherwise known as an abdominal series, are usually the initial study obtained in a patient with abdominal symptoms. Studies include an upright chest radiograph, a supine abdominal or kidney-ureter-bladder (KUB) film, and a left lateral decubitus abdominal radiograph. The goal of these films is to rule out free intra-abdominal air, delineate the severity of bowel distention, and possibly identify the location of obstruction.

Plain films are diagnostic in only 50% to 60% of cases of SBO and are only 66% sensitive in proven cases of SBO by experienced radiologists.[15] In addition, specificity has been reported to be low because both mechanical and functional large bowel obstructions may show similar findings on plain radiographs. Nevertheless, they remain a vital initial radiographic tool because of their low cost, availability, noninvasiveness, and value as a gauge of disease progression (Fig. 68–2).

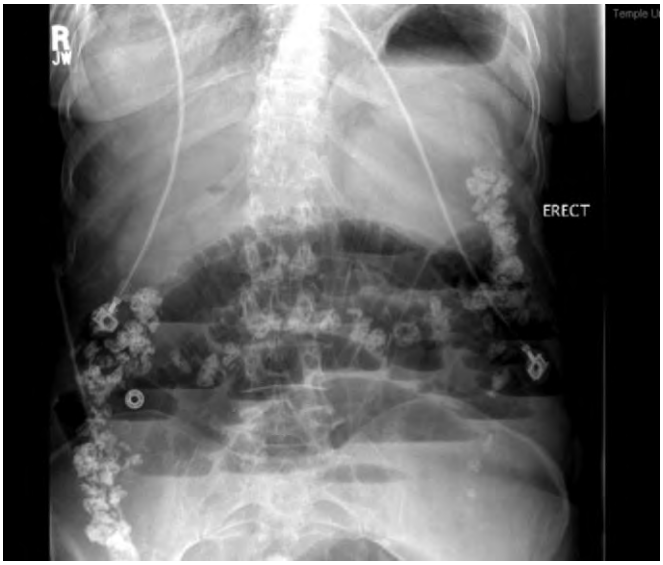

Figure 68–2. Upright abdominal radiograph showing multiple dilated small bowel loops with air-fluid levels.

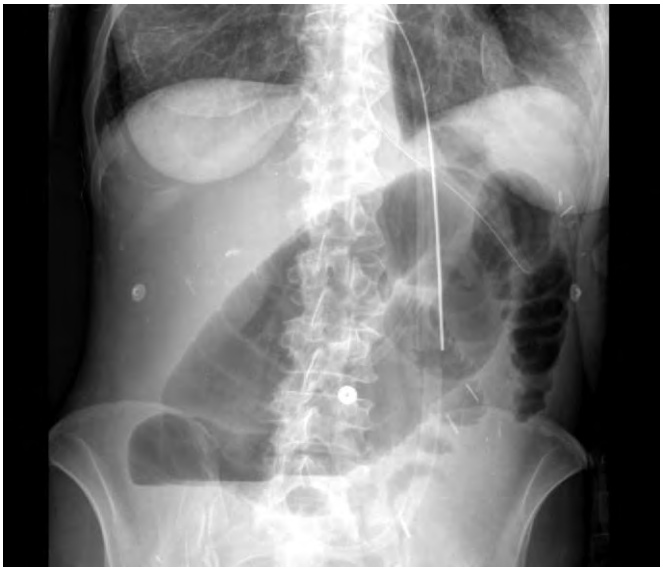

Figure 68–3. Plain abdominal radiograph showing extremely distended small bowel loops with very minimal air in the colon, representative of high-grade obstruction.

Patterns suggestive of SBO include multiple loops of small bowel filled with gas or fluid and a moderate amount of gas in the colon. The finding of colonic gas indicates partial SBO, early complete SBO, or ileus. This pattern is often nondiagnostic and may require further investigational studies such as computed tomography (CT). A more definitive diagnosis of SBO can be made when dilated gas- or fluid-filled small bowel loops are seen with minimal or no gas in the colon[16] (Fig. 68–3)

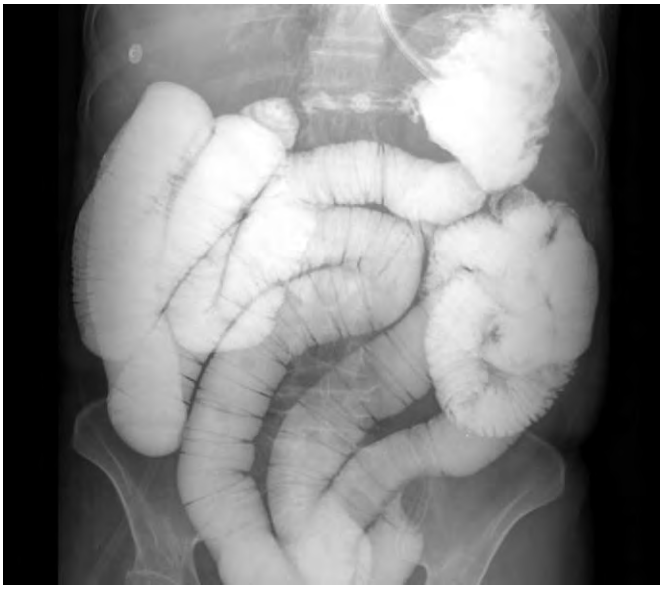

Figure 68–4. Small bowel follow-through film showing distention of multiple small bowel loops, representative of distal obstruction.

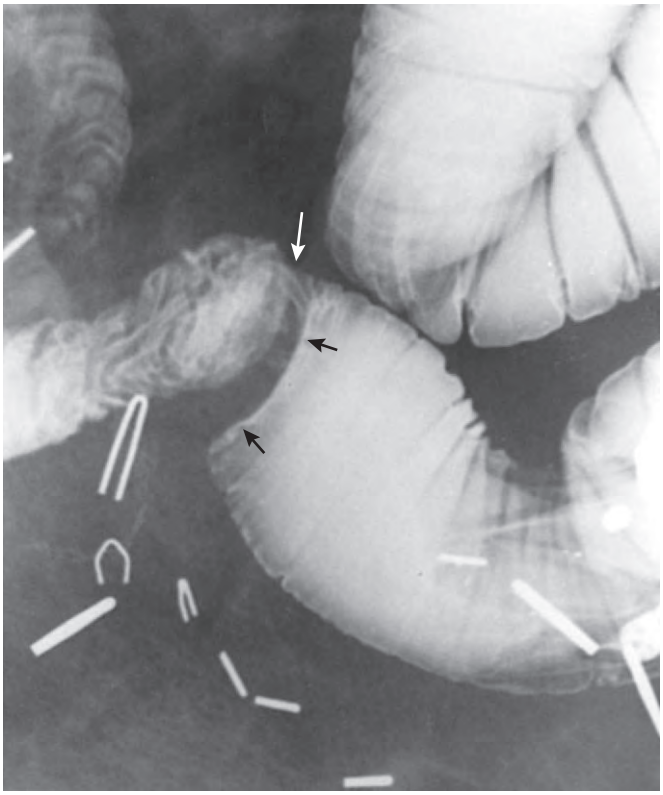

Figure 68–5. Partial small bowel obstruction with an adhesive band at the transition point *(white arrow)* between dilated proximal bowel and decompressed distal bowel. The *black arrows* point to the site of constriction caused by the band.

Contrast Radiographs

Barium films can be used for small bowel evaluation by either oral ingestion of contrast, as for **small bowel follow-through,** or as a retrograde study by way of an enema (Fig. 68–4). In the setting of high-grade SBO, these techniques have some limitations, such as dilution of barium as a result of fluid-filled dilated loops of bowel, which results in poor elucidation of mucosal detail. In addition, slow transit of contrast through the obstructed bowel may prohibit identification of sites of partial blockage or smaller lesions.[17]

Enteroclysis allows intubation of the jejunum and direct infusion of contrast boluses toward the site of obstruction regardless of the degree of peristalsis in the dilated proximal bowel. This technique has been shown to be extremely predictive of obstruction, as well as its absence, its site, and its cause. A positive diagnosis is made when a transition in luminal size is seen (Fig. 68–5). The upper limit of normal small bowel diameter by enteroclysis is 3 cm in the jejunum and 2.5 cm in the ileum.[17] This method can be especially helpful in discriminating between various causes of obstruction such as adhesions, tumors, and radiation.[18]

However, the use of enteroclysis is limited because of requirements for conscious sedation, nasojejunal tube placement, experienced staff, and extensive, time-consuming radiation exposure. In addition, once barium enteroclysis is performed to rule out obstruction, secondary imaging studies are obscured by the barium contrast. Therefore, small bowel follow-through with fluoroscopy is adequate is most situations.[19]

The therapeutic effect of water-soluble contrast is controversial. Some have shown that oral diatrizoate meglumine (Gastrografin) may have a therapeutic effect on SBO[20] and predict the need for early surgical intervention. It has been used as a mode of differentiating partial from complete SBO, thereby leading to operative intervention sooner when the latter situation is identified. After 24 hours, an operation is performed if Gastrografin is not found to have passed into the colon. In patients with partial SBO treated conservatively, hospital stay was found to be shorter and tolerance of a soft diet was noted to occur earlier. The incidence of surgery for SBO, however, was not found to be affected by Gastrografin administration.[21]

Computed Tomography

CT can be a valuable tool in the work-up for SBO. It is helpful in distinguishing SBO from other causes of bowel dilatation and can aid in the decision-making process between operative and nonoperative therapy. Although the sensitivity of CT may be as low as 48% in identifying low-grade obstruction, it is reported to be as high as 81% for high-grade obstruction.[22] CT is also very successful in delineating the cause of obstruction in greater than 90% of cases[19] and in diagnosing ischemic bowel, as well as its precipitating factors, including bowel volvulus, torsion, and intussusception (Fig. 68–6). Additionally, CT is a particularly helpful study for diagnosing external and internal hernias, such as an obturator hernia.

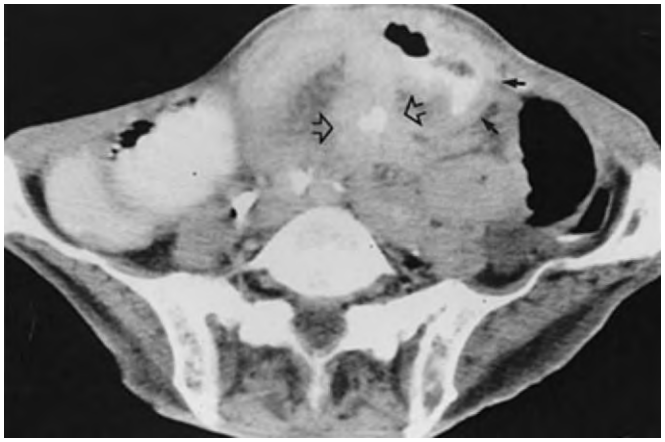

Figure 68–6. Computed tomography scan of the lower part of the abdomen. Dilated bowel loops surround a large mesenteric mass *(open arrows).* In one bowel loop, wall thickening is demonstrated *(solid arrows).*

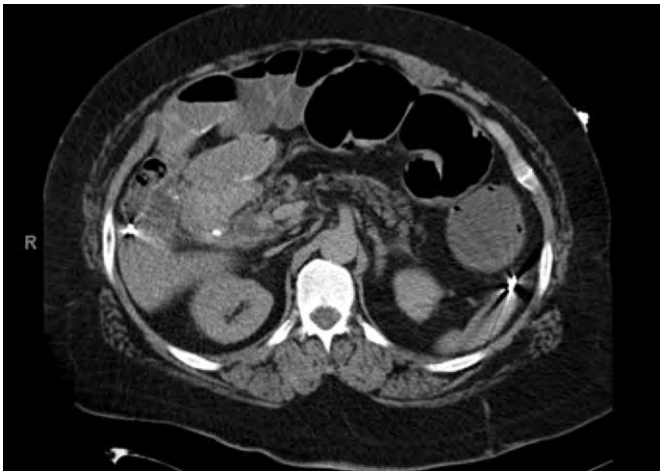

Figure 68–8. Computed tomography scan of the upper part of the abdomen showing high-grade or complete bowel obstruction with decompressed colon.

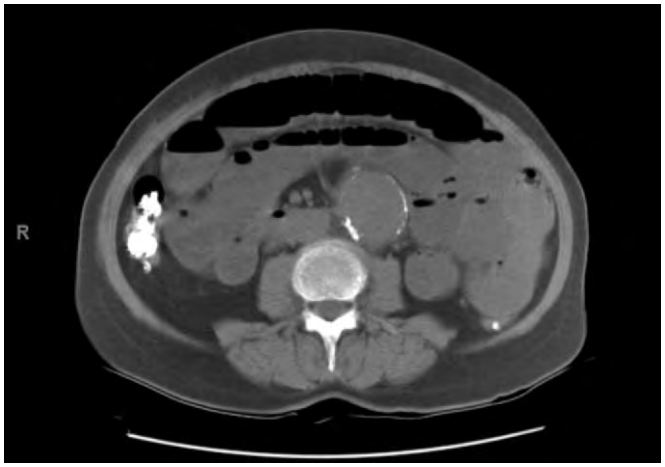

Figure 68–7. Computed tomography scan of the abdomen showing high-grade partial distal small bowel obstruction.

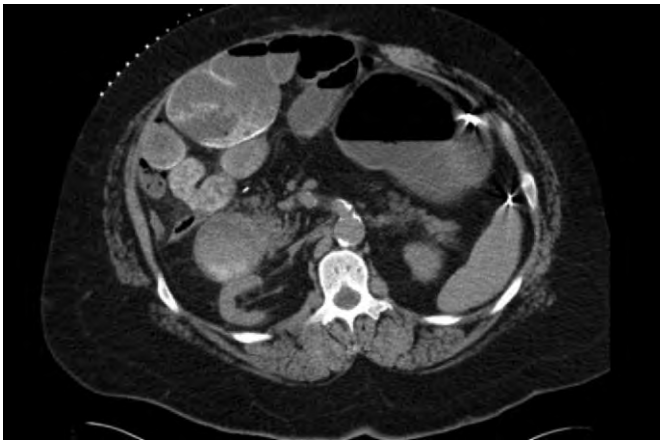

Figure 68–9. Computed tomography scan of the upper abdomen showing dilated loops of proximal small bowel with air-fluid levels adjacent to less dilated, more distal loops of small bowel.

Findings of partial SBO on CT include mildly dilated small bowel loops (>2.5 cm in diameter) with an ill-defined transition point and incompletely collapsed distal bowel in the setting of a moderate amount of gas and fluid in the colon (Figs. 68–7 to 68–9). To distinguish partial SBO from early high-grade SBO, oral contrast is expected to enter the colon within 6 hours, which may be confirmed by follow-up radiography or CT.[23]

For chronic, intermittent partial SBO, CT performed during the symptomatic period may be diagnostic. Alternatively, CT enteroclysis in this setting better delineates findings that may otherwise be missed, such as adhesions or small tumors, but still require surgical intervention. CT enteroclysis combines infusion of water-soluble contrast via a nasointestinal tube into the jejunum with CT imaging. This technique may also improve the low-yield results in cases of low-grade SBO by improving mucosal detail and the distensibility of the small bowel.

When high-grade obstruction, volvulus, torsion, intussusception, other causes of strangulation, or ischemia or infarction is not apparent on CT, conservative management with avoidance of an operation is reasonable. This strategy may prevent significant morbidity and mortality in patients who are at high risk for general anesthesia and abdominal surgery.

In cases of closed-loop obstruction, the involved segment of bowel is nearly completely filled with fluid, and the more proximal portion of the bowel is likely to contain air-fluid levels. The mesentery may also show a whorl sign, suggestive of twisted mesenteric vessels.[24] As for bowel strangulation, its findings are those of ischemic bowel, represented by ascites, a thickened wall, increased

mural attenuation, and the target sign when intravenous contrast is administered. Additionally, pneumatosis, portal venous gas, mesenteric congestion, and hemorrhage may be seen in advanced ischemia.[19]

Another useful situation for CT imaging of SBO is in patients with preexisting pathology, such as abdominal malignancy or inflammatory processes. As a fairly noninvasive, reproducible, and readily available study, it serves a generally useful purpose as an early diagnostic study after initial plain radiographs are obtained. In addition, in the acute setting of evaluation for abdominal pain in the emergency department, CT is a reliable initial study to rule out other causes of pain.

MEDICAL TREATMENT

A patient in whom SBO is diagnosed should be admitted to the hospital, hydration instituted, electrolytes corrected, and a nasogastric tube placed. If the diagnosis is **partial** SBO with no evidence of complete obstruction, strangulation, or ischemia, conservative, nonoperative management may be instituted. Such management entails ensuring adequate intravenous hydration, close monitoring of urine output with or without a Foley catheter, nasogastric tube drainage, and frequent assessment of the patient's abdominal examination. A central venous pressure or pulmonary capillary wedge pressure monitor may also be necessary for fluid management in more complex cases. Approximately 80% to 90% of partial SBO cases resolve spontaneously with conservative measures.

In cases of postoperative SBO, long-tube decompression, such as with a Miller-Abbott tube, may be helpful. This topic is discussed further in the following section.

Long-Tube Decompression

Long-tube decompression has been used since the 1930s when Wangensteen reported advancing a long tube into the jejunum to the point of obstruction during exploratory laparotomy. Recovery was seen in 80% of these patients with no other intervention.[25] Later, Abbott and Johnston passed the Miller-Abbott tube via the nose into the duodenum and inflated the distal balloon, which then allowed the tube to reach the point of obstruction by peristalsis. This technique was successful in relieving the obstruction in 80% of cases.[26] A major disadvantage was the time delay inconvenience caused by the dependence on peristalsis for advancement of the tube to the appropriate position.

In the 1970s and 1980s, endoscopic placement of long tubes into the small bowel was introduced and eliminated the need to wait for spontaneous migration of the tube. This technique was reported to take as little as 20 minutes for placement into the jejunum,[27] with immediate decompression. Success rates were reported to be as high as 90%.[28]

SURGICAL TREATMENT

Surgery is indicated early in the management of complete SBO or high-grade partial SBO. If there is any indication of bowel incarceration, strangulation, or ischemia, an urgent operation should be performed after adequate resuscitation. Exceptions to early operative intervention may be cases of inflammatory bowel disease, radiation enteritis, and some cases of carcinomatosis in the absence of clinical signs of deterioration. These situations may best be managed conservatively in light of the limited benefits and potential high risks associated with operative management.

In cases of nonoperative management of partial SBO, factors prompting surgical intervention include (1) worsening abdominal pain and distention; (2) findings of peritonitis, fever, and leukocytosis; (3) failure of resolution of complete obstruction within 12 to 24 hours; and (4) failure of improvement of partial obstruction after 48 to 72 hours or progression to complete obstruction. Most cases of partial SBO secondary to adhesions resolve when managed conservatively, with only 10% to 20% requiring operative correction.

The decision to operate for SBO is not as straightforward in cases of early postoperative obstruction. Most surgeons initially manage these cases expectantly up to 4 weeks before operative intervention is performed. If reoperation is attempted before this time, dense and vascular adhesions may cause significant morbidity with an increased risk for enterotomy and bleeding. Pickleman and Lee reported resolution of postoperative obstruction in 96% of patients within 2 weeks, with the unlikelihood of resolution after 10 days.[29] Certainly, if symptoms or physical findings worsen during the waiting period, as well as the previously mentioned laboratory or radiologic abnormalities, surgical intervention should be implemented in timely fashion.

Laparoscopic Versus Open Adhesiolysis

Since laparoscopic cholecystectomy was introduced in the 1980s, increasing experience by surgeons has broadened the use of minimally invasive techniques in both elective and urgent situations. Laparoscopic adhesiolysis was first described in 1991,[30] and many other reports have been published ever since. Advantages over laparotomy include less postoperative pain, shorter time to return of bowel function, shorter hospital stay, shorter recovery time, fewer wound complications, and decreased adhesion formation. Although no prospective randomized trials comparing laparoscopic and open adhesiolysis for SBO are available at present, retrospective studies, albeit with short follow-up, indicate the safety of laparoscopy with the aforementioned benefits in the appropriate patient population.

Laparoscopy should be avoided in patients with peritonitis or free air requiring emergency exploration. Emergency laparoscopic adhesiolysis has been reported to result in a 36% conversion rate to laparotomy versus 7% when performed electively.[31] In addition, the degree of abdominal distention, bowel diameter (<4 cm),[32] and site of obstruction are important factors when considering laparoscopy. A correlation between the number of previous abdominal operations and successful laparoscopic adhesiolysis is controversial.[33]

Regardless of the method of surgery, adequate resuscitation of patients preoperatively is invaluable. Electrolytes should be corrected, urine output closely monitored, usually with a Foley catheter, and a nasogastric tube placed for decompression. Antibiotics should also be given approximately 1 hour before an incision is made.

Operative Treatment

The surgical approach depends on the suspected cause of obstruction, as well as the intra-operative findings. If adhesions are the presumed cause, laparoscopy or laparotomy is performed with careful and gentle handling of the inflamed, distended, and edematous bowel and friable mesentery. Once the point of obstruction is located and the adhesions released, the entire bowel should be inspected, and depending on the severity and comorbid conditions of the patient, placement of gastric or enteral draining tubes or feeding tubes (or both) should be considered. For example, when faced with a particularly lengthy or complex case, placement of a draining gastrostomy tube may allow early postoperative removal of the nasogastric tube and prevent its potential complications.

If an incarcerated or strangulated hernia is the culprit, the contents should be reduced after induction of general anesthesia if it can be accomplished without difficulty. Before repair of the defect, the visceral contents should be inspected to ensure viability, particularly in cases of suspected strangulation and ischemia.

When mass lesions are the cause of obstruction, partial bowel resection is performed with or without primary anastomosis, as determined on a case-by-case basis. In less common cases of obstruction from carcinomatosis or radiation, intestinal bypass may be warranted as a palliative measure. Obstruction secondary to Crohn's disease should be resected if minimal inflammation is present and fibrosis is the major component of this mostly isolated area of disease.

Prevention of Adhesion

Adhesions after abdominal surgery are the most common cause of SBO. In particular, colorectal surgery is noted to be one of the largest offenders, especially after proctocolectomy and ileal pouch–anal anastomosis. In addition to the morbidity and mortality caused by SBO and its treatment modalities, the financial burden is also noteworthy. In 1996, more than $3.2 billion was paid by Medicare for adhesion-related complications, and more than $1.3 billion was attributed to adhesiolysis costs in 1994 in the United States.[34] In fact, recurrent SBO developed in approximately a third of patients who underwent adhesiolysis for SBO, with most occurring in the first 5 years postoperatively. However, a quarter were found to have SBO complications more than 10 years later.

Various substances and methods have been used for the prevention of adhesions over the past 100 years. Technical efforts such as gentle tissue handling, minimal use of foreign materials, careful hemostatic measures, and prevention of infection, ischemia, and desiccation have failed to achieve satisfactory results. Substances have also been used with minimal success, including amniotic fluid, bovine cecum, shark peritoneum, fish bladder, vitreous of calf's eye, lubricants, gels, polymers, and various physical barriers.

One notable form of physical barrier is a sodium hyaluronate–based bioresorbable membrane, Seprafilm, which persists in the abdomen for 5 to 7 days.[35] It has been studied in multiple large populations undergoing colorectal surgery. Studies showed decreased incidence, severity, and extent of adhesions after abdominopelvic procedures involving colorectal and gynecologic surgery at the locations of application.[36] In a large, prospective, randomized, multicenter, single-blind controlled study, it also was found to cause fewer cases of adhesive SBO requiring surgery. The number of cases of SBO, however, was not different from that of the control group.[37] Other anti-adhesive substances and techniques are also undergoing extensive research for safety and efficacy.

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Chapter

69

Volvulus of the Stomach and Small Bowel

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The term *volvulus* derives from the Latin word *volvere,* meaning to turn or roll. Clinically, *volvulus* refers to a greater than 180-degree twisting of a hollow organ about its mesentery and results in luminal obstruction, impaired venous return, and eventually ischemia. Though much less common than volvulus of the cecum and sigmoid colon (discussed elsewhere), small bowel volvulus and gastric volvulus are clinical problems that when not recognized promptly, can lead to necrosis of the involved organ with resultant high morbidity and mortality.

SMALL BOWEL VOLVULUS

Etiology

Small bowel volvulus is typically categorized as primary or secondary. Primary small bowel volvulus is relatively rare in the United States but is one of the most common causes of small bowel obstruction in many African and Asian populations. The reported annual incidence ranges from 1.7 to 5.7 per 100,000 population in Western countries as compared with 24 to 60 per 100,000 population in Africa and Asia.[1] Young adults are primarily affected, with a strong male preponderance. Small bowel volvulus is responsible for less than 5% of small bowel obstructions in Western series[2-4] and over half of small bowel obstructions in some African and Asian series.[5,6] The incidence of small bowel volvulus varies not only by country but also by region within certain countries and correlates with lower socioeconomic status.[7] These patterns have been attributed to the high-fiber, vegetarian diet consumed in these populations, as well as to the high proportion of laborers and farmers, who tend to eat infrequent, large meals.[7,8] An increased incidence of small bowel volvulus has been observed during Ramadan, when Muslims ingest large quantities of high-fiber food after prolonged fasting.[8] The incidence of small bowel volvulus is also higher in regions with endemic parasitism, which is known to increase bowel motility.[1] A particularly high incidence of small bowel volvulus was discovered in a Ugandan tribe that consumed a large amount of a beer rich in serotonin,[9] and laxative bowel preparation has been described as a precipitating factor.[10] In 80% of cases the intestinal torsion is clockwise, as it is for midgut volvulus associated with congenital malrotation.[11] However, although congenital malrotation can rarely be manifested in delayed fashion as midgut volvulus, only a minority of adolescent and adult patients with primary small bowel volvulus have an identified lack of mesenteric fixation. Anatomically, the small bowel in high-risk populations is longer and has a longer mesentery with a narrower insertion and a lack of mesenteric fat.[11] Interestingly, patients with small bowel volvulus are not usually emaciated but rather have firm, muscular abdomens, which theoretically might limit the mobility of bowel in the anterior-posterior plane.[5] Whether these observed differences are causative or merely correlative is unclear. Taken together, however, such observations support a popular theory that rapid filling of a segment of proximal intestine with high-bulk chyme pulls it down into the pelvis and displaces empty distal bowel upward, thereby initiating the torsion.

In contrast, secondary small bowel volvulus is much more common than primary small bowel volvulus in the United States. In secondary small bowel volvulus, the intestine is twisted around an underlying point of fixation; as the loop fills with fluid, peristalsis exacerbates the torsion. By far the most common point of fixation is a postoperative adhesion. Case reports have described a number of other causes, however, including internal hernias,[12] tumors,[13] mesenteric lymph nodes,[14] Meckel's diverticulum,[2] and pregnancy.[15] In the most recently published Western series, Roggo and Ottinger from Massachusetts General Hospital (MGH) reported 35 patients with small bowel volvulus; these patients represented 4% of all small bowel obstructions over the 10-year study

Table 69–1 Modern Series of Small Bowel Volvulus

Author	Roggo	Ghebrat
Country	USA	Ethiopia
Study period	1980-1990	1995-1997
Number of patients	35	51
Male-female ratio	1:1.2	12:1
Average age	67	37
Primary small bowel volvulus	14%	92%
Gangrenous small bowel	46%	18%
Mortality overall	9%	12%
Mortality from gangrene	17%	NS

NS, not stated.

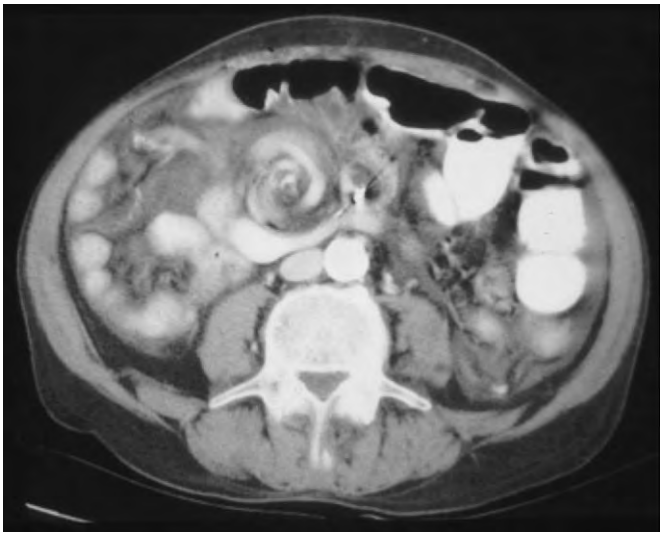

Figure 69–1. Abdominal computed tomography scan with a "whirl" sign in a patient with small bowel volvulus secondary to postoperative adhesions.

period (1980 to 1990).[2] In five patients (all men), the volvulus was primary. In 29 of the remaining 30 patients, the volvulus was secondary to postoperative adhesions. Unlike primary small bowel volvulus, secondary small bowel volvulus affected both sexes equally and mainly older adults. This study is compared with a contemporary series by Ghebrat et al. from Ethiopia[5] in Table 69–1, which illustrates some of the differences between primary and secondary small bowel volvulus.

Diagnosis

Clinically, the findings in patients with small bowel volvulus are nonspecific. Patients have signs and symptoms of small bowel obstruction that are usually sudden in onset. Central abdominal pain is almost always present.[1,2,5] In some cases, careful questioning may elicit a previous history of intermittent obstructive symptoms such as crampy epigastric or periumbilical abdominal pain. "Pain out of proportion" to the degree of obstruction should raise suspicion of vascular compromise, as should fever, tachycardia, peritoneal signs, acidosis, and leukocytosis. However, none of these signs alone are sensitive or specific enough to reliably rule bowel ischemia in or out. For example, in the MGH series, 9 of 35 patients (26%) with small bowel volvulus had peritoneal signs and two thirds of these patients had gangrenous bowel; 10 of the 26 patients without peritoneal signs had gangrenous bowel.[2]

Plain films are usually nonspecific and demonstrate dilated loops of bowel or air-fluid levels, or both. However, in a closed-loop obstruction such as volvulus, the loops may be filled with fluid and have little or no air. Thus, plain films may reveal a "gasless" abdomen or even be interpreted as normal.[16] In patients with gangrenous bowel, plain films may reveal pneumatosis or portal venous gas. However, these findings are notoriously insensitive and late signs. Gastrointestinal contrast studies may show a corkscrew pattern or an abrupt "bird beak" at the point of obstruction, and angiography may demonstrate a spiraling pattern of the mesenteric vessels.[14] However, these modalities have largely been replaced in the evaluation of acute small bowel obstruction by computed tomography (CT), which is rapid, noninvasive, and widely available. CT findings characteristic of a closed-loop obstruction include a radial distribution of dilated bowel loops converging toward a point of torsion or a C- or U-shaped loop of horizontally oriented, fluid-filled bowel.[17] The rotation of the mesentery may generate a "whirl" sign, which is virtually pathognomonic for small bowel volvulus (Fig. 69–1). Mesenteric thickening may be present as a result of previous intermittent, incomplete volvulus. Though not specific for volvulus, small bowel wall thickening, pneumatosis, portal venous gas, and free intraperitoneal fluid suggest small bowel ischemia.

Treatment

Evidence of ischemia mandates immediate exploration and resection of the involved, gangrenous small bowel. Suspicion of volvulus clinically or radiographically should also prompt immediate exploration because of the associated risk for ischemia. In Western series, up to 50% of patients with small bowel volvulus will require resection for gangrenous small bowel.[2] The rarity of small bowel volvulus in our society may lead to a delay in diagnosis and a higher incidence of gangrenous small bowel than in Asian and African series. Overall mortality in patients undergoing exploration for small bowel volvulus ranges from 10% to 35%,[1] which is considerably higher than that for small bowel obstruction in general. These overall mortality rates are attributable to the large proportion of patients with gangrenous bowel, in whom mortality rates are between 20% and 60% in most series.[1]

For patients without ischemic bowel, the optimal treatment is less clear. No prospective, randomized

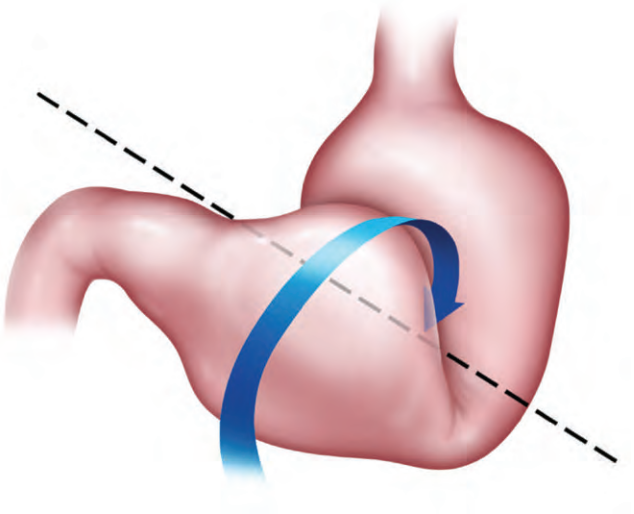

Figure 69–2. Organoaxial rotation occurs when the stomach rotates around a transverse line between the pylorus and gastroesophageal junction.

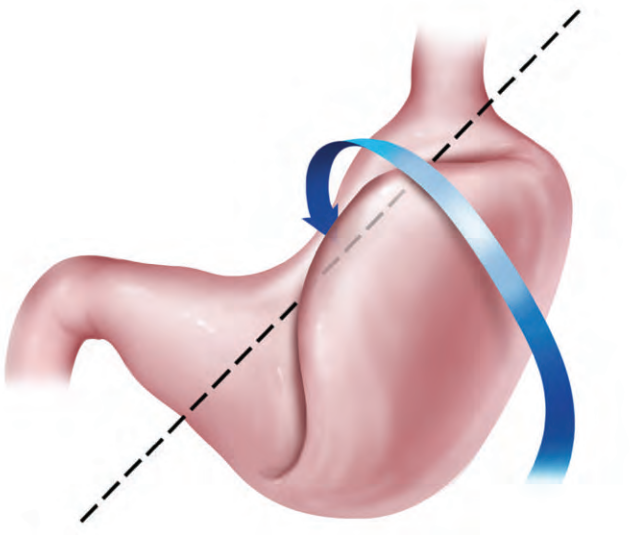

Figure 69–3. Mesenteroaxial rotation occurs when the stomach rotates around a longitudinal line parallel to the gastrohepatic omentum.

studies or even retrospective studies have addressed the issue of recurrence. Most studies describe simple detorsion without resection but rarely include long-term follow-up. The risk for recurrent volvulus is therefore not well established. Intestinopexy of a long segment of bowel is technically difficult and not recommended. In neonatal midgut volvulus caused by malrotation, intestinopexy is not routinely performed, and rates of recurrence are considered acceptably low. It is believed that the formation of intraperitoneal adhesions after laparotomy should prevent most recurrences. However, some authors have recommended resection of involved, nongangrenous intestine in order to prevent recurrent volvulus,[1] although the risk for short-gut syndrome prohibits this approach if a long segment of bowel is involved.

GASTRIC VOLVULUS

Etiology

Similar to small bowel volvulus, gastric volvulus occurs when the stomach or a portion of the stomach is rotated at least 180 degrees along its transverse or longitudinal axes. Gastric volvulus can be classified according to anatomy, etiology, or onset (acute or chronic). As defined by Singleton, organoaxial rotation is the most common (two thirds of cases) and occurs when the stomach rotates around a transverse line between the pylorus and the gastroesophageal junction (Fig. 69–2).[18] Mesenteroaxial rotation is less common (one third of cases), and the stomach rotates around a longitudinal line parallel to the gastrohepatic omentum (Fig. 69–3).

In 10% to 30% of cases the gastric volvulus is considered primary and results from laxity of the stomach's ligamentous attachments (gastrohepatic, gastrocolic, gastrolienal, and gastrophrenic).[19] Primary gastric volvulus has been seen in association with congenital asplenia and with "wandering spleen."[20] Primary gastric volvulus is usually mesenteroaxial, with the pylorus rotating anteriorly (more common) or posteriorly from right to left.[21] Rarely, the fundus rotates around the same axis. As the stomach fills with fluid, the torsion is exacerbated. This type of volvulus is usually incomplete (less than 180 degrees) and is accompanied by chronic or intermittent symptoms.[19]

In the majority of cases, gastric volvulus is secondary to another anatomic abnormality, the most common of which is diaphragmatic hernia. Gastric volvulus is therefore commonly referred to as an intrathoracic "upside-down" stomach. Most cases of secondary gastric volvulus are organoaxial, with the greater curvature rotating up into the chest either anteriorly (more common) or posteriorly with respect to the fixed duodenum and esophagus.[19] Despite the rich blood supply of the stomach, strangulation can occur with torsion greater than 180 degrees and is much more common with organoaxial than with mesenteroaxial volvulus.[22] Paraesophageal hiatal hernia is the most common cause in adults as well as in children, whereas congenital diaphragmatic hernia (left-sided Bochdalek) is an additional common cause in children.[23] However, gastric volvulus has also been described in association with traumatic diaphragmatic hernia, diaphragmatic eventration,[24] and even Morgagni hernia.[25] Although secondary gastric volvulus is typically intrathoracic and occurs as a result of diaphragmatic hernia, secondary intra-abdominal gastric volvulus has also been reported to occur as a result of tumors[26] and after a variety of surgical procedures, including Nissen fundoplication[27] and gastric banding.[28]

Diagnosis

The clinical manifestation of acute gastric volvulus can be quite dramatic. In 1904, Borchardt described the triad

of epigastric pain, retching with an inability to vomit, and difficulty or inability to pass a nasogastric tube. This triad describes acute organoaxial volvulus; the gastroesophageal junction is open in acute mesenteroaxial volvulus, and nasogastric tube placement should not be difficult. For patients with intrathoracic gastric volvulus, the abdominal findings may be minimal. Rather, the "gastrothorax" may cause chest pain, shortness of breath, and symptoms secondary to mediastinal compression, including arrhythmia and tamponade.[22,29,30] When gastric strangulation or perforation has occurred with either intra-abdominal or intrathoracic gastric volvulus, signs of gastrointestinal bleeding and septic shock may be evident.

In contrast, the signs and symptoms of chronic gastric volvulus may be vague and intermittent, or it may be an incidental finding on an imaging study. Symptoms of chronic primary gastric volvulus include upper abdominal discomfort, vomiting, early satiety, and dysphagia.[19,31] In addition to these obstructive symptoms, patients with chronic intrathoracic gastric volvulus may describe postprandial chest pain or shortness of breath. The differential diagnosis is broad and includes many much more common diseases, such as gastroesophageal reflux disease and peptic ulcer disease.

Radiographically, the diagnosis of primary gastric volvulus may be difficult to establish because the volvulus is often intermittent. Plain films may demonstrate a spherical stomach on supine views and a double air-fluid level on upright views. A retrocardiac air-fluid level on a lateral chest radiograph is highly suggestive of secondary gastric volvulus with an intrathoracic stomach. In the right clinical situation, further imaging studies may not be necessary. However, an upper gastrointestinal contrast study will confirm the diagnosis by demonstrating a contrast-filled stomach above a normally located gastroesophageal junction with narrowing at the site of the volvulus (Figs. 69–4 and 69–5).

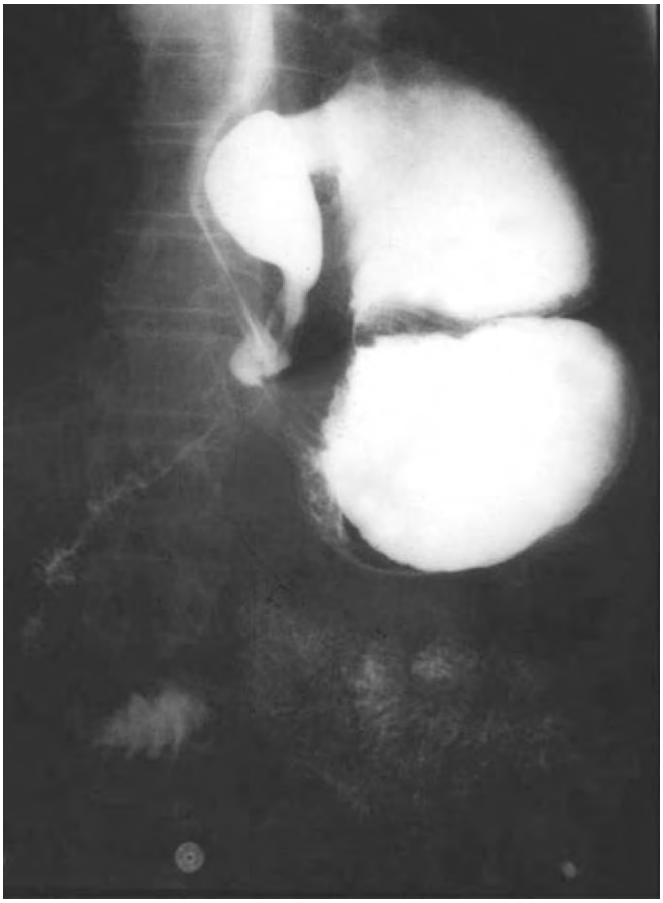

Figure 69–4. Upper gastrointestinal contrast study demonstrating a paraesophageal hernia with organoaxial volvulus. The greater curvature is intrathoracic, and the pylorus is in close proximity to the normally positioned gastroesophageal junction.

Treatment

For acute gastric volvulus, the traditional treatment is emergency laparotomy with reduction of the volvulus. Mortality rates as high as 30% to 50% have been reported for this condition, with the major cause of death being sepsis secondary to gastric strangulation.[19,22] Strangulation leads to gastric necrosis with or without perforation and requires resection by either local excision, subtotal gastrectomy, or even total gastrectomy. Other reported complications include ulceration, gastrointestinal hemorrhage, omental avulsion, splenic rupture, and pancreatic necrosis. Once the volvulus has been reduced and emergency conditions addressed, the goal of surgery is to prevent recurrence by fixing the stomach to the abdominal wall and correcting any predisposing conditions. Anterior gastropexy is easily accomplished by placement of a gastrostomy tube. The short gastric vessels should be preserved, if possible, both to retain their blood supply and to help anchor the greater curvature. In the case of gastric volvulus secondary to diaphragmatic hernia, the diaphragmatic defect should be repaired, although in septic or medically high-risk patients, reduction and gastropexy alone may be safer and sufficient, particularly in those with limited life expectancy. Otherwise, the best way to repair the diaphragmatic defect is debatable. Although retrospective data suggest that prosthetic mesh prevents recurrence, the risk for infection in the setting of gastric necrosis may be increased, and mesh should therefore be used selectively.[32]

For chronic gastric volvulus, the more important issues are whether and when to operate. It is difficult to know the percentage of patients with a diaphragmatic hernia and intrathoracic stomach who will progress to acute gastric strangulation. However, the high morbidity and mortality associated with such strangulation justify expeditious repair, even in asymptomatic patients. In contrast, chronic primary gastric volvulus is often intermittent and is much less likely to become strangulated. In the pediatric population, primary gastric volvulus has been successfully managed with nonoperative "postural" therapy and does not routinely require surgical intervention.[33]

More recently, endoscopic and laparoscopic approaches to both acute and chronic gastric volvulus have been popularized. In select cases of acute gastric

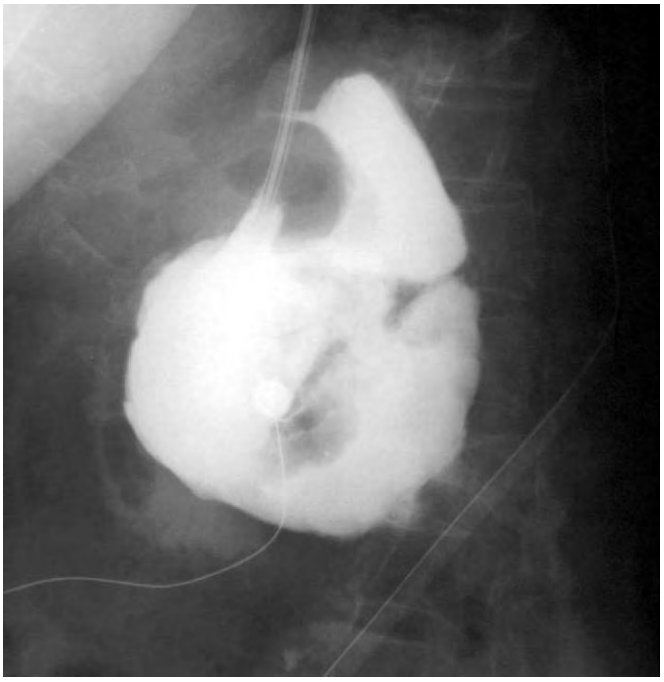

Figure 69–5. Upper gastrointestinal contrast study demonstrating a paraesophageal hernia with complete obstruction of the stomach because of volvulus. The patient was found to have gastric necrosis at exploration.

volvulus without gastric necrosis, gastric decompression—either by placement of a nasogastric tube or endoscopically—may convert an emergency to an urgent operation or even avoid an operation altogether. Endoscopic reduction of an intrathoracic stomach is relatively difficult. Various techniques have been described, including the use of two endoscopes[34] and expansion of an intragastric balloon.[35] Once the stomach has been reduced, gastropexy is relatively simple and is achieved by placement of a percutaneous endoscopic gastrostomy (PEG) tube. In the first description of endoscopic reduction, two PEG tubes were placed to help prevent recurrent volvulus.[36] Purely endoscopic techniques, however, are best reserved for high-risk patients because these techniques do not address the underlying pathology. In contrast, laparoscopic approaches[37] and combined laparoscopic and endoscopic approaches[38] have the potential to combine minimally invasive techniques with repair of the diaphragmatic defect. Although no randomized, controlled studies have been conducted, Teague et al. compared the results of open (13 patients) and laparoscopic (18 patients) repair in patients with acute or chronic gastric volvulus. Laparoscopic repair was technically difficult (three conversions to open procedures) but was safe and associated with a shorter hospital stay.[39]

SUMMARY

Small bowel volvulus and gastric volvulus are uncommon problems in this country and are often diagnosed in delayed fashion. Early recognition and treatment may help prevent the morbidity and mortality associated with small bowel and gastric ischemia.

ACKNOWLEDGMENT

The authors acknowledge William M. Thompson, MD, for providing the radiographic images of small bowel and gastric volvulus.

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Chapter

70

Crohn's Disease: General Considerations, Medical Management, and Surgical Treatment of Small Intestinal Disease

D. Wayne Overby · Mark J. Koruda

GENERAL CONSIDERATIONS, MEDICAL THERAPY

Crohn's disease is a transmural inflammatory disease that can involve any part of the gastrointestinal tract from the mouth to the anus. Despite the large body of published literature and ongoing study dedicated to Crohn's disease, it remains an incurable disease of unknown etiology. Clinicians are faced with the difficulty of diagnosing and treating patients with a heterogeneous disease that has an array of features and manifestations.

Epidemiology

Wide variations in the incidence and prevalence of Crohn's disease have been reported. These differences may be due to diagnostic variations compounded by variations in reporting, or they may be due to real differences in genetic and environmental factors among geographically distinct populations.[1] Interestingly, these differences seem to follow political borders rather than natural boundaries. There have been studies showing increasing incidence at greater latitudes, but these results have not been universally observed.[1,2] Differences related to socioeconomic status have also been reported, with increasing affluence imparting increased risk, but this association has not been borne out in more recent studies. Moreover, it is useful to remember that with differences in affluence come differences in diet, hygiene, and population density,[2] all of which are the essence of cultural westernization.

The prevalence of Crohn's disease in North America has been estimated to be 26.0 to 198.5 cases per 100,000 people (recently, 144 to 198 cases per 100,000). Given the prevalence reported in the two most recent studies and given a population estimated to be 300 million, there are 400,000 to 600,000 cases of Crohn's disease in North America. Recent studies have demonstrated higher prevalence rates with relatively stable rates of incidence, thus suggesting that patients may be living longer with the disease. The incidence of Crohn's disease in recent studies has varied from 3.1 to 14.6 cases per 100,000 person-years. Again assuming a population of 300 million, Crohn's disease is diagnosed in 9000 to 44,000 people in North America yearly. There appears to be a slight female preponderance, with female prevalence ranging from 50% to 60% in most studies. The mean age at diagnosis in most North American cohorts is between 33 and 39 years, with the disease being diagnosed in the majority of patients in their second or third decade of life; a second peak was found in the sixth or seventh decade in roughly half of cohorts, which has given rise to the idea of bimodal distribution of disease with regard to age.[1] The second peak may be due to differences in environment leading to differences in disease expression or variations in diagnosis, or it may in fact represent a delay in diagnosis as the disease relapses.[1,2]

Natural History

The severity of disease observed in any group of patients with Crohn's disease will exist on a continuum from asymptomatic, to medical or surgical remission, to mild, moderate, or severe disease. There are European and North American cohorts that are probably the best-studied populations outside specialty referral centers. These studies indicate that among patients in their first year after diagnosis, 80% had high disease activity, 15% had low activity, and 5% were in remission.[3] At any point in time after the first year, examination of a group of patients with Crohn's disease will find a majority (approximately 65%) in remission, with another 25% experiencing low activity and 10% experiencing high activity; 13% will have chronically active disease. About 43% of cohort patients required steroids during the course of their disease, whereas 10% of patients in any given year required steroids and 30% of patients in any given year required sulfasalazine or 5-aminosalicylate products. Up to 57% of patients required at least one surgical resection. In most patients, Crohn's disease has a relapsing and remitting course, with relatively small numbers of patients experiencing prolonged remission or unremitting disease.[1] Mortality in patients with Crohn's disease is slightly increased in cohort studies with long-term follow-up; the absolute difference in survival at 20 years was 6% to 7%.[4-6] The most unfortunate aspect of Crohn's disease may be that it strikes the majority of patients in the prime of their lives, which increases the potential for early long-term or permanent disability, so aside from direct medical costs, there are indirect costs associated with decreased productivity.[7]

Risk Factors and Pathogenesis

Respected authors bemoan the lack of knowledge regarding the underlying causes of Crohn's disease. It is generally accepted that a combination of environmental and genetic factors are at work to produce altered mucosal integrity of the gastrointestinal tract and complex alterations in local and systemic immune response.

Environmental Factors

A number of environmental factors have been implicated in Crohn's disease, including microorganisms of both infectious and commensal varieties; smoking; various components of diet; medications, including antibiotics, nonsteroidal anti-inflammatory drugs, and oral contraceptives; and hygienic factors, with increasing hygiene imparting increased risk. It is generally accepted that cigarette smoking, though not a cause, makes Crohn's disease worse, but no other single environmental factor or combination of environmental factors has been convincingly implicated as causative. One widely held hypothesis suggests that Crohn's disease is manifested when genetically predisposed individuals are exposed to an environmental trigger or triggers.[8-11]

Genetic Factors

As for genetic predisposition, it has long been known that there exist familial aggregations of inflammatory bowel disease. The finding that disease concordance is much higher in monozygotic twins (44%) than dizygotic twins (3.8%)[12] adds weight to the argument that genetics plays a significant role in the development of inflammatory bowel disease while at the same time suggesting a potentially complex relationship between environmental factors, genetic susceptibility, and incomplete phenotypic penetrance.[13] Recent studies using DNA screening and linkage analysis of members in affected kindreds have identified nine genetic susceptibility loci for inflammatory bowel disease (*IBD1* to *IBD9*). Mapping of the *IBD* loci led to the identification of a gene that increases susceptibility to Crohn's disease.[14]

Variants of a gene in the *IBD1* locus (16q12), which was named *NOD2* on discovery and later renamed *CARD15* (for caspase activation and recruitment domain), cause susceptibility to ileal Crohn's disease; *CARD15* polymorphisms are not linked to ulcerative colitis. The *CARD15* gene product and the pathway in which it is involved have been studied extensively. After stimulation with lipopolysaccharide or proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), the *CARD15* gene is expressed in cells such as monocytes, macrophages, dendritic cells, and small intestinal Paneth cells (Paneth cells are most numerous in the terminal ileum). The *CARD15* gene product is a cytoplasmic protein that probably acts as a pattern recognition receptor for a breakdown product of the peptidoglycan that is a cell wall component of gram-negative and gram-positive bacteria; the proteolysis occurs in phagocytes and the resulting substance is called muramyl dipeptide. Muramyl dipeptides are subsequently transported into the cytoplasm of cells, where they bind to the CARD15 protein, which in turn activates a signaling cascade that leads to translocation of nuclear factor κB (NF-κB) into the nucleus. Translocation is followed by activation of NF-κB responsive genes, which leads to the production of proinflammatory cytokines. In this way, CARD15 is a part of the innate immune system. It may be that the CARD15 polymorphisms found in patients with Crohn's disease lead to decreased cellular apoptosis, which could in turn cause the overexpression of NF-κB that is seen in Crohn's lesions. Although CARD15 variants increase susceptibility to Crohn's disease, the relationship is complex and not fully understood.[12-14]

The three common mutations that account for 82% of mutated alleles of the *CARD15* gene can be found in up to 50% of patients with Crohn's disease, but they can also be found in 20% of normal individuals, so *CARD15* mutations are neither necessary nor sufficient for expression of the disease; *CARD15* variants account for only 20% of the genetic susceptibility to Crohn's disease in white individuals, whereas *CARD15* variants are absent in Asian and sub-Saharan African populations. However, when compared with normal individuals, the odds ratio for the development of Crohn's disease in heterozygous carriers is 2 to 3, and for homozygous carriers it is 20 to 40. Questions about the benefit of genetic screening of

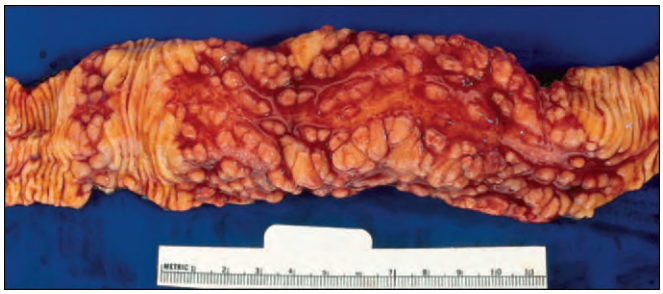


Figure 70–1. Segmental resection of small bowel showing cobblestoning ulceration in Crohn's disease. (From Hart J: Non-neoplastic diseases of the small and large intestine. In Silverberg SG, DeLellis RA, Frable WJ, et al [eds]: Silverberg's Principles and Practice of Surgical Pathology and Cytopathology, vol 2, 4th ed. Edinburgh, Churchill Livingstone, 2006, p 1391.)

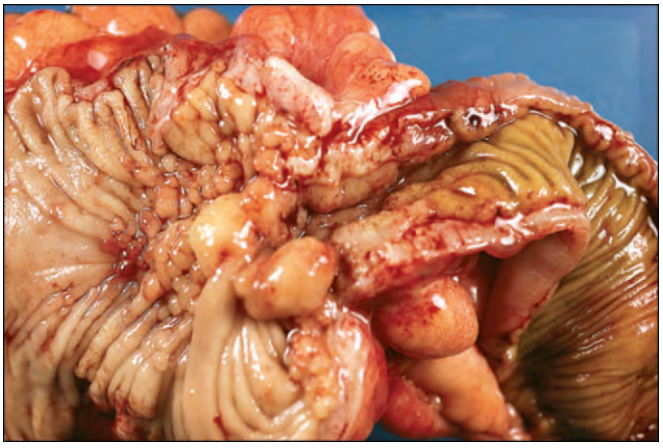


Figure 70–2. Crohn's ileitis with formation of a short stricture. (From Hart J: Non-neoplastic diseases of the small and large intestine. In Silverberg SG, DeLellis RA, Frable WJ, et al [eds]: Silverberg's Principles and Practice of Surgical Pathology and Cytopathology, vol 2, 4th ed. Edinburgh, Churchill Livingstone, 2006, p 1390.)

the general population or family members of carriers are sure to arise; detailed answers to such questions are beyond the scope of this text, but the bottom line answer is that there is no benefit.[13,14] For a more detailed understanding of the current work regarding genetic susceptibility to Crohn's disease, the authors recommend reading the references cited for this section.

Pathology

Crohn's disease is a transmural inflammatory disease with discontinuous lesions that can involve any part of the gastrointestinal tract from the mouth to the anus, but most commonly it involves the ileocecal region. The relapsing and remitting course of Crohn's disease is marked by pathologic changes that are manifested in the clinical course; as the disease flares and abates, the gross and microscopic findings change.

Gross Features

The active phase of the disease is marked initially by the formation of aphthous ulcers that can involve any part the gastrointestinal tract mucosa. The ulcers are small, flat, and soft with a whitish center and red border. As the inflammation continues, the ulcers deepen; eventually they become transmural, and in turn they may lead to deep fissures that can cause abscess formation, fistulization, and in rare cases, free perforation as penetration occurs. The ulcers are scattered at first, but as they progress, they coalesce; the islands of normal mucosa that remain give the mucosal surface a cobblestone appearance (Fig. 70–1). When the involved organ is intestine, continued inflammation causes thickening of the bowel wall with narrowing of the lumen, concomitant thickening of the adjacent mesentery, and wrapping of the outer surface by fat that creeps from the mesentery. The mesenteric involvement includes engorged lymphatic channels and enlarged lymph nodes. As the disease abates and heals, fibrosis and stricture of previously inflamed areas can occur (Fig. 70–2).[8,15,16]

Anatomically, the disease is discontinuous and segmental, which has given rise to the descriptive term *skip lesions;* 29% of patients have disease confined to the small intestine, in 27% it is confined to the colon, and 41% have disease involving both the colon and small intestine, so overall, 70% of patients with Crohn's disease have small bowel involvement.[17] Although the exact incidence and prevalence of upper gastrointestinal Crohn's disease is not known and such involvement is historically rare, it is thought that improvements in diagnostic techniques have led to an increasing incidence in recent reports. Careful examination and biopsy of the upper gastrointestinal tract in patients with known distal disease will reveal histologic evidence of proximal Crohn's disease in a significant number (in as many as 30% to 50% of patients in recent studies), although many will lack upper gastrointestinal symptoms. Upper gastrointestinal Crohn's disease has been most frequently found in the gastric antrum and duodenum, with only rare involvement of the esophagus and remainder of the stomach.[18]

Microscopic Features

The microscopic pathologic changes begin as inflammatory cells, including lymphocytes, macrophages, and neutrophils, aggregate; in the intestine, such aggregations are associated with intestinal crypts. These cellular aggregations represent microabscesses that underlie the superficially appearing aphthous ulcers and penetrate to form fissures (Fig. 70–3). Continued influx of inflammatory cells may lead to noncaseating granulomas with multinucleated giant cells, which is the lesion that is essentially pathognomonic for Crohn's disease (Fig. 70–4). However, the reported incidence of these granulomas varies widely, and they are absent in 50% or more of Crohn's patients, which means that finding granulomas

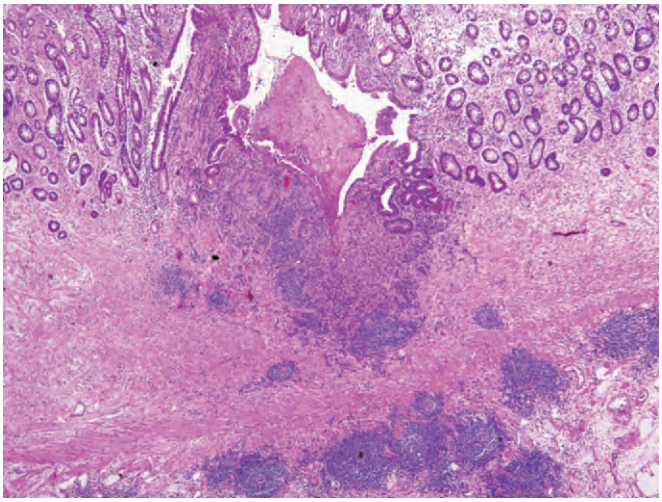


Figure 70–3. Fissuring ulceration extending into the submucosa with associated abundant chronic inflammation. This is a characteristic lesion of Crohn's disease and can progress to form a fistula (ileal resection, hematoxylin-eosin stain). (From Dilworth HP, Montgomery E, Iacobuzio-Donahue CA: Non-neoplastic and inflammatory disorders of the small intestine. In Iacobuzio-Donahue CA, Montgomery E [eds]: Gastrointestinal and Liver Pathology. Philadelphia, Churchill Livingstone, 2005, p 172.)

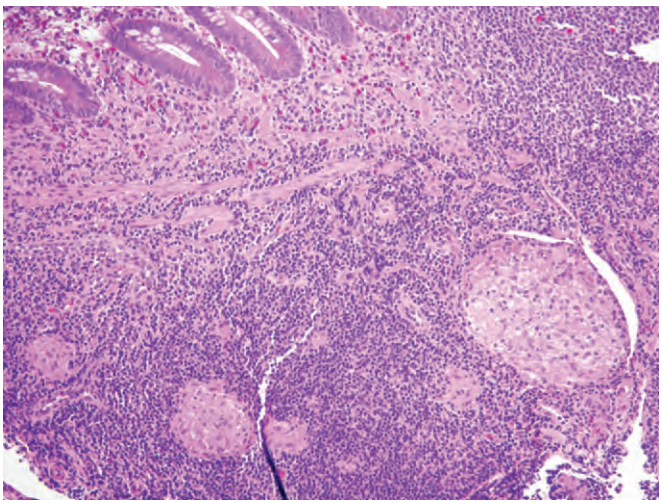


Figure 70–4. Multiple submucosal granulomas *(bottom)* embedded in a large lymphoid aggregate (ileal biopsy, hematoxylin-eosin stain). (From Dilworth HP, Montgomery E, Iacobuzio-Donahue CA: Non-neoplastic and inflammatory disorders of the small intestine. In Iacobuzio-Donahue CA, Montgomery E [eds]: Gastrointestinal and Liver Pathology. Philadelphia, Churchill Livingstone, 2005, p 170.)

helps rule the disease in but the absence of granulomas does not rule the disease out.[15,16,19]

Clinical Features

The variability that is evident in every aspect of Crohn's disease underlies the heterogeneity of its findings. The nature, location, and extensiveness of the gastrointestinal lesions give rise to the assortment of gastrointestinal symptoms while dictating the disease's severity and clinical course. Extraintestinal manifestations are a frequent accompaniment of the gastrointestinal disease.

Classification of Crohn's Disease

As it becomes obvious that Crohn's patients are a heterogeneous group, it follows that different subgroups will manifest their disease in different ways; these variations in the natural history and clinical features among subgroups will affect a clinician's interpretation of a patient's prognosis and the treatment decisions. In addition to aiding clinicians, a better understanding of the variables that create the different subgroups may lay the groundwork for understanding the relationship between the environmental and genetic factors that underlie Crohn's disease.[20] Attempts to develop a reasonably simple and objective method for categorizing patients with Crohn's disease led to the Vienna classification system, which groups patients on the basis of age (<40 or ≥40), disease location (terminal ileum, colon, ileocolon, upper gastrointestinal), and disease behavior (inflammatory, stricturing, penetrating).[21] Recent studies that used the Vienna classification system to examine Crohn's disease in a variety of settings have provided significant insight into its clinical findings.

Manifestations

Crohn's disease will be diagnosed in the majority of patients, on the order of 70%, within a year of becoming symptomatic; however, the time between symptom onset and diagnosis can be much longer, with 14% of patients having at least 5 years between symptom onset and diagnosis. Patients who are older at diagnosis tend to have a longer time between the onset of symptoms and diagnosis of their disease. Time to diagnosis will typically be shorter in younger patients, and there tends to be a higher proportion of patients with a young age at disease onset in referral centers.[22] As stated earlier, almost all patients (95%) will have active disease during the first year after diagnosis, whereas only 35% of patients will have active disease in any following year.[3] There are differences reported in the initial location of disease, although studies agree that the greatest proportion of patients will have disease involving the small intestine or a combination of the small and large intestine at diagnosis.[22,23] In a substantial number of patients (85%) the location of the diseased segment will be the most stable aspect of Crohn's disease over time; inflammation will tend to extend and regress within the involved segment and does not usually extend to other segments.[23] Most patients will have strictly inflammatory versus stricturing

or penetrating disease,[23,24] although referral centers, which tend to see more complicated disease at initial contact, will have a greater proportion of patients with stricturing and penetrating disease at diagnosis.[22] In sharp contrast to anatomic location, which tends to remain stable over time, disease behavior in an individual patient tends to progress over time, with the majority of patients who initially have strictly inflammatory disease progressing to stricturing or penetrating disease over the course of their illness.[23,24] Studies have found that the initial location of disease correlates with later disease behavior; isolated small bowel disease is more likely to be associated with strictures, colonic and ileocolonic disease is more likely to be associated with penetration,[23-25] and in long-term (20 years) follow-up, complications develop in 94% of patients with terminal ileal disease versus 78% of patients with colonic disease.[24]

With the aforementioned findings in mind, there is a logical progression to the typical gastrointestinal and extraintestinal manifestations of Crohn's disease.

- Abdominal pain—The abdominal pain experienced by patients with Crohn's disease is usually obstructive in nature, which gives rise to intermittent, crampy pain. It is caused by the narrowing of the lumen of the gastrointestinal tract, usually small bowel, that develops as segments become inflamed and eventually stricture. It occurs as an initial symptom with similar frequency (approximately 60% to 70% of patients) across age groups and genders.[26-28]
- Diarrhea—Diarrhea may be caused by decreased absorption in inflamed segments; in particular, decreased absorption of bile acids and steatorrhea may be an underlying cause in patients with terminal ileal disease. Resection of the terminal ileum and ileocecal valve may be causative in surgically treated patients. As an initial symptom, it occurs with a frequency similar to abdominal pain (roughly 60% to 70% of patients).[26-28]
- Bleeding—Bleeding is not a constant feature of Crohn's disease, but it may still be the initial symptom in a significant number of patients (23.5% in one large series). The bleeding may be slight and detectable only with Hemoccult testing. Severe acute hemorrhage is rare (0.9% to 6%); in most studies it is more common in patients with colonic involvement, although it may emanate from any part of the gastrointestinal tract from the upper to the lower, which is why localization of the bleeding will be of extreme importance in treatment.[29,30]
- Weight loss—Weight loss and malnutrition obviously follow on the heels of abdominal pain, obstruction, and malabsorption. It is a part of the initial symptom complex in about 25% to 30% of adults. It is, significantly, almost twice as frequent in children.[26-28] The specifics of malnutrition in patients with Crohn's disease are covered later in the chapter.
- Fever—Fever may be due to ongoing inflammation of diseased segments, dysregulation of systemic immunity, or infection secondary to penetrating disease. It occurs as an initial symptom in approximately 15% of patients.[27,28]
- Fatigue/malaise—Malaise is probably caused by both malnutrition and dysregulation of the immune system, which changes the balance of immune cells and the inflammatory mediators that they release. It occurs in roughly 10% to 15% of patients.[27,28]
- Perianal disease—Although this chapter is focused on upper gastrointestinal and small bowel Crohn's disease, it is worth mentioning that perianal disease is frequently (about 10% of the time[27,28]) a part of the initial symptom complex, and in some (in as many as 5% of patients) it will be the sole indicator of Crohn's disease.[31]
- Extraintestinal manifestations—There are a number of chronic inflammatory disorders of unknown etiology that are diagnosed in patients with inflammatory bowel disease so frequently (in up to 50% of patients in some studies) that they are considered to be extraintestinal manifestations of the disease. Of those found in Crohn's disease, the most common are iritis/uveitis (0% to 6.4%), primary sclerosing cholangitis (0.4% to 1.2%), ankylosing spondylitis (excluding asymptomatic sacroiliitis, 1.2% to 8%), peripheral arthritis (12.8% to 23%), pyoderma gangrenosum (0.6% to 1.2%), and erythema nodosum (1.9% to 7.2%). There is some disagreement among recent studies regarding the overall (from 6% to 40%) and individual incidence of these disorders, which is due at least in part to different study populations and study methodologies. Many studies do attempt to separate and compare the rates of occurrence of the various extraintestinal manifestations of Crohn's disease versus ulcerative colitis, and the most constant difference is a higher rate of primary sclerosing cholangitis in ulcerative colitis than in Crohn's disease.[32-34]

Laboratory Findings

Traditionally, the diagnosis of inflammatory bowel disease has relied on clinical, endoscopic, histopathologic, and radiologic findings. Although it is true that the etiology and pathophysiology of inflammatory bowel diseases remain incompletely solved mysteries, it is becoming clear that a dysregulated immune response develops in genetically predisposed individuals exposed to one or more environmental factors. It is reasonable to expect quantifiable evidence of this dysregulation in the form of clinical laboratory abnormalities that are both generalized with respect to inflammation, such as leukocytosis, and specific to inflammatory bowel disease, such as the formation of unique serum antibodies that can be measured as markers in serologic tests.[35]

Nonspecific measures of inflammation include an elevated white blood cell count, platelet count, erythrocyte sedimentation rate, and C-reactive protein. Although these findings usually correlate with increased Crohn's disease activity,[36] their usefulness is limited, both in initial diagnosis and in monitoring of disease activity, because of their lack of specificity.

A number of antibodies to both self and non-self proteins that occur in patients with inflammatory bowel disease have been identified. The best studied

antibodies by far are perinuclear antineutrophil cytoplasmic antibodies (pANCAs), which are found primarily in patients with ulcerative colitis (48% to 82% of patients) and less frequently in patients with Crohn's disease (5% to 20% of patients), and anti–*Saccharomyces cerevisiae* antibodies (ASCAs), which are found primarily in patients with Crohn's disease (48% to 69% of patients) and less frequently in patients with ulcerative colitis (5% to 15% of patients). A number of other antibodies have received attention, including antibodies to outer membrane porin C (anti-OmpC), which are antibodies to the *Escherichia coli* cell wall protein and are found in patients with Crohn's disease; antibodies to I2, which are antibodies to an antigen derived from the DNA of *Pseudomonas fluorescens* and are found inside macrophages from the intestinal mucosa of patients with Crohn's disease; and antibodies to pancreatic antigens, which are found in patients with Crohn's disease. To date, a single serologic test that discriminates patients with inflammatory bowel disease from those without it or that discriminates patients with Crohn's disease from those with ulcerative colitis and does so with high sensitivity and specificity has not been found.[35] There is evidence that using panels of serologic tests, for instance, combining pANCA plus ASCA or combining pANCA, ASCA, and anti-OmpC, will increase their specificity, but at the expense of decreased sensitivity. The specificity and sensitivity for diagnosing Crohn's disease and ulcerative colitis in adults when pANCA and ASCA are combined are on the order of 95% and 50%, respectively.[35,37-39] Studies of the utility of serologic testing in patients with inflammatory bowel disease are ongoing, and the degree of utility will probably be a moving target for years to come as new antigens are identified and compared with or combined with tests for other antigens and validated.

In addition to their potential usefulness in diagnostic testing, investigations that identify antibodies unique to patients with inflammatory bowel disease may lead to a better understanding of the underlying causes of the disease or to better immunomodulatory treatments directed more specifically at points of immune system dysregulation. Serologic testing has the potential to identify patients who are susceptible to the development of inflammatory bowel disease, to identify subgroups of patients who will have more or less aggressive forms of disease, and to predict or monitor response to therapy.[35,38] For a more detailed understanding of serologic testing in inflammatory bowel disease, the authors recommend reading the references cited for this section.

Radiographic Imaging

Gastrointestinal imaging continues to evolve on all fronts, including imaging of the small intestine. Various forms of contrast-enhanced axial imaging using computed tomography (CT) and magnetic resonance imaging (MRI) vie with better techniques in ultrasound to improve on the results that can be obtained with conventional barium studies of the small intestine. In the future, some combination of these modalities may eventually supplant barium studies of the small intestine for the diagnosis of small bowel Crohn's disease in much the same way that push endoscopy has largely replaced barium studies for evaluation of the mucosa of the upper and lower gastrointestinal tract.

All endoscopic and radiographic imaging studies used in Crohn's disease attempt, with varying degrees of effectiveness, to accomplish one or more of the following goals: confirm the diagnosis; localize lesions while gauging their extent, severity, and degree of inflammatory activity; identify the presence of extraintestinal manifestations; and ultimately aid in medical and surgical decision making.[40]

Small Bowel Follow-Through and Enteroclysis

In many clinical situations, push endoscopy has replaced barium studies as the preferred method for evaluating the mucosa of the upper gastrointestinal tract and colon.[41] On the other hand, "conventional" radiographic studies using intraluminal contrast agents, either small bowel follow-through or small bowel enteroclysis (also known as small bowel enema), are still considered to be first-line studies for the evaluation of small bowel disease in general and Crohn's disease in particular.[42-45] Small bowel follow-through is performed after the oral administration of barium; the protocol for the examination is variable between operators and institutions, with some performing a few plain radiographs and others performing extensive fluoroscopic evaluations with multiple compression views to separate bowel loops in order to provide detailed anatomic information and assessment of motility. Enteroclysis is performed by introducing the barium suspension directly into the small intestine via a tube; when compared with small bowel follow-through, the technique for enteroclysis is more uniform between operators.[44,46] There is still debate about which conventional radiographic method is best when evaluating the small bowel to make or exclude the diagnosis of Crohn's disease, and there is literature to support both views; it is likely that the aforementioned operator and institutional variability accounts for some of the perceived difference and that preferences reflect local demands by clinicians and available expertise.[41] Although enteroclysis does not evaluate gastroduodenal disease and is considered to be more uncomfortable for the patient, it is generally accepted that it produces superior small bowel images with better mucosal detail.[42,46] That being said, a detailed, fluoroscopy-based small bowel follow-through, augmented to demonstrate the distal ileum if necessary, is adequate for the initial assessment of small bowel Crohn's disease. The sensitivity and specificity of small bowel enteroclysis for the diagnosis of Crohn's disease have been reported to be 93% to 100% and 97% to 98%, respectively.[41]

A number of possible radiologic findings can be seen on small bowel follow-through and enteroclysis in patients with Crohn's disease; given the heterogeneity of the disease, it follows that these findings can appear in combination and can vary significantly from patient to patient. Imaging of the terminal ileum is of particular importance because many patients have disease involving this part of the gastrointestinal tract and disease may be

limited to the terminal ileum on initial evaluation. Findings seen on small bowel follow-through and enteroclysis (Figs. 70–5 and 70–6) include discrete ulcers, fissures or longitudinal ulcers, fistulas and sinus tracts, cobblestoning, thickened and distorted mucosal folds, wall thickening; enlargement of the ileocecal valve, short or long and single or multiple areas of luminal narrowing with pre-stenotic dilation, and skip lesions, which are areas of diseased bowel interspersed with areas of normal bowel or asymmetric involvement of a portion of bowel.[44]

Cross-Sectional Imaging in Crohn's Disease

Traditional push endoscopy, which is increasingly being supplemented with capsule endoscopy, and barium studies are currently the preferred methods for diagnosing the more subtle mucosal lesions associated with early Crohn's disease. However, when evaluating the transmural, extramural, or extraintestinal extent of disease, cross-sectional imaging, CT for the majority of providers and MRI for a growing number, has distinct advantages over intraluminal imaging modalities and can compensate for the limitations of conventional imaging. Moreover, as cross-sectional imaging technology continues to improve with faster image acquisition times and increased resolution, its role in imaging of Crohn's disease will probably grow.[40] In a comparison of spiral CT and conventional enteroclysis, the sensitivity and specificity of CT for the diagnosis of Crohn's disease were reported to be 94% and 95%, respectively, versus 96% and 98% for enteroclysis.[47] MRI has a similar profile. Both MRI and CT are probably less sensitive than conventional radiographic studies for early lesions.[40]

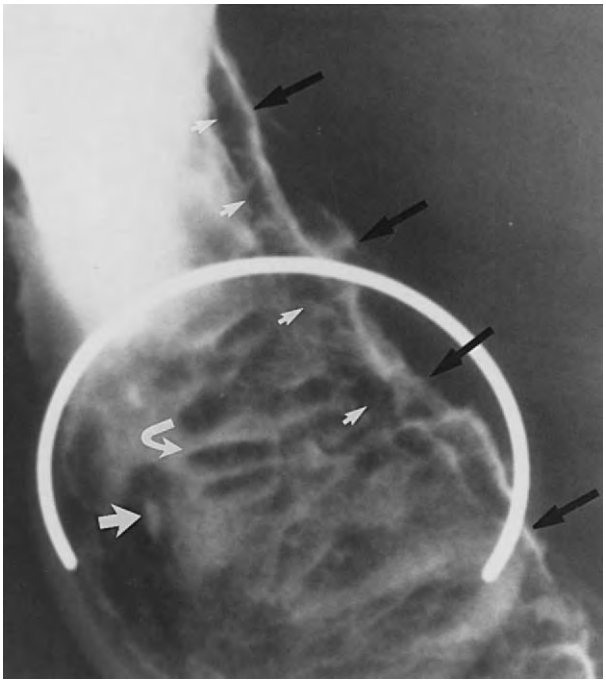


Figure 70–5. This image of the terminal ileum contains a long mesenteric border ulcer *(black arrows)* with a radiolucent line along its luminal aspect *(small white arrows).* Interrupted, thickened folds *(curved arrow)* are present. Aphthoid ulcers have enlarged and deepened *(large white arrow).* (From Herlinger H, Caroline DF: Crohn's disease of the small bowel. In Gore RM, Levine MS [eds]: Textbook of Gastrointestinal Radiology, vol 1, 2nd ed. Philadelphia, WB Saunders, 2000, p 732.)

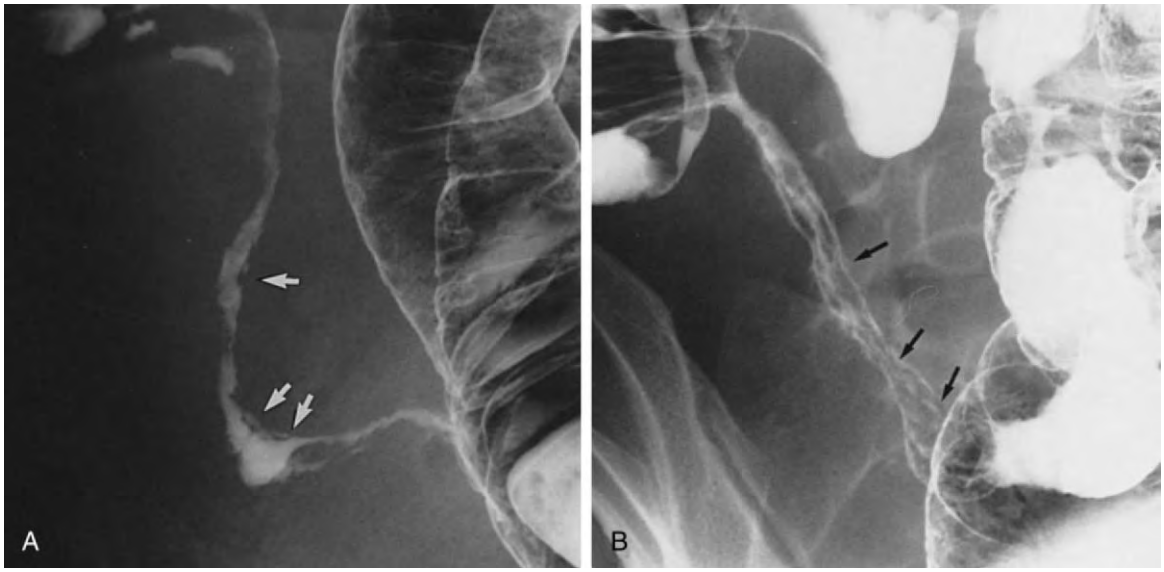


Figure 70–6. Narrowed terminal ileum in active Crohn's disease. **A,** There is marked narrowing of the terminal ileum with probable tiny ulcers *(arrows).* **B,** Enteroclysis in double contrast widens the lumen to reveal an extensively fissured stenotic stage of advanced Crohn's disease *(arrows).* (From Herlinger H, Caroline DF: Crohn's disease of the small bowel. In Gore RM, Levine MS [eds]: Textbook of Gastrointestinal Radiology, vol 1, 2nd ed. Philadelphia, WB Saunders, 2000, p 735.)

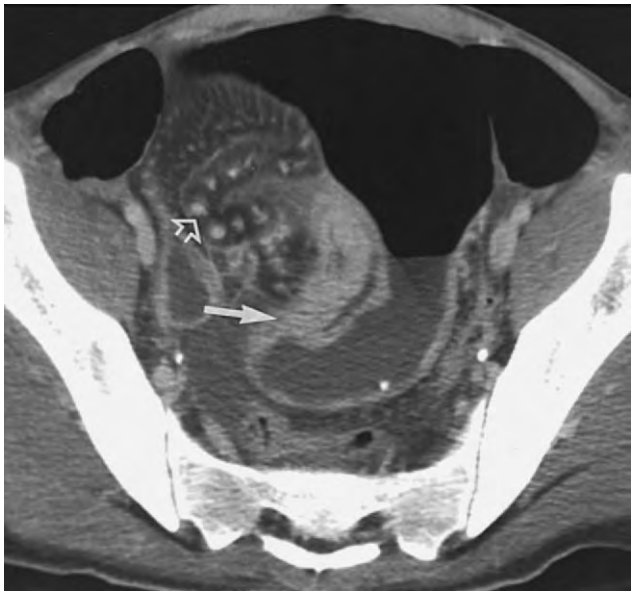


Figure 70–7. High-grade obstruction as a result of Crohn's disease. Computed tomography demonstrates a grossly dilated, gas-filled small bowel proximal to a narrowed, thick-walled, enhancing segment of Crohn's disease *(solid arrow)* that was causing obstruction. Dilated vessels are seen in the mesentery *(open arrow).* (From Herlinger H, Caroline DF: Crohn's disease of the small bowel. In Gore RM, Levine MS [eds]: Textbook of Gastrointestinal Radiology, vol 1, 2nd ed. Philadelphia, WB Saunders, 2000, p 737.)

When using CT and MRI for Crohn's disease, a combination of intravascular and intraluminal contrast is generally used. The intraluminal contrast may be positive (high attenuation, e.g., diatrizoate meglumine [Gastrografin] in CT, iso-osmolar polyethylene glycol solution in MRI) or negative (low attenuation, e.g., methylcellulose in CT, dilute barium in MRI); the lumen must be clean and fully distended with contrast because undistended bowel loops can mimic abscesses, masses, enlarged lymph nodes, or a segment with wall thickening. Full luminal distention requires a large volume of contrast (1.5 to 2 L or more) given relatively rapidly (over a period of 45 to 90 minutes); it can be given orally or via a nasogastric/jejunal tube. Motion artifacts can be problematic, so antiperistaltic agents may be given before scanning, particularly with MRI. In addition, rapid distention with large volumes of intraluminal contrast can induce reflex atony, and faster multidetector scanners allow the acquisition of images during a single breath hold. Please see referenced material for descriptions of CT and MRI scanning protocols.[40,48]

Cross-sectional images (Figs. 70–7 and 70–8) should be analyzed for the following[40,49]:

- Length of involved segments.
- Skip lesions.
- Wall thickening—Normal wall thickness is 1 to 2 mm for distended small intestine and 3 mm for colon. Bowel wall thickness exceeding 4 to 5 mm is considered abnormal. Bowel wall thickening is the most consistent feature of Crohn's disease on cross-sectional imaging. Adequate distention with intraluminal contrast is a necessity.
- Degree of enhancement and patterns of attenuation—After the administration of intravenous contrast, active lesions have increased enhancement, which is a marker of inflammation; alternating layers of mural enhancement and attenuation (double-halo or target sign) can also be seen in active lesions.
- Stenosis and pre-stenotic lesions—The small bowel lumen is normally 2.5 cm in diameter; luminal dilation proximal to areas of stenosis and luminal narrowing is easily identified on cross-sectional imaging. Adequate distention with intraluminal contrast is required because inadequate contrast beyond stenotic lesions may lead to underestimation of more distal disease.
- Abscess and fistula—A phlegmon or abscess is easily identified on cross-sectional imaging; however, CT and MRI are less sensitive in identifying fistulas and sinus tracts than conventional enteroclysis is.
- Fibrofatty proliferation—Also known as creeping mesenteric fat, it is seen adjacent to involved bowel segments as slightly increased attenuation on CT and slightly decreased attenuation on MRI.
- Increased vascularity of the vasa recta (comb sign).
- Mesenteric adenopathy—Abnormally large mesenteric lymph nodes from 3 to 8 mm can be identified; nodes larger than 10 mm should increase suspicion for carcinoma and lymphoma.
- Early-stage lesions—Small aphthous ulcers, subtle distortions of bowel folds, and slight enlargement of lymph follicles may not be appreciated on cross-sectional imaging because of limitations in spatial resolution.

Ultrasound

The idea that ultrasound is useful in the diagnosis of abdominal surgical diseases, particularly in those that involve transmural inflammation and wall thickening of hollow viscera, should not seem unusual given its usefulness in cholecystitis and appendicitis; it is no surprise that the use of ultrasound for the assessment of a variety of inflammatory disorders of the small and large intestine is gaining increasingly widespread acceptance. Although transabdominal ultrasound for the evaluation of Crohn's disease is well supported in the literature and is becoming more commonplace in Europe, it remains a rarity in the United States. The oft-cited advantages of ultrasound, including cost, availability, noninvasiveness, and lack of ionizing radiation, have been augmented by technologic advances that have improved resolution. These improvements not only allow good cross-sectional imaging of the gut wall but, like CT and MRI, also allow examination of the surrounding mesentery and abdominal cavity for evaluation of extramural disease manifestations. It is now possible to visualize, localize, and gauge the extent of transmural inflammation while

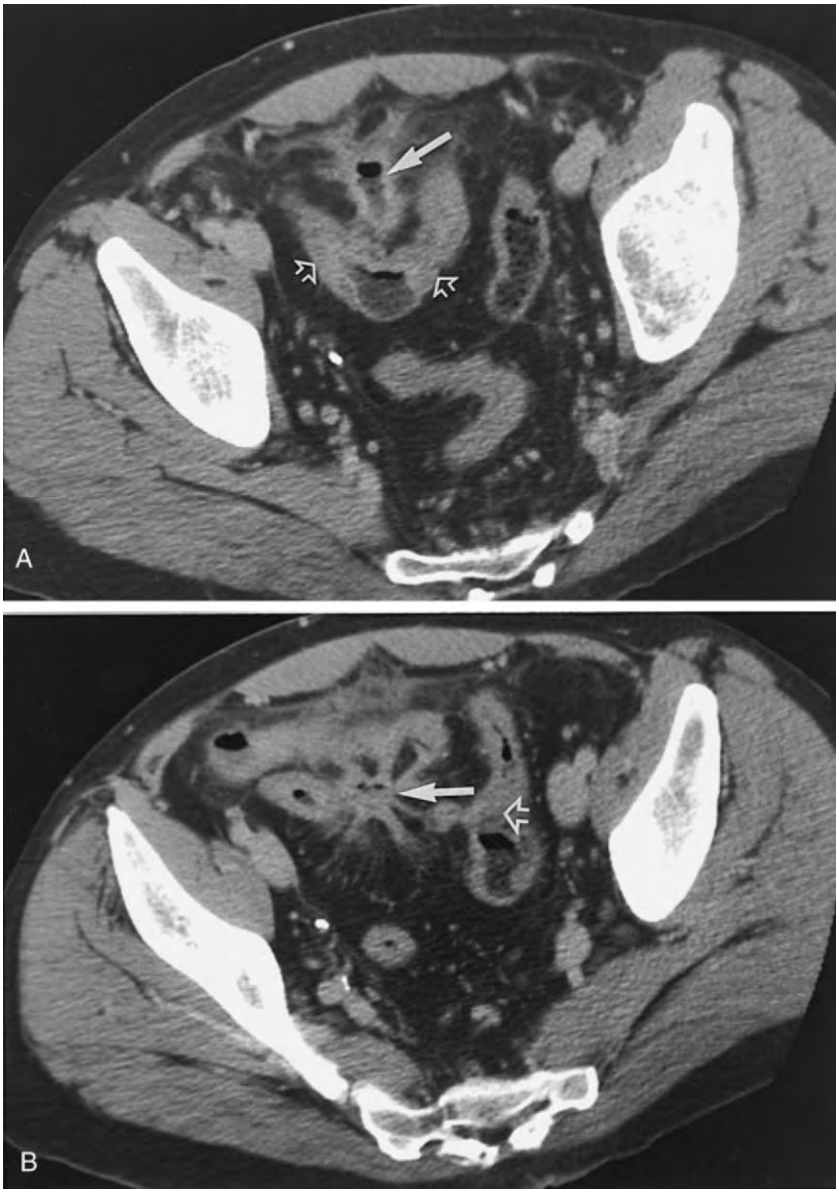


Figure 70–8. Ileal Crohn's disease with tracts and abscesses. **A,** A gas-containing mesenteric abscess *(solid arrow)* is close to transmural Crohn's disease of the terminal ileum *(open arrows).* **B,** Top of the abscess in the mesentery *(solid arrow)* with a fistula to the adjacent Crohn's disease–involved ileum *(open arrow).* Multiple tracts are related to the abscesses. (From Herlinger H, Caroline DF: Crohn's disease of the small bowel. In Gore RM, Levine MS [eds]: Textbook of Gastrointestinal Radiology, vol 1, 2nd ed. Philadelphia, WB Saunders, 2000, p 740.)

detecting extraintestinal complications such as strictures, abscesses, and fistulas. Techniques that use anechoic intraluminal contrast or intravenous contrast agents with Doppler ultrasound will probably improve ultrasound's diagnostic capabilities even more. As is so often the case with complex ultrasound studies, their advantages can be offset by the degree of expertise required of the ultrasound technologists and radiologists; this shortcoming can lead to concerns regarding intraoperator variability and can engender questions regarding the applicability of study results to widespread practice. In addition, like CT and MRI, ultrasound is not sensitive enough to detect the subtle mucosal lesions that may be the only radiographic sign of early disease. Furthermore, ultrasound has been found to be less effective in the imaging of Crohn's disease localized to the anorectum. Finally, patient characteristics that make transabdominal ultrasound technically difficult in other settings, such as obesity or intraluminal gas, make transabdominal ultrasound in Crohn's disease more difficult as well. Even so, recent prospective studies comparing the accuracy of bowel ultrasound as the first imaging procedure in diagnosing Crohn's disease with the accuracy of endoscopy, radiologic studies, or surgical exploration followed by pathologic examination of the surgical specimens found sensitivities and specificities of 76% to 88% and 98% to 100%, respectively, results that support continued investigation.[50]

Endoscopy

Radiology and endoscopy have complementary roles in the diagnosis and subsequent management of Crohn's disease[51]; despite continued evolution in the state of the art for both, neither has gained primacy.

Push Endoscopy

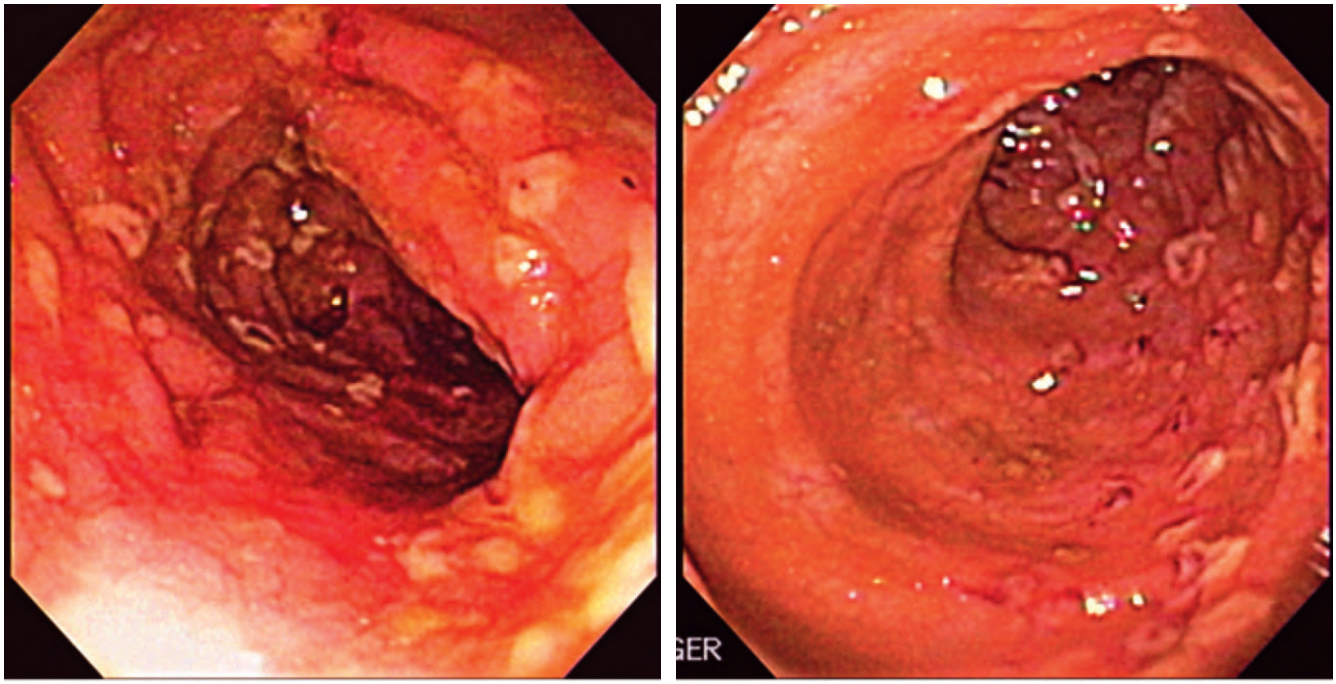
The advantages afforded by push endoscopy, including colonoscopy with ileoscopy and esophagogastroduodenoscopy, in the diagnosis and management of Crohn's disease are many: the ability to detect subtle mucosal lesions, which in many cases are the only sign of early disease; the ability to obtain biopsy samples for histologic examination; and increasingly, the ability to perform intraluminal therapeutic interventions.

Patients with Crohn's disease most commonly have abdominal pain and chronic diarrhea as their initial complaints. The majority of patients with chronic diarrhea will undergo some type of endoscopy, and if the remainder of the antecedent clinical evaluation is suggestive of inflammatory bowel disease, colonoscopy with the addition of ileoscopy is a good first choice of diagnostic procedure[51] because it can help differentiate between Crohn's disease and ulcerative colitis on the basis of mucosal changes, disease distribution, and histology (multilevel biopsy specimens that include the terminal ileum, along with histologic examination, significantly increase the diagnostic sensitivity and specificity of endoscopy in inflammatory bowel disease[52]).

In the differentiation of Crohn's disease from ulcerative colitis, the most important colonoscopic findings are aphthous ulcers (Fig. 70–9), cobblestoning, and discontinuous lesions.[53] In addition, terminal ileal involvement and rectal sparing are strongly suggestive of Crohn's disease. Although there may be "backwash ileitis" on ileoscopy in patients with ulcerative colitis, this finding is observed in the setting of pan-colitis with continuous involvement of the colon from the rectum to the cecum[52,54]; in patients with inflammatory bowel disease and isolated terminal ileal involvement, the diagnosis of Crohn's disease is secure.[55,56] Because rectal involvement is essentially a prerequisite for the diagnosis of ulcerative colitis, rectal sparing, which occurs in about 40% of patients with Crohn's disease, is useful in differentiation between the two forms of inflammatory bowel disease, although there are caveats: the rectal mucosa may appear normal despite histologic evidence of pathology on biopsy, and rectal sparing can occur in up to 40% of medically treated patients with ulcerative colitis.[57]

Because Crohn's disease may involve the upper gastrointestinal tract, esophagogastroduodenoscopy plays a role in diagnosis and management. Indeed, because the frequency of upper gastrointestinal tract Crohn's involvement seems to be much higher than previously reported, the role that upper endoscopy plays will probably increase. For example, in patients with indeterminate colitis, involvement of the upper gastrointestinal tract provides strong evidence in favor of Crohn's disease; in patients with known Crohn's disease who have upper gastrointestinal symptoms, upper endoscopy can facilitate diagnosis of the underlying cause, whether it be Crohn's or some other disease; and it is certainly possible that patients might have Crohn's disease isolated to the upper gastrointestinal tract.[58,59]

The use of endoscopy in the clinical management of Crohn's disease subsequent to diagnosis is evolving. With regard to monitoring of disease activity after initiation of



A B

Figure 70–9. **A** and **B,** Multiple aphthous ulcers seen in recurrent Crohn's disease in the neoterminal ileum of the ileocolonic anastomosis 3 months after resection. (From Krok KL, Lichtenstein GR: Inflammatory bowel disease. In Ginsberg GG, Kochman ML, Norton ID, et al [eds]: Clinical Gastrointestinal Endoscopy. Philadelphia, WB Saunders, 2005, p 317.)

medical therapy, endoscopy does not have a firmly established role. Although endoscopic indices of disease activity have been developed and validated, with the most extensively studied being the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the newest being the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD), they have not seen widespread use for a variety of reasons. Though reliable and reproducible, CDEIS is complex, which limits its use in clinical trials and day-to-day practice. The SES-CD is probably easier to use, but because of its recent development, it is has yet to be widely applied. Neither CDEIS nor SES-CD has been shown to correlate especially well with clinical disease activity, nor have studies shown that steroid-induced clinical remission is closely linked to mucosal healing. In contrast, studies of treatment with immune modulators such as infliximab and azathioprine have shown correlation between mucosal healing and clinical improvement, so evidence of healing on endoscopy is becoming an important therapeutic target.[60,61] When considering surveillance after curative resection, endoscopic severity evaluated with the Rutgeerts' score predicts the likelihood of symptomatic recurrence.[61] Endoscopy also has an important role in cancer surveillance in patients with long-standing colonic Crohn's disease.[62] From an interventional perspective, endoscopic balloon dilation with or without steroid injection may offer an alternative to surgical therapy for primary and postsurgical Crohn's strictures, although randomized controlled trials are needed for comparisons of safety and efficacy with more standard therapies.[63]

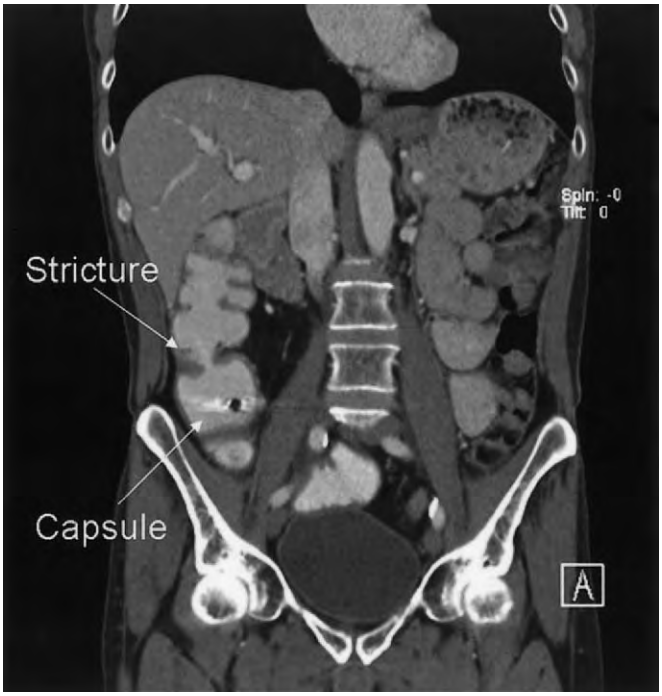


Figure 70–10. Abdominal computed tomography scan illustrating Crohn's stricture of an ileocolonic anastomosis trapping a video endoscopy capsule.

Wireless Video Capsule Endoscopy

Wireless video capsule endoscopy requires a system made up of several components. There is a single-use capsule 26 mm long by 11 mm in diameter that contains a color camera chip, lens, light source from a light-emitting diode, radiofrequency transmitter, antenna, and batteries. Two images are acquired every second, for a total of about 50,000 in an 8-hour study. The images are sent to a belt-worn receiver with a 5-gigabyte hard drive. Images are then downloaded to a computer workstation and viewed as continuous video, with viewing and interpretation typically requiring 1 to 2 hours. Study length is dictated by the capsule's battery life, so the belt is worn for approximately 8 hours after ingestion of the capsule, during which time patients are able to continue their normal daily activities. The capsule's movement is completely passive and relies on peristalsis to progress distally, and it is designed to be passed spontaneously.[64,65] Studies report complete evaluation of the small intestine in as few as 50% and as many as 85% of cases, with most studies reporting 65% to 80% success rates.[66]

Before the introduction of wireless capsule endoscopy in the year 2000, a majority of the small intestine's length was essentially inaccessible to endoscopy performed in the nonsurgical setting. A subsequent pilot study in 2002 reported the use of capsule endoscopy for obscure gastrointestinal tract bleeding, and it has rapidly become the test of choice for obscure small bowel bleeding.[64]

Because 70% of patients with Crohn's disease have involvement of the small intestine[25] and subtle mucosal lesions may be the only signs of early disease, it follows that capsule endoscopy could be extremely useful in the diagnosis and subsequent management of Crohn's disease. Early investigators were understandably reluctant to use the capsule in Crohn's patients; given the capsule's size and the propensity for stricture formation in Crohn's disease, the fear of capsule-induced mechanical obstruction must have loomed large.[67] The rate of "non-natural excretion," that is, capsules requiring endoscopy or surgery for removal, has been reported to be as low as 0% and as high as 15%, depending on study indications and patient populations.[66,68] Even so, a number of studies have been completed in which the diagnostic utility of capsule endoscopy was evaluated in patients with Crohn's disease.[68] Capsules that do not pass spontaneously in patients with Crohn's disease are usually due to strictures (Fig. 70–10), with many of these patients having undergone radiographic studies before ingestion that showed no evidence of stenosis. To reduce the likelihood of retained capsules and possibly obviate the need for radiographic studies before capsule ingestion, a similarly sized, dissolvable "patency capsule" has been developed. When they are retained, wireless endoscopy capsules do not usually cause acute small bowel obstruction; instead, the diagnosis is typically made several days after ingestion based on patient suspicion and intermittent obstructive symptoms. Separate from concerns about obstruction caused by

capsules, other problems inherent in the interpretation of these studies in patients with Crohn's disease still remain[64,68]:

- Study results from institutions with special expertise in capsule endoscopy may not be generalizable to everyday practice.
- Prospective studies to determine the sensitivity, specificity, accuracy, and positive and negative predictive values have not been completed for want of a clear nonsurgical gold standard for diagnosis and for want of a group of prospective patients with long-term follow-up.
- Capsule endoscopy gives information about mucosal lesions and possibly stenosis, leaving aside information about wall thickening or any extraluminal findings.
- The commonality and importance of scattered mucosal breaks, aphthous ulcers, or erosions in various groups of patients, from asymptomatic volunteers to those with suspected or known Crohn's disease, need to be determined, and diagnostic standards need to be created and validated.

Despite these problems, capsule endoscopy is destined to become an important part of the armamentarium for the diagnosis and management of Crohn's disease.

Medical Therapy

All modes of therapy for Crohn's disease have similar goals, which are to reduce symptoms while maintaining or improving patient quality of life. As previously stated, patients with Crohn's disease are usually initially seen with active disease, so typically, a sequential approach to therapy is used in which remission is first induced and then maintained. Current medical regimens require careful consideration of disease location and the level of disease activity (mild, moderate, or severe). Therapy should be individualized according to the patient's disease activity, as well as response to and tolerance of the medical intervention (Fig. 70–11).[20]

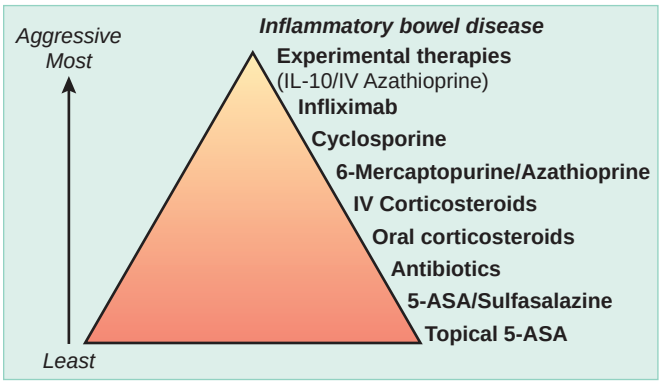


Figure 70–11. Therapeutic pyramid for escalation of medical therapy for Crohn's disease. ASA, acetylsalicylic acid. (From Johns Hopkins University Crohn's Disease Resource Web Page. Copyright Johns Hopkins 2000.)

Inducing Remission in Patients with Active Disease

Corticosteroids have long been used to induce remission in patients with Crohn's disease, and randomized controlled trials have proved the effectiveness of conventional steroids such as prednisone in patients with mild or moderate disease. However, the benefits of conventional steroid treatment may be offset by serious adverse effects in some patients (giving rise to steroid-intolerant patients), little or no improvement in others (steroid-resistant patients), and disease flares during or shortly after tapering (steroid-dependent patients). More than 35% of patients treated acutely with conventional steroids will become steroid dependent or steroid resistant. Budesonide is a corticosteroid with extensive first-pass liver metabolism that results in low systemic bioavailability, which gives it the potential to reduce side effects; the oral version for use in Crohn's disease (inhaled versions are used for the treatment of allergic rhinitis and asthma) is an enteric-coated, controlled-release formulation. Unfortunately, budesonide is effective in a limited number of patients: 30% to 40% of patients will not respond, and studies show that it is useful in patients with ileal and right-sided colonic disease, but not in those with left-sided colonic disease.[20,69] Steroids are not useful in maintaining remission.[70]

Aminosalicylates, including 5-aminosalicylic acid (mesalamine and the controlled-release forms Asacol and Pentasa) and sulfasalazine (a sulfonamide antibiotic, sulfapyridine, linked to mesalamine), can be used selectively to induce remission. Sulfasalazine has been proved effective for inducing remission in patients with colitis or ileocolitis and mildly to moderately active Crohn's disease; it is not useful in maintaining remission. The studies evaluating mesalamine, including Asacol and Pentasa, in active Crohn's disease have been mixed, and experts disagree with regard to their usefulness in inducing and maintaining remission, although they are still considered to be first-line therapy at many centers.[20,69,71]

Antibiotics, including metronidazole and ciprofloxacin, are currently used clinically and have been studied singly, together, and in combination with budesonide for induction of remission (although not for maintaining remission) in mild to moderately active Crohn's disease. Metronidazole has not been proved to be superior to placebo for inducing remission, although one Scandinavian crossover trial found it to be as effective as sulfasalazine.[69,72] The data for ciprofloxacin in Crohn's disease are mixed; controlled trials have shown the superiority of ciprofloxacin over placebo for inducing remission, but another showed that in combination with metronidazole, it is less effective than prednisone. Combinations with budesonide and prednisolone have not been demonstrated to be more effective than monotherapy with these agents.[71,72] Besides inconsistently proven efficacy, significant side effects can occur with the long-term use of either drug, and the development of antibiotic-resistant organisms is a justifiable concern.[20]

For patients with mild to moderate disease that fails to respond to first-line treatment with steroids

(including budesonide) or sulfasalazine or for patients with more severe disease, treatment with immunomodulators is appropriate.[69] *Azathioprine* is the prodrug of 6-mercaptopurine, which is a precursor to intracellular purine antimetabolites that have an antiproliferative effect on mitotically active lymphocyte populations. Multiple randomized studies and a meta-analysis of these studies support the use of azathioprine and 6-mercaptopurine in the treatment of active Crohn's disease, although it may take 4 to 8 weeks for them to begin to take effect.[69,73] Side effects include pancreatitis, bone marrow suppression, allergic reactions, and increased rates of infection.[73]

Methotrexate is a folic acid structural analogue that competitively inhibits the binding of dihydrofolic acid to the enzyme dihydrofolate reductase, which is involved in purine and pyrimidine synthesis; thus, the drugs impair DNA synthesis. The relevant mechanism of action in inflammatory bowel disease, however, has not been fully elucidated.[73] Methotrexate has been shown in randomized controlled trials to be more effective than placebo in treating active Crohn's disease and will induce remission in a significant proportion of patients with corticosteroid- and azathioprine/6-mercaptopurine–resistant disease; it usually requires at least 4 to 6 weeks to take effect.[69,73,74] Liver toxicity is the most serious potential side effect in patients taking methotrexate, and nausea is a common complaint. In addition, methotrexate is teratogenic and an abortifacient.[73]

Infliximab is a chimeric mouse-human monoclonal antibody against TNF-α. In a study that established the use of infliximab in Crohn's disease, a single infusion allowed 33% of patients to enter remission as compared with a placebo rate of 4%, it improved disease in 81% as compared with 17% of controls, and response to infliximab can be seen in as little as 1 to 2 weeks.[69] The effectiveness of infliximab has led to the development of a number of new biologic agents for the treatment of Crohn's disease, including a variety of antibodies with TNF-α as their target, as well as antibodies to interleukins, interferon-γ, and leukocyte adhesion molecules, all of which are in various phases of clinical trials.[75]

Maintaining Remission

A vitally important goal of therapy for Crohn's disease is maintenance of remission. Daily azathioprine and 6-mercaptopurine have been proved in randomized controlled trials to be more effective than placebo in maintaining remission after medical induction; a retrospective study suggests that azathioprine may prevent recurrence after surgery as well.[74] Because of their side effects, potential for significant toxicity, and toxicity-monitoring requirements, important questions remain concerning the discontinuation of azathioprine and 6-mercaptopurine therapy. A recent study of patients with Crohn's disease in remission for at least 42 months found that withdrawal of azathioprine led to an 18-month relapse rate of 21% versus 8% in the group randomized to continue treatment.[69] Another study found that the efficacy of azathioprine is maintained over a period of at least 5 years.[74] Weekly methotrexate has a proven role in maintaining remission of Crohn's disease, with its use generally preceded by methotrexate induction; the optimum duration of therapy has yet to be confirmed, although it is suggested that it could be effective for 3 to 4 years. Given methotrexate's primary adverse effects, it is best avoided in patients with risk factors for liver disease or established liver disease and in those desiring to conceive.[69,74] Infliximab infusions given every 8 weeks have been shown to be effective in maintaining remission in those who respond to the initial infusion. Patients may form antibodies to infliximab, and these antibodies are responsible for acute and delayed hypersensitivity reactions, as well as loss of responsiveness in those who responded previously; this has led to the use of concomitant immunosuppression in Crohn's patients receiving infliximab.[69,74,75] Steroids are not effective in maintaining remission of Crohn's disease, although budesonide can prolong the time to relapse. The use of 5-aminosalicylates for maintaining remission is controversial, with current evidence not supportive of their use in medically induced patients, although they do show some promise in maintaining remission in surgically treated patients.[69,74]

Because most patients will relapse after medical induction, a reasonable approach to maintenance would include azathioprine, 6-mercaptopurine, methotrexate, or infliximab and, in select cases, budesonide (in patients with distal small intestinal or right-sided colonic disease, with the understanding that the treatment effect will probably last less than a year).[69] Infliximab is very expensive (the average third-party reimbursement per dose administered to a 70-kg patient is more than $5200),[76] so it should probably be reserved for patients refractory to other agents, thus leaving azathioprine, 6-mercaptopurine, and methotrexate for most patients. Given the toxicity profiles of infliximab and the immunosuppressive agents, it is reasonable to give patients at least one trial free of maintenance therapy; if symptoms recur within 6 to 12 months, repeat induction should be followed by maintenance therapy with the aforementioned agents indefinitely as patient tolerance allows.[69,71]

Nutrition

Nutrition is an important consideration in the care of patients with Crohn's disease, both in terms of supportive care, which is directed at correcting malnutrition, and potentially as an alternative means of treatment.[77]

Malnutrition

Deficiencies in macronutrients (protein, energy) and micronutrients (vitamins, minerals, and electrolytes) are common in patients with Crohn's disease.[78] The degree of malnutrition depends on disease location, extent, and activity. The long-term malnutrition seen in patients with Crohn's disease may have a multitude of consequences, including growth failure and pubertal delay in children, bone loss, delayed healing of fistulas, poor wound healing after surgery, and increased susceptibility to infection.[79] Assessment of nutritional status includes a

history, physical examination, and laboratory studies focusing on intake, body mass index, serial body weight, muscle wasting, edema, serum albumin, and iron studies; more detailed assessment may include anthropometry and the use of scoring systems such as the Subjective Global Assessment.[77] Factors that contribute to malnutrition in patients with Crohn's disease include the following[78]:

- Anorexia—Decreased appetite is probably due to the high levels of inflammatory cytokines, such as TNF-α, that result from dysregulation of systemic immunity.
- Bowel obstruction—Caused by stricture or abscess.
- Abdominal pain—Caused by inflammation or obstruction.
- Malabsorption—Caused by altered or reduced absorption as a result of inflammation, postinflammatory changes, or surgical resection.
- Losses from the gut—Protein-losing enteropathy may develop in patients with mucosal injury; components of serum, including proteins, iron, lipids, and trace elements, are lost intraluminally because of leaky capillaries in inflamed areas of bowel.
- Direct drug effects and drug-nutrient interactions.
- Increased metabolic requirements, particularly in the setting of complicated disease.
- Prescription of restricted diets.

Specific nutrient deficiencies include the following:

- Vitamin B_{12} (cobalamin)—Deficiency is secondary to decreased absorption of the vitamin B_{12}–intrinsic factor complex in diseased or resected ileum. Vitamin B_{12} deficiency may contribute to anemia in Crohn's patients, and it is a cofactor in homocysteine metabolism (for more detail, see discussion of folate later).[78]
- Calcium—Patients with Crohn's disease do have malabsorption of calcium as a result of complexes formed with unabsorbed intraluminal fats and decreased absorption of vitamin D (a fat-soluble vitamin), although serum calcium levels are maintained by the action of parathyroid hormone, potentially at the expense of bone density. Osteopenia is common in patients with Crohn's disease, with steroid use, along with patient factors such as genetics, contributing to the problem.[77,78,80]
- Fat-soluble vitamins—The adequacy of vitamins A, E, D, and K may be affected as a result of fat malabsorption secondary to disease affecting any part of the small intestine and as a result of alterations in bile acid metabolism, particularly with terminal ileal disease or resection.[81]
- Folate—Folate deficiency is common in patients with Crohn's disease; it is caused by dietary deficiency, increased utilization, and drug treatments, including sulfasalazine, which can bind folate and thereby make it unavailable for absorption, and methotrexate, which is a folic acid antagonist. Inadequate levels of folate may play a role in development of anemia in patients with Crohn's disease. Increased levels of folate may have a protective effect with regard to the development of dysplasia and colorectal cancer, so decreased levels may be another factor in the increased cancer risk seen in Crohn's patients. Folate is a cofactor in homocysteine metabolism, and deficiency may lead to elevated plasma homocysteine levels, which may induce a hypercoagulable state and increase the incidence of thromboembolic events in patients with inflammatory bowel disease.[77]
- Iron—Deficiencies may result from loss secondary to intraluminal bleeding, from decreased absorption because of small bowel disease or resection, and from dietary restrictions, all of which can contribute to the anemia seen in Crohn's disease.[82]
- Selenium—A number of studies have demonstrated decreased selenium concentrations in Crohn's disease patients with a concomitant decrease in glutathione peroxidase activity; the catalytic action of this enzyme protects cells from oxidative damage by lipid peroxides.[80,83]
- Zinc—Deficiencies are difficult to assess because serum levels correlate poorly with total-body zinc stores, but deficiencies are thought to be fairly common in patients with Crohn's disease as a result of decreased absorption or increased loss because the diets of adults with Crohn's disease typically contain a similar amount of zinc as the diets of control subjects. In addition to detrimental effects on wound healing, severe zinc deficiency leads to clinical features of acrodermatitis, such as alopecia, anorexia, diarrhea, dermatitis, poor growth, and impaired immune function.[84]

Supportive nutritional therapy is aimed at improving the nutritional status of the malnourished patient, and unless absolutely contraindicated, the enteral route is preferred. Oral or tube feeding supplementation with protein, calories, and micronutrients can be implemented with any number of commercially available formulas; the decision about which oral or tube feeding formula to use should be based on cost, palatability, and patient tolerance. Initial electrolyte monitoring and replacement are important in severely malnourished patients to prevent the refeeding syndrome. Given its cost and potential for complications, total parenteral nutrition (TPN) as a means of nutritional supportive care should be limited to short-term use in those with bowel obstruction or fistulas, with long-term use reserved for those with short-gut syndrome; there is some, albeit limited, evidence to support the use of TPN in severely malnourished Crohn's disease patients in preparation for surgery.[77]

Nutrition as Primary Therapy

There is evidence to support the use of restricted diets based on enteral nutrition formulas as therapy to induce remission of Crohn's disease, and although potential mechanisms of action such as decreased antigenic presentation have been postulated, the physiology underlying the treatment effect is unknown. There are three meta-analyses and a Cochrane review of randomized

control trials involving enteral therapy as primary treatment of Crohn's disease.[77] They have found that elemental formulations do not have greater efficacy than nonelemental formulations do in induction of remission and that enteral nutrition is not as effective as steroids for induction of remission.[85] Although enteral nutrition has not been compared with placebo, the response rates in studies to date have been greater than one would expect from placebo.[77] Given the side effects associated with steroid treatment and the benign nature of nutritional therapy, there is continued interest in enteral nutrition as primary therapy for Crohn's disease.[77,85]

SURGICAL THERAPY

In addition to general considerations and medical therapy for Crohn's disease, this chapter focuses on surgical therapy for Crohn's disease involving the small intestine. Studies that have monitored patients with Crohn's disease after diagnosis have found variable rates for the requirement for intestinal surgery, but the rates are consistently high[86]; 57% of patients studied in a population-based American cohort required at least one surgical resection,[1] whereas 78% of patients in the National Cooperative Crohn's Disease Study required surgery by 20 years after symptom onset.[87] Because the majority of patients with Crohn's disease have small bowel involvement, a discussion focused on the surgical management of small bowel Crohn's disease is of particular importance. However, surgical management of Crohn's disease can be made complicated by the potential for involvement of any part of the gastrointestinal tract, the segmental nature of involvement, the likelihood of recurrence requiring multiple procedures, penetrating disease causing abscesses and fistulas, adhesions, malnutrition, and medical therapy with immunosuppressive agents. Indications for surgical therapy and subsequent decisions with regard to technique must be carefully considered.

Indications

Surgical therapy for diseased segments does not cure Crohn's disease; therefore, it should be used only to treat complications that are not amenable to medical therapy, and with the potential for recurrence and the need for reoperation in mind, all procedures should be performed with consideration for the conservation of small intestinal length. Indications for operative intervention are directly related to the site of intestinal involvement (Box 70–1)[88]:

- Failure of medical therapy—Medical therapy has failed when maximal medical therapy proves inadequate, successful medical induction is followed by failure of maintenance therapy, and significant complications related to medical treatment develop. As medical therapies improve, definitions for failure of medical therapy will continue to evolve.
- Penetrating disease—Patients with a penetrating pattern of disease may also require surgical therapy. Although penetrating disease is not always an absolute indication, it may require operative intervention if complicated (see Box 70–1). If feasible, abscesses may be treated by percutaneous drainage and systemic antibiotics, thereby delaying definitive surgery until it can be safely performed.
- Free perforation—Although a rare complication, perforation requires immediate surgical intervention.
- Obstruction—Obstruction as a result of single or multiple, sometimes lengthy strictures may require stricturoplasty or resection; patients should be decompressed and resuscitated before surgery.

Box 70–1 Indications for Surgery in Patients with Crohn's Disease

Failure of medical treatment
- Persistence of symptoms despite corticosteroid therapy for longer than 6 months
- Recurrence of symptoms when high-dose corticosteroids are tapered
- Worsening symptoms or new onset of complications with maximal medical therapy
- Occurrence of steroid-induced complications (cushingoid features, cataracts, glaucoma, systemic hypertension, aseptic necrosis of the head of the femur, myopathy, or vertebral body fractures)

Obstruction
- Intestinal obstruction (partial or complete)

Penetrating disease
- Fistula if
  - Drainage causes personal embarrassment (e.g., enterocutaneous fistula, enterovaginal fistula, fistula in ano)
  - Fistula communicating with the genitourinary system (e.g., enterovesical or colovesical fistula)
  - Fistula producing functional or anatomic bypass of a major segment of intestine with consequent malabsorption and/or profuse diarrhea (e.g., duodenocolic or enterorectosigmoid fistula)
- Inflammatory mass or abscess (intra-abdominal, pelvic, perineal)
- Free perforation

Hemorrhage

Carcinoma

Fulminant colitis with or without toxic megacolon

Growth retardation

Adapted from Sartor RB, Sanborn WJ (eds): Kirsner's Inflammatory Bowel Diseases. Philadelphia, WB Saunders, 2004:597.

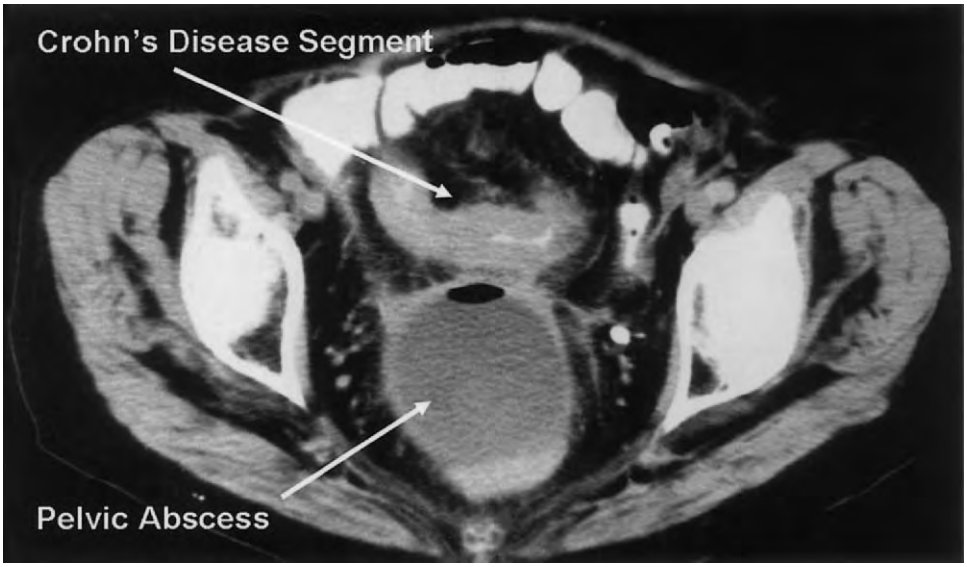


Figure 70–12. Pelvic abscess associated with diseased ileum.

- Other less frequent complications such as massive gastrointestinal hemorrhage, cancer, toxic megacolon, and growth retardation are also indications for surgery.

Preoperative Evaluation and Preparation

Proper preparation of a patient with Crohn's disease for surgery cannot be overemphasized. Every effort should be made to optimize the patient's medical status before surgery, including identifying and mitigating any medical comorbid conditions. If infectious complications secondary to penetrating disease are suspected, cross-sectional imaging is essential because it allows identification of potential abscesses. To minimize the risk for anastomotic leak and the need for diversion, any abscesses that are found should be drained, with percutaneous techniques if possible, before embarking on operations that may require resection (Fig. 70–12). In some instances, complete evaluation of the entire gastrointestinal tract should be undertaken preoperatively to localize areas affected by disease; such evaluation can be accomplished with a combination of endoscopy, contrast studies, cross-sectional imaging, and capsule endoscopy. Complete evaluation of the gastrointestinal tract may not be possible when emergencies arise, which leaves intraoperative evaluation as the primary means of diagnosis. When urgent or emergency intervention is required, patients should not be denied appropriate resuscitation, antibiotics for treatment or surgical prophylaxis, or thromboembolism prophylaxis.

Any patient in whom construction of an intestinal stoma is even a remote possibility should be adequately prepared for the eventuality. Preparation should include preoperative consultation with an enterostomal therapist and, at the very least, marking of an appropriate site or sites for the potential stoma. Blind intraoperative selection of an intestinal stoma site frequently leads to inappropriate placement; a location that is too close to an incision, in a body crease, or in a belt line can make postoperative stoma management difficult.

When operative therapy can or must be delayed, attention should be paid to assessing and correcting malnutrition and metabolic abnormalities. If patients have lost more than 5% of their baseline weight in the preceding 3 months or if they have an albumin concentration that is less than 3.0 g/dl, their nutritional status puts them at increased risk for perioperative complications, and if possible, they should be considered for nutritional intervention before surgery. The enteral route is always preferred if it can be tolerated and when disease complications allow. There is limited evidence to support the use of TPN in the preoperative setting, although a severely malnourished patient may benefit.[88]

With regard to mechanical bowel preparation, a number of randomized controlled trials and meta-analyses have concluded that it is not beneficial and potentially harmful in colorectal surgery[89]; it should certainly be avoided in small bowel procedures.

Patients with suppressed adrenal function because of treatment with corticosteroids should continue steroid treatment in the perioperative period, and although the use of superphysiologic so-called stress-dose steroids in patients who are not critically ill is of unproven benefit, it is still recommended by some experts,[88,90] which should not be confused with steroid use in critically ill patients with hypotension requiring vasopressors, in whom current and mounting evidence suggests that testing for adrenocortical insufficiency and treatment with stress-dose steroids may be beneficial.[91]

Operative Strategies and Techniques

Abdominal Incision

In patients with Crohn's disease who are undergoing abdominal operations, the importance of selection and placement of incisions cannot be overemphasized. Many of these patients will require multiple abdominal operations during the course of their disease. Some will

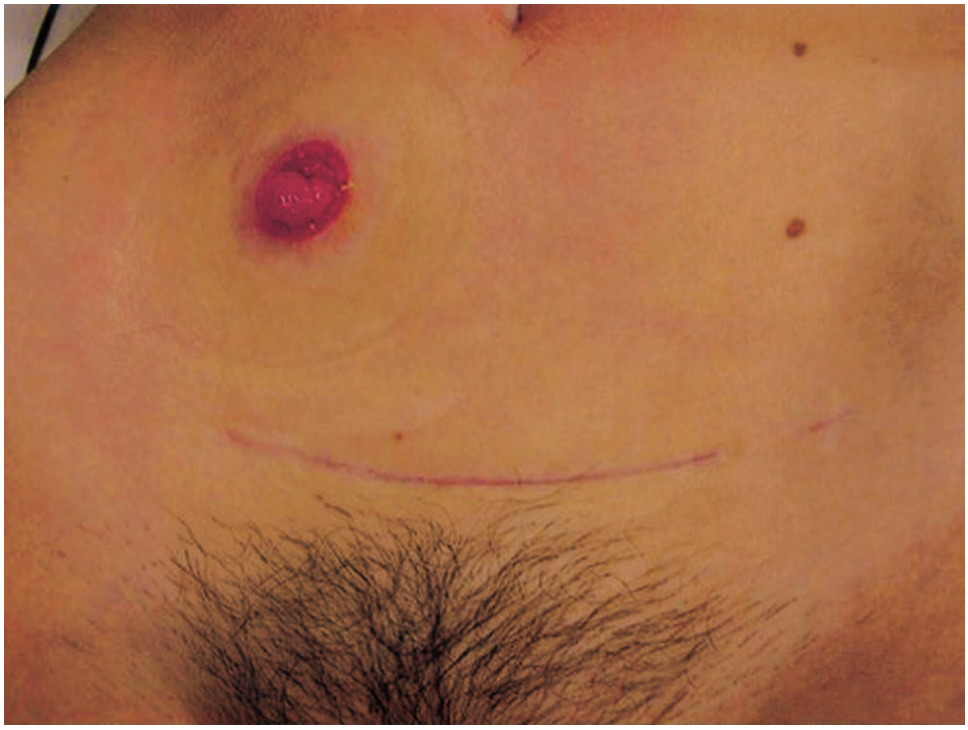


Figure 70–13. Pfannenstiel incision and diverting ileostomy.

require a stoma, if not at the time of their initial procedure, then in the future, so the placement of scars may potentially have long-term consequences. Transverse incisions or incisions off the midline for either open or laparoscopic surgery should be avoided because scars at these sites may preclude their use for future stoma placement; moreover, because future laparotomies may require an incision that is entirely different from the initial transverse incision, the patient may be put at increased risk for hernia formation.

In our practice, a low, transverse Pfannenstiel incision has been used in more than 300 Crohn's disease patients with excellent results. It is a useful approach for procedures involving the small intestine, the lower part of the abdomen, and the pelvis, and with the use of mechanical retractor systems and headlights, access to the upper part of the abdomen may be achieved. The incision yields excellent cosmetic results with a negligible rate of hernia in our hands, and the literature reports similarly low hernia rates (0% to 3.7% versus as high as 42% with midline incisions).[92,93] It allows ample room to pack away the abdominal contents, and it facilitates stoma placement (Fig. 70–13). We use a retractor consisting of two elastic rings connected by a clear plastic sleeve to facilitate exposure through these smaller incisions (Alexis Wound Retractor, Applied Medical, Rancho Santa Margarita, CA, 92688) (Fig. 70–14).

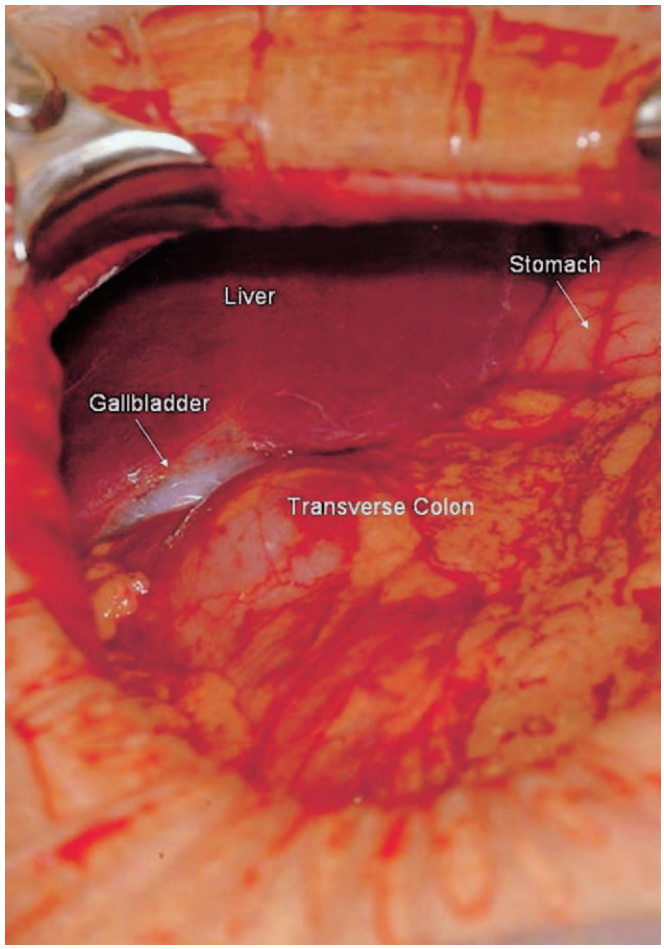


Figure 70–14. Exposure afforded by a Pfannenstiel incision.

Abdominal Exploration and Identification of Diseased Segments

Complete exploration of the abdomen with a focus on identifying diseased segments of the gastrointestinal tract should be performed. Crohn's involvement may be

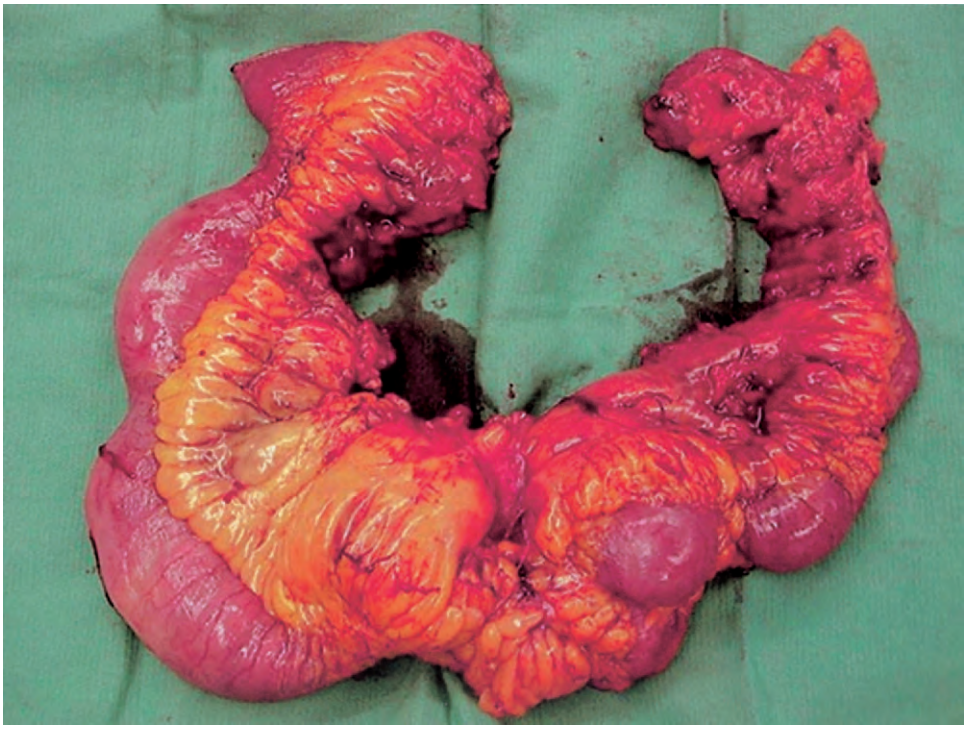


Figure 70–15. Specimen from ileocecectomy for Crohn's disease depicting serosal hyperemia and extension of mesenteric fat onto the serosal surface, which is commonly referred to as "fat wrapping" or "creeping fat."

obvious with thickened bowel wall and adjacent mesentery, serosal hyperemia, and extension of mesenteric fat onto the serosal surface, commonly referred to as "fat wrapping" or "creeping fat" (Fig. 70–15). If the mesenteric border is examined by visual inspection and palpation, more subtle disease may be identified at sites where the bowel wall becomes indistinguishable from the mesentery.[94] Another method for identifying clinically significant obstructing disease that we use infrequently involves the use of a Foley catheter; after creating an enterotomy over a known area of disease or stenosis that is to be resected or is to undergo stricturoplasty, an 18-French Foley catheter on an introducer is placed in the lumen, and the small bowel is telescoped onto the Foley catheter until the duodenum or ileocecal valve is reached. After inflating the balloon to 2 to 2.5 cm in diameter, it is gently pulled through the small intestine; strictures are identified when passage of the balloon is arrested.[95]

Bowel Resection Versus Stricturoplasty

Surgical techniques for the treatment of small intestinal Crohn's disease can be broadly classified into two groups: those that involve bowel resection and those that do not. Because surgery does not cure Crohn's disease nor prevent its recurrence, surgical strategies are focused on relieving its symptoms and complications while minimizing the amount of intestine that is removed.

Historically, the surgical approach to Crohn's disease was much like the surgical approach to cancer; a complete resection for cure with wide surgical margins and even intraoperative frozen sections to identify microscopic involvement seemed logical and was widely practiced. However, significant recurrence rates were seen even after extensive resections. It has since been established that recurrence is not negatively affected by disease at the surgical margins or positively affected by increased length of resection. This understanding, as well as the fear of iatrogenic short-bowel syndrome, has led to a bowel-sparing approach to surgical therapy for Crohn's disease that has made short-bowel syndrome in modern centers very rare[86] (one study of 464 patients with Crohn's disease undergoing surgery found that 21 [5%] had residual intestine <180 cm with just 7 of them requiring home TPN[96]). The bowel-sparing approach to surgical therapy for Crohn's disease has evolved to include techniques that avoid resection altogether. The application of stricturoplasty to small bowel stenoses caused by Crohn's disease is a relatively recent innovation, with the first report being published in 1982 by Lee and colleagues.[97] Since then, multiple studies have shown it to be safe and effective without an increased risk for recurrence.[86,95]

Indications for stricturoplasty include single or multiple fibrotic strictures within diffusely involved segments of small bowel, previous extensive (>100 cm) resections of small bowel, short-bowel syndrome, rapid recurrence of disease with obstruction (within 12 months), duodenal strictures, and strictures at previous anastomotic sites. Contraindications to stricturoplasty include perforation of the small bowel with or without peritonitis; phlegmonous inflammation, abscess, or fistula at the intended stricturoplasty site; likelihood of tension on closure of the stricturoplasty; and location of the intended stricturoplasty site in close proximity to a segment requiring resection.[95]

Given the contraindications to stricturoplasty, it is obvious that resection continues to be an important part of the surgical armamentarium in the treatment of Crohn's disease. A common indication for resection continues to be small bowel obstruction, and in many cases of obstruction, resection may be the treatment of choice, particularly in those with septic complications or those that involve the terminal ileum. Other indications for resection include penetrating disease with or without sepsis, major hemorrhage, and carcinoma.

Stricturoplasty Techniques

There are two main types of stricturoplasty: the Heineke-Mikulicz technique and its variations and those involving some form of side-to-side anastomosis. Stricture length is perhaps the most important consideration when choosing the type of stricturoplasty to be performed. Short strictures, or those less than 10 cm in length, may be treated with the Heineke-Mikulicz technique. Longer strictures or many short strictures close together require side-to-side techniques; the Finney stricturoplasty can be used with strictures that are 10 to 25 cm long,[95] and Michelassi and Upadhyay report using side-to-side isoperistaltic stricturoplasty in diseased segments averaging 51 cm and as long as 109 cm.[98]

The Heineke-Mikulicz stricturoplasty is performed by opening the antimesenteric wall of the strictured bowel longitudinally through all layers and reorienting the incision so that it is closed transversely with seromuscular interrupted or running absorbable suture (Fig. 70–16). Variations include the following[95,99]:

- Judd stricturoplasty, which allows longitudinal elliptical resection of a small portion of bowel wall, followed by transverse closure in situations in which there is a small area of penetration or damaged wall within a short stricture (Fig. 70–17).
- Moskel-Walske-Neumayer stricturoplasty, which uses a Y-shaped enterotomy rather than a longitudinal one, followed by transverse closure, which helps avoid undue suture line tension when performing stricturoplasty in segments with mismatched diameters, such as those with pre-stenotic dilation (Fig. 70–18).

Techniques for longer strictures that involve the use of side-to-side anastomosis include the following[95,99]:

- Finney stricturoplasty, which is performed by creating a longitudinal antimesenteric enterotomy, which is then oriented in side-to-side fashion by creating a U-shaped bend, followed by closure with absorbable suture in running fashion beginning on the posterior wall (Fig. 70–19).
- Jaboulay stricturoplasty, which is similar to the Finney technique in many respects in that it orients the intestine in a U shape, but instead of a single antimesenteric enterotomy, two separate enterotomies are made with the most strictured portion left unopened; subsequent closure creates a side-to-side enteroenterostomy (Fig. 70–20).

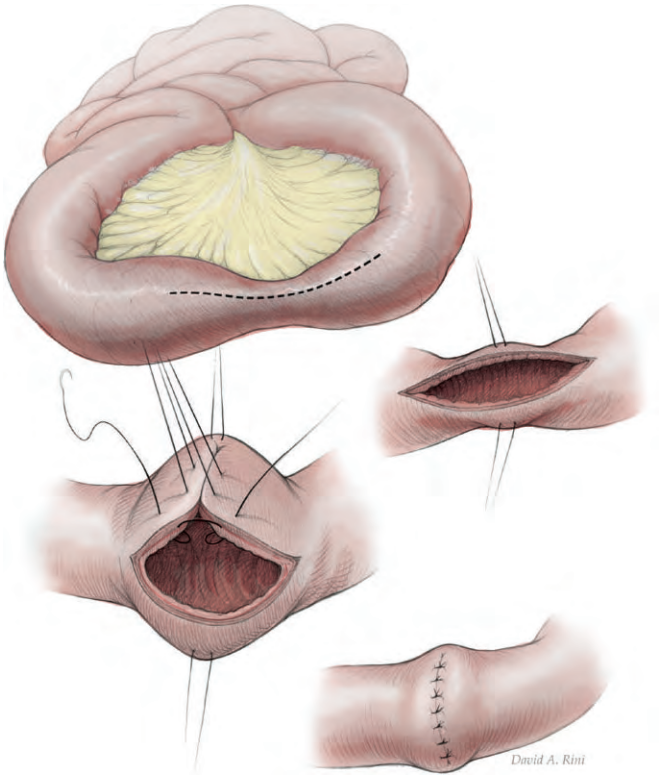


Figure 70–16. Heineke-Mikulicz stricturoplasty using an interrupted Gambee stitch. A longitudinal enterotomy over the stricture is followed by transverse closure. (From Talamini M: Stricturoplasty in Crohn's disease. In Cameron JL [ed]: Current Surgical Therapy, 8th ed. Philadelphia, CV Mosby, 2004, p 117.)

- Side-to-side isoperistaltic stricturoplasty, which is begun by dividing the small bowel mesentery at the midpoint of the affected segment, followed by division of the bowel itself between atraumatic bowel clamps; the proximal loop is then placed over the distal loop, antimesenteric enterotomies are made, the ends of the small bowel are tapered to avoid any blind pouches that could result after closure, and a running two-layer closure results in a long enteroenterostomy (Fig. 70–21).[95,98,99]

Bowel Resection and Anastomotic Techniques

After gaining safe entry into the abdomen, mobilizing diseased segments as required, and identifying the extent of diseased segments as described earlier, the proximal and distal margins may be divided with a linear cutting gastrointestinal stapler. If there is significant obstruction with dilated, fluid-filled loops, it may be necessary to decompress the intestine before stapling by milking the small bowel contents proximally or distally, followed by the application of atraumatic bowel clamps or umbilical tape, or by careful enterotomy and suction. The mesentery may be taken just beneath the small bowel; because it is often thickened, shortened, and hyperemic, this can present a technical challenge.

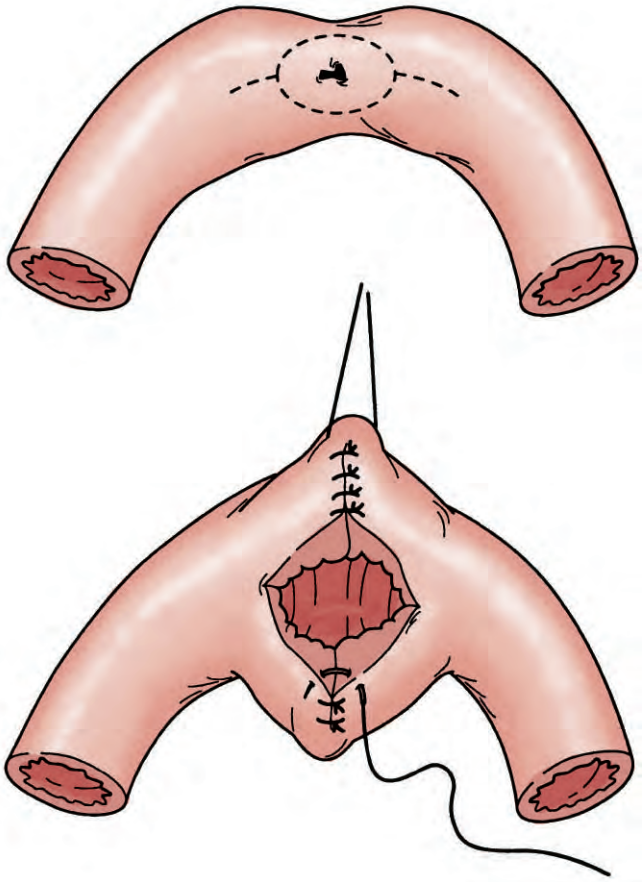


Figure 70–17. Judd stricturoplasty. The fistulous site is resected as part of the longitudinal enterotomy, which is then closed transversely. (From Michelassi F, Hurst RD: Stricturoplasty in Crohn's disease. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. St Louis, CV Mosby, 2001, p 134.)

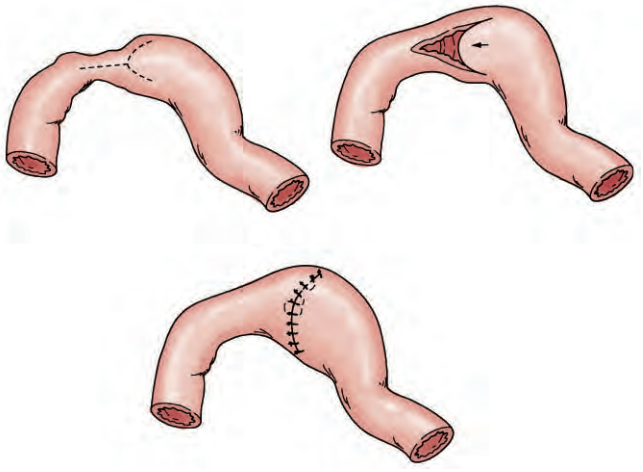


Figure 70–18. Moskel-Walske-Neumayer stricturoplasty. A Y-shaped enterotomy is performed before transverse closure. The Y-shaped enterotomy facilitates tailoring the large lumen of the proximal intestinal loop into the small lumen of the distal loop. (From Michelassi F, Hurst RD: Stricturoplasty in Crohn's disease. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. St Louis, CV Mosby, 2001, p 134.)

After resection, the decision to perform a primary reanastomosis, a primary reanastomosis with a proximally placed loop stoma for diversion, or resection with an end stoma depends on factors such as urgency or emergency, stability of the patient in the operating room, patient nutritional status, the degree and temporality of steroid use, the condition of the bowel undergoing resection and anastomosis, and the condition of the abdomen in general, with septic complications such as abscess being of particular concern.[88] As in any bowel anastomosis, close attention must be paid to all technical details, including the blood supply to the bowel undergoing anastomosis, ensuring a tension-free anastomosis, consideration of proximal and distal bowel diameter, and avoidance of any distal obstruction. Although resection and anastomosis may be performed in areas of active disease and small ulcers should not place the anastomosis at risk, wherever possible, large longitudinal ulcers should not be incorporated into the anastomosis.[100]

With regard to recurrence and the need for reoperation, there is some evidence to support the superiority of a functional end-to-end stapled anastomosis over other stapled or hand-sewn techniques. Moreover, complication rates are low, the technique is quick and easy to perform, and it lends itself well to anastomosis of bowel with different calibers.[65] We typically use a 75-mm linear cutting stapler to create the common channel and close the remaining defect with a noncutting linear stapler.

A summary of salient issues regarding resections in patients with Crohn's disease includes the following points:

- Resection of gross disease is appropriate.
- Wide margins and frozen sections are unnecessary.
- The available evidence does not absolutely compel the use of any appropriate stapled or sewn anastomotic technique.

Stoma Formation

All patients undergoing operative therapy for Crohn's disease should be reasonably prepared, including mental preparation and stoma site marking, for the possibility of stoma creation to the extent dictated by clinical circumstances. Although permanent stomas are rarely required in the treatment of small bowel Crohn's disease, a poorly placed or constructed stoma, even if temporary, is at best a daily inconvenience and at worst a source of major morbidity.[101]

Selection of the stoma site is the first step in stoma construction; ideally, site selection occurs before surgery. Consultation with a certified enterostomal therapist can facilitate all aspects of patient preparation and stoma management, including ideal site selection. In general, stomas should be located within the rectus muscle. A scar-free portion of the abdominal wall should be chosen to allow good appliance seal. Care should be taken to avoid bony prominences such as ribs or the iliac crest. Evaluation of the stoma site should be performed by taking into account the proposed incision and using a template of the stoma appliance with the patient lying, sitting, and standing, especially in obese individuals,

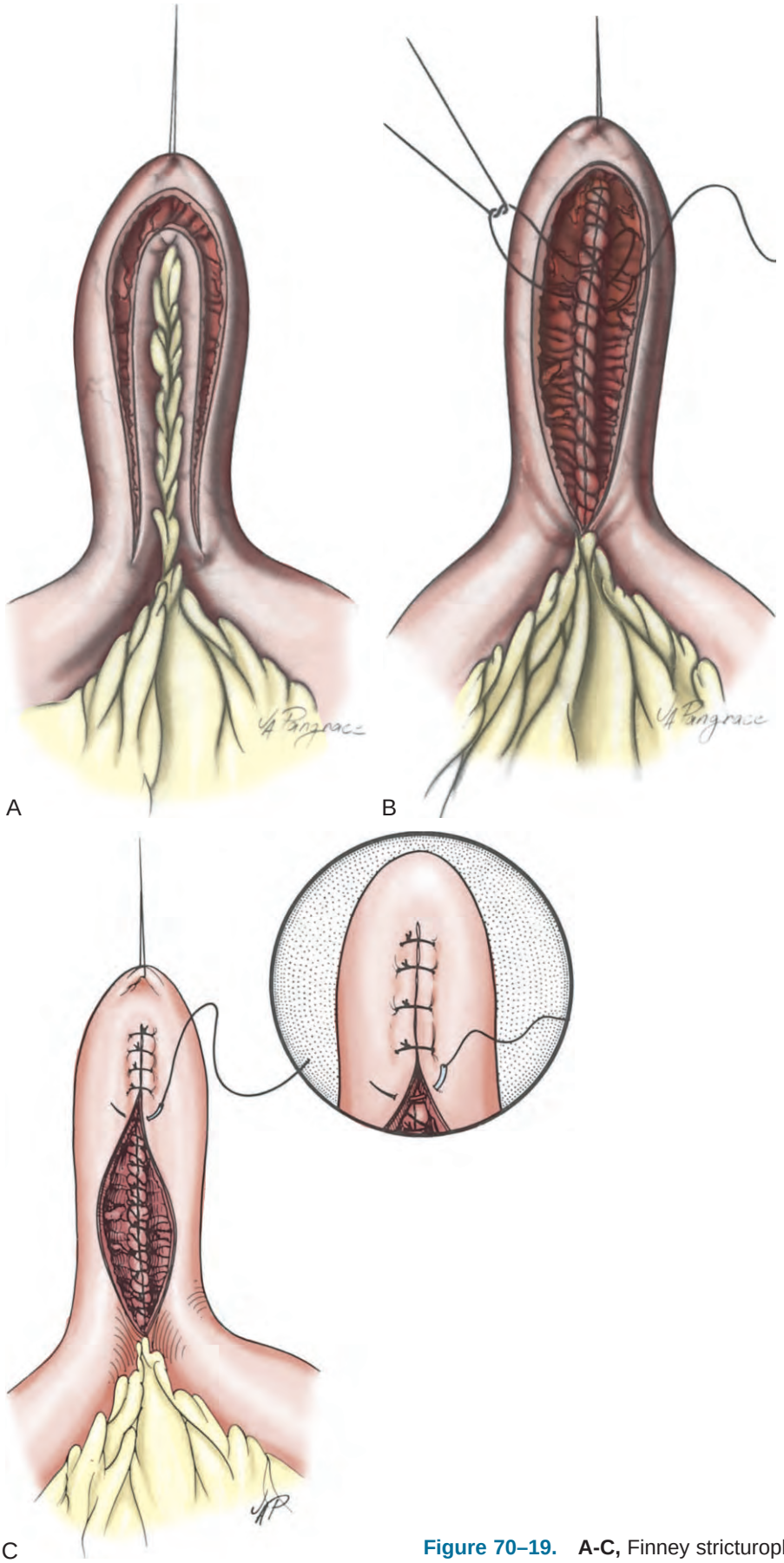


Figure 70–19. **A-C,** Finney stricturoplasty. Enteroenterostomy is performed after the affected bowel is folded onto itself into a U-shape. (From Talamini M: Stricturoplasty in Crohn's disease. In Cameron JL [ed]: Current Surgical Therapy, 8th ed. Philadelphia, CV Mosby, 2004, pp 118-119.)

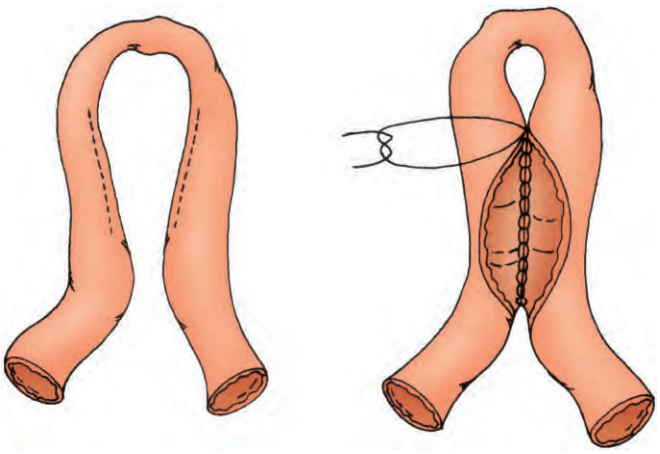


Figure 70–20. Jaboulay stricturoplasty. Two separate enterotomies are made, with the most strictured portion left unopened. Subsequent closure creates a side-to-side enteroenterostomy. (Adapted from Tichansky D, Cagir B, Yoo E, et al: Strictureplasty for Crohn's disease: Meta-analysis. Dis Colon Rectum 43:911, 2000.)

because shifting of the abdominal wall can reveal creases or protrusions that can interfere with appliance seal and the patient's ability to see or reach the stoma site. If the patient has a history of multiple abdominal operations, abdominal sepsis, the potential for a shortened mesentery, or other factors that could interfere with the bowel reaching a proposed stoma site, several alternative sites should be chosen and marked. Marking should be done with indelible ink, and the marking should be reinforced in the operating room immediately before surgery by re-inking or lightly scratching the skin so that the mark can be found after preparing the abdomen.[101]

Standard techniques are used to create and mature the end or loop stoma (we do not use bars in the creation of our loop stomas): a 2-cm disk of skin is sharply excised, the subcutaneous fat is opened to the level of the rectus fascia, a cruciate incision is made with electrocautery in the anterior rectus sheath, the rectus muscle is spread in the direction of its fibers, the posterior sheath and peritoneum are opened with a cruciate incision, the tract is dilated with two fingers, the bowel is brought through the abdominal wall with the mesentery

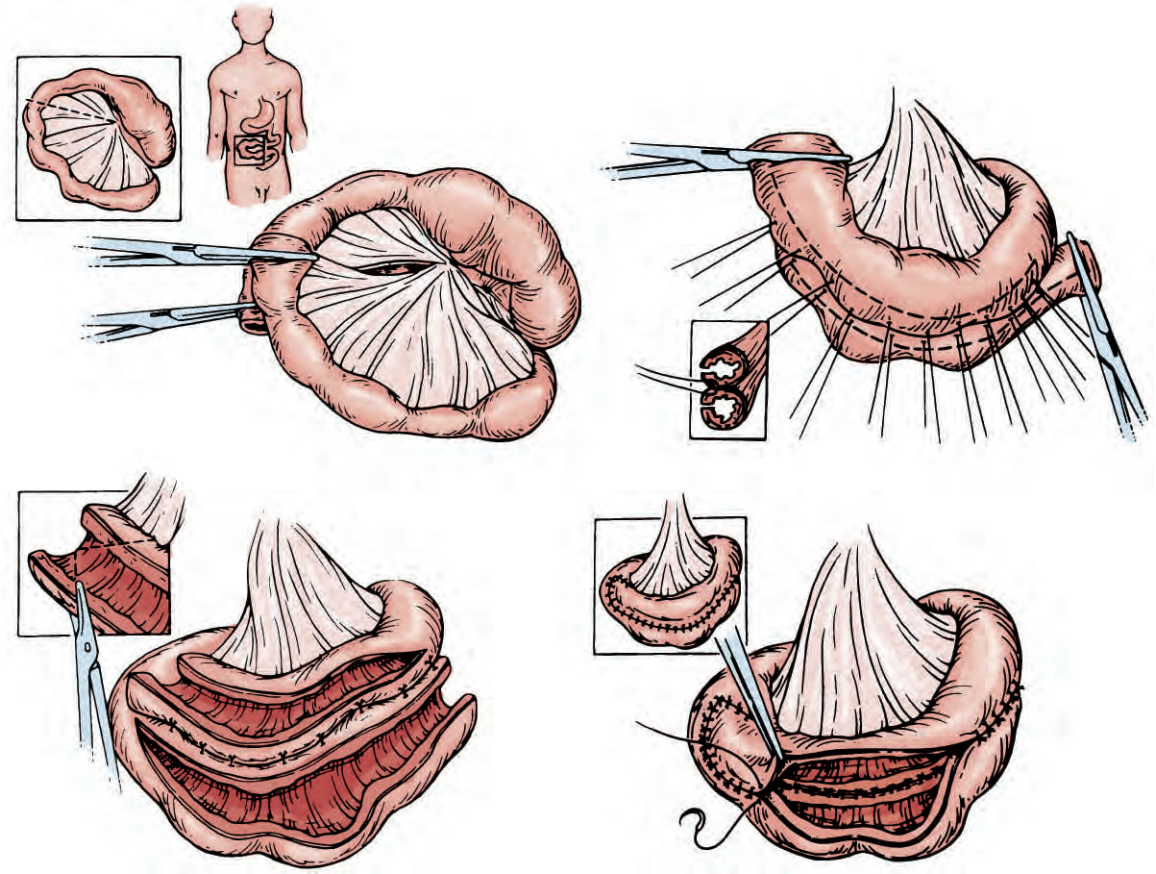


Figure 70–21. Side-to-side isoperistaltic stricturoplasty. A long side-to-side isoperistaltic enteroenterostomy is performed after dividing the diseased intestinal segment and moving the proximal loop over the distal loop in a side-to-side fashion. (From Michelassi F, Hurst RD: Stricturoplasty in Crohn's disease. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. St Louis, CV Mosby, 2001, p 136.)

cephalad to ensure that the dependent portion of the stoma is well formed, the abdominal incision is closed, the bowel is opened, and the stoma is matured so that 2 to 3 cm of everted bowel projects from the abdominal wall.[101] It is important to pull the fascia to the midline with a midline incision or caudad with a Pfannenstiel incision before creating the abdominal wall defect to ensure that all openings are aligned, thus preventing kinking of the bowel, which can lead to obstruction or ischemia of the stoma.

Bypass Procedures

Intestinal bypass or exclusion procedures are rarely, if ever indicated in the treatment of Crohn's disease that involves the jejunum and ileum. However, treatment of Crohn's disease of the duodenum may require bypass procedures such as gastrojejunostomy or duodenojejunostomy.[94]

Laparoscopic Surgery in Crohn's Disease

Crohn's disease presents an array of challenges to surgeons approaching treatment of the disease laparoscopically, including multiple previous abdominal operations, intense inflammation, mesenteric thickening, penetrating disease, and segmental involvement. Patients, many of whom are acutely aware of the high likelihood that they will require surgical therapy at some point in the course of their disease, are eager to pursue laparoscopic approaches that promise better cosmetic outcomes and reduced recovery time. The laparoscopic, laparoscopically assisted, or hand-assisted approach in Crohn's disease may lend itself to diagnosis in cases in which previous attempts at work-up have been nondiagnostic; to diversion in the treatment of more distal disease, particularly in complicated disease; and to resection using primarily hand-assisted techniques and the endoscopic Ligasure (10-mm Ligasure Atlas or 5-mm Ligasure V), which allows safe laparoscopic division of the thickened mesentery. Although the overwhelming majority of evidence to date supporting the benefits of laparoscopy over open approaches has not come from prospective randomized controlled trials, there do seem to be advantages in terms of blood loss, postoperative pulmonary function, duration of postoperative ileus, and length of hospital stay. Characterization of the long-term results after laparoscopic surgery for Crohn's disease awaits adequate numbers of patients with long-term follow-up.[102]

Indications for laparoscopic surgery are essentially the same as those for open surgery. Contraindications to a laparoscopic approach include the following[102]:

- Diffuse peritonitis
- Acute obstruction with distention accompanied by dilated of loops of intestine
- A history of multiple previous laparotomies or known dense intra-abdominal adhesions
- Coagulopathy not correctable at the time of surgery
- Portal hypertension with known intra-abdominal varices

Management of Complicated Small Bowel Crohn's Disease

The Vienna classification system groups Crohn's disease patients on the basis of age (<40 or ≥40), disease location (terminal ileum, colon, ileocolon, upper gastrointestinal), and disease behavior (inflammatory, stricturing, penetrating).[21] Because surgical therapy does not cure Crohn's disease, it is used only to treat complications that are not amenable to medical therapy.[88] Although any of the three types of disease behavior may require surgical therapy, the most common indications involve stricturing or penetrating types of disease behavior.

Stricturing Disease

Patients with Crohn's disease and a primarily stricturing pattern of disease behavior may have an array of symptoms with a wide range of severity reflecting the degree of underlying obstruction, from chronic and low-grade to acute and high-grade or complete. Patients may have abdominal pain, nausea, vomiting, distention, and even obstipation leading to food avoidance, weight loss, failure to thrive, malnourishment, or hospital admission for medical or surgical therapy. Patients with obstructive symptoms caused by stricturing disease who require admission should be initially treated with nonoperative therapy, including bowel rest, nasogastric suction, and resuscitation. If patients have evidence of active disease on colonoscopy or contrast radiography, it is reasonable to treat them with aggressive medical therapy because inflammation may contribute to the partial obstruction. A low-residue diet may reduce the incidence of subsequent episodes of partial bowel obstruction. Patients with recurrent bouts of partial obstruction, those who fail to respond to nonoperative therapy, and patients with complete bowel obstruction require surgery.[103] It bears mentioning again that to the extent possible dictated by the urgency of their operation, patients should always be resuscitated and decompressed before their arrival in the operating room.

The decision to treat strictures with resection or stricturoplasty will be influenced by a variety of factors, including the surgeon's comfort and experience with stricturoplasty techniques for strictures of various length; patient factors such as malnutrition, steroid use, or sepsis; concomitant penetrating disease with phlegmon, abscess, fistula, or free perforation; and the condition of the bowel to be treated. Many authors advocate stricturoplasty as the first choice for patients with almost any type of stricturing disease, including complicated strictures or anastomotic strictures, whereas others argue that resection should generally be the first choice, with stricturoplasty being reserved for patients with short-bowel syndrome or those with multiple recurrences. Depending on the clinical scenario, patients may be served best by a combination of resection and stricturoplasty.

Enteric Fistulas

Patients with Crohn's disease and a primarily penetrating pattern of disease behavior are subject to the formation of fistulas, which are abnormal passages from

a normal cavity or hollow organ to a free surface (external fistulas) or to another cavity or hollow organ (internal fistulas). Fistulas involving the small intestine are discussed in this chapter. Examples include small intestine to small intestine (enteroenteric); small intestine to colon (enterocolonic); small intestine to any part of the urogenital tract, including the bladder (enterovesical), ureters (enteroureteral), and vagina (enterovaginal); and small intestine to skin (enterocutaneous fistula). The transmural nature of Crohn's disease leads to fistula formation, and although downstream obstruction or stricture is not a prerequisite for fistula formation, obstruction may contribute to fistula formation or decrease the likelihood that a fistula will heal. In a recent population-based study, fistulas developed in 35% of patients with Crohn's disease, with 20% of the fistulas being perianal (which is considered in another chapter).[104,105] A prospective study of the features, indications, and surgical treatment in 513 consecutive patients affected by Crohn's disease from 1985 to 1996 found that although fistulas were present in nearly a third of patients, they were rarely the primary indication for operative therapy.[96] This indicates that many of the fistulas found in patients with Crohn's disease, particularly those between loops of small bowel, will be asymptomatic and found incidentally on radiographs or during surgical exploration for treatment of septic complications or obstruction. However, small bowel fistulas may cause complications requiring surgery when long segments of bowel are bypassed, thereby leading to diarrhea or malabsorption; when the genitourinary or biliopancreatic systems are involved; or when the fistula results in external drainage.[100] Medical therapy has shown little promise in the treatment of Crohn's disease–induced enteric fistulas until recently; immunomodulator therapy for enteric fistulas, particularly with infliximab, has been modestly successful in the treatment of enteric fistulas, although the majority of patients in studies to date had perianal disease. It is probably justifiable to give patients who are otherwise reasonably well a trial of medical therapy, but not at the exclusion of indicated surgical therapy.[106]

Enteroenteric Fistulas

Crohn's disease–induced fistulas from one loop of small bowel to another are usually, in and of themselves, of little clinical consequence, although the active disease and inflammation that are the underlying cause typically require treatment. A simple enteroenteric fistula that encompasses a short length of bowel between connections may be found incidentally on radiographs, on abdominal exploration, or in a resected specimen and does not require further surgical intervention. An enteroenteric fistula can be symptomatic and require surgical therapy if a long section of small bowel is bypassed. Short-segment fistulas that are in close proximity should not be separated, but taken en bloc. Long-segment fistulas in which en bloc resection would sacrifice significant bowel length should be separated close to bowel that will undergo resection while leaving the possibility of primary repair for the healthy segment. Most ileocecal fistulas behave clinically like enteroenteric fistulas and are treated similarly.[88,104]

Ileosigmoid Fistulas

Ileosigmoid fistulas occur in up to 6% of all Crohn's disease patients and in 16% to 26% of Crohn's disease patients with internal fistulas. They are generally the result of penetration from the small intestine into the sigmoid, and the sigmoid is not usually affected primarily by Crohn's disease. As with enteroenteric fistulas, ileosigmoid fistulas are frequently asymptomatic, but they can be associated with abdominal pain, diarrhea, and malabsorption. Commonly, they are not detected with endoscopic or contrast studies. These fistulas can generally be treated without sigmoid resection by taking down the fistula and, after débridement of the sigmoid, closing the colon primarily. Sigmoid resection is reasonable if colonic Crohn's disease is present or if technical difficulties prevent easy primary closure, such as local inflammation with rigidity and thickening of the colonic wall, a large defect after débridement, or involvement of the colon wall close to the mesentery. If sigmoid resection is required, primary reanastomosis for restoration of intestinal continuity can usually be performed; temporary proximal diversion may be necessary in patients with long-term steroid use or extensive inflammation that precludes safe primary closure of the fistula defect.[88,100,104]

Enterovesical and Enteroureteral Fistulas

The reported incidence of fistulas from the gastrointestinal tract to the genitourinary system in patients with Crohn's disease has been 1% to 8%.[107] They originate most commonly from the ileum, colon, or rectum; they may also result from anastomotic leak after resection.[104] Although they may be the initial complaint in patients with Crohn's disease, they typically occur in patients with established disease. Common symptoms include dysuria, urinary urgency, urinary frequency, suprapubic discomfort, pneumaturia, and fecaluria. Chronic or recurrent urinary tract infections and urogenital tract infections such as prostatitis or epididymitis may give rise to fever and hematuria.[107] The diagnosis should be suspected in a patient with history, physical examination, and laboratory findings that are typical. The diagnosis can be confirmed and the lesion localized with the aid of cystoscopy, plain radiography, including small bowel follow-through or small bowel enteroclysis, or axial imaging with CT or MRI.[104] The fistulas rarely close spontaneously, and although medical therapy may be mitigating, definitive treatment generally requires surgical therapy. The dome of the bladder is most commonly involved and the trigone is usually spared, thus allowing a relatively straightforward approach. The basic operative steps are division of the fistula, resection of the involved portion of bowel, and débridement and primary closure of the bladder with postoperative Foley catheter drainage.[88,100]

Enterocutaneous Fistulas

Most enterocutaneous fistulas in patients with Crohn's disease occur in the postoperative setting; the involved bowel is essentially normal, and the fistulas, which tend to drain through surgical scars, are the result of anastomotic leak after resection or unrecognized bowel injury. Although reported numbers vary, it seems that spontaneous enterocutaneous fistulas that are the direct result of penetration from a diseased segment of small bowel to the exterior are relatively rare. *Even though it may be difficult to definitively say which is more common, it is worth considering that spontaneous enterocutaneous fistulas that occur before a patient has undergone surgery or after a patient is far removed from surgery are probably the result of penetrating Crohn's disease and that those that occur in the postoperative setting are probably the result of surgical misadventure.* These observations necessarily have an impact on decision making with regard to treatment of enterocutaneous fistulas because postoperative fistulas involving bowel not affected by Crohn's disease will behave differently from spontaneous fistulas that are the result of penetration from bowel affected by Crohn's disease. Fistulas that are not a direct result of Crohn's disease should respond to conventional treatment in a fairly predictable fashion; long, low-output fistulas have an increased probability of closing with nonoperative therapy such as bowel rest, strategies to decrease the output of the gastrointestinal tract, and TPN support, whereas short, high-output fistulas are more likely to require operative therapy. In contrast, spontaneous fistulas that are the direct result of penetrating Crohn's disease rarely close without operative therapy, although as mentioned earlier, newer medical therapies with immunomodulators such as infliximab may be of benefit. Of course, operative therapy should not be delayed when there is distal obstruction, if fistula output or wound care becomes difficult to manage, or if medical treatment has obviously failed. Operative therapy relies on division of the fistula, resection of the involved bowel, débridement of the entire fistulous tract, and safe repair of the ensuing bowel defects.[88,106]

Enterogenital Fistulas

Fistulas from the rectum to the vagina are common in women with Crohn's disease (9% of all fistulas observed in a recently published, population-based study[105]), and although fistulas from the small intestine to the female genital tract, including enterovaginal, enterosalpingeal, and enterouterine, do occur, they are less common. Symptoms of an enterovaginal fistula include malodorous vaginal discharge and passage of air from the vagina; enterosalpingeal and enterouterine fistulas may be difficult to identify preoperatively, with diagnosis occurring at the time of abdominal exploration. The common themes continue, including division of the fistulous tract with resection of involved bowel and débridement of the victim organ, although effort should be made to preserve reproductive, endocrine, and sexual function, especially in women of childbearing age.[94]

Abscesses

Abscesses in patients with Crohn's disease are common (reports indicate that 10% to 30% of patients with Crohn's disease will have an abscess at some point in their illness[108]); they can be an intermediate step in the formation of fistulas, and like fistulas, they may be the result of penetrating disease from a segment of bowel affected by Crohn's disease, or they may be the result of surgical misadventure (see Fig. 70–12). Patients may have few, if any symptoms because the abscesses are frequently contained in loops of bowel, between leaves of mesentery, by abdominal viscera, in the retroperitoneum, or in the pelvis; symptoms may also be quelled by medical therapies such as steroids or immunomodulators. If patients do have signs and symptoms, they are those typical of intra-abdominal infections, including fever, ileus or obstruction, abdominal pain, tenderness, or a palpable mass. Diagnosis and localization are aided most by axial imaging. Classically, treatment was strictly operative, with abscess drainage as a first stage followed by bowel resection as a second stage. With the advance of radiographically guided percutaneous techniques, abscesses can be effectively drained outside the operating room; concomitant medical therapy for any active Crohn's disease, along with resuscitation, antibiotics for systemic infection, nutritional support, and bowel rest as indicated, can be administered. If the abscess cavities collapse and the patient's Crohn's disease is controlled, no further therapy may be needed. If operative therapy is required, the patient will benefit in terms of physiologic preparedness and technical ease, which may make the operation less extensive, preserve bowel length, and allow restoration of bowel continuity without diversion in a single stage.[30,108]

Ureteral Obstruction

The majority of cases of ureteral obstruction in patients with Crohn's disease are not caused by stones, with 50% to 73% of cases of ureteral obstruction in patients with Crohn's disease being acalculous. Acalculous ureteral obstruction was seen in 4.7% to 14.3% of Crohn's patients who had diagnostic intravenous pyelography studies performed; in contrast, intravenous pyelograms performed on asymptomatic Crohn's patients reveal acalculous ureteral obstruction in 18% to 50% of those tested, which suggests that acalculous obstruction in these patients is a more prevalent problem that probably goes unrecognized fairly frequently. When symptoms do occur, they can be nonspecific, with patients reporting urinary frequency and urgency, flank pain, and fever and, on examination, a palpable abdominal mass is possible. The results of urinalysis and culture are often normal. The diagnosis is most often confirmed with axial imaging. The inflammation associated with ileocecal disease is usually the cause of acalculous ureteral obstruction, so it occurs more commonly on the right and less commonly on the left or bilaterally. Current recommendations advocate a staged approach to treatment consisting of medical control of active Crohn's disease, ureteral stenting for significant obstruction, and

percutaneous drainage of any associated abscess, followed by resection of diseased bowel and ureterolysis as required if nonoperative therapy fails.[107]

Free Perforation

Free perforation in patients with Crohn's disease is rare; as alluded to in the sections on abscess and fistula, the adhesions that are a result of the transmural inflammatory nature of Crohn's disease create an environment around affected segments that does not favor free perforation. Free perforation usually occurs in Crohn's patients with toxic colitis, distal obstruction, or cancer and after endoscopy or surgery. Perforation in patients with prodromal signs and symptoms will generally be heralded by a sudden worsening in their clinical course; as usual, such assumptions are dangerous in patients treated with steroids and immunomodulators, in whom a high index of suspicion is required for diagnosis. Plain films showing free air confirm the diagnosis, and in cases in which the diagnosis goes unsuspected, CT scans will show the same. It should go without saying that emergency exploration is required when free perforation is suspected; while the operating room is being prepared, the patient should be resuscitated, treated prophylactically with broad-spectrum antibiotics, receive stress-dose steroids if appropriate, have laboratory tests performed, including blood type and crossmatch, and be marked for stoma placement. Débridement and primary repair of gastroduodenal perforation or resection with primary anastomosis after jejunoileal perforation is often possible, and proximal diversion with a loop or end stoma should be considered if conditions are unfavorable.[30]

Crohn's Disease of the Duodenum

As stated previously, the exact incidence and prevalence of upper gastrointestinal Crohn's disease are not known, and even though it is historically rare, the incidence has increased in recent reports. Careful examination and biopsy of the upper gastrointestinal tract in those with Crohn's disease will reveal histologic evidence of disease in as many as 30% to 50% of patients, although many will lack upper gastrointestinal symptoms. The duodenum can be primarily affected by Crohn's disease, or it can be secondarily affected as the victim organ of penetrating disease (Fig. 70–22). Symptoms of duodenal involvement include dyspepsia or epigastric pain, anorexia, and proximal obstructive symptoms such as early satiety, nausea, vomiting, and weight loss. Complications of proximal Crohn's disease are similar to those found with more distal disease; inflammation, strictures, and fistulas (almost all of which are the result of penetration into a normal duodenum) occur along with an increased risk for cancer in areas of long-standing disease. Because the majority of patients with upper gastrointestinal disease have concomitant lower gastrointestinal disease and because medical therapy for proximal Crohn's disease has not been well studied, the course of medical treatment is typically determined by the clinical course of the distal disease. Many of the principles of surgical

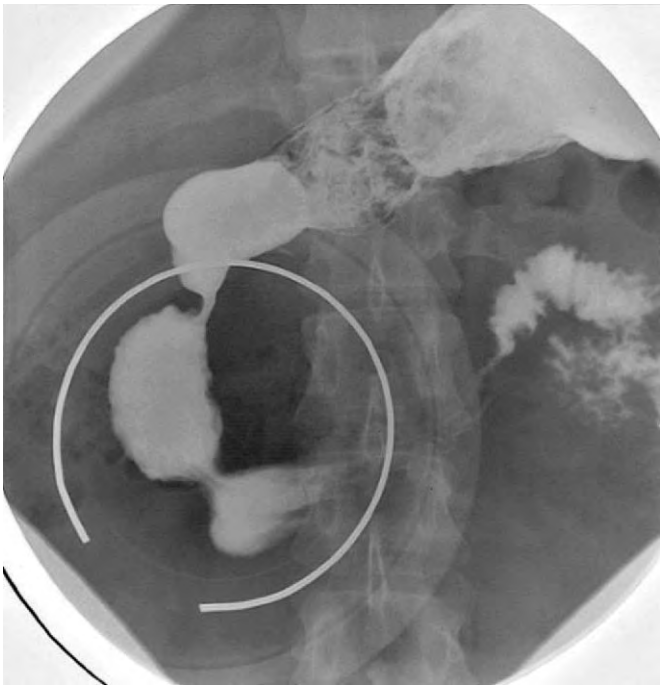


Figure 70–22. Upper gastrointestinal series demonstrating multifocal Crohn's disease of the duodenum.

management discussed in previous sections apply to complicated duodenal disease: after medical therapy has been instituted for active Crohn's disease, the patient should receive nutritional support with preference given to the enteral route; frank abscesses that are accessible should be percutaneously drained; fistulas should be divided and the bowel segments from which they arose should be resected; minimal débridement of the duodenum may allow primary closure with the Heineke-Mikulicz technique, although more extensive débridement may require a duodenojejunostomy, gastrojejunostomy, or Roux-en-Y anastomosis for reconstruction; and strictures can be treated with a stricturoplasty when technically feasible or may require a duodenojejunostomy, gastrojejunostomy or Roux-en-Y anastomosis for reconstruction.[109]

Postoperative Care

In most respects, the postoperative care of patients who have undergone surgery for Crohn's disease is not different from that in patients who have undergone any other type of gastrointestinal surgery. Routine use of postoperative nasogastric suction is not required for distal procedures, but it may be considered for procedures involving the upper gastrointestinal tract. If stress-dose steroids were required, they can be tapered quickly if the patient is not critically ill.[94]

Recurrence of Crohn's disease after resection, which usually occurs at the site of surgical anastomosis, is seen in almost all patients when they are monitored long-term. First, there is endoscopic recurrence, which in a significant number of patients is followed by

symptomatic recurrence. One study found endoscopic evidence of Crohn's disease recurrence in 73% of patients 1 year after surgery, with only 20% of patients having symptoms; when observations were repeated 3 years after surgery, the endoscopic recurrence rate had increased to 85%, and symptoms were present in 34%. Perhaps the most important measure of recurrence is the need for reoperation, with about half of patients undergoing ileocolonic resection requiring reoperation within approximately 10 years of surgery.[86]

There is evidence to support the use of some types of medical therapy to prevent both endoscopic and symptomatic recurrence of Crohn's disease after surgery. Besides being inappropriate for maintenance therapy in nonsurgical Crohn's patients, steroids have proved ineffective for prophylaxis against disease recurrence in the postoperative setting. Sulfasalazine has not been shown to be consistently helpful in preventing postoperative recurrence. Although there is evidence to support the efficacy of other 5-acetylsalicylate preparations in the maintenance of postsurgical remission in Crohn's disease, the overall beneficial effect of mesalamine is small. Only a modest benefit has been shown with azathioprine and 6-mercaptopurine in the postoperative setting, but because there is much stronger evidence supporting their use in maintenance therapy after medically induced remission, they are probably justified in high-risk postoperative patients.[65,86]

Finally, smoking cessation is advised in all postoperative Crohn's disease patients; smokers have double the rate of recurrence, and smokers who quit have decreased rates of recurrence.[65]

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Chapter

71

Ileostomy

Riaz Cassim · David W. McFadden

HISTORICAL PERSPECTIVES

An ileostomy is a communication constructed between the distal part of the small intestine and the abdominal wall. It may be temporary or permanent and is classified according to the anatomic configuration upon creation. When performed after removal of the entire colon and rectum, it takes the form of a permanent end ileostomy. With the growing popularity and success of restorative proctocolectomy for ulcerative colitis, familial adenomatous polyposis, and low rectal cancer, the number of permanent ileostomies being performed has shown a downward trend.[1] Protection of these low-lying anastomoses has brought about the need for temporary diversion of the intestinal contents. This has been accomplished with the use of a temporary loop ileostomy.

The first recorded case of creation of an ileostomy is credited to Baum in 1879 for relieving an obstruction secondary to cancer of the ascending colon.[2-4] During the early half of the 20th century the ileum was simply brought out several inches through the abdominal wall for subsequent drainage.[5] Initially, the ileum was exteriorized via the inferior portion of the abdominal incision. It was not until the 1930s that the ileostomy was created through a separate right lower quadrant incision.[2] Healing was achieved by the formation of scar tissue between the serosa of the small bowel and the abdominal wall. This led to inflammation of the exposed serosa and ultimately resulted in stricture formation at the ileostomy exit site and subsequent intestinal obstruction with signs of abdominal cramping, voluminous ileostomy output, and hypovolemia. This condition was termed *ileostomy dysfunction* and was described by Warren and McKittrick in 1951.[6] In an effort to expedite healing and prevent irritation of the abdominal wall, Dragstedt in 1941 started covering the ileostomy with a skin graft, which led to a long and unsightly stoma.[4]

Ileostomy, as we know it today, has been around only for past 50 years. Dr. Bryan N. Brooke described it in 1952 when he inverted the end of the ileum before maturing the stoma in the operating room, and it has thus come to bear his name.[2,7,8] In 1953 Turnbull advised a similar technique whereby the seromuscular layer of the distal half of the exteriorized small bowel was removed and the mucosal tube was everted over the proximal half, thereby covering the exposed serosa.[2,8,9]

Significant advances were made by the development of a practical ileostomy appliance in 1936. Strauss, a Chicago surgeon, Koenig, his patient, and Rutzen, who made it commercially available, share the credit.[2,8,10] In addition, a major step in ileostomy care was establishment of the first ileostomy club by Turnbull at the Mount Sinai Hospital in New York.[2,10,11] As of 2001 there are over 450 chapters in the United Ostomy Association with 25,000 members. Turnbull also initiated the training program for enterostomal therapists in 1961 at the Cleveland Clinic.[2,9,10]

INDICATIONS

Total proctocolectomy with a permanent end Brooke ileostomy still remains the gold standard operation for patients with ulcerative colitis and familial polyposis. An end ileostomy may be potentially reversible if it is deemed that an ileoanal anastomosis may be hazardous, such as in patients with severe malnutrition, peritoneal contamination, or vascular compromise. A total abdominal colectomy with end ileostomy can then be performed, with completion proctectomy and ileoanal pouch anastomosis done as a second-staged precedure.[1]

Many conditions require temporary decompression and diversion after colorectal surgery. Few studies have compared the morbidity and mortality associated with diverting loop colostomy and loop ileostomy for protection of a colorectal anastomosis, and the results have been divided.[12-16] Rullier et al. have shown that the morbidity after loop ileostomy construction and closure, including the risk for reoperation, is significantly lower for loop ileostomy than for loop colostomy.[16] Other studies have also shown excellent results with loop ileostomy.[17,18] Quality of life, although altered in all patients with stomas, is less impaired after a loop ileostomy because the effluent is odorless and the stoma is less bulky and less prone to prolapse.[13,19-21]

A temporary loop ileostomy may be warranted for the following conditions[15,22,23]:

- Anastomotic factors
  - Protecting a complicated anastomosis, such as coloanal and ileoanal anastomoses
  - Proven anastomotic leakage at surgery
  - Technical difficulties, such as incomplete staple rings and tension
  - Anastomosis in an irradiated field
  - Anastomosis in the presence of mild peritonitis or contamination
  - Multiple distal anastomoses
- Crohn's disease
- Carcinomatosis with distal obstruction
- Abdominal trauma
- Congenital anomalies

PHYSIOLOGY

An ileostomy starts to function 48 to 72 hours after construction. A mature ileostomy produces between 400 and 700 mL of effluent per day. This volume remains relatively constant for an individual. The contents are weakly acidic (pH 6.1 to 6.5). Sodium excretion is 60 to 120 mEq/day, which is two to three times higher than in normal feces. Equilibrium is established by renal conservation of salt and water.[24] If the ileostomy output is excessive and leads to dehydration, the urine becomes concentrated and acidic. This may result in the formation of uric acid calculi, which have been reported in 3% to 13% of ileostomates.[11,25]

Cholelithiasis after permanent ileostomy has been reported in up to 30% of patients.[25,26] Patients older than 50 years and females are at a slightly higher risk for unknown reasons.[26] Cholesterol stones are precipitated by disruption of the enterohepatic circulation of bile acids by removal or inflammation of the terminal ileum.[27]

PREOPERATIVE PREPARATION

The thought of a stoma, whether permanent or temporary, is frightful and anxiety provoking for most patients. It is important to relieve patient fear about living with a stoma. Providing patients with literature on their disease and the proposed surgery is often helpful. Getting a patient in touch with ostomy support groups, especially with an individual of similar age, gender, and socioeconomic status, will aid the patient in realizing that a normal life is possible with an ileostomy.

Proper positioning of the stoma and meticulous surgical technique are the two most important factors that ensure success with a well-functioning ileostomy. A preoperative visit with the enterostomal therapist is essential. The latter can provide important preoperative counseling and perform proper marking of the stoma site, which has a direct bearing on the subsequent outcome of the ileostomy and management.[28,29] Ileostomy effluent is liquid, corrosive to the skin, and voluminous. An ileostomy that is properly located will often prevent complications such as leakage resulting in skin breakdown, prolapse, and peristomal hernia.[29,30]

Typically, the ileostomy is positioned in the right lower portion of the abdomen through the rectus abdominis muscle. This point usually corresponds to a third of the distance on an imaginary line stretching from the umbilicus to the right anterior superior iliac spine. The stoma should lie on the bulge of the infraumbilical skin fold.[21] Another way to determine the location is to draw a vertical line through the umbilicus and another horizontal line through the inferior margin of the umbilicus. The faceplate of the appliance is positioned in the right lower quadrant so that it abuts against the two imaginary lines. The opening of the faceplate usually corresponds to the outer half of the rectus muscle.[22]

Previous scars, bony prominences, the waistline, the beltline, the inguinal crease, the costal margin, the umbilicus, and skin folds should be avoided if at all possible. These sites interfere with proper placement and management of the ileostomy appliance and thus lead to poor clinical outcomes. The faceplate of the ileostomy appliance should be placed on the patient and its appropriateness confirmed by having the patient bend, stand, sit, and lay down. In patients who are obese, it should be placed at the level of the umbilicus or higher for ease of management. Ostomates have to be able to visualize the stoma if they are to participate effectively in stoma care. Once the ideal stoma site has been determined, it is marked with a permanent marking pen or preferably by intradermal injection of methylene blue dye.

TECHNIQUES

For an optimal outcome one must focus on potential complications and postoperative care while constructing an ileostomy. Adhering to the basic surgical principles of gentle tissue handling, good hemostasis, and prevention of tension will ensure good results. Placing the ileostomy in the main incision should be condemned because this prevents the placement of a well-fitting appliance and leads to a higher incidence of wound infection, dehiscence, and incisional hernia.[28]

END ILEOSTOMY

The patient is placed in the supine or the perineolithotomy position, depending on the resection being performed (Fig. 71–1). A hypodermic needle is used to scratch a mark at the preoperatively marked stoma site in the right lower part of the abdomen because if the site is marked with a pen, it will be erased with vigorous surgical preparation. For most operations, a midline approach passing to the left of the umbilicus is preferable to help minimize scars and preserve the remaining quadrants of the abdomen should revision or relocation of the ileostomy be required in the future. Such an approach is particularly important in patients with Crohn's disease.

Preparation of the terminal or distal ileum is an important aspect of the procedure. The ileocolic artery is divided as part of the right colectomy, but the

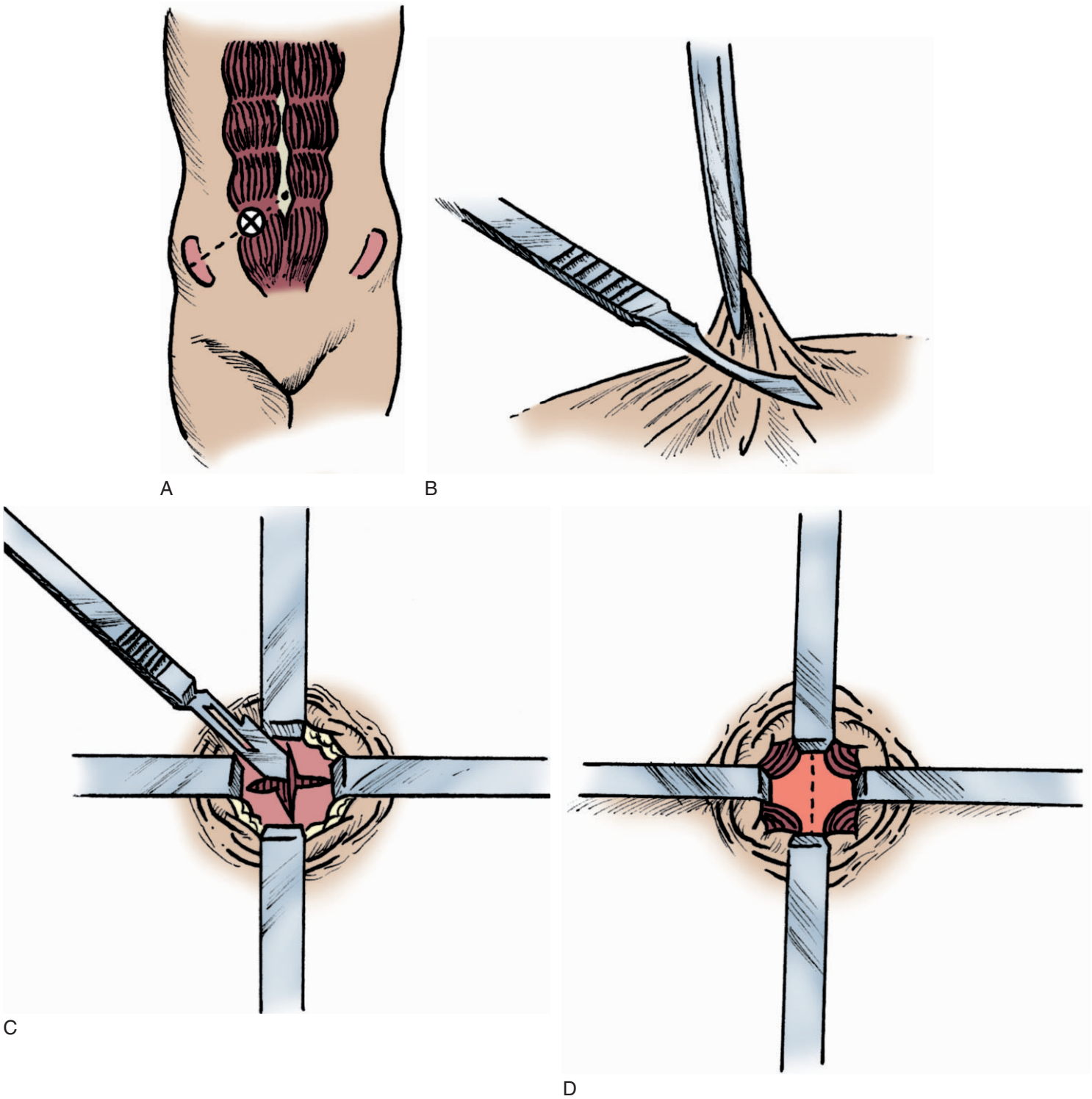
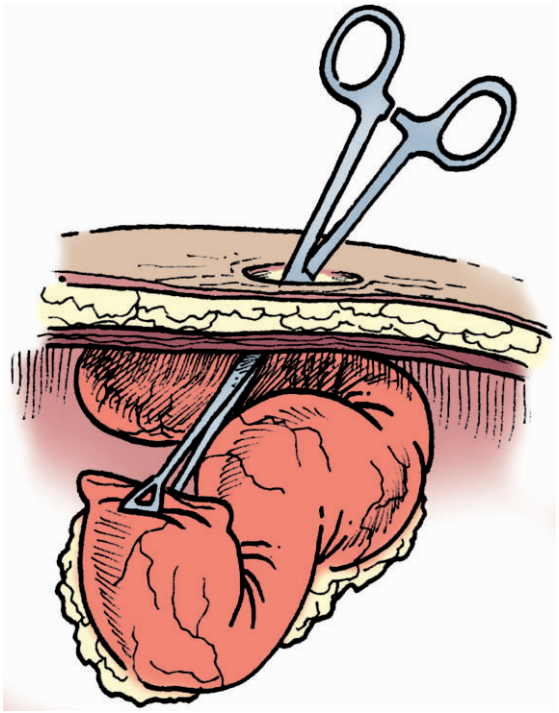


Figure 71–1. Technique of end ileostomy (Brooke) construction. **A,** Ileostomy site marked preoperatively in the right lower quadrant (a third of the way between the umbilicus and the anterior superior iliac spine, overlying the rectus muscle). **B,** Two-centimeter disk of skin excised with a scalpel. **C,** Anterior fascia divided via a cruciate incision. **D,** Posterior rectus sheath divided longitudinally after spreading the rectus muscle.



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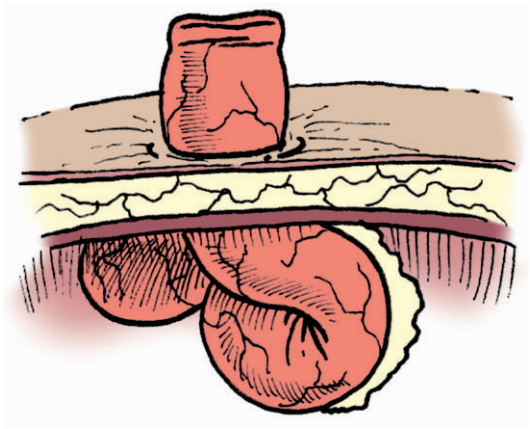

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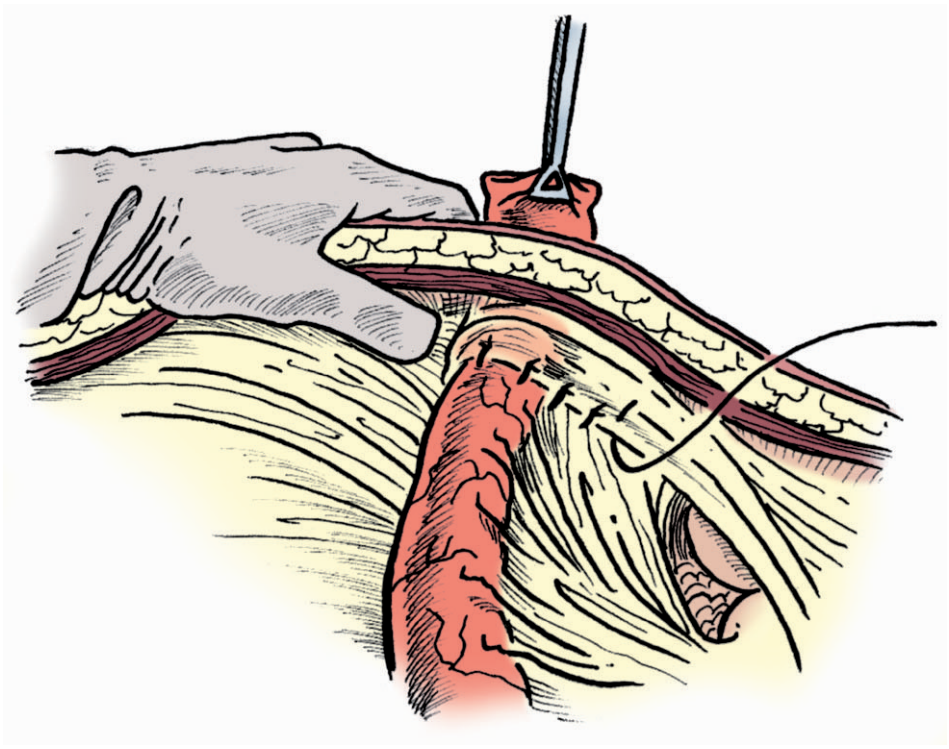
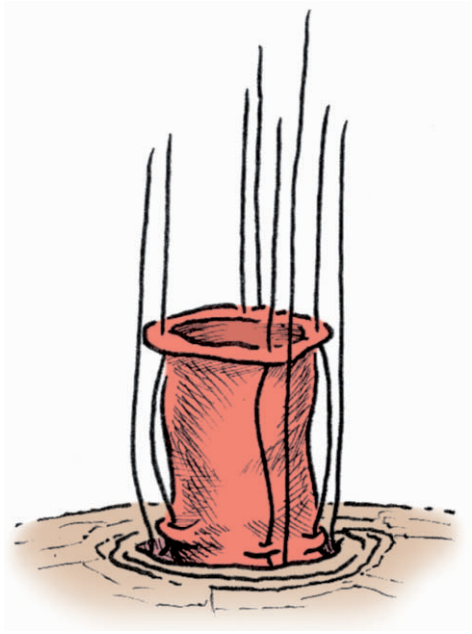


G

Figure 71–1, cont'd. **E,** Ileum delivered through the ileostomy site with a Babcock clamp. **F,** Ileum protruding 2 to 3 cm above the anterior abdominal wall without tension. **G,** Intraperitoneal fixation of the ileum and its mesentery.

Continued



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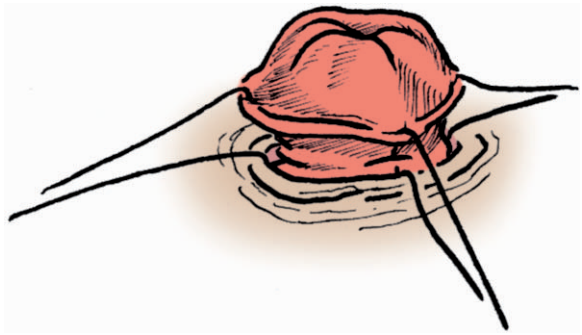

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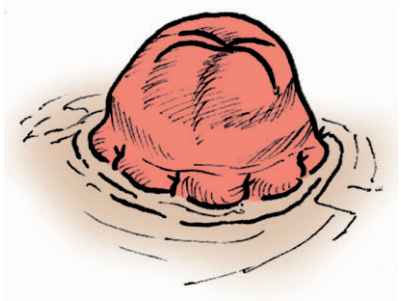

J

Figure 71–1, cont'd. **H** and **I,** Placement of three-point sutures in each of the four quadrants helps evert the ileal mucosa. **J,** Matured ileostomy.

remaining small bowel mesentery and vascular arcades are preserved. The mesentery of the distal small bowel is mobilized along the right posterior abdominal wall all the way to the duodenum to ensure adequate mobilization and construction of a tension-free stoma. Once the ileum is exteriorized, it should lay there without any mechanical effort.

After the appropriate resection has been performed, the ileum is divided with a GIA stapler or between clamps. It is important to preserve as much terminal ileum as possible, especially in patients with benign disease.[1] The bowel is divided 2 to 3 cm proximal to the ileocecal valve and should be free of any visible inflammatory changes, which is important in patients with Crohn's disease. The distal 2 to 3 cm of ileum to be exteriorized is cleansed of its mesentery so that eversion can take place without difficulty.

Before making a skin incision at the stoma site, all layers of the abdominal wall are apposed to reduce the shearing effect of the layers of the abdominal wall on the stoma. Such shearing predisposes to stenosis. Apposition is achieved by placing clamps on the cut edge of the fascia, peritoneum, and dermis of the skin and applying traction to keep the layers at the same level. A 2-cm disk of skin is removed at the previously marked stoma site and can be effectively accomplished by grasping and elevating the skin with a Kocher clamp and removing the skin with a horizontal sweep of the knife. The subcutaneous fatty tissue is divided and not excised to help provide support for the ileostomy, as well as the appliance.[1] In obese patients, a cylinder of subcutaneous fatty tissue may be excised to provide room for the bulky exteriorized bowel. With good retraction the anterior rectus sheath is easily identified and incised in a cruciate fashion. The rectus muscle is separated in the direction of its fibers with scissors or a blunt clamp. The posterior rectus sheath is identified and made prominent by pushing it through the separated rectus muscle fibers with the index and middle fingers introduced through the midline abdominal wound. A vertical incision is made in the posterior sheath. The newly constructed stoma opening should permit the passage of two fingers.

Babcock clamps are introduced into the peritoneal cavity through the stoma opening and used to grasp and deliver the end of the ileum out onto the abdominal surface. About 4 cm of ileum should be exteriorized and should lie without tension. Greater lengths of ileum need not be exteriorized because the everted ileostomy does not have to be more than 2 cm in height. Care is taken to ensure that the mesentery of the distal portion of the small bowel is not twisted, the divided edge of the mesentery points cephalad, and the proximal portion of the small bowel occupies the left side of the abdomen.

If the ileostomy is to be permanent, intraperitoneal fixation of the bowel and mesentery to the posterior rectus sheath is performed. Such fixation helps distribute the tension evenly around the stoma. Three or four interrupted sutures with fine (4-0) absorbable material are used. Seromuscular bites are taken through the ileum and secured to the parietal peritoneum. This step is omitted in patients with Crohn's disease because inadvertent full-thickness bites through the bowel may lead to the development of fistulas. The right lateral aspect of the abdomen is left open. However, closure may be accomplished by suturing the mesentery of the distal ileum to the anterior abdominal wall. This maneuver is believed to prevent herniation of the small bowel around the intra-abdominal portion of the ileostomy. Superiorly, the mesentery may be sutured to the falciform ligament to ensure complete closure. It is important to completely obliterate this space. If there is any tension on the

mesentery, it is better to leave the defect wide open. Alternatively, performing an extraperitoneal ileostomy can close this defect.[29] Closure of the lateral abdominal space has not been shown to decrease the subsequent development of small bowel obstruction.[31,32]

Once it is deemed that the ileostomy is viable and there is no twist in the small bowel mesentery, the midline incision is closed. The skin is approximated and the incision is covered so that it is protected from coming in contact with the intestinal contents, which would increase the risk for wound infection.

The staple line is divided with a knife or electrocautery. Fresh bleeding from the mucosal edges ensures viability of the ileostomy. Maturation is begun by placing a three-point stitch in each of the four quadrants.[1] Fine (3-0 or 4-0) absorbable sutures are used for incorporating full-thickness bites of the open end of the ileum, a seromuscular bite just proximal to the anterior fascia, and finally a bite through the dermis of the skin. By placing traction on these sutures the ileum is easily everted. Before tying down the sutures, one or two further sutures are placed in each quadrant. These are simple sutures that incorporate full-thickness bites of the edge of the open bowel and the dermis of the skin. Tying down all the sutures should result in a "rosebud" or spigot formation. Sutures through the full thickness of the skin should be avoided because scarring will prevent the application of a watertight appliance seal. The ileostomy should be protruding 1 to 2 cm above the abdominal wall to allow the placement of a well-fitting appliance. This is extremely important because the ileal effluent is very irritating and, if allowed to bathe the peristomal skin, will result in skin breakdown.

The skin surrounding the stoma is painted with skin adhesive, and a transparent ileostomy appliance is placed and allowed to hang to the right side of the patient. This facilitates emptying of the appliance in the immediate postoperative period, as well as inspection of the stoma without having to remove the ileostomy bag. The opening in the faceplate should be 2 mm wider than the stoma to allow for postoperative edema. The appliance is usually changed after the second postoperative day once the midline dressing is removed. If there is leakage around the appliance at any time, the device should be changed immediately.

LOOP ILEOSTOMY

A loop ileostomy is also located in the right lower quadrant (Fig. 71–2). The site is chosen preoperatively just as for an end ileostomy. At the completion of the appropriate procedure a loop of bowel is chosen for creation of the diverting ileostomy. It should be as distal as possible in the small intestine at a point where the bowel can be brought up onto the abdominal wall without tension. The proximal or distal limb should be marked with a suture so that orientation is maintained before maturation of the stoma.

A small opening is created in an avascular part of the mesentery at the apex of the loop. A ¼-inch Penrose drain is placed through this opening to help place traction and deliver the bowel to the anterior abdominal wall. The skin incision for the stoma site is made exactly as for an end ileostomy. Subcutaneous fat may have to be removed to accommodate the two loops of bowel along with its mesentery.

Some authors prefer to position the proximal limb in the dependent inferior position, but such positioning requires twisting the mesentery of the small bowel. Although placing the functional proximal end inferiorly theoretically achieves complete diversion and drainage, this is easily and very well achieved by maturing the stoma with the proximal end more prominent as described.

Because the stoma will be temporary, there is no need to anchor it to the posterior sheath. The Penrose drain is substituted for a commercially produced plastic ileostomy bridge, which is available in different lengths. This rod is anchored to the skin with nonabsorbable sutures and should protrude just beyond the stoma so that it does not interfere with proper placement of the ileostomy appliance. After ensuring that the bowel is oriented properly, the abdominal incision is approximated and protected. The small bowel is opened by making an incision two thirds of the way along the antimesenteric wall of the distal loop just above the skin surface. Three-point anchoring sutures are placed toward the proximal limb as described for the Brooke ileostomy. Three such sutures are placed, one on each side of the mesentery and the third bisecting these. The remaining bowel wall, including the distal limb, is matured by using simple fine absorbable sutures that incorporate full-thickness bites of the cut end of the bowel and the dermis of the skin, which should result in an accentuated proximal limb and a recessive crescent-shaped distal limb flush with the skin. A watertight ileostomy appliance is placed in the operating room. The ileostomy bridge is removed after about a week when the edema has partially subsided and the ileostomy is functioning.

DIVIDED-LOOP ILEOSTOMY

In 1984, Abcarian and Prasad described their experience in constructing a modified loop ileostomy (Fig. 71–3). The segment to be exteriorized is identified and the ileum is divided near the apex of the loop with a GIA stapler. The proximal end is pulled through the right lower quadrant stoma opening, and 5 cm is exteriorized. The antimesenteric staple line of the distal limb is brought up through the same opening and positioned cephalad to the proximal limb. The entire staple line of the proximal limb is removed and the stoma constructed as for an end Brooke ileostomy. One corner of the recessive limb staple line is excised, and it is matured as a mucous fistula flush with the skin, thus allowing for distal decompression. Two transitional sutures are placed between the adjoining walls of the two limbs to create a completely diverting, perfectly circular stoma, which allows for a better appliance fit.[25,33]

END-LOOP ILEOSTOMY

This rarely performed procedure should be in the armamentarium of all abdominal surgeons because it can be

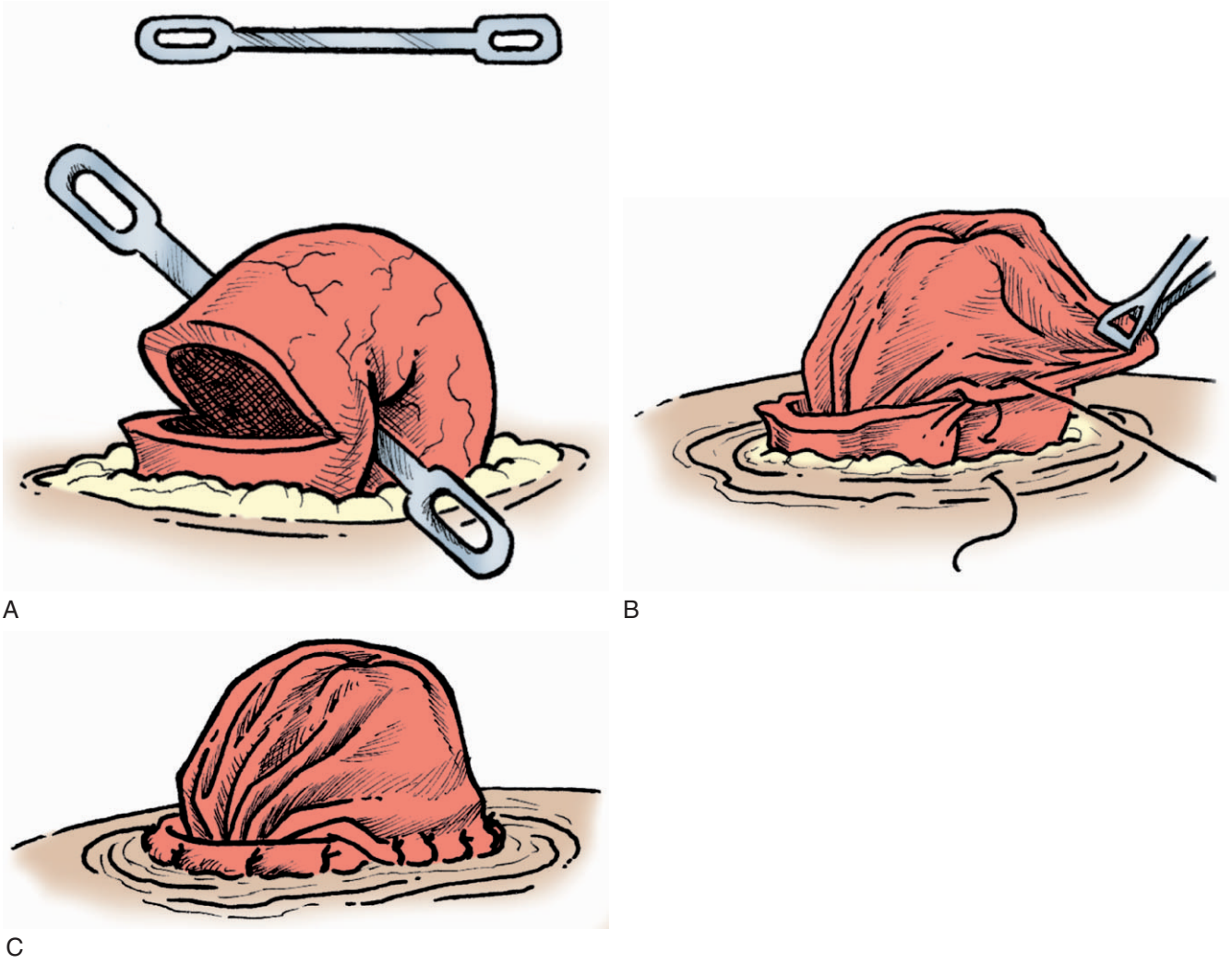

Figure 71–2. Maturation of a loop ileostomy. **A,** Commercially available plastic rod (shown separately) supporting the ileal loop. A transverse incision is made along the distal limb at the level of the skin. **B,** Eversion of the prominent proximal limb with three-point sutures. **C,** Fully matured loop ileostomy (shown without the plastic rod).

of great benefit when tension on the mesentery of the small intestine precludes construction of a viable end Brooke ileostomy (Fig. 71–4). This circumstance can be seen in patients with Crohn's disease who possess a thick short mesentery, in morbidly obese patients with thick anterior abdominal walls,[1] or in abdominal catastrophes in which edema and circulatory deficiencies prevent safe construction of an end ileostomy.

The distal part of the small bowel is transected as for an end ileostomy. The staple line may be oversewn and reinforced with absorbable seromuscular suture. A segment of bowel proximal to the closed end is chosen so that it can be exteriorized through the stoma opening on the right lower abdominal wall without tension. The construction then proceeds exactly as it would for a loop ileostomy. If the stoma is to be permanent, the bowel and its mesentery are anchored to the peritoneum and the posterior sheath with fine absorbable sutures.[22,25]

CLOSURE OF A LOOP ILEOSTOMY

Closure can be accomplished in most cases by a local procedure, thus eliminating performance of a formal celiotomy (Fig. 71–5). Closure is undertaken once it is ascertained that the distal anastomosis has healed completely and its integrity has been confirmed by contrast studies. In most cases the loop is closed a minimum of 6 weeks after the initial procedure to allow adequate tissue healing and softening of intra-abdominal adhesions. In a nonrandomized prospective study, Menegaux et al. have shown that temporary small bowel stomas may be closed safely on postoperative day 10 in healthy patients.[34]

The patient is positioned supine and a circumferential skin incision is made close to the mucocutaneous junction. Allis clamps can be used for vertical traction on the ileostomy. Circumferential subcutaneous dissection is carried out with electrocautery or scissors to reach the

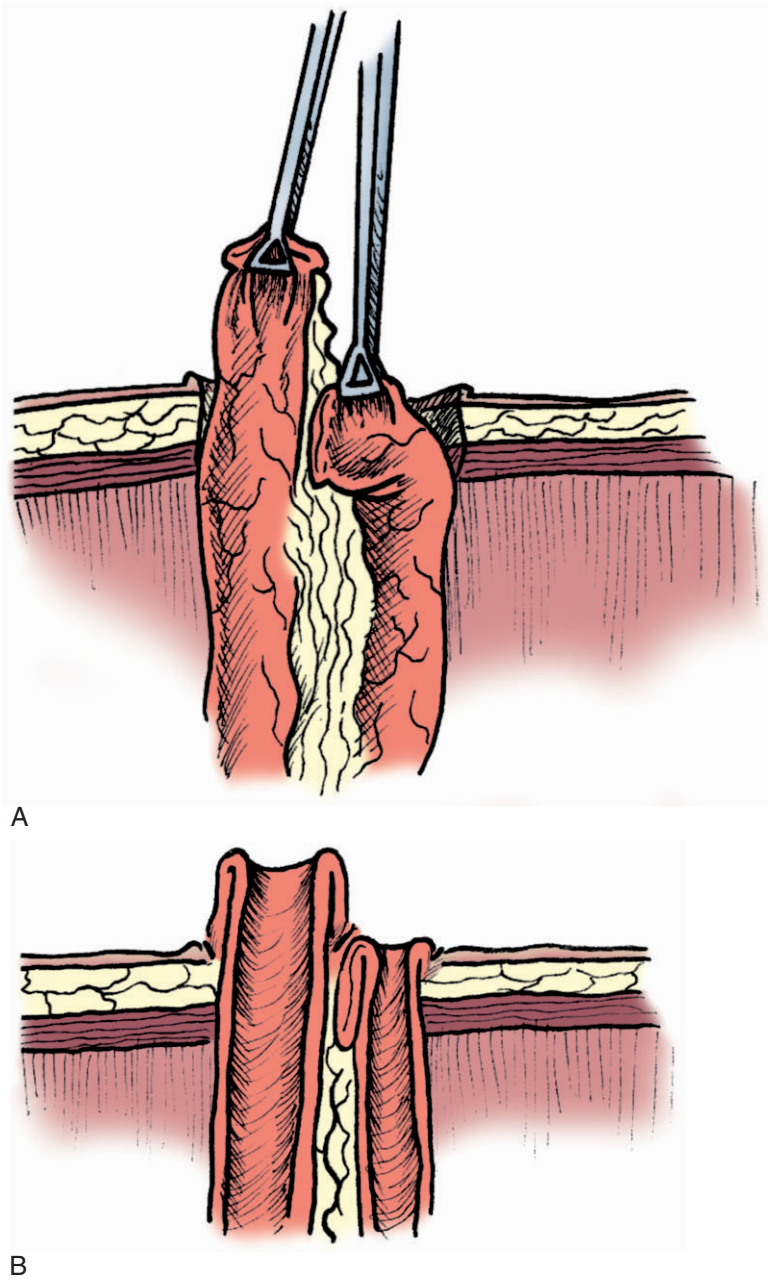

Figure 71–3. Divided-loop ileostomy. **A,** Proximal limb of the divided ileum delivered as for an end ileostomy. Only the antimesenteric border of the distal limb is brought up to the skin surface. **B,** On maturation it appears as an end ileostomy.

base of the ileostomy and identify the anterior fascia. Care is taken to prevent injury to the small intestinal wall or mesentery. The anterior sheath is incised close to the bowel wall to gain access to the peritoneal cavity. The intestine is circumferentially freed from peritoneal attachments by sharp dissection. The excess scar and skin are trimmed away from the bowel wall. The closure can be accomplished in various ways. The enterotomy can be closed transversely via a two-layer hand-sewn technique with an inner full-thickness layer and an outer seromuscular layer. Fine absorbable sutures are used for both layers. Alternatively, a linear stapler can be used to accomplish the same transverse closure.

If there is any concern about luminal narrowing, a linear cutting stapler is used to form a stapled side-to-side functional end-to-end anastomosis. The antimesenteric walls are aligned, and a GIA stapler is deployed to create the anastomosis. With a second GIA stapler placed transversely, the excess skin and ostomy opening are transected to complete the anastomosis.[1,29] No major difference in morbidity has been demonstrated between stapled and sutured closure, although stapled closure can be accomplished faster.[35] Hasegawa et al. have shown that postoperative bowel obstruction is less common after staple than after suture closure.[36]

The small bowel is returned to the peritoneal cavity and the fascia approximated with nonabsorbable suture. The subcutaneous space is thoroughly irrigated. The skin can be packed open or loosely approximated with staples and intervening Telfa wicks to drain the subcutaneous

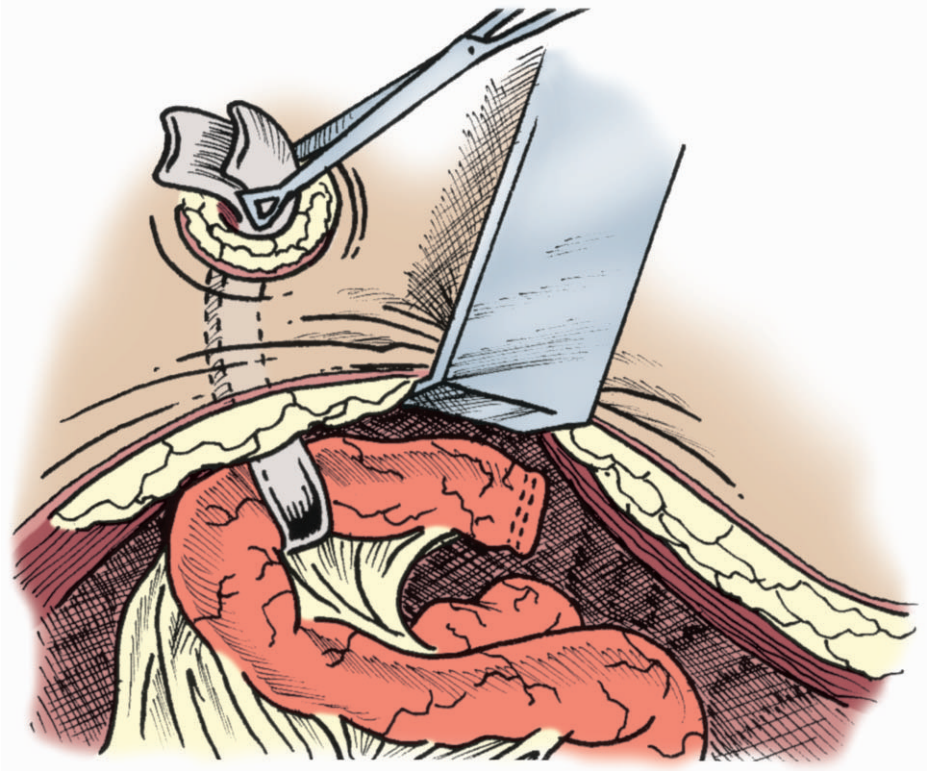

Figure 71–4. End-loop ileostomy. A loop of ileum proximal to the stapled end is delivered through the stoma site. Maturation takes place as for a loop ileostomy.

space. They can be removed after 48 to 72 hours. Sutton et al.[37] propose closing the skin with circular subcuticular nonabsorbable suture. The suture is tightened to draw the wound edges together while leaving a small 5- to 10-mm central defect, which allows the subcutaneous space to drain and heal by secondary intention. The suture is removed around the 14th postoperative day. They performed such a closure in 51 patients, with wound infections developing in none of them.

COMPLICATIONS OF ILEOSTOMY

Meticulous surgical technique and proper location of the stoma can minimize complications attributable to ileostomy construction and closure. The reported complication rates vary from 7% to 76%.[17,18,38-45]

Stoma Necrosis

Stoma ischemia with necrosis has been reported in 1% to 5% of patients undergoing construction of an ileostomy.[17,18,21,31,32,46] It is more often seen in the obese and after emergency procedures.[46] The most common cause is devascularization secondary to overzealous skeletonization of the terminal ileum for eversion. The viability of the stoma should be ascertained in the operating room. If the mucosa appears dusky, the ileostomy should be revised before leaving the operating suite. If discovered postoperatively (usually within 48 hours), one must determine the depth of viability, which can be accomplished by placing a test tube through the stoma opening and illuminating the lumen with a flashlight. If the ischemia is limited to the subcutaneous space and above the fascia, the patient can be treated by observation with revision performed later if stenosis develops. If the necrosis extends below the peritoneum, immediate revision is required.

Bowel Obstruction

Small bowel obstruction can occur after creation or closure of the ileostomy. It is important to differentiate between mechanical blockage because of food indiscretion (high-fiber foods), which occurs more distally at the stoma site just below the fascial level, and more proximal obstruction from intra-abdominal disease, such as adhesions, internal herniations, and recurrent strictures secondary to Crohn's disease. Bowel obstruction may also be caused by skin-level stoma stenosis as a result of ischemia. The clinical signs and symptoms are the same regardless of the cause and include cessation of ileostomy output, abdominal distention, crampy abdominal pain, nausea, vomiting, and dehydration. Patients with partial obstruction may have increased output. Treatment begins by instituting aggressive resuscitation, intravenous hydration, and nasogastric decompression. Kodner[22] proposed a logical algorithm to deal with this complication. A Foley catheter (24 French) is inserted into the stoma and held in place by partially inflating the balloon. Irrigation is performed with 50 ml of warm water. If there is return of food particles, the irrigation is carried out slowly until the return is clear and the mechanical food obstruction is relieved. If the initial fluid return is clear, one can

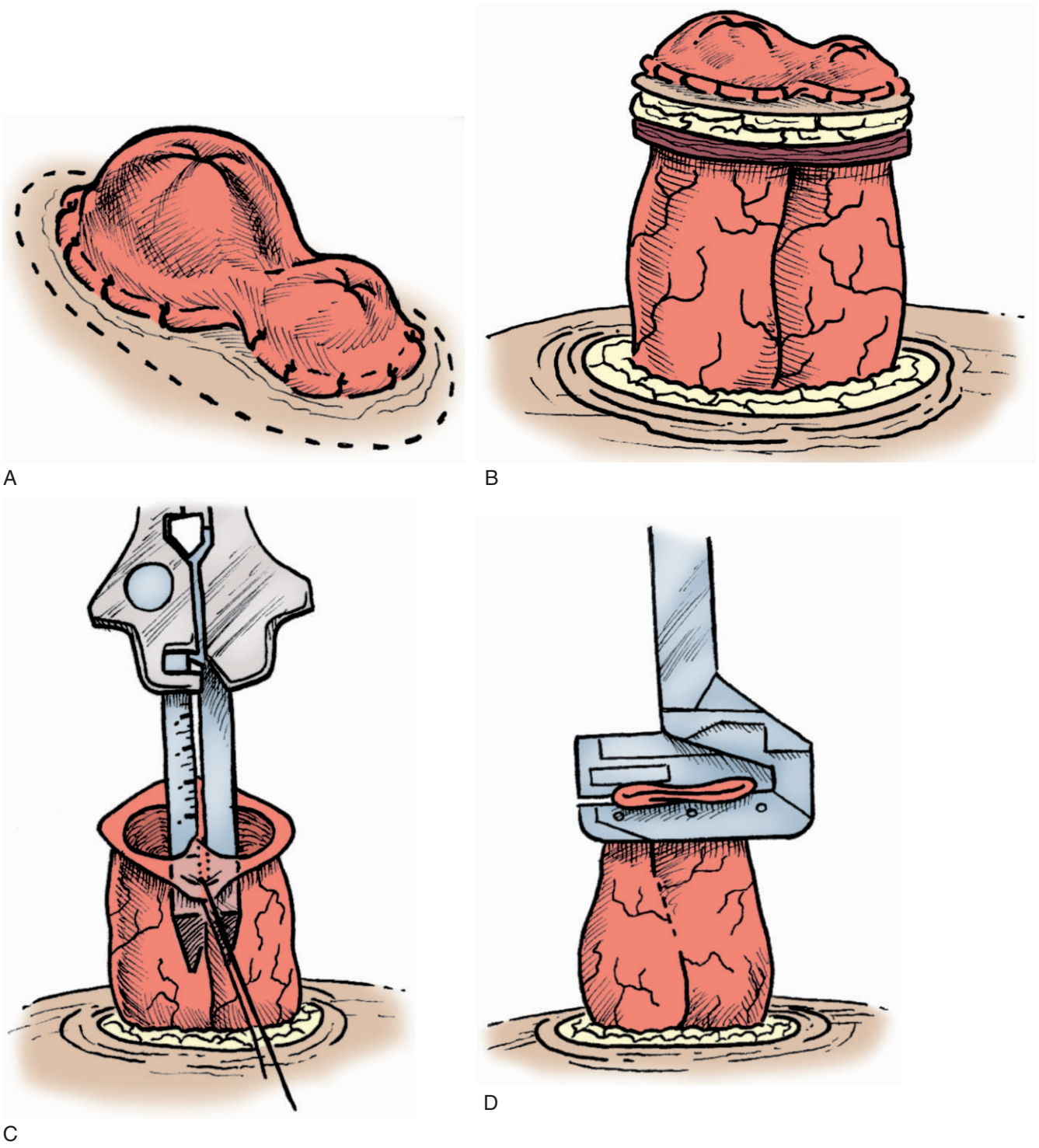

Figure 71–5. Loop ileostomy closure. **A,** Skin incision made around the ileostomy close to the mucocutaneous junction. **B,** Stoma and small bowel elevated after the intraperitoneal adhesions are divided. **C** and **D,** Stapled side-to-side anastomosis.

assume a proximal obstruction and perform a water-soluble contrast study to delineate the site of obstruction. This may be therapeutic if the obstruction is due to food particles. Patients should show signs of rapid improvement within 24 to 48 hours after conservative therapy. If any signs of impending bowel ischemia are present, early surgery is the prudent course.

Bowel obstruction has been reported in 3% to 17% of patients with ileostomies.[42,43,47-50] Feinberg et al.[42] had an 11% incidence of bowel obstruction after creation of a loop ileostomy. Senapati et al.[43] reported a bowel obstruction rate of 11.4% after ileostomy closure; two thirds of these obstructions were treated conservatively, whereas 11 (4.2% of all ileostomy closures) patients

required operative intervention. In Feinberg and colleagues' study, no patient had bowel obstruction after resection with anastomosis, and such treatment was better than a hand-sewn anastomosis or simple closure, although it did not reach statistical significance.

Mucocutaneous Separation

The newly matured stoma may separate from the surrounding skin if the tissue is friable, as in patients taking high-dose steroids, stoma site infections, and excessive tension on the maturing sutures. Management is conservative, with aggressive enterostomal therapy provided until the skin opening heals and a new mucocutaneous junction forms.[1]

Stoma Stenosis

Stomal stenosis develops in 2% to 10% of ileostomies.[21,31,32] It may occur if the fascial opening is made too small. The surgeon's middle and index fingers should pass through the stoma opening in the abdominal wall to ensure an adequate aperture size. Skin-level stenosis develops as a result of stomal ischemia or subcutaneous infection. Initial management is gentle dilation, which can be accomplished with Hegar dilators. If there is no relief from obstructive symptoms, surgical revision is undertaken. The stenosis may be corrected with a local procedure by taking down the mucocutaneous junction, dissecting down to the fascia, and making the opening larger with re-creation of the stoma. Laparotomy may be necessary if exteriorization of the bowel was initially inadequate.

Stoma Retraction

Retraction has been reported in 3% to 17% of all ileostomies.[17,18,21,31,36,46] Goldblatt et al. reported that 30% of their revisions were performed because of stenosis and retraction.[51] Tension on the small intestinal mesentery and lack of fixation of the mesentery and bowel to the peritoneum may result in this complication. A flush stoma may also occur as a result of weight gain and is seen in morbidly obese patients, who have a higher rate of stoma retraction.[52] With a skin-level ileostomy the effluent leaks onto the surrounding skin, causes breakdown, and prevents secure application of the appliance. It may be managed with skilled enterostomal therapy, but many patients require revision of the stoma.

Stoma Prolapse

Ileostomy prolapse has been reported in 0% to 11% of patients.[13,17,21,31,32,53,54] Causes include too large an abdominal wall fascial opening, lack of fixation of the mesentery to the abdominal wall, and placement of the ileostomy outside the rectus muscle or in previous incisions. It is usually associated with a parastomal hernia.[54] The prolapse may be intermittent or fixed. If the appliance can still be applied without leakage and the prolapse is stable and not bothersome to the patient, it need not be corrected. Repair is accomplished by a local approach that involves resecting the excess ileum and re-creating a Brooke ileostomy. Laparotomy for intraperitoneal fixation may be needed to preserve bowel length.

Parastomal Hernia

Parastomal hernia is seen less frequently after ileostomy than after colostomy construction.[53-55] It affects 1.8% to 28.3% of end ileostomies and 0% to 6.2% of loop ileostomies.[55] Patients with poor tissue characteristics, such as obesity, use of high-dose steroids, chronic obstructive pulmonary disease, malnutrition, raised intra-abdominal pressure, and previous herniations, are at risk.[53,54,56] No difference in incidence rates has been demonstrated with regard to location of the stoma through the rectus muscle, fascial fixation, or closure of the lateral space.[55-58]

The majority of patients are asymptomatic. Operative indications include symptoms of small bowel obstruction, localized discomfort, an enlarging mass, and poor appliance fit that may result in leakage of effluent and peristomal skin breakdown. About 30% of patients with peri-ileostomy hernias require operative repair.[59]

Repair may be accomplished by direct fascial approximation, prosthetic mesh repair, and relocation of the stoma to new site. Although fascial reapproximation is the simplest option because it avoids a formal laparotomy, it carries with it an unacceptably high rate of hernia recurrence (46% to 100%).[55,59,60] The prosthetic mesh may be placed intraperitoneally or as a fascial onlay. There is a small risk of mesh infection and erosion into the bowel (3%).[59] Recurrence rates after mesh repair are reported to be between 0% and 39%.[55,59,60] Reiger et al., in their series of 41 patients who underwent 51 repairs, showed that the lowest recurrence rates were seen after stoma relocation (24%).[60] The reported rates vary between 0% and 76%.[55,59,60] If the hernia defect is large, the ileostomy can be relocated via the paraileostomy incision and thereby avoid a formal laparotomy. No clinical trials have compared the aforementioned procedures, and the reported numbers are small.[55]

Laparoscopic repair of paraostomy hernias has been reported, but the series are small and not limited to paraileostomy hernias. Recurrence rates of 0% to 44% are reported.[61-63] Safadi reviewed 11 studies with a total of 37 patients and added 9 of his own. He described a recurrence rate of 44.4% within 6 months of the operation.[61] As experienced is gained and techniques are refined, the results may improve. The advantage of this approach is that it avoids stoma relocation and reduces postoperative pain and wound complications.

Peri-ileostomy Fistula

The incidence of peri-ileostomy fistula is unknown. Older studies reported rates of 24% to 40%.[51,64] A fistula may result from recurrent Crohn's disease, operative

injury when an anchoring stitch incorporates the full thickness of the bowel wall, ischemic injury to the stoma, or ill-fitting appliances.[65] Greenstein et al.[66] reported a series of 214 patients with an ileostomy constructed for Crohn's disease. Parastomal fistulas developed in 14 patients (6.5%), and all cases were a consequence of recurrent Crohn's disease.

Because fistulas pose a difficult proposition of maintaining a secure ostomy appliance, treatment consists of reconstruction of the ileostomy either at the same location or at a new one, depending on the complexity of the fistula.[66] Medical therapy has not been successful in treating these fistulas, although infliximab may be of benefit.

Hemorrhage and Peri-ileostomy Varices

Trauma to the stoma from ill-fitting appliances may cause mucosal tears or shallow ulcers that result in troublesome bleeding. These lesions heal spontaneously with proper stomal care and enterostomal therapy.

Sclerosing cholangitis leading to cirrhosis is seen in patients with inflammatory bowel disease. These patients may manifest parastomal varices in addition to anorectal and esophageal varices. Local treatment with sclerosing agents or variceal ligation provides temporary control. Definitive treatment consists of portosystemic shunting or selective splenorenal shunting.[67,68]

Peri-ileostomy Skin Problems

Peristomal skin irritation has been reported in 15% to 79% of patients with an ileostomy.[42,53,54,69] It commonly accompanies flush or retracted stomas, which result in poor appliance fit and leakage of effluent. Skin problems are seen more frequently after emergency procedures because preoperative stoma positioning is not usually possible.[52] The peristomal skin may secondarily become infected with bacterial or fungal organisms (11%), most commonly *Candida albicans*.[30] Treatment consists of local antifungal powder and enterostomal therapy.

Paraileostomy skin ulceration can be secondary to recurrent Crohn's disease or be a manifestation of pyoderma gangrenosum. The latter is due to underlying active inflammatory disease and resolves after removing the diseased segment of bowel. Aggressive enterostomal therapy is needed in the interim.[69]

Ileostomy Diarrhea

Increased ileostomy output may be seen with gastroenteritis, partial small bowel obstruction, radiation enteritis, short-bowel syndrome, and Crohn's disease.[54] Ileostomy effluent totaling greater than 1000 ml/day may lead to dehydration and sodium depletion requiring hospitalization and intravenous fluid replacement. In the first month after construction of a new ileostomy, dehydration secondary to stomal water and electrolyte loss is common. Treatment includes intravenous fluid resuscitation, dietary manipulation, antidiarrheal agents, and fiber. The risk of dehydration requiring hospitalization from a loop ileostomy can be as high as 20%.[42,54] Chronic dehydration leads to acidic urine and predisposes to the formation of uric acid calculi.[54]

CONCLUSION

Living with an ileostomy is a major life-altering event for patients. With thorough preoperative preparation, patient education, meticulous surgical technique, and patient access to enterostomal therapy, complications can be prevented and the patient's quality of life improved.

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Chapter

72

Suturing, Stapling, and Tissue Adhesives

John Migaly • Rolando Rolandelli

The healing of a bowel anastomosis proceeds in a stepwise, time-dependent fashion. At the time of transection of the bowel, there is an immediate inflammatory response elicited by activation of the clotting cascade, recruitment of platelets, and perpetuation of the inflammatory cascade via the elaboration of inflammatory mediators stored in platelet granules. Neutrophils are subsequently recruited into the wound. During these first 3 to 5 days, termed the inflammatory phase of wound healing, the collagen matrix undergoes degradation by metalloproteinases. It is in this initial phase that the integrity of the anastomosis depends almost entirely on technical factors, suture materials, or the integrity of stapled margins of bowel.[1]

Around the fifth postoperative day there is a crucial switch from collagen degradation to collagen deposition, which corresponds to the transition from the inflammatory phase to the fibroplasia phase (Fig. 72–1). The fibroplasia phase reaches its maximal level at day 7.[2] Any delay or impairment of the fibroplasia phase can result in the potentially catastrophic consequence of anastomotic dehiscence.[3] Indeed, it is at the end of the first postoperative week that anastomotic dehiscence usually occurs and becomes clinically evident.

Although it may seem that surgical stapling devices have completely supplanted hand-sewn suturing of bowel anastomoses, hand suturing remains a crucial skill in every surgeon's armamentarium. Certain situations are not amenable to surgical stapling, and it is in these situations that the surgeon's facility with suturing techniques can vastly affect the outcome of an intestinal anastomosis.

Hand suturing uniformly invokes an inflammatory response from dragging the suture material through the bowel. The choice of suture material used by surgeons is not based on a strong preponderance of scientific evidence. Everting and inverting anastomoses have come in and out of favor over the last 2 centuries, as have many anastomotic techniques.

SURGICAL SUTURING AND TECHNIQUE

Suture Material

All sutures produce some degree of inflammation as they are dragged through tissues. The degree of inflammation corresponds to the amount of collagenases and metalloproteinases produced in the local wound environment and the subsequent loss of tensile strength in both the wound and the suture material itself.[4]

The ideal suture material should elicit minimal tissue reaction and be easy to handle and tie without fraying. It should also be relatively easy to sterilize while maintaining all of the ideal characteristics after sterilization.[5]

The type of suture used has traditionally been tailored to the particular layer of the intestinal tract that the suture material is being used to approximate. Chromic catgut is the most commonly used as an inner layer of suture in a two-layer intestinal anastomosis.

In the 1950s, Madsen studied 12 different suture materials and concluded that absorbable suture materials display a marked tissue reaction with delay of collagen formation.[6-8] Because chromic catgut is reabsorbed between 18 and 21 days, it is not the material of choice for single-layer applications such as bilioenteric anastomoses.[9] The absorbable synthetic sutures of polydioxanone (PDS) and polyglyconate (Maxon) are the commonly used sutures in these anastomoses because of their longer retention time in wounds and sustained breaking strength.

The absorbable synthetic suture materials polyglactin (Vicryl) and polyglycolic acid (Dexon) are used interchangeably with chromic catgut but have the added benefits of decreased inflammatory response and increased strength. The downside of these sutures is that they are braided and produce more drag across the intestinal wall.

Silk suture is still the traditional nonabsorbable suture most commonly used for intestinal anastomoses, and it

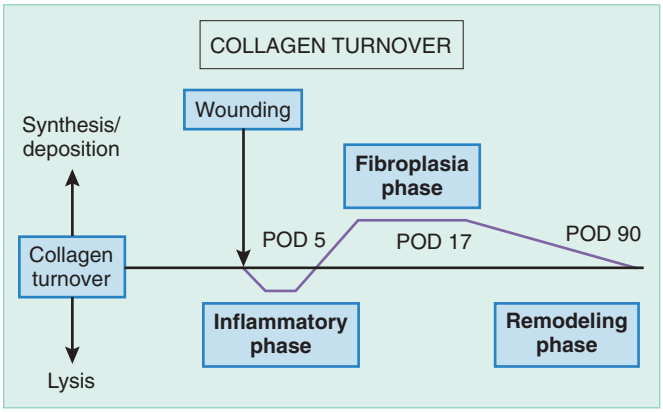

Figure 72–1. Collagen deposition and lysis as a function of time in intestinal healing. POD, postoperative day. (From Migaly J, Lieberman J, Long W, et al: Effect of adenoviral-mediated transfer of transforming growth factor-beta1 on colonic anastomotic healing. Dis Colon Rectum 47:1703, 2004.)

was lauded as the most reliable suture by Halstead as far back as 1913.[10] Silk is used most often as the outer layer of a two-layer anastomosis and is most commonly used as an interrupted seromuscular stitch.

In conclusion, in two-layer anastomoses, the inner layer is usually an absorbable suture such as chromic catgut, Dexon, or Vicryl, with the outer seromuscular stitch being silk. If a one-layer anastomosis is to be performed, a nonabsorbable suture such as silk is used. Bilioenteric anastomoses are commonly performed as one-layer anastomoses with more durable absorbable synthetics such as PDS or Maxon.

Suture Material and Infection

As in the case of any implantable foreign body, suture material can potentiate bacterial infection in an intestinal anastomosis. The particular properties of a suture determine its ability to thwart or encourage bacterial infection. Bacterial adherence is variable among the various suture types.

Chu and Williams examined 10 types of suture ranging from absorbable to nonabsorbable, monofilament to braided, and synthetic to natural origins and quantitatively determined the adhesion of radiolabeled bacteria to these various sutures. They found that PDS sutures exhibited the lowest affinity to the adherence of *Escherichia coli* and *Staphylococcus aureus*. Dexon sutures exhibited the highest affinity to these species.[11]

Katz et al. confirmed these results and, furthermore, demonstrated via an in vivo model of wound infection that suture materials potentiate bacterial growth and cause infection in mice. They injected suspensions of staphylococci into subcutaneous pockets in mice and found that 10^9 bacteria were necessary to cause wound infection in mice in the absence of suture whereas only 10^5 were necessary to elicit significant wound infection in the presence of suture. They also found that the inflammatory response and infectivity scores correlated nicely with the adherence indices of the various types of suture. The fastest removal of bacteria was from nylon, and the slowest was from silk.[12] Consideration should be given to the type of suture used in the event of gross fecal soilage.

Suture Material and Tumor Cell Adherence

Both in vitro and animal data support the theory that certain suture materials support the growth of tumor cells more than others do.[13] Using a rodent model, Reinbach demonstrated that radiolabeled tumor cells adhere more avidly to silk suture used to close enterotomies of the colon than they did to PDS sutures.[14] Further investigation is obviously warranted before deciding which suture truly conveys an oncologic advantage in bowel anastomoses.

Methods of Suturing

Suture lines can be created either in a simple or interrupted fashion or in a continuous or running manner. The advantage of a continuous suture is that the suture line is more watertight, with the disadvantage being that the integrity of the entire suture line is based on one stitch. Hemostasis is also improved with a continuous suture, with the converse effect being that continuous suturing may constrict anastomotic blood flow more than interrupted suturing does.

Regardless of whether the suture is run in continuous or interrupted fashion, a bowel anastomosis must adhere to the following principles. The anastomosis must be watertight and must have mucosal apposition. The submucosa, which supplies much of the strength to a bowel anastomosis, must be incorporated into the closure. Care must be taken to not strangulate the edges of the bowel during closure in order to avoid stricture or necrosis and subsequent anastomotic leakage.

Lembert Suture

Lembert suture is the most commonly used suture in gastrointestinal surgery (Fig. 72–2). It is used as the outer layer of a two-layer bowel anastomosis and is also used to repair seromuscular tears in the bowel wall. The stitch is started approximately 3 to 4 mm lateral to the incision and placed at a right angle to the long axis of the incision. It incorporates only the seromuscular layer; care must be taken to not incorporate the full thickness of the bowel wall. The tip of the needle is brought out close to the edge of the incision and is then reinserted in the apposing wound edge and brought out 3 to 4 mm lateral to the wound edge. The suture is then tied down to a tension that approximates the tissue, but not tight enough to tear the tissue. The most commonly used material for a Lembert suture is either silk or PDS suture. This stitch can be performed in an interrupted or continuous manner.

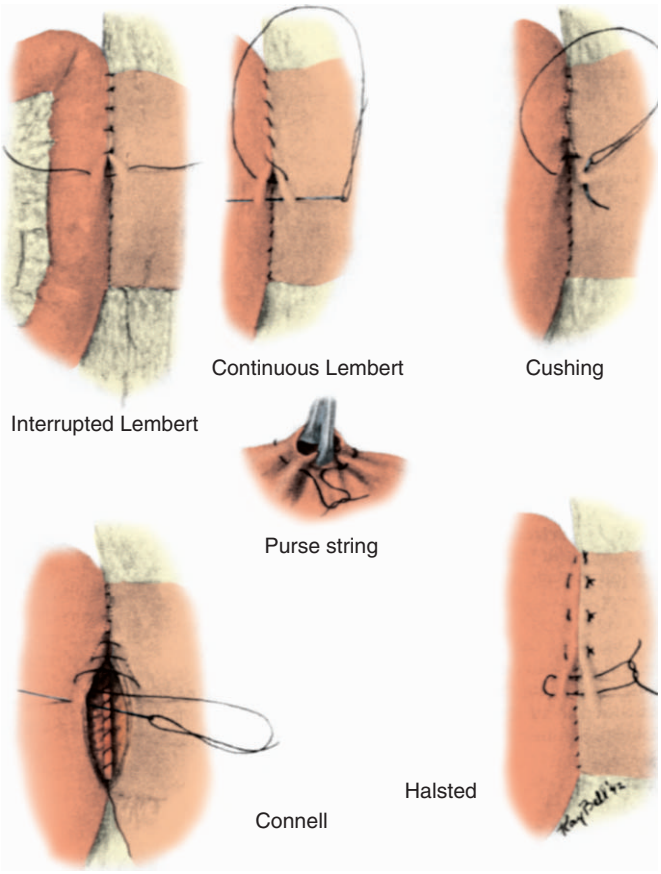

Figure 72–2. Common methods of intestinal suturing. (From Orr TG: Operations of General Surgery, 2nd ed. Philadelphia, WB Saunders, 1949.)

Horizontal Mattress Suture (Halsted Suture)

A horizontal mattress suture, or Halsted suture, is predominantly used for seromuscular apposition in multilayer bowel anastomoses (see Fig. 72–2). The suture is passed through the seromuscular layer 2 to 3 mm lateral to the wound edge and brought out at the wound edge; the needle is then passed through the opposing edge of the wound and brought out 2 to 3 mm lateral. On that same side of the wound approximately 2 mm distal, the suture is passed through both edges of the wound to create two free ends of the suture on one side of the wound edge with the loop of the suture on the other side. This stitch is particularly useful in damaged, inflamed, or abnormal tissue where a Lembert suture pulls through the tissue. Because the horizontal mattress stitch distributes tension in a plane perpendicular to that of a Lembert suture, it allows for apposition of tissues with less crushing effect on them.

Purse-String Suture

A purse-string suture is used to invert appendiceal stumps or to secure feeding tubes or drainage tubes in place. It is basically a circular continuous Lembert suture about a fixed point or opening in the gastrointestinal tract. It is most commonly performed with nonabsorbable suture (see Fig. 72–2).

Connell Suture

The Connell suture is a full-thickness, usually continuous suture that allows for the mucosa to be inverted into the lumen of a bowel anastomosis (see Fig. 71–2). The suture is started at the edge of the anastomosis and brought, full thickness, from inside to out on one side and then outside to in on the opposite side. The suture is tied so that the knot is inside the lumen. The suture is then passed through the tissues from inside to out on one side to begin the Connell stitch. On the other limb of the anastomosis the suture is driven through the tissues, full thickness, from outside to in. On the inside of the bowel lumen the stitch is advanced 2 to 3 mm along the wall and then driven through the bowel wall from inside to out on the *same* side. With the suture now on the outside of the bowel, the next throw is performed on the opposite side in an identical manner. This creates a U-shaped, full-thickness, running inverted suture line. It usually serves as an inner layer of a two-layer anastomosis. Absorbable sutures such as chromic or Vicryl are generally used for these applications.

Inverted Versus Everted Intestinal Anastomosis

The concept of inverting versus everting intestinal anastomoses has long been debated. The overwhelming majority of hand-sewn anastomoses are currently performed in an inverting fashion in either one or two layers.

Gambee and associates, in 1956, published a 156-patient series of various large bowel anastomoses in which they used a single-layer, full-thickness, interrupted, inverting technique with silk suture (Fig. 72–3).[15] They reported five deaths as a result of anastomotic leaks with a mortality of 3%. The incidence of all anastomotic complications was 8.6%, with the majority being radiographic leaks that were not clinically evident.

In 1966, Getzen published a clinical series of 136 everted gastrointestinal anastomoses in which only one leak occurred (resulting in death).[16] Getzen compared inverting and everting bowel anastomoses in a canine model. In 293 anastomoses in dogs, there was no evidence of mucocele or fistula formation. Anastomotic edema was more pronounced in the everted group up to 21 days after surgery. The tensile strength of the inverted anastomosis was two thirds that of the everted group up to 21 days after surgery. Anastomotic strength was comparable in the two groups after 21 days. There were no deaths attributable to everted mucosa.[17]

As with any other wound, the ideal form of intestinal healing is by primary intention. This is accomplished when the individual layers of the intestine reconnect at each side of the anastomosis. Of all layers, the submucosa is particularly important because it harbors fibroblasts, which will produce the collagen that ultimately holds the anastomosis together. Inversion of the anastomosis presents the ends of mucosa to the lumen, where

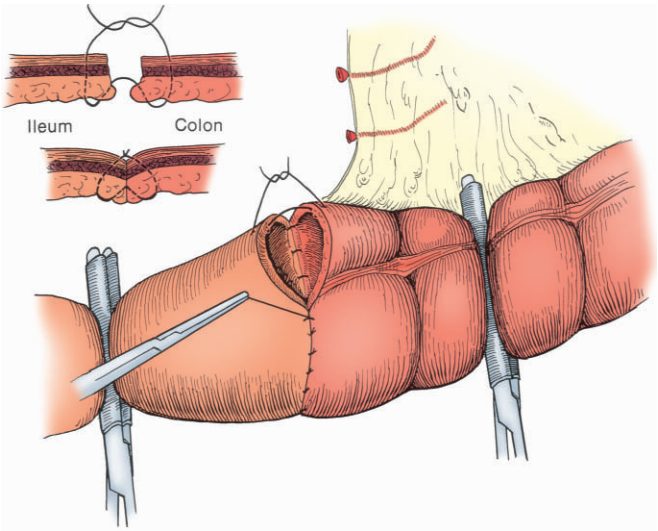

Figure 72–3. The Gambee method of intestinal suturing involving the use of interrupted, inverting sutures. (From Gambee LP, Garnjobst W, Hardwick CE: Ten years' experience with a single layer anastomosis in colon surgery. Am J Surg 92:222, 1956.)

they are further degraded until the submucosa of one side is apposed to the submucosa on the other side. In an inverted anastomosis, the exposed submucosa tends to become adherent to any surrounding structure, thereby eliciting adhesions and delaying healing into a secondary-intention process. It is from this experience that most surgeons have adopted the inverting method for intestinal anastomosis.

STAPLERS AND STAPLING TECHNIQUES

Surgical staplers have become the standard for the creation of bowel anastomoses. In 1826, Henroz first described a device made from two rings that would approximate two open ends of bowel. He successfully tested the device on dogs.

One of the first stapling devices used in humans was the Hültl stapler (Fig. 72–4). This stapler was used to close the stomach during gastrectomies. The array of staplers now available has virtually eliminated the need for hand-sewn anastomoses and has subsequently reduced operative times drastically.

Modern-day staplers deliver staples of either fixed or variable staple height. Linear staplers deliver staples of fixed height, whereas circular staplers can be adjusted to variable heights. A vascular stapler has a closed staple length of 1.0 mm. Tissue staplers have "blue" cartridges and "green" cartridges, which are used for thin tissues and thick tissues, respectively. The closed staple length of a "blue" stapler is 1.5 mm, and it is used for standard tissues such as the small bowel, colon, and esophagus. The closed staple length of a "green" stapler is 2.0 mm. These staplers are used for thicker tissues such as the stomach or rectum. Variable-length staplers are discussed later.

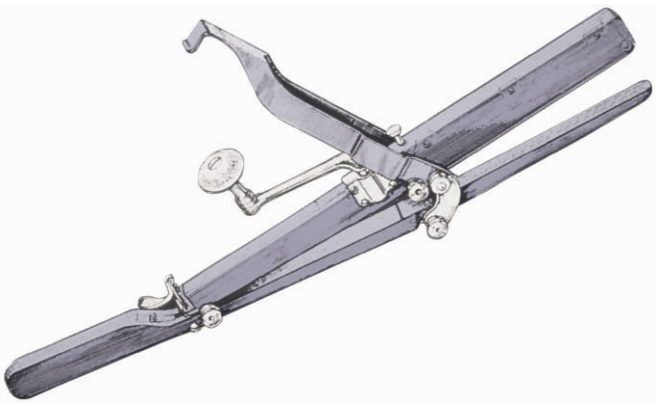

Figure 72–4. Depiction of the Hültl stapler. (From Feil W, Lippert H, Lozac'h P, et al: Atlas of Surgical Stapling. Heidelberg, Germany, Johann Ambrosius Barth, 2000.)

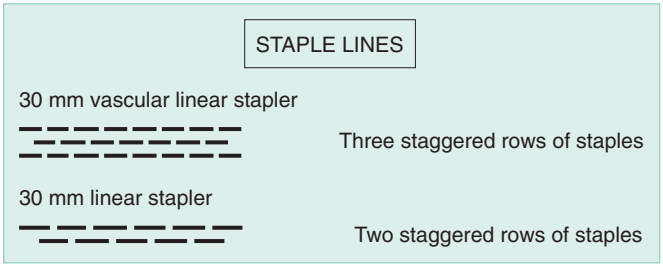

Figure 72–5. Vascular staple lines versus intestinal staple lines. (From Feil W, Lippert H, Lozac'h P, et al: Atlas of Surgical Stapling. Heidelberg, Germany, Johann Ambrosius Barth, 2000.)

Tissue staplers deliver two staggered rows of staples, whereas vascular staplers are used to divide large-caliber vessels while maintaining hemostasis. Vascular staplers deliver three staggered rows of staples (Fig. 72–5).

Types of Staplers

Linear staplers (TA staplers) deliver a double staggered row of staples. They are used in a wide variety of situations, including closure of a hollow viscus, such as the common enterotomy in a side-to-side bowel anastomosis, closure of gastrotomies, and division of large vessels (Fig. 72–6). They can be of variable staple length or fixed staple length, and they can be articulating and nonarticulating.

Linear cutters (GIA staplers) both transect and resect tissues by delivering two double staggered rows of staple lines and deploying a knife to divide the tissue between the staple lines (Figs. 72–7 and 72–8). They are used for a variety of gastrointestinal procedures, such as the formation of enteroenterostomies and gastroenterostomies and the resection of solid organs such as the liver or pancreas.

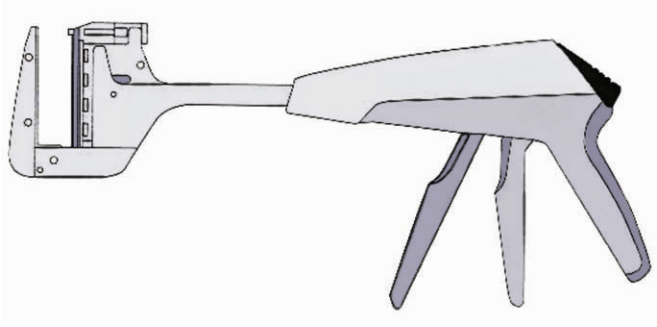

Figure 72–6. Depiction of a TA stapler. (From Feil W, Lippert H, Lozac'h P, et al: Atlas of Surgical Stapling. Heidelberg, Germany, Johann Ambrosius Barth, 2000.)

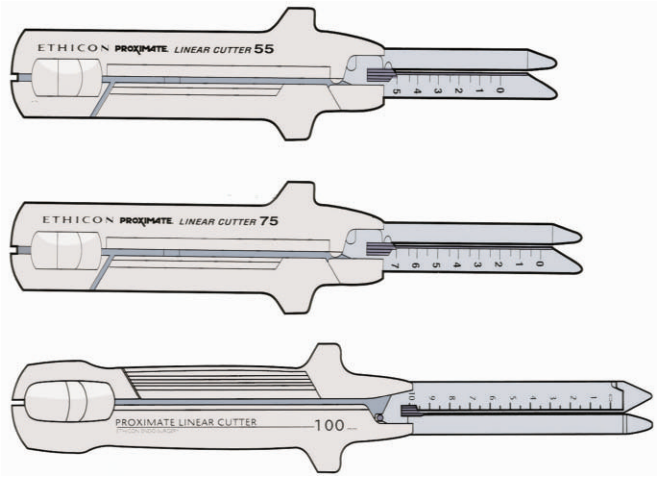

Figure 72–7. Various sizes of linear cutting staplers. (From Feil W, Lippert H, Lozac'h P, et al: Atlas of Surgical Stapling. Heidelberg, Germany, Johann Ambrosius Barth, 2000.)

Circular staplers (EEA, ILS, PPH staplers) are used for inverted end-to-end and end-to-side anastomoses. These staplers usually have a detachable head and lay down a circular, double staggered row of staples. The staples can be variably tightened to a closed length of 2.5 to 1.0 mm, depending on the thickness of the tissue. Circular staplers with nondetachable shafts are used to suspend and excise prolapsed hemorrhoidal tissue.

Techniques/Pitfalls in Surgical Stapling

Functional End-to-End Anastomosis

A functional end-to-end anastomosis (Fig. 72–9), first described in the 1960s, involves apposing the antimesenteric surfaces of two segments of bowel and placing each arm of the GIA stapler in each lumen and firing the stapler to create a common lumen.[18] The lumen is examined and the staples are checked for hemostasis; bleeding points along the staple line in the lumen may be

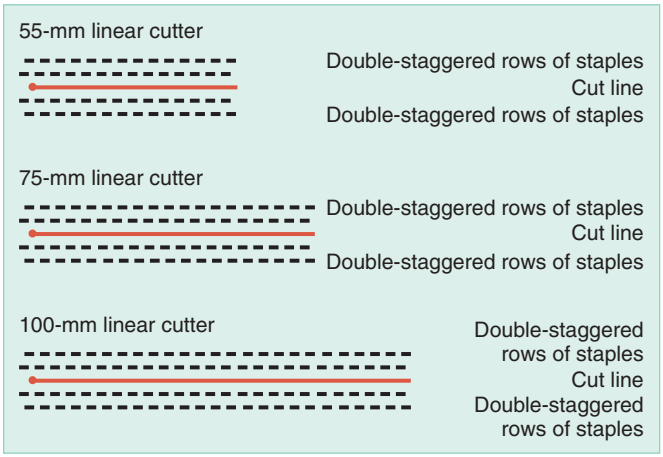

Figure 72–8. Configuration of the staple lines of linear cutting staplers in relation to the knife. (From Feil W, Lippert H, Lozac'h P, et al: Atlas of Surgical Stapling. Heidelberg, Germany, Johann Ambrosius Barth, 2000.)

controlled with 3-0 PDS figure-of-eight sutures. Application of cautery above the staple lines should be discouraged because the current is transmitted along both sides of the staple line and thus can subsequently harm otherwise healthy tissue below the staple line. The common enterotomy is grasped, full thickness, at its edges with Allis clamps to ensure that the serosa and muscularis do not slip under the staple after the stapler is approximated. A single firing of the TA stapler is used to close the common enterotomy. Before firing the TA across the common enterotomy, an important technical point is to ensure that the anterior termination and posterior termination of the GIA staple line are staggered to avoid the crossing of three staple lines.[19] When multiple staple lines cross at the same point, the staples may not close properly, which could lead to anastomotic leakage (see Fig. 72–9).

Stapled End-to-End Anastomosis

This type of anastomosis is performed with a circular stapler (EEA) and is commonly used for the creation of a coloproctostomy but also for esophagostomies and gastroenterostomies. In the case of a colorectal anastomosis, the proximal end of the two ends to be anastomosed is opened, and EEA sizers are placed into the lumen to assess the size of the stapler to be used. Optimal size for these anastomoses should be either 29 or 31 mm. Care should be taken to not create serosal or muscular tears in the colon. Muscular tears of the colon may not always be evident because they might be hidden by the mesentery. The anvil for the EEA is then placed into the open end of the colon, and a Prolene purse-string suture is placed around the rod of the anvil and tied tightly around the rod. If there are any gaps in the purse-string suture, the staple line might be incomplete and a leak could ensue. A mattress suture may be placed around the

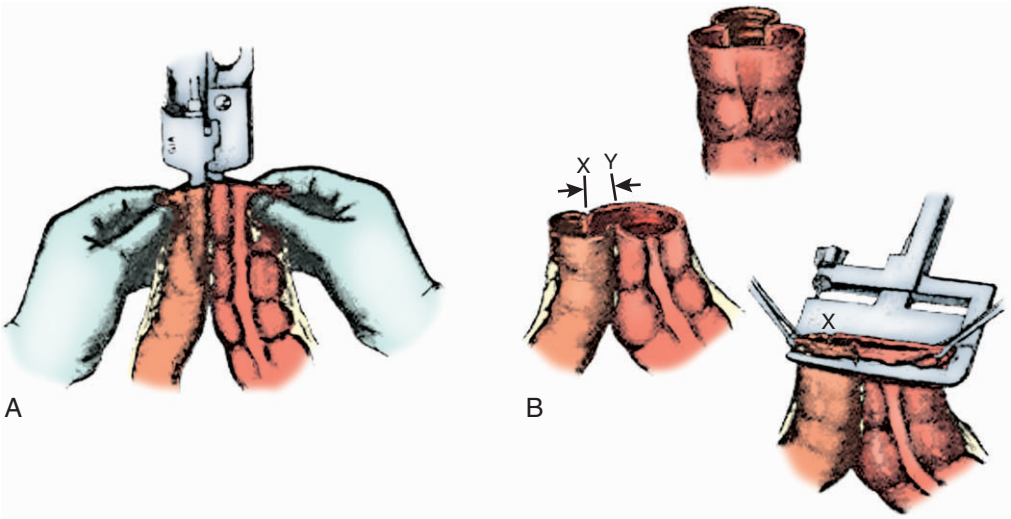

Figure 72–9. Example of a side-to-side, functional end-to-end stapled intestinal anastomosis. When closing the common enterotomy, care must be taken to stagger the anterior and posterior staple lines. (From Chassin JL, Rifkind KM, Turner JW: Errors and pitfalls in stapling gastrointestinal tract anastomoses. Surg Clin North Am 64:447, 1984.)

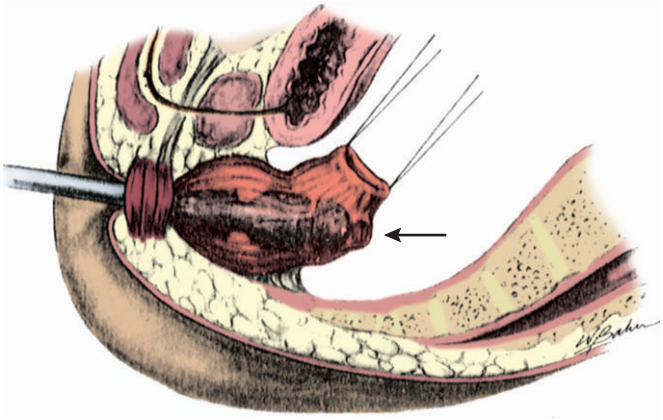

Figure 72–10. When passing a circular stapler for a coloproctostomy, care must be taken to follow the contour of the rectum and sacrum to avoid inadvertently pushing the stapler through the back of the rectum. (From Chassin JL, Rifkind KM, Turner JW: Errors and pitfalls in stapling gastrointestinal tract anastomoses. Surg Clin North Am 64:451, 1984.)

rod to reinforce the purse-string suture. Care must be taken to ensure that the both ends of the bowel are freed up because any fat incorporated into the staple lines may predispose the anastomosis to leakage. The blood supply should also not be too close to the ends for fear of intraluminal bleeding after the stapler is fired.

The stapling device is inserted into the rectum transanally. Care must be taken to follow the contour of the rectum and sacrum to avoid perforating the back wall of the rectum (Fig. 72–10). At the top of the rectum, the stapler should be positioned so that the pin of the EEA comes out right in the middle of the staple line at the portion of rectum that has been cleaned rather than advancing the pin at any other point, such as through the mesorectum. Once the pin is advanced, the anvil and stapler are engaged and the device is screwed tightly. Before firing the EEA, the stapler should be gently rotated to ensure that no other tissue, such as vagina or bladder, has been inadvertently incorporated into the staple line.

Hand-Sewn Versus Stapled Bowel Anastomoses

Beart and Kelly randomized 80 patients to hand-sewn versus stapled coloproctostomies and found no differences in postoperative complications.[20]

In a prospective multicenter randomized study, Docherty et al. compared manually constructed and stapled colorectal anastomoses in 732 patients.[21] Despite a significant increase in radiologic leak rates in the sutured group (14% versus 5%), there was no difference in clinical anastomotic leak rates, morbidity, and postoperative mortality. Univariate analysis correcting for tumor stage demonstrated that the rate of tumor recurrence and cancer-specific mortality was higher in the sutured patients (7.5% and 6.5%, respectively) and in patients with anastomotic leaks.

A meta-analysis of 13 studies that examined manual versus stapled colon and rectal anastomoses found no differences in leak rate, morbidity, mortality, and cancer recurrence. It did, however, demonstrate a higher rate of intraoperative technical problems and a higher rate of anastomotic strictures after stapled anastomoses.[22] This higher rate of stricture in stapled anastomoses is contraintuitive based on the fact that in animal models, the blood flow rate through stapled anastomoses is significantly higher than the flow rate through the standard two-layer and the Gambee anastomoses.[23]

Another observation in experimental animals is that stapled anastomoses tend to heal by secondary intention as compared with hand-sewn anastomoses, which heal by primary intention.[24] This is most noticeable in the functional end-to-end type. Leakage from this anastomosis tends to take place at its closure with the TA stapler and often occurs weeks after being created rather than in the typical first week. During reoperation, the anastomosis is found to be attached by the TA line to some raw surfaces of the laparotomy.

TISSUE ADHESIVES

Ever since the first use of fibrin powder for hemostasis in 1909, the utility of fibrin and fibrin glue products has rapidly increased in a wide spectrum of different areas of surgery.[25,26] Though more commonly used for hemostasis, skin grafting, bone sealing, and other straightforward tissue repairs, its use in the formation of sutureless anastomoses or in the reinforcement of bowel anastomoses is controversial.

Fibrin glue promotes the coagulation of blood by accelerating the conversion of fibrinogen to fibrin. Fibrin glue contains fibrinogen, plasma proteins, factor VIII, aprotinin, and calcium chloride. It is generally packaged as two separate vials that need to be mixed before use. The first vial usually contains fibrinogen, factor VIII, and plasma proteins. The second usually contains thrombin, calcium chloride, and aprotinin. As the two components are mixed, factor VIII is activated and fibrin is subsequently cross-linked, which results in the hemostatic effect and more importantly has effects of varying degree on wound-breaking strength and tissue adhesion.

Data on fibrin glue reinforcement of surgical anastomoses are inconsistent but seem to point to a detrimental effect on bowel anastomoses. In a rat model of intestinal anastomosis, sutureless anastomoses performed with fibrin glue were associated with a higher leak rate than traditional sutured anastomoses were. Furthermore, the bursting pressure of the fibrin glue anastomoses, when compared with sutured anastomoses, was lower at 4 and 7 days postoperatively, which is the critical period in intestinal healing and is also the period associated with anastomotic leakage.[27]

Reinforcement of intestinal anastomoses with fibrin sealant also has a detrimental effect on anastomotic strength. Van der Ham demonstrated in a rat model that reinforcement of the suture lines in intestinal anastomoses had a detrimental effect on anastomotic strength, bursting pressure, and hydroxyproline content. Thus, these anastomoses were both physiologically and biologically inferior.[28,29] These results were duplicated by Byrne, who showed quite clearly not only the negative effects on bursting pressure but also impressive rates of perianastomotic adhesions, toxic sepsis, and death in rats.[30]

Microscopically, there is an intense perianastomotic inflammatory reaction, and levels of hydroxyproline and subsequently collagen are significantly lower in the fibrin glue anastomoses.[28-30] More importantly, high levels of fibrin have been found to inhibit macrophage migration.[31] Fibrin has also been shown to predispose to residual abscess formation in rat peritonitis models. Fibrin inhibits neutrophil phagocytosis of radiolabeled bacteria through a reversible, but dose-dependent mechanism.[32] Thus, fibrin not only acts as an inhibitor to macrophage migration but also inhibits neutrophil function and thus can be a potential nidus for bacterial infection.

In conclusion, the routine use of tissue adhesives for the reinforcement of bowel anastomoses cannot be recommended.

Octyl-2-cyanoacrylate (Dermabond), commonly used for superficial lacerations, was evaluated in a rat model of high-risk and uncomplicated intestinal anastomoses. The results confirmed that there was no significant advantage to the use of octyl-2-cyanoacrylate over the use of traditional intestinal anastomoses in either uncomplicated or high-risk anastomoses. No appreciable difference was noted in gross perianastomotic appearance, adhesions, or hydroxyproline concentrations in rats with and without the use of octyl-2-cyanoacrylate. There was, however, a marked reduction in postoperative day 7 anastomotic bursting pressure in the rats that received octyl-2-cyanoacrylate.[33] This is, of course, significant because it coincides with the fibroplasia phase of anastomotic healing and thus the period for anastomotic leakage should wound healing be altered. The use of octyl-2-cyanoacrylate cannot be recommended at this time.

SUTURELESS INTESTINAL ANASTOMOSES

Biofragmentable Anastomosis Ring

In 1985, Thomas G. Hardy, Jr. described a biofragmentable anastomosis ring (Valtrac) intended to facilitate sutureless intestinal anastomosis.[34] The device consists of two identical circular rings composed of Dexon and 12% barium sulfate. Prolene sutures are used to create purse-string stitches at the two cut ends of the bowel, and the sutures are tightened around the rings after the rings are placed inside the bowel lumens (Fig. 72–11). The device is closed by applying pressure to both sides of the anastomosis. An audible or palpable click of the device signifies proper closure of the device. The device is broken down and passed in stool at some later time.

Hardy et al. validated the feasibility and safety of this device in a dog model.[34] The safety and efficacy of the Vatrac device for human use was examined in a prospective, randomized, multicenter clinical study involving 438 patients. The patients were randomized to sutured or stapled intestinal anastomoses versus use of the biofragmentable anastomotic ring. There were no significant differences in age, gender, or comorbidity. The overwhelming majority of patients underwent oncologic resections. In 13% of the patients, a technical complication such as a serosal tear or inability to fit the device into the lumen of the bowel precluded use of the device. No difference was found in the postoperative complications of anastomotic leak, fistula, hemorrhage, wound infection, ileus, or small bowel obstruction between groups. There was no advantage or difference in length of stay,

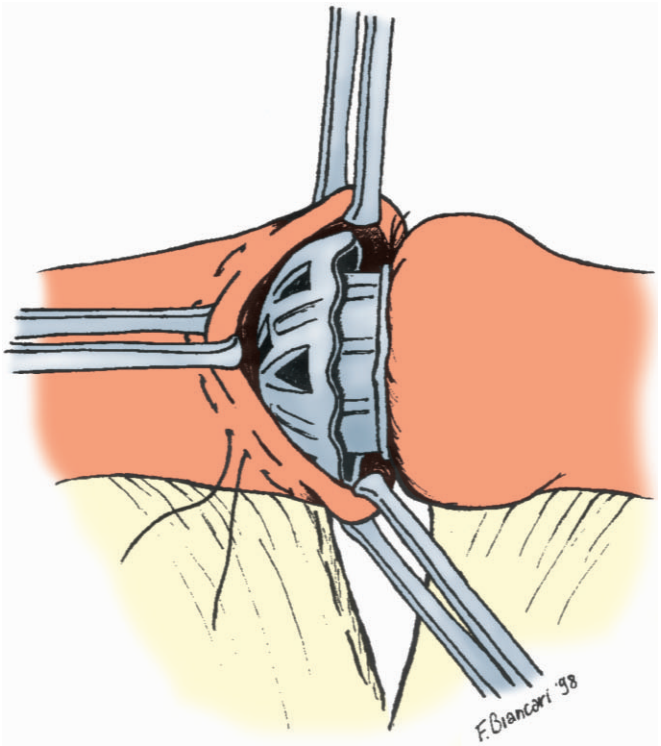

Figure 72–11. Example of the biofragmentable anastomosis ring. (From Di Castro A, Biancari A, Brocato R, et al: Intestinal anastomosis with the biofragmentable anastomosis ring. Am J Surg 176:473, 1998.)

diet, or return to bowel function.[35] Therefore, the biofragmentable anastomosis ring was found to be at least as efficacious as traditional sutured or stapled anastomoses. Di Castro et al. published similar results in a retrospective series of 453 patients with anastomoses created by the biofragmentable anastomosis ring in both elective and emergency situations.[36] They reported a 3% anastomotic leak rate with a 1% rate of reoperation. There were no postoperative intestinal obstructions, but late anastomotic strictures requiring endoscopic dilatation developed in four patients.

The use of biofragmentable anastomosis rings is not superior to traditional suturing or stapling; it does, however, offer a slightly quicker method of anastomosis and allows uniformity of bowel anastomoses throughout the small and large bowel.

CONCLUSION

At the present time, it is not possible to categorically state which is the ideal method of intestinal anastomosis that will work well in every patient. Therefore, it is up to the surgeon to decide in the course of an operation which method is most appropriate. Much of this decision-making process is based on well-established scientific principles. However, part of the decision is also based on the surgeon's skill and experience. Our current inability to scientifically test these factors places them in the realm of art. As in many other biologic processes, further technologic progress will enable us to apply scientific principles even to what is now considered the art of surgery.

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Chapter

73

Gastric, Duodenal, and Small Intestinal Fistulas

Michael S. Nussbaum · David R. Fischer

The word *fistula* comes from the Latin meaning "pipe" or "flute" and is defined as an abnormal communication between two epithelialized surfaces. Gastrointestinal fistulas continue to cause significant morbidity and mortality, even though many factors important in their management are known. Over the past 35 to 40 years, the mortality associated with gastrointestinal fistulas has diminished from approximately 40% to 60% to about 15% to 20%.[1] This improvement in prognosis is attributable to general advances in fluid and electrolyte/acid-base therapy, blood administration, critical care, ventilatory management, antibiotic regimens, and nutritional management. Formerly, malnutrition and electrolyte imbalance were the causes of death in the majority of these patients. In the present era of fistula treatment, mortality is largely attributable to uncontrolled sepsis and sepsis-associated malnutrition.

The mechanism of fistula formation is varied. Congenital fistulas are caused by errors in development. Acquired fistulas may occur as a result of inflammatory disease, abdominal trauma, surgical complications, radiation, and benign or malignant neoplasm. Spontaneous causes account for 15% to 25% of gastrointestinal fistulas and include radiation, inflammatory bowel disease, diverticular disease, appendicitis, ischemic bowel, perforation of gastric and duodenal ulcers, pancreatic and gynecologic malignancies, and intestinal actinomycosis or tuberculosis. The remaining 75% to 85% of gastrointestinal fistulas are of iatrogenic origin and occur as a result of technical complications of surgical procedures and trauma. Such complications include dehiscence of anastomoses, mechanical injury to the gastrointestinal tract during dissection, cautery injury, retractor injury, indwelling tubes, and misplacement of a suture through the bowel during abdominal closure. Other technical complications resulting in fistulas are those that occur at delayed periods after surgery, such as intraperitoneal bleeding and abscess formation with or without suture line dehiscence. Fistulas may also develop after drainage of a percutaneous abscess, with a connection created between the intestine and abdominal wall.

Treatment of patients with gastrointestinal fistulas requires an understanding of metabolic and anatomic derangements. For patient mortality to be minimized, nutrition, volume, and electrolyte derangements must be promptly corrected. Additionally, ongoing losses must be anticipated and prevented. Malnutrition is easier to prevent than correct. Once established, malnutrition is difficult to correct, especially in the face of continuing sepsis. After the initial stabilization period, including control of sepsis and establishment of nutritional support, management can be divided into phases, starting with determination of the anatomy of the fistula and the likelihood of spontaneous closure. This may then be followed by definitive surgical therapy for a fistula that does not close spontaneously, but a waiting period of at least 6 weeks is usually required. The final process is healing. The critical points in successful management of gastrointestinal fistulas are recognition of the fistula, control of infection and further contamination, restoration of fluid and electrolyte losses, and re-establishment of a positive nutritional balance before undertaking major definitive corrective procedures.

GENERAL CONSIDERATIONS

Gastrointestinal fistulas result from perforations that communicate with adjacent organs or intestine (internal fistulas) or communicate externally with the abdominal wall (enterocutaneous fistulas). Although they may resolve spontaneously, specific intervention or operative therapy may be needed. The small intestine's length, as well as its unique convoluted anatomy, predisposes it to involvement in a variety of diseases, and almost any surgical procedure involving the abdomen can result in iatrogenic injury to the small intestine and subsequent fistula formation. The development of a fistula between

the small intestine and an internal structure can be a life-threatening event, as with exsanguination from an aortoenteric fistula or cholangitis from communication with the intestine and subsequent bacterial contamination of the biliary tree. Other fistulas, particularly internal fistulas between loops of small intestine, may be asymptomatic. Enterocutaneous fistulas are the most common form of small intestinal fistula. Though not usually lethal, an enterocutaneous fistula mandates careful and multitiered management to avoid further complicating the well-being of the patient.

Multiple factors make a gastrointestinal fistula a complex and potentially lethal condition. First, the patients in whom such fistulas develop are usually systemically ill. Sepsis is a recognized antecedent risk factor for the development of a gastrointestinal fistula, and the high metabolic requirement of the septic state can preclude spontaneous closure of the fistula. In fact, sepsis is often secondary to the factor leading to the fistula itself. Malnutrition is also a common occurrence that results both from the hypermetabolic state of the septic, postoperative patient and from the large volume of protein-rich fluid produced, and subsequently lost, by the small intestine. Fluid and electrolyte abnormalities, including hypovolemia, hypokalemia, hypomagnesemia, and metabolic acidosis, are common and result from the continued loss of intestinal fluid. Such losses are not limited to fistulas communicating externally because internal fistulas, such as enterocolic fistulas, can bypass the normal intestinal continuity and overwhelm the absorptive capacity of the recipient organ. Malabsorption and malnutrition from bacterial overgrowth may complicate gastrocolic or enterocolic fistulas. Finally, local wound excoriation and discomfort from the enzymatically active intestinal effluent can complicate potential abdominal wall reconstruction and recovery after surgical attempts to repair a fistula. Furthermore, operating on a fistula before control of sepsis and nutritional optimization can lead to increased mortality and often further fistula formation.

ETIOLOGY

Gastric and Duodenal Fistulas

The vast majority of gastric and duodenal fistulas still occur after surgical, endoscopic, or interventional procedures. Postoperative anastomotic or suture line leaks account for 80% to 85% of all fistulas. Basic general surgical principles of adequate blood supply, lack of tension, no distal obstruction, and uncompromised technique are essential. External fistulas that occur in conjunction with large abdominal wall defects are particularly difficult to treat and often require multiple staged operations, with mortality rates of 20% to 60%.[2] Before 1950, greater than 60% mortality was observed in patients with gastric and duodenal fistulas, but as of 1975, with improved perioperative care and the advent of total parenteral nutrition (TPN), the mortality rate had decreased to just below 25%.[3] The gastric and duodenal fistula rate of just 0.6% at this time was ascribed in part to the liberal use of catheter duodenostomies after gastrectomy.[3] Around 1990, Schein and Decker noted a 17% mortality rate for gastric and duodenal fistulas, with a 13% mortality rate for duodenal stump fistulas.[2] Reconstruction of the common bile duct uncommonly results in duodenal injury and fistula. Numerous comparisons of sutured versus stapled anastomoses show comparable results, without an obvious superiority of either. The ease of stapler use does not compensate for edematous or inflamed tissues, for which better tissue approximation may be achieved with hand-sewn techniques, although anastomoses in these types of tissue may be doomed to failure no matter which technique is used. Postoperative leaks from gastric staple or suture lines after ulcer surgery have accounted for most perforations in the past. However, the decline in gastric resection for ulcer disease, along with the broad application of new endoscopic and laparoscopic techniques for other diseases, accounts for many other newer causes of perforation.

Gastric operations for morbid obesity include vertical banded gastroplasty, Roux-en-Y gastric bypass, gastric banding with adjustable prosthetics, and the duodenal switch procedure. Gastric staple line disruption may develop in the early postoperative period or can occur many months after surgery. Importantly, early anastomotic leaks after gastrojejunostomy in this patient population are highly morbid and often lethal. A high index of suspicion is required to detect these leaks, and they should be controlled early in the process. Mortality may occur even before the development of a fistula. Internal gastric fistulas after gastric stapling are well known, with subsequent weight gain after a fistula has formed between the proximal gastric pouch and the distal part of the stomach. For gastric bypasses, the 10% to 30% incidence rate of internal fistula formation after simple stapling has been reduced to 3% to 6% by either gastric division after stapling or up to three applications of the stapler without division.[4,5]

In a series of 318 partial gastrectomies, Pickleman et al. reported a 1.3% anastomotic leak rate, all from gastrojejunostomy and without any duodenal stump leaks. After total gastrectomy with Roux-en-Y esophagojejunostomy, anastomotic leaks occurred in 4.8%.[6] A perforation rate of 1.5% has been reported after vertical banded gastroplasty for morbid obesity,[7] and a rate as high as 6% has been reported after divided gastric bypass, again from the gastrojejunostomy.[8] Gastric perforation is also a risk in patients who have undergone splenectomy as a result of greater curvature partial-thickness ligatures with devascularization. The incidence of eventual perforation at stapled gastric closures may be increased with the use of cautery to control bleeding at the stapled edge, intersecting staple lines within an anastomosis, and the use of a stapler on a thickened, edematous gastric wall, which causes overcompression, tearing, and devascularization at the line of closure. In such tissue, a hand-sewn closure more adequately approximates tissue without excessive tension.

Duodenal stump leakage has been long feared, although the overall incidence has declined, in part because of the decreased use of antrectomy for ulcer disease and the increased use of reliable staplers for

duodenal division and closure. Duodenal stump leakage is more common after difficult gastric resections, for example, after antrectomy for giant duodenal ulcer disease.[9] Reports indicate a very low incidence of stump leakage after gastric resection. In a high-risk patient, morbidity and mortality can be decreased and possibly prevented by placement of a duodenostomy tube along with closed suction drains external to the duodenum. Duodenal diverticulectomy or lateral duodenotomy for periampullary procedures may result in leakage in edematous or inflamed tissue or with poor hand-sewn technique. Biliary tract surgery is not usually associated with duodenal injury, with the exception of dissection of a markedly inflamed or chronically fibrotic gallbladder, an adherent choledochal cyst, or an unsuspected duodenal diverticulum.

Gastrojejunocolic internal fistula, a rare complication after distal gastrectomy with gastrojejunostomy, is due to marginal ulceration causing perforation at the gastrojejunostomy and a fistula to the adjacent transverse colon. Typical symptoms include diarrhea, pain, gastrointestinal bleeding, and weight loss. Neoplastic causes of internal fistulas are uncommon. Gastrocolic fistulas have resulted from gastric ulcer erosion and invasion of the transverse colon by gastric adenocarcinoma or lymphoma. Primary hepatic flexure or transverse colon adenocarcinoma may in rare instances invade and create a fistula to the duodenum or stomach.

The ongoing extension of laparoscopic techniques to gastric surgery has not eliminated the risk of perforation. Veress needle insertion for establishing pneumoperitoneum may result in the perforation of any intra-abdominal organ, as can the other varied techniques of abdominal access for laparoscopy, especially in a reoperative abdomen. Laparoscopic fundoplication and laparoscopic Heller myotomy are now widely used for the surgical management of gastroesophageal reflux disease and achalasia, respectively. Although morbidity rates are low, the esophagus or stomach may be perforated during the procedures, with the majority occurring in the first 10 to 25 fundoplications or myotomies performed by the surgeon. The incidence of esophageal or gastric perforation during fundoplication ranges from 0.3% to 1.9%,[10-12] with a large retrospective review of 2453 procedures by Perdikis et al. showing an overall incidence of 1.0%.[13] These perforations are acquired in at least four ways:

1. During retroesophageal dissection, the gastric fundus that is adherent to the left crus of the diaphragm may be lacerated during the right-to-left dissection through fatty tissue.
2. Direct injury can be inflicted on the anterior aspect of the stomach with graspers while retracting in a caudad and anterior direction. These graspers are often temporarily out of the laparoscopic field of view. The fundus may also be lacerated as a result of excessive tension while maneuvering it behind the esophagus.
3. Esophageal bougie insertion can cause perforation at the gastroesophageal junction or along the greater curvature.
4. Full-thickness suture placement while securing the fundoplication, with eventual tearing of the gastric wall, may result in delayed recognition of the perforation.

Laparoscopic fundoplication may also result in delayed gastric perforation along the greater curvature from inadvertent thermal or cautery injury during division of the short gastric artery. If the diaphragmatic crura are not approximated adequately, the fundoplication can herniate into the chest during postoperative straining, vomiting, or heavy lifting, with subsequent gastric ischemia and perforation. Laparoscopic revision of a previous fundoplication requires more gastric traction and division of adhesions, with a 3% risk for gastric laceration.[14] Other laparoscopic procedures that have caused perforation include diaphragmatic hernia repair, paraesophageal hernia repair (perforation in 6%), Heller myotomy, splenectomy, pyloromyotomy, and gastrostomy tube placement. The laparoscopically placed adjustable silicone gastric band, positioned around the proximal part of the stomach for the treatment of morbid obesity, has also resulted in gastric perforation in less than 1% of patients.[15,16]

Laparoscopic cholecystectomy may produce duodenal injury if the duodenum and gallbladder are densely adherent to one another as a result of either direct cutting action or cautery and thermal injury. Laparoscopic cholecystectomy may also result in colonic injury by the same mechanisms. In addition, improperly insulated instruments may cause electrical arcing to the duodenum, small bowel, or colon with resultant perforation. These injuries may not be immediately apparent. Coincident bile spillage from the gallbladder may also mask a duodenal injury. Likewise, duodenal perforation and bile duct injury may coexist. Laparoscopic bile duct exploration usually risks cystic duct or common bile duct injuries more than injuries to the duodenum. However, advanced procedures such as antegrade sphincterotomy and antegrade stent insertion may also result in duodenal injury.

Crohn's disease is a rare cause of gastrocolic, duodenocolic, or duodenocutaneous fistulas. Primary gastric or duodenal involvement is reported in less than 1% of patients with Crohn's disease; duodenocutaneous fistulas may develop from the first or second portion of the duodenum. However, most gastric or duodenal fistulas are internal and result from involvement of primary Crohn's disease of the transverse colon or, more commonly, from recurrence at the ileocolic anastomosis after previous resection. Those with gastrocolic fistulas have a 40% incidence of vomiting, which may be feculent; duodenocolic fistulas are often asymptomatic, with only a 4% incidence of vomiting, which is not usually feculent.[17]

Inflammatory fistula formation can result from gallstone erosion through the gallbladder and migration into the contiguous second portion of the duodenum, which causes a persistent cholecystoduodenal fistula. It may remain asymptomatic (as should a similar surgically created cholecystojejunostomy) but should be suspected in patients with the uncommon finding of gallstone ileus

with distal small bowel obstruction because of the stone. Renogastric fistula has been reported secondary to a staghorn calculus.[18] Duodenal hematomas may also lead to fistula formation. Severe necrotizing pancreatitis requiring necrosectomy, with subsequent open packing or closed drainage, has resulted in both gastric and duodenal fistulas. These fistulas may already exist at the time of initial laparotomy, or they may develop as late as 1 to 3 months later, either from the inflammatory process or from an iatrogenic cause. Although they may be more frequent after open packing, spontaneous closure is common (up to 54%).[19,20]

The capacity and compliance of the stomach make endoscopic examination routine, with a low incidence of injury. However, endoscopic polypectomy or attempts at tumor removal with a snare and cautery may cause either immediate full-thickness perforation or deep penetration with thermal injury to the remaining tissue and subsequent delayed perforation. Similar injury may occur with the use of thermal contact methods (heater probe, multipolar electrocoagulation, laser) or dilute epinephrine injections into bleeding ulcers and arteriovenous malformations, with exacerbation of the injury by successive treatments. Esophageal dilatation performed with a semirigid dilator over a wire has caused gastric perforation from the end of the wire. Percutaneous endoscopic gastrostomy tube placement, though often routine, has also resulted in perforation, either from dislodgment of the tube before complete gastric adhesion to the abdominal wall or from trauma during placement. Lack of adhesion to the abdominal wall may be more common in immunosuppressed patients taking steroids, for instance. Gastric necrosis may also occur as a result of ischemia and subsequent gastric leakage from a tube that is pulled too tight. Improper tube placement along the posterior wall below the greater curvature, while the stomach is distended, can result in excessive tension on the posterior gastric wall when traction is applied, with subsequent leakage into the lesser sac. Tube placement that is too proximal in the stomach has also caused perforation because of excessive gastric wall tension and eventual tube dislodgment through the wall. In addition, tube insertion may perforate the adjacent jejunum or transverse colon and result in a persistent gastrojejunal or gastrocolic fistula, even after the gastrostomy tube has been removal. This complication may also require early laparotomy to address peritonitis and sepsis. A percutaneously placed gastrostomy tube results in a thin fibrous cylinder connecting the stomach to the anterior abdominal wall; manual replacement of the gastrostomy tube can perforate this cylinder and give liquid feeding solutions direct access to the peritoneal cavity, with resultant peritonitis. Gastrostomy tube placement may cause a persistent gastrocutaneous fistula that enlarges through erosion or infection of fascia and skin. These fistulas may be difficult to control, with continued drainage of gastric fluid onto the surrounding skin. The substitution of a larger gastrostomy tube will not control the leakage and usually results in enlargement of the opening. Persistent drainage may require either tube removal or placement of a smaller tube, along with direct or nasogastric suction until the tract contracts down around the tube. Surgical closure is required for a persistent gastrocutaneous fistula that does not respond to such measures.

Because many endoscopic duodenal procedures involve the second portion of the duodenum, perforation is usually retroperitoneal. Failure to recognize an injury or a delay in treatment markedly increases morbidity and mortality. Perforation after endoscopic retrograde cholangiopancreatography (ERCP) with ampullary sphincterotomy for stone extraction or biliary stent placement is one of the more frequent postendoscopic indications for urgent surgical intervention. Repair of the distal bile duct, as well as repair of the duodenum, may be required. Controlled leaks confined to the retroperitoneum can often be monitored with very close clinical observation in stable patients. Retroperitoneal perforation is more common during therapeutic ERCP, with an incidence of 0.6% to 1.8% and a mortality rate of up to 25%.[21,22] Delayed duodenal perforation from the biliary stent itself may be caused by partial extrusion and impingement of the end of the stent on the distal second or proximal third portion of the duodenum, with eventual erosion and perforation. Proximal stent migration into the common bile duct may cause a choledochoduodenal fistula to subsequently form if the stent reenters the duodenum away from the papilla. Similarly, pancreatic duct stents may produce a pancreaticogastric fistula with proximal migration of the stent into the gastric antrum. Other procedures at risk for the development of duodenal perforation include endoscopic polyp or tumor removal, push enteroscopy, endoscopic ultrasound with transduodenal biopsy, and endoscopically assisted transgastric jejunal feeding tube placement.

An aortoduodenal fistula involving the third portion of the duodenum must be suspected in any patient with a previous abdominal aortic graft and upper gastrointestinal bleeding or a patient with graft infection without gastrointestinal bleeding. An aortogastric fistula may occur intra-abdominally in a patient with a ruptured abdominal aortic aneurysm without previous aortic surgery,[23] as well as intrathoracically after esophagectomy at the esophagogastric suture line (treated successfully by direct repair and endovascular graft placement).[24] Reconstruction of the inferior vena cava with a stented polytetrafluoroethylene (Teflon) graft has also resulted in a fistula to the adjacent duodenum.[25]

Percutaneous transhepatic wire and biliary stent placement may lead to duodenal perforation. However, a transhepatic biliary drain also provides effective duodenal decompression if subsequent operative repair is needed. Because of the proximity of the duodenum and inferior vena cava, caval filter placement has resulted in duodenal penetration from the filter hooks. Percutaneous drainage of upper abdominal abscesses uncommonly results in duodenal injury. Swallowed foreign bodies that are small enough to traverse the pylorus may not escape the duodenum; typically, toothpicks and fish bones may penetrate the duodenum and form a phlegmon or an abscess. Stiff feeding tubes or nasogastric tubes passing through the pylorus have also resulted in duodenal perforation.

Nonoperative causes of perforation include strangulated paraesophageal hernia, foreign body ingestion, and

esophageal intubation with gastric overpressure. Gastric adenocarcinoma may uncommonly result in perforation. Treatment of gastric lymphoma with chemotherapy or radiation (or both) has caused perforation along with cytoreduction. Mycotic infection with eventual gastric perforation has been reported in immunosuppressed heart, lung, and liver transplant recipients.[26]

Small Intestinal Fistula

Small intestinal fistulas can form in a number of ways. External small intestinal fistulas (enterocutaneous fistulas) are by far the most frequent type of small intestinal fistula. Enterocutaneous fistulas most commonly follow postoperative complications and are often the result of technical errors at the time of an abdominal procedure. Of 35 fistulas originating in the jejunum or ileum reported by MacFadyen and associates, 75% drained externally.[27] The ileum is the most common site of origin of an enterocutaneous fistula. Reber and colleagues found that of 120 small intestinal enterocutaneous fistulas, 72 originated from the ileum and 48 from the jejunum.[28] Enterocutaneous fistulas can be classified according to the daily volume of drainage. A high-output fistula drains 500 ml/day or more of fluid. In most instances, a high-output fistula is associated with greater morbidity and mortality and a decreased likelihood of spontaneous closure. Soeters and associates found that patients with high-output fistulas had a greater incidence of malnutrition and fluid and electrolyte disturbances.[3] Mortality increased, and the rate of fistula closure was low. In contrast, excellent results with high-output fistulas were reported in Graham's series, in which 35 of 39 consecutive patients underwent spontaneous fistula closure with a 3% mortality rate.[29] In general, high-output fistulas usually originate from a proximal portion of the small intestine. Conditions that are independent of the surgical technique, such as previous intestinal irradiation, intra-abdominal sepsis, or the presence of diseased or ischemic intestine, can also give rise to external fistulas. Enteroenteric or enterocolic fistulas develop almost exclusively from the transmural inflammation associated with Crohn's disease.

Webster and Carey proposed five general mechanisms for fistula formation[30]:

Congenital A rare form of congenital small intestinal fistula involves complete failure of the vitellointestinal duct to obliterate, which results in an enterocutaneous fistula to the umbilicus. When incomplete obliteration of the duct occurs, the enteric portion of the duct is the usual portion that persists and forms a Meckel diverticulum. Rarely, the entire omphalomesenteric duct remains patent and forms an external fistula. The diagnosis should be suggested by the appearance of fecal material at the umbilicus after postnatal slough of the umbilical cord.

Trauma Traumatic injury to the small intestine that results in fistula formation usually occurs from an internal source, such as a swallowed fish bone, toothpick, or metallic object. Erosion of these objects into an adjacent loop of small intestine results in an internal enteroenteric fistula. Major penetrating trauma, such as knife or bullet wounds, rarely results in fistula formation because these cases are usually explored surgically and the intestinal injuries repaired. Locally unexplored knife wounds, however, have resulted in the development of an enterocutaneous fistula when minor intestinal injuries were not diagnosed in timely fashion.

Infection An abscess or invasive intestinal infection may erode through the intestine and create a fistula. Amebiasis, coccidiomycosis, tuberculosis, cryptosporidiosis, actinomycosis, and salmonellosis have all been implicated in the development of intestinal fistulas. Intestinal perforation at the ileum from tuberculosis and typhoid fever is still occasionally seen, especially in countries where these diseases are endemic. *Actinomyces* is a common cause of enterocutaneous fistulas after appendectomy. Fistulas may also result from the proximity of the small intestine to an abscess involving a solid organ, such as when rupture of a perinephric abscess results in a nephroenteric fistula.

Perforation or Injury with Abscess Perforation of the intestinal wall by tumor, inflammation, or operative injury may result in the local formation of an abscess. A fistula may develop if this abscess subsequently erodes into an adjacent structure. Most enterocutaneous fistulas develop as a result of injury to the small intestine during surgery or from exposure of the bowel to a large abdominal defect or prosthetic mesh used to repair such defects. An enterocutaneous fistula rarely develops spontaneously. In fact, most develop after an abdominal surgical procedure. In most large series, 60% to more than 90% of enterocutaneous fistulas were caused by operative complications. Faulty operative technique involving injury to the intestine during handling, lysis of adhesions, or abdominal fascial closure often results in fistulas. In addition, enterocutaneous fistulas may be caused by leakage from an intestinal anastomosis or enterotomy closure. Fistulas may also develop as a result of percutaneous drainage of an intra-abdominal abscess. After perforation, an abscess may develop at the site of injury and then drain either internally into another loop of intestine or externally through the abdominal wall or wound. Commonly, a fistula has been found to have feculent drainage from the wound after the wound is opened for a presumed wound infection.

Inflammation, Irradiation, or Tumor The small intestine and an adjacent structure can become densely adherent from chronic inflammatory conditions, abdominal radiation injury, or tumor erosion. Subsequent degeneration of the common wall results in fistula formation. Inflammatory bowel disease, particularly Crohn's disease, is well known to create enteroenteric, enterocolic, perineal, enterocutaneous, and other fistulas in this fashion. In Crohn's disease, the diseased intestine makes fistula formation after anastomosis more likely. Although a spontaneous external fistula can develop as a direct result of Crohn's disease, most occur only after a previous

operation has caused the diseased intestine to adhere to the abdominal wall. Postoperative fistulas in the setting of Crohn's disease are just as likely to develop after simple exploration, bypass, or appendectomy as after primary resection. Fistula formation after laparotomy is usually an early complication, especially when arising from an anastomosis, whereas a late fistula generally indicates recurrent Crohn's disease. Erosion of the intestine by a foreign body such as swallowed objects or polypropylene mesh, abdominal wall dehiscence with evisceration, and strangulation of a hernia with infarction and perforation of the intestine have all been implicated in the development of external fistulas. Enlarging carcinomas of the stomach or colon may adhere to and erode into adjacent small intestine with some frequency. Fistula formation is particularly apt to occur after irradiation of a pelvic malignant lesion. Fistulas that arise secondary to radiation injury rarely, if ever close spontaneously.

DIAGNOSIS OF PERFORATIONS AND FISTULAS

Acute intraoperative perforations are best handled by maintaining a strong index of suspicion for technical errors, recognizing the injury before the end of the procedure, and immediately repairing, suturing, or reinforcing weakened tissues. Especially during prolonged laparoscopic procedures, the tendency for potential injuries must be recognized and overcome. Serosal injuries should be carefully examined and sutured. Intraluminal instillation of methylene blue and saline or direct endoscopic examination can demonstrate a small perforation or provide reassurance that an area of concern is not a full-thickness injury.

Postoperatively, unrecognized perforations caused during surgery or leaks that develop at suture or staple lines are manifested as instability or failure to improve as expected. A gastrointestinal fistula can be obvious in some patients and extremely difficult to identify in others. Fistula formation is frequently heralded by fever and abdominal pain until gastrointestinal contents discharge through an abdominal incision or the umbilicus. Spontaneous fistulas from neoplasm or inflammatory disease usually develop in a more indolent manner. Enterocutaneous fistulas often have intestinal contents or gas exiting from a drain site or through the abdominal incision after an operation. The drainage fluid is usually typical of intestinal contents, with obvious bile staining, and intestinal gas may accompany the effluent. At times the initial fistula drainage may initially appear clear rather than yellow or green, and the fistula may be misdiagnosed as a seroma or wound infection. At other times a heavy purulent component may also mask the enteric communication and instead suggest a wound infection. If the drainage persists and the diagnosis is uncertain, the patient may be given activated charcoal or indigo carmine by mouth and the drainage inspected for these substances.

Endoscopic gastroduodenal perforations are suspected when fever, tachycardia, or abdominal tenderness is present after the procedure. Initial chest and abdominal radiographic films may demonstrate free intraperitoneal air or retroperitoneal air outlining the duodenal wall. Unexplained fever, ongoing or new tachycardia, hypotension, worsening leukocytosis, new or continuing abdominal pain, persistent ileus, and persistent oliguria all raise suspicion for a pathologic intra-abdominal process.

STAGING/CLASSIFICATION

Gastrointestinal fistulas can be classified by their anatomic characteristics, and they are either internal or external (enterocutaneous). The actual anatomic course of the fistula should be defined. Typically, the name of a fistula is derived from the involved and connected organs or structures. Examples include gastrocolic, jejunoileal, and aortoenteric fistulas. In general, the anatomy of a fistula will suggest the cause and help predict whether spontaneous closure will occur.[31,32] Fistulas can be classified physiologically in terms of output over a 24-hour period. They can be classified as low (less than 200 ml/day), moderate (200 to 500 ml/day), and high (greater than 500 ml/day).[3,31] An accurate measure of fistula output, as well as the chemical make-up of the effluent, can provide assistance in preventing and treating metabolic deficits and correcting ongoing fluid, electrolyte, and protein losses. The anatomic and etiologic factors are much more important in predicting spontaneous closure than the actual output of the fistula. The underlying disease process will help in prognisticating both the closure rate and mortality.

External or enterocutaneous fistulas are by far the most common type of small intestinal fistula and are usually readily recognizable. In contrast, internal fistulas that communicate between the intestine and another hollow viscus or structure may not be suspected for some time because the symptoms may be minimal or may mimic the underlying disease process. Relatively rare, such fistulas have been reported between adjacent segments of the gastrointestinal tract, as well as between the small intestine and the biliary tree, genitourinary system, and arterial and venous trees.

COMPLICATIONS

The loss of gastrointestinal contents either prematurely by diversion to the body surface or by "short-circuiting" within the gastrointestinal tract may result in profound fluid and electrolyte deficits, the specific nature of which depends on the portion of the gastrointestinal tract whose contents are lost. Malabsorption with severe nutritional and vitamin deficiencies may also ensue. Fistulas are commonly associated with one or more abscesses, which often drain incompletely with fistulization. Therefore, persistent sepsis may occur as a result of contamination of a normally sterile space or organ system by gastrointestinal flora traversing the fistula. Gastrointestinal hemorrhage, intestinal obstruction, and excoriation and erosion of the skin by gastrointestinal secretions may also complicate the course of a patient with a fistula. These problems may be superimposed on other

abnormalities inherent to the underlying disease that produced the fistula.

Fluid and Electrolyte Abnormalities

Fluid and electrolyte disturbances occur commonly in patients with enterocutaneous fistulas. Secretions from the salivary glands, stomach, duodenum, pancreas, liver, and small intestine amount to 8 to 10 L/day, and this fluid is rich in sodium, potassium, chloride, and bicarbonate. The degree of volume depletion and electrolyte imbalance depends on the anatomic location of the fistula and can vary from 50 to 3000 ml/day.[27] Duodenal fistulas are particularly prone to volume and electrolyte loss, and aggressive fluid management is necessary for patients with such high-output fistulas. A distal fistula, such as one arising from the terminal ileum in a patient with Crohn's disease, is usually associated with less fluid loss because considerable absorption occurs in the proximal part of the gut.

Fluid and electrolyte imbalances were noted in 35 of 128 patients with gastrointestinal fistulas reported by Soeters and associates from 1970 to 1975.[3] The most common abnormalities were hypovolemia, hypokalemia, and metabolic acidosis. Hypokalemia occurs primarily from potassium loss in the fistula effluent, although hypovolemia also contributes by causing renal retention of sodium in exchange for potassium secretion. Sepsis contributes to the hypovolemic state by altering the metabolic rate and increasing insensible water loss through fever. Metabolic acidosis is generally caused by the loss of pancreatic juice rich in bicarbonate and is thus more common with proximal intestinal fistulas. Gastric fistulas, especially in conjunction with gastric outlet obstruction, will cause a hypokalemic, hypochloremic metabolic alkalosis secondary to the loss of a large volume of hydrochloric acid.

Patients with fistulas causing fluid and electrolyte abnormalities have a higher mortality rate.[33] Advances in critical care, invasive monitoring, and aggressive fluid and electrolyte management can reduce this early mortality considerably, as evidenced by data from the Massachusetts General Hospital. Before 1960, nearly all patients at this institution died when an electrolyte deficit complicated a fistula involving the small intestine. Improvements in therapy and control of sepsis have resulted in a substantial decrease in the mortality rate.[3]

Malnutrition

The small intestine contains fluid rich in ingested nutrients and endogenous proteins, such as enzymes and albumin. Thus, malnutrition develops in almost all patients with a small intestinal fistula if the absorptive surface area is bypassed or the enteric contents are lost externally. Nutritional deficiency may be exacerbated by the extra metabolic demands of sepsis or additional surgery. Soeters and associates reported moderate to severe malnutrition in 86 of 128 patients.[3] Before the introduction of TPN, 74% of patients with intestinal fistulas exhibited malnutrition, and 59% of these patients died.

Sepsis

With advances in fluid replacement, management of electrolyte deficits, and nutritional support, sepsis remains the major determinant of mortality in patients with fistulas of the small intestine. Most fistulas develop after contamination of a sterile space by gastrointestinal bacteria. Abscesses not only cause but can also complicate fistulas of the intestine. Uncontrolled abdominal sepsis can lead to bacteremia, local and distant infection, and multisystem organ failure. Local extension usually results in wound infection. Distant bacterial seeding may cause splenic and hepatic abscess or endocarditis. Large defects in the abdominal wall predispose the patient to repeated episodes of sepsis and consequently a high mortality rate. In a large series by Schein and Decker, the overall mortality rate associated with fistulas of the small bowel was 33%.[34] However, when a large abdominal wall defect accompanied the fistula, the mortality rate rose to 60%, with the main cause of death cited as infection.

Abdominal Wall and Wound Abnormalities

Skin erosion and excoriation commonly occur from an externally draining gastrointestinal fistula. The local digestive action of the gastrointestinal secretions, particularly pancreatic enzymes, can result in considerable discomfort to the patient. The degree of local skin excoriation depends on the output and contents of the fistula effluent and is most severe with proximal intestinal fistulas. Malnutrition contributes to this process by delaying the formation of scar or granulation tissue.

Other Complications

Other complications of small intestinal fistulas occur with less frequency. Massive gastrointestinal hemorrhage can result from the formation of a fistula between the small intestine and a blood vessel. One or more "herald bleeds" may be a prelude to exsanguinating hemorrhage. More commonly, anemia develops chronically and is associated with slow blood loss from a friable fistula tract. Colonization and overgrowth of the small intestine by colonic bacteria can occur with enterocolic fistulas and may result in malabsorption and severe, malodorous diarrhea. Distal obstruction of the fistula tract from adhesions or other disease can develop and result in an increase in fistula output or failure of the proximal tract to close. Finally, carcinoma has been reported in chronic fistulas, especially those associated with Crohn's disease. It is believed that chronic irritation of the epithelium promotes the development of such malignancies.[35]

MANAGEMENT

Management of a gastrointestinal fistula is a difficult and complex process. However, if one uses a systematic

approach in dealing with these difficult problems, their treatment becomes manageable and potentially rewarding. In general, management can be compartmentalized into five stages: stabilization, investigation, decision, definitive therapy, and healing.[36]

The ultimate goal when treating gastrointestinal fistulas is restoring continuity of the gastrointestinal tract. However, most fistulas are not treated simply by taking the patient back to the operating room. Rather, many weeks and perhaps months of care is often required to manage most patients successfully. As just outlined, management of patients with such fistulas can be conceptualized as a series of steps to control life-threatening abnormalities rapidly and to intervene in a timely and controlled manner with convalescent or surgical care. Although these steps address the physical well-being of the patient, one should not underestimate the impact of a fistula on mental and emotional health. A gastrointestinal fistula places a great deal of stress on a patient's self-esteem. Therefore, family members, social workers, and mental health professionals can play a vital role during the prolonged convalescence that is typical with this disease process.

The present approach and understanding of fistula management have developed significantly over the past 40 years. In their classic paper in 1960, Edmunds, Williams, and Welch called attention to the serious nature and the high mortality of such fistulas and pointed out the relationship between infection, malnutrition, fistula output, and mortality.[33] In addition, they advocated earlier surgical intervention for all high-output fistulas and recommended total resection of the fistula with end-to-end anastomosis or complete bypass of the fistula when resection was not possible. With early correction of fistulas, malnutrition and its attendant complications were thereby less likely to develop. The overall mortality in their series was 44%.[33] Modern fistula management has evolved significantly and mortality has decreased substantially. Urgent surgery in a debilitated, malnourished patient is rarely necessary nowadays.

Stabilization

As outlined earlier, the first step in the management of any intestinal fistula is stabilization of the patient, which is usually accomplished within the first 24 to 48 hours of management. These patients are typically in a vulnerable state of health. They may be febrile and septic from what was thought to be a wound infection that was treated by opening the wound. The wound drainage contains succus entericus and the patient may be deteriorating. Alternatively, they may be immunocompromised secondary to ongoing therapy (e.g., cancer radiation treatment, chemotherapy) or additional infectious processes. Therefore, the most important priority is to stabilize the patient. Patients typically require correction of obligate third-space losses, as well as emesis, fistula output, urine output, or a combination of these and other causes. Initial efforts should be directed toward intravenous fluid resuscitation, control of infection, ongoing measurement of fistulous and urine output, and protection of the surrounding skin. The incision should be examined for fascial integrity, and any remaining subcutaneous collections should be drained. Thereafter, attention is shifted to identification of the fistulous source, the nature of the tract, and associated fluid collections or abscesses.

Resuscitation

Restoration of a normal circulating blood volume and correction of electrolyte and acid-base imbalances are top priority. Rehydration usually requires isotonic fluid until the patient is euvolemic again. Depending on the site of the fistula, replacement of fistula output varies. High-output fistulas, those exceeding 500 ml/day, continue to result in the highest mortality rate, up to 35%, because of malnutrition, electrolyte imbalance, and sepsis. Moderate-output fistulas range from an output of 200 to 500 ml/day, whereas low-output fistulas produce less than 200 ml/day and are associated with low mortality rates and high spontaneous closure rates. Small bowel, pancreatic, and biliary losses are isotonic. Colonic losses may be hypotonic, and gastric fistulas may be associated with the classic hypokalemic, hypochloremic metabolic alkalosis. Although certain patterns can be predicted, electrolyte levels in an aliquot of the fistula output, as well as electrolyte levels in the patient's serum, should be measured and corrected appropriately according to the particular electrolyte profile. Because most patients require considerable volume replacement, close monitoring of the patient's physiologic parameters is essential to ensure the safety and efficacy of therapy.

The natural course of an improperly managed high-output fistula is dehydration, electrolyte abnormalities, malnutrition, infection and sepsis, renal failure, and death. Initial management should address any existing hypovolemia; anemia; hypoalbuminemia; sodium, chloride, or potassium depletion; and acid-base disorders. Strict intake and output measurements are essential, and central venous pressure monitoring and urinary catheterization are especially helpful with high-output fistulas. Invasive monitoring is often necessary because it is usually difficult to estimate antecedent fluid deficits accurately. A central venous catheter can be extremely useful in this capacity and provides the additional benefit of supplying access for parenteral nutrition. The patient's urine output should be restored to greater than 30 ml/hr, assuming that renal function has not been impaired. In patients with cardiovascular impairment or evidence of shock, a pulmonary artery catheter may be needed to guide ongoing fluid repletion after initial fluid boluses have not resulted in adequate urinary output.

Ongoing fluid losses should be fully replaced, and potassium, calcium, phosphorus, and magnesium deficits should be corrected. These electrolyte deficits may take time to correct because the measured serum levels reflect only a small percentage of what can be a massive depletion of intracellular ions. Sodium bicarbonate administration may be required to correct the metabolic acidosis that usually develops with a high-output or proximal fistula. Because the deficit in circulating blood volume is

caused primarily by extracellular fluid losses, replacement should be in the form of an isotonic solution. Normal saline or lactated Ringer's solution is most appropriate for this purpose. However, specific parenteral fluids may be selected on the basis of the initial electrolyte levels. Transfusion of red blood cells may be necessary because of chronic blood loss and anemia of chronic disease. To optimize the patient's hemodynamic status, blood transfusion may be required. There is no specific hemoglobin or hematocrit level that requires transfusion; rather, transfusion should be based on the patient's overall hemodynamic status, oxygen-carrying capacity, and oxygen delivery.

Often, these patients are in a severe catabolic state and have extremely low protein and albumin levels. This is important for several reasons. First, patients will have low capillary oncotic pressure, which may contribute to profound edema, especially after resuscitation has begun. Severe hypoalbuminemia will take weeks to correct through nutritional repletion alone. Supplemental intravenous salt-poor albumin administration for a limited period will help increase oncotic pressure and minimize edema and may improve wound healing.[37] More importantly, however, the patient is in a state of nutritional emergency. For this patient to be stabilized and to potentially heal the fistula, positive nitrogen balance must be achieved. If nutritional therapy is not started early, these patients are at great risk for multisystem organ failure, infection, and other complications of severe malnutrition that could lead to death. An initial infusion of albumin will not correct these problems, and nutritional repletion will take weeks to accomplish.

Nutrition

Ongoing nutritional assessment and institution of nutritional support have improved the overall outcome in patients with small intestinal fistulas. The signal study in 1964 by Chapman et al. emphasized that the key to successful management was to "get control of fistula," combat sepsis, and from the very beginning maintain adequate nutritional support.[38] They stressed the vital role of nutrition and reported a decreased mortality rate of 14% in patients treated with an excess of 3000 calories per day via a combination of intravenous (peripheral administration of protein hydrolysates) and tube feedings and 55% mortality in patients receiving a suboptimal nutritional regimen. They also emphasized that supportive and surgical treatment go hand in hand; the two are not mutually exclusive. Their indications for operative closure of the fistula included the presence of distal intestinal obstruction, continued massive loss of fluid from the fistula despite control of the infection and an adequate nutritional regimen, and persistence of the fistula even without high losses over a prolonged period. In a follow-up report in 1971, Sheldon et al. documented the success of such a treatment regimen and noted that most patients could be given adequate nutrition by standard methods such as tube and enterostomy feedings. At the time of their report, TPN was a new technique that had been used only in a select few patients.[39] Roback and Nicholoff reported closure of 73% of enteric fistulas in patients with adequate caloric supplementation, but only 19% healed when nutritional support was inadequate.[40]

Provision of sufficient calories and protein is necessary to minimize further skeletal muscle breakdown and organ dysfunction. Fluid, electrolyte, and trace element losses must be repleted. With the widespread advent of parenteral nutrition in the 1970s, the overall reduction in mortality to a range of 15% to 20% was achieved consistently in a variety of reports. In their reviews of large series of patients, Reber et al. in 1978 (786 patients) and Soeters and associates in 1979 (404 patients) reported that the addition of parenteral nutrition in large scale to the treatment of gastrointestinal fistulas improved the spontaneous closure rate.[3,28] Parenteral nutrition, however, had no impact on fistula mortality; maintenance of adequate nutrition with more conventional methods was equally effective.[3,28] Nevertheless, parenteral nutrition has greatly simplified the nutritional management of patients with gastrointestinal fistulas. Once a patient is both malnourished and septic, it becomes quite difficult to replete such a patient. Even though these patients often have abdominal abscesses and bacteremia, parenteral nutrition is safe and the overall incidence of septic complications from the central line or parenteral nutrition is no greater than that in other clinical situations.

It is much better to begin to provide nutritional support as soon as the patient is stabilized. Full caloric and nitrogen replacement can be provided within a few days of instituting nutritional support.[37] Nutrition can be given by several routes. Frequently, these patients may be too ill to eat, or they cannot consume enough calories even if they can take some oral nutrition. Usually, either enteral tube feeding or parenteral nutrition will be required. The choice of which to use depends on the fistula anatomy. It is advantageous to provide at least a portion of the calories through the enteral route because the gastrointestinal tract is a much more efficacious way of providing nutrition, maintaining the intestinal mucosal barrier and immunologic integrity, and stimulating hepatic protein synthesis, which has been found to be of critical value in determination of the outcome in fistula patients.[41] Thus, whenever possible, enteral nutrition is preferable to parenteral nutrition and probably decreases the incidence of multisystem organ failure and sepsis if administered appropriately.

Enteral nutrition is not without complications, however, and the process should be closely monitored. Complications such as diarrhea, aspiration, and bowel ischemia are not uncommon without careful clinical monitoring. Enteral nutrition can be given for upper gastrointestinal fistulas, especially when the feeding tube can be placed beyond the fistula (for instance, a feeding tube placed beyond the ligament of Treitz for a gastric, duodenal, or pancreatic fistula). In general, feeding tubes should be placed when possible beyond the ligament of Treitz to decrease the potential risk for aspiration. Enteral feeding should also be used for distal fistulas (e.g., a colonic fistula), as long as feedings do not significantly increase fistula output. On the other hand, parenteral nutrition can be a valuable tool in the

treatment of fistulas as well. Patients with small bowel fistulas may not be able to tolerate enteral nutrition without increasing fistula output. In these cases and in others in which patients cannot tolerate enteral feeding, parenteral nutrition is indicated. In patients with a persistent adynamic ileus and before the fistula tract is well established, parenteral nutrition is very useful. Parenteral nutrition techniques and advantages are well known, although complications also occur with some frequency. In the Reber et al. study of 91 patients with gastrointestinal fistulas managed with TPN, 28% had complications, with catheter-related sepsis and subclavian vein thrombosis occurring most frequently.[28] Hyperglycemia is common when initiating TPN in patients with gastrointestinal fistulas. New-onset hyperglycemia in a patient with an established TPN regimen should alert the treating physician to the possibility of new or ongoing sepsis (e.g., intra-abdominal abscess, wound infection, line sepsis, pneumonia).

The presence of a gastric or duodenal fistula will not usually permit oral alimentation, unless it is of low output and eating does not markedly worsen losses. If a feeding tube beyond the ligament of Treitz or a tube jejunostomy is in place, enteral nutrition should be started; with normal small and large intestinal function, all nutritional needs can be met. However, the presence of distention or diarrhea will limit the rate of tube feeding and may necessitate parenteral nutrition and fluid repletion. TPN via central venous access enables the delivery of full caloric and fluid requirements, unless poorly controlled hyperglycemia or hypercapnia limits caloric delivery. Those with low-output fistulas require 30 to 35 kcal/kg/day, with 1.0 to 2.0 g protein per kilogram body weight per day. Those with high-output fistulas require more calories—up to 1.5 to 2.0 times normal energy expenditure, with a protein supply of 1.5 to 2.5 g/kg/day.[37] This is especially the case with duodenal fistulas because of the loss of gastric, duodenal, biliary, and pancreatic exocrine protein-rich secretions. Short-turnover protein (prealbumin, retinol-binding protein, transferrin) levels should be measured at least weekly to assess the adequacy of protein delivery. An ongoing catabolic state will adversely affect short-turnover protein levels, even with maximal protein delivery. Those with high-output fistulas may benefit from twice the recommended daily allowance of vitamins, trace elements, and zinc and up to 5 to 10 times the daily requirement for vitamin C.[37] The daily delivered volume should include both maintenance fluids and ongoing fistulous losses.

Historically, high output from a fistula was a relative contraindication to enteral nutrition. Both human and animal data, however, suggest that even these complicated fistulas can be adequately managed with enteral nutrition, although the parenteral route may still succeed in further reducing fistula output. Enteral nutrition, both orally and by tube feeding, has been used increasingly when treating small intestinal fistulas because of its trophic effect on the intestine. The overall success with nutritional supplementation by the enteric route rivals that of parenteral nutrition. Indications for enteral supplementation depend on the site of the fistula and the extent of the remaining small intestine that can be used for absorption. By using a combination of enteral nutrition techniques along with parenteral nutrition, adequate caloric and nitrogen intake should be achieved rapidly. As little as 20% to 25% of the nutrition supplied enterally is usually sufficient to provide the advantages of enteral nutrition, and the remainder can be supplied via parenteral nutrition. Conversely, the decreased fistula output that usually accompanies the institution of parenteral nutrition can greatly simplify the management of high-output fistulas. In addition to this adjunctive role in conjunction with parenteral nutrition, tube feeding continues to be an important measure in the complete nutritional management of some fistula patients with distal and low-output fistulas, when the fistulas are nearly healed, or when parenteral nutrition is difficult or impossible to institute. The ability to provide TPN may also be limited by recurrent line infections, which can lead to endocarditis, or the lack of adequate access sites secondary to thrombosis in patients maintained on long-term TPN. A single-lumen catheter dedicated solely to TPN is preferable and may decrease infectious and thrombotic complications.

Because both enteric and parenteral feeding has advantages and disadvantages, the source of nutritional supplementation should depend on the individual patient and the surgeon's preference and experience. In most cases, parenteral nutrition should be instituted as soon as possible. Thereafter, steps to localize the fistula and control infection can be taken. Normal intestinal motility and function generally return once abdominal sepsis is controlled and fluid and electrolyte imbalances are corrected. If the fistula location is such that enteric access and alimentation are possible, enteral nutrition can be instituted and parenteral nutrition phased out. By using a combination of approaches, adequate nutrition can be maintained throughout the patient's course.

Control of Sepsis

Uncontrolled sepsis remains the major factor contributing to mortality in patients with small intestinal fistulas. Aggressive management of all ongoing infections and careful surveillance for new septic foci are thus absolutely necessary for successful management. Tachycardia, persistent fever, and leukocytosis usually portend inadequate control of the fistula or abscess formation. Frequent physical examination and judicious use of ultrasonography and computed tomography (CT) are mandatory.

Advances in patient monitoring, correction of fluid, electrolyte, and acid/base imbalances, and the use of parenteral nutrition have largely alleviated electrolyte disturbances secondary to high-output fistulas and malnutrition. In the present era, mortality is mostly determined by uncontrolled sepsis and sepsis-associated malnutrition. Malnutrition in the presence of uncontrolled sepsis cannot be treated without effective surgical drainage of the septic source. As long as uncontrolled sepsis persists, the patient's condition will continue to deteriorate. The stabilization phase often involves control of a septic source. Typically, drainage of an intra-abdominal abscess is required, which is ideally accom-

plished in an image-guided, percutaneous fashion. In addition, fistula drainage must be controlled and the skin of the abdominal wall protected. Local control is an extremely important component of the early management of a fistula. Discontinuation of oral intake and initiation of parenteral nutrition are important steps. Placement of a nasogastric tube or a nasoenteric tube positioned proximal to the fistula may be helpful with enteric fistulas involving the duodenum or proximal jejunum. Egress of the fistula output from the abdominal cavity must be facilitated with an immature enterocutaneous fistula because inadequate external drainage results in internal loculation, abscess formation, or peritonitis. It is extremely important to prevent the severe local skin excoriation that frequently develops around the site of an enterocutaneous fistula. Fistulas that have been controlled with a tube should cause minimal injury to fascia, subcutaneous tissue, and skin. Such injuries typically include perforations with abscesses that have been percutaneously drained or have been converted at surgery to a controlled fistula with an indwelling tube or an adjacent drain.

Drainage should be collected to measure the output and provide a gauge for fluid and electrolyte replacement. The method of controlling fistula drainage must be individualized for each patient. Precautionary steps should be instituted early because once excoriation is present, healing is difficult in the presence of ongoing drainage. A fistula should be exteriorized on a flat portion of the abdominal wall with avoidance of bony prominences and skin folds. This permits secure application of an ostomy bag or other device to collect and monitor fluids and protect the skin. Specialized nursing assistance by an enterostomal therapist or wound care specialist is frequently necessary and can be quite helpful in the management of these often complex wounds. Drainage with a single catheter placed into the site generally fails because the catheter becomes occluded or the volume of fluid expelled with peristalsis exceeds the capacity of the catheter. In some instances, a sump suction catheter can be placed through the external opening and gentle continuous suction applied to control fistula drainage (a sump catheter can be constructed by inserting a soft rubber catheter in the wound with an angiocatheter placed in the side of the rubber catheter to create a sump system by applying low continuous wall suction through the catheter). A surrounding ostomy appliance can then be placed around the tube to collect any excess drainage. When fistula drainage has been controlled, the sump catheter should be gradually withdrawn or progressively replaced with smaller-caliber tubes. This allows the tract to contract and close. Sump suction can eventually be replaced by gravity drainage in most patients. D'Harcour and associates reported an 81% overall closure rate with this method in 147 patients with both high-output (93 patients) and low-output (54 patients) fistulas.[42]

One useful modification of fistula wound management has been described by Suripaya and Anderson (Fig. 73–1). A disposable ileostomy bag with adhesive backing is fitted to the fistula site.[43] The opening in the ileostomy bag is cut to fit the fistula as exactly as possible. Two 18-French or larger catheters with multiple side perforations are tied together and passed into the fistula through the open end of the bag. All perforations are placed within the fistula below skin level. A third 18-French catheter with multiple perforations is placed in the ileostomy bag, and the open end of the bag is tied securely around all three catheters. One of the two catheters within the fistula and the catheter lying free in the bag are set for continuous suction at a minimum of 40 mm Hg of negative pressure. The adjacent catheter in the fistula serves as an air vent. When functioning, the bag is completely collapsed, and fluid leaking from the tract is immediately aspirated away. The surrounding skin must be protected from excoriation and erosion because skin breakdown can cause discomfort and also increase metabolic requirements. Protection can best be accomplished by attaching a disposable ostomy appliance with either a Stomahesive or a karaya ring around the fistula. The surrounding skin can be protected with Stomahesive paste, karaya gum powder, aluminum paste, tincture of benzoin, or zinc oxide/menthol cream.

Alternatively, a wound vacuum (V.A.C. [vacuum-assisted closure] device) drainage system works very well to control fistula drainage and protect the skin (Fig. 73–2). With negative pressure application to the wound, the V.A.C. apparatus allows for excellent control of drainage, minimizes the size of the abdominal wound, simplifies management by decreasing the frequency of dressing changes, and may actually promote healing of the fistula.[44,45] By simplifying wound care and control of output, patients can be discharged from the hospital sooner and the V.A.C. can easily be managed in a home care or extended care setting. For the majority of enterocutaneous fistulas, this has become our method of choice for controlling fistula drainage and protecting the surrounding skin.

The therapeutic use of appropriate antibiotics for intra-abdominal abscess and sepsis should be carefully reserved for septicemia and cholangitis, as well as in preparation for surgery. Once signs of intra-abdominal sepsis have occurred, the use of antibiotics does not obviate the necessity of treating the process surgically or via percutaneous drainage. Adequate drainage of an abscess cavity must be accomplished. If possible, general anesthesia and major surgical procedures should be avoided or postponed until the patient's condition has stabilized. Although drainage of the abscess must be complete, it is important to choose the least traumatic procedure that is consistent with this goal. Ultrasound and CT are most often used to search for peritonitis or an intra-abdominal abscess. These two modalities not only localize such processes but also permit guided percutaneous drainage, an invaluable procedure in a critically ill patient who may not tolerate an operative procedure (Fig. 73–3). Abdominal exploration may be required in septic patients who are losing ground, even if diagnostic studies have not pinpointed an abscess. If exploratory laparotomy is required for drainage, it is best to avoid definitive operative repair of the fistula because such attempts are usually unsuccessful in the setting of adjacent sepsis. Failure of repair may make subsequent attempts more difficult and possibly result in spread of

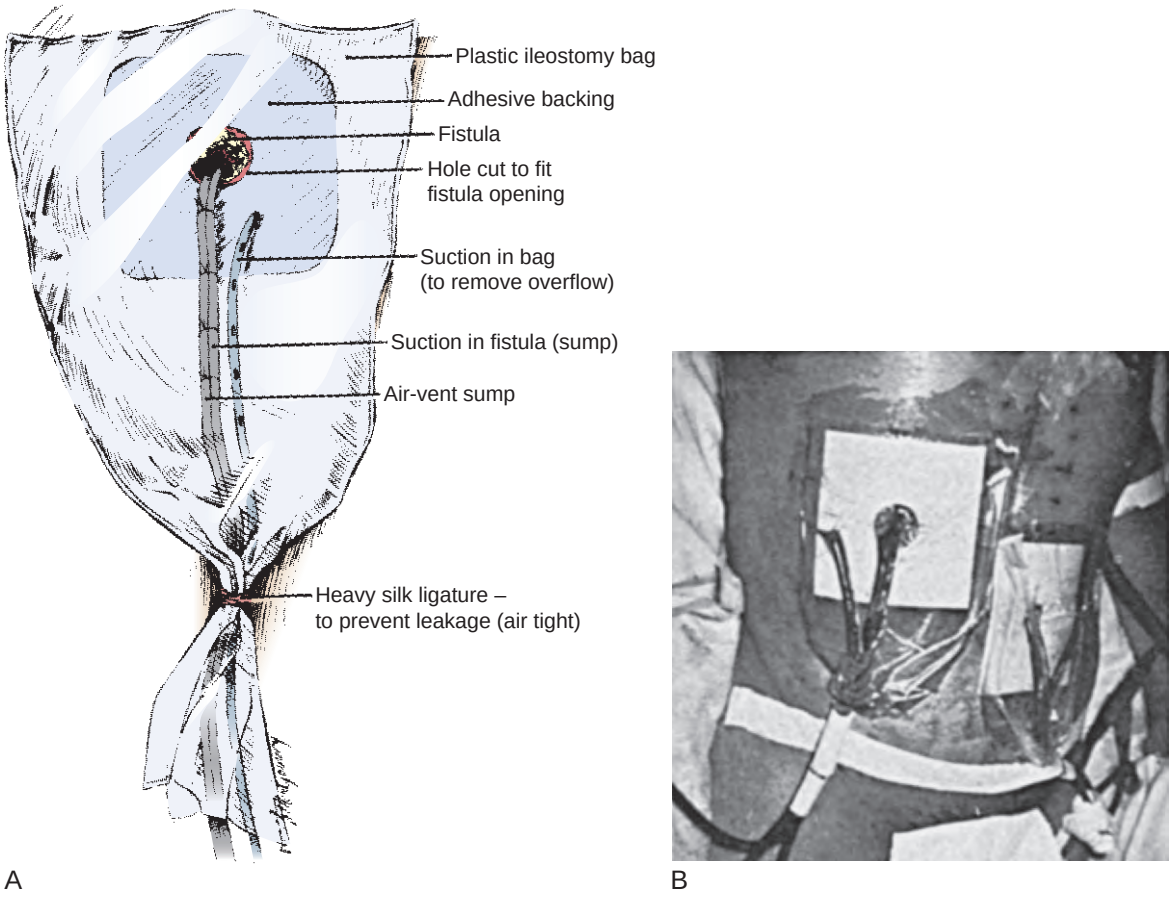

Figure 73–1. Enterocutaneous fistula drainage device. **A,** Components of the suction device. **B,** Bag collapsed by negative suction. (From Suriyapa C, Anderson MC: A simple device to control drainage from enterocutaneous fistulas. Surgery 70:456, 1971.)

infection to previously uninvolved areas of the abdomen. Control of the fistula should be established during the operation by allowing complete drainage to the skin surface or by actually exteriorizing the fistula.

The fistula effluent should be cultured for both bacteria and fungi. Sputum, urine, wound, and blood cultures, including those from central venous lines, should also be obtained. Wound or drain site collections should be evacuated. The wound should be débrided of all grossly infected and necrotic tissue. Culture results and the eventual patient systemic response should modify subsequent antibiotic therapy, particularly if *Enterococcus,* resistant gram-negative bacteria, or fungus is cultured. Percutaneous drainage can often temporize the situation until the patient's condition stabilizes and may, in some cases, lead to eradication of the fistula.

Once sepsis is controlled or when no sepsis is present, parenteral/enteral nutrition should result in improved nutritional status and allow skin lesions to heal and the future operative field to become quiescent. Early operative intervention in the presence of malnutrition is not necessary and may be detrimental. Even if the regimen of bowel rest in conjunction with intravenous and enteral nutrition does not lead to successful spontaneous fistula closure, the patient is generally in better nutritional and metabolic condition to withstand an operation to correct the fistula.

Pharmacologic Support

Use of the long-acting somatostatin analogue octreotide for decreasing pancreatic and enterocutaneous fistulous output has been popularized during the 1990s. An inhibitory effect on gastric, biliary, and pancreatic secretions is generally observed in clinical use. With typical subcutaneous dosages of 100 to 250 μg every 8 hours, fistulous output is reduced by 40% to 60% after the first day regardless of fistula site or volume of output.[46] Side effects are not usually severe and include hyperglycemia, decreased bowel motility, and elevated cholesterol levels. Placebo-controlled studies indicate that octreotide decreases fistula-related complications, reduces fistulous output, and decreases fistula healing time and the time required for TPN.[47] Octreotide has been shown to promote fistula closure within a significantly shorter time than TPN alone does, even with malignant enterocutaneous disease, and is particularly helpful in decreasing secretions in high-output fistulas to a manageable

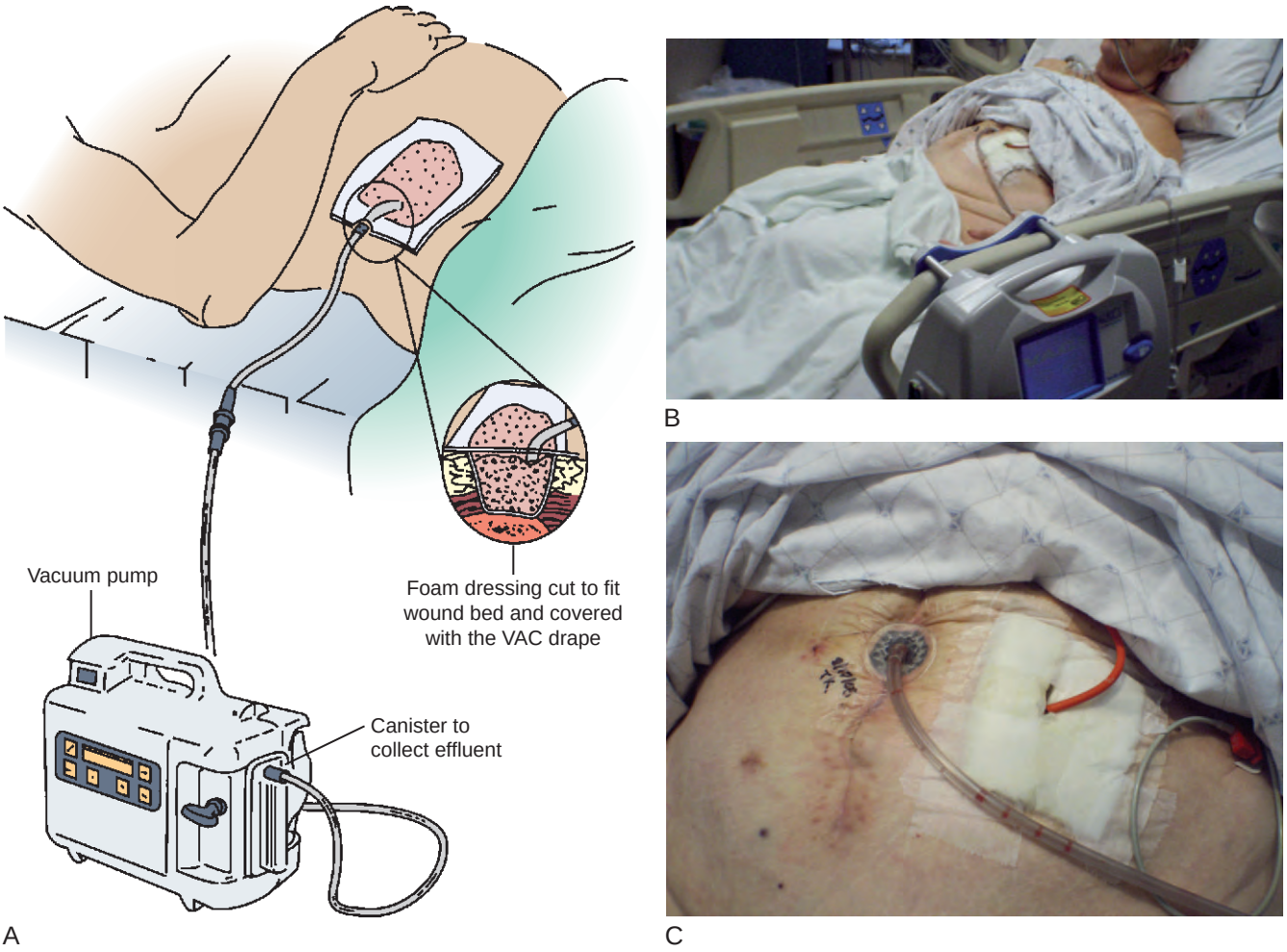

Figure 73–2. **A,** The wound V.A.C. apparatus allows for excellent control of drainage, minimizes the size of the abdominal wound, and simplifies management. (From Cro C, George KJ, Donnelly J, et al: Vacuum assisted closure system in the management of enterocutaneous fistulae. Postgrad Med J 78:364, 2002.) **B,** Wound V.A.C. on a patient with a gastrocutaneous fistula (see Fig. 73–3). **C,** Control of gastrocutaneous fistula with the wound V.A.C. apparatus.

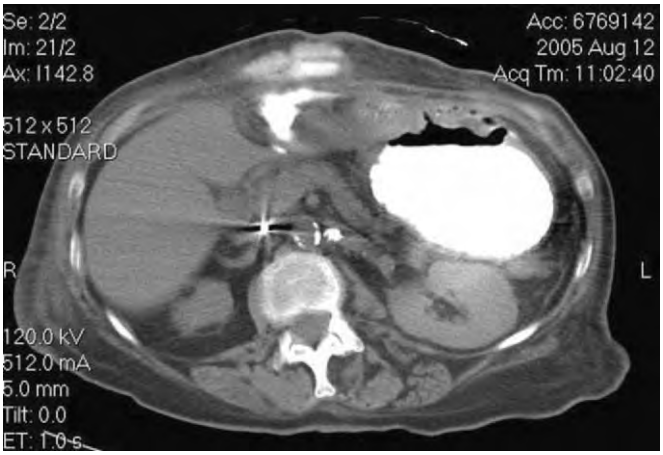

Figure 73–3. Computed tomography scan demonstrating free air and contrast extravasation from the stomach into an anterior intra-abdominal abscess after vagotomy, antrectomy, and Billroth II gastrojejunostomy for a giant duodenal ulcer.

level.[48-50] However, the mortality rate, hospitalization time, and overall fistula closure rate were not improved, although even in the fistulas that eventually required operative closure, octreotide in general both reduced their output and simplified management.

Proton pump inhibitors or histamine H_2 receptor antagonists are advisable both to reduce gastric acid production and to reduce gastric secretions. These medications may be useful in decreasing fistula output, particularly with proximal fistulas or when the amount of gastric secretions is high. Patients with refractory fistulas related to Crohn's disease have been successfully treated with short courses of cyclosporine. In five patients with a total of 12 fistulas, Hanauer and Smith used an infusion of 4 mg/kg/day for 6 to 10 days, followed by oral dosing at 8 mg/kg/day adjusted to maintain serum cyclosporine levels of 100 to 200 ng/ml.[51] All fistulas responded to cyclosporine infusion with decreased drainage and improvement in both local inflammation and patient comfort. Complete resolution occurred in 10 of the 12

fistulas after a mean of 8 days. Therapy was continued for a mean of 6 months, with five recurrences, two of which were related to inadequate cyclosporine serum levels. Similar results with cyclosporine were reported by Present and Lichtiger.[52] Side effects consisted of infectious complications, mild hypertension, paresthesias, and hirsutism. Although useful for short-term treatment, long-term administration of cyclosporine is generally avoided because of the potentially septic complications of immunosuppression, as well as hypertension and nephrotoxicity. In addition, the use of immunosuppressive drugs such as cyclosporine may theoretically impair healing of the fistula.

Azathioprine and 6-mercaptopurine are both effective in treating active Crohn's disease and in maintaining remission, with the cumulative dose being the primary factor in predicting response. Associated small bowel fistulas may also improve with such treatment. Adverse reactions such as leukopenia, pancreatitis, and nausea may preclude therapy with these agents. Combination therapy with tacrolimus and either azathioprine or 6-mercaptopurine may be useful when treating perineal fistulas related to Crohn's disease. In one study involving 11 patients, 7 had a complete response and 4 had a partial response.[53] The most common side effects with such combination therapy are nausea, paresthesias, nephrotoxicity, and tremor.

More recently, infliximab (Remicade), a chimeric monoclonal antibody to tumor necrosis factor-α, was developed as treatment of Crohn's disease. Infliximab is effective in closing fistulas in patients with Crohn's disease. In a randomized, multicenter trial investigating infliximab administered intravenously at 0, 2, and 6 weeks and dosed at 5 mg/kg for the treatment of 94 adult Crohn's patients with chronic fistulas, partial resolution of multiple lesions occurred in 68% and complete closure occurred in 55% of patients.[54] Other studies also support the efficacy of infliximab in treating Crohn's disease–related small bowel fistulas.[55,56] In 282 patients with fistulizing Crohn's disease, infliximab, 5 mg/kg every 8 weeks, significantly reduced hospitalizations, surgeries, and procedures in comparison to placebo.[57] Complications of this therapy occur in more than 60% of patients and include headache, abscess, upper respiratory tract infection, and fatigue.

Investigation

The next phase of management is investigation. After stabilization is accomplished in the first 24 to 48 hours, investigation usually takes place over the next 7 to 10 days. Investigation implies a thorough evaluation of the gastrointestinal tract, definition of the anatomy of the fistula, and identification of any complicating features such as abscess, stricture, or distal obstruction.[31,32] Investigative studies should be designed to not only determine the presence and location of the fistula but also provide information regarding its cause. This objective can be accomplished by several investigational methods. Oral administration of indigo carmine or charcoal can be used to demonstrate the presence of a connection between the gastrointestinal tract and the abdominal wall or urinary bladder. These tests, however, prove only the presence of a fistula and do not identify its site or source. Probably the most important first test is a fistulogram, which will define the length and width of the fistula, as well as its anatomic location. A fistulogram can be performed by inserting a small catheter through the drainage site into the fistula tract and then slowly injecting water-soluble contrast under fluoroscopy (Fig. 73–4). It is best performed by the responsible surgeon in collaboration with the radiologist. The value of the procedure is enhanced by close involvement of the surgeon

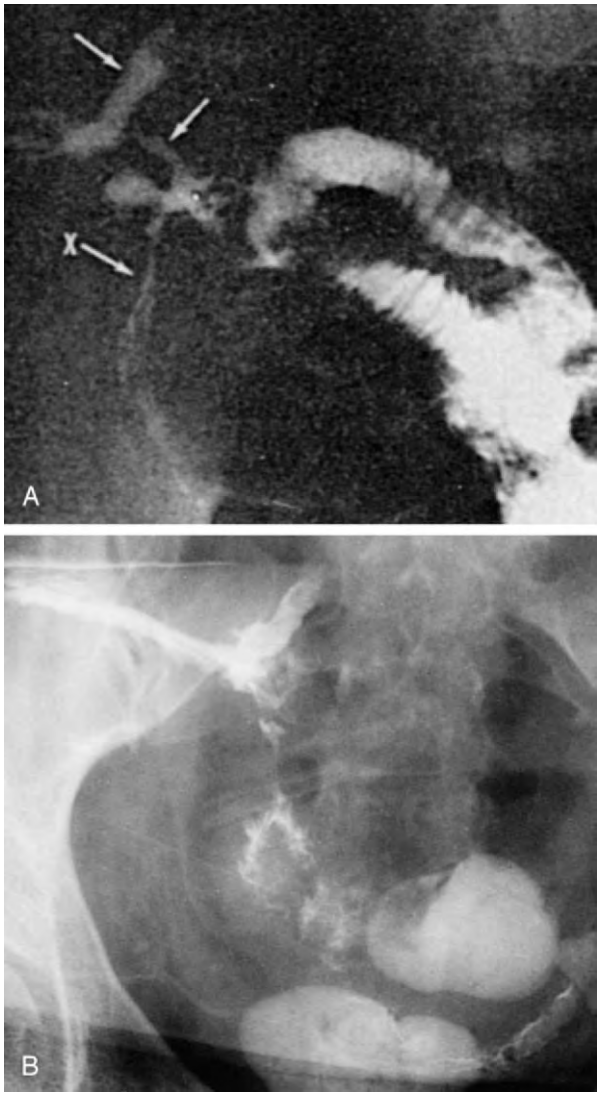

Figure 73–4. **A,** Fistulogram. Injection of a cutaneous fistula demonstrates several tracts *(arrows)* leading to the ileum. Crohn's disease is present in one loop *(arrow with X).* **B,** Fistulogram demonstrating an enterocutaneous fistula in a patient after appendectomy for acute perforated appendicitis. **(A,** From Goldfarb WB, Monafo W, McAlister WH: Clinical value of fistulography. Am J Surg 108:902, 1964.)

and the radiologist as the study is performed. The procedure is safe and can be performed even in seriously ill patients.[58,59]

Fistulography performed early in the course of the disease will help determine (1) the site of the fistula, (2) intestinal continuity with the fistula, (3) the presence or absence of distal intestinal obstruction, (4) the nature of the intestine immediately adjacent to the fistula, and possibly (5) the presence or absence of an intra-abdominal abscess. Other tests such as an upper gastrointestinal series with small bowel follow-through and barium enema are helpful in further elucidating the exact anatomy and location of the fistula. Performing the fistulogram first is prudent because contrast from an upper gastrointestinal series, contrast enema, or even CT may make it difficult, if not impossible to interpret a fistulogram until all of the contrast has passed. Fistulography should be followed by a complete contrast study of the gastrointestinal tract either orally or through existing intraluminal tubes. Such study is valuable both for identifying the internal source of the fistula and for defining its size and complicating factors such as distal obstruction. The fistulogram should always be performed before the complete contrast study because the latter will not usually define the fistula and may decrease visualization or make fistulography impossible. Internal fistulas may be more difficult to evaluate. Patients with enteroenteric fistulas often suffer a delay in diagnosis because of a lack of symptoms or symptoms that mimic the primary disease or event creating the fistula. An internal small intestinal fistula may be asymptomatic, particularly if the amount of absorptive area bypassed by the fistula is small. Other internal fistulas may not be readily recognized because the symptoms may mimic those of the primary disease. For example, an enteroenteric fistula, which is most often secondary to Crohn's disease, is frequently accompanied by abdominal pain, diarrhea, weight loss, or fever. These symptoms are similar to those accompanying an acute exacerbation of Crohn's disease itself. Thus, at times the diagnosis is not made until surgery in these patients. If the colon is involved with the fistula, a fluoroscopic water-soluble or barium enema will assist in definition of both the fistula and any associated colonic disease.

Additional useful tests in the early stage of investigation are CT and ultrasonography. These tests can further define the anatomy of the vicinity of the fistula and evaluate for any ongoing or unrecognized intra-abdominal processes or abscesses, as well as distal obstruction. A CT scan will be required in almost all patients for these reasons, especially to rule out any undrained collections. CT scanning with oral and intravenous contrast media is highly sensitive and specific for intra-abdominal free air and will assist in locating the fistula and identifying adjacent fluid collections and concomitant bowel obstruction. The use of CT, however, within the first week after surgery is associated with the expected presence of postoperative air within the abdominal cavity and thus may be difficult to interpret. Obviously, extravasation of intraluminal contrast on CT examination is diagnostic of perforation. CT and ultrasound are useful adjuncts when an intra-abdominal abscess is suspected (Fig. 73–5). Significant fluid collections should be drained, preferably under CT or ultrasound guidance via a percutaneous route, and an indwelling catheter left in the cavity. This then permits subsequent examination of the cavity under fluoroscopy with water-soluble contrast to assist in delineation of the fistula tract. Although the site of perforation may not be identified on initial injection because of inflammation, subsequent examinations after several days of drainage will often show the site of the fistula. CT scanning is highly recommended for suspected duodenal perforations; no other imaging modality is currently better at demonstrating gas in the retroperitoneum surrounding the duodenum, which is a diagnostic sign of perforation. An elevated serum amylase level may accompany duodenal perforation after ERCP and give the impression of pancreatitis, thus leading to a delay in diagnosis with an increase in the mortality rate.[22]

Intravenous pyelography and retrograde pyelography may be helpful in defining a nephroenteric fistula, whereas cystoscopy is usually a more accurate method for determining the presence of an enterovesical fistula. In general, CT is the most sensitive study for identifying a colovesical or enterovesical fistula. ^{99m}Tc-labeled hepatoiminodiacetic acid (HIDA) scanning or ^{111}In-labeled leukocyte scintigraphy may have an advantage over conventional radiography in certain proximal enterocutaneous or biliary-enteric fistulas.

Endoscopic evaluation, including colonoscopy, esophagogastroduodenoscopy, and ERCP, may be helpful in certain specific clinical situations. However, endoscopy is not usually advisable if an acute perforation is suspected and should generally be delayed until the acute inflammatory process has resolved. Endoscopic examination of the stomach and duodenum may occasionally be used to identify a fistulous source and to take biopsy samples of adjacent tissue for exclusion of malignancy. Billroth II anatomy will usually preclude duodenal examination, although enteroscopy through the afferent jejunal limb is possible by highly skilled endoscopists. ERCP will allow the diagnosis of fistulas connecting the gallbladder or biliary tract to the duodenum or stomach. For suspected gastrocolic or duodenocolic fistulas, colonoscopy may identify the involved site and enable a biopsy to be performed to diagnose inflammatory bowel disease or malignancy. The fistulous output may be analyzed for electrolytes and cultured to determine drug sensitivities, as well as assayed for bilirubin and amylase for comparison with serum values.

In the rare circumstance when perforation has not been excluded by noninvasive tests and the patient's condition is not improving or is worsening, diagnostic laparotomy should be considered. Morbidity and mortality rates are only increased by a delay under these circumstances. Diagnostic laparoscopy may be useful to rule out perforation after a previous laparoscopic procedure or after an endoscopic procedure. It is not usually appropriate in a septic, hypotensive patient and does not enable a satisfactory examination of the retroperitoneal duodenum. As mentioned previously, early laparoscopy for tachycardia or unexplained fever is essential to prevent mortality from an anastomotic leak after gastric bypass surgery.

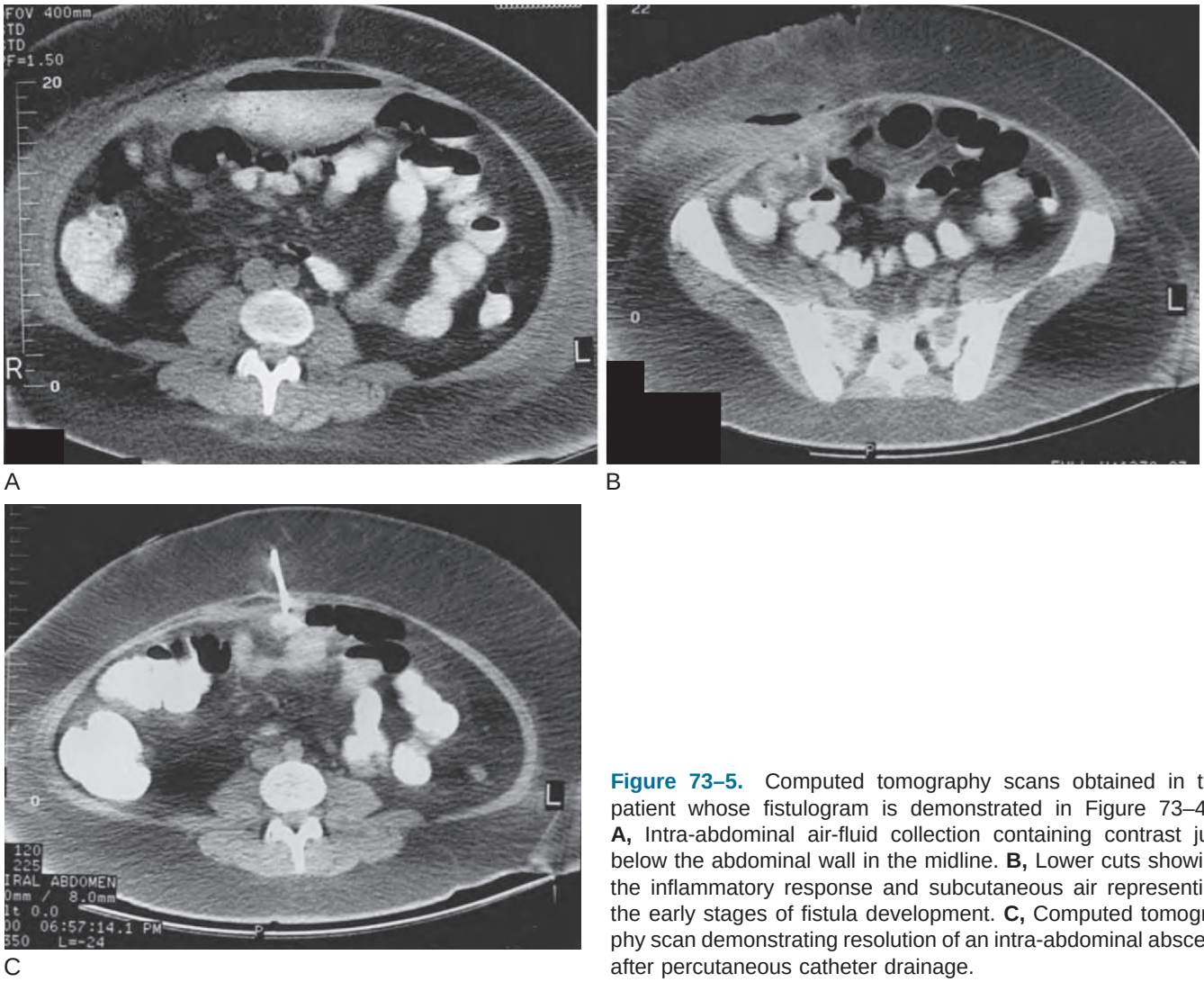

Figure 73–5. Computed tomography scans obtained in the patient whose fistulogram is demonstrated in Figure 73–4B. **A,** Intra-abdominal air-fluid collection containing contrast just below the abdominal wall in the midline. **B,** Lower cuts showing the inflammatory response and subcutaneous air representing the early stages of fistula development. **C,** Computed tomography scan demonstrating resolution of an intra-abdominal abscess after percutaneous catheter drainage.

Decision

The next step in fistula management is a decision on management and the timing of such management. When one is making these decisions, the likelihood of spontaneous closure must be determined. The likelihood of closure depends on several factors. The first is anatomic location. In general, anatomic locations that are favorable for closure are the oropharynx, esophagus, duodenal stump, pancreas, biliary tree, and jejunum. Alternatively, unfavorable locations include the stomach, lateral duodenum, ligament of Treitz, and the ileum. As mentioned previously, nutritional status is very important. Patients with poor nutritional status, as measured by overall assessment, albumin, short-turnover proteins (serum transferrin, thyroxin-binding prealbumin, retinol-binding protein), injected skin antigens, and other factors, are much less likely to close a fistula no matter what the anatomic location.[41] More importantly, if a patient's nutritional status is poor, the mortality rate is higher. Another important factor is the presence or absence of sepsis. The absence of sepsis has a positive predictive value for closure, whereas the converse is true in the presence of sepsis. Elimination of sepsis should be considered a necessity for spontaneous closure. The cause of the fistula is also predictive of closure. Postoperative fistulas and fistulas secondary to appendicitis or diverticulitis are likely to close. Fistulas associated with active Crohn's disease are unlikely to close until the Crohn's disease is quiescent. Fistulas associated with cancer will usually require excision of the tumor along with the fistula. In addition, the presence of a foreign body will prevent closure of the fistula without operative intervention.

After sepsis has been controlled and diagnostic studies have been completed, management of a fistula should follow a conservative course. An opportunity for spontaneous healing should be permitted. It is important to provide adequate nutritional support and to aggressively investigate any new onset of signs of sepsis during this convalescent period. The duration of conservative treatment must be individualized. If a positive nitrogen balance is maintained, fistula output decreases, and no septic complications develop, nonoperative manage-

ment may be continued. The spontaneous closure rate of enterocutaneous fistulas in several large series ranged from 32% to 80%.[27,28] Reber and associates reported that more than 90% of small intestinal fistulas that closed did so within a month.[28] Less than 10% closed after 2 months, and none closed spontaneously after 3 months. Thus, a reasonable management plan may consist of at least 1 month of nonoperative management, with reasonable extensions should the fistula show signs of slow but continued healing. Delaying surgery allows peritoneal reaction and inflammation to subside, thus making a definitive surgical procedure easier and safer. Delaying repair also permits nutritional optimization, thereby decreasing the likelihood of postoperative wound complications. A postoperative enterocutaneous fistula usually extends hospitalization by 2 to 3 months, but this period may shorten somewhat with refinements in TPN, administration of somatostatin analogue, and wider availability of outpatient nursing care. In fact, many patients are candidates for discharge home or to a skilled nursing facility during the convalescent period because of the availability of these agents in such settings.

The condition of the bowel or other organ involved in the fistula is also important. Healthy adjacent tissue is a favorable factor. Other favorable factors include a small fistula, quiescent disease, and the absence of an abscess. On the other hand, total disruption of the bowel negates closure, as does distal obstruction, abscess, malignancy or irradiation (or both), epithelialization of the fistula tract, and active disease. Typically, a long fistula tract (longer than 2 cm) is more likely to close than a short fistula tract. Similarly, a thin, narrow tract is a favorable prognostic indicator (i.e., less than 1 cm^2). Therefore, short, wide tracts are unlikely to close spontaneously.[31,32] Nutrition has been mentioned as an important factor in stabilization and spontaneous closure. The short-turnover proteins can provide prognostic information. Specifically, a serum transferrin level less than 200 mg/dl predicts a low likelihood of spontaneous closure.[41]

Failure of an enterocutaneous fistula to close spontaneously is associated with a number of factors (represented by the acronym *FRIENDS*): the presence of a *foreign body* within the tract or adjacent to it, previous *radiation* exposure of the site, ongoing *inflammation* (most commonly from Crohn's disease) *or infection* that contributes to a catabolic state, *epithelialization* of the fistula tract (particularly if the fistula tract is less than 2 cm long), *neoplasm, distal intestinal obstruction,* and pharmacologic doses of *steroids.* Fistulas associated with a concurrent pancreatic fistula also have a low rate of spontaneous closure, as do those occurring in the presence of malnutrition or adjacent infection. As mentioned, the loss of intestinal continuity or the presence of abdominal wall defects makes operative correction more likely. Vigorous attempts to identify each of these confounding factors and to modify their influence may increase the success of nonoperative strategies, but operative intervention is generally necessary when they are present.

Campos et al. analyzed prognostic factors for closure of external duodenal fistulas and found that the odds of spontaneous closure were (1) three times greater with low-output fistulas than with high-output fistulas, (2) five times greater with postoperative fistulas than with fistulas associated with inflammatory bowel disease or trauma, and (3) two times greater with duodenal fistulas than with jejunoileal fistulas.[60] For duodenal fistulas, spontaneous closure was observed in 33%, with an overall mortality rate of 36%. Williams et al. found that even high-output lateral duodenal fistulas spontaneously closed in 63% with TPN and eradication of sepsis.[61] Their median output was 1480 ml/day, with a median time to closure of 29 days and an overall mortality rate of 15%. Kuvshinoff et al. found that seven of eight gastric fistulas closed spontaneously but only one of four duodenal fistulas did so; approximately 50 days was required for closure.[41]

After considering all the aforementioned factors, one determines whether to observe the fistula for spontaneous closure or plan early surgery after stabilization. When one determines that the fistula is likely to close and does not operate, if the fistula has not closed after 4 to 5 weeks without sepsis, an operation will probably be required. General wisdom holds that a fistula that has not closed by 4 to 6 weeks is unlikely to do so and surgery is indicated. The decision to operate is tempered by the patient's condition and the state of the abdomen. In particular, when faced with a firm, indurated abdomen, it is better to stabilize the infection, nutrition, and fluid balance in this circumstance and wait until the abdomen is soft, without significant induration, to maximize the chance for operative success and minimize the risk of creating new enterocutaneous fistulas. In certain cases then, the period of waiting may be greater than 6 weeks.

Definitive Therapy

The next important decision is to determine whether definitive operative therapy is necessary and the timing of such therapy. In situations that are favorable, between 80% and 90% of fistulas that are going to close spontaneously will close within 4 to 5 weeks. When spontaneous closure is unlikely or has not occurred within 4 to 5 weeks, an operation will be required. When operative therapy has been chosen, the operation must be carefully planned. Whenever possible, the operation should not take place until the patient is stable, not septic, and in an adequate nutritional state. The most favorable time to reoperate on patients is either within 10 days of diagnosis or after 4 months.[32]

Gastric and Duodenal Perforations and Fistulas

Endoscopically produced gastroduodenal perforations are appropriately referred for surgical management when a free perforation is recognized by the presence of intra-abdominal air on radiographic films. However, retroperitoneal duodenal perforations that occur during ERCP and sphincterotomy have been treated both medically and surgically, depending on the size of the perforation and the patient's response. Loperfido et al. reported 12 retroperitoneal perforations in a series of 2769 ERCP procedures; 6 were treated nonoperatively,

with one death.[21] From a surgical standpoint, Bell et al.[22] warned that patients with perforations diagnosed within 24 hours of surgery had a mortality rate of 13% whereas delay beyond 24 hours increased mortality rates to 43% because of sepsis or multiorgan failure. If medical therapy is undertaken for a small, contained perforation, close monitoring should be performed, with surgical exploration initiated within 24 hours for perforations that do not improve or that worsen.

Acute intraoperative gastric or duodenal perforations should be repaired during the course of the operation. This simple principle presupposes both that the perforation is recognized and its repair is possible. In particular, laparoscopic surgical procedures may produce perforations that are not recognized at that time. Frequently, if recognized, such injuries can be repaired with laparoscopic suturing techniques. However, in some situations laparoscopic repair of gastric or duodenal lacerations may be quite difficult to perform, particularly if the surgeon is not expert in advanced laparoscopic maneuvers. Conversion to laparotomy in these circumstances to ensure a safe repair reflects good surgical judgment rather than failure. Initial complications tend to breed subsequent complications, which are minimized by prompt and thorough treatment of the initial problem.

Gastric perforation occurring during a surgical procedure can usually be primarily repaired with an inner layer of continuous absorbable suture and an outer layer of interrupted silk suture. Alternatively, a stapler may be used if the anatomy is appropriate and the tissues are not inflamed or markedly edematous. During laparoscopic procedures, serosal lacerations are often visible; methylene blue instillation via a nasogastric tube will reveal extravasation. Intraoperative endoscopy with air insufflation and distal occlusion under saline irrigation may be even more accurate in identifying a leak. Manual distal occlusion and removal of the insufflated air by suction at the conclusion of the test are essential because air insufflation of the intestine can make the remainder of the procedure very difficult. Serosal lacerations may be sutured laparoscopically if amenable, but laparotomy is appropriate for difficult anatomy or poor exposure.

Usually, patients with perforations that are recognized in the immediate postoperative period should be returned to the operating room for repair. For initial laparoscopic procedures, repeat laparoscopy may be appropriate to diagnose the perforation and to close it, if possible. Laparotomy will often be required for satisfactory identification, washout, and closure. With both laparoscopic and open procedures, anastomotic leaks will frequently occur later, about 1 week after surgery. The decision to operate will be influenced by the ability to drain associated abscesses percutaneously and the presence of peritonitis. Focal collections that are adequately drained, with a good systemic response and only local tenderness, may continue to be observed for eventual closure. Ongoing sepsis, poorly drained collections, or generalized peritoneal signs should mandate reexploration, débridement, drainage, and management of the perforation.

Surgical options for gastric perforation include simple closure, partial gastric excision with reclosure, or partial gastrectomy. An indurated stomach with extensive inflammation will make resection hazardous; in this situation, an omental patch of the perforation should be considered. Placement of a drain or sump in the area may convert the perforation to a controlled fistula if the repair or patch leaks again. Placement of a gastrostomy tube, if possible, will permit gastric decompression and avoid the prolonged use of a nasogastric tube with its risk for sinusitis. Placement of the gastrostomy tube through the area of perforation may be optional if closure or excision cannot be safely accomplished. Consideration should be given to placement of a feeding jejunostomy tube (or a combined gastrostomy-jejunostomy tube). A leaking gastroduodenostomy may be treated by distal gastric resection with conversion to a Billroth II gastrojejunostomy.

Perforations that are recognized in the first several days postoperatively should usually be treated by reoperation and closure or by anastomotic revision. More typically, nearly 1 week after surgery, the onset of fever, tachycardia, respiratory failure, and acidosis with ileus and pain will suggest a leak or abscess. After CT-guided percutaneous drainage, with appropriate antibiotic therapy, the perforation will often heal. Failure to resolve shifts the focus to management of a fistula. An early leak after gastric bypass surgery should be recognized and repaired as soon as possible to prevent significant morbidity and mortality. This complication usually requires revision of the anastomosis and drainage.

Repair of ERCP-induced duodenal perforations should be performed as soon as possible after diagnosis and hemodynamic and respiratory stabilization. Delay increases the friability and edema of the duodenum and increases retroperitoneal contamination and the possibility of damage to the small and large intestine and mesentery. A midline laparotomy is advised to allow access to all of the small bowel and mesentery. Wide kocherization of the second portion of the duodenum, with mobilization of the hepatic flexure if needed, allows close inspection of the second and third retroperitoneal portions. In most cases with an early diagnosis, local débridement of the wound edges with suture closure will close the duodenal defect. If the perforation occurred during sphincterotomy, the location of the bile duct must be determined before suture closure. If the duct location is uncertain, cholecystectomy may be performed, and a small catheter can be passed through the cystic duct stump into the distal common bile duct and duodenum. For a significant ampullary injury, proximal bile drainage with either a T-tube or a tube cholecystostomy should be considered. Proximal decompression is accomplished with a gastrostomy tube. Internal duodenal decompression can be achieved with either a retrograde tube duodenostomy (placed through the proximal jejunum) or a combination gastrostomy-jejunostomy tube, with the distal end cut short appropriate to a duodenal tip location. The duodenal repair is reinforced with omentum, if possible, and a local closed suction drain will, in many cases, facilitate evacuation of the fluid. It also serves to convert any subsequent leakage to a controlled fistula. A

feeding jejunostomy should be created for postoperative enteral nutrition. With a delay in the diagnosis of duodenal perforation, there may be widespread inflammation or necrosis in the retroperitoneum that extends under the transverse mesocolon and small bowel mesentery. Much of this can be accessed by hepatic flexure mobilization, but a counterincision beside or below the small bowel mesentery may be needed to adequately débride and drain the areas of necrosis. Sump drain placement under the small bowel mesentery and near the duodenum generally permits good drainage; the sumps may be gradually withdrawn later after tube checks and CT scans demonstrate healing.

Pyloric exclusion has been used successfully in trauma patients with extensive duodenal injury, with diagnosis delayed more than 24 hours after injury, and after initial primary duodenal repair with subsequent breakdown and a high-output lateral fistula. Closure of the pylorus, gastrojejunostomy, gastrostomy, and feeding jejunostomy without vagotomy are performed in the expectation that the pylorus will reopen within 3 to 6 weeks, although subsequent intra-abdominal abscesses may require drainage. This technique may be most suitable for nontrauma patients with a delayed diagnosis of duodenal perforation in which the bowel wall is markedly thickened, friable, and inflamed and where other options, such as closure, serosal patching, or tube duodenostomy, are not thought to be adequate (see Chapter 53 on duodenal trauma).

Gastroduodenal fistulas that develop in association with necrotizing pancreatitis and necrosectomy may be treated during laparotomy or by subsequent percutaneous drainage. Tsiotos et al. treated two gastrocutaneous fistulas 1 month after necrosectomy by percutaneous drainage, with eventual closure.[19] Duodenal fistulas were treated by tube duodenostomy or Roux-en-Y duodenojejunostomy; late-developing duodenal fistulas were treated by percutaneous drainage. Ho and Frey used primary closure and delayed external drainage for gastric fistulas after necrosectomy and treated duodenal fistulas with pyloric exclusion or external drainage.[20]

If the gastric or duodenal defect is too large to allow primary closure or the fistula originates in conjunction with the ampulla and pancreatic duct, a Roux-en-Y gastrojejunostomy or duodenojejunostomy is a flexible and valuable technique for dealing with such difficult gastric or duodenal fistulas. It is best used in the absence of ongoing infection, when sufficient time has been allowed, and the jejunum is pliable and not edematous. Although mucosa-to-mucosa apposition is best, hand sewing the end of the Roux limb even with the chronically thickened tissue around a fistula usually results in healing. A feeding jejunostomy distal to the enteroenterostomy should always be considered.

Treatment of a duodenal stump fistula is based on the condition of the stump and surrounding tissue and the surgeon's judgment. Options include primary suture closure, mobilization of the stump with resuture or stapling, lateral tube duodenostomy for duodenal decompression, direct tube drainage through the fistula, a serosal patch, or the use of a Roux jejunal limb. Duodenal fistulas that are associated with recurrence of Crohn's disease at an ileocolic anastomosis are managed by resection of the recurrent disease with reanastomosis. The duodenal end of the fistula is débrided and primarily closed, and omentum is interposed to separate it from the new anastomosis. Difficult duodenal closure has been managed by either a jejunal serosal patch or duodenojejunostomy. Primary colonic Crohn's disease with either a gastric or duodenal fistula is similarly treated by resection of the primary source and closure of the fistula, with duodenojejunostomy reserved for large residual defects.

Internal gastrocolic or duodenocolic fistulas from colon carcinoma are generally managed by partial colon resection, as well as resection of the involved stomach or duodenum, along with primary closure. Large duodenal defects require a patch or duodenojejunostomy. A gastrojejunocolic fistula is treated by a partial gastrectomy that includes the anastomosis and by excision of the involved jejunum and colon. Reconstruction may be performed by either reanastomosis of the jejunum with a more distal loop gastrojejunostomy (to include truncal vagotomy if ulcer related) or conversion to a Roux-en-Y gastrojejunostomy. The colon may be anastomosed, or a proximal colostomy may be performed if extensive local inflammation is present.

For repair of both perforations and fistulas, the use of fibrin sealant as an adjunct should be considered. It has been used successfully in the transthoracic repair of esophageal perforations to anchor a pleural flap over the sutured repair. Bardaxoglou et al. also reported successful use of fibrin sealant for esophageal perforations, combined with absorbable mesh.[62] Lau et al. compared sutured repair and fibrin sealant with a gelatin sponge for the treatment of perforated ulcers and also compared laparoscopic and open techniques.[63] They did not find any significant differences between sutured and fibrin sealant repair. These results, combined with successful reports of nonoperative fistula closure with the use of fibrin sealant, suggest a broader role in operative management.

Enterocutaneous Fistulas

Many enterocutaneous fistulas close spontaneously if infection is controlled, nutrition is adequate, and distal obstruction is not present. Definitive operative correction remains the final step in the management of nonhealing small intestinal fistulas. As with the duration of medical management, the surgical procedure needs to be individualized. Direct suture closure of the fistula is associated with a high incidence of breakdown and fistula recurrence.[28] This operation is rarely useful except as a last resort in patients with dense abdominal adhesions from previous surgeries or in medically moribund patients. In most cases, the preferred operation is resection of the involved segment of intestine and primary end-to-end anastomosis. This technique was successful in 57 of 66 patients reported by Reber and colleagues.[28] In the setting of extensive sepsis, primary anastomosis may not be appropriate. In these circumstances, exteriorization of both the proximal and distal ends of the intestine

may be performed. It is critical that the proximal end be constructed as a standard everted Brooke stoma so that a proper appliance can be fitted and the subsequent effluent adequately managed.

If the fistula is not deemed appropriate for resection, such as when it develops as a complication of a deep pelvic procedure, staged approaches involving bypass should be considered. A simple side-to-side anastomosis proximal and distal to the fistula is inadequate, as is unilateral (proximal or distal) exclusion of the involved segment. Bilateral exclusion with isolation of *both* the proximal and distal portions of the involved intestine is necessary for effective defunctionalization of the fistula. In a staged procedure, the fistulous segment is left in situ, or the ends are exteriorized as mucous fistulas; the afferent and efferent bowel loops are anastomosed to restore intestinal continuity. Alternatively, if the efferent loop cannot be mobilized, the intestine proximal to a distal ileal fistula can be divided and anastomosed to the transverse colon. The fistulous segment is again returned to the pelvis or exteriorized as a mucous fistula. This technique is not as satisfactory as complete exclusion but works reasonably well if the ileocecal valve is competent. Optimally, the staged procedure is completed when the fistula segment is removed at a later date, although this is not always possible.

Gastrointestinal fistulas associated with large abdominal defects are not only the most difficult to manage surgically but also the most likely to result in mortality. The wound V.A.C. works well to keep these wounds smaller and easier to manage and frequently closes even large abdominal wall defects. Musculocutaneous flaps and the application of abdominal wall reconstruction techniques involving component separation and prosthetic materials may be required to obtain adequate coverage.

Enteroenteric Fistulas

An internal fistula refers to a communication between the small intestine and some other organ or structure within the peritoneal cavity. An enteroenteric fistula occurs when the small intestine joins with either another segment of small intestine or the colon. Most enteroenteric fistulas are caused by Crohn's disease, although colonic diverticulitis and colon cancer can also be antecedent events. Fistulas develop in direct proportion to the length of the involved intestine. Fistula formation in Crohn's disease begins with serosal cohesion of healthy small or large bowel to the diseased intestinal segment. The process is usually gradual and results in internal perforation and subsequent fistula formation as the ulcer penetrates through the newly formed common wall. Free perforation and generalized peritonitis are unusual. Ileocecal fistulas are most common because of the high percentage of patients with Crohn's disease who have chronic inflammation of the terminal ileum. The jejunum and duodenum are involved less frequently.

Careful evaluation is needed to diagnose an enteroenteric fistula because abnormalities may be subtle, reported as generalized complaints, or even absent. Symptoms such as diarrhea, abdominal pain, weight loss, and fever are not specific and are frequently caused by the underlying disease process, as well as the fistula. Abdominal tenderness or a mass may be noted on physical examination. In some patients there may be evidence of obstruction. Enteroenteric fistulas are often serendipitously diagnosed on a small bowel series or barium enema obtained for evaluating vague abdominal discomfort or dysfunction (Fig. 73–6). Sometimes the fistula is not discovered until laparotomy. In others with Crohn's disease, long-term parenteral nutrition, bowel rest, and the use of pharmacologic therapy that includes 6-mercaptopurine, cyclosporine, or infliximab has been successful in resolving certain types of fistulas.[51-57] This outcome contrasts greatly with the natural history of these fistulas before such pharmacologic innovation. For instance, a 1974 study involving 63 patients with Crohn's disease and enteroenteric fistulas found that 52 ultimately required surgery.[64] However, surgical intervention is still necessary in many patients because of refractory disease or intolerance to medications and their side effects.

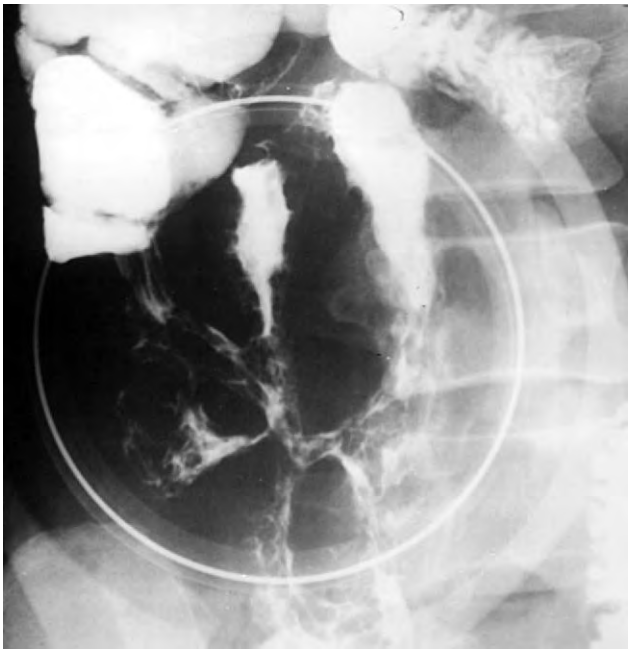

Figure 73–6. Small bowel series demonstrating a complex "starburst" enteroenteric fistula.

When surgical intervention is warranted, the operative procedure of choice is en bloc resection of the diseased intestine in continuity with the fistula tract. If inflammation or an abscess is present, primary resection may be unwise. In such a situation, proximal diversion or percutaneous drainage of any associated abscess cavity is prudent. Resection of the diseased intestine and fistula should be delayed for 6 weeks, if possible, to allow the inflammatory process to subside. Nutritional support during this time is essential.

Any resection, whether primary or as part of a staged procedure, should be confined to the involved segment of intestine to conserve overall bowel length. Extensive resection does not appear to protect against further

Figure 73–7. Fistulogram demonstrating an enterovesical fistula in a patient with long-standing ileal Crohn's disease (the *arrow* indicates a fistula tract). (From Tassiopoulos AK, Baum G, Halverson ID: Small bowel fistulas. Surg Clin North Am 76:1175, 1996.)

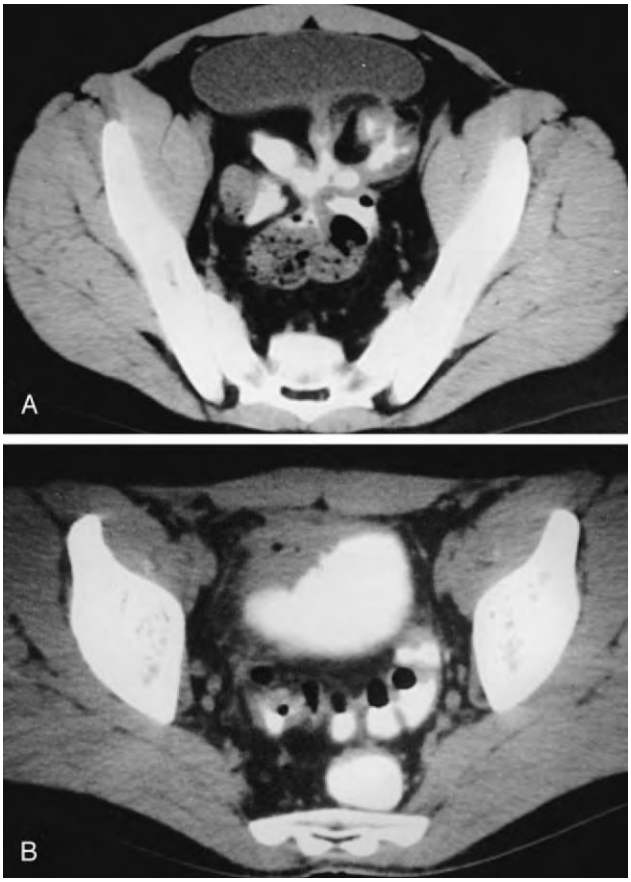

Figure 73–8. Computed tomographic scans in patients with enterovesical fistulas **A,** Complex enteroenteric and enterovesical fistula. **B,** A loop of small intestine is adherent and causing significant inflammation on the wall of the bladder with subsequent fistula formation.

complications and only increases the likelihood of subsequent malabsorption. This is particularly true in Crohn's disease, in which repeat laparotomy, intestinal resection, and subsequent absorptive loss are common and could result in short-gut syndrome.

Enterovesical Fistulas

Although a colonic communication with the urinary bladder caused by diverticulitis or colon cancer is seen with some frequency, fistula formation between the small intestine and the bladder is rare. More than half of all enterovesical fistulas occur as a complication of Crohn's disease; however, radiation injury to the small bowel can also result in their formation. An ileovesical fistula develops in 2% to 4% of patients with regional enteritis, usually as a late manifestation of their disease. Such fistulas tend to be long, narrow, and tortuous (Fig. 73–7). Many seem to maintain patency only intermittently. The fistula frequently tracks downward from the ileum in the right iliac fossa. The uterus does not function as an anatomic barrier to such fistula tracts as it does with the short, localized fistulas resulting from diverticulitis or rectosigmoid cancer. Thus, enterovesical fistulas have an even distribution among the sexes.

More than 80% of patients with enterovesical fistulas have urinary symptoms such as fecaluria or pneumaturia.[65] Evidence of bladder irritability and subsequent dysuria are common. In a few patients fulminant sepsis may develop because of contamination of the urine with intestinal organisms. The presence of an internal fistula involving the urinary tract can be confirmed by the appearance of charcoal or indigo carmine in the urine after administration. Cystoscopy is helpful in establishing or confirming the diagnosis. The most consistent finding is an area of bullous edema, usually on the posterior-lateral wall or the fundus of the bladder. In some patients, the fistula opening can be directly visualized. Biopsy should be performed to evaluate for unusual causal processes such as tuberculosis or cancer.

CT is the most accurate and efficient radiographic means for diagnosing an enterovesical fistula (Fig. 73–8). Barium contrast studies of the gastrointestinal tract often do not demonstrate the fistula but are invaluable in determining the nature of the underlying disease process and assessing its extent. Intravenous pyelography and cystography are rarely useful in evaluation of the fistula itself. They may be important as a means of demonstrat-

ing bilateral renal function and evaluating abnormalities of the upper urinary tract.

In the absence of obstruction, inflammation, or abscess, the preferred treatment of an enterovesical fistula is resection of the diseased intestine and involved portion of the bladder. Removal of the fistula is particularly important to prevent continued contamination of the urinary tract. A primary anastomosis is used to restore intestinal continuity, and the bladder wall is closed. As with other fistulas, if an inflamed intestine or mass makes resection unsafe, transection plus cutaneous diversion of the proximal and distal intestinal segments is recommended.

Nephroenteric Fistulas

Fistulas between the gastrointestinal system and the upper urinary tract are rare. Primary renal disease causes most nephrogenic fistulas. As with bladder fistulas, the colon is more frequently involved than the small intestine. When a small bowel fistula is present, anatomic proximity appears to be the prime determinant of the affected segment of intestine. Therefore, the duodenum is most often involved, whereas nephrojejunal fistulas are rare.

Bissada and associates analyzed a group of 43 patients with nephroenteric fistulas identified over a period of several decades. Before 1945, fulminant infections were responsible for fistula formation in 21 of 26 patients.[66] Renal tuberculosis and bacterial infections were equally responsible, whereas obstructing renal calculous disease was a rare finding. With the advent of effective antimicrobial agents, however, tuberculosis has become a rare cause of fistulization. Bacterial infections are still an important antecedent event but are now almost always associated with secondary staghorn calculi. Since 1945, renal trauma has become the second most common cause of nephroenteric fistulas, and it accounted for 35% of the cases reported in this series. Penetrating, blunt, and iatrogenic types of trauma have all been reported to result in the formation of a fistula. Rarely, fistulas arise spontaneously from the alimentary tract, primarily in association with diverticulitis.

The symptom complex associated with a nephroenteric fistula is determined by the nature of the underlying renal disease, the rapidity with which the fistula forms, and the presence of associated conditions such as diverticulitis or perinephric abscess. Often, development of the fistula is insidious. The patient appears chronically ill and debilitated. There are invariably manifestations of a chronic urinary tract infection with chills and fever, and fulminant sepsis is not uncommon. Flank pain, tenderness to palpation, or a mass may be present. Pneumaturia, fecaluria, nausea and vomiting, and watery purulent diarrhea are frequent symptoms. Dehydration and uremia develop in the more advanced stages of the disease. Hyperchloremic acidosis may occur as urine electrolytes are reabsorbed in the gastrointestinal tract.

As with enterovesical fistulas, oral administration of charcoal or indigo carmine can confirm a suspected fistula between the intestine and the urinary tract. Barium contrast studies are usually ineffective in demonstrating nephroenteric fistulas.[66] An intravenous pyelogram can be helpful, but only if the involved kidney remains functional, which is uncommon. Invasive pyelography, both retrograde and antegrade, is sensitive in diagnosing nephroenteric fistulas, with dye often passing into the intestine, especially if the fistula is large. Retrograde pyelography combined with cinefluorography is most commonly performed. When obstruction precludes a retrograde approach, percutaneous access to the renal pelvis followed by antegrade pyelography is useful. CT remains an important radiographic adjuvant to the evaluation and management of nephrogenic fistulas by diagnosing associated perinephric abscesses and thus should always be performed.

Treatment of a nephrogenic fistula is initiated by correcting fluid and electrolyte imbalances and anemia, along with administering broad-spectrum antibiotics. Nutritional support should begin by the parenteral route to help correct further debilitation. Urinary obstruction, if present, should be relieved either by retrograde placement of a ureteral catheter or by a temporary nephrostomy tube. A perinephric abscess must be drained if present.

Medical management alone rarely results in closure of the fistula. The involved kidney is often dysfunctional or nonfunctional and thus continues to be a nidus for ongoing infection and inflammation. The affected intestine generally has extensive inflammatory changes. In most cases, therefore, nephrectomy with intestinal resection is the procedure of choice. Primary intestinal anastomosis can be carried out, depending on the severity of disease.

Procedures conserving the involved renal parenchyma are reserved for nephrogenic fistulas detected before severe renal functional impairment has occurred. Conservation is more likely to be appropriate for fistulas of traumatic origin. If the contralateral kidney has adequate function, the outcomes associated with surgical intervention are good, with perioperative mortality occurring in less than 10% of patients.

Enterovaginal Fistulas

Fistulas from the small intestine to the vagina are rare. As with colovaginal fistulas, enterovaginal fistulas are more likely to occur in women who have undergone a hysterectomy. Enterovaginal fistulas are usually caused by regional enteritis, radiation enteritis, granulomatous disease, or rarely, malignant tumors.

Most patients have a purulent or feculent vaginal discharge. Gas may also be intermittently expelled from the vagina. Associated intra-abdominal sepsis is common and may cause fever, chills, and abdominal pain. Enterovaginal fistulas can lead to hypovolemia and severe fluid and electrolyte abnormalities, particularly when the drainage is profuse. Speculum examination generally confirms the diagnosis by revealing vaginal erosion and drainage of intestinal contents. CT scanning, as well as contrast studies of the small intestine or vagina, may also be diagnostic. In more subtle cases, a suspected fistula between the intestine and the vagina may be identified by placing

a tampon in the vagina before the oral administration of charcoal or indigo carmine.

Management of an enterovaginal fistula is similar to that for an enterocutaneous fistula. Local drainage through sump drains placed through the vagina may allow adequate control of sepsis and fistula output. If sepsis is eradicated, fistula output is low, and adequate nutrition is provided, an enterovaginal fistula may close without an operation. Spontaneous closure of a fistula associated with Crohn's disease, however, is rare. Resection of a cuff of vaginal tissue along with the fistula and involved intestine is the preferred surgical approach. A primary intestinal anastomosis should be performed if the surrounding inflammation permits. The vaginal defect may be left open to allow external drainage of the pelvis postoperatively.

Enterouterine, Enterocervical, and Enterofallopian Fistulas

On rare occasion, a fistula forms between the intestine and the uterus, cervix, or fallopian tube. Enterouterine fistulas have been reported to occur secondary to various pelvic malignancies or as an unusual sequela to a long-standing ectopic pregnancy. The thick muscular wall of the uterus makes the development of such fistulas unusual. Appropriate treatment of the underlying disease together with a hysterectomy is usually indicated.

Fistulas to the cervix generally develop secondary to radiation therapy to the cervical stump and occur only when a previous supracervical hysterectomy has been performed. Fistulas from the intestine to the fallopian tube can result from endometriosis, tuberculosis, and lymphogranuloma venereum. Rarely, an ectopic pregnancy can rupture into the intestine and cause lower gastrointestinal bleeding.[67]

Aortoenteric Fistulas

The most common fistula between the arterial tree and the small intestine arises from the aorta. Complications of aortic aneurysms and their repair are by far the most frequent cause of this entity, although such fistulas have occurred after other abdominal procedures. Spontaneous or primary aortoenteric fistulas usually occur when the plaque of an atherosclerotic aortic aneurysm ruptures into the intestine. On rare occasion, mycotic, tubercular, or traumatic aneurysms may also rupture into the small bowel. The duodenum is most often involved when a spontaneous fistula develops. Reckless and associates reviewed 131 spontaneous aortoenteric fistulas and found that rupture into the third portion of the duodenum occurred in 57.6% of cases whereas the remainder of the small intestine was involved in only 8%.[68]

Secondary aortoenteric fistulas complicate 2% to 4% of all aortic reconstructions and generally involve aortoiliac or aortofemoral prosthetic grafts. The fistulas usually occur at the level of the proximal aortic anastomosis, and most rupture into the duodenum. If the fistula occurs at the anastomosis between the prosthesis and the iliac arteries, the ileum is the most commonly involved segment of intestine.

Two processes can cause secondary aortoenteric fistulas and result in different clinical manifestations. A direct communication between the intestine and the arterial lumen ultimately leads to massive gastrointestinal hemorrhage. Initially, bleeding is intermittent and is rarely exsanguinating. Such episodic bleeding, known as *herald* or *sentinel* bleeding, is generally painless and may cause chronic anemia. Melena or hematemesis in any patient with an aortic prosthesis should be assumed to be from an aortoenteric fistula until proved otherwise. Several months may elapse between the initial bleeding episode and the inevitable massive hemorrhage. The second form of secondary fistula is known as a *paraprosthetic-enteric* fistula. In this type of aortoenteric fistula, the intestine communicates with a perigraft abscess or aneurysm and not directly with the arterial lumen. Most of these patients have manifestations of sepsis. In a group of 21 patients with such fistulas, O'Mara and Imbembo noted 14 with sepsis, 4 with gastrointestinal hemorrhage, and 3 with abdominal pain.[69] Although a distinct clinical entity, a paraprosthetic fistula ultimately leads to a direct communication with the arterial lumen and subsequent hemorrhage if untreated.

The mechanism by which aortoenteric fistulas develop is controversial. A combination of mechanical and infectious factors probably contributes in most instances. Mechanical injury to the intestine can occur from the trauma of the adjacent arterial pulsation. This is more apt to transpire when the intestine has become fixed to the area of anastomosis, which may be avoided by separating the intestine from the aorta with interposed omentum or surrounding tissues. After the intestine has been sufficiently traumatized, leakage of intestinal contents occurs, with subsequent infection and enzymatic digestion at the suture line. The localized septic process ultimately leads to suture line disruption. Other methods of fistula formation have been hypothesized, including aneurysmal degeneration of the graft with subsequent mechanical erosion into the intestinal wall. Occasionally, a false aneurysm develops at the suture line and ultimately ruptures into the intestine. False aneurysms are usually a consequence of technical errors during the graft anastomosis, but they can also result from infected grafts.

Although the presence of an aortoenteric fistula may be suspected clinically, extensive evaluation and confirmation may not be possible if severe hemorrhage is present. In such instances, immediate laparotomy and proximal control of the aorta are priorities. Fortunately, most aortoenteric fistulas are associated with multiple episodes of limited gastrointestinal bleeding. These patients should be prepared for an urgent operation, but there is generally enough time to perform further diagnostic investigation. Upper gastrointestinal endoscopy should be performed initially to exclude common causes of hemorrhage, such as peptic ulcer disease or esophageal varices. The actual erosion into the intestinal wall can often be seen if the endoscopist is instructed to examine the distal end of the duodenum. Biopsy of such an erosion is absolutely contraindicated. CT is sensitive in evaluating the retroperitoneum for suspected aortoenteric fistulas. CT has the advantages of rapid imaging

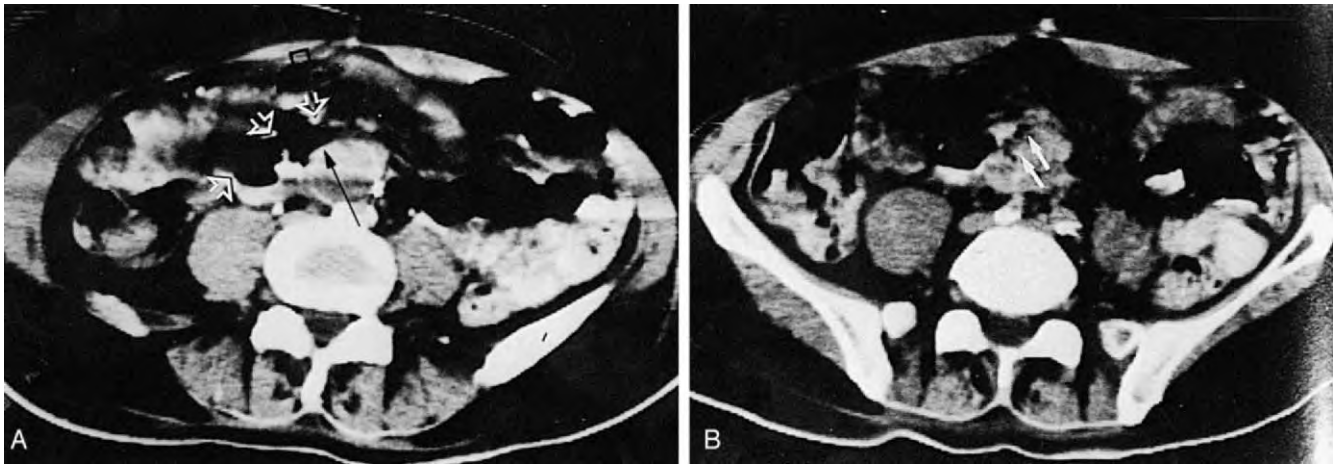

Figure 73–9. Computed tomographic scan of aortoenteric erosion. **A,** Apparent erosion of an aortic graft *(black arrow)* into the overlying duodenum *(open arrows).* **B,** Perigraft air *(arrows).* (From Bernhard VM: Aortoenteric fistulas. In Rutherford RB [ed]: Vascular Surgery. Philadelphia, WB Saunders, 1989, p 530.)

and wide availability (Fig. 73–9). Because it is a noninvasive study, CT does not require technical expertise and does not cause patient discomfort, thereby avoiding the potentially disastrous consequences of raising the patient's blood pressure. CT may demonstrate loss of the normal fatty plane between the aortic graft and the duodenum, a finding indicative of a probable fistula. It may also reveal a false aneurysm at the anastomosis or the presence of a periaortic gas or fluid collection.

When the diagnosis remains elusive, aortography should be performed. Aortography is particularly useful if there is active hemorrhage or if a false aneurysm is suspected. Extravasation of contrast material into the intestine or retroperitoneum confirms the diagnosis. If endoscopy, CT, and aortography fail to find the suspected fistula, upper and lower gastrointestinal barium contrast studies can be performed. Barium evaluation should be postponed until after endoscopy, CT, and aortography, however, because residual barium decreases the sensitivity of these procedures. Barium studies may demonstrate a sinus tract from the intestine. The presence of an intestinal diverticulum or ulcer may result in a false-negative evaluation. If the patient is febrile or a perigraft infection is suspected, blood for culture should be drawn from both upper and lower extremity veins. Positive blood cultures, particularly if limited to the lower extremities, are predictive of a poor clinical outcome.[70]

Management of an aortoenteric fistula, once confirmed, consists of early and aggressive operative intervention. Removal of the prosthesis and extra-anatomic bypass should be coupled with broad-spectrum antibiotics appropriate for the multiple enteric organisms usually present. Conventional wisdom holds that the presence of infection at the prosthetic site precludes less involved procedures such as local closure of the fistula or replacement of the prosthesis. In a series reported by O'Mara and associates, a recurrent aortoenteric fistula developed in all four of the patients treated by initial repair of the fistula, but without extra-anatomic bypass.[71] By contrast, five of the seven patients who had the prosthesis removed, followed by an axillobifemoral bypass, lived and did well. However, there have been successful reports of in situ repair of the aorta with prosthetic grafts or cryopreserved aortic homografts. Walker and colleagues reported excellent overall results with in situ replacement of the abdominal graft and primary closure of the duodenal fistula in 20 patients. Of the 18 survivors, 15 had no further complications.[72] Vogt and associates reported a similar low operative mortality rate and no complications of reinfection when in situ cryopreserved aortic homografts were used to replace the infected aortic prosthesis.[73] The intestinal defect can be débrided and primarily closed in most cases, but bowel resection and end-to-end anastomosis may be necessary or technically easier in some patients.

The survival rate in patients with aortoenteric fistulas is poor, often because of exsanguinating hemorrhage or associated cardiovascular or renal impairment. The mortality rate has been reported to be as high as 50%. A multicenter retrospective study of 98 patients found an improved mortality rate of 24% in patients with aortoenteric fistula or infection treated by axillobifemoral bypass and aortic exclusion. Bypass patency rates at 2 and 5 years were reported to be 82% and 65%, respectively, and limb salvage was achieved in 90% and 82% of patients, respectively, over the same time course.[74]

General Considerations

When planning the operation for fistula patients, the surgeon should allow adequate time for a difficult and prolonged procedure. Depending on the complexity of the abdominal wound, component release and other reconstructive maneuvers may be required to achieve closure of the abdominal wall. It is frequently helpful to enlist the expertise of a plastic surgeon for closure of the abdominal wound (Fig. 73–10A). The component separation release technique is useful for the reconstruction

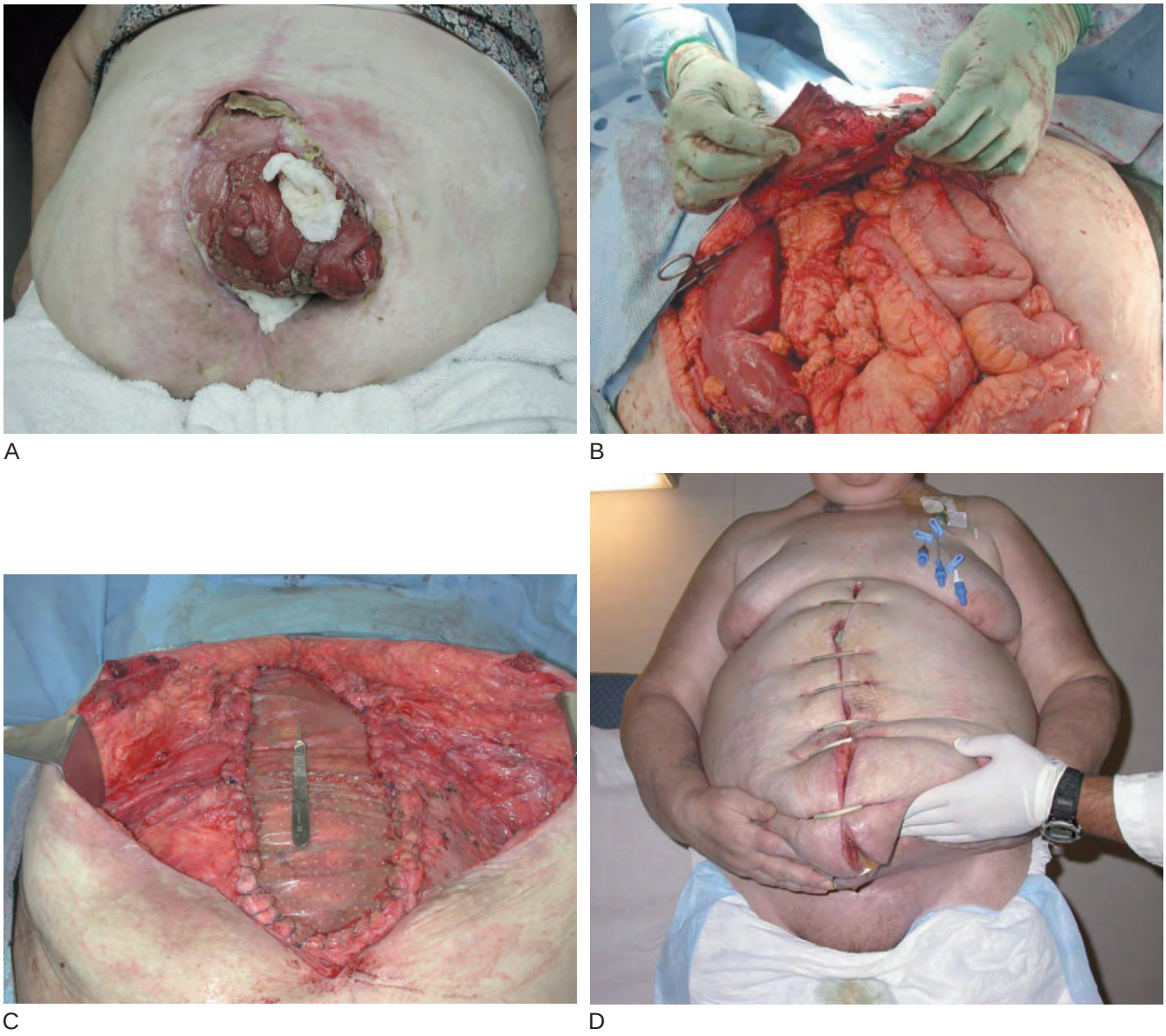

Figure 73–10. **A,** Enterocutaneous fistula with epithelialization of the tract and a large abdominal wall defect. **B,** The entire intestinal tract has been mobilized and complete enterolysis performed. **C,** The large abdominal wall defect is closed with a combination of abdominal wall and small intestinal submucosa (Surgisis Gold). **D,** Completed resection of the fistula and abdominal wall closure with loose closure of the skin and the use of retention sutures.

of large abdominal wall defects, especially when contaminated conditions exist in which the use of prosthetic material may be contraindicated. Thus, preoperative consultation and evaluation by the plastic and reconstructive surgery team should be considered. Preoperative preparation should include a mechanical bowel preparation whenever feasible, preoperative abdominal wall preparation with antiseptic (e.g., chlorhexidine) scrubs beginning at least 24 hours in advance, and perioperative antibiotics directed toward bowel and skin flora, as well as any specific organisms identified by recent culture and sensitivity information.

Whenever possible, a new incision or extension of the previous incision over "virgin" abdominal wall will make reentry into the abdominal cavity easier and safer. Once the peritoneal cavity is entered, the entire intestinal tract should be mobilized, and complete enterolysis should be performed if possible, especially is there is any question of distal obstruction (see Fig. 73–10B). A useful adjunct during this portion of the operation is to use laparotomy pads soaked in saline solution to "rehydrate" the adhesions before attempting adhesiolysis. By using a combination of gentle compression and palpation with one hand and sharp dissection with either scissors or a scalpel in conjunction with the use of copious amounts of saline-soaked sponges, one can usually carry out complete mobilization of the involved intestine. In general, an intestinal fistula cannot be repaired primarily; such repair usually

results in recurrence. Fistulas require complete resection back to healthy tissue with enteroenterostomy. If the anastomosis is performed on healthy bowel, the choice between a stapled or hand-sewn anastomosis does not matter. More importantly, the anastomosis should be under no tension, there must be adequate blood supply, and distal obstruction cannot be present. A feeding jejunostomy or nasoentric tube should be placed. Ongoing nutritional repletion is an extremely important constituent of a successful outcome, and most patients will not be able to take enough calories by mouth during the postoperative recovery period. A gastrostomy tube may also be a useful adjunct in the postoperative period. Depending on the state of the intestinal tract, the extent of enterolysis required, and the underlying process that led to fistula formation, prolonged postoperative ileus will commonly occur, and decompression via a gastrostomy tube, while downstream enteral nutrition is given, may be very beneficial. Because of the usual extensive nature of the dissection during such operations, the formation of intra-abdominal adhesions is likely. Methods for decreasing intra-abdominal adhesions, such as the use of hyaluronic acid–carboxymethylcellulose membrane (Seprafilm), may be beneficial in preventing postoperative complications.[75] Finally, abdominal wall closure is extremely important to allow the best chance for success and to prevent recurrent fistulization. It is essential that the abdominal wall be closed with autologous tissue (using component separation or musculocutaneous flaps) or an absorbable prosthesis consisting of either small intestinal submucosa (Surgisis Gold) (see Fig. 73–10C) or dermis (AlloDerm) or with a permanent prosthesis that is resistant to infection such as titanium mesh (TiMesh). Assistance by surgeons with specific skills in abdominal reconstruction (plastic and reconstructive surgery) is often quite helpful in these situations, and their advice and consultation should be readily sought (see Fig. 73–10D).

Healing

Most postoperative fistula patients are in a profoundly catabolic state in the early postoperative period and are at risk for nutritional complications. Again, optimal nutrition is as important postoperatively as preoperatively. Supplemental nutrition via enteral, parenteral, or a combination is frequently required, and with time, the patient can be transitioned to complete intake by mouth. Even when a patient cannot tolerate full caloric intake via the enteral route, providing a portion of the nutrition enterally remains an important objective. It may be useful to cycle tube feeding at night once the patient is eating in an attempt to stimulate appetite. Meals from home also occasionally help with appetite stimulation. A dietitian consultation can be very helpful as well. A period of home tube feeding or, if necessary, home parenteral nutrition is not unreasonable in these patients because re-establishing normal eating habits may be a long process. The final phase of the treatment of fistulas, then, is healing, and this phase is highly dependent on good nutrition after a well-performed operation. If the patient cannot tolerate at least 1500 kcal/day enterally, parenteral nutrition should be continued until this goal is achieved. Once enteral intake approaches this range, the parenteral nutrition can be weaned.

The overall mortality rate if one includes all fistulas is approximately 20%. Mortality with a postoperative fistula is not as high. Postoperative fistulas are associated with less than 2% mortality and approximately 12% morbidity. Delayed complications may include short-bowel syndrome, depending on the extent of the intestinal resection, previous resections, and the underlying disease state (i.e., Crohn's disease). In patients with a marginal amount of bowel remaining, some intestinal adaptation may occur, and with time, weaning of parenteral nutrition may be possible. As a general guide, approximately 90 cm of small intestine with an intact ileocecal valve may be adequate to prevent short-bowel syndrome, whereas 150 cm may be necessary when the ileocecal valve has been resected. The surgeon must be vigilant for recurrent fistulas postoperatively. These patients are also highly susceptible to adhesive small bowel obstruction. It is generally prudent to manage early postoperative small bowel obstruction in these patients with long-tube decompression and TPN rather than risk further complications with another operation in the early postoperative period.

SUMMARY

Management of intestinal fistulas provides a surgeon with multiple challenges. Careful attention must be paid to the physiologic, metabolic, and immunologic derangements in these patients. An organized and tolerant approach to the stabilization, investigation, planning and implementation of medical and surgical therapy, and healing phase should allow for a successful outcome in the majority of patients.

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Chapter

74

Internal Hernias—Congenital and Acquired

Mohammad K. Jamal · Eric J. DeMaria

Small bowel obstruction (SBO) is a common surgical emergency that accounts for nearly 20% of acute surgical admissions and often requires definitive operative treatment. The diagnosis of SBO is relatively straightforward in most instances and is based on a history of nausea, vomiting, and abdominal pain. Physical examination in most cases reveals vital signs suggestive of hypovolemia and a distended abdomen with high-pitched bowel sounds. The diagnosis of SBO is confirmed with plain radiographic films and in some instances computed tomography (CT) scans of the abdomen, which typically show air- and fluid-filled distended small bowel loops with or without a transition zone—denoting a complete or partial bowel obstruction.

Initial treatment of SBO involves nasogastric tube decompression, aggressive replacement of fluids, and correction of electrolyte imbalance. Surgical exploration should not be delayed because bowel incarceration or strangulation can occur. Strangulated obstructions are surgical emergencies and, if not diagnosed and properly treated, lead to vascular compromise resulting in bowel ischemia and further morbidity and mortality. Because as many as 40% of patients have strangulated obstructions, differentiating the characteristics and causes of obstruction is critical to proper patient treatment. The leading causes of SBO include adhesive disease (50% to 75%), malignancies (20%), abdominal wall hernias (10%), and inflammatory bowel disease (10%).

Internal hernias, either congenital or acquired, account for a small percentage of SBO cases (0.6% to 5.8%).[1-5] This condition involves herniation of a viscus, usually small bowel, through a normal or abnormal aperture within the peritoneal cavity. This herniation may be intermittent or persistent and may pose a diagnostic challenge given the rare nature of its occurrence. Only rarely is an internal hernia accurately diagnosed preoperatively. Because of the risk for strangulation of the hernia contents, even small internal hernias are dangerous and may be lethal. However, as a result of their rarity, discovery of an internal hernia at laparotomy may be confusing to an unsuspecting surgeon who is not familiar with this abnormality, and thus appropriate management may be compromised.

CONGENITAL INTERNAL HERNIAS

Congenital internal hernias are the result of malformation of the peritoneum and, in some instances, malrotation of the midgut during the embryonic period. A paraduodenal hernia (PDH) is the most common variety of congenital internal hernia, followed by the transmesenteric and transomental varieties. Others, including Foramen of Winslow and paracecal hernias, are extremely rare and are briefly discussed at the end of the section.

Paraduodenal Hernia

Also known as a paramesocolic hernia, PDH accounts for nearly 53% of the 500 published series of all internal hernias and was first described by Neubaur in 1786.[6-10] One hundred years later, Treitz and Waldeyer additionally described *hernia retroperitonealis*—several peritoneal folds and fossae through which small bowel could potentially herniate. The pathogenesis of PDH is controversial, but two theories regarding its origin appear to be most popular.[11] In a report by Moynihan in 1889, it was proposed that paraduodenal fossae were congenital and the hernia was acquired by gradual enlargement of an existing fossa. In 1923, Andrews disputed this theory and proposed that PDH forms as a result of a congenital anomaly in development of the peritoneum that arises during midgut rotation. As a consequence, small bowel becomes invaginated into an avascular, and therefore unsupported, segment of the left mesocolon. The resulting small bowel thus becomes trapped between the posterior abdominal wall, with the mesocolon and inferior

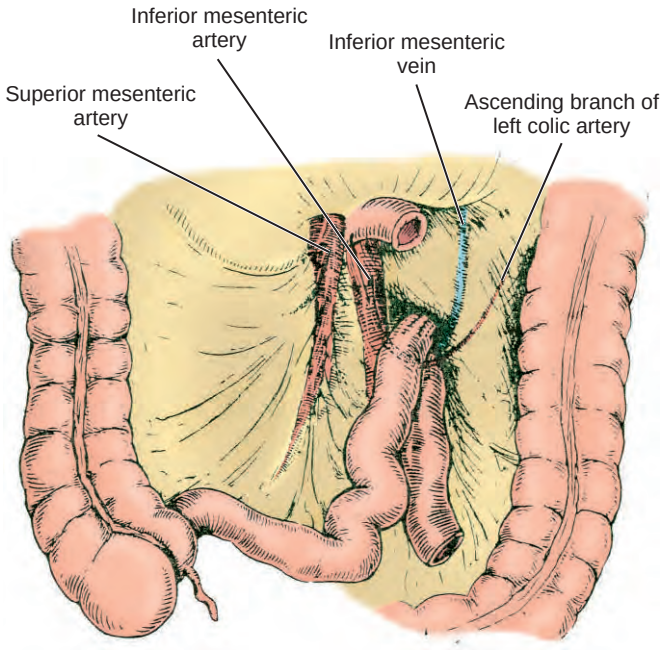

Figure 74–1. Left paraduodenal hernia. The opening of the hernia sac lies above the ascending branch of the left colic artery and the inferior mesenteric vein. The sac lies behind the left mesocolon. (From Newsom BD, Kukora JS: Congenital and acquired internal hernias: Unusual causes of small bowel obstruction. Am J Surg 152:279-285, 1986.)

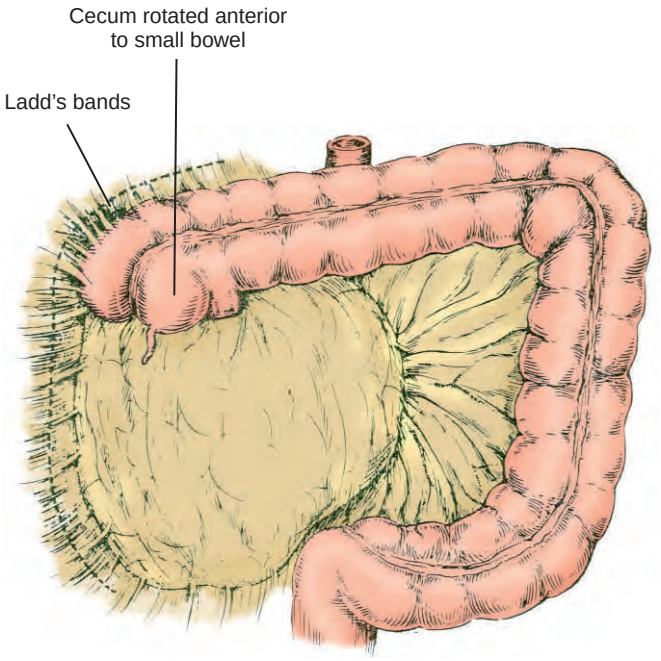

Figure 74–2. Right paraduodenal hernia. This hernia is caused by failure of the small bowel to rotate to the left with the right colon continuing to rotate anterior to it. This results in trapping of the small bowel behind the right mesocolon when fusion with the retroperitoneum occurs. The *dotted line* represents the plane opened to mobilize the right colon and reduce the hernia. (From Newsom BD, Kukora JS: Congenital and acquired internal hernias: Unusual causes of small bowel obstruction. Am J Surg 152:279-285, 1986.)

mesenteric vein (IMV) forming the anterior wall of the hernia sac.

Of the published cases of PDH, nearly 75% were left sided with a male-to-female ratio of 3:1.[11] The average age at diagnosis is reported to be between the third and fourth decades of life. A left PDH contains most of the small bowel, with the afferent limb being the fourth part of the duodenum and the efferent limb being the terminal ileum (Fig. 74–1). The small bowel invaginates into the fossa of Landzert, which lies to the left of the fourth portion of the duodenum. After formation of the hernia, the colon usually retains its normal position. Several other possibilities exist—the colon can undergo malrotation, the left colon can lie on the right side of the hernia, or if it is on a long mesentery, there is the potential for colonic volvulus.[12-14]

A right PDH similarly originates from abnormalities arising during the second phase of embryonic intestinal rotation; it results in arrest of further rotation of the pre-arterial segment of the gut in the right side of the abdomen (Fig. 74–2). Continued rotation of the postarterial segment leads to entrapment of small bowel behind the right colonic mesentery, with the superior mesenteric artery forming the anterior edge of the hernia sac.[15]

Clinical Findings

PDH may be asymptomatic and be discovered incidentally at laparotomy, at autopsy, or during radiologic studies for other unrelated causes.[11,16,17] More commonly, PDH is manifested as acute SBO on a background of recurrent chronic, vague abdominal pain. The abdominal pain associated with a left PDH is typically left sided but can be variable in location and sometimes even right sided.[18] The pain is often exacerbated by eating and postural changes and relieved by lying supine. It is postulated that the pain arises from recurrent incarceration of the hernia contents and is relieved by spontaneous reduction of the hernia.[5] Weight loss is variable and may be severe if symptoms are present for a long time. In its most malignant form, PDH may be associated with bowel strangulation with a resultant increase in death. On occasion, a tender left-sided abdominal mass may be palpable during an acute episode.

Diagnosis

The diagnosis of PDH generally requires a high index of suspicion and is usually made by upper gastrointestinal barium contrast study. The small bowel is found clustered to the left of the midline with a well-circumscribed edge that corresponds to the hernia sac.[5,11,19-21] Passage of contrast may be delayed with a change in position of the patient. There is usually a mass effect causing

displacement of the posterior wall of the stomach, duodenojejunal flexure, and transverse colon. In some instances, a CT scan may detect a PDH by showing a similar clustering of small bowel loops in the retroperitoneum.[8,22] Upward displacement of the IMV by the hernia contents may also be noted on intravenously enhanced CT scans or arteriography.[5,22] A barium enema may be performed in stable patients to rule out colonic malrotation.

However, all radiologic studies may be normal, especially in chronic intermittent cases because the hernia may reduce spontaneously. These investigations are most often diagnostic during an acute episode. In a literature review of nearly 32 cases reported by Tong and colleagues,[22] a preoperative diagnosis through either small bowel follow-through or CT scan was made in 23 (72%) of the 32 patients, but 14 (61%) had an acute manifestation. Given the rarity of symptoms, an incidental diagnosis of PDH is relatively infrequent and usually made at the time of abdominal exploration.

Treatment

The lifetime risk for bowel incarceration associated with PDH is around 50%. Incarceration can result in increased morbidity and mortality, and therefore these hernias should be treated if found incidentally.[11,15,20,23] Treatment of PDH follows the basic principles of hernia surgery—reduction of the contents, resection of the hernia sac, restoration of normal bowel anatomy, and repair of the hernia defect. Initial exploration of the abdomen will often reveal the classic empty abdomen sign, with only a segment of the ileum present in the abdominal cavity and the remainder encased in the hernia sac to the left of the midline. The small bowel may be manually reduced if the hernia orifice is large enough and the defect can be closed with nonabsorbable suture.[11,23] If the small bowel is edematous, the hernia orifice is tight, or adhesions within the sac prevent manual reduction of the contents, the hernia orifice can be widened by excising the avascular plane to the right of the IMV. Care should be taken to avoid damage to this structure and the left colic artery, both of which lie in close proximity to the anterior edge of the orifice.[24]

If the hernia orifice cannot be widened, the sac should be opened along the anterior wall and the contents reduced. A decompressive enterotomy is sometimes beneficial to evacuate the contents of the incarcerated bowel, thus allowing easy reduction. The sac should then be excised from the left of the IMV toward the left colon while taking care to preserve the marginal artery of Drummond. In cases of obvious bowel strangulation, the appropriate length of small bowel should be resected and a decision made regarding reanastomosis or creation of an end ostomy, depending on the hemodynamic stability of the patient and the overall condition of the involved bowel segments.

More recently, several authors have reported laparoscopic repair of both right and left PDH.[19,25,26] However, the role of laparoscopy in the diagnosis and treatment of PDH is relatively recent, and to date, experience with this modality is limited.

Transmesenteric Hernia

A transmesenteric hernia (TMH) is an intraperitoneal hernia that may be either congenital or acquired. As the name suggests, TMH consists of protrusion of a loop of bowel through an aperture in the mesentery (Fig. 74–3). It accounts for nearly 5% to 10% of all cases of congenital internal hernia and occurs more commonly in the pediatric age group. When found in children, TMH is often associated with intestinal atresia or mesenteric ischemia and occurs near the ligament of Treitz or the ileocecal valve.[15,27] In contrast, most TMHs in adults are related to predisposing factors, including previous surgery, abdominal trauma, and peritonitis. A common type of TMH occurs after an iatrogenically created mesenteric defect, such as after gastrectomy or Roux-en-Y gastric bypass (RYGBP). These hernias are discussed in more detail in the section on acquired internal hernias.

TMH was first reported by Rokitansky in 1836 as an autopsy finding in which the cecum alone herniated through a hole near the ileocolic angle. Several others, including Loebl in 1844 and then Turel in 1932, described variations of TMH through the transverse mesocolon and sigmoid colon, respectively.[28] Several etiologic hypotheses for the occurrence of idiopathic mesenteric defects causing TMH have been proposed in the surgical literature, three of which have gained relative acceptance. Federschmidt in 1920 stated that these defects represented partial regression of the dorsal mesentery in humans. Menegaux, on the other hand, postulated the presence of fenestrations during developmental enlargement of an inadequately vascularized

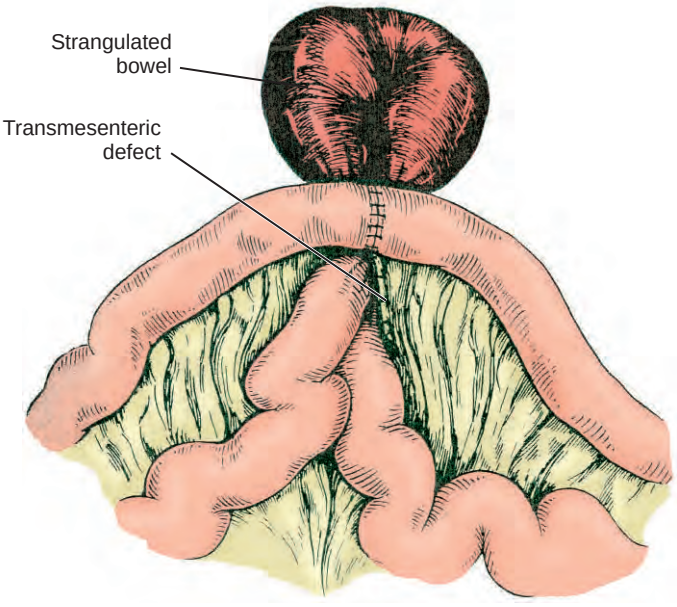

Figure 74–3. Transmesenteric hernia caused by herniation of a loop of small bowel through an unclosed mesenteric defect after small bowel resection. (From Newsom BD, Kukora JS: Congenital and acquired internal hernias: Unusual causes of small bowel obstruction. Am J Surg 152:279-285, 1986.)

area as a cause of TMH. Judd, Kiebel, and Mall believed that because the greater part of the gut is displaced from the abdominal cavity into the umbilical cord in fetal life, considerable pressure might displace the colon along the path of least resistance and gradually force it through the delicate mesentery. Another theory by Macklin assumes that when two epithelial layers are apposed with a deficient intervening supportive stroma of connective tissue, coalescence inevitably takes place, with development of a space or defect.

There is no sex and age predominance in the occurrence of TMH. In a collective review by Janin et al., nearly 70% of reported TMHs occurred through defects in the small bowel mesentery.[28] Ileocecal defects accounted for 53% of these and 37% of the entire group of TMHs. These ileocolic defects are typically circular or oval, lie in the area of the mesentery between the ileocolic artery and the last ileal branch of the superior mesenteric artery, and range in size from 2 to 3 cm. Transverse mesocolic defects, on the other hand, are bound by the vascular arch formed by the middle and left colic arteries, whereas defects of the sigmoid mesocolon are usually circular and lie immediately above the superior rectal vessels.

Clinical Findings

The clinical manifestations of TMH are similar to those of any other case of SBO—crampy abdominal pain, nausea, vomiting, and abdominal distention. These patients most frequently have right-sided abdominal tenderness but, occasionally, diffuse pain accompanied by various degrees of abdominal distention is noted. Patients typically appear to be severely ill and may rapidly progress to a shock-like state concurrent with mesenteric ischemia and bowel necrosis. A palpable abdominal mass is sometimes present, usually sausage shaped and tympanitic, and a localized succession splash may be elicited over it.

Because most mesenteric defects are small and there is no limiting hernia sac, a large portion of the small bowel can herniate through a tight opening. The resulting pressure of the herniated bowel and its thickened mesentery compresses the vessels in the free margins of the mesenteric defect and results in early incarceration and strangulation of the loop forming the margin of the defect. This may explain why the latter may be found to be gangrenous whereas the herniated bowel may not even be strangulated. Furthermore, the herniated segment of bowel or a redundant sigmoid can freely undergo volvulus, a condition more commonly seen in TMH than in other types of internal hernias.

Diagnosis

TMHs are more difficult to diagnose than other internal hernias. Based on a history of bowel obstruction, a CT scan may show a cluster of small bowel loops, SBO, and central or posterior displacement of the colon. Mesenteric vessels may be stretched, crowded, and engorged and have a *whorl sign*. Furthermore, the major mesenteric trunk may be displaced by herniated small bowel loops. Signs of volvulus or mesenteric ischemia, including bowel wall thickening, twisting of the mesenteric vessels (the whorl sign), engorged blood vessels, and mesenteric ascites, may be the predominant CT findings and denote a delayed diagnosis.[29,30] In patients with acquired TMH after gastrectomy or RYGBP, a retro-anastomotic TMH can be detected on CT scan as an abnormal position of an efferent loop of the gastrojejunostomy, an obstructed afferent or efferent loop (or both), or clumped and fixed jejunal loops in the left upper portion of the abdomen. Rarely, small bowel herniation occurs through a peritoneal defect in the pouch of Douglas as a result of previous hysterectomy.[29]

Treatment

Nasogastric decompression, aggressive preoperative fluid replacement, and correction of electrolyte disturbances are essential before surgical exploration. Laparotomy is mandated in all cases of TMH given the high incidence of incarceration and strangulation. Treatment is dependent on viability of the bowel—if the herniated loops are gangrenous, resection is mandatory, with or without primary anastomosis. If the bowel is viable, reduction of the incarcerated loops plus repair of the defect with interrupted nonabsorbable suture is recommended. Furthermore, if a mesenteric defect is discovered during laparotomy for an unrelated cause, it is imperative that it be closed with a similar technique.

Transomental Hernia

Transomental hernias typically represent less than 5% of all internal hernias. Only a handful of cases have been reported in the surgical literature.[15] As the name suggests, internal herniation of a viscus, typically small bowel, occurs through an opening in the gastrocolic omentum (Fig. 74–4). The actual cause of the omental rent is unknown, but inflammatory, traumatic, circulatory, and congenital mechanisms have all been implicated. A variant of this hernia, the *internal double omental hernia,* has been reported by some authors and denotes herniation of the small bowel through an opening in the gastrocolic omentum and exit through the gastrohepatic omentum.[31,32]

Management consists of simply releasing the constricting ring of omentum, which typically tends to be stiff and fibrous, and resecting or reducing the bowel, depending on its viability.[33,34]

Miscellaneous Congenital Internal Hernias

Foramen of Winslow hernias are rarely encountered. Only 117 cases have been reported in the world literature through 1977[35] (Fig. 74–5). In cases reported since 1966, the cecum was the most commonly herniated viscus, followed by the small bowel.[36] Preoperative diagnosis of a Foramen of Winslow hernia is generally established in less than 10% of cases. In some instances, an epigastric mass and radiographic evidence of a retrogastric mass containing air are suggestive of this entity.[9] Management involves manual reduction of the hernia

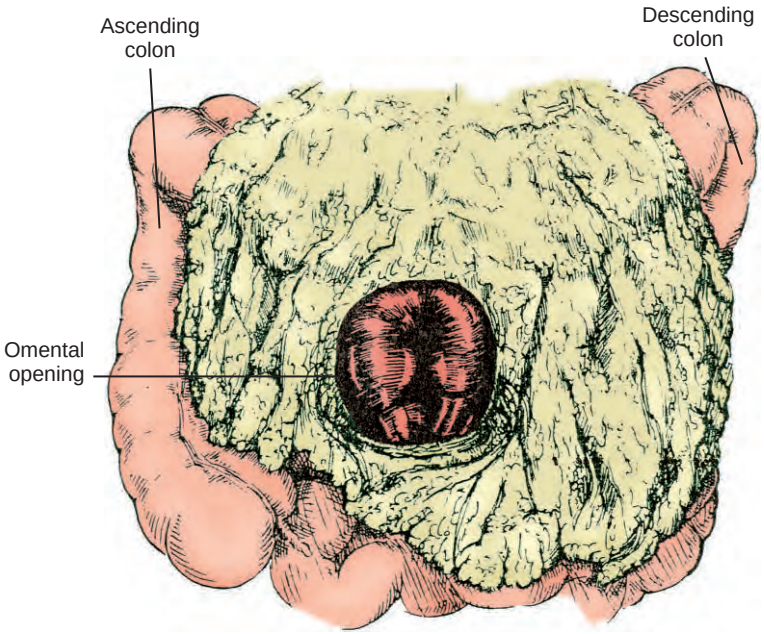

Figure 74–4. Transomental hernia with strangulation of a loop of bowel through the transomental hernia defect. Management consists of simply cutting the constricting ring around the bowel and resection of involved bowel. (From Newsom BD, Kukora JS: Congenital and acquired internal hernias: Unusual causes of small bowel obstruction. Am J Surg 152:279-285, 1986.)

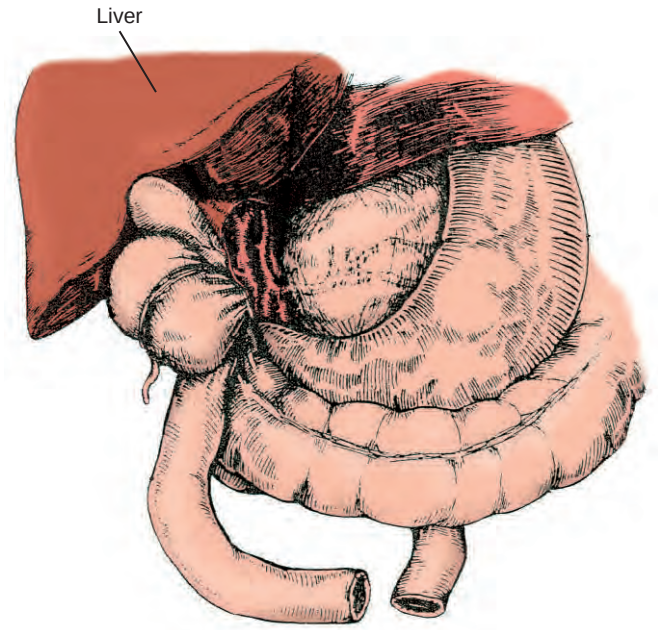

Figure 74–5. Foramen of Winslow hernia. The mobile right colon has been shown to be incarcerated through the opening into the lesser sac. The neck of the sac contains vital structures that must be preserved when repairing these hernias. (From Newsom BD, Kukora JS: Congenital and acquired internal hernias: Unusual causes of small bowel obstruction. Am J Surg 152:279-285, 1986.)

contents, which sometimes requires opening of the lesser sac for counterpressure or decompressive enterotomy. A wide Kocher maneuver may at times be necessary to enlarge the hernia opening. Attempts at closure of the opening are not generally recommended, although fixation of a mobile cecum is advised.[35,37-39]

Paracecal hernias, as well as herniation into fossae of the sigmoid mesentery, account for a small percentage of internal hernias. Others, including herniation through fossae or defects in the broad ligament and foramina in the falciform ligament, are extremely rare varieties of internal hernia.[40-43]

ACQUIRED INTERNAL HERNIAS

Acquired internal hernia (AIH) refers to herniation of a viscus, most commonly small intestine, through iatrogenically created defects in the peritoneum after major abdominal surgery, including Roux-en-Y reconstructions after gastrectomy, gastric bypass, esophageal replacement, and pancreatic and hepatobiliary surgery. With the recent increase in the number of certain bariatric surgical procedures performed in the United States, especially RYGBP, the incidence of AIH has risen in recent years. Therefore, herniation after gastric bypass will be discussed in this section as a representative AIH.

Nearly 150,000 bariatric surgical procedures are performed in the United States each year, the majority of which involve RYGBP. With the advent of minimally invasive techniques, the associated morbidity with this relatively high-risk procedure has decreased somewhat. When compared with the open procedure, there has been a reduction in incision-related complications such as wound infections and incisional hernias after laparoscopic gastric bypass; other complications, including the risk for anastomotic leak and SBO, have remained essentially unchanged or have increased in certain series. SBO is a known complication of gastric bypass surgery, with an incidence varying anywhere from 1.3% to 5% in several series of experienced bariatric surgeons using the open technique.[44-48] The incidence of bowel obstruction

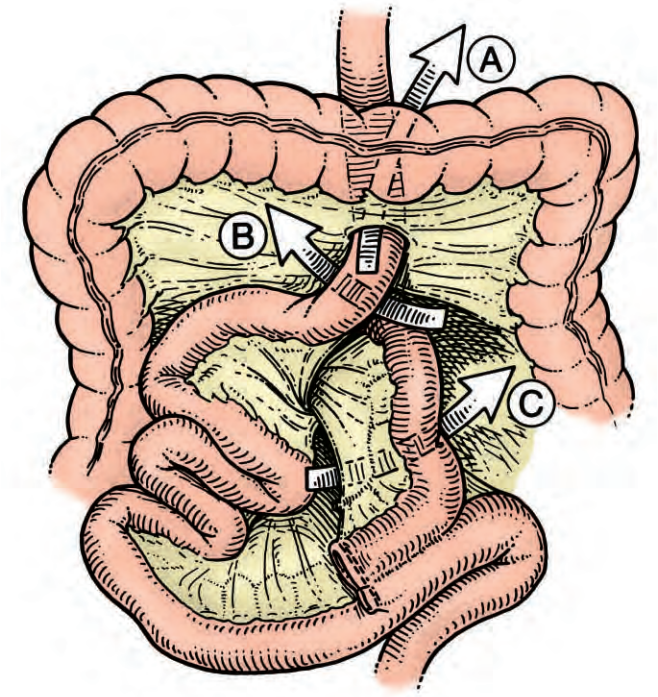

Figure 74–6. Internal hernia after a retrocolic Roux-en-Y gastric bypass. Potential sites of internal herniation of small bowel include the mesocolic mesenteric defect (A), the Petersen defect (B), and the jejunojejunostomy mesenteric defect (C). (From Schweitzer MA, DeMaria EJ, Broderick TH, Sugerman HJ: Laparoscopic closure of mesenteric defects after Roux-en-Y gastric bypass. J Laparoendosc Adv Surg Tech A 10:173-175, 2000.)

appears to be similar in earlier series of laparoscopic gastric bypass—anywhere from 1.5% to 3.5%, with most obstructions caused by internal hernias.[49,50] Other unrelated causes of SBO in gastric bypass patients include adhesions, incarcerated ventral hernias, and rarely, intussusception of the jejunojejunostomy.

The technique of laparoscopic gastric bypass has not been standardized, and there are several variations in the technique. The laparoscopic approach may involve the use of a circular stapler, linear stapler, or a hand-sewn technique for the two anastomoses; the Roux limb may be placed in antecolic or retrocolic fashion, with or without closure of the mesenteric defect; the enterotomies may be closed by suture or staples; and finally, the trocar sites may or may not be closed. It is closure of the several different mesenteric defects that may prevent internal herniation of small bowel in these patients. Internal herniation in gastric bypass patients can occur through any of the two mesenteric defects when an antecolic approach is used and through any of the three defects when a retrocolic approach is used. These potential hernia defects occur at the jejunojejunostomy, the mesocolic window, and Petersen's space (Fig. 74–6).

An enteroenterostomy mesenteric defect is created as a standard step in essentially all variations of gastric bypass, and in our practice, it is closed with a running absorbable suture. If an antecolic approach is used, an opening is created in the gastrocolic omentum, and the Roux limb is brought over in an antecolic and antegastric fashion. If the greater omentum is especially thin, the Roux limb can be passed anterior to it without a window. In the retrocolic approach, a window is created in the transverse mesocolon, and the Roux limb is brought through the lesser sac in retrogastric fashion to the transected pouch. Mesenteric defects are again routinely closed in our practice with running absorbable suture, beginning at the medial edge of the mesocolic window and running superiorly over the Roux limb, with incorporation of the bowel serosa and closure of the base of the Petersen defect.

The debate between proponents of antecolic and retrocolic gastric bypass continues among bariatric surgeons. Several authors have reported a higher incidence of internal hernia after laparoscopic RYGBP—this difference is probably explained by the absence of adhesion formation after a minimally invasive approach.[51-53] In the series reported by Champion and Williams, the incidence of SBO from all causes was 4.5% in the retrocolic group and 0.43% in the antecolic group.[51] Seventy-one percent of the obstructions in this group of 711 patients were caused by internal hernias. Furthermore, the incidence of bowel obstruction in the group with sutured mesenteric defects was slightly lower (4.1%) than in those with an unsutured mesenteric defect (4.5%). In another report by Higa et al., the incidence of SBO from an internal hernia was 3.1% in a group of 63 patients undergoing retrocolic RYGBP.[52] The site of internal hernias varied—they occurred at the mesocolon (70%), jejunal mesentery (22%), and Petersen's space (8%) in that order. Although most patients were symptomatic, 5% of internal hernias were incidental findings at the time of another surgical procedure.

Clinical Findings

The diagnosis of AIH is difficult, and radiologic evaluation is often nondiagnostic. The presence of colicky, postprandial left upper quadrant abdominal pain after gastric bypass should raise suspicion of an obstruction. The location of the abdominal pain generally correlates with the side of internal herniation, with left upper quadrant pain occurring when the small bowel herniates through the defect to the patient's left side and right upper quadrant pain typically being seen when the small bowel herniates to the right side of the defect. Other symptoms may include nausea, emesis, and abdominal distention. Although similar symptoms may be seen in other pathologic conditions, including a marginal ulcer or SBO from other causes, persistence of such symptoms, even in the absence of radiologic findings, generally mandates exploration.

Diagnosis

Patients with acute intermittent abdominal pain should be evaluated initially with plain films. An obstructed bowel gas pattern with air-fluid levels is sometimes

enough evidence of an internal hernia that urgent exploration is required. Others with vague abdominal pain can be investigated with contrast-enhanced upper gastrointestinal series with small bowel follow-through or CT, or with both. A high index of suspicion is required for proper diagnosis and management of these patients. In a series reported by Blachar et al., 463 patients were investigated for complications after RYGBP.[54] The incidence of internal hernia after gastric bypass was 3%, whereas SBO from other causes developed in nine patients.

Several important features diagnostic of internal hernia that are found on upper gastrointestinal series include a cluster of small bowel loops seen in the mid or left upper portion of the abdomen.[54] This cluster is relatively fixed and remains high on erect radiographs, which reveal stasis and delay in passage of contrast material. The CT appearance of internal hernias often depends on their location, although clustering of dilated small bowel loops with crowding and congestion of the mesenteric vessels is seen in all instances. In cases of herniation through the transverse mesocolon, the herniated cluster of bowel is located posterior relative to the stomach and may exert a mass effect on its posterior wall. Furthermore, herniations through the small bowel mesentery cause the clustered bowel to press against the abdominal wall with no overlying omental fat and thereby result in central displacement of the colon. A Peterson-type hernia is difficult to diagnose because it has neither a confining sac nor a characteristic location, and the only clues to its presence may be engorgement and crowding of the mesenteric vessels and evidence of SBO.

Treatment

On diagnosis of AIH, exploration is mandatory and can be performed laparoscopically by experienced surgeons with minimal morbidity and complications.[51,52,55,56] The biliopancreatic limb and the common channel should be run from the ligament of Treitz to the ileocecal valve. The Roux limb should be identified and the entire length run from the gastrojejunostomy to the enteric anastomosis. Any herniated segment of small bowel should be reduced, and any mesocolic and jejunojejunostomy mesenteric defects should be closed with nonabsorbable running suture. Controversy exists regarding closure of Petersen's defect, with some authors recommending interrupted closure of this mesenteric defect to prevent internal herniation postoperatively.

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Chapter

75

Mesenteric Arterial Trauma

Rao R. Ivatury

EPIDEMIOLOGY

Injuries to the mesenteric arteries are rare and occur in less than 1% of all trauma admissions. No mesenteric arterial injuries were found in a collective review of 3705 arterial injuries from World War II, the Korean War, and the Vietnam War, as reported by DeBakey and Simeone, Hughes, and Rich and associates.[1-3] This rarity is also substantiated by civilian series reported by several authors.[4-16] In a recent multi-institutional study, Asensio and colleagues[16] could collect only 250 patients with these injuries over a period of 10 years from 34 participating trauma centers. It is evident that even an established trauma surgeon may not have a large experience dealing with these difficult lesions.

SURGICAL ANATOMY

The superior mesenteric artery (SMA) originates about 1.5 cm below the celiac axis and is the second branch of the abdominal aorta; it is located at approximately the level of L1. Surrounded by the portal vein, pancreas, and duodenum, the SMA soon disappears under the neck of the pancreas. The zones of the artery as described by Fullen and associates[7] in 1972 were based on the collateral circulation and the extent of ischemia resulting from injury or ligation of the different portions of the artery (Fig. 75–1). Zone I extends from the origin of the artery at the aorta to the first major branch (inferior pancreaticoduodenal artery). Loss of this portion of the artery leads to maximal ischemia. Zone II extends from the inferior pancreaticoduodenal artery to the origin of the middle colic artery. Injuries in this area lead to severe ischemia. Zone III extends distal to the origin of the middle colic artery to the origin of the segmental branches. Zone IV is the region of the artery termed by segmental names: ileocolic, right colic, and so forth. The collateral circulation of the SMA is not as well developed as that of the celiac axis and the inferior mesenteric artery (IMA). Superior and inferior pancreaticoduodenal branches of the celiac axis and the SMA and the marginal artery of Drummond between the SMA and IMA are the usual collateral channels. These vessels, however, are inconstant and variable, thus making the SMA essentially an end artery.

OPERATIVE EXPOSURE AND MANAGEMENT DECISIONS

Operative exposure of the SMA is very difficult because of its high location and a dense celiac plexus and lymphatics around the origin of the artery. Active bleeding from the region behind the pancreas may be an indication of SMA injury in zone I. This zone is best approached by dividing the pancreas at its neck anterior to the mesenteric vessels. Further exposure is facilitated by medial visceral rotation (Figs. 75–2 and 75–3). Rotation is commenced by incising the avascular line of Toldt on the left colon, dividing the lienosplenic ligament, and rotating the left colon, spleen, tail and body of the pancreas, and stomach toward the midline. The left kidney may also be mobilized and reflected medially (Mattox maneuver) to gain access to the proximal infradiaphragmatic aorta and its first two branches (the celiac axis and SMA). Transection of the dense celiac and peripancreatic venous plexus is also required. This medial visceral rotation, especially when the left kidney is included, does take time and experience to perform. Potential pitfalls are damage to the spleen, kidney, and renal pedicle during the maneuver. In addition, the resulting altered anatomy may prove confusing to an inexperienced operator.

Injuries with hematoma below the transverse mesocolon can be approached by several methods. Dividing the mesocolon and performing an extended Kocher maneuver with extension along the third portion of the duodenum allow one to palpate the SMA. The Cattell-Braasch maneuver, in which the root of the small bowel mesentery is dissected in a diagonal line to the junction of the third and fourth portions of the duodenum and reflected cephalad, also exposes the SMA pulsations for dissection and isolation. Injuries to the distal zones of the

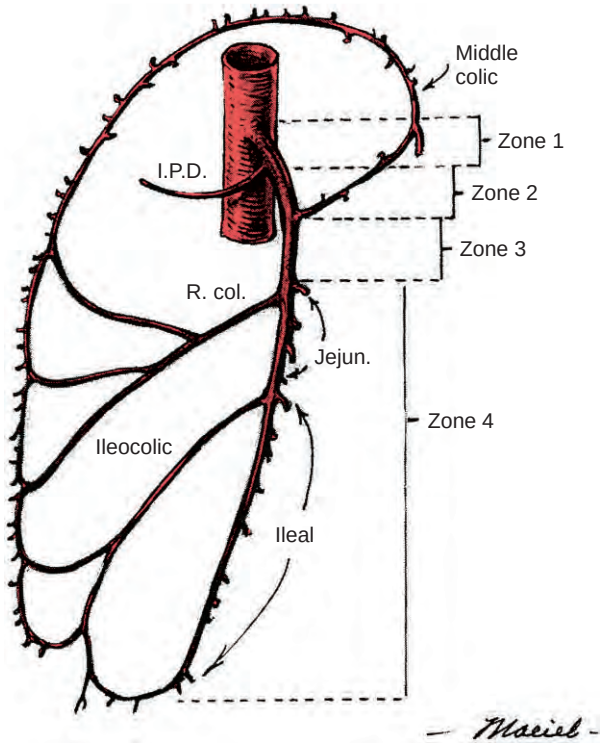

Figure 75–1. Fullen's anatomic classification of injuries to the superior mesenteric artery based on the location of the injury in relation to the main arterial branches. I.P.D., inferior pancreaticoduodenal artery; R. col., right colic artery. (From Fullen WD, Hunt J, Altemeier WA: The clinical spectrum of penetrating injury to the superior mesenteric arterial circulation. J Trauma 12:656-663, 1972.)

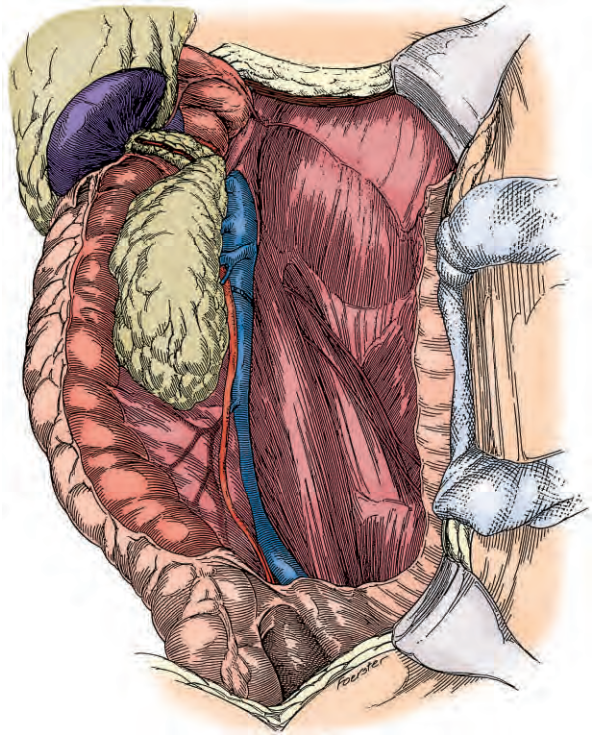

Figure 75–2. Left medial visceral rotation. The descending colon, left kidney, spleen, and distal pancreas are mobilized en bloc to expose the suprarenal aorta in the retroperitoneum. (From Rutherford RB: Atlas of Vascular Surgery—Basic Techniques and Exposures. Philadelphia, WB Saunders, 1993.)

SMA can be approached directly. The frequent presence of associated injuries to other abdominal vessels and intra-abdominal organs and the severe associated hypotension may make it necessary to compress the aorta under the diaphragm while the patient is resuscitated with transfusions. Aortic compression can be performed initially with a sponge stick or the assistant's fingers. Longer periods of compression may necessitate enlargement of the aortic isthmus in the diaphragm, mobilization of the aorta, and the application of a Satinsky clamp (Fig. 75–4). The dense celiac plexus of nerves and lymphatics and the long hiatal fibers of the diaphragm make the dissection difficult and time-consuming. One useful technique is to divide the left crus of the diaphragm at the 2-o'clock position, widen the aortic isthmus, bluntly dissect the distal portion of the thoracic aorta, and then apply a clamp on the suprarenal aorta.[5] A left anterolateral thoracotomy and occlusion of the descending aorta may be faster and easier.

Frequently, these patients will have major associated injuries causing extensive blood loss and hemodynamic instability. Onset of the critical "triad of death," namely, hypothermia, acidosis, and coagulopathy, is often the rule rather than the exception and is precipitated by associated abdominal injuries, multiple transfusions, the need for aortic compression, and dilutional coagulopathy. In these circumstances, it is prudent to institute "damage control" principles.[17] Rapid termination of the laparotomy is the goal. Ligation of the SMA is usually reserved as a means to control life-threatening hemorrhage or exsanguination in these circumstances. The morbidity associated with SMA ligation is high, but because the patient may not tolerate a prolonged vascular replacement at this time of physiologic exhaustion, placement of a temporary arterial shunt between the ends of the divided SMA is the preferred approach.[18] Javed shunts or any vascular shunt available in the operating room will serve the purpose. If none is immediately available, intravenous infusion tubing will be a good substitute. This will maintain SMA flow distally and avoid mesenteric ischemia. These shunts are well tolerated for at least 24 hours. A heparin-bonded shunt, if available, is another option. Control of contamination is achieved by rapid closure of bowel perforations. In these patients the abdomen is usually left "open" by the placement of a "Vac-Pac" dressing. The patient is transferred to the intensive care unit (ICU) for resuscitation. This ICU phase of "damage control" will focus on correction of the hypothermia, acidosis, and coagulopathy. Acidosis is reversed by aggressive blood and fluid resuscitation. It must be remembered that ligation of the SMA and superior mesenteric vein (SMV) may cause profound bowel

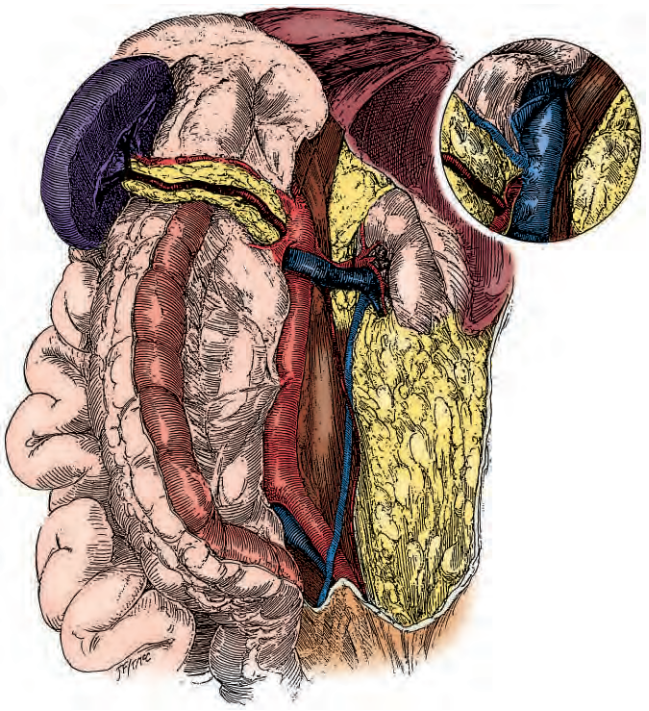

Figure 75–3. Modified left medial visceral rotation. The left kidney is left in situ in the retroperitoneum while the rest of the viscera are mobilized. With division of the left crus of the diaphragm *(inset),* this maneuver gives better exposure of the proximal celiac axis and superior mesenteric artery. (From Rutherford RB: Atlas of Vascular Surgery—Basic Techniques and Exposures. Philadelphia, WB Saunders, 1993.)

Table 75–1 Survival After Superior Mesenteric Artery Injury

Author	No. of Patients	No. of Survivors (%)
Fullen, 1972	8	5 (62.5%)
Graham, 1978	45	27 (60.6%)
Lucas, 1981	15	10 (66.7%)
Kashuk, 1982	6	4 (66.7%)
Sirinek, 1983	20	14 (70%)
Accola, 1986	22	7 (31.8%)
Asensio, 2000	28	13 (46.4%)
Davis, 2001	15	8 (53.3%)
Tyburski, 2001	41	20 (48.8%)
Asensio, 2001	250	153 (61.2%)
Total	*450*	*261 (58%)*

Adapted from Feliciano DV: Injury to abdominal aorta and visceral arteries. In Rich NM, Mattox KL, Hirshberg A (eds): Vascular Trauma, 2nd ed. Philadelphia, Elsevier, 2004, pp 219-314.

edema and increase the need for massive volume replenishment. Intra-abdominal hypertension and abdominal compartment syndrome are common complications in these circumstances and must be carefully watched for by frequent measurement of bladder pressure as a surrogate for intra-abdominal pressure.[19] It is our practice to perform decompressive laparotomy if bladder pressure is greater than 20 mm Hg with organ dysfunction.

More definitive SMA repair is usually undertaken at the second laparotomy, when the patient is in a better physiologic state. Injuries to zone III and beyond the middle colic branch and those at the origin of zone IV before the origin of the enteric branches should be repaired primarily. Distal zone IV injuries involving segmental branches to the small and large bowel may be ligated. Only occasionally it is possible to perform lateral arteriorrhaphy of the SMA. Bypass grafting to the proximal SMA is ideally performed as a short graft taken directly off the infrarenal aorta. SMA bypass may be performed safely with a synthetic graft, even in the face of a contaminated field,[5] unless the injury involves a high-velocity missile. This graft is routed through the root of the mesentery of the small bowel to anastomose with the mid or distal part of the SMA.[5] It is imperative that the aortic suture line be protected from adjacent bowel by omentum or a retroperitoneal flap to prevent an aortoenteric fistula in the future.[5] After successful mesenteric revascularization, bowel viability must be critically assessed. There is no single good test to determine bowel viability after revascularization. Ballard and associates[20] found that in patients who were revascularized for acute mesenteric ischemia, the overall accuracy of clinical judgment, intravenous fluorescein, and intraoperative Doppler was 50%, 56%, and 0%, respectively. Bulkley and colleagues[21] also found fluorescein to be the best tool to assess viability. A recent study reported that clinical judgment alone had an overall accuracy of 87% and a predictive value of only 69% versus 100% overall accuracy, sensitivity, and predictive value for laser Doppler flow measurements of the bowel mucosa.[22] There should be a low threshold for second-look or third-look laparotomy, especially if the patient fails to improve in the early postoperative period.

RESULTS

As indicated earlier, SMA injury is rare and the majority of series in the literature included less than 25 patients per report (Table 75–1). A recent study of these injuries, conducted under the auspices of the multi-institutional trials committee of the American Association for the Surgery of Trauma, was published by Asensio and coauthors. This is the largest series yet reported, and 250 patients were analyzed during a 10-year period from 34 participating centers. The majority of SMA injuries occurred as a result of penetrating trauma (52%) and were predominantly in Fullen zone IV (112). Zone I, II, and III injuries totaled 51, 35, and 42, respectively. Twenty-two percent of patients underwent primary repair, and 16 (7%) underwent interposition grafts consisting of 10 (4%) autogenous reverse saphenous vein grafts and 6 (2%) polytetrafluroethylene grafts. Forty-four of 206 patients (21%) underwent planned second-look procedures, and 9 died during their hospitalization.

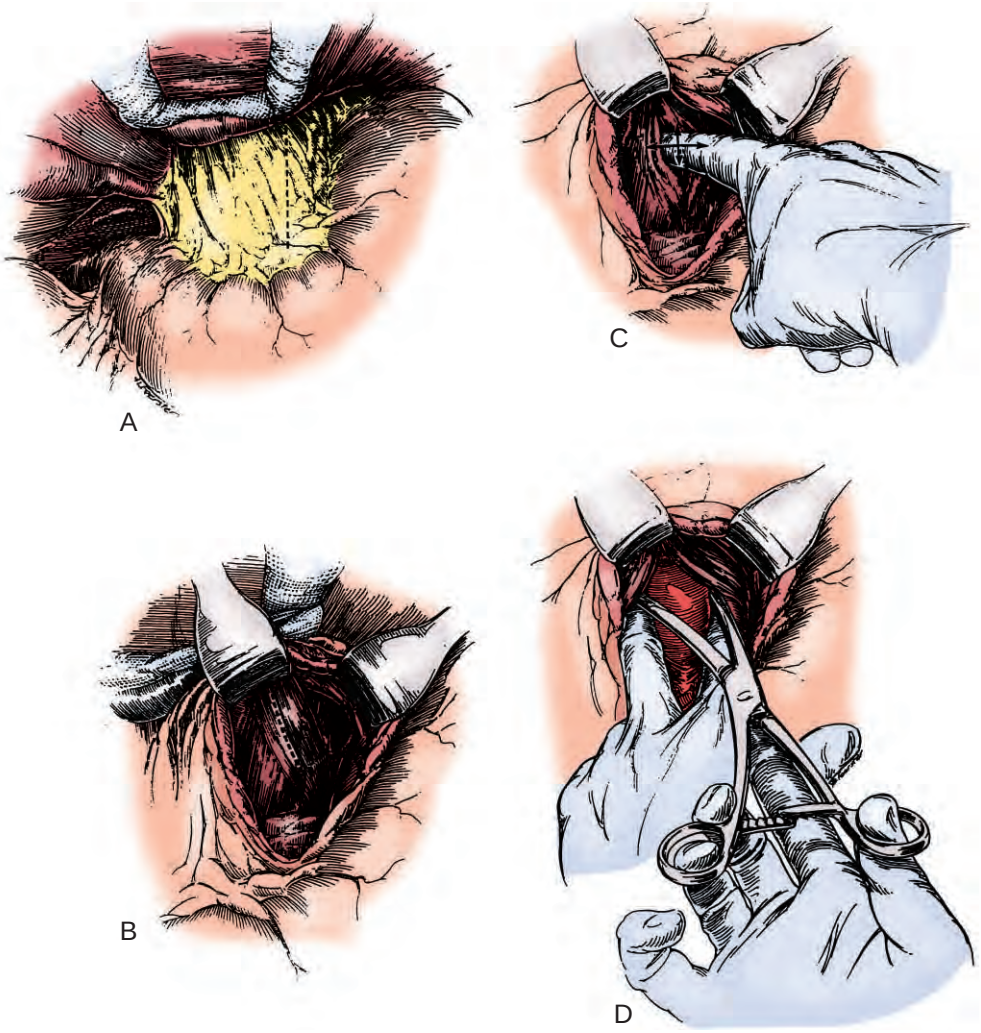

Figure 75–4. Sequential maneuvers for rapid exposure of the supraceliac aorta. **A,** Longitudinal opening in the lesser omentum. **B,** Blunt dissection of the left crural fibers. **C,** Freeing of the aorta from the surrounding loose areolar tissue with a finger. **D,** Guiding the occluding vascular clamp in over two fingers until its tips "touch bottom" on the vertebral body behind the aorta. (From Rutherford RB: Atlas of Vascular Surgery—Basic Techniques and Exposures. Philadelphia, WB Saunders, 1993.)

Overall mortality was 39% (97 of 250); of these patients, 69 (71%) died in the operating room or within the first 24 hours of admission, either from exsanguination or injury-related causes; the other 28 patients (29%) succumbed as a result of complications in the postoperative period. As might be expected, Fullen zone I injuries had the highest mortality (76.5%). This report should be carefully studied for its detailed account of the outcome after these injuries.

Interesting case reports describe some sequelae from injury to the superior mesenteric vessels.[23-28] Radonic et al.[23] described two cases of SMA-SMV fistula from penetrating trauma that were diagnosed by angiography and treated operatively. Deitrick et al.[26] reported a proximal SMA–portal vein fistula that was embolized by angiographic methods. Miglietta et al.[27] presented a case of traumatic SMA–duodenal fistula from a gunshot wound of the abdomen. At the initial laparotomy a hematoma around the SMA was not explored. One month later the patient experienced massive upper gastrointestinal hemorrhage. Immediate exploratory laparotomy revealed a large fistula between the SMA and the duodenum, but the patient could not be resuscitated after an intraoperative cardiac arrest. These cases illustrate the importance of careful exploration of the SMA and its surrounding hematoma at the initial laparotomy.

In summary, injuries to the mesenteric arteries are associated with high mortality. Most result from penetrating trauma, but blunt injury, usually to the SMA, does occur. Proximal injuries to the celiac artery or SMA are manifested as intraperitoneal bleeding or a central retroperitoneal hematoma. All central retroperitoneal hematomas should be explored so that major vascular injuries are not missed. In cases of extreme blood loss with accompanying coagulopathy, acidosis, and hypothermia, damage control principles yield the best results, with temporary intravascular shunting of the SMA being the preferred approach. Planned second- and

third-look laparotomy is crucial for early detection of bowel nonviability. Interventional techniques, combined with improved abdominal imaging, can also be effective in avoiding laparotomy entirely and dealing with delayed complications such as arteriovenous fistulas and pseudoaneurysms.

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Chapter

76

Reoperative Surgery of the Stomach and Duodenum

Bruce Schirmer ▪ C. Joe Northup

Reoperative surgery of any type is always more difficult than operating on virgin tissue. Scarring from previous surgery means, at best, additional time and dissection to establish appropriate tissue planes to perform the operation. At worst, it predisposes the patient to more serious consequences, including significant intraoperative bleeding, leading to transfusion and increasing the risk of postoperative infection. Damage to organs in the dissection process through such scar tissue may leave the patient with unrecognized perforations or organ injury that may result in disastrous postoperative complications, such as leak, abscess, fistulas, sepsis, and death.

Although clinical circumstances may force the performance of a reoperation on an emergent or urgent basis, when reoperative surgery is elective, the surgeon must take into consideration the need to avoid severe intraoperative scarring as much as possible. The most important rule to follow to minimize the consequences of scarring from previous surgery is *waiting an adequate period of time* since the last laparotomy to perform further abdominal surgery.

This chapter examines the aspects of reoperative surgery of the stomach and duodenum that the authors believe are particularly important for optimizing the outcomes of such procedures. In some situations, the procedures are performed only as a last resort when medical therapy has failed. In other situations, reoperative surgery has a stronger and more effective track record for success. This chapter focuses on elective reoperative surgery or surgery for longer term complications or failures of previous upper digestive system operations. Emergent reoperation of the stomach and duodenum may be required for immediate complications of recently performed surgery. These types of operations are not dealt with for the most part in this chapter because they essentially constitute immediate complications and treatment of complications of the initial operation. These complications are discussed in most circumstances in the various chapters covering the index operation. The focus in the present chapter is on reoperations that are done at a later date after the original operation. For the most part, these are elective procedures, but semiurgent ones for commonly occurring late problems of previous gastroduodenal surgery also are discussed as appropriate.

The types of reoperations are grouped according to the disease type for which they are being performed. These categories include peptic disease, gastroparesis and motility disorders, gastroesophageal reflux disease, bile reflux gastritis, cancer, bariatric surgery, and obstructive processes of the distal duodenum or segments of intestine draining a gastrojejunostomy.

GENERAL PRINCIPLES OF REOPERATIVE SURGERY

Although the individual operation planned as a reoperative procedure has varying degrees of success, and indications are based on previous outcomes data, the success of most reoperative operations depends on adhering to certain basic principles (Box 76–1). Most reoperative procedures are performed based on background knowledge of the likelihood of success of a repeat operative procedure achieving the intended goal. As with any operative procedure, reoperations have a higher degree of success the more severe the symptoms and the more likely the cause of the symptoms can be correlated with a clearly definable anatomic abnormality or pathology. Procedures that have variable success, particularly when the goal is eradication of nonspecific symptoms, should be avoided or performed only when a good benefit-to-risk ratio can be established.

Information Acquisition and Preparation

Preparation for reoperative surgery should always include obtaining as complete as possible records from

Box 76–1 Basic Principles of Reoperative Surgery

- Potential benefits must outweigh risks or likely outcome without intervention.
- Confirm that there is an anatomic and not a functional problem.
- Obtain all possible information regarding previous operations.
- Define the anatomy by radiographic, functional, and endoscopic studies as indicated.
- Allow an adequate amount of time to pass to minimize previous operative scarring, which can prevent ease of operation and increase complications.
- Be certain of blood supply to remaining tissues, especially anastomoses.
- Do not leave sections of the upper gastrointestinal tract without adequate drainage of luminal contents.
- Provide for a fail-safe mechanism of nutrition should postoperative complications occur.
- Assess the success of a reoperative procedure constantly as it is in progress. Do not hesitate to stop if more harm than good is being done. Do not leave the patient worse off than before.
- Anticipate that complications, such as leaks, may occur, and prepare for their possibility intraoperatively.

earlier operative procedures. Recent complete nonsurgical medical records also must be obtained. Attention to the details of which, if any, major blood vessels were divided during previous surgery may prove helpful in planning the appropriate reoperative approach. Knowledge of the relative location of Roux limbs and afferent and efferent intestinal limbs relative to other abdominal organs enables the initial dissection process to proceed with confidence based on such information.

Preoperative assessment of the current gastroduodenal anatomy is essential before embarking on any reoperative procedure of the upper gastrointestinal system. Such assessment often requires radiographic studies, endoscopy, or both. The surgeon should be certain he or she has a firm grasp on the existing anatomy of the stomach and duodenum, to as great an extent as possible, before embarking on an elective reoperation.

Assessment and Counseling

The patient and his or her current condition must be assessed carefully by a thorough history, physical examination, and review of the records and imaging studies. It is important for the surgeon to make a recommendation for reoperative surgery when there is a clear anatomic indication for the operation. In several areas of reoperative upper digestive surgery, such as bariatric surgery and antireflux surgery (see later), relying solely on symptoms or a patient's desire for further improvement of their symptoms as a basis for performing reoperative surgery may lead to a poor ultimate outcome from the reoperation. If a previously well-constructed operation remains intact, there is little reason to think that revising it would likely improve the situation.

After a thorough review of all pertinent information, the surgeon must make an assessment and recommendation as to whether reoperation is indicated. A thorough counseling session by the surgeon with the patient is necessary to discuss the relative merits or lack of merits of reoperative surgery. Such counseling sessions can be multiple if the initial encounter occurs at a time when appropriate and needed imaging studies or other laboratory evaluations are still pending.

Because reoperative surgery carries increased risks for complications, it must be entered into with significant planning and with careful contemplation on the part of the surgeon as to the risks and potential benefits of the procedure. The potential benefits are often less likely to be as good as the original procedure, if a revision is planned. Similarly, the risks are almost always increased. This combination puts the burden of proof on the surgeon to counsel the patient appropriately as to these parameters and to advise reoperation only when the likelihood of success is clear, and the danger of life-threatening complications is mitigated as much as possible.

Technical Aspects of Performing Reoperative Surgery

Open Surgery

The multiply-operated abdomen presents a challenge for all surgeons. Adhesion formation and subsequent obstruction is a frequent indication for surgical intervention. A careful approach must be undertaken to enter a previously operated abdomen. The typical approach is first to identify an area that would tend to have fewer adhesions or an unoperated area. Typically, the most superior aspect of the midline adhesion is often the best place to approach the adhesions associated with a previous scar. Inadvertent injury to the liver is generally less of a problem than injury to a piece of small intestine or colon. We advocate the use of sharply entering the abdomen to avoid any risk of thermal injury from cautery. When the fascia has been identified, Kocher clamps can be placed on the fascia with gentle traction by an assistant. The surgeon should apply gentle countertraction on the bowel and sharply take down adhesions from the abdominal wall. Adhesiolysis should be completed to the point where the operative goals can be accomplished. There is no benefit in taking down unnecessary adhesions.

Historically, attempts have been made to reduce the development of obstruction from intraoperative adhesions, including bowel plication and long intestinal tubes. Careful surgical technique remains the most effective method of adhesion prevention. Removal of foreign material, careful handling of tissues, adequate hemostasis, and avoidance of unnecessary dissection are the most efficient methods to prevent adhesions.[1,2]

Newer, bioresorbable materials have been shown to provide some benefit in reducing the severity or formation of adhesions. Cohen et al.[3] prospectively showed a reduction in adhesion formation and a decrease in severity using a hyaluronate-based barrier. In another prospective trial, Becker et al.[4] also showed a significant decrease in incidence, extent, and severity of postoperative adhesions with a similar product. Pharmacologic agents, such as anticoagulants and anti-inflammatory agents, have not reliably decreased adhesion formation.

When a surgeon performs an operation in which there is a high likelihood of returning, consideration must be given to adhesion prevention. Surgeons may want to consider using a hyaluronate-based barrier in these situations. Future advances in bioresorbable materials may improve their benefit in adhesion prevention further and possibly result in a decrease in the risk of postoperative bowel obstruction.

Laparoscopic Surgery

Since the advent of the laparoscopic era of performing general surgery operations, there is no question that a laparoscopic approach results in considerably less intra-abdominal adhesions than a celiotomy. Laparoscopy is currently the best approach a gastrointestinal surgeon can use to prevent significant and difficult postoperative adhesion formation. Not all operations described in this chapter are amenable to a laparoscopic approach, however, unless the surgeon has considerable expertise in laparoscopic surgery. Each individual operation must be assessed for the potential to apply a laparoscopic technique if possible, and such a decision must be based on the patient's previous operations, reports of the intra-abdominal condition at the time of those procedures, and the skill of the surgeon in performing laparoscopic surgery. Although most primary upper gastrointestinal operations are routinely performed laparoscopically by skilled laparoscopic gastrointestinal surgeons, reoperative surgery is approached more often using a celiotomy because of the time element and extreme technical difficulty encountered in using laparoscopy for revisional surgery of the foregut. Nevertheless, for bariatric and antireflux operations, there is a considerable body of published experience with successful use of a laparoscopic approach for revisional operations.

Laparoscopic Technique With the increasing use of laparoscopy, one of the most challenging barriers remains the previously operated abdomen. The initial difficulty is the approach to obtaining intra-abdominal access. The surgeon may choose a closed (Veress needle) or open (Hasson trocar) approach. An open versus closed approach has not shown any significant differences in the ease of use or the complication rate when entering the abdomen.[5,6] The open approach to laparoscopy is often thought to be safer with better visualization of the tissues. The open approach tends to be more complicated, however, when a trocar is inserted away from the midline. Also, in an overweight or morbidly obese patient, the open approach results in several technical problems, including the fact that the incision needs to be larger to allow for safe entry into the peritoneal cavity. The larger incision is subsequently more prone to leak gas from the pneumoperitoneum.

Our approach of choice is to use the Veress needle in an unoperated field or area of the abdomen. Optimal areas for safe entry to the reoperated abdomen are the right or left upper quadrants, 1 to 2 cm below the costal margin. Through a small incision, a tracheotomy hook is used to elevate the fascia, and the Veress needle is inserted. Initial aspiration should be performed to evaluate for any potential organ violation. Aspiration of gross blood or enteric contents should prompt a change in entry location or a conversion to an open procedure, and the damaged organ should be repaired. Structures underlying any site of attempted peritoneal access always must be given special attention on reentering the abdomen.

When adequate pneumoperitoneum has been achieved, a bladeless trocar is inserted. After the initial trocar is placed, a telescope is inserted to confirm intra-abdominal placement. The bowel should be carefully inspected directly below and surrounding the initial entry site to identify any possible injury.

After entry, the extent of adhesion formation must be assessed. The first priority is the placement of an additional operating port. An area of the anterior abdominal wall must be identified that is free of adhesions and safe for placement of an operating trocar. If no space is readily apparent, consideration must be given to converting to an open procedure. After a second operating port is placed, a careful adhesiolysis is begun. We prefer first to free enough space to be able to place a third trochar an adequate distance from the first operating port, preferably on the opposite side of the abdomen. This allows for a grasper to apply gentle, downward traction, while bluntly and sharply dividing adhesions to the anterior abdominal wall.

We use 5-mm ports and a 5-mm 30- to 45-degree angled laparoscope. An angled scope allows for visualization of the adhesions at different perspectives and decreases the chance of injury to adherent intestine. Additionally, using a 5-mm telescope allows for movement of the camera from port to port to inspect adhesions and organs from a different viewpoint.

Adhesiolysis should be continued until the surgical objective can be accomplished. Excessive adhesiolysis places the patient at greater risk for a bowel injury. Little benefit is gained by doing a total abdominal adhesiolysis, and this only lengthens the procedure time. Omental adhesions to the anterior abdominal wall are common-

place in the previously operated abdomen and relatively easy to divide. Bowel adhesions may be more difficult, and care should be taken to avoid an enterotomy at all costs because recognition of enterotomy with a laparoscopic approach may be more difficult than with open surgery. We sometimes divide the peritoneum to dissect the bowel down off the abdominal wall still densely adherent to the peritoneum if this would prevent injury. Small bowel interloop adhesions also are a technical challenge and must be divided carefully. Probably the most difficult situation technically in reoperative laparoscopic enterolysis involves an area of the abdominal wall where previously placed mesh exists that was used to repair an incisional or ventral hernia. In such situations, bowel can be so tightly stuck to the mesh as to preclude its safe enterolysis using a laparoscopic approach, and conversion to an open approach is necessary.

Bowel Injury During Laparoscopic Enterolysis Management of a bowel injury during laparoscopy varies depending on the procedure being performed. Any enterotomy that occurs can be repaired with primary repair with interrupted sutures. Any large tear in the intestine must be evaluated carefully for resection. Typically, an enterotomy of greater than or equal to 50% of the lumen should be resected. A colon injury also can be managed with primary closure with laparoscopy.

In patients undergoing laparoscopy with multiple previous operations, we require patients to have a bowel preparation before surgery. Bowel preparation allows for decreased contamination if an injury occurs and decreases bowel "bulk" to allow for increased intraoperative space.

A missed bowel or gastric injury during laparoscopic enterolysis is a major complication that usually results in significant morbidity for the patient. The patient often presents with severe abdominal pain and peritonitis. Sepsis also may be a complicating accompanying problem. The patient should be re-explored immediately and undergo resection or primary repair of the injury, placement of drains if indicated by tissue quality, and diversion of the gastrointestinal stream if needed for severe injuries.

Nutritional Issues and Access

A final note is needed for reoperative surgery of the upper gastrointestinal system. Because nutritional intake is based on food or nutrients passing through these organs if an oral route of postoperative nutrition is expected (as it usually is), the operation must be highly likely to guarantee that eventuality in the relatively immediate postoperative period. If there is a significant likelihood that oral feeding may be precluded by a typical and common postoperative complication resulting from the reoperation, the burden is also on the surgeon to make provisions for a reliable enteral feeding access to be placed at the time of the operation for postoperative use. This access is usually an operatively placed gastrostomy or jejunostomy tube, depending on the operation performed.

PEPTIC DISEASE

Gastric Outlet Obstruction After Pyloric or Duodenal Ulcer Surgery

Gastric outlet obstruction after a previous operation for obstructing peptic ulcer may occur as a result of technical problems with the anastomosis, postoperative scarring, recurrence of the peptic disease with ulceration resulting in anastomotic scarring, or functional disorders of gastric emptying, the most common of which is postvagotomy syndrome with poor gastric emptying. Patients typically present with nausea, vomiting, early satiety, and postprandial pain. Patients can be extremely miserable if the nausea and vomiting are severe. Secondary dehydration and abnormalities in electrolytes, such as hypokalemia, also may develop. Malnutrition may be present. Gastric outlet obstruction at the level of the anastomosis may present as vomiting of clear gastric juice with undigested food contents. Obstruction at a level beyond the anastomosis, or of the efferent limb of a gastrojejunostomy, manifests more typically as bilious vomiting.

The diagnosis is strongly suggested by the clinical picture and secondarily reinforced by plain radiographs showing a distended gastric remnant. Definitive diagnosis is confirmed by contrast upper gastrointestinal series. Unless perforation is suspected, barium is the oral contrast medium of choice for improved visualization in perhaps a large reservoir of gastric secretions and as a less dangerous material if any aspiration of vomitus were to occur. Upper endoscopy may be helpful in determining the degree and level of obstruction of an anastomosis, although it often can be inaccurate in determining emptying ability of the anastomosis.

For more chronic situations, in which poor gastric emptying is intermittent and of varying severity, solid and liquid radionuclide gastric emptying studies should be performed to assess the emptying capacity of the stomach. Patients who present with delayed gastric emptying by radionuclide studies, but who have a patent anastomosis confirmed by upper gastrointestinal series, must be presumed to have primarily a functional gastric emptying disorder rather than an anatomic outlet obstruction. These patients should be managed medically whenever possible, with prokinetic agents being the mainstay of therapy. The reader is directed to the subsequent section on gastroparesis for further details.

In a situation in which a pyloroplasty or Billroth I procedure has been performed, and in which the pyloric channel has become re-obstructed, conservative measures of eliminating any potential causes of recurrent ulcer, such as smoking, nonsteroidal anti-inflammatory drugs, and steroids, and treatment for existing *Helicobacter pylori* in the stomach, must precede reoperation and be given an adequate trial to determine if they alone may provide adequate relief of the obstructive process. Balloon dilation of a scarred pylorus may provide satisfactory relief in some situations, particularly when the recurrent ulcer disease or cause has been eliminated or successfully treated. Balloon dilation may be done endoscopically or fluoroscopically.

When conservative measures at reopening the pyloric region have failed, the operative procedure of choice for relieving this obstruction is a gastrojejunostomy. *Trying to resect the stenotic and scarred pylorus is difficult, dangerous, and contraindicated for benign disease.* Adding a vagotomy is indicated only if recurrent peptic ulceration has occurred at the pyloric channel area, contributing to the re-stenosis. Often, adding a vagotomy is detrimental to the overall result of the operation because it greatly inhibits gastric emptying through the newly created gastrojejunostomy. Patients should be tested and treated for the presence of *H. pylori* before undergoing reoperation, even if other causes for the recurrent ulcer exist. Eradication of the bacteria must be confirmed by hydrogen breath testing.

Operative Technique

Gastrojejunostomy for an obstructed pyloric outflow must emphasize several principles:

1. The anastomosis must be adequately large. We prefer to use a 60-cm length linear stapler to perform the anastomosis or duplicate sequential firings of a 45-cm length stapler. This creates an anastomosis of at least 4 to 5 cm in length.
2. The location of the anastomosis should be dependent to allow maximum gravitational drainage. This means creation of the gastrojejunostomy on the posterior surface of the stomach, with a retrocolic location of the jejunal limb (Fig. 76–1).

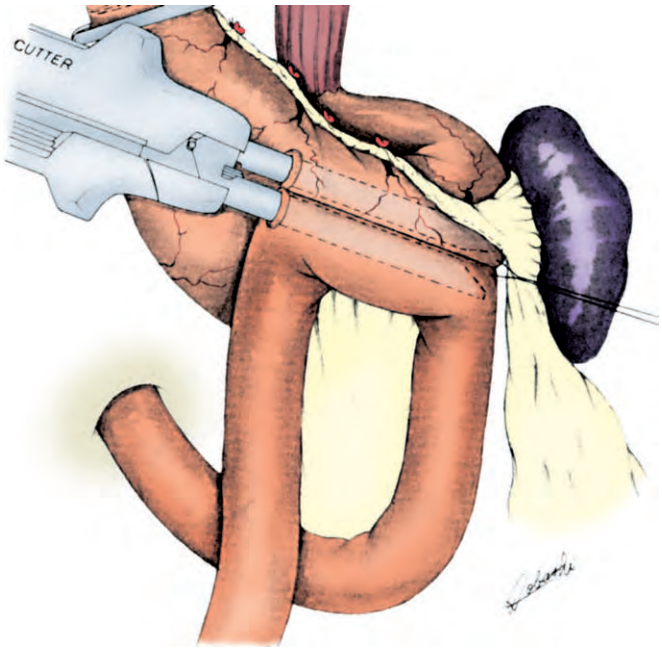

Figure 76–1. Stapled gastrojejunostomy. Creation of a stapled Billroth II anastomosis. Note the preferred method of placing the staple line in a posterior position to improve gastric emptying. (From Feil W, Lippert H, Lozac'H P, et al [eds]: Atlas of Surgical Stapling, New York, Thieme Medical Publisher, 2000, p 132.)

3. The critical outflow to the stomach is not the anastomosis size itself, but the patency of the efferent limb of a gastrojejunostomy. To ensure that the lumen of the efferent limb is open to drainage, the bowel should be tacked to the posterior surface of the stomach 1 to 2 cm beyond the anastomosis to prevent kinking downward of the efferent limb and limiting the surface area for drainage. The tacking stitches should serve to stent open the lumen of the efferent limb.
4. A smooth and unobstructed passageway of the afferent and efferent limbs of the gastrojejunostomy through the mesentery of the transverse colon should be assured. Similarly, the mesenteric opening needs to be sutured to the sides of the bowel to prevent herniation of other loops of bowel superior to the level of the colon mesentery.

Gastric Outlet Obstruction at the Site of a Surgical Gastrojejunostomy

In a patient with a previous antrectomy or subtotal gastrectomy of some portion and a gastrojejunostomy, reobstruction at the site of the anastomosis may occur immediately after surgery or later. Immediate postoperative issues involve technical problems, anastomotic edema, distal efferent loop obstruction, or other kinking or obstruction of the efferent limb of intestine draining the stomach. These complications are discussed elsewhere. Chronic causes of gastric outlet obstruction after a previous gastrojejunostomy include efferent limb obstruction, marginal ulcer at the anastomosis with scarring, and simply stenosis of the anastomosis.

Patient presentation with this anatomic problem is similar to that of gastric outlet obstruction after stenotic pyloroplasty, but vomitus is bilious if the anastomosis is patent to the afferent limb of the gastrojejunostomy. This most often is true. Diagnosis is by upper gastrointestinal series or by endoscopy. The upper gastrointestinal series gives a better anatomic picture of the situation and a better analysis of gastric emptying. Passage of an endoscope through an anastomosis may suggest patency, but functional emptying may be seriously compromised despite the ability to pass an endoscope through the anastomosis. This is especially true if there is an element of obstruction of the efferent intestinal drainage limb, not appreciated by endoscoping the anastomotic area alone.

Initial measures to improve stenotic gastrojejunostomy involve medical therapy to treat and eliminate any marginal ulcer present. Endoscopy with anastomotic dilation is often helpful to relieve symptoms while medical therapy has a chance to reverse the obstructing ulcer process. Eradication of *H. pylori* also is important in this situation, as are other measures to eliminate causes of recurrent ulcer of the stomach (mentioned previously).

Stenosis of the anastomosis is unusual without accompanying reulceration. It may occur on the basis of foreign body reaction to anastomotic staples or sutures, however, or on the basis of chronic ischemia. These causes can

produce a progressive stenosis of the anastomosis, which is usually amenable to treatment with multiple dilations.

Marginal ulcer may cause obstruction at the site of a previous gastrojejunostomy. Diagnosis is usually by endoscopy because contrast studies often do not clearly identify the presence of a marginal ulcer. The site of the ulcer is normally at or just beyond the anastomosis, and this must be confirmed on endoscopy as well. Endoscopic dilation and fluoroscopic dilation may prove successful in treating these obstructions.[7] The presence of a marginal ulcer and a more chronic pattern of stenosis are factors that decrease the likelihood of success using balloon dilation alone. If dilations have failed, and a marginal ulcer persists, a barium radiograph should be performed before reoperation to confirm the marginal ulcer has not fistulized to surrounding structures, such as the transverse colon. This situation is rare, but important to determine if present preoperatively. At times, such a fistula is small and difficult to visualize on the contrast study. Severe scarring in the area of the anastomosis and adherence of an adjacent organ to the area may suggest the presence of such a fistula, even if it is not seen clearly on the contrast study. Such fistulas represent an indication for reoperation because conservative measures are not likely to result in healing.[8]

A minimally invasive approach that has been used in treating fistulas elsewhere in the gastrointestinal tract, but that is currently little proved as a definitive treatment for marginal ulcer fistulas at a gastrojejunostomy site, is fibrin glue injection of the fistula tract to produce occlusion of it. Fibrin glue has been shown to be effective in closing some enterocutaneous fistulas,[9] but its role in treating marginal ulcer fistulas is as yet unproven.

Confirmatory determination of the obstruction site to be at the area of the anastomosis is done with the upper gastrointestinal series, but also may be accomplished with endoscopy. Obstruction of the efferent limb of the gastrojejunostomy may result from stenosis and kinking of the bowel as it exits through the transverse colon mesentery or may be on the basis of postoperative intra-abdominal adhesions, internal hernia, or other less common causes that produce bowel obstruction. Operative treatment of this condition is much more likely, and balloon dilation usually has little role if the obstruction is much beyond the anastomosis.

Operative Technique

Operative treatment of an obstruction at a previous gastrojejunostomy site includes adherence to the following general principles:

1. If a vagotomy was not performed at the initial gastrojejunostomy, a completion vagotomy is indicated in the setting of marginal ulceration. Most incomplete vagotomies result from inaccurate identification of the posterior vagus nerve, which may lie considerably away from the posterior esophageal surface, coursing over the top of the diaphragmatic crura. Dissection further up the right side of the esophagus in the mediastinum often allows the surgeon to find, identify clearly, and follow the posterior vagus trunk. Intraoperative frozen section confirming neural tissue and skeletonization of the distal 5 cm of esophagus are crucial components of completion vagotomy.
2. The area of the previous anastomosis is usually best resected, to eliminate the scarred and obstructed portion of the stomach containing the previous anastomosis. The more proximal stomach is used for creation of the gastrojejunostomy. If resection is substantial, the surgeon may wish to perform a Roux-en-Y drainage of the stomach because this allows a greater length of intestine to reach the more proximal stomach. In addition, resection that includes the jejunal portion of the gastrojejunostomy predisposes to the use of a Roux limb for drainage because the bowel already is divided. Another factor in favor of using a Roux limb for any resection beyond the mid body of the stomach is to prevent potential bile reflux esophagitis.
3. Either the Roux limb or the gastrojejunostomy must be created without any tension on the anastomosis.
4. The efferent limb of the gastrojejunostomy or the Roux limb itself must lie in a position such that the outlet pathway of the bowel is not kinked or in any way obstructed.
5. Orienting the gastrojejunostomy in an isoperistaltic fashion is favorable, but not essential, to good emptying. Either retroperistaltic or isoperistaltic orientation to the stomach functions as long as the efferent limb is widely patent.
6. The bowel must be sutured to the transverse colon mesentery as it passes through it, to prevent postoperative internal hernias of other loops of bowel through the defect. Excessive suturing, especially running permanent suture lengths, may result in stenosis at this site, however.

Postgastrectomy Dumping and Diarrhea

Postgastrectomy dumping is a manifestation of the loss of pyloric control of gastric emptying and is present, to a greater or lesser extent, after any gastric resection with gastrojejunostomy or pyloroplasty. Rapid emptying of food into the jejunum results in the release of vasoactive amines and peptides, including insulin.[10] The vasoactive amines cause early dumping, which occurs within 30 to 60 minutes of eating and consists of physical manifestations including tachycardia, mild hypotension, and symptoms of nausea, abdominal pain and fullness, weakness, dizziness, and a sick feeling after meals with a high osmotic content. The major offending types of foods are calorically dense ones, such as sweets. Eating and drinking at the same time exacerbates symptoms. Late dumping occurs 2 to 4 hours after eating and is characterized by diaphoresis, tachycardia, light-headedness, and confusion. Hypoglycemia often, but not always, is present. Glucagon-like polypeptide (GLP-1) has been implicated as a vasoactive amine contributing to early and late dumping syndrome.[11]

Treatment for postgastrectomy dumping is nonoperative. In almost all situations, the patient can adjust food

intake and speed to ameliorate symptoms. Separating eating from drinking, avoiding high-calorie foods and concentrated sweets, and eating slowly prevent most severe symptoms of dumping. If dumping proves still refractory even with these measures, subcutaneous octreotide is effective in reversing the symptoms of dumping.[12] Longer acting intramuscular dosing of the drug has been shown to prevent the need for subcutaneous injections three to four times a day[13] with equal efficacy. Usually patients experience a decrease in dumping severity as time passes after surgery. Similarly, patients usually can be tapered off octreotide after a several-month course of treatment. For severe cases, the drug is effective long-term, but side effects, which often lead to its discontinuation, include diarrhea and gallstone formation.[14]

Postgastrectomy diarrhea is a sequela of the postprandial dumping that follows the loss of pyloric-controlled gastric emptying after gastric resection. It may be exacerbated further by vagotomy. Diarrhea typically follows mild to more severe dumping symptoms by about 30 minutes and can be as debilitating as the dumping. Following the same approach of alteration of eating pattern that is used to treat dumping often improves the diarrhea as well. Octreotide is less useful for diarrhea alone, whereas antidiarrheal agents are usually of some symptomatic benefit. Adaptation and time usually also are helpful for this condition.

Operative treatments of reversing short segments (10 to 15 cm) of intestine, previously advocated in past decades as a treatment for postprandial dumping (proximal segment of bowel reversal) or diarrhea (more distal small bowel reversal), are no longer generally advocated for the treatment of these conditions and are now rarely used by surgeons working on the upper gastrointestinal tract.[15] Nonoperative therapy usually results in enough improvement of symptoms to satisfy most patients. The conditions usually improve with time, and the ability to obtain an adequate experience in such procedures is so rare as to preclude most surgeons from obtaining expertise in them. Despite the occasional reports of success with such operations, many surgeons have found that these operations often are associated with a high incidence of bowel obstruction, stenosis, and not appreciably greater improvement in symptoms than less aggressive nonoperative measures. One relatively recent report described elimination of dumping when an isoperistaltic 10- to 12-cm segment of jejunum was placed as an interposition graft as an alternative to Billroth I reconstruction after distal gastrectomy for gastric cancer.[16]

The amount of nonbariatric gastric surgery that is done for benign gastric disease, such as peptic disease, has decreased greatly over the past several decades. Medical therapy is often adequate to relieve many of the symptoms of peptic ulcer and cure the disease without surgical therapy. Patients who still require surgery for benign gastric disease, although less numerous, still may manifest the same severe complications and symptoms that made gastric surgery difficult in the past. For those patients, appreciating the experience of past decades helps in planning any needed reoperative surgery.

GASTROPARESIS AND GASTRIC EMPTYING OR MOTILITY PROBLEMS

Gastroparesis

Gastroparesis is defined as poor intrinsic gastric emptying resulting from a lack of peristaltic activity. Most patients with gastroparesis have this condition secondary to another medical condition, such as diabetes, vagotomy, collagen vascular disease, viral illness, medications, Parkinson's disease, hypothyroidism, or amyloidosis. Rarely, patients have primary gastroparesis, and this is part of an overall neural or smooth muscle disease of the gut that manifests itself as overall pseudo-obstruction or ileus, rather than isolated gastroparesis. Gastroparesis is often idiopathic as well.

Patients with gastroparesis present with early satiety, vomiting of undigested food, abdominal pain, nausea, and food intolerance and aversion. Patients with idiopathic cases, believed sometimes to result from a viral illness, may develop sudden severe symptoms. Other secondary causes are usually more insidious in onset except for postvagotomy patients. These patients have perhaps the most profound symptoms and are perhaps the one subgroup of patients with gastroparesis for whom reoperative surgery may be indicated for severe symptoms.

The diagnosis of gastroparesis is made by the clinical syndrome and symptoms accompanied by a documentation of solid food and liquid food delayed emptying using radionuclide gastric emptying studies. Such studies are considered the gold standard for confirming the presence of delayed gastric emptying of solids and liquids. Gastroparesis can be mistaken for rapid gastric emptying, and gastric emptying studies are necessary sometimes to define clearly the cause of patient symptoms.[17]

Gastroparesis is mentioned here largely as a warning to surgeons that the primary and best therapy for such patients is *medical*. Prokinetic agents, either erythromycin or metoclopramide, are the medications of choice for treating gastroparesis. Erythromycin, a macrolide antibiotic, has a chemical structure similar to the gastrointestinal regulatory peptide motilin. Erythromycin exerts gastric-specific contractile stimulation and assists in gastric emptying. It has been shown to be effective for short-term and long-term use. Side effects include cramping. Metoclopramide is a procainamide derivative that acts to stimulate the entire gastrointestinal tract by antagonism of peripheral dopamine receptors and increasing acetylcholine release from the myenteric plexus. It is the most commonly prescribed prokinetic agent available in the United States today and is effective for gastroparesis. The side effects of long-term metaclopramide use are its major detraction; these include extrapyramidal side effects and nightmares particularly in elderly patients, dystonic reactions in young patients, and hyperprolactinemia.

Reoperative surgery for causes of gastroparesis is uncommon and generally limited to cases of severe postvagotomy gastroparesis.[18] Diabetic gastroparesis is usually treated adequately with medical therapy. Nutritional

compromise occasionally may occur, however, secondary to the disease. In such situations, placement of enteral access is needed for management of the disease. Such enteral access must be a *jejunal* feeding tube, not a gastrostomy. Placement of nutrients directly into the stomach not only does not guarantee they will reach the intestine before being vomited but also exacerbates symptoms of the gastroparesis. Surgeons are urged to use a conservative approach to patients with idiopathic gastroparesis because these individuals may resolve their disease spontaneously over months to years and should not be subjected to irreversible gastric resection, which could compound subsequent upper gastrointestinal symptoms.

Patients with severe persistent symptoms of gastroparesis, who have had the disease for a long time, who have a known cause for the disease, who have experienced nutritional compromise, and who have a poor quality of life secondary to the problem occasionally may be considered candidates for surgical therapy. Most individuals who fit this description have postvagotomy gastroparesis, and so reoperative surgery is the norm. In such patients, removal of most of the stomach, leaving only a small gastric reservoir that cannot serve as a large atonic pouch to store food, is indicated. The operation resembles the Roux-en-Y gastric bypass (RYGB) that currently is the most frequent operation performed for morbid obesity except that the distal stomach is resected. Near-total gastrectomy with Roux-en-Y gastric drainage is relatively successful in relieving symptoms in this patient population. One study by Echauser et al.[19] showed nearly 80% relief of symptoms for patients undergoing near-total gastrectomy for postvagotomy motor disorders of the stomach. Even this radical surgical approach to gastroparesis is not guaranteed to restore a good quality of life to the patient, but it remains the only surgical option for the most severely affected patients.

Reports have arisen regarding the use of gastric electrical stimulation for the treatment of gastroparesis. Although symptomatic relief has been achieved in patients, data showing pacing produces an increase in gastric emptying by radionuclide testing are still lacking.[20] This treatment modality still must be considered an experimental procedure.

Roux Limb Syndrome

The Roux limb syndrome, described previously in the surgical literature, is manifested by symptoms of early satiety, bloating, upper abdominal pain, and vomiting after eating. Patients who have this syndrome have had previous gastric resection with vagotomy and often had a second operation to convert the gastric drainage from a loop gastrojejunostomy to a Roux-en-Y drainage. The cause of the Roux syndrome was attributed to a primary motor disorder of the Roux limb by some authorities. Other authors, including us, believe the vagotomy itself was the primary reason for the symptoms and the dysfunction.[21] Evidence to support this position derives from the fact that patients who did have Roux syndrome, and who underwent subsequent near-total gastrectomy with Roux-en-Y drainage, usually were relieved of symptoms with the same frequency as patients with gastroparesis. As a result of improvements in medical treatment for peptic ulcer disease, the performance of gastric resection with vagotomy has decreased markedly over the past 3 decades, and this situation is now rarely encountered in clinical practice. The numerous morbidly obese patients who have undergone RYGB, without vagotomy, without producing a large number of patients with the Roux syndrome, lends further evidence to the fact that the vagotomy and gastroparesis were likely the underlying cause of the symptoms experienced in the past by patients given the diagnosis of the Roux limb syndrome. If such patients are encountered today, they should be managed in a similar fashion as patients with gastroparesis, reserving surgical therapy for patients refractory to medical management, and using near-total gastrectomy as the surgical procedure of choice if reoperation is performed.

GASTROINTESTINAL NEOPLASMS

Adenocarcinoma of a Gastric Remnant

Patients who have undergone previous distal gastrectomy for benign peptic ulcer disease are at risk for cancer of the remaining gastric remnant. This risk has been well documented in the surgical literature.[22] The occurrence of tumors is on average several decades after the original operation, however. Routine screening endoscopy for all such patients is recommended starting 20 years after surgery. Should a suspicious lesion be found on gastroscopy in this setting, multiple biopsy specimens of the lesion should be obtained. The highest likelihood for yield of a correct diagnosis is when biopsy specimens are taken at the edge of the ulcerated lesion, not in the often necrotic central portion of a tumor ulcer. Completion gastrectomy is the surgical treatment of choice and is curative in nearly all cases that are diagnosed by endoscopic screening.

Patients who have had previous gastric resection for adenocarcinoma are at risk for local recurrence. Surveillance endoscopy in this patient population is performed on a 6- to 12-month basis, until several years of disease-free interval have passed. Then endoscopic frequency is decreased. If a recurrent cancer is diagnosed, reoperative surgery with total gastrectomy and en bloc radical resection including an R2 nodal dissection as indicated is the procedure of choice. Achievement of an R0 status is the goal of resection. Roux-en-Y esophagojejunostomy is indicated for reconstruction, and a feeding jejunostomy is placed for assurance of enteral access and feeding capability should any problems arise at the esophagojejunostomy anastomosis. Results of resection for recurrent gastric adenocarcinoma show a high incidence of ultimate death from recurrent cancer.[23] If recurrent gastric cancer has progressed beyond the realm of feasible curative re-resection, options for palliation of the problem include laparoscopic gastrojejunostomy[24] and endoscopic placement of metallic stents.[25]

Recurrent Stromal Cell Tumor

Gastrointestinal stromal cell tumors, known in the past as leiomyomas of the gastrointestinal tract, have variable malignant potential. Their tumor biology behavior mimics sarcomas, in the sense that local recurrence is the most common manifestation of recurrent neoplastic disease. If such a situation occurs for a previously resected gastric stromal tumor, radical re-resection is indicated to cure the condition. A 5-cm proximal and distal margin of resection is optimal, if possible. Intraoperative frozen section of the margins of the resected specimen is appropriate to help confirm the adequacy of surgical excision of the recurrent tumor. Neither radiation nor chemotherapy has much efficacy in this disease; surgery remains the only chance for complete cure. If the tumor has extended into surrounding structures, en bloc resection including the spleen, distal pancreas, and colon or wedge resection of the left hepatic lobe may be necessary. Reconstruction usually is achieved with a Roux-en-Y gastrojejunostomy or esophagojejunostomy. Recurrent stromal cell tumors have a penchant for repeat recurrence, and the potential for cure is markedly diminished over that of initial resection.[26]

Recurrent Desmoid Tumors

Desmoid tumors, which are commonly associated with patients with familial colon polyposis and Gardner's syndrome, are a difficult surgical problem. They are generally slow-growing tumors and manifest themselves by creating symptoms of obstruction or pain. They tend to occur in the mesentery of the small bowel.

Diagnosis is usually by suggestive clinical picture and computed tomography. A mass in the mesentery of the small bowel is diagnostic. Desmoids most commonly involve the bowel distal to the duodenum, but may occur in the area of the celiac axis or duodenum. In such cases, they tend to be difficult tumors to remove completely because they often present at a stage where perivascular invasion of major mesenteric arteries, such as the superior mesenteric artery or branches of the celiac axis, is involved. Radical excision with vascular reconstruction is occasionally possible, but often tumor extent and invasion preclude this option as well. Debulking of the tumor has some benefit, but offers only palliative therapy.[27] Because desmoid tumors are so difficult to cure, a high index of suspicion for their presence must be maintained in patients at risk for the disease.

GASTROESOPHAGEAL REFLUX DISEASE

Reoperation for failed antireflux surgery is becoming increasingly commonplace, especially at major referral centers for complex gastrointestinal problems. During the mid-1990s, the incidence of fundoplication performed in the United States dramatically increased with the availability of a laparoscopic option for the procedure. The number of procedures increased by approximately 800% between 1989 and 1999.[28] Foregut surgeons now are seeing an increasing number of patients who have developed problems from their initial operation and present as potential candidates for revisional surgery. Patients who develop recurrent symptoms after previous antireflux surgery do so because the operation may have failed for the following reasons:

1. Recurrent diaphragmatic herniation with migration of the wrap to an intrathoracic location
2. Slippage of the wrap with recurrent gastroesophageal reflux
3. Inadequacy of the wrap or disruption of the wrap with recurrent gastroesophageal reflux
4. Inadequate length of abdominal esophagus at the original operation, with the wrap placed around the proximal stomach, preventing adequate increase in lower esophageal sphincter pressure and resulting in subsequent recurrence of gastroesophageal reflux
5. Stenosis of the wrap area with persistent postoperative dysphagia

The symptoms that generally occur after failure of antireflux surgery differ. Symptoms should be a guide to suspicion of one of the above-listed failures of the previous fundoplication. Symptoms alone are notoriously unreliable for confirming the presence of a failed previous fundoplication, however, and the surgeon must confirm the presence of recurrent disease and the anatomic problem with the fundoplication before offering reoperation to the patient. Only with such information can a rational plan for reoperation be constructed and the appropriate counseling occur regarding the likelihood of success of the revisional operation.

Recurrent and persistent epigastric pain after a previous fundoplication should raise the suspicion that recurrent herniation of the wrap through the diaphragm and into the mediastinum has occurred. This is the classic symptom of recurrent diaphragmatic herniation. An upper gastrointestinal series is usually diagnostic and may be the only test needed in this setting before reoperation is recommended. Recurrent herniation of the wrap into the chest does not always manifest with significant symptoms. Hashemi et al.[29] reviewed the University of Southern California series of repairs of large paraesophageal hernias by obtaining a routine upper gastrointestinal series an average of 27 months postoperatively for patients undergoing repair of type III hiatal hernias with fundoplication. Patients who had a previous laparoscopic repair had a 42% incidence of recurrent hernia, and more than half had few, if any, symptoms.

Reoperation for recurrent diaphragmatic herniation can be performed through the abdomen or through the chest. If multiple previous upper abdominal operations have been performed, the latter approach may allow a technically easier repair. Left thoracotomy, reduction of the herniated wrap back into the abdomen, and crural diaphragm repair are indicated in this setting. Use of reinforcing mesh is still controversial, but may be considered if the diaphragm tissue is of poor quality. Mesh must be placed so as to avoid potential erosion into the esophagus. Materials that have a smooth surface (e.g., Gore-Tex or composite meshes) are preferred to

materials with an open weave configuration (e.g., Prolene or Marlex).

Repair of the reherniation also can be accomplished with high likelihood of success through the abdomen. Our experience has been that performance of this recurrent surgery may require an open incision, depending on the severity of scarring at the diaphragmatic hiatus. A previous operation done via celiotomy usually requires another open approach. If the previous antireflux operation was done laparoscopically, however, and scarring in the area of the diaphragm is not excessive, we have repaired the recurrent herniation successfully with a laparoscopic approach. The same consideration must be entertained for the use of a nonadherent mesh material to reinforce the crural repair through the abdomen and when a laparoscopic approach is used. Mesh should be securely fixed with sutures, not stapled or tacked to the diaphragm.

Patients who present with symptoms resembling recurrent gastroesophageal reflux after a previous fundoplication should be assessed carefully to determine that recurrent reflux is present. Patients are often restarted on proton pump inhibitor therapy for presumed recurrent reflux after surgery when vague or nonspecific symptoms that could be reflux are voiced to the patient's internist or gastroenterologist. Lord et al.[30] showed that at a mean time of 28 months after fundoplication, 43% of symptomatic patients were taking acid suppression medications, and only 24% of patients taking acid suppression medications had abnormal 24-hour pH studies.

If a patient complains of symptoms of recurrent reflux, full evaluation of the patient and the previous operation is indicated. Minimum tests include an upper gastrointestinal series to assess for potential disruption of the wrap, herniation of the wrap into the chest, or gross reflux on contrast agent ingestion. If the upper gastrointestinal study shows a clear problem with the wrap, some surgeons proceed to reoperation. A pH test is the gold standard for documenting recurrent reflux in this setting. Upper endoscopy should be liberally performed, especially if considerable time has passed since the first operation, or if there is any concern that Barrett's esophagitis may have developed in the interim. Upper endoscopy also gives good information regarding the current position of the wrap and further enhancing information regarding diaphragmatic herniation. Lord et al.[30] reported that endoscopic assessment of the fundoplication was the most significant factor associated with an abnormal pH test, documenting the accuracy of endoscopy to assess a disrupted wrap.

Our general recommended approach to the reevaluation of patients with a failed antireflux operation is to obtain an upper gastrointestinal series and upper endoscopy and proceed with pH testing if those studies do not show gross herniation of the wrap into the chest. Adding a repeat esophageal manometry in this setting is controversial and should be based on the patient's symptoms. Any symptoms that suggest atypical pain, esophageal spasm, or dysphagia are indications for a preoperative manometry study before reoperative surgery.

The outcomes of reoperation for failed antireflux operations are generally good. The largest series in the literature was reported by the group from Emory.[31] In their series of 1892 patients who underwent fundoplication at Emory, 2.8% required reoperation. Most reoperations occurred within 2 years of the initial procedure. Transdiaphragmatic wrap herniation was the most common reason (61% of cases) for reoperation in that group. A group of 231 patients had fundoplication done elsewhere, and in that group transdiaphragmatic herniation was the problem in 47% of cases. Slipped or disrupted wraps were found in 19% and 18% of the two groups and were the second most common reason for failure. Most of the reoperations were done laparoscopically (70%). Mortality for the series was 0.3%. Intraoperative perforation occurred in 17% of the laparoscopic cases and 29% of the open cases. Postoperative complication rates were 11.7% for the laparoscopic cases and 40.3% for the open cases. Relief of postoperative symptoms to the mild or absent category was achieved in 73% to 89% of patients. Failure of the reoperations requiring a second reoperation was reported in 8% of patients, with transdiaphragmatic herniation again being the leading cause of failure.

Other reports of reoperative surgery for failed fundoplication also have shown relatively good results, although never as good as the initial operation. Neuhauser and Hinder[32] reported results of 100 consecutive patients undergoing reoperative surgery for failed fundoplication. Only 52% of the patients had a previous laparoscopic operation. These authors performed reoperative laparoscopic fundoplication in 83% of cases. There was a 30% perioperative or postoperative complication rate, however, and the authors cautioned that such reoperative surgery is a major surgical technical challenge. Byrne et al.[33] described their experience with 118 patients undergoing reoperative antireflux surgery, with 101 of the 118 being able to be done laparoscopically. Heartburn was relieved or minimal in 84%, and regurgitation was relieved or minimal in 87% of patients. Patients having preoperative dysphagia were improved in 25 of 32 cases. Rosemurgy et al.[34] reoperated on 64 patients: 28% owing to hiatal failure, 19% owing to wrap failure, and 33% owing to failure of both. Most (76%) reoperations were done laparoscopically. Improvement in dysphagia was observed in 100% of symptomatic patients, improvement of reflux was seen in 79%, and improvement of both when both were present was seen in 74% of patients. Heniford et al.[35] reoperated on 55 patients. They did 37 of the procedures laparoscopically and had a 12.7% complication rate and an average hospitalization of 4.6 days; greater than 90% of patients experienced good to excellent symptom relief. Dutta et al.[36] reported a series of 28 redo fundoplications, most for symptoms of gastroesophageal reflux disease. All but two were done laparoscopically, with an average operating room time of less than 1 hour. Three patients required reoperation for reherniation of the wrap.

Reoperation for failed fundoplication can be performed with good symptomatic and overall outcomes. Patients must be cautioned that the reoperations have a higher complication rate and a slightly lower symptomatic improvement rate than the initial operation.

Success at performing reoperations laparoscopically depends on the severity of previous scarring and the surgeon's skill and persistence. These reoperations should be performed by surgeons with extensive laparoscopic and antireflux surgical experience.

Technical Aspects of Revisional Antireflux Surgery

Revisional antireflux surgery poses a significant technical challenge. The following are recommendations for successful laparoscopic performance of the operation:

1. The initial approach should be as for all previously operated abdomens, with care being taken to avoid organ injury on accessing the abdomen.
2. The most difficult initial organ dissection plane is the one between the inferior surface of the left lobe of the liver and the anterior proximal stomach. Dissection of the liver off the stomach without excessive violation of Glisson's capsule and significant bleeding is important. If liver parenchymal violation occurs, often the liver retractor can be positioned to place direct pressure on the area of the injury, tamponading any bleeding and achieving hemostasis as the operation progresses. Significant liver laceration warrants the placement of a closed-suction drain in the area at the completion of the operation to drain any potential bile leak. Liver surface hemostasis, if difficult, can be enhanced by high-energy electrocautery applied 1 to 2 mm off the surface of the liver to seal the tissue. The argon beam coagulator is even more effective if significant areas of capsular disruption have occurred. If one uses this instrument during laparoscopic surgery, the abdomen must be vented while the energy source is turned on.
3. The fundoplication position and the relationship to the diaphragmatic crura must be assessed. Usually is it evident if the problem is wrap herniation through the diaphragm, wrap disruption, or wrap misplacement.
4. Sutures used to create the wrap should be identified and cut, loosening the wrap.
5. The fundoplication should be taken down carefully and completely. Tissue planes should be confirmed. If any question exists as to the location and edge of the esophagus, an intraoperative endoscope or lighted bougie can facilitate location of its borders. Nonlighted bougies also are helpful if neither an intraoperative endoscope nor lighted bougie is available.
6. Conversion to an open incision should be performed if the tissue planes of the gastric fundus, the borders of the esophagus, or the borders of the diaphragmatic crura are not clearly seen. It is hoped that this decreases the incidence of intraoperative organ injury.
7. The fundus must be redissected to achieve good mobilization, and the retroesophageal area must be maximized for adequate room to pass the wrap.
8. Abdominal esophageal length must be 2 cm at rest. Mobilization of the esophagus to achieve this length must be performed. An esophageal lengthening procedure rarely is necessary. If so, we have successfully used a circular then linear stapler laparoscopically, similar to a laparoscopic vertical banded gastroplasty (VBG) being done for morbid obesity.
9. Re-repair of the crura is almost always necessary. Poor tissue quality of the crura should raise the consideration of placement of a soft mesh across the lower crura, not in contact with the esophagus, for reinforcement of the closure.
10. The wrap must be constructed over a dilator, preferably one No. 54 to 60 French size.
11. Any concerns for injury to the esophagus or stomach should be tested by air insufflation using an endoscope intraoperatively.
12. The wrap, when reconstructed, should be placed as high as possible on the esophagus and fixed to the crura of the diaphragm in revisional surgery. This placement should help prevent a second hiatal failure.
13. If a hiatal failure is still of concern, anterior gastropexy may help prevent gastric migration upward into the mediastinum.

The most important of these principles are summarized in Box 76–2.

BARIATRIC SURGERY

Revisional bariatric surgery should be performed only by an experienced bariatric surgeon. Laparoscopic revisional bariatric surgery requires extremely advanced laparoscopic skills, significant bariatric surgical experience and skill, and an efficient and supportive operating room team that is well equipped for such a surgically challenging operation. A skilled laparoscopic first assistant is a necessity for all bariatric surgery, but particularly revisional surgery.

Box 76–2 Major Principles of Reoperative Antireflux Surgery

Expect the plane between the undersurface of the left lobe of the liver and the stomach to be difficult to dissect cleanly.

Identify the source of the failure—wrap slippage, disruption, diaphragmatic hernia, or combination.

Clearly identify the esophagus.

Take down the wrap.

Confirm adequate length of abdominal esophagus.

Reconstruct the operation, and test for leaks or organ injury.

Patient Selection

Based on supply, demand, and public health concerns, one can make a strong case that revisional bariatric surgery is rarely indicated. Currently more than 23 million people in the United States are candidates for bariatric surgery, and less than 1% of them receive surgical therapy annually. There is a shortage of well-trained bariatric surgeons, especially those who perform the operation laparoscopically, for the patient demand. Use of surgeon time and medical facility resources for revisional bariatric surgery is, in light of these facts, of debatable merit. The practice of medicine and surgery holds care of the individual patient as the paramount concern, however, and as such, revisional surgery may be appropriate at times.

All bariatric operations have some failures. A figure of approximately 10% is often used in discussions regarding the "failure rate" of various well-established bariatric operations. The reasons for failure may vary. These reasons must be assessed carefully and understood before reoperative surgery is entertained or offered. If the failure is *primarily of the operation,* consideration for reoperation is appropriate. If the failure is *primarily of the patient and the patient's eating habits and compliance,* reoperation has little likelihood of succeeding any more than the initial failed operation. Surgical ego, compassion for a noncompliant patient who is upset with his or her current condition, and the incentive to perform a technically challenging operation all should be avoided in such situations and should not lead the surgeon to offer reoperation to a patient who has failed a previous bariatric operation because of behavioral and eating issues.

Reoperation should be considered in a situation where the operation has failed. The surgeon must define this anatomic failure. Reoperation is based on correcting the previous failure or safely revising the first operation to another bariatric procedure appropriate for the patient and his or her needs, expectations, and eating patterns. It is wise to have several counseling sessions with patients who request reoperative surgery. A dietary history not only from the patient, but also from the patient's family is appropriate in this setting. The patient needs to have demonstrated the appropriate behavior after the initial failed operation.

Any patient who is a candidate for reoperative surgery, if the surgery is to produce further weight loss, must meet the National Institutes of Health criteria for qualifying for weight loss surgery. The patient must have a body mass index (BMI) of greater than 40 kg/m^2 without weight-related comorbid medical problems or a BMI greater than 35 kg/m^2 with a comorbid problem. Psychological stability, motivation, documentation of previous appropriate behavior after the initial operation, and no medical conditions making the reoperation of excessively high risk are criteria that we mandate before reoperative bariatric surgery.

Failed Vertical Banded Gastroplasty

The VBG was the most popular bariatric operation performed in the 1980s. By 1990, it had fallen out of favor largely because of the poor long-term weight loss record of the operation[37] and because a considerable percentage of patients also develop progressive stenosis of the gastric outlet,[38] prompting conversion to a high-calorie liquid diet.[39] Multiple reports exist in the bariatric surgical literature documenting the ability to convert patients with previously failed VBG operations successfully to RYGB. Jones[40] reported only a 13% complication rate for a series of 141 patients undergoing reoperative surgery to convert from failed bariatric procedures to RYGB. Sugerman et al.[41] performed conversion of 53 VBG procedures with complications to RYGB, achieving 67% excess weight loss. The complication rate was high—about 50% for the series, including 20 marginal ulcers. Cariani et al.[42] also reported a high incidence of complications after reoperative surgery for VBG or failed RYGB, totaling greater than 55% between early and late complications. Reoperative surgery, especially bariatric surgery, carries increased risk for infection, wound complications, pulmonary complications, and intra-abdominal crises from leaks above that seen for initial operations.

Most reoperative surgery for failed VBG has been done using a celiotomy approach. Some surgeons have performed this operation laparoscopically, however. Gagner et al.[43] reported laparoscopically converting 27 patients with failed open or laparoscopic gastroplasty, adjustable gastric banding, or RYGB to a new or revised RYGB. The average BMI for these patients decreased from 43 kg/m^2 to 36 kg/m^2, and the complication rate was 22%. There are increasing reports of small experiences in the bariatric surgical literature where surgeons have used a laparoscopic approach successfully to convert a failed previous bariatric operation to a RYGB. These failed procedures are most often VBG or laparoscopic adjustable gastric banding (LAGB). Technical considerations when performing a conversion of a VBG to a RYGB, whether laparoscopic or open, are as follows:

1. Dissection of the left lobe of the liver off the area of the band, on the lesser curvature of the stomach, is usually the most difficult tissue plane encountered.
2. The proximal gastric pouch must be clearly identified.
3. The new gastric pouch must be made above the level of the band. This is not usually difficult because the existing pouch above the band is usually distended and of more than adequate size to divide and still have an adequate proximal gastric pouch.
4. A decision to resect or leave the distal portion of the existing proximal pouch above the band must be made. If it is left in place, the opening through the band must be adequate to drain this isolated gastric segment. If it is resected, the band and the section must be completely resected, with the distal resection line below any previous staple lines.

The failed fixed banding procedure of the VBG also has been successfully revised to placement of an adjustable gastric band. The adjustable gastric banding

procedure is the most common bariatric operation performed throughout the world outside the United States and is gaining popularity in this country. O'Brien et al.[44] placed an adjustable band to revise failed gastroplasty and other procedures for 50 patients. The 3-year weight loss was 47% of excess weight. The early complication rate of placement of these bands, done via a celiotomy, was considerably increased versus band placement as a primary operation (17% versus 1.1%), always done laparoscopically. Late (2% versus 18%) complication rates were lower for the revision series than for initial LAGB.

Failed Laparoscopic Adjustable Gastric Banding

Reports in the literature that have described reoperation for failed LAGB have usually taken the approach of using only one other alternative operation for this problem. Conversion of a failed LAGB to a laparoscopic RYGB was performed by Mognol et al.[45] for 70 patients. They reported a conversion rate of only 4.3%, an operative time of 4 hours, hospital stay of 7 days, complication rate of 14.3% early and 8.6% late, and no deaths. Excess weight loss averaged 70%, and more than 60% of patients achieved a BMI less than 33 kg/m^2. These results are excellent and are similar to the results reported by Calmes et al.[46] for a series of 49 patients converted from LAGB or VBG to laparoscopic RYGB. They had no conversions, operating room time was 3.25 hours, morbidity was 20%, and nearly 75% of patients achieved a BMI less than 35 kg/m^2.

The use of a laparoscopic biliopancreatic diversion to treat patients with failed weight loss after LAGB was reported by Fielding.[47] Having performed a large series of LAGB procedures, surgeons reoperated on 5.4% of the initial LAGB group who had their bands removed for a variety of reasons. They performed the biliopancreatic diversion 38 times laparoscopically and 20 times via celiotomy. They also performed a laparoscopic duodenal switch procedure for 21 patients. In this entire group, excellent weight loss of 40% excess weight was achieved with only a 6.3% complication rate and no mortality.

Failed Roux-en-Y Gastric Bypass

RYGB may fail for several reasons. If the surgeon does not divide the stomach in creating the proximal gastric pouch, there is a significant incidence of disruption of the gastric staple line with regain of weight and associated development of marginal ulceration at the site of the gastrojejunostomy. MacLean et al.[48] reported the incidence of such staple line disruption in 29% of cases followed up to 8 years. Our own experience with not dividing the stomach in the first few years of performing RYGB was a 5% incidence of staple breakdown per year, which accumulated to 25% by 5 years' follow-up. It is now commonly accepted in bariatric surgery that dividing the stomach to create the proximal gastric pouch results in fewer long-term complications from staple line breakdown.

If staple line breakdown is the reason for the failure of the RYGB, reoperation is indicated to redivide the stomach at or above the original staple line. Care must be taken by the surgeon not to leave an isolated undrained closed section of stomach between staple lines. If staple line identification intraoperatively is difficult, we have used upper endoscopy to help define the proximal edge of the staple line. If confirmation of a preexisting staple line can be done only from the distal stomach, we have no concerns about creating a small gastrotomy in the distal stomach during revisional gastric surgery to identify with absolute certainty the level of the previous staple line. This maneuver is useful for all types of reoperative gastric surgery, not just bariatric. The gastrotomy is easily closed later.

Failed RYGB has been treated by adding a malabsorptive component to the original procedure by Fobi et al.[49] and Sugerman et al.[50] Fobi's group[49] performed a distal RYGB, decreasing the absorptive length of the alimentary tract in half. They reported an excessive protein malnutrition incidence of 23% in the 65 patients for whom this was done. Weight loss was from a BMI of 42 kg/m^2 to 35 kg/m^2. Sugerman's group[50] similarly found adding malabsorption to significant restriction can be problematic when they created a distal RYGB with only a 50-cm common channel after failed gastric bypass. All five reported patients developed protein-calorie malnutrition, and two died of hepatic failure. Creation of a 150-cm common channel in 22 patients resulted in only 3 developing protein-calorie malnutrition and reoperation to lengthen the common channel. Bariatric surgeons must be aware of the *significant* potential morbidity that may result from adding a malabsorptive operation on to an already present restrictive one.

There is a trend in the bariatric field, especially by bariatric surgeons or their colleagues who perform advanced intraluminal endoscopic surgery, to consider reoperating on patients after RYGB who have regained weight or failed to lose adequate weight and who have a larger than 1-cm gastrojejunostomy. The reasoning is that the enlarged anastomosis has allowed excess food intake and weight regain. Initiatives of performing endoscopic intraluminal suturing to narrow the gastrojejunostomy anastomotic opening have begun in several centers.[51] Endoscopists use the same endoscopic tissue suturing device that has been used to treat gastroesophageal reflux disease endoscopically for several years in some centers. The latter experience has been less than satisfying and does not compare in efficacy with laparoscopic antireflux surgery. The major concern with this reoperative procedure is that to date there is *no direct evidence* anywhere in the bariatric literature that a smaller anastomosis produces improved weight loss after RYGB. The experience with failed VBG should have taught bariatric surgeons that a small anastomosis does not guarantee good prolonged weight loss. Similarly, no study has been published showing that reoperation to narrow the anastomosis has any efficacy. Endoscopists who venture into this arena should be aware of the lack of evidence substantiating these procedures. Until proved effective (including lack of placebo and associated diet and

exercise effects), these procedures must be considered experimental.

Failed Malabsorptive Procedure

Few reports of reoperative surgery for biliopancreatic diversion or duodenal switch operations exist. This is largely because the operation usually produces satisfactory weight loss. The reoperations that do occur usually are due to the consequence of protein-calorie malnutrition and the need for repeated episodes of parenteral nutrition and persistent hypoalbuminemia. This situation is corrected by revision to increase the length of the common channel. Surgeons usually revise the operation to make a considerably longer common channel, but there are no clear guidelines for the amount or percentage that the surgeon must increase the common channel to avoid residual protein-calorie malnutrition and still preserve some degree of weight loss. Cases must be individualized, and the surgeon does well to err on the side of safety in restoring adequate digestive function in these situations.

All bariatric operations may fail for a variety of reasons. The success with reoperation, as noted earlier for many of the reported series, is usually only modest. It is typical for the reoperative candidate to have a BMI in the low to mid 40s and to have some additional weight loss to achieve a BMI near 35 kg/m^2. Achieving a BMI less than 30 kg/m^2 is unusual based on most reported experiences. Many reoperations are done via an open celiotomy approach. Performance of laparoscopic reoperation should be restricted to only surgeons with significant advanced laparoscopic experience in bariatric surgery. Overall, the complication rates of reoperative bariatric surgery are considerably higher than the rates reported for initial procedures. Because of this combination of facts, the bariatric surgeon is cautioned to be particularly selective in offering reoperative surgery for failed previous bariatric operations. The concerns elaborated earlier regarding patient rather than operation failure always must be heeded when assessing a patient for reoperative bariatric surgery.

BILE REFLUX GASTRITIS

Enterogastric reflux is within the normal pattern of gastrointestinal physiology. The gastric mucosa is relatively resistant to modest amounts of bile, and gastritis normally does not occur with such quantities of bile. If bile reflux is excessive, however, bile gastritis may occur. Patients with this problem typically have epigastric abdominal pain, nausea, and bilious vomiting. The diagnosis of bile reflux gastritis requires first that no concurrent obstructive process is present. Such problems include afferent limb syndrome, efferent limb obstruction after gastrojejunostomy, more distal bowel obstruction, and gastroparesis, particularly postvagotomy gastroparesis. Upper gastrointestinal series, endoscopy with careful examination and biopsy of the gastric mucosa, gastric emptying studies, and quantitative assessment of the amount of enterogastric reflux all should be performed in patients suspected to have bile reflux gastritis. Radionuclide scintigraphy of the biliary tree is helpful in quantitating the amount of bile reflux. In most cases, an underlying cause for the patient's symptoms can be found after such a battery of tests. Often the problem is not true bile reflux. The surgeon must *avoid* operating on patients for this condition without a complete evaluation. Performing reoperative surgery for presumptive bile reflux when the true cause of the problem is gastroparesis leads to poor outcomes and persistently symptomatic patients.

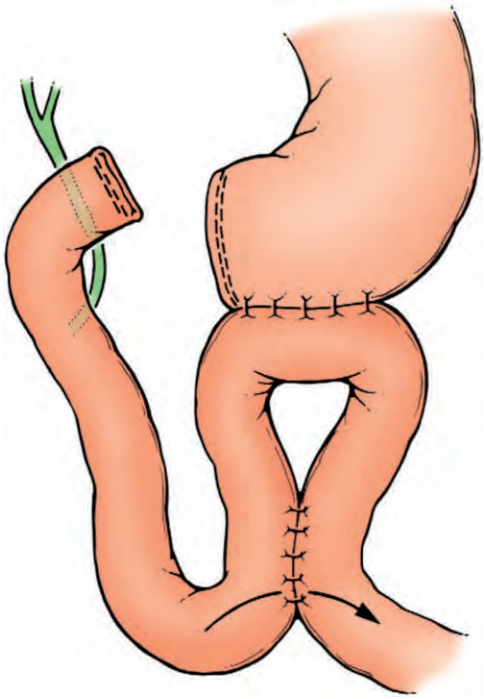

Figure 76–2. Braun's enteroenterostomy. Anastomosis between afferent and efferent limbs for surgical management of bile reflux gastritis. (From Madura JA: Postgastrectomy problems: Remedial operations and therapy. In Cameron JL [ed]: Current Surgical Therapy, 7th ed. Philadelphia, Mosby, 2001, p 92.)

Treatment of a patient with true bile reflux gastritis is based on the existing anatomy. If the patient has a gastrojejunostomy, the options include conversion to a Roux-en-Y drainage or creation of a Braun enteroenterostomy between the afferent and efferent limbs of bowel. This is performed by simply creating a side-to-side anastomosis between the afferent and efferent limbs draining the stomach (Fig. 76–2). Typically, the distance is 30 cm away from the gastrojejunostomy. Vogel et al.[52] reported excellent reversal of alkaline reflux gastritis by use of the Braun enteroenterostomy in a group of 30 patients.

The duodenal switch operation, first described by DeMeester et al.[53] for the treatment of this condition, treats bile reflux gastritis when there is no gastrojejunostomy or previous gastric resection. The duodenal switch is performed by dividing the duodenum 2 to 3 cm distal to the pylorus, then performing an anastomosis of the duodenal stump to a Roux-en-Y loop of jejunum (Fig.

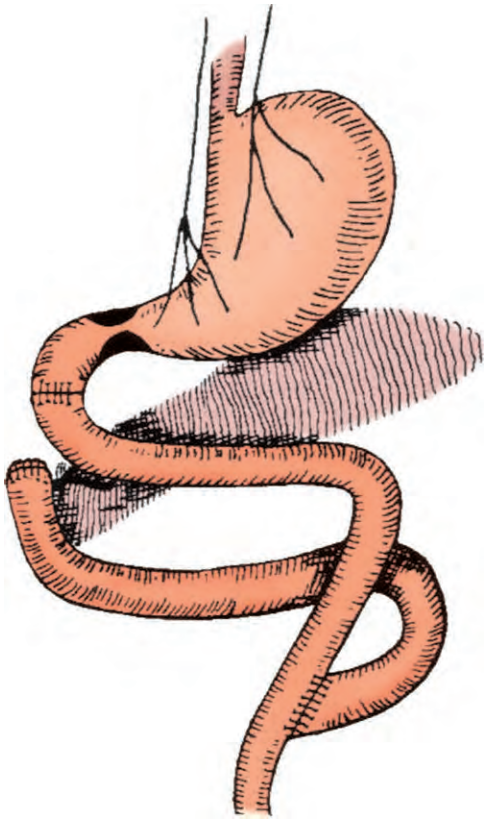

Figure 76–3. Duodenal switch procedure. The duodenum is transected 2 to 3 cm distal to the pylorus and anastomosed to a Roux-en-Y limb.

76–3). The enteroenterostomy of the Roux limb is typically at least 75 cm downstream to avoid any potential for bile reflux under normal circumstances. Marginal ulceration is a common problem after this operation, and consideration should be given to long-term proton pump inhibitor therapy postoperatively.

AFFERENT LIMB SYNDROME

Afferent limb syndrome is the term used to describe the partial obstruction of the afferent limb of a gastrojejunostomy after previous gastric resection and Billroth II gastrojejunostomy. The afferent limb contains the biliary and pancreatic secretions carried from the duodenum. Obstruction to drainage of the afferent limb may arise as a result of any obstructive process, benign or neoplastic. Early obstruction after a recent operation is usually the result of technical error in creating the gastrojejunostomy, with resulting kinking of the efferent limb. More chronic obstruction may result from progressive scarring of the afferent limb as it passes through the transverse colon mesentery; adhesion formation with stricture, chronic volvulus, or internal hernia; or any other chronic obstructive process.

Symptoms of the afferent limb syndrome commonly include postprandial epigastric and right upper quadrant pain, followed by bilious vomiting with simultaneous relief of the pain. The pain occurs as a result of the increased biliary secretions causing distention of the duodenum and afferent limb. When the limb pressure is sufficient to decompress into the stomach, bilious vomiting results. Because the syndrome is usually slowly progressive, it may cause enough partial obstruction of the drainage of the bile and pancreatic juice to elevate bilirubin and amylase. Chronic obstruction in the afferent limb also may result in a chronic diarrhea syndrome from bacterial overgrowth. Pancreatitis also has been reported.[54] Diagnosis of the afferent limb syndrome is often a clinical one. Radiographic studies, including upper gastrointestinal series or computed tomography with oral contrast administraton, often clearly delineate the problem and are usually diagnostic.

Treatment of afferent limb syndrome is reoperative, and the operative findings should dictate the procedure performed. If simple adhesiolysis resolves the problem, and the intestine is not chronically scarred and narrowed, that is all that is indicated. If the afferent limb is chronically scarred near the gastrojejunostomy, however, which is usually the case, surgical treatment is division of the bowel just proximal to the obstruction point and creation of a Roux-en-Y drainage of the stomach by reanastomosing the proximal end of the divided afferent limb to the jejunum 50 to 75 cm beyond the gastrojejunostomy. Closure of the mesenteric defect completes the procedure.

HOSTILE ABDOMEN

A taxing challenge a surgeon faces is the *hostile abdomen*. This term is used to describe an abdomen in which tissue planes are obscured, and bowel mobility is limited or absent. Severe scarring and carcinomatosis are the most common reasons for such an abdomen. Bowel obstruction is a common occurrence with abdominal or pelvic cancer. Patients develop an obstruction with a prevalence of 5.5% to 42% with ovarian cancer and 10% to 28.4% with colorectal cancer.[55] A complete obstruction requires operative intervention regardless of the patient's history. Most operative management of this situation would not involve reoperation on the stomach or duodenum, but often a gastrostomy tube is placed at the time of such procedures to help decompress the stomach; this may be the only option for patient palliation in the presence of an abdomen filled with carcinomatosis. Indications for placement of a gastrostomy tube are listed in Box 76–3. This is not a comprehensive list, but includes the most frequent indications for gastrostomy.

Gastrostomy tube placement is generally a straightforward procedure. Care must be taken to choose an area of the stomach that most easily reaches the anterior abdominal wall; this is usually the greater curvature area in the proximal body area of the stomach. The traditional Stamm gastrostomy serves adequately in almost all cases. Janeway gastrostomies, created from a greater curvature tube of stomach anastomosed to the skin, are indicated only as a permanent feeding access.

When encountering diffuse carcinomatosis in the setting of an obstructed gastrointestinal tract, the surgeon is wise to do as little as necessary and feasible to

Box 76–3 Indications for Gastrostomy

- As an alternative to nasogastric intubation during operations in which a prolonged postoperative ileus is expected
- As a means of long-term enteral access for patients who cannot eat without assistance
- For patients with obstructing lesions of the hypopharynx or esophagus
- As a reliable means of decompressing the stomach and giving enteral nutrition after esophageal and bariatric surgery
- Palliative decompression for distal obstructing lesions in which resection or bypass is not technically feasible or medically indicated

improve the patient's remaining time. Bowel obstruction in patients with metastatic cancer is often considered a relatively terminal event, with median survival following being 3 months.[56] Patients with terminal cancer who are unfit for an operation may benefit from nonoperative management of a malignant obstruction. Analgesics, antiemetics, and antisecretory medications have been shown to provide an alternative management of a chronic obstruction.[57] Surgery is an appropriate option in low-risk to moderate-risk patients. Only 30% of patients with malignant bowel obstruction have prolonged postoperative symptom relief after surgical intervention.[58]

When a lysis of adhesions is attempted in a patient with multiple previous operations, the patient is at great risk for multiple enterotomies. In contrast to an enterotomy during a standard dissection, an enterotomy in a "frozen abdomen" is much more hazardous. The bowel injury may be extremely difficult to close if the intestine cannot be safely mobilized to allow for adequate closure. Also, there is a slightly greater risk for luminal narrowing from a repair of a bowel injury that is poorly visualized and mobilized. When multiple enterotomies have been made, or no progress is being safely made, consideration must be given to backing out of the operation. This is a difficult decision for any surgeon to make. Although the original operative goals may not have been accomplished, consideration must be given to avoiding causing further morbidity to the patient.

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Chapter

77

Radiation Enteritis

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Radiation therapy or combined chemoradiation therapy is a widely accepted adjuvant or neoadjuvant treatment modality for various tumors. Despite steady technical improvements in irradiation techniques, the major drawback is the unnecessary irradiation of normal tissue in close vicinity to the tumor, which can result in radiation toxicity such as radiation enteritis, an entity that can occur in an acute or chronic form.

This chapter attempts to shed some light on the pathogenesis of radiation-induced toxicities or complications and discusses possible future treatments for patients suffering from this condition. Moreover, new technical developments in radiation oncology and radiochemotherapy that will improve the protection of nonmalignant tissue and hence decrease the complication rate of radiation therapy without compromising the tumor-killing activity of these methods are discussed as well.

BACKGROUND

Radiation is a common adjuvant and, more recently, a neoadjuvant therapy in the multimodality approach to the treatment of various abdominal and pelvic cancers and has been proved in multiple studies to be an important tool for destroying cancer cells. Besides these beneficial effects, radiation also affects normal and healthy tissue surrounding the targeted tumor, such as the small and large intestine, liver, kidney, and lung.[1-9]

Radiation enteritis is one of the most feared complications of abdominal and pelvic irradiation. The mucosa and submucosal vasculature of the intestine are most sensitive to radiation and might sustain severe acute or chronic damage leading to malabsorption, strictures, and fistulas, with considerable impact on the patient's quality of life.[10]

The amount of radiation required to produce clinical signs of enteritis varies with the treatment regimen and from patient to patient. Because of the current trend of combined chemotherapy and radiation therapy, the incidence of radiation enteritis is increasing.[11]

Clinicians are usually confronted with the sequelae of early and late complications of radiation enteritis and therefore need a detailed understanding of the mechanisms leading to early and late radiation enteritis.

INCIDENCE

Radiation enteritis is a relentless disease process reflecting widespread bowel involvement. The first patient with radiation-induced enteropathy was described by Walsh in 1897, only 2 years after Roentgen's description of ionizing radiation.[12,13]

According to the literature, the exact incidence of radiation enteropathy is not known. However, since the 1980s, the incidence of acute enteritis appears to have increased because more than 50% of patients with cancer receive radiotherapy as a component of their treatment.[14-18]

The incidence of *acute* radiation enteritis shows great variation and has been reported in the literature as being between 20% and 80%.[19,20]

The exact incidence of *chronic* radiation enteritis remains controversial and ranges from 0.5% to 36% with an average of 5%.[16,21-23] However, the prevalence seems to be underestimated in the literature because of losing track of patients, patient death as a result of malignancies, and differences in treatment regimens.[12,15,22] Moreover, one has to bear in mind that this wide variation is also due to different factors such as radiation dose per fraction and total dose of radiation and to patient-related predisposing factors such as location and size of the treatment volume, hypertension, diabetes mellitus, and preexisting vascular or pelvic inflammatory disease.[16,24]

A total radiation dose of less than 4000 cGy (4000 rad) rarely causes deleterious effects on bowel mucosa and hence radiation enteritis (1 Gy is equivalent to 100 cGy or 100 rad).[15,16] If the dose does exceed 5000 cGy, the complication rate increases significantly. Doses of radiation producing clinical damage in up to 5% or in up to 50% of patients within 5 years are termed $TD_{5/5}$ or $TD_{50/5}$, respectively, depending on the volume of irradiated tissue. The range is 60 to 75 Gy for the esophagus, 45 to 50 Gy for the stomach, 45 to 65 Gy for the small bowel and colon, and 55 to 80 Gy for the rectum.[25]

In addition, the use of certain adjuvant chemotherapeutic agents such as 5-fluorouracil (5-FU), doxorubicin, actinomycin D, and methotrexate increase the likelihood of enteritis secondary to radiation therapy. A history of laparotomy and previous abdominal operations also increases the risk for enteritis, probably because of adhesions that tether portions of the small bowel into the irradiated field.

ETIOLOGY

Roentgen rays have their most destructive effect on rapidly dividing cells such as bowel epithelium, and as a consequence many of these epithelial cells die during radiotherapy. Cells in other tissues are sublethally damaged and die off later when entering the mitosis phase.

The pathophysiologic effect behind radiation-induced cell death is the deposition of energy in the anatomic structure of the chemical constituents of cells.[16] Disruption of the DNA helix or abnormal reconstitution of the genetic code will result in cell death or cell dysfunction. Radiation injury will subsequently occur in the mucosa, submucosa, muscularis propria, and serosa as a function of cell turnover in these tissue layers.

Therefore, three distinct phases of radiation effects have been identified:

1. *Acute phase:* primarily affecting the mucosa
2. *Subacute phase:* predominantly affecting the submucosa
3. *Chronic phase:* affecting all layers of the bowel wall

During radiation therapy, adjacent healthy tissues are invariably located within the irradiated field and therefore represent the main dose-limiting factor of radiation therapy. The small bowel appears to be one of the most radiosensitive organs of the abdomen because of the high number of proliferating cells, the extensive vascular network, and important metabolic activities.[16] However, its mobility seems to be somewhat protective. The most sensitive cells of the bowel wall are those of the crypt of Langerhans in the small intestine.

Late radiation injuries more frequently involve the immobile and fixed terminal ileum. Because the jejunum, except for its upper portion and the proximal ileum, is relatively protected by its mobility, repeated exposure of selected small bowel segment is avoided.[16,22]

Predisposing Risk Factors

Many factors are thought to predispose to radiation injury. Dose-escalating techniques in radiation oncology, combined with chemotherapy and thin-built patients, are associated with a higher risk of sustaining small bowel injury.[26,27] Thin patients, especially females, and the elderly have an increased amount of small bowel in the pelvic cul-de-sac.[12,26,28,29] They also have a decreased amount of subcutaneous tissue, which would allow greater depth of penetration of ionizing radiation.

Any previous operation or pelvic infection may cause intra-abdominal fixation of the small bowel and thereby expose the same segment of bowel to the radiation field. This situation is predominantly seen after rectal surgery because of the development of more adhesions as a result of a high level of physical injury to the gut serosa and increasing microbial leakage through the intestinal wall into the peritoneum, unsuccessful reperitonealization, and the impaired vasculature of small bowel loops in the sacral cavity.[30] Low splanchnic blood flow as seen in congestive heart failure or conditions associated with vascular occlusion or narrowing predisposes to radiation-induced injury. Moreover, DeCosse et al. demonstrated a significant association between hypertension, diabetes, and cardiovascular disease and the subsequent development of radiation enteritis.[31,32]

PATHOPHYSIOLOGY AND HISTOPATHOLOGIC FEATURES

The gut wall is damaged by ionizing radiation either directly or indirectly. The direct effect of intestinal irradiation is loss of regenerating cells within the crypts of the intestinal epithelium.[16,22,30,33] Indirectly, damage to the fine vasculature of the intestine may progress to obliterative vasculitis and cause ischemia of the bowel many years after radiation therapy.

Early Histologic Findings

The first 2 weeks after radiation therapy is characterized by four early histologic findings. The first is *mucosal ulceration*. In early stages these ulcers are small and shallow but get bigger and deeper in the later stages and thereby lead to perforation and fistulization. The second histologic feature consists of *epithelial atypia*. Radiation-induced fine mutation is the single important factor involved in malignant transformation of intestinal epithelium in humans. The third finding is termed *ileitis cystica profunda*, which is defined by the presence of cystic glandular structures in the intestinal wall below the muscularis mucosae. Its mechanism remains controversial, but it has been suggested that fragmentation of the muscularis mucosae leads to herniation of epithelium into deeper layers of the intestinal wall. Moreover, mucosal trapping during the re-epithelialization phase of deep ulcers has been proposed as a potential explanation. The fourth characteristic is *serosal thickening*. This finding reflects an increased amount of fibrous connective tissue and edema. Its pathogenesis, however, is controversial. It is believed that radiation-induced vascular permeability is followed by edema, intestinal protein deposition, and subsequent fibrosis. These histopathologic findings decrease gradually and remain constant for 20 weeks on. Other features such as vascular sclerosis, intestinal fibrosis, and lymph congestion are virtually absent at 2 weeks but with time increase and reach a constant level 8 to 14 weeks after irradiation.

Late Histologic Findings

Late histologic features include three distinct entities. The first is characterized by vascular sclerosis. The struc-

tural and functional alterations in blood vessels consist of three stages: *early* (hours to days after irradiation), *intermediate* (4 weeks after irradiation), and *late* (4 to 6 months after irradiation). During the *early stage* an inflammatory reaction takes place with deletion of capillaries secondary to substances released by the damaged endothelial cells. The *intermediate phase* is characterized by destruction and obliteration of capillaries, sloughing of endothelial cells, and the formation of focal thrombi. Plasma proteins accumulate in the extravascular space and possibly lead to hyalinization, which is also seen histologically. In the *late phase* several histologic entities are observed, such as necrosis of the vessel wall, ulcerations, and thrombosis. Thickening of the vessels and media necrosis induce total vascular occlusion and disruption. The second late histologic finding is *intestinal wall fibrosis* as a result of deposition of collagen in the intestinal wall. Several pathophysiologic mechanisms have been discussed and are briefly outlined. Radiation has a direct effect on collagen and components of the extracellular matrix such as glycosaminoglycans. Cell injury or cell death involved in the production or degradation of collagen leads to fibrosis. Moreover, vascular and lymphatic damage contributes to the ongoing fibrosis. Some authors suspect nonspecific inflammatory or autoimmune processes. The third characteristic is *lymph congestion*. Loss of the epithelial barrier of the bowel leads to exposure of deeper layers of the bowel wall to intraluminal contents, which induces a severe inflammatory reaction. In late radiation enteropathy, fibrotic constriction of lymph vessels, rather than their direct damage, is the cause of obstructed lymph flow and consequent dilation.

MOLECULAR BIOLOGY OF RADIATION ENTERITIS AND MICROCIRCULATION

Recent progress in molecular biology has led to new concepts of the pathogenesis of radiation enteritis. The first concept involves *apoptosis,* which is defined as an active mode of cell death characterized by chromatin and cytoplasmic condensation as a result of the activation of DNA endonucleases and transglutaminases. It is controlled by regulatory genes such as *p53, bcl-2, ced-3, ced-4,* and *ced-9.* Under normal physiologic conditions, both small intestinal and colonic epithelia undergo a low rate of spontaneous apoptosis.

Animal experiments have shown that exposure to low-dose radiation leads to an increase in the rate of apoptosis of intestinal crypt cells, especially stem cells of the crypts. The rate of apoptosis was dose dependent and depended on the expression of tumor suppressor genes in stem cells.[34-36]

Paris et al. demonstrated in mouse models that microvascular endothelial cell apoptosis is the primary lesion leading to stem cell dysfunction.[37]

Garcia-Barros et al. provided evidence that tissue and tumor response to radiation is also determined by microvascular sensitivity to radiation. Their studies indicated that microvascular damage in response to radiation occurs at clinically relevant dose ranges.[27] Another concept comprises the pathogenesis of fibrosis. Herskind et al. investigated the role of cytokines in radiation enteritis.[38] They found that transforming growth factor β (TGF-β) is of particular importance in extracellular matrix deposition and development of tissue fibrosis.

Ionizing radiation activates translation of the gene coding for TGF-β. Radiation induces the formation of hydroxyl radicals that stimulate the production of TGF-β_1. This cytokine remains elevated even at 26 weeks after radiation, especially in vascular endothelial cells, fibroblasts, and smooth muscle cells and is mainly implicated in the pathogenesis of fibrosis.[39,40] Immunohistochemical studies of bowel mucosa showed that TGF-β_1 is primarily located in intestinal villi or at the top of colonic crypts.[41-43] Animal experiments demonstrated increased TGF-β immunoreactivity in the small intestine. It acts as a potent fibrogenic and proinflammatory cytokine that leads to connective tissue hyperplasia and increased leukocyte migration and activation in the intestinal wall.[44] The molecular or chemical inhibition of TGF-β_1 caused less structural injury and significantly decreased intestinal wall fibrosis when exposed to high doses of radiation.[44] Further studies have demonstrated a prominent role of TGF-β in the pathogenesis of not only radiation-induced enteritis but also radiation-induced organ dysfunction and fibrosis.[1-9] These radiation-induced processes are strikingly similar to the pathogenesis of known clinical entities characterized by an excess of fibrosis, such as scleroderma,[45-47] idiopathic pulmonary fibrosis,[48-50] diabetic nephropathy,[51] and membranous glomerulonephritis.[52]

RADIATION AND THE MICROCIRCULATION

Recent evidence showed that radiation is leading to significant microcirculatory perturbations, eventually causing microvascular dysfunction and organ damage. It was demonstrated that irradiation causes an increase in leukocyte–endothelium interaction and vascular permeability, a similar process seen during inflammation or ischemia/reperfusion injury. [45,53-62] This finding was also substantiated in histologic studies in which irradiated intestinal tissue showed a significant interstitial accumulation of polymorphonuclear leukocytes.[63] The inhibition of leukocyte adhesion to endothelial cells through the administration of antibodies directed toward specific adhesion molecules resulted in a significant reduction in radiation-induced tissue damage.[45,53-58,62,64] This radiation-induced intestinal inflammatory process at the microcirculatory level was also inhibited by the application of oxygen–free radical scavengers such as SOD.[65]

NATURAL HISTORY AND CLINICAL FEATURES

According to the aforementioned pathologic changes, radiation enteritis is manifested as acute radiation enteritis or late radiation enteropathy with early and late symptoms, respectively.

The *acute phase* occurs during the course of irradiation and results from direct radiation-induced depletion of the actively proliferating intestinal crypt cells with concomitant inflammation of the lamina propria. The clinical symptoms of acute radiation enteritis consist mainly of diarrhea, abdominal pain, anorexia, malaise, and vomiting, all of which are usually self-limited. These symptoms disappear after 2 to 6 weeks and require only symptomatic treatment. They are dependent on the rate and duration of time over which radiation is applied rather than on the total dose. This stage frequently remains subclinical despite marked mucosal damage.

The symptoms of *late radiation enteropathy* occur after a variable latency period averaging 2 to 3 years with a range of 6 months to 20 years. The symptoms are the result of progressive occlusive vasculitis and diffuse collagen deposition and fibrosis.

Symptoms of late radiation enteritis consist of abdominal pain as a result of obstruction secondary to radiation-induced strictures or perforation and necrosis. The onset of symptoms is often insidious, and they are mostly due to changes in intestinal transit and include intermittent diarrhea and constipation. Fistulization between the bowel and pelvic organs, such as the bladder, vagina, or other bowel segments, causes pneumaturia, feculent vaginal discharge, and rapid passage of undigested food in stool, respectively. Moreover, intestinal malabsorption, bile salt malabsorption, anemia, and hypoalbuminemia have been observed. Multiple segments of small bowel can be involved simultaneously.[14]

Abscesses can occur as well, usually in the pelvis, and may cause signs of sepsis. Intestinal perforation may cause acute peritonitis, but this complication is uncommon. Significant intestinal bleeding occurs rarely as a result of ileal ulcerations, but rectal bleeding from radiation proctitis is relatively common.[66]

A four-point injury scale from 0 to 4 has been introduced by O'Brian et al.[30] for the classification of radiation-induced bowel injury: *0,* no complaints; *1,* mild diarrhea (controlled by diet and reassurance); *2,* marked diarrhea and rectal pain, which are relieved by antidiarrheal pain medications or antibiotics; and *3,* severe complications, including fistula formation, perforation, or stricture. The Radiation Therapy Oncology Group (RTOG) introduced a gastrointestinal morbidity scoring system with five grades: *0,* no symptoms; *1,* mild diarrhea, cramping, bowel movements five times daily, slight rectal discharge; *2,* moderate diarrhea and colic, bowel movements more than five times daily, excessive rectal mucus or intermittent bleeding; *3,* obstruction or bleeding requiring surgery; and *4,* necrosis, fistula, or perforation.

It is important to stress that radiation can lead to the development of secondary radiation-induced malignancies, synchronous radiation lesions, or recurrent malignant disease.[67-77] The pathophysiologic mechanisms of radiation-related carcinogenesis and malignant transformation have been studied intensively.[78,79] In a series of 51 patients, Galland and Spencer reported that 47% remained symptom-free at a median follow-up of 1 year. In the remainder, new radiation-related GI problems developed. In none of the patients who were initially seen with bleeding did new problems develop. In comparison, 33% of the patients with strictures and 89% of those with perforation or fistula formation went on to manifest new lesions. Patients whose initial manifestation was fistulas also appeared to be at increased risk of having synchronous radiation lesions at the time of diagnosis. These patients were at increased risk of dying as a result of recurrent malignant disease within a relatively short period.[26-29,80]

Associated collateral radiation damage, frequently underestimated, has been described in the urinary tract system, specifically in the bladder. Other injuries include radiation myelitis, osteitis pubis, pathologic fractures, and atheromatous changes in blood vessels within the radiation field.[32]

Most deaths are due to recurrent disease or the effects of radiation on the gut. Galland and Spencer reported in their study that radiation enteritis was responsible either directly or indirectly for the death of 23 of the 37 patients who died. Nine of these patients died with no evidence of their original tumor.[26,27]

DIAGNOSIS

Establishing the diagnosis of radiation enteritis can be challenging and should include a detailed history and physical examination, followed by laboratory tests and radiologic imaging studies.

The clinical findings in a patient suffering from radiation enteritis can range from subtle symptoms to malabsorption and bowel perforation, as described earlier in the section on natural history. The physician should be guided by a high index of suspicion and eliminate all possible differential diagnoses.

A complete blood count should be obtained when patients are bleeding or suffering from malabsorption. Moreover, a metabolic panel is essential for patients with vomiting or diarrhea. To establish the cause of diarrhea, stool cultures should be obtained, as well as stool volume and stool fat studies. Measurement of bile acid absorption by synthetic gamma-labeled bile acid might be useful.[81] Its absorption and enterohepatic circulation are identical with that of taurine-conjugated bile acids; however, it cannot be deconjugated. Therefore, its absorption is sensitive and specific for terminal ileal function. However, this test is cumbersome to perform and not usually available for clinical use on a routine basis. Measurements of changes in intestinal permeability may be useful in the diagnosis of chronic intestinal damage. Intestinal permeability to large molecules such as chromium-ethylenediaminetetraacetic acid is increased in acute radiation enteritis, but there have been no reports on chronic radiation enteritis.[82]

An acute abdominal series is needed to evaluate for obstruction and ileus. Barium contrast studies provide better mucosal detail and can identify areas of stricture, as well as fistulas. Mendelson and Nolan and Sellink and Miller described the radiologic findings after a single-contrast barium infusion technique, enteroclysis.[83,84] This method seems to be more sensitive and specific for radiation-induced changes and has been shown to be superior to the conventional follow-through examination in demonstrating stenotic segments and mucosal pathol-

ogy because of optimal bowel distention.[20,83] In addition, information regarding GI motility can be obtained. However, with the advancement of modern technology, these small bowel imaging studies have been partially replaced by MRI-enteroclysis, multislice CT-enteroclysis, and sono-enteroclysis.[63,85-87]

Abdominal and pelvic CT scans are the best studies to confirm obstruction and perforation and to exclude extraintestinal processes, including possible abscesses.

Endoscopy allows mucosal biopsy, which can reveal classic histologic changes consistent with radiation injury, as described earlier.

Many studies have addressed the radiologic features of chronic radiation enteritis in an attempt to identify specific radiologic signs.[19,88,89] Many of them used barium follow-through techniques, whereas others used enteroclysis as the preferred method.

A pathologic fold pattern in the ileum as a result of submucosal edema was observed in 71% of patients.[19] Approximately 50% of patients had no fold pattern at all because of mucosal atrophy. Mural thickening and stenosis were also found. More than 70% of patients showed delayed intestinal transit with dilatation of the jejunum and proximal ileum. These findings were associated with hypoperistalsis of the affected ileal loops. More than half of the patients showed dilatation of the proximal ileum with a maximum diameter of 60 mm. In more than two thirds of all cases an associated dilatation of the jejunum was noted. Radiologic features reflecting the presence of adhesions are known as fixed bowel loops that can be displaced only by deep palpation or as mucosal tacking associated with focal adhesions.

Puddling of barium in the terminal ileum or a segmental saw-toothed appearance of the small bowel is commonly seen. Kinking of bowel loops was attributed to by some authors to mesenteric shortening or adhesions and wall thickening.[83,88,89]

Multiple studies, however, have shown that the extent of the disease is clearly underestimated by radiologic methods when the radiographic results are compared with data obtained during laparotomy. Nonetheless, there is good correlation between intraoperative and radiologic findings with regard to the presence and site of strictures and adhesions.[83] Poor correlation was observed for peritoneal metastases extrinsic to the bowel wall.[20]

PROGNOSIS

It is generally believed that radiation enteritis is a progressive disease. The median latent period between radiation therapy and intestinal symptoms is usually 6 to 24 months with a range between 1 month and 37 years.[27-29,45,90]

Gilinsky et al. reviewed patients with radiation-induced proctosigmoiditis and found that those who had not received blood transfusions had a higher rate of spontaneous remission. In contrast, patients whose symptoms were so severe that transfusions were required rarely experienced remissions and were more likely to undergo surgery.[91] Galland and Spencer reported new radiation-induced GI problems in 39% of patients (20 of 51). Ten patients underwent surgery, 5 of whom died.[16]

No new problems developed in patients whose initial manifestation was bleeding, as opposed to 33% of patients with strictures and 89% of patients with perforation or fistula formation as their initial symptom.[27] Harling and Balslev found cumulative 10-year survival rates of 37% and 64% in patients with perforation or fistula versus bleeding or stricture.[27]

Hatcher et al. made similar observations that patients whose initial manifestation was fistulas appear to be at increased risk of having synchronous radiation lesions at the time of diagnosis, as well as at increased risk of dying.[80] They estimated that additional complications become apparent in about half of those surviving the initial lesion. Harling and Balslev found in their study that during an observation period of 14 years (from 1972 to 1986), 23% of all deaths (13 of a total of 75 deaths) were related to radiation complications and 47% were due to recurrent malignant disease.[90] The cumulative 10-year survival rates were 58% for the entire series of 136 patients, not including those who died from radiation enteritis.[90] However, the 10-year survival rate of patients presenting with bowel perforation or fistulae compared to those presenting with bleeding or stricture was 37% and 64%, respectively.[90]

All investigative groups have confirmed that the risk for new radiation-induced lesions is greater in patients who initially have perforation or fistula than in patients with initial bleeding or stricture. Moreover, life expectancy was poorer in patients with fistulas. The presence of a fistula seems to imply wider dissemination of the destructive process and an excessive rate of recurrent disease.[26,80] However, Perez et al. did not support this finding.[92]

Galland and Spencer and Harling and Balslev reported a 40% to 60% 5-year survival rate.[26,90] Galland and Spencer showed that radiation enteritis was responsible either directly or indirectly for the death of 23 of 37 patients. Nine of these patients had no evidence of their original tumor.[26] It has also been reported that small bowel injuries carry more than four times the mortality than colorectal injuries do[93]; however, this observation was not confirmed by others.[94]

Regimbeau et al. estimated that approximately one third of all patients suffering from chronic radiation enteritis will need to undergo surgery at one point.[23] Furthermore, they found that reoperation was more common in the conservative surgical group of patients who did not undergo bowel resection (50%) compared to those patients who underwent bowel resection (34%).[23] Reoperations were associated with a higher mortality rate overall.[23]

Libotte et al. reviewed the clinical and survival data of 108 patients with radiation enteritis at a median follow-up of 11 years. The median time of occurrence of severe radiation-induced lesions (obstruction, perforation) after radiotherapy was 18 months, 9 months for rectal bleeding and 10.5 months for mild symptoms.[95] They showed that patients with rectal bleeding had a poorer prognosis than did those with mild symptoms but an equivalent prognosis to patients with severe complications.[95]

The development of radiation-induced malignancy is a pivotal factor in the patient's prognosis. It has been shown experimentally that colonic adenocarcinoma will

develop in 47% of rats after having been exposed to 4500 rad.[96] Galland and his group examined colonic resection specimens from 26 patients with radiation-induced colitis and found a significant increase in the prevalence of dysplasia and other premalignant changes.[27,97] The relative risk for the development of colonic carcinoma after radiotherapy has been calculated as being 2 to 3.6 in women who undergo irradiation for gynecologic cancer.[98]

MANAGEMENT OF RADIATION ENTERITIS

Methods of Prevention

Prophylactic measures that help reduce the incidence of radiation enteritis include methods to exclude the small bowel from the pelvis, such as reperitonealization, omental transposition, or placement of absorbable mesh slings.[99-101] The small bowel is a mobile structure that can be altered by a variety of positions and techniques, including the prone, Trendelenburg, and decubitus positions.[14] Das et al. studied the efficacy of a belly board device that resulted in a 70% reduction in small bowel volume within the irradiated pelvic field.[102] Ferguson described the use of omental pedicle grafts.[103]

The use of radioprotectant chemicals during radiotherapy is an evolving strategy of clinical importance. Amifostine was the first cytoprotectant approved by the Food and Drug Administration for ovarian cancer patients receiving cisplatin-based chemotherapy and for the prevention of xerostomia in patients undergoing radiation therapy for head and neck cancer.[104-106] The protection of normal cells is believed to occur predominantly by scavenging of free radicals. Active metabolites of amifostine react with free radicals in competition with oxygen.[107] Pretreatment with amifostine in clinical trials reduced the frequency of cyclophosphamide-induced neutropenia and nephrotoxicity and the neurotoxicity of platin compounds.[108] Halberg et al. reported that the intraluminal administration of amifostine during intraoperative radiation therapy produced localized radioprotection and reduced duodenal damage.[109] Despite all these promising results, there is still controversy regarding the selectivity of amifostine because some studies have shown variable degrees of tumor protection as well.[110,111] A few phase I and II studies suggest that amifostine could be beneficial in limiting the radiation damage.[112] Superoxide dismutase, a free radical scavenger, has been used successfully to reduce radiation-induced complications.[65]

Numerous pharmacologic interventions have been reported to reduce the symptoms of radiation enteritis. Diarrhea associated with abdominal irradiation has been positively affected by sucralfate. A randomized, placebo-controlled trial of 70 patients who were treated by pelvic irradiation for bladder and prostate cancer showed that patients who received sucralfate during radiation therapy had statistically significant reductions in both the acute and chronic symptoms of radiation enteritis when compared with patients who received placebo.[113,114]

Glutamine-enriched enteral formulas, as well as hormones such as bombesin, growth hormone, glucagon-like peptide 2, and insulin-like growth factor 1, have proved useful in preventing symptoms of acute radiation enteritis.[115-117]

Novel Techniques in Radiotherapy and Combined Radiotherapy/Chemotherapy

The goal of all new technologic changes in the field of radiation oncology is to allow safe administration of greater radiation doses to the tumor and achieve an increased rate of cure with acceptable normal tissue toxicity. The irradiation technique must prevent unnecessary irradiation of tissues outside the tumor-containing areas.

Radiation enteritis can be minimized by using special ports to deliver optimal treatment specifically to the tumor and not to the surrounding tissues. Radiopaque markers such as titanium clips could be placed during laparotomy to further delineate and identify the area of interest for future, more targeted radiation therapy.

Frykholm et al. have found that technically, a two-field radiation approach cannot spare the surrounding tissues to the same extent as three or four fields can,[118] and hence two types of conformal radiation therapy have evolved and been introduced into clinical practice*: three-dimensional conformal radiation (3DCRT)* and *intensity-modulated radiation therapy (IMRT).*

Traditional radiation therapy techniques, including 3DCRT with uniform radiation intensity or with simple beam fluence–modifying devices such as wedges, do not provide a method for sparing critical structures that push into the target or that are partially or fully surrounded by a target or combination of targets. True 3DCRT dose distributions are now possible, in large part because of continuing advances in computer technology that have led to the development of sophisticated *three-dimensional radiation treatment planning (3DRTP)* systems with inverse planning capabilities and computer-controlled radiation therapy delivery systems equipped with a multileaf collimator. Such planning and delivery systems have made the implementation of 3DCRT with modulated radiation fluence practical. The ultimate goal of 3DCRT is to conform the spatial distribution of the prescribed dose to the three-dimensional target volume (cancerous cells plus a margin for spatial uncertainties) while at the same time minimizing the dose to surrounding normal structures (RTOG, The National Cancer Institute Guidelines for the Use of Intensity-Modulated Radiation Therapy in Clinical Trials).

IMRT represents a new paradigm in radiation therapy that requires knowledge of patient immobilization, multimodality imaging, setup uncertainties and internal organ motion, tumor control probabilities, normal tissue complication probabilities, three-dimensional dose calculation and optimization, and dynamic beam delivery of nonuniform beam intensities. This new process of planning and treatment delivery shows significant potential for further improving the therapeutic ratio and reducing toxicity. The radiation beam is broken into beamlets for which the intensity can be adjusted individually. Up to now, however, it is not clear whether IMRT will fulfill the expectations that it has raised,[119,120] and hence further studies need to be conducted and evaluated.

Adjuvant (postoperative) and *neoadjuvant* (preoperative) radiotherapy for resectable rectal cancer, for example, has been studied extensively.[17,121-125] In terms of neoadjuvant therapy, a meta-analysis of 4000 patients found that both a *short-term course* (25 Gy in 5 fractions, common approach in Europe) and a *long-term course* (45 Gy in 25 fractions, commonly applied in the United States) of radiation therapy were equally effective in reducing local recurrence.[126,127] Neoadjuvant radiation therapy using 25 Gy with daily fractions of 5 Gy, administered within 1 week followed by surgery the next week, is a widely used treatment for patients with resectable rectal cancer.[18,121,128,129] Nevertheless, the high dose per daily fraction (5 Gy) led to significant impairment of bowel function.[130]

This regimen was changed to 2.5 Gy per fraction twice daily for 5 days preoperatively and provided excellent results in terms of local tumor control without marked late morbidity. This modification was called non–down-staging *hyperfractionation* and was thought to be safe for the treatment of selected patients. Hypofractionation with greater doses per fraction led to an increase in the occurrence of radiation-induced damage.[131]

Kupelian et al. reported a clinical trial of 166 patients with early-stage prostate cancer who were treated with hypofractionated intensity–modulated radiotherapy delivering 2.5 Gy/fraction (total of 70 Gy) in comparison to 116 patients who were treated with 3DCRT delivering 2.0 Gy/fraction (total of 78 Gy). Rectal toxicity was observed in only 5% of patients treated with IMRT as compared with 12% in a group of patients treated with 3DCRT.[132]

The German Rectal Cancer Study Group trial published by Sauer et al. provided evidence that preoperative or neoadjuvant chemoradiation has numerous potential advantages over postoperative chemoradiation, such as less toxicity, a lower incidence of radiation enteritis, a lower rate of local recurrence, and a lower rate of anastomotic stricture after surgery.[17,133] It was suggested that this should be the preferred treatment for patients with locally advanced and low-lying rectal cancer. The theoretical background for the advantage of preoperative radiotherapy in comparison to postoperative treatment has been discussed in various publications.[121,122] Despite all positive aspects of preoperative chemoradiotherapy in the treatment of rectal cancer, Sauer et al., for example, pointed out the possibility of overtreating early-stage tumors (TNM stage I). Despite the use of endorectal ultrasound, approximately 18% of the patients (stage I) had been over-staged during the initial evaluation and received unnecessary postoperative chemoradiotherapy.[17,134] The percentage of unnecessary postoperative chemoradiation was even higher if those patients with stage IV disease (7%) and those with unknown TNM stage (6%) were included. This important issue illustrates the importance of correct preoperative clinical staging, which might improve with the additional use of MRI, leading to better patient selection.[135]

Preoperative combined-modality treatment with conventional radiation doses and fractionation plus concurrent 5-FU–based chemotherapy has yielded better results than preoperative radiation therapy has alone.[17,18,133] Patients with clinical T3 rectal tumors or positive lymph nodes, or both, are commonly treated with combined-modality treatment, followed by surgery and four cycles of postoperative chemotherapy.[136,137] This concept, however, is not completely accepted and is being currently investigated as part of the European Organization for Research and Treatment of Cancer (EORTC) trial.[104,138-140]

Other studies have investigated the effect of conventional fractionation, hypofractionation, accelerated and hyperfractionated regimens, and radiation dose escalation techniques and found that with concurrent chemoradiotherapy, either the dose of the chemotherapeutic drug or the radiation dose needs to be reduced to avoid significant GI complications such as ulceration or hemorrhage without affecting the tumoricidal effects of both radiation therapy and chemotherapy.[119,141-145]

New drug-radiation combinations with such drugs as *capecitabine, raltitrexed, oxaliplatin,* and *irinotecan* are currently being investigated in several trials.[145,146] In addition to these cytotoxic drugs, novel targeted biologic agents, including *epidermal growth factor inhibitors* and *vascular endothelial growth factor inhibitors,* have been shown to enhance the antitumor effect of both radiation therapy and chemotherapy.[146]

The time interval between the completion of radiation therapy and definitive surgery turned out to be a pivotal factor for achieving maximal tumor response to radiation in order to achieve R0 resections or perform sphincter-sparing operations.[147,148] Grann et al. recommended a minimum of 4 weeks.[147] This was supported by the Lyon R90-01 randomized trial.[149] Beets-Tan and coworkers determined the applicability of MRI in predicting tumor-free resectability of the primary lesion.[150]

Because pancreatic cancer is only moderately sensitive to radiation, doses of 50 to 50.4 Gy can be applied safely in combination with chemotherapy. Early experimental trials initially stated that doses of 70 Gy and higher can be administered to patients with pancreatic cancer when given without chemotherapy.[145,151] However, at these high doses, the radiosensitivity of adjacent organs considerably limited the option of percutaneous radiation therapy. A significant number of radiation-induced toxicities occurred.[151] Moreover, radiotherapy alone did not improve the overall survival rate. *Intraoperative radiation therapy (IORT)* using fast electrons allows the application of high radiation doses to the tumor and tumor bed while protecting adjacent organs and tissues.[152] However, such treatment did not translate into improved overall survival rates. Nevertheless, IORT might help reduce the percutaneous radiation dose to 40 to 50 Gy, thereby significantly reducing the frequency of radiation-induced toxicity.[152]

Treatment Options

Conservative/Symptomatic Management

Treatment of acute radiation enteritis is directed toward controlling the symptoms.[81] Antispasmodics and analgesics, including opiates, may alleviate the abdominal pain and cramping. The use of steroids is of uncertain value. Conservative measures such as the administration of intravenous fluids, bowel rest, and antidiarrheal drugs are indicated.[30,153] Dietary manipulation, including oral

elemental diets, has been advocated to ameliorate the symptoms of radiation enteritis. Diets low in milk, fat, and lactose had beneficial effects in patients with acute radiation enteritis.[12] Loiudice and Lang showed that administration of total parenteral nutrition (TPN) to patients with chronic small bowel problems was superior to a low-residue diet in clinical improvement and immunologic and radiologic parameters.[154] The addition of methylprednisolone appeared to enhance the effects of TPN.[12,154-156] In contrast, Silvain and co-workers found that TPN alone was not superior to surgical management, with clinical radiation enteritis recurrence rates of 34% and 47% at 1 and 2 years, respectively.[157] Although TPN corrected nutritional deficits effectively and deferred surgery in some patients, radiation enteritis remains an unpredictable progressive disease.[157]

Acute enterocolitis may be mediated by prostaglandin, at least in part. In a small prospective study, Mennie et al. found that aspirin as an inhibitor of prostaglandin E synthesis caused a significant decrease in diarrhea and abdominal pain.[158] Cholestyramine (4 to 12 g/day), which binds bile salts, has also been found to be effective.[159] Kilic et al. reported that sulfasalazine (2 g/day) was effective in reducing the symptoms of acute radiation enteritis.[160] Probiotics have been found to be effective in preventing various gastrointestinal diseases, especially radiation-induced enteritis.[161]

In the acute phase of radiation proctitis, hydrophilic stool softeners may help control mucous diarrhea, whereas sitz baths and perineal compresses have been used in an attempt to ease tenesmus if analgesics fail. Steroid retention enemas are helpful for both acute and chronic radiation proctitis. Jacobs et al. found that the administration of oral or rectal Salazopyrin alleviated the symptoms of acute and chronic radiation proctitis in 37 of 40 patients.[162] Moreover, hemorrhagic radiation proctitis can be alleviated by the topical application of formalin. If the bleeding is refractory to local formalin treatment, argon plasma coagulation has been shown to be an effective and safe treatment.[163-165] In addition, bipolar electrocoagulation or endoscopic laser coagulation has been described for the management of hemorrhagic radiation injury or radiation-induced mucosal vascular lesions.[166,167]

Surgical Management

Before definitive surgical treatment is considered, it is important that the extent of both the original malignancy and the radiation damage be established and any sepsis, malnutrition, or biochemical abnormalities be corrected.[35]

Radiation enteritis is one of the most challenging problems in GI surgery. The operations are complex and prone to complications.[168]

Operative interventions may be required in only a subgroup of patients with chronic effects of radiation enteritis. This subgroup of patients represents just a small percentage (2% to 3%) of the total number of patients who have undergone abdominal or pelvic irradiation.[153]

Indications for surgery include obstruction, fistula formation, perforation, and bleeding. Complete bowel obstruction as a result of strictures is the most common indication for surgery. Surgeons are frequently confronted with dense adhesions, unexpected problems, and fragile irradiated tissues that are difficult to handle and poor to heal.[153]

Caution must be exercised when operating on patients with previously irradiated bowel because the vascular injury may be widespread and not readily recognizable by gross inspection of the intestine. The risk for dehiscence of the anastomosis, however, is not negligible. Extensive adhesiolysis should be avoided if possible. Perforation should be treated by resection and anastomosis. When the anastomosis is thought to be unsafe, ostomies should be created. The utility of frozen section or laser Doppler flowmetry for assessment of blood flow at the anastomosis site is of limited value.[169]

Bowel perfusion at the resection borders is usually assessed by gross examination, color, capillary refill, and bleeding tendency, depending on the surgeon's experience.

If resection and anastomosis are planned, at least one end of the anastomosis should be from intestine outside the irradiated field. An incidence of anastomotic breakdown as high as 50% has been reported after resection and anastomosis involving diseased segments of bowel because of the poor healing properties of irradiated tissue.[28,29]

In a retrospective analysis from 1970 to 1982, Wobbes et al. showed 27 patients who were operated on for stenosis, perforation, fistulization, and chronic blood loss of the small bowel after radiotherapy for malignant disease.[170] Bypass procedures in the form of ileotransversostomies were performed on 20 patients who presented with either obstruction or fistulization. Two patients died postoperatively. In contrast, 4 of 7 patients who underwent bowel resection for perforation, fistulization, or obstruction died of intra-abdominal sepsis. The researchers concluded that a bypass procedure should be performed if possible. In case of resection, the anastomosis should be done during a second operation. Obstruction caused by rigid and fixed pelvis incorporating small intestinal loops is best treated by bypass procedures.

Regimbeau et al. retrospectively studied 109 patients, from 1984 to 1994, who were operated on for radiation enteritis. Of these patients, 68% had been irradiated for gynecologic carcinoma, 28% for digestive cancer (24 colorectal cancer and 4 anal cancer), 7% for urologic carcinoma, and 4% for Hodgkin's disease, cutaneous neoplasia, and soft tissue carcinoma.[23] The operative mortality was approximately 5%. Thirty-three patients (30%) experienced postoperative complications, including anastomotic leak in 11 patients. Overall survival, after a mean follow-up of 40 months in patients without cancer recurrence, was 85% at 1 year and 69% at 5 years after surgery. Overall survival was influenced by the nature of the treatment, with 51% and 71% 5-year survival after conservative and resection treatment, respectively. Despite high initial mortality and morbidity rates, life expectancy in patients who underwent bowel resection was superior to conservative surgical treatment.[23] They and other investigators said that bypass procedures are associated with a higher relative risk of radiation-induced cancer in the irradiated bowel that is not resected but left in place.[27,98] However, the bypass operation is a valid surgical alternative for patients with high risk of short-gut

syndrome and poor medical condition.[23] Regimbeau et al. mentioned in their publication that reoperation after the first surgical procedure was mandatory for approximately 40% of their patients because of recurrence of gastrointestinal symptoms. The mortality and morbidity rate was higher for those patients. They also found a higher reoperation rate among patients who were treated conservatively without resection of small bowel.[23] Onodera et al. retrospectively analyzed 48 patients who underwent small bowel resection for intestinal obstruction and pull-through reconstruction for proctitis. They postulated that generous small bowel resection of affected bowel is a safe procedure for small bowel injury, whereas rectal resection is best dealt with by restorative proctectomy.[171]

Multiple resections and bypass of large segments of intestine will eventually place the patient at risk for short-bowel syndrome, as well as dependence on TPN. The use of TPN has been described as a life-prolonging measure; however, the long-term outcome of patients who have radiation enteritis and receive home TPN is dismal, with 5-year survival rates of only 36%.[157] Most of these patients died because of complications due to radiation therapy. The others had cancer recurrences.

In a retrospective study, Scolapio et al. reviewed 225 patients requiring home TPN for various diseases; 32 patients suffered from radiation enteritis. The overall 5-year survival probability was 60%, irrespective of age and underlying disease. The 5-year survival of patients with home TPN suffering from radiation enteritis was only 54%.[172] Therefore, efforts to preserve the remaining intestinal length may be warranted in an attempt to avoid the metabolic and nutritional consequences of further major resections or bypass procedures. Dietz and co-workers presented the use of strictureplasty for the management of patients with obstructing complications of radiation enteritis.[172] Three patients presented with small bowel obstruction and enterocutaneous fistula, two patients with chronic small bowel obstruction and rectovaginal fistula. Four patients required home TPN. Strictureplasty was successfully performed on all patients. All patients who were dependent on home TPN were eventually weaned from TPN. The authors pointed out that strictureplasty procedures should not be recommended as a primary surgical procedure for the treatment of perforation, hemorrhage, or fistula. It may be considered a useful option if resection would be likely to induce short-bowel syndrome.[173]

SUMMARY

Radiation enteritis is a serious complication of abdominal or pelvic irradiation and should be understood as a progressive and chronic disease with early and late clinical symptoms. The clinical manifestations range from mild diarrhea to severe complications such as bowel obstruction, fistula formation, and hollow viscus perforation. Management of this relentless disease varies from supportive care to surgical intervention, depending on the initial clinical symptoms. New molecular and microcirculatory insights into the pathomechanism of radiation enteritis can lead to novel therapeutic concepts for preventing rather than treating this relentless disease.

Improved long-term survival after radiotherapy should be achieved primarily by better tumor control. The use of novel techniques in radiation oncology, such as IMRT combined with new cytotoxic and biologic agents, might lead to improved protection of nonmalignant tissue without compromising the tumor-killing activity of these methods. Other methods such as hypofractionation, accelerated and hyperfractionated regimens, concurrent chemoradiotherapy, and neoadjuvant and adjuvant chemotherapy might help reduce GI complications without affecting the tumoricidal effects of the therapy.

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Chapter

78

Short-Bowel Syndrome

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Intestinal failure refers to a condition that results in inadequate digestion or absorption of nutrients, or both, so that an individual becomes malnourished and requires specialized medical and nutritional support.[1] Short-bowel syndrome is a type of intestinal failure caused by a shortened remnant after intestinal resection. The pathophysiologic changes that occur in short-bowel syndrome relate primarily to the loss of intestinal absorptive surface and more rapid intestinal transit (Box 78–1). The consequences of malabsorption of nutrients include malnutrition, diarrhea, steatorrhea, specific nutrient deficiencies, and fluid and electrolyte abnormalities. These patients are at risk for other specific complications, including an increased incidence of nephrolithiasis, cholelithiasis, and gastric hypersecretion. The clinical manifestations of short-bowel syndrome vary greatly among patients and depend on intestinal remnant length, location, and function; the status of the remaining digestive organs; the presence or absence of the ileocecal valve; and the adaptive capacity of the intestinal remnant. Thus, short-bowel syndrome is not entirely dependent on a given length of remaining intestine.

The prevalence of short-bowel syndrome is 3 to 4 per million, and thousands of patients are now surviving with short-bowel syndrome.[1] This condition occurs in about 15% of adult patients who undergo intestinal resection, with three fourths of these cases resulting from massive intestinal resection and one fourth from multiple sequential resections.[2] Massive intestinal resection continues to be associated with significant morbidity and mortality, primarily related to the underlying diseases necessitating resection.[2,3] About 70% of patients in whom short-bowel syndrome develops are discharged from the hospital, and a similar percentage are alive 1 year later.[4] This improved survival rate has been achieved primarily by the ability to deliver long-term nutritional support. The long-term outcome of these patients is often determined not only by their age and underlying disease but also by complications related to the management of short-bowel syndrome.

FACTORS INFLUENCING OUTCOME

Intestinal remnant length is the primary determinant of outcome in patients with short-bowel syndrome. The length of the small intestine in adults varies between 12 and 20 ft (360 to 600 cm), depending on how it is measured and the height and sex of the individual. The duodenum measures 10 to 12 inches (25 to 30 cm). The length of the small intestine from the ligament of Treitz to the ileocecal junction is about 16 ft (480 cm), with the proximal two fifths being jejunum and the distal three fifths being ileum. Resection of up to half of the small intestine is generally well tolerated. Although short-bowel syndrome may develop in patients with less than 180 cm of small intestine, or about a third the normal length, permanent parenteral nutrition (PN) support is likely to be needed in patients with less than 120 cm of intestine remaining without colon in continuity and less than 60 cm remaining with colonic continuity (Table 78–1).[4,5]

The site of resection is also an important factor. Patients with an ileal remnant generally fare better than those with a jejunal remnant. The ileum has specialized absorptive properties for bile salts and vitamin B_{12}, unique motor properties, a hormone profile different from that of the jejunum, and a greater capacity for intestinal adaptation.[6,7] The presence of the ileocecal junction improves the functional capacity of the intestinal remnant.[7] Although previously this had been attributed to a barrier function and transit-prolonging property of the ileocecal valve, this advantage may actually be related to the specialized property of the terminal ileum itself.

The status of the other digestive organs also contributes to outcome. The stomach influences oral intake, mixing of nutrients, transit time, pancreatic secretion, and protein absorption. Pancreatic enzymes are important in the digestive process and particularly influence fat absorption. The colon absorbs fluid and electrolytes, slows transit, and participates in the absorption of energy from malabsorbed carbohydrates. When compared with

Box 78–1 Pathophysiologic Consequences of Massive Resection

General

- Malnutrition and weight loss
- Diarrhea and steatorrhea
- Vitamin and mineral deficiencies
- Fluid and electrolyte abnormalities

Specific

- Cholelithiasis
- Gastric hypersecretion
- Liver disease
- Nephrolithiasis

Table 78–1 Intestinal Length and Nutritional Prognosis

Intestinal Anatomy	Intestinal Length to Avoid Permanent Parenteral Nutrition
End-jejunostomy (type 1)	100 cm
Jejunocolic anastomosis (type 2)	65 cm
Jejunoileocolic anastomosis (type 3)	30 cm

Adapted from Messing B, Crenn P, Beau P, et al: Long term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 117:1043, 1999.

an end-jejunostomy (type 1 anatomy), a jejunoileal anastomosis with an intact colon (type 3 anatomy) is equivalent to 60 cm of additional small intestine, and a jejunocolic anastomosis (type 2 anatomy) is equivalent to about 30 cm of small intestine.[5]

A variety of conditions requiring intestinal resection lead to short-bowel syndrome (Table 78–2).[8] Patients with underlying inflammatory disease may have impaired intestinal function. The cause of resection will also influence the outcome because of the effect on other digestive organs. Long-term treatment and survival are influenced by the patient's age and other morbid conditions. Underlying disease will also influence these parameters.

INTESTINAL ADAPTATION

The small intestine is able to adapt to compensate for the reduction in absorptive surface area caused by intestinal resection.[9-11] This process occurs within the first year or two after resection and improves intestinal absorptive capacity (Fig. 78–1).[11] Whether the adaptive response can be significantly accelerated or augmented is not clear. The overall intestinal adaptive response results from changes in intestinal structure, function, and motility.

Table 78–2 Causes of Short-Bowel Syndrome

Postoperative	52 (25%)
Irradiation/cancer	51 (24%)
Mesenteric vascular disease	46 (22%)
Crohn's disease	34 (16%)
Other benign causes	27 (13%)
Total	210

From Thompson JS, DiBaise JK, Iver KR, et al: Short bowel syndrome as a postoperative complication. J Am Coll Surg 201:85, 2005.

Structural adaptation after intestinal resection involves all layers of the intestine.[9,10] Mucosal DNA and protein synthesis and crypt cell proliferation are increased within hours after resection. Both the total number of cells and the proportion of proliferating cells are increased in the crypt. Enterocytes migrate at a faster rate along the villus. Villus lengthening occurs by an overall increased number of cells. Rates of apoptosis, or programmed cell death, increase in both crypt and villus enterocytes after resection. However, the proliferative stimulus dominates, so adaptation occurs. The ratio of crypts to villi may also increase. Microvilli along the epithelial surface increase as well. Overall, mucosal weight increases.

The thickness and length of the muscle layers also increase after resection, primarily as a result of hyperplasia rather than hypertrophy of the muscle cells.[9] Muscle adaptation, however, occurs at a later time than mucosal adaptation and only after more extensive resection. These changes in the components of the intestinal wall result in marked thickening of the intestinal wall, as well as increased intestinal circumference and length. Thus, there is an overall increase in mucosal surface area because of both villus hypertrophy and the increases in length and circumference of the remnant.

Intestinal motor activity is also altered by intestinal resection.[6] The canine small intestine demonstrates a biphasic motor response to varying degrees of distal resection. There is initial disruption of motor activity, followed by adaptation. In the distal segment of the intestinal remnant after limited resection and more generally after 75% resection, motility recordings are initially dominated by recurring bursts of clustered contractions.[12] With extensive resection, these clusters are prolonged and associated with baseline tonic changes. With limited resection, there is evidence of progressive motor adaptation with eventual slowing of transit and return of migrating motor complex (MMC) cycling. This adaptation is less apparent after massive resection. Motor adaptation

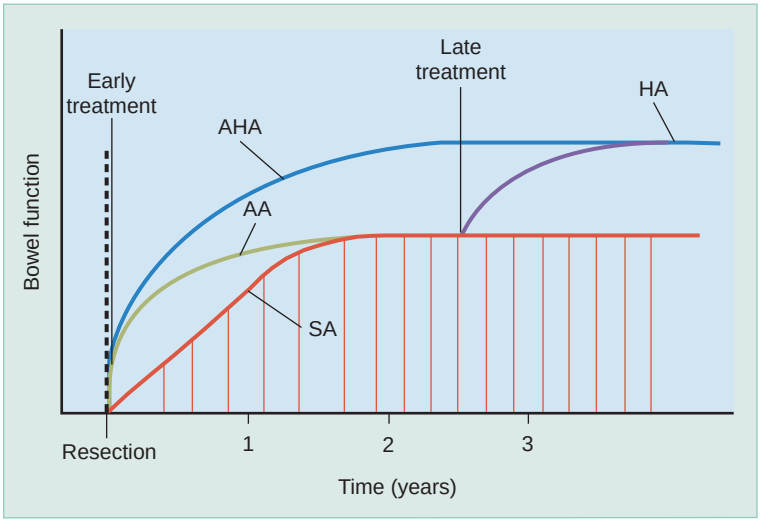

Figure 78–1. Schematic presentation of intestinal adaptation. AA, accelerated adaptation; AHA, accelerated hyperadaptation; HA, hyperadaptation; SA, spontaneous adaptation. (From Jeppesen PB: Clinical significance of GLP-2 in short bowel syndrome. J Nutr 133:3721, 2003.)

is more prominent in the jejunum than in the ileum. These changes are accompanied by modest alterations in smooth muscle contractility. Clinical reports also demonstrate a biphasic adaptive motor response during the first year after resection. There is disrupted motor activity in the first few months after resection, but these changes occur only after extensive resection (remnant shorter than 100 cm). Long-term human studies demonstrate a shorter duration of the MMC cycle and fed pattern after resection.[13]

Functional adaptation has been well documented after resection,[1,5,14,15] and structural adaptation increases intestinal absorptive surface area. Both structural adaptation and motor adaptation lead to prolonged transit time. Although the formerly accepted theory of improved absorption by individual enterocytes was discounted, more recent studies suggest that certain transport capabilities do improve. Within months of resection, diarrhea diminishes and nutritional status improves.

The mechanism of intestinal adaptation has been studied extensively but is still not entirely understood. The degree of structural adaptation is related to the extent and site of resection.[9,10] Adaptation is greater with more extensive resection, and the ileum has a greater adaptive capacity than the jejunum does. Subsequent resection elicits a further adaptive response. Luminal nutrients and secretions and growth factors are important for achieving the maximal response but are not essential for adaptation to occur (Box 78–2).[9,10] The early molecular events associated with this hyperplastic response are being investigated.[16,17] Intestinal resection results in increased levels of a variety of gene products in enterocytes within hours. There is an immediate increase in genes that encode transcription factors, not only genes that influence cell proliferation but also those that augment nutrient trafficking, as well as heat shock genes, which maintain normal cellular function. Many of these are novel genes not normally present in intestinal epithelium. The specific triggers for these events are not clear, and there are obviously many candidates. Currently, there is clinical interest in manipulating the adaptive response pharmacologically.

Box 78–2 Factors Influencing Intestinal Adaptation

- Gastrointestinal regulatory peptides
- Luminal contents
  - Nutrients
  - Secretions
- Systemic factors
  - Growth factors
  - Hormones
  - Cytokines
- Tissue Factors
  - Immune system
  - Mesenchymal factors
  - Mesenteric blood flow
  - Neural influences

MEDICAL MANAGEMENT

The early management of a patient with short-bowel syndrome is that of a critically ill surgical patient who has recently undergone intestinal resection and other concomitant procedures. Thus, control of sepsis, maintenance of fluid and electrolyte balance, and initiation of nutritional support are important in the early management of these patients. For patients who have survived this early phase, the primary goals of management are to maintain adequate nutritional status, maximize the absorptive capacity of the remaining intestine, and prevent the development of complications related to both the underlying pathophysiology and the nutritional therapy.

Maintain Nutritional Status

The most important therapeutic objective in the management of short-bowel syndrome is to maintain the patient's nutritional status. This usually requires PN support in the early period after surgery. Fluid and electrolyte losses from the gastrointestinal tract may be great during the early postoperative period and must be monitored and replaced as soon as possible. Enteral nutritional support should be started as soon as possible when the ileus has resolved. With time, an increasing amount of nutrients are absorbed by the enteral route. This is important for maximizing intestinal adaptation and preventing complications related to PN. As their condition improves and intestinal adaptation occurs, many patients can absorb the necessary nutrients entirely by the enteral route. The length of the intestinal remnant and the status of the colon have important prognostic implications in this regard (see Table 78–1).

The ability of patients with short-bowel syndrome to maintain adequate caloric intake enterally is determined by a variety of factors, including intestinal remnant length and location, any underlying intestinal disease, and the status of the remaining digestive organs.[15,18] Whether there is continuity in the intestinal tract or a stoma is also an important consideration. Diarrhea and perianal complications may markedly diminish oral intake. Patients with stomas are more likely to have a greater percentage of their calories taken enterally. Hyperphagia develops in many patients with short-bowel syndrome to overcome inefficient absorption.[19]

Many patients with short-bowel syndrome require long-term PN for survival, and this therapy has considerable expense and morbidity. Patients without malignancy have 1-, 3-, and 5-year survival rates of about 90%, 70%, and 60%, respectively.[4] One third of deaths are related to the underlying disease, 50% to other supervening disease, and 10% to 15% to PN therapy. Sepsis and liver disease related to PN are important factors in long-term survival.

The incidence of sepsis varies from 0.1 to 0.3 episodes per patient year of PN. Sepsis may be associated with catheter thrombosis. The need for prolonged therapy makes vascular access a long-term problem, and catheters may eventually need to be placed in the azygos, hepatic, or inferior vena cava veins.

End-stage liver disease develops in about 15% of long-term adult PN patients and is associated with a survival time of about 1 year without liver transplantation.[20,21] Although the etiology of the liver disease is not completely understood, it appears to be a multifactorial process that is initially reversible but ultimately leads to severe steatosis, cholestasis, and cirrhosis. Liver disease occurs more frequently in children than adults. Provision of enteral nutrients may prevent this problem, but overfeeding is a predisposing factor. Control of sepsis and bacterial overgrowth is important to minimize this liver disease. Patients with abnormal liver function test results while receiving PN should undergo abdominal ultrasound for evaluation of the gallbladder and bile ducts and should have a liver biopsy performed as appropriate.

Maximize Enteral Nutrient Absorption

Because the morbidity associated with nutritional support in patients with short-bowel syndrome is related primarily to PN, maximizing enteral absorption of nutrients is important for long-term survival. Furthermore, diarrhea and stomal fluid losses can also be important clinical problems that affect the patient's quality of life. Thus, it is beneficial to ensure that the patient's intestinal remnant is functioning optimally and absorbing nutrients and fluid.

The optimal diet for patients with short-bowel syndrome remains controversial. Provision of nutrients in their simplest form to minimize digestion has been one strategic approach. Simple sugars and dipeptides and tripeptides are rapidly absorbed from the intestinal tract. However, partially hydrolyzed diets appear to be just as effective and are less expensive. Complex carbohydrates reduce the osmotic load, but concentrated sugars, such as fruit juices, should be avoided because they generate a high osmotic load. Whether the diet should have a high-fat or low-fat content is another issue. There appears to be increasing agreement that patients with colon should have a low-fat (20% to 30% of calories), high-carbohydrate (50% to 60% of calories) diet but that patients with an end-enterostomy do not require fat restriction (30% to 40% of calories). Fat absorption obviously requires more digestion unless the fat is supplied in the form of medium-chain triglycerides. The ability to absorb these nutrients improves with time, so the diet may need to be continually modified. Specific problems such as lactase deficiency are often present, and the diet should be altered appropriately. Ingestion of a glucose-electrolyte oral rehydration solution with a sodium concentration of at least 90 mmol/L will optimize water and sodium absorption in the proximal jejunum and prevent secretion into the lumen.

Minimizing gastrointestinal secretions and controlling diarrhea are also important goals for maximizing absorption. Both histamine H_2 receptor antagonists and proton pump inhibitors are effective in controlling gastric hypersecretion, correcting malabsorption, and improving nutritional status in patients with short-bowel syndrome. Furthermore, cimetidine may also increase intestinal adaptation. Somatostatin and its long-acting analogue octreotide have been investigated for the management of severe refractory diarrhea in short-bowel syndrome. They improve diarrhea by prolonging small intestinal transit time and reducing salt and water excretion. Part of the beneficial effect may also be related to a reduction in gastric hypersecretion. Although these therapeutic agents are beneficial in the short term, it is not clear whether they continue to be effective after a few months, and they may have some potential deleterious effects. Somatostatin may exacerbate steatorrhea because of impaired pancreatic exocrine function. Other potential adverse effects of octreotide are inhibition of intestinal adaptation and the development of cholelithiasis. Recent evidence supports the use of ox bile and cholylsarcosine, a synthetic conjugated bile acid, as replacement therapy because they improve fat absorption without exacerbating diarrhea.

Box 78–3 Restoration of Intestinal Continuity

Advantages

- Absorptive capacity increased
- Energy absorbed from short-chain fatty acids
- Infectious complications reduced
- Transit time prolonged
- Stoma avoided

Disadvantages

- Bile acid diarrhea
- Dietary restrictions
- Nephrolithiasis increased
- Perianal complications

From Thompson JS: Intestinal resection and the short bowel syndrome. In Quigley EMM, Sorrell MF (eds): Medical Management of the Gastrointestinal Surgery Patient. Baltimore, Williams & Wilkins, 1994, p 327.

Another important aspect of dietary management is to provide a diet that will maximize the intestinal adaptive response.[9,10,18] Provision of fat and dietary fiber may be particularly important in this regard. Long-chain and short-chain fatty acids appear to have a greater trophic effect on the intestine than medium-chain fatty acids do. Although these nutrients directly stimulate intestinal adaptation, nutrients also stimulate intestinal adaptation through endocrine and paracrine effects.

Pharmacologic therapy for short-bowel syndrome is a rapidly expanding area of investigation. Recent evidence suggests that provision of the appropriate diet, nutritional supplements such as glutamine, and growth factors such as growth hormone improves intestinal absorption and perhaps modifies the adaptive response in patients with established short-bowel syndrome.[22] However, which of these components is actually responsible for improved absorption is controversial. Growth hormone and glutamine do not have a consistent beneficial effect.[23,24] Currently, glucagon-like peptide-2 appears to have the most promise for promoting absorption and adaptation.[11] Epidermal growth factor also stimulates intestinal adaptation and may soon be studied in clinical trials.[25]

An important clinical issue is whether to establish intestinal continuity in patients who have a colonic remnant. There are both advantages and disadvantages to restoring continuity (Box 78–3). The colon may improve intestinal absorption by increasing the absorptive surface area, deriving energy from short-chain fatty acids, and prolonging transit time, particularly if the ileocecal valve is intact. Avoiding a stoma also improves quality of life. However, the response of the colon to luminal contents is somewhat unpredictable. Bile acids may cause a secretory diarrhea. Perianal problems can be quite disabling and decrease the patient's oral intake. Oxalate is absorbed primarily in the colon, and restoring continuity places the patient at increased risk for the formation of calcium oxalate stones. Serum and intestinal fluid markers have been investigated as a means of predicting the response of the individual patient to restoring continuity, but none is generally available and useful. Distal reinfusion of enteral contents into a mucus fistula to assess the functional outcome has some usefulness, but it is cumbersome. Not all patients who initially have a stoma created eventually have continuity restored with a satisfactory outcome.[26] This decision should be considered on an individual basis and depends on the length of the intestinal remnant, the status of the ileocecal valve and the colon, and the patient's overall condition. Generally, at least 3 ft of small intestine is required to prevent severe diarrhea and perianal complications. Restoring continuity, however, should always be given strong consideration because of possible improvement in absorption.

Prevent Complications

Metabolic complications are common in patients with short-bowel syndrome because of their tremendous fluid and electrolyte losses and the need to replace these losses with specialized solutions. Intravascular volume has to be maintained to prevent dehydration and renal dysfunction. Hypocalcemia is a common problem related to poor absorption and binding by intraluminal fat. Maintaining adequate calcium and magnesium levels and vitamin D supplementation are important to minimize bone disease. Hyperglycemia and hypoglycemia are frequent complications of patients receiving a large amount of their calories parenterally. Both metabolic acidosis and metabolic alkalosis can occur. A specific problem is D-lactic acidosis, which results from bacterial fermentation of unabsorbed nutrients, particularly simple sugars. Lactate reduces colon pH, thereby permitting the growth of acid-resistant anaerobes capable of producing D-lactate. Impaired metabolism of D-lactic acid may also contribute to elevated serum D-lactic acid levels. This diagnosis is suggested by an unexplained metabolic acidosis and associated neurologic symptoms, such as confusion and somnolence. D-Lactic acid is not measured by standard laboratory techniques for lactic acid determination. Thus, an increased anion gap but normal lactate level in the appropriate clinical setting mandates measurement of D-lactic acid. D-Lactic acidosis is treated by minimizing overall caloric intake or by instituting a low-carbohydrate diet. Administration of intestinal antibiotics may be appropriate, but the optimal duration of such treatment is unclear, and recurrence rates are significant.

Specific nutrient deficiencies need to be prevented and monitored closely, including iron and vitamin deficiencies, as well as deficiencies in micronutrients such as selenium, zinc, and copper. Because fat is poorly absorbed, fatty acid deficiency can also occur. Although medium-chain fatty acids can supplement the diet enterally, parenteral lipids are required in patients who

depend primarily on that route. Serum free fatty acid levels and triene-to-tetraene ratios may need to be monitored periodically to determine the need for supplementation and response to treatment. In general, enteral intake must greatly exceed the absorptive needs to ensure that these needs are being met.

Catheter-related sepsis is an important problem that often necessitates rehospitalization and replacement of catheters. Attention to technique and meticulous patient education are important to prevent this complication. Most infections are due to *Staphylococcus* species, but gram-negative bacteria and fungi are also associated with line sepsis. An attempt at line sterilization before removal is appropriate when infections are caused by coagulase-negative staphylococci and gram-negative bacteria. Repeated placement of catheters can lead to catheter thrombosis, which is the other common problem. In patients who require PN permanently, this may become an important factor in the patient's survival because vascular access may not be achievable indefinitely.

PN-induced liver disease is another potential long-term problem.[20,21] It can be minimized by providing as large a portion of the calories as possible enterally, avoiding overfeeding, using mixed fuels (less than 30% fat), and preventing specific nutrient deficiencies. Treating bacterial growth and preventing recurrent sepsis are also important. Ursodeoxycholic acid administration may likewise be beneficial.

Bacterial overgrowth is another long-term complication associated with both intestinal disease and resection. It may result from impaired motility or stasis caused by obstructive lesions (Fig. 78–2). Achlorhydria is also a contributing factor. Bacterial deconjugation of luminal bile salts impairs bile salt reabsorption. Bacteria also metabolize intraluminal vitamin B_{12}. Depending on the bacterial species present, secretory diarrhea may occur as well. Bacterial overgrowth requires a high degree of suspicion to make the diagnosis. This complication should be suspected when a patient's absorptive capacity and stool habits change acutely. It may result from a mechanical obstruction or a blind loop, which can be relieved by surgery. However, it is often a primary motor abnormality and requires intermittent therapy with antibiotics. Colonization of the lumen with acidophilus or other nonpathogenic organisms is another potential therapy.[27]

Cholelithiasis occurs in 30% to 40% of patients with intestinal insufficiency.[28,29] Factors that predispose these patients to gallstone formation include altered hepatic bile metabolism and secretion, gallbladder stasis, and malabsorption of bile acids. Depending on the dominant mechanism, either mixed pigment stones or cholesterol stones may occur. Long-term PN is an important contributing factor causing altered hepatic bile metabolism and gallbladder stasis. Patients receiving PN are susceptible to the development of cholelithiasis and hepatocellular dysfunction and thus require careful clinical evaluation.[28,29] Biliary sludge forms within a few weeks of initiating PN if there is no enteral intake, but it rapidly disappears when enteral nutrition is resumed. Intestinal mucosal disease and resection, particularly of the ileum, cause bile acid malabsorption, which leads to lithogenic bile and the formation of cholesterol stones. The risk for cholelithiasis is significantly increased if less than 120 cm of intestine remains after resection, the terminal ileum has been resected, and PN is required. The incidence of cholelithiasis can be minimized by providing nutrients enterally whenever possible. Patients totally dependent on PN may be treated with intermittent cholecystokinin injections to prevent stasis and the formation of sludge. Administration of intravenous lipids also stimulates gallbladder emptying. Cholelithiasis may lead to complications in a higher number of patients with short-bowel syndrome than in the general population and also requires more complicated surgical treatment. Thus, several authors now recommend prophylactic cholecystectomy in these patients when laparotomy is being undertaken for other reasons.[29]

Nephrolithiasis also occurs with some frequency. Calcium oxalate stones form as a result of increased oxalate absorption from the colon.[29] Oxalate is normally bound to calcium in the intestinal lumen and is not absorbed. Decreased availability of calcium secondary to reduced intake or binding by intraluminal fat leaves free oxalate in the lumen. Thus, the oxalate is absorbed in the colon and forms calcium oxalate in the urine. Nephrolithiasis is unusual in patients after intestinal resection and jejunostomy but occurred in a fourth of such patients with an intact colon within 2 years of

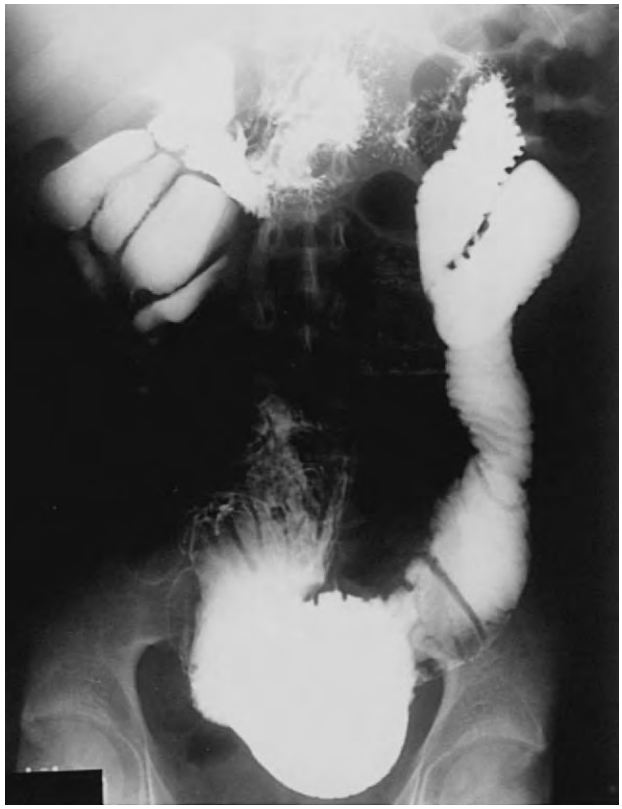

Figure 78–2. Contrast study of a patient with short-bowel syndrome. The shortened remnant lies primarily in the left side of the abdomen with a large dilated segment in the pelvis. Contrast has passed into the right colon beyond this area.

resection. Nephrolithiasis can be prevented by maintaining a diet low in oxalate, minimizing intraluminal fat, supplementing the diet with calcium orally, and maintaining a high urinary volume. Foods with high oxalate content include chocolate, tea, cola, spinach, celery, carrots, and other fruits and vegetables. Cholestyramine, which binds oxalic acid in the colon, is another potential treatment.

Gastric hypersecretion is a potential problem in patients with short-bowel syndrome. Massive intestinal resection can cause gastric hypersecretion as a result of parietal cell hyperplasia and hypergastrinemia. This phenomenon is usually transient and lasts several months. The etiology has not been elucidated but may involve loss of an inhibitor from the resected intestine. The associated hyperacidity exacerbates malabsorption and diarrhea. Clinical development of peptic ulcer disease may also occur and is seen in about a fourth of patients undergoing massive resection.[26] Treatment of gastric acid secretion may improve absorption but also prevents peptic ulcer disease. Control of acid secretion by H_2 receptor antagonists or proton pump inhibitors should be initiated in the perioperative period after resection and maintained until the increased acid production resolves. Some patients, however, continue to have symptoms of peptic ulcer disease that eventually require surgical intervention. Gastric resection therapy should be avoided when possible. A highly selective vagotomy may be the most desirable procedure if feasible.

SURGICAL MANAGEMENT

The primary goal of surgical therapy for short-bowel syndrome is to increase intestinal absorptive capacity, which can be achieved either by improving absorption by existing intestine or by increasing the area of absorption (Box 78–4). Recruiting additional intestine into continuity, relieving obstruction, or slowing intestinal transit will often improve absorption. The intestinal lengthening procedure is feasible in selected patients. The most significant increase in length, however, is potentially achieved by intestinal transplantation. The choice of surgical therapy for short-bowel syndrome is influenced by intestinal remnant length and caliber and the clinical condition of the patient (Table 78–3).[3]

Preserve and Maximize the Intestinal Remnant

An abdominal reoperation is required in about half the patients with short-bowel syndrome after discharge from the hospital.[26] Intestinal problems are the most common indication. An important goal with any reoperation in patients with short-bowel syndrome is to preserve the length of the intestinal remnant. Several strategies can be used when further intestinal disease requires surgery.[30] Resection can often be avoided by intestinal tapering to improve the function of dilated segments, performing stricturoplasty for benign strictures, and using serosal patching for certain strictures and chronic

Box 78–4 Surgical Strategies for Short-Bowel Syndrome

- Preserve and maximize remnant
  - Avoid resection
  - Restore continuity
  - Recruit additional intestine
- Improve intestinal function
  - Relieve obstruction
  - Taper dilated bowel
  - Slow intestinal transit
- Increase absorptive area
  - Intestinal lengthening
  - Intestinal transplantation

Table 78–3 Surgical Approach to Short-Bowel Syndrome

Intestinal Remnant	Clinical Condition	Surgical Options
Adequate length with normal diameter	Enteral nutrition (remnant >120 cm in adults, >60 cm in children)	Optimize intestinal function, recruit additional length
Adequate length with dilated bowel	Bacterial overgrowth, stasis	Treat obstruction, intestinal tapering
Marginal length with normal diameter (remnant 60-120 cm in adults, 30-60 cm in children)	Rapid transit, need for parenteral nutrition	Recruit additional length, reversed intestinal segment, artificial valve, colon interposition
Short length with normal diameter (remnant <60 cm in adults, <30 cm in children)	Need for parenteral nutrition	Optimize intestinal function
Short length with dilated bowel	Need for parenteral nutrition	Intestinal lengthening
Short length	Complications of parenteral nutrition	Intestinal transplantation

From Thompson JS: Surgical approach to the short bowel syndrome: Procedures to slow intestinal transit. Eur J Pediatr Surg 9:263, 1999.

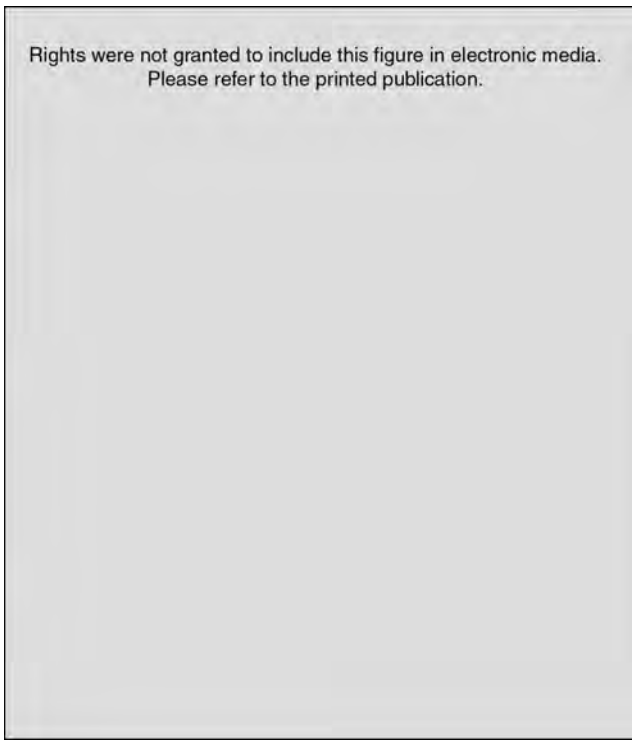

Figure 78–3. Techniques for preserving intestinal length include tapering of dilated segments rather than resection **(A)**, stricturoplasty for strictures **(B)**, and serosal patches for strictures and perforation **(C)**. (From Thompson JS: Recent advances in the surgical treatment of the short bowel syndrome. Surg Ann 22:110, 1990.)

perforations (Fig. 78–3). Resections should be limited in extent when they cannot be avoided. An end-to-end anastomosis is favored both to prevent blind loops and to maximize functional length of the intestine. Depending on the previous operations performed, patients occasionally have intestinal segments that can be recruited into continuity at the time of reoperation. This should always be given careful consideration. The length, location, and characteristics of the remnant should be carefully documented at the time of any operation.

Stricturoplasty is most often performed in the fashion of a Heineke-Mikulicz pyloroplasty. The stricture is incised longitudinally and closed transversely. The incision extends at least 1 cm proximal and distal to the stricture, but larger incisions may be required to achieve a satisfactory orifice. The enterotomy can be repaired with either a single-layer or a two-layer anastomosis. Longer strictures or multiple closely associated strictures can be opened with a side-to-side stapled anastomosis. Blind loops should be avoided, however.

Serosal patching is performed by apposition of an adjacent serosal surface, usually either small intestine or colon, to a nonhealing fistula, stricture, or other focal defect. A single-layer seromuscular-to-seromuscular anastomosis is created in either an interrupted or continuous fashion. The serosal patch becomes covered by normal mucosa from adjacent tissue. This technique is most applicable to smaller defects because contraction of the patch does occur and could lead to a stenotic segment.

Improve Intestinal Function

Improve Motility

Patients with short-bowel syndrome have a propensity for the development of dilated intestine secondary to chronic obstruction or intestinal adaptation. Dilated intestine may lead to stasis and bacterial overgrowth, which can further aggravate the malabsorption associated with the short remnant. Mechanical obstruction at an anastomosis or from adhesions or strictures related to the underlying disease process should always be sought in these patients and corrected with the techniques mentioned previously. These dilated segments, however, are often not associated with distal obstruction. Tapering dilated segments improves motility by permitting closure of the lumen during contraction of the wall, which improves peristalsis. Simple imbrication of the redundant bowel is the preferred method, although longitudinal transection plus removal of intestine along the antimesenteric border has also been performed. A continuous nonabsorbable suture line is usually most expeditious, particularly for lengthy segments. Excisional techniques are easily performed with stapling devices but can also be performed with bowel clamps. Tapering enteroplasty improves intestinal function in patients with short-bowel syndrome.[3] Blind loops should be sought and eliminated, preferably by revision of the anastomosis rather than resection.

Prolong Intestinal Transit

Procedures designed to prolong intestinal transit time have been evaluated experimentally and performed clinically, but their efficacy remains questionable (Fig. 78–4).[31,32] Most of the reports are anecdotal. These adjunctive procedures are often performed during the adaptive phase; hence, it is difficult to determine whether the improvement in nutritional status and absorption was due to the surgical procedure or the normal adaptive process. Three procedures have been attempted in sufficient numbers to be considered, including reversed intestinal segments, colon interposition, and artificial sphincters (Table 78–4).

Reversed Intestinal Segments Reversing segments of intestine to slow intestinal transit is the surgical procedure that has been reported most extensively. The antiperistaltic segment functions by inducing retrograde peristalsis distally and disrupting the motility of the proximal part of the intestine. In addition, disruption of the intrinsic nerve plexus slows myoelectrical activity in the distal remnant. Reversed segments also alter the hormonal milieu after resection.

Most experimental studies of antiperistaltic segments demonstrate slowed intestinal transit, improved absorption, reduced weight loss, and prolonged survival after intestinal resection, but some reports do not show a

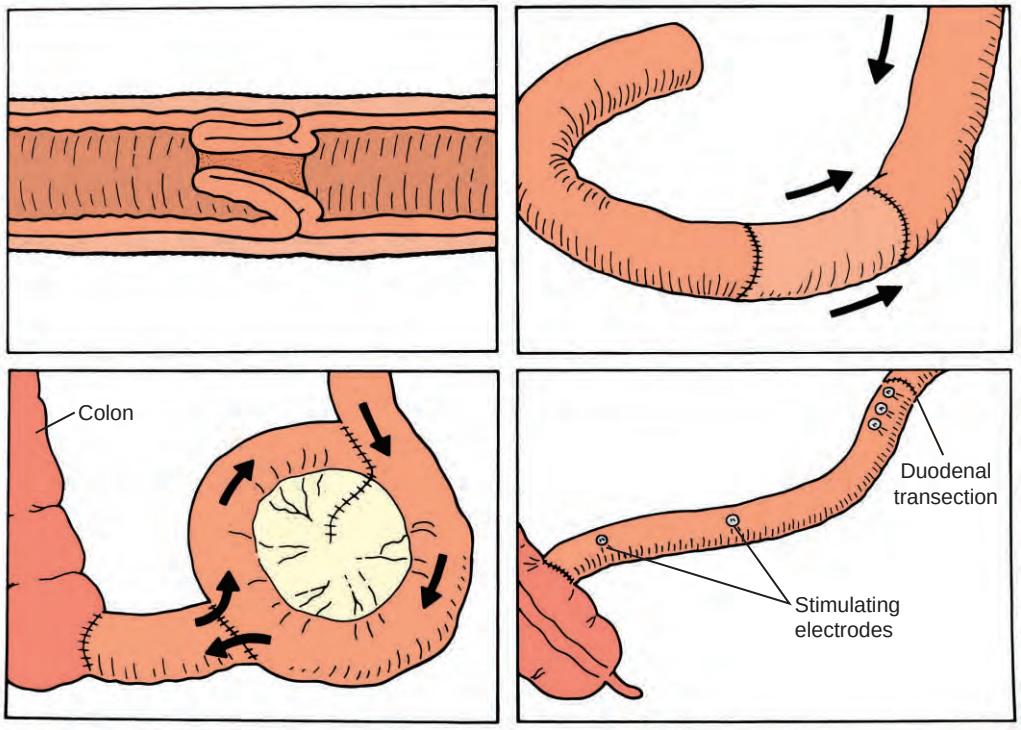

Figure 78–4. Techniques for slowing intestinal transit: intestinal valve *(upper left)*, antiperistaltic segment *(upper right)*, recirculating loop *(lower left)*, and intestinal pacing *(lower right)*. (From Thompson JS, Rikkers JS: Surgical alternatives for the short bowel syndrome. Am J Gastroenterol 82:97, 1987.)

Table 78–4 Clinical Experience with Procedures to Prolong Transit for Short-Bowel Syndrome

Procedure	Number of Patients	Number of Children (%)	Number of Patients with Clinical Improvement (%)
Reversed segment	55	6 (11)	45 (81)
Intestinal valve	12 (6)*	1 (16)	4 (67)
Colon interposition	12	11 (92)	6 (50)
Pouch or loop	4	1 (25)	1 (25)
Intestinal pacing	1	0 (0)	0 (0)

*Six procedures performed as a staged approach for intestinal lengthening.
From Thompson JS: Surgical approach to the short bowel syndrome: Procedures to slow intestinal transit. Eur J Pediatr Surg 9:263, 1999.

beneficial effect.[33,34] The variable outcomes may be explained by several factors, including variation in the extent of resection, timing of the procedure, and the use of different lengths of antiperistaltic segments. Reversed segments performed simultaneously with 75% resection in canines blunted the normal adaptive response, which may be related to the altered hormonal response.[35]

The ideal antiperistaltic segment slows transit without causing complete obstruction. Several technical details are important. The optimal length of the reversed segment would appear to be about 10 cm or less in adults and 3 cm in children. The reversed segment should be created as distal in the small intestinal remnant as feasible. Care must be taken to avoid complete rotation of the mesentery to prevent intestinal ischemia.

Antiperistaltic segments have been reported clinically in more than 50 patients, about 90% of whom were adults.[31] In these anecdotal reports, clinical improvement with slowed intestinal transit and increased absorption has been reported in 80% of patients. Transient obstructive symptoms and anastomotic leak are potential problems. The length of the segment has varied from 5 to 15 cm in these reports. Performance of this procedure in patients with Crohn's disease does not appear to

influence recurrence rates. Long-term function has been demonstrated.

Intestinal Valves The effect of valves and sphincters on intestinal motility involves several different mechanisms. They create a partial mechanical obstruction, disrupt the normal motor pattern of the small intestine, and prevent retrograde reflux of colonic contents.[31] In experimental studies, intestinal valves and sphincters have been shown to prolong transit time, increase absorptive capacity, and extend survival, although the results have been inconsistent. Effective valves usually result in some dilation of the proximal part of the intestine and may cause, at least transiently, obstructive symptoms. Potential complications include necrosis of the valve, complete obstruction, and intussusception. Durability of the sphincter function of valves has been questioned.

Several different techniques for creating intestinal valves and sphincters to replace the ileocecal valve have been reported, including external constriction of the intestine, segmental denervation, and intussusception of intestinal segments to increase intraluminal pressure, with the latter being used most frequently. Intussuscepted valves should be 2 cm in length if retrograde and 4 cm if the intussuscepted valve is prolapsed antegrade. We have generally created a retrograde sphincter similar to that used in the continent ileostomy procedure, but it is only 2 cm in length.[3]

The reported clinical experience with intestinal valves and sphincters is less extensive than that with reversed segments. Nipple valves were recently used in six infants to cause dilation of the intestine so that subsequent intestinal lengthening could be performed.[33] Intussuscepted valves were reported as primary treatment in five adults and one infant with short-bowel syndrome.[31] Four patients improved markedly, one had questionable benefit, and takedown of the valve was required in the other. Ileocolic nipple valves were lost in a third of patients monitored for more than 5 years in one study, again raising the issue of durability.

Colon Interposition Interposing a colonic segment in the small intestinal remnant in either an isoperistaltic or antiperistaltic fashion retards intestinal transit. Isoperistaltic interposition is performed proximally and functions by slowing down the rate at which nutrients are delivered to the distal portion of the small intestine.[31] The antiperistaltic colon interposition is placed distally, similar to the reversed small intestinal segment. Interposed colonic segments absorb water, electrolytes, and nutrients, in addition to their effect on intestinal transit. Although it has been suggested that interposed colon might develop structural and functional similarities to the small intestine, this has not been substantiated.

In experimental studies, isoperistaltic colon interposition generally resulted in slower transit time, less weight loss, and improved survival after resection. Results with antiperistaltic colon interposition, however, have been less consistent. The length of colon interposed seems to be less critical than with reversed segments.

The use of colon interposition has been reported in 12 patients, 11 of whom underwent isoperistaltic interposition.[32] All but one of the patients were infants younger than 1 year. The interposed colon segment varied between 8 and 24 cm in length. All patients were PN dependent preoperatively. Six (50%) patients demonstrated sustained clinical improvement; the other six, including the one with the antiperistaltic colon, did not improve and subsequently died of sepsis or hepatic failure. Colonic stasis with bacterial overgrowth may have contributed. This experience suggests that isoperistaltic colon interposition may have some merit.

Other Approaches Intestinal pouches and recirculating loops would theoretically prolong transit time by permitting prolonged exposure of luminal nutrients to the intestinal absorptive surface. In experimental studies, however, these procedures have not improved absorption or survival rates after massive resection. Four clinical reports involving recirculating loops have been disappointing as well.

Intestinal pacing in a retrograde fashion has also been investigated as a means of prolonging transit time. Retrograde electrical pacing promotes peristalsis in a reverse direction but also alters proximal intestinal motility, possibly through a hormonal mechanism. Postprandial retrograde pacing in canines improved absorption and intestinal status. In the one reported attempt to achieve retrograde pacing in a patient with short-bowel syndrome, the pacemaker failed to stimulate the intestine.

Choice of Procedure Procedures designed to slow intestinal transit should be applied cautiously in patients with nearly adequate remnant length and demonstrated rapid transit. They should be considered only after maximal adaptation has occurred. Reversed intestinal segments and artificial valves have the greatest appeal as procedures to slow intestinal transit. Antiperistaltic segments should be used in patients with longer remnants. The 10-cm segment still leaves sufficient remnant for absorption. Valves should be considered in patients with shorter remnants because less bowel is used. In one experimental study, an intestinal valve was more effective than an antiperistaltic segment in prolonging transit time after resection. The efficacy of these procedures remains questionable, however, and other approaches have been even less encouraging. Furthermore, these procedures are applicable to only a small proportion of patients with short-bowel syndrome.

Increase Absorptive Area

Dilated intestinal segments may be amenable to an intestinal tapering and lengthening procedure. Theoretically, such a procedure has the advantage of not only improving motility and reducing stasis but also improving intestinal absorption by the increased absorptive area. The primary technique was initially described by Bianchi[34] (Fig. 78–5). More recently, an alternative technique called serial transverse enteroplasty (STEP) has been reported[36,37] (Fig. 78–6). In these approaches the

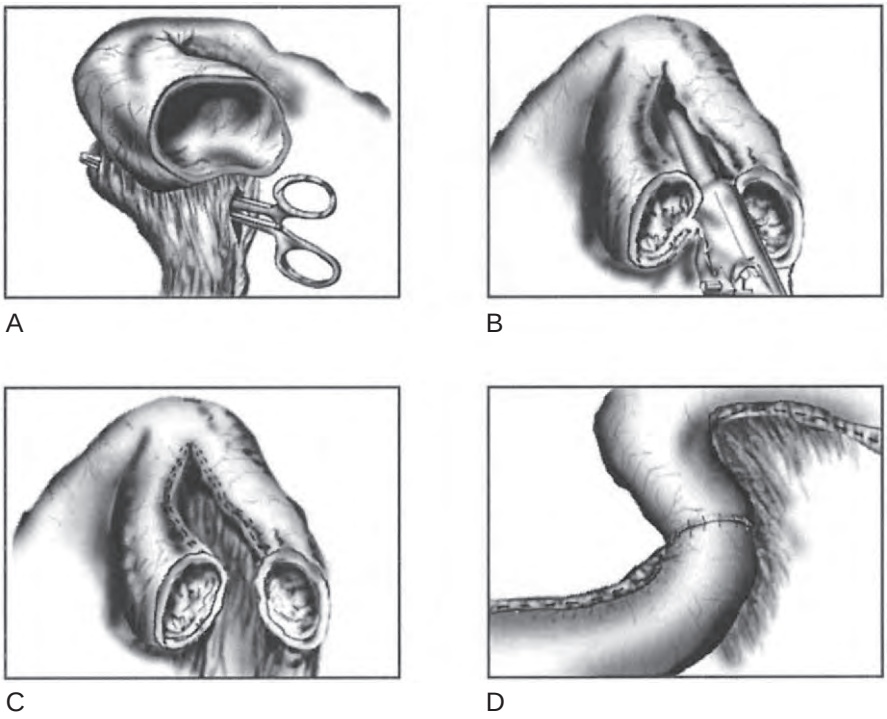

Figure 78–5. The Bianchi procedure. Longitudinal dissection between the blood vessels on the mesenteric border **(A)** permits the use of staples to divide the intestine longitudinally **(B** and **C)**. The two parallel segments are then anastomosed end to end **(D)**. (From Thompson JS: Surgical rehabilitation of the intestine in short bowel syndrome. Surgery 135:465, 2004.)

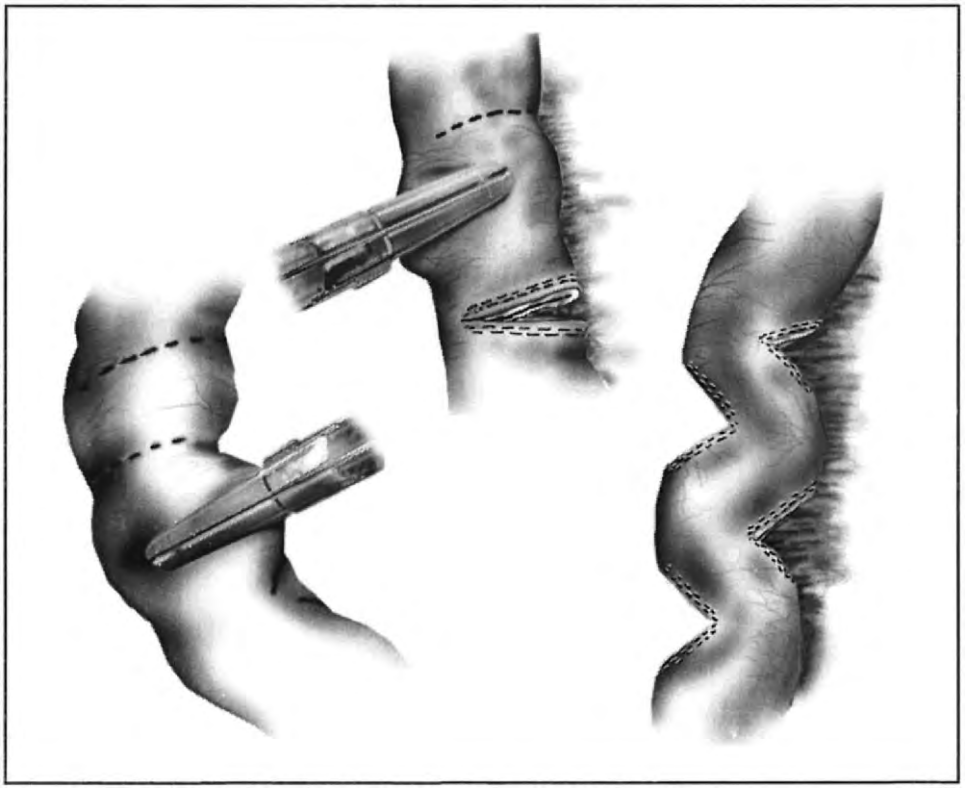

Figure 78–6. The STEP procedure. Several transverse applications of a linear stapler from opposite directions on the bowel wall allow the intestine to lengthen with reduced diameter. (From Thompson JS: Surgical rehabilitation of the intestine in short bowel syndrome. Surgery 135:465, 2004.)

dilated segments are tapered, and the redundant intestine is preserved and restored into continuity for additional length.

In experimental studies, intestinal lengthening by the Bianchi procedure prolongs transit time but does not clearly improve absorption in the short term.[38] Intestinal lengthening causes motor disruption in the proximal portion of the intestine and alters the hormonal response to resection. The jejunum may yield better results than lengthening of ileum. Improved nutrition

has been demonstrated in an animal model after the STEP procedure.[36]

The Bianchi procedure is performed by transecting distal to the dilated segment to be tapered. Dissection is performed longitudinally for about 5 cm on the mesenteric edge of the bowel between the terminal branching vessels to create a space that permits longitudinal division of the bowel with a stapler. A hand-sewn anastomosis can also be used. If the diameter of the bowel permits, the staple line can be imbricated as well. This procedure is repeated until the desired length is achieved. The two parallel longitudinal segments can then be anastomosed end to end to halve the diameter and double the length of the segment. Intestinal lengthening of segments from 5 to 90 cm has been reported. Obviously, longer segments are at greater risk for complications.

The STEP procedure involves serial transverse applications of a linear stapler from alternating directions to divide the bowel perpendicular to the long axis of the intestine. The length and spacing of the transverse division are determined by the diameter of the intestine. Multiple stapler applications are required. The net result is an increase in length and a reduction in diameter. This procedure is less complicated than the Bianchi procedure because it avoids the extensive mesenteric dissection and the additional anastomosis. It is feasible for very short segments and those near the ligament of Treitz.

Intestinal lengthening, primarily the Bianchi procedure, has now been reported in more than 100 patients.[34,37,39,40] After an initial prolonged ileus, significant improvement in absorptive capacity and nutritional status has been reported in 90% of these patients in the short term. Potential complications, however, such as necrosis of divided segments, anastomotic leak, and obstruction develop in up to 20% of patients. Gastrostomy tubes are often placed because of the prolonged dysmotility that occurs. Although short-term results have been encouraging, emerging long-term results suggest that about half the patients undergoing this procedure have a sustained benefit for up to 10 years.[39] The initial experience with the STEP procedure has been favorable.[37,40] Initial short-term results in 10 patients have demonstrated the feasibility and safety of the technique in the clinical setting. The outcome of these procedures is heavily influenced by patient selection in terms of age, remnant length, hepatic function, and requirement for PN. Thus, these procedures should be applied cautiously.

One of the limitations of lengthening procedures is that they can be applied only to a fairly select group of patients. Obviously, the procedures should be considered only if bacterial overgrowth or other signs of malabsorption are identified that appear to be related to the dilated segment. The intestinal diameter should be at least 4 cm to provide an adequate lumen size after tapering. Sequential operations, first using a procedure such as an artificial valve to produce intestinal dilation and then performing the lengthening at a later time, have been used to expand the applicability of this technique. The vascular anatomy must be favorable for the Bianchi procedure. Effort is also being directed at recruiting additional vascular supply to permit further lengthening. The STEP procedure should markedly increase the applicability of intestinal lengthening.

INTESTINAL TRANSPLANTATION

The development of intestinal transplantation must be placed in the context of patients and physicians faced with catastrophic clinical circumstances in the absence of reliable alternatives. The mortality rate of patients requiring PN for benign disease has been estimated at 5% to 25% per year, or about 15% at 3 years.[41] For infants, the risk for PN-induced liver disease is especially great. It is estimated that half the deaths in children receiving PN are due to liver failure.[42] Currently, intestinal transplantation is applied as rescue therapy for patients with life-threatening complications of intestinal failure. In 2001 the U.S. federal government through the Centers for Medicare and Medicaid Services (CMS) approved payment for intestinal transplantation at select centers.

Indications

Indications for intestinal transplantation are restricted to life-threatening complications of intestinal failure, with the most common complication being the development of liver disease. It is important to determine whether the liver disease is reversible. If the liver disease is found to be irreversible, based on either biopsy findings or clinical features such as massive splenomegaly, ascites, encephalopathy, or gastrointestinal bleeding, the patient should undergo combined liver–small bowel transplantation. Greater emphasis has recently been placed on considering isolated small bowel transplantation for patients with potentially reversible PN-induced liver disease. Regardless of the type of transplant required, early referral and listing are important to ensure the patient the greatest opportunity to obtain a transplant.

The other common indications for intestinal transplantation are an irreversible permanent PN requirement along with episodes of sepsis or loss of venous access. Septic episodes that would prompt consideration for intestinal transplantation are typically catheter related. Patients who have undergone multiple hospitalizations related to catheter sepsis, often requiring intensive unit care with the need for vasopressors, fall in this category. Other indications for intestinal transplantation are multiantibiotic-resistant bacteremia or metastatic infection in sites such as the tricuspid valve or brain. Loss of venous access typically implies an inability to place a catheter in the subclavian or intrajugular veins and the use of extemporaneous sites such as the hepatic veins or the inferior vena cava. A transplant evaluation is strongly recommended in patients with known poor survival on PN, such as those with microvillus inclusion disease, intestinal aganglionosis, or desmoid tumors that have previously been eviscerated. Today, with improved outcomes and large numbers of patients dying on the waiting list, greater responsibility is being placed on the treating physician to make earlier referral to a transplant center.

The transplantation evaluation process for patients with intestinal failure requires a multidisciplinary group of health care professionals, including surgeons, gastroenterologists, dietitians, social workers, and nurse specialists. The evaluation process also incorporates an assessment of the feeding program that the patient is currently receiving. Contrast studies of the small and large bowel are frequently performed. A liver biopsy is performed in patients with evidence of liver dysfunction to help select the appropriate type of transplantation procedure. During the evaluation process, other problems are addressed, including worsening liver failure, sepsis, difficult vascular access, and septic episodes. After being identified as a potential candidate, the patient is placed on an active transplantation waiting list.

Operative Procedure

The donor operation begins similarly regardless of the organs being removed. Potential organ donors are matched with recipients according to blood type, size, and medical necessity. Most patients with short-bowel syndrome have a loss of peritoneal domain, thus requiring the donor to be about 50% smaller than the potential recipient. Recent success with reduced-size intestinal transplants has challenged these donor size guidelines. Donors should be ABO blood group identical, although exceptions to this rule have been reported.[43] Human leukocyte antigen matching and a negative T-cell crossmatch may be beneficial, particularly for recipients of isolated small bowel allograft. Donor logistics often prevent this type of testing from being performed prospectively.

Removal of the intestine for isolated small bowel transplantation involves removal of the liver and small bowel together, after which they are separated on the back table.[44] The donor operation for a future liver–small bowel transplantation is relatively similar, but no hilar dissection is performed. The colon and stomach are mobilized out of the field, and the liver–small bowel composite is removed en bloc, with care taken to remove as much aorta proximal to the celiac axis as possible.[44]

Back-table preparation for an isolated small bowel graft involves removing the duodenum–head of the pancreas from the portal vein and superior mesenteric artery. For liver and small bowel grafting procedures, the preparation involves removal of the distal pancreas and spleen. The numerous intercostal arteries are ligated, and the distal end of the aorta is oversewn. Critical for a liver–small bowel graft is that no hepatic hilar dissection take place so that the hepatobiliary-duodenal complex remains undisturbed.[44]

The recipient operation typically makes use of previous incisions. For isolated small bowel transplantation, the infrarenal aorta is isolated, and the arterial anastomosis for the small bowel graft is typically performed between the donor superior mesenteric artery and the infrarenal aorta.[44] Venous drainage can be systemic or portal, but systemic drainage is preferred whenever liver disease is present. An enterostomy is created to decompress the small bowel and to facilitate biopsy. A loop ileostomy is the most common type of stoma created for both liver–small bowel and isolated small bowel transplantation.

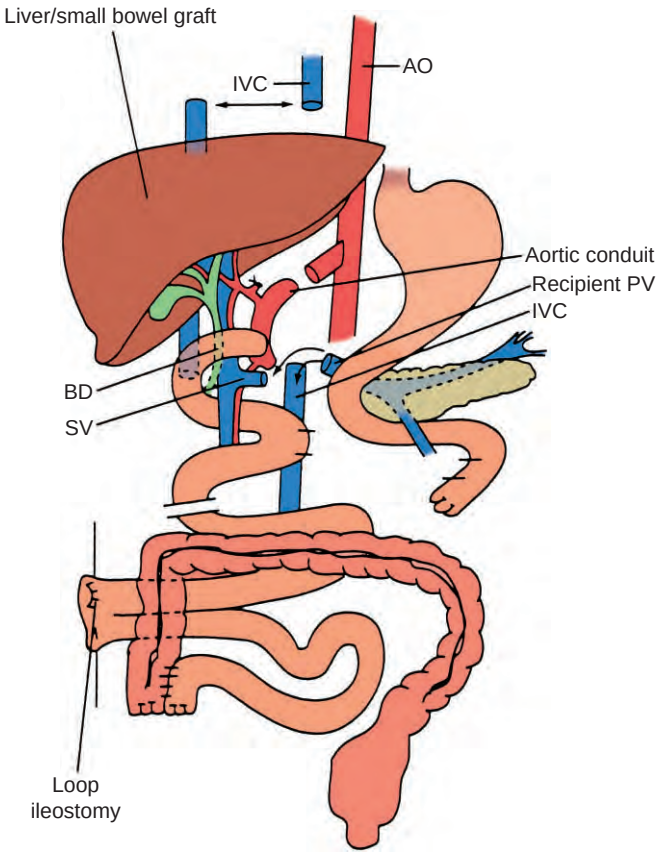

Figure 78–7. Diagram of a liver–small bowel allograft. This diagram demonstrates the intact hepatobiliary duodenal complex. AO, aorta; BD, bile duct; IVC, inferior vena cava; PV, portal vein; SV, splenic vein. (From Deroover A, Langnas A: Surgical methods of small bowel transplantation and liver-bowel transplantation. Curr Opin Organ Transplant 4:335, 1999.)

The liver–small bowel transplantation surgical technique leaves the donor hepatic hilar structures undisturbed and the hepatic-duodenal-biliary system intact (Fig. 78–7). The advantage of this approach is that it limits the necessary back-table dissection, prevents any torsion around the portal vein after implantation, and virtually eliminates any possible biliary tract complications after transplantation. The liver–small bowel composite allograft is implanted orthotopically. Arterial inflow is through the donor aortic conduit, and a native portacaval shunt is created to decompress the recipient's viscera. Under certain circumstances, particularly when the native foregut is diseased or dysfunctional, complete abdominal evisceration is performed before implantation of the donor organs. With evisceration of the native foregut the operation is often referred to as a multivisceral transplant. The proximal gastrointestinal anastomosis is frequently performed between the remnant proximal part of the stomach and the donor jejunum.

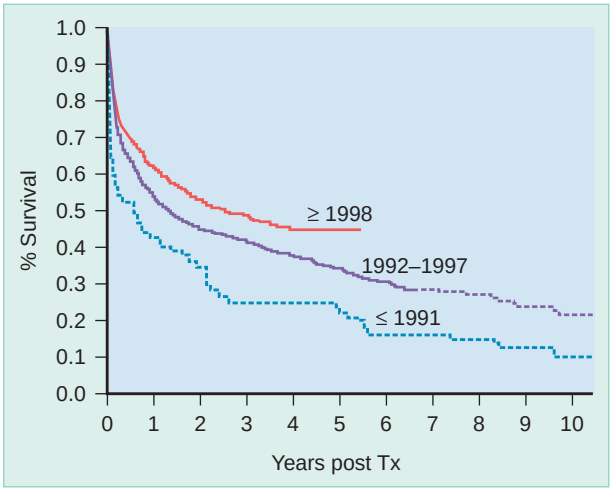

Figure 78–8. Graft survival rates after intestinal transplantation have improved over time. (From Grant D, Abu-Elmagd K, Reyes J, et al: 2003 Report of the intestine transplant registry: A new era has dawned. Ann Surg 241:607, 2005.)

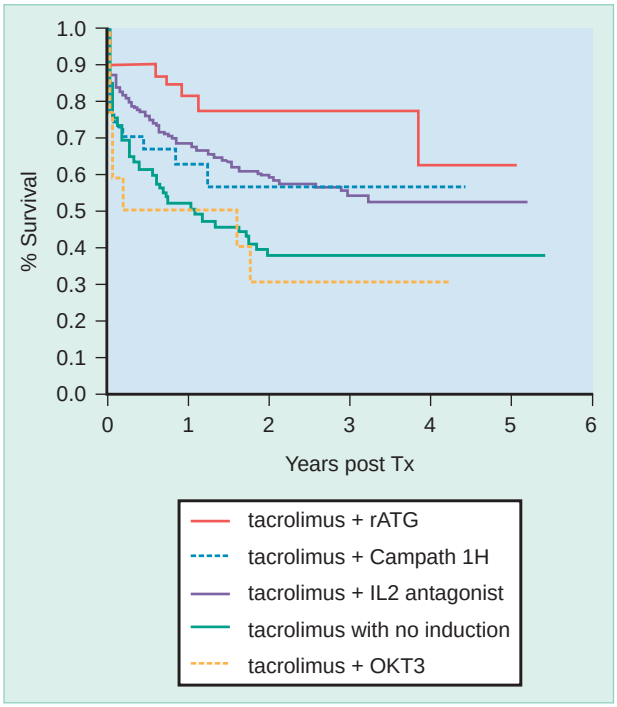

Figure 78–9. Graft-survival rates plotted according to the type of immunosuppressive protocol with particular reference to induction therapy. ATG, antithymocyte globulin; IL2, interleukin-2. (From Grant D, Abu-Elmagd K, Reyes J, et al: 2003 Report of the intestine transplant registry: A new era has dawned. Ann Surgery 241:607, 2005.)

After transplantation, the cornerstone of immunosuppressive management is the administration of tacrolimus and steroids. The majority of intestinal transplant programs now make use of some form of induction therapy, either with biologic agents such as Thymoglobulin or with interleukin-2 receptor blocking agents.[45-47] Reports have been made of other drugs being administered, including sirolimus, alemtuzumab (Campath 1H), and mycophenolate.[48] Numerous other agents are given as prophylaxis for infection, in particular, broad-spectrum antibiotics, antifungal agents, and antiviral drugs.

Outcome

Worldwide, based on published data from the 2003 Intestinal Transplant Registry (ITR) contributed by 61 programs in 10 countries, 989 transplants have been performed in 923 patients.[49] According to ITR data, isolated intestinal transplantation was performed 433 times and an intestinal allograft transplanted with a liver 556 times. Thirty-two grafts were obtained from living donors, including an identical twin and a triplet. In 2001 the CMS approved intestinal transplantation as therapy for patients with life-threatening complications of intestinal failure.

A total of 484 of the 923 patients reported in the ITR who underwent any type of intestinal transplantation are alive. The longest survivor has been on an enteral diet for over 14 years. Patient and graft survival has also steadily increased over time (Fig. 78–8). The ITR results also demonstrated factors important in improving patient and graft survival.[49] In a log-logistic model, factors associated with improved patient and graft survival included transplantation of a patient coming from home and the use of induction therapy (Fig. 78–9). As expected, programs that have performed at least 10 transplantations have better patient survival rates than do programs that have performed less than 10 transplantations. Patients who are called in from home have much higher survival rates, which should encourage physicians to refer patients earlier. Clinical experience remains confined to a small number of programs, with 83% of the cases performed at 10 institutions. The most common causes of death after intestinal transplantation included sepsis, multiorgan system failure, graft thrombosis, rejection, and post-transplantation lymphoma.

Rejection episodes continue to be a major problem in small bowel transplantation, even with tacrolimus-based immunosuppression combined with some form of induction therapy. The incidence of transplant rejection remains variable. According to the ITR, graft rejection rates were 57% for intestine grafts, 39% for combined intestine and liver grafts, and 48% for multivisceral grafts.[49] Contemporary single-center reports demonstrate even further reductions in rejection rates. At the University of Pittsburgh, Thymoglobulin induction combined with tacrolimus has resulted in a 44% rejection rate in the first month, whereas patients receiving interleukin-2 receptor blocking agents combined with tacrolimus at the University of Nebraska had a rate of about 5%.[45,47] These rates of rejection are now similar to those seen in recipients of heart, liver, and kidney transplants. The diagnosis of rejection is based on histologic findings. Mild rejection is diagnosed by the findings of

mild cryptitis, increased inflammatory infiltrated lamina propria, and apoptosis of crypt cells (Fig. 78–10). A diagnosis of moderate rejection is made when villus blunting develops in addition to the findings associated with mild rejection. Serious rejection is diagnosed when there is not only severe blunting but also complete loss of mucosal lining and severe crypt cell destruction. Biopsy of the small bowel allograft is performed either on a protocol basis or when changes in clinical findings occur. Clinical findings that could be associated with rejection include diarrhea, increased stoma output, bloody diarrhea, abdominal pain, or an intolerance to feedings. Unfortunately, a noninvasive marker for the diagnosis of rejection episodes is not available.

Infections after organ transplantation are generally frequent as a result of two important factors in these patients: increased levels of immunosuppression and an allograft colonized with enteric organisms. Common sites of bacterial infection include the central line, surgical wound, and intraperitoneum. Bacteremia or fungemia may also develop as a consequence of allograft rejection, infectious enteritis, or preservation injury. With any of these bowel injuries, there can be loss of mucosa with eventual translocation of enteric organisms.

The primary viruses that cause infections after intestinal transplantation include herpesviruses such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV). A variety of strategies have been proposed to either prevent or diagnose both CMV and EBV infection. Molecular monitoring for both EBV and CMV DNA in blood is now routine in most transplant programs. Prophylactic measures include infusions of pooled immunoglobulins and antiviral drugs such as ganciclovir. The intestinal graft is the most common site of CMV infection. Treatment is based on the use of antiviral drugs such as ganciclovir or foscarnet.

Post-transplant lymphoproliferative disease (PTLD) is an EBV-associated process that occurs after all solid organ transplantations. Intestinal transplant recipients appear to be at higher risk for PTLD than do recipients of other organ transplants, probably in part because of the high level of immunosuppression needed to control rejection, as well as the relatively young age of recipients. The reported incidence of PTLD after intestinal transplantation is between 7% and 29%.[45-47,49] Treatment of PTLD often involves lowering of immunosuppression and the use of antiviral agents as a first line of therapy. Newer treatments being proposed include the use of a low-dose cyclophosphamide (Cytoxan) regimen to control PTLD without the side effects of more traditional chemotherapeutic regimens.[50] Rituximab, a monoclonal antibody directed at CD20-positive B cells, is now being used to treat PTLD. Recently, the use of blood tests to measure qualitative and quantitative amounts of EBV DNA in the peripheral blood of transplant recipients has been advocated.[51] Measurements of EBV DNA are used

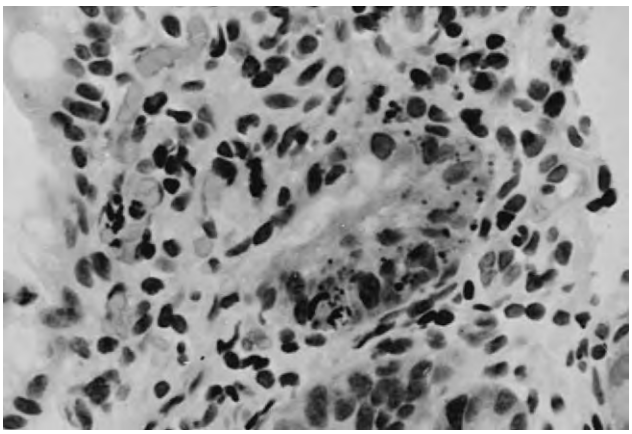

Figure 78–10. Photomicrograph of intestinal rejection in a transplanted intestinal graft. Apoptosis is a prominent feature. A single crypt is seen in the center with multiple apoptotic cells.

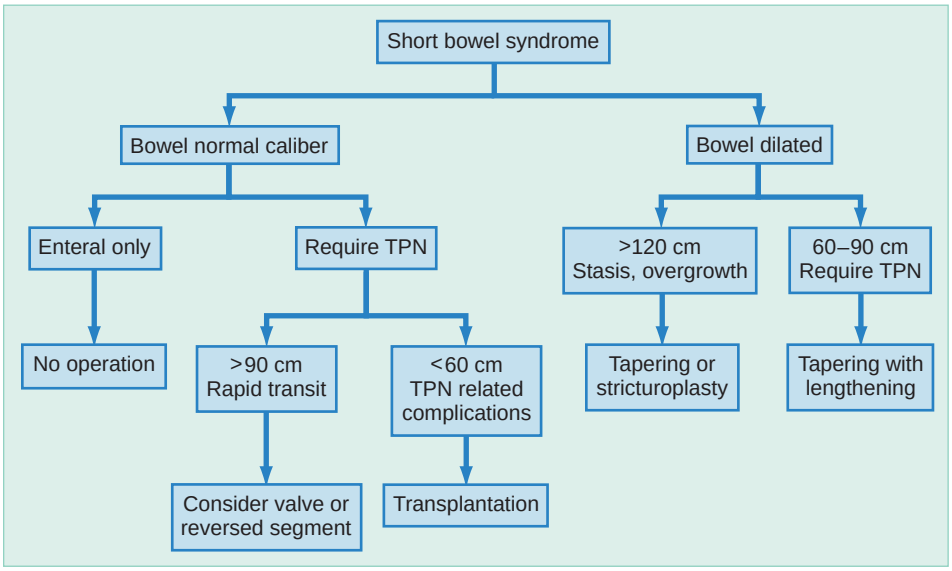

Figure 78–11. Surgical management of short-bowel syndrome. TPN, total parenteral nutrition. (From Thompson JS, Langnas AN, Pinch LW, et al: Surgical approach to the short bowel syndrome: Experience in a population of 160 patients. Ann Surg 22:600, 1995.)

in the hope of identifying PTLD before it becomes clinically evident so that less toxic preemptive therapy can be administered.

Graft-versus-host disease has been a relatively uncommon clinical event after intestinal transplantation. Its incidence was 7% in one series.[45] The diagnosis is based on traditional histopathologic criteria of skin, native gastrointestinal tract, or mucosa. Treatment of graft-versus-host disease is based primarily on increases in immunosuppression.

The functional status of the small bowel allograft is the foremost factor in determining the long-term quality of life for recipients. According to the ITR, enteral autonomy develops in 81% of recipients. Data also demonstrate that intestinal transplantation becomes cost-effective in comparison to PN at 2 years.[52]

The increasing experience and improved outcome of intestinal transplantation support the clinical use of this treatment modality. Although the potential morbidity of transplantation is greater than that of nontransplant surgical procedures, so too is the benefit. Intestinal transplantation is potentially applicable to a greater number of patients with short-bowel syndrome than nontransplant procedures are. All these procedures should be performed only in carefully selected patients (Fig. 78–11).

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Chapter

79

Gastrointestinal Carcinoid Tumors

Cletus A. Arciero ▪ Elin R. Sigurdson

Lubarsch first described carcinoid tumors in 1888.[1] Oberndorfer used the term "karzinoide" in 1907 to describe a tumor that was more indolent behaving than adenocarcinoma.[2] Since these early discoveries, carcinoid neoplasms have been described in most organs in the body. Carcinoid neoplasms are neuroendocrine tumors that span the realm from benign to malignant. They are derived from enterochromaffin cells, or secretory cells found within respiratory and gastrointestinal epithelial tissues. These cells, which belong to the amine precursor uptake decarboxylase (APUD) system, are often argentaffinic (silver staining), are usually argyrophilic (silver staining only with the addition of a reducing agent), and produce a wide array of biogenic amines, neuropeptides, and peptide hormones. Although gastrointestinal neuroendocrine tumors are rare, carcinoid tumors are the most common of them.

INCIDENCE AND EPIDEMIOLOGY

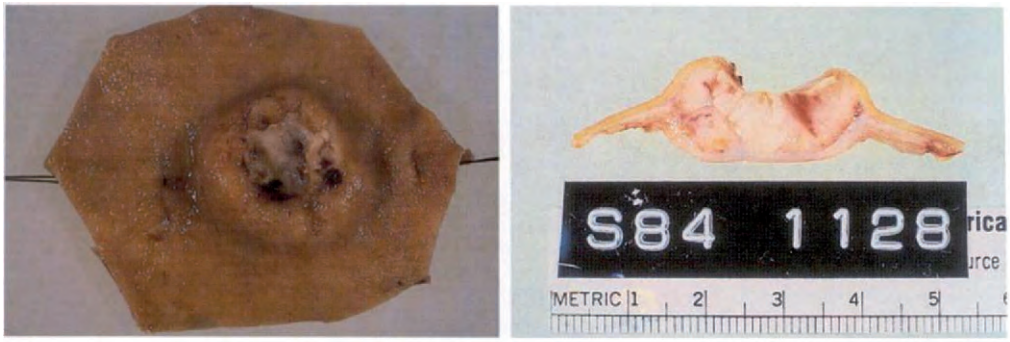
The incidence of gastrointestinal carcinoids in the United States is estimated to be 2.47 to 2.58 per 100,000, with similar rates noted in Europe and Japan.[3] The incidence of carcinoid tumors is higher in African Americans, who have rates of 3.98 to 4.48 per 100,000. Necroscopy studies have shown that upward of 0.65% to 1.2% of all patients examined exhibit evidence of a small intestine carcinoid.[4] However, because of their often indolent course, far fewer diagnoses are made. The tumor occurs most commonly in the fifth to sixth decade of life with a slight predilection for females (55 : 44 female-to-male ratio). Sixty-seven percent of all carcinoids arise in the gastrointestinal tract, with the majority (25.3%) of the remaining occurring in the tracheobronchial tree.[3]

Gastrointestinal carcinoids are distributed via embryologic origins: foregut, midgut, and hindgut. Foregut carcinoids account for approximately 7% of all carcinoids, whereas midgut and hindgut carcinoids represent 62% and 30% of all carcinoids, respectively. Because of the preponderance of APUD cells within the ileum and appendix, the most common sites are the appendix (35%) and small intestine (23%), followed by the rectosigmoid (12%) and colon (6%). The majority of the small intestine carcinoids occur within 2 ft of the ileocecal valve. Both foregut and midgut carcinoids are associated with a second, synchronous primary carcinoid tumor of similar embryologic origin in 25% of cases. Non-neuroendocrine, synchronous cancers are discovered in 17% to 53% of patients with carcinoid tumors.[5]

Some patients have a genetic predisposition to carcinoid tumors. First-degree relatives of patients with carcinoid have an increased relative risk (RR = 3.6) for development of a carcinoid tumor.[5] There is also a notably increased risk for carcinoid tumors in those who have a well-educated social background (RR = 2.8) and reside in a major metropolitan region (RR = 1.39).[5]

PATHOLOGY

Carcinoid tumors are composed of enterochromaffin cells (which are cells that stain with chromaffin). Grossly, these tumors are well-circumscribed, round, submucosal lesions that reveal a yellow coloration when sectioned because of the high lipid content of the tumors (Fig. 79–1). They are typically small (<2 cm) and multicentric. Microscopically, carcinoid tumors are pathologically categorized by the presence of small, uniform cells in orderly bands or ribbons (Fig. 79–2). They have benign cytologic features with rare mitotic figures. The cytoplasm is marked by the abundant presence of neurosecretory granules, and immunohistochemical staining reveals numerous peptides. The exact microscopic features of carcinoid neoplasms vary according to their origin. Foregut tumors are mostly argyrophilic, whereas midgut tumors are mostly argentaffinic. Hindgut tumors appear to be a mix, with 60% to 70% being argyrophilic, 8% to 16% being argentaffinic, and the rest having no



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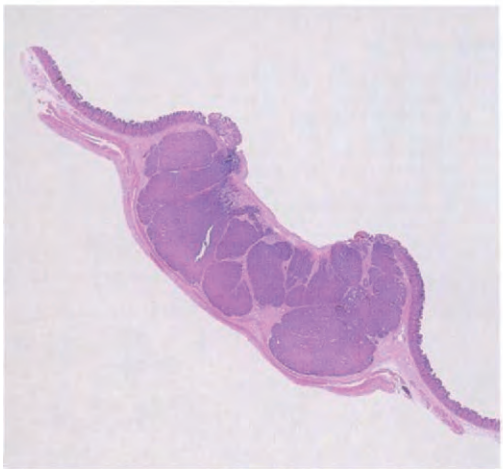
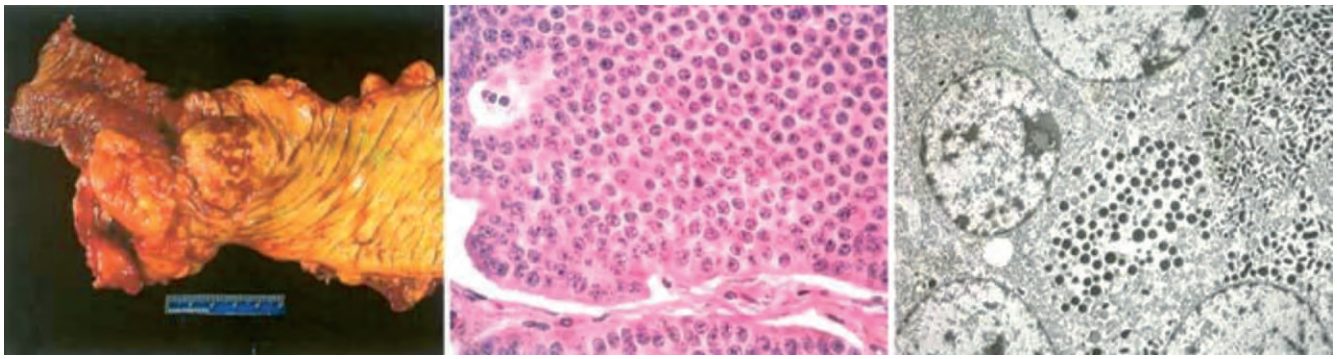


C

Figure 79–1. Gastric carcinoid tumor. **A,** Large, ulcerated tumor (gross). **B,** Fixed specimen (gross). **C,** Low-power histologic study showing a large tumor with mucosal ulceration but confined to the wall of the stomach. (Courtesy of Edward Lee, M.D. From Koh TJ, Wang TC: Tumors of the Stomach. In Feldman M, Friedman LS, Sleisenger MH [eds]: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 7th ed. Philadelphia, WB Saunders, 2002, p 847.)



A B C

Figure 79–2. Carcinoid tumor. **A,** Multiple protruding tumors are present at the ileocecal junction. **B,** The tumor cells exhibit a monotonous morphology, with a delicate intervening fibrovascular stroma. **C,** Electron micrograph showing dense core bodies in the cytoplasm (From Liu C, Crawford JM: The gastrointestinal tract. In Kumar V, Abbas A, Fausto N [eds]: Robbins and Cotran: Pathologic Basis of Disease, 7th ed. Philadelphia, Elsevier, 2005, p 867.)

evidence of any silver staining. Carcinoid tumors have five histologic patterns: insular, trabecular, glandular, undifferentiated, and mixed.[6]

Although pathologic examination of the primary tumor cannot clearly define malignant versus benign without evidence of metastasis, certain features indicate increased aggressiveness. These more aggressive-appearing carcinoids are termed atypical/anaplastic carcinoid and have features of increased cellular atypia, high mitotic rate/activity, or necrosis. Immunohistochemical staining to detect increased levels of p21 or MIB-1, or both, can aid in determining the increased aggressiveness of a tumor.[7,8]

CLINICAL FEATURES

Carcinoid tumors are marked by their relatively slow growth and often dearth of symptoms. The median

duration of symptoms is 2 years before diagnosis. Eighty percent to 90% of patients who do have symptoms at initial evaluation are found to have metastatic or advanced disease.

The behavior of carcinoid neoplasms is dependent on the embryologic origin of the tumor. Foregut carcinoids consist of gastric and duodenal tumors. Duodenal carcinoids may cause gastrointestinal obstruction, biliary obstruction, or duodenal ulcers, although they are often discovered incidentally during endoscopy. Gastric carcinoids, 0.3% of all stomach neoplasms, can be associated with a myriad of symptoms, including abdominal pain, bleeding, and rarely, atypical carcinoid syndrome. Gastric carcinoids arise from enterochromaffin-like cells and are classified into three groups. Type I consists of gastric carcinoids associated with chronic atrophic gastritis type A. This group represents 75% of all gastric carcinoids and is marked by a lack of parietal cells, achlorhydria, and hypergastrinemia. The tumors are often less than 1 cm in diameter, diffusely involve the stomach, and metastasize in 10% of all cases, with an overall 5-year survival rate approaching 100%. The present theory is that these carcinoid tumors arise secondary to chronic stimulation by high gastrin levels and possibly mutations of the RegI alpha gene.[9] Animal models have shown a direct relationship between hypergastrinemia and carcinoid tumor formation, therefore raising the issue of the safety of using chronic proton pump inhibitors and whether antrectomy might lead to tumor regression. Patients with type I gastric carcinoid are often 70 to 80 years of age and female with symptoms of abdominal pain. Carcinoid syndrome is not seen, and these tumors usually follow an indolent course.

Type II gastric carcinoid tumors are associated with Zollinger-Ellison syndrome and familial multiple endocrine neoplasia type I syndrome. Patients in this group, 5% of those with gastric carcinoids, are younger (in their sixth decade of life), exhibit no evidence of carcinoid syndrome, and have a tumor size less than 1.5 cm with an equal gender distribution. Although metastases develop in up to 25%, the clinical course is usually indolent.

The last group of gastric carcinoids (type III) consists of sporadic carcinoid tumors. Patients in this group have larger tumors, and hepatic metastases develop in more than 65%. This group of patients (15% to 25% of those with gastric carcinoids) is associated with the development of an atypical carcinoid syndrome and have a 5-year survival rate near 50%. Indicators of tumor aggressiveness include angiolymphatic invasion, clinicopathologic type, mitotic index, Ki-67 grade, and tumor size.[10]

Midgut carcinoid tumors are the most common and include neoplasms arising from the ileum, jejunum, appendix, and proximal part of the colon. The tumors can lead to obstruction, abdominal pain, diarrhea, and gastrointestinal bleeding. Small intestinal carcinoids are also well known to cause intense fibrosing reactions leading to obstruction, ischemia, and strangulation of the small bowel and ureters (Fig. 79–3). Although carcinoid syndrome develops in only 5% to 7% of patients with midgut carcinoid, these patients represent 90% of all patients in whom carcinoid syndrome develops.

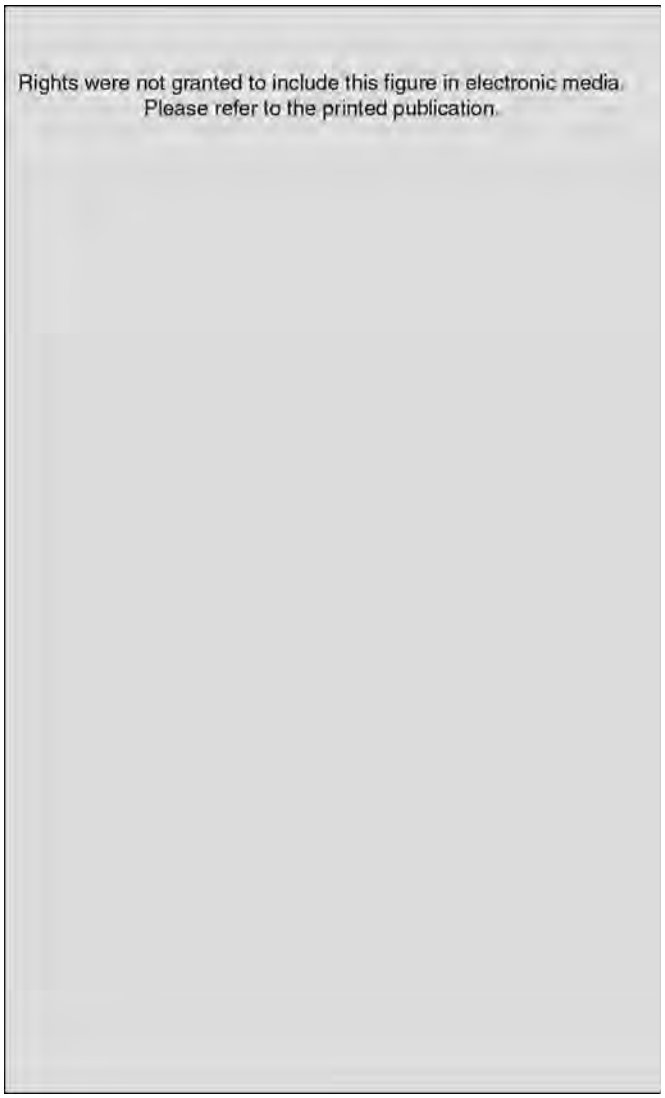


Figure 79–3. Gross pathologic characteristics of carcinoid tumor. **A,** Carcinoid tumor of the distal ileum demonstrating intense desmoplastic reaction and fibrosis of the bowel wall. **B,** Mesenteric metastases from a carcinoid tumor of the small bowel. (Adapted from Evers BM, Townsend CM Jr, Thompson JC: Small intestine. In Schwartz SI [ed]: Principles of Surgery, 7th ed. New York, McGraw-Hill, 1999, p 1245, with permission of The McGraw-Hill Companies.)

Abdominal pain is the initial complaint in 40% of patients with midgut carcinoid. This pain can be multifactorial and be due to bulky lymphadenopathy, mesenteric vascular invasion/occlusion, microvascular metastasis, hepatic metastases, or the vasoactive effects of serotonin. Patients can also have obstruction as a result of mesenteric kinking from the desmoplastic response. The fibrosis associated with midgut carcinoids can be quite extensive. Not only can intestinal obstruction occur, but retroperitoneal fibrosis can also develop and lead to ureteral obstruction and even Peyronie's disease (inflammation and scarring of the tunica albuginea).

Appendiceal carcinoid tumor is one of the most common forms of carcinoid disease and accounts for 50% of all diagnosed carcinoids. Ninety percent of appendiceal carcinoids are found via pathologic examination in patients undergoing incidental appendectomy. Another 10% undergo appendectomy for appendicitis, with two thirds of these patients having an incidental finding of a carcinoid tumor, usually located at the tip of the appendix. In general, less than 1% of all appendiceal carcinoid tumors have carcinoid syndrome as the initial clinical manifestation.

Hindgut carcinoids arise from the distal end of the colon and rectum. These nonsecretory carcinoid tumors are most often asymptomatic and discovered during colonoscopy for screening or evaluation of unrelated complaints. If symptoms are present, they are usually due to the increased size of the tumor, and these patients will often have symptoms similar to those with colorectal adenocarcinoma (bleeding, changes in bowel habits, or obstruction).

Carcinoid Syndrome

Malignant carcinoid syndrome is a clinical entity marked by flushing, diarrhea, abdominal cramping, wheezing, heart valve dysfunction, and pellagra. Although classically described as the hallmark of a carcinoid tumor, carcinoid syndrome occurs relatively infrequently. It is found in 10% to 18% of all patients with carcinoid tumors, but the incidence increases to 40% to 50% in patients with advanced disease.[11]

Carcinoid syndrome is based on the biochemical behavior of the tumors involved. Carcinoid tumors are neoplasms of peptide- and amine-producing cells, the enterochromaffin or Kulchitsky cells. These cells produce a large number of substances, including serotonin, tachykinins, and histamine. Ultimately, it is the metabolism of tryptophan that leads to the development of carcinoid syndrome. In carcinoid tumors that produce large amounts of serotonin, dietary tryptophan is diverted for this purpose. It is the actions of serotonin that lead to many of the manifestations of carcinoid syndrome. The syndrome develops in the presence of hepatic metastasis, which precludes hepatic inactivation of the active metabolites of serotonin.

The development of carcinoid syndrome is related to the embryologic origin of the original tumor. Midgut carcinoids are the most common source of carcinoid syndrome because these tumors produce high levels of serotonin. More than 90% of all patients suffering from carcinoid syndrome have a midgut primary. Foregut carcinoids, on the other hand, lack the aromatic amino acid decarboxylase required to convert 5-hydroxytryptamine (5-HT) to serotonin and therefore cannot produce the classic carcinoid syndrome. Hindgut carcinoids also lack the ability to convert tryptophan to serotonin, and thus even if metastatic lesions are present, carcinoid syndrome will not develop.

The symptoms associated with carcinoid syndrome include cutaneous flushing, which occurs in 85% of affected patients. This flushing, which has diverse patterns, including diffuse erythematous, violaceous, prolonged, and bright red patches, is possibly caused by the release of various kinins. The flushing lasts 2 to 10 minutes in patients with facial flushing and can last 2 to 3 days in those whose flushing occurs throughout their body. There may also be an associated tachycardia and hypotension. This rash can increase in duration as the disease progresses. Onset of the rash has been linked to eating, alcohol intake, defecation, emotion, palpation of the liver, and induction of anesthesia. General anesthesia can induce a carcinoid crisis marked by the sudden release of catecholamines from the tumor, acute hypotension, flushing, and bronchospasm. Pretreatment with octreotide can help avoid this anesthetic complication.

The diarrhea associated with carcinoid syndrome is directly related to serum serotonin levels; serotonin stimulates secretin release, which results in an increase in intestinal motility and decreased intestinal absorption. This watery, nonbloody diarrhea affects 80% of patients with carcinoid syndrome and is the symptom described by patients as the most debilitating. It is associated with abdominal cramping, and the number of daily bowel movements ranges from a few to more than 30.

Bronchospasm develops in 10% to 20% of patients with carcinoid syndrome. This wheezing/dyspnea often occurs during flushing episodes. However, treatment with β-adrenergic agonists can worsen the situation by triggering an intense, prolonged symptomatic vasodilation.

The valvular disease associated with carcinoid syndrome is a result of valvular fibrosis secondary to high concentrations of circulating amines. Serotonin is thought to be a major cause of the fibrosing reaction via stimulation of fibroblasts and fibrogenesis. Fibrous plaques develop on the endocardium of the valvular cusps, cardiac chambers, and occasionally, the intima of the pulmonary arteries or aorta (or both). The right side of the heart is the most commonly affected because of pulmonary inactivation of the humoral substances before exposure to the left side of the heart.

Other symptoms that can develop include venous telangiectasia, pellagra as a result of diversion of dietary tryptophan, and muscle wasting secondary to protein malnutrition.

Atypical or variant carcinoid syndrome is a syndrome that occurs in patients with gastric carcinoid tumors. These patients experience cutaneous flushes that are patchy and highly pruritic. Diarrhea, bronchospasm, and cardiac lesions are rare. It is thought that the syndrome is secondary to large release of histamine from the tumor rather than serotonin.

DIAGNOSIS

Laboratory Studies

Biochemical testing can often be the cornerstone of diagnosing a carcinoid tumor preoperatively. The 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) is a helpful laboratory study. This test has a

sensitivity of 75% to 100%, with the greatest sensitivity in patients with midgut carcinoids. Consumption of a large amount of tryptophan-containing food before urine specimen collection can confound the test results. Therefore, dietary intake must be controlled for accurate measurements. The sensitivity is decreased somewhat in patients with foregut and hindgut tumors. Foregut tumors generally lack aromatic amino acid decarboxylase; therefore 5-HIAA secretion is relatively unhelpful. However, 5-HT urinary secretion is increased and, with foregut tumor, has a sensitivity of 60%.[12,13]

The serum chromogranin level is another biochemical assay that parallels urinary 5-HIAA. Although the sensitivity and specificity are not well supported for all gastrointestinal carcinoids, studies indicate that chromogranin A is 100%, chromogranin B is 85%, and chromogranin C is 5% specific for carcinoid tumor.[14] Chromogranin A and an associated protein neurokinin A have also been used as a prognostic indicator, with increasing levels correlating with decreased survival.[13]

Although serum serotonin levels are increased in patients with carcinoid tumors, its specificity is low. Other markers such as substance P, neurotensin, human chorionic gonadotropin, and neuropeptides K and PP have not been useful.

Several provocative tests have historically been used to aid in the diagnosis of carcinoid. An epinephrine provocation test involves the use of escalating doses of epinephrine to produce carcinoid syndrome. A pentagastrin provocation test similarly involves the use of pentagastrin to stimulate a flushing response. Neither of the tests is commonly used.

Imaging Studies

Radiographic imaging of primary carcinoid tumors is difficult because of the small size of most tumors and their common submucosal location. A large proportion of these tumors are also located within the small bowel, which is historically difficult to image. Common approaches to the diagnosis of carcinoid tumors are based on the features of the tumors themselves. Gastric and rectal carcinoids are often asymptomatic and are thus most commonly imaged on screening or diagnostic endoscopy. The advent of endoscopic ultrasound has aided in the characterization of these tumors.

Barium studies, including small bowel series and enteroclysis, have shown good success in the diagnosis of larger carcinoid tumors of the small bowel (Fig. 79–4). The submucosal location of carcinoid tumors actually lends itself to more accurate localization with contrast studies, especially enteroclysis, than with conventional sectional imaging, such as computed tomography (CT).[15] Barium studies can also display the characteristics of a carcinoid tumor, including target signs of ulcerated tumors and angulation or narrowing from fibrosis. These characteristics, however, are shared by many other small bowel tumors, thus decreasing the specificity of barium studies.

The most commonly used radiologic examination in patients with a carcinoid neoplasm is CT. Primary tumor localization is rare with CT because of its submucosal location and often small size. CT is effective at identifying the mesenteric stranding/fibrosis that often accompanies carcinoid tumors, as well as mesenteric nodal involvement. The desmoplastic response can also cause changes in the mesenteric vasculature that can be identified with CT-angiography. The advent of three-dimensional CT imaging/reconstruction has likewise aided in the radiographic identification of small bowel tumors, including carcinoids.[16] CT is most effective for identifying hepatic metastasis, with sensitivity greater than 85%.[17,18] Metastatic carcinoid tumors are highly vascular and hence display bright enhancement during arterial-phase imaging.

The role of magnetic resonance imaging (MRI) in the diagnosis of a primary carcinoid tumor is limited, and it

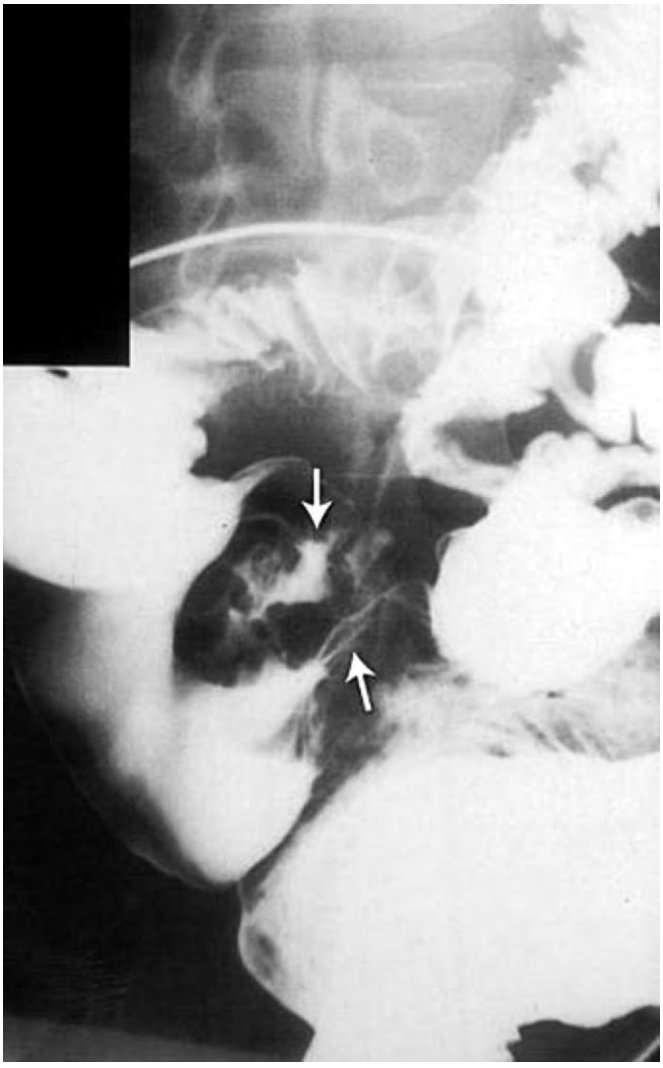


Figure 79–4. A barium radiograph of a carcinoid tumor of the terminal ileum demonstrates fibrosis with multiple filling defects and high-grade partial obstruction *(arrows).* (Courtesy of Melvyn H. Schreiber, M.D., The University of Texas Medical Branch.)

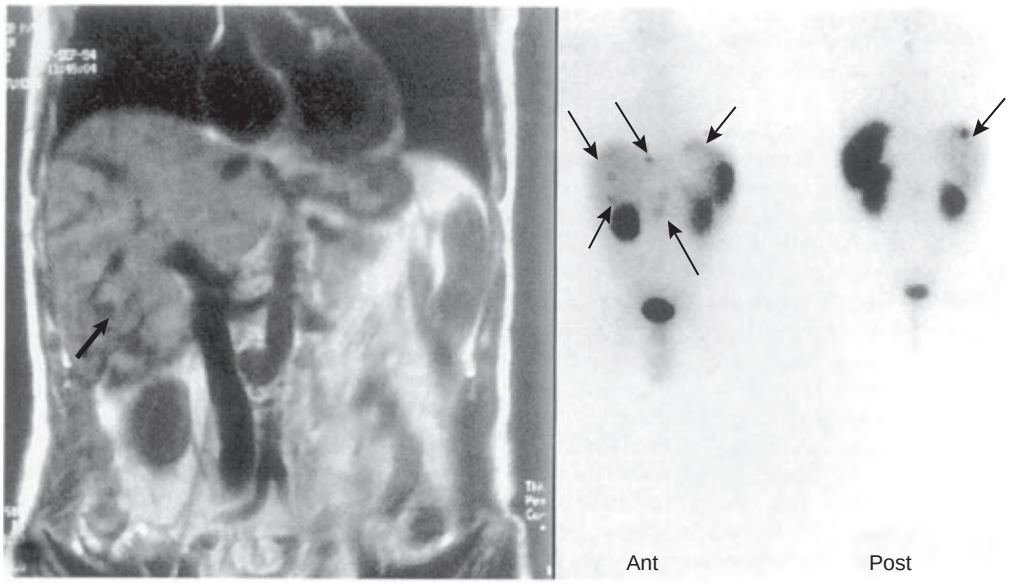


Figure 79–5. **A,** Magnetic resonance image showing a single focus of metastatic disease *(arrow)* in the right lobe of the liver in a patient with a carcinoid tumor and elevated 5-hydroxyindoleacetic acid. **B,** A ^{111}In-labeled pentetreotide scan of the same patient shows multiple hepatic lesions and two involved para-aortic lymph nodes. These findings were confirmed at laparotomy. Radionuclide activity in the kidneys, spleen, and bladder is evident. (From Anthony T, Kim L: Gastrointestinal carcinoid tumors and the carcinoid syndrome. In Feldman M, Friedman LS, Sleisenger MH [eds]: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 7th ed. Philadelphia, WB Saunders, 2002, p 2160.)

adds little or no information above that provided by CT. In the assessment of hepatic metastases, MRI has recently been shown to be more effective than either CT or somatostatin receptor–based scintigraphy (SRS) (Fig. 79–5).[19]

SRS has been used to image carcinoid tumors. Based on ^{111}In-labeled diethylenetriamine pentaacetic acid (DPTA)-D-Phe1-octreotide, Octreoscan uses a somatostatin analogue to obtain 80% to 90% sensitivity and specificity in identifying carcinoid neoplasms (see Fig. 79–5).[20] Various ligands have been used, including octreotide, pentetreotide, and lanreotide, with octreotide showing the greatest sensitivity for carcinoid tumors.[21] The technology is most effective in somatostatin receptor–positive carcinoid tumors, thus limiting its use in tumors that are nonfunctional. The technology is also limited in patients who do not exhibit carcinoid syndrome, for whom the sensitivity is only 60% for identification of the primary tumor.[22] The addition of single-photon emission computed tomography (SPECT) has increased the sensitivity of SRS in the detection of abdominal carcinoid.[23,24] SRS technology is also well suited to monitor response to treatment and progression of disease.

Positron emission tomography (PET) has had mixed results in imaging carcinoid tumors.[25] 2-Deoxy-2-[^{18}F]fluoro-D-glucose (FDG)-PET appears to be sensitive and specific in identifying carcinoid tumors that exhibit high proliferative activity or are poorly differentiated. However, for tumors that have low proliferative activity and are well differentiated, somatostatin-based imaging is much more sensitive and specific.[26] FDG-PET has shown some utility in identifying the retroperitoneal fibrosis that may develop in patients with carcinoid neoplasms.[27] FDG-PET should be used in patients with suspected or known carcinoid who have negative somatostatin receptor imaging.[21,28] A newer modality that has found improved success with PET technology is 5-HT–PET. 5-HT–PET has shown improved accuracy in comparison to both FDG-PET and conventional CT.[29] In a direct comparison of FDG-PET, 5-HT–PET, Octreoscan, and conventional imaging (CT/MRI), researchers report that conventional imaging is the most sensitive technique.

Another modality that has been tested for the evaluation of patients with carcinoid tumors is ^{131}I-metaiodobenzylguanidine (MIBG) scans. Limited studies have shown results roughly equivalent to those of CT, with a sensitivity of 55% to 70% and a specificity of 95%.[22,30] This scan may be especially helpful in patients who are being maintained on long-term octreotide therapy or who have had previously unrevealing Octreoscan findings.

TREATMENT AND OUTCOME

Surgery is the only cure currently available for patients with carcinoid tumors. The extent of resection is based on the location of the tumor within the gastrointestinal tract, the size of the tumor, the presence/absence of metastatic disease, and the presence/absence of

symptoms. The embryologic origin also determines not only the surgical approach but also the overall prognosis. Patients with foregut carcinoids can expect 5-year survival rates of 74%, 40%, and 18% for locoregional, nodal, and metastatic disease, respectively. The 5-year survival rates with midgut (80%, 75%, 35%) and hindgut carcinoids (76%, 46%, 19%) reveal the differences.[3]

Locoregional Disease

Duodenal carcinoid tumors are extremely rare, and therefore there is no standard surgical approach. Duodenal carcinoid tumors smaller than 1 cm should be treated by endoscopic or local resection. Although tumors 1 to 2 cm in diameter can be removed endoscopically, it is recommended that transduodenal resection be performed.[31] In tumors larger than 2 cm, more aggressive resection should be undertaken, which may entail segmental resection or pancreaticoduodenectomy with en bloc lymph node dissection. The overall 5-year survival rate for patients with duodenal carcinoids is 60%, but patients with tumors larger than 2 cm have a much higher rate of recurrence and lower survival than those with smaller tumors.[31,32]

Resection of gastric carcinoids is based on the type of tumor. Type I and II gastric carcinoids small than 1 cm in diameter can be treated by local excision or endoscopic removal, followed by endoscopic surveillance every 6 to 12 months. Therapy for lesions 1 to 2 cm in diameter is variable. Some report using antrectomy to remove gastrin stimulation along with local excision of the tumor or tumors, whereas others approach all tumors larger than 1 cm in diameter with resection via gastrectomy, partial or total.[22,33,34] However, the success of this approach is still unknown. Tumors 2 cm or larger in diameter should be resected via partial or total gastrectomy, depending on their location. The prognosis for patients with type I and II gastric carcinoids is excellent, with a nearly 100% 5-year survival rate.

Type III gastric carcinoids are much more aggressive. These tumors should be treated by partial/total gastrectomy and lymph node dissection.[22,33] Despite this aggressive surgical approach, 5-year survival rates are closer to 50%, in part because of the large percentage of patients initially seen with metastatic disease.

Carcinoid tumors of the jejunum and ileum should be treated by segmental resection and en bloc lymphadenectomy. This approach should be undertaken even in patients with metastatic disease in an attempt to avoid the fibrotic complications that are often associated with primary small bowel carcinoids.[35] Patients with localized disease have a 5-year survival rate of 75%, which drops to 59% to 65% for nodal disease and to less than 36% for metastatic disease.[34] Patients with recurrent disease may live many years.

Treatment of carcinoid tumor of the appendix is largely based on its excellent prognosis and the likelihood of metastatic disease. Tumors that are smaller than 2 cm and do not involve the base can be safely removed via appendectomy alone. If the base is involved in an otherwise low-risk tumor, cecectomy can be performed. Tumors that are 2 cm or larger in diameter or have mesoappendiceal invasion should be treated by right colectomy.[36] Overall, the rate of lymphatic spread of appendiceal carcinoid is very low, and such spread is rare in tumors smaller than 2 cm in diameter.[36] Five-year survival rates are 94% for patients with localized disease, 85% for nodal disease, and 34% for metastatic disease.[3,37]

Carcinoid tumors of the colon should be managed in the same manner as colonic adenocarcinoma. Therefore, all tumors of the colon should be treated by segmental colectomy and resection of the accompanying lymph nodes.[38] Five-year survival rates for colonic carcinoid range from 71% in patients with locoregional disease to 20% in those with metastatic disease.[3]

Rectal carcinoids that are smaller than 1 cm in diameter can be treated by local excision, often endoscopically. Tumors larger than 2 cm in diameter should be treated by radical resection, either low anterior resection or abdominoperineal resection. The role of the more radical resection has been questioned because of the lack of a survival benefit over local excision.[39] Overall, 5-year survival rates are 81% for patients with locoregional disease, 47% for nodal disease, and 18% for metastatic disease.[3] Management of rectal carcinoid tumors that are 1 to 2 cm in diameter is more controversial. Researchers have proposed that poor prognostic markers such as muscular invasion, ulceration, or symptoms at diagnosis should lead to radical resection rather than local excision.[34]

These guidelines for resection of carcinoid tumors are not absolute; individual clinical scenarios must be considered when deciding on the treatment plan and extent of resection.

Metastatic Disease

Surgical Therapy

The approach to the treatment of patients with metastatic disease is based on symptoms. Patients whose only symptoms are mild diarrhea may be successfully treated with oral codeine. However, the role of surgical intervention for metastatic disease has increased in modern times. The biologic activity of carcinoid neoplasms lends itself to aggressive treatment of metastatic disease.

Most patients with carcinoid tumors should undergo resection of the primary tumor regardless of metastasis. Such resection aids in avoiding complications from growth of the primary tumor in terms of bleeding, obstruction, and abdominal pain, especially with midgut carcinoids because of their propensity to cause intense fibrosing reactions. Even large tumors that are locally advanced with nodal disease are usually amenable to surgical resection.[40]

Patients with hepatic metastases may also benefit from surgical intervention. By using a resection or ablative approach to hepatic metastases, the patient can be palliated and even enjoy a long-term survival benefit. Surgical therapy for metastatic carcinoid tumors is aimed at removing more than 90% of the tumor burden via either anatomic or wedge resections, with acceptable morbidity

and mortality rates of 15% and 1.2%, respectively.[40] By using this cytoreductive approach, symptoms from metastatic carcinoid are reduced in 95% of patients, with a median symptom-free duration of 45 months. Five-year survival rates improve from 40% to 50% in patients who do not undergo surgery to 60% to 82% in patients after hepatic resection of their metastatic disease.[41,42]

Patients whose tumor is unresectable or in whom reduction of greater than 90% of the tumor burden is not feasible may be palliated with techniques of hepatic therapy. Palliation methods include radiofrequency ablation (RFA), cryotherapy, hepatic arterial occlusion, embolization, and chemoembolization.

RFA has found success as an ablative technique for colorectal metastases. Its application to metastatic carcinoid has also been shown to be effective in patients with unresectable hepatic disease or as an adjunct to resection. In one study, the use of RFA for metastatic carcinoid provided symptomatic relief in greater than 80% of patients, and 41% showed no progression of disease during a short follow-up period.[43] Cryotherapy has also provided good symptomatic relief for up to 100% of patients with metastatic carcinoid.[44] Both modalities have relatively short-term response rates, but they can be successfully used on multiple occasions in patients with recurrent disease.

Ablative techniques that are based on vascular occlusion or embolization have also been studied. Their ability to induce tumor necrosis has largely been unsuccessful because of the rich collateral circulation within the liver. Hepatic arterial vascular occlusive therapy produces biochemical and tumor response rates of 37%. Embolization, often with gelatin, has shown slightly better results. Chemoembolization combines inflow disruption with the local administration of chemotherapeutic agents. This technique has led to a reduction of symptoms in 60% to 100% of patients with carcinoid syndrome and a biochemical response in 57% to 91%.[45] However, the results of these therapies have been mostly symptomatic and short lived. Patients undergoing either of these therapies are also subject to complications after occlusion/embolization, including abdominal pain, fever, fatigue, and even carcinoid crises as a result of the sudden release of hormones from the targeted lesion or lesions.

Orthotopic liver transplantation has also been performed in patients with metastatic carcinoid; however, its true role in the treatment of patients with metastatic carcinoid remains unclear. There have been limited attempts at liver transplantation in this patient population, but with significant morbidity and mortality and high rates of recurrence. Recently, researchers have attempted to define a more select group of patients for transplantation. Patients who appear to have the greatest survival rates are those with well-differentiated tumors that exhibit low proliferative activity. In this select group, orthotopic liver transplantation can yield a 5-year survival rate of up to 69%.[46]

Medical Therapy

Systemic treatment of patients with advanced carcinoid tumors has focused mainly on relief of the symptoms of carcinoid syndrome. The most commonly used therapy for such patients is somatostatin receptor–mediated hormonal therapy. The somatostatin receptors are blocked with a somatostatin analogue, thereby relieving the flushing, diarrhea, and other symptoms of carcinoid syndrome. The most commonly prescribed agent has been octreotide. Octreotide administration leads to resolution or a reduction in symptoms, including flushing (53% complete response, 32% partial response) and diarrhea (25% complete response, 49% partial response). However, the short half-life (2 to 4 minutes) of octreotide necessitates continuous infusion or twice-daily subcutaneous injections.

Newer analogues with longer half-lives have recently been developed with similar response rates. Lanreotide is administered every 10 to 14 days, whereas depot octreotide is given just once monthly. Side effects of the treatment include sinus bradycardia, arrhythmias, gallbladder stones, steatorrhea, hypothyroidism, and hypoglycemia.

Although designed to reduce the symptoms of carcinoid syndrome, there has been some objective tumor responses noted with somatostatin analogues. A biochemical response is seen in 27% to 72% of patients with carcinoid treated with somatostatin analogues; however, the actual tumor response is only 2%. Tumor stabilization has been noted in nearly 50%, but over a relatively short follow-up period of 5 months.[22]

Systemic treatment with interferon has been examined as possible systemic therapy for patients with advanced carcinoid disease. The mechanism that has been proposed is interferon's ability to inhibit cellular proliferation, inhibit angiogenesis, and enhance immune cell–mediated cytotoxicity. Trials including interferon alfa and gamma and human leukocyte interferon have been performed. Treatment with either human leukocyte interferon or interferon alfa has resulted in biochemical responses but little tumor response. The results were less favorable for combination therapy consisting of interferon alfa and gamma, for which no response was noted. The combination of interferon alfa and octreotide led to a reduced risk for tumor progression, without any survival benefit.[47]

Various studies have examined the effects of systemic chemotherapy, both single agent and combination, in patients with metastatic carcinoid with little success. A more recent phase II trial examined docetaxel as a potential therapeutic agent.[48] Although the therapy was well tolerated, there was minimal tumor response, and only a small proportion of patients experienced even a biochemical response. To date, systemic chemotherapy has failed to have a role in the treatment of metastatic carcinoid disease.

Biologic therapies are currently being examined for a potential role in the treatment of metastatic carcinoid tumors. Epidermal growth factor receptor (EGFR)-based therapy has shown success in solid tumors such as lung, breast, colon, and head and neck cancers. Recent basic science research has shown that gefitinib, which targets EGFR, induces apoptosis, growth inhibition, and cell cycle arrest.[49] These findings indicate that EGFR-based treatments may be an effective therapy in the future.

Case reports and small series have reported the use of hormone receptor–mediated radiation therapy for metastatic carcinoid tumors. Peptide-targeted therapies include ^{131}I-MIBG–octreotide; ^{177}Lu-, ^{111}In-, and ^{90}Y-labeled somatostatin analogues; and more recently, bombesin and neuropeptide Y (Y1) analogues. Research to date has shown some success with these therapies, although the success is often noted to be equivalent to that of treatment with nonradiolabeled somatostatin analogues. Most reports show short-term stabilization of disease, with greater than half of all treated patients reporting some symptomatic relief.[50,51] However, tumor response rates (complete and/or partial) have been low, 23% to 30%. Combined peptide approaches are being used in an attempt to improve tumor and patient response to therapy.[51]

External beam radiotherapy has had some limited role in the treatment of advanced carcinoid disease. As a palliative procedure for bulky disease, brain metastasis, spinal cord compression, and bony metastasis, radiation therapy has shown some benefit.

FUTURE DIRECTIONS

Gastrointestinal carcinoid tumors have varied manifestations and clinical courses. Advances in molecular biology will continue to aid the clinician in determining what clinical course a particular tumor will take. The application of high-throughput genomic and proteomic analysis to the pathologic examination of tumors, as well as the application of this technology to the serum of patients with carcinoid disease, will possibly enable a more accurate prognosis.

Advances in peptide receptor–aided imaging will enable more accurate and earlier diagnosis of carcinoid tumors. Possibly, the use of multiple markers in a single radionuclide-based scan will permit the localization of small carcinoid tumors that currently remain unrecognized and undiagnosed.

The emerging field of biologic therapies may also aid in the treatment of patients with advanced or metastatic disease, or both. Phase III trials of EGFR-targeted therapies are hoped to produce exciting results. There are numerous other potential biologic therapies that have yet to be discovered and examined.

Overall, gastrointestinal carcinoid is a variable disease process because of its varied embryologic origin. Surgical resection is the only chance for cure. As the expansion of molecular biology and biologic therapy continues, treatment options for this disease will improve.

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Chapter

80

Gastrointestinal Stromal Tumors

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Although rare, gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract. Understanding and treatment of these tumors have improved dramatically over the last several years. Enhanced diagnostic specificity and recognition of the pathophysiology and natural history of this previously poorly defined clinical entity have resulted in novel treatment approaches. Initially managed as a surgical disease with a relatively poor prognosis, a greater understanding of GIST pathobiology has transformed therapeutic options and led to an improved prognosis for patients with advanced disease. The present management of this GI tumor could potentially serve as a paradigm for the combined surgical management of a solid tumor with molecularly specific, targeted therapeutics enhanced by optimal pharmacologic and pharmacodynamic properties.

HISTORICAL PERSPECTIVE AND NATURAL HISTORY

The true incidence of GIST has been somewhat obscured by the fact that until recently this clinical entity was ill defined. It is now recognized as the most common mesenchymal tumor of the GI tract, with an estimated annual incidence of approximately 6000 cases per year. Previous reported series of GI sarcomas, particularly those compiled before the year 2000, were dominated by the defining nomenclature of smooth muscle tumors (leiomyosarcoma and leiomyoblastoma). It is now recognized that many of these tumors that were previously reported as smooth muscle neoplasms have distinctive pathologic features and could be retrospectively reclassified as GIST. As suggested by Mazur and Clark, who first introduced the term stromal tumor,[1] these neoplasms are probably not derived from a direct smooth muscle cell lineage. Further advances in the defining pathology of GIST indicated that GIST cells originate from the same precursor cell as the interstitial cells of Cajal (ICC), the GI myenteric plexus pacemaker cell, and therefore have characteristics of both smooth muscle and neural differentiation, as evidenced by morphology and immunophenotype.[2]

Strict criteria for recognition of GIST have now enabled retrospective studies to be performed to evaluate the prognosis and natural history relevant to clinical care. A variety of different tumor-related variables have been assessed by both univariate and multivariate analysis to determine their importance in outcome prediction, as well as malignant potential. The most significant prognostic features of the primary tumor are size and mitotic index (Table 80–1).[3] These two primary tumor categories allow reliable risk assessment, although other tumor features that are surrogates of proliferation, such as Ki67 expression, have also been found to be helpful in risk modeling. These patient risk profiles suggest that greater than 50% of high-risk tumors will recur within 10 years after initial diagnosis, the majority within 3 years. In contrast, low-risk/very-low-risk tumors have a less than 5% probability of recurrence, with the intermediate-risk category being less predictable and therefore necessitating very close follow-up. At the time of diagnosis approximately a third to a half of all clinically detected GISTs are either overtly malignant by virtue of demonstrated metastatic disease or high risk for malignant behavior, and approximately two thirds will have pathologic features suggestive of potential malignant behavior, such as larger size or increased mitotic index.[4,5] For this reason, classification of GIST into benign versus malignant is often problematic, and therefore GIST in aggregate represents a biologic continuum, with even small contained tumors historically noted to recur 15 to 20 years after initial diagnosis. Obviously, this risk stratification strategy provides important guidelines for the necessity of

Table 80–1 Gastrointestinal Stromal Tumor Risk Assessment

Risk of Recurrence	Tumor Size (cm)	Mitotic Index (50 HPF)
Very low	<2	<5
Low	2-5	<5
Intermediate	<5	10-16
	5-10	<5
High	>5	>5
	>10	Any
	Any	>10

HPF, high-power field.

long-term patient follow-up and radiologic surveillance, as well as consideration of more aggressive primary tumor management directed toward high- and intermediate-risk groups.

Tumor location has also been linked to prognosis, with primary gastric GISTs seeming to fare better than those of small bowel or rectal origin.[6] The rare GIST of the retroperitoneum, mesentery, or omentum will similarly generally display a malignant aggressive course when compared with those of primary gastric origin.

PATHOLOGY

Elucidation of the pathology of GIST has been closely paralleled by therapeutic advancements. As the specific diagnosis of GIST has been defined by morphology, ultrastructure, and immunohistochemistry, the true incidence and prevalence of this tumor are now more accurately reflected in population studies.[7] The annual incidence of GIST is approximately 5000 to 6000 cases in the United States yearly. The incidence statistics are more reliable at this time because in the past many of these tumors were reported as GI smooth muscle tumors. It is now evident that through ultrastructural studies and lineage-specific immunomarkers, GIST cells have features in common with ICC, with both GIST and ICC staining positive for KIT (CD117).[8] Although approximately 95% of GIST cells stain positive for KIT, a variety of other immunomarkers can also be demonstrated, including BCL-2 (80%), CD34 (70%), muscle-specific actin (50%), smooth muscle actin (35%), S-100 (10%), and desmin (5%).[9] The differential diagnosis of GIST includes a number of different mesenchymal tumors such as schwannomas, leiomyomas, and leiomyosarcomas; however, morphology and KIT staining will generally establish the diagnosis.

The majority of GISTs are composed of a uniform population of spindle cells (approximately 70% of cases), with epithelioid cells (20% of cases) and a mixed variety (10% of cases) accounting for the rest (Figs. 80–1 to 80–3). The spindle cells are generally arranged in short fascicles but can align in a schwannian pattern. Most

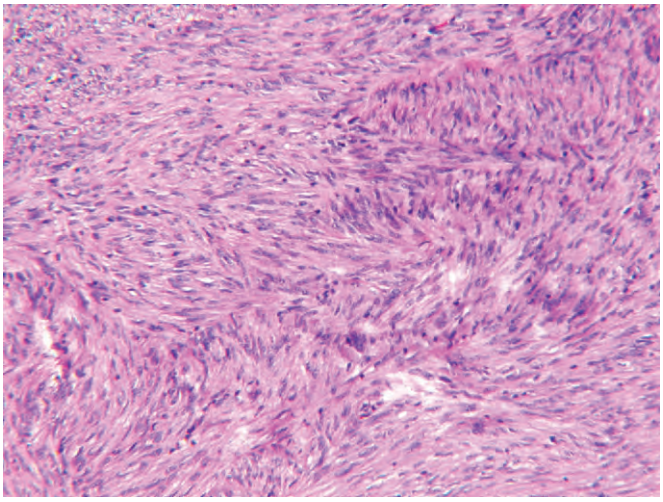

Figure 80–1. Spindled GIST. Although the histologic patterns of GIST vary, many demonstrate short interlacing fascicles of spindled cells with indistinct cytoplasm, uniform nuclei, and a variable degree of matrix production.

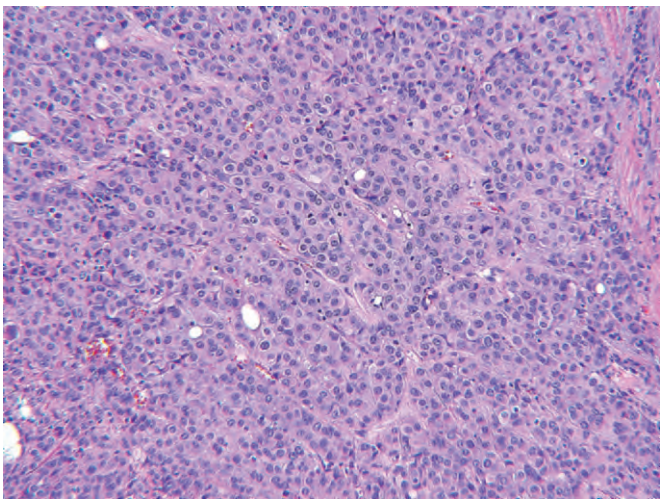

Figure 80–2. Epithelioid GIST. In contrast to spindle cell GIST, the epithelioid variant is composed of polygonal cells with abundant eosinophilic cytoplasm and well-defined cytoplasmic borders.

GISTs have a uniform cytology, and marked cytologic pleomorphism is uncommon. Approximately 5% of cases can have a prominent myxoid stroma. Nuclear atypia is more common in epithelioid GISTs and often represents a malignant phenotype. The use of KIT immunostaining has been helpful in the diagnosis of GIST; however, it is possible that because of technical issues, such as overstaining with inappropriately titered KIT antibodies, there may be instances of false-positive reporting. The possibility of overstaining is important to consider because KIT-negative, desmin-positive tumors, such as desmoid tumors or leiomyosarcoma, may have similar

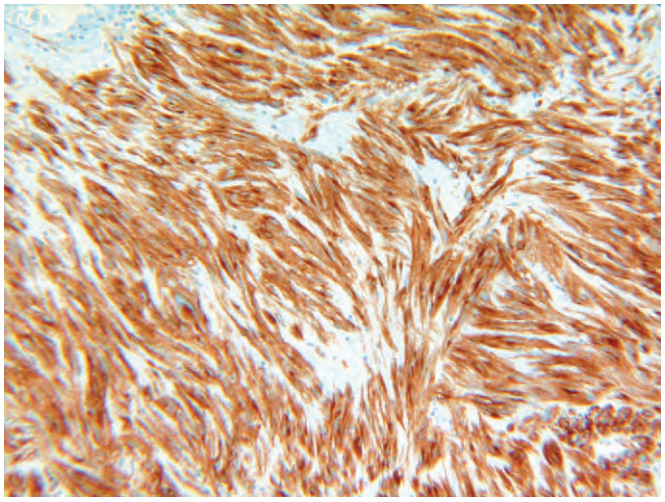

Figure 80–3. CD117 immunohistochemistry. GIST stains uniformly with CD117.

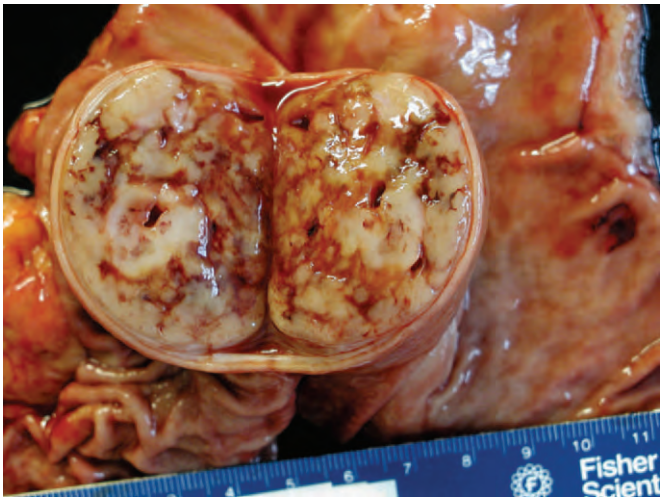

Figure 80–4. Photograph of a small submucosal gastric GIST after partial gastric resection.

spindle cell morphology. It is also important to note that the overall intensity of KIT staining, which may be cytoplasmic, membranous, or paranuclear, is not related to either prognosis or response to therapeutic KIT-specific inhibition.

As with most spindle cell neoplasms, adequate tissue is essential for making an accurate diagnosis. In the case of a primary GIST that is surgically resectable, it is not recommended that an immediate transabdominal tissue biopsy be performed because tumor cell exfoliation after biopsy manipulation can lead to tumor recurrence. Tissue can, however, be safely obtained by endoscopic core biopsy when necessary.

When assessing malignant potential, the pathology of GIST is somewhat unreliable in that malignant potential is more closely related to risk stratification (see the section on natural history and Table 80–1), which is based mainly on mitotic index and tumor size rather than tumor morphology and pleomorphism. However, cytogenetic analyses of GIST have provided some clues with regard to the malignant phenotype. Karyotypes from two thirds of GISTs demonstrate either monosomy 14 or partial loss of 14q, with at least two regions of 14q deletions appearing to be hot spots and representing probable areas of tumor suppressor genes.[10] In addition, loss of the long arm of chromosome 22 is present in 50% of GISTs and is often associated with progression to a borderline or malignant lesion. Losses on chromosomes 1p, 9p, and 11p are more significantly found in malignant GISTs. Common pathways for the genetic changes that have been observed in the development and progression of GIST are KIT or platelet-derived growth factor receptor-α (PDGFR-α) mutation → 14q deletion → 22q deletion → 1p deletion → 8p gain → 11p deletion → 9p deletion → 17q gain.[10]

Approximately 5% of GISTs will be KIT negative by immunostaining, yet by all other morphologic/clinical criteria these tumors can be classified as GISTs. They are generally a rather heterogeneous group of tumors consisting mostly of tumors containing mutations in PDGFR. This small subset of GISTs characterized by negative KIT staining is more likely to be of epithelioid histology, be nongastric in location, and have activating PDGFR-α mutations. A few of these weakly positive or non–KIT-staining GISTs will have evidence of KIT mutations on genotyping, and in rare instances there will be no discernible mutations in either PDGFR-α or KIT, thus suggesting that a KIT-negative GIST can arise through alternative oncogenic mechanisms.[11] An adequate tumor sample in the clinical instance of KIT negativity should be evaluated by genotyping because a mutation in KIT or PDGFR-α can be diagnostic and has important therapeutic implications. In addition, new tumor markers of GIST, such as DOG1 (discovered on GIST-1) and protein kinase C-θ, can be helpful in the differential diagnosis in difficult cases.[12,13]

CLINICAL EVALUATION

GIST is most commonly diagnosed in adults 50 to 80 years of age, with a mean age of 60. The male-to-female ratio is approximately 1:1. The majority of patients with GIST are symptomatic, with the most common symptoms being abdominal pain, early satiety, and bloating related to the presence of a space-occupying mass. GI bleeding and anemia are frequently noted and are due to erosion of mucosa by the tumor, even though GISTs originate within the muscular layer of the bowel wall and are often manifested by evidence of an extrinsic mass. The most common location is the stomach (60% to 70%), followed by the small bowel (20% to 25%), colorectum (5%), and esophagus (5%). Rarely, cases of GIST originating within the retroperitoneum, omentum, appendix, gallbladder, pancreas, and mesentery have been described. Approximately 20% of GISTs are asymptomatic and discovered incidentally by radiographic imaging or endoscopy, or

they may be an unexpected surgical finding (Fig. 80–4). These incidental tumors are often asymptomatic, noncystic submucosal masses most commonly found during endoscopy. Recommendations for management of an asymptomatic incidental GIST with regard to biopsy or resection are not based on large cohort follow-up studies. However, in general, even a subcentimeter, submucosal suspected GIST should undergo biopsy or be removed, or both, if the clinical situation allows because of the necessity for long-term observation and the potential for malignant clinical progression based on the defined risk profile.

The clinical work-up for a suspected GIST should follow the pattern for evaluation of any patient with an undiagnosed intra-abdominal mass. Although some GISTs are small submucosal solid tumors found incidentally, the majority are larger than 5 cm and are symptomatic because they are a space-occupying abdominal mass. GI bleeding and the insidious anemia of chronic blood loss are not uncommon with large necrotic GISTs. The initial work-up should consist of a history and physical examination, which may reveal the presence of a palpable abdominal mass, followed by a cross-sectional abdominal imaging study, usually a contrast-enhanced computed tomography (CT) scan. Routine chest radiographs and blood work, including liver function tests, are indicated. Endoscopy, endoscopic ultrasound, and possibly endoscopic biopsy can be recommended if the clinical situation warrants because the majority of GISTs are of gastric origin. Early surgical involvement should address the potential for complete resection, and in patients with locally advanced or metastatic disease, consultation with medical oncology, evaluation for systemic therapy with imatinib mesylate, and close surgical follow-up should be considered. Close surgical follow-up is especially important for patients with large GISTs involving bowel mucosa, which may subsequently bleed either intra-abdominally or intraluminally as a manifestation of rapid tumor response after the initiation of systemic therapy.

Percutaneous core or intraoperative biopsy of a suspected GIST that is localized and presumed to be resectable is not necessary. These tumors tend to be soft, well vascularized, and friable, and tumor spill or spontaneous rupture portends a poor prognosis and compounds the difficulty of treatment decisions. Conversely, it is relatively safe to biopsy the tumor by endoscopic means, either by direct visualization of a mucosal component or by endoscopic ultrasound guidance. Image-guided percutaneous tumor biopsy is considered as part of the work-up, however, for a metastatic tumor or a primary tumor that is marginally resectable. Additionally, careful biopsy and tissue diagnosis can be considered when immediate tumor resection could lead to considerable morbidity or functional disability. In this instance the possibility of tumor down-staging with a preoperative neoadjuvant targeted therapy regimen should be considered. Although data regarding the efficacy of this combined neoadjuvant approach are insufficient, it has the theoretical benefit of organ preservation and function-sparing management of some GISTs, such as those originating in the rectum or the pancreas.

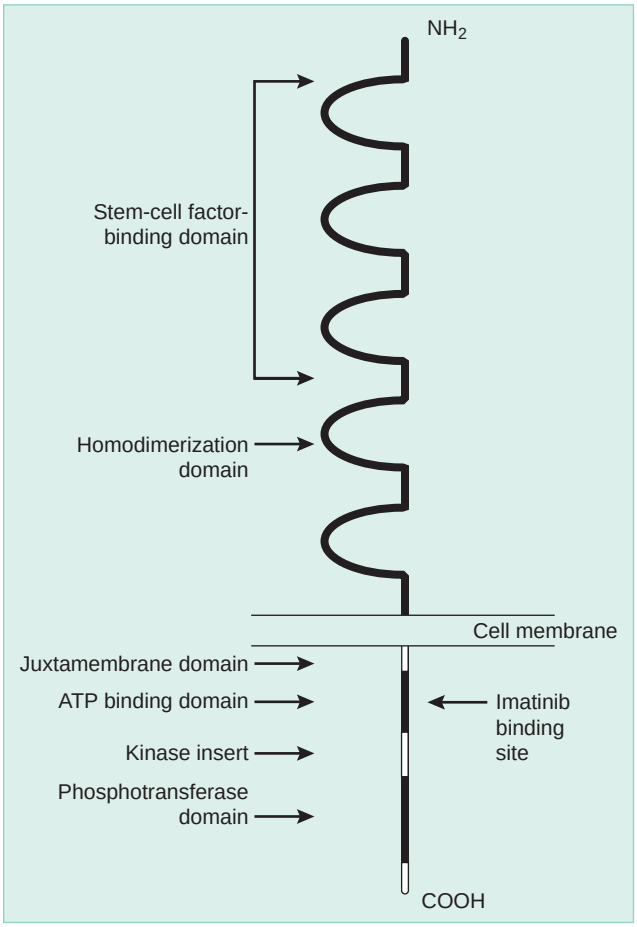

Figure 80–5. The structure of the transmembrane KIT receptor tyrosine kinase. (From Joensuu H, Fletcher C, Dimitrijevic S, et al: Management of malignant gastrointestinal stromal tumors. Lancet Oncol 3:655-664, 2002.)

MOLECULAR BIOLOGY OF GASTROINTESTINAL STROMAL TUMORS

Greater insight into the pathogenesis and subsequently the pathobiology of GIST has altered the diagnostic parameters and therapeutic implications for this mesenchymal tumor. These tumors are nearly universally characterized by the expression of KIT, a transmembrane receptor tyrosine kinase encoded by the c-kit proto-oncogene and recognized by the immunohistochemical stain for CD117, an antigen to an epitope on the extramembranous portion of the KIT molecule (Fig. 80–5).[14]

The c-kit gene is a cellular homologue of the v-kit oncogene found in the genome of the feline sarcoma virus.[15] Stem cell factor is the natural ligand for KIT, and under normal physiologic conditions, two molecules of KIT form a dimer by binding to two molecules of the ligand, with the resulting dimerization leading to activation of the intracellular tyrosine kinase. Ligand-independent activation of the KIT kinase leads to signal transduction abnormalities favoring proliferation and enhancement of cell survival mechanisms.[16] Structurally,

the KIT molecule has an extracellular domain of five immunoglobulin-like repeats and a tyrosine kinase domain split by a variable kinase insert that separates the adenosine triphosphate binding site and the phosphotransferase regions, thus placing this receptor kinase in the same category as similar type 3 tyrosine kinase receptors such as macrophage colony-stimulating factor and PDGF.[17]

A seminal event in the definition of GIST initially reported by Hirota et al. and subsequently verified by a number of investigators was identification of a c-kit gain-of-function mutation by gene sequencing in the majority of these tumors.[18] These in-frame mutations are noted early in GIST tumorigenesis and are important drivers of the malignant phenotype. The gain-of-function kinase activity results in ligand-independent KIT autophosphorylation and constitutive activation and is probably a hyperproliferative transforming event. The mutations are often physically located within 11 amino acids (Lys-550 to Val-560) in the juxtamembrane domain (exon 11) and can be characterized as either deletions, point mutations, or insertions. In the unusual event that these mutations occur in a germ cell line, the family lineage is characterized by instances of multiple GISTs.[19] Further compelling evidence for KIT mutation in the pathogenesis of GIST has been substantiated by transfection experiments of mutated KIT leading to cellular clonal transformation of the transfectant.[20] In addition, there is a transgenic mouse model of a KIT mutation leading to spontaneous GISTs that are morphologically similar to the human counterpart.[21]

The reported frequency of KIT mutations in GIST is variable and depends on the methodology used, but a mutational event probably occurs in 85% to 90% of malignant GISTs.[22] In addition, these mutations generally occur in exonic hot spots: 11 (intracellular juxtamembrane region), 9 (extracellular domain), and rarely 13 or 17 (both found in the intracellular portion of the receptor).[23] It is also notable that KIT mutations were found in 85% of a series of morphologically benign GISTs found incidentally, and these tumors ranged in size from 4 to 10 mm.[24] This suggests that mutated KIT is an early sign of genomic instability and may not be prognostically important in predicting the extent of malignant behavior. KIT mutations are distinctive, however, and have not been found in morphologically similar tumors, such as leiomyomas or leiomyosarcomas, thus making this mutation pathognomonic for GIST.[25]

TARGETED THERAPY

Enhanced appreciation of the pathobiology of this mesenchymal tumor, particularly with regard to autonomous kinase activation, has prompted clinical trials involving pharmacologic exploitation of the dysregulated KIT receptor tyrosine kinase.[26] Imatinib mesylate (Gleevec), a rationally designed small-molecule oral drug that is a selective inhibitor of type 3 tyrosine kinases, showed remarkable efficacy in preclinical studies against the KIT oncoprotein. This activity was manifested by antiproliferative effects and a measurable decrease in the tyrosine phosphorylation of KIT in KIT-expressing malignant cell lines.[27] These compelling preclinical data fostered interest in conducting the first clinical application of imatinib mesylate in a solid tumor, which resulted in a dramatic response in a patient with inoperable bulky metastatic GIST.[28] This report was followed by multi-institutional proof of the principal trial of imatinib mesylate in previously treated, unresectable patients with confirmed and measurable recurrent metastatic GIST. The study resulted in 147 patients being treated; 54%, 28%, and 14% demonstrated partial and durable responses, stable disease, and progressive disease, respectively.[29] It is important to note that all these patients had KIT expression confirmed by CD117 staining, thus emphasizing the important selectivity of this drug.[30] This clinical benefit has continued to be durable after a median follow-up of 3 years, with approximately 85% of patients still taking the drug. This study served as the basis for a registration study leading to Food and Drug Administration approval of imatinib mesylate for GIST patients with metastatic or recurrent disease.

Because the GIST clinical trial experience serves as a paradigm as one of the first in human trials to demonstrate efficacy for a designed small-molecule molecularly targeted therapeutic agent, evaluation of its pharmacodynamics and resistance patterns has potential applicability to other drugs of this classification. One interesting and clinically relevant response factor resides within the c-kit gene itself. The majority of GISTs sampled from patients in the initial metastatic disease trials with imatinib mesylate were found to harbor KIT mutations, with exon 11 being the most common site detected. The response to imatinib mesylate, as well as event-free and overall survival, was adversely affected by the presence of either an exon 9 mutation (extracellular portion of KIT) or wild-type KIT (Fig. 80–6).[31] The presence of wild-type KIT in approximately 10% of the patients in this series of KIT genomic mutational analyses was perplexing because the dysregulated KIT oncoprotein was initially thought to be the sole kinase driver of the transformed proliferative phenotype. A partial explanation for the GIST malignant phenotype without KIT mutant protein may be found in the recent identification of PDGFR-α gain-of-function mutations in GIST samples.[32] It appears that PDGFR-α mutations and KIT mutations are mutually exclusive, and in a series of GIST genotyping, 4.7% of patient samples were noted to have PDGFR-α mutations involving domains homologous to those often mutated in KIT (Fig. 80–7).[31] The uncommon patient with a PDGFR-α mutation can have a GIST that is morphologically and clinically identical to those with a KIT mutation. Some of these patients have a documented response to imatinib mesylate, thus implying that this drug can be clinically useful in inhibiting two different kinases. A small percentage of GISTs do not demonstrate a mutation in either KIT or PDGFR. The mechanism of malignant transformation and expression of the malignant phenotype is probably multifactorial in these GISTs and may be related to increased kinase activity downstream of the KIT receptor or amplification of the KIT gene or the KIT gene product. Knowledge of the GIST genotype can also have therapeutic implications because

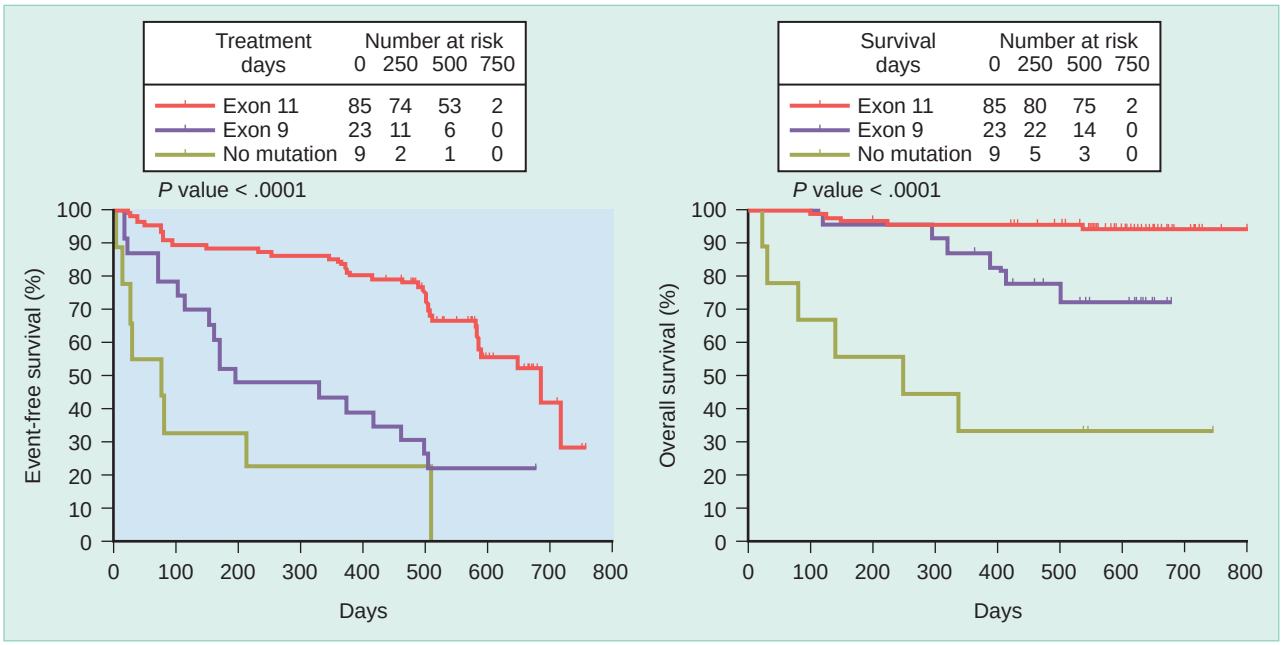

Figure 80–6. The GIST kinase genotype correlates with event-free and overall survival, as demonstrated by the Kaplan-Meier estimate of the probability of event-free and overall survival for patients with KIT exon 11 mutation, KIT exon 9 mutation, or no mutation of KIT or PDGFR. (From Heinrich M, Corless C, Demetri G, et al: Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumors. J Clin Oncol 21:4347, 2003.)

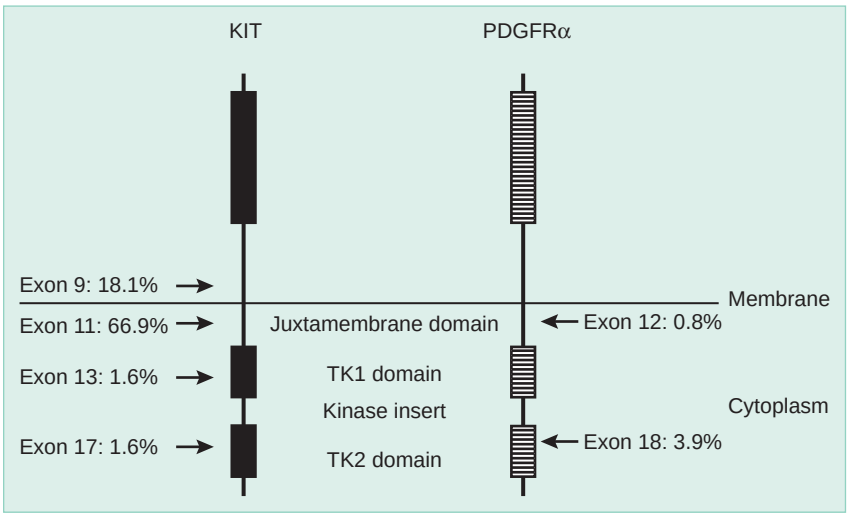

Figure 80–7. Structure of KIT and PDGFR-α. The locations of GIST kinase mutations are shown in relationship to the structural features of the proteins. GIST from 9 (7.1%) of 127 patients had no detectable KIT or PDGFR-α mutation. (From Heinrich M, Corless C, Demetri G, et al: Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumors. J Clin Oncol 21:4343, 2003.)

GIST patients harboring a KIT mutation outside of exon 11 are less likely to respond to imatinib mesylate. They may therefore be candidates for alternative therapies as they become available. It is especially important, however, to emphasize that approximately 5% of GISTs will be KIT "negative" by CD117 immunostaining. These KIT-negative GISTs, when compared with KIT-positive GISTs, are more likely to have epithelioid morphology, arise in the omentum/peritoneal surface, and contain PDGFR mutations. These GISTs may contain imatinib mesylate–sensitive clones, and therefore patients with morphologically and clinically confirmed KIT-negative GIST should not be denied a trial of imatinib mesylate therapy.[5,11] Because of the success of imatinib mesylate therapy in the management of GIST, the present recommendations in the work-up of a KIT-negative GI mesenchymal tumor with histopathology suggesting a spindle, epithelioid, or mixed variant of GIST are to evaluate tumor tissue for KIT or PDGFR-α mutations. Thus, genotype screening in this particular patient population may provide clinically actionable information.[33] Investigations into the molecular mechanisms of GIST response are ongoing with broad-based implications for specific targeted therapeutics in other solid tumor models. Data

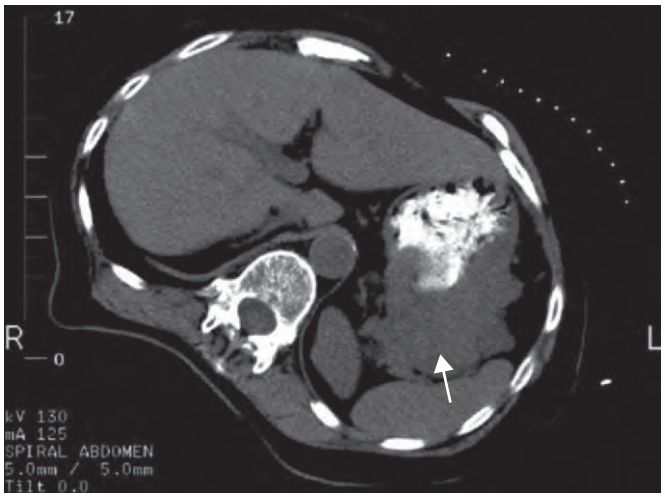

Figure 80–8. Computed tomographic scan of a primary gastric GIST (*arrow*). Note the extrinsic mass effect on the stomach.

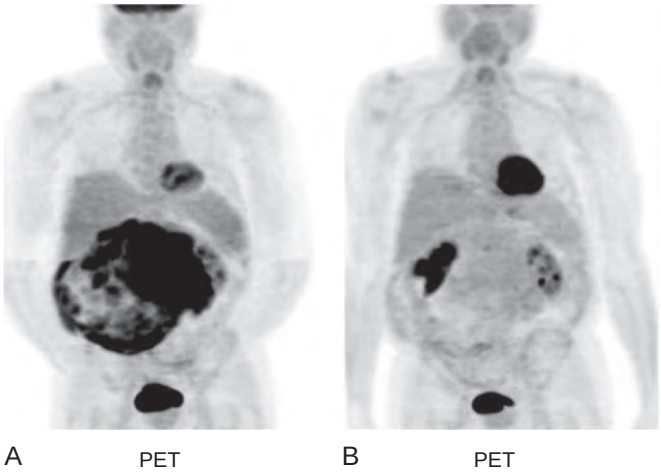

Figure 80–9. ^{18}F-fluorodeoxyglucose (FDG)–positron emission tomographic (PET) scan indicating a large bulky primary GIST before **(A)** and after **(B)** imatinib mesylate administration. The decreased FDG concentration in the tumor was noted within several weeks after initiation of drug therapy.

generated from evaluation of downstream signal transduction pathways suggest differential expression of signaling intermediates depending on the type of KIT mutation, and robust genomic-based platform arrays have identified differential-response gene expression signatures associated with GIST cells sensitive to imatinib mesylate. It is conceivable that future evaluations will provide enough data so that GIST patients can be phenotyped by tumor biopsy before and just after administration of imatinib mesylate to determine whether they will respond to single-drug therapy or whether alternative or combination therapies will be necessary to optimize their outcome.

IMAGING

Cross-sectional imaging, particularly in the initial workup of a patient with suspected primary or recurrent GIST, is the diagnostic procedure of choice. A contrast-enhanced (oral and intravenous) CT scan is recommended and generally allows assessment of the extent of the primary, as well as the potential presence of metastatic disease. The typical primary GIST will be manifested as an intestinal-based mass with the bulk of the tumor extrinsic to the bowel, thus often providing an opportunity for complete resection, even in patients with a large primary tumor (Fig. 80–8). In many instances the primary tumor, although large, may be pedunculated, particularly if originating from the stomach. Guidelines for follow-up after successful GIST surgical resection, as recommended by the National Comprehensive Cancer Network, are as follows: CT of the abdomen/pelvis performed every 3 to 6 months for 3 to 5 years and annually thereafter, except in patients with very-low-risk primary GIST, in which case less frequent follow-up is required.[33] The frequency of metastasis of GIST to the lung is quite low, and therefore routine screening chest CT is not necessary.

Standard image-based response criteria are being reevaluated in light of the information available for GIST patients treated with imatinib mesylate. These characteristic CT scan changes in GIST, consistent with a favorable response to a molecularly targeted agent, include a change in density of the measurable tumor to a more myxoid or hypodense appearance rather than a definitive decrease in size. This response can take place within a month of initiation of therapy and can be quantitated by measurement of Hounsfield units. Within 2 months of therapy a decrease in tumor size, usually confirmed by comparing the sum of the longest diameters of all target measurable lesions or a 15% decrease in density, can be considered predictive of a beneficial response, although a maximal decrease in tumor size may take 6 months or longer. Conversely, drug resistance may be manifested as the appearance of a small intratumoral nodule without a change in overall density or size of the tumor mass. Lessons learned about the clinical usefulness of these measurable response criteria may have more universal applicability to assessment of specific targeted therapy for other solid tumors as increasing numbers of these agents become clinically available.

Functional imaging with ^{18}F-fluorodeoxyglucose (FDG)–positron emission tomography (PET) can be an important adjunct to standard CT by assessing early changes in metabolic activity in GIST. FDG-PET can provide an immediate and sensitive measure of response in GISTs, which are generally PET avid tumors.[34] Imatinib mesylate may have a dramatic effect on abrogation of GIST cell glycolysis, and these measurable decreases in glucose uptake by the tumor can be visualized within hours of initiation of therapy and can be predictive of long-term response by comparison to the standard uptake value. This may be particularly helpful in the assessment of neoadjuvant treatment (Fig. 80–9). If FDG-PET is being considered as a diagnostic modality to

monitor continued response, detect recurrence, or complement an ambiguous CT scan, a baseline PET scan should be obtained before initiation of therapy.

SURGICAL MANAGEMENT

Surgical management of GIST is based on sound oncologic principles, and before the introduction of imatinib mesylate as an effective systemic therapy, surgical resection was the only viable therapeutic option. However, approximately 50% of all GIST patients will have evidence of overt malignant disease at initial evaluation, and survival after surgical management of these patients has historically been quite poor. Because of the low incidence of GIST there is a paucity of information regarding the results of surgical resection from retrospective data. In several reported series, optimal patients with primary tumors predominantly gastric in origin and treated by complete tumor resection still had a relatively poor reported 5-year survival rate of approximately 50%.[35,36] Tumor size is a predominant factor in surgical resection series for primary GIST, and patients with tumors larger than 10 cm have reported survival rates in the 20% range at 5 years. There continues to be attrition in resected GISTs during prospective follow-up, with one series reporting only 10% of resected patients being free of disease after a median follow-up of 68 months.[37] The median time to recurrence after resection of a primary GIST is 2 years, but in subsets with small tumor size or slowly proliferating GIST, metastases can develop more than 10 years after diagnosis, and therefore all these patients require life-long follow-up.

Of patients with primary disease at initial diagnosis, approximately 75% will undergo complete resection. The most common sites of disease failure after complete resection are the peritoneal cavity and the liver. The finding of an extra-abdominal site is quite uncommon. Approximately half to two thirds of GIST primaries will have disease failure within the liver, and nearly 40% of patients will have the liver as the only site of failure. Generally, hepatic involvement is multifocal; however, one series of 34 patients reported a 5-year survival rate of 30% after hepatic resection.[38] Surgical resection for recurrent GIST has found limited use with rare long-term success, even after complete tumor removal or ablation. Palliative surgery for bleeding or obstruction can be entertained as a viable alternative in a patient with limited disease and a good performance status.

The goal of surgery in the management of primary GIST is complete gross resection with an intact pseudocapsule. At laparotomy the abdomen should be carefully explored for any evidence of metastatic disease on the peritoneal surfaces or in the liver. GISTs should be handled gently and with care to avoid rupture. GISTs are generally exophytic, tend to displace adjacent structures, and despite the CT appearance, can often be lifted away from surrounding organs. En bloc resection is infrequently necessary and only when there is evidence of dense adherence to adjacent organs. Segmental resection of the stomach or intestine can be performed with the intent of negative margins. Partial or wedge gastrectomy is a viable option because GIST cells do not manifest submucosal spread, as is common with adenocarcinoma. Lymphadenectomy is unnecessary because lymph node metastases are rare. The value of microscopically negative resection margins, especially in a large tumor, is questionable since margin status does not appear to be a prognostic indicator for recurrence when it has been evaluated as a meaningful risk factor. This may be because these large extrinsic tumors tend to shed cells into the peritoneal cavity, so local/regional recurrence is predicted more by tumor size than by resection margin. The value of reoperative surgery for microscopically positive margins is unproven and should depend on many factors, such as tumor size, potential morbidity, and the availability of adjuvant therapy. Laparoscopic wedge resection may be used for small GISTs (<2 cm) when the risk for rupture is minimal, but data on this approach are lacking.

Surgical considerations for the management of GIST have recently undergone considerable change. Although surgical resection remains the standard form of treatment of primary GIST, the efficacy of the KIT-targeted oral agent imatinib mesylate has transformed therapeutic considerations into a multimodality paradigm. There is increasing awareness that GIST needs to be managed with the combined expertise of pathology, surgery, medical oncology, and imaging in the initial evaluation and subsequent management. It is reasonable, then, to evaluate surgical considerations and outcomes with respect to pre–imatinib mesylate and post–imatinib mesylate time frames. Traditional sarcoma-based polychemotherapy and irradiation have historically been ineffective in the treatment of GIST, and surgical management in general has been associated with disappointing results in terms of recurrence-free and overall survival for high-risk GIST patients, particularly for large and highly proliferative tumors. Imatinib mesylate is a rationally based therapeutic agent that was developed as an antagonist to the KIT receptor on GIST cells and has shown remarkable effectiveness against metastatic and unresectable GIST.[39] Addition of this drug to surgical management decisions in GIST leads to the possibility of effective adjuvant therapy for improving long-term outcomes. Furthermore, surgical debulking of slowly responding, stable, or partially responding large primary or recurrent GISTs after "neoadjuvant" administration and assessment of response to imatinib mesylate may enhance long-term disease control in GIST patients with large tumor burdens. Advantages of this combined approach could also lead to organ preservation, an important consideration for GIST patients with primary tumor location in the proximal stomach, rectum, or duodenum. The results of ongoing clinical trials will probably provide more concrete recommendations for the surgical management of GIST and become part of the care standard in the future.

ADJUVANT THERAPY

Surgery is the primary initial treatment of resectable GIST, but it is seldom curative in patients with a high risk for recurrent disease. Surgery is even less effective in

patients with locally recurrent or metastatic disease. Before the availability of imatinib mesylate the only treatment of GIST, other than surgical resection, was conventional chemotherapy and radiotherapy. However, lack of efficacy has been a constant in studies evaluating these modalities in the management of GIST patients.[40] The recent availability of an effective systemic therapy raises the issue of its potential use as adjuvant or neoadjuvant treatment in conjunction with surgical tumor resection with the objective of either cytoreduction of disease before surgery or improvement in long-term survival after successful resection. Other than anecdotal experience, data on the combined use of imatinib mesylate and surgical resection are lacking. Clearly, patient selection factors for adjuvant trial design are critical. Patients typically at high risk for recurrence, such as those with tumors larger than 10 cm or tumors with greater than five mitoses per 50 high-powered fields, are obvious candidates for such a trial. Patients with other risk factors, such as tumor perforation or rupture or a known specific drug-sensitive genotype, might also be considered for clinical trial participation. Presently, three national cooperative group trials are evaluating imatinib mesylate as adjuvant or neoadjuvant therapy.[39] One is already completed with the results pending for a phase II trial design of postoperative imatinib mesylate in high-risk patients, another is an ongoing phase II randomized postoperative trial for high- and intermediate-risk patients with comparison to placebo, and the third is an ongoing neoadjuvant design for patients with bulky primary or resectable recurrent/metastatic GIST. The possibility of pharmacologic debulking with imatinib mesylate, followed by surgical resection, may be a rational strategy for organ preservation, in vivo drug sensitivity testing, optimization of therapy for focal metastatic disease, and abrogation of emerging drug-resistant clones. Short follow-up clinical experience has suggested the usefulness of limited surgery in some patients with multiple-site recurrent disease whose tumor demonstrated a mixed pattern of response to imatinib mesylate and in whom resection or ablation was successful in removing unresponsive sites while the bulk quiescent residual disease was managed successfully with continued imatinib mesylate therapy. At this time the optimal dose plus duration of imatinib in the surgical adjuvant or neoadjuvant strategy has not been defined, and this combination in treating GIST in standard actual practice awaits elucidation in clinical trials.

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Chapter

81

Gastrointestinal Lymphomas

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Despite recent advances in the diagnosis and treatment of non-Hodgkin's lymphoma (NHL), this disease remains the sixth leading cause of cancer-related deaths in the United States, with an approximate 5-year survival rate of 56%.[1] An estimated 56,000 cases of NHL will occur in the United States in 2005, and approximately 19,000 will die of the disease.[1] The incidence of NHL has increased rapidly, almost doubling, since the early 1970s, probably because of an increased incidence of human immunodeficiency virus (HIV) infection and environmental and toxic exposure.[1,2] However, the incidence stabilized in the 1990s, primarily as a result of a decline in acquired immunodeficiency syndrome–related malignancy.[1]

NHL classically originates in lymph node basins, but it may occur as extranodal lymphoma or lymphoma arising within a solid organ in up to 30% of cases.[3] The gastrointestinal (GI) tract is the most common site of extranodal disease and accounts for approximately 20% of all NHL and approximately half of extranodal NHL.[2,4] Requirements for the diagnosis of primary GI lymphoma include absence of palpable lymphadenopathy, normal bone marrow biopsy and peripheral blood smear, absence of mediastinal lymphadenopathy on chest radiographs, disease grossly confined to the affected viscus, and absence of hepatic or splenic involvement unless via direct extension of the primary tumor.[5] This chapter focuses on lymphomas occurring in the stomach and small intestine, the two most commonly affected organs of the digestive tract worldwide.

INCIDENCE AND EPIDEMIOLOGY

GI tract lymphomas may occur in any part of the digestive tract from the oral cavity to the rectum, and the incidence appears to depend on geographic location.[2] In Western and Middle Eastern regions, the stomach is the most commonly affected site, followed by the small intestine, colon, pancreas, and all other sites; however, in other parts of the world such as India, Africa, and the South Pacific, intestinal lymphoma is the predominant form, followed by the stomach, colon, and other organs (Table 81–1).[2,6]

Gastric Lymphoma

In the United States the stomach is the most common site of GI lymphoma and accounts for more than half of the lymphomas of the GI tract. Yet it is relatively uncommon and accounts for less than 15% of primary gastric neoplasms and 2% of all lymphomas.[6-8] Gastric lymphomas tend to occur in patients older than 50 years, with a peak incidence in the sixth and seventh decades, and they are two to three times more common in men.[6,7] However, recent studies have demonstrated that the disease is occurring more commonly in an increasingly younger age group, predominantly because of increased incidence in HIV-infected patients.[6] Gastric lymphomas most frequently occur in the gastric antrum or distal body, but they may arise from any portion of the stomach.[7,9]

Small Intestinal Lymphoma

Lymphoma of the small intestine is the second most common extranodal lymphoma of the GI tract in the United States. It is the third most common primary neoplasm of the small bowel and accounts for 15% to 20% of malignant small bowel tumors, 5% of all lymphomas, 4% to 12% of all NHLs, and 20% to 30% of primary GI lymphomas.[7,10,11] Small intestinal lymphomas, like gastric lymphomas, tend to occur in patients older than 50 years; however, it is the most common intestinal neoplasm in children younger than 10 years, thus resulting in a bimodal distribution.[7,11] Small bowel lymphoma is most commonly located in the ileum, the site of the highest concentration of gut-associated lymphoid tissue.[7]

CLINICAL FEATURES

The typical signs and symptoms of GI lymphoma are often nonspecific and commonly mimic other abdomi-

Table 81–1 Frequency and Sites of Extranodal Lymphomas in Series from Different Countries

	USA (1972)	The Netherlands (1989)	Denmark (1991)	Canada (1992)	Hong Kong (1984)	Pakistan (1992)	Egypt (1994)	Switzerland (1997)
Stomach	24	23	19	24*	39	10	10	36
Small intestine	8	5	9	—	24	17	5	11
Colon and rectum	5	7	2	—	—	10	6	4
Head and neck	21	23	8†	34	22	18	23	19
Orbit	2	3	1	4	1	<1	<1	5
Central nervous system	2	6	7	10	—	2	1	1
Lung, pleura	4	5	5	1	—	—	—	1
Bone	5	3	9	4	4	2	11	3
Soft tissue	9	2	3	5	3	—	—	1
Breast	2	2	1	2	—	—	—	3
Skin (except mycosis fungoides)	8	2	11	4	3	8	4	6
Genitourinary tract	3	4	6	5	8	12	6	5

*Including all gastrointestinal sites.
†Waldeyer's ring and tonsils not included.
From Zucca E, Roggero E, Bertoni F, Cavalli F: Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol 8:727-737, 1997.

nal pathologies, such as gastritis, peptic ulcer disease, and pancreatic or gallbladder disorders, as well as other neoplasms.[6] The most common initial symptom of both gastric and intestinal lymphomas is abdominal pain; additional symptoms may include early satiety or abdominal fullness, fatigue, diarrhea, nausea, vomiting, and indigestion (Table 81–2).[8,12] Lymphoma of the small intestine is more likely to cause intussusception, obstruction, or perforation than gastric lymphoma is. In fact, approximately 30% to 50% of patients will have an abdominal emergency, with perforation present in up to 25% of cases.[2,5] Over half of patients with GI lymphoma will exhibit anemia secondary to chronic occult blood loss; overt bleeding is uncommon.[7] Constitutional B symptoms, which include fever, weight loss, and night sweats, are rare (less than 12% of patients) unless systemic disease is present.[8] Because of the insidious onset and nonspecific nature of many of these symptoms, it is often months or years before the diagnosis is made.[4] Physical examination is normal in approximately 55% to 60% of patients, with abdominal tenderness encountered in 20% to 35% and a palpable mass in 17% to 25%.[6] Other physical findings may include fever, lymphadenopathy, jaundice, hepatomegaly, and splenomegaly.[6]

PATHOLOGY

Appropriate management of GI lymphomas requires determination of the stage and subtype of the lymphoma, as well as consideration of morphology, genetic alterations, and immunophenotype.[2] There are several classification systems for GI lymphomas (Table 81–3). In the World Health Organization (WHO) classification, the most common NHL arising in the GI tract is diffuse large B-cell lymphoma (DLBCL) (55%), followed in frequency by extranodal marginal cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (40%), Burkitt's lymphoma (3%), and follicular, mantle cell, and enteropathy-type T-cell lymphomas (<1% each) (Table 81–4).[2]

Diffuse Large B-Cell Lymphoma

DLBCL is the most common type of NHL, extranodal lymphoma, and GI lymphoma. It may occur as de novo disease, but it may also arise from or coexist in a background of low-grade MALT lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, or follicular lymphoma (Fig. 81–1).[2,13] DLBCL is often manifested as a tumor mass replacing the normal architecture of its tissue of origin and is most commonly located in the stomach or ileocecal region (Fig. 81–2).[2] There are several morphologic variants of DLBCL that are distinguished by histologic, cytogenetic, and molecular genetic features; patterns of gene expression dictate the prognosis.[14,15] A Bcl-2 gene mutation, commonly involved in a (14;18)(q32;q21) translocation, is present in 10% to 40% of DLBCLs, and a Bcl-6 gene mutation with a (14;3)(q32;q27) rearrangement may occur in

Table 81–2 Symptoms at Diagnosis in Patients with Primary Gastrointestinal Non-Hodgkin's Lymphoma*

	Stomach (*N* = 277)		Small Bowel (*N* = 32)		Ileocecal Region (*N* = 26)		Multiple GI Sites (*N* = 24)	
Symptom†	*No. of Patients*	*%*	*No. of Patients*	*%*	*No. of Patients*	*%*	*No. of Patients*	*%*
Pain	216	78.0	24	75.0	20	76.9	14	58.3
Loss of appetite	131	47.3	13	40.6	6	23.1	14	58.3
Loss of weight‡	68	24.5	11	34.4	4	15.4	6	25.0
Bleeding	50	18.8	2	6.3	3	11.5	2	8.3
Vomiting	52	18.1	10	31.3	2	7.7	5	20.8
Night sweats	31	11.2	4	12.5	5	19.2	11	45.8
None	10	3.6	—	—	—	—	—	—
Diarrhea	10	3.6	4	12.5	5	19.2	7	29.2
Constipation	9	3.2	8	25.0	6	23.1	3	12.5
Fever	6	2.2	2	6.3	2	7.7	1	4.2
Perforation	5	1.8	3	9.4	—	—	—	—
Ileus	—	—	12	37.5	5	19.2	1	4.2
B symptoms (fever, night sweats)	33	11.9	5	15.6	3	11.5	6	25.0
Median time to diagnosis (days)	93		135		76		142	

*Major sites only.
†More than one possible.
‡Not considered a B symptom but caused by non-Hodgkin's lymphoma.
From Koch P, del Valle F, Berdel WE, et al: Primary gastrointestinal non-Hodgkin's lymphoma: I. Anatomic and histologic distribution, clinical features, and survival data of 371 patients registered in the German Multicenter Study GIT NHL. J Clin Oncol 19:3861-3871, 2001.

Table 81–3 Comparison of Gastrointestinal Lymphoma Classifications

WHO	REAL	Working	Lukes-Collins	Kiel	Rappaport
Extranodal marginal zone lymphoma (MALT)		Small cleaved cell type	Small cleaved cell type	Immunocytoma	Well-differentiated lymphocytic
Follicular lymphoma	Follicular center lymphoma	Small cleaved cell type	Small cleaved cell type	Centroblastic/centrocytic, follicular and diffuse	Nodular poorly differentiated lymphocytic
Mantle cell lymphoma				Centrocytic	Intermediately or poorly differentiated lymphocytic, diffuse or nodular
Diffuse large B-cell lymphoma	Diffuse large B-cell lymphoma	Large cleaved follicular center cell	Large cleaved follicular center cell	Centroblastic, B-immunoblastic	Diffuse mixed lymphocytic and histiocytic
Burkitt's lymphoma	Burkitt's lymphoma	Small noncleaved cell, follicular center cell	Small noncleaved follicular center cell	Burkitt's lymphoma with intracytoplasmic immunoglobulin	Undifferentiated lymphoma, Burkitt's type

MALT, mucosa-associated lymphoid tissue; REAL, Revised European-American Lymphoma; WHO, World Health Organization.
From Mercer DW, Robinson EK: Stomach. In Townsend CM (ed): Sabiston's Textbook of Surgery: The Biological Basis of Modern Surgical Practice. Philadelphia, Elsevier, 2004, pp 1265-1321.

Table 81–4 Frequency of Organ Involvement

Gastrointestinal Lymphoma	Stomach	Small Intestine	Colon*	Pancreas*
Diffuse large cell lymphoma	55	55	60	60
MALT lymphoma	40	20	15	
Burkitt's lymphoma	3	5	15	15
Peripheral T-cell lymphoma	0	15	10	5
Mantle cell lymphoma	<1	0	1	10
Follicular lymphoma	<1	0	1	10

*Relative frequency of particular malignancies estimated from small case series in the literature.
MALT, mucosa-associated lymphoid tissue.
Adapted from Koniaris LG, Drugas G, Katzman PJ, et al: Management of gastrointestinal lymphoma. J Am Coll Surg 197:127-141, 2003.

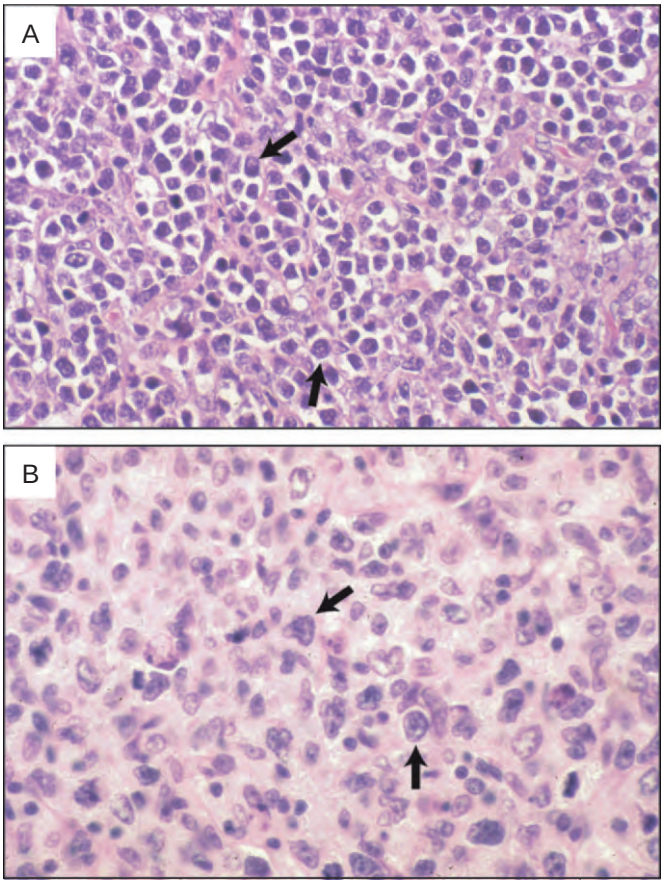

Figure 81–1. Diffuse large B-cell lymphoma of the stomach showing a monotonous high-grade infiltrate of large centroblast-like cells *(arrows)* under low **(A)** and high-power **(B)** magnification. (Courtesy of Mary R. Schwartz, M.D., Baylor College of Medicine.)

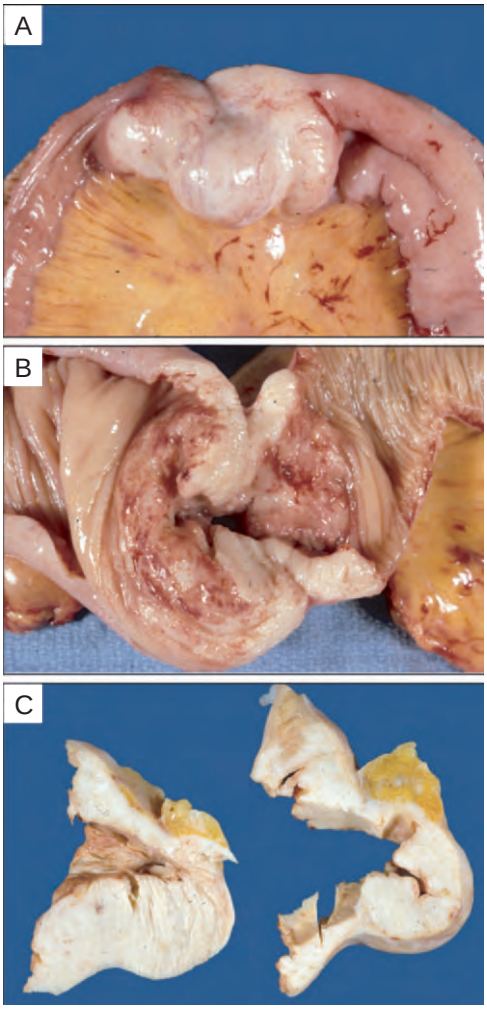

Figure 81–2. Diffuse large B-cell lymphoma of the jejunum demonstrating the external aspect **(A),** the mucosal aspect **(B),** and cross sections showing transmural involvement and expansion of the wall by lymphoma **(C).** (Courtesy of Mary R. Schwartz, M.D., Baylor College of Medicine.)

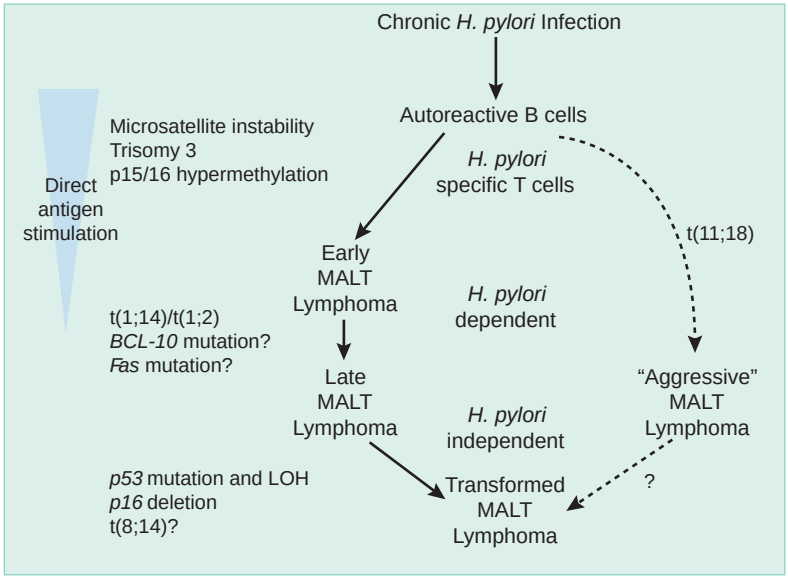

Figure 81–3. Schematic presentation of the pathogenesis of MALT lymphoma. LOH, loss of heterozygosity. (From Du M, Isaccson PG: Gastric MALT lymphoma: From aetiology to treatment. Lancet Oncol 3:97-104, 2002.)

approximately 30% to 40% of cases; variabilities in survivin expression and p53 mutations have also been described.[14-16] The Bcl-2 protein is involved in the prevention of apoptosis, and recent evidence suggests that overexpression of it is associated with decreased overall, disease-free, and relapse-free survival.[15] In contrast, overexpression of the Bcl-6 protein, which normally regulates T-cell–dependent antigen responses, is associated with increased overall survival.[14]

MALT Lymphoma

MALT lymphomas were first described in 1983 and have since been reclassified as extranodal marginal zone lymphomas of the MALT type.[17] The stomach, which is paradoxically devoid of organized lymphoid tissue, is the site most frequently affected by MALT lymphomas.[18] These gastric tumors are thought to arise from MALT acquired as a result of chronic inflammation, most commonly gastritis associated with *Helicobacter pylori* because more than 90% of patients with gastric MALT lymphoma are infected with this bacterium.[4] Chronic activation of tumor-infiltrating T-cells is responsible for B-cell activation, with subsequent oligoclonal and monoclonal proliferation in an *H. pylori* strain–specific manner.[17] Once an active, proliferating monoclonal B-cell population develops, reactive oxygen species released at the site of inflammation contribute to an accumulation of oxidative stress and resultant genetic abnormalities.[9]

Genetically, two predominant translocations, t(11;18)(q21;q21) and t(1;14)(p22;q32), are implicated in the development of MALT lymphoma.[19] The t(11;18)(q21;q21) translocation, which fuses the inhibitor of apoptosis *(IAP2)* gene to the MALT 1 *(MLT)* gene, is detected in approximately 21% to 60% of gastric MALT lymphomas.[20] The resultant IAP2-MLT fusion protein is associated with nuclear localization of Bcl-10, a protein with transforming and proapoptotic functions

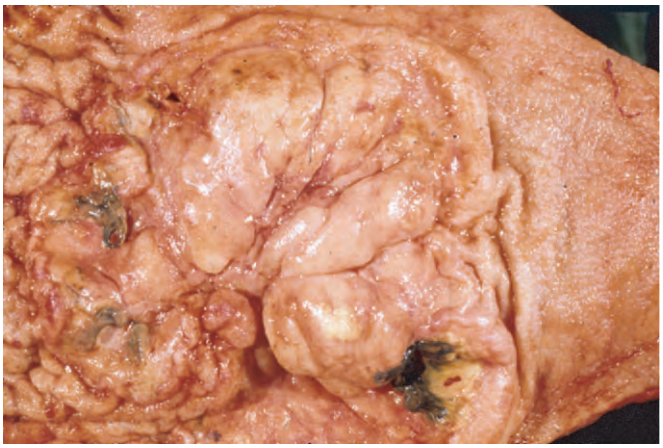

Figure 81–4. Gastric MALT lymphoma, gross photograph. (Courtesy of Mary R. Schwartz, M.D., Baylor College of Medicine.)

normally localized in the cytoplasm, as well as activation of the nuclear factor kappa B (NF-κB) pathway, which results in antigen-independent growth and disease dissemination.[17] This translocation is associated with resistance to *H. pylori* eradication, lymphoma regression, and more aggressive, advanced stages of disease.[7,17] The t(1;14)(p22;q32) translocation, which occurs in less than 5% of gastric MALT lymphomas, transfers the Bcl-10 gene to the immunoglobulin heavy chain promoter region and thereby results in a similar pattern of Bcl-10 overexpression and nuclear localization, activation of the NF-κB pathway, and an association with more advanced stages of disease.[20] Mutations leading to the formation of MALT lymphoma are summarized in Figure 81–3.

Gastric MALT lymphoma is often multifocal, with most tumors located in the antrum or distal body of the stomach (Fig. 81–4).[9] Histologically, there is diffuse

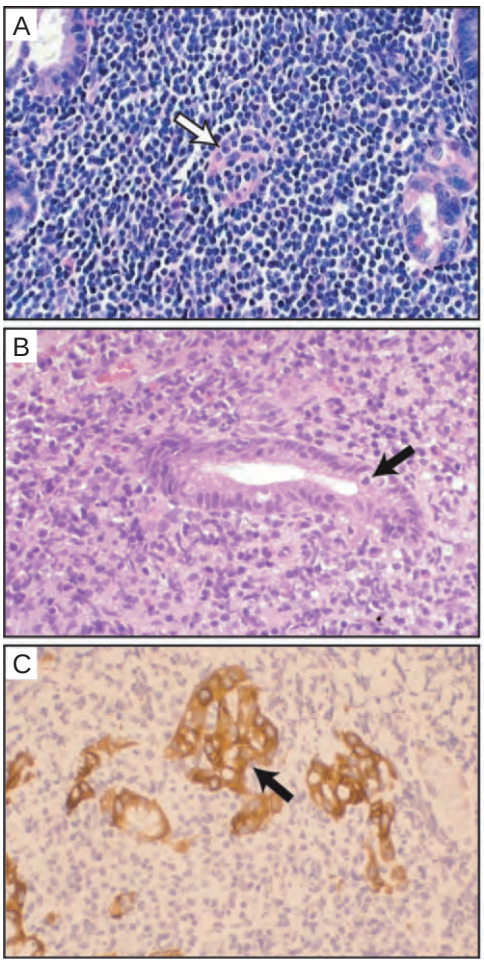

Figure 81–5. Histopathologic characteristics of MALT lymphoma. **A,** Monocytoid, lymphocytic infiltrate with lymphocytes infiltrating the epithelial component (lymphoepithelial lesion) *(arrow).* (Courtesy of Suimin Qiu, M.D., The University of Texas Medical Branch.) **B,** Low-grade MALT lymphoma of the stomach demonstrating lymphoepithelial lesions *(arrow),* and **C,** keratin immunohistochemical stain demonstrating lymphoepithelial lesions with infiltration and partial destruction of glandular structures by lymphocytes *(arrow).* (Courtesy of Mary R. Schwartz, M.D., Baylor College of Medicine.)

permeation of the lamina propria with germinal centers; neoplastic cells infiltrate the marginal zone around reactive lymphoid follicles and invade gastric glands, with the formation of characteristic lymphoepithelial lesions (Fig. 81–5).[9,13] The neoplastic MALT lymphoma cells generally express B-cell markers, including CD20, CD22, and CD79a, but they lack markers expressed by other B-cell neoplasms, such as CD5, CD10, CD23, and Bcl-6.[13,19]

Burkitt's Lymphoma

Burkitt's lymphoma is an aggressive lymphoma that may occur as endemic (in equatorial Africa) or sporadic disease.[2] It has a well-established association with Epstein-Barr virus infection.[7] Burkitt's lymphoma generally

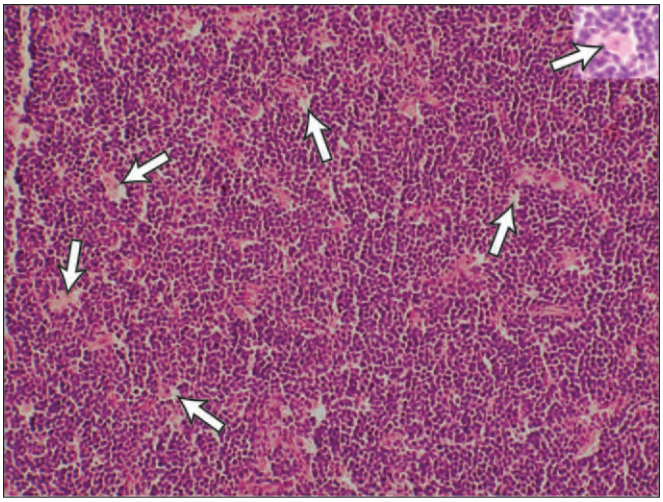

Figure 81–6. Low-power view of Burkitt's lymphoma with monotonous lymphocytic infiltrate and scattered clear spaces (starry sky appearance) *(arrows).* Clear spaces are actually large histiocytes *(inset).* (Courtesy of Suimin Qiu, M.D., The University of Texas Medical Branch.)

affects younger populations than other types of gastric lymphoma do and is typically located in the cardia or body of the stomach or the terminal ileum.[7,13] Apoptosis and mitosis are common within the tumor, which attracts circulating macrophages and thereby results in the classic "starry sky" appearance (Fig. 81–6).[13] Burkitt's lymphoma generally expresses CD10, CD20, CD79a, and Bcl-6 but lacks Bcl-2. Rearrangement of the *c-myc* oncogene is typical of this lymphoma.[21]

Follicular Lymphoma

Follicular lymphoma is most commonly a systemic disease, but it may rarely be manifested as localized GI tract involvement.[13] There is an apparent predilection for the duodenum, and differentiation from MALT lymphoma is often difficult because of the lymphoepithelial lesions common to both.[13] Transformation of follicular lymphoma to diffuse large B-cell disease may occur in as many as 32% of patients and carries a poor prognosis.[22] The most useful markers for the diagnosis of follicular lymphoma are CD10, Bcl-6, and Bcl-12.[13] Additionally, up to 85% of tumors will demonstrate a t(14;18)(q32;q21) translocation leading to Bcl-2 overexpression.[23]

Mantle Cell Lymphoma

Mantle cell lymphoma, in contrast to other forms of GI lymphoma, tends to be manifested as polyposis predominantly involving the small bowel (Fig. 81–7).[24] There is an infiltrate of small or medium-sized cells with irregular nuclei and little cytoplasm, and lymphoepithelial lesions are rare (Fig. 81–8).[13] Unlike other lymphomas, the tumor cells tend to compress rather than infiltrate.[13] Typical tumor markers include CD5, CD20, CD79a, and cyclin D1.[13,24]

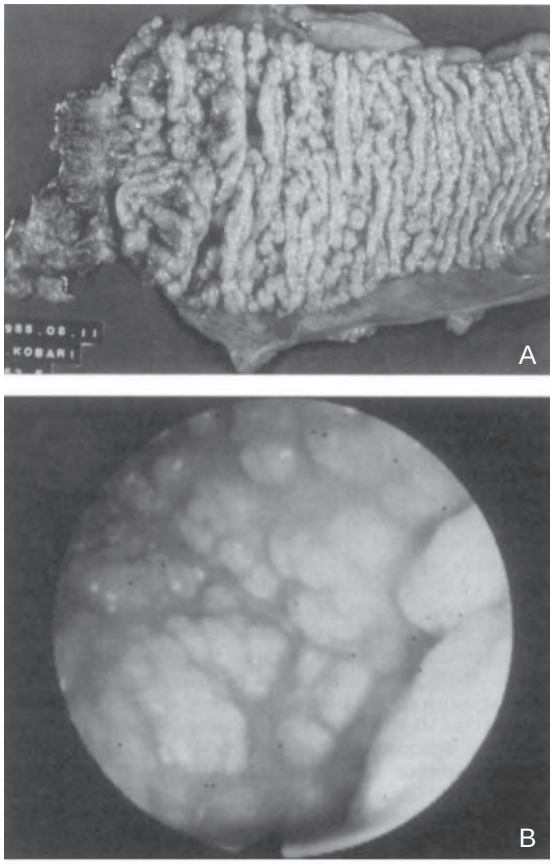

Figure 81–7. Growth manifestations of multiple lymphomatous polyposis. **A,** A surgically resected rectum shows a myriad of confluent polyps and the formation of giant folds. **B,** Endoscopic examination of the duodenum shows numerous polyps that were densely present with the same lesions extending throughout from the esophagus to the rectum. (From Hashimoto S, Nakamura N, Kuze T, et al: Multiple lymphomatous polyposis of the gastrointestinal tract is a heterogenous group that includes mantle cell lymphoma and follicular lymphoma: Analysis of somatic mutation of immunoglobulin heavy chain gene variable region. Hum Pathol 30:581-587, 1999.)

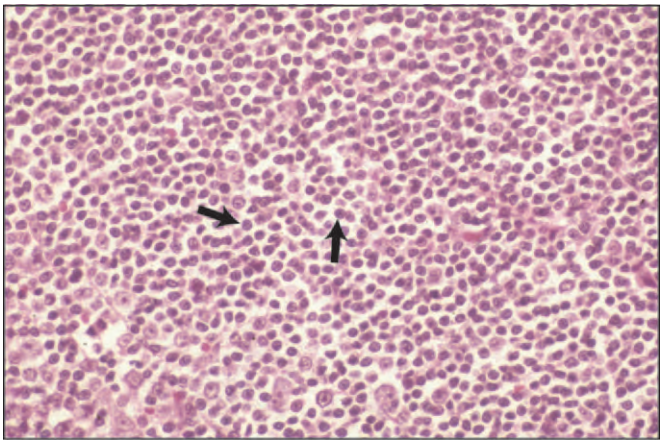

Figure 81–8. Mantle cell lymphoma of the stomach demonstrating the characteristic diffuse infiltration of small- to medium-sized cells with little cytoplasm *(arrows).* (Courtesy of Mary R. Schwartz, M.D., Baylor College of Medicine.)

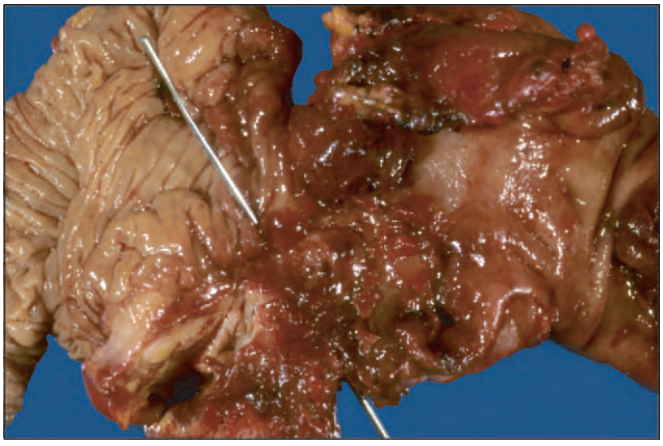

Figure 81–9. Duodenal T-cell lymphoma with circumferential ulceration extending from the pylorus to the ampulla. (Courtesy of Mary R. Schwartz, M.D., Baylor College of Medicine.)

Enteropathy-Type T-Cell Lymphoma

Enteropathy-type T-cell lymphoma (ETL) is an unusual lymphoma variant most commonly localized to the jejunum and ileum.[25,26] A well-defined relationship exists between celiac disease and the development of ETL, and compliance with a gluten-free diet reduces the risk for lymphoma in these patients.[25,27] Perforation is a frequent complication of ETL.[28] Circumferential ulceration of the mucosa is common with this lymphoma, and a heavy eosinophilic and histiocytic infiltrate may obscure tumor cells, which are generally blastic with prominent nucleoli (Fig. 81–9).[29] Adjacent normal bowel generally demonstrates villus atrophy and crypt hyperplasia.[30] ETL exhibits variable tumor markers, which may include CD3, CD4, CD8, and TIA-1.[29] A summary of the immunophenotypes characteristic of various GI lymphomas is shown in Table 81–5.

GRADING

Grading GI lymphomas is important for determination of the prognosis and proper treatment strategy for the disease. GI lymphomas are considered to be low-grade, indolent NHL or high-grade, aggressive NHL by the new WHO classification.[8] Low-grade lymphomas are almost always a derivative of MALT and are thus termed low-grade MALT lymphomas. High-grade lymphomas contain low-grade MALT components in about a third of cases and represent progression of disease; in the remaining two thirds of high-grade tumors, the disease may have progressed from low-grade lesions or may have arisen as a de novo high-grade tumor.[8] Low-grade lymphomas are generally composed of a diffuse infiltrate of small- to medium-sized lymphocytes demonstrating monoclonality. In contrast, high-grade lymphomas appear histologically as large numbers of transformed blasts that

Table 81–5 Common Immunophenotypes of Gastrointestinal Lymphomas

Lymphoma	CD3	CD4	CD5	CD8	CD10	CD20	Bcl-2	Cyclin D1
Diffuse large B-cell lymphoma	–	–	–	–	±	+	±	–
MALT lymphoma	–	–	–	–	–	+	+	–
Mantle cell lymphoma	–	–	+	–	–	+	+	+
Follicular lymphoma	–	–	–	–	+	+	±	–
Burkitt's lymphoma	–	–	–	–	+	+	–	–
Enteropathy-type T-cell lymphoma	+	+	–	+	–	–	–	–

Adapted from El-Zimaity HM, Wotherspoon A, de Jong D: Interobserver variation in the histopathological assessment of MALT/MALT lymphoma: Towards a consensus. Blood Cells Mol Dis 34:6-16, 2005.

Box 81–1 TNM Classification of Gastric Lymphoma

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1 Tumor invades the lamina propria or submucosa
- T2 Tumor invades the muscularis propria or subserosa
- T3 Tumor penetrates the serosa (visceral peritoneum) without invasion of adjacent structures
- T4 Tumor invades adjacent structures

Lymph Node (N)

- NX Regional lymph node(s) cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in perigastric lymph node(s) within 3 cm of the edge of primary tumors
- N2 Metastasis in perigastric lymph node(s) more than 3 cm from the edge of the primary tumor or in lymph nodes along the left gastric, common hepatic, splenic, or celiac arteries

Distant Metastasis

- MX Presence of distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Adapted from Green FL, Page DL, Fleming ID, et al: AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2001.

Box 81–2 Ann Arbor Classification System for Primary Lymphomas

Stage	Definition
I	Involvement of a single extranodal site or a single lymph node region or structure
II	Involvement of two or more lymph node regions or lymph structures on the same side of the diaphragm
III	Involvement of lymph node regions or lymph node structures on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues with or without associated lymph node involvement

Adapted from Koniaris LG, Drugas G, Katzman PJ, et al: Management of gastrointestinal lymphoma. J Am Coll Surg 197:127-141, 2003.

may coalesce in clusters or sheets, ultimately effacing the residual low-grade elements.[8]

STAGING

No consensus has been reached on the optimal system for staging GI lymphoma, but the TNM staging system (as proposed for gastric carcinoma, Box 81–1) is commonly used in surgical applications.[7] The Ann Arbor classification system (Box 81–2) was modified by Musshoff[5] for staging of GI lymphomas (Box 81–3), and both are still commonly applied. Accurate staging often requires evaluation by endoscopy, ultrasonography, chest radiography, bone marrow biopsy, and computed tomography (CT).[6]

DIAGNOSIS

A high index of suspicion is required to make the diagnosis of GI lymphoma because the clinical and radiologic

Box 81–3 **Musshoff's Criteria for Staging of Gastric Lymphomas**

Stage	Definition
IE	Lymphoma restricted to the GI tract on one side of the diaphragm
IE_1	Infiltration limited to the mucosa and submucosa
IE_2	Lymphoma extending beyond the submucosa
IIE	Lymphoma additionally infiltrating lymph nodes on the same side of the diaphragm
IIE_1	Infiltration of regional lymph nodes
IIE_2	Infiltration of lymph nodes beyond the regional nodes
IIIE	Lymphoma infiltrating the GI tract and/or the lymph nodes on both sides of the diaphragm
IVE	Localized infiltration of associated lymph nodes together with diffuse or disseminated involvement of extra-GI organs

Adapted from Ahmad A, Govil Y, Frank BB: Gastric mucosa-associated lymphoid tissue lymphoma. Am J Gastroenterol 98:975-986, 2003.

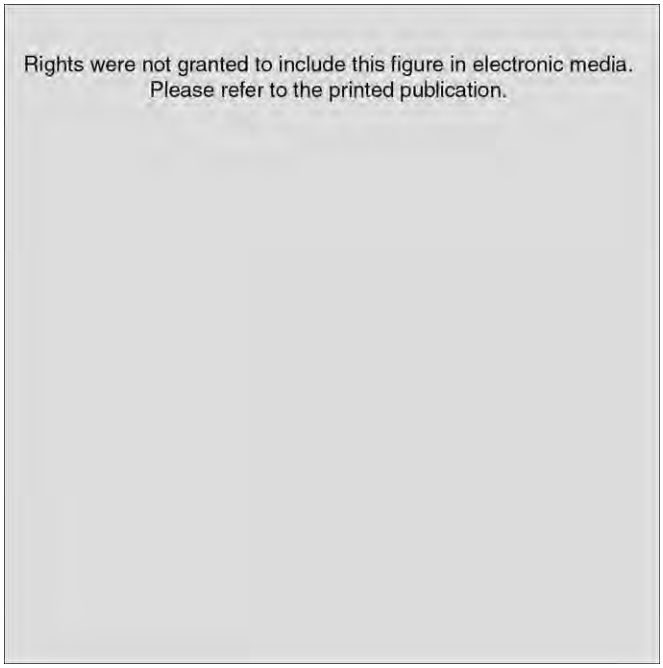

Figure 81–10. Gastric lymphoma manifested as gastric ulceration with atypical erythematous surrounding mucosa. (From Tytgat GNJ: Upper gastrointestinal endoscopy. In Yamada T [ed]: Atlas of Gastroenterology. Philadelphia, Lippincott, Williams & Wilkins, 2003, pp 823-840.)

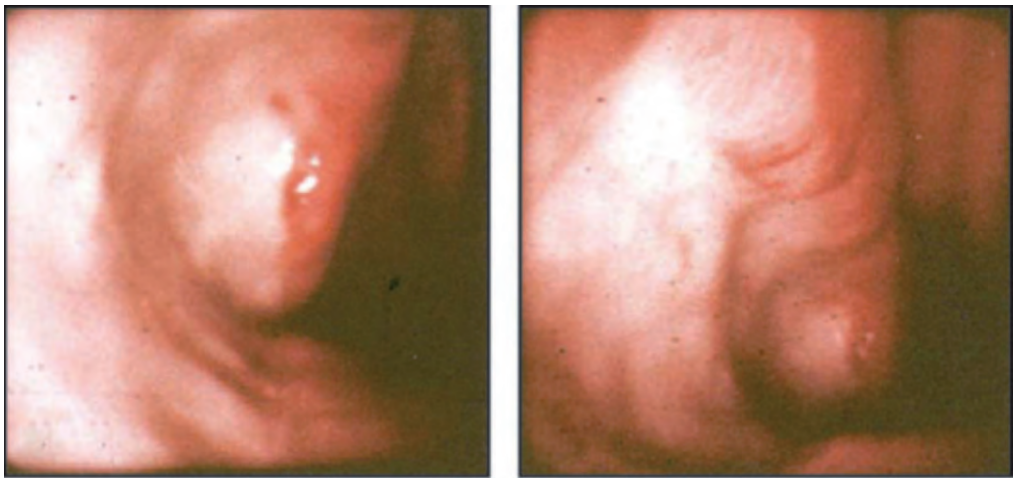

Figure 81–11. **A** and **B,** Endoscopic appearances of MALT lymphoma, exophytic type. A large friable, nodular mass with evidence of bleeding is located in the antrum of the stomach. This lesion proved to be a MALT lymphoma. (From Ahmad A, Govil Y, Frank BB: Gastric mucosa-associated lymphoid tissue lymphoma. Am J Gastroenterol 87:975-986, 2003.)

features are often vague. A careful physical examination should include palpation of all lymph node regions and evaluation of the abdomen for palpable masses or hepatosplenomegaly.[8] Laboratory evaluation should include a complete blood count with differential, routine biochemical assays, lactate dehydrogenase level, and serum protein electrophoresis.[8] Once the diagnosis of GI lymphoma is established, evidence of metastatic disease should be sought by performing an upper airway examination, bone marrow biopsy, and CT of the chest and abdomen to evaluate for lymphadenopathy; any enlarged lymph nodes should be biopsied.[7]

Gastric Lymphoma

The diagnosis of gastric lymphoma is generally made by upper endoscopy and biopsy, with a diagnostic yield of approximately 90%.[31] The most frequent endoscopic finding is ulceration in both low-grade and high-grade lesions (Fig. 81–10). Diffuse infiltration and polypoid masses are also common findings (Fig. 81–11).[31] Such appearances are mistaken for benign conditions such as gastritis or peptic ulcer disease in approximately 50% of patients with low-grade disease and 25% of patients with high-grade disease, thus reinforcing the importance of

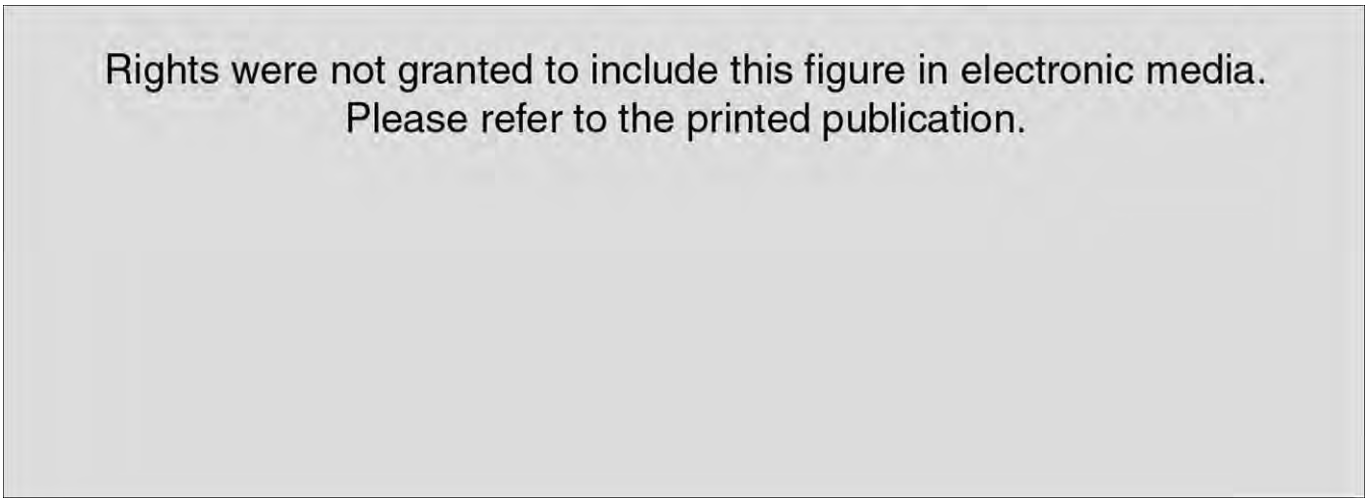

Figure 81–12. A radial ultrasound image obtained at 12 MHz shows an advanced gastric lymphoma producing diffuse gastric wall thickening involving all layers of the stomach. (From Kimmey MB, Vilmann P: Endoscopic ultrasonography. In Yamada T [ed]: Atlas of Gastroenterology. Philadelphia, Lippincott, Williams & Wilkins, 2003, pp 1042-1054.)

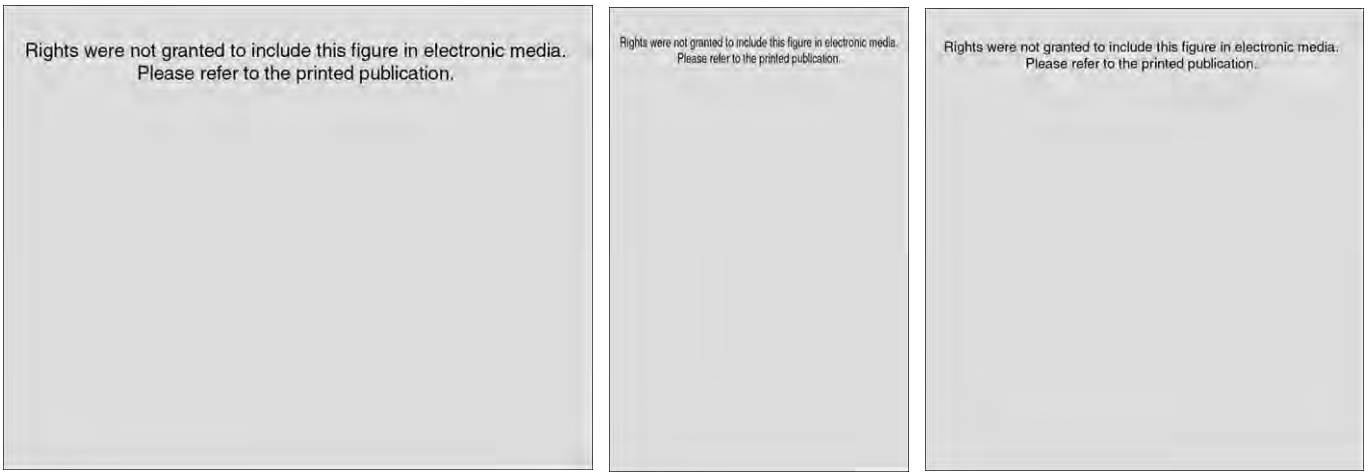

Figure 81–13. The utility of contrast imaging of gastrointestinal lymphomas. **A,** Double-contrast radiography showing a severely constricted lesion in the ileum that was subsequently diagnosed as MALT lymphoma. **B,** Double-contrast radiography revealing an ulcerative lesion with mucosal destruction in the terminal ileum, later diagnosed as diffuse large B-cell lymphoma. **C,** Small bowel lymphoma complicating celiac disease with a mass in the right iliac fossa. (**A** and **B,** From Nakamura S, Matsumoto T, Takeshita M, et al: A clinicopathologic study of primary small intestine lymphoma: Prognostic significance of mucosa-associated lymphoid tissue–derived lymphoma. Cancer 88:286-294, 2000; **C,** from Ciclitira PJ: Celiac disease. In Yamada T [ed]: Atlas of Gastroenterology. Philadelphia, Lippincott, Williams & Wilkins, 2003, pp 331-340.)

biopsy for tissue diagnosis.[31,32] Endoscopic ultrasound is an important adjunct for detecting intramural tumor infiltration and determining tumor stage and is considered to be more reliable than routine CT scanning (Fig. 81–12). The sensitivity of lymph node detection is more variable, with 45% to 90% accuracy.[31] *H. pylori* testing should be performed on biopsy samples and, if negative, confirmed by serology.[7]

Intestinal Lymphoma

In approximately 30% to 50% of patients, the initial manifestation of small bowel lymphoma is an abdominal emergency.[2] As many as 90% of small bowel lymphomas are diagnosed intraoperatively, either as part of a treatment plan or to establish a diagnosis.[33] Commonly used preoperative imaging modalities include CT of the abdomen and pelvis, lymphangiography, gallium scanning, upper GI series, barium enema, upper endoscopy, and colonoscopy; the appropriate work-up depends on the suspected location of the tumor, and decisions should be made on an individual basis (Fig. 81–13).[33]

TREATMENT

Initial treatment of both gastric and intestinal lymphomas should take into account *H. pylori* status because approximately 70% to 80% of MALT lymphomas and a variable

Table 81–6 *Helicobacter pylori* Treatment

Regimen 1	Regimen 2	Regimen 3
Omeprazole (20 mg, twice a day) Amoxicillin (1 g, twice a day) Clarithromycin (500 mg, twice a day)	Omeprazole (20 mg, twice a day) Metronidazole (500 mg, twice a day) Clarithromycin (500 mg, twice a day)	Omeprazole (20 mg, twice a day) Tetracycline (500 mg, 4 times a day) Metronidazole (500 mg, 4 times a day) Bismuth (525 mg, 4 times a day)

Treatment duration is 10 to 14 days. Regimen 1 is the treatment of choice. Regimen 2 is for penicillin-allergic patients. Other proton pump inhibitors may be substituted at equivalent dosages. Eradication rates exceed 85% with all three regimens.
From Kahl BS: Update: Gastric MALT lymphoma. Curr Opin Oncol 15: 347-352, 2003.

number of DLBCLs regress after *H. pylori* eradication in patients harboring the bacterium.[34] Currently, management of gastric lymphoma takes a predominantly conservative, nonsurgical approach, whereas treatment of many intestinal lymphomas involves a multidisciplinary approach with surgical management being a key component of therapy.

Gastric Lymphoma

Optimal treatment of gastric lymphoma depends on *H. pylori* status, disease stage, degree of large cell transformation, and the presence of genetic mutations such as t(1;14), t(11;18), or Bcl-10 overexpression.[16] The indolent nature of low-grade MALT lymphomas lends itself to conservative treatment, with antibiotic therapy being the sole initial agent, given that the patient can be monitored closely.[35] Approximately 77% of patients with gastric MALT lymphoma will experience complete remission after *H. pylori* eradication.[9] Remission is generally achieved within 12 months of therapy, but a latent period of up to 45 months may occur, with a relapse rate of less than 10%.[9] Current *H. pylori* eradication therapy should include a 2-week regimen of either (1) omeprazole or lansoprazole, clarithromycin, and amoxicillin; (2) omeprazole or lansoprazole, metronidazole, and clarithromycin; or (3) omeprazole or lansoprazole, bismuth, metronidazole, and tetracycline (Table 81–6). Strict endoscopic surveillance with biopsy is recommended 2 months after treatment and at least twice per year for 2 years to monitor for regression.[35] Indicators of possible failure of *H. pylori* eradication include lymphomas of stage IIE and above, stage IE_2 cases that involve the muscularis propria or serosa, lymphomas demonstrating t(11;18)(q21;q21) or t(1;14)(p22;q32) translocations or nuclear expression of Bcl-10, or lymphomas associated with underlying autoimmune disorders.[9] However, eradication should still be pursued in these patients. An algorithm for the management of MALT lymphoma is presented in Figure 81–14.

There are no treatment guidelines for the management of patients who experience antibiotic failure. Surgical therapy is highly curative for localized tumors, but many gastric lymphomas disseminate widely within the mucosa, with frequent tumor relapse in the gastric stump and eventual need for total gastrectomy, which has a significant impact on quality of life.[9] Thus, a multimodal approach consisting of any combination of chemotherapy, radiation therapy, and surgery is common.[4] Chemotherapy with a single alkylating agent, such as cyclophosphamide or chlorambucil, is useful either alone or as an adjunct to surgical resection for *H. pylori* eradication–resistant MALT lymphomas.[9,35] Combination chemotherapy with CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine], and prednisone), with the possible addition of rituximab (a chimeric monoclonal antibody against the CD20 B-cell antigen), is preferred for the treatment of high-grade MALT lymphoma or DLBCL.[35-37] MALT lymphomas are also highly radiosensitive, and the use of low-dose localized radiation alone is highly effective in the management of lymphomas unresponsive to *H. pylori* eradication, with a 5-year survival rate of greater than 90%.[9] The combination of surgery and radiotherapy has been advocated for management of low-grade disease, with the addition of chemotherapy for high-grade disease, but no consensus has been reached.[4,36]

Intestinal Lymphoma

Patients with lymphoma of the intestine who are *H. pylori* positive benefit from eradication therapy, as with gastric lymphoma.[11] Initial management of stage I or II small bowel lymphoma should otherwise include segmental surgical resection with regional lymph node excision, regardless of patient age or lymphoma type, given the increased risk for perforation and obstruction associated with these tumors (Fig. 81–15).[2] An aggressive multimodal therapeutic approach combining both surgical resection and polychemotherapy can improve the outcome in patients with all intestinal lymphoma variants, but decisions on the appropriate course of therapy must be made on an individual basis.[11,38] The most commonly applied chemotherapy regimen for patients with intestinal DLBCL or MALT lymphoma is CHOP, with the addition of rituximab in those with mantle cell or follicular variants.[2,11] Treatment of Burkitt's lymphoma is similar to CHOP, with the substitution of methotrexate for prednisone.[2] T-cell lymphomas are notoriously chemotherapy resistant; the best chance for cure in this patient population is achieved by enrollment in clinical trials.[2] Radiotherapy is infrequently used in the treatment of intestinal lymphomas because of a high risk of late complications.[38]

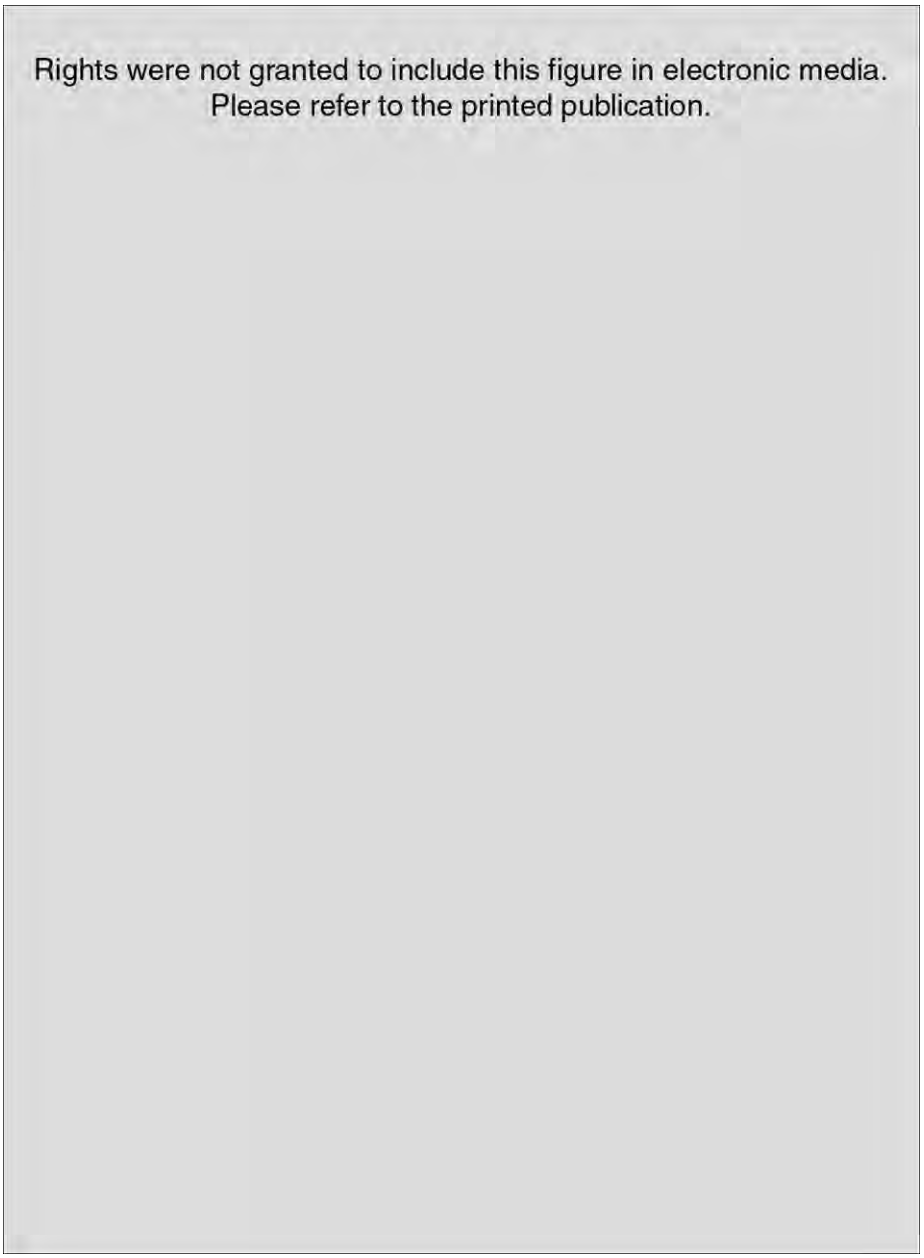

Figure 81–14. Algorithm for the management of primary gastric lymphoma. **A,** Low grade; **B,** high grade. (From Yoon S, Coit DG, Portlock CS, et al: The diminishing role of surgery in the treatment of gastric lymphoma. Ann Surg 240:28-37, 2004.)

PROGNOSIS

Factors affecting prognosis in patients with GI lymphoma include lymphoma type, grade, stage, location, molecular markers, genetic rearrangements, and age of the patient. MALT and MALT-derived lymphomas have the best overall prognosis, regardless of location.[2,11] Gastric lymphomas have a better overall prognosis than intestinal lymphomas do; 5-year survival rates for tumors localized to the stomach are approximately 91% for low-grade, 73% for secondary high-grade, and 56% for primary high-grade tumors, whereas the 5-year survival rate for aggressive small intestinal lymphomas is approximately 25% to 30%.[5,6,39] Intestinal B-cell lymphomas are associated with a better prognosis than those of T-cell origin, with average 5-year survival rates of 75% and 25%, respectively.[5,40]

SUMMARY

GI lymphomas are a diverse group of neoplasms that are often associated with vague symptoms that imitate common intra-abdominal pathologies; a high degree of suspicion is frequently required to make the diagnosis. Many advances have been made in the diagnosis and management of GI lymphomas over the past decade. The importance of *H. pylori* infection to the development of lymphomas has only recently been realized, and this realization has revolutionized treatment of the disease. Gastric lymphoma, once a surgical disease, is now managed conservatively, with *H. pylori* eradication being central to treatment. Although surgery remains the mainstay of treatment of small intestinal lymphoma, *H. pylori* eradication has proved to be a useful adjunct in its management as well.

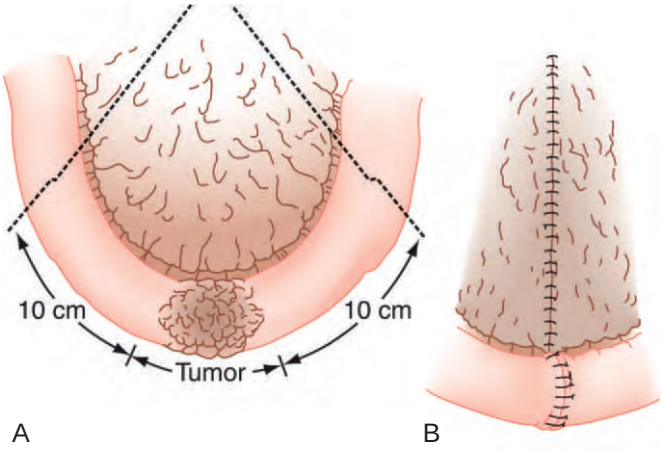

Figure 81–15. Segmental surgical resection of the small intestine. **A,** Malignant tumors should be resected with a wide margin of normal bowel and a wedge of mesentery to remove the immediate draining lymph nodes. **B,** End-to-end anastomosis of the small bowel and repair of the mesentery. (Adapted from Thompson JC: Atlas of Surgery of the Stomach, Duodenum and Small Bowel. St Louis, Mosby–Year Book, 1992, p 299.)

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Chapter

82

Surgical Conditions of the Small Intestine in Infants and Children

Marshall Z. Schwartz ▪ Ahmed Mami

Conditions of the small intestine in infants and children can be categorized into congenital abnormalities and acquired abnormalities. These two categories combined represent the majority of abdominal surgical emergencies in infants and young children. They are also the major cause of mortality. The advent of new and better imagining technologies has led to more precise and earlier diagnosis. For example, detailed fetal ultrasonography and fetal magnetic resonance imaging are more precise than they were 5 to 10 years ago. In addition, new minimally invasive surgical approaches have allowed for more rapid recovery.

Congenital abnormalities refer to developmental anomalies such as malrotation. Acquired abnormalities are entities that evolve after birth.

Congenital abnormalities covered in this chapter include malrotation, intestinal atresia, duplications, meconium obstruction, and omphalomesenteric duct remnants. Acquired lesions include necrotizing enterocolitis and intussusception.

Over the past 8 to 10 years two significant changes have occurred in the evaluation and treatment of many of the conditions discussed in this chapter. Imaging technology and techniques have continued to improve, which allows for more precise diagnosis. Although it could be stated that the usual approach to surgical problems in children is minimally invasive (i.e., through very small incisions), the use of laparoscopic techniques with very small ports (3 mm) and instruments has become common in pediatric surgery.

MALROTATION

The term *malrotation* refers to incomplete midgut rotation and fixation during in utero development. Thus, a more appropriate term would be *incomplete rotation*. The midgut, which is supplied by the superior mesenteric vessels and extends from the duodenojejunal junction to the midtransverse colon, remains unfixed and suspended on a narrow mesentery. This abnormal anatomy predisposes the midgut to life-threatening volvulus. Although this condition was first described by Mall in 1898,[1] it was William Ladd who described the currently used principles of malrotation repair in 1936.[2]

The primitive gut is recognized as a straight tube in the fourth week of embryologic development (Fig. 82–1). Rapid growth plus elongation of the midgut starting in the fifth week leads to herniation of the midgut with the superior mesenteric vessels as its stalk. This results in the formation of a physiologic umbilical hernia at the base of the umbilical cord. The midgut undergoes 270-degree counterclockwise rotation around the superior mesenteric vessels. This initial rotation results in the normal position of the duodenojejunal flexure in the left upper quadrant at the level of the gastric antrum. The duodenojejunal flexure becomes fixed to the posterior abdominal wall by the ligament of Treitz. As a result of this rotation and fixation, the third portion of the duodenum lies posterior to the superior mesenteric artery (SMA). In the 10th week the herniated intestinal loop begins to return to the abdominal cavity. The cecocolic loop undergoes another 270-degree counterclockwise rotation around the SMA, which leads to the normal position of the cecum in the right lower quadrant. Subsequently, the ascending colon and descending colon become fixed to the posterior abdominal wall. During the fourth and fifth weeks of gestation, the small intestine mesentery attaches itself to the posterior abdominal wall in a broad base extending diagonally from the duodenojejunal flexure to the cecum.

There are several degrees of rotational abnormality. Nonrotation is characterized by failure of counterclockwise rotation after return of the midgut to the

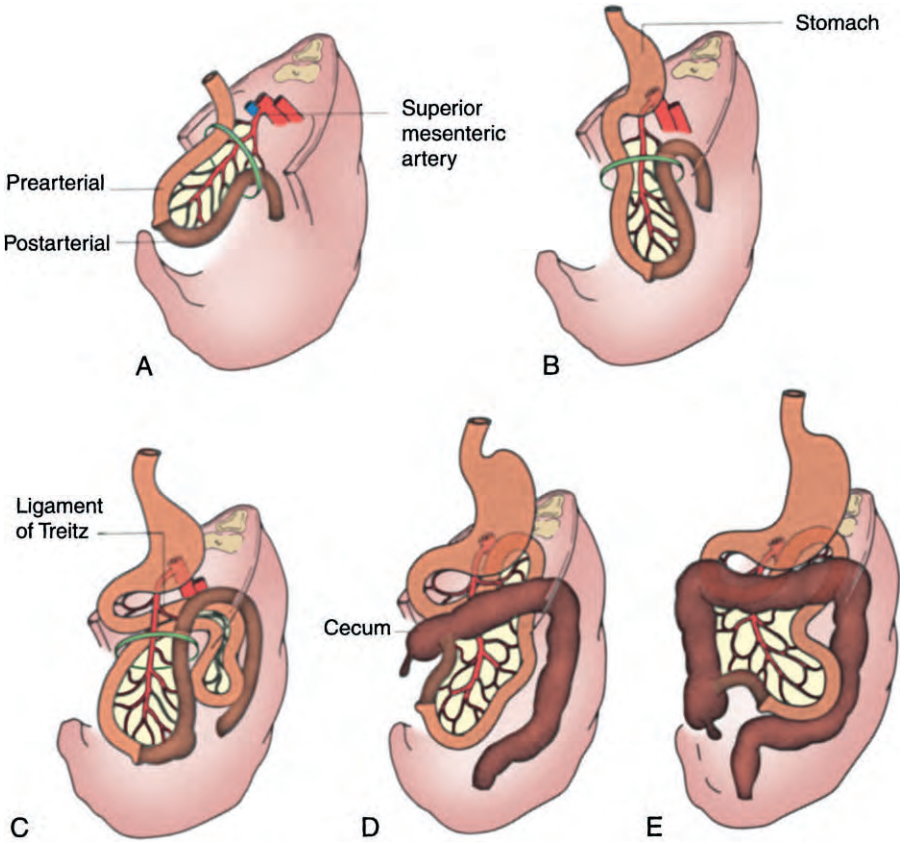


Figure 82–1. Normal midgut rotation is shown beginning in the 5th gestational week **(A)** through completion of the process in the 12th week **(E)**. (From Ashcraft KW, Holder TM [eds]: Pediatric Surgery. Philadelphia, WB Saunders, 1999.)

abdominal cavity (Fig. 82–2A). In incomplete rotation, the counterclockwise rotation is arrested at around 180 degrees. These are the most common forms of malrotation. The small intestine lies on the right side with the duodenojejunal flexure to the right of the vertebral column, and the duodenum has a corkscrew configuration. The large intestine lies on the left side with the cecum at abnormal locations, usually in the midline. Other forms of fixation anomalies may be due to failure of fixation of the ascending colon in the right hypochondrium. Associated with this abnormal fixation is a narrow intestinal mesentery and Ladd's bands. Ladd's bands represent the retroperitoneal attachments that normally fix the cecum and ascending colon to the posterior abdominal wall. Because the right colon is more medial, the bands extend across the duodenum from the right upper quadrant to the cecum and ascending colon. In reverse rotation, part of the rotation occurs in a clockwise direction around the SMA (see Fig. 82–2D). The duodenum assumes an anterior position and the colon lies posterior to the duodenum and the SMA. If the counterclockwise rotation extends beyond 270 degrees, the cecum comes to rest in the left hypochondrium position (see Fig. 82–2E). This rare form is called hyper-rotation. Other forms of fixation anomalies may be due to failure of fixation of the ascending or descending colon to the posterior abdominal wall. In this condition, the small intestine is at risk of entrapment in the potential space between the mesocolon and the posterior abdominal wall and is referred to as a mesocolic or paraduodenal hernia (see Fig. 82–2F). Lesser degrees of malrotation may affect only the cecocolic loop. Although the duodenum may lie in a normal position, the cecum remains unfixed and in an abnormal position with Ladd's bands. These patients are at risk for duodenal obstruction and cecal volvulus.

Patients with malrotation have a 30% to 62% risk of having associated anomalies, and most involve the gastrointestinal tract.[3] Five percent to 26% are associated with duodenal or other small intestinal atresias. Other less common anomalies include imperforate anus, cardiac anomalies, duodenal web, Meckel's diverticulum, and trisomy 21. Rare associations include biliary atresia, esophageal atresia, mesenteric cyst, Hirschsprung's disease, and craniosynostosis. Malrotation is always present in infants with congenital diaphragmatic hernia, omphalocele, and gastroschisis.

Malrotation is documented in 0.5% of autopsy studies,[4] although the incidence of clinically symptomatic malrotation is estimated to be 1 in 6000 live births.[5] Malrotation may initially be recognized at any age, but in approximately 90% of patients symptoms develop before 1 year of age, with 50% to 75% appearing within the first month of life.[6-8]

Malrotation can be totally asymptomatic and discovered only during work-up for an unrelated condition or during an autopsy examination. The initial symptoms depend on the cause. Neonates typically have bilious emesis, which may be the only initial symptom of midgut volvulus. If the diagnosis is delayed and the bowel

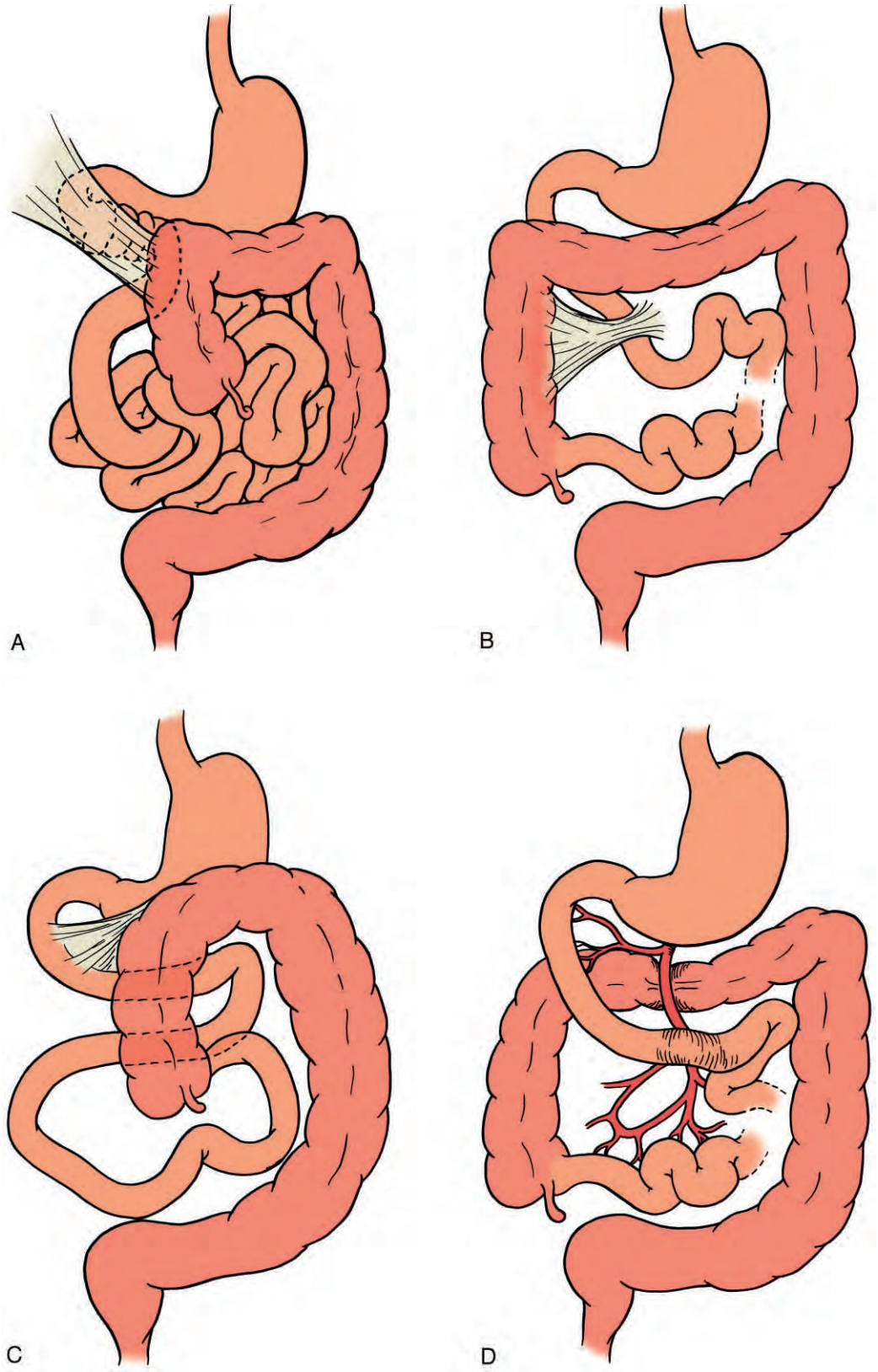


Figure 82–2. **A,** Complete nonrotation of the midgut. Neither the duodenojejunal junction nor the cecum has rotated around the superior mesenteric artery (SMA). All of the small bowel lies to the right of the SMA, and all of the colon lies to the left. This anomaly is the most frequent type of malrotation, and the risk for midgut volvulus is ever present. **B,** Nonrotation of the duodenojejunal junction with normal rotation of the cecum. This abnormality may be manifested clinically as duodenal obstruction as a result of abnormal mesenteric (Ladd's) bands from the colon across the anterior duodenum. **C,** Normal rotation of the duodenojejunal junction with nonrotation of the cecum. These patients are at risk for midgut volvulus. **D,** Reverse rotation of the duodenojejunal junction passing ventral rather than dorsal to the SMA, followed by reverse rotation of the colon (the cecum rotating dorsal rather than ventral to the SMA). This abnormality may be manifested clinically as obstruction of the transverse colon.

Continued

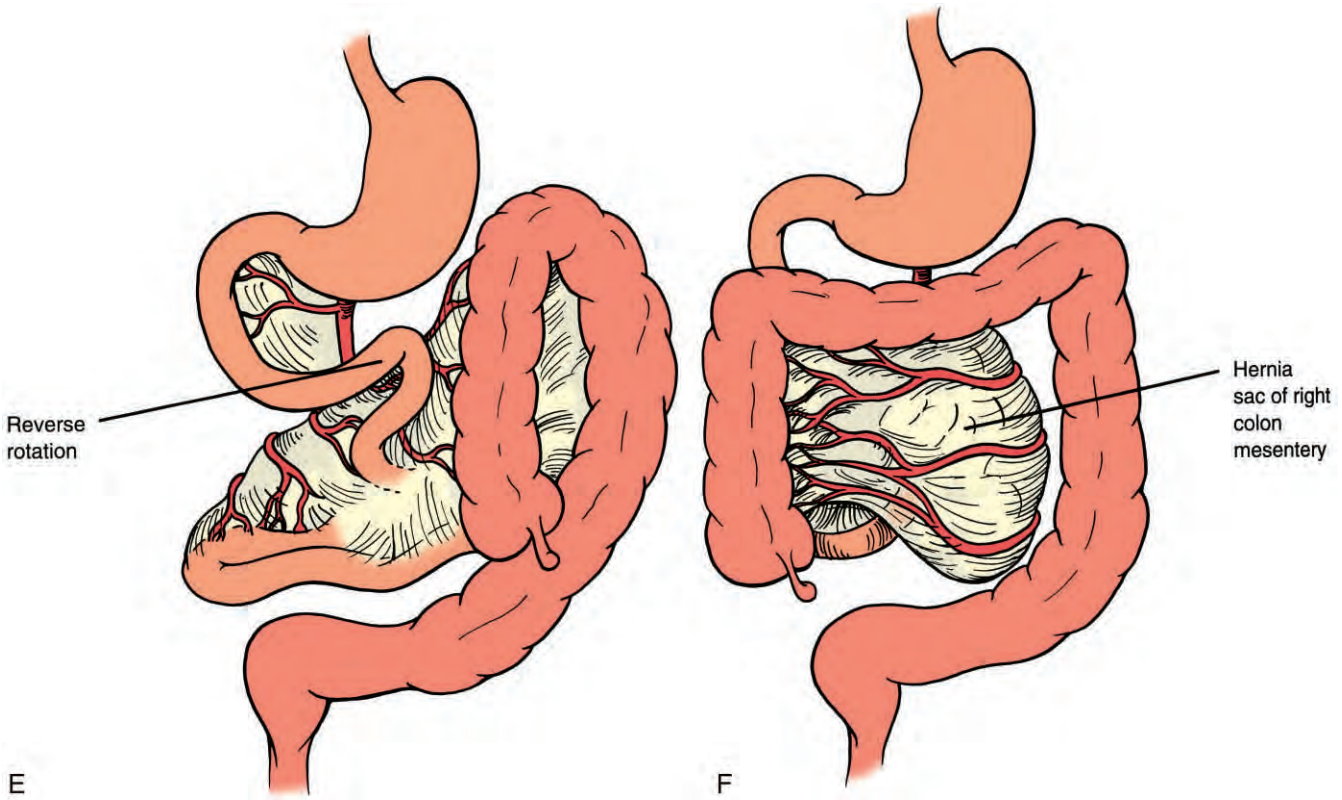


Figure 82–2, cont'd. **E,** Reverse rotation of the duodenojejunal junction (passing ventral rather than dorsal to the SMA), followed by normal rotation of the colon. **F,** A paraduodenal hernia sac is created by the mesentery of the colon as the cecum passes over the small intestine to lie in the right lower quadrant. (From Oldham KT, Colombani PM, Foglia RP [eds]: Surgery of Infants and Children: Scientific Principles and Practice. Philadelphia, Lippincott-Raven, 1997.)

becomes ischemic, the infant will demonstrate systemic signs such as increasing lethargy with poor perfusion, temperature instability, cardiopulmonary compromise, and low urine output. The patient may deteriorate to septic shock and multiorgan failure with other signs such as melena, hematemesis, and peritonitis. Hematologic studies may show metabolic acidosis, thrombocytopenia, and leukopenia. Malrotation without volvulus may be manifested as chronic, vague abdominal pain, with or without intermittent bilious emesis, and failure to thrive.

Successful treatment of malrotation depends on early diagnosis. The acute onset of bilious vomiting in a neonate is a sign of malrotation until proved otherwise. It demands immediate radiologic evaluation. The gold standard test for the diagnosis of malrotation is an upper gastrointestinal contrast study. Malrotation is diagnosed by an abnormal position of the ligament of Treitz. The normal location is typically to the left of the vertebral column and posterior to the stomach. In the absence of a ligament of Treitz, the duodenum remains to the right of the spine. Another possibility is that the duodenojejunal flexure crosses to the left of the vertebral column but lies below the level of the gastric antrum. Volvulus can be diagnosed by contrast-enhanced upper gastrointestinal series showing a corkscrew configuration of the upper portion of the small intestine (Fig. 82–3) or a "bird's beak" appearance at the third portion of the duodenum (Fig. 82–4). It must be emphasized that plain abdominal radiographs are not helpful in ruling in or out midgut volvulus.[4] The abdominal radiograph may show a wide range of abnormalities, including a dilated stomach and proximal duodenum, similar to a "double-bubble" sign, a paucity of abdominal gas, or dilated bowel loops with multiple air-fluid levels, or the radiograph may appear normal. A contrast enema study is not part of the work-up for malrotation. The presence of a normally located cecum in the right lower quadrant does not rule out malrotation. Abdominal ultrasonography may be used to study the position of the superior mesenteric vein (SMV) in relation to the SMA. Normally, the SMV lies to the right of the SMA. An abnormal position of the SMV in relation to the SMA may indicate the presence of malrotation with volvulus.

Children who are acutely ill with peritonitis need emergency surgery without radiologic studies. Patients who are symptomatic from volvulus as a result of malrotation should undergo nasogastric decompression, be resuscitated with intravenous fluid, and receive broad-spectrum antibiotics. Blood samples should be sent for laboratory analysis, including a complete blood count and type and crossmatching. The patient should be taken to the operating room urgently. Unnecessary delay may further compromise the bowel and lead to infarction.

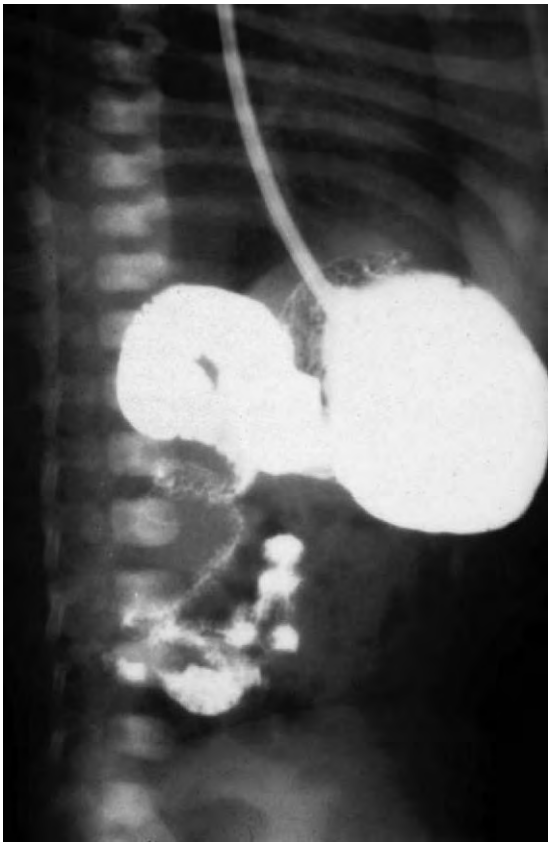


Figure 82–3. Midgut volvulus. A spot film from an upper gastrointestinal series demonstrates a distended, contrast-filled stomach with corkscrew configuration of the proximal part of the small bowel. (Courtesy of A. B. Campbell, MD, St. Christopher's Hospital for Children.)

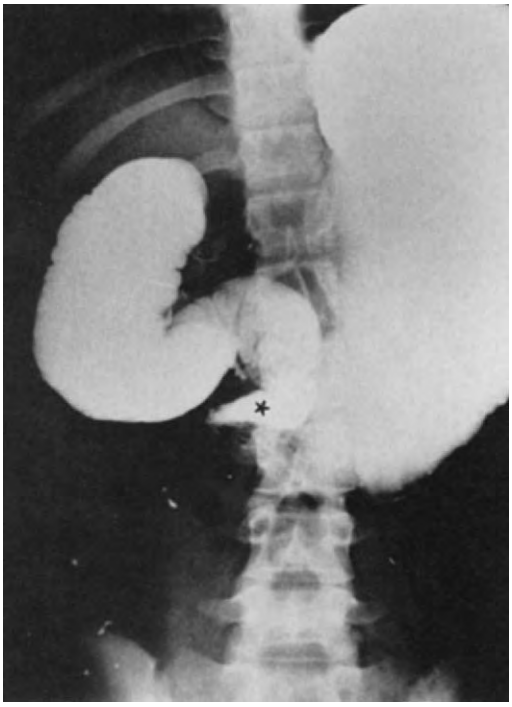


Figure 82–4. This upper gastrointestinal contrast study shows malrotation with volvulus. The "beak" is illustrated by the *asterisk*. Note the malposition of the distal duodenum as well. (From Oldham KT: Pediatric abdomen. In Greenfield LJ, Mulholland M, Oldham KT, et al [eds]: Surgery: Scientific Principles and Practice. Philadelphia, Lippincott-Raven, 1997.)

Children with vague chronic symptoms or children who are symptom-free should undergo elective correction.

The standard approach to correction of malrotation has been via a right upper quadrant transverse incision. However, a Ladd procedure in the absence of volvulus can be performed laparoscopically as long as there is no question of bowel compromise. The entire small intestine is eviscerated and carefully examined for the presence of volvulus (Fig. 82–5). If volvulus is present, it should be reduced by counterclockwise rotation as necessary because volvulus usually occurs in a clockwise direction. The bowel is assessed for viability. Mild to moderately ischemic bowel resumes its normal color after reduction of the volvulus. Bowel with uncertain viability should be wrapped with warm moist gauze sponges for at least 15 minutes. Frankly gangrenous bowel should be resected and a stoma or stomas fashioned. Bowel with marginal viability should be left in continuity if possible with a view to perform a second-look operation 24 to 36 hours later. At the second operation any necrotic bowel should become obvious, and further resections may be necessary. After reducing the volvulus if it is present, Ladd's bands, which represent the posterior peritoneal attachments of the right colon that cross over the duodenum, should be divided on the lateral aspect of the duodenum (Fig. 82–6). Widening of the mesenteric base is necessary, and the duodenum is mobilized and straightened by dividing the abnormal ligament of Treitz and Ladd's bands. The duodenum is carefully examined for intrinsic obstruction. If there is any doubt, a balloon catheter can be passed transorally and manipulated into the upper jejunum. An inability to pass the catheter or to pull the catheter back with the balloon inflated indicates the presence of intrinsic obstruction. Incidental appendectomy should be performed to avoid diagnostic confusion in the future because the cecum will be placed in the left lower quadrant. The intestine is returned to the abdominal cavity, starting with the duodenum and proximal jejunum, which are placed on the right side, and ending with the terminal ileum and cecum, which are placed in the left hypochondrium.

Postoperative care of these patients includes nasogastric decompression and intravenous fluid until return of bowel function. Prolonged ileus is not unusual postoperatively, especially if volvulus was present. Postoperative complications include bleeding and recurrent volvulus. The latter is rare if the initial operation is technically complete. The most serious complication is short-gut syndrome as a result of volvulus and bowel necrosis requiring extensive small bowel resection.

The operative mortality of Ladd's procedure ranges from 3% to 9%,[3] with the higher mortality being

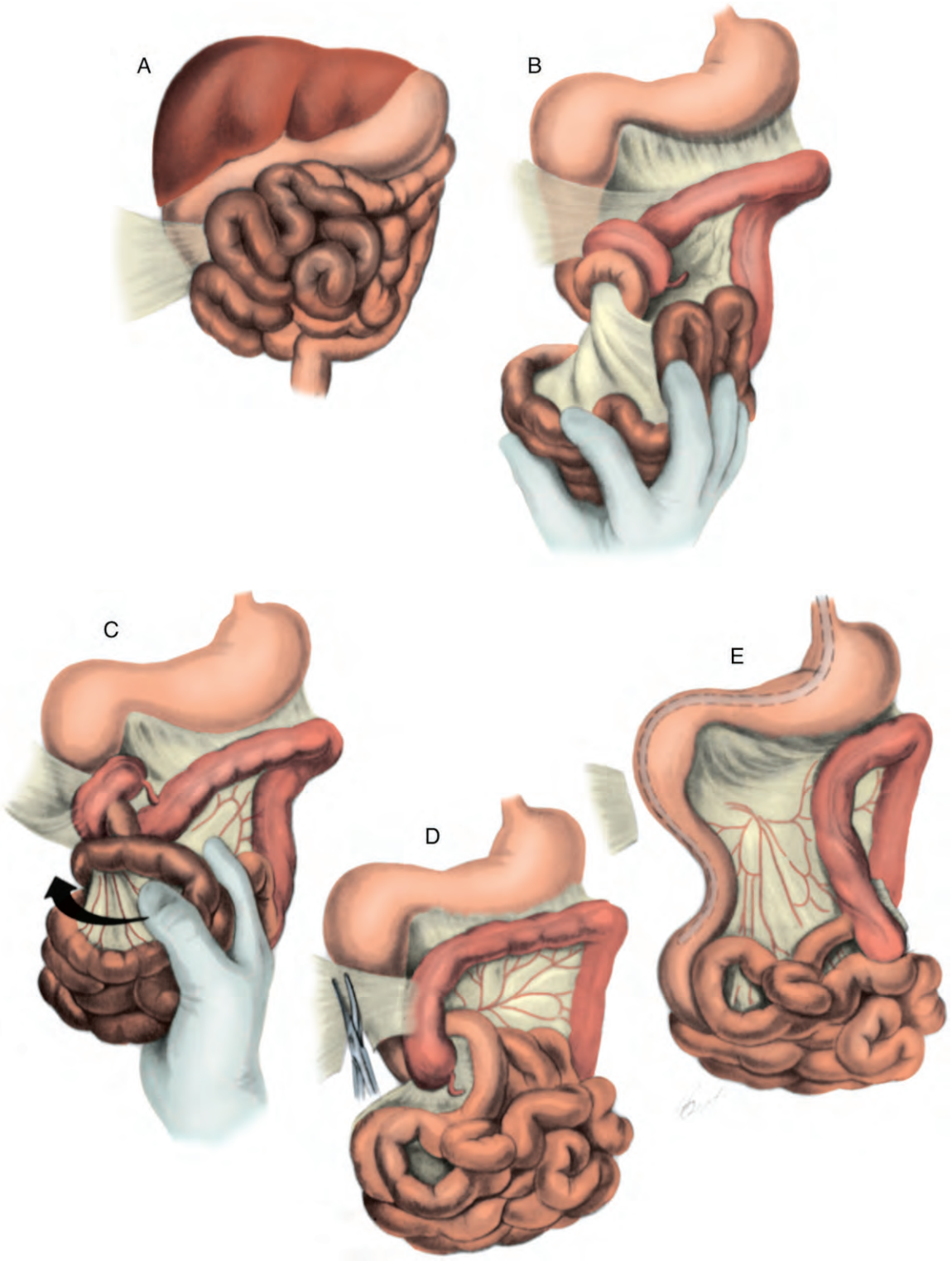


Figure 82–5. Malrotation of the intestine. **A,** Appearance of the viscera as the abdominal cavity is opened. The small intestines are seen at once and seem to hide the colon. Vascular compromise of the intestine may be obvious. **B,** The entire intestinal mass is delivered out of the wound and drawn downward to reveal the base of the mesentery. Coils of intestine or ascending colon are wrapped around the root of an incompletely anchored mesentery. The volvulus has taken place in a clockwise direction. The descending duodenum is dilated because of extrinsic pressure from Ladd's bands or peritoneal folds that cross it. **C,** The volvulus is reduced by taking the entire intestinal mass in the hand and rotating it counterclockwise (in most cases). **D,** With reduction of the volvulus, the cecum lies in the right paravertebral gutter. The peritoneal folds from the cecum obstruct the duodenum. The folds are incised close to the lateral serosal border of the duodenum. The underlying superior mesenteric pedicle is identified and carefully preserved. **E,** Appearance of the intestines and ascending colon at the end of surgery. The duodenum descends along the right gutter. The small intestines lie on the right side of the abdomen, and the cecum and ascending colon are in the midline or left side of the abdomen. The superior mesenteric artery and its branches are left exposed as shown. A nasogastric tube has been passed into the jejunum to exclude intrinsic obstruction. (From O'Neill JA Jr, Rowe MI, Grosfeld JL, et al [eds]: Pediatric Surgery. St Louis, Mosby–Year Book, 1998.)

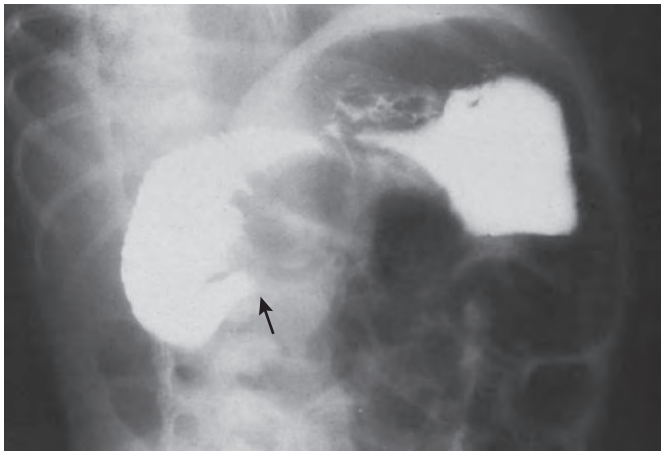


Figure 82–6. Ladd's bands. This upper gastrointestinal contrast study demonstrates the site of Ladd's bands. Cutoff of contrast is marked by an *arrow*.

associated with complete small intestinal necrosis, prematurity, or other serious congenital abnormalities.[9]

ATRESIA AND STENOSIS

Atresia and stenosis are among the most common causes of neonatal intestinal obstruction.[10] The reported incidence of jejunoileal atresia is about 1 in 1000 live births with a range of 1 in 300 to 1500 live births.[11-15] The most widely accepted cause of these defects is a localized intrauterine vascular accident leading to necrosis and resorption of the affected segments.[13] The vascular event can be thrombosis, embolism, intussusception, or volvulus. The general acceptance of this etiology is based in part on animal studies in which in utero occlusion of mesenteric vessels led to atresia.[13,16] The association of atresia with certain disease states such as gastroschisis and midgut volvulus adds weight to the ischemia/necrosis theory.[17]

The gender ratio is equal. Jejunal atresia is slightly more common than ileal atresia. In 80% to 90% of cases the atresia is isolated. However, in up to 20% of cases atresias are multiple.[10,18] Hence, it is important to evaluate the whole intestine for other atresias. In one study, about a third of patients had associated anomalies, predominantly gastrointestinal.[19] An important comorbid condition that can be overlooked in infants with jejunoileal atresia is cystic fibrosis. The reported incidence is 10% to 20%.[18-21] White infants with jejunoileal atresia have more than 210 times the risk for cystic fibrosis than white infants in the general population do.[22] These children should be screened routinely for cystic fibrosis.[20,23]

Small intestine atresias have been classified into four types (Fig. 82–7), and the outcome can vary significantly depending on the type. Intestinal atresia is being diagnosed more frequently with prenatal ultrasonography.[19] The more proximal small bowel atresias can be associated with maternal polyhydramnios as a result of decreased fetal intestinal absorption of amniotic fluid.[24] Ultrasonography may show dilated, fluid-filled intestinal loops. Antenatal diagnosis permits earlier recognition, which allows for more effective parental counseling and appropriate preparation for surgical intervention postnatally.[25] At the time of delivery, bile staining of amniotic fluid is associated with intestinal obstruction.[26]

Infants with atresia or stenosis usually have bilious vomiting on the first day of life. However, in about 20% of cases, the vomiting may be delayed for 24 hours.[13,27] The higher the obstruction, the earlier the vomiting. Abdominal distention is more pronounced with distal obstruction. More than 60% of these infants fail to pass meconium in the first day of life.[10,13] They may have grayish mucoid contents in the rectal vault. Other associated symptoms and signs include fever, dehydration, aspiration pneumonia, and unconjugated hyperbilirubinemia. The latter may be due to impairment of the enterohepatic circulation.[18] Examination of the abdomen may also reveal signs of peritonitis or ischemia, such as tenderness, edema, and erythema of the abdominal wall. The clinical manifestations of intestinal stenosis are more subtle, with intermittent partial bowel obstruction, malnutrition, and failure to thrive. The initial findings in infants with intestinal stenosis may be unremarkable, but higher-grade bowel obstruction ultimately develops and requires surgical intervention.

Abdominal radiographs show gas- and fluid-filled bowel loops with absence of gas distally (Fig. 82–8A). In proximal obstruction, there are fewer distended bowel loops. Distal ileal atresia may be difficult to differentiate from meconium ileus or colonic obstruction. In patients with atresia or meconium ileus, a contrast enema will show a microcolon and small, unused distal ileum (see Fig. 82–8B). In meconium ileus, some of the contrast may outline the impacted stool and thus make the diagnosis. In colonic atresia, contrast will not demonstrate the cecum or ileocecal valve. Ten percent of patients with atresia have meconium peritonitis from in utero bowel perforation.[10,18]

Management of infants with atresia includes intravenous fluid, decompression of the stomach, withholding of enteral feeding, and administration of antibiotics. After resuscitation the infant is taken to the operating room for exploratory laparotomy. The goals of the operation are to restore intestinal continuity after resection of the atretic segment while preserving intestinal length. Through a right upper or lower quadrant transverse incision, the small bowel is eviscerated. A transition point is usually identified. Normal saline is injected distal to the transition point and milked more distally to rule out other obstructions. If the proximal dilated bowel appears ischemic and nonviable, it should be resected. Resection of massively dilated proximal bowel may expedite bowel recovery postoperatively. A tapering procedure may be performed in the proximal bowel segment. It is important to note that in atresia the proximal blind end is dilated and hypertrophied with ineffective peristaltic activity.[28] It is also deficient in mucosal enzymes and muscular adenosine triphosphate.[29] Although dysmotility resolves after removal of the obstruction, recovery may take longer in patients with very dilated bowel loops. The

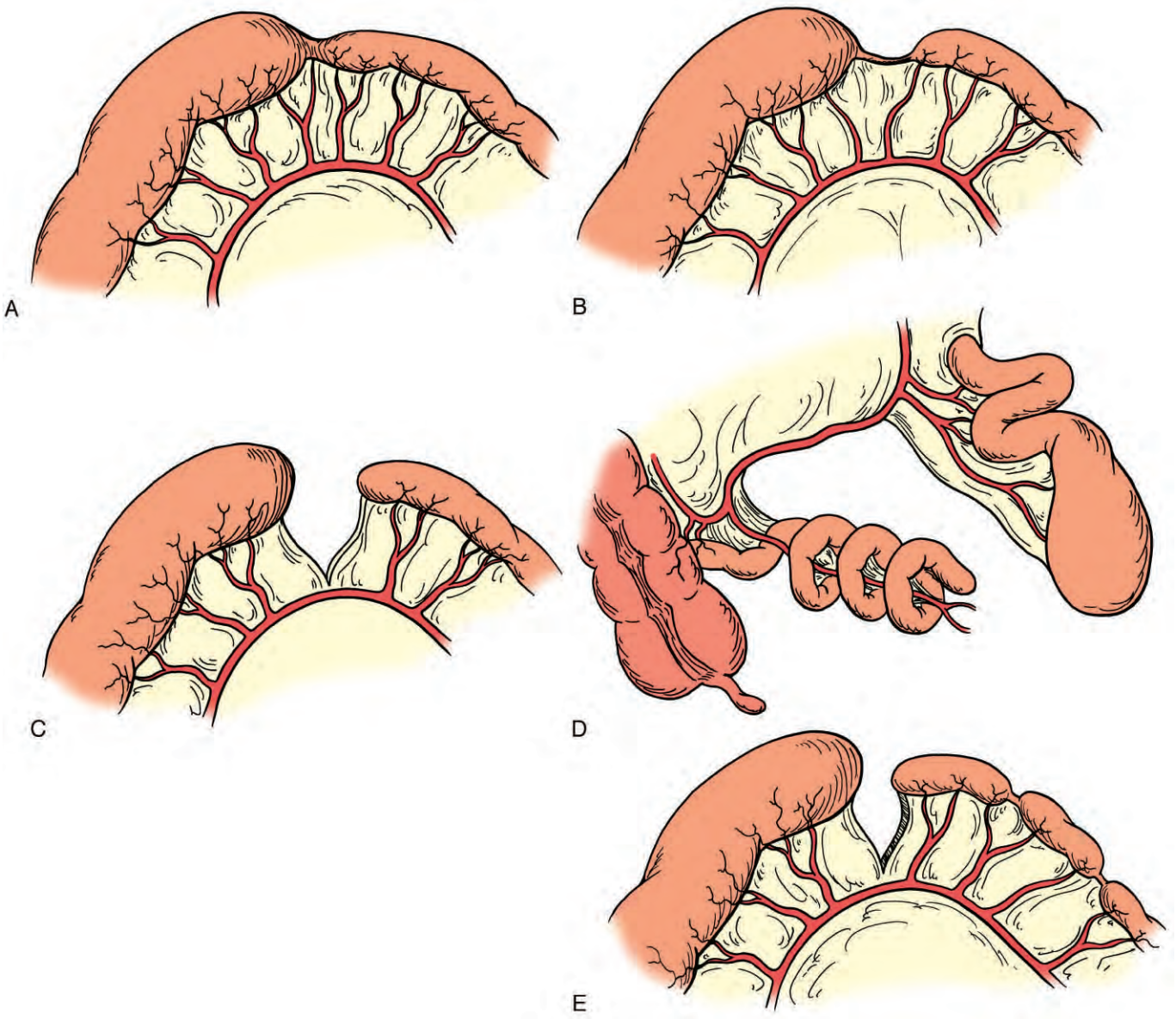


Figure 82–7. Classification of intestinal atresia. **A,** Type I, membranous atresia with intact bowel and mesentery. **B,** Type II, blind ends separated by a fibrous cord. **C,** Type IIIa, blind ends separated by a V-shaped mesenteric defect. **D,** Type IIIb, "apple peel" atresia. **E,** Type IV, multiple atresias ("string of sausages"). (From Oldham KT, Colombani PM, Foglia RP [eds]: Surgery of Infants and Children: Scientific Principles and Practice. Philadelphia, Lippincott-Raven, 1997.)

tapering procedure can be performed by resecting a part of the antimesenteric side of the bowel with a stapling device. Another technique to reduce the caliber of the proximal part of the bowel is imbrication of the antimesenteric side with running suture. Studies suggest that bowel plication may prevent disturbed intestinal transit postoperatively.[30] Continuity of the bowel is achieved by an end-to-oblique anastomosis after opening the distal part of the bowel and making a longitudinal antimesenteric incision to accommodate the difference in size between the proximal and distal bowel loops. Simple atresias of the small intestine can be managed with "laparoscopic assistance" by identifying the anatomy laparoscopically, bringing the atretic ends out through an enlarged umbilical port incision, performing the anastomosis extraperitoneally, and replacing it back through the umbilicus.

Infants with gastroschisis and intestinal atresia present a special problem. Atresia may be missed initially because of thick peel obscuring the bowel. It is preferred that the gastroschisis defect be repaired initially and the atresias be addressed after a period of bowel decompression and parenteral nutrition to give the peritoneal and bowel inflammation time to resolve. However, early enterostomy may be needed, especially in patients with complicated distal atresia.[31,32]

Postoperatively, parenteral nutrition is started pending return of bowel function. Proximal atresias tend

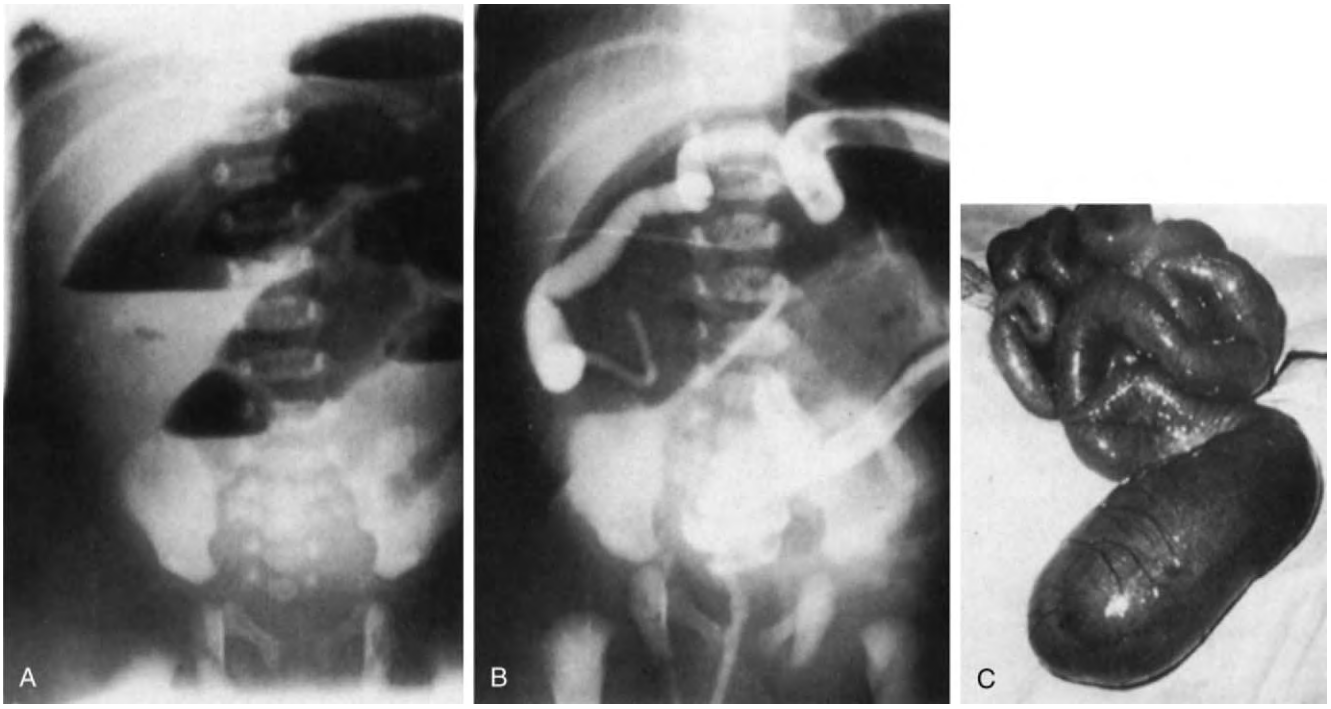


Figure 82–8. Ileal atresia. **A,** Erect abdominal radiograph showing distended intestinal loops with air-fluid levels. **B,** Contrast enema demonstrating a microcolon (unused), suggestive of small bowel obstruction. **C,** Atresia of the ileum (type IIIa) at laparotomy. (From O'Neill JA Jr, Rowe MI, Grosfeld IL, et al [eds]: Pediatric Surgery. St Louis, Mosby-Year Book, 1998.)

to take a longer time before return of bowel motility. Enteral feeding is started when the infant shows signs of return of bowel function. Passing of gas and stool together with decreasing and clearing of the gastric aspirate is a good indicator of return of bowel function.

The prognosis in these patients is excellent, with survival rates of 90%, as opposed to a mortality rate of 90% before 1952.[13] The reduction in mortality is probably due to improvements in neonatal care, nutrition, and surgical techniques. Anastomotic leak or stricture requiring surgical intervention develops in 10% to 15% of infants.[33] These patients are also at risk for adhesive bowel obstruction and necrotizing enterocolitis (NEC); however, these complications are infrequent. Extensive resection of the bowel can lead to short-bowel syndrome. Adaptation and recovery of bowel motility take 12 to 24 months in these patients.

DUPLICATIONS AND CYSTS OF THE SMALL INTESTINE

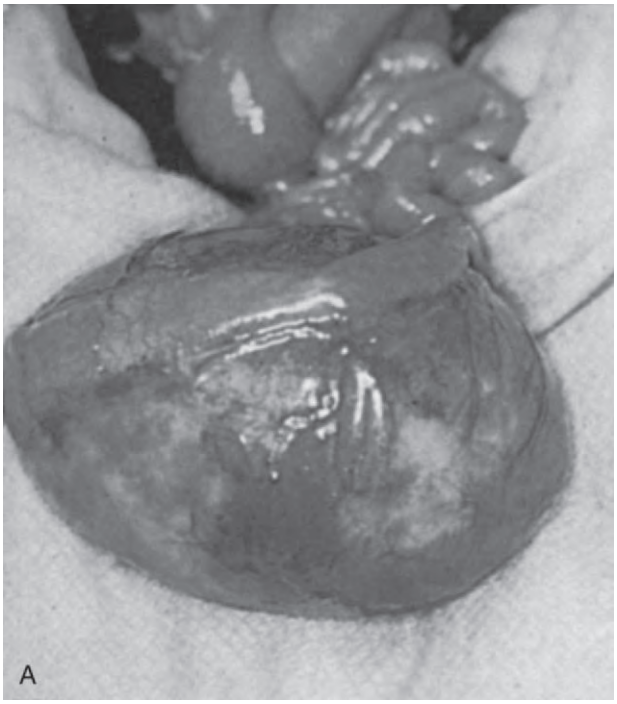
Three forms of cystic structures can be associated with the small intestine. Abnormalities that are in direct contact with the small intestinal wall are referred to as duplications because they contain all three layers of bowel. Two forms of duplication can occur. The most common is a spherical structure referred to as a *cystic duplication* (Fig. 82–9). These lesions do not have communication with the lumen of the normal small intestine. Another form of duplication is a *tubular duplication* (Fig. 82–10).

These duplications parallel the normal bowel lumen and share a common wall and blood supply with the adjacent bowel. They have a higher incidence of communication with the existing lumen of the small intestine and have a significant incidence of ectopic gastric mucosa.[34]

The second category of cystic structures consists of cysts that arise in the mesentery of the bowel, whereas the third category includes cysts that involve the omentum. Several theories have been proposed to explain the origin of these structures, but because of the numerous types of cysts in and around the small intestine, there is no common theory that best explains all of them.

The small intestine is the most common location for enteric duplications and accounts for more than half of such anomalies.[35] Twenty percent of the remaining duplications occur in the thorax and 5% are found at the junction of the thorax and abdomen. Seventy-five percent of enteric cysts do not communicate with the lumen of the bowel.[36] It is important to emphasize that both tubular and cystic duplications of the bowel share a common wall and a common blood supply with the adjacent normal intestine. It is also relevant that 25% of duplications contain ectopic tissue.[37] The most common ectopic tissue is gastric mucosa.

The clinical findings vary significantly, depending on the size and site of the duplication or cyst. Cystic duplications of the bowel are typically manifested as partial small bowel obstruction as a result of the cyst gradually



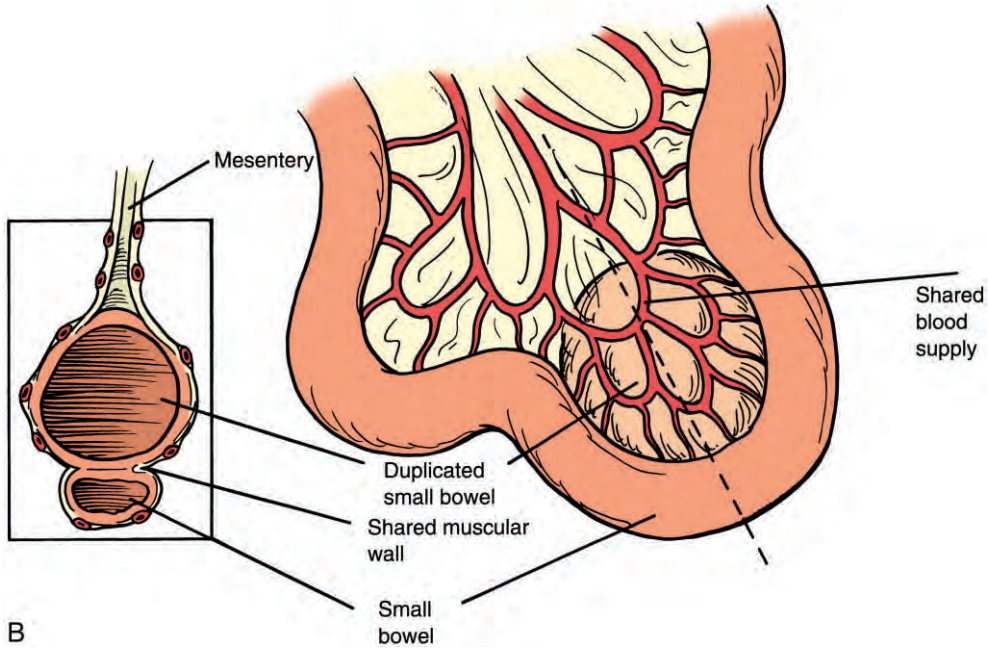


Figure 82–9. **A,** Large cystic duplication of the small intestine. (From Ashcraft KW, Holder TM [eds]: Pediatric Surgery. Philadelphia, WB Saunders, 1999.) **B,** Small bowel duplication in cross section demonstrating the common wall, shared blood supply, and intramesenteric location. (From Oldham KT, Colombani PM, Foglia RP [eds]: Surgery of Infants and Children: Scientific Principles and Practice. Philadelphia, Lippincott-Raven, 1997.)

enlarging and compressing the adjacent lumen. Tubular duplications of the bowel may likewise cause bowel obstruction. However, bleeding is also a common manifestation because of the high incidence of ectopic gastric mucosa with secondary ulcer formation. Very large mesenteric or omental cysts can be manifested as a palpable mass producing vague abdominal symptoms or pain.

Treatment of duplications of the small intestine depends on the specific findings and circumstances. Cystic duplications of the small intestine usually require resection of the adjacent bowel because of the shared common wall and blood supply. Tubular duplications that are relatively short (under 20 cm) can be resected along with the adjacent intestine. If the tubular duplication is extensive, which would result in major loss of

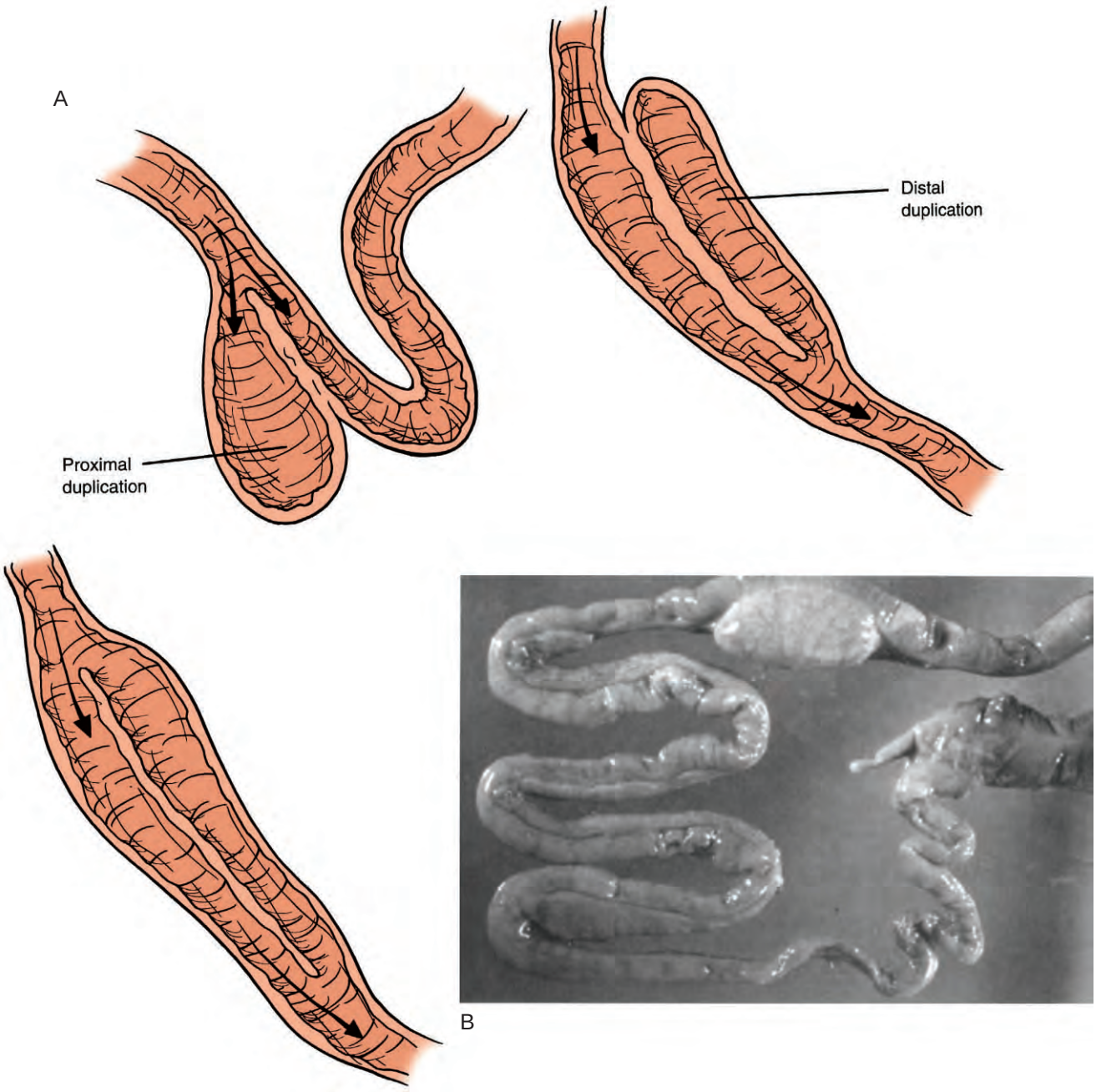


Figure 82–10. **A,** Schematic depiction of the various forms of communicating tubular duplications: duplication communicating proximally and forming a bulbous mass, duplication communicating distally and remaining clinically asymptomatic, and duplication communicating proximally and distally. **B,** Autopsy specimen showing a tubular small bowel duplication involving a portion of the ileum and much of the jejunum. (From Oldham KT, Colombani PM, Foglia RP [eds]: Surgery of Infants and Children: Scientific Principles and Practice. Philadelphia, Lippincott-Raven, 1997.)

normal small intestine, the duplication can be opened along its longitudinal direction and the mucosa of the duplication excised. Any communication with the adjacent normal small intestine would have to be closed.

Omental cysts can readily be removed by excising the adjacent omentum. Very large cysts can be decompressed by aspiration of fluid and therefore require less of an abdominal incision for removal. Treatment of cysts within the mesentery of the small intestine can be difficult if they are extensive and large. Every effort should be made to carefully dissect a mesenteric cyst to achieve complete removal. However, such dissection may not be safe because of extensive involvement of the blood supply to the small bowel. In these circumstances it may be necessary to leave some of the cyst behind.

The overall outcome of treatment of these cysts should be excellent. Recurrence is likely only in large mesenteric cysts, where complete excision might compromise the blood supply to the normal small intestine, and extensive tubular small intestinal duplications.

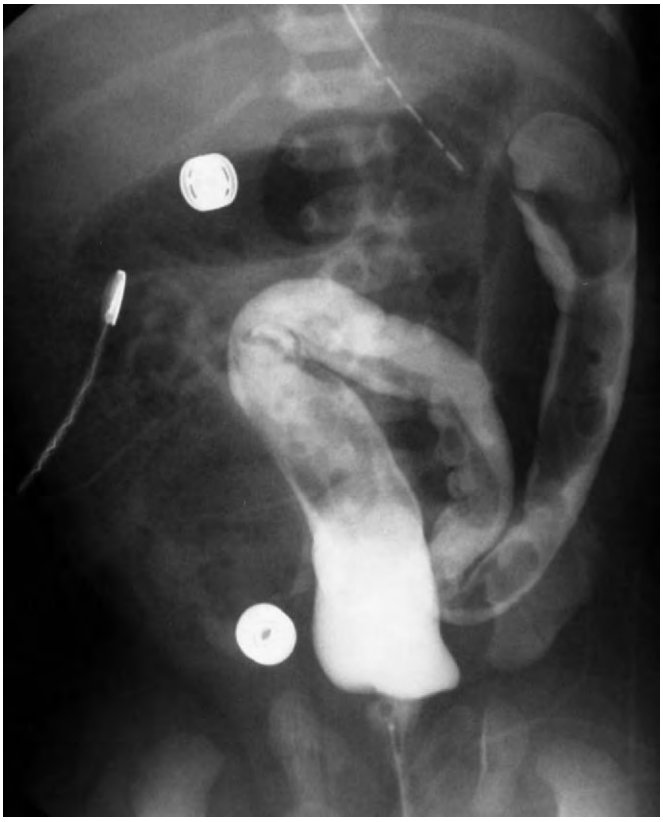


Figure 82–11. Image from a water-soluble contrast enema demonstrating an intraluminal meconium plug extending from the transverse colon to the rectum, as well as a small left colon. (Courtesy of A. B. Campbell, MD, St. Christopher's Hospital for Children.)

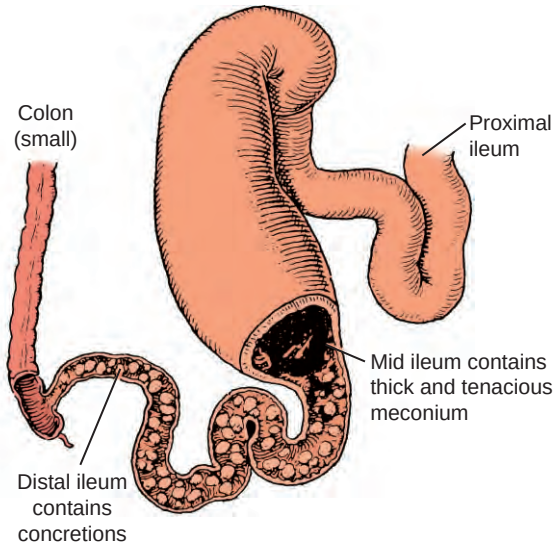


Figure 82–12. Schematic of meconium ileus. (From Lloyd DA: Meconium ileus. In Welch KJ [ed]: Pediatric Surgery, Chicago, Year Book Medical Publishers, 1986.)

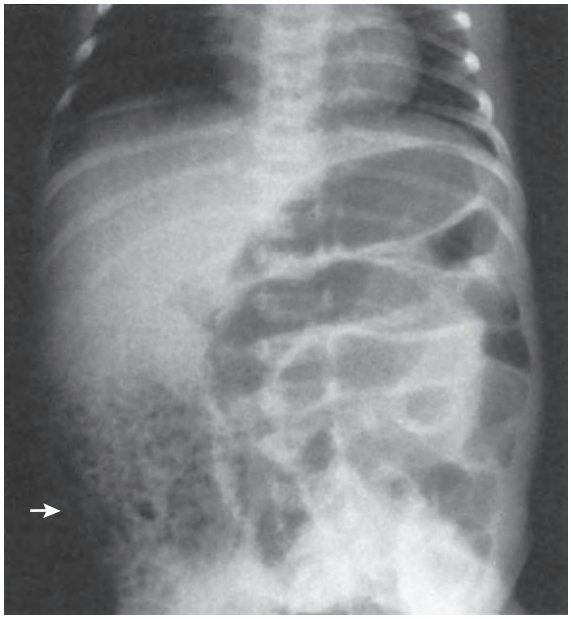


Figure 82–13. Plain abdominal radiograph of meconium ileus with distended loops of bowel and a mass of meconium *(arrow)* with a "ground glass" appearance from mixed air and stool. (From Ashcraft KW, Holder TM [eds]: Pediatric Surgery. Philadelphia, WB Saunders, 1999.)

MECONIUM SYNDROMES

Intestinal obstruction secondary to meconium impaction occurs frequently. In a newborn infant, entities such as meconium plug syndrome and small left colon syndrome can develop. These conditions involve meconium impaction in the descending and rectosigmoid colon. A water-soluble contrast enema is performed for diagnosis and treatment (Fig. 82–11). Passage of the meconium plug generally resolves the problem, with recurrence being uncommon.

Meconium ileus is a much more complicated entity characterized by meconium impaction beginning at the terminal ileum and extending proximally for various distances (Fig. 82–12). It can involve up to a third to half of the small intestine. Almost all infants with meconium ileus have cystic fibrosis with secondary pancreatic exocrine enzyme deficiency, which leads to thick, tenacious meconium. Cystic fibrosis, an autosomal recessive disease, results in chloride transport abnormalities produced by a defect in chromosome 7. The thickened secretions also affect the biliary tract, pancreas, and most commonly, the respiratory tract. Approximately 10% to 20% of cystic fibrosis patients will have meconium ileus.[38]

Meconium ileus is usually manifested at birth as abdominal distention and bilious vomiting. Plain abdominal radiographs demonstrate dilated bowel loops with a "ground glass" appearance in the right lower quadrant (Fig. 82–13).[39] These infants require resuscitation with intravenous fluids, bowel decompression, and broad-spectrum antibiotics. If there is no evidence of complicated meconium ileus, a water-soluble contrast enema should be performed. This study may be therapeutic as well as diagnostic. If meconium ileus is present, the goal of the study is to reflux the contrast past the obstructing

meconium and free it from adherence to the mucosa. A more hypertonic solution or a mucolytic substance (e.g., 4% Mucomyst) may enhance the effectiveness of the procedure. The success rate is 50%, but it is dependent on the length of bowel impacted with meconium.[40] Failure to relieve the obstruction after a few attempts is an indication for exploratory laparotomy.

A subset of these patients have complicated meconium ileus, which refers to evidence of perforation with free air, a meconium cyst, or atresia secondary to in utero perforation. The findings on the first day of life are indicative of bowel perforation, meconium peritonitis, volvulus, or atresia. Abdominal radiographs may show free air, free fluid, or calcifications in addition to bowel obstruction. A contrast study may be contraindicated in patients with complicated meconium ileus, or it may be performed for diagnosis only. If laparotomy is necessary, the usual approach is to irrigate the obstructing meconium with 4% acetylcysteine solution, which can be performed via a proximal enterotomy. The inspissated meconium may be gently milked out through the enterotomy or into the colon. Only a small subset of patients may require bowel resection and primary anastomosis. It would be unusual, but if the distal part of the bowel cannot be cleared of the obstructing meconium, an ostomy and mucous fistula should be created. The mucous fistula can be used to irrigate the bowel distally. Infants with complicated meconium ileus are managed operatively, with resection of atretic or necrotic bowel and exteriorization enterostomies possibly being required. The most complicated form is a meconium cyst secondary to in utero perforation (Fig. 82–14). In this situation the perforation does not close, and a large cyst that often fills the entire peritoneal cavity can develop. In such circumstances, finding the two ends of the bowel in the setting of generalized inflammation may be difficult.

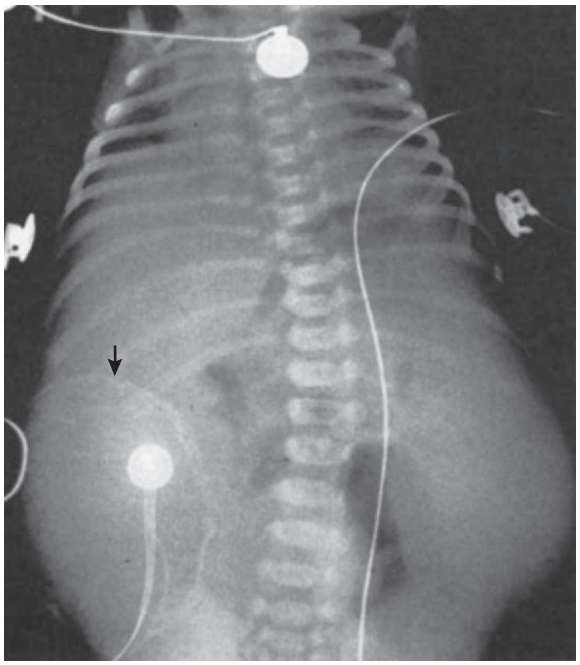


Figure 82–14. Abdominal radiograph of meconium peritonitis with a giant pseudocyst demonstrating calcification *(arrow)* in the cyst wall. (From Ashcraft KW, Holder TM [eds]: Pediatric Surgery. Philadelphia, WB Saunders, 1999.)

Spontaneous prenatal bowel perforation may lead to a condition known as meconium peritonitis. Postnatally, an abdominal radiograph may show scattered areas of calcification in the peritoneal cavity. In many cases the perforation seals and heals in utero and does not result in any postnatal bowel sequelae. The presence of pneumoperitoneum, intestinal obstruction, or clinical deterioration mandates surgical intervention, which usually involves resection of atretic or necrotic bowel with exteriorization.

MECKEL'S DIVERTICULUM AND OTHER OMPHALOMESENTERIC DUCT REMNANTS

The omphalomesenteric, or vitelline, duct is a remnant of the embryonic yolk sac. Remnants of these structures are the most common postnatal anomalies of the gastrointestinal tract (Fig. 82–15). The most frequently occurring residual of the yolk sac is a diverticulum arising from the antimesenteric border of the distal ileum, which has come to be known as *Meckel's diverticulum.* Knowledge of these omphalomesenteric duct remnants is important because complications related to these structures are numerous and may be life-threatening. It is estimated that a remnant of an embryonic yolk sac is present in 1% to 4% of all infants.[41] Although the incidence of omphalomesenteric duct remnants (especially Meckel's diverticulum) is high, the risk for development of symptoms from these anomalies is relatively low. The apparent risk of a complication developing as a result of Meckel's diverticulum is approximately 4%, with 80% of these patients initially being seen at younger than 10 years of age.[42]

Partial or complete failure of involution of the omphalomesenteric duct results in various residual structures, depending on the stage in which this process fails to progress.[41] The portion of the omphalomesenteric duct that does not become atretic will persist and develop along with the remainder of the gastrointestinal tract. Persistent patency of the omphalomesenteric duct can be determined by the 10th week of gestation.

There are many abnormalities that result from remnants of the embryonic yolk sac, and the various abnormalities can generally be categorized as either a patent omphalomesenteric (vitelline) duct, Meckel's diverticulum, omphalomesenteric cyst, omphalomesenteric duct remnants at the umbilicus, omphalomesenteric band, or vitelline blood vessel remnants.

Patent Omphalomesenteric (Vitelline) Duct

This structure represents a persistent connection between the distal ileum and the umbilicus and accounts for approximately 2.5% to 6% of the spectrum of

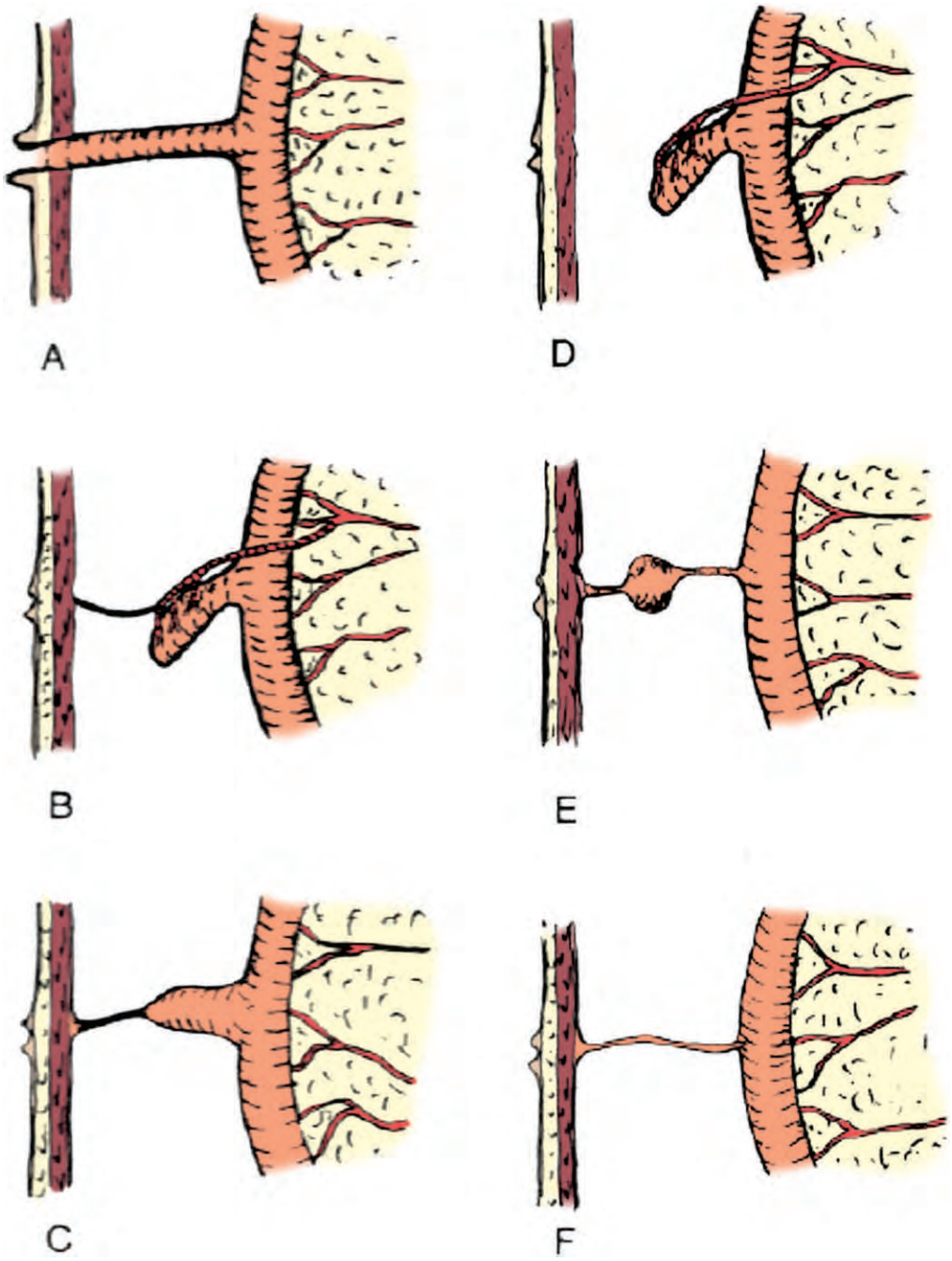


Figure 82–15. Illustrated are some of the more common residual congenital abnormalities that result from the embryonic yolk sac. **A,** Patent omphalomesenteric duct representing a communication from the terminal ileum to the umbilicus. **B,** Meckel's diverticulum with a patent right vitelline artery illustrated as a cord to the undersurface of the umbilicus. **C,** Meckel's diverticulum with a cord connecting the tip of the diverticulum to the undersurface of the umbilicus. The cord (band) represents the distal residual of the omphalomesenteric duct. **D,** Typical appearance of Meckel's diverticulum with persistence of the vitelline artery. **E,** Involution of the proximal and distal ends of the omphalomesenteric duct with a residual cord or band and central preservation of the omphalomesenteric duct resulting in a mucosa-lined cyst. **F,** Intraperitoneal band from the ileum to the undersurface of the umbilicus representing involution without resolution of the omphalomesenteric duct. (From Wyllie R, Hyams J [eds]: Pediatric Gastrointestinal Disease. Philadelphia, WB Saunders, 1999.)

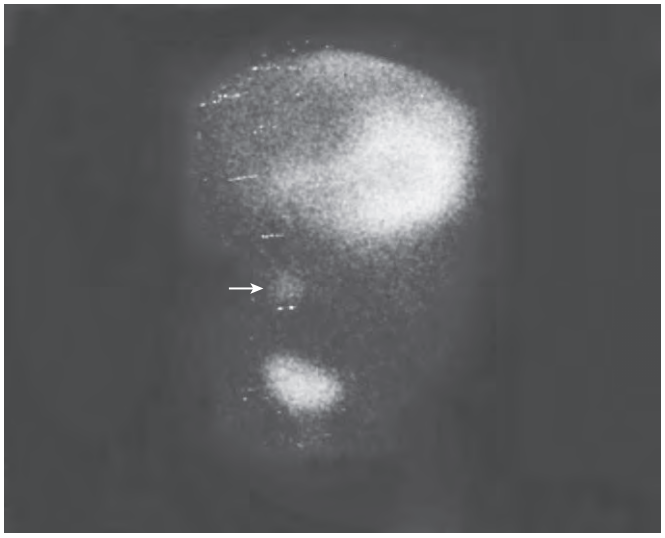


Figure 82–16. Typical appearance of a positive Meckel scan with an area of increased uptake above the area of the bladder in the lower midportion of the abdomen *(arrow)*.

omphalomesenteric duct remnants. Of interest is that males predominate by a ratio of 5 to 1.[43] Ectopic gastric mucosa is identified in approximately a third of patients with a complete fistula. Clinical manifestations of the anomaly usually appear in the first 2 weeks of life. After separation of the umbilical cord, drainage from the umbilicus (which has the appearance of intestinal contents) occurs. Once a diagnosis is made, resection of the entire omphalomesenteric duct is indicated.

Meckel's Diverticulum

This congenital abnormality is the most common of the embryonic yolk sac remnants and represents at least 80% of all of these anomalies. Meckel's diverticulum contains all three layers of the intestinal wall and is typically located within 40 to 50 cm of the ileocecal valve. However, this distance is related to age. The diverticulum originates from the antimesenteric border and is typically 3 to 6 cm in length. Of considerable significance is the presence of ectopic tissue within Meckel's diverticulum. This tissue can include gastric, duodenal, or colonic mucosa, as well as pancreatic tissue.[44] In the majority of patients who become symptomatic as a result of Meckel's diverticulum, the symptoms are caused by this ectopic tissue. A bleeding Meckel's diverticulum is diagnosed with a technetium 99 pertechnetate uptake scan ("Meckel's scan"), which identifies gastric mucosa (Fig. 82–16).

Treatment of Meckel's diverticulum depends on symptoms or anatomic findings at the time of incidental identification. Patients who have symptoms from Meckel's diverticulum such as bleeding or obstruction require resection of the diverticulum. With the presence of gastric mucosa or other ectopic mucosa or tissue, complete resection may require a sleeve resection of the attached small intestine. If the ectopic tissue is contained in the tip of the Meckel diverticulum, amputation at the antimesenteric border of the bowel will result in complete resection. In patients who are asymptomatic or in whom Meckel's diverticulum is incidentally identified at the time of abdominal exploration, removal is indicated if ectopic tissue can be palpated within the diverticulum or if there is a very narrow base, which would be associated with a high potential for obstruction.

Omphalomesenteric Cyst

Involution of the omphalomesenteric duct at the umbilicus and at the ileal end of the duct results in a mucosa-lined cyst. The cyst can be located in the intraperitoneal or preperitoneal space and may become quite large. Most often they are associated with secondary infection, which requires initial drainage and subsequent excision.

Omphalomesenteric Duct Remnants at the Umbilicus

These remnants are uncommon but, when present, are identified within the first 1 to 2 weeks of life. Identification occurs when the umbilical stalk falls off and a polypoid mass covered by mucosa is present at the umbilicus. If an omphalomesenteric duct remnant is identified at the umbilicus, it should be excised.

Omphalomesenteric Band

This abnormality results from involution of the omphalomesenteric duct without disappearance of the tissue. As a result, a solid cord connecting the ileum to the undersurface of the umbilicus is present. This abnormality generally becomes evident as the cause of intestinal obstruction.

Vitelline Blood Vessel Remnants

Occlusion but failure of involution of this structure also results in a fibrous cord within the peritoneal cavity. This remnant becomes clinically evident by producing intestinal obstruction as a result of twisting of a segment of small intestine around the band.

In general, treatment of symptomatic omphalomesenteric duct remnants is resection; however, symptoms from these remnants can be vague and difficult to diagnosis. Radiographic and clinical evidence of bowel obstruction in the absence of previous surgery or other clear-cut etiology suggests the presence of remnants of the omphalomesenteric duct as the cause of the bowel obstruction. If a symptomatic Meckel's diverticulum is identified and there is no evidence of perforation, the current approach is to remove the diverticulum laparoscopically.

NECROTIZING ENTEROCOLITIS

NEC is the most common and the most lethal surgical emergency affecting the gastrointestinal tract in premature infants. This entity was first described in 1967[45] and became more common as neonatal intensive care units

(NICUs) became more advanced in supporting premature infants. NEC produces various degrees of ischemic necrosis affecting the large and small intestine and usually involves the watershed areas of the bowel, namely, the terminal ileum and the cecum. The degree of involvement may be limited to the mucosa, or it can be more extensive and lead to total intestinal necrosis. NEC tends to be patchy and can affect both the large and small intestine in 44% of cases.[46] The most severe form of the disease leading to pan-necrosis develops in 20% of patients. The mortality rate of this disease is 13 per 100,000 live births, with a case fatality rate ranging from 20% to 40%.[47] Although more than 90% of affected patients are born prematurely, the disease can also affect full-term infants. It is estimated that NEC develops in up to 10% of premature infants weighing less than 1500 g.[48] Despite the high incidence of this disease, the pathogenesis remains elusive. Prematurity, low birth weight, and excessive feeding are known risk factors. These infants are usually stressed and may have had poor intestinal perfusion as a result of a number of causes, such as asphyxia, patent ductus arteriosus, exchange transfusion, catheterization of the umbilical artery or vein, anemia, systemic infection, and cardiac anomalies. Premature infants have an immature intestinal mucosal barrier that predisposes them to bacterial translocation.[49] In addition, they have an immature immune system with a reduction in both specific and nonspecific immune defense mechanisms.[50] Premature infants also have impaired gut motility and higher gastric pH, which puts them at risk for bacterial colonization.[51] Moreover, many of them are colonized with nosocomial bacteria from their stay in the NICU. Enteral feeding also provides the substrate for bacterial overgrowth. Formulas increase the risk for development of NEC 20-fold in comparison to breast milk. Formulas lack immunoglobulins, lactoferrin, macrophages or platelet-activating factor, acetylhydrolase, and numerous other peptides that are present in breast milk.[52] However, studies have shown the efficacy of hypocaloric feeding in reducing the risk for NEC in premature infants by "conditioning" the immature gut.[53]

Patients usually have nonspecific signs such as apnea, bradycardia, hemodynamic and temperature instability, hypoglycemia, and lethargy.[54] Initial gastrointestinal signs include abdominal distention, increased gastric residuals, vomiting, and Hemoccult-positive stools, which may become frank blood as the disease progresses. In infants with more advanced disease, signs of peritonitis develop as a result of bowel necrosis and perforation. There may be discoloration, edema, and tenderness of the abdominal wall, and a mass may be palpable. Multiorgan failure with hypotension, poor urinary output, and worsening respiratory status may develop. Metabolic acidosis and falling platelet counts are ominous signs. Abdominal radiographs may demonstrate pneumatosis intestinalis (Fig. 82–17), which is the hallmark of NEC.[55] However, absence of pneumatosis intestinalis does not rule out the diagnosis because it is usually a transient finding.

Other radiologic findings include dilated bowel loops, which may be persistent and fixed, diminished bowel gas, portal venous gas, and ascites. Fixed, dilated bowel loops and ascites may be signs of intestinal necrosis. Abdominal radiographs may show free intraperitoneal air, indicative of bowel perforation (Fig. 82–18). This sign is best demonstrated on a left lateral decubitus radiograph as air between the liver and the lateral abdominal wall.

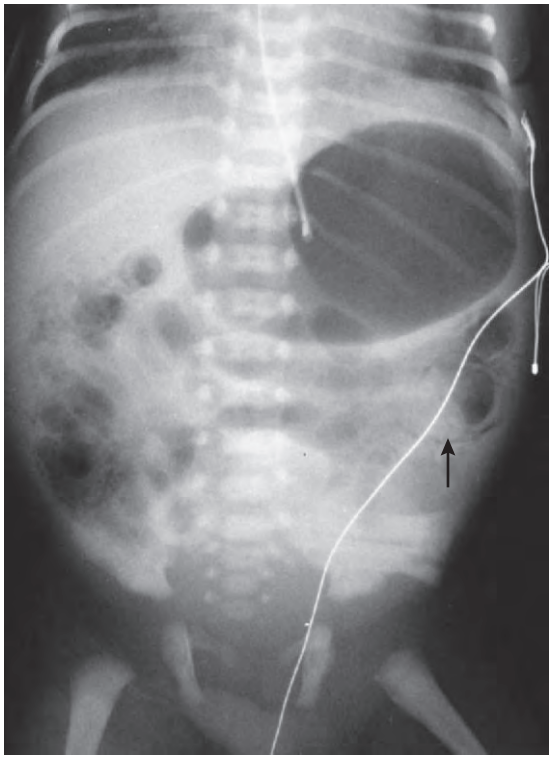


Figure 82–17. Patterns of intestinal pneumatosis. A supine abdominal radiograph in a neonate with necrotizing enterocolitis demonstrates submucosal (right hemiabdomen) and linear intramural pneumatosis *(arrow)*. (Courtesy of A. B. Campbell, MD, St. Christopher's Hospital for Children.)

When NEC is diagnosed or suspected, medical therapy is initiated and includes discontinuation of enteral feeding, placement of an orogastric tube for intestinal decompression, intravenous fluids, and broad-spectrum antibiotics. It is necessary to obtain serial abdominal radiographs, a complete blood count, and platelet counts (typically every 6 to 8 hours) to monitor the infant's status and look for free intra-abdominal air as an indicator for surgical intervention. Sixty percent to 70% of infants improve with medical management. However, infants who fail to improve with maximal medical management or continue to deteriorate with persistent metabolic acidosis, significant thrombocytopenia, and hemodynamic instability may need surgical exploration. Currently, the only absolute indication for surgical intervention is free intra-abdominal air as an indication of bowel perforation. Other "relative" indications are persistent metabolic acidosis, profound thrombocytopenia, a palpable abdominal mass, abdominal wall erythema, and portal venous gas. However, none of these signs, by themselves, are indications for surgery. The objectives of surgery are to resect nonviable bowel while preserving as much viable bowel as possible to avoid

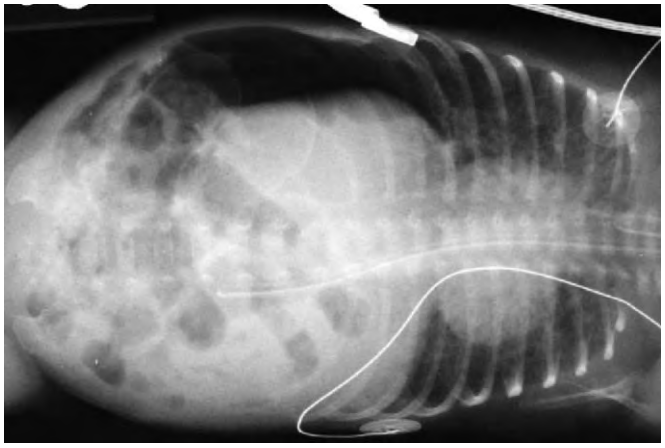


Figure 82–18. Pneumoperitoneum in necrotizing enterocolitis. An abdominal radiograph in the left lateral decubitus position demonstrates a large amount of free intraperitoneal air and extensive intestinal pneumatosis. (Courtesy of A. B. Campbell, MD, St. Christopher's Hospital for Children.)

creating short-bowel syndrome. Exploratory laparotomy is generally performed through a right supraumbilical or infraumbilical transverse incision. The entire gastrointestinal tract is inspected. Infants with the most severe form of the disease have their entire bowel affected (NEC totalis), which may result in an "open and close" procedure. If more than one area of nonviable bowel is present, multiple resections with primary anastomosis and proximal diversion at the point of the first bowel resection may be required. If multiple affected areas are of questionable viability but not frankly necrotic, a proximal diverting enterostomy may be indicated, followed by a "second look" 24 to 48 hours later. A technique described by Lessin et al. to treat multiple bowel involvement involves multiple resections of nonviable segments and lining up the remaining viable segments of the intestine over a feeding tube without anastomosis.[56] Contrast studies have shown that the segments undergo autoanastomosis. This technique avoids multiple stoma-related complications and further loss of intestinal length with closure and may help avoid a reoperation.[56] If only a single bowel segment is affected, this area is resected with the formation of a proximal ostomy and distal mucus fistula. The ostomy is usually brought through the lateral aspect of the incision. Another important technique is placement of peritoneal drains, which was first reported in 1975.[57] Although this technique was originally described as a temporizing procedure for very-low-birth-weight premature infants, subsequent reports have described it as the primary and sole operative intervention.[58,59] With more experience in using this approach, it appears to be more beneficial in infants with pneumoperitoneum who weigh less than 1000 g. It involves placing one or two Penrose drains at the bedside through a small incision in the lower abdominal quadrants. Bowel continuity is evaluated later with contrast studies. Azarow et al. compared the survival rate of neonates with NEC who weighed less than 1000 g and were treated by either laparotomy or percutaneous peritoneal drains. The survival rate in the peritoneal drainage group was 69% as opposed to only 22% in the laparotomy group.[60] Placement of peritoneal drains for increasing ventilatory requirements because of severe abdominal distention in the absence of free peritoneal air offers rapid stabilization. However, the mortality remains high in this group of critically ill patients.[61] A major sequela of NEC is the formation of stenosis or strictures of the small and large bowel. Strictures develop in 29% to 35% of infants after NEC. After recovery from NEC, all infants require a contrast enema or a distal colostogram before stoma take-down. Strictures are resected at the time of reversal of the ostomy. Recurrence of NEC is seen in less than 6% of patients.[62] The mortality associated with NEC has improved because of advances in neonatal and surgical care. It is estimated that 50% of premature infants weighing less than 1000 g and 75% weighing less than 1500 g survive an episode of NEC.[63] The long-term outcome after NEC treated at one tertiary NICU was favorable, with 83% of infants subsequently attending school full-time and only 14.3% suffering from developmental delay.[64]

INTUSSUSCEPTION

Intussusception is a process whereby the intestine telescopes into itself. The telescoping bowel segment is referred to as the intussusceptum. Although it was first described by Paul Barbette of Amsterdam in 1674,[65] it was not until nearly 200 years later that the first successful operation for intussusception (in a toddler) was performed.[66] The incidence of intussusception is highest between 4 and 10 months of age, and 80% to 90% of cases occur between 3 and 36 months.[67] Nearly all intussusceptions in infants and toddlers are idiopathic. That is, there is no clear etiology. In addition, most are ileocolic or ileoileocolic. Upper respiratory tract infections or gastroenteritis (adenovirus and rotavirus have been implicated) have been thought to be contributory to the development of "idiopathic" intussusception.[68] Hypertrophy of Peyer's patches can be seen at surgery, but no single etiologic factor predominates. Approximately 5% to 10% of cases have a true pathologic lead point.[69] The older the toddler, the more likely there will be a lead point.[70] The most common lead point is Meckel's diverticulum. Other lead points include polyps, the appendix, intestinal duplication, foreign bodies, and tumors such as hamartomas associated with Peutz-Jeghers syndrome. Children with Henoch-Schönlein purpura may have intussusception with submucosal hemorrhage acting as a lead point. Patients with cystic fibrosis may be at risk for recurrent intussusception, and these children tend to be older than the usual age at which it occurs.[68]

The typical history is that of sudden, short-duration, cyclic crampy abdominal pain. During these episodes the infant cries inconsolably with the knees drawn up. Between episodes the infant is asymptomatic. After the development of intussusception, lymphatic and venous obstruction of the intussusceptum occurs and leads to congestion (Fig. 82–19). Subsequently, swelling develops

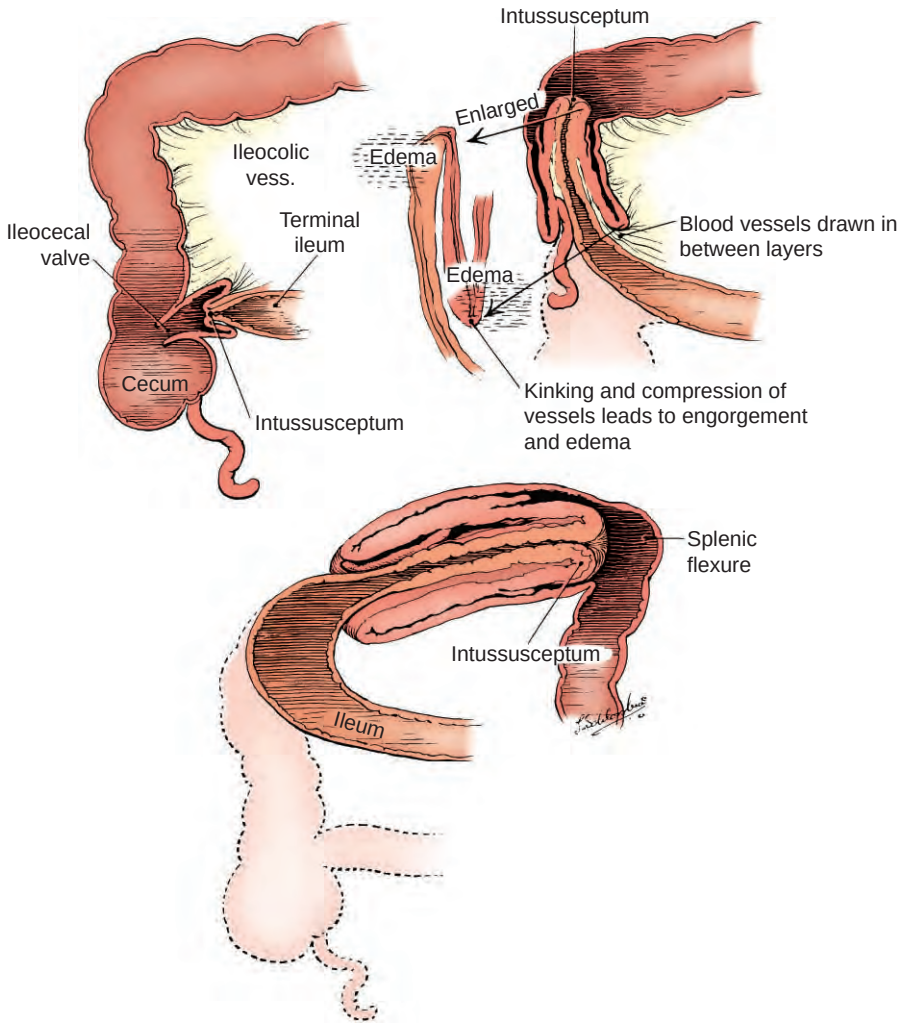


Figure 82–19. Development of an intussusception. Most intussusceptions in infants and children are of the kind shown here. The intussusception begins at or near the ileocecal valve without an obvious local anatomic lesion to cause it. From the first moment there is simultaneous interference with patency of the alimentary canal and with the vascular supply of the intussusceptum. The drawings indicate the manner in which the mesenteric vessels are drawn between the layers of the intussusception and compressed. The slight interference with lymphatic and venous drainage that occurs almost immediately results in edema and an increase in tissue pressure. This further increases resistance to the return of venous blood, the venules and capillaries become enormously engorged, and bloody edema fluid drips into the lumen. The mucosal cells swell into goblet cells and discharge mucus, which after mixing in the lumen with the bloody transudate, forms a "currant jelly" stool. Edema increases until venous inflow is completely obstructed. As arterial blood continues to pump in, tissue pressure rises until it is higher than arterial pressure, and gangrene ensues. The drawings indicate the sharp U-shaped turns of the intestine and mesenteric vessels at either end of the intussusceptum. The outer coat of the intussusceptum (middle layer of the intussusception) is isolated between the two sharp bends and understandably is the first to become gangrenous. Gangrene appears in this coat near the tip of the intussusception and progresses back toward the neck of the intussusceptum. Rarely, the intussuscipiens is damaged. (From Ravitch MM, Welch KJ, Benson CD, et al [eds]: Pediatric Surgery, 3rd ed. Chicago, Year Book, 1979.)

and results in impairment of arterial flow and mucosal necrosis. This produces the classic "currant jelly" stool. On examination the child may show signs of dehydration or lethargy, depending on the length of time that has passed and whether bowel necrosis is present. A sausage-shaped mass may be palpable in the right upper quadrant. The presence of peritoneal signs is ominous and mandates operative intervention. In 60% to 90% of cases, rectal examination demonstrates either occult or gross blood.[71]

Abdominal radiographs may be normal or show a paucity of gas in the colon and dilated small bowel loops (Fig. 82–20). Ultrasonography has been used more frequently to diagnose intussusception. It may show a kidney-shaped mass in the longitudinal view or a target sign in the transverse view (Fig. 82–21). A barium contrast enema was the "gold standard" for diagnosis, and in over 50% of cases, hydrostatic pressure was successful in reducing the intussusception (Fig. 82–22). However, this treatment strategy changed in 1990 as a result of a report

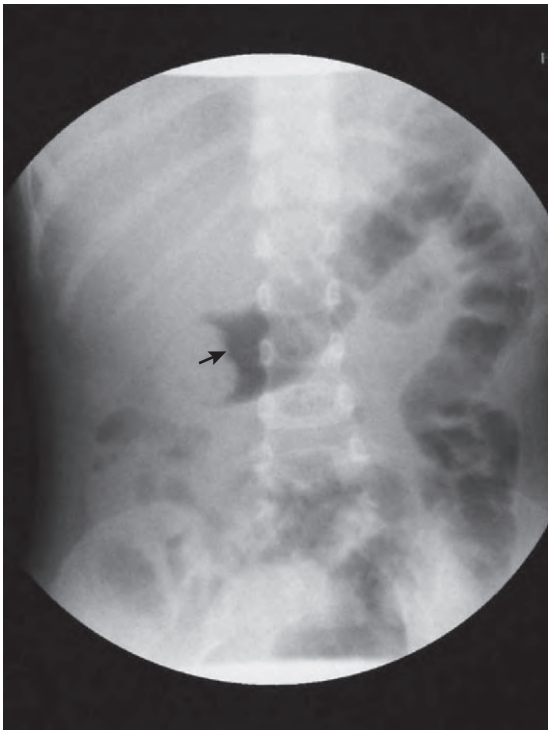


Figure 82–20. Ileocolic intussusception. A scout film for a contrast enema demonstrates a rounded soft tissue mass in the right upper quadrant with central radiolucency along the inferior margin of the liver. This pseudotumor suggests the presence of intussusception. (Courtesy of A. B. Campbell, MD, St. Christopher's Hospital for Children.)

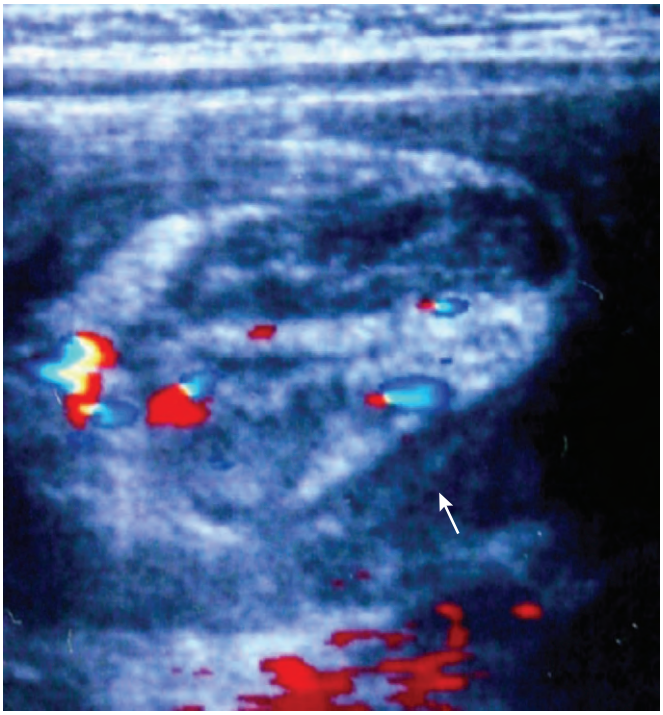
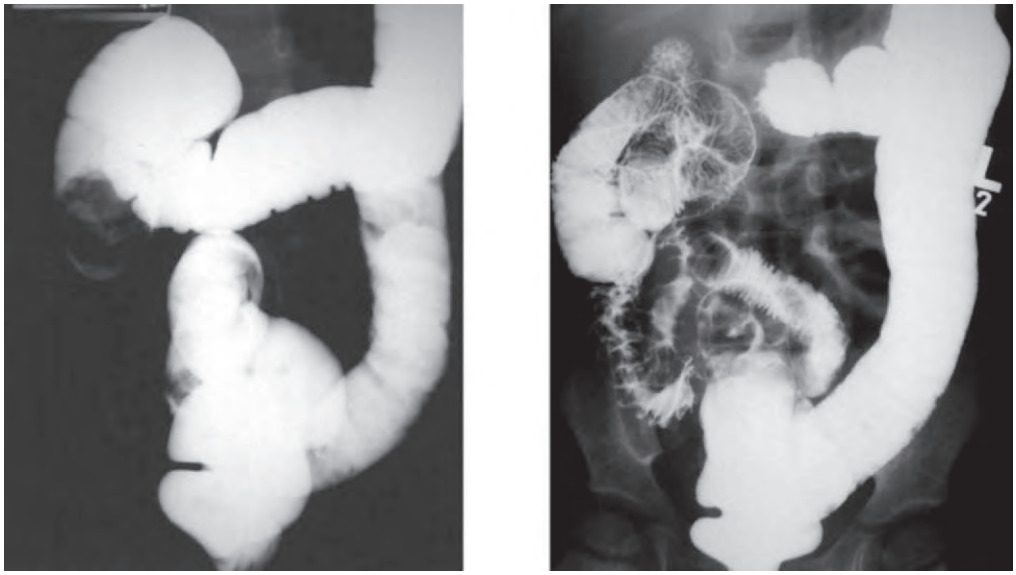


Figure 82–21. Intussusception, color Doppler imaging. A cross-sectional color Doppler ultrasound image of intussusception demonstrates the typical target appearance with compression of an eccentric small bowel segment, a hypoechoic peripheral colon wall *(arrow)*, echogenic mesenteric fat, and incidental mesenteric lymph nodes. Brisk flow is noted within the mesenteric vessels centrally. (Courtesy of A. B. Campbell, MD, St. Christopher's Hospital for Children.)



A B

Figure 82–22. Barium enema reduction of intussusception. **A,** A filling defect in the ascending colon is shown. **B,** The intussusception is successfully reduced with reflux of contrast into the small bowel. (Courtesy of A. B. Campbell, MD, St. Christopher's Hospital for Children.)

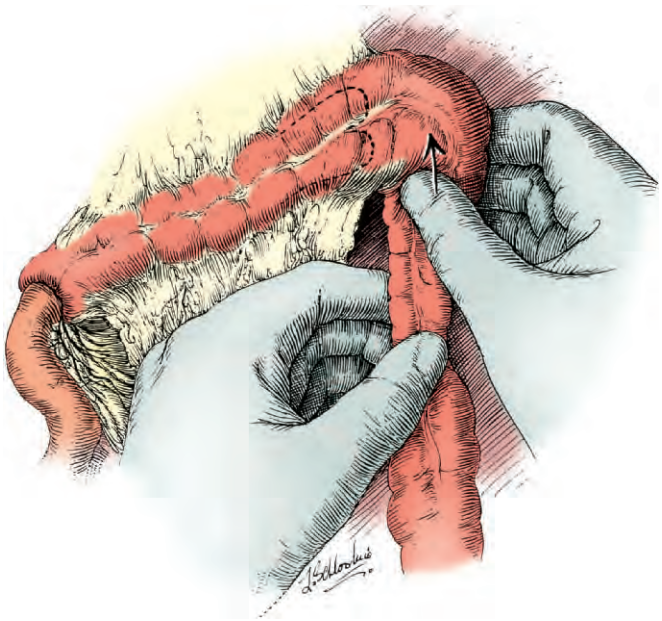


Figure 82–23. Manual reduction of intussusception. If a barium enema fails or intussusception is encountered during laparotomy for intestinal obstruction, manual reduction is required. The intestine is occluded immediately distal to the intussusception with the fingers of one hand and stripped proximally with the fingers of the other. In effect, this maneuver increases intraluminal pressure just as an enema does. The intestine should not be pulled. If reduction is not readily achieved, resection and anastomosis should be performed. (From Ravitch MM, Welch KJ, Benson CD, et al [eds]: Pediatric Surgery, 3rd ed. Chicago, Year Book, 1979.)

from a Chinese group describing air-contrast enema as a diagnostic and therapeutic tool.[72] The intussusception is reduced under fluoroscopic guidance. The patient receives intravenous fluid and antibiotics before the procedure. Successful reduction is confirmed by reflux of air (or barium) into the small bowel. The success rate with air or barium reduction should exceed 70%. Failure of reduction or the presence of peritonitis mandates operative intervention, which can be performed laparoscopically or by a standard approach. If done laparoscopically, reduction is accomplished by gently pulling the intussusceptum from the intussuscipiens. In the open approach an infraumbilical transverse incision is made. The intussusception is reduced by applying gentle pressure retrogradely in a distal-to-proximal direction and milking the intussusceptum out of the intussuscipiens (Fig. 82–23). After operative reduction the bowel is carefully inspected for viability and the presence of a "lead point." The intussuscepted bowel may be congested and edematous. Observation over a 10- to 20-minute period may be necessary to assess viability. If the lead point was Meckel's diverticulum or a polyp, it should be resected. Intussusception may recur in 5% to 10% of cases after successful hydrostatic reduction.[68] In contrast, the reported recurrence rate after operative reduction is 1% to 4%.[68,73] Recurrence is usually managed by hydrostatic reduction. Repeated episodes of intussusception mandate operative intervention to look for a lead point. Bowel perforation is a serious complication that occurs in 0.2% of cases treated by hydrostatic reduction and requires emergency surgery. If there is necrosis of the intussuscepted bowel or operative reduction is impossible, resection is necessary. Usually, an end-to-end anastomosis can be safely performed.

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Chapter

83

Anatomy and Physiology of the Mesenteric Circulation

Steven B. Goldin ▪ Alexander Rosemurgy

This chapter discusses the anatomy of the mesenteric arterial circulation, including common normal arterial variations.[1] Collateral pathways between the major arterial vessels and their clinical significance are also discussed. Reviewing embryonic developmental anatomy[2] simplifies understanding of the arterial anatomy. Venous anatomy is detailed elsewhere in this text. The intestine serves a variety of functions, including digestion, absorption of fluids and nutrients, secretion of fluids and hormones, and propulsion of enteric contents, and it forms a barrier that contributes to host defense mechanisms. This chapter also concentrates on regulation of mesenteric blood flow. Detailed understanding of the physiologic factors that augment blood flow to and from the intestinal circulation requires a closer look at the arteriolar, capillary, venule, and venous anatomy. For purposes of this discussion, the mesenteric circulation designates blood flow only to the intestinal circulation, and the splanchnic circulation refers to blood flow to any of the gastrointestinal organs or structures within the peritoneal cavity as seen in Figure 83–1.

EMBRYOLOGY

The foregut structures of the digestive tract, including the esophagus, stomach, duodenum, liver, gallbladder, and pancreas, develop when the embryo is approximately 4 weeks old. These structures receive blood flow from the celiac artery, which begins at the proximal ends of the vitelline arteries near the seventh cervical vertebra. With growth of the embryo, the celiac artery migrates caudally to T12. The midgut begins just distal to the entrance of the ampulla of Vater and extends to the proximal two thirds of the transverse colon. The midgut's vascular supply is from the superior mesenteric artery (SMA). The midgut develops from two limbs called the cephalic and caudal limbs. During development of the midgut, there is rapid elongation of these limbs and its mesentery, as well as counterclockwise rotation of approximately 270 degrees around the SMA, as seen in Figure 83–2A. This rotation occurs just after the SMA has given off its duodenal branches. Therefore, the proximal SMA branches to the small bowel originate on the right side of the SMA, whereas distally, branches to the small bowel originate on the left side of the SMA. Likewise, the colonic branches of the SMA, which branch off distally from the SMA, originate from the right side of the SMA, as shown in Figure 83–2B. The hindgut gives rise to the distal third of the transverse colon, extends to the upper part of the anal canal, and terminates in the cloaca. The blood supply to the hindgut is via the inferior mesenteric artery (IMA). The cloaca is divided into an anterior portion, called the primitive urogenital sinus, and a posterior portion, called the anorectal canal, by the urorectal septum, as seen in Figure 83–3. Descent of the urorectal septum to the cloacal membrane results in formation of the perineum, as well as a posterior anal membrane and an anterior urogenital membrane. The anal membrane contacts the anal pit, or proctodeum, which has an ectodermal origin. Therefore, the upper portion of the anal canal has an endodermal origin, whereas the lower portion is of ectodermal origin. Accordingly, the upper portion of the anal canal is supplied by the IMA, with the lower portion being supplied by the systemic circulation.

ANATOMY

The small intestine, or small bowel, extends from the pylorus in the right upper quadrant to the cecum in the right lower quadrant. A large fold of peritoneum that extends from the posterior abdominal wall suspends the small bowel within the peritoneal cavity and prevents significant rotation. This fold of peritoneum is called the mesentery and contains arteries, veins, nerves, lymphatic vessels, lymph nodes, and fat. The small bowel mesentery begins at its base, just to the left of the second lumbar vertebral body, and extends inferiorly and obliquely to

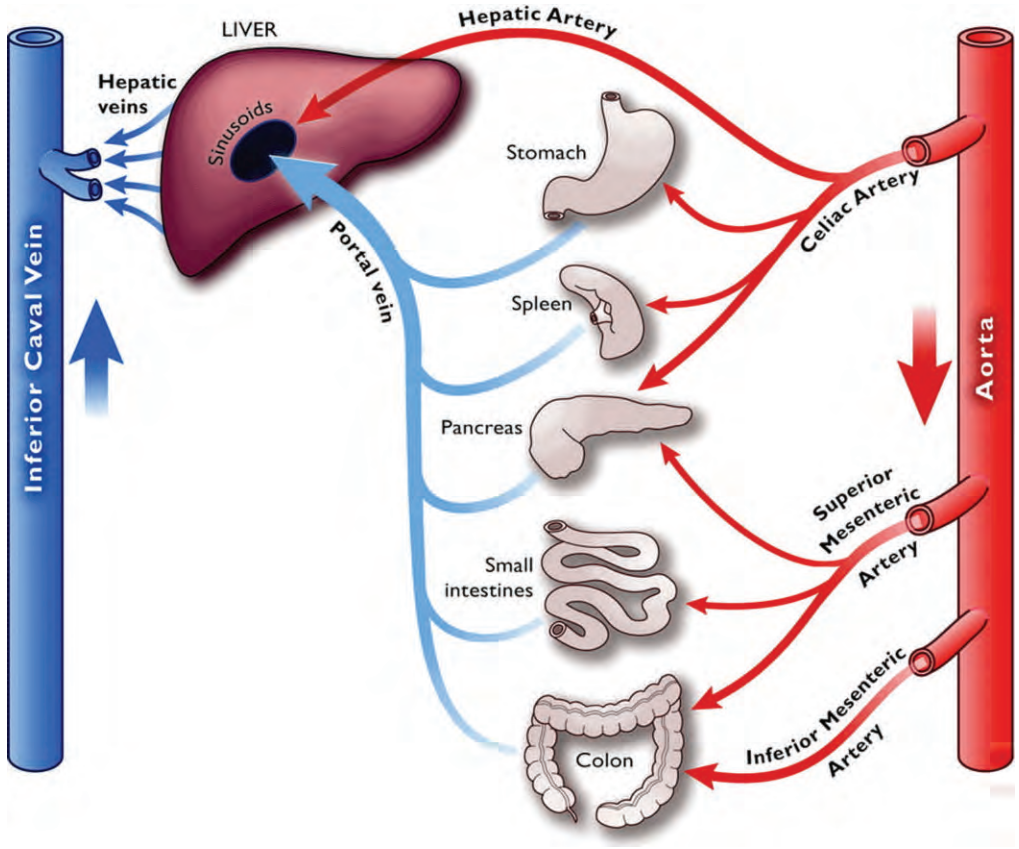

Figure 83–1. Schematic representation of the splanchnic circulation. (From Gelmen S, Mushlin PS: Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 100:434-439, 2004.)

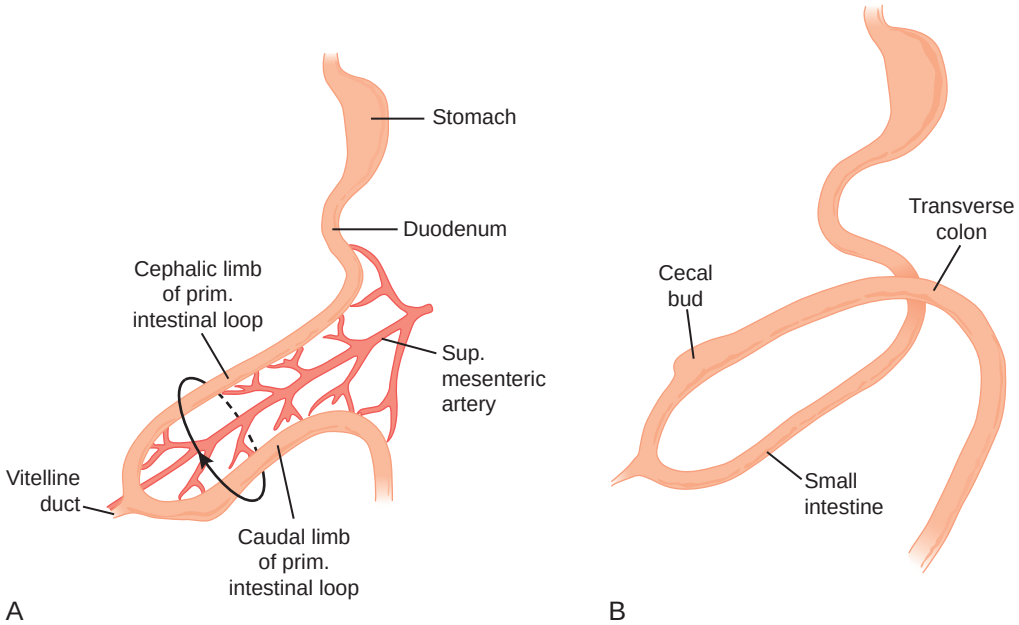

Figure 83–2. **A,** Schematic drawing of the primitive intestinal loop before rotation (lateral view). The superior mesenteric artery forms the axis of the loop. The *arrow* indicates the direction of the counterclockwise rotation. **B,** Similar view as in **A,** but showing the primitive intestinal loop after 180-degree counterclockwise rotation. Note that the transverse colon passes in front of the duodenum. (From Sadler TW: Langman's Medical Embryology, 7th ed. Baltimore, Williams & Wilkins, 1995.)

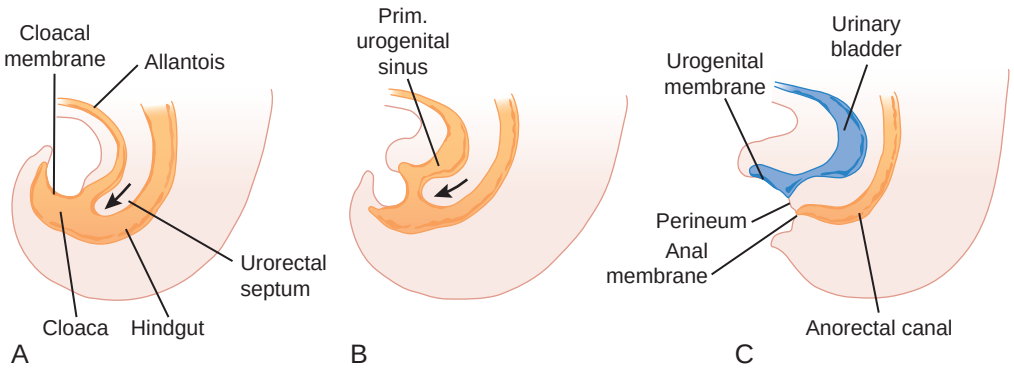

Figure 83–3. **A-C,** Drawings of the cloacal region in embryos at successive stages of development. The *arrows* indicate the route of descent followed by the urorectal septum. Note the anorectal canal and perineum. (From Sadler TW: Langman's Medical Embryology, 7th ed. Baltimore, Williams & Wilkins, 1995.)

the right toward the iliac fossa. The mesentery attaches in a fan-like pattern to the entire length of the small bowel along one side termed the *mesenteric border of the small bowel*. In humans, the total length of the duodenum is approximately 20 cm, and that of the jejunum and ileum is 260 cm. The duodenum begins at the pylorus and extends in a C-loop fashion to the duodenojejunal junction, which is located just to the left of the second lumbar vertebra and is supported by the ligament of Treitz. The jejunum makes up approximately two fifths of the length of the small bowel, with the remaining three fifths constituting the ileum. There is no clear anatomic demarcation between the jejunum and ileum.

The colon, which begins in the right lower quadrant and extends in a question mark pattern throughout the abdominal cavity to reach the rectum, also has mesenteric attachments composed of similar elements. The length of the human colon is approximately 110 cm. The cecum is the first portion of the colon and begins at the ileocecal valve. It is approximately 6.3 to 7.5 cm long and 7.5 cm wide. Like the small bowel, it is completely covered by peritoneum, but it differs from the small intestine by not having a mesentery. The vermiform appendix is attached to the cecum 2.5 cm below the ileocecal valve and may vary in length from 2.5 to 23 cm. The appendix may be located in a variety of locations, including the pelvis and retrocecal area, or it may be directed superiorly and to the left. The appendix is completely covered with peritoneum and has a mesentery, which furnishes its blood supply. The ascending colon is continuous with the cecum and located on the right side of the abdomen. It ascends toward the inferior surface of the liver, where it turns medially to make the hepatic flexure. The ascending colon and hepatic flexure are retroperitoneal structures. The transverse colon begins at the hepatic flexure and crosses the peritoneal cavity. It is an intraperitoneal structure and has a mesentery, which makes its location and relationship to other structures variable. The transverse colon ends at the splenic flexure, which is usually higher than the hepatic flexure. It is also a retroperitoneal structure. The descending colon begins at the distal end of the splenic flexure, where it courses retroperitoneally and inferiorly on the left side of the abdomen until it reaches the left iliac fossa and becomes the sigmoid colon. The sigmoid colon is intraperitoneal and has a mesentery. It is S-shaped, starts in the left iliac fossa, and continues to the rectum. The

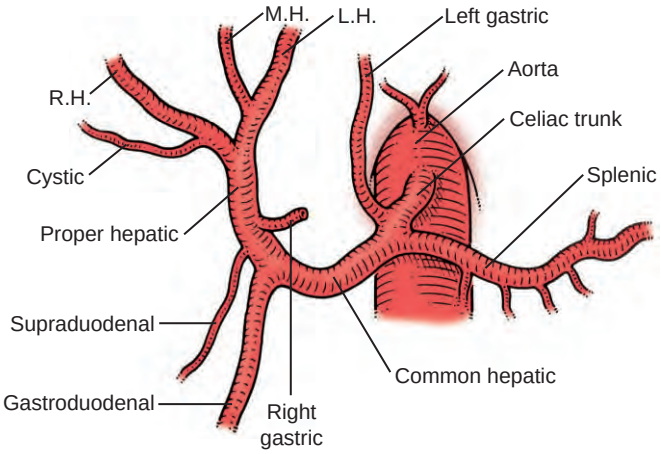

Figure 83–4. Major branches of the celiac trunk. L.H., left hepatic artery; M.H., middle hepatic artery; R.H., right hepatic artery. (From Blumgart LH, Hann LE: Surgery of the liver and biliary tract. In Blumgart LH, Fong Y [eds]: Surgical and Radiologic Anatomy of the Liver and Biliary Tract, 3rd ed. London, WB Saunders, 2000.)

rectum is approximately 15 cm long and begins at the midsacral area. It then follows the curve of the sacrum and coccyx into the pelvic cavity.

Mesenteric attachments, as mentioned, contain all the blood vessels going to the viscera. Clinically understanding the relationship of the vasculature, mesentery, and bowel is extremely important. Resectional strategies are based entirely on the blood supply. The mesentery contains a large number of collateral blood flow pathways, which also have extremely important clinical implications that will be described in subsequent sections.

Celiac Axis

The celiac artery is the largest branch of the abdominal aorta and it supplies the embryologic foregut. It leaves the aorta at a 90-degree angle between T12 and L1 just after the aorta has penetrated the diaphragm. There is considerable variability in both the celiac artery and the SMA, as described later. Classically, the celiac artery trifurcates into the left gastric, splenic, and common hepatic arteries, as seen in Figure 83–4. Multiple

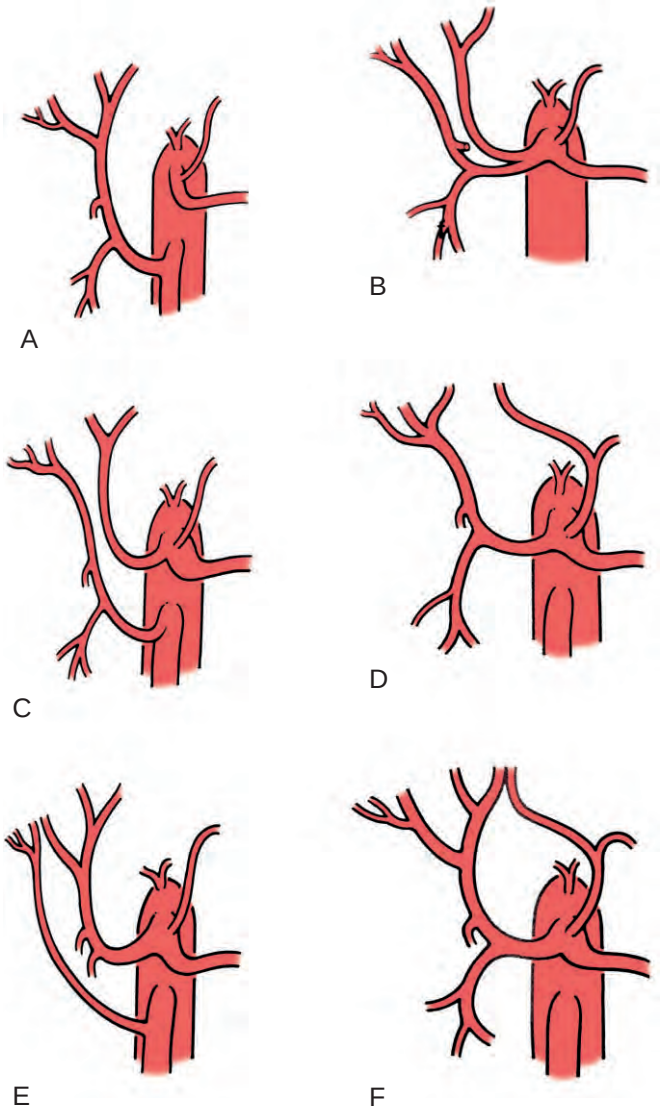

Figure 83–5. Hepatic artery variation. In 25%, the right hepatic artery arises partially or completely from the superior mesenteric as seen in **A, C,** and **E.** A similar proportion of individuals have a variation in the left hepatic artery, with flow arising from the left gastric artery as seen in **D** and **F.** Rarely, the right or left hepatic arteries originate independently from the celiac trunk or a branch after a very short common hepatic artery origin from the celiac as seen in **B** and **C.** The gastroduodenal artery may originate from the right hepatic artery as seen in **B** and **C.** (From Blumgart LH, Hann LE: Surgery of the liver and biliary tract. In Blumgart LH, Fong Y [eds]: Surgical and Radiologic Anatomy of the Liver and Biliary Tract, 3rd ed. London, WB Saunders, 2000.)

anatomic variations of the celiac artery and SMA branches are common and are shown in Figure 83–5. Within the lesser omentum, the left gastric artery first sends branches to supply the distal portion of the esophagus. It then follows a course along the lesser curvature of the stomach and anastomoses with the right gastric artery, which is a branch off the common hepatic artery. The common hepatic artery is also visualized and first gives off a variable number of branches to the pancreas before the branching of the right gastric artery and the gastroduodenal artery. The common hepatic artery then becomes the proper hepatic artery, which subsequently divides into the right and left hepatic arteries supplying the liver. Before dividing, the proper hepatic artery often gives off branches to the duodenum, including a retroduodenal artery that follows the common bile duct. In approximately 75% of individuals, the cystic artery originates from the right hepatic artery. In approximately 20%, the right hepatic artery may not originate from the proper hepatic artery or is lacking. In the majority of these individuals, the blood supply to the right lobe of the liver originates from the SMA and is called a *replaced right hepatic artery.* If both a right hepatic artery and a supply vessel from the SMA are present, the latter vessel is termed a *recurrent* or *accessory right hepatic artery.* The replaced and accessory right hepatic arteries usually run just posterior, inferior, and lateral to the bile duct and can be injured during pancreaticoduodenectomy and other procedures that involve the porta hepatis if care is not taken to assess their presence. Another 20% of individuals will also have an aberrant left hepatic artery. In this case, some of the blood supply to the left lobe of the liver originates from the left gastric artery and runs with the hepatic branch of the vagus nerve through the lesser omentum to the left lobe of the liver. Rarely, the entire arterial supply to the liver originates from the SMA. The right gastric artery, as mentioned, courses on the lesser curvature of the stomach to anastomose with the left gastric artery. The gastroduodenal artery courses posterior to the duodenum and usually divides into the superior pancreaticoduodenal and right gastroepiploic arteries. The superior pancreaticoduodenal artery divides into duodenal and pancreatic branches. The duodenal branch courses between the pancreas and duodenum anteriorly and continues caudally to anastomose with a branch of the inferior pancreaticoduodenal artery. The superior pancreaticoduodenal artery runs on the posterior surface of the head of the pancreas. The right gastroepiploic artery runs along the greater curvature of the stomach in the greater omentum and eventually communicates with the left gastroepiploic artery. The last branch of the celiac artery is the splenic artery. It courses toward the spleen and lies on the cephalad boarder of the pancreas, which it also supplies. Just before reaching the spleen, the splenic artery gives off multiple short gastric branches to supply the stomach, as well as the left gastroepiploic artery, which courses along the greater curvature of the stomach inferiorly to anastomose with the right gastroepiploic artery.

Superior Mesenteric Artery

The SMA supplies the entire embryologic midgut and is the second largest intra-abdominal branch of the aorta. It branches off the aorta 0.5 to 1.5 cm caudal to the celiac artery. In approximately 1% of individuals, the SMA and celiac arteries arise from a common trunk. The SMA and celiac vessels may also communicate by the artery of Buhler if this embryologic remnant has not been

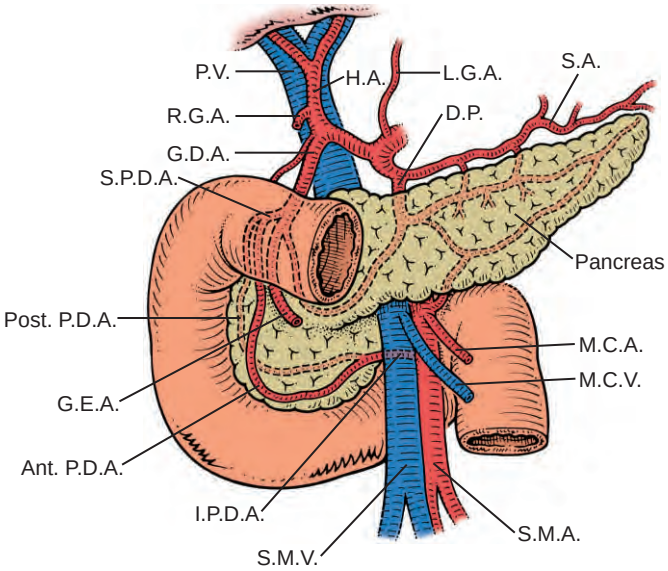

Figure 83–6. Arterial vascular arcades supplying the duodenum and pancreas. Ant. P.D.A., anterior pancreaticoduodenal artery; D.P., dorsal pancreatic artery; G.D.A., gastroduodenal artery; G.E.A., right gastroepiploic artery; H.A., hepatic artery; I.P.D.A., inferior pancreaticoduodenal artery; L.G.A., left gastric artery; M.C.A., middle colic artery; M.C.V., middle colic vein; Post. P.D.A., posterior pancreaticoduodenal artery; P.V., portal vein; R.G.A., right gastric artery; S.A., splenic artery; S.M.A., superior mesenteric artery; S.M.V., superior mesenteric vein; S.P.D.A., superior pancreaticoduodenal artery. (From Blumgart LH, Hann LE: Surgery of the liver and biliary tract. In Blumgart LH, Fong Y [eds]: Surgical and Radiologic Anatomy of the Liver and Biliary Tract, 3rd ed. London, WB Saunders, 2000.)

obliterated. The SMA leaves the aorta at a 20- to 30-degree angle posterior to the body of the pancreas at L1. The artery then passes inferiorly and just medial and anterior to a small portion of the uncinate process of the pancreas, where it gives off its first branch, the inferior pancreaticoduodenal artery, as seen in Figure 83–6. This vessel usually arises on the right side because of a relative lack of rotation of this part of the vessel during development. The artery then passes anterior to the third portion of the duodenum, where it divides into anterior and posterior branches that anastomose with pancreaticoduodenal branches of the superior pancreaticoduodenal artery previously described. After passing the duodenum, the SMA enters the root of the mesentery. Other major SMA branches seen in the majority of patients include multiple jejunal and ileal branches and the ileocolic, right colic, and middle colic vessels. There are approximately 12 to 20 jejunal and ileal branches. They run in the mesentery and form a series of arcades before reaching the intestines. The mesentery is longer in the ileum, and there are more arcades in this area. The last ileal artery also forms arcades with the branch supplying the cecum and thus forms a collateral circulation with the ileocolic artery. The ileocolic artery often has a common takeoff with the right colic artery and sends branches to the ascending colon and the ileum. The branch to the ileum supplies the cecum and appendix, with the appendiceal artery usually passing posterior to the ileum and entering the mesoappendix, or the mesentery of the appendix. The ascending branches of the ileocolic artery join the right colic artery, which again divides into ascending and descending branches that anastomose with the ileocolic vessels as mentioned and the middle colic artery. The middle colic artery is usually the second branch of the SMA and supplies the transverse colon. It forms collateral anastomoses to the right and left colic arteries. The right colic artery, as mentioned, is a branch of the SMA, but the left colic branches are derived from the IMA. The middle colic artery arises as a common right-middle colic vessel in approximately 50% of people. In approximately 40%, the right colic comes directly off the SMA. The ileocolic artery may originate directly from the SMA or arise as a common vessel with the right colic artery.

Inferior Mesenteric Artery

The IMA, like the celiac artery and SMA, arises from the anterior surface of the aorta; it is located approximately 3.8 cm proximal to the bifurcation of the aorta into the common iliac arteries at L3. The IMA supplies the embryologic hindgut. It courses approximately 3.5 cm before branching and is approximately 0.5 cm in diameter. It supplies the distal third of the transverse colon, the splenic flexure, the descending colon, the sigmoid colon, and the proximal part of the rectum. Its branches include the left colic, three or four vessels to the sigmoid colon, and the superior rectal vessels. The left colic artery branches ascend on the descending colon and anastomose with branches of the middle colic artery from the SMA at the splenic flexure. The sigmoidal branches form arcades that anastomose with the left colic artery and the superior rectal artery. The superior rectal artery supplies blood to the wall of the upper two thirds of the rectum and to the mucosa of the lower third of the rectum.

Celiac Axis–Superior Mesenteric Arterial Communications/Collaterals

Approximately 20% of individuals will have greater than 50% stenosis of the celiac artery at the time of death.[3] The majority of these patients are asymptomatic[4] because of the presence of rich collateral vessels from the SMA. The network of collaterals between the celiac artery, SMA, and IMA is demonstrated in Figure 83–7. The most common collateral pathways surrounding the duodenum and pancreas are shown in Figure 83–6 and involve the pancreaticoduodenal vessels and the dorsal pancreatic artery.[5] The pancreaticoduodenal arcades course anterior and posterior through the head of the pancreas, which they supply along with the duodenum.[6,7] Both the anterior and the posterior pancreaticoduodenal arcades are fed by the gastroduodenal artery from the cephalad direction. These arcades communicate with the SMA via separate inferior pancreaticoduodenal arteries from the

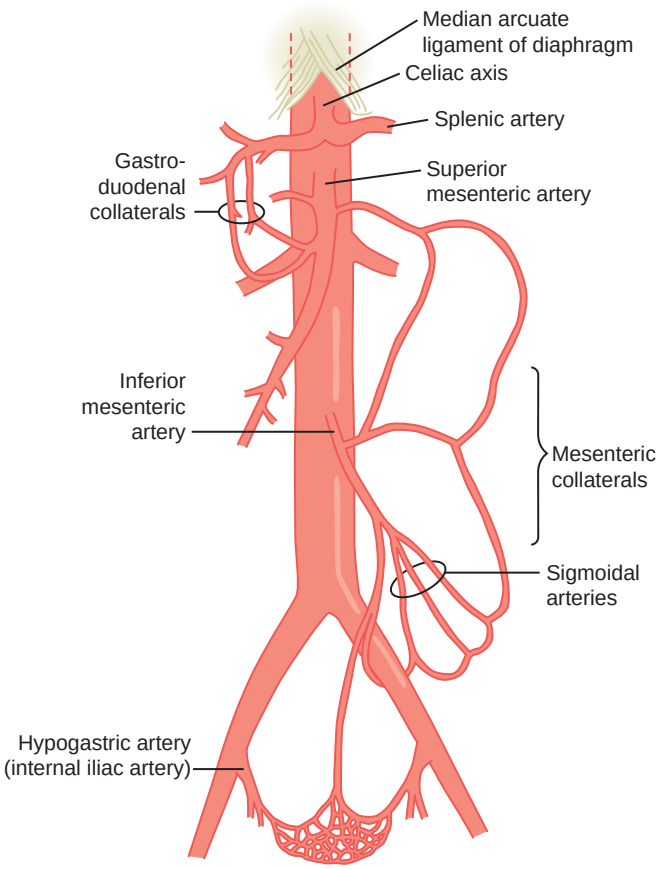

Figure 83–7. Schematic depiction of the major visceral vessels and collateral pathways. (Adapted from Hanson KJ: Mesenteric ischemia syndromes. In Dean RH, Yao JST, Brewster DC [eds]: Current Diagnosis and Treatment in Vascular Surgery. Englewood Cliffs, NJ, Appleton & Lange/ Prentice Hall, 1995, p 264.)

SMA. The dorsal pancreatic artery may arise from a variety of sites, including the splenic artery (39%), the right hepatic artery (12%), the SMA (14%), the celiac artery (22%), or another vessel (13%).[8] This artery has numerous connections between the celiac artery and SMA. The dorsal pancreatic artery also divides into two right and one left branch, with one of the right branches joining the pancreaticoduodenal arcades. The other right branch supplies the uncinate process of the pancreas. The left branch becomes the transverse pancreatic artery, which communicates with caudal pancreatic vessels supplied by the splenic artery. A fourth branch of the dorsal pancreatic artery runs below the inferior border of the pancreas and communicates with the SMA or with branches from the SMA. The collaterals that form may be extensive and a variety of unusual pathways may exist in light of the large variety of hepatic arterial anatomic variants that exist.[5]

Superior Mesenteric–Inferior Mesenteric Arterial Communications

As for the celiac axis, it is not uncommon for the SMA (30%) and IMA (30%) to be stenotic at the time of death.[3,9] Collateral circulation therefore plays a large role in maintaining visceral health. Besides the communicating arcades just described for these vessels, there are a variety of other important vascular communications between the SMA and IMA. The marginal artery of Drummond is located peripherally in the mesentery of the colon. It is usually a continuous arterial pathway along the colon. An anastomosis between the middle and left colic arteries is present in 95% of people and occurs at the splenic flexure of the colon. The location of these anastomoses is designated Griffiths' point. This artery may also be lacking in the proximal portion of the descending colon just beyond the splenic flexure in 5%, in the sigmoid colon in 20%, and at the rectosigmoid junction in an even larger number. Likewise, there is a critical point of Sudeck that occurs between the last sigmoidal branch and the superior rectal artery. When undertaking colonic resection, it is important to ensure adequate blood supply to both ends of the bowel, and rectal resections should include a portion of the sigmoid colon taken above this potential critical point to ensure adequate vascular supply at the anastomosis. Other important vascular communications include the meandering mesenteric artery (MMA), which is its preferred name. The MMA is present in approximately two thirds of the population. It has also been called the central anastomotic artery of the colon, the accessory middle colic artery, the mesomesenteric artery, the middle-left colic collateral, the arch of Riolan, the arch of Treves, and the artery of Drummond (not the marginal artery of Drummond). The MMA is a communication between a branch leaving the SMA just proximal to the middle colic artery and a branch of the ascending left colic artery.

Inferior Mesenteric–Hypogastric Communications

The rectum receives three main sources of blood flow. The superior rectal arteries arise from the IMA and have been described. The two other vessels are the middle and inferior rectal vessels, as seen in Figure 83–8. The superior rectal artery is largely responsible for supplying the upper two thirds of the rectum, but its branches course submucosally and anastomose with branches from the inferior rectal artery in the anal columns. The middle rectal arteries are branches of the internal iliac arteries and supply the muscular layer of the lower third of the rectum. The inferior rectal arteries are branches of the internal pudendal arteries and supply the lower end of the anal canal, where they anastomose with the superior rectal vessels. The mesenteric circulation is therefore in communication with the systemic circulation via these vessels, which can provide a route of collateral circulation.

Rare Communicating Vessels

Occasionally, other collateral pathways also play significant roles. The splenic artery may supply a branch to the left colic artery, and the iliolumbar branches and superior and inferior epigastric vessels may provide important collaterals via the circumflex iliac and femoral arteries. Parietovisceral communications may also exist.

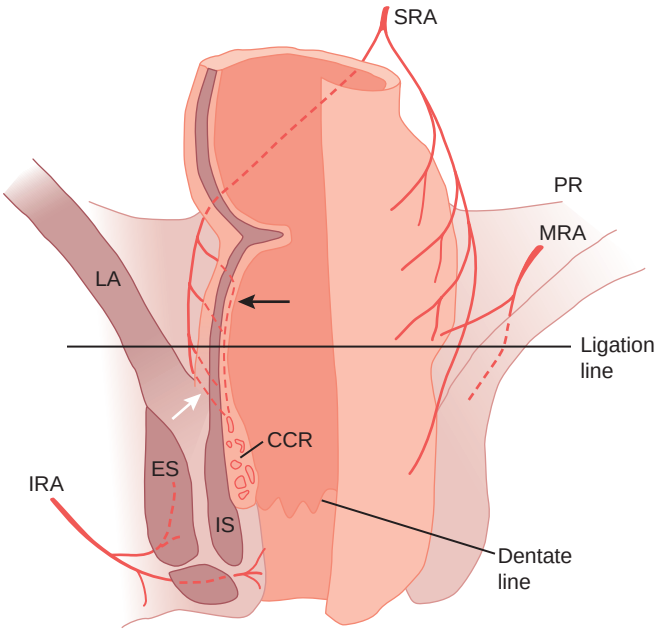

Figure 83–8. Schematic illustration of the rectum and anal canal. The rectal wall has been removed on the right side to demonstrate the transmural course of the branches of the superior rectal artery (SRA). The middle rectal artery (MRA), inferior rectal artery (IRA), corpus cavernosum recti (CCR), levator ani muscle (LA), internal sphincter muscle (IS), external sphincter muscle (ES), and peritoneal reflection (PR) are shown. The *black arrow* indicates longitudinal submucosal branches; the *white arrow* indicates transmural "piercing" branches of the SRA. (From Aigner F, Bodner G, Conrad F, et al: The superior rectal artery and its branching pattern with regard to its clinical influence on ligation techniques for internal hemorrhoids. Am J Surg 187:102-108, 2004.)

CLINICAL CORRELATIONS

Understanding the mesenteric collateral circulation is fundamental to comprehending a variety of disease processes and the compensatory issues that occur in individuals. Chronic blockage of any single mesenteric vessel is usually inconsequential if the collateral pathways are functional. Blockage of the celiac artery usually results in blood flow being routed through the SMA via the pancreaticoduodenal arcades and the dorsal pancreatic vessels that communicate with the gastroduodenal and left gastroepiploic arteries to supply the liver, stomach, pancreas, duodenum, and spleen. Likewise, blockage of the SMA will usually result in blood being routed via the same vessels, as well as the MMA and IMA, to supply the small bowel and right colon. Blockage of the IMA is usually compensated for by blood flow through the MMA, marginal artery of Drummond, and collateral vessels from the inferior and superior rectal arteries.

Acutely, the hypogastric or internal iliac arterial collateral circulation plays an insignificant role. Critical ischemia from acute occlusion can result from single-vessel disease in the absence of adequate collateral circulation or when multiple vessels are involved. The individual is also much more apt to compensate appropriately when the blood flow disturbance occurs slowly or chronically than when blood flow through a major mesenteric vessel is abruptly or acutely stopped. Likewise, it is important for an operating surgeon to be cognizant of the locations of the anastomosing systems. As mentioned, these communicating systems may be lacking and compounded by disease processes in the native vessels. Segmental colectomy may interrupt critical anastomotic networks between the SMA and IMA and result in acute ischemia in patients with severe mesenteric occlusive disease. Similarly, a Whipple operation in a patient with chronic celiac occlusion can cause hepatic ischemia by interrupting collateral arterial flow from the SMA through the pancreaticoduodenal arcades.

The mesenteric artery most frequently occluded by chronic vascular disease is the IMA. Abdominal aortic aneurysm repair usually results in sacrifice of the IMA. Understanding the collateral circulation is imperative to prevent the development of ischemic colitis in these patients. Likewise, if the SMA is severely diseased and the midgut is receiving a large proportion of blood from the MMA, sacrificing this vessel during aneurysm repair can result in infarction of the small bowel and right colon.

PHYSIOLOGY OF THE MESENTERIC CIRCULATION

The major arterial vessels to the splanchnic system include the celiac axis, SMA, and IMA. In the resting or unfed state, these vessels receive approximately 20% to 25% of cardiac output.[10,11] Approximately 25% of the splanchnic circulation flows directly to the liver, with the remaining 75% of blood flow reaching the liver via the portal system. The splanchnic circulation contains approximately a third of the total blood volume, which makes it the circulatory system's largest reservoir. Branches of the celiac artery, SMA, and IMA penetrate the bowel wall and continue to divide into smaller vessels that result in a vascular plexus within the submucosa.[12] At rest, approximately 70% to 80% of the blood flow is distributed to the mucosa, 15% to 25% is directed to the muscular and serosal layers, and the remaining 5% is distributed to the submucosal layer.[13,14] Sixty percent of the blood flow to the mucosa supplies the epithelial cells in the terminal villi, with the remaining 40% supplying the crypts and goblet cells.[13]

Arterioles are arteries approximately 25 μm in diameter. They are the main resistance vessels to the intestine and are composed of three layers, including an outer tunica adventitia, the tunica media, and an inner tunica intima. The adventitia contains nerve cells that are capable of augmenting the tone of the media, which is composed of a thick layer of smooth muscle. This muscle responds to a variety of neurohumoral stimulatory signals, as described later in this chapter. The intima contains endothelial cells.

Arterioles continue to divide, and at approximately the third-order division they become vessels that supply the tips of the mucosal villi and feed a capillary system.

The capillaries, or exchange vessels, allow for the transfer of particles less than 3 nm in size, such as fluid, electrolytes, nutrients, and oxygen, between cells and the bloodstream. A valve-like mechanism located between arterioles and capillaries controls the entry of blood into capillaries. These valves control blood flow into nutrient beds where exchange takes place, but they have no significant effect on vascular resistance. These valves are, however, responsible for physiologic shunting whereby blood flow is redistributed between nutrient beds. The capillaries coalesce to form venules located in the center of each villus and course along the arterial pathways in reverse.

Venules and veins serve as capacitance vessels and contain the majority of blood in the mesenteric circulation. The small bowel venous system contains approximately 300 to 400 ml of blood that can be readily diverted into the systemic circulation. The walls of capacitance vessels are much thinner than the walls of resistance vessels. These walls, however, do contain smooth muscle, which can significantly affect vessel tone and blood volume within these vessels.

Resistance vessels (arterioles) and capacitance vessels (venules) have different sensitivities to various stimuli, including sympathetic, baroreceptor, and chemoreceptor stimulation.[15-17] These vessels are also innervated by entirely separate sympathetic neurons, which allows for differential control.[18] An increase in venous sympathetic activity results in increased tone within this system and the shifting of a large quantity of blood from the mesenteric circulation to the general circulation. This increased venous tone is also reflected on the capillary bed and results in increased hydrostatic pressure causing an influx of fluid from the capillaries into the bowel, which may be manifested as bowel wall edema.

CONTROL MECHANISMS

Multiple control mechanisms of splanchnic blood flow exist, with some degree of interdependency between them. Control mechanisms may be either extrinsic or intrinsic. Extrinsic mechanisms are systemic, whereas intrinsic mechanism function locally. Both mechanisms affect mesenteric blood flow by altering arteriolar smooth muscle vascular tone.[19]

Extrinsic Control of Splanchnic Blood Flow

Extrinsic control begins with hemodynamic parameters, including cardiac output, blood pressure, and blood volume. Inadequate perfusion results in reduction of blood flow to the intestine. Extrinsic mechanisms may also be neuronal, humoral, or combinations of both. Neuronal control mechanisms include the autonomic reflexes. The intestine is directly innervated by both the sympathetic and parasympathetic nervous systems. Stimulation of the sympathetic and parasympathetic nervous systems results in vasoconstriction and vasodilatation, respectively. Sympathetic activity is the most important single determinant of intestinal blood flow and consists of both adrenergic fibers and nonadrenergic, noncholinergic fibers that result in vasoconstriction and vasodilatation, respectively. These fibers originate in the brainstem or medulla. Afferent fibers also arise in the intestine and regulate blood flow by releasing neurohumoral substances. These substances are released by a variety of stimuli, including heat, ischemia, and hypoxia. These fibers also connect to the medulla via the vagus nerve and provide feedback to the sympathetic nervous system.[20]

The sympathetic nervous system tonically innervates small arteries, submucosal arterioles, and the myenteric and submucosal plexuses in the small intestine. Norepinephrine, adenosine triphosphate, and neuropeptide Y are the neurotransmitters released from synaptic vesicles in these nerves. Activation of nicotinic or muscarinic receptors by various drugs augments or diminishes the release of norepinephrine.

Functionally, the parasympathetic nervous system does not play a significant role in augmenting blood flow, although three types of parasympathetic nerves exist and travel with the vagus nerves. The parasympathetic nervous system's main role involves intestinal motility. The neurotransmitter in all three parasympathetic pathways is acetylcholine,[21] which does causes vasodilation. The receptors are located on the endothelium, and activation of these receptors results in the release of nitric oxide from the endothelium. Nitric oxide then diffuses to the vascular smooth muscle, where it results in vasodilation. Vasoactive intestinal polypeptide (VIP) may also play a role as a second messenger to acetylcholine.

Intrinsic Control of Splanchnic Blood Flow

Intrinsic regulation involves the intramural nervous system, endothelial signal transduction, and paracrine secretion of vasoactive substances. The response depends on the receptor status of the tissue in the region of the vasoactive material. Mucosal perfusion is largely regulated by products of the endothelium, mainly the vasodilators prostaglandin I_2 and nitric oxide and the vasoconstrictor endothelin. The intrinsic sympathetic tone is mediated by norepinephrine.[22] The resultant blood flow is determined by contributions from the aforementioned factors.

Intrinsic control involves both metabolic and myogenic mechanisms. Metabolic control links the available blood supply to the nutritional needs of the tissue. Cellular by-products and oxygen depletion result in vasodilation and an increase in tissue perfusion. Myogenic control mechanisms are related to transmural pressure. Increased vascular transmural pressure results in diminished blood flow because of increased vascular resistance and arteriolar vasoconstriction, whereas decreased vascular transmural pressure results in increased blood flow because of diminished vascular resistance and arteriolar vasodilation. The metabolic and myogenic control mechanisms therefore exist to ensure autoregulation of blood flow to the intestine, which remains constant between perfusion pressures of 30 and 100 mm Hg.

Direct intraluminal contact of a variety of agents and intramural neurotransmitters (Box 83–1) also affects

Box 83–1 Agents That Alter or Possibly Alter Mesenteric Blood Flow*

Vasoconstriction

Increased sympathetic tone (adrenergic), decreased parasympathetic tone (cholinergic), catecholamines (except in liver and muscle), angiotensin I, II, and III, antidiuretic hormones, calcium, dopamine (high dose), endothelin-1, epinephrine, leukotrienes, motilin, neuromedin U, neuropeptide Y, norepinephrine (high dose), oxytocin, peptide YY, vasopressin, phenylephrine, potassium, prostaglandin B_2, D, F_1, $F_{2\alpha}$, H_2, serotonin (high dose), somatostatin, thromboxane A_2, vasopressin, methoxamine, metaraminol, propranolol, digoxin, ergotamine, platelet-activating factor, increased P_{O_2}, decreased P_{CO_2}, increased pH, decreased metabolites (K^+, lactate, adenosine, etc.)

Vasodilation

Decreased sympathetic tone, increased parasympathetic tone, acetylcholine, adenosine, adenosine diphosphate, adenosine triphosphate, bradykinin, calcitonin gene–related peptide, carbon dioxide, cholecystokinin, dopamine (low dose), gastric inhibitory peptide, gastrin, glucagon, glucocorticoids, glucose-dependent insulinotropic peptide, histamine, hydrogen, insulin, kallikrein, magnesium, neuromedin N, neurotensin, endothelium-derived relaxing factor, nitric oxide, endothelium-derived hyperpolarizing factor, nitroglycerin, norepinephrine (low dose), catecholamines (only in liver and muscle), opiates (enkephalins), pituitary adenylate cyclase–activating polypeptide, prostacyclin, prostaglandin E and I, secretin, serotonin (low dose), substance P, thrombin, thyrotropin-releasing hormone, uridine triphosphate, vasoactive intestinal polypeptide, xenin, adrenomedullin, xenopsin, phentolamine, isoproterenol, pentagastrin, tolazoline (Priscoline), papaverine, nitroprusside, caffeine, sodium nitrite, aminophylline, decreased P_{O_2}, increased P_{CO_2}, decreased pH, increased metabolites

Unknown or Variable Effects

Bombesin, chromogranin A, chromogranin B, cryptins, cholecystokinin, duodenal cholecystokinin-releasing peptide, duodenal secretin-releasing peptide, enteroglucagon, galanin, gastrin-releasing polypeptide, glucagon, glucagon-like peptides, guanylin, incretins, monitor peptides, neuromedin B, neuromedin C, pancreastatin, pancreatic polypeptide, sorbin, trefoil peptides

*Vasoconstriction diminishes blood flow, whereas vasodilation increases blood flow.

mucosal blood flow.[23,24] The actual role that these agents have in vivo in the local regulation of blood flow is largely uncertain. Increased blood flow occurs with local vasodilation in the submucosal vascular network and can be triggered by a variety of substances that work through both cholinergic and noncholinergic pathways.[25] The observed vasodilation is a result of inhibition of sympathetic activity by VIP-containing sensory neurons.

RESTING STATE

Vascular tone is mediated by a variety of mechanisms, including neural mediators, circulating humoral mediators, paracrine and autocrine mediators, and metabolic vasodilators. Neural and humoral mediators have their largest effect on the heart and large vessels and less effect on the microvasculature in the intestine. Paracrine and metabolic mediators have their greatest effect on the microvasculature and significantly less effect on larger vessels. Metabolic autoregulation plays a significant role in modulating vascular tone in the resting state.

DIGESTION

During digestion, blood flow to the gastrointestinal organs increases and is called postprandial intestinal hyperemia. This increased flow is probably required to maintain intestinal function and integrity.[26-28] The intestinal response to a meal includes an increase in blood flow to the submucosal arterioles.[29] This increase in flow may be up to 200% of the resting state flow.

There are two phases of the response to food: the anticipatory phase and the postprandial phase.[10,26] During the anticipatory phase, mesenteric vascular resistance is increased in response to higher sympathetic activity.[30,31] The increased sympathetic activity causes an increase in cardiac output, blood pressure, heart rate, and splanchnic and renal vascular resistance. The postprandial phase begins as the stomach fills with food.

Postprandially, the mesenteric vasculature dilates and blood flow in the SMA increases within 5 minutes by as much as 60%.[32,33] This increase in mesenteric blood flow occurs as a result of redistribution from the extremities.[34] Peak flow occurs 30 to 90 minutes after ingestion and then declines over a period of 2 to 3 hours.[35] The major increase in blood flow is largely to the mucosal layer and is determined by both neurohumoral and paracrine agents released secondary to chemical and mechanical stimuli,[10,25,26,36-38] as well as digested food (protein, lipid, carbohydrates), bile, and chime.[25] Lipids in combination with bile salts produce the greatest net increase in blood flow, whereas the response to carbohydrates occurs quickest.[35] Distention of the bowel lumen does not affect blood flow.[38,39] Various peptides and hormones, including cholecystokinin, secretin, gastrin, serotonin, and bradykinin, may also contribute to postprandial hyperemia.

Postprandial hyperemia cannot occur simultaneously in the entire gastrointestinal tract. Vasodilation of the entire mesenteric circulation would result in the capacity to accommodate a blood flow of 4 to 5 L/min

(majority of cardiac output). Therefore, blood flow to the mesentery increases in a sequential manner, with areas containing food receiving the majority of flow.[38,40] According to some reports, hyperemia occurs in the segment containing food,[25,41,42] and once the chyme passes a particular region in the intestinal tract, blood flow returns to baseline.[30,43]

AUTOREGULATORY ESCAPE

Blood flow is maintained at normal levels during a variety of physiologic conditions, including those with elevated sympathetic activity and catecholamine levels. This process is called splanchnic autoregulation and acts via multiple mechanisms as described earlier. As long as mean blood pressure remains higher than 70 mm Hg, intestinal blood flow is not dependent on blood pressure. Blood flow may initially decrease under the vasoconstrictor effects, but then it gradually returns toward normal. Resumption of blood flow is most likely a result of local metabolic factors that result in vasodilation, including ischemia. Blood flow, under such circumstances, is preferentially increased to the submucosa over the mucosa, which probably explains why the mucosa may sustain ischemic damage with the bowel still remaining viable if flow is restored. When blood pressure drops below 70 mm Hg, intestinal perfusion will have a linear relationship to blood pressure. Below a pressure of 40 mm Hg, the bowel will become ischemic and sustain injury.[44]

DOPAMINE

Administration of low-dose dopamine (<5 μg/kg/min) produces preferential dopaminergic and β-adrenergic effects over α-adrenergic effects. Activation of these receptors results in dilation of the splanchnic circulation and a net increase in splanchnic blood flow.[45,46] This blood flow, however, is redistributed away from the gut mucosa,[47] and although net splanchnic flow increases, mucosal ischemia worsens. Mucosal ischemia results in increased translocation of microorganisms and endotoxins into the portal circulation. Dopamine also increases hepatic ischemia, which results in decreased clearance of proinflammatory cytokines. To conclude, low-dose dopamine probably worsens mesenteric ischemia.[48-50] Besides being harmful to the gastrointestinal tract, recent evidence also suggests that dopamine is not useful in the treatment or prevention of renal dysfunction and is harmful to the endocrine, immunologic, and respiratory systems in critically ill patients.[51] The long upheld practice of administering low-dose dopamine to improve renal function and mesenteric perfusion should be abandoned.

CATECHOLAMINES

Sympathetic stimulation is a major determinant of tone in both the arterial resistance vessels and venous capacitance vessels. Table 83–1 lists some commonly used intravenous agents, including catecholamines, that augment mesenteric vascular blood flow. Vascular tone is largely dependent on the type of receptors stimulated. Receptor stimulation depends on the type of catecholamine and its concentration at the receptors. Understanding the effects of catecholamines on mesenteric blood flow

Table 83–1 Commonly Used Intravenous Agents That Augment Mesenteric Vascular Blood Flow*

Agent	Mechanism of Action in Normovolemic Patients
Amrinone	Direct inhibition of phosphodiesterase results in increased cAMP and vasodilation
Dobutamine	Mild β_2 stimulation
Dopamine	Dopaminergic effects at 1 μg/kg/min†
	Predominately β effects between 3 and 10 μg/kg/min
	Combined α and β between 10 and 20 μg/kg/min
	Predominately α at >20 μg/kg/min
Epinephrine	Renal vasoconstriction at less than 1 μg/min
	Cardiac β stimulation between 1 and 4 μg/min
	Increasing α stimulation between 5 and 20 μg/min
	Predominantly α at >20 μg/min
Isoproterenol	Pure β-agonist
Nitroglycerin	Directly relaxes arteries and veins
	Venodilation predominates at doses <50 μg/min
	Arterial vasodilation predominates at doses >200 μg/min
Nitroprusside	Directly dilates arteries and veins
Norepinephrine	Predominately α effects
Papaverine	Blocks angiotensin II– and vasopressin-mediated vasoconstriction
Phenylephrine	Pure α-agonist

*Generally, vasoconstriction occurs with stimulation of α-receptors, which diminishes mesenteric blood flow, whereas vasodilation occurs with stimulation of β-receptors, which increases mesenteric blood flow. These effects, however, are dependent on the location of the receptors, which is shown in Figure 83–9; the density of receptors in the mesenteric arterial and venous circulation, which is shown in Table 83–2; the affinity of the agent for the receptor subtype; the plasma concentration of other agents; the preexisting tone of the mesenteric vessels; and the volume of blood in the circulation. The effects of catecholamines administered during hypovolemia depend on the blood volume in the splanchnic reservoir.

†See text specific to dopamine action on mesenteric vascular flow.

cAMP, cyclic adenosine monophosphate.

requires a full understanding of catecholamine actions on the entire splanchnic circulation.[11] The receptors located on various splanchnic beds are detailed in Table 83–2 and shown in Figure 83–9. The hepatic arterial vascular bed contains mainly α_1-, a smaller quantity of α_2-, and an intermediate number of β_2-receptors.[52] The hepatic capacitance vessels, including the sinusoids, have α-adrenergic receptors, and the hepatic veins have both α- and β_2-adrenergic receptors. Activation of α-receptors results in vasoconstriction, whereas activation of β_2-receptors results in vasodilation. The intestinal resistance (arterial) vessels have roughly equal numbers of α_1- and β_2-receptors and a lesser number of α_2-receptors. The mesenteric venous system contains largely α_1-, a smaller number of α_2-, and a questionable number of β_2-receptors. Activation of α-receptors results in venoconstriction and a decrease in venous capacitance, whereas activation of β_2-receptors results in venodilation and an increase in venous capacitance.

Sympathetic activity causes a variety of hemodynamic consequences, including an increase in cardiac output. This increased output is dependent on an increase in blood volume, which largely comes from the splanchnic circulation. When arterial flow decreases, pressure within the venous capacitance vessels also decreases. The decrease in venous pressure is minimized by elastic recoil in the veins, which maintains a pressure adequate to force the splanchnic vascular volume into the systemic circulation. This phenomenon of elastic recoil can function even as arterial inflow is decreased. These two methods of venoconstriction are also responsible for the decreased splanchnic flow and shift of blood volume from the splanchnic circulation to the systemic circulation with exercise or hemorrhage. With mild exercise, there is a 35% decrease in splanchnic blood volume. In cases of moderate hemorrhage, approximately 65% of the total splanchnic blood volume can be directed into the systemic circulation.[53]

Table 83–2 Vascular Bed Receptor Subtypes

	Receptor Subtype		
Vascular Bed	α_1	α_2	β_2
Mesenteric arterial	+++	++	−−−
Hepatic arterial	+++	+	−−
Mesenteric venous	+++	+	−?

From Gelman S, Mushlin PS: Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 100:434-439, 2004.

SUMMARY

Nature has developed a mesenteric circulatory system that is rich in collateral circulation. A significant survival advantage is probably held by animals and people who foster a rich blood supply to their mesenteric circulation. Understanding the blood supply to the mesenteric circulation is critical for clinicians and especially surgeons, for all resectional and other procedures performed within the abdomen have the potential to result in

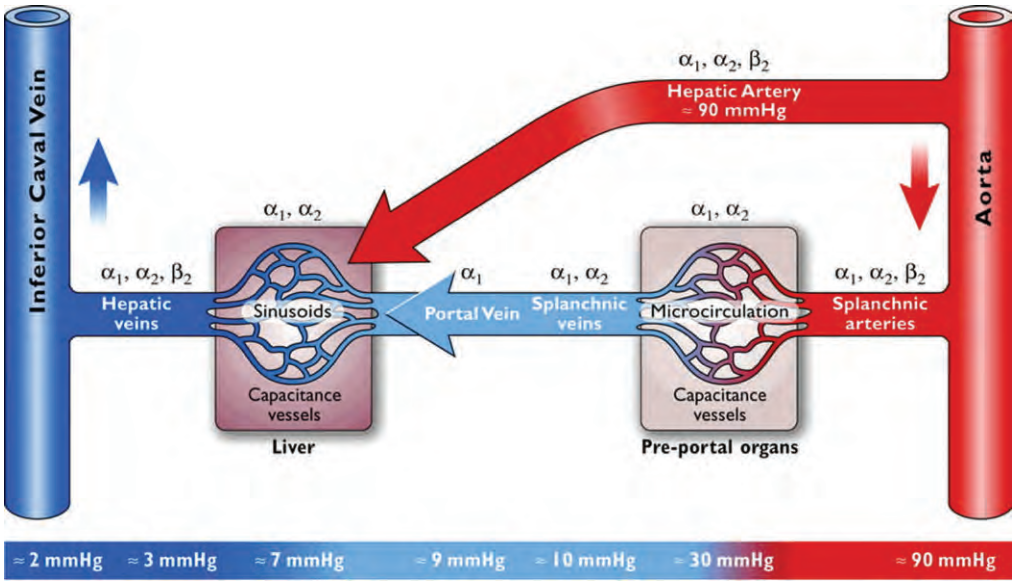

Figure 83–9. Diagrammatic representation of the splanchnic vasculature. Splanchnic arteries represent all arterial vessels of the preportal organs; splanchnic veins represent the pooled venous blood from all these organs. The distribution of adrenoceptor subtypes (α_2, β_2) and approximate intravascular pressures are shown for corresponding segments of the splanchnic vasculature. (From Gelmen S, Mushlin PS: Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology 100:434-439, 2004.)

ischemia of the mesenteric organs if done without attention to their vascular supply. The complexity of the situation grows exponentially when dealing with the multitude of pathologic states that can affect vessel patency, as well as the variety of anatomic variations, including the presence of collateral vessels.

Regulation of mesenteric blood flow is an extremely complex process that involves a variety of control mechanisms operating at multiple levels. Adding to the complexity, these control mechanisms directly influence and augment each other. Changes that occur within humans after ingestion of a meal further complicates the scenario. Clinically, it is essential to understand where various receptors are located and their function when stimulated. It is also crucial to understand the effects of various pressor agents on both the systemic and mesenteric systems and realize that progress is still being made in understanding the effects of these agents. The best example of this continues to be dopamine. Low-dose dopamine was once touted as being a drug that improves both renal and mucosal blood flow. Recent studies have now shown that it is actually harmful and should not be used for this indication. With the extremely large number of chemicals and hormones that directly affect the mesenteric circulation and the large number of disease states that affect patients, there will probably be further important changes in the manner in which we practice medicine in the future.

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Chapter

84

Mesenteric Ischemia

Anthony J. Comerota ▪ Matthew Todd Miller

Mesenteric ischemia is a frequently lethal condition resulting from critically reduced perfusion to the gastrointestinal tract. It has acute and chronic forms that involve both the arterial and venous sides of the circulation. Common to all forms of mesenteric ischemia are the diagnostic difficulties and challenging management decisions accompanying these patients. First described in the 1500s, diagnosis and management of mesenteric ischemia consisted of abdominal exploration with resection of the involved bowel, but the diagnosis was often made too late to save the patient. In 1950, using the newly delineated principles of vascular surgery, Klass[1] performed an early abdominal exploration with superior mesenteric artery (SMA) embolectomy in a patient with acute mesenteric ischemia. Although the patient died of acute heart failure during the postoperative period, the significant advance of visceral revascularization was apparent when normal bowel was observed at autopsy. In the years that followed, numerous cases of successful mesenteric embolectomy with patient survival were reported, and operations were developed for revascularization of patients with acute and chronic mesenteric ischemia.[2] It is conceptually important that physicians involved in the care of patients with mesenteric ischemia, especially acute mesenteric ischemia, recognize that the major advances in care and the improved survival of these patients have been achieved as a result of revascularization of the ischemic bowel.

Despite the remarkable advances in vascular surgical technique, vascular imaging, percutaneous intervention, and surgical critical care, mesenteric ischemia remains a complex and often disheartening disease. Acute mesenteric ischemia is a life-threatening vascular emergency that requires a high degree of clinical suspicion and early intervention to avoid a poor outcome. Unfortunately, recent reports indicate that its incidence is on the rise.[3,4] Mesenteric ischemia accounts for 0.1% of hospital admissions and 1% to 2% of admissions for abdominal pain.[5] One population-based study showed the incidence of mesenteric ischemia to be 9 per 100,000 person-years; however, as anticipated, the incidence increases substantially with age.[6] The reported mortality ranges from 24% to a high of 96%, with an average of 69%.[7]

The mesenteric arterial circulation comprises three major aortic branches with multiple collaterals: the celiac axis, the SMA, and the inferior mesenteric artery (IMA). The celiac axis consists of three major branch vessels to the foregut: the common hepatic, left gastric, and splenic arteries. The SMA supplies blood flow to the majority of the small intestine and the right colon and a portion of the transverse colon. Finally, the IMA is responsible for blood flow to the remaining transverse, descending, and sigmoid colon. The arterial collaterals with their anastomotic arcades often allow for compensatory intestinal blood flow when one or more of the major visceral arteries becomes diseased or occluded, most commonly as a result of chronic disease. Therefore, patients with acute or, more often, chronic disease may be protected from intestinal ischemia because of their collateral circulation (Fig. 84–1). It is commonly observed that in patients with chronic mesenteric ischemia, two of the three major visceral arteries are diseased, and these patients have symptoms of intestinal ischemia. However, patients with acute arterial occlusion of one major artery, usually the SMA, experience severe symptoms because the compensatory collateral circulation is inadequate.

The splanchnic circulation receives approximately 25% of the resting and 35% of the postprandial cardiac output.[8-10] Seventy percent of the mesenteric blood flow is directed to the mucosal and submucosal layers of the bowel, with the remainder supplying the muscularis and serosal layers.

Not surprisingly, the mucosal layer of the bowel wall is the most severely affected by acute mesenteric ischemia, and abnormalities have been observed as early as 10 minutes after arterial occlusion in experimental models.[11] Mucosal integrity is compromised early, and bowel wall edema, loss of capillary integrity leading to bacterial translocation and endotoxemia, and exudation of fluid into the bowel lumen ensue. The mucosa sloughs, with ulcerations left in the bowel wall. Up to this point the intestine remains viable; however, if the

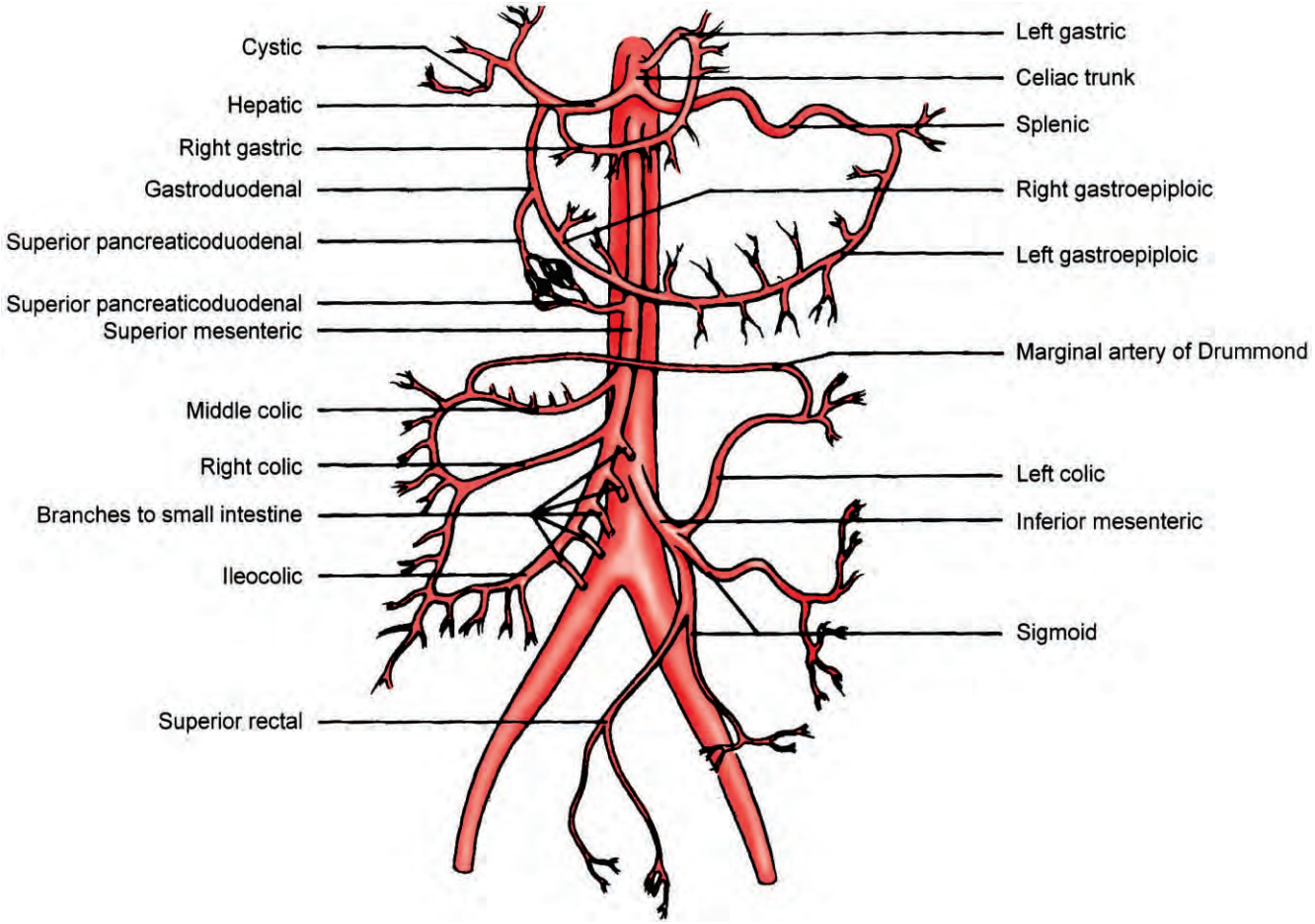


Figure 84–1. The mesenteric circulation. (From Schwartz LB, Davis RD Jr, Heinle JS, et al: The vascular system. In Lyerly HK, Gaynor JW Jr [eds]: The Handbook of Surgical Intensive Care, 3rd ed. St Louis: Mosby–Year Book, 1992, p 287.)

ischemia progresses, there is ongoing necrosis of the muscularis and serosal layers of the bowel wall, at which point the involved segment is no longer salvageable.

Although acute mesenteric ischemia results in profound illness, correcting the ischemia and reperfusing the ischemic bowel can cause further deterioration because of myocardial depression and a generalized systemic inflammatory response. Escape of oxygen free radicals, myocardial depressant factor, and other products of tissue injury into the circulation contributes to the reperfusion phenomenon, which can lead to disseminated intravascular coagulation and multiorgan system dysfunction. This is mentioned not to discourage mesenteric revascularization, but to emphasize the importance of expedient diagnosis and reversal of the ischemia. Hypoxia disrupts bowel wall metabolism and thereby causes cellular damage leading to profound vasoconstriction, which further compromises tissue perfusion, even after large-vessel revascularization. Early intra-arterial infusion of vasodilators has improved mesenteric revascularization and resulted in more favorable outcomes.[2,8,12,13] A limited experience with infusion of superoxide free radical scavengers has shown benefit in reducing mesenteric reperfusion complications[14]; however, the benefit of superoxide free radical scavengers remains under investigation.

ACUTE ARTERIAL MESENTERIC ISCHEMIA

Unfortunately, the prognosis of patients with acute mesenteric ischemia is poor and, in most communities, has not changed during the past 30 or more years. This is true despite the surgical, technical, endovascular, and pharmacologic advances that have occurred during the same time frame. This state of affairs should cause one to reflect on the disease process, appreciate the benefit of revascularization, and recognize that delay in diagnosis is costly and that traditional approaches to these difficult patients require modifications to improve outcomes.

Insight can be gained by reviewing advances in the management of mesenteric ischemia and putting them into the perspective of personal and clinical experience. Personal observation has revealed that patients who undergo emergency exploratory laparotomy without a definitive diagnosis preoperatively have a prohibitively

high mortality rate. A common scenario in these patients is resection of ischemic bowel without mesenteric revascularization. Absent a preoperative diagnosis and knowledge of patients' underlying anatomy and pathophysiologic contributors to their mesenteric ischemia, attempts at revascularization are often unsuccessful and are generally ill advised. On the other hand, in patients in whom the diagnosis is made preoperatively and who undergo hemodynamically guided aggressive resuscitation with appropriately planned revascularization that addresses the anatomic and pathophysiologic causes of the mesenteric ischemia, the likelihood of survival is maximized.

These clinical observations are supported by a number of animal experiments performed by Boley and colleagues.[15-17] They demonstrated that when mesenteric blood flow is reduced, either from a systemic cause or from mesenteric obstruction, vascular resistance increases within several hours as a result of mesenteric vasoconstriction. If normal mesenteric blood flow could be promptly restored, the vasoconstriction was immediately reversible. If, however, vasoconstriction was present for several hours, it remained even after large-artery mesenteric occlusion was corrected because of the profound vasospasm. These experiments were followed by others demonstrating that small-vessel mesenteric vasoconstriction was relieved by the intra-arterial infusion of papaverine into the SMA; therefore, a method of treating the vasoconstriction was proposed.

These experimental observations ultimately led to an aggressive diagnostic and revascularization approach to acute mesenteric ischemia. The improved outcomes with precise diagnosis and revascularization and the recent literature demonstrating the benefit of percutaneous techniques form the basis for the recommendations outlined in Figure 84–2. Early diagnosis is essential and is most often achieved by having a low threshold for arteriography and placement of a catheter for the infusion of papaverine. Using this approach of early arteriographic diagnosis with catheter-directed papaverine infusion, Boley et al.[2] and Clark and Gallant[18] reduced the mortality to less than 50% in patients with acute intestinal ischemia. Even in the subset of patients with acute SMA embolism in whom the diagnosis was made promptly (≤12 hours), Boley et al.[19] reported a 33% mortality rate. Though high, this is considered a substantial improvement over what had traditionally been reported.

Embolic Occlusion

Embolic occlusion of the SMA accounts for 40% to 50% of cases of acute mesenteric ischemia.[3,12] Most emboli originate in the heart and are secondary to myocardial infarction, cardiac arrhythmia, endocarditis, cardiomyopathy, ventricular aneurysm, valvular disorders, or depressed left ventricular function as a result of ischemic heart disease (Box 84–1). Rarely, a paradoxical embolus traveling through a patent foramen ovale from a thrombus in the venous system is the cause. Most mesenteric emboli lodge in the SMA because it branches from the aorta at an oblique angle, as opposed to the celiac artery, which is nearly perpendicular to the axis of the aorta. More than 50% of emboli lodge in the mid to distal segment of the SMA. The SMA tapers after major branch points, and emboli are commonly found distal to the middle colic artery. Less than 15% of emboli occlude the SMA at its origin.

The point of occlusion affects the magnitude and distribution of the ischemia that it produces. Occlusion at the origin of the SMA causes intestinal ischemia extending from the ligament of Treitz to the transverse colon, whereas occlusion distal to the middle colic artery preserves the right colon and proximal part of the small bowel. As emphasized earlier, the key to successful management of patients with acute mesenteric ischemia is a high index of suspicion leading to early diagnosis, aggressive resuscitation, and early mesenteric revascularization.

Patients with acute SMA embolism usually have sudden and dramatic symptoms that reflect the abruptness of the occlusion and the severity of ischemia distal to the embolus because of the absence of collateral

Box 84–1 Etiology and Distribution of Mesenteric Ischemia

Acute Mesenteric Ischemia

- Emboli (50%)
  - Arrhythmia
  - Valvular disease
  - Myocardial infarction
  - Hypokinetic ventricular wall
  - Cardiac aneurysm
  - Aortic atherosclerotic disease
  - Iatrogenic
- Thrombosis (25%)
  - Atherosclerotic disease
- Nonocclusive (5% to 15%)
  - Pancreatitis
  - Heart failure
  - Sepsis
  - Cardiac bypass
  - Burns
  - Renal failure
  - Medications
- Venous occlusion
  - Hypercoagulable state
  - Sepsis
  - Compression
  - Pregnancy
  - Portal hypertension
  - Malignancy

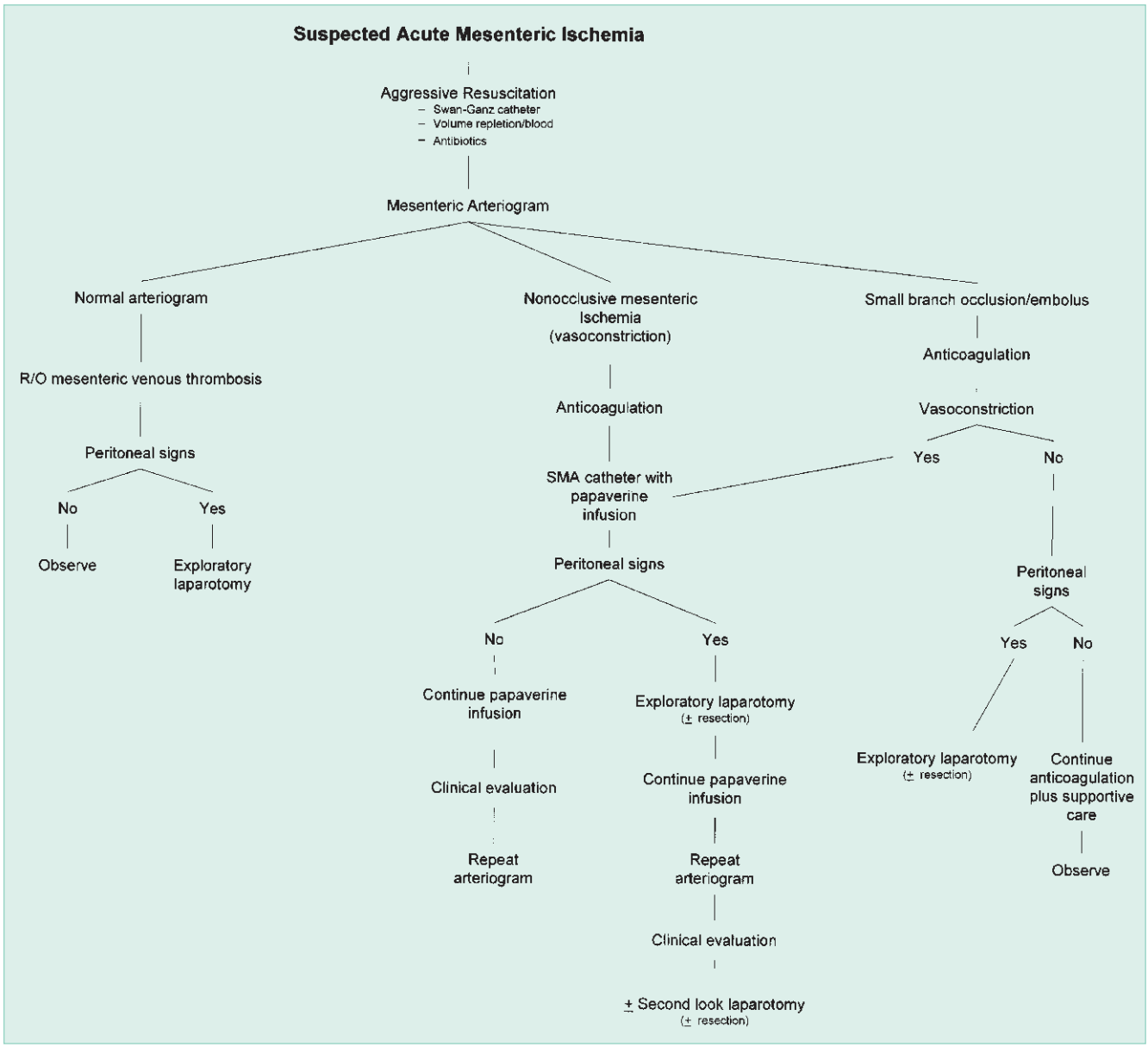
Chronic Mesenteric Ischemia

- Atherosclerotic disease
- Arterial hyperplasia/dysplasia
- Inflammatory disease

circulation. As with all forms of acute mesenteric ischemia in patients who are evaluated early after the onset of occlusion, their complaints of severe abdominal pain contrast markedly with the absence of physical findings. Rectal examination is not generally helpful because the presence of occult blood is typically a late occurrence. Early on the pain may be colicky in nature, but it then becomes constant. Nausea and vomiting may occur in some patients and, less commonly, diarrhea, which may lead to diagnostic confusion.

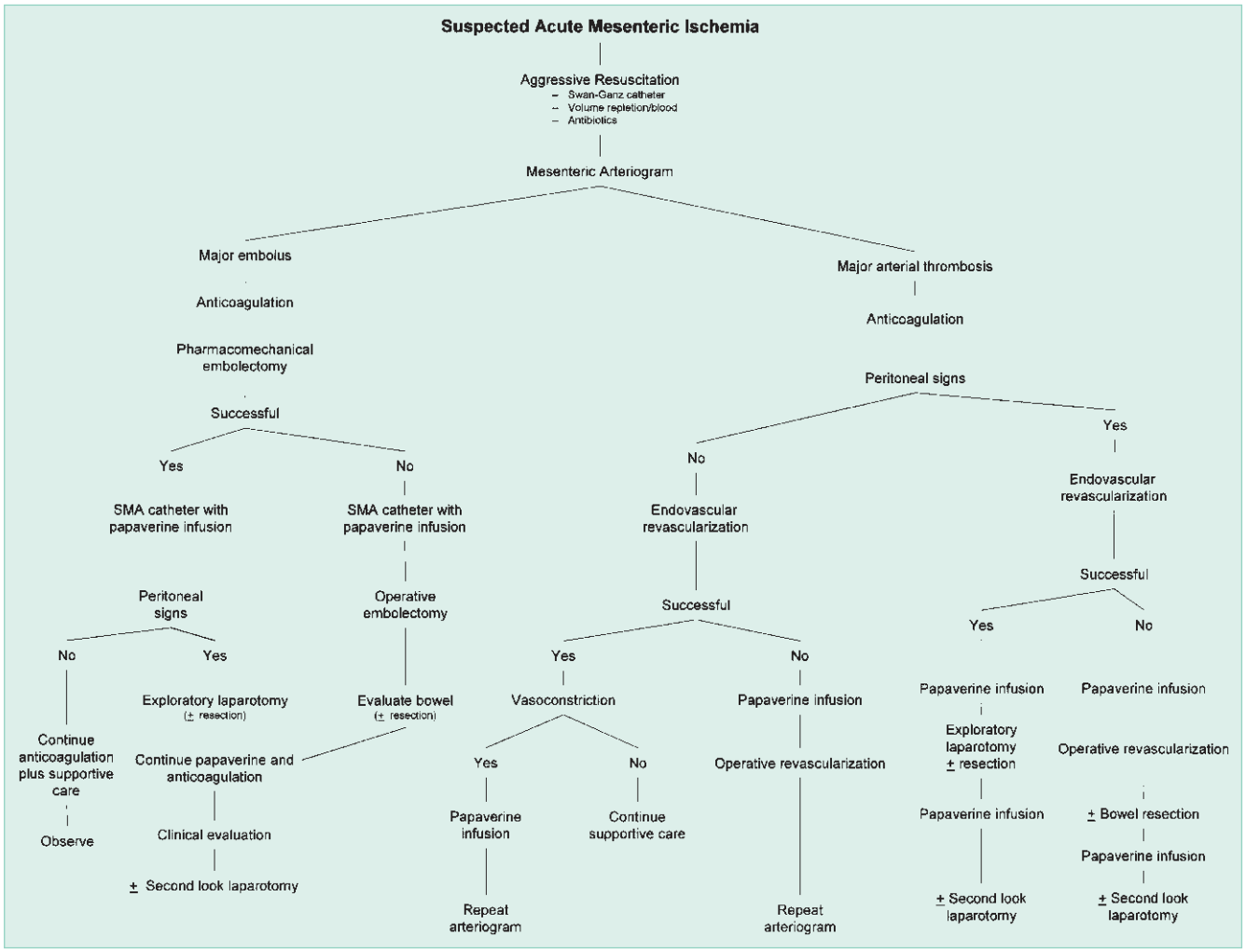
Thrombotic Occlusion

Acute thrombotic occlusion generally occurs in conjunction with chronically diseased vessels and may have a somewhat more insidious onset because of previously developed collateral circulation. These patients account for 25% to 35% of cases of acute mesenteric ischemia. A history of general abdominal discomfort, anorexia, and perhaps symptoms of postprandial abdominal pain, weight loss, and food aversion before their acute episode assists an astute clinician in differentiating between acute thrombotic versus acute embolic occlusion in some patients. Unfortunately, such a history is not found consistently because many patients with acute thrombotic occlusion have no symptoms until the occlusive event. This may be due to rupture of a previously noncritical atherosclerotic plaque that abruptly occludes the vessel, a pathophysiologic catastrophe similar to embolic occlusion because the patient may not have had significant stenosis before the acute event.



A

Figure 84–2. **A** and **B,** Recommended treatment of acute mesenteric ischemia. R/O, rule out; SMA, superior mesenteric artery.



B

Figure 84–2, cont'd.

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia, which accounts for approximately 20% of all cases of acute mesenteric ischemia, has manifestations similar to those of mesenteric arterial thrombosis, but it occurs with patent mesenteric arteries. Splanchnic vasoconstriction is the underlying pathophysiologic process and is precipitated by hypoperfusion from medications, depressed cardiac output, or renal or hepatic disease.[13] When blood pressure in the bowel falls below a critical pressure of 40 mm Hg, ischemia develops and eventually leads to infarction and bowel necrosis.

Diagnosis of nonocclusive mesenteric ischemia can be especially difficult in hospitalized patients, who are often critically ill and unable to complain because of either ongoing sedation or intubation. The diagnosis is often delayed because their clinical manifestations may be wrongfully attributed to their underlying critical illness. Older patients who have acute myocardial infarction, congestive heart failure, dysrhythmia, sepsis, or hypovolemia or use splanchnic vasoconstrictors are at increased risk for nonocclusive mesenteric ischemia. Other patient populations at particularly high risk are hemodialysis patients and those with a recent history of cardiopulmonary bypass, major abdominal surgery, pancreatitis, aortic dissection, or burns.[20,21]

Diagnosis

Early diagnosis is the key to successful management of most diseases and is especially true for acute mesenteric ischemia. Acute arterial mesenteric ischemia results from a number of causes (see Box 84–1), which if uncorrected often lead to intestinal infarction. Recognition of acute mesenteric ischemia can be difficult because most patients have nonspecific symptoms of abdominal pain. *Abdominal pain out of proportion to the findings on physical examination and persisting beyond 2 to 3 hours* is the classic picture. Diarrhea, nausea, vomiting, and anorexia can also be part of the initial symptom complex. Fifteen

percent of patients report melena or hematochezia, and occult fecal blood is found in at least half the patients.[22] Leukocytosis is common. However, with delay in diagnosis and progression of ischemia to full-thickness bowel wall injury, the manifestation is one of an acute abdomen, with findings of distention, guarding, rigidity, and hypotension, consistent with overt peritonitis and its septic consequences.

The patient should have intravenous access established with blood drawn and sent for a complete blood count with differential, electrolytes, evaluation of renal and hepatic function, blood urea nitrogen, creatinine, amylase, lipase, prothrombin time, activated partial thromboplastin time, and cardiac enzymes. Frequently, the laboratory findings are consistent with hemoconcentration resulting from the patient's hypovolemia and dehydration. The white blood cell count is often elevated and metabolic acidosis is present. Hyperamylasemia and elevations in lactate dehydrogenase, aspartate aminotransferase, and creatine phosphokinase levels are common. If hyperkalemia and hyperphosphatemia are present, bowel infarction should be suspected.[23] An electrocardiogram is performed and the patient placed on a monitor to evaluate cardiac rhythm. Depending on the history and physical findings, a nasogastric tube can reduce further abdominal distention and vomiting. Patients with cardiac disease who are hypovolemic should have a Swan-Ganz catheter placed to assist in monitoring their resuscitation.

Plain Films

Plain films of the abdomen (supine, upright) and the chest (anteroposterior) are obtained, predominantly to exclude other processes such as bowel obstruction or free air as a result of perforation. Up to 25% are normal in appearance. Portal venous gas is an advanced finding that suggests intestinal necrosis. Suspicious findings on plain films include a nonspecific ileus pattern with dilated, fluid-filled loops of bowel, thumbprinting, separation of bowel loops (edematous mesentery), intramural gas, and free air. In the majority of cases, however, plain films are nondiagnostic.[24,25]

Ultrasonography

Although duplex ultrasonography can be helpful in patients with chronic mesenteric ischemia, its utility in patients with acute mesenteric ischemia is limited. Even when requested for elective evaluation of patients with chronic ischemia, up to 40% cannot be adequately assessed because of body habitus or bowel gas.[26] These limitations are magnified when ultrasonography is attempted in patients with acute mesenteric ischemia. Abnormalities such as calcification, thrombus, and arterial stenosis or occlusion can occasionally be identified in the acute setting, assuming that the patient can cooperate, does not have dilated bowel that interferes with sound wave penetration, and has a favorable body habitus. Though able to evaluate the proximal mesenteric circulation, duplex evaluation of peripheral mesenteric perfusion is indirect and based on the velocity profile of the proximal artery.[27] Duplex sonography may have its greatest utility after revascularization[28] because patients with persistent abnormalities face high mortality with graft failure; therefore, planned reintervention to preserve mesenteric perfusion is prudent.

Computed Tomography

Computed tomography (CT) has rapidly become the initial diagnostic test for most patients with abdominal disease. It is a quick (approximately 19 seconds to scan the abdomen and pelvis), noninvasive, easily tolerated test that can show the indirect findings of arterial bowel ischemia and may show the arterial occlusion or mesenteric venous thrombus. Moreover, it is available in most institutions.

Findings on CT scans associated with bowel ischemia include dilation of the bowel lumen, bowel wall thickening, abnormal bowel wall enhancement, arterial occlusion, venous thrombosis, and intramural or portal venous gas. Dilation of an ischemic bowel segment suggests interruption of normal peristaltic activity. Symmetrical bowel wall thickening greater than 3 mm in a distended segment of bowel suggests ischemia. Greater degrees of bowel wall thickening should raise suspicion of mesenteric venous thrombosis (MVT). Oral contrast should be avoided in patients with suspected mesenteric ischemia because it may obscure subsequent arteriographic imaging of the mesenteric vasculature, which usually leads to the definitive diagnosis. Intravenous contrast is useful in demonstrating the heterogeneity of the ischemic bowel wall (lack of bowel wall enhancement)[29] and may show occlusion of mesenteric arteries if given by rapid bolus administration. Correlation between ischemia and CT scan findings is delineated in Table 84–1.[30]

Taourel et al.[31] reported a sensitivity of 64% and specificity of 92% for the CT diagnosis of acute arterial mesenteric ischemia. However, CT is the diagnostic technique

Table 84–1 Correlation Between Pathologic Damage and Computed Tomography Findings

Pathologic Damage	CT Findings
Vasoconstriction	Wall hyperdensity Absence of wall enhancement
Increased capillary permeability	Wall thickening Bowel dilation
Mucosal cellular necrosis	Pneumatosis Gas in mesenteric vein branches Gas in portal vein branches
Transmural bowel necrosis	Pneumoperitoneum Retropneumoperitoneum Ascites

From Angelelli G, Scardapane A, Memeo M, et al: Acute bowel ischemia: CT findings. Eur J Radiol 50:37-47, 2004.

of choice for acute MVT, with a sensitivity exceeding 90%.[32,33] As CT scan technology has advanced, three-dimensional reconstructions of the aorta and its branches show additional detail, which has improved the sensitivity and specificity to 94% to 96%.[31,34] As the technology continues to evolve, newer-generation scanners will further improve diagnostic capability. The limitations and risks of CT angiography center around patients with renal insufficiency or contrast allergies, limitations of contrast volume, and metal artifacts obscuring the area of interest.

Magnetic Resonance Angiography

When compared with catheter arteriography, current contrast-enhanced (gadolinium) three-dimensional magnetic resonance angiography (MRA) performs favorably in the common and proper hepatic arteries, the splenic artery, the SMA, and the portal, superior mesenteric, and splenic veins. Agreement is poor, however, for evaluation of the intrahepatic arteries, the SMA branches, and frequently the IMA, and catheter-directed arteriography remains necessary for detailed evaluation of these branch vessels.[35] However, because of the compromised clinical status of many patients and the need for urgent diagnosis, MRA is not often the procedure of choice.

MRA is frequently used for the evaluation of patients suspected of having chronic mesenteric ischemia since it can provide both anatomic and functional information regarding mesenteric perfusion. Because deoxyhemoglobin is paramagnetic and oxyhemoglobin is not, an increase in deoxyhemoglobin reduces the T2 of blood. By using this effect, patients with chronic mesenteric ischemia have been shown to have a decrease in the percentage of oxygenated blood in the superior mesenteric vein.[36] MRA spares patients the side effects of ionizing radiation and contrast toxicity.[27]

Arteriography

Catheter-directed contrast arteriography has been and remains the method of definitive diagnosis for acute and chronic mesenteric ischemia. Through the arteriographic access, catheter-based interventions are being performed with increased frequency in both patients with acute disease and those with chronic disease. Arteriograms establish the diagnosis; assist in differentiating between acute embolic, thrombotic, or nonocclusive mesenteric ischemia as the cause; and allow proper planning of the revascularization procedure. Anteroposterior (AP) and lateral views of the aorta and the mesenteric branches are required for proper arteriographic evaluation. The lateral view is particularly important to examine the proximal celiac artery and SMA, which overlap the aortic contrast column on AP views.

Acute embolic occlusion of the SMA is characterized arteriographically by abrupt occlusion of the artery, usually at a branch point where the vessel tends to narrow (Fig. 84–3). If imaged acutely, a meniscus sign (crescent) is often observed. If secondary thrombosis occurs proximal to the embolus, the classic meniscus sign of embolic occlusion will be obscured. The specific location of the occlusion depends on the size of the embolus, with the most common location being just distal to the middle colic artery, at which point the SMA rapidly narrows. Because these patients generally have a cardiac source for the embolus and peripheral atherosclerosis is not etiologically related to their mesenteric ischemia, the aorta and other arteries may show little atherosclerotic disease. Emboli rarely lodge in the proximal SMA (<15%).

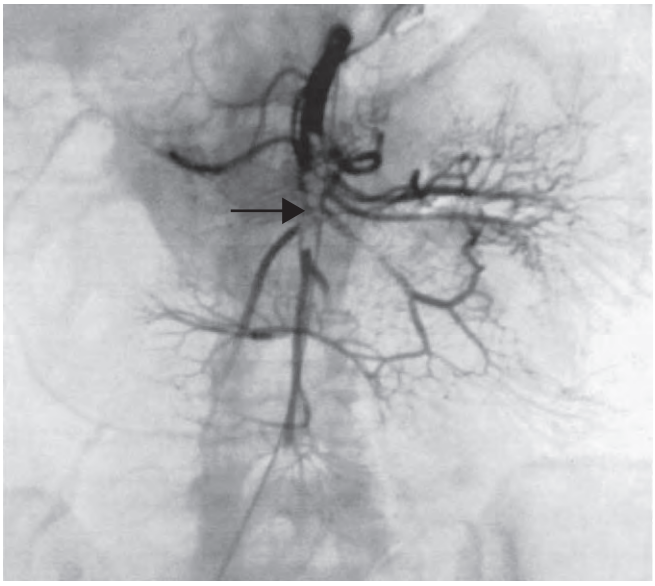
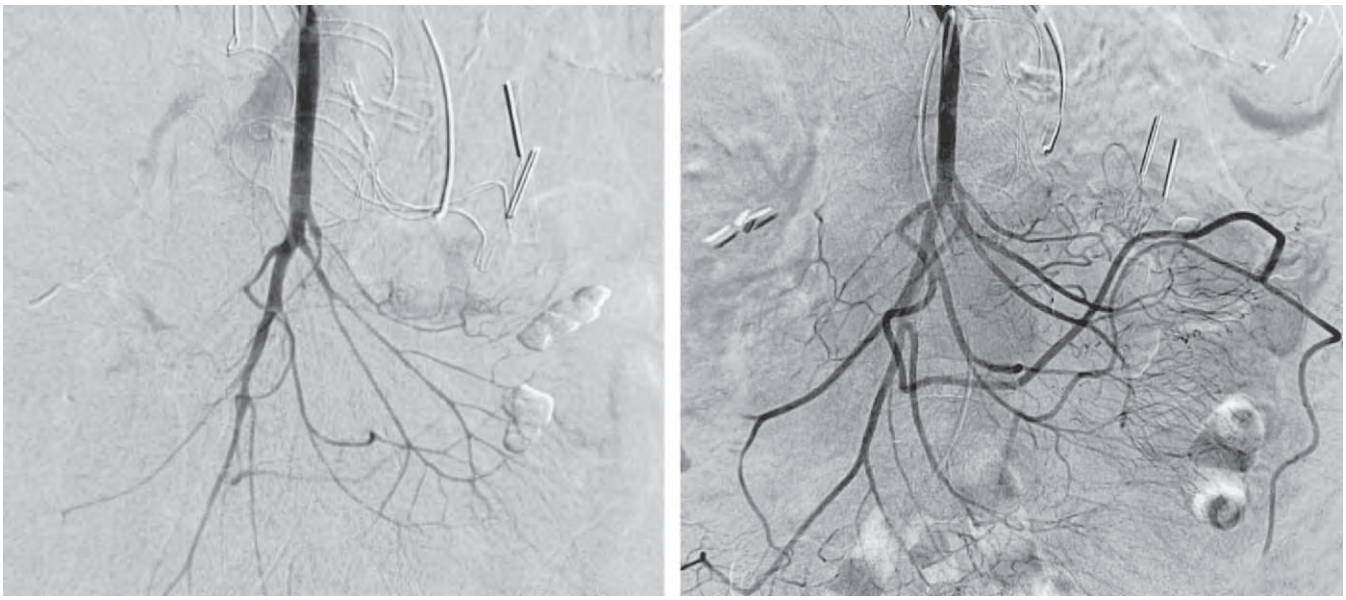


Figure 84–3. Acute embolus (*arrow*) occluding the superior mesenteric artery. (From Hladík P, Raupach J, Lojík M, et al: Treatment of acute mesenteric thrombosis/ischemia by transcatheter thromboaspiration. Surgery 137:122-123, 2005.)

Acute thrombotic occlusion usually occurs in an artery with significant underlying atherosclerosis. Atherosclerotic plaque most frequently develops at branch points of arteries from the aorta, most commonly at the origin of the celiac artery, SMA, and IMA. When segmental occlusion occurs as the result of chronic disease, the chronicity of the process is suggested by the development of collateral circulation to the distal branches. Delayed arteriographic imaging is often required to properly opacify the distal vessels. Patients with mesenteric arterial thrombosis frequently have more advanced atherosclerotic disease in their abdominal aorta and its branches than do those with acute embolic occlusion.

The diagnosis of nonocclusive mesenteric ischemia is typified by diffuse spasm of the SMA branches with intermittent areas of narrowing and dilation. Perfusion is markedly compromised because the intense distal vasospasm causes high peripheral resistance, with frequent reflux of contrast into the aorta. The distal mesenteric arterial arcades are not usually visualized. Patients with acute critical illness, those taking vasopressors, and those who are hypovolemic can demonstrate these arteriographic findings as a result of the body's physiologic response to hypovolemia. Additionally, acute proximal mesenteric arterial occlusion is often followed by distal



A B

Figure 84–4. Arteriogram of a patient with typical nonocclusive mesenteric ischemia. **A,** Characteristic distal pruning of the mesenteric arcades. **B,** Repeat arteriogram after 24 hours of papaverine infusion demonstrating improved (normal) distal perfusion.

vasospasm, thus compounding the severity of the intestinal ischemia. This underscores the need for rapid and effective resuscitation of these patients, performed most efficiently while monitoring their cardiopulmonary hemodynamics. Aggressive rehydration reduces the compensatory mesenteric vasoconstriction and decreases the nephrotoxic effects of the contrast agent.

Patient Management

Effective management of patients with mesenteric ischemia is linked to (1) early diagnosis, (2) aggressive resuscitation, (3) early revascularization, and (4) ongoing supportive care. Resuscitative efforts should begin immediately on suspicion of the diagnosis because these patients often have multiple medical comorbid conditions and associated cardiac disease. Early and aggressive resuscitation is aimed at correcting the patient's hypovolemia and low cardiac output. A Swan-Ganz catheter is frequently required to gauge the patient's response. Because the mucosal layer of the bowel wall is the most sensitive to ischemia, bacterial translocation should be anticipated and intravenous antibiotics used to treat the associated bacteremia. Catheter-directed papaverine to reverse the often severe mesenteric vasospasm is initiated early after arteriography. Anticoagulation is given to prevent propagation of mesenteric thrombus. The most expedient evaluation of patients with acute arterial mesenteric ischemia is mesenteric arteriography. Further delay caused by relatively insensitive or nonspecific diagnostic testing puts the patient at greater risk for a poor outcome. Once the nature of the mesenteric ischemia is delineated, a specific plan for revascularization can be initiated. A treatment-specific algorithm is summarized in Figure 84–2.

A normal arteriogram should include its venous phase and be followed by a CT scan, if not already performed, to exclude the diagnosis of MVT. If the diagnosis of MVT is excluded, the patient should be aggressively supported and observed. If peritoneal signs are present, exploratory laparotomy should be performed.

Approximately 20% of patients with acute mesenteric ischemia will have a nonocclusive mesenteric vasospastic phenomenon alone. This is generally associated with low cardiac output or a history or present condition of congestive heart failure and treatment with a digitalis preparation. Associated hypovolemia in patients receiving vasopressors and those undergoing operative coronary revascularization who were on cardiopulmonary bypass round out this clinical scenario. The arteriogram generally shows diffuse vasospasm with marked narrowing of the major branches of the SMA (Fig. 84–4), often with the "string of lakes" appearance. Because of the high outflow resistance in the SMA, reflux of contrast into the aorta is common. In addition to aggressively correcting the low cardiac output, terminating vasoconstrictor use, and discontinuing digitalis preparations, intra-arterial papaverine infusion at 30 to 60 mg/hr is the treatment of choice. In the absence of peritonitis, supportive care with anticoagulation and continued papaverine infusion is recommended. The arteriogram is repeated at 12- to 24-hour intervals, and the papaverine infusion is discontinued once the vasospasm has resolved.

Ideally, patients who demonstrate evidence of peritonitis should undergo exploratory laparotomy, with appropriately conservative resection of necrotic bowel

during the papaverine infusion. Postoperatively, the infusion is continued and repeat arteriography is performed. Depending on the patient's clinical evaluation, a second-look laparotomy is considered. In the event that abdominal surgery has been performed without arteriography, clearly necrotic bowel is expeditiously resected, and then arteriography with papaverine infusion is performed. Second-look laparotomy is considered.

Patients who have embolic occlusion of a small branch are also treated with anticoagulation to avoid additional thromboemboli. Associated vasoconstriction is treated with catheter-directed papaverine. In the absence of peritonitis, patients can be observed. In the presence of peritoneal signs, exploratory laparotomy is performed.

During the past several years, remarkable technologic advances have been made with percutaneous interventions. Patients who have major embolic occlusion or major thrombotic occlusion of their visceral vessels can often be approached with a percutaneous, pharmacomechanical method to dissolve or extract the embolus or thrombus and correct an underlying stenosis, if found.[37-41] Combining plasminogen activators with mechanical thrombus disruption and suction extraction can often restore perfusion more quickly and potentially with less morbidity than is the case with standard operative techniques. Because vasospasm is frequently associated with acute mesenteric occlusion, SMA catheter infusion of papaverine should be used to relieve the vasospasm. In the presence of peritonitis, exploratory laparotomy with appropriate resection is performed. The papaverine infusion is continued to relieve ongoing vasospasm and improve bowel perfusion, and anticoagulation is continued to avoid additional embolic or thrombotic events. A second-look laparotomy is planned if the condition of the bowel wall is tenuous at the time that the abdomen is closed. If a second-look laparotomy has been planned and the patient is clinically improving, the repeat laparotomy should be delayed to allow maximal improvement.

If catheter-based pharmacomechanical techniques are unsuccessful in the management of an acute SMA embolus, the catheter should be left in the proximal SMA and papaverine infusion initiated, followed by an expedient operative thromboembolectomy. After perfusion is restored to the bowel, it should be carefully examined for areas of irreversible ischemia. Areas of necrosis should be resected. If there is no irreversible ischemia and blood flow is restored, it can be anticipated that bowel wall perfusion will improve, with good prospects for ultimate bowel viability. Papaverine infusion is continued postoperatively and a repeat arteriogram performed to assess reperfusion and the degree of ongoing vasospasm.

In patients with major arterial thrombosis, anticoagulation should be initiated to minimize progressive thrombotic occlusion of branch vessels. Endovascular revascularization is recommended, including balloon angioplasty and stenting (if necessary) of the celiac artery, SMA, or IMA, or any combination of these arteries. Intra-arterial lytic therapy can be used to clear the acute thrombus[37,38] and unmask an underlying lesion, which should be corrected with adjunctive angioplasty and stenting.[39,42] If the endovascular approach is successful, the completion arteriogram is evaluated for mesenteric vasoconstriction. If present, a catheter is left in place and papaverine infusion continued with subsequent repeat arteriography. In the absence of vasoconstriction, continued supportive care is offered. If endovascular revascularization is unsuccessful, the catheter is left in the SMA for intra-arterial papaverine infusion if a portion of the artery is available for catheter positioning. The patient is then taken to the operating room for operative revascularization. A repeat arteriogram is performed postoperatively and the catheter appropriately repositioned if continued papaverine infusion is indicated.

Patients with peritoneal signs require exploratory laparotomy. Before operating, however, endovascular reconstruction is attempted. If successful, a papaverine infusion is initiated before exploratory laparotomy. Postoperatively, the papaverine infusion is continued and a second-look laparotomy performed, if appropriate.

In the absence of successful endovascular reconstruction, the patient is taken to the operating room for operative revascularization while papaverine is being infused into the SMA. Bowel infarction is often more extensive with arterial thrombosis than with embolic occlusion and has been observed from the duodenum to the transverse colon. Performing an adequate thrombectomy of a diseased visceral artery is difficult and not usually successful as an isolated procedure. Antegrade or retrograde bypass of the diseased artery is generally warranted to restore perfusion. Autologous vein grafts are preferred if bowel resection is required; however, synthetic grafts have fewer problems with compression and kinking,[43] although their use is discouraged in patients with questionable bowel viability. McMillan et al.[44] reported 3-year patency rates of 93% for antegrade grafts, 95% for retrograde grafts, 95% for saphenous vein grafts, and 89% for synthetic grafts. Outcomes were not as favorable in the experience of Cho et al.,[45] who reported 5- and 10-year patency rates of 57% and 46%, respectively, for all grafts. When the SMA beyond an occlusion is an adequate target for revascularization, it appears that a single bypass is all that is required in the majority of cases.[46] After operative revascularization, the bowel is inspected for areas of necrosis and appropriate resection performed. The papaverine infusion should be continued through the new conduit, with subsequent arteriography and a second-look laparotomy performed if indicated.

ACUTE MESENTERIC VENOUS THROMBOSIS

MVT accounts for 5% to 15% of patients with mesenteric ischemia.[47] The superior mesenteric vein is most commonly involved, frequently with extension of thrombus into the portal vein. Interestingly, the inferior mesenteric vein is most often spared.[48] The patient's clinical findings depend largely on the extent of thrombosis, the mesenteric veins involved, and the degree of bowel wall ischemia. Unfortunately, the mortality rate in these patients remains high, up to 50% in some reports.

Although patients with acute MVT have a more abrupt symptom onset than do patients with subacute and chronic mesenteric venous occlusion, the diagnosis remains difficult. Most commonly, patients complain of midabdominal colicky pain, which suggests small bowel involvement. Because of the diffuse and nondescript nature of their symptoms, most patients delay seeking medical care for 2 or more days after symptom onset.[49] Nausea, vomiting, diarrhea, and anorexia frequently accompany their abdominal discomfort. Although findings of occult blood in the stool are present in half of the patients,[50] gross bleeding such as hematemesis, hematochezia, or melena occurs in approximately 15%.[51]

Because of the generalized nature of the patient's symptoms and the relative infrequency of MVT, the definitive diagnosis is often delayed. The past medical history or family history is often informative because venous thromboembolism is part of the history in half of the patients.[48-50]

Physical findings are frequently similar to those in patients with early arterial mesenteric ischemia. Their abdomen is soft, without tenderness or peritoneal signs, and in the early stage the abdominal examination is often unimpressive save for some abdominal distention. Fever, muscular guarding, and rebound tenderness are indicators of more advanced disease progression and bowel infarction leading to peritonitis. Bowel infarction ultimately develops in 30% to 60% of patients with acute MVT.

Because of fluid sequestration within the bowel wall and lumen and the development of ascites, hypotension with hemodynamic instability is often part of the clinical picture. Patients first seen in this advanced clinical condition have a poor prognosis.[51,52]

Blood tests are obtained but are not generally helpful. Elevation of the white blood count with a shift toward immature white cells can be found in 50% to 65% of patients.[51] Serum amylase is usually normal, and serum lactate is elevated only in patients with advanced bowel ischemia and suggests necrosis.

Plain abdominal films are often the initial diagnostic test and are generally of little value. Although abnormalities can be found in 50% of patients,[47] the findings are nonspecific. Thumbprinting, when seen, is indicative of the mucosal edema resulting from venous congestion. Pneumatosis intestinalis, portal vein gas, and free air in the abdomen usually represent bowel infarction.[52]

CT of the abdomen with intravenous contrast is the diagnostic test of choice for patients with suspected acute MVT. A definitive diagnosis can be made in more than 90% of patients. Harward et al.[50] reported 90% sensitivity of abdominal CT with observation of a luminal venous thrombus. However, if one includes other characteristic findings of the bowel wall, such as thickening, pneumatosis, or streaking of the mesentery, CT sensitivity increases to nearly 100%.[33,52] Magnetic resonance venography is used less commonly, but when properly performed, it is highly sensitive.

Depending on the timing of the examination, color duplex ultrasound of the mesenteric veins can be helpful. If performed early, before significant bowel distention, a sensitivity of 80% or greater can be anticipated.[53]

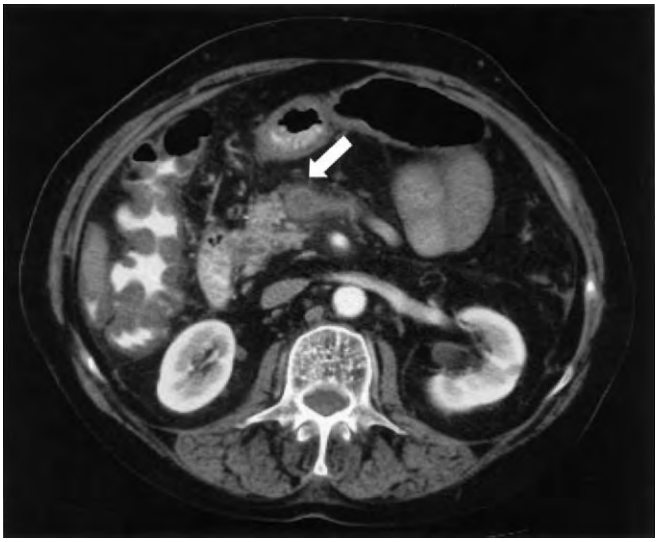


Figure 84–5. Computed tomographic scan of a patient with mesenteric venous thrombosis showing a thrombosed superior mesenteric vein at the splenic vein junction *(arrow),* streaking of the mesentery, and bowel wall thickening.

Selective mesenteric arteriography is not frequently used to establish the diagnosis of MVT, although it may be helpful in the management of these patients. Findings such as incomplete filling of the mesenteric veins, prolonged opacification of the arterial arcades, and the presence of thrombus or nonfilling of the superior mesenteric, splenic, or portal vein (Fig. 84–5) are seen in these patients. Most report a sensitivity of 70% to 80%.[54,55]

Treatment is generally directed at limiting progressive venous thrombosis, reducing the risk for bowel necrosis, and performing timely resection in those with irreversible bowel ischemia. Unfortunately, because of delay in diagnosis, the diffuse nature of the thrombosis, and the rarity of this condition, treatment directed at restoring patency to the thrombosed veins is unusual. In light of the rapid technologic advances in percutaneous interventions, which incorporate pharmacologic and mechanical methods of thrombus dissolution/extraction, it appears reasonable, if not advisable to initiate a strategy of thrombus dissolution/extraction to restore venous drainage because with the traditional care of anticoagulation alone, these patients continue to face a mortality rate ranging from 15% to 50%.[48,50,55,56] The diagnosis of MVT should trigger a search for an underlying thrombophilia. Such an evaluation includes factor V Leiden, prothrombin gene mutation, antiphospholipid/anticardiolipin antibodies, antithrombin III, protein C, protein S, factor VIII levels, hyperhomocysteinemia, paroxysmal nocturnal hemoglobinuria, and assessment for an underlying myeloproliferative disorder.

Rapid initiation of systemic anticoagulation is important. In patients with localized or diffuse peritoneal irritation, exploratory laparotomy is indicated. Laparoscopy

should be avoided in these patients because the increased abdominal pressure associated with the pneumoperitoneum further diminishes mesenteric blood flow.

On entering the abdomen, the superior mesenteric and portal veins should be assessed to determine the relative age of the thrombus. If the large veins appear to have an acute thrombus within them, thrombectomy is recommended, followed by bolus infusion of a recombinant tissue plasminogen activator (rt-PA) solution. The authors use a high-volume, low-dose solution of rt-PA, typically diluting 2 mg in 50 ml and infusing the entire 2-mg dose. Necrotic bowel is conservatively resected with preservation of viable intestine. The patient is treated with heparin intraoperatively and anticoagulation is continued postoperatively.

Associated arterial vasospasm should be evaluated by arteriography and treated with catheter-directed papaverine into the SMA, which improves perfusion to the ischemic bowel and reduces the necessity for additional resection. Patients treated for MVT have a high risk of recurrence (35% to 70%),[49] most frequently within 30 days, thus emphasizing the need for early and persistent anticoagulation.

Patients surviving the acute episode of MVT face chronic mesenteric venous hypertension with a subsequent risk for varices. This post-thrombotic venous hypertension occurs most commonly in patients with persistent large-vein mesenteric thrombosis, which further supports a strategy to remove the thrombus in patients with acute large-vein MVT. Some have reported success with transhepatic portography and instillation of a plasminogen activator directly into the thrombus.[57,58] Unfortunately, thrombolytic agents have been used infrequently in these patients because of the perceived risk for hemorrhage. The success of thrombolysis is often compromised by the delay in diagnosis. Intrathrombus thrombolytic therapy and, alternatively, intra-arterial thrombolytic therapy via the SMA should be considered in patients with thrombosis of large mesenteric veins when the potential benefit outweighs the risk of bleeding.

CHRONIC MESENTERIC ISCHEMIA

Chronic mesenteric ischemia is most commonly the result of advanced atherosclerotic disease of multiple mesenteric arteries. Because of the good collateral circulatory network that exists between the mesenteric vessels, symptomatic chronic mesenteric ischemia is rare. Risk factors for its development are the same as those for atherosclerotic disease in general: a positive family history, smoking, hypertension, and hypercholesterolemia. Generally, when symptomatic disease does occur, there is a female preponderance. Nonatherosclerotic causes of chronic mesenteric ischemia are less frequent and include inflammatory arterial disease, middle aortic syndrome, celiac artery compression (median arcuate ligament syndrome), chronic aortic dissection, aortic coarctation, fibromuscular dysplasia, and neurofibromatosis.

The finding of mesenteric artery atherosclerotic disease does not necessarily indicate intestinal ischemia. Significant atherosclerotic obstruction of the mesenteric arteries has been observed in 6% to 10% of individuals at autopsy.[59] In patients who undergo abdominal aortography, which is a select group of patients who are more likely to have occlusive disease, obliterative disease of the celiac or mesenteric artery has been found in 14% to 24%.[60] Although visceral artery stenosis is frequent, symptoms resulting from visceral arterial occlusive disease are uncommon because of the extensive collateral circulation.

As imaging techniques are becoming more common and stenosed visceral arteries detected more frequently, a temptation exists to correct "asymptomatic" visceral arterial stenosis. This approach is not prudent in light of the natural history study of asymptomatic intestinal arterial occlusive disease performed by Thomas and colleagues.[61] They identified 60 patients with significant mesenteric artery occlusive disease and monitored these patients for a mean of 2.6 years. In none of the 45 patients with one- or two-vessel mesenteric arterial occlusive disease did signs or symptoms of intestinal ischemia develop. Fifteen patients had severe three-vessel disease. During follow-up, fatal intestinal infarction developed in one patient and symptoms of intestinal angina in three.

The natural history of asymptomatic mesenteric occlusive disease appears to be reasonably documented. It has been our experience, which is supported by the literature, that few if any of these patients require mesenteric revascularization.

Clinical Features and Diagnosis

The classic picture of patients with chronic mesenteric ischemia is postprandial abdominal pain leading to an aversion to food and resulting in weight loss. The pain has been characterized as intestinal angina or, in the authors' parlance, intestinal claudication. The pain is characteristically diffuse and often midabdominal, midepigastric, and crampy in nature. The pain generally develops within 15 to 45 minutes after eating, with the severity frequently related to the size of the meal ingested. The authors have observed early-onset pain with foregut (celiac artery distribution) ischemia, with later-onset pain occurring with more diffuse ischemic disease. Because of the association of abdominal pain with food ingestion, fear of eating develops and leads to the characteristic weight loss and subsequent malnutrition.

Other symptoms of nausea, vomiting, and diarrhea have accompanied chronic mesenteric ischemia. Bloating has also been observed. Symptoms of constipation and findings of occult blood in the stool and ischemic colitis represent hindgut ischemia. Because none of these symptoms or signs is specific for chronic mesenteric ischemia, the majority of these patients will have been subjected to an extensive diagnostic evaluation before referral to a vascular surgeon. If a complete evaluation has not been performed, conditions that produce

abdominal pain and weight loss more commonly than visceral ischemic disease does should be excluded before plans for revascularization.

Evaluation of the mesenteric arteries frequently begins with a noninvasive mesenteric duplex scan. This should be performed with the patient in a fasted state because mesenteric outflow resistance changes with food intake and increases in bowel gas.

The most frequent criterion used to identify celiac artery stenosis is a peak systolic velocity of 200 cm/sec or higher, which has been reported to have a sensitivity of 75% and a specificity of 89%.[62] The same investigators reported that a peak systolic velocity of 275 cm/sec or higher predicted 70% to 99% stenosis of the SMA with a sensitivity of 89% and a specificity of 92%. The absence of a Doppler signal in the SMA represents occlusion. Others have reported an end-diastolic velocity of 45 cm/sec or higher to be the best indicator of 50% or greater stenosis of the SMA, with a sensitivity of 100% and specificity of 92%.[63] Retrograde flow in the common hepatic artery is a reliable indicator of severe proximal celiac artery occlusive disease.[64]

Aortography with AP and lateral views has been the diagnostic technique of choice. Lateral aortograms are important for evaluation of the origin of the mesenteric vessels. CT angiography is rapidly becoming the preferred technique for contrast visualization of the aorta and its branches. Contrast-enhanced (gadolinium) MRA is useful in patients with dye allergy and renal compromise.

Laboratory tests to evaluate the malabsorption that may accompany intestinal ischemia, such as stool fat content, D-xylose tolerance, and vitamin B_{12} absorption, may yield positive results; however, they are nonspecific and not generally useful in the overall management of these patients.

Mesenteric Revascularization

Although it is generally true that patients with symptomatic chronic mesenteric ischemia have at least two, if not three intestinal vessels diseased, this is not always the case. Patients with single-vessel occlusive disease who do not have adequate collateral circulation from other mesenteric arteries will suffer chronic mesenteric ischemia. The authors have successfully revascularized a single celiac artery, and others have reported similar findings.[65]

As with all vascular reconstruction, patient selection and the physician's judgment, combined with operative skill, play an important role in overall success. Dogma should be replaced by intelligent decision making based on knowledge of the disease process, awareness of the current options for revascularization, both endovascularly and operatively, and the patient's inherent risk.

Surgical Revascularization

Because chronic symptomatic mesenteric ischemia is relatively unusual in the majority of vascular practices, few physicians have broad-based experience with surgical mesenteric revascularization. There is a wide range of operative techniques, and the one chosen should be based on the patient's anatomy, disease distribution, and associated comorbid conditions and the surgeon's comfort and expertise with the available technique.

Mesenteric Artery Endarterectomy

Endarterectomy of the SMA and the celiac artery was initially performed in retrograde fashion, often attempting a "blind endarterectomy" through a distal arteriotomy.[66] The technique served its purpose during the formative years of vascular surgery. Though occasionally successful, this approach is often complicated by failure, and blind endarterectomy is no longer acceptable in any area of the vascular tree. An improved technique popularized by Wylie et al.[67] advocates complete exposure of the aorta from below the renal arteries to the supraceliac aorta. Such exposure is most reliably accomplished through an extended retroperitoneal approach. A "trapdoor" aortic incision is made from above the celiac artery and extended laterally and then medially below the SMA. The atherosclerotic plaque of the aorta and the orifices of the celiac artery and SMA is then removed by the technique of endarterectomy. Because the plaque in the SMA often extends beyond the orifice of this vessel, subsequent SMA arteriotomy, endarterectomy, and patch angioplasty are frequently required (Fig. 84–6). Although good results are reported by those experienced in this technique, most vascular surgeons are not comfortable with this exposure and extensive dissection and are more likely to encounter complications. The risks associated with suprarenal aortic clamping during visceral endarterectomy include cholesterol embolization, renal failure, and paraplegia, as well as higher pulmonary and cardiac risk.

Aortomesenteric Bypass

On the basis of previous reports, many vascular surgeons favor multivessel revascularization for chronic mesenteric ischemia.[67-71] There seems to be an intuitive advantage to multivessel revascularization; however, others have convincingly argued that the single most important artery is the SMA and that successful bypass to the SMA will provide durable relief with outcomes equivalent to those of multivessel repair.[46,72] Furthermore, the controversy regarding antegrade versus retrograde bypass continues. The correct answer to these important questions for any given patient lies in the judgment of the treating physician. Success is likely for those who make appropriate judgments based on the distribution of disease, the patient's anatomy, and other clinical factors. For example, isolated revascularization of the IMA has been shown to be successful in properly selected patients. The degree of benefit from single-vessel revascularization is related to the number and quality of collateral channels to other portions of the ischemic gut.

Even the proponents of isolated SMA bypass recommend multivessel revascularization in patients in whom (1) the SMA is diffusely diseased, (2) there is a question of durability with a single bypass, and (3) a previous

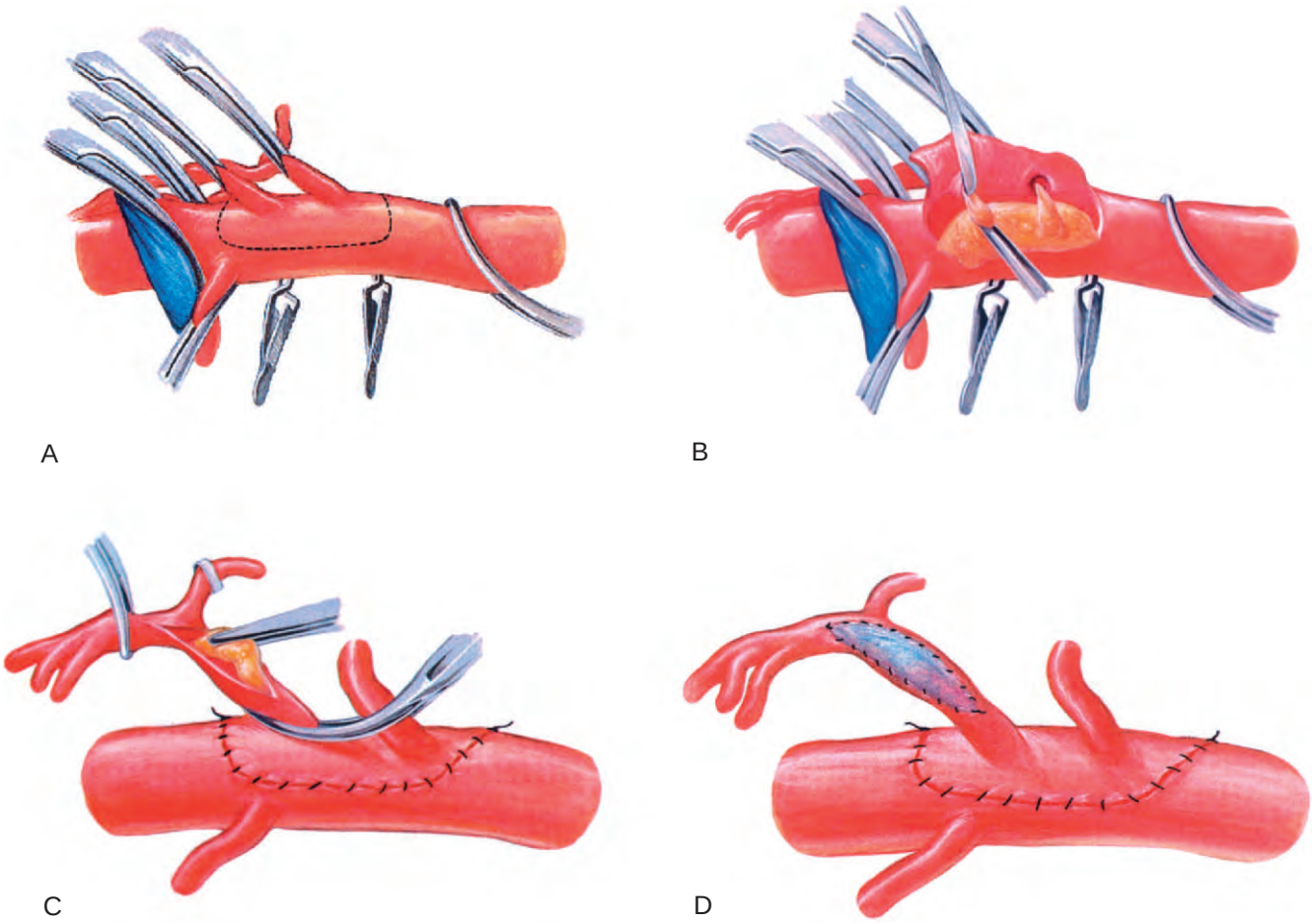


Figure 84–6. Transaortic endarterectomy for celiac and superior mesenteric stenosis. Exposure is obtained through a left thoracoabdominal retroperitoneal approach. **A,** Trapdoor aortotomy. **B,** Removal of orifice lesions from branches. **C,** After completion of transaortic endarterectomy, superior mesenteric artery (SMA) endarterectomy is completed through a separate incision (if needed). **D,** Vein patch closure of SMA. (From Wylie EJ, Stoney RJ, Ehrenfeld WK: Manual of Vascular Surgery, vol 1. New York, Springer-Verlag, 1980, pp 215-217.)

abdominal operation (especially gastrectomy and colectomy) has potentially interrupted the normal collateral connections between the superior mesenteric and celiac vascular beds.[65]

The antegrade aorta-to-celiac or aorta-to-SMA bypass is usually performed through a transperitoneal approach. The supraceliac aorta is generally soft and has much less atherosclerotic disease than the infrarenal aorta does. It is exposed by retracting the left lobe of the liver to the right after division of the triangular ligament. The gastrohepatic ligament is divided, and after entry into the lesser sac, the esophagus (which has a nasogastric tube coursing through it) is mobilized, encircled with a 1-inch Penrose drain, and retracted to the left. The diaphragmatic crura and median arcuate ligament are divided to expose a generous portion of the supraceliac aorta. The proximal celiac artery is also exposed during the course of this dissection, usually during transection of the median arcuate ligament.

The SMA is exposed through an incision at the base of the transverse mesocolon. Occasionally, the duodenum can be mobilized to aid exposure as the SMA exits from beneath the pancreas. A variety of techniques have been used, including anastomosing a 12×6 or 14×7 aortic bifurcation graft. The celiac and SMA anastomoses have been variously performed in an end-to-end or end-to-side fashion. Most frequently, the celiac revascularization is accomplished with an end-to-side anastomosis to the right hepatic artery and the SMA revascularization with an end-to-side anastomosis to the infrapancreatic SMA. Many surgeons tunnel the SMA bypass behind the pancreas, but anterior to the renal vein. A useful technique is sequential mesenteric revascularization with a single 8-mm graft, which revascularizes the celiac artery with a side-to-side anastomosis and the SMA with an end-to-side anastomosis.[69]

Mesenteric bypass from the mid infrarenal aorta to the SMA (Fig. 84–7) should be avoided because of the likelihood of kinking once the viscera are replaced after the procedure. The concept of the shortest graft being the best does not necessarily hold for mesenteric bypasses. The choice of graft material is often debated among

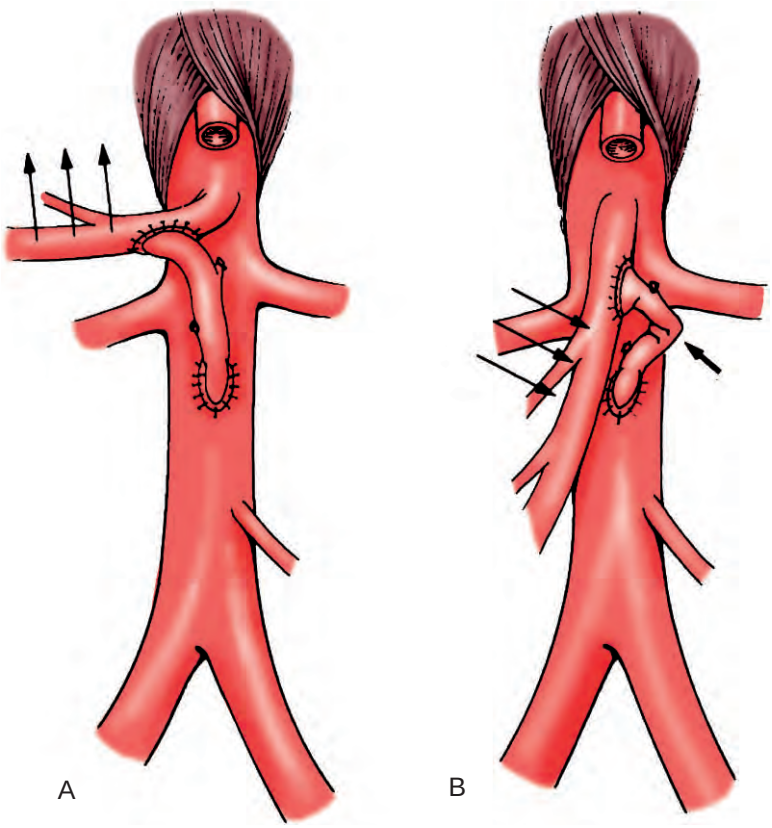


Figure 84–7. Illustration of the potential for kinking when using short saphenous vein grafts from the infrarenal aorta to the superior mesenteric artery. (From Taylor LM, Moneta GL, Porter JM: Treatment of chronic visceral ischemia. In Rutherford RB [ed]: Vascular Surgery, 5th ed. Philadelphia, WB Saunders, 2000, p 1536.)

surgeons. Although autogenous grafts are inherently more attractive from an infection and thrombogenicity perspective, they are subject to kinking and compression and may not be of adequate size to carry the blood flow required for the intestines. Normal SMA blood flow usually exceeds 750 ml/min,[73] and saphenous vein grafts of average size (<6 mm in diameter) rarely carry more than 500 ml/min.

Retrograde Bypass

Visceral bypass grafts originating from the distal infrarenal aorta or the iliac arteries offer the advantage of anatomic familiarity to all vascular surgeons and limit the amount of dissection required to achieve revascularization. Several authors have suggested that retrograde bypasses are not as durable as antegrade revascularization; however, avoidance of the common pitfalls leading to graft kinking and improvement in patient selection may eliminate many of these disadvantages.[74,75] Even proponents of antegrade bypass recognize that in certain clinical conditions retrograde bypasses are indicated: (1) emergency revascularization in patients undergoing laparotomy for acute mesenteric ischemia (an autogenous vein should be the conduit), (2) an inaccessible supraceliac aorta because of previous surgery or inflammation, (3) severe cardiac disease with contraindications to supraceliac aortic clamping, and (4) the need for simultaneous infrarenal aortic and mesenteric revascularization.[76]

Selection of the section of distal infrarenal aorta or iliac artery should be based on the distribution of atherosclerotic disease. If the infrarenal aorta and iliac artery are severely diseased, they should be replaced, with the mesenteric graft originating from the aortic prosthesis.

The most proximal suitable segment of the SMA as it passes from beneath the pancreas should be used. This maximizes the outflow bed and minimizes the likelihood of graft kinking.

The SMA anastomosis is performed first. If the conduit is autogenous vein, the viscera are returned to the abdomen and the graft placed under mild tension while constructing the aortic or iliac anastomosis (Fig. 84–8). If a prosthetic is used, it is configured in a gentle curve with the goal being to reduce the risk for graft kinking. The right hepatic artery is often a good target for celiac revascularization. Mobilization of the duodenum with a Kocher maneuver to expose the right hepatic artery or the use of a retropancreatic tunnel with the graft approaching the right hepatic artery from the left side of the abdomen provides a proper configuration that reduces the chance of graft kinking and maximizes technical success (Fig. 84–9).

Endovascular Revascularization

Operative reconstruction for mesenteric ischemia is a large operation that is usually performed on a patient with multiple risk factors who is often malnourished.

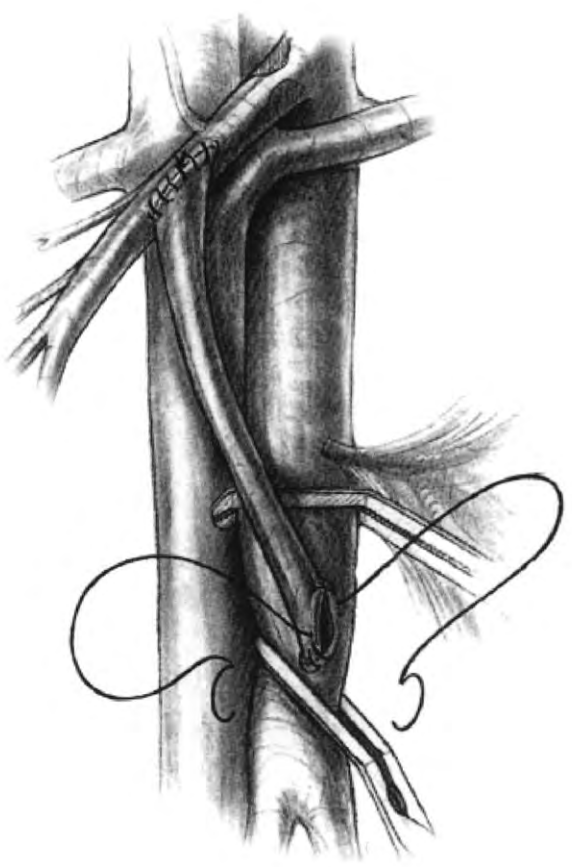


Figure 84–8. Retrograde infrarenal aorta–superior mesenteric artery bypass with autologous vein. (From Zarins CK, Gewertz BL: Atlas of Vascular Surgery. New York, Churchill Livingstone, 1989, p 107.)

Percutaneous techniques of mesenteric revascularization are intuitively attractive if they can be performed successfully with low complication rates. Tables 84–2 and 84–3 review operative and endovascular revascularization procedures for chronic mesenteric ischemia. In most operative reports, there appears to be nearly uniform early patency. However, early patency in operated patients is not usually based on objective imaging, but rather on operative observation and clinical follow-up. In contrast, endovascular procedures are always accompanied by completion arteriography, which offers more objective assessment of technical success and patency.

Procedure-related morbidity is considerably less with the endovascular approach, although it may not be readily apparent by a review of selected literature. This difference in significant morbidity may be hidden by the definition of procedure-related complications. As an example, the brachial artery approach is associated with a frequent need to repair the brachial puncture site, typically performed under local anesthesia. The authors plan to perform brachial artery repair in all patients undergoing this approach. However, when reviewing procedure-related complications, the need for a brachial artery repair is often considered numerically equivalent to renal failure, a respiratory complication, or acute myocardial infarction.

Balloon dilation of the SMA was first reported in 1980 by Furrer et al.[98] Early results have been encouraging, with technical success reported in up to 80% of patients along with symptomatic relief and improvement of nutritional status.[87,88,99,100] Current results of endovascular techniques have improved (see Table 84–3) as the technology has advanced and low-profile balloons and stents and better pharmacotherapy have become available. The high brachial approach is preferred by some because it offers a mechanical advantage in advancing balloon catheters and stents (if necessary) into the mesenteric arteries, especially the SMA. The celiac artery is externally surrounded by the dense fibers of the arcuate ligament and the crus of the diaphragm. Therefore, angioplasty alone is less likely to be effective and stenting is required more frequently. Generally, balloon angioplasty is all that is recommended, assuming that an arteriographically good result is observed. Indications for mesenteric artery stenting include (1) residual stenosis of 30% or greater, (2) an obstructing dissection or flap after percutaneous transluminal angioplasty, and (3) recurrent stenosis within 12 months of balloon dilation.[94] When these guidelines have been observed, technical success rates of 96% to 100% have been reported.[94,96] Procedure-related mortality is low and has been reported as 0% in most series. The hospital stay is short for most patients, and an increasing number are being treated as outpatients. Few, if any, require intensive care monitoring.

Figure 84–10A and B shows an arteriogram of a patient with postprandial abdominal pain and an associated 30-lb weight loss. High-grade celiac artery and SMA stenosis is apparent, and the IMA is occluded. The patient had minimal improvement of the celiac stenosis with angioplasty alone, but an excellent anatomic result of angioplasty and stenting of the SMA. The completion arteriogram in the AP view (see Fig. 84–10C and D) shows excellent collaterals to the celiac branches via the pancreatic duodenal and gastroduodenal arteries. After the procedure, the patient became asymptomatic.

The important end point is improvement in symptoms and long-term clinical success. This has been observed in approximately 85% with a mean follow-up of about 26 months (see Table 84–3). Repeat angioplasty and stenting (if necessary) for recurrent disease can generally be performed with equally low complication rates and has been associated with good technical and clinical success.

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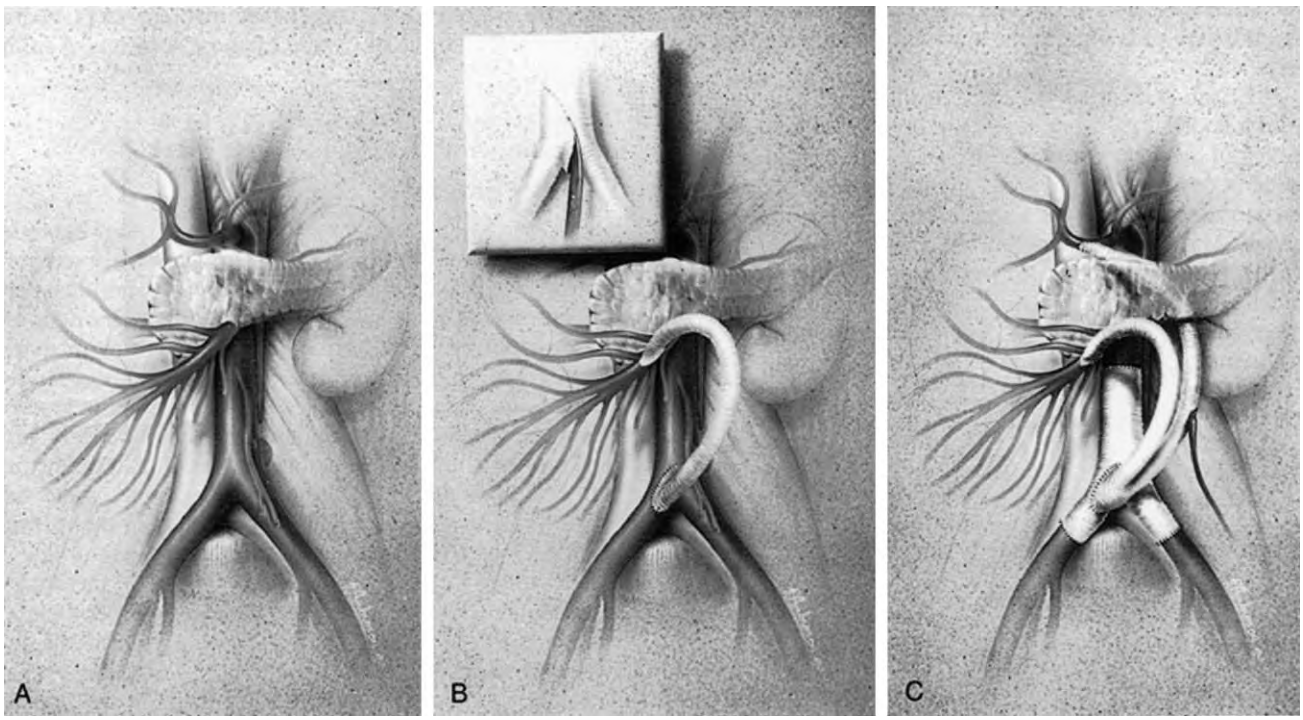

Figure 84–9. **A,** Exposure of the infrarenal aorta and the superior mesenteric and celiac arteries. **B,** Method of infrarenal aorta–superior mesenteric artery (SMA) bypass. *Inset,* method of forming the graft origin from an aortic bifurcation graft. **C,** Method of infrarenal aortic graft placement with bypass to the SMA and hepatic artery. Note the reimplantation of the inferior mesenteric artery. (From Taylor LM, Porter JM: Treatment of chronic intestinal ischemia. Semin Vasc Surg 3:193, 1990.)

Table 84–2 Literature Review of Surgical Revascularization in Patients with Chronic Mesenteric Ischemia

Author	Year	*N*	Vessels Revascularized	Immediate Clinical Success	Follow-up (mo)	Long-Term Clinical Success	Operative Complications	Operative Mortality	Long-Term Patency
Kieny R, et al.[72]	1990	53	62	NA	102	91% (48)	4% (2)	2% (1)	NA
Cormier JM, et al.[77]	1991	91	131	NA	69	NA	9% (8)	3% (3)	91% (83)
Cunningham CG, et al.[78]	1991	74	140	88% (65)	71	86% (64)	35% (26)	12% (9)	NA
McAfee MK, et al.[79]	1992	56	116	89% (50)	60	90% (50)	41% (23)	10% (5)	90% (50)
Calderon M, et al.[80]	1992	20	36	100% (20)	36	100%	20% (4)	0	100% (20)
Christensen MG, et al.[81]	1994	65	65	NA	55	68% (44)	NA	2% (1)	NA
Gentile AT, et al.[46]	1994	24	24	100% (24)	40	89% (21)	NA	0	89% (21)
Johnston KW, et al.[75]	1995	21	37	NA	120	NA	19% (4)	0	86% (18)
McMillan WD, et al.[44]	1995	16	24	92% (15)	35	97% (15)	31% (5)	6% (1)	89% (14)
Moawad J, et al.[68]	1997	24	38	96% (23)	29	78% (19)	46% (11)	4% (1)	78% (19)
Mateo RB, et al.[82]	1999	85	NA	92% (78)	57	81% (69)	45% (38)	8% (7)	81% (69)
Kihara TK, et al.[83]	1999	42	66	NA	36	96% (40)	30% (13)	10% (4)	65% (27)
Foley MI, et al.[84]	2000	29	29	97% (28)	44	NA	NA	3% (1)	79% (23)
Park WM, et al.[85]	2002	98	179	93% (91)	60	92% (90)	21% (21)	5% (5)	NA
English WP, et al.[86]	2004	34	NA	NA	42	94% (32)	NA	9% (3)	89% (30)
TOTAL		732	947	394	44,271	512	155	41	374
MEAN				93%	61	87%	27%	6%	85%

NA, not available.

Table 84–3 Literature Review of Endovascular Revascularization of Patients with Chronic Mesenteric Ischemia

Author	Year	*N*	Vessels Revascularized	Technical Success	Immediate Clinical Success	Follow-up (mo)	Long-Term Clinical Success	Complications	Mortality Rate	Long-Term Patency
Sniderman KW[87]	1994	13	20	91% (12)	85% (11)	NA	82% (11)	8% (1)	0	NA
Hallisey MJ, et al.[88]	1995	15	23	93% (14)	88% (13)	28	75% (11)	0%	0	75% (11)
Allen RC, et al.[89]	1996	19	24	95% (13)	79% (15)	39	86% (16)	11% (2)	5% (1)	NA
Maspes F, et al.[90]	1998	23	41	90% (21)	77% (18)	27	88% (20)	9% (2)	0	NA
Nyman U, et al.[42]	1998	5	6	83% (4)	100% (5)	21	80% (4)	40% (2)	0	40% (2)
Sheeran SR, et al.[91]	1999	6	13	83% (5)	92% (5)	16	75% (4)	0	8% (1)	83% (5)
Kasirajan K, et al.[92]	2001	28	32	89% (25)	NA	36	66% (18)	18% (5)	11% (3)	73% (20)
Pietura R, et al.[93]	2002	6	9	100% (6)	100% (6)	12	100% (6)	NA	0	100% (6)
Matsumoto AH, et al.[94]	2002	33	47	87% (29)	88% (29)	38	97% (32)	13% (4)	0	97% (32)
Steinmetz E, et al.[95]	2002	19	19	100% (19)	93% (18)	31	94% (18)	16% (3)	0	100% (19)
Sharafuddin MJ, et al.[96]	2003	25	26	96% (24)	88% (22)	11	92% (23)	12% (3)	0	92% (23)
Chahid T, et al.[97]	2004	14	17	100% (14)	100% (14)	29	93% (13)	14% (2)	0	NA
TOTAL		206	277	186	156	5587	176	24	5	118
MEAN				90%	88%	29	85%	12%	2%	86%

NA, not available.

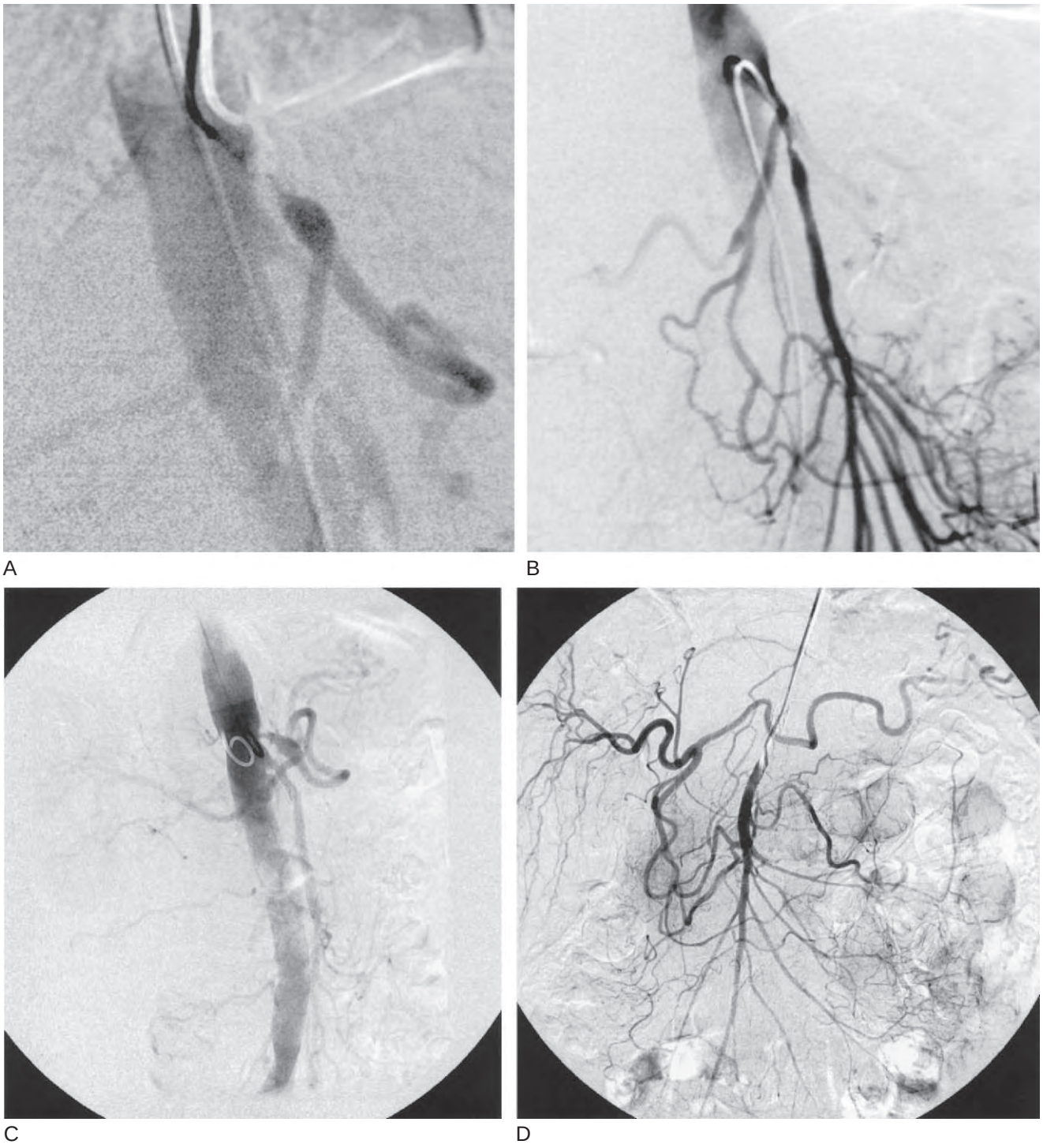

Figure 84–10. Abdominal aortograms of a woman with a 4-month history of postprandial abdominal pain, weight loss, and food avoidance. **A,** Lateral aortogram demonstrating high-grade stenosis of the origin of the celiac artery. **B,** Lateral aortogram demonstrating stenosis of the superior mesenteric artery (SMA) and no visualization of the inferior mesenteric artery. **C,** Lateral aortogram after percutaneous intervention with angioplasty of the celiac artery and angioplasty and stenting of the SMA. Note the residual stenosis of the celiac artery but good technical result of the SMA. **D,** Anteroposterior arteriogram after SMA angioplasty and stenting showing excellent filling of the celiac branches via collaterals (pancreaticoduodenal and gastroduodenal arteries). The patient remains asymptomatic 1 year after the procedure.

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Chapter

85

Aortoenteric Fistula and Visceral Artery Aneurysms

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AORTOENTERIC FISTULA

Aortoenteric fistula (AEF) remains an uncommon, but potentially lethal problem that typically arises from the progressive growth of an abdominal aortic aneurysm (AAA) or, more commonly, as a complication of aortic reconstructive surgery. Early recognition and diagnosis rest on a high index of suspicion, although timely and accurate diagnosis remains difficult despite improvements in diagnostic technology. Prompt treatment can be lifesaving and prevents severe enteric hemorrhage, multisystem organ failure, or limb amputation. Recent advances in surgical and endovascular techniques, as well as perioperative care, continue to improve both the morbidity and mortality associated with AEF.

Classification

An AEF is an abnormal communication between the aorta and any gastrointestinal lumen. The classification of AEFs is based on the underlying pathophysiology, and they are categorized into either *primary* or *secondary* types. Primary AEF reflects erosion of an AAA or, in unusual circumstances, erosion of an atherosclerotic aorta into an overlying segment of intestine. Foregut, midgut, and hindgut fistulas have all been reported in the literature. The third and fourth segments of the duodenum are most commonly involved (70%) because of their close approximation to the infrarenal aorta and their fixed immobile position in the retroperitoneum.[1] Although the true incidence of primary AEF is not known, autopsy studies have found them to be present in 0.04% to 0.07% of specimens involving an atherosclerotic aorta, whereas 0.69% to 2.36% have been discovered in the presence of native aortic aneurysms.[2,3] *Secondary* AEFs are more frequently observed clinically, with an overall incidence of between 0.36% and 1.6%.[4] They typically occur after surgery on the aorta, particularly graft replacement for an AAA or atherosclerotic occlusive disease, endarterectomy, and renal or visceral artery bypass procedures. Two different types of *secondary* fistulas may develop. The first is a *graft-enteric fistula,* which originates from partial disruption of the proximal graft-aortic anastomosis. The other is a *graft-enteric erosion,* in which the bypass prosthesis directly erodes into the adjacent enteric wall. It is believed that despite a low overall incidence in the published literature, the actual occurrence of AEFs may be higher than reported. *Secondary* AEF is more commonly seen than *primary* types because of the number of aortic reconstructions performed. Recently, AEF has also been associated with endovascular aortic graft placement.[5]

Pathogenesis

Aortic wall pathology accounts for over three quarters of all *primary* fistulas and usually develops from the pulsatile enlargement of an AAA. In addition to atherosclerotic aneurysmal disease, enlargement secondary to an underlying aortic dissection can lead to AEF. More worrisome are inflammatory arteritides and infective mycotic aneurysms, tuberculosis, and syphilis, which can be initiating events of aorta-to-enteric fistulas.[2] The remainder of *primary* AEFs are thought to begin with gastrointestinal rather than aortic disease processes, including penetrating peptic ulcers, bowel wall ischemia, infection, foreign body erosion, trauma, operative injury, neoplasia, pancreatic pseudocyst, gallstones, and radiation therapy.[2,6,7]

Secondary AEFs involve a more complicated series of events ultimately leading to a similar result. Two specific mechanisms help explain the pathogenesis of these AEFs. The first involves degeneration of a proximal aortic suture line to a prosthetic graft. The etiology of such a breakdown of this anastomosis can be multifactorial, including a technical error with an insufficient amount of healthy tissue incorporated in the suture line, aneurysmal enlargement above the anastomosis when the original graft replacement was too distal from the

renal arteries, suture failure, although this is quite infrequent today, or pseudoaneurysm formation secondary to infection. All of these processes lead to localized arterial disruption and, with a progressive increase in size, can erode into nearby enteric structures and result in a *graft-enteric fistula,* which accounts for three quarters of all AEFs.[8] Because pseudoaneurysm formation after graft insertion may be the initiating event for AEF formation, yearly postoperative ultrasound scans of prosthetic aortic grafts is performed by many clinicians.

A second mechanism of AEF development involves postoperative direct erosion of a prosthetic graft into overlying adherent bowel. Long-standing contact between bowel and pulsatile prosthetic material eventually leads to thinning of the overlying bowel wall, ischemic degeneration, and enteric wall perforation and ultimately results in soilage of the underlying vascular graft. Gastrointestinal proteolytic and bacterial enzymes then erode more surface area along the graft with extension to the proximal suture line. Although the prosthetic graft itself is quite resistant to bacterial and lytic breakdown, the native aortic tissue at the anastomosis is not nearly as hardy. Eventually, a small disruption of the aorta at the anastomosis takes place and leads to bleeding from the aorta along the outside of the prosthesis and into the enteral opening with associated gastrointestinal bleeding. This process is known as *graft-enteric erosion*. The development of a *secondary* AEF without graft placement, for instance, after non–graft-related aortic reconstruction such as endarterectomy, is seen in only about 2% of patients.[8]

Surgical intervention for a ruptured AAA and for aortic atherosclerotic occlusive disease results in higher rates of secondary AEF development,[9] most likely because of the lack of an aneurysmal wall to cover the prosthetic graft in the latter circumstance and a large retroperitoneal hematoma and possible visceral wall ischemia in the former.

Several important principles can be used to prevent secondary AEF formation after aortic surgery. It is clear that direct contact between prosthetic grafts and enteric structures is key to the development of AEFs. Therefore, every effort should be made to place viable, healthy, autologous tissue between these two structures, and several options are available at the time of surgery to do so. Most commonly, in the case of AAA, the native aneurysmal wall is sufficient to cover the graft material, although this can be challenging at its most proximal point where the aortic anastomosis is located. This area, however, is usually just above the duodenum and the beginning portions of the jejunum. Although there may not be sufficient aneurysmal wall for coverage, this area should still be covered by reattaching the posterior layer of peritoneum. A greater challenge involves the placement of an aortofemoral or aortoiliac graft for occlusive disease when there is no aneurysmal wall at all to cover the prosthetic graft. This situation is especially problematic when a proximal end-to-side anastomosis is performed and more of the graft is extending anteriorly into the peritoneal cavity. In such circumstances, when insufficient retroperitoneal fat and posterior peritoneum are available to cover the graft, an omental flap can be mobilized and interposed between the graft and overlying bowel. It should cover all of the graft and be sutured in place to maintain its protective position. Correct length of the graft during insertion for any aortic procedure should be ensured so that there is no redundancy and angulation, which can also be associated with graft erosion.

Occasionally, in a hostile abdomen that has undergone previous laparotomies or has endured radiation therapy, incidental enterotomies may occur during aortic dissection. They characteristically involve the small bowel, and if they are small and without extensive spillage, aortic reconstruction can proceed safely. Similarly, associated open cholecystectomy can be performed for symptomatic cholelithiasis after the aortic procedure is completed.[10]

Perioperative administration of prophylactic antibiotics effective against gram-positive organisms, such as a first-generation cephalosporin, is routine clinical practice. Similarly, antibiotic irrigation of the abdominal cavity before closure is routinely performed. Although most primary graft infections are thought to result from prosthetic contamination at the time of placement, infection as a result of transient bacteremia from other sources may also develop, especially infection by anaerobic or gram-negative organisms.[11]

Clinical Findings

One of the most challenging aspects about AEFs is the difficulty of making a correct and timely diagnosis, which remains critical to effective resuscitation and successful treatment. Indeed, only a third of all AEFs are correctly diagnosed before surgical intervention.[4] The timing of the clinical manifestations of an AEF is quite variable and ranges from a few weeks to several years after the initial aortic reconstructive surgery.[12] Probably because of gender differences in the prevalence of AAAs, men with AEFs outnumber women by a ratio of 4:1.[13] The diagnosis of AEF is most often considered during evaluation for gastrointestinal bleeding because up to 64% of patients are seen in this manner.[2,14] Conversely, however, AEF is a rare cause of the bleeding inasmuch as less than 5% of patients with previous aortic surgery and gastrointestinal bleeding have an AEF as the underlying cause.[15] In those who do, an initial herald bleeding event is considered characteristic of AEF.[3] This may be manifested in a number of ways but commonly involves brisk upper and lower gastrointestinal bleeding. Rarely is this initial episode life-threatening, and some time is available to arrange for an endoscopic evaluation.[15] Although the initial event may be self-limited, subsequent uncontrolled fatal hemorrhage will occur if a correct diagnosis is not made and the cause left untreated.

More frequently seen is gastrointestinal hemorrhage with signs and symptoms of systemic infection. Hematemesis and fever are the two most common initial symptoms associated with a graft-enteric fistula, whereas melena and fever (sepsis) are more often seen with graft-enteric erosions.[8] Along with fever and leukocytosis, infection as an initial manifestation of AEF may be found

in 25% of patients. When present, sepsis with AEF is usually more severe than prosthetic graft infection alone. Seen less often than bleeding is abdominal pain. Primary AEF patients may complain of insidious abdominal pain, possibly related to an underlying cause such as peptic ulcer disease or neoplasia. Physical examination of patients with primary AEF reveals a palpable abdominal aneurysm in only 30%. Uncommonly, septic embolization to the lower extremities may occur and result in ischemic changes. Rarely do patients have the classic triad of gastrointestinal bleeding, abdominal pain, and a pulsatile abdominal mass.[16]

Aortoesophageal fistulas have been considered a separate pathologic entity. Like AEFs in other enteric sites, underlying aortic pathology and aortic surgery account for a large percentage of cases. Unique to esophageal fistulas, lesions of the esophagus and foreign body erosion constitute an equally prevalent number of cases. The typical site of aortic involvement in these circumstances is the thoracic aorta. Aortoesophageal fistulas remain rare, with a large proportion of cases being found at autopsy. The classic constellation of symptoms, or *Chiari's triad* (midthoracic pain, sentinel arterial hemorrhage, and subsequent exsanguination), is ascribed to this type of fistula. Like other types, upper gastrointestinal bleeding is the most common initial symptom, followed by chest pain and dysphagia.

Diagnosis

Diagnosis of an AEF may be difficult and depends on a high index of suspicion because the clinical findings may be subtle.[17] In any patient with a surgical history of bowel or aortic reconstruction and gastrointestinal hemorrhage, AEF should be considered. Attention to the patient's hemodynamic stability should take highest precedence, with unstable patients requiring immediate aggressive resuscitation followed by operative exploration of the abdomen. Patients with intermittent or self-limited bleeding can safely undergo a short preoperative work-up to assist in planning for corrective AEF surgery. Despite the spontaneous initial cessation of bleeding from many AEFs, early rebleeding occurs in 40% of patients, thus limiting the time available to arrive at an accurate diagnosis. It should be remembered that the only test that has 100% diagnostic accuracy is exploratory laparotomy.[8]

Esophagogastroduodenoscopy (EGD) remains the first and most frequently performed test in patients suspected of having an AEF.[18] EGD may best be conducted in the operating room with a qualified vascular surgeon present for patients with a high suspicion of AEF because manipulation of a quiescent AEF can lead to brisk and life-threatening bleeding. Essential to complete EGD is visualization of the fourth portion of the duodenum because it overlies the aorta and previously placed prosthetic grafts. Findings on EGD may range from mucosal surface changes to complete bowel perforation with visible prosthetic graft and active arterial bleeding. There are no therapeutic options during endoscopy to stop the bleeding. It serves only as a diagnostic procedure. Unless other definitive gastrointestinal pathology is found on EGD to explain the gastrointestinal bleeding, an indeterminate EGD cannot exclude an AEF in patients with prosthetic aortic grafts or those with aneurysmal aortas.

After EGD, computed tomography (CT) is the next most used tool (50%) in the work-up of AEF, and it has both high sensitivity (94%) and high specificity (85%).[18,19] CT scans are helpful because of their ability to image not only the aorta but also the entire retroperitoneum and bowel wall, as well as spatial relationships between the two. In patients who have previously undergone aortic reconstruction, abnormal perigraft findings may include air bubbles, fluid, obliteration of soft tissue planes, and a pseudoaneurysm. Considerable overlap does exist between CT findings in aortic infection and AEF.[19,20] Though pathognomonic, oral or intravenous contrast leak is a rare finding. Perigraft air or fluid more than a few weeks after an aortic operation is strong evidence of an AEF.[21]

Angiography is best used for preoperative planning before necessary vascular reconstruction. It rarely reveals a graft-enteric erosion or specific vascular defect, which is usually covered with thrombus, and is rarely diagnostic.[22] Angiography may document other graft characteristics that can cause overlying bowel erosion, such as a pseudoaneurysm or kink in the prosthesis.[23] The use of magnetic resonance imaging may be helpful for prosthetic graft infection; however, few convincing data have been published regarding its efficacy in the diagnosis of fistulas, and its utility in critically ill patients is also likely to be limited.

Nuclear imaging, including technetium 99m and indium 111 scans, offer high sensitivity for the diagnosis of AEF, but the associated false-positive rate may be unacceptably high for routine use (Fig. 85–1). Their applicability may be of benefit by using red blood cells to suggest the location of active gastrointestinal bleeding or in differentiating aortic graft infection with radiolabeled white blood cells.[24,25] Limited experience with ^{18}F-2-deoxy-D-glucose positron emission tomography (FDG-PET)

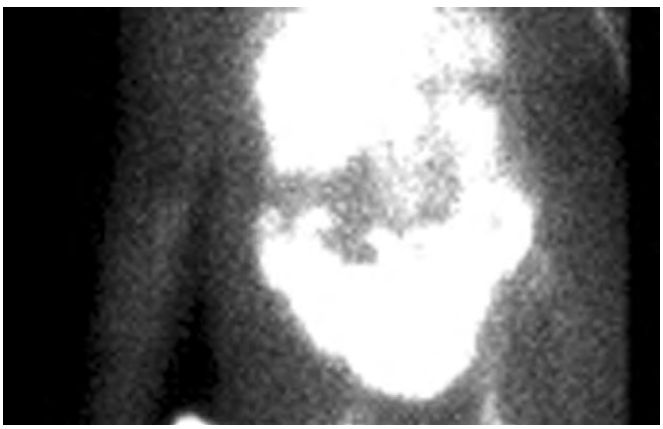


Figure 85–1. Red blood cell–labeled nuclear scan demonstrating diffuse blood in the small bowel without localization of the source of arterial bleeding.

scanning for AEF has been reported in patients with subtle signs of graft compromise.[26]

Ultrasound evaluation of the aorta and periaortic structures may be useful to screen for an aneurysm or pseudoaneurysm after surgery; however, its use in detection of AEFs is limited and therefore not recommended. Other modalities for bowel imaging, such as plain films and barium swallow, are seldom helpful for diagnosis or localization of fistulas and may interfere with other imaging because of barium artifacts.[11]

Surgical Treatment

The initial approach to patients suspected of having an AEF or those with an established diagnosis begins with an appreciation of the patient's cardiovascular status and underlying comorbid conditions. Central to planning of treatment is an appraisal of the survivability of these gravely ill patients after another major operation. Placement in an intensive care unit before and after surgery, central venous access, intra-arterial pressure monitoring, appropriate fluid resuscitation, correction of electrolyte abnormalities, and blood transfusions as needed should be undertaken. Antibiotic coverage is typically empirical until tissue culture results are available; however, appropriate coverage for gram-negative organisms, enteric bacterial species, and *Staphylococcus aureus* should be initiated.

The present standard of treatment of both primary and secondary AEFs remains surgery. Without surgery, a patient harboring an AEF will ultimately succumb to bleeding or sepsis. The primary aim of operative intervention is to stop active bleeding and prevent potential life-threatening hemorrhage. After successful vascular control, the surgeon can then address the enteric defect, infection control, and vascular reconstruction with preservation of distal blood flow.

Patients with any degree of hemodynamic instability should be resuscitated quickly and taken to the operating room without delay or extensive work-up. The initial approach should be through a midline laparotomy from the xiphoid to the pubis symphysis. Retroperitoneal exposure is an alternative approach to a diseased aorta and to avoid a hostile abdomen. However, limited visualization of the right iliac artery or graft limb and involved bowel make it a less than ideal choice for a patient in extremis. The first priority on abdominal entry should be proximal vascular control, which will in most cases best be accomplished through supraceliac aortic exposure and control. After proximal control, if the patient is hemodynamically stable, distal aortic or iliac artery control can be established. In unstable patients, distal control can be achieved through placement of occlusion balloon catheters, either through the open aorta or via a transfemoral approach. Once proximal and distal control is established, infrarenal dissection is undertaken and aortic cross-clamping performed in the infrarenal position to avoid prolonged mesenteric and renal ischemia. If hemostasis is present, systemic heparinization is induced before cross-clamping to prevent distal arterial thrombosis.

If there is no active bleeding, examination of the gastrointestinal tract should be performed. Beginning with the stomach and looking for evidence of peptic ulcer disease, a methodical running of the bowel should continue distally with particular attention paid to the area at the ligament of Treitz. Dissection of the bowel directly overlying the aorta should be performed sharply. Once the dense adhesions are freed, the AEF should be isolated and bowel repair or resection carried out as necessary. Because there is no definitive method of restoring bowel continuity, the operative anatomy should dictate the method selected. Enteric spillage into the operative field should be minimized by either clamping or oversewing any obvious defects. Small defects may be amenable to a transverse, two-layered repair, whereas segmental resection to healthy tissue is needed in other patients. Serosal patch placement and end-to-end, end-to-side, or Roux-en-Y anastomosis may be required for fistulated bowel.

Management of the aortic portion of the AEF should begin with extensive débridement of any infected retroperitoneal soft tissue. Intraoperative tissue Gram stain and culture will help in identifying the degree of infection and bacterial pathogens. Once clear tissue margins are ensured, full exposure through meticulous sharp dissection of the native aorta for primary AEF or the prosthetic graft for secondary AEF is performed. It is essential that dissection along the length of the aorta or graft be extended to well-incorporated healthy and uninfected tissue. The type of AEF will guide the manner in which the aorta is handled and the definitive reconstruction performed. If an AEF is not discovered at the usual location near the ligament of Treitz, the entire small bowel and colon should be assessed to look for other unsuspected pathology.

Primary Aortoenteric Fistula

Treatment of a primary AEF, once vascular and enteric control is established, rests on the degree of infection found at surgery. With more proximal AEFs involving structures such as the duodenum, it is possible for the bacterial inoculum to be lower than for AEFs involving more distal structures such as the colon. Nevertheless, historical studies report that up to 30% of primary AEFs may harbor infection.[27] In most cases, primary AEFs can be attributed to the progressive evolution of an aneurysmal aorta. Primary AEFs, as a result of either an aneurysmal or gastrointestinal etiology, may be repaired by either in situ graft placement or extra-anatomic bypass (EAB). Patients' medical comorbid conditions and cardiovascular instability usually dictate the use of a prosthetic graft. The use of antibiotic (rifampin)-impregnated grafts may lower the risk for infection. Alternatively, in stable patients, autologous aortoiliac bypass with superficial femoral veins is an available option.[28] In an operative field in which gross contamination or purulence is encountered, EAB is the safer alternative, although it prolongs the operative time. The key tenet in repair remains adequate débridement of all infected tissue and placement of healthy tissue between the aortic reconstruction and overlying bowel.

Secondary Aortoenteric Fistula

Of the *secondary* AEFs, aortoenteric erosions are the easier to treat. As in *primary* AEFs, the involved bowel is treated by either repair or resection. Because the aortic graft is only secondarily contaminated, excision of this segment of graft plus in situ replacement of it with another prosthetic graft is usually satisfactory. Treatment of *secondary* AEFs caused by associated aortic anastomotic disruption can be significantly more complicated because they generally involve more extensive prosthetic infection and less normal aortic tissue. Traditionally, a single operation addressing both graft excision and creation of an EAB has been associated with a high level of morbidity and mortality. In an effort to lower complications secondary to the long cross-clamp times required to perform both phases of the operation, a reversed staging approach has been adopted by some, with favorable results reported in the literature.[4] Reversed staging begins with placement of an EAB, followed by excision of the infected graft 1 to several days later.[4,9] Use of the reversed staging approach, however, depends on patient stability. Those with active bleeding or profound sepsis cannot undergo this sequence and require urgent graft excision. When possible, staging allows for decreased intraoperative blood loss, as well as avoidance of the metabolic and hemodynamic consequences of prolonged interruption of perfusion to the lower extremities. Though performed in two separate operations, each stage remains a challenging step in full reconstruction. The typical EAB includes an axillofemoral and femorofemoral bypass with preservation of pelvic blood flow in a retrograde manner from the common femoral arteries. Patients with previous bifemoral grafting and extension of infection into the groin present much more of a challenge because of the need to excise the existing anastomoses and then select new sites for distal graft placement, usually tunneled lateral to and downstream from the previous reconstruction. Once the EAB is completed, the patient is returned to the intensive care unit, where resuscitation and antibiotic coverage are continued. One to several days later, the patient is returned to the operating room for removal of the infected prosthetic graft and repair of the enteric defect.

Before graft excision, the enteric defect should be repaired or resected and gastrointestinal continuity reestablished. After complete exposure of the prosthetic graft and proximal and distal aorta, excision of the involved graft and radical débridement of infected perigraft tissue are performed. Complete removal of aortic tissue at the proximal suture line is required. If necessary to obtain viable aortic tissue because of infectious involvement extending to the renal arteries, separate revascularization with antegrade bypasses to the renal arteries can be performed. Fortunately, this is a rare occurrence. Insufficient débridement of the proximal aorta adjacent to the anastomosis has been associated with later aortic stump blowout and death from recurrent bleeding.[29] Recent studies, however, show a reduction in this complication with meticulous closure technique and the onlay of healthy autologous tissue. The stump and area of excised graft are optimally covered with an omental flap. The distal end of the aorta, after graft excision, is oversewn with monofilament polypropylene suture to prevent disruption. Thorough irrigation of the entire abdomen is required before abdominal closure. Specimens of all prosthetic and perigraft tissue should be taken for culture to help in tailoring the selection of postoperative antibiotics.

In situ reconstruction remains an important option for patients in whom EAB is not possible. Recent advances in replacement graft options have renewed interest in this type of repair, with a greater than 22% survival benefit over extra-anatomic repair.[2,30] The risk for aortic stump blowout after EAB is reported to be as high as 16% and can be avoided by using this approach.[2] Additionally, the amputation rate is 14% lower with in situ revascularization.[18] Currently, several choices of replacement conduit are available for reconstruction. Autologous tissue is ideal when reconstruction takes place in a known infected field. One useful type of autologous tissue is the superficial femoral vein used to reconstruct the aortoiliac system. An advantage over other venous tissue is its larger diameter. However, proper vein harvesting and construction of the bifurcation may be time-consuming and can lead to longer lower extremity ischemic times.[28] Saphenous vein, when sewn into a larger-diameter conduit through panel or spiral techniques, may be suitable, even for aortic replacement. Arterial allografts are seldom used because of the known risk for late aneurysmal degeneration. The use of cryopreserved homografts has been successfully reported in the literature, albeit with limited clinical experience. Authors using homografts as replacement conduits cite the inherent infection-fighting ability of this conduit, as well as its ability to function as a temporizing conduit, with definitive reconstruction performed in a delayed manner after the infection has cleared.[31] Rifampin-impregnated Dacron prosthetic grafts have demonstrated better protection against reinfection when used during in situ reconstruction.[32,33] Newer manufacturing techniques of antibiotic bonding with collagen or gelatin allow for longer antibiotic availability at the in situ site.[34]

Occasionally, in patients in whom aortic grafting was performed for occlusive disease or in patients with bilateral lower extremity amputations, graft excision without revascularization may be possible. In such circumstances, preoperative noninvasive vascular studies and arteriography can be helpful in determining the degree of available collateral circulation. Cases in which an end-to-side graft was initially placed may be handled by graft excision with aortic endarterectomy and patch closure, provided that thorough débridement of infected aortic tissue has been performed.

Endovascular Therapy

Endovascular therapies for AAA have not prevented the later development of an AEF. Such techniques, however, may also provide new options for interventions in the treatment of AEF. Despite the less invasive nature of endovascular surgery, AEF after stent deployment has been reported in the literature.[35-37] Specific aneurysmal

characteristics that may lend to the later development of an AEF after stent placement include the ongoing presence of an AAA under endotension, treatment of inflammatory aneurysms, the choice of stent, migration or kinking of endovascular devices, and unrecognized occult *primary* AEF.[37]

The therapeutic use of endovascular devices for AEF may be most helpful in the setting of acute, life-threatening hemorrhage, where timely operative control may be hindered by extensive adhesions and a hostile abdomen. Successful use of balloon control of aortic hemorrhage in a situation involving traumatic AEF has been reported.[38,39] Temporizing the bleeding from an AEF may also be accomplished through transcatheter coil embolization before operative intervention and open repair.[40] The use of endovascular repair in the presence of known aortic infection or AEF should be individualized to the patient because there is no current consensus on treatment in these circumstances. Successful stent placement in the presence of an AEF has been reported; however, recurrence of infection and fistula hemorrhage continue to be clear risks.[41-44] Stent repair of AEF is not definitive therapy because débridement and removal of associated retroperitoneal infection are not possible.[45] The use of more novel techniques, including the combined application of an aortic stent and endoscopic injection of fibrin sealant, has also been reported.[46,47] In the future, stent placement in patients with a known AEF may possibly be indicated as a bridge to definitive open repair once the acute, life-threatening circumstances are controlled or for palliative reasons.[48,49]

Results

The natural, untreated clinical course of *primary* AEF remains eventual death from gastrointestinal hemorrhage. Surgical approaches short of closure of the enteric defect, removal of infection, and vascular reconstruction, such as local patch repair or aneurysmorrhaphy, are complicated by reinfection and increased mortality.[50]

Secondary AEF follows a similar course if left untreated. Several options are currently available to handle this type of AEF, including the traditional method of fistula takedown and bowel repair, followed by graft excision, débridement, and EAB. The reversed staging technique still maintains these surgical principles but allows for reduced lower extremity ischemia times by EAB construction before intra-abdominal decontamination and repair. This method has produced improved results over the traditional technique, with an AEF cure rate of 70% (>3 years postoperatively) and 18% mortality.[4] Graft excision may be performed without revascularization, as potentially indicated for patients with occlusive disease, but it still carries a high mortality rate. More recently, renewed interest in in situ graft replacement has emerged, with investigators reporting improved surgical outcomes with appropriate patient selection and a range of bypass graft choices. A 20% reduction in mortality has been reported with in situ replacement versus EAB.[2]

Reinfection, graft occlusion, amputation, aortic stump blowout, and need for revision surgery are still seen. In a meta-analysis of *secondary* AEF by Pipinos et al., a third of patients undergoing AEF surgery suffered complications.[8] In another subset group, revision of graft placement was required in 40%, and recurrent *secondary* AEFs developed in 34%. Aortic stump rupture and anastomotic rupture occurred in 19% and 7%, respectively.[8] Amputation complicating AEF ranges from 6% after in situ repair, to 8% with lower extremity revascularization before graft excision, to 20% after EAB.[18]

Despite improvements in surgical technique and perioperative care, AEF remains a rare complication that is difficult to diagnose and treat. The majority of published data regarding AEF are in the form of small-volume, retrospective analyses or case reports, with multiple different practice standards applied. Definitive conclusions regarding any single method or technique are more difficult because of this lack of data. Death after AEF occurs in 30% to 40% of patients. Thirty-day survival rates after surgical treatment range from 13% to 86%, with an average of 33%. Overall, morbidity and mortality rates have been relatively unchanged and remain higher than seen with prosthetic graft infection. Quality of life after AEF and reconstruction has not been studied in the current literature.

VISCERAL ARTERY ANEURYSMS

Visceral artery aneurysms are relatively rare lesions. However, they are clinically important because of the potential for rupture and life-threatening hemorrhage. An increased frequency of abdominal imaging has brought to attention more visceral aneurysms than has previously been reported.[51,52] Although there is a paucity of prospective natural history data on which to base treatment recommendations, general guidelines for intervention have been developed. Newer techniques for treatment have expanded the available options for patients with visceral artery aneurysms.

Splenic Artery Aneurysms

Incidence

Splenic artery aneurysms (SAAs) are the most common visceral artery aneurysms found intra-abdominally. Only aortic and iliac artery aneurysms are more frequent. It is difficult to define the exact incidence of SAAs, with postmortem studies suggesting an incidence ranging from 0.1% to 10%. An average prevalence of 0.8% is suggested, with SAAs developing more commonly in multiparous women.[53,54] Improved and more frequently used radiographic imaging modalities are likely to increase the frequency of diagnosis of such aneurysms.

Pathogenesis

The exact etiology of SAA is not completely understood. Multiple underlying disorders are thought to be associated or directly responsible for SAA formation. Abbas et

al. reported the presence of hypertension (50%), obesity (28%), smoking (28%), and hypercholesterolemia (22%) in 217 patients with SAAs.[55] Historically, the most commonly implicated condition is arteriosclerosis. More recently, however, it has been suggested that the arteriosclerotic changes are secondary alterations in the composition of the vascular wall that are possibly associated with abnormal hemodynamic flow patterns.[56] Commonly seen in patients with SAAs is the presence of arterial fibrodysplasia, thus supporting a causative role of medial layer degeneration in the formation of these aneurysms.[54,57] Portal hypertension, cirrhosis, and splenomegaly are linked to the development of SAAs because of their contribution to elevated portal pressure and an increased diameter of the splenic artery. Accordingly, orthotopic liver transplantation has also resulted in an increased incidence of SAAs, probably because of the same mechanism. Other pathologic conditions that can lead to the development of SAAs include connective tissue disorders such as Marfan's syndrome, inflammatory states, and infection. Pseudoaneurysms can occur after traumatic injury to the abdomen, whereas chronic pancreatitis with pseudocysts leads to a 10% incidence of false aneurysms of the splenic artery.

A history of multiple pregnancies is common in women with SAAs. A recent analysis showed an average of 3.5 pregnancies in women with SAAs.[55] No single cause has explained the relationship between pregnancy and aneurysm development. Molecular and physiologic data suggest a predilection of the splenic artery to respond to changes of pregnancy, including hormonal effects and blood flow changes.[53]

Most SAAs appear saccular and may occur anywhere along the vessel. Typically, they are found along the main trunk or branch points, with multiple aneurysms occurring in up to 20% of patients. Smaller SAAs, such as those associated with systemic disease, may be found within the spleen itself. SAAs may vary in size considerably but largely fall between 2 and 3 cm. Calcification of the aneurysms occurs commonly and is found in up to 90% of splenic aneurysms.[55]

Clinical Findings

The majority of patients with SAAs are asymptomatic at the time of diagnosis. Those who do have symptoms at diagnosis are often found to have another cause for their complaints. Typical symptoms that may raise suspicion for SAA include vague, radiating left upper quadrant or epigastric pain that is exacerbated by positional changes. Episodic abdominal discomfort may be related to distal embolization of thrombus resulting in splenic infarction. SAAs are usually found incidentally by plain film radiography, CT, or arteriography for unrelated reasons. Calcification outlining the aneurysm sac tends to appear curvilinear and at the expected location of the splenic artery in the left upper quadrant.

The lifetime risk for SAA rupture may be as high as 10%, although some series have reported mortality rates as high as 25%.[58,59] Patients at increased risk for rupture include pregnant, multiparous women during the third trimester, cirrhotic patients, and those with connective tissue diseases. Symptomatic SAAs are typically due to intraperitoneal rupture. The phenomenon of *double rupture* refers to temporary lesser sac containment of a bleeding aneurysm resulting in transient symptoms, followed by breakthrough exsanguination into the rest of the abdominal cavity leading to hemodynamic collapse. SAAs may rarely rupture into adjacent structures such as the bowel, biliary tract, and splenic vein and result in occult bleeding. Symptomatic SAAs found in pregnant women have ruptured. The correct diagnosis, however, is difficult to make and can be confused with other obstetric, gynecologic, and general surgical conditions, thereby delaying emergency treatment. Mortality in pregnant women after ruptured SAAs has historically been reported to be as high as 70%, with fetal salvage being rare.[53,60]

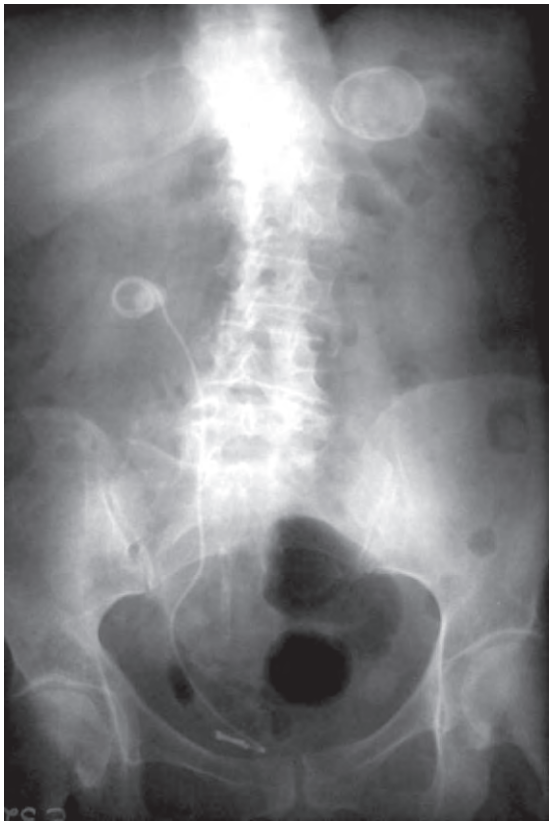
Diagnosis

Diagnosis of a symptomatic SAA rests on clinical suspicion. The initial clinical findings may lead to an evaluation for other intra-abdominal conditions first, with incidental identification of an SAA on radiographic studies. Plain abdominal radiographs may identify concentric calcifications in the left upper quadrant that suggest the presence of an aneurysm. CT scans, CT angiography, and duplex ultrasound will also be useful in the identification and diagnosis of an SAA (Fig. 85–2). Arteriography is not usually needed for identification of an aneurysm but can be helpful for operative planning before elective surgical repair. In patients in whom other modalities do not clearly define the precise vessel of origin, selective arteriography can provide the definitive diagnosis.

Treatment

The indications for treatment of an SAA have become better defined. Although definitive management of asymptomatic SAAs does not involve a fixed size cutoff for operative intervention, in good-risk patients, intervention is appropriate when the diameter of the aneurysm exceeds 2 cm. Lesions in young patients or women of childbearing age or aneurysms with progressive enlargement should be repaired electively. SAAs that are found during pregnancy are best treated at diagnosis because of the high mortality in the mother and fetus if rupture occurs. Symptomatic aneurysms should be repaired on an emergency basis.

Surgical treatment of SAAs may be individualized for each patient because several approaches are available for repair. Surgical techniques include aneurysm ligation, resection, and resection with splenectomy when the aneurysm is close to the hilum of the spleen. Because of the abundant collateral blood supply to the spleen via short gastric arteries, arterial reconstruction is not necessary. Aneurysm exclusion, accomplished through proximal and distal artery ligation, is all that is required and the preferred approach in most circumstances. Aneurysmorrhaphy, or opening of the aneurysm and oversewing the inflow and outflow vessel, is performed when adequate exposure of the proximal or distal splenic artery is



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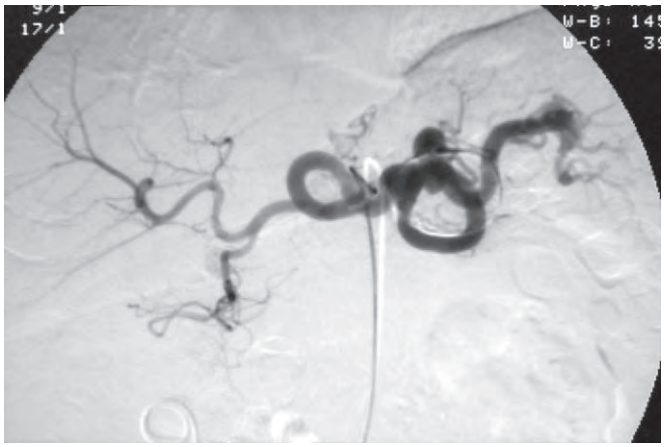

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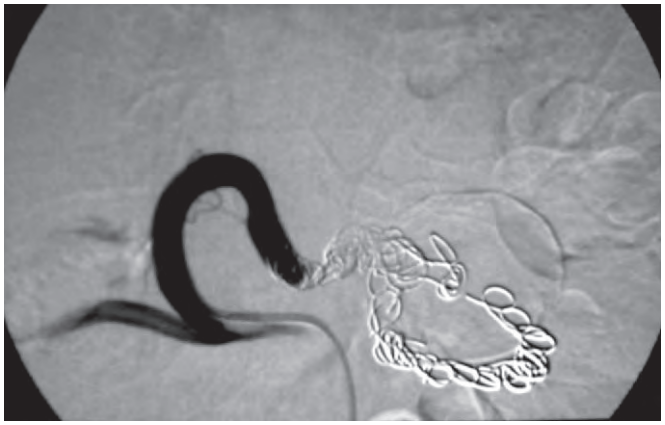

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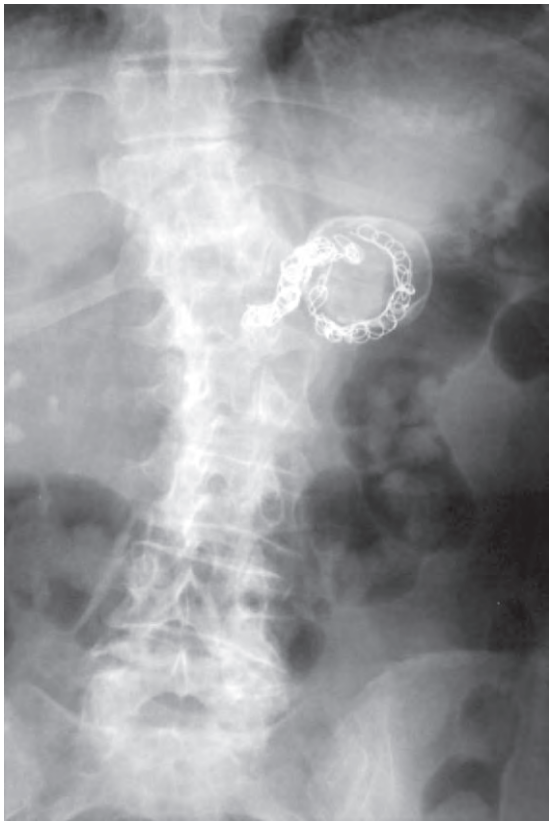


D

Figure 85–2. **A,** A plain abdominal radiograph shows a large calcified aneurysm in the left upper quadrant. **B,** Selective angiography of the celiac artery identifies signet-ring opacification of a splenic artery aneurysm. Thrombus on the inside of the aneurysm induces flow of contrast within the outer edges of the aneurysm. **C,** Coil embolization within the splenic aneurysm induces thrombosis of the aneurysm and occlusion of the mid and distal splenic artery. **D,** An abdominal roentgenogram illustrates the coils within the curvilinear structure of the splenic aneurysm.

not possible as a result of surrounding inflammation. Proximal ligation alone is not recommended because retrograde blood flow can potentially continue to enlarge an SAA. Splenectomy may be needed in cases in which an SAA is near the hilum or is encroaching on the parenchyma and might make exclusion hazardous. Splenectomy is not generally recommended, however, because of loss of splenic function and host resistance. A laparoscopic approach using any of these methods has been performed successfully.[61]

The characteristics of the SAA also define the manner in which exposure and subsequent aneurysm treatment are carried out. Ruptured aneurysms, patients with previous abdominal surgery and extensive adhesions, or those with severe inflammation from recent pancreatitis may make the operative approach technically challenging. SAAs are usually best approached surgically through the lesser sac with exposure and control of the proximal splenic artery. Patients with rupture and instability because of blood loss may benefit from proximal control of the splenic artery at its takeoff from the celiac trunk, after which evacuation of the contained hematoma in the lesser sac will allow easier dissection and identification of the aneurysm. Pregnancy can complicate surgery further, with the gravid uterus displacing the abdominal viscera superiorly. Cesarean delivery may be required before definitive therapy because the majority of SAAs rupture during the third trimester.

SAA embolization is an alternative endovascular technique for repair with a high reported success rate of 85%.[62] This method may be ideal for patients who are unfavorable candidates for either open or laparoscopic repair. Postembolization risks are real, however, and consist of incomplete aneurysm obliteration, coil migration, end-organ ischemia, and pain from splenic infarction.[63] Recently, stent graft exclusion of SAAs has been reported in carefully selected, high-risk patients who would benefit long-term from spleen salvage.[63-65] Endovascular stent graft placement requires sufficient normal proximal and distal splenic artery anatomy for graft anchoring. Additionally, feeding vessels to the aneurysm sac may not allow for complete endovascular exclusion and thus may contribute to a persistent endoleak.

The results of SAA treatment remain favorable, with low mortality rates in elective patients. Complications after surgery relate specifically to the performance of splenectomy when required. Recurrence after repair is rare and contingent on the technique used. Earlier diagnosis of SAA, continuing improvements in minimally invasive surgery, and endovascular stent graft placement should reduce the number and complexity of emergency aneurysm repairs in the future.

Hepatic Artery Aneurysms

Incidence

Hepatic artery aneurysms (HAAs) have historically been rare, with an incidence of approximately 0.4%.[66] They account for up to 20% of all splanchnic artery aneurysms.[67] The recent application of percutaneous procedures for biliary disease and the increased use of radiologic procedures performed for other reasons have increased the number of identified HAAs. Such aneurysms have the potential for rupture and continue to pose a threat for major hemorrhage and possible death.

Pathogenesis

Multiple different causes are responsible for the development of HAAs. Previously, an infectious cause was largely responsible for the formation of most HAAs. This incidence has decreased significantly, with only 10% presently related to infection, typically as a result of intravenous drug use or endocarditis.[68] Improvements in antimicrobial therapy have most likely also reduced this number. A significant number of HAAs found are false aneurysms, probably related to operative or percutaneous instrumentation and traumatic injury. Systemic inflammatory arterial diseases, infection, pancreatitis, liver transplantation, pregnancy, and portal hypertension have been associated with aneurysm formation. Medial degeneration and arteriosclerosis are factors in a significant number of HAAs.

Approximately 80% of HAAs are extrahepatic, with the common hepatic artery accounting for 63%. The remainder are most often seen to involve the intraparenchymal, right hepatic artery.[68] One third of HAAs are associated with aneurysms of other visceral arteries.[55] Hepatic aneurysms are usually solitary, with multiple aneurysms more frequently seen in patients with inflammatory arteriopathies, such as polyarteritis nodosa. Larger aneurysms tend to be saccular, whereas smaller ones are more fusiform in shape.

Clinical Findings

HAAs are seen twice as frequently in men as women. Both extremes of age are affected; however, patients average between 50 and 60 years of age at diagnosis. Traumatic causes may affect a younger population. Because a larger number of HAAs probably exist without being diagnosed, the majority of aneurysms are asymptomatic. Patients who do report complaints and are later found to have lesions typically have vague, right upper quadrant abdominal pain suggestive of other causes. The extreme manifestation of symptomatic HAA occurs after rupture, where peritonitis and hemodynamic compromise are usually seen. Other less common manifestations include jaundice and biliary colic secondary to extrahepatic biliary compression and obstruction. Aneurysms may also erode or rupture into adjacent organs or biliary ducts and cause massive gastrointestinal hemorrhage and hematobilia. Most often, hematobilia results from rupture of false aneurysms related to trauma. Fever is commonly seen with hematobilia. Physical examination rarely yields specific findings, and abdominal bruits are seldom found. Patients with long-standing fistulas from aneurysm rupture may have signs of chronic anemia. Quincke's triad of jaundice, abdominal pain, and hematobilia is not seen with any regularity.[69]

Diagnosis

Unless ruptured, most HAAs are not correctly diagnosed initially because other factors account for the symptoms and the HAA is an incidental finding. Some radiographic signs may indicate the presence of an HAA. Calcification of the aneurysm sac may be seen on plain films or CT. Compression of adjacent structures, such as bowel lumen or biliary ducts, can also be identified radiographically.

There are no accepted screening tests for HAA. Duplex ultrasonography and CT remain the primary methods of investigation when an aneurysm is suspected. Arteriography will effectively diagnose an HAA, but its role should most often be limited to preoperative evaluation of hepatic artery perfusion and surgical planning.

Treatment

Although aneurysm size has not been definitively correlated with the potential for rupture, HAAs carry the highest risk for rupture (44%) of any visceral aneurysm, and the mortality associated with rupture is greater than 35%.[70,71] Accordingly, aneurysm repair is recommended for all medically fit patients.

Operative planning is aided by arteriography in elective patients. Most importantly, the location of the aneurysm along the hepatic artery determines the approach. A subcostal incision or midline laparotomy is appropriate for most HAAs. Early proximal vascular control of the common hepatic artery should be carried out. Realizing the relationship of the foregut collateral vessels to an extraparenchymal aneurysm allows for determination of the need for revascularization of blood flow to the liver. Aneurysms proximal to the gastroduodenal artery takeoff may be treated by exclusionary ligation on both sides of the aneurysm with or without excision of the aneurysm.[66] An exception to this recommendation is the rare occluded superior mesenteric artery (SMA), which would limit collateral flow through the gastroduodenal artery.[66] HAAs found distal to the gastroduodenal artery involve more careful operative planning. The risk for liver necrosis after proper hepatic artery ligation can be avoided by arterial reconstruction. Arterial revascularization in such circumstances is required. A useful way to test for potential postligation liver ischemia is temporary intraoperative artery occlusion and parenchymal assessment. Multiple strategies to reconstruct the hepatic artery are available and include the use of primary end-to-end anastomosis with an autologous vein interposition graft, splenohepatic or aortohepatic bypass, and prosthetic graft placement.[71-73] Right or left hepatic artery aneurysm repair should be approached in a similar reconstructive manner. If ligation is required, adjunctive cholecystectomy is advocated to avoid postoperative necrosis of the gallbladder. Rarely, partial liver resection may be required to treat HAAs.

Advanced experience with endovascular stent graft placement makes it an attractive option in some patients. Its application may be particularly useful for intrahepatic aneurysms, small aneurysms, hostile abdomens, and patients who cannot tolerate open procedures. Percutaneous transcatheter embolization has also been used successfully in the management of HAAs but carries its own inherent risks, including parenchymal necrosis and hepatic abscess.[74] This option appears less appealing than graft placement.

Superior Mesenteric Artery Aneurysms

Incidence

Superior mesenteric artery aneurysms (SMAAs) are the third most frequent visceral aneurysms, after SAAs and HAAs. Aneurysms of the SMA and its branches have an incidence of less than 0.01%.[75] An increase in the number of reported aneurysms is likely to be seen as routine CT scans are increasingly being performed for a variety of other reasons. SMAAs are important because of their potential for rupture and the risk that they pose to small and large bowel supplied by the SMA.

Pathogenesis

Unlike other aneurysms, trauma and atherosclerosis do not account for the majority of SMAAs. Interestingly, the SMA is associated with an infectious etiology more frequently than any other muscular artery. Historically, an infectious cause was thought to be responsible for up to half of these aneurysms; however, recent reports do not support this high number of mycotic aneurysms. When infection is the underlying cause, *Streptococcus* is most commonly involved and may be related to left-sided bacterial endocarditis. Collagen vascular disorders and systemic syndromes affecting the arterial vasculature may also contribute to SMAA development in selected patients. Atherosclerosis has not been accepted as the primary cause of SMAA development; however, its presence is seen in a number of aneurysms.[76]

Clinical Findings

Similar to other visceral aneurysms, vague, intermittent abdominal pain is the leading complaint in patients found to have an SMAA. Unlike the silent nature of other abdominal aneurysms, SMAAs typically produce symptoms. Oftentimes, the symptoms may be similar to an episode of acute mesenteric ischemia. A pulsatile, mobile, epigastric mass may be found in a significant number of patients. The ability to displace the mass manually helps distinguish it from AAAs. A strong clinical suspicion should be present for patients with this type of manifestation and documented bacterial endocarditis. Ruptured SMAAs will probably cause cardiovascular collapse unless they are temporarily contained. Rupture into gastrointestinal structures does not occur routinely.

Diagnosis

Unlike other visceral aneurysms, calcification of SMAAs is not routinely seen and thus limits the usefulness of plain abdominal radiographs. Cross-sectional imaging is the preferred method of diagnosing these aneurysms, with CT scanning or duplex ultrasound yielding the most

accurate results. The role of arteriography is limited to preoperative planning and specific delineation of the celiac artery, inferior mesenteric artery, and surrounding collateral vessels.

Treatment

Operative repair of SMAAs is indicated in all patients because of the significant risk for rupture. Aneurysmorrhaphy and simple ligation are both acceptable surgical approaches. In cases in which appreciable collateral circulation has developed in response to a progressively diseased SMA, ligation proximal and distal to the aneurysm can be performed without enteric blood flow compromise. If, however, sufficient collateral flow has not developed because of stenosis in either the celiac or inferior mesenteric artery, reconstruction should be performed. Autologous vein and prosthetic routes are both acceptable and may be bypassed from the infrarenal or supraceliac aorta. In some cases, concomitant bowel resection may be required despite adequate resection and reconstruction.

Transcatheter embolization may be applied to a select group of patients who are at high risk for complications during open surgical repair. These patients should have excellent collateral flow on arteriography, and postprocedural clinical monitoring for bowel viability is warranted. Limited reports of successful embolization and stent graft placement in high-risk patients are available. There will probably be increased application of these techniques in the future.

Celiac Artery Aneurysms

Incidence

Celiac artery aneurysms (CAAs) are not well studied in the current literature, presumably because of a low overall incidence in the population. A prevalence of 5.9% has been reported, with two thirds of aneurysms found in men.[77] As with other visceral aneurysms, better and more frequent cross-sectional imaging should increase the radiographic identification of asymptomatic patients with CAAs. The importance of a CAA is related to its potential rupture and subsequent risk for death.

Pathogenesis

Unlike SAAs and HAAs, exposure to traumatic injury is uncommon in the development of CAAs. Historically, infection was thought to be a common cause of their development; however, atherosclerosis is currently the most common precursor. Other factors in the development of CAAs may include celiac axis instrumentation and medial degeneration. The frequency of associated aneurysms in other arteries may be as high as 38%.[78]

Clinical Findings

Demographically, CAAs are similar to other visceral artery aneurysms. Most aneurysms are asymptomatic before diagnosis, but epigastric pain seems to occur in a significant number of patients. Other common findings may include abdominal bruits or pulsatile masses.[79] Previously, a high incidence of CAA rupture was reported; however, a recent reappraisal does not seem to support this finding. Stone et al. reported a 6% rupture rate in a series of 18 patients, which is significantly lower than historical reports.[77] The risk for rupture has not been attributable to known risk factors. When ruptured, CAAs typically have symptoms similar to other visceral aneurysms. Intra-abdominal bleeding with hemodynamic compromise is likely to occur rapidly. The initial manifestation of a CAA may include acute mesenteric ischemia secondary to embolization of a mural thrombus within the aneurysm sac.[80]

Diagnosis

Incidental diagnosis during work-up for other disease most commonly identifies CAAs. Calcifications may be present in a small percentage of CAAs and helps in its diagnosis through plain roentgenographic studies. Ultrasound can also be useful for diagnosis. CT scanning was shown to identify 67% of CAAs in one series and is the preferred noninvasive imaging modality for CAAs.[77] Previously, arteriography was considered essential for work-up; however, its utility is effectively limited to preoperative planning.

Treatment

Not much data are available on which to base management recommendations for asymptomatic CAAs. The risk for rupture is difficult to measure in these patients, with recent reviews yielding a low overall rupture rate. The influence of aneurysm size on rupture is not clearly defined, but a size of 2 cm or greater in diameter has been recommended as a cutoff for operative treatment.[77] However, given the potential for mortality if rupture occurs (up to 40%), patients with CAAs should undergo operative intervention if they are medically fit.[78] A ruptured CAA is handled similar to other visceral aneurysms in the abdomen. Emergency surgery with early ligation of the CAA controls hemorrhage without significant ischemic threat to the liver or bowel. After proximal control is achieved, antegrade bypass revascularization from the aorta to the common hepatic and splenic artery should be attempted if the patient is hemodynamically stable.

Patients eligible for elective aneurysm resection should undergo revascularization. Reconstruction of the celiac trunk may be performed through several techniques. Either aortoceliac bypass after aneurysmectomy or aortohepatic/aortosplenic bypass should be performed. Autologous saphenous vein and prosthetic conduit are reasonable alternatives, especially with a short celiac artery. Some have suggested that prosthetic grafting may have better long-term patency than saphenous vein grafts.[77]

The use of endovascular stent grafts and embolization is currently not well reported. The short length of the celiac artery and acute angulation at its bifurcation may

limit the use of stent grafts in the near future for this indication.

Inferior Mesenteric Artery Aneurysms

Inferior mesenteric artery aneurysms are quite rare, and there are no recent reports of an increased incidence in the current literature. They will probably continue to be identified as incidental findings on cross-sectional imaging with CT or arteriography. Symptoms of these aneurysms are similar to those of other visceral aneurysms. Colonic ischemia as a result of embolization or rupture is possible, but rare. Aneurysmectomy with ligation of the inferior mesenteric artery is probably adequate treatment. The relative ease of access to this vessel would appear to make treatment recommended for all identified aneurysms. Future application of transcatheter embolization or stent grafting remains to be seen.

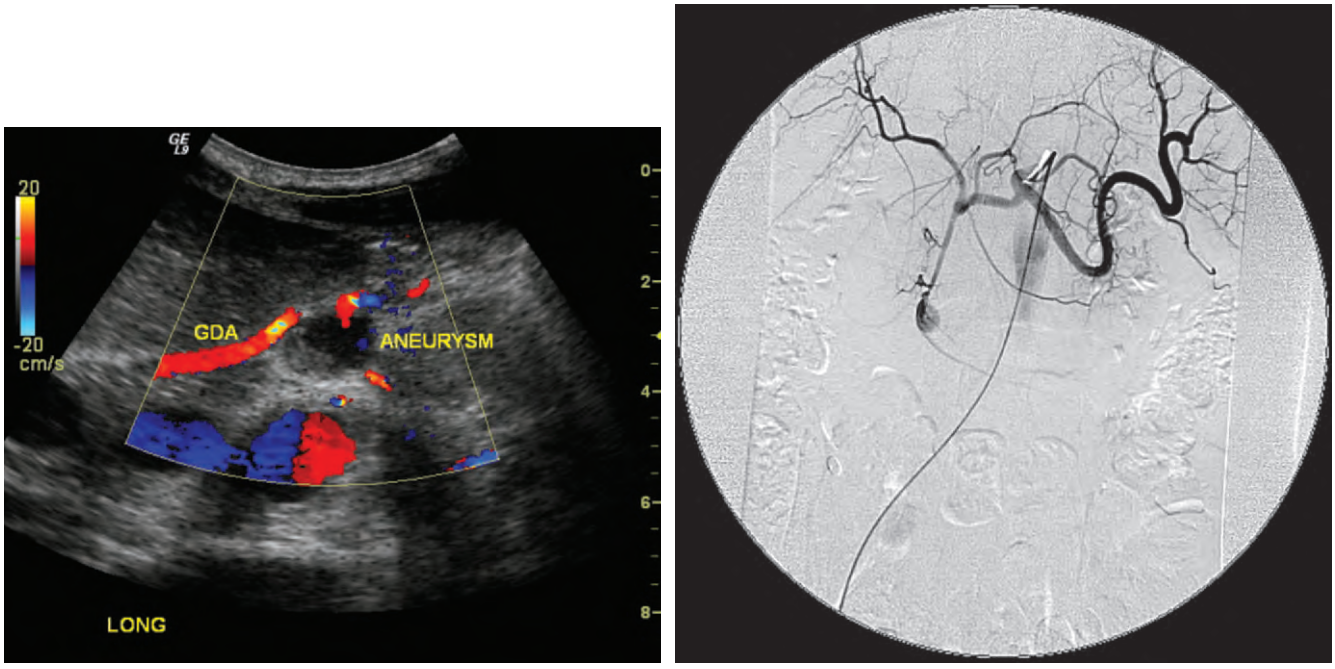
Mesenteric Artery Branch Aneurysms

Gastroduodenal, Pancreaticoduodenal, and Pancreatic Artery Aneurysms

Aneurysms of arteries providing collateral flow between the celiac and superior mesenteric systems are rare. Pancreaticoduodenal artery aneurysms account for only 2% to 3% of all splanchnic artery aneurysms.[81] When present, epidemiologic factors are similar to those for aneurysms found at other sites, including a gender propensity for development in men. The risk for rupture associated with these branch aneurysms is quite high (50% to 80%), and the resultant mortality exceeds 50%.[82,83]

Multiple causes exist for the development of these aneurysms; however, localized inflammation from pancreatitis is the most commonly theorized underlying cause. Pancreatitis is present in up to 60% of patients with gastroduodenal artery aneurysms and 30% of those with pancreaticoduodenal aneurysms.[79] The presence of a pancreatic pseudocyst may contribute to the arteriosclerosis leading to aneurysm formation.

The rarity and asymptomatic or nonspecific symptomatic nature of these aneurysms present a challenge for timely diagnosis and intervention. Most of them are small and nonpalpable. Physical examination alone is therefore rarely of diagnostic value before the aneurysm becomes quite large or has ruptured.[84] When calcified, the diagnosis may be suggested by its presence on an abdominal roentgenogram. Abdominal ultrasonography performed for ill-defined abdominal pain may identify the unsuspected vascular lesion (Fig. 85–3). Similarly, an abdominal CT scan can both identify these mesenteric branch aneurysms and provide an accurate measurement of their size (Fig. 85–4). In other circumstances, the diagnosis is mostly dependent on appropriate clinical suspicion and more objective subsequent evaluation. Mesenteric angiography is the definitive diagnostic modality because it not only confirms the diagnosis but also provides a necessary road map with which an appropriate therapeutic decision can be made. With



A B

Figure 85–3. **A,** A longitudinal abdominal color duplex ultrasound demonstrates an aneurysm of the gastroduodenal artery (GDA) and an echogenic thrombus within it. **B,** Selective angiography of the celiac trunk shows the aneurysm with retained contrast in the distal portion of the gastroduodenal artery.

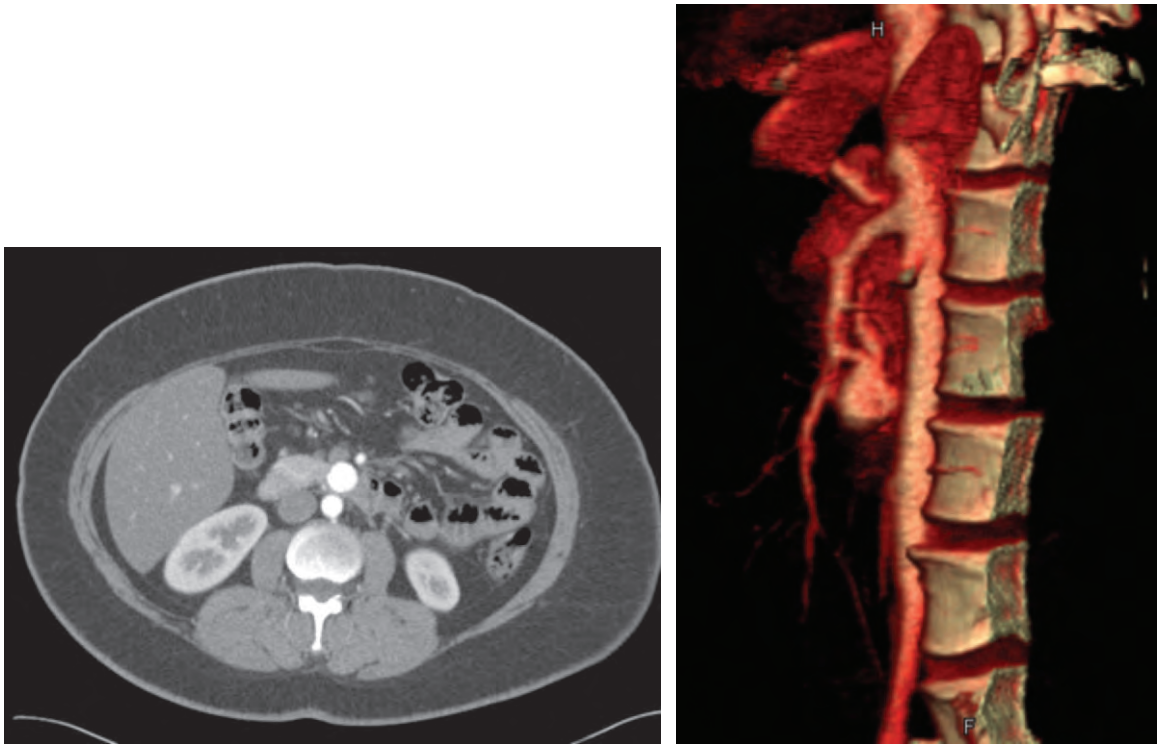


Figure 85–4. **A,** An abdominal computed tomography (CT) scan of the midabdomen with intravenous contrast identifies an aneurysm of the inferior pancreaticoduodenal artery lying between the underlying aorta and the smaller superior mesenteric artery above it. **B,** A sagittal three-dimensional reconstruction CT angiogram illustrates the inferior pancreaticoduodenal artery aneurysm arising posterior to the superior mesenteric artery.

improvements in technology, magnetic resonance angiography is also a useful noninvasive alternative to arteriography. Patients with hypotension and an evident surgical abdomen may require surgical intervention without the opportunity for a definitive preoperative diagnostic evaluation.

Most aneurysms are associated with nonspecific symptoms before the final correct diagnosis is made. Epigastric pain is the most common complaint, and it may initially appear clinically as pancreatitis. Rupture occurs with hemorrhage typically into the stomach or duodenum. Intra-abdominal cavity rupture is unusual. Rarely, obstructive jaundice may result from compression of the biliary ductal system by the expanding aneurysm. Preoperative diagnosis is rarely correctly made without a high index of suspicion. Typically, this group of ruptured aneurysms is identified at laparotomy for refractory gastrointestinal hemorrhage.

As with most visceral aneurysms, intervention is indicated when the risk for rupture and exsanguinating hemorrhage is thought to be greater than the potential risks associated with surgical or other interventional procedures. The risk for rupture of aneurysms is believed to be proportional to the size of the aneurysm.[81] Interestingly, Neville et al. found that 37% of ruptured pancreaticoduodenal aneurysms were less than 1.0 cm and there were no differences in size between ruptured and unruptured aneurysms.[85] Once such an aneurysm is diagnosed, surgical excision with or without vascular reconstruction or embolization is recommended because of the unpredictability of rupture of these aneurysms. Surgical excision is the treatment of choice. Surgical treatment of this group of aneurysms may be more difficult, however, because of the enteric erosion found in most cases and their location within the parenchyma of structures such as the pancreas. Additionally, the presence of pancreatic pathology, including pseudocysts, must be addressed at the time of surgery. A Kocher maneuver will usually be necessary for adequate exposure to ligate the aneurysm. Dissection of the aneurysm sac may be tedious and hazardous in the presence of pancreatitis. In such a situation, ligation of the feeding vessels to the aneurysm sac should suffice as treatment. In only rare cases will pancreatic resection be required. Surgical resection with revascularization is recommended in patients with significant celiac axis occlusion in order to prevent intestinal ischemia and death. If celiac or superior mesenteric artery stenosis is not an issue or if the collateral circulation is adequate, excision or ligation without vascular repair would be appropriate and is less technically demanding.

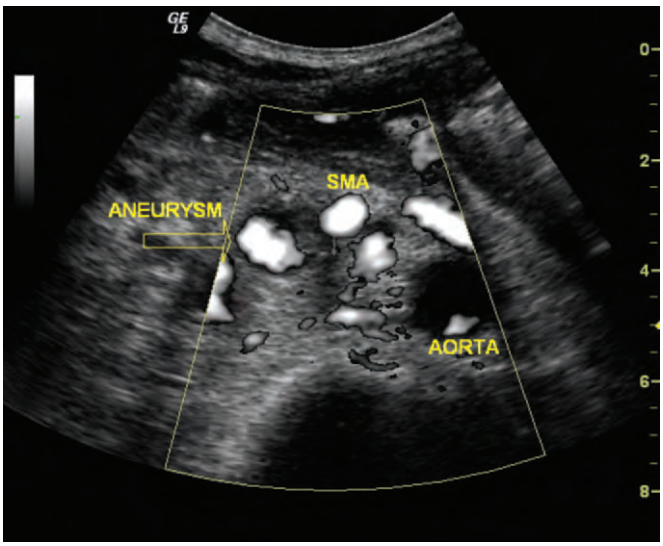
Transcatheter embolization can be used in unstable patients, those with high operative risk because of comorbid conditions, and those with unfavorable anatomy. The

presence of significant collateral circulation in this region may contribute to ineffective treatment with resultant rebleeding or rupture. The use of endovascular stent occlusion with embolization and thrombin injection has also been reported to be successful for these aneurysms.[86] Additional studies are needed to assess outcomes with these techniques.

Gastric and Gastroepiploic Artery Aneurysms

Aneurysms of these branch vessels occur with similar rarity as other branch aneurysms. Their origins may be related to a variety of initiating events, and no single cause is identified. Trauma, infection, congenital predisposition, medial degeneration, and other causes are plausible for their development.

Typical symptoms include epigastric pain and gastrointestinal complaints related to irritation or compression. Intraluminal rupture of an aneurysm may result in profound hematemesis in a significant number of patients.[87] Up to 30% of patients may have an abdominal rupture requiring laparotomy for control of bleeding.[88] Significant mortality is associated with rupture of these branch aneurysms.[83] Operative treatment includes ligation of the involved vessel and the aneurysm when technically possible. Aneurysms within the wall of the stomach may require partial gastric resection.



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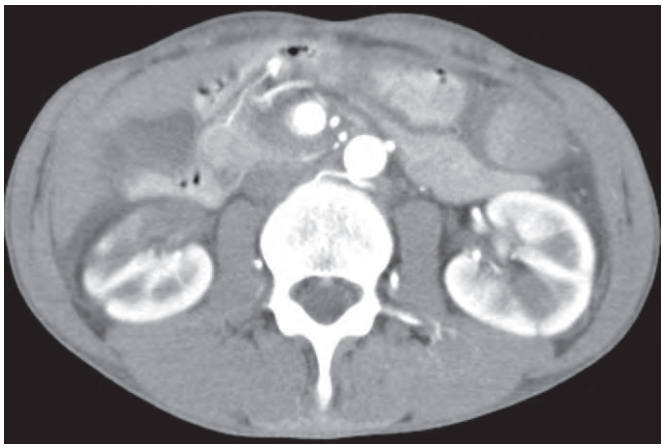

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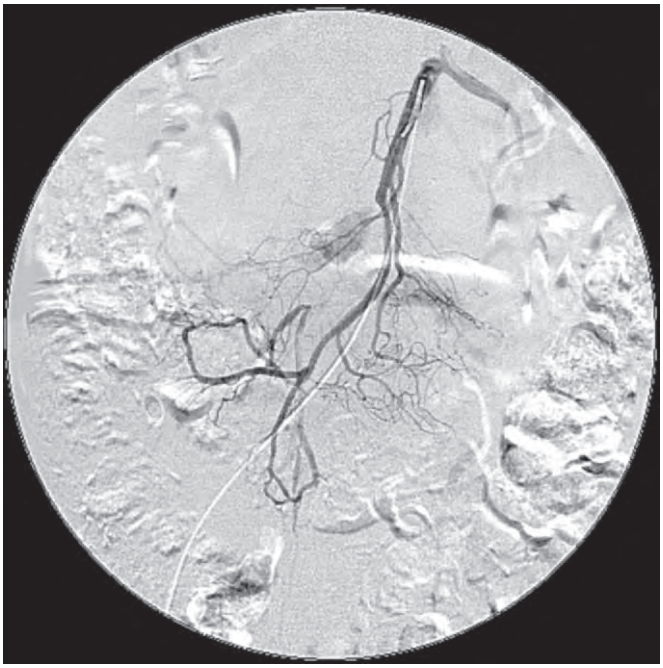

C

Figure 85–5. **A,** Transverse lower abdominal power-flow duplex ultrasound showing an ileocolic aneurysm lateral to the superior mesenteric artery (SMA). **B,** A computed tomography scan with contrast demonstrates the large size of the ileocolic aneurysm and nonopacified thrombus within it. **C,** Selective angiogram of the SMA showing retained contrast within the ileocolic aneurysm with contrast filling the distal vessel and extrinsic compression and medial displacement of the SMA.

Jejunal, Ileal, and Colic Artery Aneurysms

This group of aneurysms is rare and typically seen as small, solitary lesions. Multiple lesions in a single patient may be found with systemic vasculitides, including polyarteritis nodosa.[89] There remains no single cause for the presence of these lesions, and congenital as well as degenerative arterial disease probably contributes to their progression. Most aneurysms remain relatively silent clinically and may be found initially at surgery for other disease. As with other aneurysms, cross-sectional imaging, including CT, duplex ultrasonography, and arteriography, can help in the diagnosis (Fig. 85–5). Arteriography may be particularly important in identifying the presence of multiple aneurysms before treatment. Rupture is difficult to predict; however, aneurysms of colic arteries are thought to rupture more commonly than those associated with the small bowel.[90,91]

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Part

1

Pancreas

Chapter

86

Anatomy, Physiology, and Embryology of the Pancreas

Dale E. Bockman

The healthy, mature pancreas functions silently to produce digestive enzymes and hormones. It usually comes to notice only when a pathologic alteration produces symptoms, frequently involving pain. Pancreatic access and pancreatic surgery are difficult because of the gland's retroperitoneal location in an area replete with major blood vessels and branches and multiple nerves, lymphatics, and ducts, interference with any of which can inhibit normal function.

The pancreas originates during early development of the gastrointestinal system, then differentiates and grows to produce a large gland stretching approximately 15 cm from the duodenum toward the spleen along the posterior body wall. It weighs approximately 90 g normally. Its size may decrease with diabetes or increase with chronic pancreatitis. The exocrine pancreas produces and releases digestive enzymes into the duodenum. Hormones, including insulin, are released from the endocrine portion into the blood vascular system.

Tracking the development of the pancreas from its first appearance in the primitive gut to the acquisition of its mature form can provide some understanding of its relationship with adjacent structures. Furthermore, examination of the developmental stages of the organ reveals cellular changes that are key to understanding regressive changes that may accompany pathologic alterations, which often are treated surgically.

EARLY ANATOMIC FORMATIONS

The pancreas and liver begin as epithelial buds from the primitive gut and reach their mature form through proliferation and differentiation of multiple cell types. Early in embryonic development the endoderm folds into a tube, the anterior part of which is the foregut. At the same time the precursors of major blood vessels form in the surrounding mesenchyme, which is important in early pancreatic development. The primitive aorta, paired anteriorly and fused into a single vessel in the region of the foregut, lies immediately dorsal to the gut. Primitive vitelline veins lie ventral to the gut. The primitive gut and the primitive vessels are, at this stage, tubes consisting solely of a single layer of epithelium. Interaction of the epithelium of the aorta with that of the gut induces proliferation of endodermal epithelium and the beginning of differentiation to form the dorsal primordium of the pancreas (Fig. 86–1). A similar inductive process occurs where vitelline vein endothelium touches gut endoderm to produce ventral buds. The proliferating pancreatic buds express the *Pdx1* gene,[1] providing an early marker of pancreatic differentiation.

The epithelium of the dorsal and ventral buds proliferates to form the growing dorsal and ventral pancreatic primordia (Fig. 86–2). The liver, gallbladder, and associated ducts also develop from the right ventral

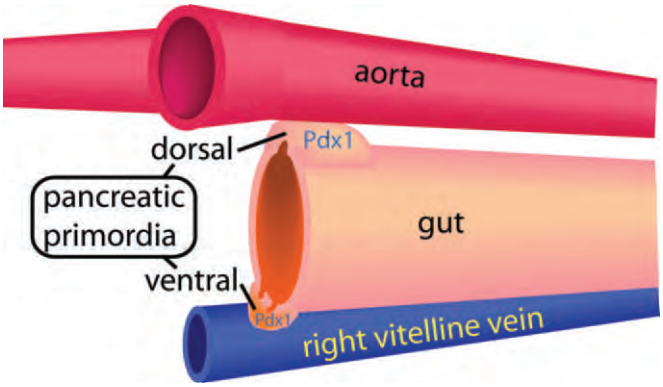

Figure 86–1. Induction of the pancreatic primordia. The epithelial interaction of aorta and gut has produced the dorsal pancreatic bud. The aorta, which originally is paired anteriorly, becomes single with development. Only the right vitelline vein is shown. The right vein persists to form the hepatic portal vein. Epithelial interaction between the vitelline veins and the gut produces primordia. The one associated with the right vitelline vein persists and develops as the ventral primordium.

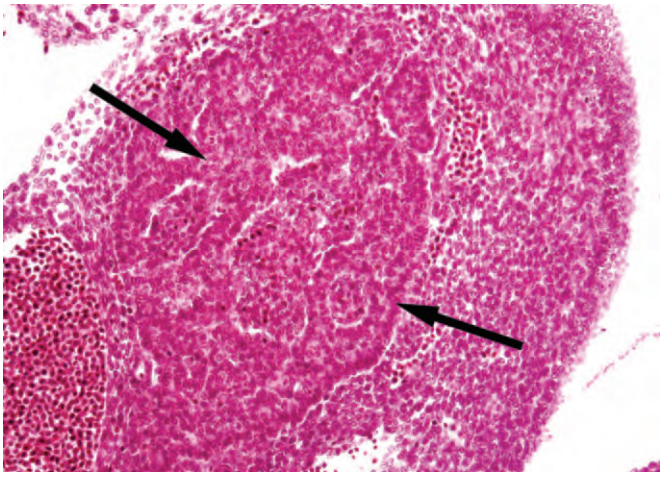

Figure 86–3. Histologic section of pancreatic primordium. The epithelium grows into surrounding mesenchyme as branching primitive tubules. The tubules anastomose in places, producing circular continuity (*arrows*).

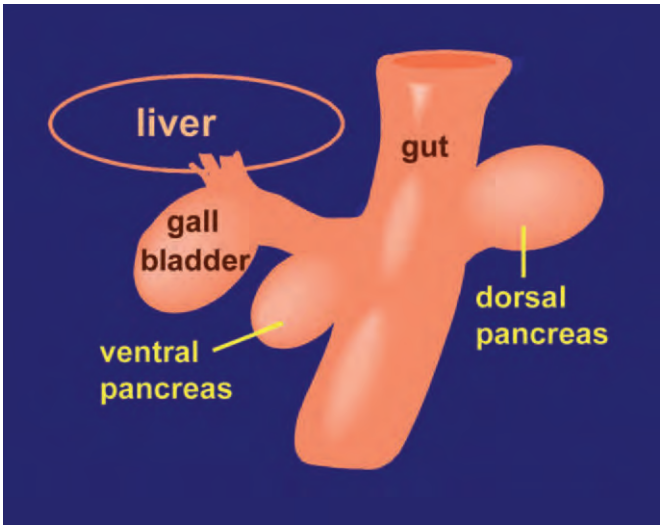

Figure 86–2. Early development of the pancreatic primordia. The dorsal and ventral primordia grow and begin the differentiation of different cell types. The liver, gallbladder, and bile duct also develop from the ventral primordium. (From Bockman DE, Freeny PC: Anatomy and anomalies of the biliary tree. Laparosc Surg 1:92-104, 1992.)

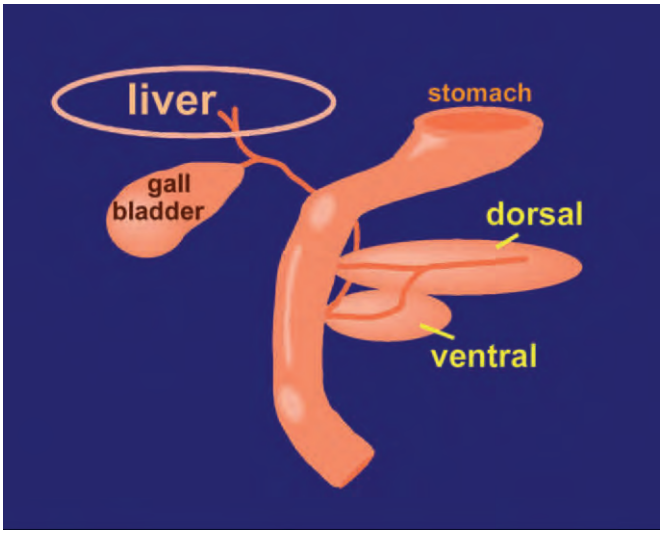

Figure 86–4. Diagram of later development of the pancreatic primordia. The ventral pancreatic primordium swings around to the same side as the dorsal. The primordia fuse, as do their ducts. The duct from the liver and gallbladder (primitive bile duct) maintains a close association with the duct of the ventral pancreatic primordium. (From Bockman DE, Freeny PC: Anatomy and anomalies of the biliary tree. Laparosc Surg 1:92-104, 1992.)

primordium. The epithelium expands as primordial tubules that branch as they grow into the surrounding mesenchyme. Mesenchyme is cellular at first. Adult connective tissue is derived from mesenchyme. Cells become more dispersed as differentiation toward adult extracellular matrix proceeds. Extracellular matrix plays a distinct role in the changes accompanying chronic pancreatitis and pancreatic cancer.[2]

Although some differentiation in genetic expression begins, the epithelial cells remain morphologically similar for some time. The branched primordial tubules, which appear as primitive ducts, may reunite within the primordium to form circular continuities (Fig. 86–3).

Further development of the gastrointestinal tract brings the embryonic ventral pancreas to the same side of the gut as the dorsal pancreas (Fig. 86–4). Fusion of

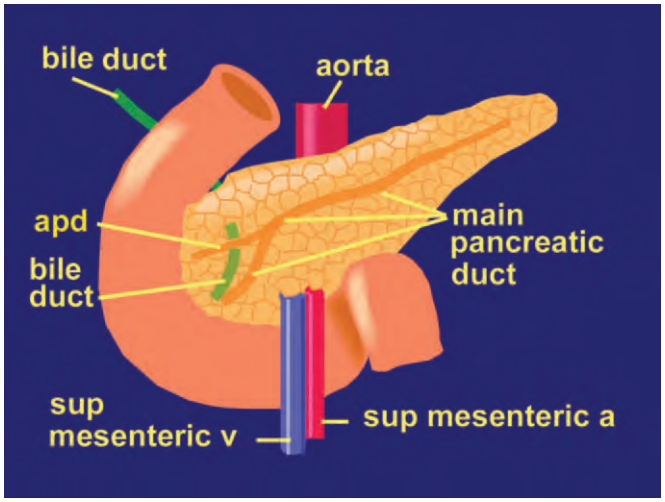

Figure 86–5. Basic associations of the mature pancreas. The head is tucked into the curvature of the duodenum. The previously separate dorsal and ventral primordia have fused completely. The main pancreatic duct develops from the duct of the ventral pancreas plus the distal part of the duct from the dorsal pancreas. The accessory pancreatic duct (apd) consists of the rest of the duct from the dorsal pancreas. The bile duct empties in common with the main pancreatic duct at the major papilla in the duodenum. If the accessory duct is patent, it empties into the duodenum at the minor papilla. The uncinate process laps around the superior mesenteric artery (sup mesenteric a) and vein (sup mesenteric v).

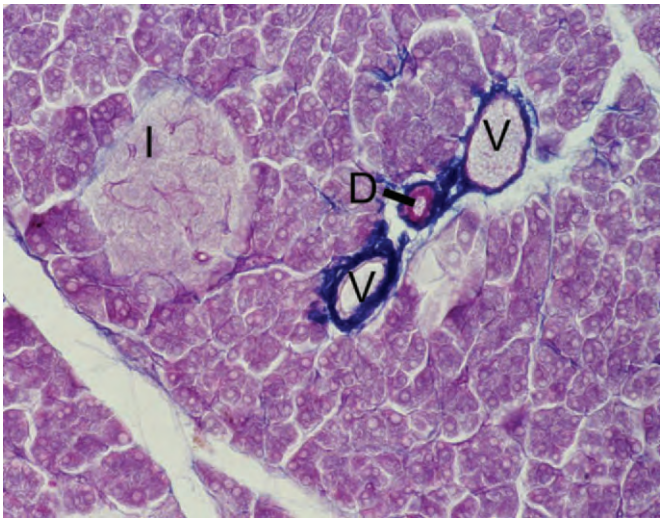

Figure 86–6. Histologic section through normal adult pancreas. Most of the figure is occupied by acinar tissue. One islet of Langerhans (I) is shown. Connective tissue is stained dark blue. It is present in moderate amounts around blood vessels (V) and a small duct (D). It is not prominent between acini and in the islet.

the two precursors takes place. Just as primitive ducts reunite within each primordium, the enlarging ducts that will drain the exocrine products of the pancreas into the duodenum anastomose with each other. The epithelial cells lining the main ductal pathways differentiate into mature duct cells. The duct of the ventral pancreas and the part of the duct of the dorsal pancreas that continues into the tail become the main pancreatic duct (Fig. 86–5). The bile duct retains its original association with the ventral primordium, entering into the duodenum with the main pancreatic duct at the major duodenal papilla. The part of the duct of the dorsal pancreas between the anastomosis and the gut becomes the definitive accessory pancreatic duct.

The pancreas initially grows within a free mesentery, but subsequent changes convert it into a retroperitoneal organ. Rotation of the gut moves the duodenum from the midline to the right side, its middle segment pressed against the dorsal abdominal wall. The pancreas, carried along in the duodenal mesentery, similarly acquires a retroperitoneal position as the mesenteric layers fuse.

Its location at the dorsal abdominal wall just posterior to the diaphragm places the pancreas into close association with a myriad of major vessels and nerves. The aorta gives off the celiac trunk on leaving the thoracic cavity and before passing along the dorsal surface of the pancreas. The superior mesenteric artery arises dorsal to the pancreas to pass ventrally over the duodenum. The superior mesenteric vein, paralleling the artery, passes to the dorsal surface of the pancreas where it is joined by the splenic vein to form the hepatic portal vein. The thinner part of the pancreas over the superior mesenteric–hepatic portal vein is its neck, separating the head from the body.

The endocrine and exocrine components of the pancreas derive from the same population of cells. Differentiation of the cells comprising the primitive ducts leads along three main pathways. At intervals cells bud off the primitive ducts, proliferate into spheroidal groups, lose their contact with the lumens, and become the islets of Langerhans. At the ends and along the sides of the primitive ducts, differentiating cells produce the spheroidal and elongate collections that constitute the acini. The remaining cells stay approximately in their original relationship to become the mature ducts.

In the mature pancreas, acinar tissue is most prominent (Fig. 86–6). Islets of Langerhans are interspersed among the acinar tissue, as are smaller (intralobular) ducts.

EARLY CELLULAR CHANGES

Early in embryonic development proliferation and differentiation of primitive duct cells produce the precursors of islets of Langerhans. The islet cells produced include those capable of expressing insulin, glucagon, somatostatin, or pancreatic polypeptide. Cells expressing each of these products are present by 14 weeks' gestational age.[3] During the early stages of islet formation, some of the cells express markers for duct cells at the same time they express insulin; that is, they represent an intermediate stage between duct cells and mature islet cells. The duct markers disappear with increased age.

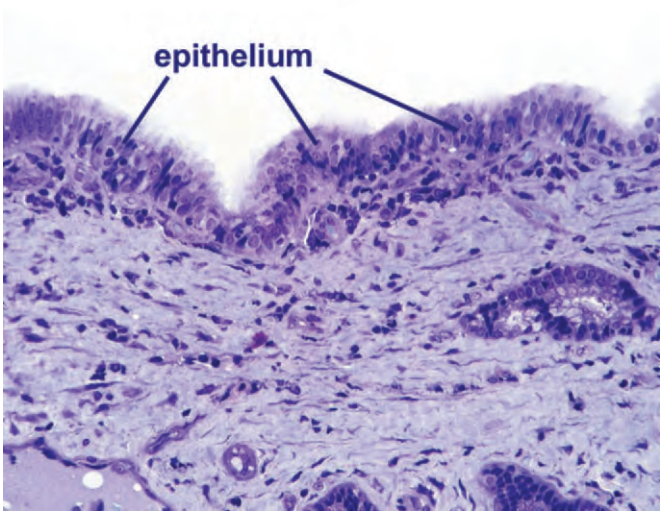

Figure 86–7. Light micrograph through a pancreatic duct. A continuous, single layer of epithelium separates the lumen (top) from the underlying connective tissue, which provides strength and substance for the wall. (From Bockman DE, Muller M, Buchler M, et al: Pathological changes in pancreatic ducts from patients with chronic pancreatitis. Int J Pancreatol 21:119-126, 1997.)

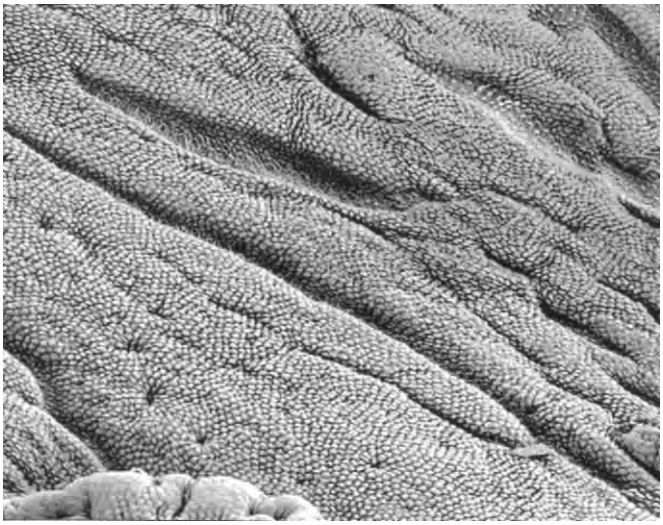

Figure 86–8. Scanning electron micrograph showing the luminal surface of a pancreatic duct. (From Bockman DE, Muller M, Buchler M, et al: Pathological changes in pancreatic ducts from patients with chronic pancreatitis. Int J Pancreatol 21:119-126, 1997.)

The rate of cellular proliferation of islet cells decreases with time.[3] Early islet cells proliferate more slowly than their primitive duct cell precursors, and proliferation becomes progressively slower with increasing gestational age. Islet cells maintain the ability to divide in the adult pancreas despite their low proliferative index.[4,5]

Distinct islets consisting of clumps of multiple cells are observed in the mesenchyme surrounding primitive ducts by 16 weeks' gestation.[3] A pattern is established that includes not only spheroidal accumulations of many islet cells (see Fig. 86–6) but also smaller numbers or single cells scattered within the pancreatic parenchyma. Single islet cells may be retained within ducts.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Ductal Epithelial Cells

Mature ducts form a barrier between the secretion products they carry in their lumens and the surrounding extracellular matrix. The epithelium constitutes a continuous layer lining the ducts (Fig. 86–7). Ductal epithelial cells lie side-by-side with the apposing membranes at the luminal surface joined by tight junctions. Therefore interchange of fluid and ions between duct lumen and extracellular space must be a transcellular event regulated by the cells traversed. Larger ducts present a smooth, undulating surface toward the lumen (Fig. 86–8). Tightly joined ductal cells display microvilli projecting into the lumen between tight junctions (Fig. 86–9). In the absence of pancreatic disease, the ducts are surrounded by a connective tissue matrix with a small number of cells (see Fig. 86–7). With disease, however, such as chronic pancreatitis, the epithelial barrier may be missing in places,[6] with accumulation of inflammatory cells and proliferation of blood vessels exposed directly to the

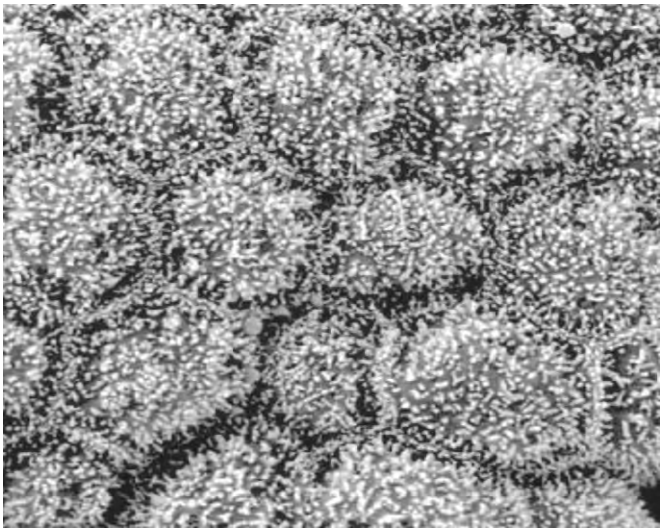

Figure 86–9. Scanning electron micrograph showing the luminal surface of a pancreatic duct at higher resolution than Figure 86–8. The epithelial cells are packed together in an approximately hexagonal array. The edges of the epithelial cells, joined by tight junctions, project slightly. The luminal surface of each cell displays short microvilli. (From Bockman DE, Muller M, Buchler M, et al: Pathological changes in pancreatic ducts from patients with chronic pancreatitis. Int J Pancreatol 21:119-126, 1997.)

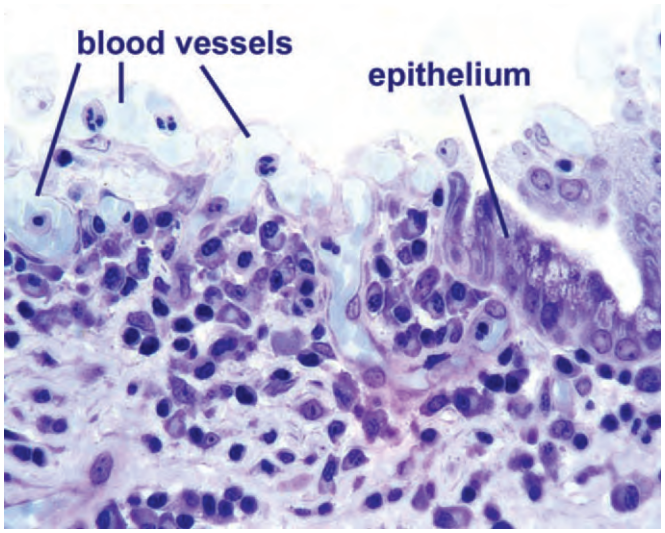

Figure 86–10. Histologic section of a pancreatic duct from a patient with chronic pancreatitis. The epithelium is not continuous; it has been breached. A large number of blood vessels are exposed directly to the lumen, and inflammatory cells are numerous. (From Bockman DE, Muller M, Buchler M, et al: Pathological changes in pancreatic ducts from patients with chronic pancreatitis. Int J Pancreatol 21:119-126, 1997.)

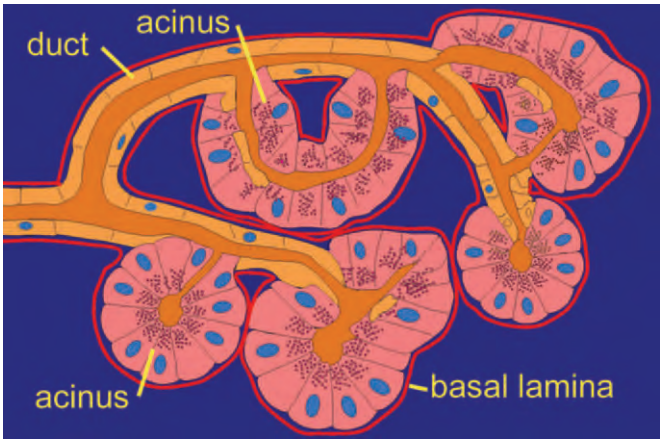

Figure 86–11. Diagram to show some of the relationships of acini to ducts. Acini may be simple spheroidal arrangements of acinar cells distributed along or at the termination of ducts. Acini also may be complex. Some may join a lumen at two ends, producing circular continuity. A continuous basal lamina is found at the base of the acinar cells. The basal lamina and tight junctions between acinar cells at the lumen provide a barrier between the lumen and the surrounding extracellular matrix. Digestive enzymes, stored as zymogen granules in the apex of acinar cells, are secreted into the lumen on stimulation. Centroacinar cells are duct cells within acini. (From Bockman DE: Histology and fine structure. In Beger HG, Warshaw AL, Büchler MW, et al [eds]: The Pancreas, Vol 1. Oxford, Blackwell, 1998, p 20.)

lumen (Fig. 86–10). In this condition interchange of substances and cells between lumen and the extracellular space of the pancreas can occur without the regulation normally provided by the ductal epithelium.

Acinar Cells

Acinar tissue constitutes the greatest proportion of the mature normal pancreas. Like islet cells, early acinar cells are derived from primitive ducts. Continued proliferation and differentiation produce the cells specialized to synthesize, store, and secrete digestive enzymes. Acinar cells are present by the 4th month of gestation. However, the relative proportions of enzymes change with time. At birth, trypsinogen levels are less than normal adult levels, lipase is only a fraction of adult levels, and amylase is almost absent.[7] Enzymes are synthesized in an abundant rough endoplasmic reticulum prominent in the base of acinar cells and packaged in the Golgi apparatus for storage. Many of the enzymes are stored in granules as precursor products (zymogens) mainly in the apex of acinar cells. Stimulation of the acinar cell releases zymogen granules at the cell membrane bordering on the acinar lumen. Activation of the enzymes occurs on entry into the duodenal lumen where enterokinase acts on the pancreatic juice conducted there through the pancreatic ductal system. Trypsin is activated, in turn activating other zymogens.

Pancreatic ducts branch and rebranch, producing progressively more and smaller ducts. The smallest ducts are intimately associated with acini. Some duct cells form tight junctions with adjacent acinar cells. The result is a continuous lumen, surrounded by a continuous epithelium, from the ductal system through the acinar system (Fig. 86–11). A duct may terminate on an acinus that is formed by a spheroidal accumulation of acinar cells. Alternately, a duct may contact one acinus, then continue on the other side to contact a second acinus.[8] Acini can be elongate, bifurcated, or multilobed. An acinus may contact a duct at two places, forming a looped lumen (see Fig. 86–11). Small ductal cells that are located within an acinus are referred to as *centroacinar cells.* Acini are grouped into microscopic lobules. Collections of these microscopic lobules are grouped together and surrounded by connective tissue septa to produce the lobulated pattern visible on the pancreatic surface with the naked eye. Once established, and in the absence of disease, the relative proportions of components are maintained in a steady state.

Dysfunctional Cellular Changes

Imposition of abnormal conditions on the pancreas leads to transdifferentiation, in which fully differentiated cells revert to another cell type. Relative proportions of components change when abnormal situations alter factors modulating cellular behavior. Some of the change can occur by necrosis and apoptosis. If, for example, acinar cells die while other cell types survive, their proportion decreases.

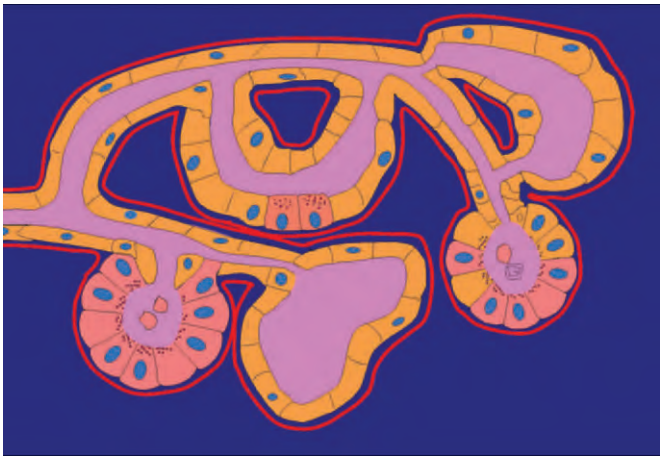

Figure 86–12. Diagram to illustrate the formation of a tubular complex by transdifferentiation of acinar cells to duct cells. Zymogen granules are sparse. Cells are lower and lumens are enlarged from the normal configuration. Cell loss occurs. The result is the appearance of collections of ducts. Compare with Figure 86–11. (From Bockman DE: Histology and fine structure. In Beger HG, Warshaw AL, Büchler MW, et al [eds]: The Pancreas, Vol 1. Oxford, Blackwell, 1998, p 20.)

A more complex change that occurs is the transition of cells backward along the path differentiation has taken. Acinar and islet cells transdifferentiate to ductal cells.[9,10] The result is clusters of small ducts, called *tubular complexes* (Fig. 86–12). Tubular complexes may be produced by obstruction of the ductal system or by genetic abnormalities. They are common in chronic pancreatitis and pancreatic cancer.

Cell markers and morphology change as acinar cells revert to a ductal phenotype,[11-13] signaling the expression of different sets of genes. Furthermore, the cells that have secondarily acquired the ductal phenotype exist in the population that is susceptible to malignant transformation.[14-16]

Cellular Membrane Function

Cell membranes regulate the transport of substances into and out of pancreatic cells, thereby controlling the physiology of the organ. The population of receptors contained in their membranes determines the response of the cells to relevant ligands. The integrity of cell membranes must be maintained to allow channels to function normally, providing precise levels of appropriate substances within the cells, at rest and during stimulation.

Pancreatic cells react to many hormones and neurotransmitters.[17] Among the variety of receptors contained in their membranes are receptors for cholecystokinin, secretin, and acetylcholine.

Release of secretin from the duodenum results in the secretion of bicarbonate-rich fluid into the ductal system. Secretin interacts with its receptor on the surface of ductal cells. Bicarbonate, generated within the cell through the action of carbonic anhydrase, is expelled into the duct lumen through the apical membrane via an exchange with chloride.[17] The channel that supplies the lumen with chloride ions is the cystic fibrosis transmembrane conductance regulator that is defective in cystic fibrosis.

Release of cholecystokinin results in secretion of digestive enzymes from acinar cells. Stimulation of secretion is accompanied by increased concentrations of intracellular calcium ions within acinar cells. The membranes of zymogen granules fuse with the apical membrane, releasing the contents of the granules into the acinar lumen. It is likely that the main interaction on the basolateral membrane of human acinar cells is not between cholecystokinin and its receptor but between acetylcholine and its receptor. Human acinar cells do not react to cholecystokinin the same as in some species.[18] Rather, it is likely that receptors for cholecystokinin on afferent fibers of the vagus nerve are activated, initiating stimulation of pancreatic secretion by vagal cholinergic pathways.[19]

Ligands and receptors normally interact within certain limits of concentration. In unusual situations the limits are exceeded. Supramaximal stimulation of acinar cells with the cholecystokinin analogue caerulein, a procedure that produces experimental acute pancreatitis, makes their cell membranes permeable to large molecules, suggesting a mechanism for the initiation of acute pancreatitis. Perhaps overstimulation via the vagus nerve damages acinar membranes, allowing early events characteristic of pancreatitis.[20]

Blood Supply

The abundant blood supply of the pancreas comes from branches of the aorta that also serve adjacent abdominal organs (Fig. 86–13). Arteries originating in the aorta branch to serve liver, stomach, spleen, and intestine in common with the pancreas. The celiac and superior mesenteric arteries constitute the primary arteries from which others are derived. The splenic and common hepatic arteries branch from the celiac. Dorsal and greater pancreatic arteries, in addition to smaller ones, branch from the splenic artery. The gastroduodenal artery branches from the common hepatic to form anterior and posterior superior branches that form loops by anastomosing with anterior and posterior pancreaticoduodenal branches of the inferior pancreaticoduodenal artery, a branch of the superior mesenteric artery (see Fig. 86–13). Arteries running in the region where the head of the pancreas apposes the duodenum supply both organs.

Abundant anastomoses of arteries provide alternate routes of circulation. The microcirculation within the pancreas is supplied by arteries that continue to branch. The arteries that penetrate the surface of the pancreas do not parallel the main ductal system. They derive from a peripheral location distinct from the ducts that originate in the duodenum and branch from central locations within the pancreas.[21] Part of the microcirculation supplies the ductal system. Vessels are numerous in the connective tissue surrounding ducts. A capillary plexus supplies the acinar tissue and drains into the venous system.

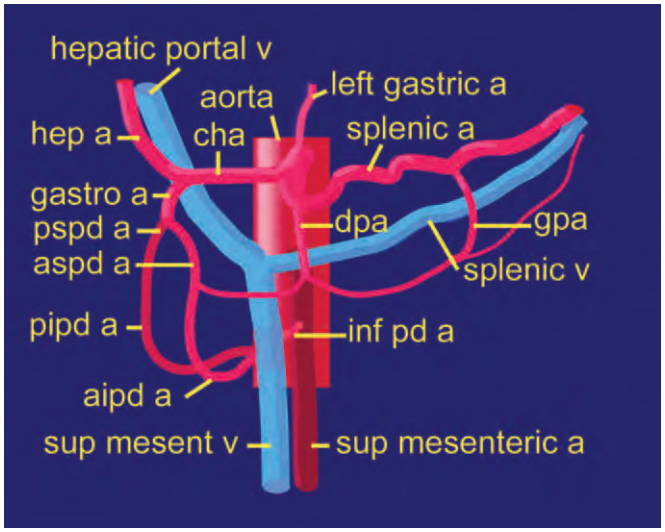

Figure 86–13. Diagram showing some of the major blood vessels associated with and supplying the pancreas. The dorsal pancreatic artery (dpa) and greater pancreatic artery (gpa) and smaller branches supply the pancreas from the splenic artery, which arises from the celiac trunk. The common hepatic artery (cha) also derives from the celiac trunk, giving rise to the gastroduodenal artery (gastro a). The anterior (aspd a) and posterior (pspd a) branches of the superior pancreaticoduodenal artery, from the gastroduodenal artery, anastomose with the anterior (aipd a) and posterior (pipd a) branches of the inferior pancreaticoduodenal a (inf pd a). These arcs and their branches supply the head region of the pancreas as well as the duodenum. The inferior pancreaticoduodenal artery branches from the superior mesenteric artery, a major branch of the aorta. The superior mesenteric vein (sup mesent v) unites with the splenic vein dorsal to the pancreas to form the hepatic portal vein.

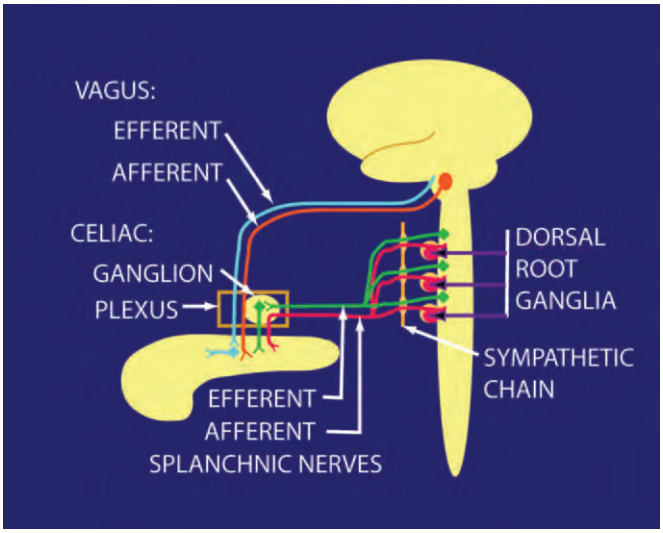

Figure 86–14. Stylized representation of the major nerves serving the pancreas. The vagus nerve carries parasympathetic (efferent) fibers and sensory (afferent) fibers to and from the brain directly. The fibers pass through the celiac plexus without synapse. Parasympathetic fibers synapse on nerve cell bodies within the pancreas. Splanchnic nerves carry sympathetic (efferent) fibers and sensory (afferent) fibers whose cell bodies are in dorsal root ganglia. Sympathetic fibers synapse on nerve cells bodies of secondary neurons in celiac ganglia, part of the celiac plexus. The sensory fibers can serve as the afferent arm of reflexes and under pathologic conditions as a route for pain impulses. The efferent fibers stimulate secretion and regulate blood flow.

The perfusion of the islets of Langerhans is much greater than that of acinar tissue.[22-23] One or more arterioles enter the islet to branch into a prominent capillary plexus (see Fig. 86–6). The fenestrated capillaries of the islets empty directly into the acinar capillary plexus.

Veins of the pancreas drain eventually into the hepatic portal system (see Fig. 86–6), so may become involved in the spread of pancreatic cancer to the liver. Cancer may invade the hepatic portal vein along its path dorsal to the pancreas.

Lymphatic System

The lymphatic system of the pancreas complements the drainage system provided by veins and serves as a route for cellular migration. Lymphatic vessels lie mostly in the connective tissue septa of the pancreas. They are not particularly numerous, they have thin walls, and they tend to collapse when not in situ, so they are difficult to observe. A few intralobular lymphatic vessels drain into the interlobular plexus. These, in turn, coalesce into larger vessels which tend to parallel the blood vessels serving the pancreas.[24] Lymphatic vessels emerge on the surface of the pancreas to enter lymph nodes. Efferent vessels from multiple nodes empty eventually into the thoracic duct.

In the normal situation the lymphatics carry mostly excess interstitial fluid so could be considered to serve as an overflow.[24] In pathologic situations, other things gain access and are conducted. Lymph-borne metastases of pancreatic cancer are found in primary and secondary lymph nodes interposed between the pancreas and the thoracic duct. Lymph nodes surround the pancreas and lie before and along the sides of the aorta and its branches. Many of the nodes are associated with blood vessels and may be described according to the vessel. Celiac, splenic, hepatic, gastroduodenal, pancreaticoduodenal, and superior mesenteric groups of nodes are described. Suprapancreatic and infrapancreatic groups lie immediately outside the pancreas.[24] Numeric designation and grouping are also used to describe nodes of importance to metastasis.[25]

Nervous System

Nerves control normal pancreatic function and serve as pain pathways and routes of cancer spread in the presence of disease. The principal nerve groups serving the pancreas are parts of the sympathetic and parasympathetic divisions along with their accompanying sensory fibers (Fig. 86–14). Sympathetic fibers carried primarily in the

splanchnic nerves originate in the intermediolateral cell column of the spinal cord. Accompanying sensory fibers have their cell bodies in the dorsal root ganglia. Parasympathetic fibers are carried with accompanying sensory fibers in the vagus nerve, which is attached to the brain. Sympathetic innervation affects pancreatic vasculature. Parasympathetic innervation modulates secretion. However, normal control of pancreatic function is complex and relies on simultaneous regulated activity of all mechanisms, so that a defect in one component can affect another. Physiologic control of and response by the pancreas is mediated in part by peptidergic innervation.[26,27] Among these neurotransmitters are substance P, neuropeptide Y, calcitonin gene-related peptide, and vasoactive intestinal polypeptide.

Splanchnic and vagus nerves pass through a plexus of nerve fibers and ganglia distributed around the base of the celiac artery. The sympathetic fibers synapse on secondary neurons in the celiac ganglia in addition to contributing to the celiac plexus. The parasympathetic fibers and sensory fibers pass through the celiac plexus without synapse. Parasympathetic fibers synapse on cell bodies of secondary neurons that form ganglia within the pancreas.

The pancreas is connected to the enteric neural system in addition to the brain and spinal cord. The enteric nervous system is an organized and interconnected network of nerve cell bodies and fibers found within and regulating the alimentary tract proper. Nerve cells in the lower stomach and duodenum extend fibers into the pancreas. A direct connection is thereby established between the enteric nervous system and that of the pancreas.[28]

Nerve fibers combine in the celiac plexus and are distributed to the substance of the pancreas as networks surrounding the arteries of supply.[29] The nerves that are distributed thus are mixed; that is, a nerve may contain sympathetic, parasympathetic, and sensory fibers. The nerves are mainly unmyelinated; that is, unlike the larger nerves supplying muscles in which nerve fibers are surrounded by layers of myelin, the nerve fibers in the pancreas are surrounded immediately by Schwann cells and contained in a protected environment[30,31] that is separated from the surrounding milieu by a perineurium (Fig. 86–15).

On direct intense stimulation of nerves, or because of damage to the perineurium and nerve fibers by invasion of pancreatic cancer or chronic inflammation accompanying chronic pancreatitis, pain may be induced and sustained. A logical approach to the treatment of unremitting pain is to interrupt the pathway conducting it. Common approaches have been to block the celiac plexus or to interrupt the splanchnic nerves since they are the principal pathways for pain conduction from the pancreas.[32]

The severity and breadth of pain generation may lead to incorporation, at least potentially, of other nerves that are less central to pain conduction from the pancreas.[33] It is possible that sensory nerves in the vagus may contribute to pain generation under appropriate circumstances. The pancreas lies on the posterior abdominal wall, and pancreatic cancer may extend from the pancreas proper to involve spinal nerves. Branches of the phrenic nerve could become involved in pain transmission.

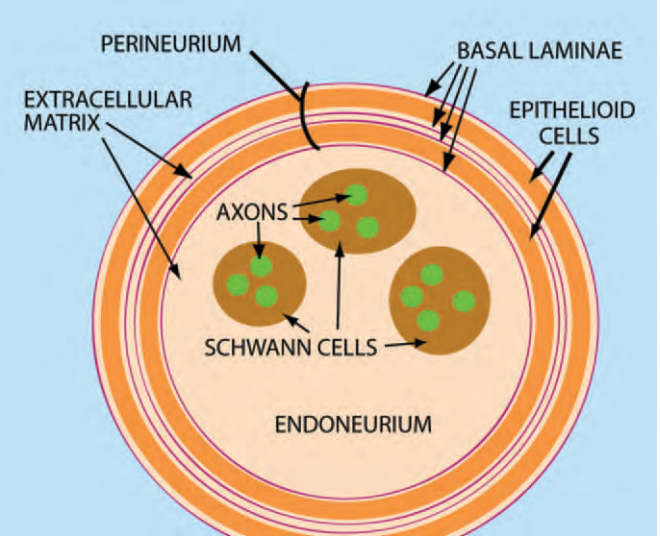

Figure 86–15. Stylized diagram of the components of a pancreatic nerve. Nerves in the pancreas are mainly unmyelinated. Afferent and efferent (sympathetic and parasympathetic) fibers may be included in the same nerve. Before the nerve ends are reached, the nerve bundles are surrounded by a multilayered perineurium that separates the inside (endoneurium) from the surrounding tissue. A specialized microenvironment is thereby maintained in the healthy nerve. The perineurium is composed of layers (here two) of epithelioid cells, basal laminae outside and inside each layer, and extracellular matrix between the layers. Individual nerve fibers are further supported and protected by surrounding Schwann cells. The interruption of the integrity of nerves by invasive cancer and chronic inflammatory cells is likely a cause of chronic pain.

After the nerve fibers carrying the impulses enter the spinal cord, they are carried to the brain where they are interpreted as pain. These are thought to travel primarily in the spinothalamic tract. There is some evidence, however, that fibers in the dorsal columns of the spinal cord may also carry chronic pain and that interruption of these fibers can provide relief.[34-36]

REGULATION OF THE PANCREAS

Development and physiology of the pancreas are tightly regulated. The normal situation is for a fully developed pancreas to respond to meals by aiding digestion and helping utilize or store glucose. To achieve this state, a long series of events, beginning in the embryo, depends on the serial expression and suppression of different genes. At the end of the differentiative process, normal function is controlled by a myriad of agents signaling among the participating components. Maintenance of normal function depends on the integrity of barriers

(individual cell membranes, epithelial layers, basal laminae) that make possible precise control.

Events that reach beyond these normal parameters lead to pancreatic disease. For the most part, the trigger for the diseases is not known. However, it is possible to recognize the deviations from normal: degeneration of acinar and islet cells and their transdifferentiation to ductal cells, alteration and expansion of the extracellular matrix, origin and extension of cancer, invasion of inflammatory cells, altered circulation, and damage to nerves. The possibility for improved treatment of pancreatic disease lies in the ability to determine what causes these deviations from normal.

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Chapter

87

Acute Pancreatitis

Scott F. Gallagher ▪ Colleen E. Jaffray ▪ Michel M. Murr

It is fascinating to conjecture how an inflammatory process in a retroperitoneal gland can produce abnormalities in so many organs.

Reginald Fitz 1889[1]

The first plausible explanations of the pathogenesis of acute pancreatitis were hypothesized by Halsted, Osler, and Opie, contemporaries at Johns Hopkins Hospital. In 1925, Sir Berkeley Moynihan declared that "acute pancreatitis is the most terrible of all the calamities occurring in conjunction with the abdominal viscera," which still holds true today.[2,3] Acute pancreatitis has widely variable clinical and systemic manifestations spanning the spectrum from a mild, self-limiting episode of epigastric pain to severe, life-threatening, multiorgan failure including sepsis, renal failure, acute respiratory distress syndrome, and death.

Despite decades of research and clinical trials, treatment remains essentially supportive as opposed to therapeutic that will treat or prevent pancreatic inflammation, the root of the problem. Improved outcomes are clearly linked to advancements in supportive care Currently, the only effective therapeutic interventions address the complications of acute pancreatitis, most commonly biliary sepsis, pancreatic necrosis, pseudocysts, infection, and sepsis; the latter account for mortality rates in excess of 50% to 80%.[4-6]

The advent and integration of minimally invasive surgery, including advanced endoscopic, radiologic, and interventional techniques, are changing the management of complicated, acute pancreatitis. Incorporation of these modalities has brought into question the use and timing of operative management for pancreatic necrosis, pseudocysts, and gallstones.

NOMENCLATURE (ATLANTA CLASSIFICATION)

Pancreatologists adapted a uniform nomenclature and classification for acute pancreatitis that became known as the *Atlanta Classification*. This was devised to establish a clinical classification system for interinstitutional comparisons and academic investigations.[4] In addition, this classification eliminates confusing, variable, local terminology and such terms as *phlegmon, infected pseudocyst, hemorrhagic pancreatitis,* and *persistent acute pancreatitis.* The definitions are as follows:

- *Acute pancreatitis* is an acute inflammatory process of the pancreas with variable involvement of other tissues or remote organ systems.
- *Mild acute pancreatitis* is associated with minimal organ dysfunction and an uneventful recovery (Fig. 87–1A).
- *Severe acute pancreatitis* is associated with distant organ failure and/or local complications such as necrosis, abscess, or pseudocyst.
- *Acute fluid collections* occur early in the course of acute pancreatitis, are located in proximity to the pancreas, and always lack a wall of granulation/fibrous tissue (see Fig. 87–1B).
- *Pancreatic necrosis* is a diffuse or focal area(s) of nonviable pancreatic parenchyma, which is typically associated with peripancreatic fat necrosis (see Fig. 87–1C).
- *Pancreatic abscess* is a circumscribed intra-abdominal collection of pus, usually near the pancreas, containing little or no pancreatic necrosis, that arises as a consequence of acute pancreatitis or pancreatic trauma.
- *Acute pseudocyst* is a collection of pancreatic fluid enclosed by a wall of fibrous or granulation tissue, which arises as a consequence of acute pancreatitis, pancreatic trauma, or chronic pancreatitis (see Fig. 87–1D).

PATHOGENESIS AND PATHOPHYSIOLOGY

Acinar Cell Injury

Normal pancreatic anatomy and physiology are discussed in Chapter 86; however, it is important to discuss the

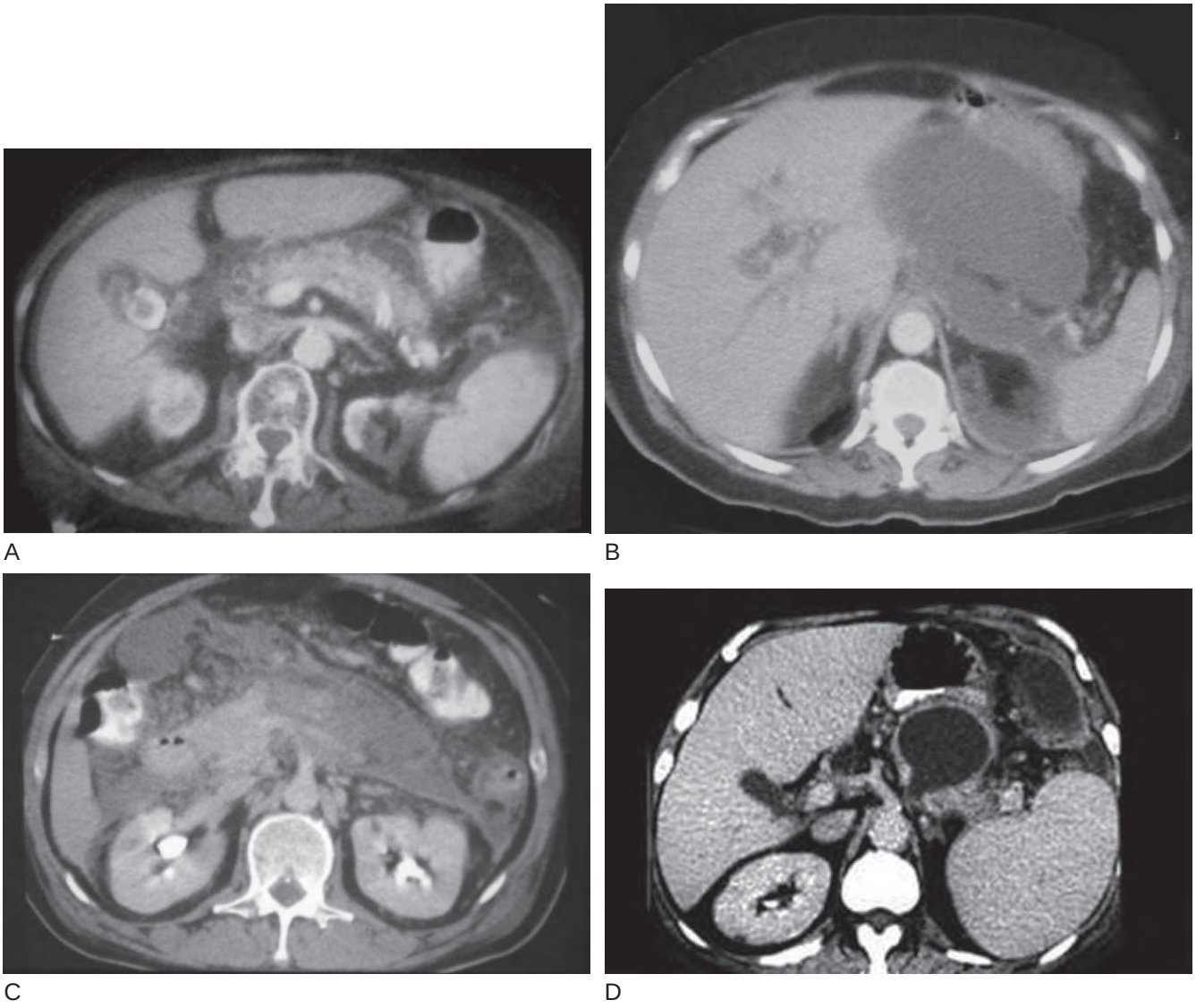


Figure 87–1. **A,** In mild acute pancreatitis, the fully enhanced pancreas shows interstitial edema; mild fat stranding is seen in the peripancreatic tissues. (**A,** From Simms M, Johnson D: Diagnosis of necrotizing pancreatitis using contrast-material–enhanced CT. Probl Gen Surg 13:14, 1996.) **B,** Acute fluid collections are poorly defined collections in the lesser sac and are a distinct clinical and radiologic entity from pancreatic pseudocysts. **C,** Necrotizing pancreatitis is characterized by the absence of enhancement of the parenchyma with intravenous contrast. The head of the pancreas enhances with contrast, whereas the body and tail do not. Note the moderate amount of fat stranding in the peripancreatic soft tissues. **D,** A pancreatic pseudocyst has a well-defined wall of fibrous or granulation tissue and contains clear pancreatic fluid. Note the absence of inflammation in the surrounding tissues.

intracellular events that govern trafficking of proteases and enzymes within acinar cells. During acute pancreatitis, the orderly packaging of digestive enzymes and proteases is disrupted, thereby resulting in colocalization of digestive zymogens and lysosomal hydrolases. The subsequent, premature activation of trypsinogen leads to acinar cell injury.

Under these conditions, intracellular calcium is increased thereby inhibiting autolysis of trypsinogen. Hence, trypsinogen remains activated and propagates acinar cell injury.[7-9] The precipitating event that leads to colocalization and acinar cell injury remains elusive. Observational hypotheses such as the "common channel theory" suggesting that bile reflux into the pancreatic duct induces acinar cell injury have not been supported by rigorous scientific data.

Local Inflammation

Acinar cell injury induces an influx of polymorphonuclear leukocytes into the perivascular pancreatic

parenchyma occurs. Within hours, hyperactivated monocytes are attracted to the site of acinar cell injury and propagate the inflammatory process through production of inflammatory mediators. As this vicious cycle feeds on itself, the ongoing acinar cell injury leads to an amplified inflammatory process, which results in the local and systemic overproduction of interleukins, tumor necrosis factor, nitric oxide, complement, platelet activating factor, free radicals, as well as other macrophage and leukocyte products. Despite their role in the propagation of acute pancreatitis, cytokines (including tumor necrosis factor and interleukin-1) have no direct effect on acinar cells and cannot initiate acute pancreatitis.[10]

Systemic Inflammation and Distant Organ Injury

Although cytokines alone cannot initiate acute pancreatitis, they play a central role in its systemic propagation. Extrapancreatic, macrophage-derived cytokine production in the lungs and liver is associated with histomorphologic organ injury and dysfunction.[11-14] Pancreatic enzymes that gain access to the systemic circulation via the inflamed retroperitoneum induce cytokine production from resident macrophages in distant organs, and a significant body of work suggests that these enzymes are the link between local inflammation and systemic manifestations of acute pancreatitis.[15-17] The mechanisms that initiate and terminate the systemic propagation of acute pancreatitis are poorly understood and warrant further investigation.

ETIOLOGY

Nearly 90% of all episodes of acute pancreatitis are attributable to gallstone disease and alcohol abuse. Geographic variation exists in the United States with urban areas tending to have more alcohol-related acute pancreatitis, whereas gallstone-induced pancreatitis predominates in other areas of the United States as well as in Europe and parts of Asia. Some suggest that alcohol-induced pancreatitis is more common in the United States due to social differences in the perception of alcoholism. Further etiologies of acute pancreatitis and clinical associations are listed in Box 87–1. The most common are briefly discussed, including biliary tract stones, alcohol, postprocedural, trauma, hyperlipidemia, hyperparathyroidism/hypercalcemia, hereditary, pancreas divisum, infection, medications, pregnancy, and idiopathic.

Controversy exists regarding the exact pathophysiology linking an impacted stone in the ampulla to acute pancreatitis; however, increased pressure in the pancreatic duct likely either promotes colocalization of digestive enzymes and lysozymes or causes transductal efflux of pancreatic enzymes directly into pancreatic parenchyma. Although choledocholithiasis can be demonstrated in only 20% of patients with acute pancreatitis, an impacted stone can be demonstrated in only 2% of these patients. Nevertheless, gallstones can be found in the stool of most patients (90%) with gallstone pancreatitis indicating that by the time patients seek medical attention, the offending gallstone may have already passed into the intestinal tract.

The precise pathophysiology is unclear. Several experimental models suggest alcohol increases pancreatic exocrine and protein secretion while increasing ampullary resistance. Alcohol is also associated with ductal hypertension, proteinaceous precipitates, and stones.

The most common cause of postprocedural acute pancreatitis (3% to 4%) is endoscopic retrograde cholangiopancreatography (ERCP). With awareness and experience, its occurrence can be minimized through gentle contrast injection into the pancreatic duct.

Box 87–1 Etiology of Acute Pancreatitis and Clinical Associations

- Biliary tract stone disease
- Ethanol/alcohol abuse
- Trauma
  - Postprocedural
    - Post-ERCP
    - Postoperative
  - Direct blunt trauma
- Hyperparathyroidism/hypercalcemia
- Hyperlipidemia
- Hereditary pancreatitis
- Infections
  - Viral
  - Parasitic
  - Fungal
  - Bacterial
- Mechanical obstruction
  - Tumors
  - Pancreatic divisum
  - Duodenal obstruction
- Medications
  - Antibiotics: sulfonamides, tetracyclines
  - Calcium
  - Cardiovascular: clonidine, quinidine, warfarin
  - Diuretics: furosemide, thiazides, ethacrynic acid, diazoxide
  - Steroids: estrogen, glucocorticoids
  - Other: azathioprine, cimetidine, methyldopa, phenformin
- Pregnancy
- Scorpion *(Tityus trinitatis)* venom
- Idiopathic

ERCP, endoscopic retrograde cholangiopancreatography.

Postoperative acute pancreatitis occurs from retraction or manipulation during procedures on adjacent organs, as well as from extraabdominal procedures (i.e., cardiothoracic and orthopedic operations). Most likely, hypoperfusion occurs in the pancreatic bed during the latter procedures and leads to acinar cell injury.

Although hyperamylasemia is not rare after major blunt abdominal trauma, it is rarely (<5%) associated with the full clinical presentation of acute pancreatitis.[18]

Hereditary hyperlipidemias (including hyperlipoproteinemia types I and V) rarely cause pancreatitis. The cause is unclear, especially since hypertriglyceridemia may be absent between episodes of pancreatitis. It is hypothesized that excess free fatty acids generated by the action of pancreatic lipases within the pancreatic microcirculation initiate acinar cell injury.

Although uncommon, the association of pancreatitis and hypercalcemia often secondary to hyperparathyroidism is documented. Calcium, a known secretagogue for exocrine pancreatic enzymes, may trigger trypsinogen activation and delay its autodigestion within acinar cells.

Hereditary or familial pancreatitis exhibits an autosomal dominant inheritance pattern with incomplete penetrance and is linked to a single point mutation in the trypsinogen gene (7q35) that prevents trypsinogen autolytic inactivation.[19] The sentinel acute pancreatitis event recurs and progresses into chronic pancreatitis, which leads to gland destruction.[7]

Pancreas divisum is a normal variant in 5% to 7% of the population and results from the failure of ventral and dorsal pancreatic ductal fusion during embryonic development. Most patients with pancreas divisum do not develop pancreatitis. For those who do, elimination of gallstone disease is the first step in the management algorithm. Once other etiologies have been excluded, a dorsal pancreatic duct sphincterotomy may relieve symptoms.

In the past, a handful of infections including mumps and *Ascaris lumbricoides* were associated with acute pancreatitis; however, the acquired immunodeficiency syndrome epidemic with its subsequent opportunistic pathogen superinfections and their treatment with toxic medications have expanded the etiologic differential diagnosis of acute pancreatitis. For example, cytomegalovirus as well as antiretroviral and antitubercular medications has been linked to acute pancreatitis.

A growing list of medications is associated with acute pancreatitis (see Box 87–1). Suffice it to say that an exhaustive review of medications should be undertaken once biliary tract disease, alcohol, and other common causes of pancreatitis have been excluded.

Although acute pancreatitis has been linked to pregnancy (0.1%), most include patients with gallstones, alcohol use, or other risk factors.

In some series idiopathic pancreatitis has been reported to be as high as 40%; however, this is truly uncommon, as shown by several recent clinical trials. Specifically, biliary sludge or microlithiasis has been implicated in up to 75% of previously classified idiopathic acute pancreatitis and 83% of unexplained biliary pain.[20,21]

CLINICAL PRESENTATION

The spectrum of clinical presentations of acute pancreatitis is broad. Fortunately, 90% to 95% of patients simply experience a mild, self-limiting bout of acute pancreatitis. Though much less common, 5% to 10% of patients develop a severe, life-threatening episode associated with a prolonged hospitalization, intensive care unit (ICU) stay, and increased morbidity. Patients with severe, acute pancreatitis account for more than 80% of deaths and should be treated aggressively.

The cardinal symptom of acute pancreatitis is the insidious onset of constant epigastric pain, which often radiates to the back; however, other symptoms including anorexia, nausea, emesis, abdominal mass, or fever are often present. Patients with severe, necrotizing acute pancreatitis may develop jaundice, hypotension, shock, and signs of retroperitoneal hemorrhage, specifically an ecchymotic discoloration of the flank (Grey Turner's sign), the umbilicus (Cullen's sign), or the inguinal ligament (Fox's sign).

DIAGNOSIS

Laboratory Tests

Serum amylase and lipase remain the most widely used laboratory tests. The sensitivity of amylase is relatively low since there are multiple causes of hyperamylasemia unrelated to acute pancreatitis (Box 87–2).[22] However, concurrently increased lipase and amylase in the setting of abdominal pain increases the sensitivity and specificity of diagnosing acute pancreatitis to 90% and 95%, respectively.[22,23] Although diagnostic, serum amylase and lipase levels have not been found to correlate with pancreatitis severity. Fractionation of plasma amylase isoenzymes and the calculation of fractional amylase excretion may be helpful in patients with nonpancreatic sources of hyperamylasemia or with renal failure. Nevertheless, the advent of computed tomographic (CT) scan has rendered these latter tests nearly obsolete.

Radiologic Studies

Although the classic sentinel loop in the left upper quadrant and a diffuse ileus are commonly seen on abdominal roentgenograms, neither is pathognomonic. Nonetheless, plain films remain an essential part to exclude other diagnoses in the work-up, including perforated viscus or renal calculi.

Abdominal ultrasound (US) is rapid, inexpensive, and noninvasive. Although operator dependent, it provides information on the gallbladder as well as the biliary ductal system. Although it can detect pancreatic edema, overlying distended bowel limits visualization and renders it suboptimal for staging acute pancreatitis.

Contrast-enhanced dynamic CT with intravenous and oral contrast has an integral role in the diagnosis and management of acute pancreatitis. Not only does CT minimize the impact of operator experience, but it also provides a wealth of anatomic data so often missed or omitted on US. Findings on CT include pancreatic

Box 87–2 Hyperamylasemia Unrelated to Acute Pancreatitis

- Abdominal
  - Acute appendicitis
  - Biliary tract disease and gallstones
  - Intestinal obstruction and ischemia
  - Liver diseases
  - Pancreatic fistula
  - Peritonitis
  - Pregnancy
  - Perforated viscus
- Impaired amylase secretion
  - Renal dysfunction
  - Nephrolithiasis
  - Macroamylasemia
  - Bisalbuminemia
- Metabolic disorders
  - Diabetic ketoacidosis
- Salivary gland disorders/injury
  - Calculi
  - Hypersecretion
  - Irradiation sialadenitis
  - Mumps
  - Parotitis
- Trauma
  - Burns
  - Cerebral trauma
  - Multiple trauma

edema, peripancreatic fluid collections, mesenteric fat stranding, inflammation, biliary tract stones, and bile duct size. Absence of enhancement (>3 cm or >30% of gland) is the hallmark of pancreatic necrosis (see Fig. 87–1C). Additionally, extravisceral gas (Fig. 87–2), pneumoperitoneum, free fluid in the pelvis or gutters, and hemorrhage into the lesser sac are critical findings. Most important, CT scanning provides a tool for staging of pancreatic and peripancreatic inflammation.

Balthazar identified criteria for CT findings in acute pancreatitis: A, normal; B, pancreatic edema; C, peripancreatic fat abnormalities; D, single fluid collection; and E, multiple fluid collections or gas. Later, Balthazar incorporated pancreatic necrosis into a CT severity index (0 to 10). Patients with CT index greater than 7 had a 17% mortality, whereas patients with a CT index less than 3 had no mortality.[24]

An alternative to CT is magnetic resonance imaging using gadolinium and magnetic resonance cholangiopancreatography (MRCP). Their use has been relatively limited and not well-studied. MRCP is an option where ERCP is not technically feasible as a diagnostic modality; however, MRCP precludes the interventional aspects of ERCP.

ERCP is rarely indicated in mild, uncomplicated acute pancreatitis. It is, however, important for diagnostic and therapeutic intervention for severe, acute pancreatitis and its complications. Specifically, ERCP provides an essential tool in our armamentarium to remove impacted stones, decompress the biliary tree, and delineate pancreatic ductal anatomy.

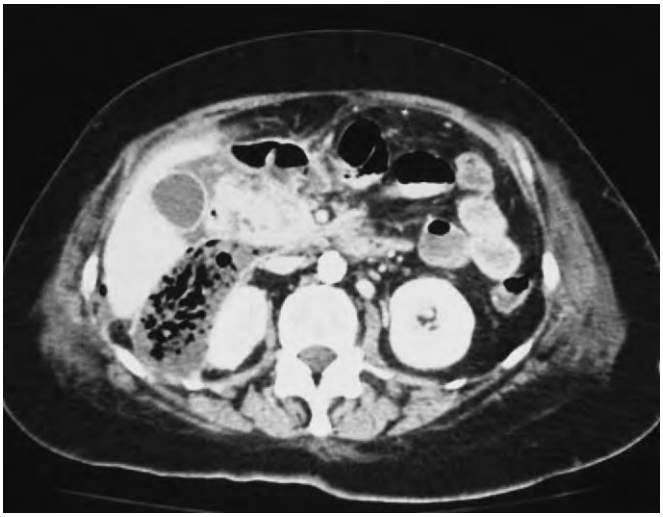


Figure 87–2. Acute pancreatitis complicated by extravisceral air in a fluid collection that was predominantly located in the right pericolic gutter suggestive of perforated viscus or infected necrotizing pancreatitis.

PROGNOSTIC INDICATORS

Because of the variability and seeming unpredictability of acute pancreatitis, clinical scoring systems have been developed to predict the severity of acute pancreatitis and, as important, for patient stratification and enrollment in clinical trials.

Ranson's criteria is the most commonly used scoring system and is based on 11 clinical and laboratory parameters measured within the first 48 hours of admission to the hospital (Table 87–1).[25] Patients with one or two criteria have a predicted mortality of less than 1% compared to patients with three criteria (10%) or four criteria (15%); with more than seven criteria, the predicted mortality approaches 50%. Although specific to acute pancreatitis, complete assessment with this one-time score may not be available until 48 hours after admission.

Modified Glasgow criteria are based on eight clinical and laboratory parameters measured within 48 hours of admission (Table 87–2).[26] Its limitations are similar to Ranson's criteria.

Acute Physiology and Chronic Health Evaluation (APACHE)-II scoring system (Box 87–3)[27] incorporates 12 physiologic and laboratory parameters as well as age and comorbid conditions to estimate severity of any disease process. Specifically, a score greater than 9 signifies severe, acute pancreatitis. The APACHE-II scoring system overcomes the shortcomings of Ranson's criteria such that it can be determined on a daily basis; however, it

Table 87–1 Ranson's Criteria

Ranson's Criteria	Nonbiliary Acute Pancreatitis	Biliary Acute Pancreatitis
Admission		
Age (yr)	>55	>70
WBC count (×1000/mm^3)	>16	>18
Glucose (mg/dl)	>200	>220
AST (IU/L)	>250	>250
LDH (IU/L)	>350	>400
Within 48 Hours of Admission		
Hematocrit decrease (points)	>10	>10
BUN increase (mg/dl)	>5	>2
Base deficit (mEq/L)	>4	>5
Fluid replacement (L)	>6	>4
PaO_2 (mm Hg)	<60	<60
Calcium (mg/dl)	<8	<8

AST, aspartate aminotransaminase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; WBC, white blood cell.

Table 87–2 Modified Glasgow Criteria: Within 48 Hours of Admission

Criteria	Value
Age (yr)	>55
WBC count (×1000/mm^3)	>15
Glucose (mg/dl)	>180
BUN (mg/dl)	>45
LDH (IU/l)	>600
Albumin (g/dl)	<3.3
PaO_2 (mm Hg)	<60
Calcium (mg/dl)	<8

BUN, blood urea nitrogen; LDH, lactate dehydrogenase; WBC, white blood cell.

remains somewhat cumbersome to calculate and is not specific for acute pancreatitis.

Multiorgan Dysfunction Score (MODS) is similar to APACHE-II; this organ-injury based scoring system has been used to predict disease severity. When applied to acute pancreatitis, a score higher than 2 predicts early mortality.[28]

MANAGEMENT OF MILD ACUTE PANCREATITIS

The mainstay of managing mild, acute pancreatitis is supportive (Fig. 87–3). Since most patients with acute pancreatitis (90% to 95%) fall into this self-limiting category, emphasis is more on determining cause and preventing recurrence. US and CT scan are important in diagnosis and radiologic staging of pancreatitis (see Fig. 87–1A); however, there is essentially no role for diagnostic ERCP. In elderly patients with an index of suspicions for malignancy, a contrast-enhanced dynamic CT should be obtained to evaluate the pancreas in conjunction with surrounding biliary tract and retroperitoneal structures.

Box 87–3 **Acute Physiology and Chronic Health Evaluation (APACHE)-II Scoring System* of Disease Severity**

A. Physiologic Variable

- Temperature
- Mean arterial pressure (mm Hg)
- Heart rate
- Respirations
- Arterial pH
- PaO_2 (mm Hg)
- Serum sodium
- Serum potassium
- Serum bicarbonate (mmol/L)
- Serum creatinine (mg/dl)
- Hematocrit (%)
- White blood cell count
- Glasgow Coma Score

B. Age Points

C. Chronic Health Points

*APACHE-II score = A + B + C.

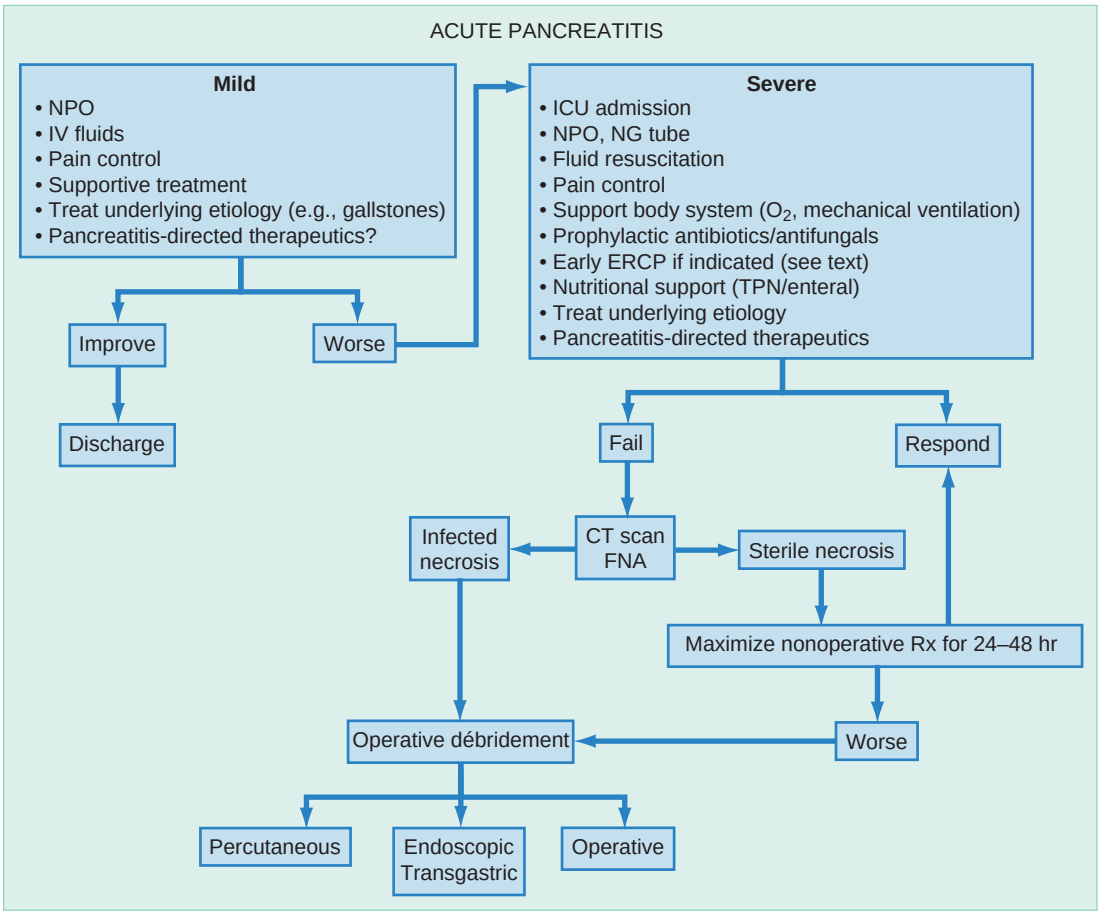


Figure 87–3. Algorithm for treatment of acute (mild to severe) pancreatitis. ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine-needle aspiration; ICU, intensive care unit; IV, intravenous; NG, nasogastric; NPO, nothing by mouth; TPN, total parenteral nutrition.

Supportive Care, Fluid Resuscitation, and Electrolyte Balance

Intravenous fluids and electrolytes should be given until the patient is able to sustain adequate fluid and nutritional intake per os. This usually includes resolution of abdominal pain with normal or normalizing amylase and lipase. The routine use of nasogastric tube decompression has not been shown to alter the course of acute pancreatitis.[29] Patient support and family education are important, especially in the setting of alcoholic pancreatitis and the need for abstinence.

Analgesia

Adequate pain control is important and may require narcotic medications. The theoretical disadvantage of morphine-induced sphincter of Oddi spasm has not been demonstrated to be clinically relevant.

Nutrition

If the patient is unable to meet adequate protein and caloric needs per os within 5 to 10 days of pancreatitis onset, supplemental feedings via a nasoenteric feeding tube is recommended. The need for parenteral nutrition is rare.

Antibiotics

There is no proven role for prophylactic antibiotics during mild, or moderate, acute pancreatitis; however, therapeutic use of antibiotics may be necessary in the event of concomitant biliary obstruction.

Operative Management

Early cholecystectomy during the same hospitalization once symptoms have subsided and cholestatic liver enzymes have returned to normal is recommended for gallstone pancreatitis. If cholestatic enzymes have not returned to normal, consideration must be given to choledocholithiasis and the use of preoperative ERCP or intraoperative cholangiography and stone extraction. Alternatively, retained common bile duct stones diagnosed with intraoperative cholangiography can be extracted by postoperative ERCP.

MANAGEMENT OF SEVERE NECROTIZING PANCREATITIS

The mainstay of management is early diagnosis, aggressive resuscitation, and staging by clinical scoring systems and radiologic imaging (see Fig. 87–3). This aggressive approach is justified to allow proper allocation of resources and prognostication. This rapidly progressing, multiorgan dysfunction occurs in approximately 10% of patients with acute pancreatitis; however, it results in 50% to 80% of mortality from subsequent organ failure and sepsis.

To date, research aimed at manipulation of the inflammatory cascade induced during severe, acute pancreatitis has failed to improve clinical outcomes. Current treatment remains largely supportive with a focus on preventing, minimizing, and correcting complications.

Supportive Care, Fluid Resuscitation, and Electrolyte Balance

Aggressive fluid resuscitation with correction of base deficit and electrolyte imbalance is the primary goal in supporting the early inflammatory and sequestration phase. Invasive cardiac monitoring may be necessary as well as endotracheal intubation as indicated for respiratory insufficiency.

Analgesia

Adequate analgesia should be routinely provided with parenteral narcotics and anti-inflammatory agents.

Nutrition

Nutritional support is extremely important as severe acute pancreatitis is one of the most catabolic conditions. Early nutrition is imperative and can be achieved initially with total parenteral nutrition until enteral access is established.[30] Use of lipids in total parenteral nutrition solutions has not been shown to worsen the course of acute pancreatitis.[31] Resumption of enteral intake or oral feeding should coincide with resolution of gastric ileus that is an early manifestation of acute pancreatitis. The theoretical fear of stimulating an already inflamed pancreas with oral or enteral nutrition is not founded in evidence-based medicine.[32] Intolerance to certain enteral formulations does not constitute worsening of pancreatitis.

Therapeutic ERCP and Management of Biliary Tract Disease

Several clinical trials have shown the benefits of early (<48 hours) ERCP in minimizing biliary tract infectious complications during severe, acute pancreatitis.[33,34] An ERCP is indicated when biliary obstruction is suspected to remove impacted stones; concomitant transpapillary stenting of the common bile duct or pancreatic duct has no impact on the course of pancreatitis. The benefits of therapeutic ERCP in experienced hands outweigh its risks in this setting.

Antibiotics

The use of prophylactic antibiotics in severe, acute pancreatitis has become controversial. Earlier clinical trials that showed benefit in reducing morbidity or mortality were poorly designed or underpowered (Table 87–3).[35-38] The widespread use of imipenem based on its high concentration in pancreatic tissue has not been substantiated in large clinical trials.[39] Nevertheless, a meta-analysis of the use of prophylactic antibiotics demonstrated a significant reduction in sepsis and mortality.[40] Recently, a well-designed trial involving 119 patients showed no benefit from prophylactic use of ciprofloxacin and metronidazole over placebo in severe, acute pancreatitis.[35] These findings prompted a large, multicenter, placebo-controlled, double-blind study of meropenem. Unfortunately, this trial was closed prematurely because of an inability to enroll enough antibiotic-naïve patients, thereby underscoring the difficulty in establishing an evidence-based role for prophylactic antibiotics in severe, acute pancreatitis.

Timing of Cholecystectomy for Gallstone Pancreatitis

Nealon et al. have now established that cholecystectomy should be delayed for patients who survive an episode of moderate to severe acute biliary pancreatitis and demonstrate peripancreatic fluid collections or pseudocysts.[41] Cholecystectomy should be delayed until either the pseudocyst resolves or, if it persists beyond 6 weeks, the pseudocyst can be drained concomitantly and safely at the time of cholecystectomy. Delayed cholecystectomy and concomitant pseudocyst management are associated with fewer septic complications, less morbidity, fewer reoperations, and fewer readmission rates and a shorter length of stay than those undergoing early cholecystectomy.[41]

Other Potential Therapeutic Options

Although a meta-analysis suggested that somatostatin reduced mortality after acute pancreatitis,[42] a more recent study did not demonstrate any benefit of octreotide treatment.[43] Many of the clinical trials designed to suppress pancreatic enzyme secretion including nasogastric decompression, glucagon, polypeptide YY, or cholecystokinin receptor antagonists have failed to definitively impact the outcomes of pancreatitis. Similarly, antiproteases and inhibition of pancreatic enzymes by gabexate mesilate were not effective.

In the past decade, experimental data implicating cytokines in the pathophysiology of acute pancreatitis prompted many clinical trials based on cytokine antagonism.[11] Lexipafant, a potent platelet activating factor inhibitor, showed promise in phase-II trials and in a European phase-III trial, which suggested significant benefit

Table 87–3 Prospective, Randomized Prophylactic Antibiotic Trials in Acute Pancreatitis

Authors, Year	No. of Antibiotics/Control	No. of Institutions	Antibiotics	Outcomes	Strengths/Weaknesses
Isenmann et al., 2004[35]	58/56	19	Ciprofloxacin, metronidazole	No difference in pancreatic infections or mortality	Prospective, randomized, adequately powered
Luiten et al., 1995[36]	52/50	16	Cefotaxime, colistin, amphotericin B, norfloxacin	Decreased local infections and mortality	Utilized selective digestive decontamination
Sainio et al., 1995[37]	30/30	1	Cefuroxime	No difference in pancreatic infections, sepsis; decreased mortality	Underpowered, single center
Pederzoli et al., 1993[38]	33/41	6	Imipenem	Decreased local infections and sepsis; no difference in mortality	Unblinded, underpowered, subgroup analysis

in patients with severe pancreatitis treated within 48 hours of pancreatitis onset.[44] Unfortunately, the double-blind, randomized, controlled, multicenter trial of lexipafant in 1518 patients with pancreatitis failed to confirm a benefit in reducing mortality or organ injury score. Although adequately powered, the study did not reach its end points due to lower than expected mortality as predicted by APACHE-II scores.[45]

Operative Management

The rationale for operative treatment of necrotizing pancreatitis is to remove necrotic peripancreatic and pancreatic tissue that may act as a reservoir for infection and sepsis. As our understanding of the role of necrosectomy in the treatment of necrotizing pancreatitis evolves, several questions arise, as follows:

1. Is necrosectomy required in patients with sterile necrosis?
2. What is the optimal timing of necrosectomy in infected necrosis?
3. What is the role of minimally invasive and image-guided interventions in the treatment of pancreatic necrosis?

Central to the first two questions is the difficulty in delineating sterile versus infected necrosis, because of their unreliable clinical symptoms and radiologic findings. Infected necrosis can be confirmed by CT-guided fine-needle aspiration of necrotic tissue followed by Gram stain and cultures. This is an important consideration, since there is literature to support delaying operative necrosectomy and maximizing supportive care in stable patients with sterile necrosis until demarcation of necrotic material occurs but not longer than 27 days.[46,47] As in many other centers, we have delayed the timing of necrosectomy in stable patients, which has dramatically reduced our utilization of fine-needle aspiration.

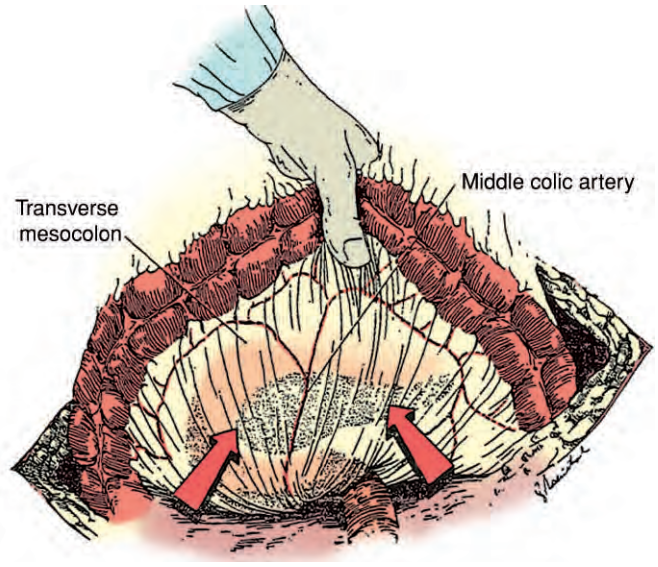
Definitive indications for operative treatment and necrosectomy are the following:

- Failure of nonoperative management with at least 48 hours of maximal ICU support
- Infected necrosis
- Extravisceral air (see Fig. 87–2)
- Hemorrhage uncontrolled by interventional techniques
- Colonic complications

The basic and universal aspect of necrosectomy is débridement of necrotic peripancreatic and pancreatic tissue. Because necrosis is an ongoing process, surgeons have addressed it in a variety of ways, as follows, after the initial necrosectomy:

- Closed packing[47]
- Open drainage[48]
- Closed high-volume lavage of the lesser sac[49]
- Repeated, planned necrosectomy with abdominal wall closure[50]

Peritoneal lavage has no place in the treatment of necrotizing pancreatitis since it addresses neither pancreatic tissue necrosis nor the removal of large particulate matter.



A

B

Figure 87–4. **A,** The lesser sac can be approached through the base of the mesocolon; attention should be paid to avoid injury to the middle colic artery. (**A,** From Del-Castillo F, Warshaw A, Rattner D: Closed packing and drainage following débridement for necrotizing pancreatitis. Probl Gen Surg 13:127, 1996.) **B,** Necrosectomy and closed packing with stuffed Penrose drains.

Necrosectomy and Closed Packing

Briefly, the lesser sac is accessed through the base of the mesocolon (Fig. 87–4A). A thorough, blunt necrosectomy is followed by packing with multiple, stuffed Penrose drains (see Fig. 87–4B).[47] Advocates of this approach cite low mortality and reduced reoperation rates and complications; however, there is a high incidence of intra-abdominal abscess formation (Table 87–4).

Necrosectomy and Open Drainage

An initial blunt necrosectomy is followed by marsupialization of the lesser sac by suturing the omentum to the abdominal wall fascia (Fig. 87–5).[48] Daily unpacking and gentle irrigation are done in the ICU or in the operating room. Advocates of this technique cite the ease by which repeated packing is done; however, the incidence of hemorrhage and fistula formation is high (see Table 87–4).

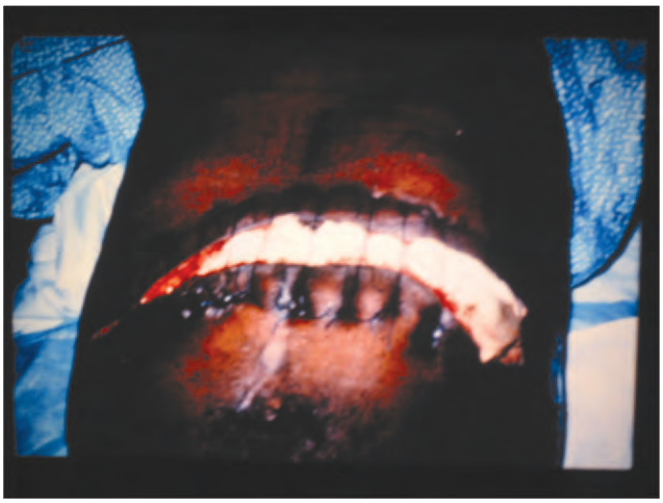


Figure 87–5. Necrosectomy and open drainage by marsupialization of the lesser sac.

Table 87–4 Comparison of Outcomes Following Operative Management of Necrotizing Pancreatitis

Necrosectomy &	Authors, Year	Reoperation, %	Abscess, %	Pancreatic Fistula, %	GI Fistula, %	Hemorrhage, %	Mortality, %
Closed drainage	Fernandez-del Castillo et al., 1998[47]	11	22	50	19	15	7
Open drainage	Bradley, 1995[48]	N/A	—	45	7	7	14
Closed irrigation	Beger et al., 1999[49]	37	20	19	13	15	13
Staged planned	Murr et al., 1987[49]	N/A	13	19	26	18	22

GI, gastrointestinal; N/A, not applicable.

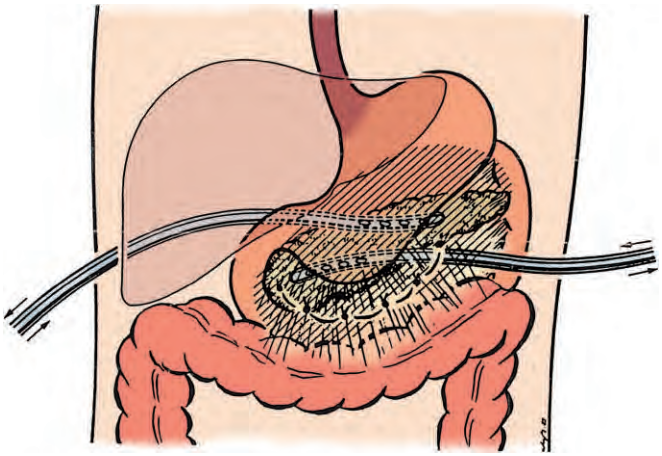


Figure 87–6. Schema of necrosectomy and closed high-volume lavage of the lesser sac. (From Rau B, Beger H: Necrosectomy and closed irrigation for necrotizing pancreatitis. Probl Gen Surg 13:142, 1996.)

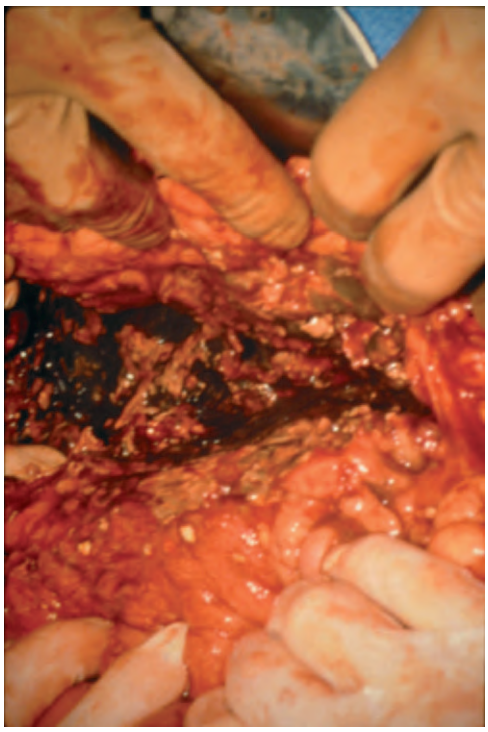
Necrosectomy and Closed Lavage

The purported benefit of this method is that it combines operative débridement (of only necrotic tissue to minimize loss of pancreatic parenchyma) with subsequent high-volume lavage of the lesser sac using a peritoneal dialysate (Fig. 87–6).[49] Similar to closed drainage, the incidence of reoperation and abscess formation is high (see Table 87–4).

Planned, Repeated Necrosectomy and Delayed, Primary Abdominal Wall Closure

The initial celiotomy and necrosectomy is followed by a planned, repeated necrosectomy every 48 hours.[50] Our preferred access is through a midline incision because of the ease of closing it. A cholecystectomy and common bile duct exploration, if indicated, are done after abdominal exploration at the initial necrosectomy; otherwise, access to these structures may be limited by edema and adhesions during later explorations. Similarly, a gastrostomy tube for decompression and jejunostomy tube for enteral feedings are also placed during the initial necrosectomy.

The lesser sac is entered through the gastrocolic ligament (Fig. 87–7A), and all areas of necrosis are unroofed and bluntly débrided (see Fig. 87–7B). Because edema and induration may mask anatomic landmarks, a CT scan is essential to direct operative access to all fluid collections, especially in the paracolic gutters and root of the mesentery. Multiple soft drains are placed in both paracolic gutters and the lesser sac. Subsequently, a nonadherent elastic drape or Adaptic gauze is used to line the lesser sac, which is then packed with moist laparotomy pads. Packing keeps the lesser sac open and readily accessible for repeated necrosectomy. Temporary abdominal closure is obtained with a zipper (Fig. 87–8) to prevent retraction of the fascia, maintain abdominal domain, and facilitate primary closure at the final operation. Planned reoperation is scheduled at approximately 48-hour intervals until the necrotic processes have been controlled or resolved. The worst outcomes occurred in patients with APACHE-II score greater than or equal to 13, extensive pancreatic necrosis, and postoperative intra-abdominal hemorrhage.



A

B

Figure 87–7. **A,** Access to the lesser sac through the gastrocolic omentum. The necrotic peripancreatic tissue has a black-gray discoloration. **B,** Débrided peripancreatic necrotic tissue during a necrosectomy. Large pieces of tissue are not amenable to small-bore catheter drainage.

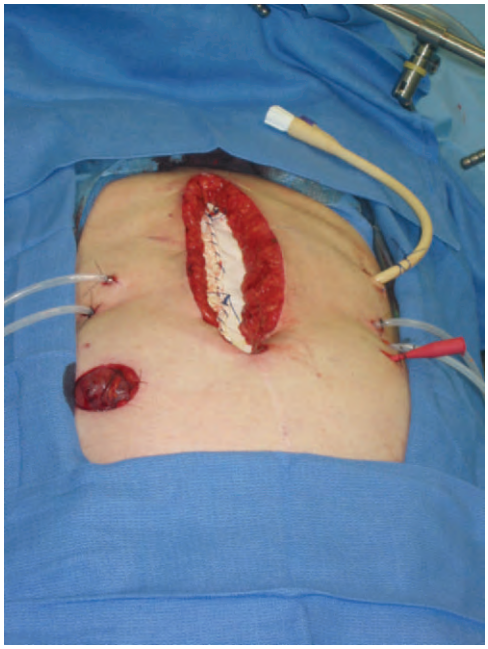


Figure 87–8. The initial necrosectomy with abdominal wall closure using a strip of Gore-Tex mesh included placing a gastrostomy tube (Foley catheter), a jejunostomy feeding tube (red catheter), and four closed-suction drains. A colostomy was also undertaken because of colonic perforation into the lesser sac.

MANAGING SEQUELAE OF ACUTE PANCREATITIS

Acute Peripancreatic Fluid Collections and Necrosis

Endoscopic management of pancreatic fluid collections and necrosis is a new and developing field. Nuances involve patient selection and determining the appropriate waiting period prior to intervention. Additionally, outcomes appear to be linked to endoscopist experience.[51]

Minimally invasive, laparoscopically directed and transgastric necrosectomy or laparoscopic cyst–gastrostomy have been undertaken in select patients.[52,53] In addition, the availability of large-bore catheters and drains has introduced the possibility of percutaneous drainage of localized fluid collections and limited pancreatic necrosis.[54] The experience with laparoscopic and percutaneous necrosectomy is rather limited but holds promise. These novel approaches seem best suited for patients, who have had a stable and uncomplicated course with predominant collections that are easily accessible through the stomach or abdominal wall.

Endocrine and Exocrine Insufficiency

Hereditary pancreatitis, alcoholic pancreatitis, and necrotizing pancreatitis have the highest risk of significant, long-term, pancreatic exocrine and endocrine dysfunction. Such insufficiency occurs in up to 50% of patients following necrosectomy for necrotizing pancreatitis.[6] Exocrine function can actually improve, whereas endocrine function does not typically recover in these patients after discharge.[6]

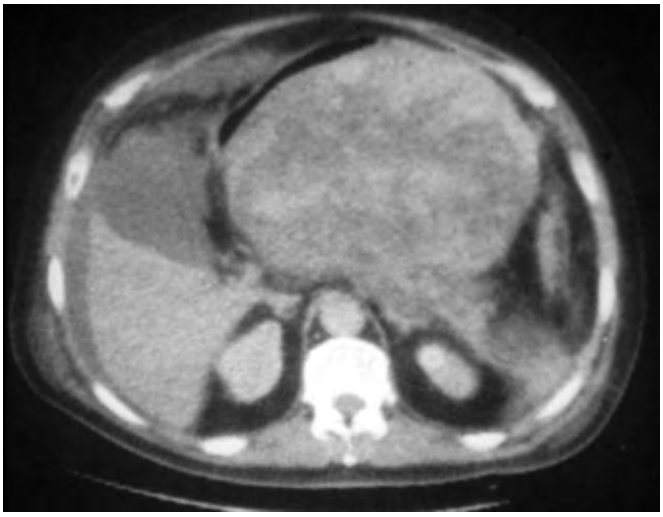


Figure 87–9. Hemorrhage into a pseudocyst can be detected on a CT scan that shows a large collection of fluid that has high density (fresh blood) within the fluid collection. (From Simms M, Johnson D: Diagnosis of necrotizing pancreatitis using contrast material–enhanced CT. Probl Gen Surg 13:17, 1996.)

Pseudocyst

Our recommended nonoperative management parallels others.[55,56] Utilizing a selective approach, two thirds of patients avoided operative pseudocyst drainage, and life-threatening complications requiring emergency operation were uncommon (7%).

Pancreatic ductal anatomy as defined by ERCP provides clear correlation with the failure and success of percutaneous pseudocysts drainage. Percutaneous drainage is best applied to patients with stricture but no pseudocyst-duct communication.[57]

With improvements in CT scanning as well as angiography and interventional radiology, most acute hemorrhage (Fig. 87–9) can be diagnosed, safely controlled, and easily managed with angiographic embolization and/or coiling. Uncommonly, operative control and packing may be required and is associated with poor prognosis.

Fistula

Pancreatic fistula as a consequence of necrosectomy or necrotizing severe, acute pancreatitis is not uncommon. Most fistulas may seal spontaneously with optimization of nutritional status and resolution of sepsis. Persistent fistulas may be associated with main pancreatic ductal disruption best characterized by ERCP. Fistulas in the

pancreatic head or a small ductal disruption may respond to transpapillary stenting. Historically, fistulas from the tail of the pancreas may require distal pancreatectomy.

FUTURE DIRECTIONS

Promising cell signaling–based research for inflammation and pancreatitis has brought forth many potential therapeutics. However, the complex inflammatory response with its inherent redundancy and genetic polymorphisms in humans underscores the complexity of translational research aimed at finding the "magic bullet" in the treatment or prevention of acute pancreatitis and other superinflammatory conditions.

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Chapter

88

Chronic Pancreatitis

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Despite major advances in the unraveling of the pathogenesis and pathophysiology of chronic pancreatitis, and although literally thousands of reports dealing with this disease have been published, chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment. Chronic pancreatitis affects about 8 new patients per 100,000 population per year in the United States, with a prevalence of 26.4 cases per 100,000 population.[1] Autopsy series, however, suggest a higher prevalence of 0.04% to 5%. Chronic pancreatitis is an inflammatory disease characterized by the progressive conversion of pancreatic parenchyma to fibrous tissue. The most frequent causes are excessive alcohol consumption and anatomic variants such as pancreas divisum, cholelithiasis, and individual genetic predisposition. In a substantial number of cases, no currently identifiable predisposing factor can be named. The morphologic and histologic changes that characterize the disease are also extremely variable. Although the term *pancreatitis* implies inflammation, acute inflammatory changes are usually episodic and often absent. It is believed that the process of fibrosis with consecutive loss of pancreatic parenchyma leads to exocrine insufficiency and maldigestion and, in advanced stages of the disease, to diabetes mellitus. In addition to exocrine and endocrine malfunction, mechanical complications occur such as the formation of pancreatic pseudocysts and duodenal and common bile duct obstruction. The peak of presentation occurs in patients between 35 to 55 years of age. Abdominal pain is the leading symptom that characteristically brings the patient to medical attention. Its presentation varies through a wide spectrum, from mild and intermittent, to constant and disabling, leading to hospitalization, inability to work, early retirement, and addiction to analgesics in devastating conditions of chronic pancreatitis. The heterogeneity of this patient population, the subjective nature of pain, and a poor understanding of its pathophysiology all are obstacles to studies directed at effectiveness of pain management. Even abstinence from excessive alcohol consumption, which seems to be the causative agent in most cases, cannot interrupt the process of continuing organ destruction.

NATURAL COURSE AND PATHOGENESIS OF PAIN IN CHRONIC PANCREATITIS

The main rationale for conservative approaches in the past derives from the assumption that most patients with long-standing chronic pancreatitis will become pain-free due to a progressive "burning out" of the organ.[2] However, studies showing that pain alleviation did not occur in more than 50% of the patients[3] as well as the unpredictability of the course of the disease,[3,4] the considerable socioeconomic implications of frequent hospitalization in these mostly young patients,[3] and last, the implementation of more customized surgical techniques has led, at least in part, to a reconsideration of this view.

Pain, by far the most common and intractable indication for medical treatment in chronic pancreatitis, is still only fragmentarily understood and a multifactorial nature is assumed, including inflammation, duct obstruction, high pancreatic tissue pressure, fibrotic encasement of sensory nerves, and a neuropathy characterized by both increased numbers and sizes of intrapancreatic sensory nerves and by inflammatory injury to the nerve sheaths allowing exposure of the neural elements to toxic substances.

DUCTAL AND PARENCHYMATOUS HYPERTENSION

The assumption that pain in chronic pancreatitis is caused by ductal hypertension is based on several observations. Ductal dilation is a common finding that is suggestive for an increased pressure in the pancreatic ductal system, which may be observed[5] in these patients. Patients with the "small duct pancreatitis" also have ductal and parenchymatous hypertension.[6] Hence, elevated intrapancreatic pressure[7] or, in other terms,

a retroperitoneal compartment syndrome yielding reduced pancreatic blood flow and reduction of the intrapancreatic pH level, especially after stimulation of the exocrine pancreatic secretion,[8] has been assumed to cause pain or to interact with its intensity. As a logical consequence of these findings, the concept of surgical and, later, endoscopic, decompression of the main pancreatic duct system arose that leads at least to temporary pain relief.[9-12]

COMPLICATIONS OF CHRONIC PANCREATITIS

In the course of chronic pancreatitis, several complications with less or more life-threatening potential may occur. Extrahepatic cholestasis as well as duodenal obstruction may be a result of an inflammatory tumor, a fibrotic scarring, or both, occurring in the head of the pancreas. Acute inflammatory episodes can lead to chronic pancreatic pseudocysts or internal pancreatic fistula to the abdominal or thoracic cavities. Finally, thrombosis of the splenic vein can occur as a result of the inflammatory reaction of chronic pancreatitis, which results in splenomegaly and localized (so-called left-sided) portal hypertension. The pathophysiology, clinical presentation, and management of these complications of chronic pancreatitis are reviewed in this chapter.

Common Bile Duct Stenosis

Biliary strictures have been recognized as characteristic complications of chronic pancreatitis. In hospitalized patients with pancreatitis, the incidence of biliary stricture accounts for about 5% to 9% and drastically increases to up to 35% in surgical series.[13-16] The main factor for the development of common bile duct stenosis is the close anatomic relationship of the distal common duct to the head of the pancreas, thereby increasing the risk of secondary common bile duct stricture in these patients by cephalic irregularities of any reason. Even though pseudocysts are common in chronic pancreatitis, compression of the common bile duct by pseudocysts is rare. The spectrum of clinical presentation of these patients ranges from being asymptomatic with only biochemical findings such as elevated alkaline phosphatase or bilirubin level, or both, to being septic with cholangitis. Interventional (i.e., surgical) therapy is clearly indicated in patients with common bile duct strictures secondary to chronic pancreatitis. Endoscopic stenting plays a role in patients who are unfit for surgery, but it is not recommended as definitive therapy, particularly with regard to the necessity of repeated endoscopic interventions due to infection, stent displacement, or stent occlusion.[17,18] Of greatest importance is to rule out that biliary obstruction in these patients is a result of a concomitant malignancy in the periampullary region.

Duodenal Obstruction

In patients requiring an operation for chronic pancreatitis, the incidence of duodenal obstruction, which can be either transient or permanent, accounts for 12%.[19] Duodenal obstruction can also occur secondarily to pancreatic pseudocysts.[20] Patients typically present with a history of nausea, vomiting, upper abdominal pain, and weight loss. Endoscopy shows a concave-shaped extraluminal impression without mucosal involvement beginning at the descending portion of the duodenum. Warshaw found that 25% of the patients with common bile duct stenosis caused by chronic pancreatitis also required surgical treatment of duodenal obstruction.[20] In duodenal obstruction, operation is indicated for patients with failure to resolve the obstruction with 1 to 2 weeks of conservative therapy, suggesting the presence of an irreversible duodenal obstruction necessitating further (surgical) treatment. The surgical procedure of choice should definitively address all the individual existing complications of chronic pancreatitis at once. Therefore, combined drainage procedures or resection are used to manage these findings. Gastric outlet obstruction can result from various mechanisms. The most frequent cause in addition to an inflammatory mass due to chronic pancreatitis is a duodenal involvement by pancreatic cancer. If surgery is indicated, the therapeutic aim should be to eliminate the cause of the duodenal stricture, such as an enlarged pancreatic head or an encasement of the duodenum by inflammatory adhesions.

Internal Pancreatic Fistulas

Pancreatic ascites and pancreaticopleural fistulas are known as *internal pancreatic fistulas*. They result from a disruption of the pancreatic duct or leakage from a pseudocyst. Internal pancreatic fistulas are rare but well-recognized conditions associated with a significant morbidity and mortality.[21,22] Misdiagnoses such as in cases of pancreaticopleural or pancreaticobronchial fistula are not uncommon. Three main types of thoracic manifestations include mediastinal pseudocysts, pancreaticopleural fistulas, and pancreaticobronchial fistulas.[23,24] Once an internal pancreatic fistula is suspected, laboratory testing of pleural effusions with special respect to their amylase concentration should be performed. Diagnostic evaluation should in particular address a possibly underlying ductal pathology. Conservative treatment may be indicated in patients with mild to moderate ductal anatomic alterations.[25,26]

Conservative treatment has an efficacy of 30% to 60%, a recurrence rate of 15%, and a mortality rate of 12%.[26,27] Interventional endoscopic therapy would be the next step in patients with persisting fistulas and pleural effusion. Endoscopic treatment is based on the concept that main pancreatic duct disruption arises as a consequence of an increase in intraductal pressure or within a pseudocyst and aims at the reduction of the ductal pressure. In most patients, a pancreatic sphincterotomy via the major papilla is performed to facilitate transpapillary endoscopic placement of a pancreatic duct stent.[28-30] In selected cases, this may be combined with the use of tissue glue for the closure of pancreatic fistulas.[31] Surgical treatment has to focus on the elimination of ductal hypertension that inhibits spontaneous closure of fistulas.

Pancreatic Ascites

Pancreatic ascites is defined as massive accumulation of pancreatic fluid in the peritoneal cavity. The level of amylase in the ascitic fluid is typically above 1000 IU/L and the ascitic fluid to serum amylase ratio is approximately 6.0.[32,33] It has been described in approximately 4% of patients with chronic pancreatitis and in 6% to 14% of those with pancreatic pseudocysts. Sometimes an attack of acute pancreatitis or a traumatic injury to the pancreas can be held responsible; however, two thirds of patients do not give a history of a recent episode of pancreatitis.[34] The establishment of diagnosis is often difficult because pain or symptoms of pancreatic disease may be absent. Especially in patients with alcohol abuse, the diagnosis may be confused with ascites due to cirrhosis and portal hypertension. Diagnostic paracentesis should be performed in every patient with ascites. If pancreatic ascites is suspected, routine tests of ascitic fluid such as cell count, culture, Gram stain, amylase, albumin, and total protein should be obtained. Once the diagnosis has been established, the evaluation of the pancreatic duct morphology is mandatory. There is agreement that endoscopic retrograde cholangiopancreatography should be performed to localize the site of leakage and to perform endoscopic therapy (transpapillary stenting of the pancreatic duct or sealing of the leak) if possible as the procedure of first choice.[29] Although there are no data on the role of magnetic resonance cholangiopancreatography for the diagnosis of this condition, this test can accurately demonstrate the normal pancreatic duct and detect any abnormalities arising from it.[35] Treatment with somatostatin or octreotide together with diuretics and repeated paracentesis may be beneficial for some patients.[36,37] The stent can facilitate healing of ductal disruptions by partially occluding the leaking duct or bypassing the pancreatic sphincter, thereby decreasing the intrapancreatic duct pressure. Some patients fail medical therapy, ultimately requiring surgery.[27] Indications for surgery include persistent or recurrent accumulation of ascites and/or sudden deterioration of clinical status. The type of surgical intervention depends on the ductal anatomy, the site of the leakage from the pancreatic duct or pseudocyst, and the operative findings.[38]

Vascular Irregularities

Portal Hypertension

Extrahepatic portal hypertension (EPH) is defined as extrahepatic hypertension of the portal venous system in the absence of liver cirrhosis. It was first described by Balfour and Steward in 1868. Representing a less common complication of chronic pancreatitis, it may be confined to either the superior mesenteric or splenic venous branch or may involve the whole splenomesentericoportal axis.[39] EPH is characterized by either a complete occlusion of branches of the venous splanchnic system (occlusive form) or a subtotal obstruction of one or more of these branches (nonocclusive form).[40,41] Clinical experience with this condition has remained limited, and no universal agreement exists on whether EPH represents a surgical risk that must be accounted for in the design of a surgical strategy for patients with chronic pancreatitis, and whether EPH per se warrants surgical intervention. Extrahepatic hypertension of the portal venous system is the most common vascular complication in chronic pancreatitis.[41,42] Every part of the splenomesentericoportal venous axis may be involved,[39] resulting in either compromise (nonocclusive variant) or obstruction (occlusive variant) of the lumen and hence of portal venous flow.[41] The pathogenesis of EPH in chronic pancreatitis may include several factors. The inflammatory process is capable of causing initial damage to vascular walls and generating venous spasm, venous stasis, and thrombosis.[43] The intimate relationship with the pancreas and the contiguous course for its entire length leaves the splenic vein most vulnerable to the inflammatory assault. Little and Moossa[43] noted that a single flare of pancreatitis was sufficient to produce splenic vein thrombosis. The most probable cause seems to be the progressive fibrosis characteristic of chronic pancreatitis, leading to progressive constriction of the splenomesentericoportal axis that passes through the pancreatic substance. Support for this assumption is evidenced by the fact that EPH in the authors' series was associated frequently with complications of adjacent organs such as duodenal obstruction or common bile duct stenosis, as pointed out by Warshaw et al.[41] Other factors contributing to EPH in chronic pancreatitis encompass extrinsic compression by pancreatic pseudocysts[44,45] or by the considerable pancreatic head enlargement observed in up to 40% of cases and caused by an inflammatory swelling of the gland, a condition referred to as *inflammatory pseudotumor*.[44,46] The portal and superior mesenteric veins are less frequently affected.[43-45] In 35 patients with chronic pancreatitis, the initial location of splenoportal venous obstruction was the splenic vein in 22 patients (63%), the portal vein in 10 (29%), and the superior mesenteric vein in 3 (9%).[44] In our series, EPH involved the splenic vein in 26 (90%) of 29, the superior mesenteric vein in 21 (72%) of 29, and the central portal vein in 7 (24%) of 29, either alone or in conjunction with other portal branches.[39] It is of note in this regard that EPH was confined in only 14 (39%) of 36 of patients to one branch of the portal venous system (either to the splenic or superior mesenteric vein). Features suggestive of EPH include common bile duct stenosis and evidence of segmental duodenal stenosis at the time of diagnosis.

Collateral routes that spontaneously form in cases of EPH involve

1. The short gastric veins (resulting in isolated fundic varices) bypassing the thrombosed splenic vein and returning the blood either through the coronary vein or via the gastroepiploic and superior mesenteric veins to the portal vein
2. Esophageal veins shifting blood less frequently to the azygos venous system in case of obstruction of the coronary vein, resulting from an obstruction of either the portal vein or the splenic vein, in case the coronary vein drains into the splenic vein (producing combined fundic and esophageal varices)
3. The left gastroepiploic vein conveying blood to the left colic and inferior mesenteric veins (yielding colonic varices at the splenic flexure)

In a literature review of EPH covering 199 patients with previous variceal bleeding, Madsen et al. found isolated gastric varices in 144 patients (75%), combined gastric and esophageal varices in 46 (23%), and colonic varices in 1 (0.5%).[47] Our data suggest no difference in the complication and death rates between surgical procedures emphasizing the resectional aspect (e.g., duodenum-preserving pancreatic head resection described by Beger [classic Whipple]) and surgical decompression by longitudinal pancreaticojejunostomy combined with a limited excision of the pancreatic head (duodenum-preserving resection of the pancreatic head according to Frey).[39] However, regardless of the surgical procedure performed, the complication rate in patients with EPH was distinctly higher than in those without.

An interesting issue is whether EPH per se represents an indication for surgery or not. Although some authors list an entrapment of the splenomesentericoportal-venous axis by an enlarged pancreatic head per se as an indication for pancreatic head resection, advocating an aggressive prophylactic treatment for possible prevention of hemorrhage from esophageal or gastric varices,[46] others have taken a more expectant stance as long as there was no evidence of variceal hemorrhage.[40] Therefore, EPH per se seems not to be an indication for surgical intervention in chronic pancreatitis unless the preoperative work-up cannot rule out a malignancy. Apart from pain, associated complications of adjacent organs (e.g., duodenal or common bile duct stenosis) still remain the main indications for surgery. In the rare circumstances where varices start to bleed, therapeutic options include interventional measures such as sclerotherapy, variceal ligation, and interventional or surgical portosystemic shunting procedures.[41,44] Splenectomy is effective only in cases of isolated splenic vein occlusion.[48] In our experience, EPH does not determine the ultimate outcome after pancreatic surgery once complications in the immediate postoperative period have been overcome. The low frequency of variceal hemorrhage observed in this study suggests that EPH in itself does not entail a major risk in long-standing chronic pancreatitis. In conclusion, the mere presence of EPH does not justify surgery in chronic pancreatitis. When surgical intervention for pancreatitis-related complications is dictated by increasing severity of symptoms, it must be borne in mind that concomitant EPH entails a considerable surgical risk, prolonging operating time, increasing intraoperative blood loss, and imposing significant complications on the individual patient. When surgery is indicated in a symptomatic patient, no definitive recommendation for a procedure can be given. Surgical strategy rather depends on pancreatic morphology than on the intent to abolish EPH.

Thrombosis of the Portal Vein with Cavernous Transformation

Dealing with patients with chronic pancreatitis and coexistent portal vein thrombosis with cavernous transformation complicates the decision-making process enormously (Fig. 88–1). Pancreatitis is the most common extrahepatic, inflammatory disease that causes portal vein thrombosis. Preoperative assessment of patients should routinely include a high-resolution computed tomographic scan and magnetic resonance device providing information with regard to arterial supply and venous drainage.

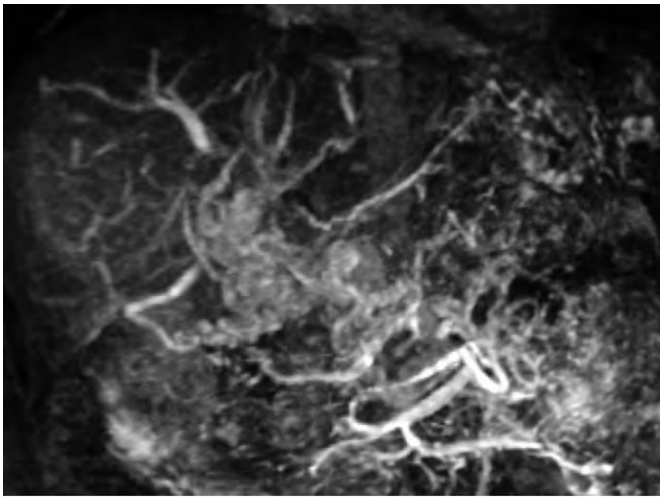


Figure 88–1. Magnetic resonance angiography of portal vein thrombosis with cavernous transformation.

As for other abdominal operations, such as surgery for gastric or duodenal ulcer disease, portal vein thrombosis with cavernous transformation was identified as a major operative risk factor, accounting for prolonged operative time and substantial intraoperative blood loss. What is the ideal operative strategy for a patient with chronic pancreatitis and an inflammatory pancreatic head tumor who has developed portal vein thrombosis with cavernous transformation? Basically, the goals of the operation in patients with or without cavernous transformation do not differ. Hence, the essential landmarks of the surgical strategy resemble those in patients without irregularities of the portal flow. However, any operation in these patients carries particular risks. This notably applies for technical steps that are associated with a dissection of portal collaterals, thereby increasing the amount of postoperative ascites. A transection of the pancreatic parenchyma above the portal vein as required for the Beger procedure, Whipple resection, and duodenum-preserving pancreatic head resection should be avoided by all means because this carries unpredictable risks.

In conclusion, EPH with coexistent cavernous transformation entails a substantial risk in pancreatic surgery for chronic pancreatitis. The mere presence of portal vein thrombosis with cavernous transformation does not justify surgery in chronic pancreatitis. When surgery is considered in a symptomatic patient, surgical strategy is determined more by pancreatic morphology than by the intent to restore portal blood flow. The approach to chronic pancreatitis with associated portal vein thrombosis with cavernous transformation is multidisciplinary,

tailoring the various therapeutic options to meet the individual patient's needs.

INDICATIONS FOR SURGICAL INTERVENTION

The indications for surgical intervention are intractable pain, complications related to adjacent organs, endoscopically not permanently controlled pancreatic pseudocysts in conjunction with ductal pathology, and neither conservatively nor interventionally tractable internal pancreatic fistula.[49-51] Occasionally the inability to exclude pancreatic cancer despite broad diagnostic work-up also requires surgery.[52] The ideal surgical approach should address all these problems.

Rationale for Drainage Procedures

Because 40% to 60% of patients with painful chronic pancreatitis exhibit ductal ectasia, decompression of the pancreatic ductal system has become one of the main therapeutic principles based on the assumption that ductal ectasia indicates intraductal hypertension.[6,10] Obstruction of Wirsung's or Santorini's duct results from single or multiple dominant strictures of the ductal system, from obstruction of the ductal lumen by calcium carbonate–containing stones, or by combination of both. The operative removal of pancreatic stones was already described at the turn of the 19th century.[53,54] Moynihan[54] claimed the underlying rationale for this operative intervention is "alleviation of pain, nausea and emesis, as well as the prevention of pancreatic atrophy." The concept of opening the pancreatic main duct with bypass of the obstruction was first described by Coffey[55] and Link.[56] The first clinical applications of this principle were independently performed by DuVal[57] and Zollinger et al.[58] Decompression of the main pancreatic duct was achieved by resection of the pancreatic tail and retrograde drainage of the pancreatic duct via a terminoterminal or terminolateral pancreaticojejunostomy. However, this procedure proved to be effective only if there was a single dominant obstruction between pancreatic tail and the ampulla of Vater. Especially in patients with alcohol abuse, which is the leading cause of chronic pancreatitis in most patients in the Western hemisphere, a single dominant stricture is found rarely. But even with patent drainage of the duct system, recurrent bouts of severe pain are frequently observed. In 1958, Puestow and Gillesby[59] presented another drainage procedure: decompression of the main pancreatic duct was performed by a longitudinal laterolateral pancreaticojejunostomy after resection of the pancreatic tail and splenectomy. Thus, even in the presence of multiple strictures ("chain of lakes"), the main pancreatic duct could be effectively drained. A modification of the Puestow-Gillesby procedure was introduced by Partington and Rochelle,[60] who performed longitudinal pancreaticojejuonstomy while at the same time avoiding splenectomy and pancreatic tail resection. The rationale for the widespread application of drainage procedures in chronic pancreatitis was the considerable morbidity and mortality rates of resectional procedures (i.e., partial pancreaticoduodenectomy) in the beginning of pancreatic surgery.

Rationale for Resectional Procedures or "Extended" Drainage Procedures

On the other hand, 15% to 40% of patients do not experience permanent pain relief after drainage operations.[9,61-63] Moreover, an inflammatory mass in the pancreatic head is considered a contraindication for a "simple" drainage operation, as associated complications of adjacent organs such as distal common bile duct stenosis or segmental duodenal stenosis require additional bypass procedures.[50,64] Finally, a reliable exclusion of malignant disease is not warranted.[12] Therefore, so-called extended-drainage operations were established as an alternative to classic resectional procedures (e.g., the Whipple or Longmire-Traverso procedure) and as opposed to so-called simple drainage operations (e.g., pancreaticojejunostomy of the Puestow-Gillesby or the Partington-Rochelle type). An inflammatory tumor of the pancreatic head arising in 30% to 50% of patients with chronic pancreatitis generates complications of adjacent organs (e.g., distal common bile duct stenosis, duodenal stenosis, and segmental portal hypertension and/or obstruction of the proximal pancreatic duct system by stones or strictures).[65] Moreover, irrespective of the width of Wirsung's duct, approximately 90% to 95% of patients suffering from chronic pancreatitis present with a problem located in the head of the pancreas (i.e., cephalic ductal alterations with or without the development of an inflammatory mass). Thus, the head of the pancreas has been referred to as the "pacemaker" of the disease.[46,66,67] First steps addressing a more customized approach to these patients were done by Beger and coworkers who inaugurated the duodenum-preserving resection of the head of the pancreas (Fig. 88–2).[68,69] This procedure includes subtotal resection of the pancreatic head following transection of the pancreas above the portal vein. Even in cases of distal common bile duct stenosis or segmental duodenal obstruction, extensive resection with decompression of the bile duct and the duodenum allows for adequate management of these organ complications, while gastroduodenal passage and common bile duct continuity may be preserved.[67,70] Identification of the intrapancreatic course of the distal bile duct is facilitated by insertion of a metal probe into the choledochal duct through a proximal choledochotomy.[71] The body of the pancreas is drained by an end-to-end or end-to-side pancreaticojejunostomy using a Roux-en-Y loop. The same jejunal loop drains the resection cavity by a side-to-side anastomosis to the rim of the resection cavity of the pancreatic head. Whipple, Longmire-Traverso, and Beger types are characterized as resectional procedures to a varying extent and require a transection of the pancreas above the portal vein. Especially in chronic pancreatitis with an inflammatory tumor of the pancreatic head, this operative step may represent the most challenging part of the

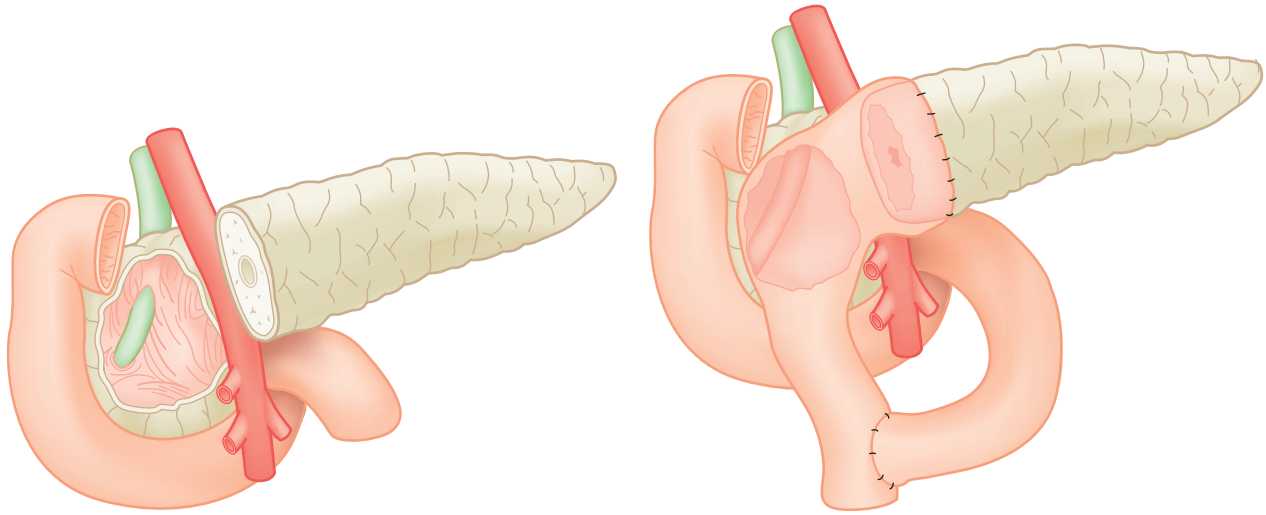


Figure 88–2. **A** and **B,** The duodenum-preserving resection of the pancreatic head, introduced by Beger, addresses the head of the pancreas referred to as the pacemaker of the disease. (**A,** From Beger HG, Buechler M: Duodenum-preserving resection of the head of the pancreas in chronic pancreatitis with inflammatory mass in the head. World J Surg 14:83-87, 1990; **B,** From Beger HG, Krautzberger W, Bittner R, et al: Duodenum-preserving resection of the head of the pancreas in patients with severe chronic pancreatitis. Surgery 97:467-473, 1985.)

operation due to displacement and/or compression of the mesenterico-portal vein axis or massive inflammatory adhesions to these vessels. Therefore, extended-drainage operations were devised that address not only the problem of intraductal and intraparenchymatous hypertension but also the morphologic alterations located in the pancreatic head while at the same time avoiding the sometimes risky maneuver of pancreatic transection. The combination of longitudinal pancreaticojejunostomy of the Partington-Rochelle–type with a transduodenal pancreaticoplasty (e.g., a surgical sphincterotomy of the orifice of the pancreatic duct) is an example of an extended-drainage procedure. This operation warranted adequate drainage of the main pancreatic duct while at the same time addressing the problem of prepapillary obstruction of the proximal pancreatic duct caused by stones or strictures.[72] Probably due to the rapid technologic advancements in interventional endoscopy with the possibility of endoscopic sphincterotomy,[73] this procedure did not gain widespread acceptance. A modified procedure communicated by Frey[68,74,75] combines a longitudinal pancreaticojejunostomy according to Partington and Rochelle[60] with a local excision of the pancreatic head drainage and duodenum-preserving excision (Fig. 88–3). This extended-drainage procedure refrains from pancreatic transection above the portal vein. For reconstruction a longitudinal pancreaticojejunostomy is employed draining the resection cavity of the head, body, and tail of the pancreas. This procedure preserves the physiologic gastroduodenal passage and the continuity of the common bile duct and therefore possesses the same physiologic approach as the duodenum-preserving resection described by Beger.[68,69] This procedure, as well as Beger's, should have considerable advantages over the various types of pancreaticoduodenectomy (e.g., Whipple or Longmire-Traverso). It can at the same time preserve exocrine and endocrine pancreatic function and is able to control complications of adjacent organs such as common bile duct stenosis, duodenal stenosis, and internal pancreatic fistulas. The extent of pancreatic head excision can be modified up to a subtotal excision including the uncinate process leading to the concept of the "Hamburg" modification of the Frey procedure (Fig. 88–4). The major advantage of drainage procedures (Frey's procedure, Hamburg modification) lies in the varying extent of resection that can be customized to the individual morphology of the pancreas.

Operative Modifications of Duodenum-Preserving Resectional Procedures

Modifying the Beger procedure, Warren and coworkers suggested to combine a duodenum-preserving pancreatic head resection with denervation of the body and tail of the pancreas by ligating and dividing the splenic vein at its junction with the superior mesenteric vein.[76] The splenic artery is divided as it approaches the pancreas from the celiac axis. Viability of the spleen is ensured through its extensive arterial and venous collateral circulation, principally the gastroepiploic and short gastric vessels. The entire flap (pancreas, splenic artery and vein, and associated nerve fibers) is freed from all tissue until the pancreas is attached only to the vessels at the hilus of the spleen. This maneuver supposedly severs all somatic and autonomic nerve fibers. Finally, a Roux-en-Y loop of jejunum is prepared and the pancreatic duct anastomosed with a small mucosal opening. Kimura et al. suggested a different modification of a duodenum-preserving pancreatic head resection with detailed

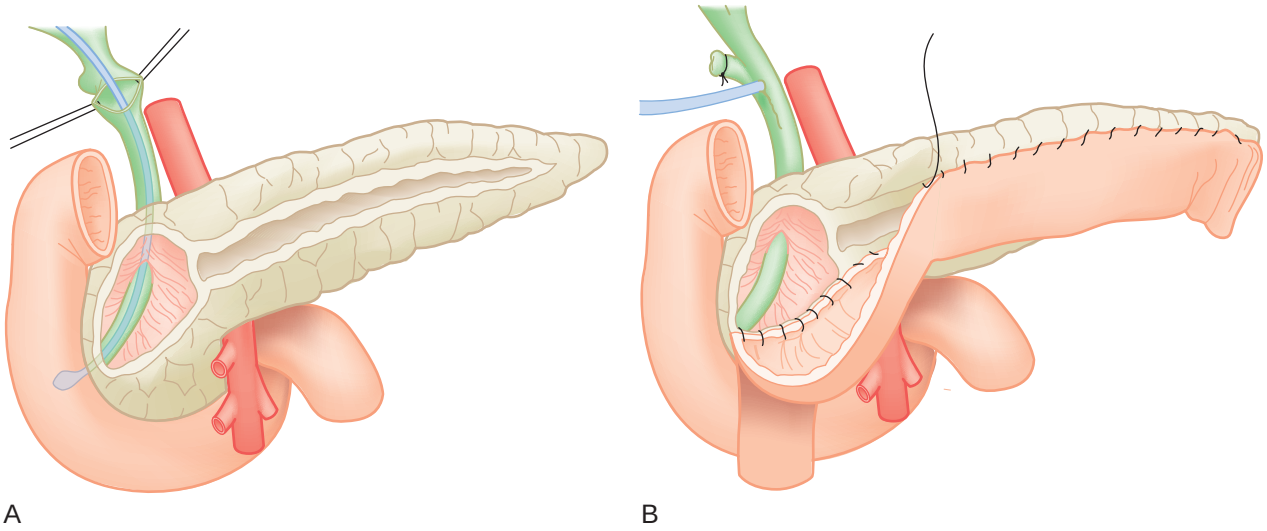


Figure 88–3. **A** and **B,** The Frey procedure. Limited local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy decompressing of the main duct in the neck, body, and tail of the pancreas. (**A,** From Frey CF, Suzuki M, Isaji S, Zhu Y: Pancreatic resection for chronic pancreatitis. Surg Clin North Am 69:499-528, 1989; **B,** Frey CF, Amikura K: Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy in the management of patients with chronic pancreatitis. Ann Surg 220:492-507, 1994.)

description of how to preserve the duodenal blood supply.[77,78] After a complete Kocher maneuver is performed, the pancreas is cut above the portal vein and removed from the third potion of the duodenum. Then the posterior surface of the pancreatic head is removed from the connective tissue membrane, which should be left intact to ensure blood flow to the duodenum. The main pancreatic duct is cut at its junction with the terminal portion of the bile duct. The pancreas is cut on the left aspect of the anterosuperior pancreaticoduodenal artery. Hence, the pancreatic tissue between the duodenum and the common bile duct is left intact to preserve sufficient blood flow to the papilla. After carefully suturing the cut surface of the pancreas with nylon monofilament strings, the remaining body of the pancreas is anastomosed in the posterior wall of the stomach. Nakao described a pancreatic head resection with segmental duodenectomy including minor and major papilla in 1998.[79] After cholecystectomy, the pancreas is divided above the portal vein. The extrapancreatic nerve plexus between the uncinate process and the superior mesenteric artery is preserved, so the inferior pancreaticoduodenal artery is preserved. The posterior inferior pancreaticoduodenal artery is ligated and divided. The anterior inferior pancreaticoduodenal artery is divided near the major papilla. The common bile duct is divided at the upper border of the pancreas. Two to three centimeters of ischemic area of the duodenum is observed including the major and minor papilla. The oral side of the duodenum is divided at 5 to 7 cm from the pyloric ring. The distal part of the duodenum is divided at the margin of the anteroinferior pancreaticoduodenal artery ligation. The gastroduodenal artery is completely spared. The length of the resected duodenum ranges from 3 to 5 cm. The reconstruction of the alimentary tract is performed with pancreaticogastrostomy, duodenoduodenostomy, and choledochoduodenostomy. Most recently, another modification (Bern procedure) has been added to the surgical armamentarium for treatment of chronic pancreatitis.[80] It combines some aspects of the Beger and Frey procedures since it refrains from transection above the portal vein but excises the pancreatic head to a much larger extent than the Frey procedure, therefore potentially preventing a recurrence and definitely decompressing the common bile duct. Early results are promising and randomized trials are under way, but late follow-up results are not available yet. It is our firm belief that the optimal surgical treatment consists of an individually tailored approach (Hamburg procedure). The head of the pancreas should always be cored out to a variable extent including a decompression of the intrapancreatic bile duct. This ensures the removal of altered tissue and includes "inflammatory altered" as well as "hypertensive" tissue. In addition, the procedure can be further customized regarding the pancreatic duct system. If ductal irregularities are present in the pancreatic head and tail, the operation can be extended as a drainage operation much in the way of a Partington-Rochelle procedure into the pancreatic tail.

Is a Drainage Operation Indicated only in Patients with Dilated Ducts?

The normal diameter of the pancreatic main duct amounts to 3 to 5 mm in relation to age.[6,10] In the surgical literature there is considerable controversy regarding the definition of a dilated or narrow pancreatic duct.[6,81] One might develop the impression that definition of a dilated or narrow duct is dependent rather on the view

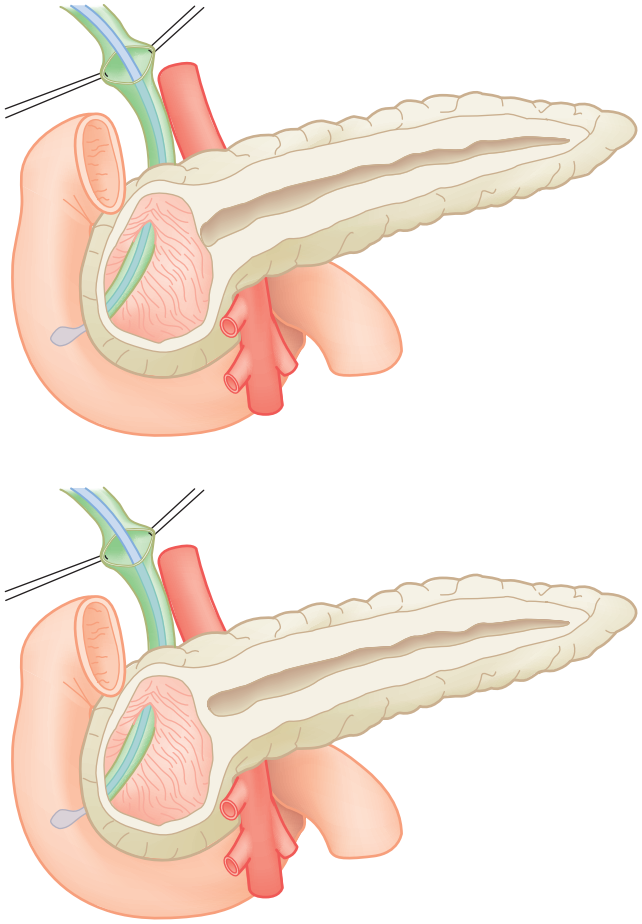


Figure 88–4. The extent of pancreatic head excision can be modified up to a subtotal excision including the uncinate process leading to the concept of the "Hamburg" modification of the Frey procedure. These procedures (original Frey, Hamburg modification) preserve the physiologic gastroduodenal passage and the continuity of the common bile duct and therefore possess the same physiologic approach as the duodenum-preserving resection described by Beger.

of the surgeon towards the technical feasibility to perform a pancreaticojejunostomy than on actual duct size. A survey among members of the American Pancreas Club revealed that most considered a duct size of a minimum of 8 mm sufficient to justify a pancreaticojejunostomy. Others regarded a duct size of 5 mm as the limit to perform a drainage operation, performing a pancreaticoduodenostomy rather than a pancreaticojejunostomy.[6] Most recently, another extended-drainage procedure has been described addressing the rare entity of sclerosing ductal pancreatitis referred to as *small duct disease* with maximal Wirsung duct diameter of less than 3 mm.[82] This operation features a longitudinal V-shaped excision of the ventral aspect of the pancreas combined with a longitudinal pancreaticojejunostomy sewn to the edge of the organ (Fig. 88–5). With this new procedure the role of distal pancreatectomy, which has until now been indicated only in sclerosing chronic pancreatitis limited to the pancreatic body and tail,[83] will be further diminished.

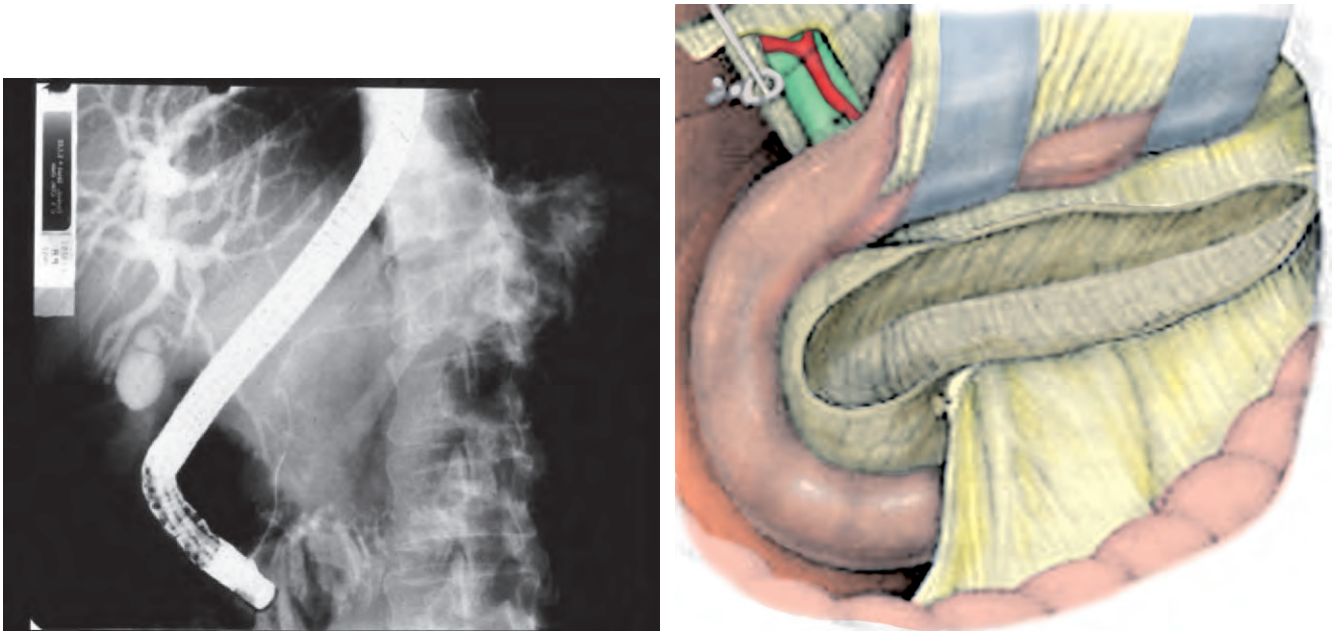
Salvage Procedures

Even though pancreatic surgery for chronic pancreatitis yields excellent results, recurrences may occur. Most frequently, recurrence develops in the remnant of the pancreatic head indicating either insufficient surgical resection of the head of the pancreas or aggressive disease. In these instances, salvage procedures may be indicated ranging from "re-do" pancreas head resections to partial pancreaticoduodenectomy (Whipple procedure, pylorus-preserving pancreaticoduodenectomy). In selected patients (i.e., re-recurrence), even total splenopancreaticoduodenectomy has to be considered. This applies, for instance, to patients in which partial pancreaticoduodenectomy, additional interventional nerve blocks, and surgical denervation fail to achieve definitive pain relief. A biliary stricture in the pancreatic head remnant after duodenum-preserving resection of the pancreatic head without morphologic proof of disease recurrence is most likely is due to ischemia of the intrapancreatic bile duct, especially if the duct was opened during the primary operation. In this case a biliodigestive anastomosis is the procedure of choice. In case of disease recurrence of the body and tail either after duodenum-preserving resection of the pancreatic head or after Whipple or Longmire-Traverso procedure, a V-shaped drainage procedure is the first-line treatment of choice.

CONCLUSION

In our opinion, the ideal procedure for chronic pancreatitis is the duodenum-preserving pancreatic head resection that can be combined with longitudinal duct drainage if ductal pathology is present in the pancreatic body or tail to varying degrees that allows a tailored concept. Looking at the present data, there is no need to transect the pancreatic axis above the portal vein. If portal vein thrombosis is present, the duodenum-preserving pancreatic head resection according to Frey is the treatment of choice. The specimen should always be sent for frozen section, and in case of malignancy, oncologic resections should be performed. In case of small duct disease (pancreatic duct diameter <3 mm), a V-shaped excision most likely will address the patients more effectively than do other procedures. If chronic pancreatitis is focused or limited to the corpus or tail of the pancreas, a spleen-preserving distal pancreatectomy is therapy of primary choice.

Pancreatic surgery is technically demanding and bears many pitfalls and potential complications. It should be left to experts in high-volume hospitals to minimize mortality and morbidity.



A B

Figure 88–5. Small duct disease. **A,** Endoscopic retrograde cholangiopancreatography showing small duct disease with a Wirsung ductal diameter of 2 mm in diffuse sclerosing chronic pancreatitis. **B,** Longitudinal V-shaped excision of the ventral pancreas for diffuse sclerosing pancreatitis with narrowing of the main pancreatic duct. Through a proximal choledochotomy, a metal probe is inserted into the duodenum. (From Izbicki JR, Bloechle C, Broering DC, et al: Longitudinal V-shaped excision of the ventral pancreas for small duct disease in severe chronic pancreatitis: Prospective evaluation of a new surgical procedure. Ann Surg 227:213-219, 1998.)

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Chapter

89

New Developments in Chronic Pancreatitis: Before Head Resection, Try Endoscopic Treatment First

L. William Traverso · Richard A. Kozarek

The principles of treatment for chronic pancreatitis are based on the following clinical and anatomic patterns:

1. The head of the gland is usually the pacemaker of chronic pancreatitis; any treatment must be designed around this area.
2. Almost every patient seeks treatment for abdominal pain (a few have chronic fistulas).
3. Surgery is considered only after all conservative treatments methods have failed.

In our institution, surgery is used only after "endotherapy" has failed. Endotherapy is an evolving concept that should be utilized only in pancreaticobiliary centers with extensive endoscopic retrograde cholangiopancreatography (ERCP) experience and where proficient management of complicated pancreatitis is already practiced.

Whether one uses surgical or endoscopic treatment, the patient will not have relief of pain unless the following criteria are met:

1. Chronic pancreatitis is documented using the 1963 Marseille definition[1] of "residual pancreatic damage, either anatomic or functional, that persists even if the primary cause or factors are eliminated." The irreversible change in the pancreas is usually fibrosis.
2. The cause of the chronic pancreatitis (e.g., gallstones, alcohol use, or autoimmune pancreatitis) must have been remedied or eliminated.
3. Imaging studies must show an anatomic defect.
4. The Cambridge classification of image severity[2] of "marked" has been documented (e.g., at least a main pancreatic duct stricture with or without stones) (Table 89–1). A schematic of the items that can be associated with a "marked" Cambridge classification is demonstrated in Figure 89–1.
5. The treatment is designed to address this anatomy, which is almost always in the pancreatic head. It is unusual for the epicenter of the disease to be isolated in the tail. Consider then a neoplastic cause or that the patient is currently abusing alcohol.
6. Once endotherapy has failed, the treatment is head resection if the patient is a surgical candidate; in our institution this is pylorus-preserving pancreaticoduodenectomy (PPPD), but there are several "head resection" techniques that are options depending on surgeon preference.

Using the algorithm just presented, the patient considered for head resection is highly selected. However, after long-term follow-up, these highly selected patients will achieve significant reduction in their disabling pain, and three fourths of them will have complete pain relief.[3] We have preferentially used PPPD for head resection in an attempt to accrue a 20-year follow-up after this procedure. If the head of the pancreas is the pacemaker of chronic pancreatitis, then removal of the entire head should produce the best pain relief. This percentage of pain relief with complete head resection should be the benchmark that other, less extensive, head resection procedures should achieve.[4]

The evolution of endoscopic therapy to treat pancreatic disorders has moderated the need for resection in

Table 89–1 Cambridge Classification of "Image Severity" for Chronic Pancreatitis

Cambridge Class Number	Description	Main Pancreatic Duct	Abnormal Side Branches
1	Normal	Normal	None
2	Equivocal	Normal	<3
3	Mild	Normal	>3
4	Moderate	Abnormal	>3
5	Marked	Abnormal*	>3

*Main pancreatic duct (MPD) terminates prematurely (abrupt, tapering, irregular); there are multiple MPD strictures; the MPD is dilated >10 mm; ductal filling defects (stones) are present; intrapancreatic or extrapancreatic "cavities" are observed; or there is contiguous organ involvement (e.g., stenoses of common bile duct or duodenum, arteriovenous fistula).
Data from Axon ATR, Classen M, Cotton PB, et al: Pancreatography in chronic pancreatitis: International definitions. Gut 25:1107-1112, 1984.

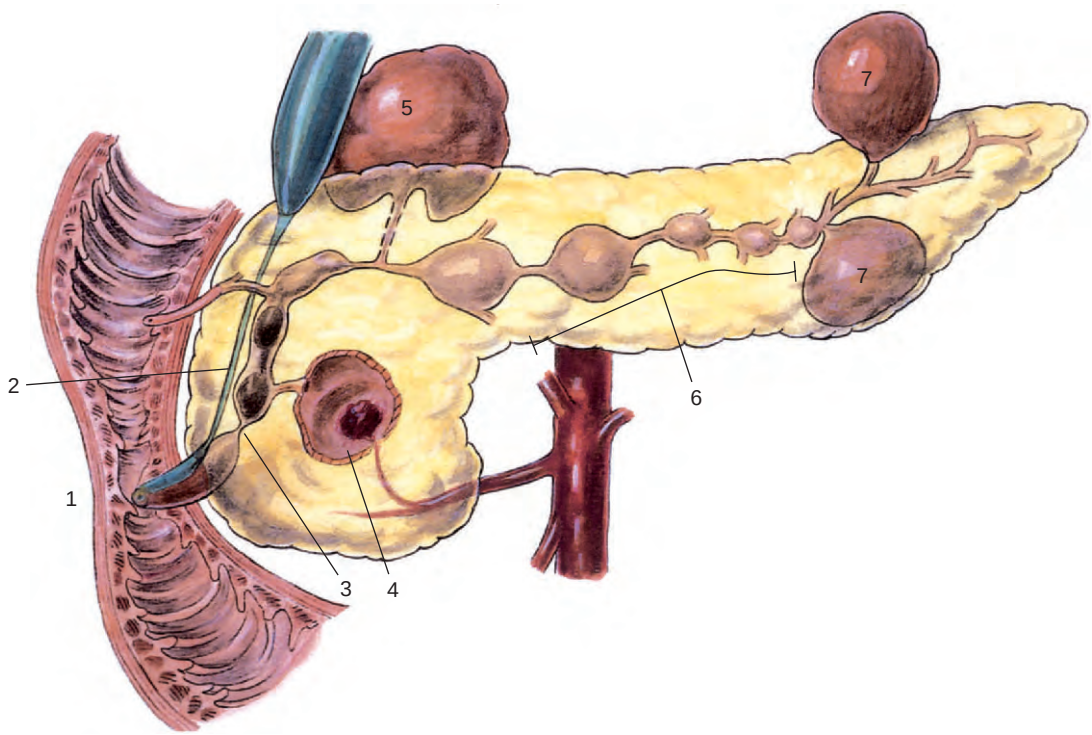

Figure 89–1. Included in this schematic are the possible complications of chronic pancreatitis that the endoscopist or surgeon may encounter when planning therapy. These items should be sought from all imaging studies. Viewing the figure from left to right, the following complications of chronic pancreatitis are depicted: (1) duodenal stenosis; (2) common bile duct stricture; (3) main pancreatic duct stricture (with ductal stones); (4) intrapancreatic pseudocyst with contained pseudoaneurysm (arterial venous connection); (5) ductal disruption at the genu with extrapancreatic pseudocyst formation; (6) chain of lakes ductal dilation; (7) distal pancreatic duct disruptions with focal extrapancreatic pseudocyst collections. (From Traverso LW: The surgical management of chronic pancreatitis: The Whipple procedure. Adv Surg 32:23-39, 1999.)

some centers. Although unable to duplicate the results of pancreatic head resection in patients with multiple strictures and stones associated with pseudotumors of the pancreatic head, endotherapy can nevertheless improve pain as well as decrease relapsing attacks of pancreatitis by approaching *obstructing calculi* and isolated *inflammatory stenoses*. This treatment is not done by endoscopists acting independently but requires access to various forms of lithotripsy, interventional radiologic support, and surgical salvage when endotherapy fails. Head resection is the final option and is the default after multiple sessions in patients where stone extraction is unsuccessful or if

the patient remains stent dependent despite repeated treatment of obstructing stenoses. But how good is endotherapy? The purpose of this chapter is to describe the efficacy for pain relief with endotherapy and, when required, salvage by head resection using PPPD.

ENDOTHERAPY TECHNIQUES

The endoscopic approach to strictures and stones presupposes access to the pancreas through the major or minor papilla. Sphincterotomy can be done using either a conventional or needle knife sphincterotome, usually with a pure cutting current to minimize the chance of cautery transmission. When approaching the pancreatic duct through the major papilla, most endoscopists undertake an initial biliary sphincterotomy to expose the pancreaticobiliary septum and help define the length of the subsequent pancreatic duct (PD) sphincter incision.[5] Slick guidewires (e.g., Tracer or Metro, or Jagwire) are used to provide access and orientation and as the "rail" for all subsequent treatment.

Prior to consideration of endotherapy one must ensure that a pancreatic stricture is benign. The patient will have already had a computed tomographic scan of the "pancreas protocol" variety, an endoscopic ultrasound, and brush cytology of any stricture potentially malignant. These anatomic criteria will have been correlated with the clinical presentation as well as blood tumor markers such as CA 19-9. Clinical follow-up is also a mandatory part of endotherapy as any neoplastic process can masquerade as chronic pancreatitis.

Benign strictures may be dilated by 4- to 6-, 5- to 7-, or 8- to 10-French dilating catheters but are more commonly treated by 4- to 8-mm hydrostatic dilating balloons. Occasionally, extremely tight strictures, particularly those associated with an upstream stone, may need to be breached by a screwlike device called a *Soehendra stent extractor*. Following dilation to a size approximating the downstream pancreatic duct, most endoscopists attempt to place a 7- to 10-French prosthesis across the stricture. This stent is usually retrieved in 2 to 4 months and, if persistent, the stricture is re-treated with additional dilation and replacement of the prosthesis. If initial stent insertion is not helpful to relieve pain, then most endoscopists seek surgical consultation. If the stent insertion is helpful, then the process can be repeated several times over a year's time frame. If the patient becomes stent dependent for symptom relief, most endoscopists consider surgical referral. In contrast to placement of a single stent for a stricture, our practice has evolved into placement of multiple smaller prostheses (5 to 7 French) across the stenosis. Not only does this allow drainage between the stents at time of inevitable stent occlusion, but also, as has been demonstrated in the endoscopic treatment of biliary strictures,[6] multiple stents appear to improve subsequent stricture patency rates.

The removal of obstructing pancreatic calculi is considerably more difficult than the endoscopic removal of bile duct stones.[7] Not only are pancreatic stones frequently associated with downstream strictures but they may also lodge at acute angulations of the duct and result in upstream ductal disruption in the form of a pseudocyst or pancreatic ascites. Approximately half of main pancreatic ductal stones can be removed after PD sphincterotomy, with or without dilation of a concomitant stricture, using conventional biliary stone baskets or an extraction balloon over a guidewires.[8] In the remaining cases, fragmentation is required.

Extremely large, impacted, and irregularly shaped calculi require fragmentation prior to removal. Although the latter can take the form of electrohydraulic, mechanical, or laser lithotripsy, most centers, including our own, prefer extracorporeal shock wave lithotripsy (ESWL).[9-13] Stones can be targeted prior to ERCP, if sufficiently calcified, or may require a baseline ERCP with insertion of a stent or nasopancreatic drain for localization. Once the stone or stones have been localized and fragmented, the fragments must be removed transampullary during an additional endoscopic procedure. Following fragment extraction, prosthesis placement is usually undertaken to minimize obstructive pancreatitis from edema at the site of previously impacted fragments or the sphincterotomy site. In addition, small side-branch calculi frequently migrate into the main pancreatic duct after decompression, and the prosthesis keeps the ductal system decompressed.

RESULTS AFTER ENDOTHERAPY FOR STRICTURE WITHOUT STONES

Multiple recent series have reported a 60% to 80% reduction in attacks of relapsing pancreatitis as well as a comparable relief in chronic pain complaints following endoscopic treatment of pancreatic strictures, although three or four treatment sessions may be required. These results are consistent with the authors' experience.

Several caveats need to be mentioned. Stents themselves can cause "ductitis" and parenchymal injury as a consequence of side-branch occlusion or direct stent pressure by the upstream end or side prongs.[14,15] Additionally, stent placement invariably leads to bacterial colonization within the ductal system. Stent occlusion can occasionally result in upstream duct blowout or even sepsis.

The results of endotherapy for pancreatic duct stricture have to be considered in two categories: persistence of stricture and symptom relief. Anatomically, stricture resolution approximates only 20% to 30% in published series, even when therapy has been undertaken for up to 1 year.[8,16,17] Clinically, most series suggest that only 10% to 20% of patients fail to get relief with initial stent placement, particularly those without upstream ductal dilation or those with multiple stones. In the remaining patients, most achieve a relatively asymptomatic level after stent removal, whereas a minority become stent dependent (15% to 20%) for pain relief. The reason for stent dependence is uncertain but may be related, in part, to location (strictures in the head are more pernicious) or the original cause (those strictures that are a consequence of severe pancreatitis with ductal disruption are often problematic).

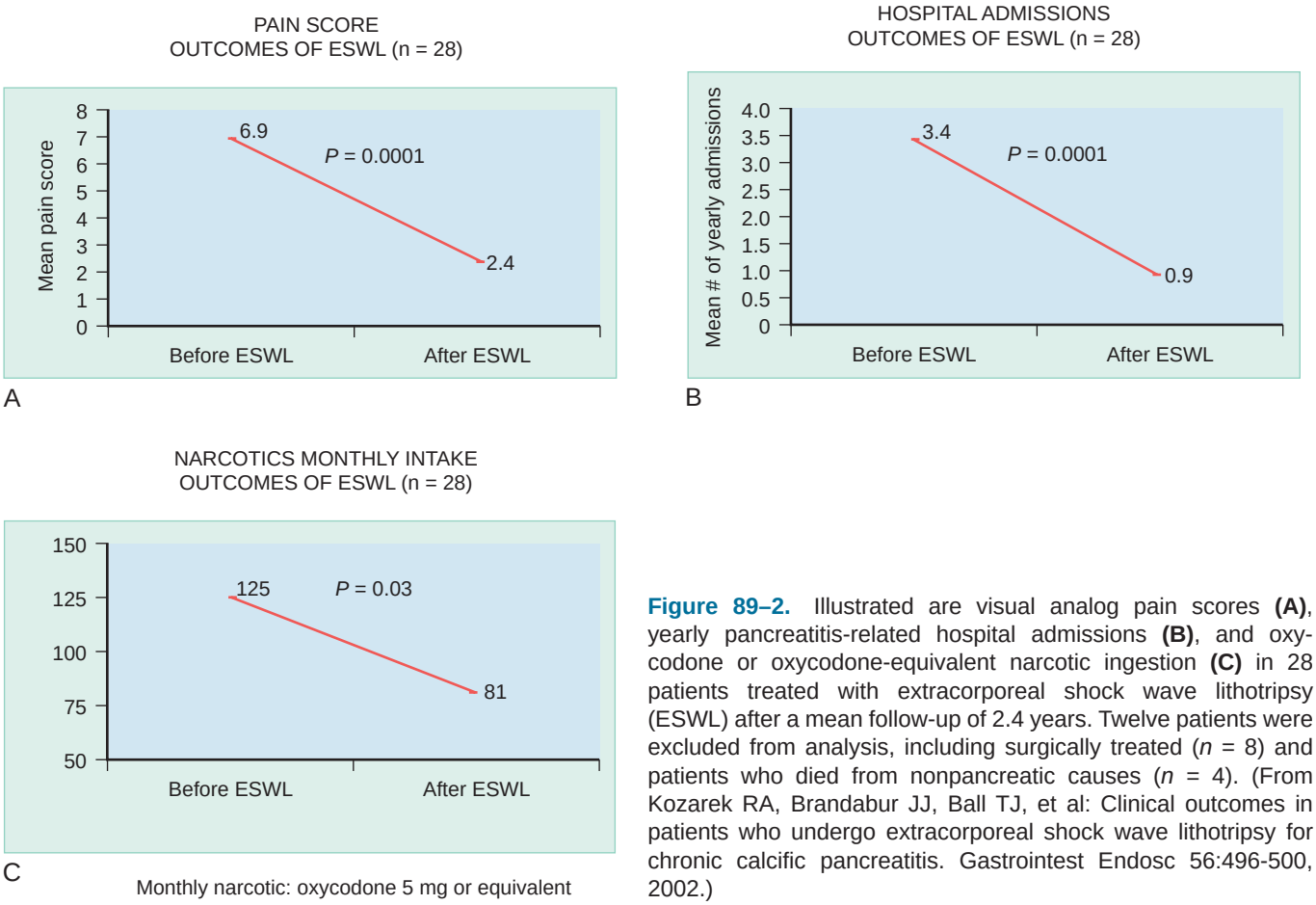

Figure 89–2. Illustrated are visual analog pain scores **(A)**, yearly pancreatitis-related hospital admissions **(B)**, and oxycodone or oxycodone-equivalent narcotic ingestion **(C)** in 28 patients treated with extracorporeal shock wave lithotripsy (ESWL) after a mean follow-up of 2.4 years. Twelve patients were excluded from analysis, including surgically treated (n = 8) and patients who died from nonpancreatic causes (n = 4). (From Kozarek RA, Brandabur JJ, Ball TJ, et al: Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc 56:496-500, 2002.)

RESULTS AFTER ENDOTHERAPY FOR STONES

About half of the patients will have strictures with stones. In contrast to some of the uncertainty associated with endoscopic treatment of pancreatic duct strictures, data are reasonably good that endotherapy for calculi is associated with short- and long-term symptom relief.[9-11,18,19] This is obviously contingent on successful clearance of stones from the main pancreatic duct, the treatment of concomitant biliary and/or pancreatic ductal stenosis, and patient selection (patients with a pseudotumor have problems not necessarily related to stones and should be excluded from endotherapy).

During the period of 1995-2000 we began our series of pancreatic duct stone extraction.[20] Thirty-five of 40 patients required a single ESWL session, while a total of 86 ERCPs were required to completely clear the main pancreatic duct. There was a 20% rate of minor procedural complications. After a mean follow-up of 2.4 ± 0.6 years, 80% of the patients avoided surgery. Four of these patients died of a cause unrelated to chronic pancreatitis. There was a statistically significant decrease in analog pain scores, oxycodone-equivalent narcotic use, and yearly pancreatitis-related admissions (Fig. 89–2).

Since that time, an additional 90 cases have been added with comparable results. The utilization of endoscopy to approach pancreatic strictures and stones since 1995 has not been associated with an increase in operative drainage or resective procedures for pancreatic duct stones; despite a relative increase in referrals for evaluation of chronic pancreatitis problems. The lack of an increase in surgical procedures may be due to endotherapy. However, as some have suggested, endotherapy might simply delay an inevitable resective or more effective decompressive procedure.

SURGICAL RESECTION TECHNIQUES

As indicated earlier we use PPPD preferentially for head resection in an attempt to document long-term pain relief after complete head resection. This information is important to support head resection in general. Except for a variety of reconstruction methods the pylorus-preserving technique is generally performed in the same manner throughout the world. The procedure removes all of the head of the pancreas and the duodenum (except the duodenal bulb) as is shown in Figure 89–3. Reconstruction in our institution is depicted in Figure 89–4. Note that the duodenojejunostomy is in an antecolic position, a position we believe minimizes delayed gastric emptying.[21,22] Delayed gastric emptying after the PPPD with this antecolic position should be less than 10%[21] and is most often associated with a pancreatic anastomotic leak.

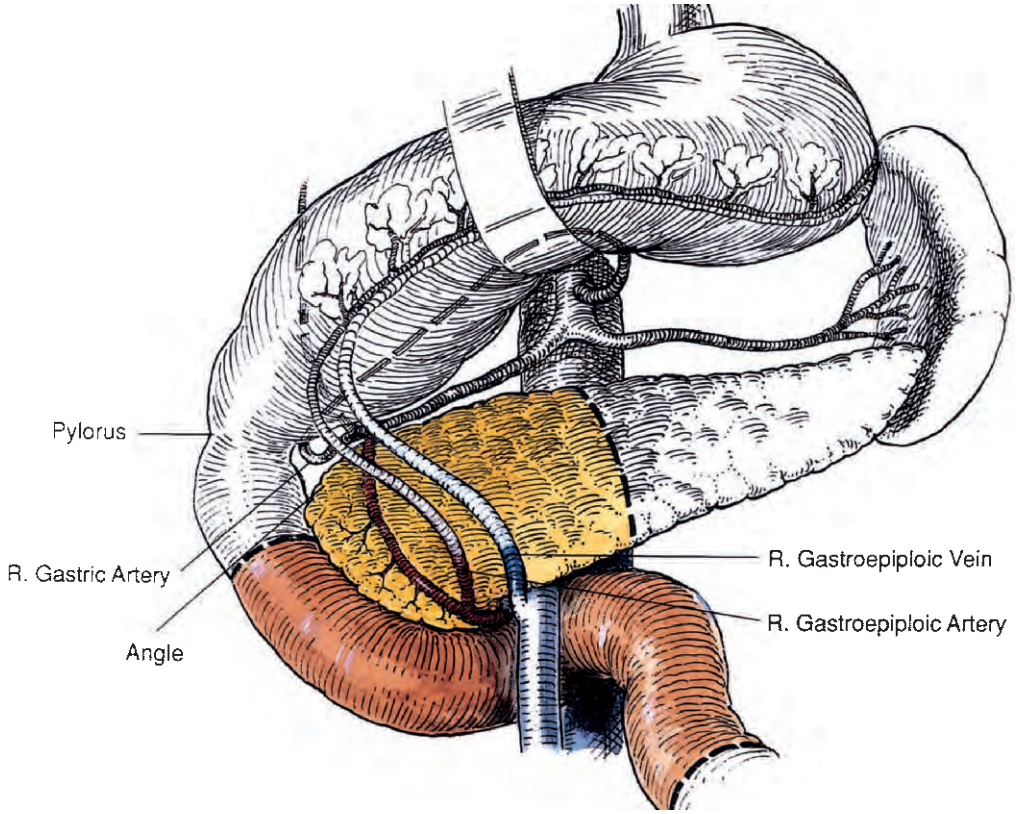

Figure 89–3. The areas in color (also outlined by *dashed lines*) indicate the area of the pancreas, duodenum (parts 2, 3, and 4), and jejunum that are resected with the pylorus-preserving pancreaticoduodenectomy. The complete head of the gland is removed. The right gastroepiploic vessels are divided near their origin as depicted by the color changes. The right gastric artery is also divided away from the stomach near its origin. This allows the neurovascular supply to the antrum and pylorus to be preserved and may minimize the incidence of delayed gastric emptying. (From a black and white photograph, in Traverso LW: The pylorus-preserving Whipple procedure for severe complications of chronic pancreatitis. In Beger HG, Buchler MW, Malfertheimer P [eds]: Standards of Pancreatic Surgery. Heidelberg, Germany, Springer-Verlag, 1993, p 397.)

RESULTS AFTER HEAD RESECTION WITH PYLORUS-PRESERVING PANCREATICODUODENCTOMY

In 1997, we reported the short- and long-term outcomes from 57 patients who had undergone pancreaticoduodenectomy for chronic pancreatitis.[3] Each of these patients had failed to respond to conservative therapy as outlined erlier. The indications for head resection in this group were as follows:

- All patients had intractable abdominal pain and we believed that they had "chronic pancreatitis" according to the Marseilles 1963 classification.
- All patients had the Cambridge image severity of "marked." To be more specific, 96% had main pancreatic duct obstruction and the 4% that did not were patients with intrapancreatic pseudocysts in the head.
- In addition to main pancreatic duct obstruction or pancreatic head pseudocyst, all patients had multiple other elements of the Cambridge classification to support head resection as listed in the footnote of Table 89–1.

The patient characteristics were as follows: 63% were male, 75% were alcohol related, 56% had pancreatic pseudocyst ("cavities") in the head, 23% had previous pancreatic operations such as pseudocyst or main ductal drainage procedures, and 33% were diabetic. The role of endotherapy was prominent in these patients. Common bile duct obstruction was observed in 65% and 47% had undergone prior common bile duct stenting. As listed previously, 96% had pancreatic duct obstruction, 39% had a documented main pancreatic duct blowout, and 35% had undergone pancreatic duct stenting that failed to achieve pain relief. In addition, 19% had required percutaneous drainage of peripancreatic fluid collections.

Ninety-seven percent of these patients underwent PPPD. Since 3% already had an anterectomy from previous ulcer surgery they were reconstructed as a standard Kausch-Whipple procedure. There was no hospital or 30-day mortality.

Follow-up was obtained in 98% of patients after a mean of 42 months. We observed a 5-year actuarial survival rate of 93%. The onset of new diabetes was interesting. In the subset of patients not diabetic preoperatively ($n = 37$), the actual 5-year diabetic occurrence

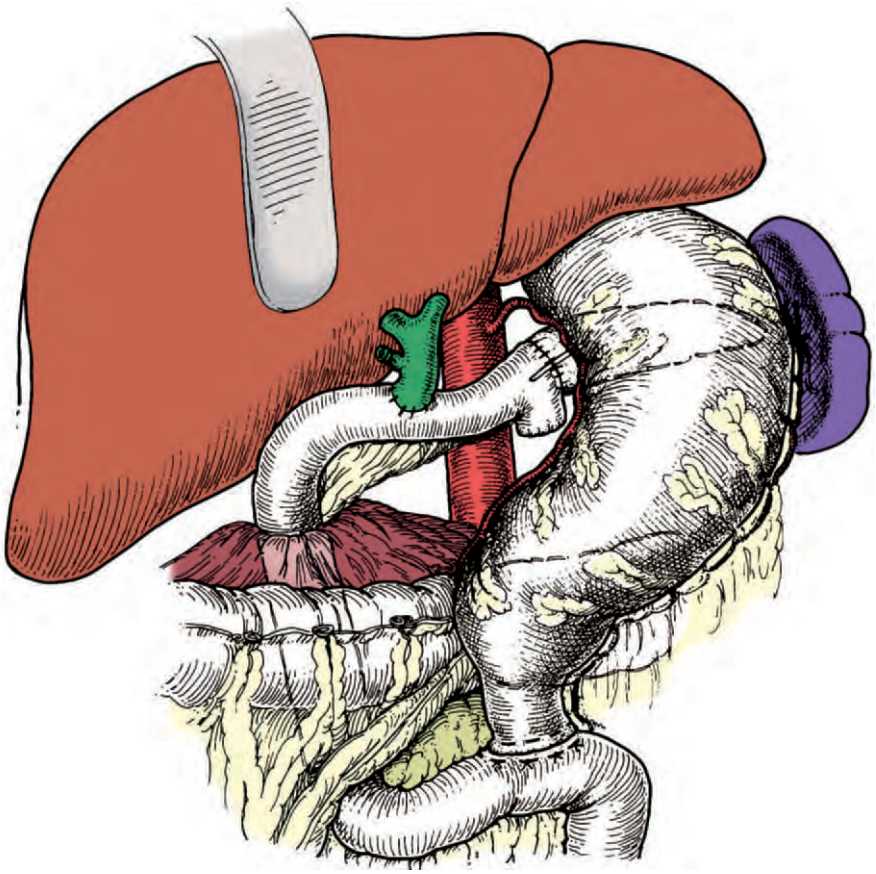

Figure 89–4. Reconstruction of the pancreatic duct and bile duct in a retrocolic fashion. The pancreaticojejunostomy can be made in a side-to-side fashion if a "chain-of-lakes" ductal pattern exists in the pancreatic remnant. The end-duodeno-to-side-jejunostomy is in an antecolic position to isolate the duodenal anastomosis from the pancreatic anastomosis and minimize delayed gastric emptying if the latter should leak. (From Traverso LW: The surgical management of chronic pancreatitis: The Whipple procedure. Adv Surg 32:23-39, 1999.)

rate was 32%. This diabetes was not a consequence of the resection because no patient became diabetic sooner than 12 months after the resection, indicating that the criteria for surgery had been accurate enough to ensure that nonfunctional pancreatic tissue had been excised. These data supported the concept that diabetes was a result of continued fibrosis in the pancreatic remnant. We did not see a predisposition for diabetes due to the pylorus-preserving procedure as has been suggested by others.[23]

Patients that were more than 1 year after their Whipple operation ($n = 43$) were then questioned after a mean follow-up period of 55 months. These patients were asked "do you still have pain and, if so, is it still disabling?" We found a surprising response. In the 96% of patients that originally had disabling pain as an indication for surgery, every patient indicated that he or she had a "good" response to surgery and that the pain was no longer disabling. In addition, 76% of the patients indicated that their pain relief was "excellent" (free of all pain). However, true to the human nature associated with those patients who develop alcohol-associated chronic pancreatitis, 14% of patients were still taking some postoperative narcotic medication (even if they did not have pancreatitis pain) and 24% had resumed drinking alcohol. In regard to activity, 93% of the patients had returned to work, school, or full activity. All patients were able to maintain their preoperative weight, and there were no patients who complained of dumping or significant diarrhea. However, 77% of the patients were taking exocrine enzymes, and 14% indicated that they had diarrhea if they did not take exocrine enzymes.

Another surprising finding was the incidence of marginal ulceration of 14% (6 of 43). Four of these six patients had undergone total pancreatectomy (an operation previously recommended in patients who were diabetic preoperatively). There was a significant correlation of peptic ulceration with the amount of resection; that is, 44% of those patients with total pancreatectomy had peptic ulceration, whereas only 6% with pancreaticoduodenectomy subsequently developed peptic ulceration. Since that time we have avoided total pancreatectomy in almost all patients regardless of their diabetic status. The often-discussed need for total pancreatectomy for small-duct pancreatitis has not been necessary in our practice. Most patients we have seen for "small ductal pancreatitis" were found to be currently drinking alcohol and did not have resective surgery (see list of resection criteria at the beginning of this chapter).

A recent review using "evidence-based medicine" examined a variety of reports that listed pain relief and sequela after all forms of head resection for chronic pancreatitis.[24] Major relief of pain was observed in 70% to 100% of patients from either the standard PD, pylorus-preserving Whipple, duodenum preserving head resection (Beger procedure), or the ventral head resection with upstream ductal drainage (Frey procedure).

These studies were difficult to compare, although many of them were randomized, controlled trials. The problem was the lack of standard selection criteria for head resection. The criteria listed in the current chapter based on imaging studies would be a great opportunity to standardize. Many head resections in Europe are done just for an inflammatory "pseudotumor" of the head without mention of ductal anatomy. The severity of chronic pancreatitis preoperatively is difficult to evaluate without imaging studies that include ductal anatomy. Without ductal anatomy it is also difficult to make an inference on endocrine and exocrine function, unless these are measured preoperatively. The evidence-based medicine review did generalize to state that none of the head resection operations appeared to delay the progression of diabetes better than another. The few prospective trials comparing the complete head resection to partial head resections suffer from low numbers (between 20 and 30 patients in each group). We believe our results (after PPPD) of good to excellent pain relief after long-term follow-up support head resection of any kind, as long as the operation can be done safely and with few long-term sequelae.

In regard to patient safety the morbidity and mortality for all of these operations are also similar. The Beger procedure appears to be practiced mainly in German-speaking countries and the Frey operation appears to be gaining popularity in North America because of less surgical difficulty. Note that any limited head resection such as the Beger or the Frey operation will result in cutting more pancreatic parenchyma than the Whipple procedure where just the neck of the gland is transected. Rapid blood loss occurs from any cut surface of the pancreas. Blood loss would be expected to be higher during parenchymal resection of these limited head resections. The estimated blood loss for the Beger procedure has not been reported. We found the average estimated blood loss for a Whipple procedure in the last 16 reports to be 964 ml while our high-volume center's average blood loss was 204 ml.[22] Since surgeons will not have the opportunity to perform many head resections, then any increased level of difficulty is an important factor in surgeon preference. The infrequency of these chronic pancreatitis cases requiring head resection and the surgical difficulty of the Whipple or the Beger procedures has led many North American surgeons to stay with the more familiar Whipple operation, not try the Beger procedure, or begin using the Frey procedure. This case volume infrequency is further compounded by the promising results of endotherapy for chronic pancreatitis. Perhaps even fewer patients will require head resection.

SUMMARY

Endotherapy for chronic pancreatitis is being used more frequently at our institution. When it fails then the patient is salvaged with PPPD with good pain relief in almost all cases. The technique of endotherapy requires endoscopic access to the pancreatic ductal system where pancreatic strictures can be dilated and stented or pancreatic stones can be removed (with or without ESWL). The technique works best for patients where pancreatic duct stones are exacerbating the pain of chronic pancreatitis. Still, most patients with strictures and no stones will have pain relief sufficient to avoid surgery. Endotherapy has become so effective that the need for surgical drainage and resections has remained constant even though the number of patients referred for problems associated with chronic pancreatitis has increased.

Resection after endotherapy is required for some patients. Generally they comprise two groups. The first group has recalcitrant stone disease behind a main pancreatic duct stricture. The second group has a main pancreatic duct stricture but no stones. Either endotherapy has no effect on their pain or they become stent dependent for pain relief. These two groups form the new and more selected subset that requires head resection. When endotherapy has failed and if the patient meets the criteria for severe chronic pancreatitis centered in the head of the gland, we have observed good to excellent relief of pain after PPPD. Long-term follow-up, which has never been available with cancer patients after the Whipple procedure, has revealed few gastrointestinal side effects from PPPD and without predisposition for diabetes. We avoid total pancreatectomy because of a higher marginal ulceration rate, even if the patient is diabetic.

From this personal experience our understanding of this disease has improved. We can select patients who will benefit from endotherapy most of the time and, if endotherapy fails, these patients can be salvaged for pain relief by head resection using a pylorus-preserving Whipple resection. After long-term follow-up of almost 5 years, the benchmark for disabling pain relief should approach 100% in properly selected patients using anatomic selection criteria. It is hoped that this benchmark could be equaled by a variety of promising operations using a more limited head resection, such as the Frey and Beger operations. First the patients should be selected with a standard list of reliable clinical and anatomic imaging criteria such as those used in this chapter. If the premise is correct that the head of the pancreas is the "pacemaker" of chronic pancreatitis, then limited head resections should approach or equal the pain relief that we have observed after the pylorus-preserving Whipple procedure.

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Chapter

90

Pseudocysts and Other Complications of Pancreatitis

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PANCREATIC PSEUDOCYSTS

A *pancreatic pseudocyst* is a localized collection of pancreatic secretions surrounded by a wall of fibrous or granulation tissue that arises as a result of acute or chronic pancreatitis, pancreatic trauma, or obstruction of the pancreatic duct by a neoplasm (Figs. 90–1 and 90–2). Pseudocysts account for about 75% of cystic lesions of the pancreas. They are distinguished from other peripancreatic fluid collections (cystic neoplasms and congenital, parasitic, and extrapancreatic cysts) by their lack of an epithelial lining, a high concentration of pancreatic enzymes within the pseudocyst, and formation at least 4 weeks after an episode of pancreatitis or pancreatic trauma (Box 90–1). Pseudocysts are formed by the inflammatory response that occurs after extravasated pancreatic secretions are walled off by the surrounding structures. The capsule of the pseudocyst can be thin fibrous tissue, which can progressively thicken as the pseudocyst matures. Frequently, the liquid contents of the pseudocyst are gradually resorbed by the body, and the pseudocyst resolves, findings indicating that the communication between the pseudocyst and the pancreatic duct has closed. Persistence of a pseudocyst implies ongoing communication with the pancreatic ductal system, regardless of whether the ductal system can be demonstrated radiographically or pathologically.

Terminology

Because pseudocysts may resemble other collections of fluid that can arise as a complication of acute pancreatitis, clear terminology is required to differentiate these different clinical entities. The International Symposium on Acute Pancreatitis, held in 1992, established consensus definitions for pseudocyst, acute fluid collection, and pancreatic abscess.[1]

Acute fluid collections form early in the course of acute pancreatitis and lack a discrete wall of fibrous or granulation tissue (Fig. 90–3). They are common in patients with severe pancreatitis and occur in 30% to 50% of cases.[2] The majority of these lesions regress spontaneously without specifically directed therapy or drainage. Most acute fluid collections do not represent a communication with the pancreatic duct. Instead, they are a serous or exudative reaction to pancreatic inflammation and trauma. Because they lack true communication with the pancreatic duct, acute fluid collections are also referred to as *pseudopseudocysts*. A fluid collection that persists for more than 4 weeks, that is usually surrounded by a well-defined wall, and that may communicate with the pancreatic ductal system is termed a *pancreatic pseudocyst*.

A *pancreatic abscess* is a circumscribed collection of purulent infected fluid that contains little or no necrotic material and arises as a complication of acute pancreatitis or trauma. A pancreatic abscess typically occurs late in the course of severe acute pancreatitis, often 4 or more weeks after the onset of symptoms. Patients have signs and symptoms of infection. The presence of a purulent exudate, a positive culture for bacteria or fungi, and little or no necrotic pancreatic material differentiate a pancreatic abscess from *infected pancreatic necrosis*, a catastrophic complication that often occurs earlier in the course of severe pancreatitis. This distinction is crucial because the mortality associated with infected pancreatic necrosis is double that of pancreatic abscess and the specific therapy for each condition is markedly different. A pancreatic abscess may be treated by percutaneous drainage in many cases, whereas infected pancreatic necrosis typically requires operative débridement.

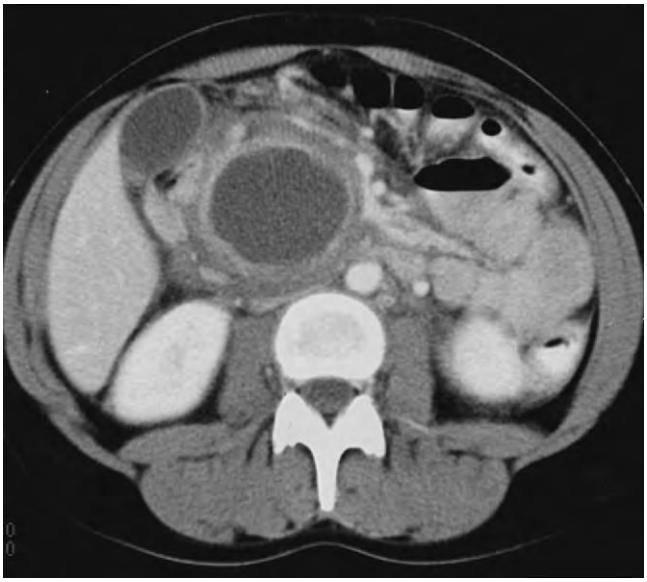

Figure 90–1. Computed tomography scan of a patient with a pancreatic pseudocyst in the head of the pancreas. The patient had symptoms of abdominal pain and nausea. The gallbladder appears distended, although the results of liver function tests were normal.

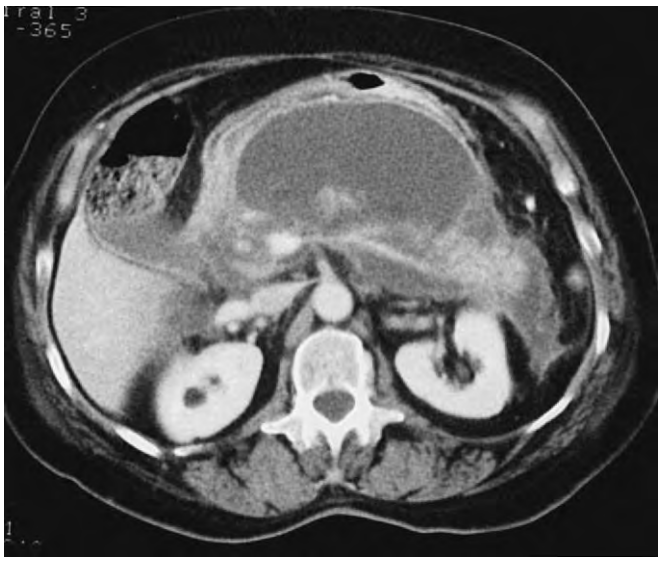

Figure 90–2. Computed tomography scan of a patient with a large retrogastric pancreatic pseudocyst. The patient had symptoms of abdominal pain, back pain, nausea, and early satiety.

Box 90–1 Cystic Lesions of the Pancreas and Peripancreatic Region

- Pancreatic pseudocyst
- Pancreatic pseudopseudocyst (acute fluid collection)
- Pancreatic abscess
- Cystic neoplasms of the pancreas
  - Serous cystadenoma
  - Mucinous cystadenoma/cystadenocarcinoma
  - Cystic islet cell tumor
  - Acinar cell cystadenocarcinoma
  - Cystic choriocarcinoma
  - Cystic teratoma
- Parasitic cysts
  - Echinococcal cyst
  - *Taenia solium* cyst
- Congenital cysts
  - Simple cyst
  - Polycystic disease
    - Isolated to the pancreas
    - Associated with polycystic kidney disease
    - Associated with von Hippel–Lindau disease
    - Associated with cystic fibrosis
- Extrapancreatic cysts
  - Duplication cyst
  - Mesenteric cyst
  - Splenic cyst
  - Adrenal cyst

Modified from Yeo CJ, Sarr MG: Cystic and pseudocystic diseases of the pancreas. Curr Probl Surg 31:165, 1994, with permission.

Etiology

Pseudocysts have historically been thought to occur in 5% to 10% of patients with acute pancreatitis. As imaging techniques have improved, particularly computed tomography (CT), our knowledge of their prevalence and natural history has improved. Pseudocysts are believed to occur in 10% to 20% of patients with acute pancreatitis and in 20% to 40% of patients with chronic pancreatitis.[3] Pseudocysts occur more commonly in males than in females, a finding that perhaps reflects the frequent occurrence of these lesions in patients with alcoholic pancreatitis. Forty-five percent to 50% of pseudocysts occur in or around the head of the pancreas, whereas the remainder are evenly distributed along the neck, body, and tail of the gland. Pseudocysts are most often solitary round or ovoid collections, but 15% of patients may have multiple pseudocysts. As mentioned, alcohol appears to be the cause of 65% of pancreatitis-related pseudocysts, and gallstones are the origin of another 15% of cases.[4,5] Trauma causes 5% to 10% of pseudocysts, and other less common causes of pancreatitis account for the remainder of cases.

Clinical Features

Abdominal pain, the most common symptom in patients with a pseudocyst, occurs in up to 90% of patients. Pseudocysts that follow an episode of acute pancreatitis are often characterized by persistence or recurrence of upper abdominal pain weeks after the initial attack. A pseudocyst may also be the source of increased or refractory pain in a patient known to have chronic pan-

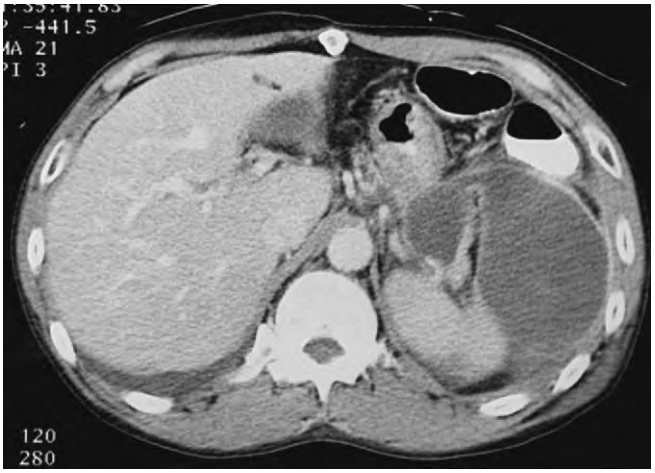

Figure 90–3. Computed tomography scan of a patient with an acute fluid collection 10 days after an episode of acute alcoholic pancreatitis. The collection is located anterior to the spleen and appears to have a thin wall. The acute fluid collection was not causing symptoms and gradually resolved with observation.

creatitis. Other common symptoms include early satiety, nausea and vomiting (50% to 70%), weight loss (20% to 50%), jaundice (10%), and low-grade fever (10%).[6,7] Physical examination reveals upper abdominal tenderness in the majority of patients, and 25% to 45% will have a palpable abdominal mass. The symptoms of early satiety, nausea, and vomiting may be secondary to gastroduodenal obstruction caused by a mass effect of the pseudocyst. Rarely, patients with pseudocysts may not seek medical attention until a secondary complication occurs. Such complications include sepsis secondary to infection, hypovolemic shock secondary to pseudocyst-associated hemorrhage, jaundice secondary to common bile duct obstruction, and severe acute abdominal pain as a result of intraperitoneal rupture of a pseudocyst.

Patients with a pseudocyst secondary to trauma may have similar symptoms at a time remote from the trauma. Pancreatic trauma is uncommon, but it may occur after blunt or penetrating injury. The ductal disruption contributing to pseudocyst formation may occur as a direct result of penetrating trauma or, more commonly, as a result of blunt trauma to the upper part of the abdomen that transects or disrupts the pancreas as it crosses anterior to the vertebral column. These injuries may be missed during initial radiologic evaluation or laparotomy, and the diagnosis of a pseudocyst is often made weeks after the initial injury.

Diagnosis

No definitive laboratory findings are available to establish a diagnosis of pancreatic pseudocyst. Elevated serum amylase and lipase concentrations may occur in half these patients. In fact, persistently elevated amylase after resolution of acute pancreatitis should prompt investigation for a pseudocyst. A few patients with a pseudocyst have mild leukocytosis, whereas others have elevated liver function test results, which may indicate some compression of the biliary tree. An abdominal CT scan is the preferred study for diagnosis of a pancreatic pseudocyst. Ultrasound examination also demonstrates many pseudocysts, and it is a less invasive test that may be used to monitor a known pseudocyst for interval size changes.[8] The use of magnetic resonance imaging (MRI) has been advocated to predict whether solid debris within a pseudocyst will prevent adequate percutaneous drainage.[9] Conventional MRI also has the potential advantage of being coupled with magnetic resonance cholangiopancreatography (MRCP) to help define pancreatic ductal anatomy relative to a pseudocyst.[10] Magnetic resonance pancreatography has shown high specificity and diagnostic accuracy in the evaluation of duct strictures and filling defects.[11] More experience is needed in the use of MRI and MRCP for the evaluation of pseudocysts.

Differentiating pseudocysts from other cystic lesions of the pancreas can be challenging. Several groups have advocated the use of percutaneous aspiration to aid in the differentiation of these structures. Lewandrowski and colleagues evaluated the intracystic fluid from 26 cystic lesions for amylase content, cytology, relative viscosity, and the serologic markers carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125).[12] The nine pseudocysts were found to have high amylase levels, negative cytologic findings, low viscosity, and low levels of CEA and CA-125. Mucinous cystic neoplasms had variable amylase concentrations, usually positive cytologic findings, high viscosity, and variably high levels of the serologic markers (Table 90–1). Serous cystic neoplasms produced fluid with intermediate results; they were low

Table 90–1 Cyst Fluid Parameters Useful in Diagnosis

Diagnosis	Amylase	Cytology	Viscosity	CEA/CA-125	CA 19-9
Pseudocyst	High	Negative	Low	Low/low	Variable
Serous cystic neoplasm	Variable	Negative	Low	Low/variable	Variable
Mucinous cystic neoplasm	Variable	Usually positive	Usually high	High/variable	High

CA 19-9, cancer antigen 19-9; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen.
Modified from Lewandrowski KB, Southern JF, Pins MR, et al: Cyst fluid analysis in the differential diagnosis of pancreatic cysts: A comparison of pseudocysts, serous cystadenomas, mucinous cystic neoplasms, and mucinous cystadenocarcinoma. Ann Surg 217:41, 1993, with permission.

in viscosity and CEA but had elevated CA-125 levels. The few cystadenocarcinomas in the group had high viscosity, high CEA and CA-125 levels, and positive cytologic findings. The Cooperative Pancreatic Cyst Study prospectively evaluated cyst fluid tumor markers and final pathology in 112 patients. Cyst CEA (>192 ng/ml) demonstrated 79% accuracy in differentiating mucinous from inflammatory cysts.[13] A European pooled analysis of cyst fluid results showed that a CEA level less than 5 ng/ml suggested a pseudocyst or serous cystadenoma with 95% specificity.[14] Furthermore, low CA 19-9 cyst fluid levels were strongly predictive of a nonmucinous cyst. Although these results indicate that some conclusions may be made about the type of cystic lesion based on cyst fluid sampling, percutaneous aspiration is not usually necessary for differentiation between pseudocysts and cystic neoplasms.

Many authors advocate the use of endoscopic retrograde cholangiopancreatography (ERCP) for the diagnosis and treatment planning of patients with pancreatic pseudocysts.[15-18] The obvious advantage of ERCP is the ability to define pancreatic ductal anatomy, of particular benefit in evaluating a pseudocyst in a patient with chronic pancreatitis. Nearly all patients with pseudocysts have some abnormality in their pancreatic ductal system, and 2% to 50% may have abnormal cholangiograms as well. A prospective study by Nealon et al. of ERCP in patients with pseudocysts found that ERCP findings changed operative management in 24 of 41 patients undergoing surgery for a pseudocyst.[19] Nineteen of the patients in the study underwent longitudinal pancreaticojejunostomy for drainage of the pancreatic duct. Unfortunately, this study had no matched controls, and therefore no conclusions regarding an outcome advantage for patients who underwent preoperative ERCP can be made.

ERCP has also been advocated as a method to determine which patients with pseudocysts are candidates for percutaneous drainage. Ahearne et al., in a 1992 study, assumed that pseudocysts associated with disruption of or communication with the main pancreatic duct required surgical drainage whereas those without these ERCP findings could be drained percutaneously.[20] This assumption may not be true. In retrospective fashion, the authors showed that patients treated according to an algorithm based on their stated assumption had fewer adverse outcomes (12%) than did patients treated in a manner that did not follow the algorithm (43% adverse outcomes). This study indicates that use of an ERCP-based algorithm can lower the incidence of adverse outcomes in patients with pancreatic pseudocysts (Fig. 90–4).

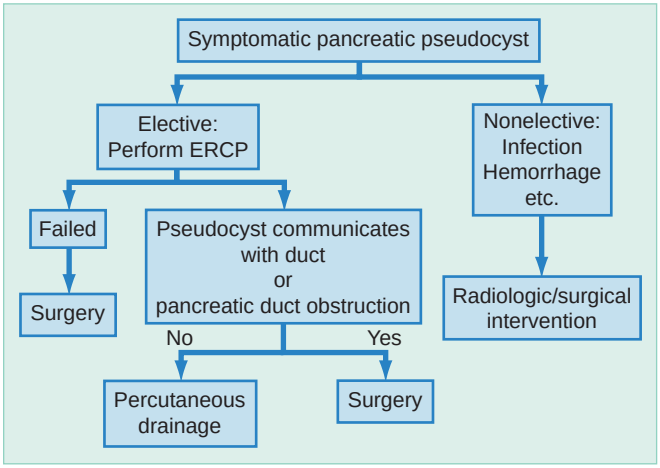

Figure 90–4. Treatment algorithm retrospectively applied to patients with pancreatic pseudocysts. ERCP, endoscopic retrograde cholangiopancreatography. (From Ahearne PM, Baillie JM, Cotton PB, et al: An endoscopic retrograde cholangiopancreatography [ERCP]-based algorithm for the management of pancreatic pseudocysts. Am J Surg 163:111, 1992.)

Natural History

Appropriate management of a patient with a pancreatic pseudocyst requires knowledge of the natural history of these lesions. Before the widespread use of ultrasonography and CT, determination of the natural history of pancreatic pseudocysts relied on other, less accurate diagnostic modalities, such as upper gastrointestinal series, physical examination, and operative and autopsy findings. Data based on these methods indicated that pseudocysts rarely regress spontaneously and that complications occur in up to half of all patients. Therefore, nonoperative, conservative therapy was not advocated in patients with known pancreatic pseudocysts.

A series of studies based on improved imaging techniques increased our understanding of the natural history of pancreatic pseudocysts and led to the era of nonoperative management of the majority of these lesions. In 1979, Bradley and colleagues reported on the natural history of pseudocysts as followed by ultrasonography.[21] Pseudocysts present for less than 6 weeks were found to resolve spontaneously in 40% of cases, although they had a 20% risk for complications. However, pseudocysts documented to be present for longer than 12 weeks did not resolve and were associated with a complication rate of 67%.

In 1990, Yeo et al. reported data from the Johns Hopkins Hospital in Baltimore that evaluated the natural history of pseudocysts by CT scan.[22] Seventy-five patients with pseudocysts were monitored with interval CT scans of the abdomen. All patients with asymptomatic pseudocysts, regardless of size, were initially managed nonoperatively. Operative intervention was performed only for persistent abdominal pain, pseudocyst enlargement, or pseudocyst complications. Nearly half (48%) of these 75 patients were successfully managed nonoperatively. At a 1-year mean follow-up, 60% of patients had complete resolution of the pseudocyst, whereas the remaining 40% had pseudocysts that remained stable or decreased in size. The only significant difference between the two

Table 90–2 Pseudocyst Size Compared with Eventual Management

Pseudocyst Size (cm)	No. of Patients	Operated (%)	Not Operated (%)
0-2	3	33	67
2.1-4	19	37	63
4.1-6	20	45	55
6.1-8	8	63	37
8.1-10	14	64	36
>10	11	73	27

From Yeo CJ, Bastidas JA, Lynch-Nyhan A, et al: The natural history of pancreatic pseudocysts documented by computed tomography. Surg Gynecol Obstet 170:411, 1990, with permission.

Box 90–2 **Management Options for Pancreatic Pseudocysts**

- Observation
- Percutaneous aspiration/drainage
- Endoscopic aspiration/drainage
- Transpapillary endoscopic drainage or stenting
- Operative approaches (open or laparoscopic)
  - Internal drainage
  - External drainage
  - Resection

groups by CT criteria was pseudocyst diameter, with pseudocysts in the nonoperative group averaging 5.8 ± 0.8 cm and pseudocysts in the operative group averaging 7.4 ± 0.6 cm ($P < .05$). Pseudocyst size correlated with the eventual need for surgery: 67% of patients with pseudocysts larger than 6 cm required operative intervention, whereas 40% of patients with pseudocysts 6 cm or smaller required surgical treatment (Table 90–2). Of the patients with pseudocysts larger than 10 cm, 27% were successfully managed nonoperatively.

These data suggested that many patients with pancreatic pseudocysts can be managed nonoperatively with careful clinical and radiologic follow-up, a practice that was confirmed by a study reported from the Mayo Clinic in Rochester, Minnesota.[23] Vitas and Sarr described 68 patients treated nonoperatively, 6 (9%) of whom had a severe complication and only 24 (35%) required operative management. The likelihood of eventual operative intervention did increase with pseudocyst size, although no strict size cutoff could be demonstrated. The success of nonoperative management was independent of the cause of the pseudocyst. The experience of these large centers and others has led to the practice of initial nonoperative management in the majority of patients with pancreatic pseudocysts. According to these data, more than 50% of patients can be expected to require no further intervention. To qualify for conservative, nonoperative management, patients should have no symptoms referable to the pseudocyst, no pseudocyst-related complications, and a stable or decreasing pseudocyst size. Patients who do not meet any of these criteria at follow-up evaluation should undergo appropriate intervention (surgical, endoscopic, or percutaneous).

Management

Patients who do not meet the criteria for conservative, nonoperative management require intervention for the pseudocyst. Associated conditions, such as ductal disruption, biliary obstruction, and chronic pancreatitis, may require concomitant intervention. The recommended management strategies for patients with pancreatic pseudocysts have changed and continue to evolve as more long-term follow-up becomes available for specific procedures. Current management options for a patient with a pseudocyst include percutaneous drainage, endoscopic drainage, operative internal or external drainage, and resection (Box 90–2)

Percutaneous approaches to pseudocyst drainage have been reported since the early 1980s. Although many early studies claimed excellent results, extended follow-up information has revealed that recurrence and failure rates for percutaneous techniques are higher than initially documented. An important distinction should be made between percutaneous aspiration and percutaneous drainage. *Percutaneous aspiration* is aimed at aspirating all pseudocyst fluid at one procedure, without leaving an indwelling drainage catheter. On reviewing the literature to date, less than 50% of patients undergoing this technique will have complete resolution of their pseudocyst.[24] The remaining patients will require repeat aspiration or a second technique (endoscopic or operative drainage). One study attempted to determine which factors could predict successful pseudocyst management with percutaneous aspiration. Patients with pseudocysts in the tail of the pancreas, with pseudocysts less than 100 ml in total volume, and with low intracystic amylase levels appeared to be the best candidates for percutaneous aspiration according to this study of 67 patients.[25] Whereas percutaneous aspiration has largely been supplanted by percutaneous drainage, it is still practiced in some centers, especially as an initial strategy to treat a pseudocyst with minimal intervention.

Percutaneous catheter drainage involves placement of an indwelling catheter into a pseudocyst by the Seldinger technique under ultrasound or CT guidance. The pseudocyst is normally entered through a flank or transgastric approach, and the tract may be dilated to accept a catheter ranging in size from 7 to 14 French. These catheters are typically irrigated or flushed with a

small amount of sterile saline two to three times a day to ensure patency, and they are left to drain into an attached bag by gravity. Contraindications to percutaneous drainage include the presence of significant pancreatic necrosis or solid debris in the pseudocyst, lack of a safe access route, pseudocyst hemorrhage, and complete obstruction of the main pancreatic duct (a controversial contraindication). One review of percutaneous drainage series reported a total recurrence rate of 7%, with 16% of patients counted as treatment failures because of the eventual need for drainage by other techniques.[26] Although most of the studies included in this review consisted of small, selected groups of patients, a large retrospective review from a single center compared patients managed percutaneously, operatively, and expectantly.[24] This review found that only 42% of patients who underwent percutaneous drainage did not require other intervention whereas 88% of patients undergoing operative intervention had a successful outcome. Ninety-three percent of the patients in the expectant group required no intervention. Patients in the expectant group had on average smaller pseudocysts (4 cm versus 7 to 9 cm in the percutaneous and operative groups), but no other significant differences. Although these data conflict with previous series reporting the success of percutaneous drainage, they do emphasize the need for an adequate period of expectant management and careful patient selection before any intervention. The authors rightly called for a prospective study comparing percutaneous and operative intervention in comparable patients. The only prospective study to date has been reported by Lang and colleagues. In this study of severe acute pancreatitis, patients were alternately assigned to either percutaneous or operative drainage.[27] Both procedures had similar rates of success, with 88% of pseudocysts ablated by operative management and 77% through percutaneous drainage. Until this study can be repeated in a more diverse group of patients, percutaneous drainage should continue to be considered an effective method of pseudocyst drainage in selected patients. Furthermore, it is a safe procedure. Most series have reported complication rates of less than 20%, with infection of the drain tract, persistent or recurrent pseudocyst, and pancreaticocutaneous fistula being the most common complications.[24,26] A recent population-based study reviewed outcomes in 14,914 patients treated by surgical or percutaneous drainage. Although selection bias was present in the study, patients treated by percutaneous drainage exhibited increased complications and a longer length of hospital stay. In the modern era of health care cost containment, these issues will certainly play a role in future treatment algorithms.[28]

Endoscopic approaches to the treatment of pseudocysts have also evolved substantially.[29] As with percutaneous methods, long-term follow-up is now becoming available. Current techniques involve the use of flexible upper endoscopy to localize and drain pseudocysts by creating a fistulous tract between the pseudocyst and the stomach or duodenum. This communication is created with electrocautery, and an endoprosthesis is left in place to stent the fistula open. Endoscopic drainage usually requires that the pseudocyst be located in the head or body of the pancreas and that it be well apposed to and bulging into the intestinal lumen. *Endoscopic ultrasound* (EUS) can be used to visualize the pseudocyst and to choose a site for drainage. Risks associated with this procedure include hemorrhage from the gastric or duodenal wall and free perforation. Endoscopic and percutaneous techniques have been combined to localize and drain pseudocysts that are adjacent to the gastric wall but do not bulge into the lumen.[30]

Traditional *transmural endoscopic drainage* has a success rate that compares favorably with that of percutaneous and operative drainage. One literature review by Beckingham and associates summarized a series of pseudocysts drained endoscopically from 1987 to 1997.[31] The review found that approximately 50% of pseudocysts were amenable to transmural drainage based on location and relation to the stomach or duodenum. Successful initial drainage was achieved in 86% of patients, whereas 11% had a recurrence requiring further intervention. About half the recurrences, or 5% of the total group, eventually required operative intervention. Endoscopic cystoduodenostomy was found to be slightly more effective than cystogastrostomy, with fewer recurrences, a finding that most likely relates to the longer patency rates of cystoduodenostomy and the smaller size of these pseudocysts. Complications after both routes of endoscopic drainage were extremely uncommon, with significant bleeding, infection, or perforation occurring in less than 2% of cases. Factors associated with successful endoscopic transmural drainage include location in the head and body of the pancreas, pseudocyst wall thickness less than 1 cm, and pseudocysts secondary to chronic pancreatitis or trauma.[32] Pseudocysts associated with severe necrotizing pancreatitis do not respond well to endoscopic drainage because solid debris obstructs the endoprosthesis.

Experience with the use of *transampullary pancreatic stents* also continues to increase, a development that has applications in the treatment of chronic pancreatitis, pancreatic ductal disruption, pancreatic fistulas, and pseudocysts. Drainage of a pseudocyst via the transampullary (transpapillary) route has been attempted in selected patients with pseudocysts shown to have an obvious communication with the main pancreatic duct by ERCP. Several groups published initial series and described similar techniques and results.[33-35] When possible, stents are placed through the ampulla, along the pancreatic duct, and into the lumen of the pseudocyst. When it is not possible to direct the stent into the pseudocyst, the tip of the stent can be placed as close as possible to the communication between the pancreatic duct and the pseudocyst; one must take care to cross any intervening strictures of the pancreatic duct. Complications associated with this procedure are rare and have included mild postprocedure pancreatitis, bleeding, and abscess formation secondary to stent obstruction. Mean follow-up in the three reported series varied from 15 to 37 months. Some patients underwent traditional transmural endoscopic drainage in addition to transampullary drainage. Initial pseudocyst drainage was successful in 81% to 94%, with 76% to 78% of patients

free of recurrence and requiring no further intervention through the period of follow-up. Clearly, transampullary drainage and pancreatic stenting may play a role in pseudocyst drainage in select patients. Prolonged follow-up of these patients for recurrence and duplication of these excellent results in other centers may lead to more widespread use of this technique.

Although favorable results may be obtained with both percutaneous and endoscopic management of pancreatic pseudocysts, not all patients have pseudocysts that are amenable to these techniques. Furthermore, patients in whom these less invasive techniques fail may require *operative intervention* for definitive treatment of their pseudocyst. Operative intervention also provides the opportunity for biopsy of the pseudocyst wall, a procedure that is necessary to exclude the possibility of a cystic neoplasm. Surgical options include internal drainage, excision of the pseudocyst, and external drainage.

The preferred operative approach for most uncomplicated pseudocysts requiring surgical intervention is *internal drainage*. The three standard options include cystojejunostomy to a Roux-en-Y jejunal limb, cystogastrostomy, and cystoduodenostomy. *Cystojejunostomy* is the most versatile technique of operative drainage and is particularly appropriate when a pseudocyst is located at the base of the transverse mesocolon and is not adherent to the posterior gastric wall (Fig. 90–5). *Cystogastrostomy* is a faster and less technically demanding procedure that is used when the pseudocyst is adherent to the posterior

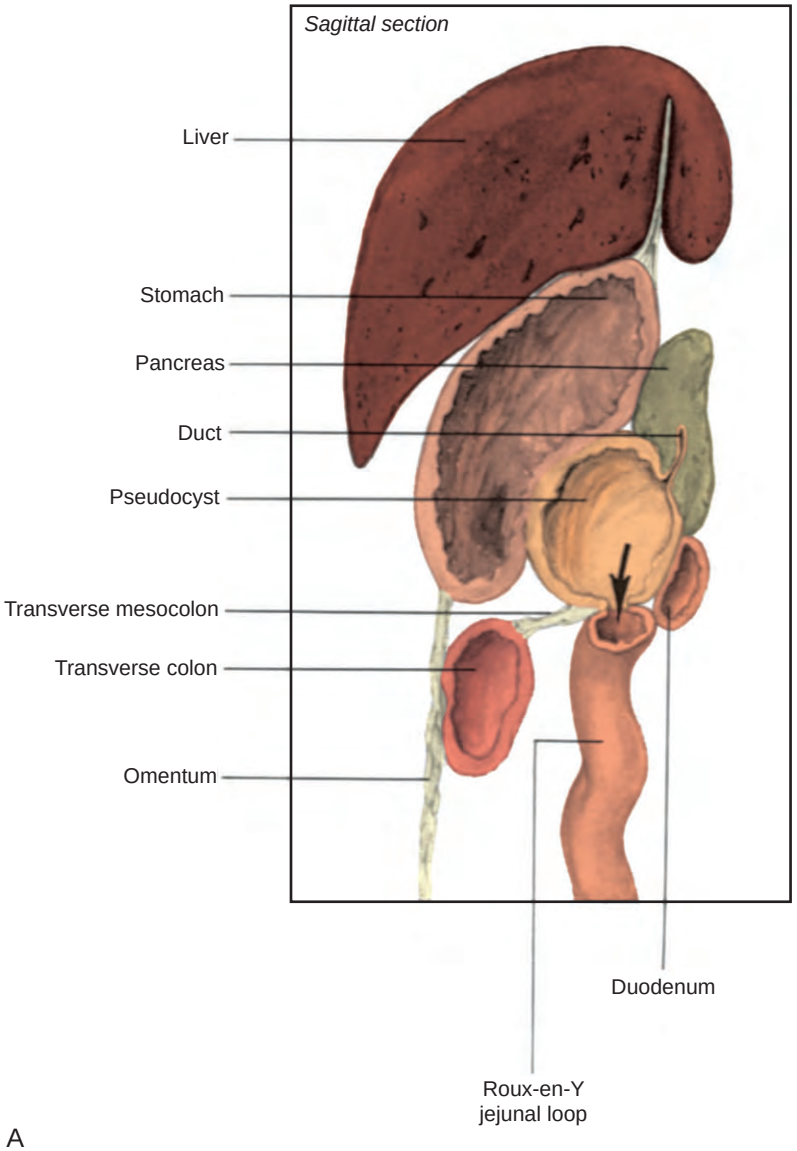

Figure 90–5. Cystojejunostomy for a pancreatic pseudocyst. **A,** Schematic of a sagittal section showing the final anatomy.

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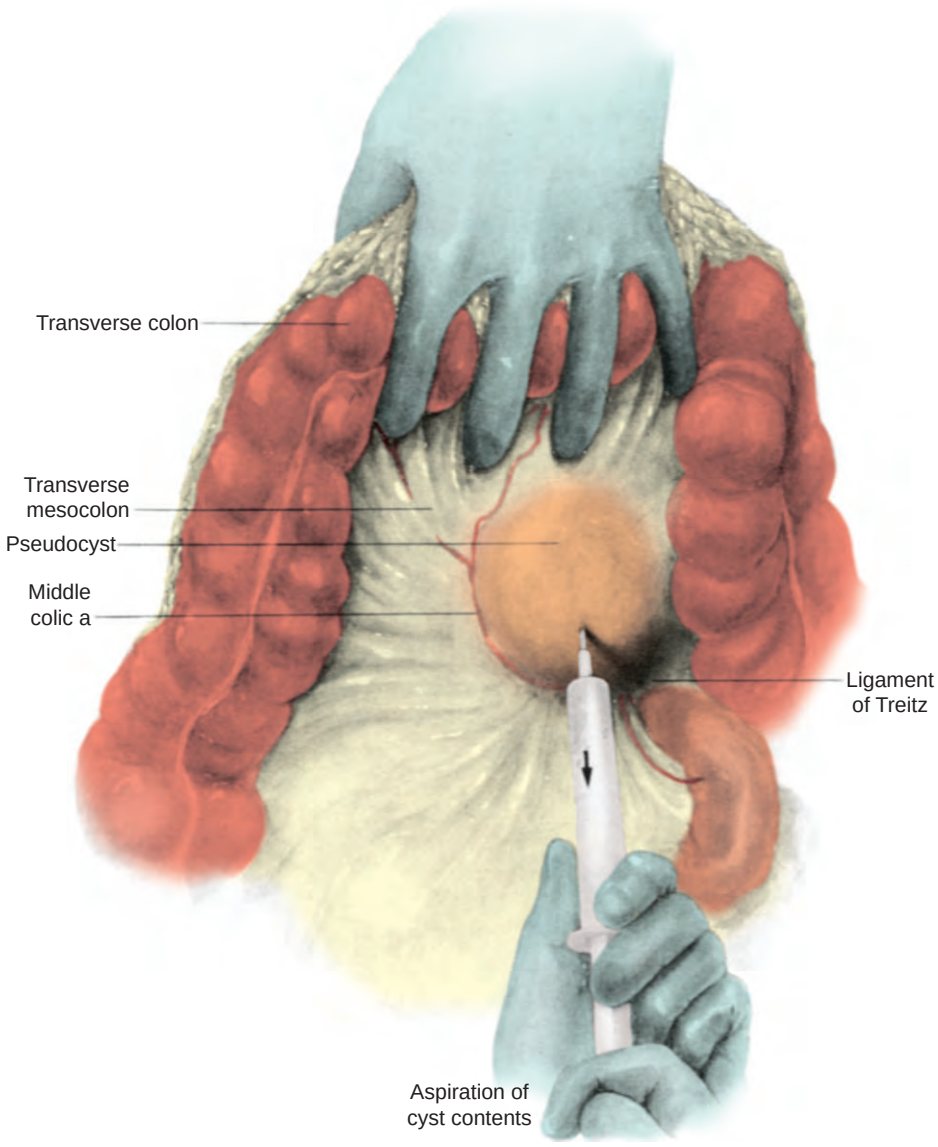
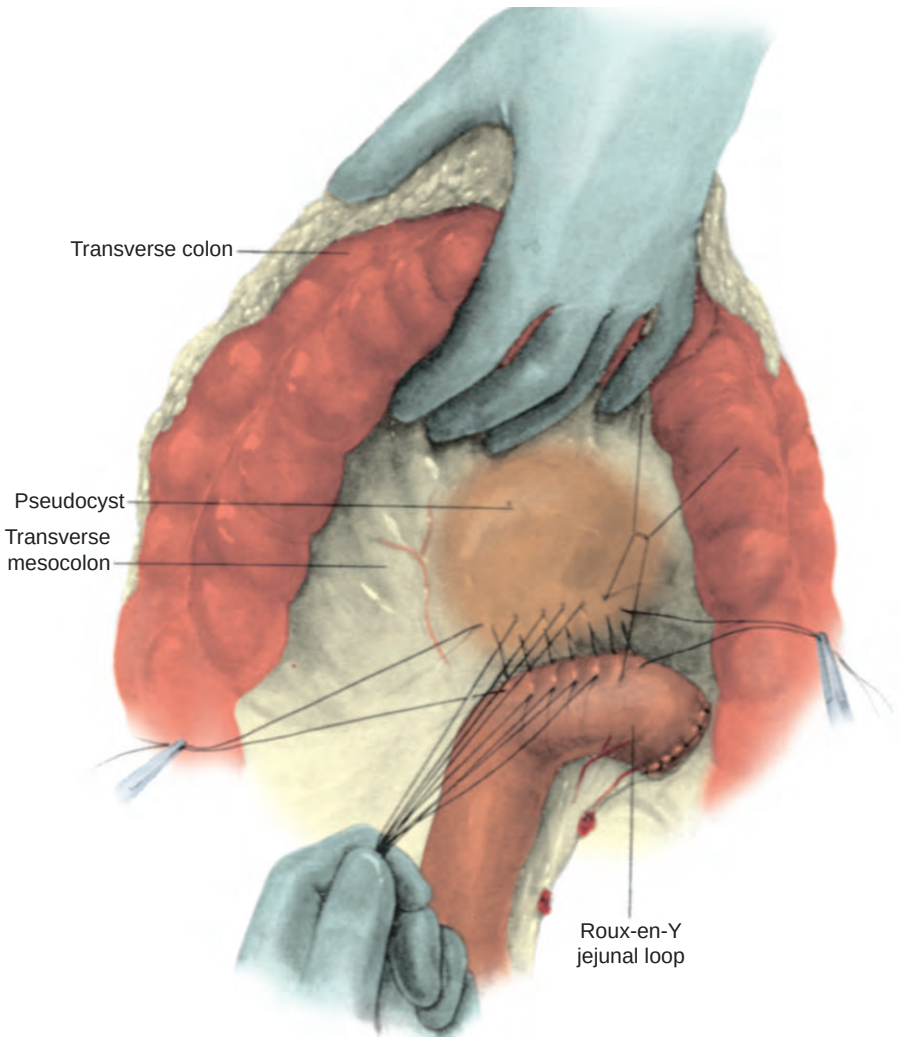


Figure 90–5, cont'd. **B,** Aspiration of a portion of the pseudocyst contents through the transverse mesocolon.



C

Figure 90–5, cont'd. **C,** Creation of the posterior outer layer of the anastomosis with interrupted silk suture.

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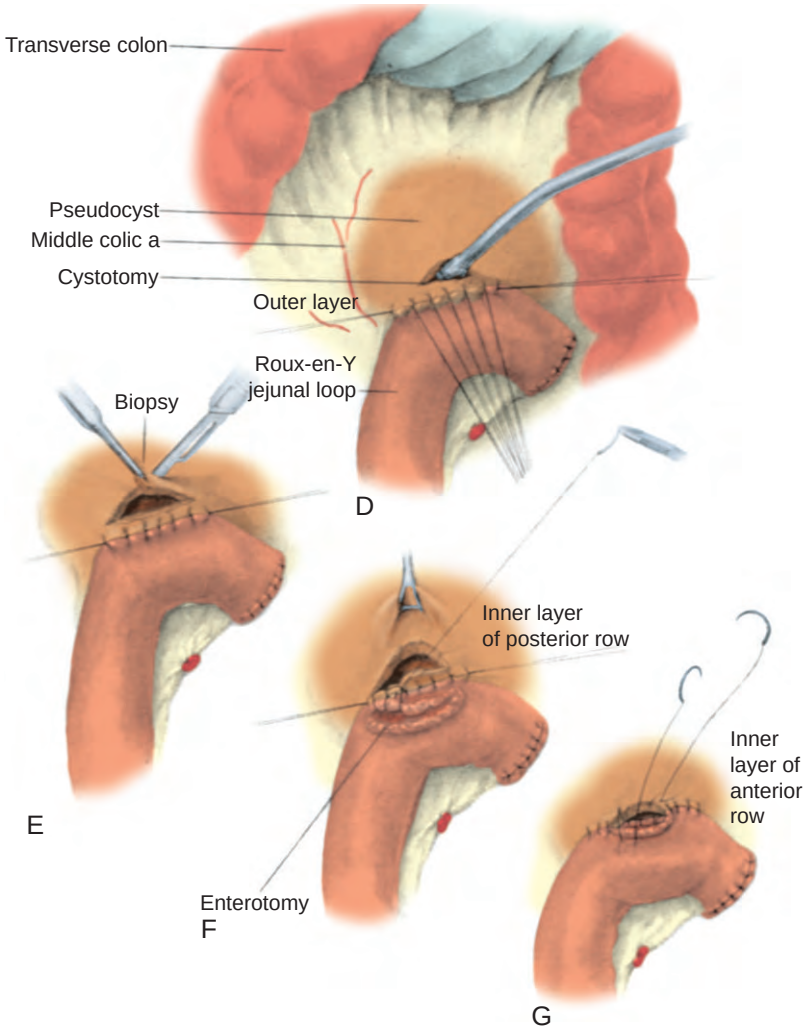
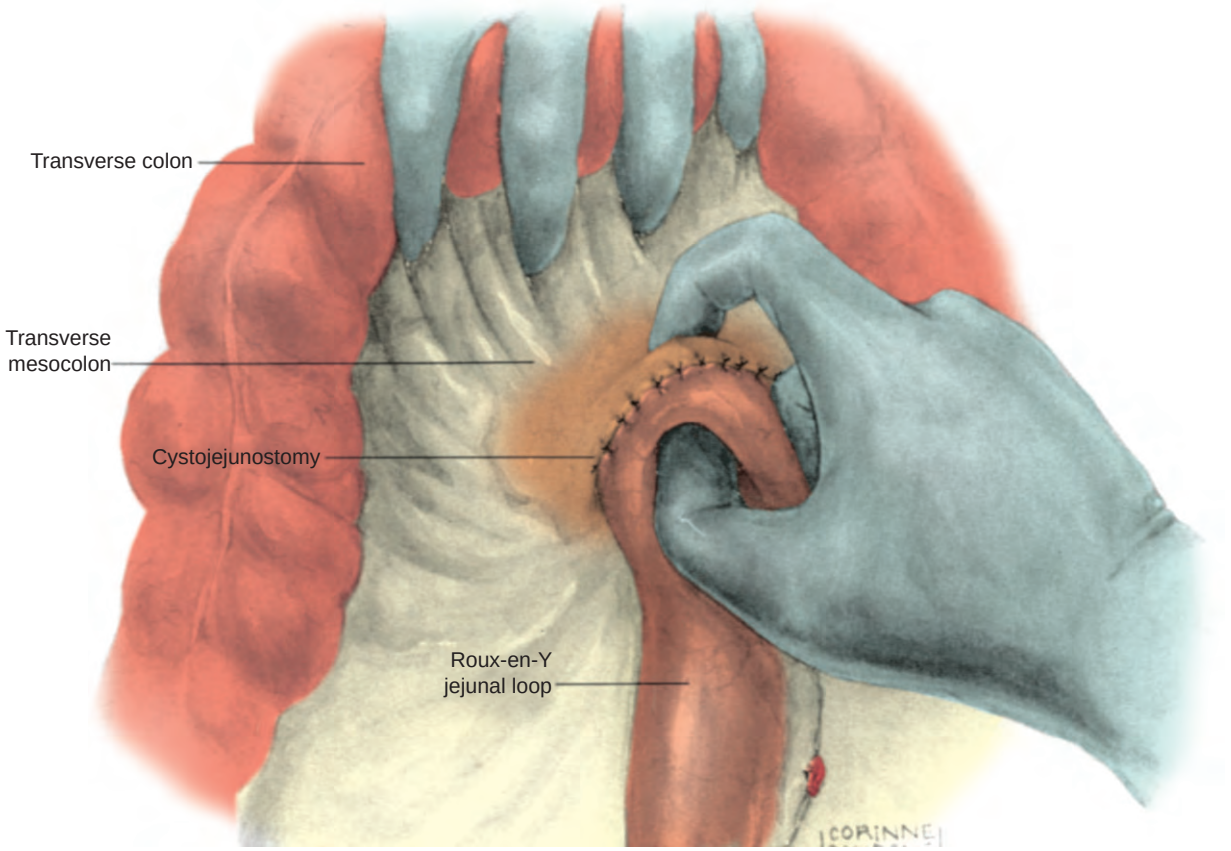


Figure 90–5, cont'd. **D,** Opening into the pseudocyst. **E,** Biopsy of the pseudocyst wall. **F,** Suturing the posterior inner layer of the anastomosis. **G,** Completing the anterior inner row of the anastomosis.



H

Figure 90–5, cont'd. **H,** After closure with an anterior outer layer of interrupted silk, the orifice of the anastomosis between the pseudocyst cavity and the Roux-en-Y jejunal loop is gently palpated. (From Cameron JL: Atlas of Surgery, vol 1. Toronto, BC Decker, 1990, p 373.)

wall of the stomach (Fig. 90–6). The least frequently used technique is *cystoduodenostomy*, which is appropriate only for pseudocysts in the pancreatic head or uncinate process that lie within 1 cm of the duodenal lumen. Cystoduodenostomy is best performed in a fashion similar to that for cystogastrostomy (i.e., by opening the lateral wall of the duodenum and creating a communication between the pseudocyst and the duodenum through a medial duodenotomy). The risk for duodenal leak and subsequent fistula makes cystoduodenostomy the least attractive method of internal drainage and thus reserved for rare use. Cystojejunostomy and cystogastrostomy have comparable morbidity, mortality, and recurrence rates.[26,36] Operative mortality in some series ranges from 0% to 5%. Cystojejunostomy has a slightly lower recurrence rate (7% versus 10%), but it is associated with significantly more blood loss and operative time. Many authors have advocated cystogastrostomy because of these technical advantages. However, Johnson et al. reported life-threatening postoperative complications, as well as two deaths, in patients with large pseudocysts (greater than 15 cm) that were treated by cystogastrostomy.[37] These complications were attributed to incomplete emptying of the pseudocyst, a finding emphasizing that complete dependent drainage is critical in any internal drainage procedure and that any solid material lining a pseudocyst should be thoroughly débrided at the time of internal drainage.

In addition to the conventional open techniques of internal drainage of pancreatic pseudocysts, several centers have performed *laparoscopic drainage procedures.* Large retrogastric pseudocysts can be drained internally by endogastric approaches, as well as by laparoscopic transgastric and laparoscopic extragastric approaches. Each allows for biopsy of the cyst wall and the opportunity for cyst débridement. Laparoscopic cystojejunostomy can be performed in select patients for better dependent drainage. A recent review of laparoscopic internal drainage revealed an operative success rate of 89% with complications occurring in approximately 7% of patients[38,39] (Fig. 90–7).

A small proportion of pseudocysts are best treated by *pancreatic resection.* Most commonly, this operation involves distal pancreatectomy for pseudocysts located in the body or tail of the gland. Peripancreatic and peripseudocyst inflammation can make distal pancreatectomy a technically challenging procedure in this setting. After distal pancreatectomy, a Roux-en-Y

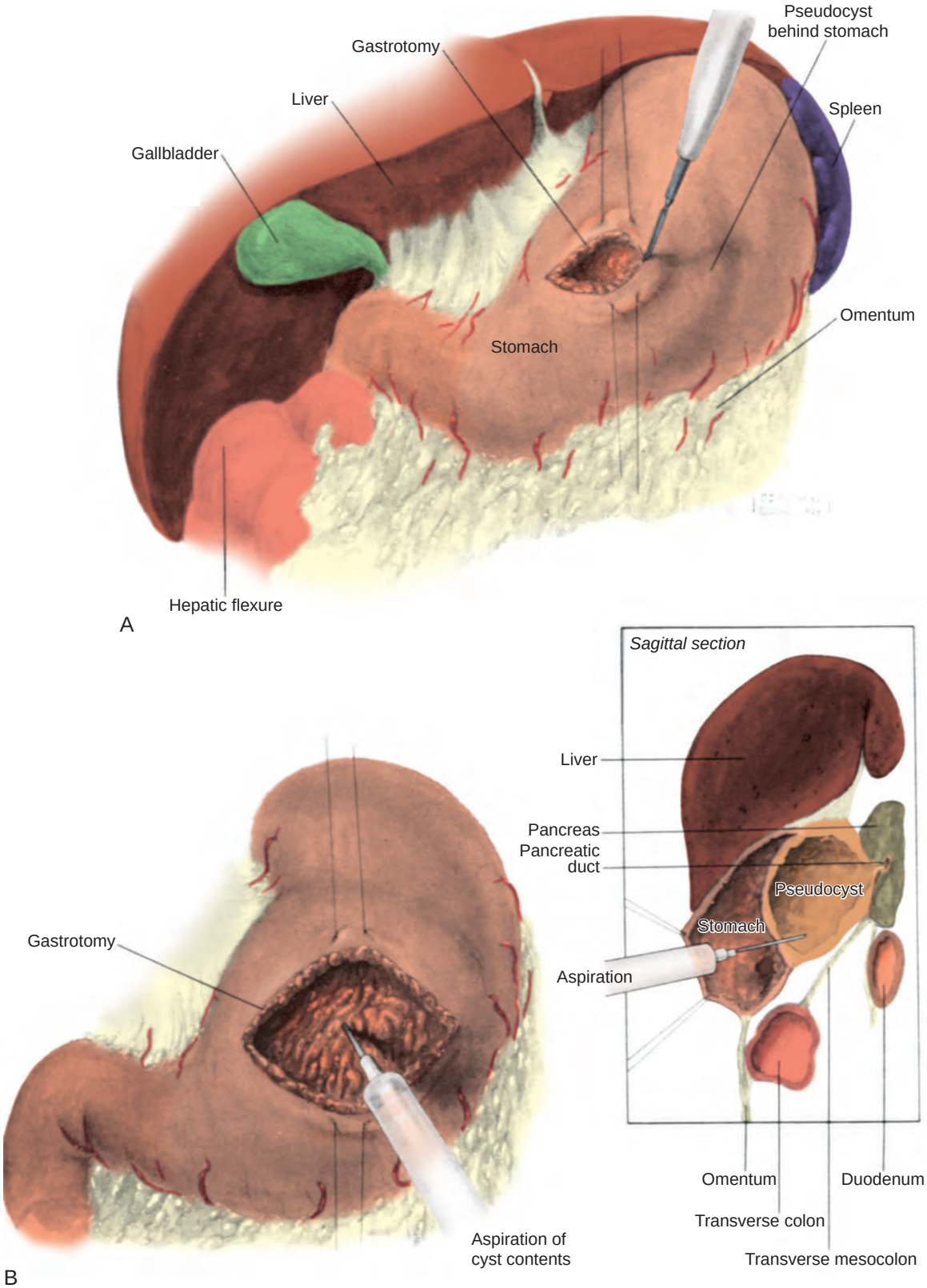


Figure 90–6. Cystogastrostomy for a pancreatic pseudocyst. **A,** An anterior gastrotomy is performed. **B,** Aspiration of a portion of the pseudocyst contents through the posterior gastric wall. The *inset* shows sagittal section anatomy.

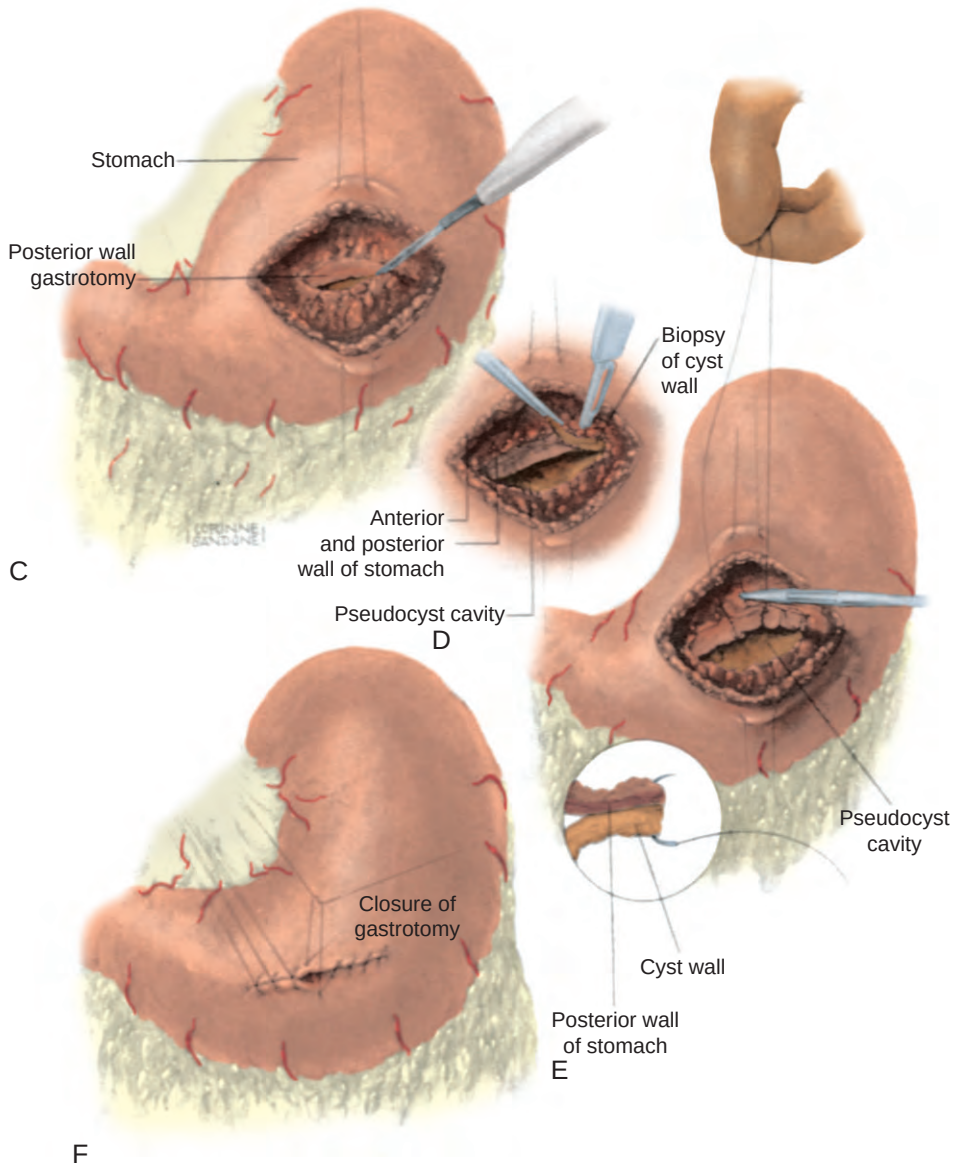


Figure 90–6, cont'd. **C,** A posterior gastrotomy creates a communication between the pseudocyst and the stomach. **D,** Biopsy of the pseudocyst wall. **E,** A running locking suture is used for hemostasis and to maintain apposition of the pseudocyst wall to the posterior wall of the stomach. **F,** Closure of the anterior gastrotomy. (From Cameron JL: Atlas of Surgery, vol 1. Toronto, BC Decker, 1990, p 381.)

pancreaticojejunostomy to the remnant pancreas may be required to decompress an obstructed or abnormal proximal pancreatic duct. In a few patients with symptomatic pseudocysts in the head of the pancreas associated with an inflammatory mass, excisional therapy may require *pancreaticoduodenectomy*. In this case, pylorus-preserving pancreaticoduodenectomy is the procedure of choice. Less commonly performed procedures, such as duodenum-preserving resection of the head of the pancreas, may be applicable in some patients.

External drainage of a pancreatic pseudocyst through an operative approach is indicated when gross infection is found at the time of surgery or when an immature, thin-walled pseudocyst is encountered that will not allow for safe internal drainage. When the pseudocyst is initially aspirated, purulent material is retrieved. At this time, the pseudocyst is isolated from the remaining abdominal viscera with moist packs, and the pseudocyst cavity is opened with the electrocautery device. The contents of the pseudocyst cavity are then completely evacuated, and the cavity is closely inspected to ensure adequate hemostasis. At least one closed-suction drainage catheter is then placed into the cavity and brought out through the abdominal wall. Appropriate antibiotic therapy should be instituted, and follow-up CT scans are obtained to ensure that the pseudocyst is entirely drained. External drainage may lead to the development of pancreaticocutaneous fistulas, most of which heal spontaneously as long as the proximal pancreatic duct is not obstructed. Total parenteral nutrition

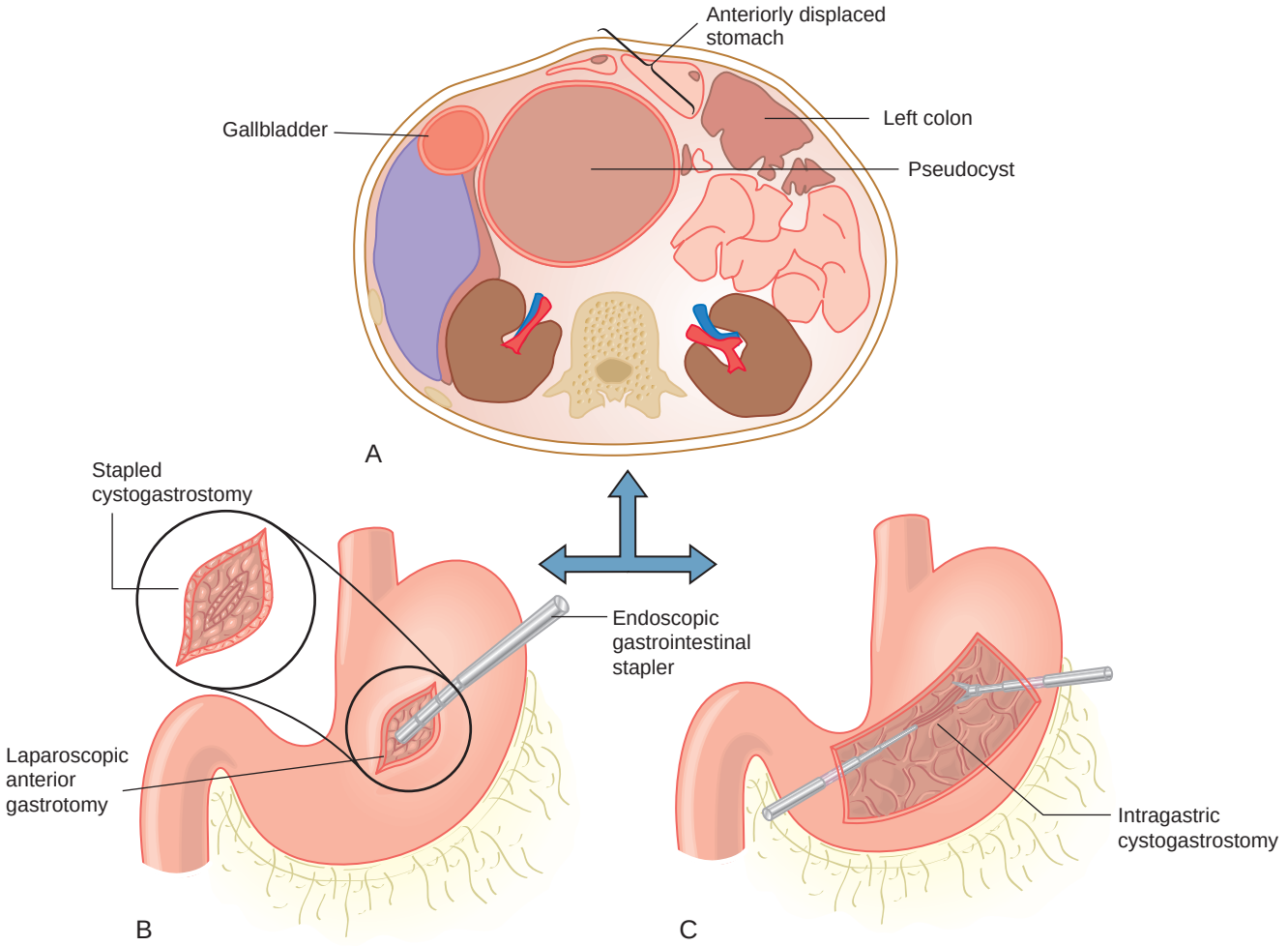


Figure 90–7. Large pancreatic pseudocyst (10 cm in size) located in the body of the pancreas **(A)**. Laparoscopic cystogastrostomy may be performed via anterior gastrotomy **(B)** or intraluminal cystogastrostomy **(C)**. (From Fernandez-Cruz L, Cesar-Borges G, Lopez-Boado MA, et al: Minimally invasive surgery of the pancreas in progress. Langenbecks Arch Surg 390:342, 2005.)

and octreotide therapy (50 to 250 µg subcutaneously three times per day) may assist in closure of a persistent pancreaticocutaneous fistula.[40] Nealon and Walser reported their experience with lateral pancreaticojejunostomy for pseudocysts associated with dilated pancreatic ducts (>7 mm) in patients with chronic pancreatitis. Forty-seven patients were treated by lateral pancreaticojejunostomy alone as pseudocyst management. Long-term pain relief was achieved in 90% of patients, with pseudocyst recurrence being observed in less than 1%.[41] This unique approach requires preoperative pancreatic duct evaluation by ERCP and appears to offer excellent results in select patients.

Complications

A review of the literature reveals that complications develop in up to 40% of patients with untreated pseudocysts, although most series report complication rates of 10% to 20%.[21-23,26,42] The most frequently reported complications include infection, hemorrhage, obstruction or compression of adjacent structures, and rupture.

Infection

An important distinction should be made between pseudocysts that are colonized or contaminated and those that are truly infected. Some pseudocysts contain small amounts of bacteria that are evident on Gram stain or culture, but the fluid from these pseudocysts is not purulent, and patients do not have clinical evidence of infection. However, in a few patients with pseudocysts (less than 5%), true *infection* can develop, as marked by fever, leukocytosis, and increased pain.[22,23] Aspiration of purulent fluid from the pseudocyst confirms the presence of an infection. The most recent Atlanta International Symposium defined these patients as having a *pancreatic abscess* and recommended that use of the term *infected pseudocyst* be avoided.[1] The bacteriology of a pancreatic abscess is highly variable, but up to 60% of these lesions contain gram-negative aerobic and anaerobic organisms.[43]

A pancreatic abscess is one clinical situation in which percutaneous drainage is clearly the treatment of choice. Success rates of up to 85% have been reported in multiple series.[44-46] Retrospective studies have shown similar

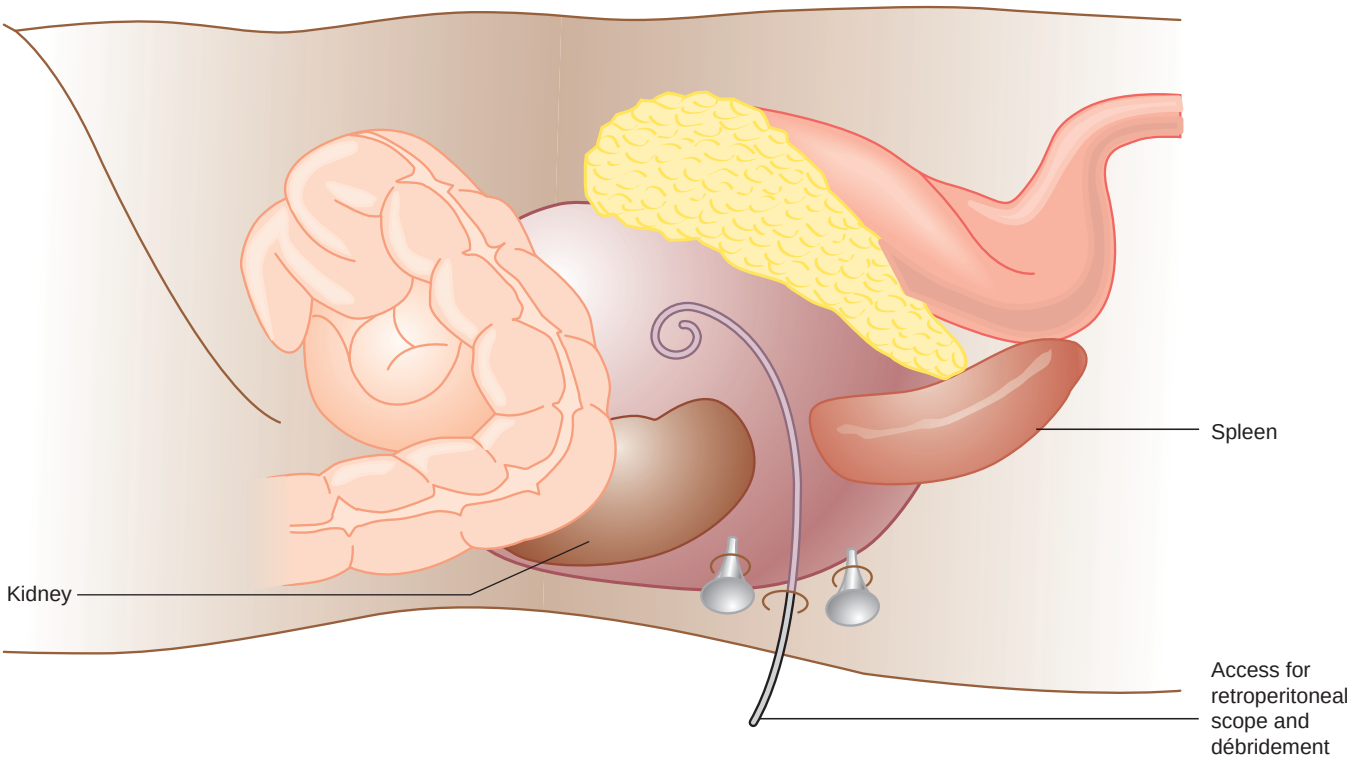


Figure 90–8. Retroperitoneal access to pancreatic necrosis. (From Fernandez-Cruz L, Cesar-Borges G, Lopez-Boado MA, et al: Minimally invasive surgery of the pancreas in progress. Langenbecks Arch Surg 390:342-354, 2005.)

success rates when comparing percutaneous and operative drainage procedures. Furthermore, the mortality rate is lower with percutaneous drainage, and a major open operative procedure is avoided. However, operative external drainage may become necessary in some patients. Percutaneous catheters often do not allow for rapid drainage of thick, purulent material or may not completely address multiloculated collections. Techniques used by interventional radiologists to upsize drainage catheters and to break up loculations are not always successful. In these cases, open operative drainage allows for complete evacuation of all infected material, and external drains may be placed under direct vision. Most recently, percutaneous endoscopic techniques have enabled débridement of necrotic tissue under direct endoscopic vision. Using previous percutaneous drainage tracts, ureteroscopes are advanced into the retroperitoneum and devitalized tissues removed under direct vision while the cavity is continually irrigated. Experience is limited to a few select centers,[47] with promising early results and minimal stress to the patient (Fig. 90–8). Because it is not often possible to predict which pseudocysts or abscesses will be successfully drained percutaneously, patients undergoing percutaneous drainage need to be closely monitored for evidence of resolution, both by clinical parameters and by follow-up imaging techniques. In patients who do not show clinical improvement or who have further progression of their symptoms and in patients who have collections that do not respond to reasonable attempts at percutaneous drainage, operative drainage should be performed.

Hemorrhage

Arterial hemorrhage may occur in up to 10% of patients with pancreatic pseudocysts.[22,23,48] The most common source of pseudocyst-associated bleeding is the splenic artery (up to 50%), with the gastroduodenal and pancreaticoduodenal arteries also accounting for a significant number of hemorrhagic events.[49] Bleeding may also occur from the portal, superior mesenteric, or splenic veins, although such bleeding occurs less commonly. The pathogenesis of arterial hemorrhage seems to follow a predictable sequence, with erosion of the vessel wall leading to pseudoaneurysm formation and eventual rupture. Massive hemorrhage is often preceded by a sentinel hemorrhage. Therefore, any degree of bleeding associated with a pseudocyst should be aggressively investigated. CT scan with intravenous contrast is an appropriate confirmatory test in a stable patient, but angiography may be necessary for diagnosis and provides a mode of treatment.

Initial management of a hemodynamically stable patient is attempted embolization of the pseudoaneurysm or source vessel, a technique performed by most skilled interventional radiologists. Most of these hemorrhages may be effectively controlled by current embolic techniques.[50-53] However, patients in whom embolic therapy fails, who rebleed, or who are hemodynamically unstable require emergency surgical exploration. Control of arterial bleeding may require associated pancreatic resection because oversewing vessels in the setting of the chronic inflammation and

enzymatic erosion associated with pseudocysts is often unsuccessful. When the responsible blood vessel can be effectively ligated, the associated pseudocyst should be externally drained with large-bore catheters. If resection is required, distal pancreatectomy, splenectomy, and splenic artery ligation are the most common procedures. Rarely, emergency pancreaticoduodenectomy may be necessary.

Obstruction

Pancreatic pseudocysts may become symptomatic as a result of the mass effect that they exert on other structures. Although *duodenal obstruction* is the most common manifestation of mechanical obstruction secondary to pseudocyst formation, obstruction of the stomach, esophagus, jejunum, and colon may be identified.[54-58] Obstruction of the mesenteric vasculature and the portal venous system (particularly the splenic vein) may lead to extrahepatic portal hypertension and subsequent splenomegaly and gastric varices.[59] Pseudocysts have also been described as obstructing other retroperitoneal structures, such as the inferior vena cava and the ureters.[60,61] In addition, reports have described pseudocysts with mediastinal and pleural extension impeding cardiac performance secondary to obstruction of preload or increased afterload.[62,63] Congestive heart failure secondary to cardiac compression by a mediastinal pseudocyst has also been reported.[64] Mechanical obstruction of any structure is a relative indication for intervention. At present, no prospective data are available on which to base recommendations for percutaneous, endoscopic, or surgical techniques.

Biliary obstruction secondary to pseudocyst formation is also well described, and it leads to such complications as jaundice, cholangitis, and biliary cirrhosis. Although biliary obstruction may be caused by direct compression of the bile duct by a pseudocyst, most patients have an associated stricture of the intrapancreatic portion of the bile duct that does not improve with pseudocyst drainage alone.[65] Evaluation of any patient with biliary obstruction and a pancreatic pseudocyst requires cholangiography before planning pseudocyst drainage. Treatment of a biliary stricture caused by concomitant chronic pancreatitis may require biliary-enteric bypass, either choledochoduodenostomy or choledochojejunostomy.

Rupture

Spontaneous rupture, the least common complication of pseudocyst formation, occurs in less than 3% of patients, but it may give rise to dramatic clinical manifestations. Spontaneous rupture of a pseudocyst into the peritoneal cavity may lead to severe acute abdominal pain as a result of chemical peritonitis. Such patients are often treated as a surgical emergency, especially those without a known pseudocyst. In patients with a known history of pseudocyst, acute abdominal pain should raise the possibility of free intraperitoneal rupture or rupture into an associated hollow viscus, most commonly a segment of the gastrointestinal tract. Rupture may be secondary to progressive expansion, but it may also indicate the presence of an infected or hemorrhagic pseudocyst. Patients with rupture and sepsis are likely to have either transenteric disruption or an infected pseudocyst that leads to contamination of the peritoneum with enteric bacteria.

Silent rupture of a pseudocyst may also occur. Some pseudocysts are presumed to resolve by rupture or fistulization into an associated portion of the stomach or small bowel, similar to operative or endoscopic enteric drainage. No further therapy is needed in these circumstances. Pseudocysts that rupture silently anteriorly into the peritoneal cavity or posteriorly into the pleural cavity may lead to the development of pancreatic ascites or pancreatic pleural effusion, respectively.[66] Management of these patients is discussed later.

CHRONIC PANCREATITIS

Chronic pancreatitis is a disease with protean clinical manifestations of varying severity, a factor that has made it a difficult disorder to define. The structural changes that have come to be associated with chronic pancreatitis were perhaps first described in 1788, when Cawley noted pancreatic calculi and fibrosis of the gland in a man who had died of malnutrition and diabetes mellitus.[67] However, not until 1963, when the first Symposium of Aetiology and Pathology of Pancreatitis was held in Marseilles, France, was a classification system developed to define chronic pancreatitis and distinguish it from acute pancreatitis.[68] Three of these symposia have now been convened, the last in 1984, and they have produced a definition of chronic pancreatitis based on clinical symptoms (recurrent or persistent abdominal pain), functional pancreatic insufficiency (endocrine and exocrine), and morphologic changes (chronic inflammation, fibrosis, and destruction of exocrine elements).[69,70] Although subsequent groups have attempted to further classify chronic pancreatitis into subgroups based on chronic calcification, chronic obstruction, and chronic inflammation (Rome, 1988), these subgroups are based primarily on histopathologic features that can be difficult to identify in all patients.[71]

Clinical Features

Pain is the initial symptom in up to 95% of patients with chronic pancreatitis and is characteristically described as a dull, boring pain in the epigastrium that may radiate to the left or the right or to the upper lumbar region of the back. The pain is often exacerbated by lying supine, by eating, and by drinking alcohol. Significant weight loss may occur as a result of not only the malabsorption associated with pancreatic exocrine insufficiency but also avoidance of eating secondary to the associated painful attacks. Patients with chronic pancreatitis may describe their pain as episodic or constant. In those with episodic pain, the pain-free intervals may shorten and the painful attacks may become longer as the disease progresses. Up to a third of patients may have spontaneous relief of their pain, an occurrence that usually indicates nearly complete loss of pancreatic exocrine function. However, one

cannot predict which patients will "burn out" and enjoy reprieve from this troublesome symptom. Narcotic addiction is a common problem in patients with chronic pancreatitis and often complicates the management of these patients. Because chronic pancreatitis is often a disease of persons with addictive personalities, such patients may fall easy prey to narcotic dependence.

The pain of chronic pancreatitis appears to be caused by several mechanisms, all of which may have different implications for treatment strategies. *Chronic inflammation* stimulating visceral afferent fibers associated with the sympathetic nervous system is a generally recognized mechanism of pain. Pharmacologic and surgical methods to disrupt transmission along these sympathetic (specifically splanchnic) fibers target this mechanism of pain. *Elevated pressure* in the pancreatic duct and the parenchyma of the gland secondary to precipitation of intraductal proteins and chronic obstruction has also been identified as a potentially correctable source of pancreatic pain. Medical therapy to decrease exocrine secretion and endoscopic and surgical drainage procedures attempt to address this elevated pressure. Evidence of *perineural inflammation* in patients with chronic pancreatitis, an observation first made in 1943 and later revisited, may also play some role in the production of pain.[72,73] Histologic examination of the glands of patients with chronic pancreatitis reveals increased size and density of pancreatic nerves, as well as destruction of the surrounding perineural epithelium by inflammatory cells. This process exposes pancreatic nerves to biologically active molecules, which may generate pain messages (Box 90–3).

Box 90–3 Treatment of Pain in Patients with Chronic Pancreatitis

- Give analgesics (cautiously)
- Discontinue alcohol
- Decrease inflammation
- Suppress secretion
  - Proton pump inhibitor
  - Pancreatic enzymes
  - Octreotide
- Relieve obstruction
  - Stent
  - Lithotripsy
  - Surgery
- Modify neural transmission
  - Medication
  - Nerve block
- Reduce oxidant stress
  - Antioxidants
  - Allopurinol

From Banks P: Epidemiology, natural history, and predictors of disease outcome in acute and chronic pancreatitis. Gastrointest Endosc 56(Suppl):S226-S230, 2002.

Chronic pancreatitis is further characterized by symptoms of *functional impairment* of the pancreas. *Diarrhea* and *steatorrhea* reflect significant exocrine insufficiency, but they do not usually occur until 90% of the secretory capacity of the pancreas is lost. *Diabetes mellitus* develops in about 50% of patients with chronic pancreatitis, and approximately half of these patients require insulin therapy. A few patients have only evidence of pancreatic endocrine or exocrine insufficiency, without pain. This situation is much more common in elderly patients. Rarely, a patient will have one of the complications of chronic pancreatitis, such as biliary or gastroduodenal obstruction, without any painful symptoms. However, such a finding is rare, and chronic pancreatitis should be diagnosed only after a careful evaluation for underlying malignant disease has been performed.

Complications

The most common reason for referral of a patient with chronic pancreatitis to a surgeon is refractory pain, specifically, pain that is not partially attributable to one of the common complications of chronic pancreatitis, such as a pseudocyst, biliary obstruction, or gastroduodenal obstruction. Patients in this group may have a pancreatic ductal abnormality that can respond favorably to operative treatment through either ductal drainage or resection. Other patients may benefit from more recently advocated techniques such as surgical denervation or duodenum-preserving pancreatic head resection. Surgical treatment of chronic pancreatitis is discussed in Chapter 88.

Although treatment of chronic pancreatitis is multidisciplinary, surgeons often play a primary role in managing the complications of this disease. Some of the common complications of chronic pancreatitis and their management are discussed in the following sections.

Common Bile Duct Obstruction

Although pancreatic inflammation and edema may cause transient partial obstruction of the common bile duct in patients with acute pancreatitis, chronic pancreatitis may lead to a fixed stricture of the intrapancreatic portion of the common bile duct (Fig. 90–9). Early recognition of this problem is essential to prevent the development of cholestasis, cholangitis, and secondary biliary cirrhosis. Furthermore, prompt investigation of biliary obstruction in patients with chronic pancreatitis may allow differentiation from periampullary malignant disease.

Common bile duct strictures caused by the characteristic inflammation and fibrosis of chronic pancreatitis in the head of the pancreas typically have a long, smooth appearance. These strictures most often involve 2 to 4 cm of the intrapancreatic common bile duct, with associated dilatation of the cephalad biliary tree. Biliary obstruction may also be associated with pancreatic pseudocysts located in the head of the gland (Fig. 90–10). Rarely, pseudocysts cause extrinsic compression of the bile duct that resolves with decompression of the pseudocyst. More commonly, patients with pseudocysts have an associated fixed fibrotic stricture of the common bile duct

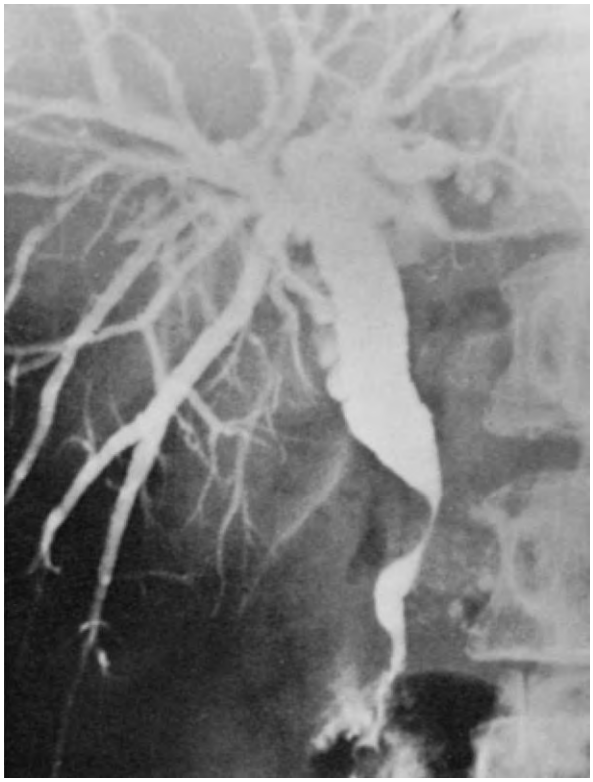


Figure 90–9. Cholangiogram of a patient with a long distal common bile stricture caused by chronic pancreatitis.

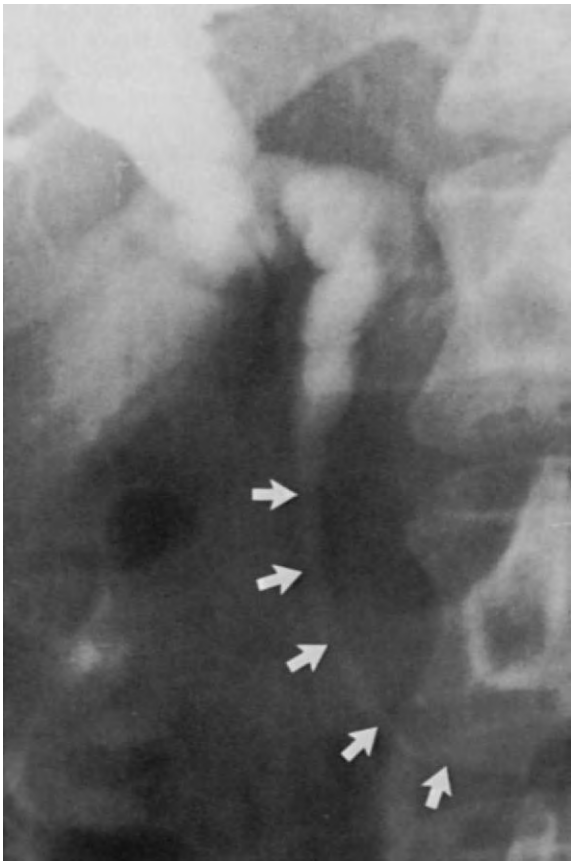


Figure 90–10. Cholangiogram of a patient with a pancreatic pseudocyst showing extrinsic compression of the common bile duct. *Arrows* indicate a narrowed distal common bile duct.

that requires a separate biliary drainage procedure. Warshaw and Rattner reviewed 21 patients with obstructive jaundice associated with a pancreatic pseudocyst.[65] Ten of these patients required biliary decompression because jaundice persisted after drainage of the pseudocyst. In a prospective study, Nealon and colleagues used ERCP to evaluate 44 consecutive patients with pancreatic pseudocysts before operative management.[19] In each of 12 patients with chronic pancreatitis and common bile duct dilatation, a fixed stricture of the intrapancreatic bile duct was identified that required a biliary drainage procedure in addition to management of the pseudocyst.

Historically, common bile duct strictures have been thought to occur in 3% to 29% of patients with chronic alcoholic pancreatitis.[74-77] However, as cholangiography has become more frequently used in patients with chronic pancreatitis, the incidence of common bile duct stricture appears to be even higher than previously thought. ERCP was used by Beger et al. to evaluate 258 patients with chronic pancreatitis; 129 (50%) of these patients were found to have a common bile duct stricture, whereas only 14% were clinically jaundiced at the time of the study.[78] In a similar study, 79 patients with moderately severe chronic pancreatitis underwent ERCP; 36 (46%) of these patients had evidence of stenosis of the intrapancreatic common bile duct.[79]

Common bile duct stricture in chronic pancreatitis may be manifested clinically in a variety of ways. As mentioned earlier, many asymptomatic bile duct stenoses may be identified by cholangiography performed for other indications. Bile duct stricture may also be suggested by laboratory abnormalities in the absence of clinical jaundice. Persistent elevation of serum alkaline phosphatase appears to be the most common abnormal laboratory finding and occurs in up to 80% of patients.[80] Associated elevations in γ-glutamyl transpeptidase can also be observed. At times, the serum bilirubin concentration may be minimally or moderately elevated and is often characterized by a rising and falling pattern. The disproportionate elevation of alkaline phosphatase relative to serum bilirubin is compatible with benign obstruction of the common bile duct in patients with chronic pancreatitis.[81] Malignant obstruction of the bile duct is more commonly manifested as marked, persistent elevation of serum bilirubin. Any elevation of serum bilirubin and alkaline phosphatase in a patient with chronic pancreatitis should suggest the presence of a common bile duct stricture.[82] Even though Beger and colleagues found laboratory abnormalities in only half the patients with ERCP-confirmed common bile duct stricture, nearly all these patients had a history of a previous episode of jaundice.[78] Although patients with chronic pancreatitis may have multiple reasons for the development of jaundice (cirrhosis, hepatitis), a history of intermittent jaundice is typical in patients with a benign common bile duct stricture. A bile duct stricture may also be associated with

abdominal pain, which may be difficult to distinguish from the typical pain of chronic pancreatitis. The initial assessment of a patient with chronic pancreatitis and refractory pain should include evaluation of the biliary tree, particularly if any of the laboratory abnormalities mentioned earlier are present. Failure to consider a common bile duct stricture may lead to failure to relieve a patient's pain despite other interventions for chronic pancreatitis. However, operative intervention limited to the biliary tract in a patient with chronic pancreatitis rarely relieves the pain completely. For example, Stabile and associates obtained adequate pain relief in only 7 of 38 patients who underwent biliary tract decompression alone.[83]

Cholangitis, a potentially life-threatening complication, occurs in approximately 10% of patients with common bile duct strictures secondary to chronic pancreatitis.[80,84] Bile cultures reveal bacterial growth, most likely gram-negative bacilli, in more than half the patients with bile duct strictures.[84,85] Nevertheless, the incidence of cholangitis remains low. The occurrence of cholangitis should lead to a search for a bile duct stricture because cholangitis is uncommon in patients with chronic pancreatitis without a biliary stricture.

Absolute indications for intervention in patients with common bile duct strictures and chronic pancreatitis include refractory pain, persistent jaundice, and cholangitis. Other conditions that may cause jaundice in a patient with chronic pancreatitis, such as cirrhosis, hepatitis, and choledocholithiasis, should be ruled out before the clinician commits to a treatment plan. However, the most important and often difficult differentiation is to determine whether the common bile duct obstruction is being caused by chronic pancreatitis or by a periampullary malignant tumor. Several important clinical features may suggest one condition or the other in the absence of a tissue diagnosis, which may be impossible to obtain without exploration and resection. Wapnick and colleagues found that patients with chronic pancreatitis as the cause of biliary obstruction were significantly younger (average age of 47 versus 62 years) and had a lower serum bilirubin level (5.6 ± 1.5 mg/dl versus 18.5 ± 2.1 mg/dl) than did patients with obstruction secondary to periampullary carcinoma.[86] Patients with obstruction resulting from chronic pancreatitis also tended to have fluctuations in their serum bilirubin level, whereas patients with carcinoma had a persistent rise in the bilirubin level until biliary decompression was accomplished. The combination of historical observations, laboratory findings, and radiologic studies, as discussed later, can differentiate some cases of benign stricture from carcinoma.

The initial imaging study in any patient with suspected biliary tract obstruction is either abdominal ultrasound or CT scan. Although both ultrasound and CT are suitable initial tests, spiral CT scan is the preferred test unless gallstone disease is strongly suspected. CT scan allows better visualization of the pancreas and thus makes it the most useful initial test in a patient with obstructive jaundice. A well-defined mass in the head of the pancreas usually indicates malignant disease. However, some patients with periampullary malignant disease do not have a defined mass. Furthermore, many patients with chronic pancreatitis have diffuse enlargement or inflammation of the head of the pancreas. Pseudocysts may also be well visualized with CT. More support has arisen for the use of MRI in the evaluation of these patients. Dynamic MRI with gadolinium enhancement has been advocated as a good method to differentiate between chronic pancreatitis and pancreatic carcinoma. However, data have not shown any clear distinguishing characteristics between enhancement of the two pathologic entities.[87] At present, MRI appears to have no advantage over CT.

Cholangiography is the definitive study for visualizing the anatomy of the biliary system. Both ERCP and percutaneous transhepatic cholangiography can be useful, although ERCP is preferred. ERCP offers the advantage of visualization of the pancreatic ductal system, which is necessary for planning operative therapy in patients with chronic pancreatitis, and direct visualization of the ampulla of Vater, which allows for biopsy if a mass is visible. Additionally, ERCP is less invasive. Both methods allow decompression of an obstructed biliary tree. Although bile duct strictures in patients with chronic pancreatitis often have a long, smooth, gradually tapered appearance, pancreatic carcinoma frequently causes an abrupt cutoff or tumor meniscus at the genu of the common bile duct. Tumors of the distal common bile duct are most often accompanied by a stricture just above the ampulla, which is not as long as the stricture associated with chronic pancreatitis. Ampullary and duodenal malignant tumors most often cause obstruction at the ampulla, the most distal portion of the bile duct. These latter tumors can be visualized with endoscopy during ERCP, and biopsy is therefore possible. MRCP has gained popularity as a noninvasive method of cholangiography.[10] Although it allows for neither decompression of an obstructed biliary system nor tissue biopsy, MRCP appears to correlate well with ERCP in defining ductal anatomy.[88-92] MRCP was studied specifically in patients with pancreatitis by Sica and colleagues.[93] They found MRCP to have 86% accuracy in characterizing pancreatic ductal anatomy relative to ERCP, with 94% sensitivity in detection of biliary anatomy, results that correspond to earlier studies. Ductal segments not detected by MRCP were defined on ERCP as normal or only slightly dilated or narrowed. Furthermore, MRCP visualized 15 of the 19 obstructed pancreatic ductal segments not seen on ERCP, and all these segments were abnormal. MRCP may play a future role in the diagnosis and planning of operative intervention for biliary obstruction in chronic pancreatitis.

Patients with chronic pancreatitis and an asymptomatic bile duct stricture, often detected during investigation of an elevated serum alkaline phosphatase level, also present a controversy in terms of indications for operative intervention. *Biliary bypass* was first suggested as the appropriate management of these patients by Warshaw and colleagues, who identified changes of secondary biliary cirrhosis in liver biopsy specimens obtained from three of four patients with long-standing asymptomatic biliary obstruction secondary to chronic pancreatitis.[94]

Afroudakis and Kaplowitz supported this finding in a series of liver biopsy specimens obtained from 24 patients who were asymptomatic and anicteric.[74] Nearly 30% of these patients had evidence of secondary biliary cirrhosis, a finding that the authors used to justify their suggestion that operative biliary decompression should be considered in any patient with a documented persistent bile duct stricture. More recently, other groups have advocated reserving operative intervention for patients with acute cholangitis, biliary cirrhosis, or persistent jaundice because their series failed to demonstrate such a high rate of biliary cirrhosis in asymptomatic patients.[76,80] Stahl and colleagues compared 20 patients with bile duct strictures who were observed without surgery with 18 similar patients who underwent operative biliary drainage.[80] The nonoperative group had no increased morbidity over an average period of 3.8 years. In a similar cohort of 648 patients monitored in South Africa by Huizinga and Baker, no cases of biliary cirrhosis were detected in patients undergoing liver biopsy for long-standing bile duct obstruction.[95]

Although the use of endoscopic and percutaneous transhepatic *stenting* procedures for the management of malignant biliary obstruction is well established and accepted, these nonoperative techniques have not been proved effective in the long-term management of benign biliary stricture. In reported series, the relapse rate after endoscopic biliary drainage is high, and surgical biliary-enteric drainage is often necessary.[95-98] Endoscopic or percutaneous techniques may be performed to relieve obstruction in patients with acute cholangitis or be used as a temporizing procedure to allow a patient time to maximize nutritional status before surgical intervention. Some series have reported traditional endoscopic stents to be patent for approximately 3 months, whereas percutaneous transhepatic biliary drains last an average of 2 months before they require exchange for obstruction.[98] Metallic biliary stents have been advocated as a possible long-term alternative in patients with chronic pancreatitis who refuse operative therapy or have significant contraindications to operative intervention.[99] Current metallic stents have an expected patency of only 8 months; thus, further improvement in these "long-term" stents will be required before they can be a durable alternative to surgical therapy.

Patients who undergo surgical procedures for biliary obstruction secondary to chronic pancreatitis are treated by either choledochoduodenostomy or Roux-en-Y choledochojejunostomy. *Choledochoduodenostomy* is preferred in many centers because it maintains the normal flow of bile, can be technically easier to perform, and leaves the jejunum free for subsequent procedures to drain the pancreatic duct. *Choledochojejunostomy*, though thought to be more technically demanding, can also be performed safely and may be necessary when choledochoduodenostomy cannot be safely performed or when the diameter of the common bile duct above the stricture is not 2 cm. In a series of 64 patients undergoing choledochojejunostomy for benign bile duct strictures Nealon and Urrutia reported no operative mortality and excellent clinical and biochemical results at more than 4 years of follow-up.[100] Transduodenal sphincteroplasty and cholecystojejunostomy are not adequate or durable drainage procedures for bile duct strictures secondary to chronic pancreatitis, and they should not be performed.

In many cases, *biliary-enteric bypass* must be accompanied by *pancreatic ductal drainage* to address refractory pain secondary to common bile duct strictures. A *side-to-side longitudinal pancreaticojejunostomy* is the most common associated procedure. If choledochojejunostomy is the biliary bypass procedure performed, a separate limb of jejunum is often used for the pancreatic-enteric anastomosis to prevent continuous bathing of the pancreaticojejunostomy with bile. Any patient undergoing operative decompression of a dilated pancreatic duct who has an associated common bile duct stricture should undergo decompression of both systems. However, performing biliary bypass as a prophylactic procedure (in patients without ductal dilatation who are undergoing pancreaticojejunostomy for chronic pain) is not necessary.[101]

Duodenal and Gastric Outlet Obstruction

Inflammatory diseases of the pancreas are often associated with transient gastroduodenal obstruction. Patients with acute pancreatitis, necrotizing pancreatitis, and pancreatic pseudocysts commonly have symptoms of nausea, emesis, and intolerance of oral intake. In these settings, evidence of duodenal stenosis may be documented by an upper gastrointestinal series or upper endoscopy. Fortunately, these symptoms are often self-limited, and the obstruction resolves as the inflammatory process improves or the space-occupying lesion (pseudocyst, pancreatic abscess) is decompressed. Bradley and Clements reported that up to 25% of patients hospitalized for acute pancreatitis have such a functional duodenal obstruction.[102]

Duodenal or *gastric outlet obstruction* rarely develops in patients with chronic pancreatitis (Fig. 90–11). Such obstruction is far less common than common bile duct or pancreatic duct obstruction. Gastroduodenal obstruction is reported to occur in only 1% of all patients with chronic pancreatitis.[54,102] However, gastroduodenal obstruction is more common in patients with severe chronic pancreatitis. Three series showed that in the subgroup of patients who require operative intervention for chronic pancreatitis, gastroduodenal obstruction may occur in 10% to 25% of such patients. Prinz and colleagues reported that in hospitalized patients undergoing operative decompression of the pancreatic duct, 8 of 55 (15%) required operative therapy for gastric outlet obstruction.[103] In the group of patients with common bile duct stricture, 25% also had coexistent gastroduodenal obstruction. Warshaw reported a 25% incidence of gastroduodenal obstruction associated with common bile duct stricture secondary to severe chronic pancreatitis.[104] Sugerman and coworkers reported on a similar group of patients with severe chronic pancreatitis that had failed to resolve with nonoperative management.[105] In this group of 28 patients, 14% required a gastrojejunostomy at the time of their procedure for chronic pancreatitis.

Like gastroduodenal obstruction in more acute inflammatory diseases of the pancreas, gastroduodenal

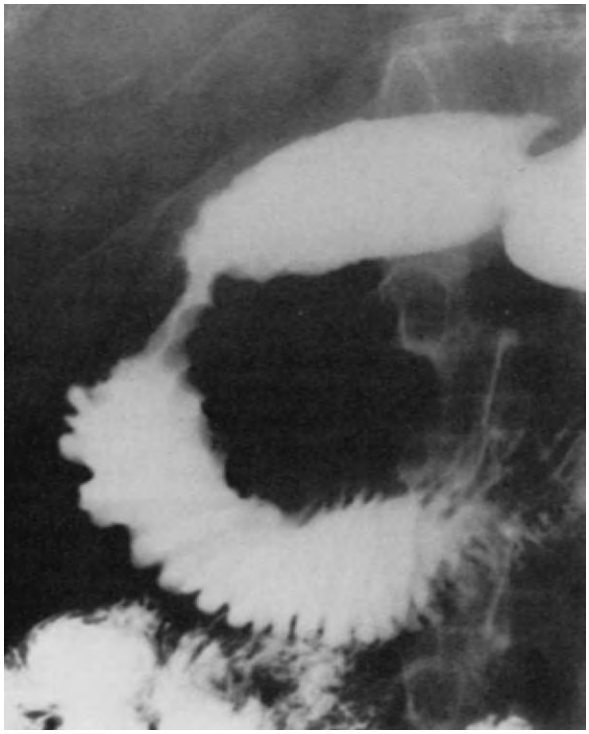


Figure 90–11. Upper gastrointestinal series in a patient with chronic pancreatitis showing a stricture at the junction of the first and second portions of the duodenum.

obstruction in chronic pancreatitis can be episodic and self-limited. These periods of obstruction often occur during exacerbations of the patient's chronic pancreatitis because inflammation and edema in the wall of the duodenum prevent normal peristalsis. Many of these patients already have chronic fibrotic changes in the duodenum that limit normal motility, and acute inflammation effectively limits the passage of enteric contents through the duodenum. These episodes generally resolve spontaneously. Persistent gastroduodenal obstruction that lasts longer than 4 weeks is an indication for further intervention.

Patients with chronic pancreatitis and gastroduodenal obstruction should be evaluated by both upper endoscopy and upper gastrointestinal series. Upper gastrointestinal series with barium may demonstrate complete gastric outlet obstruction or, more commonly, a long, fixed narrowing of the duodenum, which is a classic finding in patients with duodenal stricture secondary to chronic pancreatitis. Endoscopy is necessary to rule out other conditions that may mimic the findings of chronic pancreatitis. Peptic ulcer disease and periampullary malignant disease need to be considered, and they may be diagnosed and confirmed by biopsy performed endoscopically. CT scan should also be performed to evaluate for a pancreatic mass or pseudocyst. ERCP may be important to evaluate the pancreatic and biliary ductal anatomy. Alternatively, such evaluation may also be accomplished by MRCP because the anatomy of many of these patients does not permit intubation of the second portion of the duodenum, which is needed to accomplish ERCP.

An initial period of nonoperative management may be attempted in patients with gastroduodenal obstruction. Bowel rest, nasogastric decompression, and parenteral nutrition may allow for improvement in pancreatic inflammation and resolution of the obstruction. Persistent or recurrent obstruction after a trial of nonoperative management is an indication for surgical therapy, specifically, gastrojejunostomy. This procedure may be performed in conjunction with a biliary or pancreatic drainage procedure in patients with advanced chronic pancreatitis. In patients with chronic pancreatitis primarily involving the head of the pancreas, pancreaticoduodenectomy may be the preferred procedure to relieve pain and obstruction.

Pancreatic Ductal Disruption

Pancreatic ductal disruption is an event leading to complications of chronic pancreatitis. Ductal disruption is most often described as creating an internal pancreatic fistula (as in pancreatic ascites, pancreatic pleural effusion, and pancreaticoenteric fistula) or an external pancreatic fistula that communicates with the skin. Pseudocysts of the pancreas are also the result of disruptions of the pancreatic duct, as discussed earlier.

Pancreatic Ascites and Pleural Effusions The first report of *pancreatic ascites* occurred in 1953,[106] and it was followed by individual case reports of other patients over the subsequent 15 years. In 1967, Cameron and colleagues published the first review of 13 patients with pancreatic ascites.[107] The review established diagnostic criteria for pancreatic ascites and was followed by larger series of patients because the diagnosis was made more frequently. To date, more than 300 reports of pancreatic ascites have been published in the world literature. Parekh and Segal reported on 23 patients with pancreatic ascites or pleural effusions in 1992 and described factors that helped determine which patients would be likely to respond to conservative therapy.[108] Sankaran and Walt described 26 patients with pancreatic ascites and noted that pancreatic ascites occurred in 15% of patients with pseudocysts at their institution.[109] Lipsett and Cameron reported the Johns Hopkins Hospital experience with internal pancreatic fistulas over a 27-year period.[110] Fifty patients were included in the series, including 34 with pancreatic ascites and 7 with pancreatic ascites and pleural effusion.

Pancreatic pleural effusions have been described more recently. In the initial review of internal fistulas from the Johns Hopkins Hospital in 1967, five patients with pleural effusions were reported.[107] A subsequent update described 16 patients with pancreatic pleural effusions.[110] Most authors argue that pancreatic pleural effusions are often unrecognized because the effusions may be attributed to associated cardiac, pulmonary, or hepatic disease without fluid sampling for diagnostic studies. In fact, patients with pancreatic effusions often do not have symptoms of pancreatitis but instead have pulmonary symptoms and respiratory compromise.

The diagnostic criteria for pancreatic ascites and effusion were initially proposed by Cameron et al. in 1967.[107]

Correct diagnosis requires sampling of the fluid and assessment of amylase and albumin levels. Amylase levels are elevated relative to serum values in all patients, and fluid albumin levels are elevated to levels of 3 g/100 ml or more. Serum amylase levels may also be elevated in up to 90% of patients with pancreatic effusions or ascites, a finding that may reflect absorption of amylase from the pleural and peritoneal surfaces rather than active pancreatic inflammation.[111] Patients with markedly depressed serum albumin levels secondary to malnutrition may have fluid albumin levels less than 3 g/100 ml. The fluid of pancreatic effusion or ascites is most often clear or straw colored, but it may appear thick, chylous, or even bloody. The differential diagnosis of these internal pancreatic fistulas often includes ascites secondary to cirrhosis and malignant ascites or effusion. Patients with cirrhotic ascites generally have fluid albumin levels less than 1.5 g/100 ml and most often have low amylase levels. Distinguishing pancreatic effusion or ascites from malignant fluid may be difficult cytologically because pancreatic enzymes appear to be capable of producing metaplastic changes in serosal cells and therefore of creating false-positive results.

The pathogenesis of both pancreatic pleural effusion and ascites involves a disruption of the pancreatic duct and creation of an internal fistula into the retroperitoneum,[111] which then tracks posteriorly into the pleural space (Fig. 90–12) or anteriorly into the peritoneal cavity (Figs. 90–13 and 90–14). At times, the fistula may be contained by adjacent structures and lead to the formation

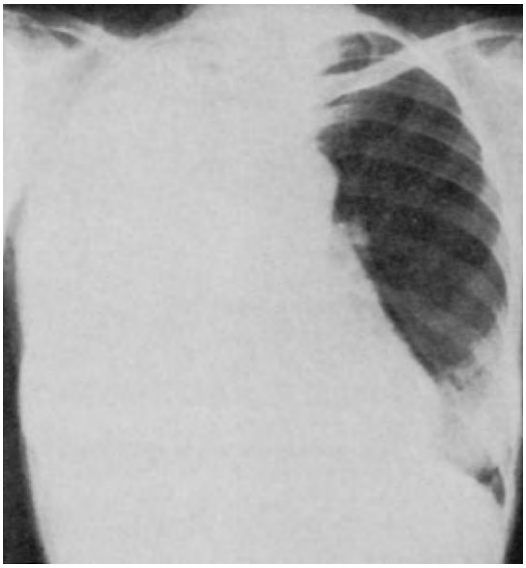


Figure 90–12. Chest radiograph of a patient with chronic massive right-sided pancreatic pleural effusion. (From Cameron JJ, Kieffer RS, Anderson WJ, et al: Internal pancreatic fistulas: Pancreatic ascites and pleural effusions. Ann Surg 184:587, 1976.)

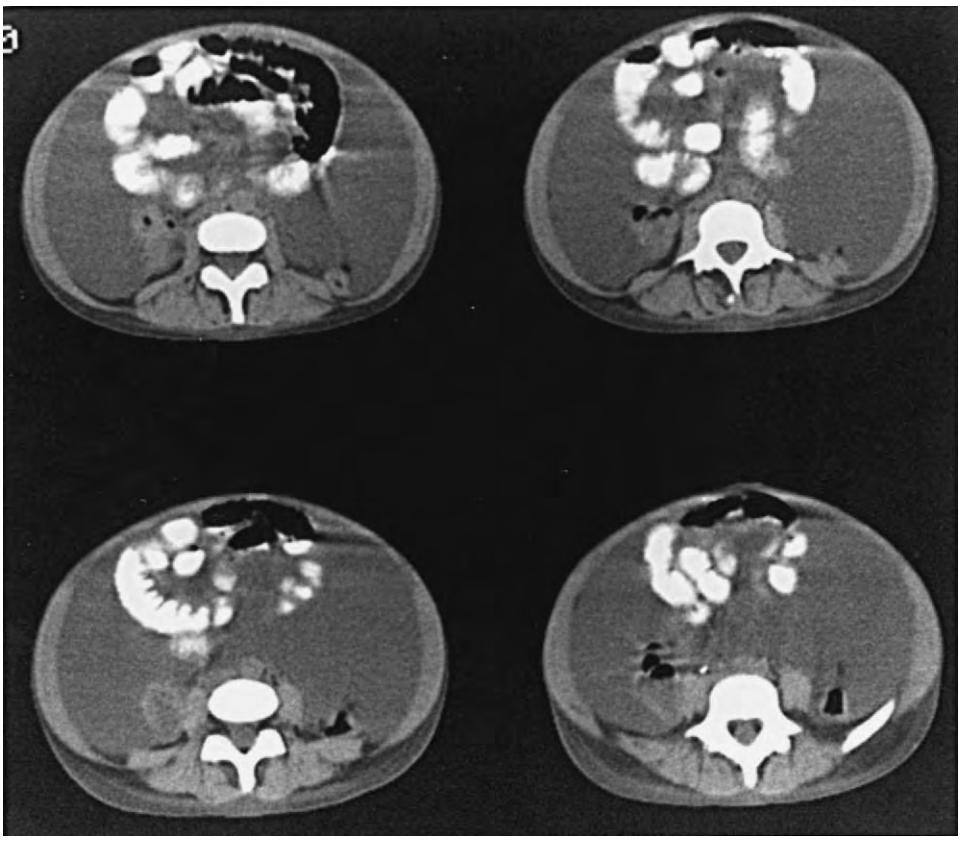


Figure 90–13. Four computed tomography scans showing extensive pancreatic ascites in a young female patient with alcoholism. The small bowel loops float centrally, and ascitic fluid fills the abdomen.

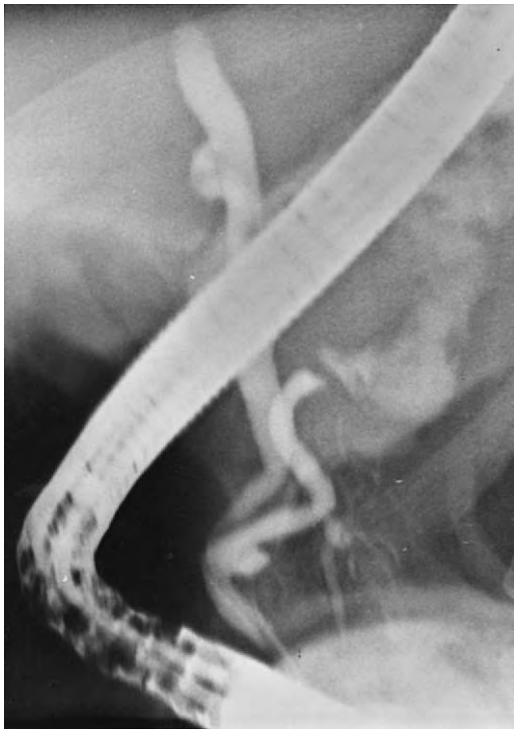


Figure 90–14. Endoscopic retrograde cholangiopancreatogram from the patient with pancreatic ascites whose computed tomography scan is shown in Figure 90–13. Contrast extravasates from the proximal portion of the pancreatic duct into the peritoneal cavity. The visualized portion of the extrahepatic biliary tree is normal.

of a pancreatic pseudocyst. Pancreatic ductal disruptions are most commonly a result of alcoholic pancreatitis, but they may be secondary to blunt or operative trauma, gallstone pancreatitis, or other causes of pancreatitis. Pancreatic ductal injury in children is most commonly the result of trauma.

Most patients with pancreatic ascites or effusions have an indolent illness that may not suggest pancreatic disease. In the Johns Hopkins series, less than 50% of patients had a history of pancreatitis.[110] Only 12% had an acute attack of pancreatitis, whereas 42% gave no history suggestive of pancreatic disease. Patients with pancreatic ascites most often have painless abdominal swelling, frequently associated with weight loss. Other causes of ascites, such as cirrhosis, Budd-Chiari syndrome, tuberculous peritonitis, and carcinomatosis, should be excluded. Patients with pancreatic pleural effusions often complain of shortness of breath that has progressed over time, as well as other respiratory symptoms. Approximately 15% of patients have both pancreatic ascites and pleural effusion.

The diagnosis of pancreatic ascites or pleural effusion is based on the diagnostic criteria discussed earlier. Initial nonoperative management is advocated in all patients. The patient should be strictly denied oral intake to limit pancreatic stimulation and exocrine secretions. Parenteral nutrition should be instituted. The somatostatin analogue octreotide has been used for the treatment of pancreaticocutaneous fistulas, and a few small studies suggest that octreotide may be effective for pancreatic ascites.[112-114] Segal and associates demonstrated that octreotide was able to lead to resolution of pancreatic ductal disruption in a small group of patients in whom conservative therapy had failed.[112] However, no prospective randomized studies have yet been performed to evaluate the use of octreotide in these conditions.

One of the principles of conservative therapy is to encourage the approximation of serosal surfaces and to limit accumulation of ascitic or pleural fluid. Paracentesis or thoracentesis should be performed intermittently to empty the pleural or peritoneal cavity. If repeated high-volume thoracentesis is necessary, tube thoracostomy may be appropriate. A trial of nonoperative therapy should be limited to 3 weeks. In a report from the Johns Hopkins Hospital, limiting the initial nonoperative phase of therapy for pancreatic ascites to 3 weeks resulted in only a single death (in a patient who refused surgery).[110] Pancreatic pleural effusions may also be treated nonoperatively for 3 weeks. Parekh and Segal attempted to identify which pancreatic fistulas will close without surgical intervention.[108] Patients in whom treatment had failed had significantly lower serum sodium and albumin levels, and the ratio of total fluid protein to serum protein was significantly higher in the treatment failures than in patients who responded to conservative therapy. ERCP was also found to be an important predictor of response to nonoperative therapy. Patients with pancreatic ductal changes indicative of severe chronic pancreatitis had a 10% or less chance of resolving their internal fistulas without surgical intervention.

Patients in whom conservative therapy fails should have their pancreatic anatomy more clearly defined. CT should be performed to assess the extent of pancreatic inflammation and to locate any pseudocysts associated with the ductal disruption. ERCP is necessary to evaluate the pancreatic ductal anatomy and to identify the location of the leak. ERCP may identify patients who may be treated by pancreatic duct stenting. Pancreatic duct stents bridging the ductal disruption have shown promise as a method to heal internal pancreatic fistulas. In the small number of reported cases, many stenting procedures have been successful, without complications.[115-118] As experience accumulates with these techniques, operative therapy may be avoided for all but the most complicated ductal disruptions. Anecdotal reports also exist of percutaneous pancreatic duct stents placed under ultrasound and fluoroscopic guidance. These techniques are unlikely to supplant the less demanding endoscopic approaches.

The choice of operative therapy is guided by pancreatic ductal anatomy. Distal pancreatic duct leaks may be addressed by *distal pancreatectomy*, a procedure that can be performed with low expected morbidity and mortality and eliminates the need for a pancreatic anastomosis. In some cases when proximal pancreatic ductal disease is present, the pancreatic remnant should be drained with a *Roux-en-Y loop*. If a direct duct leak is identified, the ductal disruption can be drained internally as a *Roux-en-Y pancreaticojejunostomy* (Fig. 90–15). When ductal disruptions are associated with a pseudocyst, the pseudocyst

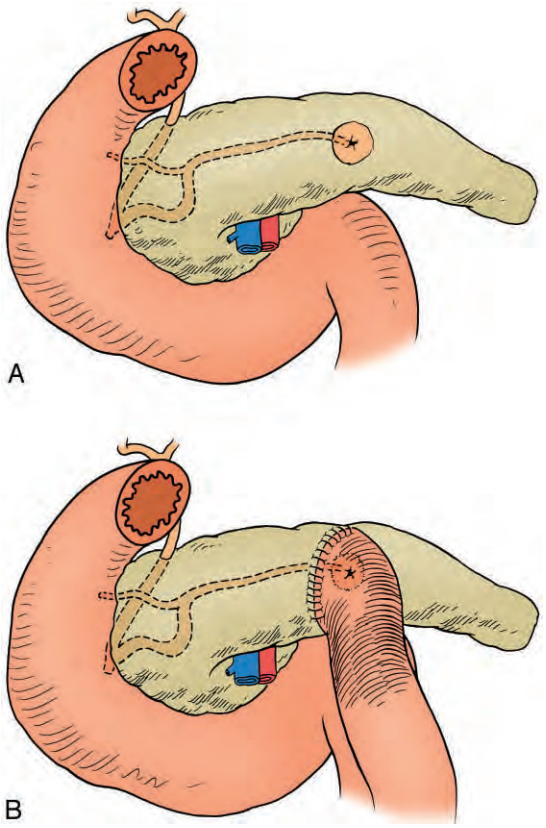


Figure 90–15. **A** and **B,** Schematic of pancreatic duct disruption and pancreatic ascites treated by anastomosing a Roux-en-Y jejunal loop to the duct leak. (From Cameron JJ, Brawley RK, Bender HW, et al: The treatment of pancreatic ascites. Ann Surg 170:668, 1969.)

may be drained either by a Roux-en-Y loop or into the stomach as a *cystogastrostomy*. These internal drainage techniques are always preferable to placement of external drains. Da Cunha and colleagues showed that external drainage procedures are commonly complicated by infection and may require reoperation in up to 50% of cases.[119] Internal drainage, in contrast, has a greater than 90% chance of success. Although early series reported high mortality rates in patients undergoing operative therapy, many of these deaths could be attributed to poor nutritional status and less refined techniques in pancreatic surgery. More recent series report a mortality rate of less than 2%.[110,119,120]

External Pancreatic Fistula

Pancreaticocutaneous fistulas may be the result of trauma, surgical resection, necrotizing and chronic pancreatitis, or percutaneous drainage of a pseudocyst associated with pancreatic duct obstruction or disruption. Most fistulas will close spontaneously with adequate nutrition, resolution of the underlying pancreatic inflammatory process, and adequate local wound care. Refractory pancreaticocutaneous fistulas warrant further evaluation with ERCP or sinograms (or both) to delineate ductal abnormalities that may preclude spontaneous closure. Broadie and colleagues reported on 38 patients evaluated by ERCP for pancreaticocutaneous fistulas. Fistulas originating from the side of the main pancreatic duct closed spontaneously within 11 weeks in 86% of patients. Side fistulas with continued pancreatic inflammation were less likely to close, with a 53% closure rate by 23 weeks. No end fistulas closed.[121]

Surgical treatment of persistent fistulas includes Roux-en-Y fistula tract–jejunostomy, pancreaticojejunostomy, or pancreatic resection. Fistula tract–jejunostomy is viewed as the safest option because it allows internal drainage in an operative field that is distant from the inflamed pancreatic bed. Best results are achieved in a stable patient with a mature fistula tract. A recent review of surgical treatment for pancreatic fistulas found that surgical closure was achieved in 90% of patients; however, operative mortality was noted in roughly 6.3% of the population.[122]

Endoscopic pancreatic duct stenting has been reported as a treatment option for refractory fistulas. Pancreatic stents successfully closed 55% of fistulas in a recent series of 97 patients with duct disruption.[123] This technique may prove to be an effective minimally invasive approach for fistula closure as technology and experience improve.

Splenic Vein Thrombosis

The splenic vein lies posterior to and closely approximated to the body of the pancreas, and it runs from the pancreatic tail to the neck of the gland. Immediately dorsal to the neck, the splenic vein joins with the superior mesenteric vein to form the portal vein. This location makes the splenic vein particularly susceptible to involvement by inflammatory diseases of the pancreas. Invasive neoplastic or inflammatory disease may lead to intrinsic damage to the venous intima or extrinsic compression secondary to edema, fibrosis, mass lesions, or lymphadenopathy. In either case, stasis of splenic vein blood flow occurs and may eventually lead to *splenic vein thrombosis*.

The importance of splenic vein thrombosis in patients with chronic pancreatitis is not completely known. Commonly used imaging techniques (particularly CT scan) have led to an increased diagnosis of splenic vein thrombosis in patients with chronic pancreatitis. Splenic vein thrombosis is clinically silent in the majority of patients. The incidence appears to be approximately 7% to 15% in patients with chronic pancreatitis, with 2% to 5% of patients having extension of the splenic vein thrombosis into the portal vein.[124,125] Splenic vein thrombosis is thought to be a relatively late complication of chronic pancreatitis.

Splenic vein thrombosis causes complications secondary to the development of extrahepatic, "left-sided" portal hypertension. Obstruction of splenic venous outflow leads to the enlargement of collateral vessels along the short gastric and gastroepiploic veins, which results in the formation of *gastric varices* along the greater curvature and fundus of the stomach, as well as *esophageal varices* secondary to increased flow to the coronary vein.

These varices do not form in all patients, and some series have reported such varices in less than 50% of patients with documented splenic vein thrombosis.[124-127] *Splenomegaly* is a related common finding in patients with splenic vein thrombosis. The most common complication of splenic vein thrombosis is *upper gastrointestinal hemorrhage* secondary to gastric or esophageal varices, which occurs in less than 10% of patients with known thrombosis.[124] Patients may also have abdominal pain or, rarely, ascites. Another important manifestation of splenic vein thrombosis is excessive *intraoperative blood loss* as a result of the enlarged venous collateral vessels. Splenic vein thrombosis should be carefully noted in patients with chronic pancreatitis who are to undergo operative therapy.

As the diagnosis of *asymptomatic splenic vein thrombosis* has increased, more information has been obtained about the natural history of this process and the indications for intervention. In a prospective study by Bernades et al., 266 patients with chronic pancreatitis were monitored for a mean period of 8.2 years.[124] These patients were screened with ultrasound for splenic vein thrombosis, which was confirmed by CT or angiography. The incidence of splenic or portal vein thrombosis was 13.2%, with varices occurring in 17% of these patients. One patient required surgery for variceal bleeding. Twenty-three patients with splenic vein thrombosis underwent no therapy, and no episodes of bleeding occurred in more than 2½ years of observation.

Treatment of patients with bleeding gastroesophageal varices secondary to splenic vein thrombosis is *splenectomy*. This operation eliminates splenic artery inflow and venous outflow, with an attendant immediate reduction in variceal blood flow. Moosa and Gadd reported a cure rate of greater than 90% in patients undergoing splenectomy at a mean follow-up of 11 months.[128] "*Nonsurgical splenectomy*" via splenic artery embolization is a nonoperative intervention that may be appropriate for selected patients with extensive comorbidity. These patients are at risk for splenic abscess. Clearly, asymptomatic splenic vein thrombosis deserves no specific intervention. Splenectomy is the treatment of choice in most patients with symptomatic gastroesophageal varices.

Pancreatic Cancer

Perhaps the most challenging aspect of the management of presumed chronic pancreatitis is distinguishing it from *pancreatic carcinoma* (Table 90–3). Patients initially seen with biliary obstruction, duodenal obstruction, or an inflammatory mass in the head of the pancreas may all have benign complications of chronic pancreatitis, but the possibility of pancreatic or other periampullary malignant disease must always be considered. Furthermore, evidence suggests that patients with chronic pancreatitis are at increased risk for the development of pancreatic cancer. Lowenfels and colleagues reported on a cohort of 2015 patients with chronic pancreatitis.[129] The risk for pancreatic cancer increased in linear fashion from the time of diagnosis of chronic pancreatitis, with the incidence increasing from 1.8% at 10 years to 4% at 20 years. Other groups have confirmed these findings in

Table 90–3 Clinical Features Distinguishing Biliary Obstruction Caused by Pancreatic Carcinoma from Chronic Pancreatitis

Feature	Pancreatic Carcinoma	Chronic Pancreatitis
History and physical examination	Persistent jaundice	Intermittent jaundice
	Weight loss	Alcohol abuse
	Older patient	Younger patient
	Palpable gallbladder (Courvoisier's sign)	Frequent attacks of pancreatitis
	Evidence of metastasis	Steatorrhea
Laboratory data	Markedly elevated bilirubin and alkaline phosphatase	Minimally elevated bilirubin
	Prolonged prothrombin time	Elevated alkaline phosphatase
	Decreased serum albumin	
Plain abdominal radiographs	Normal	Pancreatic calcifications
ERCP	Ductal cutoff (common bile duct and pancreatic duct: the "double-duct" sign)	Long, tapered stricture of the intrapancreatic common bile duct
		"Chain of lakes" appearance
		Pancreatic calculi
		Secondary and tertiary pancreatic ducts visualized
CT scan	Mass in the head of the pancreas	Diffuse pancreatic enlargement
	Dilated biliary tree	Dilated common bile duct
	Metastases	Pseudocysts
Angiography	Vessel encasement possible	Normal (usually)

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography.

similar studies and have concluded that chronic pancreatitis increases the risk for pancreatic cancer by up to three times the risk in the general population.[130,131]

Much effort has been expended to clarify which imaging modalities and diagnostic procedures best distinguish pancreatic cancer from chronic pancreatitis. Conventional CT and ERCP have traditionally been used to distinguish these two diagnoses, with a combined diagnostic accuracy of about 65% to 80%.[132] Because of the high rate of both false-positive and false-negative results, other techniques have been advocated to aid in the diagnosis. EUS is available in many centers. Advocates of this technique claim high sensitivity for the detection of pancreatic masses; Barthet and colleagues claimed 100% sensitivity in detecting pancreatic masses in patients with chronic pancreatitis.[133] Certainly, such a 100% sensitivity rate does not translate into a 100% accuracy rate. EUS is thought to be particularly helpful in the detection of masses smaller than 2 cm, many of which are missed on CT scan.[134] EUS is also reported to allow accurate characterization of the relationship of pancreatic masses to the superior mesenteric vessels and portal vein and thus to predict resectability. However, one study reported that newer high-resolution spiral CT is at least as accurate in determining resectability based on vascular involvement and that CT may be more accurate in determining involvement of the superior mesenteric artery.[135] EUS is an invasive procedure, but it may allow for the establishment of a tissue diagnosis by fine-needle aspiration cytology. However, a negative cytologic study should not delay resection in a patient with an appropriate clinical history and a mass suggestive of pancreatic cancer. Moreover, patients with chronic pancreatitis have been found to have an extremely high rate of false-positive EUS studies that detect a focal mass, so the positive predictive value of EUS for pancreatic cancer is as low as 60%.

MRCP has also been advocated for distinguishing pancreatic cancer from chronic pancreatitis. As with many of its applications, studies of the use of MRCP in diagnosing pancreatic cancer are small, and it is too early to determine the accuracy of this technique. Studies in the radiologic literature have unfortunately found similar MRI enhancement of pancreatic cancer and chronic pancreatitis, a finding that makes a definitive diagnosis difficult.[87] Other groups support the use of positron emission tomography (PET) with fluorodeoxyglucose for the diagnosis of pancreatic cancer. Rose et al. reported that PET scanning was more sensitive and specific than CT in the detection of small pancreatic tumors and that PET scan results led to a change in management in 43% of the patients in their series.[136] Unfortunately, the patients with false-positive results in this series all had chronic pancreatitis, so these findings call into question whether PET offers useful data in the diagnosis of pancreatic cancer in patients with chronic pancreatitis. Imdahl and colleagues argued that the level of glucose uptake in pancreatic masses as measured by PET allowed for differentiation of pancreatic cancer and chronic pancreatitis in a small group of patients.[137] Whether these results would make a difference in the eventual treatment is not clear because patients with concerning clinical findings all underwent resection in this series.

Clearly, no current diagnostic test is sufficiently accurate to differentiate chronic pancreatitis from pancreatic cancer. In the future, molecular genetic techniques focusing on ductal precursor lesions and the characteristic molecular fingerprint of pancreatic cancer may allow better differentiation between benign and malignant pancreatic disease. At present, patients in whom the diagnosis is unclear but the clinical symptoms of pain, jaundice, and weight loss with a noncalculous distal biliary obstruction make the diagnosis of malignant disease possible should undergo surgical exploration with planned pancreaticoduodenectomy. Because the mortality rate of pancreaticoduodenectomy has fallen significantly, particularly in experienced centers, proceeding with surgical resection is one approach.[138,139] Patients found to have chronic pancreatitis without malignant disease have also been shown to benefit from this procedure, particularly regarding quality-of-life issues.[140] Duodenum-preserving resection of the pancreatic head is another possible approach to patients with severe chronic pancreatitis.[141]

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Chapter

91

Pancreatic and Periampullary Carcinoma

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Pancreatic and periampullary carcinomas include a group of malignant neoplasms arising in or near the ampulla of Vater or in the pancreas. The initial pattern of symptoms is determined by the location of the primary lesion. Lesions that grow near the bile duct tend to cause obstructive jaundice, whereas pancreatic lesions that grow in the body or tail tend to be manifested as pain or a mass effect. The great majority of tumors that occur in these areas are adenocarcinomas arising from either the pancreas, ampulla of Vater, distal common bile duct, or duodenum.

INCIDENCE

Pancreatic and periampullary carcinomas are a major public health problem throughout most of the world. Pancreas cancer is the fourth leading cause of cancer death in the United States, with 31,800 deaths in 2005 as opposed to 163,510 deaths for lung cancer, 56,290 deaths for colorectal cancer, and 40,870 deaths for breast cancer.[1] In the United States, the incidence of pancreas cancer rose dramatically from the 1930s until the 1970s, nearly doubling. Since the mid-1970s the incidence has remained stable at about 8 to 9 cases per 100,000 population. Pancreatic cancer is a highly lethal malignancy with the yearly mortality approaching the incidence (32,180 in 2005). In the United States, demographic risk factors for pancreas cancer include age, with the majority of patients in or beyond their sixth decade of life; sex, with a slight male preponderance; and race, with African American males having the highest overall incidence.

In Europe, pancreas cancer is the sixth leading cause of cancer death, and the incidence is similar to that in the United States. The incidence in Europe has also remained stable during the past 3 decades. The Japanese, however, have seen a dramatic increase in the incidence of pancreas cancer over the past 3 decades, although the overall incidence is still less than that observed in the West. India and parts of the Middle East have the lowest recorded incidence of pancreas cancer. Worldwide, more than 200,000 people die of pancreas cancer every year.[2]

Ampullary carcinoma is the second most common periampullary carcinoma, with an overall incidence of 6 cases per 1 million or approximately 1800 cases per year in the United States.[3] Although it constitutes between 7% and 19% of periampullary carcinomas, it accounts for a higher percentage of operative cases because these lesions are more amenable to complete resection.[4,5] Distal bile duct carcinoma and periampullary duodenal carcinoma occur less frequently than pancreas and ampullary carcinoma. The actual incidence of these two carcinomas is much more difficult to estimate because they occur less frequently and are often lumped together with other malignancies. For example, distal bile duct carcinomas are often combined with all cholangiocarcinomas (perihilar and intrahepatic), as well as with gallbladder carcinoma. Likewise, periampullary duodenal carcinomas are often combined with all duodenal carcinomas or all small bowel carcinomas.

PATHOLOGY

Pathologic examination of resected pancreaticoduodenectomy specimens reveals that approximately 40% to 60% are performed for adenocarcinoma of the pancreas, 10% to 20% are performed for adenocarcinoma of the ampulla, 10% are performed for bile duct adenocarcinoma, 5% to 10% are performed for duodenal adenocarcinoma, and 10% to 20% of specimens contain only benign disease.[6,7] Because these data represent resected specimens and the resectability of pancreatic periampullary cancer is much lower, it is reasonable to assume that the pancreas is the primary site in up 80% to 90% of periampullary cancers.

Although the periampullary region can harbor a diverse array of pathologic entities, pancreatic ductal adenocarcinoma is by far the most common malignant

histology. More than two thirds of pancreatic adenocarcinomas arise in the pancreatic head, neck, or uncinate process. Other histologic types that are encountered include acinar, squamous, and islet cell tumors and tumors of nonepithelial origin. Islet cell tumors, a subgroup of neuroendocrine tumors, may be either benign or malignant and may be functional, with clinical manifestations resulting from excess hormone production. Nonfunctional islet cell tumors are usually detected because of their space-occupying characteristics. Obstructive jaundice is uncommon with benign islet cell tumors, even in the head of the pancreas, but can occur when the lesion is malignant.

Cystic neoplasms of the pancreas can also arise from the exocrine pancreas and are usually classified as serous cystadenomas, mucinous cystadenomas, or intraductal papillary mucinous neoplasms (IPMNs). Serous cystadenomas of the pancreas are thought to be benign with extremely little or no malignant potential. There have been approximately 10 reported cases in the English literature documenting what appears to be a malignancy arising from a serous cystadenoma.[8] Mucinous cystadenomas, as well as IPMNs, can be benign, premalignant, or malignant. In a single institution report of 136 pancreatic resections performed for IPMN over a 6-year period, 38% had evidence of invasive cancer.[9] Noninvasive IPMNs can be classified as adenoma, borderline, or carcinoma in situ (CIS), depending on the degree of dysplasia present. The mean age of patients with IPMN with adenoma features was 63.2 years; with borderline/CIS features, 66.7 years; and with invasive cancer, 68.1 years, thus suggesting a sequential progression.

Various sarcomas, including gastrointestinal stromal tumors (GISTs), fibrosarcomas, leiomyosarcomas, hemangiopericytomas, and histiocytomas, may also arise in the periampullary region. It is important to distinguish whether the lesion represents a GIST because of the availability of targeted therapeutics such as imatinib (Gleevec), which has a very high response rate. Thousands of patients worldwide with advanced GIST have been treated with imatinib and have achieved significant response rates, prolongation of survival, and improvement in quality of life.[10] The area around the porta hepatis, as well as the pancreas, is rich with lymphatic tissues. Lymphomas can occur in these areas and usually have ill-defined margins when compared with typical adenocarcinomas. Finally, the periampullary region may harbor sites of metastatic disease from kidney, breast, lung, melanoma, stomach, colon, and germ cell primaries, as well as from other primary sites of disease.

ETIOLOGY

More is known about the risk factors for pancreatic adenocarcinoma than for ampullary, bile duct, and duodenal adenocarcinoma.

Pancreas Adenocarcinoma

The known and suspected risk factors for pancreas adenocarcinoma can be broadly classified as established, associated, and possible. Tobacco and inherited susceptibility (which account for only 5% to 10% of cases) are considered established. Chronic pancreatitis, type 2 diabetes mellitus, and obesity are consistently found to be associated with pancreas cancer and are generally considered weak risk factors. Possible risk factors include physical inactivity, certain pesticides, and high carbohydrate/sugar intake, but the data are inconsistent and inconclusive. Cholecystectomy, cholelithiasis, coffee consumption, and alcohol have been sporadically associated with the development of pancreas cancer but are unlikely to be true risk factors (Table 91–1).

Table 91–1 Risk Factors for Pancreas Adenocarcinoma

Established	Tobacco
	Inherited susceptibility
Associated	Chronic pancreatitis
	Diabetes mellitus type 2
	Obesity
Possible	Physical inactivity
	Certain pesticides
	High carbohydrate/sugar intake

Environmental Factors and Pancreas Adenocarcinoma

The evidence linking cigarette smoking to pancreas adenocarcinoma is strong. Animal studies have confirmed the carcinogenic effects of tobacco smoke on the pancreas. Most studies have found that smoking results in about a twofold increased risk for pancreas cancer.[11-14] Most studies also confirm the anticipated finding of a dose-response relationship, with higher rates of pancreas cancer being linked to heavier smoking exposure. In a 50-year follow-up study of British physicians, pancreatic cancer rates in nonsmokers, ex-smokers, and current smokers were 21, 31, and 39 per 100,000 person-years, respectively.[15] Human autopsy studies have revealed increased hyperplastic changes with atypia in the pancreatic cells of cigarette smokers.[16]

Data reviewing the relationship of diet and pancreas adenocarcinoma are often conflicting.[11,17,18] Some studies have demonstrated an association with increased intake of total calories, as well as carbohydrates, cholesterol, meat, salt, dehydrated food, fried food, refined sugar, and nitrosamines. Fat, β-carotene, and coffee are of unproven risk, with studies demonstrating both the presence and the absence of increased risk. Some foods may have a protective effect, such as consumption of a diet high in fiber, vitamin C, fruits, vegetables, and unprepared food, but these relationships are not yet established.

Alcohol, coffee, and radiation do not seem to be significant risk factors for the development of pancreas adenocarcinoma. Findings obtained from numerous prospective cohort and case-control studies on alcohol

consumption and pancreatic cancer risk have been inconsistent, with many confounding variables present in various investigations.[19] Three case-control studies from Europe failed to demonstrate an increased risk for pancreas cancer with coffee consumption,[11] in contrast to two earlier reported series linking an increased risk for pancreas cancer with coffee consumption.[20,21] Ionizing radiation also does not seem to be associated with an increased incidence of pancreas cancer. Survivors of the atomic bombing of Hiroshima and Nagasaki have not demonstrated an increased risk for pancreas cancer.[22,23]

Host Factors and Pancreas Adenocarcinoma

Genetic syndromes that predispose patients to pancreas adenocarcinoma are the most striking examples of the contribution of host factors. Hereditary nonpolyposis colorectal cancer (HNPCC), familial breast cancer associated with the *BRCA2* mutation, Peutz-Jeghers syndrome, ataxia-telangiectasia syndrome, familial atypical multiple mole–melanoma syndrome (FAMMM), and hereditary pancreatitis are six genetic syndromes with a demonstrable increased risk for pancreas adenocarcinoma.

In the National Familial Pancreas Tumor Registry (NFPTR), individuals with two or more first-degree relatives affected by pancreas adenocarcinoma have a 16-fold increased risk for development of the disease. Although either genetic or environmental factors can be invoked, there is strong evidence that the familial aggregation has a genetic basis.[24]

Chronic pancreatitis has been associated with pancreas adenocarcinoma, but it is difficult to determine whether there is a common risk factor for the two diseases or whether chronic pancreatitis may represent an indolent manifestation of pancreas adenocarcinoma.[11,25-27] In similar fashion, type 2 diabetes mellitus is often associated with pancreas adenocarcinoma.[28,29] For both of these host factors, it is difficult to ascertain whether they are sequelae of the malignancy or whether they are truly causative factors.

Genetic Alterations and Pancreas Cancer

The majority of malignancies are the result of acquired and inherited mutations in proto-oncogenes, tumor suppressor genes, and DNA mismatch repair genes. Proto-oncogenes are normal cellular genes that when activated by a mutation or amplification into an oncogene, possess transforming properties. Tumor suppressor genes normally function to restrain cell proliferation. Loss of function of these genes by mutation, deletion, chromosome rearrangement, or mitotic recombination results in abnormal cell proliferation. When mismatch repair genes are mutated, errors in DNA replication are not efficiently repaired; as a result, simple repeated sequences are distributed throughout the genome, a condition known as *microsatellite instability,* and may lead to cancer.

As the appropriate combination of mutations accumulates within the pancreas, they may result in an invasive adenocarcinoma phenotype. In an analysis of pancreas adenocarcinoma specimens, 100% had mutations in the proto-oncogene K-*ras,* and 82%, 76%, 53%, and 10% had mutation in the tumor suppressor genes *p16, p53, DPC4,* and *BRCA2,* respectively.[30] Mutations in DNA mismatch repair genes are implicated in about 4% of pancreas adenocarcinomas.[31]

Nonpancreatic Periampullary Adenocarcinoma

Ampullary, distal common bile duct, and periampullary duodenal adenocarcinomas are less common than pancreatic adenocarcinoma and are also less well characterized in terms of their risk factors and genetic alterations. All demonstrate an increasing incidence with age. Ampullary and duodenal adenocarcinomas occur with increased frequency in patients with hereditary polyposis syndromes, including HNPCC, Peutz-Jeghers syndrome, familial adenomatous polyposis, and Gardner's syndrome. Distal common bile duct cancers make up approximately 30% of all cholangiocarcinomas, including perihilar and intrahepatic lesions. Cholangiocarcinomas are associated with several known risk factors, including age, inflammatory bowel disease, sclerosing cholangitis, choledochal cysts, and choledocholithiasis.[32]

DIAGNOSIS AND PREOPERATIVE EVALUATION

The diagnosis of a periampullary cancer is usually made on the basis of clinical findings, laboratory data, and radiologic imaging. In some cases of pancreatic or distal bile duct adenocarcinoma a tissue diagnosis is available, but the delay in definitive treatment is seldom indicated to obtain histologic confirmation of malignancy. Biopsy of a duodenal or ampullary lesion, such as a soft polypoid growth, may sometimes be of benefit if it proves to be benign and local resection is being contemplated. If the clinical findings, laboratory data, and radiologic imaging are suspicious for a malignancy, the majority of patients brought to resection will indeed have a cancerous lesion. Additionally, a negative biopsy of a periampullary mass has a significant rate of being falsely negative for carcinoma. Confirmatory biopsy is relevant if the lesion is unresectable or if neoadjuvant therapy is being contemplated.

Clinical Findings

Symptoms depend on the location of the lesion, with most patients having vague symptoms early in the course of their disease. Patients with lesions that occur near the bile duct, such as those near the ampulla, head of the pancreas, and uncinate process, are much more likely to have obstructive jaundice. Those with lesions in the body or tail of the pancreas are more likely to complain of pain.

The majority of patients with a head of the pancreas, ampullary, distal bile duct, or periampullary duodenal

adenocarcinoma have the classic constellation of jaundice, pruritus, acholic stools, and tea-colored urine. Patients with a distal common bile duct or ampullary adenocarcinoma are the most likely to have obstructive jaundice because the lesion does not need to grow to very large size before it completely obstructs the bile duct. In addition to the classic symptoms, vague upper abdominal discomfort often develops and sometimes radiates to the back. Late in the course of the disease this pain can progress to be very debilitating. Other general symptoms include anorexia, fatigue, malaise, and weight loss. Nausea and vomiting can be a sign of gastric outlet obstruction from duodenal involvement. Patients may also have acute pancreatitis secondary to obstruction of the pancreatic duct. Elderly patients with acute pancreatitis but without a history of alcohol use or gallbladder stones should be screened for a neoplasm.

Patients with pancreas adenocarcinoma involving the body or tail of the gland are more likely to have weight loss and abdominal pain as their initial complaints. These lesions can grow to a larger size before producing symptoms and are often diagnosed at a later stage with a poorer prognosis.

Physical findings on examination include scleral icterus, jaundice, and a palpable gallbladder (Courvoisier's sign). Signs of advanced disease include cachexia, palpable metastatic lesions within the liver, palpable disease in the left supraclavicular fossa near the confluence of the subclavian vein and thoracic duct (Virchow's nodule), palpable periumbilical metastatic disease (Sister Mary Joseph's nodule), and pelvic metastatic disease palpable anteriorly on rectal examination (Blumer's shelf nodule).

Laboratory Findings

In addition to the clinical signs and symptoms, patients early in the course of their disease may have subtle laboratory findings such as mildly elevated liver function test results, mildly elevated bilirubin levels, or elevated alkaline phosphatase levels, or they may have new-onset diabetes or anemia. If the disease has progressed and jaundice is apparent, patients generally have elevated serum levels of bilirubin and alkaline phosphatase, usually associated with only a mild elevation in liver transaminases. Ongoing obstruction of the biliary tree may lead to an inability to absorb vitamin K and resultant coagulopathy because of the lack of intrinsic pathway clotting factors. It is important to replete vitamin K in these patients.

There are no definitive serum markers for any of the pancreatic or periampullary adenocarcinomas. Markers that tend to be used are carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA). CA 19-9 is elevated in up to 75% of patients with pancreas adenocarcinoma, but levels are also elevated in benign conditions of the pancreas, liver, and bile ducts, as well as in smokers. CEA levels may be elevated with any of the periampullary adenocarcinomas, but more typically with bile duct and duodenal adenocarcinoma. Because nearly 100% of pancreas adenocarcinomas have a mutation in K-*ras,* several groups have tried to detect these mutations from aspirates obtained by endoscopic techniques or in stool.[33-35]

Imaging Studies

The imaging modalities most frequently used for patients with suspected periampullary cancer are right upper quadrant ultrasound (RUQ US), computed tomography (CT), magnetic resonance imaging (MRI), including magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC). The benefit of positron emission tomography (PET) has not been clearly defined. Over the past 15 years there has been a general trend away from invasive imaging studies (ERCP and PTC) toward noninvasive imaging studies. This trend has occurred for two reasons. First, there have been studies that have documented an increased rate of both preoperative and postoperative complications with the routine use of these modalities.[36,37] Second, surgeons have become more willing to operate on jaundiced patients as long as they are not septic or malnourished from their biliary obstruction.

Right Upper Quadrant Ultrasound

RUQ US is usually available at all times, especially in emergency departments. It is very sensitive for the detection of gallstones, dilatation of the biliary tree, pericholecystic fluid, and gallbladder wall thickening. The sonographer can also test for the presence of a sonographic Murphy sign, in which the patient experiences the most tenderness when the probe is pushed directly on the gallbladder fundus. RUQ US can also detect more ominous signs of advanced periampullary adenocarcinoma, including hepatic metastases, peripancreatic and hilar lymphadenopathy, and ascites. The sensitivity for actually demonstrating a pancreatic or periampullary mass is not high, and the absence of one on this imaging modality does not rule it out.

Computed Tomography

Multidetector (currently up to 64) spiral CT is probably the single most useful diagnostic and staging modality (Fig. 91–1).[38] CT has supplanted US in many centers as the initial diagnostic procedure of choice. This study gives information about the immediately adjacent vascular structures, such as the portal and superior mesenteric veins, as well as the superior mesenteric artery and celiac axis. Three-dimensional reconstructions of these vessels aid in visualizing the anatomic relationships between the vessels and the mass. Most importantly, the presence of tissue planes and the degree of circumferential involvement can be determined (Figs. 91–2 and 91–3). Additionally, information on the presence of distant metastatic disease can be gained at the same setting if the entire abdominal and thoracic cavities are scanned. These images can sometimes reveal the presence of

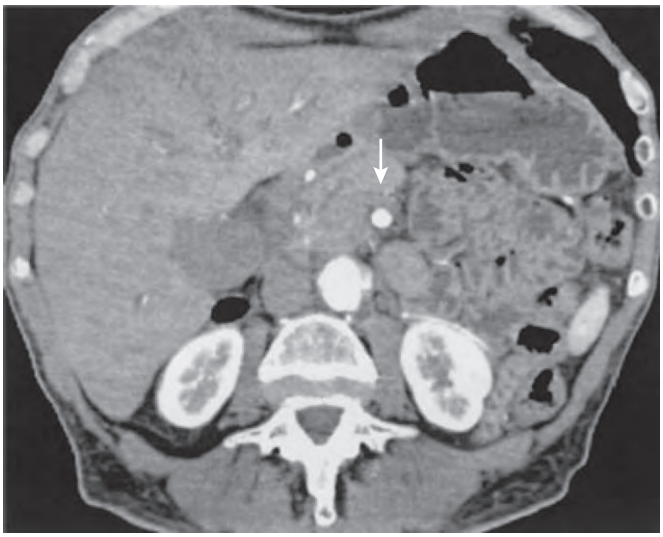

Figure 91–1. Axial computed tomography scan showing a 3-cm mass arising from the head of the pancreas. Arterial-phase axial images demonstrate loss of the periarterial plane over 90 degrees of the superior mesenteric artery *(arrow).* (From House MG, Yeo CJ, Cameron JL, et al: Predicting resectability of periampullary cancer with three-dimensional computed tomography. J Gastrointest Surg 8:280-288, 2004.)

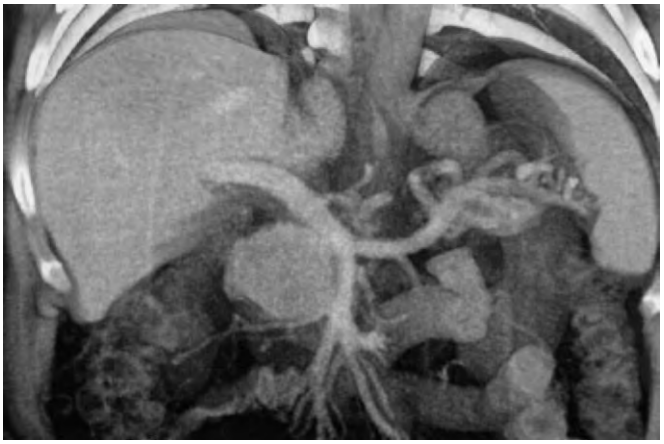

Figure 91–3. Three-dimensional axial oblique reconstruction showing a low-density mass within the head of the pancreas that abuts but does not encase the superior mesenteric vein or portal vein. The vessels appear patent with no evidence of displacement. This pancreatic adenocarcinoma was resected without the need for partial superior mesenteric vein or portal vein resection. (From House MG, Yeo CJ, Cameron JL, et al: Predicting resectability of periampullary cancer with three-dimensional computed tomography. J Gastrointest Surg 8:280-288, 2004.)

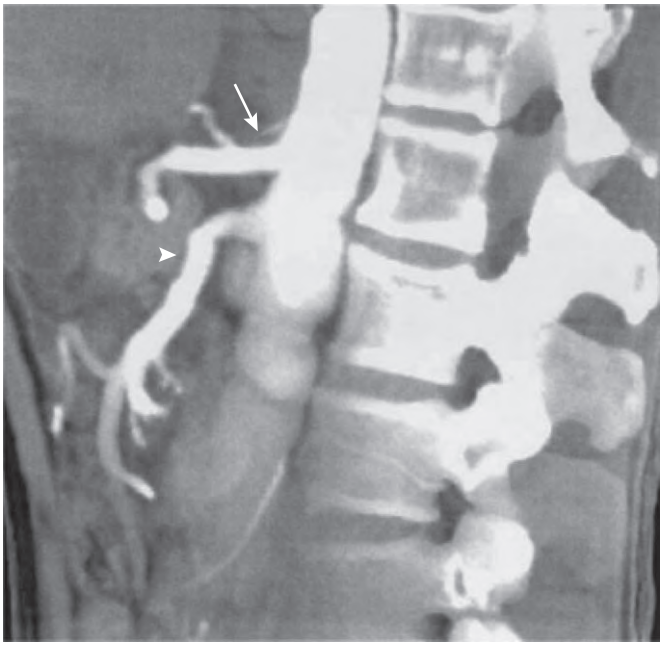

Figure 91–2. Sagittal three-dimensional computed tomographic image confirming the intimate relationship of the pancreatic mass *(arrowhead)* with the superior mesenteric artery in same patient as in Figure 91–1; however, the vessel remains completely patent. The mass does not involve the origin of the celiac axis *(arrow).* This patient underwent a margin-negative resection for pancreatic adenocarcinoma. (From House MG, Yeo CJ, Cameron JL, et al: Predicting resectability of periampullary cancer with three-dimensional computed tomography. J Gastrointest Surg 8:280-288, 2004.)

peritoneal dissemination, hepatic involvement, or pulmonary involvement. The presence of ascites, seen most readily in pelvic cuts, is usually an ominous sign.

Magnetic Resonance Imaging

When distal bile duct obstruction is suspected but no discrete mass is present on CT scan, cholangiography may be of benefit. MRCP is commonly used in this situation to image the biliary tree, as well as the pancreatic duct (Fig. 91–4). It is completely noninvasive and avoids the potential complications associated with the more invasive cholangiography modalities. MRCP has no potential for therapeutic maneuvers, such as extraction of stones or stenting, or for invasive diagnostic maneuvers, such as brushings or biopsies. Gadolinium enhancement can be used in T1-weighted sequences to study the vascular structures, which can also be three-dimensionally reconstructed. MRI and MRCP (potentially performed in a single session on the scanner) thus have the ability to provide information about tumor location, size, and extent; biliary and pancreatic ductal anatomy; and vascular involvement.

Endoscopic Retrograde Cholangiopancreatography

ERCP is sometimes required to decompress an obstructed biliary tree that is causing sepsis. The resulting images may solidify the suspected diagnosis of a pancreatic or periampullary adenocarcinoma. The classic finding of a long, irregular stricture in the pancreatic duct with distal dilatation or a cutoff of both the genu of

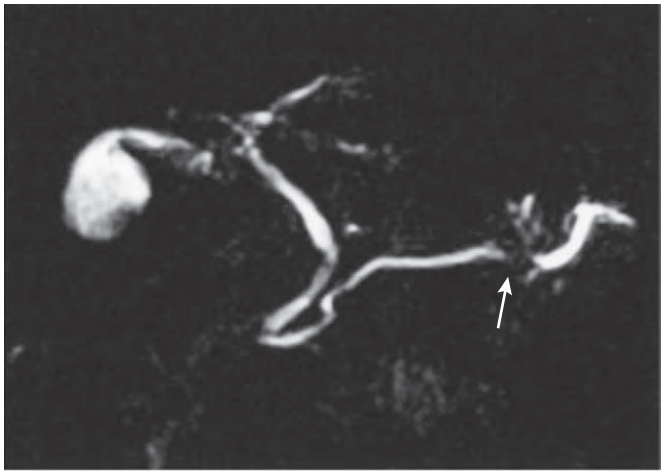

Figure 91–4. Magnetic resonance cholangiopancreatogram demonstrating stenosis of the main duct in the pancreatic body. (From Saisho H, Yamaguchi T: Diagnostic imaging for pancreatic cancer: Computed tomography, magnetic resonance imaging, and positron emission tomography. Pancreas 28:273-278, 2004.)

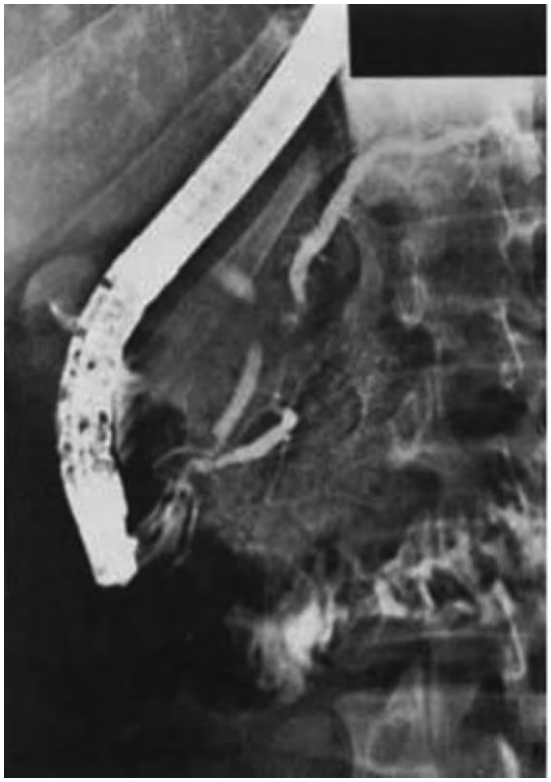

Figure 91–5. An endoscopic retrograde cholangiopancreatogram in a patient with obstructive jaundice reveals a classic double-duct sign. There is evidence of tumor at the genu of the common bile duct and the pancreatic duct. (Yeo CJ, Cameron JL: Pancreatic cancer. Curr Probl Surg 36:59-152, 1999.)

the pancreatic duct and the distal bile duct is pathognomonic of pancreas cancer (Fig. 91–5) With the current imaging capabilities of CT and MRI, diagnostic ERCP is rarely necessary to guide treatment; however, many patients still show up in the surgery clinic already having had ERCP performed and a stent inserted.

Percutaneous Transhepatic Cholangiography

PTC is another means of defining the biliary anatomy, albeit by an invasive approach. When compared with ERCP, it better defines the proximal biliary anatomy above the level of obstruction. During the cholangiogram, a percutaneous biliary drain may be inserted to drain the proximal biliary tree (Fig. 91–6). PTC is perhaps even more invasive than ERCP, and complications include intra-abdominal bleeding, as well as hemobilia. The pancreatic duct and the most distal portion of the bile duct are not usually well visualized as with ERCP.

Upper Endoscopy and Endoscopic Ultrasound

Ampullary and duodenal cancers may be directly visualized through an endoscope, and it is relatively easy to obtain a biopsy specimen for tissue diagnosis. Endoscopic ultrasound (EUS) may be performed during upper endoscopy. The duodenum, ampulla, head of the pancreas, and uncinate process of the pancreas are acoustically accessible with a probe positioned in the duodenum, whereas the body and tail of the pancreas are acoustically accessible with a probe positioned in the stomach. EUS may give information about vascular involvement (Fig. 91–7), but the decision regarding whether to explore a patient should not rely solely on this test. Fine-needle aspiration of any suspected lesions can be performed at the same time as EUS if tissue diagnosis is of benefit.

Positron Emission Tomography

The role of PET scanning is not well defined at present for pancreatic and periampullary adenocarcinoma. Some recent reports support the use of PET imaging in patients with pancreatic cancer. In a comprehensive review of the PET literature, a report suggests the value of this test.[39,40] PET imaging, however, is not routinely used presently in patients suspected of having a pancreatic or periampullary adenocarcinoma.

Tissue Diagnosis

The use of either percutaneous (US or CT guided) or EUS-guided pancreatic biopsy to evaluate a patient who appears to have a resectable pancreatic mass is somewhat controversial. Biopsy can usually be performed with rare complications, including, fistula, pancreatitis, hemorrhage, abscess, tumor seeding, and death. However, a negative biopsy in a patient with a lesion that is

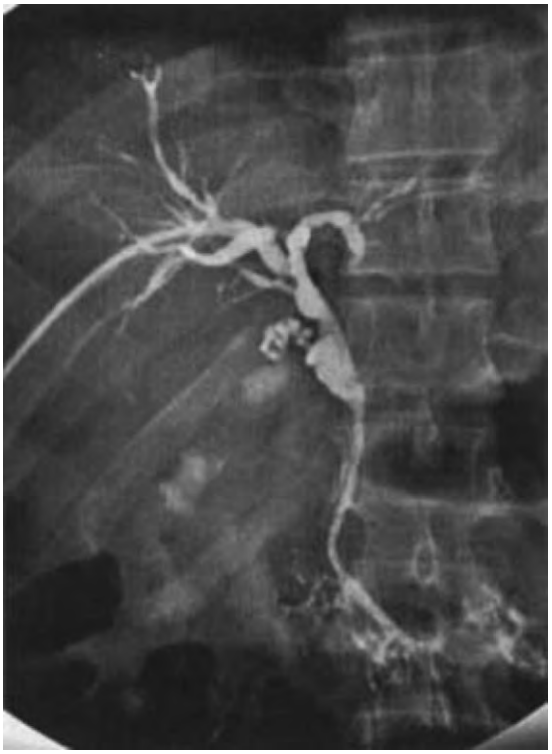

Figure 91–6. Cholangiogram obtained after placement of an internal-external percutaneous transhepatic biliary drainage catheter. The catheter traverses the obstruction in the head of the pancreas. The tip of the catheter resides in the duodenum, distal to the ampulla. (From Yeo CJ, Cameron JL: Pancreatic cancer. Curr Probl Surg 36:59-152, 1999.)

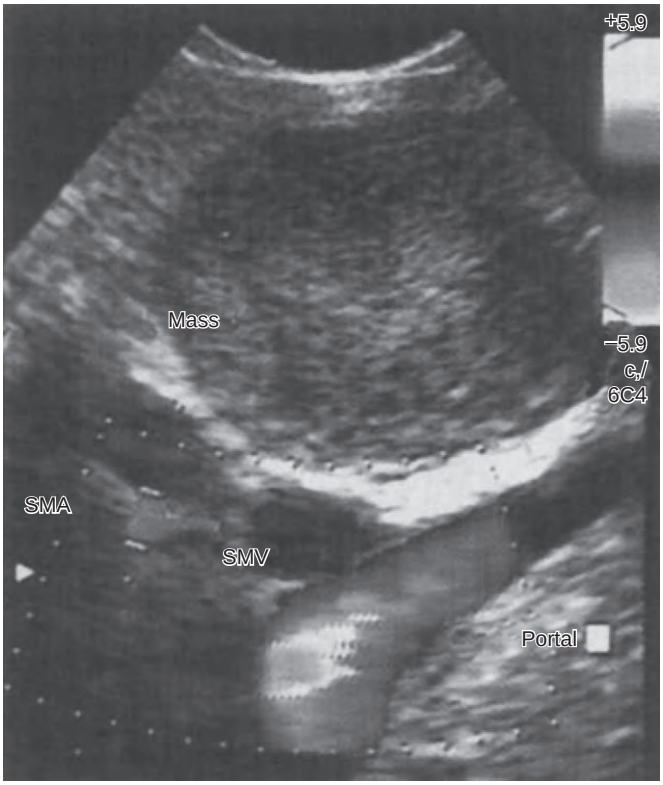

Figure 91–7. Endoscopic ultrasound image, with a linear-array echoendoscope, demonstrating a mass in the head of the pancreas with no vascular invasion of the superior mesenteric artery (SMA), superior mesenteric vein (SMV), or portal vein (Portal). (From Yeo CJ, Cameron JL: Pancreatic cancer. Curr Probl Surg 36:59-152, 1999.)

consistent with pancreatic cancer should not alter the decision to resect. Biopsy should be performed in patients whose disease is unresectable, who are being considered for palliative therapy, or in whom neoadjuvant therapy is being considered in the hope of shrinking the lesion. In special circumstances in which there is suspicion of lymphoma or metastatic disease from another site, biopsy may be of benefit, especially if the disease is best managed without resection.

Tissue diagnosis of ampullary and duodenal cancer is usually straightforward and can easily be obtained through an endoscope. The ability to obtain large and deep biopsy specimens allows better sampling. The histologic finding of a benign villous adenoma with or without dysplasia cannot reliably rule out malignancy, but it may be appropriate to perform local ampullary resection or duodenal polypectomy first and proceed to the more radical resection if visual appearance and frozen section pathologic examination support doing so. "Clamshell" or brush biopsy of distal common bile duct lesions is sometimes performed during ERCP or PTC to obtain a histologic diagnosis; however, it is often difficult to preoperatively ascertain the diagnosis because false-negative rates are near 50%.

Preoperative Staging

There is substantial overlap between diagnosis and preoperative staging, with the goal being to determine the optimal treatment of each individual patient. The mainstay of preoperative staging is multidetector spiral CT with intravenous contrast performed in both the arterial and portal venous phase. Three-dimensional reconstruction of CT scans has increased the potential to predict resectable disease because of the ability to focus on the mesenteric blood vessels commonly involved. In a study of 115 patients with periampullary cancer thought to be resectable based on preoperative three-dimensional CT, the extent of local tumor burden involving the pancreas and peripancreatic tissues was accurately defined in 93% of the patients.[41] It was 95% accurate in determining cancer invasion of the superior mesenteric vessels and accurately predicted resectability and margin-negative resection in 98% and 86% of the patients, respectively. The ability of newer-generation CT scanners to predict margin-negative resectability is dependent on its enhanced ability to assess encasement of the portal or superior mesenteric vein and encasement of the superior mesenteric, celiac, or hepatic arteries.

In addition to local extent of disease, CT is effective in detecting liver metastases that are larger than 1 cm in size. CT scans in general are not highly accurate in assessing retroperitoneal lymphadenopathy or carcinomatosis without ascites or large metastatic lesions.[38] A CT scan of the chest is often performed at the same time as the staging CT to determine whether the patient has any lung metastases, but it is rare that a patient has metastatic lung disease without evidence of metastatic disease in the peritoneal cavity.

In some centers, EUS is used to help stage patients with periampullary tumors. It is very accurate in assessing the size of the primary lesion. The ability to predict vascular involvement is controversial, with some studies reporting high sensitivity and specificity and others reporting the opposite.[42,43] EUS is not very sensitive in determining lymph node involvement or distant metastatic disease unless the lesions are quite sizable. The accuracy of findings on EUS is very operator dependent.

The use of staging laparoscopy is also controversial. Some surgeons will always use staging laparoscopy in the belief that it will save a significant number of patients the morbidity and mortality of exploratory laparotomy only to determine that they have metastatic or locally unresectable disease.[44] In general, these same surgeons believe that if patients do not undergo resection for potential cure, they are best palliated by nonoperative means. Other surgeons will not routinely perform staging laparoscopy because current cross-sectional imaging studies are sensitive and specific enough that it does not make sense to subject all patients to laparoscopy to detect the few who have unresectable disease. Some argue that gastric outlet obstruction requiring surgical intervention will develop in as many as 20% of unresectable patients and that the ability to perform hepaticojejunostomy will more durably relieve obstructive jaundice.[45] Additionally, operative chemical splanchnicectomy may be performed at the same time. Yet other surgeons will use staging laparoscopy selectively by focusing on subgroups of patients at the highest risk of having unresectable disease.[46] Patients with adenocarcinoma involving the body or tail of the pancreas are more likely to have unresectable disease because these lesions do not cause obstructive jaundice and are generally larger and more advanced at the time of diagnosis. Patients with duodenal, ampullary, and distal common bile duct adenocarcinoma are much more likely to have resectable disease.

CLINICOPATHOLOGIC STAGING

Patients with cancer of the pancreas, ampulla, distal bile duct, and duodenum are staged according to the American Joint Committee on Cancer (AJCC) staging system. These staging criteria are based on the size and extent of the primary tumor (T), lymph node involvement (N), and the presence of distant metastases (M). Patients are stratified into stage groupings that guide prognosis and treatment. Pancreas adenocarcinomas are staged with the AJCC exocrine pancreas guidelines, distal common bile duct cancers are staged with the AJCC extrahepatic bile duct guidelines, ampullary cancers are staged with the AJCC ampulla of Vater guidelines, and duodenal cancers are staged with the AJCC small intestine guidelines.

NONOPERATIVE PALLIATION

Approximately 80% to 85% of patients with pancreas adenocarcinoma are found to have unresectable disease at diagnosis because of metastatic or locally invasive disease. For the majority of patients, palliation of symptoms and improvement in quality of life are the primary purposes of any intervention. The three main symptoms needing palliation are obstructive jaundice, gastric outlet obstruction, and pain. Patients with ampullary, distal bile duct, and duodenal adenocarcinoma are more likely to have resectable disease, but if they are initially found to have advanced disease, they will also require nonoperative palliation.

Nonoperative Palliation of Obstructive Jaundice

Nonoperative palliation of obstructive jaundice may be achieved either percutaneously (see Fig. 91–6) or endoscopically during ERCP. Most centers will attempt endoscopic placement first and use percutaneous transhepatic approaches if required. Endoscopic placement is usually more comfortable for the patient and avoids trauma to the liver parenchyma and possible sequelae, including hemobilia and bile leakage. Endoscopic biliary stents may be made of plastic or metal. Plastic stents require periodic changing. Because of the size limitations of the accessory channel of endoscopes, the largest stent that can be placed is 12 French. This relatively small diameter results in periodic occlusion necessitating periodic change. In an effort to decrease stent occlusion, self-expanding metallic stents that can reach a diameter of 30 French have been developed. Metallic stents, however, eventually fail because of tumor ingrowth and, when they do fail, present a problem because they are not readily changeable. Additionally, they are more expensive than plastic stents. Covered stents are currently being developed and used and will, it is hoped, increase patency. Randomized controlled clinical trials comparing 10- or 11.5-French plastic stents with 30-French metallic stents have shown metallic stents to be associated with lower rates of cholangitis and stent replacement and fewer inpatient days.[47,48]

Nonoperative Palliation of Duodenal Obstruction

Until recently, the standard method of nonoperative palliation of duodenal obstruction was the placement of a percutaneous endoscopic gastrostomy tube. The development of expandable metallic stents deployable in the duodenum has provided another nonoperative technique for controlling gastric outlet obstruction that allows the patient to eat. Gastroduodenal stenting can be

successful in 80% to 90% of patients by providing adequate relief of obstruction.[49,50]

Nonoperative Palliation of Pain

Standard management of pain has been based on opioids and nonsteroidal anti-inflammatory agents. However, for patients to receive sufficient pain relief from narcotics, they often suffer many of the systemic side effects. US- and CT-guided celiac plexus nerve blocks have been used more recently in an attempt to specifically target the neurogenic pain caused by pancreatic and periampullary cancer. Several randomized controlled trials comparing standard oral narcotics with celiac plexus nerve blocks have demonstrated significant decreases in pain and narcotic use in patients undergoing these blocks.[51,52]

OPERATIVE PALLIATION

As discussed previously, current preoperative staging and imaging modalities allow resection in approximately 80% of patients explored for periampullary cancer. When a patient undergoes exploration and the cancer is found to be unresectable, a decision must be made regarding whether to operatively palliate the patient. Operative palliation is most beneficial in patients without widespread metastatic disease and with a life expectancy of more than several months. The potential morbidity and mortality associated with operative palliation should be weighed against the more durable palliation achieved with biliary bypass with or without gastrojejunostomy. Additionally, open chemical splanchnicectomy can be added to the operative palliative procedure.

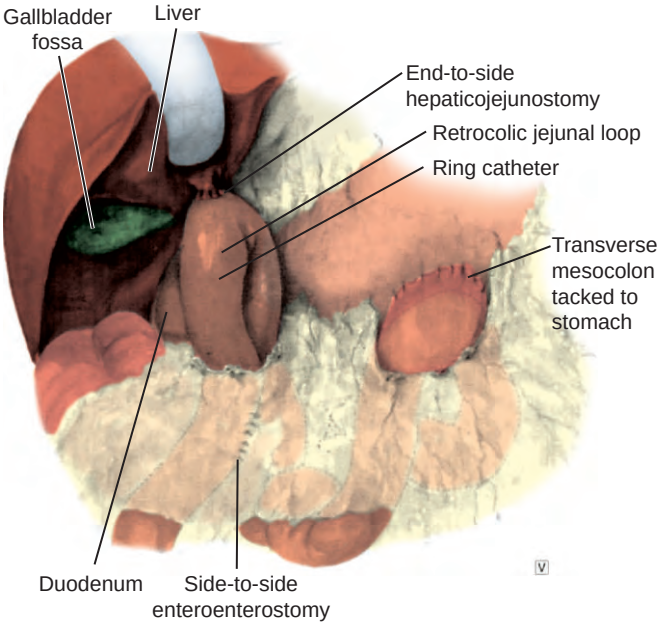

Figure 91–8. Anatomy after one method of palliative intervention. The biliary-enteric anastomosis is shown as a retrocolic end-to-side hepaticojejunostomy with a jejunal loop. A jejunojejunostomy was performed below the transverse mesocolon to divert the enteric stream away from the biliary-enteric anastomosis. Also shown is a retrocolic gastrojejunostomy. (From Cameron JL: Atlas of Surgery, vol 1. Toronto, BC Decker, 1990, p 427.)

Operative Palliation of Obstructive Jaundice

The most effective operative procedure to relieve obstructive jaundice is hepaticojejunostomy.[53,54] Other less effective operative procedures include cholecystojejunostomy or simple drainage through a T-tube inserted above the site of obstruction. Cholecystojejunostomy is prone to reobstruction because the cystic duct insertion site into the common bile duct is often close to the site of original obstruction. T-tube drainage causes a high-output biliary fistula and results in major electrolyte abnormalities. The hepaticojejunostomy is performed by removing the gallbladder and circumferentially dissecting the common hepatic duct near the bifurcation and dividing it. The anastomosis can be performed to a loop of jejunum with a Braun jejunojejunostomy between the afferent and efferent limbs (Fig. 91–8) or to a Roux-en-Y limb. In only a few patients palliated with a hepaticojejunostomy does recurrent jaundice develop before they die of their disease.[55]

Operative Palliation of Duodenal Obstruction

Periampullary cancers cause gastric outlet obstruction by compromising the lumen of the duodenum. Patients with gastric outlet obstruction who are not resection candidates and who do not have widely disseminated disease benefit from palliation, whether by operative or nonoperative stenting techniques. The role of prophylactic gastrojejunostomy is often debated. Much of the controversy stems from the discordant information on the exact percentage of patients with periampullary cancer in whom gastric outlet obstruction requiring surgical intervention eventually develops. This number ranges from 3% in some series[56] and approaches 20% in other series.[57] A prospective, randomized clinical trial was performed in 87 patients with unresectable periampullary cancer without gastric outlet obstruction in which they were randomized to undergo either retrocolic gastrojejunostomy or no bypass.[57] In none of the patients who underwent prophylactic gastrojejunostomy did gastric outlet obstruction subsequently develop, whereas symptoms requiring intervention later developed in 19% of the patients who did not undergo gastric bypass. The addition of gastrojejunostomy did increase the operative time, but it had no effect on morbidity, mortality, or length of hospital stay. The gastrojejunostomies were retrocolic, to the left of the middle colic vessels, and isoperistaltic (see Fig. 91–8). The gastrotomy was performed on the most dependent portion of the back wall of the stomach. Vagotomy is not routinely

performed after operative palliation of gastric outlet obstruction.

Operative Chemical Splanchnicectomy for Pain

Operative chemical splanchnicectomy was first introduced in the 1960s in an attempt to relieve the neurogenic pain associated with unresectable pancreas cancer.[58] A prospective randomized trial comparing intraoperative chemical splanchnicectomy with placebo in 137 patients with unresectable disease was performed by injecting 20 ml of 50% ethanol or saline through a spinal needle on either side of the aorta at the level of the celiac plexus (Fig. 91–9).[59] There were no significant differences in morbidity, mortality, or length of hospital stay. The group randomized to alcohol had significantly lower pain scores at 2, 4, and 6 months. Even the patients who did not report pain preoperatively were shown to derive a benefit from chemical splanchnicectomy postoperatively as their disease progressed.

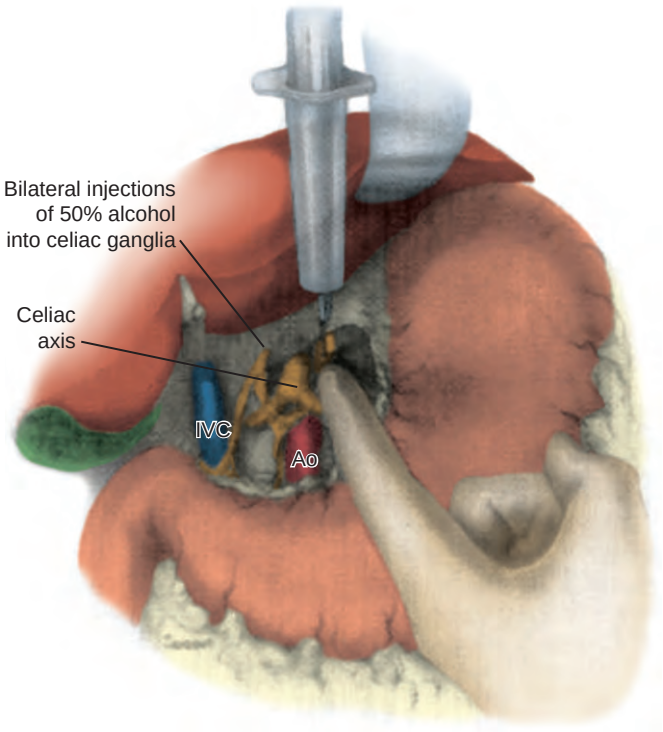

Figure 91–9. Technique of alcohol celiac nerve block in which 20 ml of 50% alcohol is injected on each side of the aorta (Ao) at the level of the celiac axis. IVC, inferior vena cava. (From Lillemoe KD, Cameron JL, Kaufman HS, et al: Chemical splanchnicectomy in patients with unresectable pancreatic cancer: A prospective, randomized trial. Ann Surg 217:447-455, discussion 456-457, 1993.)

RESECTION OF PANCREATIC AND PERIAMPULLARY CARCINOMA

Operative Technique of Pancreaticoduodenectomy

The first successful resection of a periampullary tumor was performed by Halsted in 1898 at the Johns Hopkins Hospital. He described a local ampullary resection with reanastomosis of the pancreatic and bile ducts into the duodenum in a woman with obstructive jaundice.[60] Codivilla performed the first en bloc resection of the head of the pancreas and duodenum for periampullary carcinoma, but the patient did not survive beyond the postoperative period.[61] The first successful two-stage pancreaticoduodenectomy was performed by Kausch in 1909.[62] In 1914, Hirschel reported the first successful one-stage pancreaticoduodenectomy.[63] In the first part of the 20th century, most periampullary cancers were managed by a transduodenal approach similar to that first reported by Halsted.

Whipple and colleagues in 1935 reported three successful two-stage en bloc resections of the head of the pancreas and the duodenum.[64] Over the next decade, modifications and technical refinements were made in the procedure, including the first one-stage pancreaticoduodenectomy in the United States by Trimble in 1941. The procedure was infrequently performed until the 1980s despite technical advances because of the formidable operative morbidity, mortality, and poor prognosis associated with periampullary cancer.

Exposure for a pancreaticoduodenectomy is obtained through a vertical midline incision from the xiphoid process to several centimeters below the umbilicus. Alternatively, a bilateral subcostal incision can be used. Exposure is greatly enhanced with the use of a mechanical retracting device.

The first portion of the operation focuses on assessing the extent of disease and resectability. The benefits and disadvantages of staging laparoscopy were discussed in the previous section. At open exploration, the entire liver is inspected and palpated to assess for the presence of metastases. The celiac axis is inspected for lymph node involvement. Tumor-bearing nodes within the resection zone do not contraindicate resection because long-term survival can be achieved with peripancreatic nodal involvement. The parietal and visceral peritoneal surfaces, the omentum, the ligament of Treitz, and the entire small and intra-abdominal large intestine are carefully examined for the presence of metastatic disease. Drop metastases in the pelvis are also evaluated. A Kocher maneuver is performed by elevating the duodenum and head of the pancreas out of the retroperitoneum and into the midline. The gallbladder is mobilized and the porta hepatis is assessed. The common hepatic artery and proper hepatic artery should also be assessed to confirm resectability.

The distal common hepatic duct is divided close to the level of the cystic duct entry site early during the operation. For distal common bile duct cancers or pancreatic cancers near this area, more margin on the bile duct into

the hilus of the liver may be required. The bile duct is retracted caudally, and a dissection plane is opened on the anterior surface of the portal vein. During these maneuvers, the portal structures should be assessed for a replaced right hepatic artery originating from the superior mesenteric artery. If found, this vessel should be dissected and protected from injury. If the patient appears to have an accessory right hepatic artery and a significant native right hepatic artery, the accessory vessel can often be taken. The gastroduodenal artery is next identified and occluded atraumatically. This maneuver confirms that the hepatic artery is not being supplied solely retrograde through the superior mesenteric artery collaterals (in the setting of celiac axis stenosis or occlusion).

In a classic Whipple procedure, a 30% to 40% distal gastrectomy is performed by dividing the right gastric and right gastroepiploic arteries. The antrectomy is then completed with a linear stapling device. For a pylorus-preserving pancreaticoduodenectomy, the proximal portion of the gastrointestinal tract is divided 2 to 3 cm distal to the pylorus with a linear stapling device. The right gastric artery can often be spared, but it may be taken if it allows better mobilization of the duodenum for reconstruction. The gastrointestinal tract is divided distally at a point of mobile jejunum, typically 20 cm distal to the ligament of Treitz. The mesenteric vasculature to this initial portion of the jejunum is carefully dissected and divided. Once the proximal jejunum is separated from its mesentery, it can be delivered dorsal to the superior mesenteric vessels from the left to the right side.

The superior mesenteric vein caudal to the neck of the pancreas can be identified running anterior to the third portion of the duodenum and is frequently surrounded by adipose tissue as it receives tributaries from the uncinate process and neck of the pancreas, the greater curve of the stomach, and the transverse mesocolon. In this location, the superior mesenteric vein is identified by dissecting the fatty tissue of the transverse mesocolon away from the uncinate process of the pancreas. Division of the branches emptying into the anterior surface of the superior mesenteric vein allows continued cephalad dissection. Often, a vein retractor to lift the inferior edge of the neck of the pancreas is useful for visualization (Fig. 91–10). The plane anterior to the superior mesenteric vein is developed under direct vision while avoiding branches and tumor involvement. After the plane anterior to the portal vein and superior mesenteric vein is complete, a Penrose drain can be looped under the neck of the pancreas.

Stay sutures are placed superiorly and inferiorly on the pancreatic remnant to reduce bleeding from the segmental pancreatic arteries. The pancreatic neck is then divided sharply after confirming a free plane anterior to the portal and superior mesenteric veins. The Penrose drain previously placed under the neck of the pancreas is used to elevate the pancreatic tissue to be divided and protect the underlying major veins. The main pancreatic duct should be noted so that it can be incorporated into the subsequent reconstruction.

The specimen now remains connected by the uncinate process of the pancreas. This structure is separated from the portal vein, superior mesenteric vein, and superior mesenteric artery by serially clamping, dividing, and tying the smaller branches off the portal and superior mesenteric vessels. Dissection should be performed flush with these structures to remove all pancreatic and nodal tissue in these areas but without injuring the superior mesenteric artery and vein at this level. The specimen can then be removed, and the pancreatic neck margin, uncinate margin, and common hepatic duct margins are marked for pathologic examination. To speed up analysis of these frozen section margins, the common hepatic duct margin and the pancreatic neck margin should be sampled earlier and sent for pathologic examination while the main specimen is still being removed.

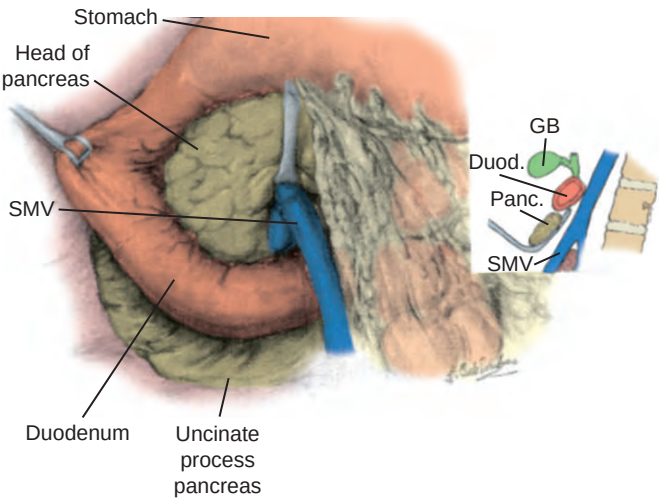

Figure 91–10. The superior mesenteric vein (SMV) can be visualized by performing an extended Kocher maneuver. At the level of the third portion of the duodenum (working laterally to medially), the SMV is the first and largest vascular structure running anterior to the duodenum. The *inset* shows the gallbladder (GB). (From Cameron JL: Rapid exposure of the portal and superior mesenteric veins. Surg Gynecol Obstet [now J Am Coll Surg] 176:395-398, 1993.)

Multiple options for reconstruction after pancreaticoduodenectomy are available. The issues and controversies surrounding the pancreatic, biliary, and gastrointestinal reconstructions are outlined by multiple papers specifically addressing these issues.

The most common reconstruction involves placing the end of the divided jejunum through a defect in the right transverse mesocolon to create a pancreaticojejunostomy, followed by hepaticojejunostomy and then duodenojejunostomy (Fig. 90–11). Some groups prefer to use a Roux limb for the pancreaticojejunostomy. The pancreatic reconnection is the most problematic anastomosis and is responsible for the majority of the morbidity and mortality associated with the procedure.

Controversy continues regarding the best type of pancreaticojejunostomy, the importance of duct-to-mucosa sutures, and the use of pancreatic duct stents. The pancreatic reconstruction can be performed with either a duct-to-mucosa anastomosis or an invagination

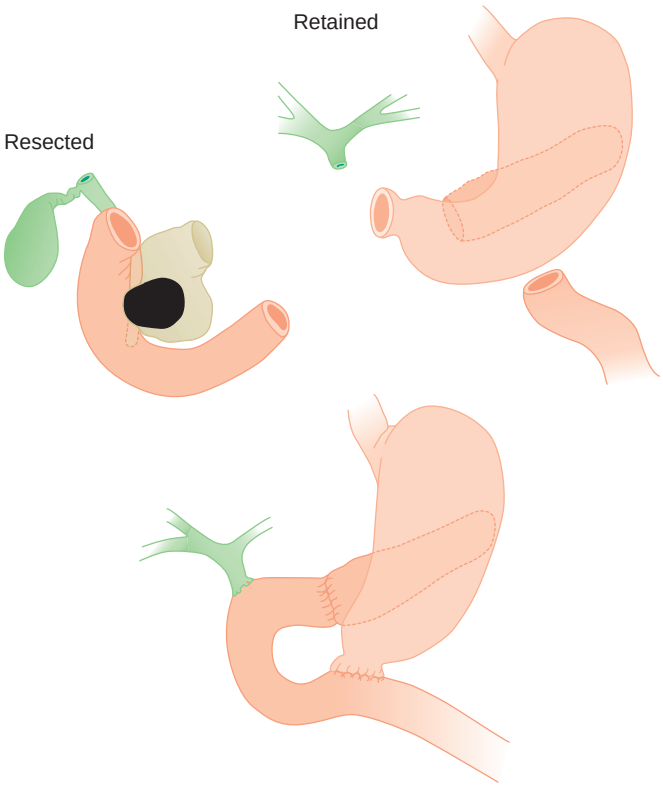

Figure 91–11. Pylorus-preserving pancreaticoduodenectomy. *Top left,* Structures resected include the duodenum (except for the initial 1 to 2 cm beyond the pylorus); the head, neck, and uncinate process of the pancreas, with tumor *(black);* the gallbladder; and the distal extrahepatic biliary tree. *Top right,* Structures retained include the entire stomach, pylorus, proximal 1 to 2 cm of the duodenum, body and tail of the pancreas, proximal biliary tree, and jejunum distal to the ligament of Treitz. *Bottom,* The reconstruction is shown as a proximal end-to-end pancreaticojejunostomy, a hepaticojejunostomy decompressed with a percutaneous transhepatic catheter, and a distal duodenojejunostomy. (From Yeo CJ, Cameron JL: The pancreas. In Hardy JD [ed]: Hardy's Textbook of Surgery, 2nd ed. Philadelphia, JB Lippincott, 1988, p 718.)

technique. With either technique, the proximal jejunal stump is brought through a defect in the mesocolon to the right of the middle colic artery. The duct-to-mucosa anastomosis is constructed in an end-to-side fashion in which the outer back row is placed with interrupted 3-0 silk sutures that incorporate the capsule of the transected pancreas and seromuscular bites of the jejunum. A small defect is then made in the jejunum to which a duct-to-mucosa anastomosis is performed that incorporates the pancreatic duct and the full thickness of the jejunum with interrupted 5-0 Maxon suture. Some surgeons prefer to stent this anastomosis with a 6-cm stent cut from a 5- or 8-French pediatric feeding tube. Three centimeters of the stent is placed in the pancreatic duct, and the other half is placed in the jejunum. The stent is held in place with one of the Maxon sutures from the back row. This stent typically passes through the intestinal tract and into the stool within a couple of weeks.

The invagination technique is performed with an end-to-end or end-to-side pancreaticojejunostomy. The pancreatic remnant is circumferentially cleared and mobilized for 2 to 3 cm to allow for an optimal anastomosis. The pancreaticojejunostomy is performed in two layers, with the outer layer consisting of interrupted 3-0 silk suture that incorporates the capsule of the pancreas and the seromuscular layers of the jejunum. The inner layer consists of running 3-0 absorbable suture that incorporates the capsule and a portion of the cut edge of the pancreas and the full thickness of the jejunum. An attempt should be made to incorporate the pancreatic duct into the inner layer for several bites to splay it open. When completed, this anastomosis invaginates the cut surface of the pancreatic neck into the jejunal lumen for several centimeters.

If the stomach is used to reconnect the pancreas, it is invaginated into the back wall of the stomach as described previously for the jejunum. In a prospective randomized trial comparing pancreaticogastrostomy with pancreaticojejunostomy, there was no difference in the leak or fistula rate between the two types of anastomoses.[65]

The biliary anastomosis is next performed with an end-to-side hepaticojejunostomy approximately 5 to 10 cm distal to the pancreaticojejunostomy. This anastomosis is performed with a single layer of interrupted absorbable suture such as 4-0 Maxon. If the patient has a percutaneous biliary stent, it is repositioned into the anastomosis. Preoperative biliary stenting remains controversial. Most groups believe that routine preoperative biliary stenting is of no benefit and carries potential risk, including an increased risk for wound or infectious complications, as well as an increased risk for pancreatic fistula formation.[66-68] Stenting can be considered in patients with obstructive jaundice who will have a substantial delay between initial evaluation and definitive surgery and in patients with cholangitis.

The third anastomosis performed is the duodenojejunostomy or gastrojejunostomy, depending on whether the pylorus has been preserved. This anastomosis can be performed 10 to 15 cm distal to the hepaticojejunostomy, proximal to the portion of jejunum traversing the defect in the mesocolon. Alternatively, it can be performed in antecolic fashion more distally on the jejunal limb, distal to where it traverses the mesocolic defect.

After the reconstruction is completed, closed suction drains are left in place near the pancreatic and biliary anastomoses. Some groups prefer not to drain and accept that if a fluid collection becomes clinically evident postoperatively, percutaneous drainage by interventional radiology may be required. They are also of the belief that closed suction drains may contribute to the development of pancreatic leak and fistula.

Postoperative management after pancreaticoduodenectomy consists of keeping the patient with nothing by mouth for 1 or 2 days and advancing the diet with liquids and then solids as tolerated. The stomach is decompressed overnight after the day of surgery with a nasogastric tube, which is usually removed the next

morning unless the output is high. The drains around the pancreatic anastomosis are typically removed once the patient has been on a regular diet and if significant amounts of amylase-rich fluid or bile are not draining.

Distal Pancreatectomy for Pancreas Cancer in the Body or Tail

Staging laparoscopy should be considered in patients with distal pancreatic cancer. If metastatic disease is found, pancreatectomy is unlikely to help in palliation of the patient. Exposure for distal pancreatectomy and splenectomy is obtained through a vertical midline incision from the xiphoid process to several centimeters below the umbilicus. Alternatively, a bilateral subcostal incision can be used. Exposure is greatly enhanced with the use of a mechanical retracting device. Folded sheets placed behind the patient underlying the spleen can also enhance exposure, especially in patients with a deep body habitus.

The lesser sac should be entered by elevating the greater omentum off the transverse colon. The splenic flexure of the colon should also be mobilized caudally and away from the spleen by dividing the lienocolic ligament. Splenectomy is usually performed with distal pancreatectomy in patients suspected of having carcinoma to obtain better margins, to remove the lymph nodes at the tip of the pancreas and the hilum of the spleen, and to avoid tedious dissection of the splenic artery and vein. The spleen is mobilized toward the midline by dividing the lienorenal ligament with the electrocautery device. The short gastric vessels in the lienogastric ligament are isolated and ligated. A plane is then developed behind the pancreatic tail and body to also mobilize the splenic artery and vein. This dissection is continued until an adequate margin is reached beyond the tumor. The splenic artery and vein are isolated at this level and suture-ligated. A row of overlapping U stitches of absorbable suture should then be placed. The electrocautery device is next used to transect the pancreatic parenchyma distal to this suture line (Fig. 90–12). A frozen section should be performed on the pancreatic margin to confirm clearance of the lesion.

Postoperative management of patients after distal pancreatectomy is usually quite straightforward. Patients are advanced on a diet as tolerated. If an operative drain is left in place, it is monitored for signs of a pancreatic leak. Removing the spleen does place the patient theoretically at increased risk for postsplenectomy sepsis, and vaccines are given either preoperatively or after recovery for pneumococcus, *Neisseria meningitidis,* and *Haemophilus influenzae.*

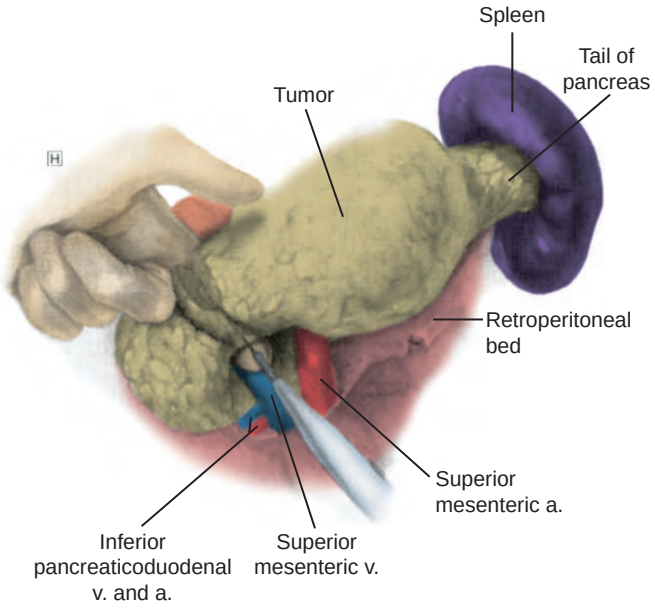

Figure 91–12. Near the completion of a distal pancreatectomy and splenectomy for a tumor in the body of the pancreas. The spleen and tail of the pancreas have been mobilized out of the retroperitoneum. The pancreatic parenchyma is being divided with the electrocautery device. (From Cameron JL: Atlas of Surgery, vol 1. Toronto, BC Decker, 1990, p 27.)

COMPLICATIONS AFTER PANCREATICODUODENECTOMY AND DISTAL PANCREATECTOMY

The mortality rate after pancreaticoduodenectomy at centers specializing in pancreatic surgery is in the 2% to 4% range. Despite the low mortality rates, especially when compared with those reported before the 1980s, the rate of postoperative complications remain high. In a series of 564 pancreaticoduodenectomies performed for adenocarcinoma, the mortality rate was 2.3% with an overall complication rate of 31%.[69] In this series, the three most common complications were delayed gastric emptying in 14%, wound infection in 7%, and pancreatic fistula in 5% (Table 91–2). Delayed gastric emptying is not life-threatening and is almost always self-limited, but it can increase the length of stay and hospital costs significantly. The great majority of patients respond to nasogastric decompression and nutritional support. Erythromycin is sometimes used to increase gastrointestinal motility.[70]

Pancreatic fistulas are not uncommon after pancreaticoduodenectomy and can lead to very severe problems, including intra-abdominal abscess and bleeding, if not properly controlled. In the majority of patients, a pancreatic leak will seal with conservative management. If closed suction drains are in place and a CT scan confirms the absence of undrained abscesses, often no other major intervention is necessary. If a CT scan demonstrates an intra-abdominal abscess, interventional radiologic techniques are usually successful at controlling the infection. If a patient is relatively asymptomatic with a controlled pancreatic leak and is on a regular diet, consideration can be given to sending the patient home with outpatient drain management. In most cases, the fistula will improve and cease within a couple of weeks. If the patient is symptomatic from the fistula or it has high

Table 91–2 Mortality and Morbidity After Pancreaticoduodenectomy and Distal Pancreatectomy in 616 Patients

	Overall ($N = 616$)	Pancreaticoduodenectomy/Total Pancreatectomy ($n = 564$)	Distal Pancreatectomy ($n = 52$)	*P* Value
Perioperative mortality	2.3%	2.3%	1.9%	NS
Overall complications	30%	31%	25%	NS
Specific complications				
Reoperation	3%	3%	4%	NS
Delayed gastric emptying	—	14%	—	—
Cholangitis	—	3%	—	—
Bile leak	—	2%	—	—
Wound infection	7%	7%	5%	NS
Pancreatic fistula	5%	5%	8%	NS
Intra-abdominal abscess	3%	3%	4%	NS
Pneumonia	1%	1%	0%	NS
Pancreatitis	1%	1%	0%	NS
Postoperative length of stay				
Mean ± SE	13.7 ± 0.4 days	14.0 ± 0.4 days	11.5 ± 2.2 days	.08
Median	11 days	11 days	7 days	

From Sohn TA, Yeo CJ, Cameron JL, et al: Resected adenocarcinoma of the pancreas—616 patients: Results, outcomes, and prognostic indicators. J Gastrointest Surg 4:567-579, 2000.

output (>200 ml/day), consideration should be given to restricting the patient's diet and using parenteral nutrition.

In a series of 52 patients undergoing distal pancreatectomy for pancreatic adenocarcinoma of the body or tail, the mortality rate was 1.9% with an overall morbidity rate of 25%. The three most common complications were pancreatic fistula in 8%, wound infection in 5%, and intra-abdominal abscess in 4% (see Table 91–2).

LONG-TERM SURVIVAL AFTER RESECTION OF PERIAMPULLARY CANCER

Survival of patients after resection of pancreatic and periampullary cancer is dependent on many factors, including the site of the primary and the stage of the disease. In a series of 616 patients who underwent resection of pancreatic cancer, pancreaticoduodenectomy was performed in 85%, distal pancreatectomy in 9%, and total pancreatectomy in 6%.[69] The overall survival rate of the entire cohort was 63% and 17% at 1 and 5 years, respectively, with a median survival of 17 months. For right-sided lesions requiring pancreaticoduodenectomy, the survival rates were 64% and 17% versus 50% and 15% for left-sided lesions at 1 and 5 years, respectively (Fig. 91–13). Factors that had favorable prognostic significance by univariate analysis were negative resection margins, tumor smaller than 3 cm, negative lymph nodes, blood loss less than 750 ml, absence of blood transfusions, well or moderate tumor differentiation, and postoperative chemoradiation.

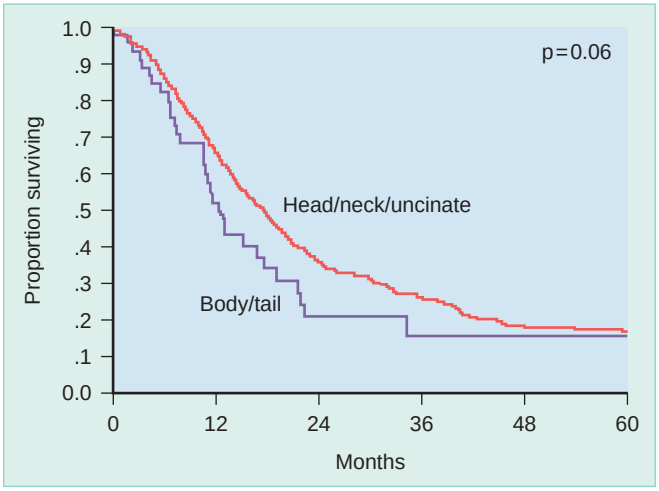

Figure 91–13. Kaplan-Meier actuarial survival curves comparing patients with head, neck, and uncinate lesions (right-sided, $n = 563$) with those who had body and tail lesions (left-sided, $n = 49$). (From Sohn TA, Yeo CJ, Cameron JL, et al: Resected adenocarcinoma of the pancreas—616 patients: Results, outcomes, and prognostic indicators. J Gastrointest Surg 4:567-579, 2000.)

An analysis was performed of 58 actual 5-year survivors from 242 consecutive patients with resected peri-

ampullary adenocarcinoma; 62% had pancreas adenocarcinoma, 19% had ampullary adenocarcinoma, 12% had distal bile duct adenocarcinoma, and 7% had duodenal adenocarcinoma.[71] The actual 5-year tumor-specific survival rates were 15% for pancreas, 39% for ampullary, 27% for distal bile duct, and 59% for duodenal adenocarcinoma. The 5-year survivors had a significantly higher rate of well-differentiated tumors, negative resection margins, and negative lymph nodes.

Some groups have advocated that patients with node-positive cancer have better survival after extended lymphadenectomy.[72] A trial was performed in which 299 patients with periampullary adenocarcinoma were randomized to standard pancreaticoduodenectomy or radical surgery in which the retroperitoneal lymph nodes were removed. For all periampullary cancer patients, those who underwent standard resection had 1- and 5-year survival rates of 78% and 25%, respectively, as compared with 76% and 31% ($P = .57$) for patients in the radical surgery group. For pancreatic adenocarcinoma patients, 1- and 5-year survival rates in the standard group were 75% and 13%, respectively, versus 73% and 29% in the radical surgery group ($P = .13$).[73]

ADJUVANT THERAPY

In 1985 the Gastrointestinal Tumor Study Group (GITSG) trial was reported and demonstrated that patients undergoing resection for pancreas cancer who received adjuvant chemoradiotherapy had better survival.[74] This prospective randomized trial compared observation (control) and split-course radiotherapy (4000 cGy, 20 fractions, over a 6-week period) with bolus 5-fluorouracil (5-FU), 500 mg/m^2 intravenously on each of the first 3 days of the 200-cGy sequence of radiotherapy, in patients with pancreas cancer. Additionally, patient receiving adjuvant therapy underwent bolus 5-FU administration every week for 2 years.

It has also been demonstrated that multiagent 5-FU–based chemotherapy regimens can be combined with radiotherapy. The group at the Virginia Mason Clinic have combined 5-FU, cisplatin, interferon alfa, and radiotherapy and have shown significant activity in the adjuvant setting, albeit with increased toxicity.[75] A randomized controlled trial performed by the European Study Group for Pancreatic Cancer (ESPAC-1) demonstrated that systemic chemotherapy alone is superior to chemoradiation therapy in the postoperative setting.[76] The role of adjuvant chemoradiotherapy in the treatment of distal bile duct, ampullary, and duodenal cancer is even less well understood than for pancreas cancer because of the relative infrequency of these diseases.

NEOADJUVANT THERAPY

A series of 193 patients with biopsy-proven pancreatic adenocarcinoma who completed neoadjuvant chemoradiotherapy and 70 patients who underwent resection without neoadjuvant therapy has been reported.[77] The exact treatment regimens varied, but 183 patients (95%) received 5-FU–based chemotherapy delivered concurrently with daily external-beam radiotherapy for a planned total dose of 4500 cGy at 180 cGy per fraction over a period of 5 weeks plus a 540-cGy boost to the tumor. Complete histologic responses were found in 6% of patients. Patients who underwent resection with minimal residual disease and those whose tumor specimens had significant tumor necrosis had significantly better survival.

The MD Anderson Cancer Center experience with neoadjuvant chemoradiotherapy for resectable pancreatic cancer was recently summarized.[78] Since 1988, four prospective neoadjuvant trials have been completed at that institution in patients with adenocarcinoma of the pancreatic head. The trials have evolved, with the first two using 5-FU as the chemotherapy component, the third using paclitaxel, and the fourth using gemcitabine. A total of 86 patients were enrolled in the most recent trial, with 58% of the resected surgical specimens showing at least 50% tumor cell kill and two with a complete pathologic response. With a median follow-up now extending more than 3 years, the median survival of resected patients was approximately 36 months.

Neoadjuvant therapy has several theoretical advantages. It allows more timely administration of chemotherapy or chemoradiotherapy to patients who are at a high risk for failure after surgical resection. It has the potential to shrink the tumor and can theoretically decrease the extent of local disease. Patients in whom disseminated disease develops during neoadjuvant treatment are unlikely to have benefited from initial resection and are spared the time commitment, morbidity, and potential mortality from resection. It may allow better selection of patients who are most likely to benefit from surgical resection.

PALLIATIVE CHEMOTHERAPY

5-FU was considered the standard therapy for advanced pancreas cancer before approval of gemcitabine by the Food and Drug Administration (FDA). Although response rates greater than 20% were reported for treatment with 5-FU, most of these reports predated the era of CT imaging and were based primarily on clinical tumor evaluation. Modern phase II trials have reported response rates of less than 10% for 5-FU alone or with leucovorin.[79,80]

Gemcitabine was approved by the FDA because of its ability to alleviate tumor-related symptoms. A pivotal phase III trial was completed to quantify this effect in patients with metastatic, symptomatic pancreatic cancer.[81] One hundred twenty-six patients who had not received previous chemotherapy for metastatic disease were randomized to weekly gemcitabine ($n = 63$) or weekly bolus 5-FU ($n = 63$). Overall survival in patients treated with gemcitabine was significantly improved over those treated with 5-FU (median survival, 5.7 versus 4.4 months, respectively; $P < .0025$). One-year survival rates were 18% for patients treated with gemcitabine versus 2% for patients treated with 5-FU.

Trials are currently ongoing in which gemcitabine is combined with other chemotherapeutic agents such as topoisomerase I inhibitors, platinums, and taxanes. Additionally, gemcitabine is being combined with molecularly targeted agents such as anti-angiogenic and epidermal growth factor receptor agents.[82]

IMMUNOTHERAPY

Immune-based therapies can exploit either the cellular or the humoral components of the immune system (or both). Strategies aimed at the cellular components recruit and activate T cells that recognize tumor-specific antigens. In a phase I trial of patients with surgically resected adenocarcinoma of the pancreas, 14 patients were treated with an allogeneic tumor cell vaccine transduced to secrete granulocyte-macrophage colony-stimulating factor.[83] No dose-limiting toxicities were encountered. This vaccine approach induced dose-dependent systemic antitumor immunity as measured by increased postvaccination delayed-type hypersensitivity responses against autologous tumors. Moreover, the three long-term survivors had the strongest postvaccination responses. This strategy is currently being evaluated in a phase II trial at Johns Hopkins.

CONCLUSION

Patients with pancreatic and periampullary cancer represent a difficult and challenging group to treat. It is clear that there is currently no single modality that can uniformly cure these patients; however, surgical resection should be attempted when appropriate because resection gives the only chance of long-term survival. Traditionally, these patients have had a poor prognosis, but with proper staging and patient selection, results are slowly improving. Resection should be performed by experienced surgeons to minimize morbidity and mortality. It is clear that there are many more developments that need to be made to improve the survival and well-being of these patients.

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Chapter

92

Neuroendocrine Tumors of the Pancreas

Daniela Ladner · Jeffrey A. Norton

The overall prevalence of functional pancreatic endocrine tumors is low, approximately 1 to 10 per million in the population.[1,2] Gastrinoma and insulinoma are the most common functional neuroendocrine tumors and account for approximately 70% to 90% of all functional pancreatic neuroendocrine tumors. Thus, somatostatinomas and other functional tumors are rare, and no endocrine surgeon has vast experience with them. Tumors are discernable from each other, in that they all produce a surplus of hormone, leading to a specific symptomatology. They can possibly present with life-threatening symptoms, which is a major reason to identify and resect these tumors. With exception of insulinomas, pancreatic endocrine tumors all are prone to malignancy. Obviously, if the tumor can be completely resected, the characteristic syndrome will resolve. However, in many individuals with these rare tumors, the extent of the disease limits the effectiveness of surgery in completely controlling the tumor. Although pancreatic endocrine tumors are malignant, they are usually low grade such that aggressive surgical extirpation is beneficial in most instances and ameliorates the symptoms even if resection is not complete. In these patients, effective medical treatments for controlling symptoms may be available and must be considered.

There are a host of pancreatic endocrine tumors other than the most frequent gastrinomas and insulinomas originating from neuroendocrine cells. Those include somatostatinomas, glucagonomas, pancreatic polypeptide–producing tumors (PPomas), vasoactive intestinal polypeptide–producing tumors (VIPomas), growth hormone–releasing factor–producing tumors (GRFomas), adrenocorticotropic hormone–producing tumors (ACTHomas), parathyroid hormone–producing tumors (PTHomas), neurotensinomas, and nonfunctional islet cell tumors. However, some researchers indicate that it is unclear whether these tumors originate from the pancreatic islets.[3] Pancreatic endocrine tumors may contain ductular structures; may produce hormones that are not produced by the normal pancreas, including gastrin and VIP; and may produce more than one hormone.[3-5] These findings suggest that pancreatic endocrine tumors originate from dedifferentiation of an immature pancreatic stem cell.[5]

It has also been proposed that pancreatic endocrine tumors originate from cells that are part of the diffuse neuroendocrine system: amine precursor uptake and decarboxylation tumors (APUDomas).[6-8] These tumor cells contain dense secretory granules; may produce multiple peptides; and usually stain positive for neuron-specific enolase, chromogranin A, and synaptophysin.[3,4,9] APUDomas comprise many neuroendocrine tumors, including carcinoids, medullary thyroid carcinoma, and pheochromocytomas.[6-8]

Microscopically, pancreatic endocrine tumors are composed of sets of small, round cells with uniform nuclei and cytoplasm (Fig. 92–1). Mitotic figures are rare, and the precise determination of malignancy cannot be made by histologic appearance.[10,11]

Recent studies suggest that there is an aggressive and nonaggressive form of pancreatic neuroendocrine tumor. The aggressive form comprises glucagonoma, somatostatinoma, and most nonfunctional tumors. It is more common in patients without multiple endocrine neoplasia (MEN) 1. It has short disease duration, large pancreatic tumors, liver metastases, and a long-term survival rate as low as 20% to 50%. Studies have shown a number of clinical and tumoral factors that are predictors of aggressive growth. These include liver metastases, lymph node metastasis, local invasion, large primary tumor size, nonfunctional tumor, and incomplete tumor resection. The further definition of other factors will likely have a significant impact on the surgical management of pancreatic neuroendocrine tumors; that is, aggressive tumors require more aggressive surgery.

The molecular pathogenesis of pancreatic neuroendocrine tumors is just being elucidated and holds promise for the identification of important parameters.

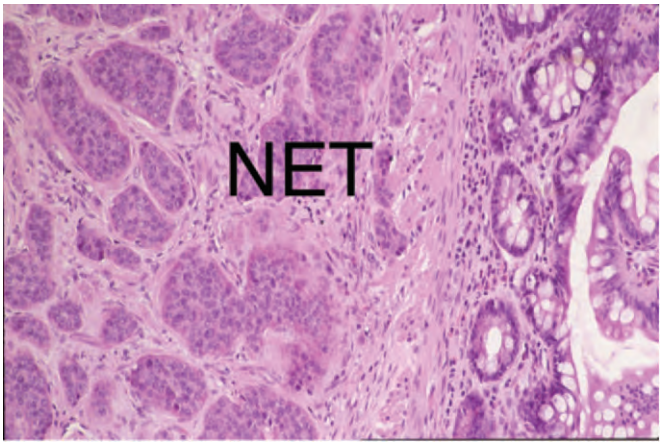


Figure 92–1. Neuroendocrine tumor (NET) within the wall of duodenum. This tumor was found to be a somatostatinoma.

Recent studies demonstrate that alterations in the tumor suppressor gene *DPC4* located on 18q21 is involved in tumorigenesis.[12] At present, no gene alteration sufficiently predicts aggressive behavior enough to allow a different more aggressive treatment strategy to be implemented.

Pancreatic endocrine tumors are classified according to the functional syndrome they produce. Every type of pancreatic endocrine tumor may be associated with MEN 1, and it is important to recognize this association because these patients generally have multiple tumors and a more indolent natural history.[13] Several studies suggest that, in addition to MEN 1, pancreatic neuroendocrine tumors are found in higher frequency in patients with von Recklinghausen's disease,[14-16] von Hippel–Lindau disease,[17] and tuberous sclerosis.[18] In patients with von Recklinghausen's disease, duodenal somatostatinoma and gastrinoma have been reported.[14-16] Of patients with von Hippel–Lindau disease, 17% had pancreatic endocrine tumors, including both adenomas and carcinomas. However, it is unusual for these tumors to be functional, and few patients have a clinical hormonal syndrome. Patients with tuberous sclerosis may have a higher incidence of insulinoma and nonfunctional pancreatic neuroendocrine tumors.

INSULINOMA

Insulinoma is a tumor of pancreatic B cells that secrete insulin. This leads to excessive insulin in the blood with resultant hypoglycemia. Hyperinsulinemia was first described in 1927. Insulinomas occur approximately in 1 per million population per year.[19] Setting them apart from other neuroendocrine tumors of the pancreas, these tumors are generally benign (90%), only 10% being malignant. They occur throughout and almost exclusively within the pancreas as solitary growths. There is usually no evidence of local invasion or locoregional lymph node metastases.[20] They present mostly as sporadic tumors (80%), or they are part of a familial syndrome (MEN 1). In the sporadic form the tumors are solitary and small (<2 cm in diameter). This makes localization often difficult.[21] The familial form, however is larger (>3 cm) and they often present with multiple tumors in the pancreas.

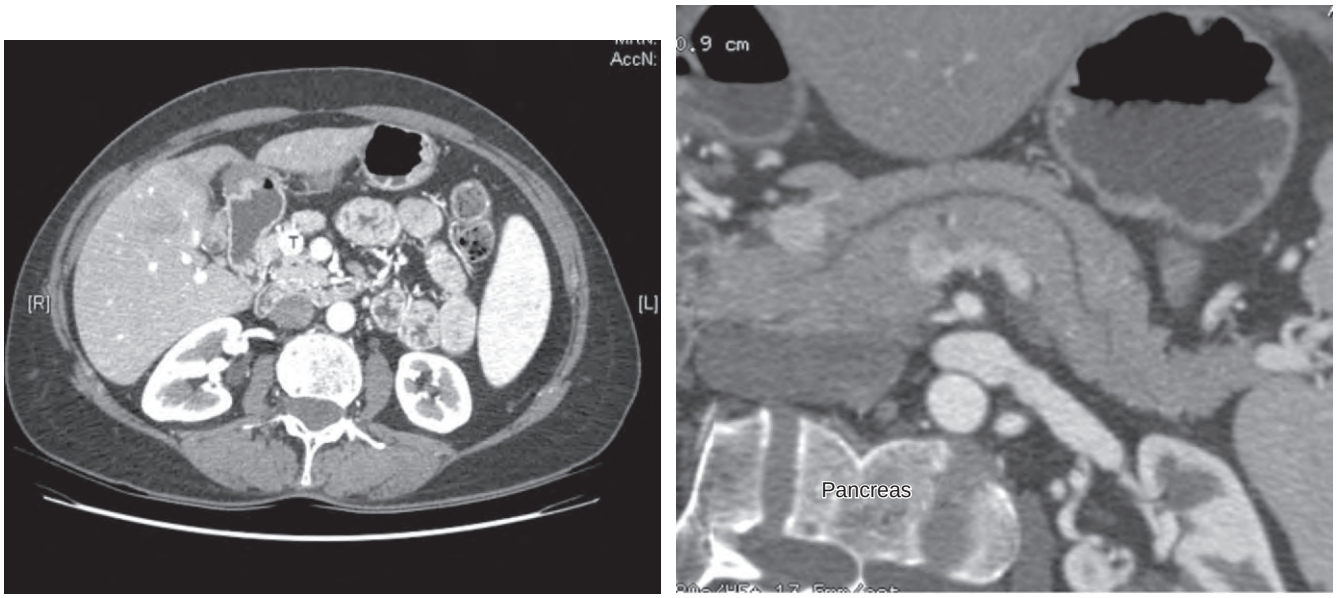
Symptoms and Diagnosis

Whipple's original triad for the diagnosis of insulinoma includes neuroglycopenic symptoms, low blood glucose (<3 mmol/L), and relief of symptoms with glucose administration. Patients with insulinoma suffer from acute neuroglycopenia. This includes anxiety, dizziness, obtundation, confusion, unconsciousness, personality changes, and seizures.[21,22] Symptoms are typically worse in the morning owing to the combination of continuous insulin production and fasting hypoglycemia; 80% of patients gain weight, usually around 20 pounds.[23] Patients may also present during an attempt to lose weight. A majority (60% to 75%) of patients are women, and many have undergone extensive psychiatric evaluation. Many have been diagnosed with a neurologic condition such as seizure disorder, cerebrovascular accident, or transient ischemic attack.[23] In a review of 59 patients with insulinoma, the interval from the onset of symptoms to the time of diagnosis ranged from 1 month to 30 years, with the median time to diagnosis being 2 years.[23] Approximately 5% to 10% of patients with insulinoma also have MEN 1, which should be excluded or included based on history, symptoms, physical examination, and biochemical findings.

Patients with suspected insulinoma may first be instructed to undergo an overnight fast in an outpatient setting. However, the gold standard test for the diagnosis of insulinoma is the 72-hour fasting test. The diagnosis of factitious hypoglycemia is a critical component of the differential and must be excluded prior to surgery.

Factitious hypoglycemia, in which exogenous insulin or oral hypoglycemic drugs are administered clandestinely, may present exactly the same symptoms as an insulinoma and may lead to an inappropriate diagnosis.[24] Factitious hypoglycemia may be suspected more often in a patient with relatives who are diabetic or in a patient associated with the medical profession, where they have access to insulin or oral hypoglycemic agents. This is seen more often in women than in men. They either take the pills or give themselves injections to induce hypoglycemia. Urinary sulfonylurea concentration should be measured by gas chromatography–mass spectroscopy to detect abuse of oral hypoglycemic drugs. Also, anti-insulin antibodies should not be detectable in those with insulinoma.[25] An increased serum concentration of proinsulin or C-peptides during hypoglycemia effectively excludes the diagnosis of factitious hypoglycemia because exogenously administered insulin does not contain these proteins and actually suppresses their endogenous production.

The diagnosis of insulinoma is difficult in patients with chronic renal failure because they may develop hypoglycemia for other reasons, but it still has been reported to occur.[26]



A B

Figure 92–2. **A,** CT of a small insulinoma (T) within the head of the pancreas. **B,** Three-dimensional reconstruction of the same CT, which shows the small hypervascular insulinoma within the head of the pancreas.

Any patient with a history of neuroglycopenic symptoms and hypoglycemia should undergo a standard diagnostic 72-hour fasting test. It is performed in the in-patient hospital setting and lasts for a maximum of 72 hours. During the fast the patient may only drink water or noncaloric beverages. The study is designed to induce symptoms of hypoglycemia in a controlled stetting so that serum levels of glucose and insulin can be measured during the occurrence of symptoms. Blood is tested for serum glucose and immunoreactive insulin concentration every 6 hours and when symptoms develop. If the patient develops neuroglycopenic symptoms such as confusion, altered mental status, dizziness or seizure, serum levels of glucose, insulin, C-peptide, and proinsulin are drawn and the fast is terminated. Dextrose is administered to relieve the symptoms of hypoglycemia.

The diagnosis of insulinoma is made if the patient develops neuroglycopenic symptoms, the serum glucose level is lower than 45 mg/dl and the concomitant serum level of insulin is higher than 5 µU/L. Elevated serum levels of C-peptide (>0.7 ng/ml) and proinsulin are confirmatory and exclude factitious hypoglycemia.[21,25] Sixty percent of patients with insulinoma develop symptoms within 24 hours after fasting begins, and almost all patients develop symptoms within 72 hours.[25]

Preoperative Localization

Sporadic nonfamilial insulinomas are difficult to precisely localize preoperatively.[27] For this reason, the diagnosis must be unequivocal before contemplating an operation. Ultrasonography is an initial study to try to localize the insulinoma. The tumor appears sonolucent compared with the more echodense pancreas. However, ultrasound images only approximately 20% of insulinomas.[28,29] It is especially limited by overlying bowel gas and in obese patients.

Spiral computed tomography (CT) with intravenous contrast and serial sections at small intervals through the pancreas (Fig. 92–2) is probably the noninvasive study of choice.[22] It images tumors based on the fact that they are hypervascular compared to the surrounding pancreas. It images approximately 40% of insulinomas.[22,30,31] It is also useful for imaging malignant insulinomas and demonstrating liver metastases.

Magnetic resonance (MR) is a newer study for imaging insulinomas. It images tumor based primarily on T2-weighted images in which insulinomas appear bright. The sensitivity is equivalent to that of CT[28,29] and increases with larger tumor size. Its utility is similar to CT, and either study should be used but not both.

Somatostatin receptor scintigraphy (SRS) or Octreoscan has become an important imaging modality for neuroendocrine tumors of the pancreas. It images tumors based on the density of type 2 somatostatin receptors. The radiolabeled octreotide binds to tumors with somatostatin receptors, causing the tumor to appear as a "hot spot" on whole-body gamma camera scintigraphy.[32] For most neuroendocrine tumors and carcinoid tumors, it is excellent and correctly identifies 90%. However, insulinomas are the exception, and they usually do not image on SRS.[33] A recent study showed that if combined with endoscopic ultrasound (EUS), the sensitivity for insulinoma was 94%, which may be useful in the future.[34]

Invasive Localization Studies

Approximately 50% of patients have small (<2 cm) insulinomas that are not detected by noninvasive imaging tests.

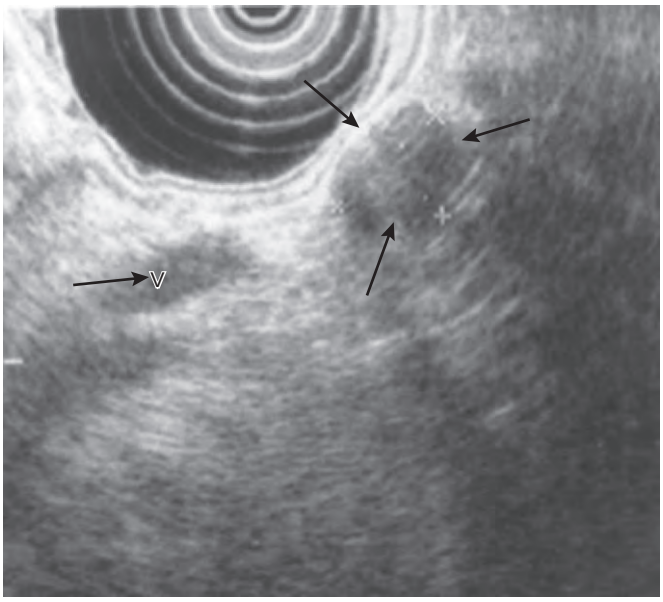


Figure 92–3. Endoscopic ultrasound with the transducer in the stomach. It demonstrates a small hypodense mass (insulinoma) within the tail of the pancreas *(arrows).* The relationship to the splenic vein (V) is also seen.

Selective arteriography of the pancreas has been useful and can identify approximately 60% of tumors based on an arteriographic blush.

EUS (Fig. 92–3) is a safe study that many suggest is the preoperative imaging study of choice because it can identify tumors as small as 2 to 3 mm.[35-37] An endoscope with a balloon is passed through the mouth and esophagus into the stomach and duodenum. The body and tail of the pancreas are visualized with the instrument in the stomach, and the head of the pancreas is seen with the instrument in the duodenum. Sensitivity for EUS ranges from 70% to 90%, and specificity is near 100%.[38-40] It is more accurate in the head of the pancreas than in the body and the tail. Despite the tremendous potential, there are some limitations. This includes false-positive findings, including accessory spleens and intrapancreatic lymph nodes, and limitations in assessment of malignancy.[41]

Portal venous sampling for insulin concentration has been used to try to localize the region of the pancreas that contains the insulinoma. It has been useful and identifies the correct region in about 80% of patients and there are few false-positive results.[19,29] However, the study is invasive in that the liver is used to enter the portal circulation, and it requires considerable expertise of the interventional radiologist. It has largely been replaced by calcium angiography.[28]

The calcium angiogram provides similar information with less difficulty, plus it may image the tumor.[42] Calcium gluconate (0.025 mEq/kg body weight of Ca^{2+}) is injected selectively into arteries that perfuse the head (gastroduodenal artery, superior mesenteric artery), body, and tail (splenic artery) of the pancreas. Calcium stimulates a marked increase in insulin secretion from the insulinoma. Insulin concentration is measured in the hepatic vein. When the artery that perfuses the insulinoma is injected, the insulin level in the hepatic vein rises, localizing the tumor to that region of the pancreas. Sensitivity for calcium stimulation is around 90%, and few false-positive results occur.[43,44] Additionally, injection of contrast material may reveal a tumor blush confirming the location of the insulinoma by imaging the tumor.

A small portion of insulinomas remain unlocalized even after all localization studies are obtained and are therefore considered occult. When the diagnosis is certain based on the fast, surgical exploration with careful inspection, palpation, and intraoperative ultrasound (IOUS) is indicated. Studies have shown that the combination of surgical exploration with IOUS identifies almost all insulinomas.[27,45-47]

Therapy

Medical treatment should prevent hypoglycemia caused by hyperinsulinemia. Acute hypoglycemia is initially normalized with intravenous glucose infusion. Hypoglycemia can be prevented while establishing the diagnosis and tumor localization by giving frequent feeds of high-carbohydrate diet, including a night meal. Cornstarch added to the diet may prolong and slow down absorption. For patients who continue to become hypoglycemic between feedings, diazoxide may be added to the treatment regimen at a dose of 400 to 600 mg orally each day. Diazoxide inhibits insulin release in approximately 50% of patients with insulinoma.[48] In some patients, calcium channel blockers or phenytoin may suppress insulin production. Octreotide binds to and activates somatostatin receptors on cells expressing them. Its usefulness to inhibit insulin release, though, has been disappointing and unpredictable.[49-51]

Long-term medical management of hypoglycemia in patients with insulinomas is generally reserved for the few patients (<5%) with unlocalized, unresected tumors after thorough preoperative testing and exploratory laparotomy and for patients with metastatic, unresectable malignant insulinoma.[49] Patients with malignant insulinomas and refractory hypoglycemia may even require the placement of implantable glucose pumps for continuous glucose infusion.[48]

Surgery is the only curative therapy for insulinoma. Since most insulinomas are benign and small, the goal of surgery is to precisely localize the tumor and remove it with minimal morbidity. The major breakthrough in surgery for insulinoma is IOUS.[46,52] It is the best intraoperative method to find and remove insulinomas.

A mechanical bowel preparation is advised. Midline or bilateral subcostal incisions allow for good exposure. Because virtually all insulinomas are located within the pancreas, an extended Kocher maneuver is performed and the lesser sac is opened, such that the entire pancreas can be examined. The tumor feels like a firm, nodular, and discrete mass. It may appear brownish-red purple, like a cherry. IOUS should be performed with a high-resolution near-field transducer like a 7.5- to 10-

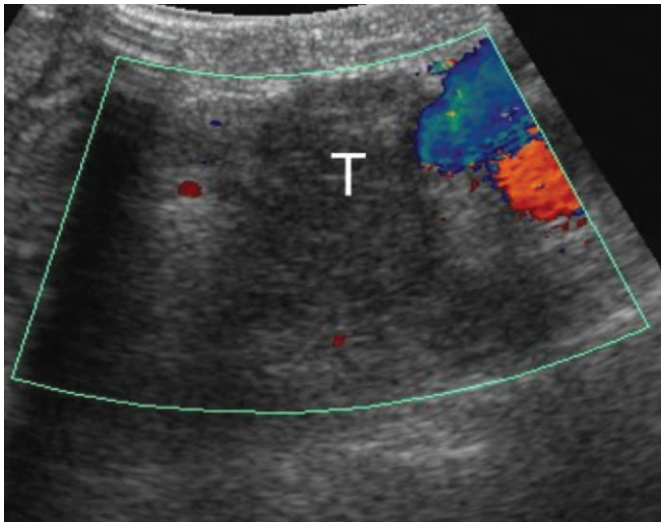


Figure 92–4. Intraoperative ultrasound (IOUS) that demonstrates a small, hypodense sonolucent tumor (T) within the head of the pancreas to the right of the superior mesenteric vein (blue) and artery (red). This tumor was an insulinoma and IOUS facilitated the enucleation.

MHz one. The tumor is sonolucent compared to the more echodense pancreas (Fig. 92–4). The tumor should be imaged in two directions to identify it as a real structure. A recent study of 37 consecutive patients showed that IOUS identified 35 (95%) and the two that were missed were in the pancreatic tail.[52]

The liver is examined for possible liver metastasis, and suspicious lesions should undergo biopsy or be excised.

Most recently for patients who have good preoperative localization and the tumor images on CT, some recommend laparoscopic resection of tumor. This has been done with good results in these patients using laparoscopic ultrasound to image the tumor and guide the resection. Clearly, patients who undergo laparoscopic resection of insulinomas have less pain, shorter hospitalization, and more rapid return to work.[53,54]

Insulinomas during pregnancy have been reported and are usually managed medically until the fetus can be delivered or the pregnancy is terminated.[55]

MULTIPLE ENDOCRINE NEOPLASIA 1

MEN 1 is inherited as an autosomal dominant disease, and tumors develop in several endocrine organs. Patients classically have four-gland parathyroid hyperplasia (94%), pituitary adenoma (35%) (mostly prolactinoma), and pancreatic neuroendocrine tumors (75%).[13] Gastrinoma and insulinoma are the most common functional neuroendocrine pancreatic tumors in MEN 1 patients, accounting for approximately 50% and 20% of the neuroendocrine tumor syndromes, respectively.[19,56] Nonfunctional pancreatic endocrine tumor and PPomas may be the most common pancreatic neuroendocrine tumors in MEN 1 patients because these tumors are almost always identified on careful histologic studies of the pancreas.[57,58] They may also have lipomas, thyroid adenomas, adrenal cortical adenomas or carcinomas, and carcinoid tumors of the entire neuroendocrine system.

Of the rare pancreatic neuroendocrine tumors, MEN 1 is present in approximately 3% of patients with glucagonoma, 1% of patients with VIPoma, 33% of patients with tumors that secrete GRF (GRFomas), and 5% of patients with somatostatinoma.[13]

Studies indicate that the genetic defect in patients with MEN 1 is localized to the long arm of chromosome 11 and linked to the skeletal muscle glycogen phosphorylase gene.[59,60] Evidence from these studies suggests that the development of endocrine tumors in MEN 1 patients conforms to Knudson's two-hit model of neoplasm formation with an inherited mutation in one chromosome unmasked by a somatic deletion or mutation of the other normal chromosome, thereby removing the suppressor effects of the normal gene.[61] In contrast, in sporadic patients with pancreatic neuroendocrine tumors, tumors do not appear to develop by homozygous inactivation of the same gene.[59]

Furthermore, growth factors have been identified in the plasma of patients with MEN 1. A circulating blood factor that was mitogenic for parathyroid cells in tissue culture has been identified,[62] and a subsequent study demonstrated that the factor was similar to fibroblast growth factor.[63] In addition, patients with MEN 1 are prone to other tumors, including bronchial, thymic, and intestinal carcinoid tumors; thyroid adenomas; adrenal adenomas; and multiple lipomas.[13] Thus, the complete pathogenesis of the multiple endocrine tumors in MEN 1 patients is not completely understood.

Diagnosis

Essentially any pancreatic neuroendocrine tumor may occur in individuals with MEN 1. Therefore, when evaluating a patient with a known neuroendocrine tumor, the possibility of unrecognized MEN 1 should be considered.

In assessing MEN 1 patients, a careful family history of first-degree relatives should be taken, also looking for other diseases such as kidney stones, hyperparathyroidism, hypoglycemia, peptic ulcer disease, diarrhea, Cushing's syndrome, and prolactinoma.

All patients younger than 40 years old who present with primary hyperparathyroidism due to hyperplasia should be screened for pancreatic endocrine tumors also, even if their family history is negative for MEN syndromes.[64]

Tests should include blood testing for serum calcium, gastrin, glucose, PP, chromogranin A, and prolactin levels. Physical examination should rule out lipomas. Screening of other family members is indicated, if suspicion of MEN 1 exists.[65]

Each patient with biochemical evidence of a neuroendocrine tumor should undergo complete radiologic assessment of disease to determine the feasibility of surgery. During the radiologic evaluation, medical management should be used to ameliorate symptoms secondary to excessive hormone secretion. It is clear that

in some patients with neuroendocrine tumors (e.g., VIPoma) advances in medical control of the hormone production have improved the surgical outcome and reduced the operative complication rate.[19]

Therapy

If MEN 1 is present, multiple neuroendocrine tumors will be identified within the pancreas,[57,58] so most experts recommend that patients with neuroendocrine tumors undergo surgery. Any neuroendocrine tumor may be malignant. Somatostatinomas and other rare pancreatic neuroendocrine tumors, unlike insulinomas, are almost always malignant.[19,66-71] Medical management can only control the signs and symptoms, and tumor resection is the only potentially curative treatment. Therefore, in patients with localized, potentially curable disease, pancreatic resection, either a Whipple procedure for pancreatic head tumors or subtotal pancreatectomy for pancreatic body and tail tumors, is indicated.

The goal of the surgical operation in a patient with an islet cell tumor is to accurately identify, stage, and remove the tumor. The surgeon should remove all tumors in a manner that allows the mortality and morbidity of surgery to be less than the natural history of the tumor. The surgeon needs to know the natural history and pathology of the neuroendocrine tumor, the expected outcome of the surgical procedure, the expected survival with the tumor resected, the immediate and long-term complication rate, and the availability of alternative medical treatments to manage the disease.[19,70]

Prognosis

Many variables associated with an individual patient have an impact on the surgical outcome. These include the extent of disease on preoperative imaging studies, whether the primary tumor is within the pancreas or duodenum, the exact area of the pancreas involved (head, body, or tail), the presence of liver or other distant metastases and whether they are resectable, the occurrence of the neuroendocrine tumor in a familial or a sporadic setting, and the simultaneous occurrence of other medical conditions that may limit the ability of a patient to undergo major surgery. Success need not be defined as cure of the hormonal syndrome. It may be decreased medication requirement, decreased symptoms, and increased length of survival. In each patient, it is clear that neuroendocrine tumors may be malignant, that surgery is an effective way of accurately staging the true extent of disease, and that surgery may be curative, even in the patients with metastatic neuroendocrine tumor.[19,72-75]

Genetic counseling and screening should be provided to families at high risk of developing the disease. These patients should enter a clinical screening program, which can enable earlier detection and treatment of MEN 1–associated tumors and prompt treatment of hyperparathyroidism.[65,76]

SOMATOSTATINOMA

Somatostatinomas are rare endocrine tumors of the pancreatic islet D cells or duodenum that secrete excessive amounts of somatostatin. Somatostatin excess causes a syndrome characterized by steatorrhea, mild diabetes, and cholelithiasis. Somatostatin is an inhibitory hormone originally discovered in the hypothalamus in 1973. It was discovered by its ability to inhibit growth hormone and thus was called *somatotropin release–inhibiting hormone*. In 1977, Ganda,[77] Larsson,[78] and their colleagues reported the first two cases of somatostatinoma. Initially, the somatostatinoma syndrome included diabetes, cholelithiasis, weight loss, and anemia. Subsequently, diarrhea, steatorrhea, and hypochlorhydria were added.[79] Somatostatin inhibits the release of most other gastrointestinal hormones. It decreases many gastrointestinal functions, including acid secretion, pancreatic enzyme secretion, and intestinal absorption. It reduces gut motility and transit time. Contrary to their duodenal counterparts, pancreatic somatostatinomas are not associated with von Recklinghausen's syndrome.[80]

Presentation

Patients with pancreatic or intestinal somatostatinoma are generally about 50 years old. There is an equal proportion of men and women. Initial symptoms are diabetes, gallbladder disease, and steatorrhea. Diabetes mellitus and glucose intolerance are reported to occur in 60% of patients with pancreatic somatostatinomas; gallstones occur in 70%; diarrhea and steatorrhea are reported in 30% to 68%; and hypochlorhydria presents in 86%. The weight loss may be secondary to diarrhea and malabsorption.

Diagnosis

In most instances, somatostatinomas have been found by accident.[10] In 75% of cases they are metastatic and larger than 5 cm at the time of diagnosis.[81] Most somatostatinomas are located in the pancreas. Despite equal distribution of islet D cells throughout the pancreas, two-thirds of the tumors are located in the head of the pancreas. Alternatively, they are in the duodenum, ampulla, or remaining small bowel. The tumor is usually found incidentally at the time of cholecystectomy or during routine imagining studies.

Diagnosis of somatostatinoma requires the demonstration of elevated tissue concentration of somatostatin or by the documentation of increased fasting plasma somatostatin levels. A level greater than 14 pmol/L is suggestive of the diagnosis of somatostatinoma.[82]

CT is a sensitive imaging study, given that the tumor is usually large at the time of diagnosis. Alternatively, MR imaging and EUS with biopsy and cytologic or somatostatin scintigraphy can be helpful in obtaining the diagnosis.[83,84] The early diagnosis of somatostatinoma may be possible with greater awareness of its existence and reliable assays for the determination of somatostatin in the blood.

Therapy

Most somatostatinomas are solitary and located within the pancreatic head or duodenum. A high proportion of these tumors are malignant. If the tumor is localized and not widely metastatic, surgical resection is the treatment of choice and the only chance for cure. This usually necessitates a Whipple pancreaticoduodenectomy. In some, the severity of diarrhea and steatorrhea correlates with the size and degree of metastatic spread of the tumor, and it improves with tumor resection.[85] Therefore, surgical debulking of metastatic disease has been advocated, but patients are few and clear benefits have not been demonstrated. Five-year survival rate of duodenal and pancreatic somatostatinomas are 30% and 15%, respectively.[86]

VIPOMA

VIPomas are generally located within the pancreas. Most VIPomas have been found in the body and the tail of the pancreas.[87] Originally, it was called *Verner-Morrison syndrome.*[88]

They secrete excessive amounts of VIP, which causes a distinct syndrome. Patients have a large-volume diarrhea, severe hypokalemia with muscle weakness, hypercalcemia, and hypochlorhydria. VIPoma typically occurs in adults. Approximately half the VIPomas are benign.[89]

Presentation

Typically, the diarrhea is large in volume (>5 L/day), and it occurs in 70% of patients.[90] It is secretory, which means that it persists despite fasting.[91] Hypokalemia is present in nearly every patient and is caused by excessive potassium losses in the diarrhea fluid. The hypokalemia causes severe muscle weakness, which is also a common symptom in these patients, and some are bedridden. Hypochlorhydria is found in 75% of patients with VIPoma and is due to inhibition of gastric acid secretion by VIP. The vasodilatory effects of VIP probably cause flushing, which occurs in a few patients. Hyperglycemia occurs in 25% to 50% of patients and is caused by overconversion of glycogen to glucose. VIP is a glycogenolytic hormone. Hypercalcemia is present in a significant proportion of patients with VIPoma.

Diagnosis

In patients with secretory diarrhea and hypokalemia suspected of having a VIPoma, a fasting plasma VIP level should be measured. Given that these tumors, when symptomatic, are usually larger than 1 cm, CT is a sensitive imaging study. MR imaging and US may also be helpful. SRS may also be useful for tumor localization.

Treatment

The first step in treating VIPoma includes the correction of the metabolic imbalance. Electrolyte losses, which result from long-standing diarrhea, should be aggressively corrected. Octreotide, a long-acting somatostatin analogue, can stop the diarrhea and correct the hypokalemia and the other metabolic derangements in most of these patients.[74] Surgical resection is the only chance for cure. IOUS may be considered for intraoperative identification. If complete surgical resection cannot be achieved, surgical debulking can be helpful, and postoperative medical treatment of the residual disease with octreotide is recommended.[92]

GLUCAGONOMA

Glucagonoma is an endocrine tumor of the pancreas that secretes excessive amounts of glucagon. This results in a characteristic syndrome that includes a rash called *necrolytic migratory erythema,* type 2 diabetes mellitus, weight loss, anemia, stomatitis, glossitis, thromboembolism, and other gastrointestinal and neuropsychiatric symptoms.[93] The rash is thought to be a consequence of severe hypoaminoacidemia. Liver disease and zinc deficiency may also add to the symptomatology.[69] Unlike other islet cell tumors, glucagonomas are almost always malignant and not resectable for cure. Tumor-related deaths occur in most patients after about 5 years of follow-up. Surgery is the only option for cure.[69] When these tumors are surgically resected, it leads to complete amelioration of all signs and symptoms.[69,94]

Patients with glucagonoma are between 50 and 60 years of age. The rash is migratory, red, and scaling and is associated with intense pruritus. It commonly occurs in the groin and lower extremities. The rash is pathognomonic of the tumor.[95,96] We demonstrated that in one patient the rash was due to markedly decreased plasma levels of amino acid, which could be completely reversed with total parenteral nutrition.[97] Others have also reported that infusion of peripheral amino acids did resolve the rash but that it did not normalize the hypoaminoacidemia.[75] Diabetes mellitus and glucose intolerance are among the most frequent findings in patients. However, about 20% of patients do not present with hyperglycemia.[98]

Weight loss and cachexia are common and may be profound. Thromboembolic symptoms occur more commonly in patients with glucagonoma. Both deep venous thrombosis and pulmonary emboli may ultimately cause death.

Diagnosis

Diagnosis is established by the measurement of elevated plasma levels of glucagon. In all patients with glucagonoma, plasma concentration is elevated (>150 pg/ml). Plasma levels greater than 1000 pg/ml are diagnostic of glucagonoma.

CT identifies the location of the tumor, which is usually larger than 4 cm (Fig. 92–5A). Glucagonomas are found within the body and tail of the pancreas. They are rarely in the pancreatic head. Seventy percent of patients present with liver metastasis at the time of the diagnosis.

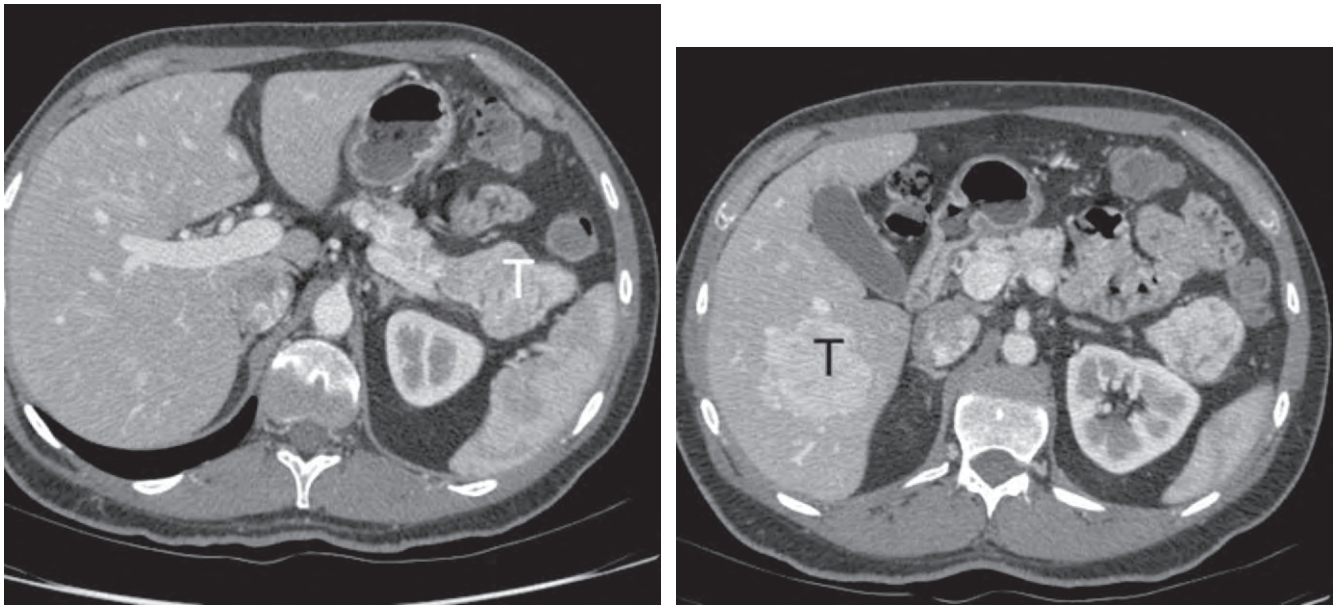


Figure 92–5. **A,** Glucagonoma (T) in the tail of the pancreas is demonstrated on CT scan. The patient presented with a rash known as necrolytic migratory erythema. **B,** The patient also had a large metastasis in the right lobe of the liver (T). He underwent a subtotal pancreatectomy/splenectomy and concomitant right hepatic lobectomy and recovered well. The rash resolved, and he has remained without imageable tumor for 2 years.

Therapy

Preoperative preparation involves controlling the diabetes, treating complications such as venous thrombosis, and improving the nutritional status, which usually also heals the rash.[99]

Surgery used for resection of the primary tumor is a subtotal pancreatectomy with splenectomy. If complete resection is not possible, surgery is used to debulk the tumor mass and to improve symptoms. Resection can also be applied to remove liver metastasis. Metastatic disease does tend to progress slowly (see Fig. 92–5B).[72] Other options include hepatic artery embolization, chemotherapy with streptozotocin and 5-fluorouracil, long-term octreotide for symptoms, and transplantation of the liver and pancreas.

GRFOMA

The GRFoma was first described in 1982.[100,101] It is a neuroendocrine tumor that secretes excessive amounts of GRF. By frequency, GRFomas occur most often in the lung (bronchus), then pancreas, jejunum, adrenal glands, and retroperitoneum.[102] Pancreatic GRFomas are large (>6 cm). One third will have metastasized at the time of diagnosis. Approximately 50% of patients with GRFomas also have Zollinger-Ellison syndrome and 33% have MEN 1. Patients present with acromegaly and a pancreatic mass. If liver metastasis or peptic ulcer disease is present, the diagnosis of GRFoma should also be considered.[100,101]

Diagnosis

The diagnosis of GRFoma is established using a plasma assay for GRF. Given that the tumor is usually large at the time of diagnosis, CT scan is a sensitive modality for diagnosis and localization.

Therapy

Surgical resection should be attempted in these patients because complete resection may be curative, and debulking may decrease symptoms and prolong survival. Octreotide therapy can relieve the symptoms of acromegaly.

CORTICOTROPIN-PRODUCING TUMOR

Malignant neuroendocrine tumors commonly secrete more than one peptide. When they produce corticotropin, patients present with Cushing's syndrome. Excessive production of corticotropin by a pituitary tumor may occur in patients with MEN but is usually mild and clinically insignificant.[103] In 5% of patients with Zollinger-Ellison syndrome, Cushing's syndrome has been reported.[103] In contrast, these patients have severe Cushing's syndrome due to ectopic production of corticotropin by the neuroendocrine tumor.[104]

Diagnosis

For the diagnosis of corticotropin-producing tumors, elevated levels of cortisol are measured in the blood. CT is used for guidance in localization.

Therapy

Corticotropin-producing pancreatic neuroendocrine tumors are usually not resectable surgically. Therefore, either debulking surgery or bilateral adrenalectomy may be indicated to control the severe signs and symptoms of hypercortisolism, given that medical management of the hypercortisolism in these patients is usually inadequate.[104]

TUMOR RELEASING PARATHYROID HORMONE–RELATED PROTEIN

Severe hypercalcemia has been reported to be due to a pancreatic neuroendocrine tumor releasing parathyroid hormone–related protein (PTHrP).[105,106] Hypercalcemia associated with pancreatic neuroendocrine tumors has also been reported to be due to the release of other substances such as VIP. In most cases, the pancreatic tumor is malignant and has spread to the liver by the time of diagnosis.

NEUROTENSINOMA

There have been reports of neuroendocrine tumors that secrete neurotensin. Neurotensin is a peptide that is found in the brain and the gastrointestinal tract. It can cause hypotension, tachycardia, cyanosis, pancreatic secretion, intestinal motility, and small intestinal secretion.

Therefore, patients with neurotensinomas present with diarrhea and hypokalemia, weight loss, diabetes, cyanosis, hypotension, and flushing.

Therapy

Patients may be cured by resection of the tumor; others have responded to chemotherapy.[107,108] Some have questioned whether a separate neurotensinoma exists. Patients with VIPoma and gastrinoma have been found to have elevated plasma levels of neurotensin. At present, it is unclear whether a separate syndrome exists.

GHRELINOMA

Ghrelin is a novel gastrointestinal hormone that exerts a wide range of metabolic functions. It promotes growth hormone release and is an important regulator of energy balance. It has been demonstrated to increase appetite and food intake and modulate insulin secretion. It has significant homology with motilin, and it stimulates gastric contractility and acid secretion. A recent study suggested that a patient had a neuroendocrine tumor of the pancreas excreting the hormone ghrelin, a so-called ghrelinoma. This hormone had not been found in any other neuroendocrine tumor of the pancreas.[109]

PPOMA AND NONFUNCTIONING NEUROENDOCRINE TUMOR

Neuroendocrine tumors that are not associated with a syndrome related to hormonal hypersecretion are referred to as *nonfunctional*. For example, PPomas secrete PP, but this hormone does not appear to cause symptoms; therefore, this tumor is considered nonfunctional. It is estimated that 10% to 25% of all neuroendocrine pancreatic tumors are nonfunctional.[3,110] They are therefore estimated to be among the most frequent neuroendocrine tumors of the pancreas.

Presentation

Typically these tumors are large when diagnosed (>5 cm), and almost all (80%) are malignant and metastatic (Fig. 92–6).[111,112] The incidence of malignancy is clearly higher than among the functioning pancreatic neuroendocrine tumors.[113] Symptoms occur secondary to mass effect. Cachexia, abdominal pain, intestinal bleeding, blockage, or hepatomegaly are common symptoms.[110] Some patients present with pancreatitis.[114]

Diagnosis

Tumors are often found incidentally during surgery.[115] Given that these tumors are usually large by the time the patient is symptomatic, CT and MR imaging are good diagnostic imaging studies. PP and chromogranin A are presently the best serum markers to identify PPomas. Nonfunctioning pancreatic endocrine tumors are differentiated from PPomas on the basis of results of the serum PP assay. Adenocarcinoma of the pancreas can be distinguished from neuroendocrine tumors by immunohistochemical staining with chromogranin A.

Therapy

Therapy includes resection of the tumor and chemotherapy. Most nonfunctioning islet cell tumors are in the head of the pancreas and require a pancreaticoduodenectomy. Debulking of hepatic tumor mass can be replaced by hepatic embolization.[116-118] Dopamine agonists have been shown to decrease circulating levels of PP and chromogranin A in patients with large unresectable islet cell tumors.[119] PPomas and nonfunctioning neuroendocrine tumors of the pancreas do not seem to differ in their biologic behavior[120,121]; however. PP and chromogranin levels may be used to monitor the result of therapy.

Prognosis

Controversy exists concerning the 5-year survival of nonfunctioning versus functioning neuroendocrine pancreatic tumors.[122] Discrepancy in studies may be due

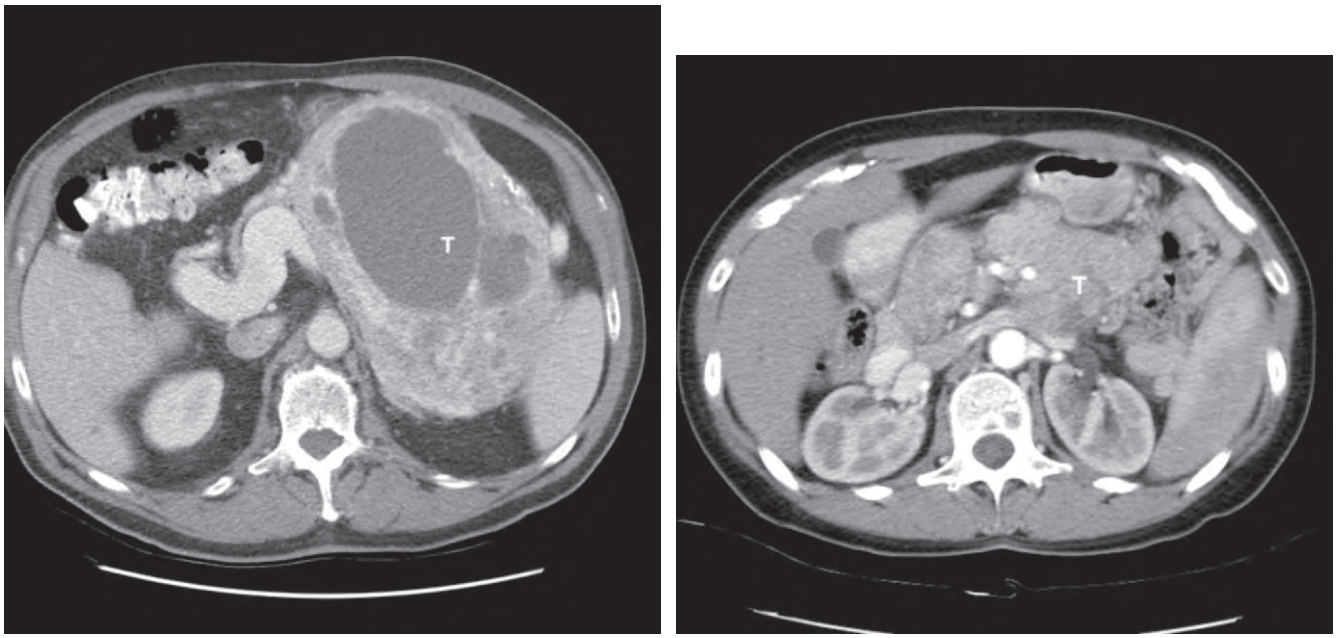


Figure 92–6. **A,** Large nonfunctional neuroendocrine tumor within the tail of the pancreas (T). This patient presented with stomach bleeding because the tumor had eroded into the posterior wall of the stomach. **B,** This patient presented with back pain. She was found to have a localized large nonfunctional neuroendocrine tumor within the body of the pancreas (T). Removal of this tumor required a total pancreatectomy/splenectomy. She has done well except that she developed small liver metastases at the 5-year follow-up.

to the small number of patients with this disease. Most likely there is no significant difference in behavior of functioning versus nonfunctioning tumors.

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Chapter

93

Primary Cystic Neoplasms of the Pancreas

George H. Sakorafas ▪ Michael G. Sarr

Although primary cystic neoplasms of the pancreas are rare neoplasms, they are being appreciated and recognized with increasing prevalence. Compagno and Oertel in 1978[1] were the first to clearly characterize histopathologically both the features and differentiation of serous and mucinous cystic neoplasms; moreover, these insightful pathologists outlined the importance of identifying the mucinous neoplasms because of their overt or latent malignant potential. Since then, many groups throughout the world have refined the classification, diagnosis, differentiation, and appropriate management of this family of unique neoplasms by recognizing the marked differences in their biologic behaviors. In 1982, Ohashi et al.[2] in Japan reported a seemingly new type of cystic neoplasm of the pancreas they termed *mucinous-secreting cancer of the pancreas*. The term *intraductal papillary mucinous neoplasm* (IPMN) has been accepted recently to describe this group of cystic pancreatic neoplasms.[3] The increasing recognition of this clinically diverse family of cystic neoplasms (especially in asymptomatic patients), primarily due to the wide availability of newer, state-of-the-art imaging techniques and the necessity to differentiate the various types of cystic neoplasms, has stimulated intense interest in these primary cystic neoplasms of the pancreas. This chapter focuses on all these aspects of these unique neoplasms.

INCIDENCE AND EPIDEMIOLOGY

Serous cystic neoplasms (SCNs) are unusual benign neoplasms composed of a single layer of cuboidal serous cells. SCNs account for about 30% of all primary cystic neoplasms of the pancreas.[4] SCNs affect women almost exclusively, with an average age at diagnosis of 62 years. Most SCNs are located in the head of the pancreas.[5] In contradistinction, mucinous cystic neoplasms (MCNs) are lined by a neoplastic mucinous epithelium that is believed to be premalignant. MCNs represent about 50% of primary cystic neoplasms of the pancreas.[4] MCNs also predominate in women (84% to 90%), with an average age at diagnosis of 53 years.[4,5] Unlike SCNs, MCNs are more common in the body/tail of the pancreas (>75%). The average size of both SCNs and MCNs is greater than 5 cm (ranging from 3 to 20 cm).[6] Patients with IPMN are usually older (mean age ~65 years), and in contrast to the SCNs and MCNs of the pancreas, IPMN has a male predominance.[3] IPMNs frequently masquerade as idiopathic chronic pancreatitis or "mucinous ductal cancer" and, indeed, were undoubtedly overlooked and misdiagnosed in the past.[7] IPMNs currently account for 17% to 25% of resections for pancreatic neoplasms in the past 5 years at the Mayo Clinic, Massachusetts General Hospital, and Johns Hopkins Hospital.[3]

CLINICAL PRESENTATION

There are no symptoms or signs that are pathognomonic of cystic neoplasms of the pancreas. Many patients (40% to 75%) are truly asymptomatic, with the cystic mass discovered only incidentally during diagnostic investigation of an unrelated abdominal complaint.[3] When the patient is symptomatic, the presentation is often nonspecific, and for SCN and MCN, the symptoms are related to the mass effect of the neoplasm; indeed, a history of acute pancreatitis is usually absent, but some complaints suggestive of acute pancreatitis may be present in up to 20% of patients. In contrast, for patients with IPMN, many present with a clinical picture of chronic pancreatitis; pain is much less prominent than the symptoms of pancreatic exocrine insufficiency. Extrahepatic biliary obstruction is distinctly unusual with any but the largest of the SCNs and MCNs in the head of the pancreas, whereas for IPMN, biliary obstruction usually suggests an associated malignant transformation.

Although most of these neoplasms occur in the body/tail of the pancreas, they do not invade the retroperitoneal nerves (causing back pain) or involve the fourth portion of the duodenum (causing distal

duodenal obstruction) despite their often large size. A complaint of abdominal fullness, often with a component of early satiety and/or vague abdominal pain, is most common. Serious systemic symptoms such as weight loss, fatigue, anorexia, and malaise are rare, unless there is malignant transformation or the patient with IPMN has pancreatic exocrine insufficiency. Unlike in ductal pancreatic adenocarcinoma, jaundice is unusual (<15%), even when lesions are in the head of the pancreas and even when the neoplasms are large. The presence of symptoms (e.g., pain, obstructive jaundice, upper gastrointestinal bleeding, hemobilia, palpable mass, and diabetes mellitus) is more common in cystic lesions with underlying invasive malignancy.[6] In this clinical setting, the median age at diagnosis is higher.[5] However, the absence of symptoms does not rule out the diagnosis of an underlying malignancy.

IPMN may present differently from other cystic neoplasms. Although some patients (~20%) with IPMNs are asymptomatic (especially those with only branch-type disease [see later]), most patients have vague abdominal pain with a clinical presentation of acute, recurrent, or, more commonly, chronic pancreatitis. This clinical presentation may be due to mucin hypersecretion, which may cause functional pancreatic ductal obstruction.[8] A lack of a history of pancreatic disease or other predisposing etiologic factors (e.g., alcohol abuse, hyperlipidemia, or family history) should be a tip-off to the astute clinician in patients with "idiopathic" chronic pancreatitis and a markedly dilated pancreatic duct.[9] When invasive carcinoma coexists in IPMN, a symptom profile similar to that of ductal carcinoma of the pancreas (e.g., pain, jaundice, weight loss, and malaise) may be present.[3] Indeed, in the past, these patients were misdiagnosed as having mucinous ductal cancer of the pancreas.[7]

PATHOLOGY AND BIOLOGIC BEHAVIOR

Currently, the spectrum of cystic neoplasms of the pancreas includes the following four categories: (1) SCNs, (2) MCNs, (3) IPMNs, and (4) unusual cystic neoplasms, which are not discussed in detail here but are outlined in Box 93–1.[10] The biologic aggressiveness of these various neoplasms is quite different and mandates a selective management approach.

SCN

SCNs, previously referred to as "microcystic" adenomas, form a well-demarcated, spongy mass (cluster) of individual small cysts (each cyst is almost always <2 cm), filled with clear, watery fluid without mucin (Fig. 93–1). The overall size of these neoplasms varies from a few centimeters to as large as 25 cm (mean, 6 to 10 cm). SCNs have a thin, almost translucent wall that usually easily separates from surrounding structures without the inflammatory or fibrous adherence expected of a post-inflammatory pancreatic pseudocyst. The cysts are lined by a single, uniform layer of cuboidal, glycogen-rich serous cells[11] with round nuclei and clear cytoplasm but without cellular characteristics of atypia or dysplasia. The much less common serous "oligocystic" adenoma has fewer (sometimes only one) cystic spaces (>2 cm), but the histopathologic appearance is similar to that of the microcystic neoplasms. The stroma separating these microcystic areas is a fibrous connective tissue that is quite vascular (on angiography) and may even be calci-

Box 93–1 Cystic Neoplasms of the Pancreas

Cystic Neoplasms

- Serous cystic neoplasm
- Mucinous cystic neoplasm
- Intraductal papillary mucinous neoplasm
- Other rare cystic neoplasms
  - Solid pseudopapillary neoplasms of the pancreas
  - Cystic islet cell neoplasms
  - Acinar cell cystadenocarcinomas
  - Cystic choriocarcinomas
  - Cystic teratomas
  - Angiomatous neoplasm (angioma, lymphangioma, hemangiothelioma)

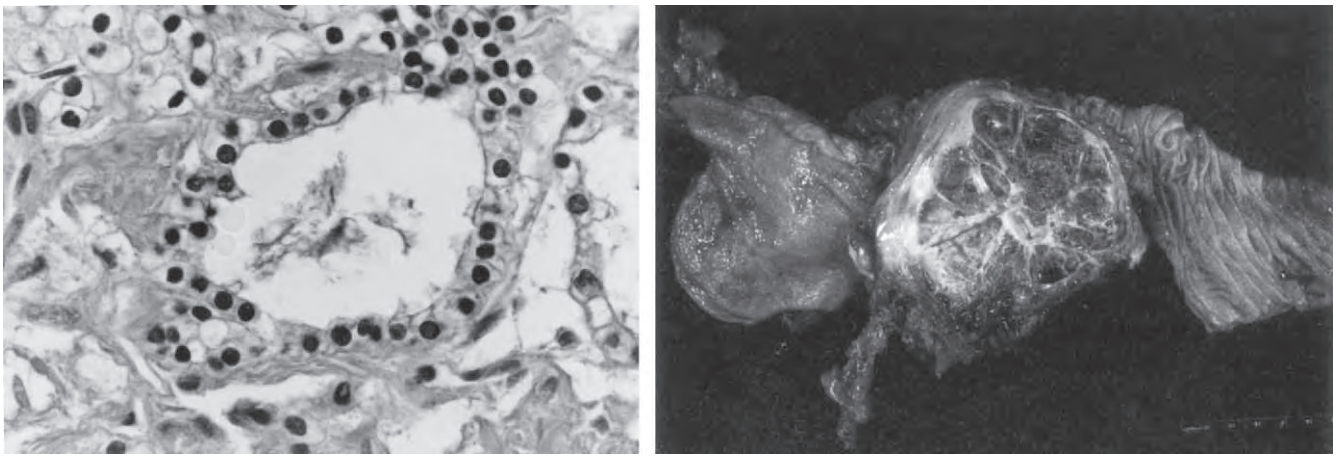
Acquired Cysts

- Parasitic cyst
  - Echinococcal (hydatid) cyst
  - *Taenia solium* cyst
- Postinflammatory cystic fluid collection
  - Pancreatic pseudocyst
  - Pancreatic pseudopseudocyst (inflammatory exudative collection)
  - Pancreatic sequestum (postnecrotic fluid collection)

Congenital True Cysts

- Simple cysts
  - Isolated pancreatic cyst
  - Pancreatic cysts associated with polycystic disease of the kidneys
  - Polycystic disease of the pancreas without related anomalies
  - Pancreatic macrocysts associated with cystic fibrosis
  - Polycystic disease of the pancreas associated with von Hippel–Lindau disease
  - Pancreatic cysts associated with polycystic disease of kidneys
- Enterogenous duplication cysts
- Dermoid cysts

Modified from Sakorafas GH, Sarr MG: Cystic neoplasms of the pancreas. In Bland KI, Sarr MG (eds): The Practice of General Surgery. Philadelphia, WB Saunders, 2002, pp 771-776.



A B

Figure 93–1. Serous cystadenoma of the pancreas. **A,** Simple serous cuboidal cells without dysplasia. **B,** Gross appearance of multiple small cysts. (**A** and **B,** From Pyke CM, van Heerden JA, Colby TV, et al: The spectrum of serous cystadenoma of the pancreas: Clinical, pathological, and surgical aspects. Ann Surg 215:132-139, 1992.)

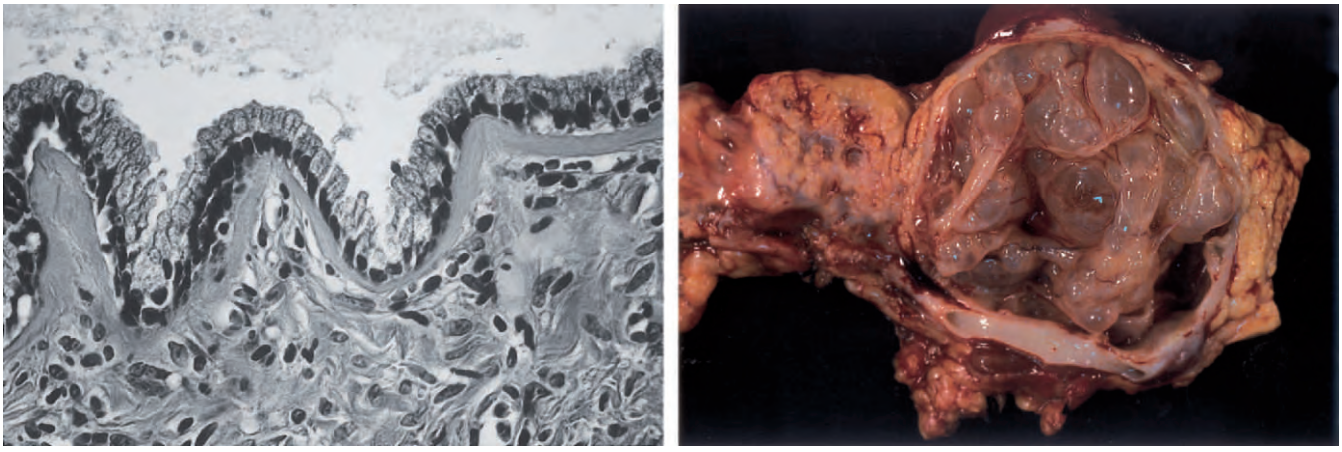


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Figure 93–2. Mucinous cystic neoplasm of the pancreas. **A,** Columnar mucinous cells line the cyst wall. **B,** Gross appearance of macrocysts with thin walls and mucinous cystic fluid. (**A** and **B,** From Sarr MG, Carpenter HA, Prabhakar LP, et al: Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas—can one reliably differentiate benign from malignant [or premalignant] neoplasms? Ann Surg 231:205-212, 2000.)

fied; indeed, this unique central calcification gives rise to a characteristic central sunburst, radial, or stellate scar pattern on computed tomography (see later). The cell of origin of SCN appears to be the centroacinar cell, possibly explaining the peripheral anatomic location of these cells within the pancreatic parenchyma.[8] Although several serous cystadenocarcinomas have been described,[12] they are "rare as hen's teeth," and thus SCNs of the pancreas should be considered (and managed as) benign neoplasms.[3]

MCN

The gross appearance of MCNs, formerly known inappropriately as "macrocystic" adenomas, is often different from that of SCNs. The individual cysts making up the mass are larger, usually larger than 2 cm, and occasionally up to 25 cm (mean size, 8 to 10 cm); MCNs generally contain fewer than six separate cysts, do not communicate with the pancreatic ductal system (Fig. 93–2), and usually are spherical. Rarely, the neo-

plasm has just one macrocyst. Typically, the cysts are not unilocular but have septa within them and may have an solid eccentric component. As with SCNs, the surrounding tissues lack an inflammatory pericystic reaction except when malignant transformation and tissue invasion have occurred.[7] MCNs contain a mucinous columnar epithelium. The characteristics of the mucinous epithelium may vary widely throughout the neoplasm with areas of a single layer of benign-appearing, mucin-secreting columnar epithelium resembling pancreatic duct epithelium (or the mucinous cells of an ovarian mucous cystadenoma) to areas of atypia, dysplasia, carcinoma in situ, and even areas of tissue invasion (invasive carcinoma). All these areas may be found within the same neoplasm (Fig. 93–3).[13] Sometimes, mucin accumulating within neoplastic lobules causes pressure necrosis of the lining epithelium, making the epithelial lining discontinuous. Incomplete, denuded epithelium may be found in 70% of mucinous cystadenomas and cystadenocarcinomas, with a mean of 40% (but as great as 98%) of the cystic wall being devoid of an epithelial lining.[14] This observation has obvious clinical implications regarding the differential diagnosis between mucinous cystadenocarcinomas, mucinous cystadenomas, and pancreatic pseudocysts, especially if the diagnosis is based on a single-site frozen-section biopsy of the cystic wall. Clearly, the distinction between benign and malignant lesions can be made only by a detailed histologic examination of the complete neoplasm after resection. The intracystic fluid is thicker and more viscous than in SCNs because it contains mucus. The epithelial cells may also stain for carcinoembryonic antigen (CEA) and serotonin, suggesting an origin from ductal or stem cells. In contrast to benign SCNs, MCNs represent a more diverse, broader, heterogeneous spectrum; these neoplasms are considered at best as potentially premalignant. Malignant degeneration within the epithelial lining of a MCN is relatively common and has been described, often after a long period.[5] Papillary invaginations are common, and multiple discontinuous areas of atypia, dysplasia, carcinoma in situ, and overtly invasive carcinoma may occur within the same neoplasm.[8,10,13,14]

Another characteristic of MCNs is the presence of ovarian stroma in the neoplasm. Indeed, some pathologists believe that the presence of ovarian stroma is required for the diagnosis of MCN.[15] Because of this requirement, virtually all MCNs occur in women, although MCN may occur rarely in men.

Many classifications for MCN have been offered. Recently, a new classification system for MCNs was offered in an attempt to differentiate (invasive) mucinous cystadenocarcinomas from both benign MCNs and the MCNs that show dysplastic changes limited to the surface epithelium (but no tissue invasion).[13] This system reliably separates this spectrum of MCNs into the following three subgroups: (1) *mucinous cystadenomas* (comprising ~65% of MCNs), which contain a uniform, single layer of benign, columnar mucinous cells; (2) *noninvasive proliferative MCNs* (~30% of MCNs), composed of a varying degree of atypia, dysplasia, papillary endothelial infolding, and even changes of carcinoma in situ in the epithelial lining but without tissue invasion; and (3)

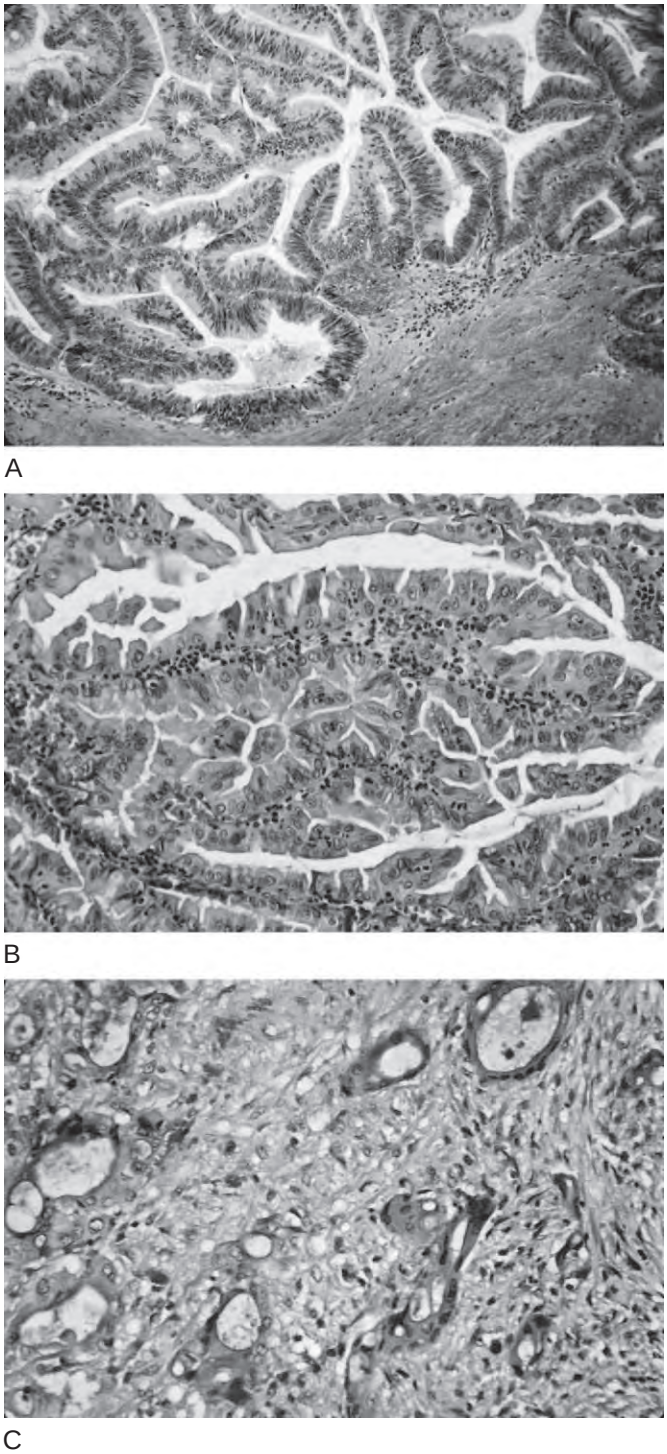

Figure 93–3. Spectrum of primary mucinous neoplasms of the pancreas. **A,** Proliferative epithelial changes with papillary fronts and low-grade dysplasia. **B,** High-grade dysplasia with papillary, polypoid intracystic growth. **C,** Mucinous cystadenocarcinoma with stromal invasion and desmoplastic response. (**A-C,** From Sarr MG, Carpenter HA, Prabhakar LP, et al: Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas—can one reliably differentiate benign from malignant [or premalignant] neoplasms? Ann Surg 231:205-212, 2000.)

mucinous cystadenocarcinomas, which may have features throughout the neoplasm of the first two groups but also contain areas of overt stromal invasion beyond the epithelium (i.e., true invasive cancer). Although the reported incidence of "cancer" in MCNs in the more recent literature has ranged from 29% to 36%, the Mayo Clinic experience is different, with only 8% of MCNs having an invasive component.[3] This dichotomy stems from the tendency of some groups to call MCNs with areas of carcinoma in situ as "cancers." As seen later, resection of such MCNs without any true invasion beyond the epithelium is curative and thus they really should not be called carcinomas as such.

The World Health Organization classifies cystic neoplasms of the pancreas in terms of two variables: (1) characteristics of the epithelium—benign, dysplastic, or carcinoma,* and (2) the presence or absence of tissue invasion beyond the epithelial lining.[16] With this classification, a specific MCN may be called *carcinoma without tissue invasion,* which seems meaningless, and a better concept may be carcinoma in situ.

Box 93–2 World Health Organization Classification of Cystic Neoplasms of the Pancreas[16]

- Serous microcystic adenoma
- Serous oligocystic adenoma
- Serous cystadenocarcinoma
- Mucinous cystadenoma
- Mucinous cystic neoplasm—borderline
- Mucinous cystadenocarcinoma
  - Noninvasive
  - Invasive
- Intraductal papillary mucinous adenoma
- Intraductal papillary mucinous neoplasm—borderline
- Intraductal papillary mucinous carcinoma
  - Noninvasive
  - Invasive

IPMN

IPMN is characterized by intraductal proliferation of neoplastic mucinous cells, which usually form papillae and lead to cystic dilation of the main pancreatic duct and/or secondary branches. These dilated neoplastic ducts contain mucus and form detectable masses, most commonly in the pancreatic head and usually in older men (>60 years old).[17] The dysplastic lesions within the IPMN are frequently diffuse and often associated with copious mucin production. Often at endoscopy, mucus can be seen exuding from a bulging papilla of Vater, when the main pancreatic duct is involved. Pancreatic ductal dilation varies from generalized dilation of the main pancreatic duct for all or part of its extent, to a more segmental dilation of the secondary and distal ducts involving a major segment of the gland, most commonly the uncinate process (the so-called branch-type IPMN).[2,14,18] The degree of duct dilation appears to be determined by either the amount of mucin production or the presence of proximal duct obstruction; however, a rare subtype of diffuse main pancreatic duct ectasia is caused by complete filling of the dilated main pancreatic duct by papillary neoplasm. Morphologically, IPMNs have four variations, which reflect the location of the small intraductal neoplasm and the amount of mucin secreted by the neoplasm.[3] They include the following: (1) diffuse main pancreatic duct ectasia; (2) segmental main pancreatic duct ectasia; (3) side-branch duct ectasia, usually located in the head or uncinate process of the pancreas; and (4) the much less common multifocal cysts throughout the gland that communicate with the pancreatic duct, variants of side-branch disease.

Histologically, IPMN is currently subdivided into the following three groups: (1) benign (adenoma), (2) borderline neoplasms (moderate dysplasia), and (3) malignant (carcinoma) (Box 93–2). The dysplastic epithelium may be flat, micropapillary, or grossly papillary (Fig. 93–4).[8] Frequently, a wide spectrum of changes of the intraductal epithelium is recognized, including normal, hyperplasia, dysplasia, and carcinoma, within the same pancreas.[18] IPMN exhibits histologically different patterns of papillae[17]: intestinal, pancreatobiliary, oncocytic papillary, and null. The prognosis of these subtypes may differ, with the pancreatobiliary type representing the more aggressive subtype and the intestinal type the indolent subtype. One group has separated IPMN based on simple hematoxylin-eosin stain into a villus "dark cell" type with a much greater propensity for malignancy and a papillary "clear cell" variety that is usually a benign, less aggressive variant. The former is also positive for staining by MUC2, a membrane-bound mucin, while the clear cell variety is MUC2 negative.[19] This histologic continuum (hyperplasia-dysplasia-carcinoma) implies a "clonal progression" with IPMN, just as like the "adenoma-carcinoma sequence" of colorectal neoplasms.[20] Recent research showed that IPMN is associated with frequent (~60% to 80%) K-*ras* point mutations, thereby establishing these mutations as a potential genetic marker in IPMN. K-*ras* mutation could be an early genetic event in the development of IPMN and other forms of pancreatic ductal transformation, as with the more typical ductal carcinoma of the pancreas. Other molecular alterations associated with IPMN are loss of heterozygosity (LOH) in 9p21 (p16) and LOH in 17p13 (p53), increased expression of cyclooxygenase-2, up-regulation of several genes such as claudin and mesothelin, hypermethylation of certain tumor suppressor genes, and increased telomerase activity. Unlike SCN and MCN, about 40% of patients at the time of diagnosis of IPMN already have an established invasive malignancy.[21] IPMN confined to the side-branch ducts are more often benign, whereas those

*Note, not the term *carcinoma in situ!*

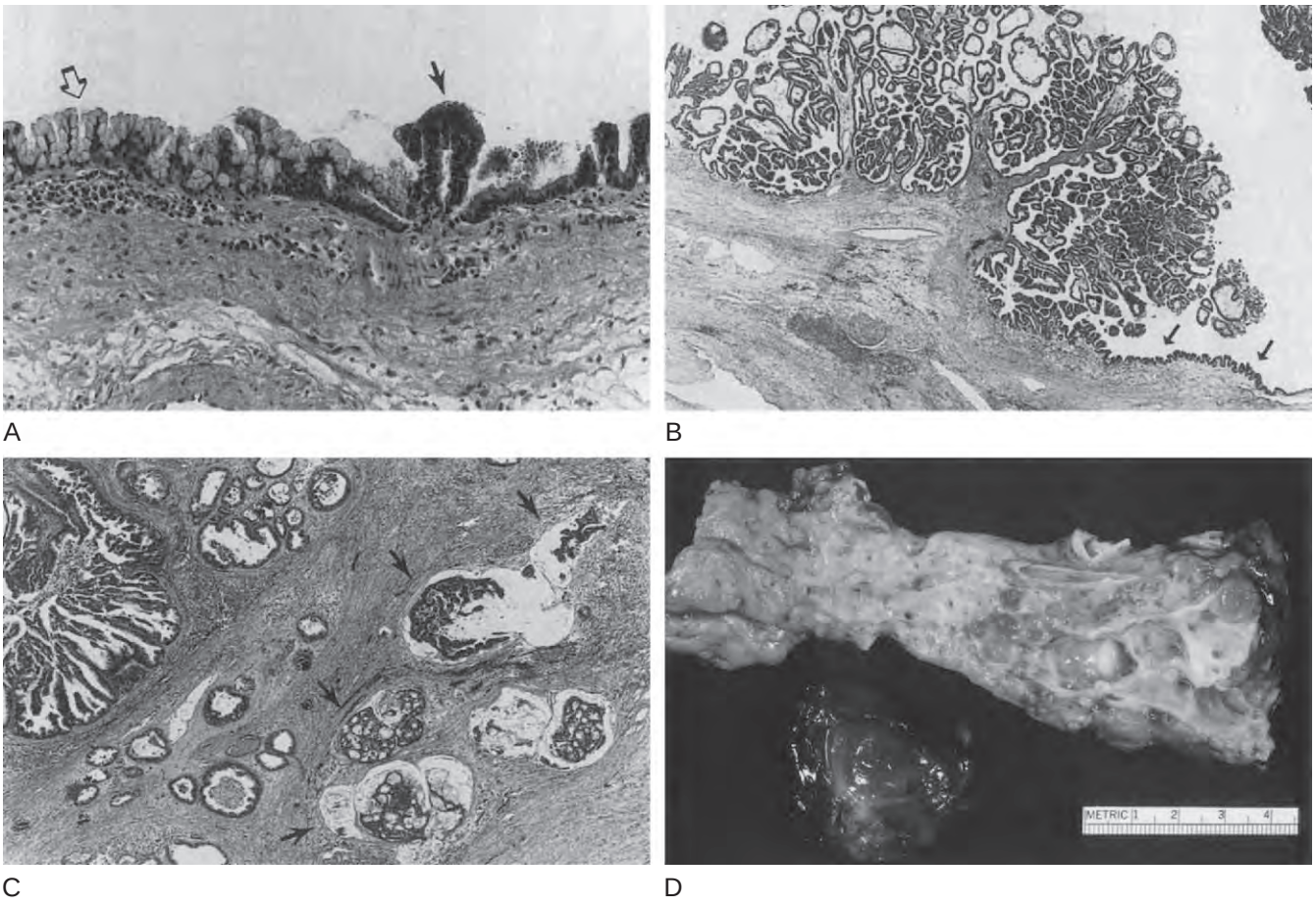

Figure 93–4. Intraductal papillary mucinous neoplasm. **A,** Ductal epithelium showing nondysplastic micropapillary mucinous hyperplasia (*open arrow*) and micropapillary dysplasia (*solid arrow*). **B,** Gross papillomatous change associated with flat micropapillary dysplasia change associated with flat micropapillary dysplasia (*arrows*). **C,** Invasive adenocarcinoma (*arrows*). **D,** Gross findings of main pancreatic duct dilation with copious intraductal mucin and ductal adenomas. (**A-D,** From Loftus EV Jr, Olivares-Pakzad BA, Batts KP, et al, and Members of the Pancreas Clinic and Pancreatic Surgeons of Mayo Clinic: Intraductal papillary-mucinous tumors of the pancreas: Clinicopathologic features, outcome, and nomenclature. Gastroenterology 110:1909-1918, 1996.)

involving the main duct are more often malignant,[22] especially those causing main duct dilation greater than 10 mm or those associated with an intraductal mass larger than 10 mm. A recent large multicenter study from Japan of 1379 patients with IPMN showed that risk factors for invasive malignancy included a main pancreatic duct greater than 7 mm and mural nodules larger than 2 mm. Similarly, for side-branch disease, risk factors for malignancy include a cyst larger than 3 cm, mural nodules larger than 2 mm, and a main pancreatic duct greater than 5 mm.[23] However, considerable overlap exists. Many IPMNs without invasive carcinoma have epithelial changes within the ducts, such as micropapillary areas with atypia, dysplasia, or frank carcinoma in situ, further establishing this disorder as a premalignant condition, and more often so than MCN.[10] Unlike typical ductal carcinoma of the pancreas,[24] these changes can be found in discontinuous areas throughout the gland, raising the question of whether IPMN represents a generalized global pancreatic duct epithelial disorder or a more localized field defect.

DIAGNOSTIC EVALUATION

Because of the markedly different biologic behavior of cystic neoplasms of the pancreas, management of each type of neoplasm differs, and therefore an accurate preoperative diagnosis of the different types of cystic neoplasms is extremely important in making the right therapeutic choices. After discovery of a cystic lesion in the pancreatic region, the three necessary diagnostic steps include the following: (1) to confirm the intrapancreatic origin of the cyst, (2) to exclude the diagnosis of a pancreatic pseudocyst, and (3) to identify those cystic neoplasms that should be resected because of overt or potential malignancy.[4]

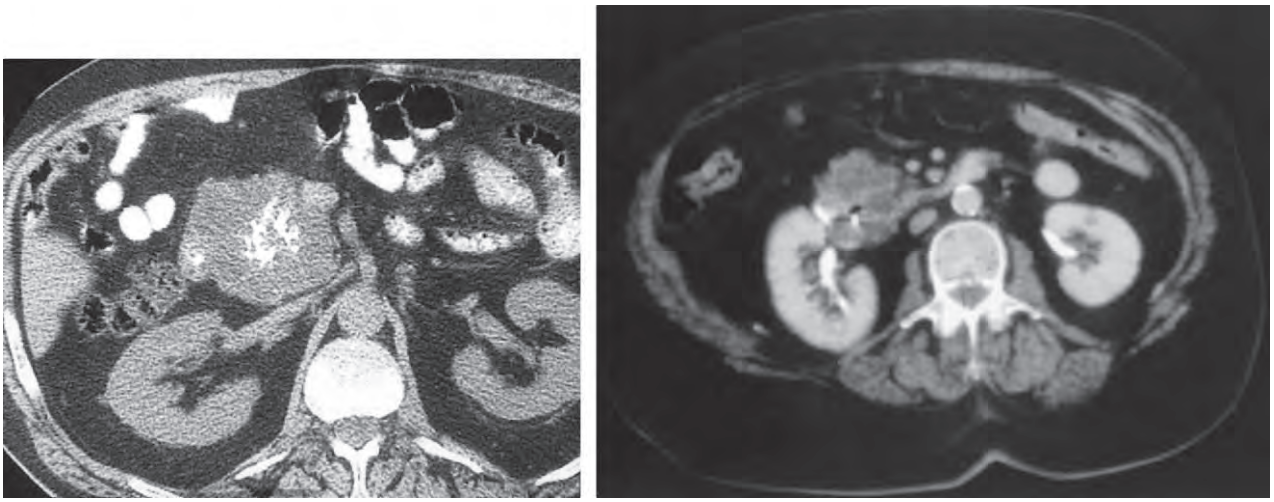

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Figure 93–5. CT of serous cystadenoma of pancreas. **A,** Note solid-appearing lesion with central starburst calcification. **B,** Microcystic mass in head of pancreas. (**A,** From Pyke CM, van Heerden JA, Colby TV, et al: The spectrum of serous cystadenoma of the pancreas: Clinical, pathological, and surgical aspects. Ann Surg 215:132-139, 1992; **B,** From Sarr MG, Murr M, Smyrk TC, et al: Primary cystic neoplasms of the pancreas: Neoplastic disorders of emerging importance—current state-of-the-art and unanswered questions. J Gastrointest Surg 7:417-428, 2003.)

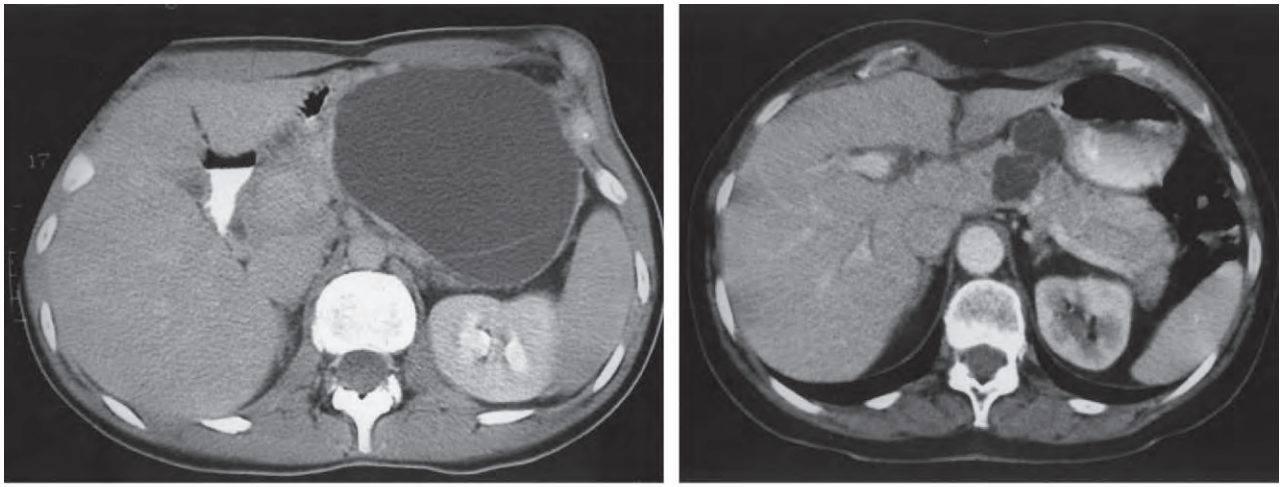
Cross-Sectional Imaging (Ultrasonography, Computed Tomography, Magnetic Resonance Imaging)

The suspicion of a cystic neoplasm is almost always first evident after a noninvasive imaging procedure (ultrasonography [US], computed tomography [CT], or magnetic resonance imaging [MRI]), often at the time of evaluation for unrelated intraabdominal disorders.

SCN SCNs have three morphologic patterns: polycystic, oligocystic, and honeycomb. The polycystic pattern is the most common (~70%) (Fig. 93–5). This pattern is characterized by a bosselated collection of multiple (usually more than six) small cysts, each of which are usually smaller than 2 cm.[3] A central fibrous scar with a characteristic stellate pattern of calcification—manifested as a central starburst calcification on imaging—occurs in up to 30% of these neoplasms and, when present, is considered virtually pathognomonic of SCNs. The honeycomb pattern (~20%) is characterized by numerous, subcentimeter cysts that often cannot be well depicted as individual cysts by cross-sectional imaging. Thus, they may appear as a solid mass, which is hypoechoic on US imaging, of low attenuation on CT, and have a high signal intensity on T2-weighed MRI. The oligocystic or macrocystic pattern is the least common (<10%). The characteristic findings of stromal hypervascularity with predominance of small cystic areas, combined with an indolent course, lack of metastases or local invasion, and an appropriate clinical setting, permits the diagnosis of SCN to be made with an accuracy approaching 95%.[10]

MCN MCNs are predominantly macrocystic (80%), but rarely they can be multilocular (20%). Generally, they are spherical in shape but may have several adjacent cysts (Fig. 93–6).[6,8] Although MCNs do not communicate with the pancreatic duct, they can cause partial pancreatic ductal obstruction. MCNs usually range from 4 to 12 cm in diameter but may reach very large sizes of up to 20 cm in diameter. The cysts have thicker, irregular walls with papillary excrescences extending into the cysts. The complex internal architecture of the cysts often allows differentiation from SCNs. Although MCNs have often been misdiagnosed as pancreatic pseudocysts in the past, MCNs usually lack the prominent extracystic inflammatory component so characteristic of pancreatic pseudocysts. Calcifications are uncommon but, when present (<20%), tend to be located in an eggshell distribution within the peripheral cyst walls. The likelihood of (invasive) cystadenocarcinoma increases if calcifications are seen. The presence of an eccentrically located mass within a cystic area, multiple papillary invaginations, a recognizable pericystic mass/reaction, extrahepatic biliary obstruction, associated metastatic liver lesions, or ascites should raise the suspicion of a mucinous cystadenocarcinoma (invasive form). In the absence of these features, differentiation of benign MCNs from the noninvasive proliferative MCNs may not be possible. The height/diameter of mural nodules/papillary invaginations may be related directly to probability of malignant degeneration.[25]

IPMN The characteristic feature of IPMN is cystic dilation of either the main pancreatic duct or a primary, segmental side-branch of the main duct, usually the uncinate lobe (Fig. 93–7). The mucinous globules or the areas of malignant transformation may appear as filling defects within the ductal system. CT scanning is probably the single best modality for evaluation of these patients



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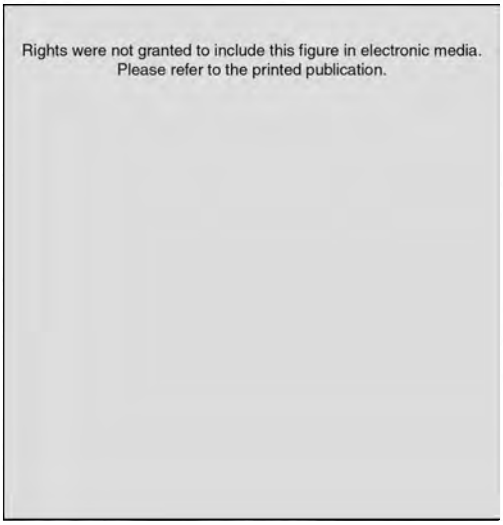


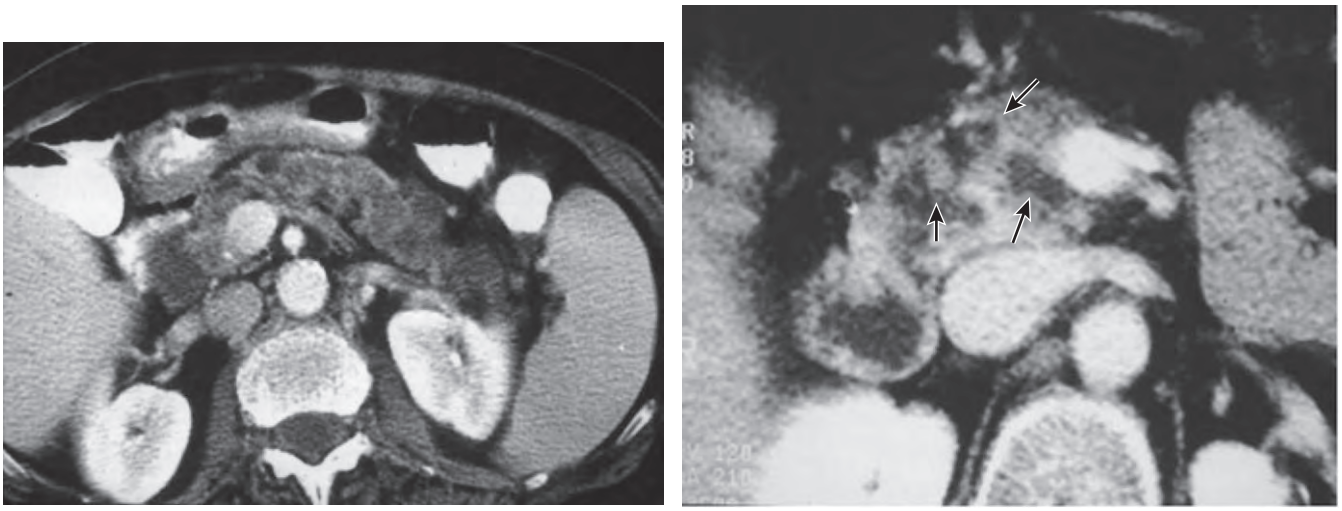
C

Figure 93–6. CT characteristics of primary mucinous cystic neoplasms of pancreas. **A,** Macrocystic neoplasm is shown. Note the septum and lack of surrounding inflammatory reaction. **B,** Several macrocystic areas (>2 cm) in mid-body of pancreas. **C,** Complex cystic mass with solid intracystic component (*arrow*)—invasive mucinous cystadenocarcinoma. (**A** and **B,** From Yeo CJ, Sarr MG: Cystic and pseudocystic diseases of the pancreas. Curr Probl Surg 31:165-252, 1994; **C,** From Johnson CD, Stephens DH, Charboneau JW, et al: Cystic pancreatic tumors: CT and sonographic assessment. AJR Am J Roentgenol 15:1133-1138, 1988.)

because it detects the location and degree of pancreatic duct dilation and may be able to differentiate IPMN from other causes of duct dilation such as chronic pancreatitis or obstructing neoplasms. Due to the improvements in imaging techniques, small cystic dilation of branch ducts with no or mild dilation of the main pancreatic duct can now be detected more accurately (branch-type IPMN).[26] The especially large IPMNs, the presence of mural nodules, and main pancreatic duct disease (in contrast to branch-type disease) are factors associated with a higher probability of underlying malignancy.[21,25,26] However, most pancreatologists agree that preoperative discrimination of benign from malignant IPMNs is difficult if not impossible.

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) has little to offer in the evaluation of SCN or MCN because these neoplasms do not communicate with the pancreatic ductal system. ERCP may be helpful, however, in the differentiation between pancreatic pseudocysts and cystic neoplasms. In contrast, in IPMN, ERCP is the diagnostic procedure of choice; it depicts the communication between the cystic dilation (or branch-duct ectasia) and the main pancreatic duct, or it reveals a markedly dilated main pancreatic duct, which may contain filling defects related to either mucinous concretions, papillary growths (intraductal papillomas), or areas of frank malignant degeneration/invasion (Fig. 93–8).[13] Often, however, the intraductal adenomas of IPMN are obscured by the mucin. The diagnosis is essentially confirmed by noting copious egress of mucin from a bulging papilla (in ≈30% of patients). ERCP may be particularly useful in the differential diagnosis between branch-type IPMN from MCN, which can be difficult on noninvasive imaging.[26,27]



A B

Figure 93–7. CT findings of intraductal papillary mucinous neoplasms of the pancreas. **A,** Main duct disease. Note dilation of the main pancreatic duct and atrophy of the parenchyma. **B,** Side-branch disease with dilation of ductal system limited to secondary branches (*arrows*). (**A,** From Loftus EV Jr, Olivares-Pakzad BA, Batts KP, et al, and Members of the Pancreas Clinic and Pancreatic Surgeons of Mayo Clinic: Intraductal papillary-mucinous tumors of the pancreas: Clinicopathologic features, outcome, and nomenclature. Gastroenterology 110:1909-1918, 1996; **B,** From Sarr MG, Murr M, Smyrk TC, et al: Primary cystic neoplasms of the pancreas: Neoplastic disorders of emerging importance—current state-of-the-art and unanswered questions. J Gastrointest Surg 7:417-428, 2003.)

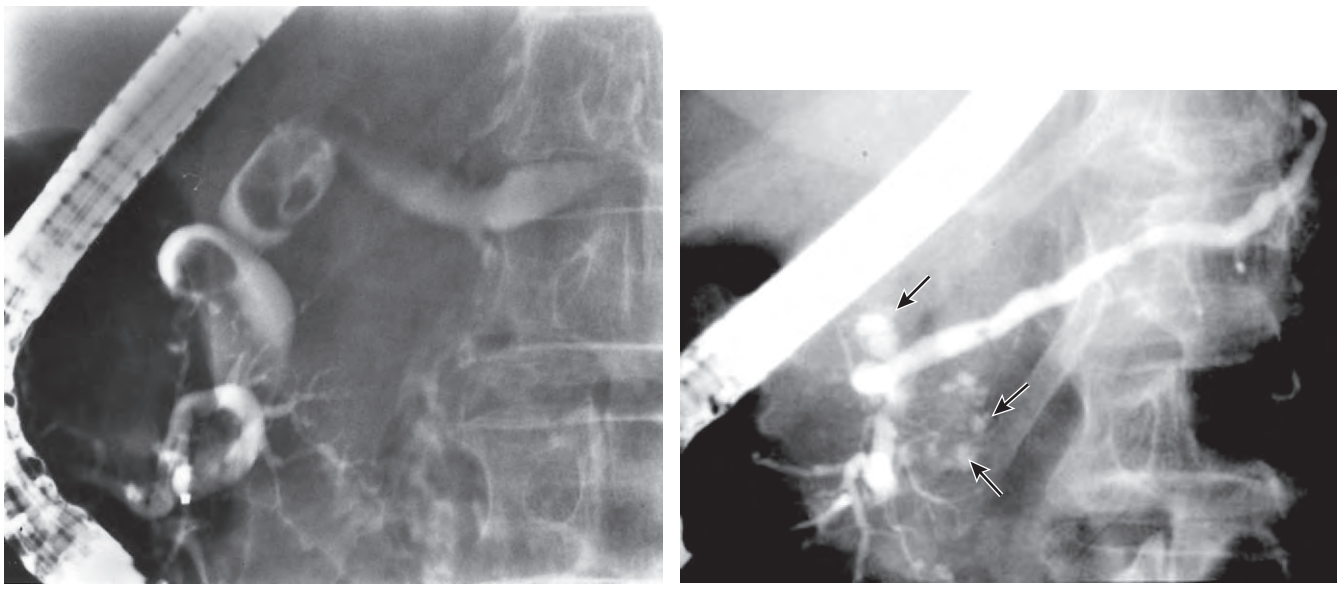


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Figure 93–8. Endoscopic retrograde pancreatography of intraductal papillary mucinous neoplasms of the pancreas. **A,** Main-duct disease. Note intraductal filling defects secondary to mucin globules. **B,** Side-branch disease. Note continuity with normal-size main pancreatic duct (*arrows*). (**A,** From Loftus EV Jr, Olivares-Pakzad BA, Batts KP, et al, and Members of the Pancreas Clinic and Pancreatic Surgeons of Mayo Clinic: Intraductal papillary-mucinous tumors of the pancreas: Clinicopathologic features, outcome, and nomenclature. Gastroenterology 110:1909-1918, 1996; **B,** From Sarr MG, Murr M, Smyrk TC, et al: Primary cystic neoplasms of the pancreas: Neoplastic disorders of emerging importance—current state-of-the-art and unanswered questions. J Gastrointest Surg 7:417-428, 2003.)

Magnetic Resonance Cholangiopancreatography

On occasion, magnetic resonance cholangiopancreatography (MRCP) may be more sensitive than ERCP in imaging pancreatic duct anatomy because filling of side-branch ducts at the time of ERCP may be obscured by intraductal plugs of mucin.[28,29] At MRCP, the presence of IPMN with mural nodules or excrescences, main pancreatic duct dilation (>15 mm), or common bile duct dilation are suggestive of dysplasia and/or malignancy; however, the absence of these mural nodules does not guarantee that the neoplasm is benign.[28] In one study, dynamic MR and MR cholangiopancreatography were found equal or slightly superior to thin-section helical CT in the evaluation of IPMN.[29]

Other Imaging Methods

Endoscopic ultrasonography (EUS) can provide detailed images of the wall and the internal architecture of the cystic lesion (i.e., septations and mural nodules, observed in MCNs), thereby facilitating the differential diagnosis from SCN.[30] Moreover, EUS can be used in image-guided fine-needle aspiration (FNA) (see later). *Intraductal pancreatoscopy* and *intraductal US* may be useful in the diagnosis and differential diagnosis of pancreatic cystic neoplasms, especially when a mass at a stenotic area of the main pancreatic duct cannot be delineated by other imaging methods (including EUS).[31] Moreover, these techniques may help assess the risk of malignancy, determine the extent of disease, allow tissue sampling, and provide therapeutic intervention.[32] However, experience with these two newer diagnostic modalities remains limited due to the technology.

Percutaneous Fine-Needle Aspiration

Fine-Needle Aspiration Cytology When positive, the characteristic cytology of SCN is that of cellular sheets of glycogen-containing, low-cuboidal cells; clear cytoplasm without vacuoles; and intracellular cytoplasmic inclusions.[33] In contrast, low-grade MCN are characterized by honeycomb sheets and clusters of mucin-containing columnar cells with, rarely, small papillary sheets.[34] In addition, MCNs have abundant mucin in their background, which is not a feature of SCNs. Because of the heterogeneity of the epithelial lining of MCNs, there may be marked discrepancies between the cytologic typing and subsequent histologic diagnosis of these neoplasms and, thus, cytologic findings only differentiate mucinous from serous neoplasms. At fine-needle aspiration cytology (FNAC), IPMNs are characterized by the presence of papillary clusters lined by mucin-containing columnar cells, usually with some degree of atypia.[34] Although low-grade MCN may demonstrate a few papillary clusters, they are not usually as tall, abundant, and striking as the clusters observed in IPMN. One major limitation of diagnostic cytology is the relatively low cellularity of the aspirated pancreatic cyst fluid, resulting in a low sensitivity (~30%), especially for SCN.[5] As a result, cytologic examination of the cyst fluid is often nondiagnostic, and FNAC has a diagnostic value only when it reveals obvious mucinous or malignant cells (specificity ~85%).[5,35] The ability to obtain directed "mini-biopsies" from the solid component of a cystic neoplasm or from the wall of the cyst increases the ability to make a differential diagnosis. Sample error is another limitation of the method. Finally, FNA may be associated with a small risk of complications (e.g., pancreatitis, theoretically neoplastic cell seeding along the needle track).

Analysis of the Cystic Fluid Biochemical analysis of the cyst contents of an FNA also may be of diagnostic value. SCNs are characterized by the absence of mucin, positive immunostaining for the cytokeratins AE1 and AE3, or positive periodic acid–Schiff reaction.[36] In contrast, a positive mucin stain or a high viscosity (mucin) reliably identifies the mucinous (premalignant or overtly malignant) mucinous neoplasms from SCN and usually from pseudocysts as well.[3] Likewise, an intracystic CEA concentration greater than 250 ng/ml reliably differentiates a mucinous from a serous neoplasm, whereas a value of less than 5 ng/ml is quite sensitive for excluding a mucinous neoplasm.[35] Other tumor markers (including CA 19-9, CA 72-4, CA 125, and CA 15.3) may be present in high concentrations in MCNs; however, their diagnostic and discriminatory values appear limited.[3] Amylase activity was a poor discriminator of differentiating most cystic masses[9]; however, a high amylase activity (>×5 serum activity) strongly suggests that the cyst is a pancreatic pseudocyst; the only exception is IPMN, in which the neoplasm involves the epithelial cellular lining of the main pancreatic ductal system (Table 93–1).

TREATMENT

Treatment varies markedly with the type (and even subtype) of cystic neoplasm of the pancreas. Each is discussed separately.

SCN

The generally benign nature of SCNs, combined with the morbidity and potential mortality of major pancreatic resectional procedures, historically led to a philosophy weighted toward observation.[36] However, uncertainty in the differential diagnosis and the reduction in perioperative mortality after major pancreatectomy observed during the last decade may account for the change of treatment policy toward a more aggressive approach. Nowadays, curative surgical resection is recommended for most all cystic neoplasms, except for an asymptomatic, benign-appearing SCN in an elderly or high-risk patient.[4,36] When SCN involve the body or the tail of the pancreas, many and probably most pancreatic surgeons suggest resection. Controversy persists regarding asymptomatic lesions in the head of the pancreas, especially in the frail or the elderly patient. Confirming these lesions confidently as benign SCNs (versus, MCNs) would allow a nonaggressive therapeutic approach (observation) in the asymptomatic patient, given the known slow pro-

Table 93–1 Differential Diagnosis of Pancreatic Cystic Neoplasms Based on Analysis of Intracystic Fluid

Cystic Lesion	Amylase Activity	CEA	Viscosity	Mucin Stain	Cytology
SCN	↓	↓	↓	Negative	Glycogen-rich cells
MCN	↓	↑↑↑*	↑	Positive	Mucinous cells
Pseudocyst	↑↑↑	↑	↓	Negative	Inflammatory cells

*Generally >250 ng/ml.
Key: ↓ = decreased, ↑ = increased.
CEA, carcinoembryonic antigen; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm.

gression of these lesions over many years.[8] In this situation, the cystic lesion might best be observed with serial, noninvasive imaging annually.[3-5] Resection (pancreatoduodenectomy, preferentially of the pylorus-preserving type) is indicated in the presence of symptoms (e.g., jaundice, pain, and early satiety) or when differentiation from an MCN cannot be made confidently.[36] There is no need for lymphadenectomy or any "extended" resection for SCN. Segmental "central" pancreatectomy and spleen-preserving distal pancreatectomy are quite reasonable procedures. Enucleation has been proposed as an alternative, but in some series, enucleation is associated with a high morbidity (≤35%) primarily related to the occurrence of postoperative pancreatic fistula.[5,36,37] Other approaches, such as cystoenterostomy, percutaneous external drainage, and percutaneous intracystic sclerosis (as used for simple hepatic cysts), are to be condemned and have no therapeutic role in this disease.

MCN

The unpredictable spectrum of multicentric metaplasia, dysplasia, carcinoma in situ, and tissue invasion implies that these lesions can dedifferentiate and transform into a life-threatening malignancy.[13] Therefore, most surgeons agree that all MCNs, whether in the proximal or distal pancreas, should ideally be removed, despite their size. For MCNs in the head of the pancreas, a formal pancreatoduodenectomy (preferentially of the pylorus-preserving type) is usually indicated. For MCNs in the body or tail region, a segmental central resection or a spleen-preserving distal pancreatectomy can be considered if there are no indications that the neoplasm has an invasive component; yet, this decision is taken at a small calculated risk (<10%) of treating an invasive malignancy without a wide resection or lymphadenectomy.[13] In many patients, a classic distal pancreatectomy with splenectomy may be the best treatment. Rarely, resection of involved adjacent structures/organs (including portal vein) may be required.[4,5] However, unlike pancreatic adenocarcinomas, malignant MCN tend to be "pushers" rather than "invaders."[5,13] Most surgeons would not perform an extended resection unless an invasive MCN was highly suspected. Lesser nonanatomic resections, such as enucleation or duodenum-preserving subtotal pancreatic head resections, although technically feasible, are suboptimal procedures, given the limitations in preoperative and intraoperative diagnosis of invasive carcinoma.

IPMNs

Because of IPMNs' latent or overt malignant potential, operative resection is indicated in all but the poor-risk patient; the aim of operative resection is to remove all the adenomatous or malignant ductal epithelium and to ensure that a recurrence in the pancreatic remnant is minimized. The basic and as yet unanswered question is whether or not IPMN represents a localized field defect limited to that segment of the gland or a global ductal abnormality with the potential to affect all of the pancreatic ductal epithelium. If this is a localized process, as with typical ductal cancer of the pancreas,[24] then a focused resection of the involved anatomic region of the gland would be indicated. In contrast, if IPMN is a global disorder of all the pancreatic ductal epithelium, probably all the pancreatic duct epithelium is at risk of malignant transformation, and therefore, in selected individuals, a total pancreatectomy would be indicated.[3,8] Total pancreatectomy, with its obligate apancreatic state, of course, has its own potential problems (brittle diabetes, exocrine insufficiency) and may not be appropriate for many patients, especially the elderly or the medically unsophisticated patient.

Currently, most experts have gravitated toward a more limited, image-guided localized but anatomic resection. When the IPMN involves branch-type duct disease, a localized but formal anatomic oncologic procedure is carried out—pancreatoduodenectomy (preferentially a pylorus-preserving procedure) for head/uncinate neoplasms and distal pancreatectomy for body/tail regions.[6,10] Management of the main duct IPMN is more controversial. When the dilation of the main pancreatic duct involves only the body and tail (~10% of patients), most pancreatic surgeons advocate a distal pancreatectomy with immediate frozen-section analysis of the proximal pancreatic margin.[3,10,38,39] If the frozen section is negative for adenomatous changes in the ductal epithelium, most surgeons do not advocate total pancreatectomy in the absence of objective evidence that the

proximal duct is involved. In contrast, if the margin is positive for invasive or noninvasive IPMN, then most surgeons would advocate a further pancreatic resection; if a tumor-free margin is not attainable without completing the pancreatectomy, most surgeons would proceed with total pancreatectomy, provided the patient is an appropriate candidate.[3] When the entire pancreatic duct is dilated, the assumption is that the disease is in the head of the pancreas. Because of this assumption (provided no intraluminal or extraluminal solid mass is evident elsewhere in the duct outside the boundaries of a pancreatic head resection), a pancreatoduodenectomy is undertaken with immediate frozen-section analysis of the distal margin. A positive margin necessitates a further "creeping" resection and, if necessary and appropriate, a total pancreatectomy is completed. Few, if any, pancreatic surgeons would advocate a nonanatomic resection for IPMN.[3]

PROGNOSIS AND FOLLOW-UP

Complete surgical excision of SCNs and of MCNs lacking any invasive component (i.e., benign MCNs and, more important, the noninvasive proliferative MCNs) ensures cure[1,13,37]; these neoplasms do not recur either locally or distally after complete surgical resection. Therefore, a regular oncologic-type follow-up program with surveillance using imaging tests or serum tumor markers is probably not necessary, thereby saving money and eliminating patient worry.[13] Most controversial is the long-term survival or patients with MCNs with tissue invasion. In the past, numerous articles have claimed survival rates higher than 50% and up to 70% for "mucinous cystadenocarcinomas"; however, these series lumped together the MCN containing a proliferative epithelium (but without tissue invasion) with the true cystadenocarcinomas. In contrast, after a careful evaluation of MCN containing true invasive carcinoma, 5-year survival rates appear to be lower (15% to 33%) but still somewhat better than those for typical ductal cancer of the pancreas.[13,40] The prognosis for nonresectable malignant MCN may be as poor as that for nonresectable pancreatic adenocarcinoma.[5] Survival may correlate with DNA cytometry.[41]

In IPMNs, the dysplastic component may remain in situ for many years. For branch-duct IPMN, several studies suggest strongly that a local anatomic resection is essentially curative. In contrast, in main-duct IPMN, occurrence in the remnant gland has been found with variable rates (0 to 10%)[3,42] provided that the frozen-section margin is negative and the resected specimen lacks invasive IPMN.[39] When the resection specimen shows invasive disease, even if the margin is negative, recurrent IPMN, either in the remnant gland or more commonly in extrapancreatic sites, occurs in 50% to 90% of patients,[21,39,42] thereby decreasing the 5-year survival to less than 50%. Invasive IPMN should be managed as an aggressive malignancy that behaves, in many respects, similar to ductal cancer of the pancreas but with a slightly better prognosis. Routine follow-up surveillance with noninvasive imaging is indicated in all patients with IPMN. The discovery of a pancreatic cyst/mass lesion may be related to the presence of a postoperative pseudocyst; a recurrence of IPMN linked to incomplete resection, a new site of IPMN; or, rarely, a cystadenocarcinoma after inadequate histopathologic examination.[5,13]

ADJUVANT/NEOADJUVANT THERAPY

If tissue invasion is present, some form of adjuvant therapy should be considered despite a "curative" resection, even if there are no nodal metastases.[13] There is anecdotal evidence that an apparently unresectable neoplasm with no metastases can become resectable after combined chemoradiation therapy.[43] However, experience remains limited, thereby precluding definite recommendations. Interestingly, patients with aneuploid neoplasms may benefit most from adjuvant chemoradiation therapy.[44]

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Chapter

94

Pancreatic Trauma

Edward E. Cornwell III · Elliott R. Haut · David Kuwayama

Pancreatic injuries, despite their relative infrequence, are regarded with great respect among experienced trauma surgeons because of their significant associated mortality and morbidity. Pancreatic injuries occur in up to 3% of patients with significant blunt abdominal trauma and a slightly higher percentage of those sustaining abdominal gunshot and stab wounds. Penetrating trauma accounts for more than 70% of pancreatic injuries and, given its anatomic location, associated injuries are the rule. The mortality rate for pancreatic injuries ranges from 10% to 25%, with the majority of deaths occurring in the first 48 hours from massive bleeding and its complications. The systemic inflammatory response syndrome, sepsis, and multisystem organ failure account for the vast majority of delayed deaths. Among patients with major pancreatic injury surviving the initial hemorrhage, nearly half will have a complication of their pancreatic wound such as abscess, fistula, pseudocyst, false aneurysm, or anastomotic leak.[1]

Patients with penetrating trauma to the pancreas experience injuries with equal frequency along the head, body, and tail of the organ.[2,3] In victims of blunt trauma, the deceleration and direct compression mechanism of injury explain why the neck of the pancreas in the prevertebral segment of the gland is the most commonly injured region.[4] The surgical management of pancreatic injury is complicated by the gland's complex anatomic relationship with the duodenum, biliary tract, splanchnic vessels, liver, spleen, vena cava, and aorta. Operative decisions are challenging because of the unforgiving nature of the gland, relative unfamiliarity with the techniques, controversy regarding the technical details, and the judgment required to decide on the extent of surgery. There should be no controversy, however, regarding the highest priority in the management of pancreatic trauma: control of hemorrhage.

DIAGNOSIS

Patients with torso trauma who manifest early indications of intra-abdominal bleeding or peritonitis require operative intervention, at which time direct evaluation of the pancreas should be carried out. The only penetrating assault with a significant likelihood of causing an isolated pancreatic injury is a posterior abdominal stab wound, and even this is quite unusual. The stable patient with blunt abdominal trauma is the person in whom timely diagnosis of pancreatic injury is most challenging.

Physical examination and evaluation of hemodynamic status still maintain a valued place in any diagnostic algorithm for patients with abdominal trauma who may have a pancreatic injury. Even anterior abdominal gunshot wounds, once uniformly accepted as a clear indication for exploratory laparotomy, are now managed selectively at some large trauma centers under the appropriate circumstances.[5,6] The initial clinical examination (vital signs, physical examination of the abdomen) becomes the main determinant of whether the patient is triaged immediately to the operating room, to other diagnostic testing, or to an observation site where serial physical examinations and monitoring can be undertaken. Important prerequisites for considering selective management of abdominal gunshot wounds rather than mandatory exploration include (1) experienced in-house surgeons who are available to take the patient to the operating room in the event of change in the initial benign clinical examination; (2) a predetermined site in the hospital that facilitates observation and serial examination (i.e., monitoring the vital signs, urine output, hematocrit, and repeated abdominal examinations); and (3) priority status that allows patients with deteriorating clinical examinations to be triaged immediately to the operating room. Serial physical examination is more universally accepted as a mainstay in the selective management of stab wounds to the anterior abdomen. Local wound exploration to determine whether a stab wound to the abdomen has penetrated the peritoneal cavity was once employed at many trauma centers, but as the stab wounds of the 1960s, 1970s, and 1980s gave way to the gunshot wounds of the 1990s and the new millennium, the number of surgeons experienced in this technique has diminished. Penetrating injuries to the back and flank as well as patients with blunt abdominal trauma

more frequently require other diagnostic adjuncts in pursuit of the determination of the need for surgical intervention or specifically to determine the presence of a pancreatic injury.[4]

Serum amylase determinations should be made routinely, and they are elevated in 80% of patients with blunt pancreatic injury.[7] This figure is much lower for penetrating wounds, but in either case an elevated amylase level mandates a directed evaluation of the pancreas. An elevated amylase level can be the result of bowel perforation, salivary gland trauma, as well as nondisruptive pancreatic injury; as such it is not a very specific test. Serum lipase may be used if there is confusion because it is not elevated when hyperamylasemia is of salivary origin. Pancreatic isoenzyme fractionation can identify salivary amylase but is often not available. It is often useful to repeat the serum amylase in patients being observed for abdominal trauma because the first blood specimens may be drawn so close to the time of wounding that a misleading normal value may result.

Additional diagnostic studies are indicated if there is suspicion of pancreatic injury. Such patients are those with amylase elevation and mild abdominal tenderness and distention. Plain or contrast radiographs offer little assistance. The focused abdominal sonogram for trauma (FAST) rapidly identifies fluid in the hepatorenal recess of Morrison.[8] As a modality that provides prompt assessment of patients with blunt trauma in the emergency department, it has essentially supplanted the diagnostic peritoneal lavage. The dynamic rapid-sequence computed tomography (CT) scan has been helpful in identifying major parenchymal (and therefore potential ductal) disruption. Although this examination is helpful, there are some important pancreatic injuries that it may miss. The study should be performed with oral contrast because occasionally a retroperitoneal rupture of the duodenum is responsible for elevation of the serum amylase without obvious signs of peritonitis.

In cases in which the clinical findings leading to the CT scan are persistent and the CT scan is equivocal or even negative, endoscopic retrograde cholangiopancreatography (ERCP) will delineate the pancreatic ductal anatomy (Fig. 94–1).[9] Although this situation occurs infrequently, ERCP can identify major ductal disruption well before clinical signs lead to laparotomy. Early identification and treatment of pancreatic injury reduce morbidity.

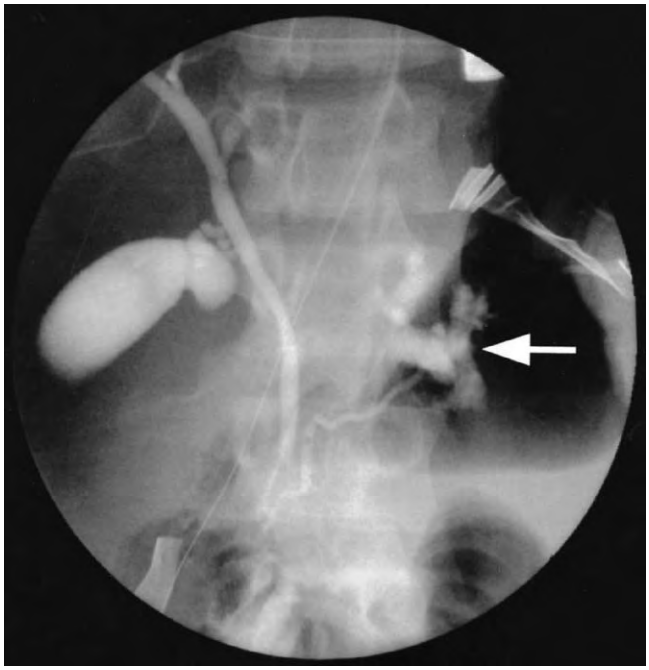

Figure 94–1. Endoscopic retrograde cholangiopancreatography performed after original damage control surgery for gunshot wound to abdomen and before re-exploration. *Arrow* shows extravasation of contrast from pancreatic duct.

INTRAOPERATIVE EVALUATION

In most patients with pancreatic injury, the diagnosis is confirmed intraoperatively. Evaluation of pancreatic trauma requires several surgical maneuvers. A Kocher maneuver entails incising the lateral peritoneal attachments to the second and third portion of the duodenum and mobilizing the duodenum and the head of the pancreas to the patient's left. This proceeds along the avascular plane to the superior mesenteric vein. Occasionally a replaced right hepatic artery is encountered as a branch of the superior mesenteric artery, and care must be taken because it can be injured during this dissection. This facilitates inspection of the posterior aspect of the head of the gland as well as the posterior wall of the duodenum and provides a view of the suprarenal inferior vena cava.

The anterior aspect of the entire gland may be evaluated by entering the lesser sac through the gastrocolic omentum. With a wide incision through that omentum and retraction of the stomach superiorly and the transverse colon inferiorly, thorough evaluation of the gland becomes possible. Any hematomas overlying the gland must be evacuated and thoroughly explored, because they frequently mask underlying severe pancreatic parenchymal or ductal injury (Fig. 94–2). Occasionally, a patient may present with severe injury to the posterior aspect of the pancreas, with the anterior capsule intact. This is seen most commonly in patients with blunt mechanisms of injury. When hematoma or contusion raises an index of suspicion for injuries that may involve the posterior aspect of the gland, an incision should be made in the peritoneum and areolar tissue along the inferior aspect of the pancreas. This most commonly applies in the prevertebral region of the pancreas. After division of the peritoneum along the inferior border of the pancreas, the surgeon's finger is slipped behind the gland to evaluate for parenchymal defects by palpation and direct visualization (Fig. 94–3).

Full evaluation of the tail of the pancreas can be facilitated by the Aird maneuver.[10] Originally described in 1955 to facilitate adrenalectomy, this procedure entails division of the avascular splenic ligaments (i.e., splenorenal, splenocolic, and splenophrenic) and mobilization of the spleen and the tail of the pancreas from the patient's left to right (Fig. 94–4).

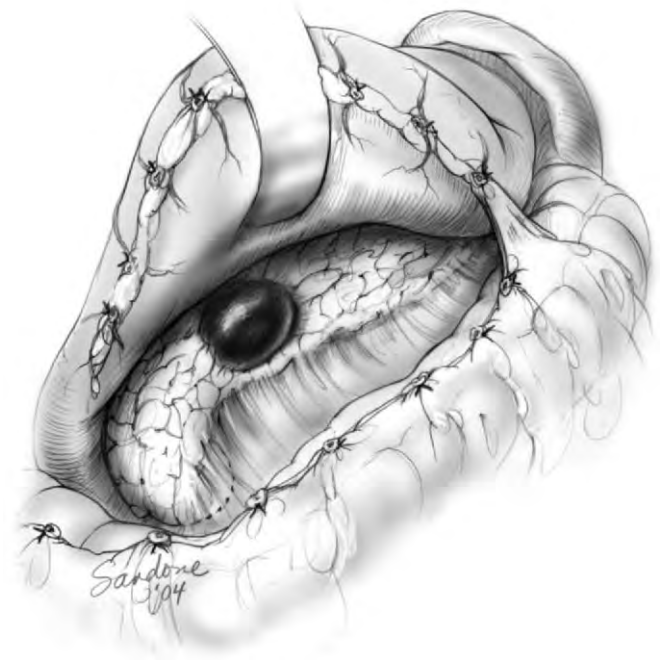

Figure 94–2. Any hematomas overlying the gland must be unroofed.

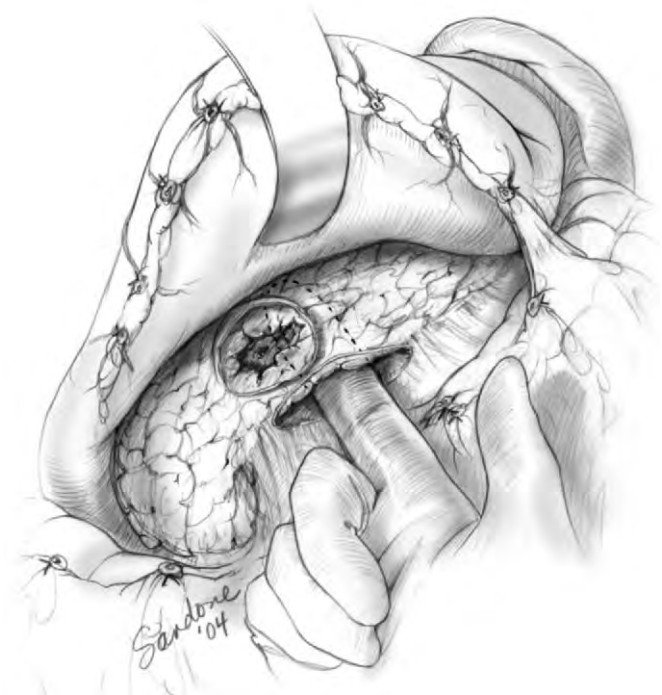

Figure 94–3. With the peritoneum along the inferior border of the pancreas divided, the surgeon's finger is slipped behind the gland to evaluate for palpable parenchymal defects.

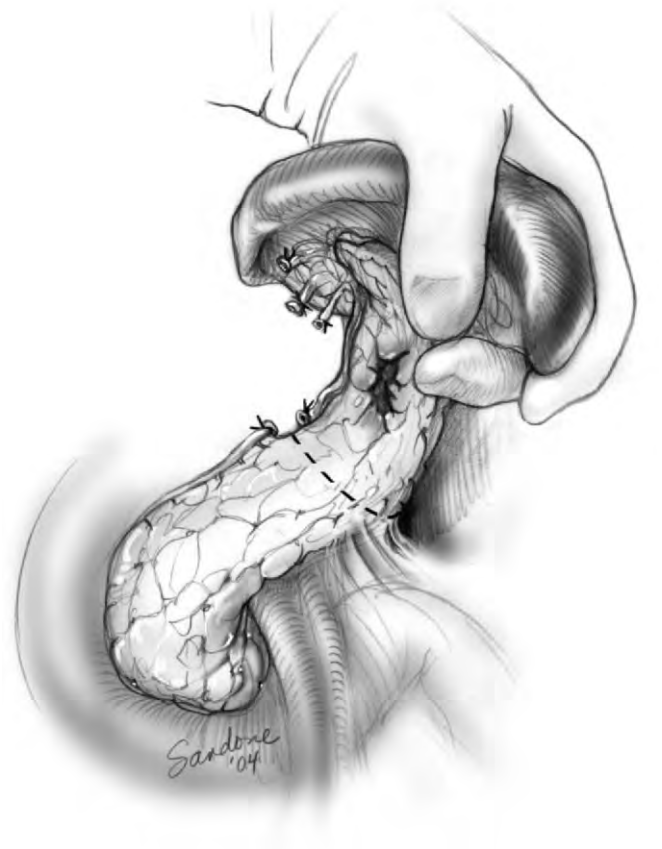

Figure 94–4. The Aird maneuver is employed to mobilize the spleen and tail of the pancreas.

OPERATIVE TREATMENT

The American Association for the Surgery of Trauma pancreatic organ injury scale grades injuries from I through V (Table 94–1). The use of a combination of the injury grade, injury location, and other concomitant injuries (especially to the duodenum) helps determine the surgical treatment for the pancreatic injury.[11] Patients with lower grade pancreatic injuries are significantly easier to manage. Observation and drainage along with débridement and meticulous hemostasis may be all that is necessary for grade I (minor contusion or superficial laceration) or grade II injuries (major contusion or laceration).

Major disruption of the pancreatic tissue requires a decision regarding the likelihood of major ductal injury. Even in major trauma centers, the gold standard ERCP is not available intraoperatively in the middle of the night. Suspicion of ductal involvement is raised by the anatomic location of the injury and the amount of local pancreatic tissue disruption. Occasionally, pancreatic juice can be seen leaking at the open ends of a duct. When major ductal injury is suspected, it should, in most instances, prompt definitive therapy. Under some

Table 94–1 American Association for the Surgery of Trauma Organ Injury Scaling: Pancreas

Grade	Type of Injury	Description of Injury
I	Hematoma	Minor contusion without duct injury
	Laceration	Superficial laceration without duct injury
II	Hematoma	Major contusion without duct injury or tissue loss
	Laceration	Major laceration without duct injury or tissue loss
III	Hematoma	Distal transection or parenchymal injury with duct injury
IV	Laceration	Proximal transection or parenchymal injury involving ampulla
V	Laceration	Massive disruption of pancreatic head

From Moore EE, Cogbill TH, Malangoni MA, et al: Organ injury scaling: II. Pancreas, duodenum, small bowel, colon, and rectum. J Trauma 30:1427-1429, 1990.

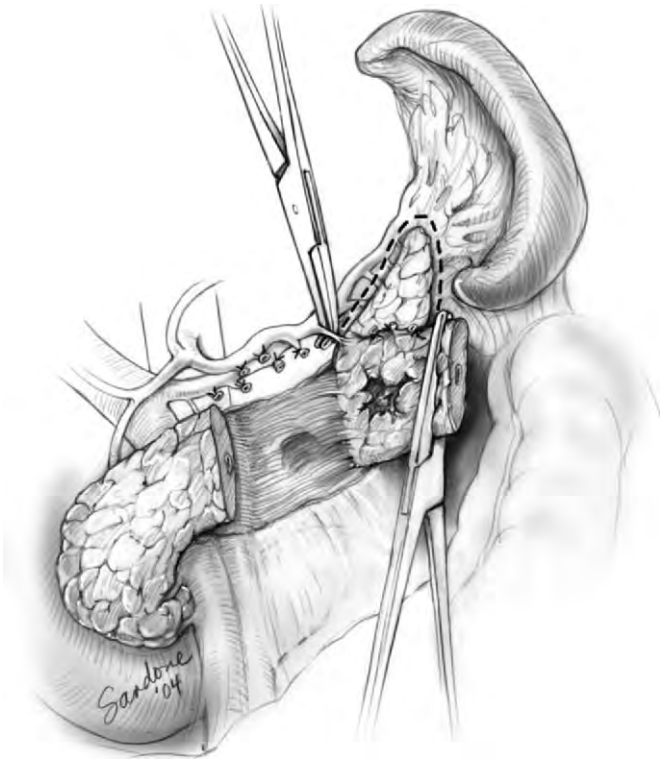

Figure 94–5. Distal pancreatectomy with splenic preservation.

circumstances, such as cardiovascular instability, drainage alone should be performed, after which the patient almost always has a pancreatic fistula.

If the duodenum is open already from the traumatic injury, then it is reasonable to perform fluoroscopic pancreatography by cannulating the ampulla to inject contrast. If there is no associated duodenal wound, the duodenum should not be opened for the sole reason of performing a pancreatogram. Another technique for performing a pancreatogram is a cystic duct cholangiogram by passing the catheter into the common bile duct and refluxing contrast into the main pancreatic duct. Adjuncts such as secretin or intravenous opiates may enhance the ability to perform a pancreatogram in this fashion.

Once the pancreatic ductal injury has been identified, the location of the injury will determine the appropriate treatment. The pancreatic duct injury can be divided into a proximal injury (in the head or neck, to the right side of the superior mesenteric vessels) and distal injuries in the distal body and tail to the left side of the mesenteric vessels. Grade III pancreatic injury with a distal transection or parenchymal injury is most easily treated by distal pancreatectomy. In the case of active ongoing hemorrhage, the most expeditious way to perform this is in combination with splenectomy. The spleen and pancreatic tail will have already been mobilized, leaving only the division of the pancreas itself, the short gastric arteries, splenic artery, and splenic vein. As with all other operations on the pancreas for trauma, the area should be widely drained with closed-suction drains to manage a possible postoperative pancreatic leak.

Many options (including staples, sutures, or electrocautery) are acceptable for transecting the pancreas and controlling the transected end of the gland; their use is based on surgeon preference. Ideally, the transected pancreatic duct should be identified and closed directly, often with either U stitch or a figure-of-eight suture. Other options include an omental patch or fibrin glue for helping control the distal pancreatic stump. The possibility of distal pancreatectomy without splenectomy (spleen-preserving distal pancreatectomy) can be considered in certain patient populations based on clinical stability and an isolated injury. The small benefit of helping to prevent overriding postsplenectomy sepsis by leaving the spleen in is often outweighed by the significant time that it takes to perform this tedious operation (Fig. 94–5).

Surgical management of severe injuries to the pancreaticoduodenal complex are some of the most complex that a trauma surgeon deals with. These grades IV and V injuries involve proximal ductal injury or massive destruction of the pancreatic head to the right of the superior mesenteric vein and are often in close association with the c-loop of the duodenum. The scope of procedure performed varies with the severity of injury, reserving the most aggressive surgical treatments for the most severe of these combined pancreaticoduodenal injuries.

There are three main goals in any surgical procedure for severe pancreatic injury. The first is to maintain

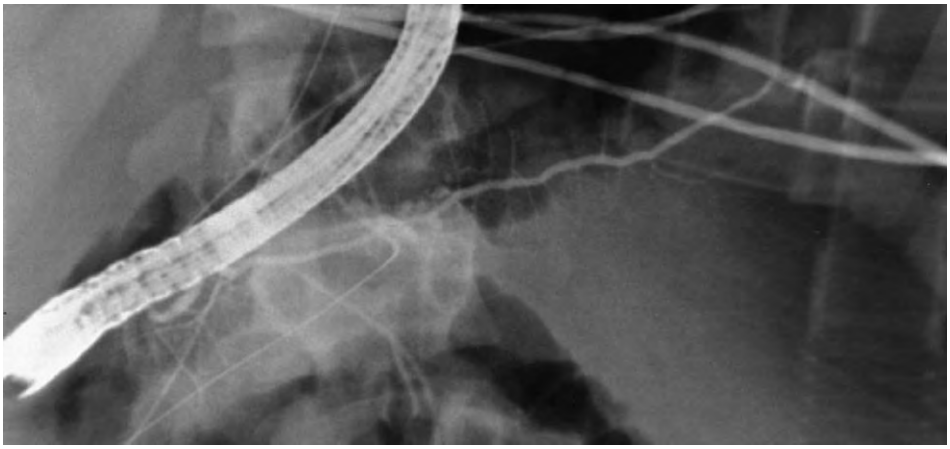

Figure 94–6. The same patient as in Figure 94–1 following placement of a pancreatic stent.

enteric flow from the pancreas and the biliary tree. The second is to divert any gastrointestinal secretions to minimize stimulation of pancreatic exocrine function. The third is to widely drain in anticipation of postoperative leaks or fistulas. The main surgical dictum for treatment of the injuries should be to perform the minimal surgical intervention necessary to adequately treat the injury and accomplish these objectives. Significant injuries to the head and neck that do not injure the major pancreatic duct are most appropriately treated with simple débridement and drainage. This approach can also be used in the hemodynamically unstable patient undergoing damage control surgery as a temporizing measure, allowing further investigation such as ERCP or magnetic resonance cholangiopancreatography after the initial operation. In the patient who is hemodynamically stable or at the second-stage operation after initial damage control, there are multiple options for dealing with injuries to the pancreaticoduodenal complex.

In the patient with pancreatic trauma, but without duodenal trauma, an extended distal pancreatectomy including the area of ductal disruption can be performed even if the pancreatic transection is to the right of the mesenteric vessels. Although this operation may leave the patient with a relative decrease in endocrine and exocrine function, it is less hazardous than attempting a Whipple procedure. If there is a very proximal transection, and there is a large portion of normal distal gland, consideration can be given to a central pancreatectomy that is performed by resecting the middle portion of the gland, débriding back to viable tissue, closing the duct on the portion closest to the duodenum, and draining the pancreatic remnant into a Roux-en-Y loop. Another possibility for a case such as this is pancreatic stenting. If at the initial operation the pancreas is widely drained and the abdomen is closed, postoperative ERCP is performed to place a pancreatic stent (Fig. 94–6). This can give the main pancreatic duct injury time to heal without performing a major pancreatic resection.

When pancreatic injuries are associated with major duodenal injuries, drainage or resection of the pancreas can be combined with suturing or stapling of the pylorus (pyloric exclusion procedure) to divert gastric flow from the duodenum.[12] Gastrointestinal continuity is then accomplished by gastrojejunostomy (Fig. 94–7). It is quite remarkable that gastroduodenal continuity is reestablished by 4 to 6 weeks after pyloric exclusion even when heavy nonabsorbable sutures or staples are used. The pyloric exclusion procedure has largely replaced the duodenal diverticulization procedure, which entails antrectomy and gastrojejunostomy, as well as drainage and decompression of the duodenal injury and drainage of the pancreatic injury.[13]

When pancreaticoduodenal trauma is so severe that hemorrhage control or extensive destruction of tissue necessitates resection of the second portion of the duodenum or the head of the pancreas, a pancreaticoduodenectomy (Whipple procedure) is indicated.[14] The avascular plane between the neck of the pancreas and the superior mesenteric vein allows for safe mobilization of the gland for resection (Fig. 94–8).

POSTOPERATIVE CONSIDERATIONS

When drainage is performed for major pancreatic injuries, the guideline for removing the drain is tolerance of regular oral feedings and the absence of high-volume or high-amylase content in the drainage fluid. A feeding jejunostomy is an important adjunct to major pancreatic injuries requiring pancreatic resection, pyloric exclusion, or the Whipple procedure because of the accumulated evidence showing the importance of early enteric feeding in maintaining the immune function of the gut in critically injured patients.

Up to one third of patients with major pancreatic injuries develop a *pancreatic fistula.* Most of these resolve spontaneously with adequate drainage. The soft evidence of a beneficial effect of somatostatin following pancreatic resection for trauma fails to justify the expense associated with its routine use.[15,16] There is more support for the concept that somatostatin may reduce the volume of output (and promote closure) once a pancreatic fistula has developed.[17] Rarely, late management of the pancreatic fistula that shows no sign of closure after many weeks of nonoperative management, or the patient who forms a pseudocyst after drain removal requires internal drainage via a Roux-en-Y jejunal limb. Postoperative

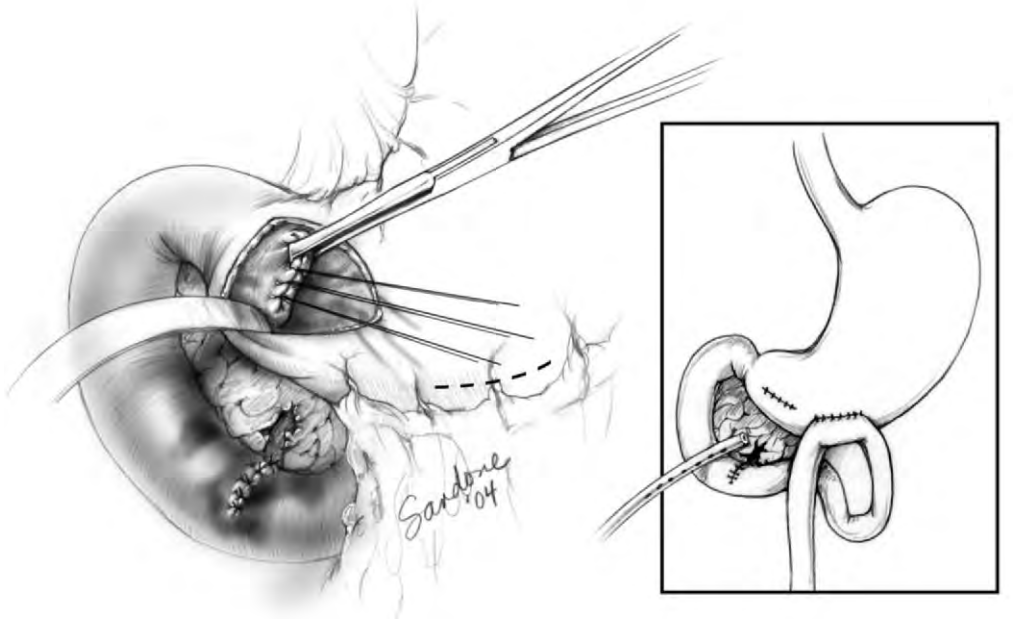

Figure 94–7. The pyloric exclusion procedure.

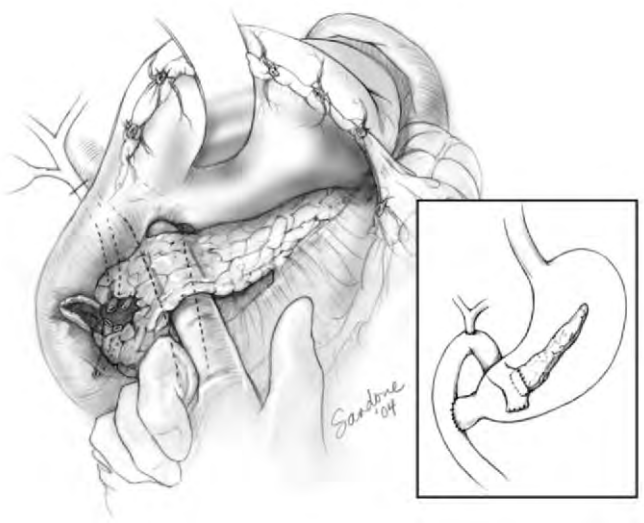

Figure 94–8. The Whipple procedure mobilizing the head of the gland.

pancreatic abscess usually demands open débridement and wide drainage. However, single, uniloculated collections in the absence of much pancreatic necrosis (as determined by dynamic CT scanning) may respond to percutaneous CT-guided drainage with large catheters.

SUMMARY

Pancreatic trauma continues to carry a significant risk of mortality and morbidity. Early physiologic stabilization and precise diagnosis (either preoperatively or intraoperatively) are the keys to optimizing outcome in these patients. The grade of the injury, and particularly the presence and location of a pancreatic ductal injury, determines the most appropriate operation (hemostasis, débridement, drainage versus resection, pyloric exclusion, or rarely pancreaticoduodenectomy).

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Chapter

95

Pancreatic Problems in Infants and Children

Charles N. Paidas · Mark L. Kayton

There is much about the pediatric pancreas that can be informative to the adult surgical specialist. Problems that are commonly seen in infants and children, such as annular pancreas, may remain occult until stumbled on in adulthood. In some instances management strategies, such as the nonoperative management of pancreatic trauma, have been demonstrated in the pediatric setting, and the adult clinician must make an informed decision as to whether to apply these approaches to adult patients.

This chapter details the surgical management of pancreatic conditions commonly seen in infancy, childhood, and adolescence. We review annular pancreas and its relation to duodenal atresia; hyperinsulinism of infancy; pancreas divisum; and the pediatric surgical strategies for chronic pancreatitis, tumors, and trauma. The safety and efficacy of endoscopic retrograde cholangiopancreatography (ERCP) in children is also discussed.

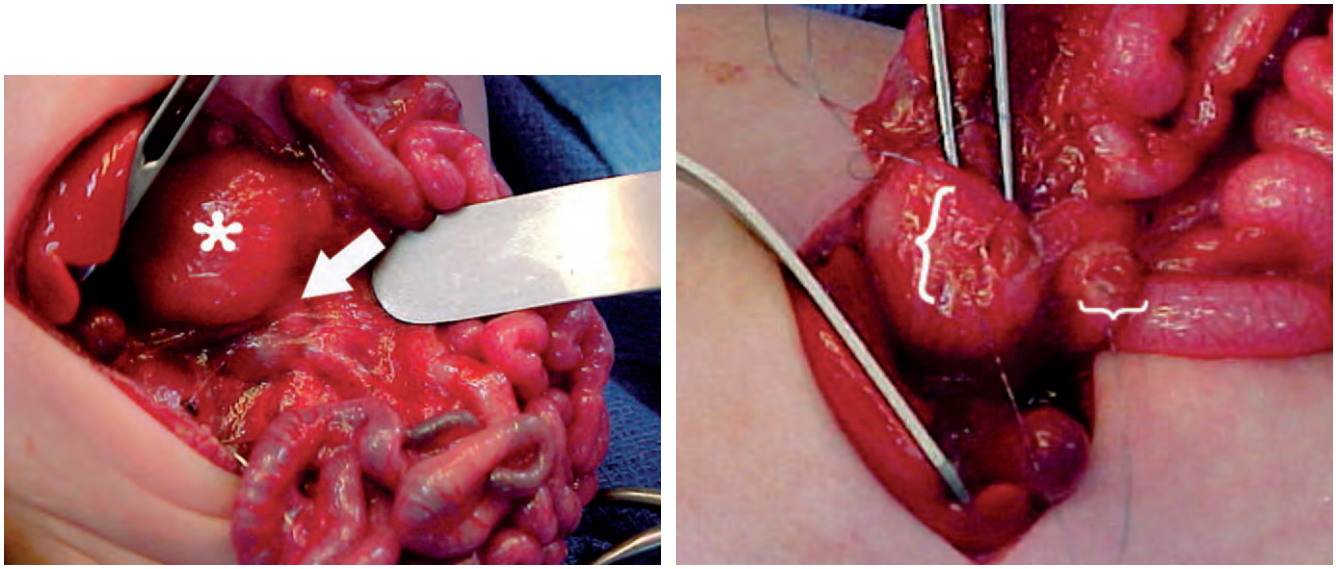
ANNULAR PANCREAS

In the fetus, the caudal portion of the developing foregut develops into the proximal duodenum as well as the dorsal and ventral pancreatic buds. At 5 weeks of gestation, rightward rotation begins to bring the ventral pancreatic bud to the right of the duodenum, where it comes to join the dorsal pancreatic bud to give rise to the head of the pancreas. The lumen of the duodenum becomes transiently obliterated with proliferation of the lining cells during the same period of development. By the 8th week of gestation, rotation of the pancreas is complete and recanalization of the duodenum has occurred.[1] Thus, it is easy to understand that any perturbation influencing the rotation of pancreatic tissue during the 5th to 8th week of gestation may also bear on the recanalization of the duodenum. Not accidentally, annular pancreas is clinically observed in association with various degrees of intrinsic duodenal stenosis and atresia. This is one of several reasons why simple division of the constricting "annulus" of pancreatic tissue is the wrong operation for this condition.

Annular pancreas generally presents in the newborn period but has been reported in an 11-year-old[2] and may be encountered incidentally in adults. Prenatal ultrasound may detect polyhydramnios or may diagnose duodenal obstruction directly, as occurred in 5 of 16 patients in a recent series from University of California at Irvine.[3] At birth, infants have a scaphoid abdomen. Radiographs showing the "double bubble" sign, classically attributed to duodenal atresia, were seen in 14 of 16 patients in the Irvine series and in all 7 of 7 in a recent Turkish series.[4] Emesis may be bilious or nonbilious; as Merrill and Raffensperger[2] noted in their classic 1976 series of 24 patients with annular pancreas, the obstruction may be above or below the ampulla of Vater. Of the 16 patients in the Irvine series, only one presented with bilious emesis, whereas 7 of 15 had bilious emesis in a report from National Taiwan University Hospital.[5]

Associated congenital anomalies should be looked for prior to, and during, operation for annular pancreas. These may include nonsurgical anomalies such as Down syndrome and operative conditions including esophageal atresia, malrotation, Meckel's diverticulum, and imperforate anus. Congenital cardiac defects must be assessed with preoperative echocardiogram prior to operation.

At operation, a transverse right upper quadrant skin incision is used. In the newborn, the proximal, obstructed, duodenal bulb may be markedly dilated, with the rim of annular pancreas visible just caudal to it (Fig. 95–1A). Repair is by duodenoduodenostomy, done in diamond-shaped fashion by making a transverse incision in the proximal duodenum and a perpendicular longitudinal incision in the distal duodenum (see Fig. 95–1B). The two ends may then be "fishmouthed" together using a single layer of interrupted, absorbable, monofilament suture. If duodenoduodenostomy is precluded by excess



A B

Figure 95–1. **A,** Appearance at laparotomy of annular pancreas with complete duodenal atresia. The dilated proximal duodenal bulb is marked with the *asterisk;* the annular pancreatic tissue is marked by the *arrow.* **B,** Construction of the diamond-shaped duodenoduodenostomy. The proximal duodenum is incised transversely and the distal duodenum, in perpendicular fashion (directions marked by *brackets*). (**A** and **B,** Courtesy of Anne C. Fischer, MD, Division of Pediatric Surgery, Johns Hopkins University, Baltimore, Maryland.)

tension or a poorly developed distal duodenum, then duodenojejunostomy should be performed.

Nasogastric or orogastric decompression is used postoperatively. Enteral feeding was reportedly started on the 8th to 9th postoperative day, on average, in the series from Irvine and Taiwan. Thus, annular pancreas, which Merrill and Raffensperger in 1976 deemed an "eminently curable lesion," is cured without ever touching the pancreas itself.

HYPERINSULINISM

Much confusion has surrounded the pathology of congenital hyperinsulinism. Reflecting this, the disease has been variously referred to as *persistent hyperinsulinemic hypoglycemia of infancy, islet cell dysmaturation syndrome,* and—most commonly—*nesidioblastosis.* Whereas the term *nesidioblastosis* classically refers to diffuse overgrowth of pancreatic islet cells, it has become clear in recent years not only that this process is not present in every infant with critical hypoglycemia but that nesidioblastosis can be identified histologically in the pancreata of infants with normoglycemia as well.[6,7] Owing largely to the work of Rahier and Fékété and colleagues in Europe, a clear algorithm for understanding, diagnosing, and treating this condition has emerged. This understanding is founded on the observation that there are two forms of congenital hyperinsulinism: a focal form and a diffuse form.

In the focal form, a genetic defect exists solely in the cells of the pancreatic lesion, involving loss of the maternal allele of chromosome 11p15 that serves to unmask a paternally derived mutation.[8] Focal adenomatous hyperplasia is the result. Pancreatic venous sampling is recommended to make the diagnosis. Antihypoglycemic medications must be held, and the blood glucose must be allowed to drop to below 3.5 mmol/L.[9] Radiologically guided, transhepatic catheter access to the portal venous system is established, at which point venous sampling for insulin and glucose is performed from the splenic, superior mesenteric, inferior mesenteric, and portal veins and from pancreatic collaterals.[10] Among 19 cases in a 1989 report from the Hospital Enfants Malades in Paris, focal insulin hypersecretion was discovered in 7 cases. If this technique is unhelpful, calcium-stimulated arteriography with sampling of the hepatic venous effluent has also been reported.[11] Supplemental imaging modalities such as computed tomography (CT), ultrasound, and intraoperative ultrasound have not yet been validated in the literature for this problem in infancy; however, positron emission tomography–magnetic resonance imaging appears promising.[12]

Treatment of the focal form of congenital hyperinsulinism is by partial pancreatectomy. Cretolle et al. have reported cure in 44 of 45 patients undergoing partial pancreatectomy following localization, and most, although not all, were found to appropriately correlate with preoperative venous localization. The authors approached lesions of the midportion of the pancreas by means of middle pancreatectomy with preservation of the head, along with Roux-en-Y jejunal loop to the transected portion of the pancreatic tail. Forty-four patients in the series had normal postoperative glucose and glucose tolerance tests as well as hemoglobin A_1C, and all patients were without exocrine dysfunction, with a reported mean follow-up of 3.7 years.[11] Curative laparoscopic enucleation of focal lesions has been reported by others.[13]

In the diffuse form of congenital hyperinsulinism, there is diffuse hyperfunction of pancreatic β cells with enlargement of their nuclei, but neither the β-cell proliferation rate nor the overall β-cell mass is increased.[6,7] Diagnosis may also be made by pancreatic venous sampling or by the observation on frozen section of diffuse enlargement of nuclei seen in all specimens. In this case, near-total pancreatectomy is required. Classic anatomic benchmarks, such as removing all pancreatic tissue up to the superior mesenteric vein, should be taken with caution in light of a pediatric autopsy study by Reyes and colleagues, who demonstrated that distal pancreatectomy taken past the mesenteric vessels, up to the left border of the pancreaticoduodenal vessels in the head of the pancreas, only accounted for removal of an average of 71.3% of the pancreas by weight, with a highly variable range of 43.5% to 95.8%.[14] The approach of Fékété et al. is to perform near-total pancreatectomy, leaving only a "small lump of pancreatic tissue in the concavity of the duodenal genu superius, with choledochal dissection."[12] Long-term complications reported following near-total pancreatectomy have included growth disturbance, glucose intolerance or overt diabetes, and variceal bleeding due to splenic vein thrombosis, the latter presenting as late as 18 years postoperatively.[15-17] Reports of long-term pancreatic exocrine deficiency are hard to find. Regeneration of the pancreas following near-total pancreatectomy in infancy has been documented.[18,19]

Early recognition of congenital hyperinsulinism is critical because, if untreated, profound hypoglycemia may lead to brain damage. The clinical manifestations of congenital hyperinsulinism ordinarily become obvious in infancy. Babies may be described as jittery, floppy, or lethargic; seizures are common, and near-death events may occur.[18,20] Diagnosis requires the presence of inappropriately elevated insulin in the setting of hypoglycemia, along with the need for continuous glucose infusion (>15 mg/kg/min) to maintain normoglycemia. The presence of low ketone bodies and an increase in blood glucose after glucagon administration may additionally be used as diagnostic criteria.[18] Medical therapy must be instituted immediately, beginning with continuous glucose administration; central venous access is helpful in this regard. Agents that may be helpful in the suppression of insulin secretion include diazoxide and somatostatin. Based on the requirement of calcium influx into pancreatic β cells to foster insulin release, it has been postulated that calcium channel blockers may work, and nifedipine was administered with apparent effect in one case.[21] Work-up must proceed while these pharmacologic maneuvers are ongoing. Operation is necessary in more than two thirds of cases.[12] The decision to operate should hinge on the demonstration of focality or, in the case of diffuse disease, on the failure of medical management.

PANCREAS DIVISUM

Pancreas divisum is a congenital anomaly, but it may manifest itself at any time during life. Alternatively, it may never be discovered until autopsy. During fetal development, as the pancreas forms from the rotation and fusion of the ventral pancreatic anlage and the dorsal pancreatic anlage, the ventral duct of Wirsung and the dorsal duct of Santorini ordinarily join. Failure of fusion of the two ducts results in pancreas divisum. In this situation, the duct of Wirsung drains the uncinate process and variable amounts of the head of the pancreas through the major papilla, while the duct of Santorini drains the remainder (usually the majority) of the pancreas through a more cephalad accessory papilla. Stenosis of one or both ducts may contribute to the development of pancreatitis.

In 1980, Cotton proposed that the presence of pancreas divisum was associated with pancreatitis.[22] He reported that, among patients with "idiopathic" recurrent pancreatitis undergoing ERCP, 25.6% were found to have pancreas divisum. In contrast, a group of patients with primary biliary disease who had ERCP over the same period manifested a 3.6% incidence of pancreas divisum. Necropsy series are cited by Cotton to show a 5% to 10% incidence in the general population. His study was provocative but flawed, insofar as the control group participants were not so-called normals but those with another disease process entirely. Nonetheless, a more recent pediatric study corroborates that of 52 children with relapsing or chronic pancreatitis, 10 had variants of pancreas divisum.[23] So whereas chronic or recurrent pancreatitis may be multifactorial, an association with pancreas divisum has not been disproved, and it may have a contributory role in some individuals.

Three important papers from, respectively, Boston Children's, University of California at San Francisco, and Vanderbilt, together present a unified concept for the surgical treatment of recurrent pancreatitis in the setting of pancreas divisum with ductal stenosis.[23-25] All recommend transduodenal sphincteroplasty of the minor papilla draining the stenotic accessory duct of Santorini and consideration of sphincteroplasty of the major papilla as well. The sphincteroplasties are done by insinuating a probe into the minor papilla and sharply dividing anterior to the probe, in gradual fashion. During the course of this sharp division, which serves to splay open the sphincter, interrupted 6-0 or 7-0 synthetic, monofilament, absorbable sutures are sequentially placed from ductal mucosa to surrounding duodenal mucosa. No stent is left. The duodenotomy, opened longitudinally, is closed transversely. The Boston Children's Hospital series indicated that dual sphincterotomies were performed in all cases and further suggested the administration of secretin (1 U/kg) to assist in the localization of a small minor papilla.

The Vanderbilt group presented follow-up on six patients after transduodenal sphincteroplasty. All had preoperative evidence by ERCP of pancreas divisum with ductal obstruction. Of the six, just one had a long-term excellent result. Another required ERCP and stenting 3 years later. Two of the six patients continued to have attacks of abdominal pain. Two others went on to have Puestow procedures, with achievement of long-term improvement. Clearly, patient selection is important in deciding who should receive sphincteroplasty. For some patients with recurrent or chronic pancreatitis and pan-

creas divisum, sphincteroplasty alone may not address the whole problem, and pancreaticoenteric anastomosis may be required.

PANCREATICOENTERIC PROCEDURES FOR CHRONIC PANCREATITIS

In stark contrast with cases of pancreatitis in adults, where the most frequent causes are alcohol and gallstones, the most common cause of pancreatitis among children in one series was trauma.[26] This was followed by congenital and drug-related etiologies.

Medical management of chronic pancreatitis revolves around the use of total parenteral nutrition (TPN), somatostatin, pain management, pancreatic enzyme replacement, and endoscopic sphincterotomy and stenting. When these fail, surgical therapy has been found helpful. There are three pancreaticoenteric anastomotic procedures described for the surgical management of chronic pancreatitis in children: (1) the Frey procedure, (2) the modified Puestow procedure, and (3) the Duval procedure.

The Frey Procedure

Although typically the least well known, the Frey procedure has a published track record in pediatric patients and should be kept in mind when considering surgical options. Designed to drain the head as well as the body and tail of the pancreas, the Frey procedure, nicely described by Rollins and Meyers,[27] involves opening the main pancreatic duct throughout its length in the neck, body, and tail of the gland, after which the head is "cored out" in continuity with the opened duct. A longitudinal anastomosis is then constructed between the gland and a Roux-en-Y limb of intestine. In a retrospective study including nine patients who underwent the Frey procedure, improvements in symptoms and in quality of life were found in seven of the nine. Notably, the average patient age was 12.8 years at the time of the Frey operation, and one patient was successfully operated on in the setting of a previous, failed Puestow. There were multiple causes of pancreatitis in this cohort, and only one of those undergoing the Frey procedure had hereditary pancreatitis.

The Modified Puestow Procedure

The modified Puestow procedure may also be successfully employed in children. DuBay and colleagues described, in 2000, its applicability to 12 cases of hereditary pancreatitis.[28] The patients were a mean of 9.3 years old (range, 2 to 16 years) and all had dilated ducts, with symptoms including either intractable pain or failure to thrive with recurrent pancreatitis. They used a two-layer, side-to-side anastomosis between the opened pancreatic duct and a retrocolic, Roux-en-Y jejunal limb. These authors found significantly decreased rates of hospitalizations after 1 and 3 years and a significant gain in percentage of ideal body weight after 3 years, for children undergoing the modified Puestow. All but 1 of the 12 patients rated their own outcome as good or excellent. One patient developed pancreatic stones postoperatively and underwent ERCP with sphincterotomy and extraction despite having had the modified Puestow 1 month prior.

Crombleholme and colleagues, in 1990, also reported favorable results using the Puestow (with splenectomy) method or the modified Puestow (without splenectomy) method in a group of 10 children (mean age, 9.4 years old [range, 4 to 16 years]) with chronic pancreatitis of varying etiologies.[29] The authors found improvement or resolution of pain in all patients with a mean follow-up of 4 years (range, 7 months to 19.75 years). The technique used was either a two-layer anastomosis where the inner layer joined ductal mucosa to jejunal mucosa using continuous 4-0 polydioxanone and the outer layer utilized interrupted 4-0 silk, or, in 3 patients, a sleeve technique wherein the pancreatic duct was opened and the entire body and tail of pancreas were placed within the Roux limb of jejunum.

The Duval Procedure

A third surgical option has been reported in a pediatric series by Weber and Keller: the Duval procedure, which is a distal pancreatectomy with Roux-en-Y pancreaticojejunostomy.[30] The authors describe, retrospectively, 16 patients who had this procedure as the primary operation, and an additional 2 who were converted to Duvals following failure of prior Puestow procedures. Mean age for the 18 patients was 8 years (range, 3 to 13 years). Half had familial pancreatitis. The extent of distal pancreatectomy was described as going generally to the superior mesenteric vessels, but intraoperative evaluation of the extent of pancreatitis in the distal gland was stated to be part of the decision-making process. Results were favorable. Of the 18 patients, 13 were weaned entirely off pain medications and required no further hospitalizations, with mean follow-up of 7.5 years.

Among these series, advocates of the Duval procedure point out that two failed Puestows were successfully converted to Duvals. In contrast, advocates of the modified Puestow included a patient who failed to improve after a Duval and so was converted to the modified Puestow. Thus, no claim can be made as to the relative superiority of one approach over the other.

TUMORS

Several pancreatic tumors are unique to pediatric patients. Presenting signs and symptoms in pediatric patients may include a mass, pain, weight loss, or hypoglycemia, but jaundice is a much less common presentation than is experienced with adults. Surgery figures prominently in the treatment of each of these conditions.

Pediatric pancreatic tumors include pancreatoblastoma, solid-pseudopapillary tumors, and primitive neuroectodermal tumors (PNETs). Lymphoid malignancies and metastatic disease may also affect the pancreas.

Other pancreatic masses and cysts such as neuroendocrine tumors, serous cystadenomas, and hydatid cysts can occur in children, and their management parallels that of the same conditions in adults.[31-33]

Pancreatoblastoma

Pancreatoblastoma usually presents in the first decade of life. Originally termed *infantile pancreatic carcinoma,* these tumors comprise both epithelial and stromal components. Pathologists look for characteristic squamoid corpuscles, which are nests of squamous-appearing spindle cells that may have keratinization. In the 1995 series by Klimstra et al., tumors were distributed similarly between males and females. Some of the tumors were identified in adults. No predilection was identified for the head versus the tail of the pancreas, but it was noted that four of six patients with tumors in the head of the pancreas died, whereas five of five with tumors in the body or tail survived.[34]

Wide local excision carries an important role in pancreatoblastoma, so the pediatric surgeon must be prepared for whatever resection is required, whether distal pancreatectomy or pancreaticoduodenectomy, even if in an infant.[35] Involvement of adjacent organs, regional nodes, and vessels is common; many patients present with metastases. Neoadjuvant and adjuvant therapy have been used. Initial diagnosis may be made by fine-needle aspiration.[36]

Primitive Neuroectodermal Tumor

PNETs are members of the Ewing's sarcoma family of tumors. Primary pancreatic PNETs, of which only 13 cases have been reported in the literature,[37-42] are aggressive tumors that typically affect patients in the second or third decades of life. The overwhelming preponderance have occurred in the head of the pancreas, which may explain why patients with pancreatic PNET, unlike those with the other pediatric histologies described here, frequently present with jaundice.

Histologically, PNETs are small round cell tumors. They share the characteristic t(11;22)(q24;q12) chromosomal translocation of Ewing's sarcoma, and this results in the *EWS-FLI1* fusion gene. Histologic diagnosis may not be straightforward, and thus obtaining enough tissue to perform molecular diagnostic studies may be critical.

All reported patients have undergone either biopsy or resection. Infiltration into surrounding organs and lymph nodes has been described. Given the similarities with Ewing's sarcoma and PNETs at other locations, chemotherapy is indicated; the only survivors reported in the literature have been those who have complied with this. Radiation has been used as well.

Solid-Pseudopapillary Tumor

In the past, solid-pseudopapillary tumors have also been termed *papillary cystic cancer* or *Frantz tumor.* It is a tumor of low-grade malignant potential, occurring more frequently in girls.[43,44] Radiographically and grossly, solid-pseudopapillary tumors have cystic and solid elements. Diagnosis may be made by fine-needle aspirate, which Nadler and colleagues have shown may be accomplished at the time of endoscopic ultrasound in an adolescent patient.[45]

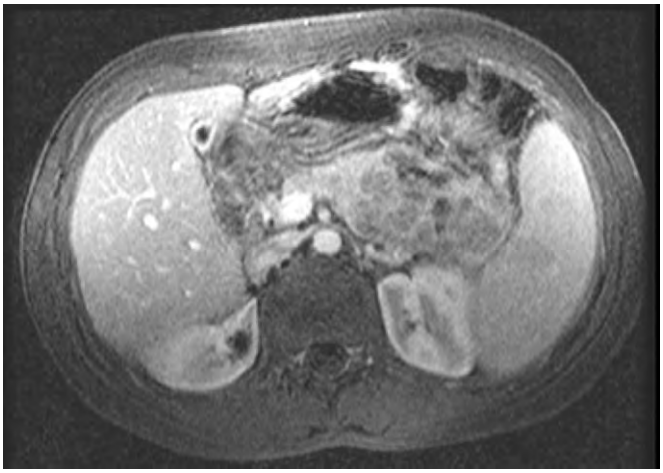


Figure 95–2. MRI showing neuroblastoma metastatic to the tail of the pancreas in a 16-year-old girl, appearing as a heterogeneous, multilobulated mass.

Solid-pseudopapillary tumors occur in all regions of the pancreas with equal frequency. They do not tend to invade adjacent organs. Depending on location, pancreaticoduodenectomy, central pancreatectomy with anastomosis of the distal portion to a Roux-en-Y jejunal loop, and distal pancreatectomy have each been applied.[44-48] Treatment is by complete excision. There is no established role for chemotherapy or radiation therapy.

Other Tumors

Lymphomas may arise in the pancreas. The pancreas also may be the site of metastatic spread of other pediatric malignancies, such as neuroblastoma (Fig. 95–2).

TRAUMA

Blunt injury to the pancreas in children typically occurs in the setting of three characteristic mechanisms. These include handlebar injuries, blows to the abdomen, or motor vehicle crashes. Hemodynamic instability after volume resuscitation of 40 ml/kg (20 ml/kg × 2) of crystalloid should prompt celiotomy, but this scenario is unusual. Ordinarily, symptoms or the presence of peritonitis or a "seat-belt" sign will lead to the performance of a CT scan. The authors have found that administration of intravenous contrast is essential to suitably visualize solid organ injury but that attempting to administer oral or intragastric contrast wastes valuable time in the trauma setting, without clinical gain. In the infant or child with limited intravenous access, intravenous

contrast can be—and on multiple occasions, has been—effectively delivered by the physician hand-pushing the contrast bolus through an intraosseous line.

Successful surgeon-directed nonoperative management of pancreatic injuries has been reported in multiple case series from the 1990s. In 1994 the Johns Hopkins group found that of 2900 children admitted for blunt trauma to a pediatric trauma center, 7 had CT-proven lacerations of the pancreas. Four of these 7 patients recovered without intervention. The remaining 3 required partial resection or operative treatment of a pseudocyst.[49] The severities of the lacerations seen on CT were not described in that report, but a subsequent review of the National Pediatric Trauma Registry by Keller and colleagues stratified 154 pediatric pancreatic injuries by severity and found that 79% of the children without major ductal injury, and 48% of the children with major ductal injury, evaded celiotomy.[50] Although encouraging, these data must be counterbalanced by a consideration of the morbidity associated with nonoperative management. Of 19 Japanese children reported in a 1999 series, nonoperative management had complications, including 2 pseudocyst ruptures secondary to patient motion and 1 death from TPN-associated complications.[51]

The data on nonoperative management highlight the observation that in some cases, even after complete transection, the pancreatic duct itself may seal. The resiliency of the duct is illustrated by a case reported by Arkovitz, in which an 8-year-old sustained a complete, ERCP-proven transection of the proximal duct. Surgical débridement and placement of two Jackson-Pratt drains—but no pancreatic resection or enteric anastomosis—were performed, and in 3 months' time complete reconstitution of the duct was demonstrated.[52] Data from the Hospital for Sick Children, Toronto, corroborate this. There, nine children had complete pancreatic transection and all were treated nonoperatively. Percutaneous pseudocyst drainage was later required in three of the nine patients. Atrophy of the body and tail were observed in some cases. However, two patients reconstituted completely normal glands.[53]

Proximal Versus Distal Duct Injuries

The decision to render operative or nonoperative treatment to a child with a ductal injury revolves, in part, on whether the injury is in the proximal duct or distal duct. The distal duct presents more straightforward surgical options since a distal pancreatectomy may be accomplished by standard suture or staple closure of the pancreatic remnant without the requirement for an enteric anastomosis. Therefore, groups at several children's hospitals have advocated early operation for distal duct transections, citing earlier return to health and obviation of the need for TPN.[54,55]

Proximal duct injuries, however, have prompted wide-ranging solutions including Whipple procedure[55] and onlay of a Roux limb of jejunum.[56] The track record of nonoperative management makes observation a more attractive alternative than complex operations for proximal ductal transection. All that may be required

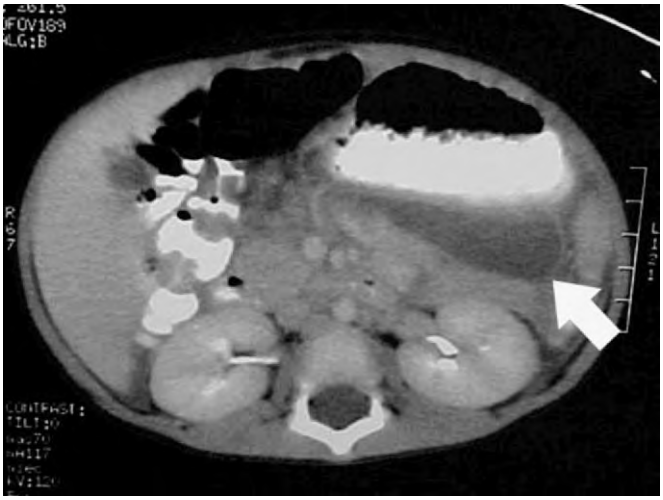


Figure 95–3. Post-traumatic pseudocyst *(arrow)* anterior to the main body of the pancreas in a young girl. The pseudocyst had a well-matured rind and was easily anastomosed to the back wall of the stomach.

is interval drainage of the potentially resulting pseudocyst.[57,58]

A noteworthy observation has been published by Canty and Weinman, who have recently described two patients with ductal injury treated by ERCP and transampullary stenting of the pancreatic duct. Both healed without pseudocyst formation. Ductal disruption occurred in the midbody in one and in the distal duct in the other, and in one case the stent did not even traverse the injury. Thus, the healing of the ductal injury is attributed to decompression of the pancreatic duct as a whole. The investigators pointed out that these cases involved ductal extravasation but not full-scale ductal transection.[59]

Options for Pseudocyst Drainage

If a pseudocyst develops, it may be dealt with by standard cystogastrostomy or cystojejunostomy (Fig. 95–3). Percutaneous drainage and internal, endoscopic drainage using a double-pigtail stent into the stomach have also been reported in children as young as 2 years old. Like open operative techniques, these methods rely on the development of a rind around the pseudocyst cavity.[60,61]

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY IN CHILDREN

The assumption that ERCP is more dangerous in children than in adults has not been substantiated by the bulk of data in the literature. Some concerns center on a 2001 study from Montreal Children's Hospital, delineating 21 ERCP procedures performed in children (mean age, 11.3 years [range, 4 to 17 years]). Although the success rate was more than 90%, the authors

reported a high complication rate of 33%. Pancreatitis occurred in four patients who underwent sphincterotomy, in one who had a strictly diagnostic ERCP, and in one in whom the ampulla could not be cannulated at all. Another patient had bleeding following sphincterotomy, requiring transfusion.[62]

However, these findings are counterbalanced by data from other centers. Allendorph et al. claimed four complications among 39 diagnostic and/or therapeutic ERCPs in children (mean age, 12.5 years [range, 6 months to 18 years]); all four complications were mild cases of pancreatitis.[63] Guelrud has reported 95% cannulation success in a series of 155 neonates and infants and 98% success among 125 children older than 1 year of age, with major complications (cholangitis and pancreatitis) occurring in only 2 patients.[64] Therapeutic ERCP may be useful for children with chronic pancreatitis, enabling papillotomy, stone extraction, and stenting with an acceptable short-term complication rate.[65]

However, for patients requiring purely diagnostic studies, the use of magnetic resonance cholangiopancreatography (MRCP) to study the pancreatic ducts has been retrospectively validated in a small pediatric series by Arcement and colleagues, who compared findings with those of ERCPs performed on the same children.[66] Given that the only complications of MRCP seem to be those of general anesthesia, MRCP is beginning to supplant ERCP when a diagnostic, not therapeutic, study is needed. For premature infants or children with respiratory concerns, overnight observation in the hospital may still be needed after anesthesia for MRCP.

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Chapter

96

Pancreas Transplantation

David B. Leeser · Stephen T. Bartlett

Since the discovery of exogenous insulin and its ability to reverse the acute effects of insulin-dependent diabetes mellitus (IDDM, or type 1 diabetes mellitus) in children afflicted with the disease, physicians have searched for ways to more closely approximate the physiologic control of blood glucose levels provided by the pancreas to prevent the secondary complications of IDDM. Type 1 diabetes is an autoimmune disease that affects young people with peak onset at age 14 years. Cases may occur at any age, with some individuals affected well into adulthood and rarely late in life. The disease process involves the destruction of the islets of Langerhans within the parenchyma of the pancreas, which leads to the inability of the body to secrete insulin in response to a glucose load and ultimately to hyperglycemic ketoacidosis. Nonphysiologic control of glucose with exogenous insulin administration has been successful at preventing the short-term complications of IDDM but has failed to prevent long-term complications of IDDM, which include retinopathy, neuropathy, and nephropathy. Advances in insulin administration techniques include long-acting insulin, insulin pumps, and multiple-dosing regimens that seek to recapitulate physiologic glycemic control. In many patients, these measures are inadequate, leaving the patient vulnerable to wide swings in blood glucose levels. This may lead to hypoglycemic unawareness in patients with longstanding type 1 diabetes. Patients with hypoglycemic unawareness lose the ability to respond to hypoglycemia with the characteristic sympathetic response. Hypoglycemia and hypoglycemic unawareness can lead to unconsciousness and seizures in patients without any prior warning signs. These episodes of hypoglycemia can be life-limiting because they cannot be treated effectively. Patients with hypoglycemia have difficulties with work and child care. Pancreas transplantation is currently the most reliable way to restore physiologic glycemic control in the type 1 diabetic, in turn preventing hypoglycemic episodes. Studies show that recipients of pancreatic allografts have stabilization and improvement of diabetic nephropathy and neuropathy and stabilization of retinal damage caused by hyperglycemia. In addition, patients become free of insulin injections, can liberalize their diet, and improve their lifestyle. Improvements in surgical techniques, immunosuppressive regimens, and patient selection has made pancreas transplant the standard by which other forms of physiologic insulin replacement should be judged.

TRANSPLANTATION OF A VASCULARIZED PANCREAS ALLOGRAFT

Candidates for Pancreas Transplantation

Candidates for pancreas transplants are type 1 diabetics with undetectable levels of C-peptide who suffer from end-stage renal disease or symptoms of hypoglycemic unawareness with progressive secondary diabetic complications. Patients with adult-onset, or type 2, diabetes suffer from a marked insulin resistance that does not respond well to pancreas transplantation. However, selected insulinopenic type 2 diabetic patients have undergone successful pancreas transplantation.[1] These patients are characterized by relative absence of insulin resistance and insulinopenia. In January 2003, the American Diabetes Association published guidelines for patient selection in pancreas transplantation. These recommendations include patients with type 1 diabetes undergoing renal transplantation or type 1 diabetic patients with the following[2]:

1. A history of frequent, acute and severe metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention
2. Clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating
3. Consistent failure of insulin-based management to prevent acute complications

The views expressed in this chapter are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or U.S. Government.

Patients should have a history of compliance with conventional treatment managed by a board-certified endocrinologist that fails to control hypoglycemia despite glucose monitoring several times each day.

Evaluation of the candidate for pancreas transplantation is completed by a multidisciplinary team that includes a transplant nurse coordinator, transplant social worker, dietitian, cardiologist, transplant nephrologist, and the transplant surgeon. Pretransplant evaluation of the candidate for pancreas transplant includes a thorough cardiac evaluation consisting of exercise stress test or dobutamine stress echocardiogram because of the frequency of undetected cardiac disease in diabetic patients. Cardiac catheterization should be performed liberally to ensure that the candidate has no significant coronary artery disease prior to undergoing transplantation to prevent any untoward intraoperative or postoperative events. Social work evaluates the patient to determine the likelihood of compliance with the medical regimen required for transplantation and identifies whether an adequate social and support structure exists for the patient. Nephrologic evaluation determines if any underlying renal disease exists that should be treated concurrently with renal transplantation at the time of pancreas transplantation. At our institution, we require a creatinine clearance of greater than 70 ml/min to proceed with pancreas transplant alone, due to the risk of subsequent renal failure once patients are placed on tacrolimus. Patients who present with end-stage renal disease are also evaluated by a nephrologist at the transplant center even though they are under the care of a community nephrologist.

Historically, pancreas transplantation was offered only to patients with established end-stage renal disease because of the morbidity of immunosuppressive medications and poor long-term graft survival of the pancreas. Since the first pancreas transplant almost 40 years ago, pancreas allograft survival rates have improved from a dismal 3% at 1 year to approach more than 90% in recent reports.[3,4] Better allograft survival in the past 25 years has prompted surgeons to successfully treat type 1 diabetic patients with pancreas transplant alone prior to the onset of end-stage renal disease secondary to diabetic nephropathy. The number of pancreas alone transplants and pancreas after kidney transplants continues to increase every year.[5] Several reports demonstrate stabilization of diabetic retinopathy along with improved visual acuity and improvement in neuropathy and nephropathy.[6,7] However, the indications for pancreas transplantation continue to be for the treatment of complications of hypoglycemic unawareness in patients without end-stage renal disease. Patients with good glycemic control with conventional insulin therapy should not risk surgery or immunosuppression if hemoglobin A_{1C} can be maintained at levels less then 7%.[8]

Cadaveric Organ Procurement and Preservation

The major source of pancreata for transplantation continues to be from cadavers that have succumbed to brain death. Potential organ donors are evaluated by local Organ Procurement Organizations that complete thorough social evaluations of potential donors for high-risk behaviors that could predispose them to blood-borne diseases. In addition, donors must be free from a history of recent malignancy, diabetes, and pancreatitis. Routine serum liver function tests (LFTs), amylase, and lipase are evaluated. Elevated LFTs, amylase, and lipase can be an indicator of foregut ischemia and injury, which may discourage the use of the organ. Most programs use age 55 years as a maximum; however, some centers selectively use pancreata from donors up to age 65 years. β-Cell mass declines after 55 years of age as normal senescent change. The minimum donor age is typically age 8 years, but many programs use donor body weight of 30 kg as the minimum cutoff rather then age. Finally, evaluation of the organ at the time of donor pancreatectomy can be essential in graft selection. Factors assessed during donor surgery are the presence of pancreatic fibrosis or fatty transformation of the pancreas. Donor factors associated with a poor outcome are body mass index higher than 30 and age older than 45 years. However, individualizing donor selection is the best policy for ensuring optimal utilization of all donor pancreata.

Cadaveric donor pancreatectomy is performed as part of a multiorgan procurement through a midline incision from the symphysis pubis, which is extended into a median sternotomy. The gastrocolic ligament is divided to enter the lesser sac and expose the anterior aspect of the pancreas. At this point, the pancreas is evaluated for signs of intraparenchymal fat, hematoma, and calcification or scarring that would preclude use of the organ for transplantation. If the organ is suitable, right medial visceral rotation to include a Kocher maneuver of the duodenum is performed to expose the inferior vena cava and aorta. Dissection is carried up to identify the left renal vein and the superior mesenteric artery (SMA). The SMA is dissected circumferentially to identify the origin of a replaced right hepatic artery if one is present. Replaced right hepatic artery does not preclude using both the liver and pancreas unless the vessel transverses the pancreatic parenchyma. Palpation for a replaced right hepatic artery should be done during mobilization of the pancreatic head. The spleen and tail of the pancreas is mobilized away from the retroperitoneum to allow for placement of slush posterior to the gland during perfusion and flushing of the organ with iced University of Wisconsin solution (UW). The aorta is isolated in the abdomen just superior to its bifurcation for placement of a cannula for perfusion with UW. The inferior mesenteric vein is also cannulated for perfusion of the portal system for hepatic allograft preservation. The gastroduodenal artery is identified, ligated, and divided. The patient is given 30,000 units of heparin prior to cannula placement and then the thoracic aorta is clamped and the portal and arterial systems flushed with cold UW solution. The venous system is vented by incising the junction of the vena cava with the right atrium. Slushed saline is packed around all organs to be harvested to surface cool the organs during perfusion with iced UW. Once perfusion is complete, the splenic artery is identified and divided just distal to its origin from the celiac axis. The portal vein is divided distal to the origin of the cardinal

vein. The common bile duct is identified, ligated as it enters the pancreas, and divided. The SMA is cut away from the aorta preserving a Carrel patch if a replaced right hepatic artery is not present. In the case of a replaced right hepatic artery, the SMA is divided just distal to the origin of the right hepatic artery. The duodenum is then flushed with dilute povidone-iodine through a nasogastric tube and then divided using a gastrointestinal stapler distal to the pylorus and at the duodenojejunal junction. The root of the mesentery is then divided using a terminal anastomosis stapler and the organ is removed. After removing all solid organs, an iliac artery and vein are removed to be used for reconstruction of the graft for transplantation. When the small bowel is procured for transplantation, it is essential to ensure that the inferior pancreaticoduodenal artery is not divided during dissection of the root of the small bowel mesentery.

Living-Donor Pancreas Transplant

Living-donor pancreas transplantation was first performed in 1978 at the University of Minnesota, the center with most of the world's experience.[9] Donor evaluation must be extensive and include a measurement of insulin and glucose levels in response to oral and intravenous glucose administration to ensure that the donor does not have a propensity to develop diabetes following distal pancreatectomy. Distal pancreatectomy was originally performed using an open technique, but in 2001, the first laparoscopic living-donor transplant was described, and more have followed.[10] In both procedures, the short gastric arterial arcade should be preserved so that the spleen can be left in place. The splenic artery is divided just distal to it origin, and the splenic vein is divided proximal to its confluence with the superior mesenteric vein (SMV) to form the portal vein. The technique involves a distal pancreatectomy with subsequent anastomosis of the donor splenic artery to the external iliac artery and anastomosis of the splenic vein to the external iliac vein. Drainage of the pancreatic duct is accomplished by fashioning a pancreaticojejunostomy or a pancreaticocystostomy.

Surgical Techniques

Pancreas transplantation can be carried out simultaneously with kidney transplantation in patients who have already progressed to end-stage renal failure (i.e., simultaneous pancreas kidney transplant [SPK]; simultaneous pancreas living-donor kidney transplant [SPLK]), following living-donor kidney transplant (pancreas after kidney transplant [PAK]), or as a pancreas transplant alone (PTA). When a simultaneous pancreas and kidney transplant is being performed, the pancreas is prepared along with the kidney. During back-table preparation of the pancreas, one of the donor's iliac arterial bifurcations is used to create a vascular conduit to the donor superior mesenteric and splenic arteries to provide arterial inflow to the pancreas. The portal vein, which will drain the pancreas, is also freed from the surrounding structures

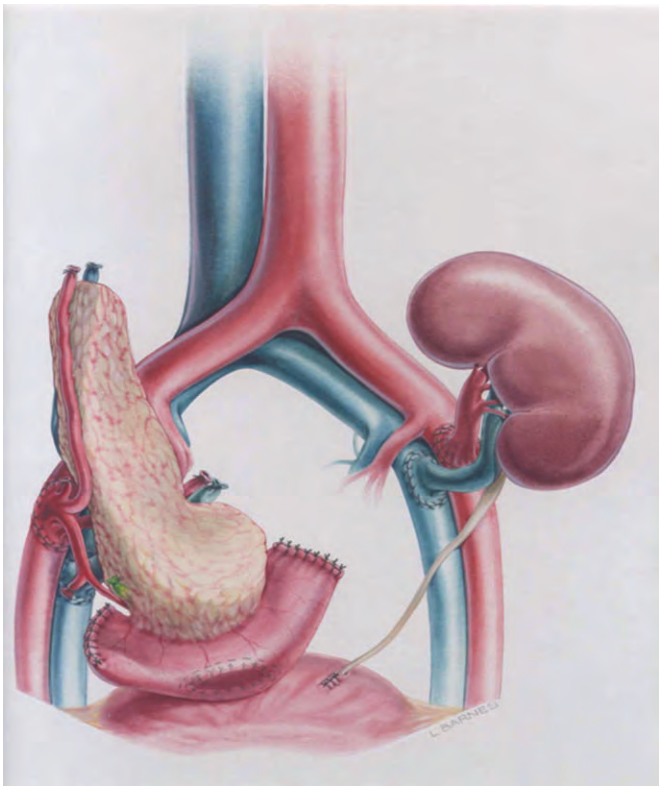

Figure 96–1. Simultaneous pancreas and kidney transplant performed with bladder drainage of the duodenum and systemic drainage of venous outflow.

to allow for the construction of an anastomosis. If the portal vein is found to be too short to create a tension-free anastomosis, then the donor iliac vein can be used as a venous graft to lengthen the portal vein. Care should be taken to avoid lengthening the vein too much as this can lead to stasis of blood in the vein and subsequent thrombosis of the pancreatic graft. Once the pancreas is prepared, a midline incision is made in the abdomen. The right iliac artery and vein are exposed through the abdominal cavity. The donor common iliac artery is anastomosed to the recipient's common iliac artery (Y-graft). If the pancreas will be drained into the systemic venous circulation, then an anastomosis is created between the portal vein and the recipient's common iliac vein (systemic drainage) (Fig. 96–1). When the pancreas is drained systemically, the head lies in the right lower quadrant of the abdomen, and the tail is directed cephalad in the right pericolic gutter. Alternatively, the SMV can be exposed at the base of the transverse mesocolon and the portal vein is connected to the recipient's portal vein via the SMV (portal drainage) (Fig. 96–2). In the case of portal drainage, the head of the pancreas lies at the base of the transverse mesocolon and the tail lies caudad toward the right lower quadrant. The organ is then reperfused and hemostasis achieved. Portal venous drainage is advocated because the insulin is delivered directly to the liver in a physiologic manner, and drainage into the liver is reported to have an immunologic advantage.[11] In addition, portal delivery of insulin

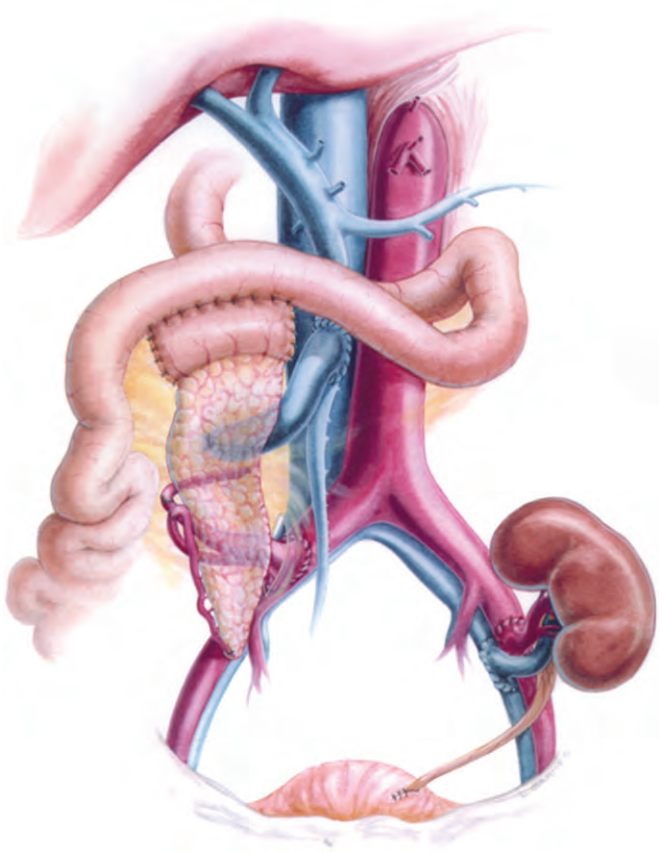

Figure 96–2. Simultaneous pancreas and kidney transplant performed with enteric drainage of the duodenum and portal venous drainage via the recipient superior mesenteric vein.

prevents hyperinsulinemia in the systemic circulation, which is more physiologic.[12] Portal venous drainage has also been linked to improved lipoprotein composition.[13] However, registry data have not shown any significant graft survival differences between patients with portal versus systemic venous drainage.[5] Currently, choice of venous drainage is based on center and surgeon preference. When performing portal drainage of the pancreas, the anastomosis between the donor portal vein and the recipient SMV must be placed high on the SMV or else SMV thrombosis may occur. At the University of Maryland, we have never had a recipient SMV or portal vein thrombosis, although it is reported in the literature.

The past decade in pancreas transplantation has seen a gradual increase in enteric drainage of the pancreas allograft. The International Pancreas Transplant Registry reports that enteric drainage of the pancreatic allograft has increased from 15% in 1994 to as high as 81% of all SPKs and 56% of PTAs at the end of 2004.[5,14] Both techniques involve resecting any excess duodenum or small bowel that accompanies the graft so that the second and third portion of the duodenum remain along with the sphincter of Oddi. In the case of bladder drainage, the portal vein coming from the pancreatic allograft is anastomosed to the external iliac vein after it is mobilized extensively with ligation and division of the hypogastric veins. Enteric drainage of the pancreatic allograft can be accomplished using a side-to-side anastomosis to the small bowel or by creating a Roux limb to exclusively drain the allograft. A two-layer hand-sewn anastomosis is constructed using an inner layer of running absorbable suture and an outer layer of interrupted silk sutures or an end-to-end anastomosis stapler can be placed through the distal duodenal limb and attached to the anvil of the stapler, which is placed in the recipient small bowel.[15] The excess donor duodenum is subsequently amputated using a gastrointestinal anastomosis stapler. Some centers continue to use the bladder for exocrine drainage of the pancreas due to the ease of monitoring urinary amylase as a marker of pancreas rejection. However, enteric drainage of the pancreas has been shown to be safe and effective in many centers. Second, the need to convert up to 24% of patients from bladder to enteric drainage in a subsequent operation is avoided in patients suffering from the complications of bladder drainage, which can include cystitis, acidosis, perineal irritation, urinary tract infection, and reflux pancreatitis.[16,17] Once the pancreas is implanted, a kidney can be placed in the left lower quadrant within the peritoneum or retroperitoneally by dissecting the peritoneum off of the anterior abdominal wall in the left lower quadrant to expose the iliac vessels on the left. We prefer to put the kidney in the retroperitoneum for two reasons: (1) the kidney is held in place by the peritoneum and cannot torse on its vascular pedicle, and (2) the pancreas and the kidney are in separate compartments should there be a peripancreatic infection or fluid collection.

POSTOPERATIVE COURSE

Care in a monitored bed by experienced staff is as effective as postoperative intensive unit care. Glucose control should normalize within the first 6 to 8 hours following transplantation, but insulin is sometimes required in the early postoperative period if the cold ischemia time was prolonged. Blood glucose levels should be checked hourly and an abrupt increase should prompt ultrasound evaluation of the pancreas to rule out technical failure, which is the most common cause of early graft loss.[5] Recipients of PTA grafts should be anticoagulated with low-dose intravenous heparin starting at 300 units per hour on arrival to the intensive care unit and increased to 400 units per hour within the next 24 hours to prevent graft thrombosis. Anticoagulation is continued with low-dose warfarin (Coumadin) for 3 months following transplantation. SPK recipients do not require anticoagulation due to the decreased platelet function induced by uremia. Patients are maintained with a nasogastric tube in place until return of bowel function.

IMMUNOSUPPRESSION

Improved results of pancreas transplantation have resulted from improved immunosuppression regimens, which are less toxic and more efficacious, in pancreas transplantation. The discovery of cyclosporine and its routine use allowed the field to grow considerably

during the 1980s; the introduction of tacrolimus led to similar sequential improvement. Currently, the standard immunosuppressive regimen at most centers includes induction with an antibody preparation, steroids, tacrolimus, and mycophenolic acid.[5] Recently, several studies have reported improved outcome with corticosteroid-free immunosuppression. The group at Nantes, France, has been using a steroid-free protocol combined with thymoglobulin induction with very low rates of rejection.[18] These results have been replicated at Northwestern University with 100% actuarial survival of pancreas allografts at 1 year using a steroid-free regimen.[4] Freise et al. also reported pancreas graft survival rates higher than 90% at 3 months using a steroid-free regimen with no difference in outcome when compared with steroid-containing protocols.[19] The Nantes group has also recently published data that show decreased insulin levels and improved cholesterol and triglyceride levels in patients receiving a corticosteroid-free regimen compared with those receiving them.[20]

The use of antibodies for induction is also becoming commonplace in pancreas transplantation. A large multicenter, prospective, randomized trial on the use of all antibody types, including interleukin-2 receptor blockers as well as T-cell–depleting agents, was recently published.[21] The findings showed a reduction in episodes of acute rejection, from 31.2% to 24.6% ($P = .28$). Biopsy-confirmed renal allograft rejection decreased from 23.0% to 13.1% ($P = .08$). The time to first episode of rejection was greater and severity of rejection lesser in the group that received induction therapy. Reducing the number and severity of rejection episodes will hopefully improve the long-term pancreas allograft survival, because the most significant predictor of chronic rejection is an episode of acute rejection with a relative risk of 4.41 ($P < .0001$), according to a study of 914 pancreas transplants at the University of Minnesota.[22] This study also found that chronic rejection was second only to technical failure as the most common cause of pancreas allograft loss.

REJECTION

Acute rejection of a pancreas allograft is heralded by increases in the lipase, amylase, or abrupt changes in glucose control in patients with enterically drained pancreata. In patients with bladder drained pancreata, a decrease in urine amylase level heralds pancreas rejection. The diagnosis of pancreatic rejection, however, should be part of the differential in any recipient who presents with symptoms of malaise, fever, or abdominal pain. As enteric drainage of the pancreas has become the standard practice at most transplant centers, advocates of bladder drainage of the pancreas have asserted that the inability to measure urinary amylase prevents early diagnosis of rejection. Both techniques require percutaneous biopsy of the pancreas under ultrasound guidance to confirm the diagnosis and histologically grade the rejection. Pancreas rejection involves an infiltration of perivascular space in the pancreas with lymphocytes. Pancreatic rejection is not similar to the insulinitis or the infiltrates of the islets of Langerhans that characterize the onset of type 1 diabetes. Finally, in many instances, the recipient of an SPK can be monitored using serum creatinine levels. Biopsy of the renal allograft can be used to confirm rejection in these cases. However, isolated pancreatic allograft rejection can occur in the absence of renal allograft rejection, so serum amylase, lipase, and glucose levels should be checked and pancreatic biopsy performed in patients with unexplained symptoms without signs of renal allograft rejection.[23] Mild rejection of the pancreatic allograft can be treated with a short course of steroids, but more advanced rejection should be treated with antithymocyte globulin or OKT3. Chronic rejection of the pancreas is characterized by fibrosis of the parenchyma of the glandular tissue that ultimately destroys the secretory capacity of the organ.[24] Currently, aside from preventing episodes of acute rejection, there is no way of treating chronic rejection. As pancreas transplantation moves into the future, chronic rejection will be foremost on the agenda to continue to improve graft survival.

RESULTS OF PANCREAS TRANSPLANTATION

According to the International Pancreas Transplant Registry maintained by the University of Minnesota Department of Transplantation, more than 23,000 pancreas transplants had been performed as of December 31, 2004.[5] More than 17,000 of these procedures had been performed in the United States. Most pancreas transplants have been performed during the past 15 years as is evident in the bar graph showing the number of transplants per year starting in 1979, at which time a very small number of transplants were being performed worldwide (Fig. 96–3). The explosion in pancreas transplantation over the past 25 years has been secondary to extraordinary improvement in outcomes. As of 1980, the pancreas allograft function at 1 year was 21% and patient survival was 67% as reported by the Internation Pancreas Transplant Registry. That contrasts markedly with the report for 2004, which shows allograft survival to be between 77% and 85% for the various different types of pancreas transplants at 1 year. Patient survival is greater than 95% in all categories. With improving 1-year graft survival and decreasing incidence of acute rejection, the long-term function of pancreas allografts can only be expected to improve.

Recent data reported in smaller series have demonstrated that even better results in pancreas transplant can be obtained. Kaufman et al. reported 1-year survival rates between 87.5% and 100% in enterically drained allografts.[4] Moreover, studies have demonstrated that a functioning pancreatic allograft stabilizes retinopathy, improves neuropathy, and allows for the regression of diabetic changes within the kidney. These results have caused the number of pancreas transplants being performed throughout the world to grow exponentially over the past 25 years. The high success rate has made the bar very high for the field of islet cell transplantation, which has made significant strides in the past 10 years.

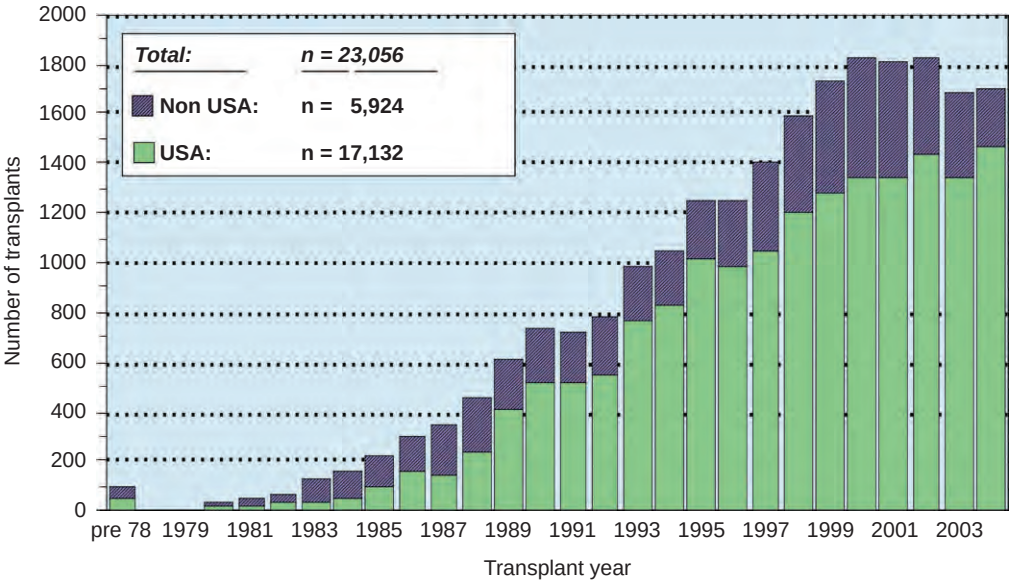

Figure 96–3. Pancreas transplants worldwide, 2003. (From Gruessner AC, Sutherland DE: Pancreas transplant outcomes for United States [US] and non-US cases as reported to the United Network for Organ Sharing [UNOS] and the International Pancreas Transplant Registry [IPTR] as of June 2004. Clin Transplant 19:433-455, 2005.)

Future improvement in pancreas transplantation will depend on the elimination of chronic immunosuppression, particularly calcineurin inhibitors, which are directly nephrotoxic and lead to long-term renal dysfunction. The next achievements in the field will involve developing a better understanding of the autoimmune disorder that underlies the development of type 1 diabetes leading to effective treatments for prevention and treatment in new cases. The progress and focus in the recent past on improving graft survival and function should now be replaced with research in improving the supply of β-cell replacement tissue. Even with 100% long-term graft function, the supply of pancreatic allografts, approximately 1200 annually, will never be enough to treat the 30,000 patients that develop type 1 diabetes each year.

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Chapter

97

Islet Transplantation

Wayne Truong · A. M. James Shapiro

Diabetes mellitus is a common endocrine disorder affecting more than 200 million people worldwide, representing 6% of the population, and is the fourth leading cause of death in North America. Although most adult patients with diabetes have type 2 disease, type 1 is the most severe form resulting from selective and progressive autoimmune destruction of insulin-producing β cells within the islets of Langerhans in the pancreas. The loss of β-cell function leads to insulin insufficiency and uncontrolled hyperglycemia.

The discovery of insulin significantly altered the fate of patients with type 1 diabetes by preventing acute lethal complications such as diabetic ketoacidosis.[1] Improved patient survival, however, allowed the development of secondary complications of diabetes including atherosclerosis, lipid disorders, proliferative retinopathy, peripheral neuropathy, and renal failure. Evidence illustrating the importance of maintaining strict glycemic control was established in 1993 with the landmark Diabetes Control and Complications Trial (DCCT) study.[2] With intensive insulin therapy, the hemoglobin (Hb)A_{1c} was 1% lower than the control group and significantly protected against microvascular complications, nephropathy, neuropathy, and retinopathy. Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) showed a significant 1% decrease in the HbA_{1c} of patients with type 2 diabetes with microvascular disease.[3] However, the cost of improved glycemic control was associated with a threefold increase in serious hypoglycemic events, including recurrent seizures and coma.[4]

Consistent glycemic control using exogenous insulin remains a challenge. Administration of insulin by subcutaneous injection is nonphysiologic and inherently limited by delayed absorption, variable blood levels, and systemic rather than portal venous delivery. Even with newer insulin analogs combined with intensive therapy, which has removed some of the delay in absorption and variability, normoglycemia is difficult to achieve. Continuous subcutaneous insulin delivery, attention to diet, and carbohydrate counting improve but do not completely normalize blood glucose levels. β-Cell replacement by whole pancreas or islet transplantation can physiologically achieve this goal.

Whole pancreas transplantation can prolong life, reverse established nephropathy,[5] and improve quality of life, but it remains too invasive for most patients. More than 21,000 whole pancreas transplants have now been performed worldwide, and recent data from the major centers report remarkable improvement in outcome, with 1-year pancreas graft survival exceeding 85% and patient survival exceeding 90%. The use of portal venous and enteric exocrine drainage as well as steroid-sparing, more potent immunosuppression strategies has also contributed to these improved outcomes.

Islet transplantation compared to whole pancreas transplants has the advantage of fewer complications and the elimination of unnecessary transplantation of the exocrine component of the gland. The Edmonton report of seven consecutive successful human islet transplants, in the year 2000, has renewed optimism in β-cell replacement as a potential cure for type 1 diabetes mellitus.[6]

HISTORY

The first attempt to transplant pancreatic tissue was in 1893, when an English surgeon grafted sheep pancreas fragments subcutaneously into a 15-year-old boy suffering from diabetic ketoacidosis (Fig. 97–1).[7] Without a clear understanding of the immune barriers at the time, the xenograft was destined to fail. Banting, according to his notebook records, also considered pancreas transplantation, but by 1920 the idea was abandoned when improved recovery of "internal secretions" led to the discovery of insulin. Diabetes was transformed from a rapidly fatal disorder, after onset of ketoacidosis, to a chronic incurable illness with end-stage secondary complications. In 1967, Lacy and Kostianovsky developed methods for islet isolation in rats,[8] and in 1972, Ballinger and Lacy were the first to reverse chemically induced diabetes using islet transplantation in rodent models.[9]

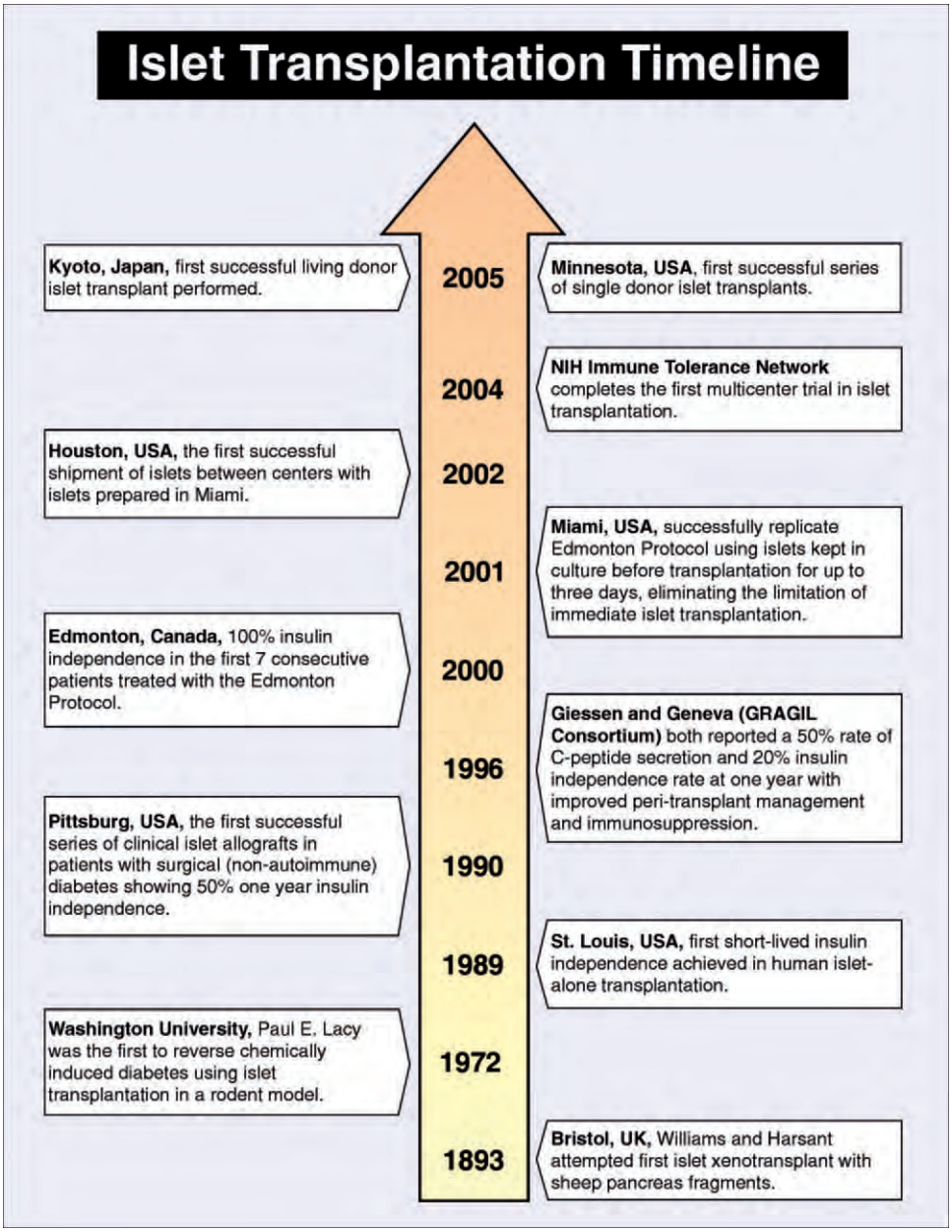

Figure 97–1. Timeline of islet transplantation.

Site of Islet Transplantation

Defining the optimal site for islet transplantation has been a challenge. The native pancreatic bed is relatively inaccessible. All other sites have the disadvantage of lower oxygenation and elevated intraislet blood pressure. The primary locations attempted in animal models include the liver, spleen, and renal subcapsule and an omental pouch. Some attempts to embolize islets to the spleen have led to significant life-threatening complications including splenic infarction, bleeding, and rupture. The dual vascular supply in the liver allows embolized islets to completely occlude venules without infarcting the transplant site. In addition, portal drainage has the potential advantage of mimicking the normal route of insulin delivery. A possible drawback of the portal site is that it exposes islets to high levels of immunosuppressive drugs and their potential toxicity as they are absorbed.[10] Even though many different sites have been tried for islet implantation, the optimal site for islet implantation has yet to be defined.

EARLY CLINICAL TRIALS

The first human islet transplants were performed in the 1970s using azathioprine and corticosteroid immunosuppression,[11] with insulin independence rarely

reported.[12] Initial attempts at islet transplantation appeared to be safe, but efforts were largely ineffective due to poor extraction and purification techniques for human islets. In 1986, Dr. Camillo Ricordi described a method for mass isolation of human and large animal islets using the so-called Ricordi chamber.[13] This semi-automated method is used today with minor modifications for successful high-yield human islet isolation. In 1989, at Washington University in St. Louis, human islets isolated using this method were able to reverse diabetes.[14] However, due to inadequate recipient immunosuppression, rejection occurred only after a few days of insulin independence. With the introduction of a steroid-free, tacrolimus (FK506)-based immunosuppression regimen, the first successful series of clinical islet allografts in patients with non-autoimmune, surgical diabetes showed long-term insulin independence up to 5 years was reported by the Pittsburgh group in 1990.[15] Up to half of the patients achieved insulin independence in these trials. During the 1990s, data from Giessen and from Geneva (GRAGIL Consortium) both reported a 50% rate of C-peptide secretion and 20% insulin independence rate at 1 year.[16] Other major centers, particularly Miami, St. Louis, Milan, Minneapolis, and Edmonton, also reported early success and demonstrated that the transplanted cells may survive for a prolonged period.

IMPROVEMENTS IN CLINICAL ISLET TRANSPLANTATION

The unimpressive results of islet transplantation in the late 1990s, as illustrated by low rates of insulin independence, were related to the islet preparation (purity of preparations and adequate islet numbers)[17] and immunosuppression (potency and toxicity especially in terms of glucose tolerance).[18] These observations provided the foundation for building newer regimens for islet transplantation, including the Edmonton protocol.

Islet Preparation

Isolation of an adequate islet mass remained a central issue for success. The average adult human pancreas weighs 70 g, contains an average of 1 million to 2 million islets of average diameter 157 μm, constituting between 0.8% and 3.8% of the total mass of the gland. The use of University of Wisconsin (UW) perfusate solution at the time of organ retrieval enhanced the yield. Careful digestion is necessary to achieve a purified preparation. Key improvements included (1) a highly purified collagenase blend (Liberase), primarily collagenase type 1 and 2, that is associated with a low endotoxin load[19]; (2) an intraductal enzyme delivery; (3) automated mechanical digestion[13]; and (4) automated refrigerated centrifuge system (COBE 2991)[20] facilitating Ficoll purification[21] (Fig. 97–2). Short-term culture and removal of all xenoproteins from the process has enhanced purity without excessive loss of islets. Final issues of islet numbers could also be overcome with the use of multiple donor pancreases. Despite the major advances, inconsistency remains in the overall success of the islet isolation procedure, which may reflect variability in donor-related factors in addition to the skills of the local procurement team.

Immunosuppression

The field of islet transplantation was rejuvenated with the Edmonton report using a steroid-free immunosuppression regimen.[6] Effective blockade of interleukin (IL)-2 with sirolimus, which inhibits T-cell expression and activation, and daclizumab, an antibody to IL-2 receptors, allows inhibition of T-cell activation and provides potent immunosuppression. The regimen of daclizumab, tacrolimus, and sirolimus may still carry some toxicity for β cells and affect carbohydrate metabolism. Daclizumab is associated with no adverse events. Sirolimus is associated with lipid abnormalities but not usually glucose intolerance and may in fact enhance insulin secretion. Although the combined use of sirolimus and low-dose tacrolimus has helped move islet transplantation forward from clinical curiosity to effective therapy for many more patients, it is recognized that these drugs are still far from ideal. Sirolimus and tacrolimus have near-ubiquitous targets of distribution and as a result lead to a number of side effects in islet recipients, including mouth ulceration, peripheral edema, a high rate of ovarian cysts in female recipients, hypertension, hypercholesterolemia, and increase in proteinuria in some patients with underlying preexisting diabetic renal damage. Lifelong immunosuppression remains a major limitation to the broad application of islet transplantation, and careful consideration of the cost-benefit analysis for each patient is required.

INDICATIONS

The major indications for islet transplantation at this time are (1) recurrent, severe hypoglycemia, particularly if decreased awareness of hypoglycemia is present, and (2) severe labile diabetes, with wide swings in blood glucose throughout the day. Current transplantation requires life-long immunosuppression and is limited to the most severe forms of diabetes.

EVALUATION AND RISK ASSESSMENT

Patients should have a realistic expectation of the outcome. Frequent hypoglycemia and glycemic lability problems are readily correctable by islet transplantation. The ability to prevent the progression of diabetic complications is unproven at this time, although given good glycemic control and correction of HbA_{1C} into the normal range, this may be a reasonable expectation. Both tacrolimus and sirolimus have nephrotoxic side effects, and these may offset the benefit of improved glycemic control. Therefore, further carefully controlled studies are required to define benefit. In addition, rapid correction of glucose control can accelerate diabetic retinopathy, at least for an initial period, and long-term

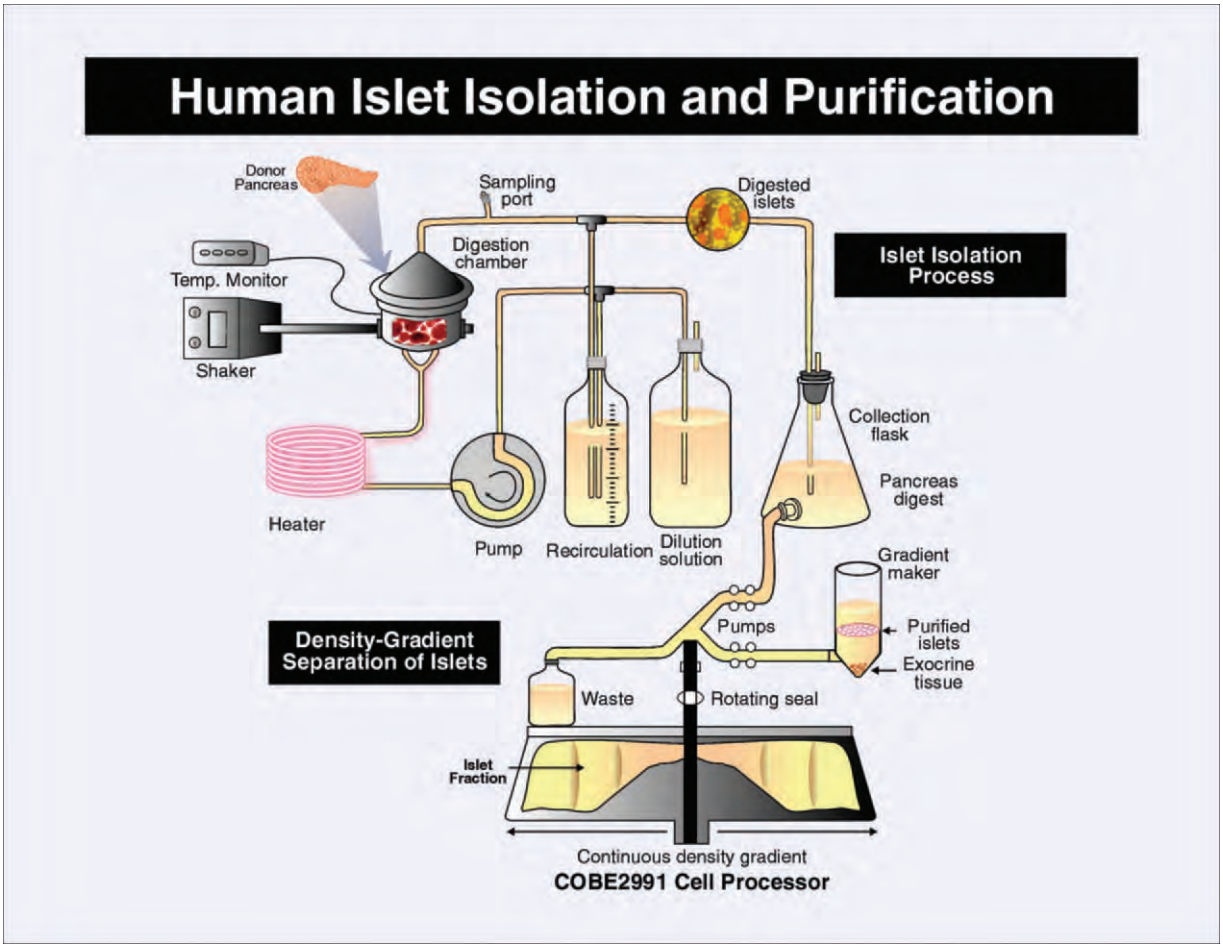

Figure 97–2. Human islet isolation and purification. Mechanical and enzymatic digestion is necessary to achieve a purified preparation. Steps include (1) a highly purified collagenase blend; (2) intraductal enzyme delivery; (3) automated mechanical digestion[13]; and (4) automated refrigerated centrifuge system (COBE 2991)[20] facilitating Ficoll purification. (Modifed from Ricordi C, Strom TB: Clinical islet transplantation: Advances and immunological challenges. Nat Rev Immunol 4:259-268, 2004.)

studies are required to define impact in control of retinopathy.

Potential complications of percutaneous islet infusion include (1) procedural risks of bleeding from the liver surface, arterial injury, or catheter tract; (2) portal vein thrombosis, which could rarely lead to disseminated intravascular coagulation, liver failure, liver transplant or even patient death; and (3) chronic immunosuppression, which may predispose patients to life-threatening infections and post-transplant malignancies. These risks must be discussed in depth with any potential candidate with careful balance of risk-benefit before proceeding. Type 1 patients with stable glycemic control are not considered candidates for islet-alone transplantation at this time.

PROCEDURE

Purified islets are introduced into the portal venous system by percutaneous, transhepatic cannulation of the portal vein under fluoroscopic guidance. It is also possible to gain access by computed tomographic guidance, by transjugular route, or with laparoscopy. A guidewire is then inserted into the main portal vein and a catheter is positioned with confirmation by venogram. Islets are suspended in heparinized solution and delivered in an intravenous bag.[22] Purified islets are infused with frequent monitoring to ensure portal pressure does not rise excessively (<22 mm Hg). The infusion is stopped if portal hypertension develops, and if it does not resolve, the infusion is discontinued. In the immediate post-transplant period, continuous intravenous insulin therapy maintaining normal blood glucose is believed to protect against islet damage caused by hyperglycemia and increased metabolic demand.[23]

ISLET TRANSPLANTATION IN THE NEW MILLENNIUM

Clinical islet transplant activity has experienced an unprecedented and exponential increase since the

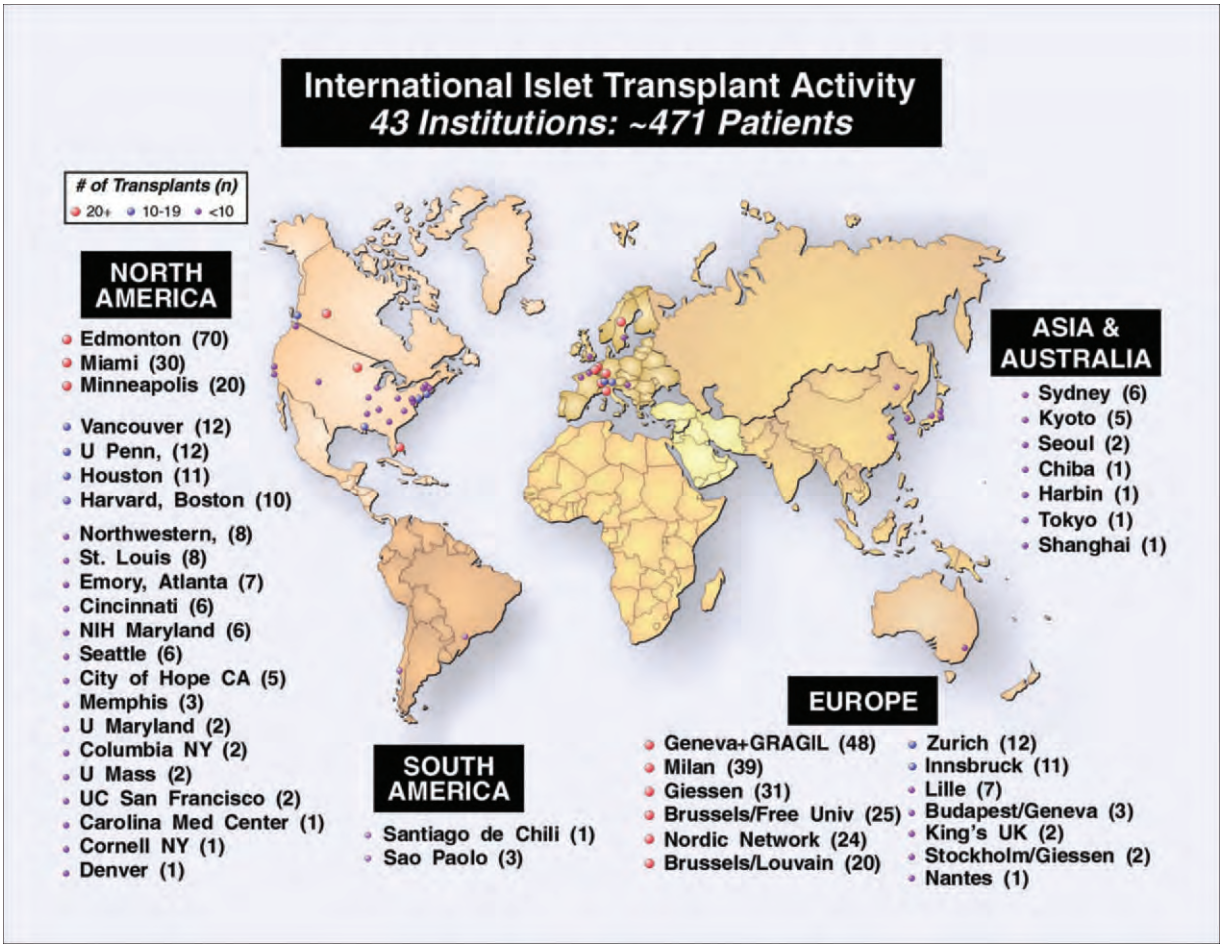

Figure 97–3. International islet transplant activity. More patients with type 1 diabetes have received islet transplants in the past 5 years than in the entire preceding 30-year history of islet transplantation, with an estimated 471 patients treated at 43 institutions worldwide.

Edmonton report in 2000, with an estimated 471 patients now treated worldwide in more than 43 institutions (Fig. 97–3). Preliminary data from the first multicenter trial in islet transplantation indicates that the *Edmonton Protocol* has been successfully replicated, with more than 80% of recipients achieving sustained insulin independence at the three most experienced sites.[24] Success was more variable (0 to 63%) at the remaining centers.

Recent advances in the field include (1) the blending of component-based collagenase constituents at the time of pancreas digestion to improve enzyme stability and reliability of isolation ("Blendzyme"); (2) the routine use of the "two-layer" oxygenated perfluorodecalin system for pancreas transportation[25]; (3) the routine use of insulin-transferrin-selenium CMRL-based islet culture while preparing the recipient for transplant[25,26]; (4) effective mechanical and physical methods to seal the catheter tract that has improved the safety of the nonsurgical, percutaneous, transhepatic, intraportal approach to islet delivery, by decreasing the risk of postprocedural bleeding[27,28]; and (5) the use of alternative immunosuppressive therapies in an attempt to enhance single-donor islet transplant success.[25,29]

Outcomes

Insulin independence after the first year of islet transplantation continue to be impressive at the three most active North American institutions, with a recent combined analysis showing 82% of a total 118 recipients in Edmonton, Miami, and Minnesota were insulin free at 1 year (Fig. 97–4).[29] However, Kaplan-Meier statistical projections reveal progressive loss of insulin independence, leaving only 50% of recipients still insulin-free at 3 years and only 15% still insulin free at 5 years. However, more than 80% of these grafts continue to demonstrate function (with endogenous C-peptide secretion) at 5 years, and patients thereby still continue to derive benefit in terms of stable glycemic control, even if insulin independence is not achieved[30] It remains to be seen whether stable improvement in glycemic control from a partially

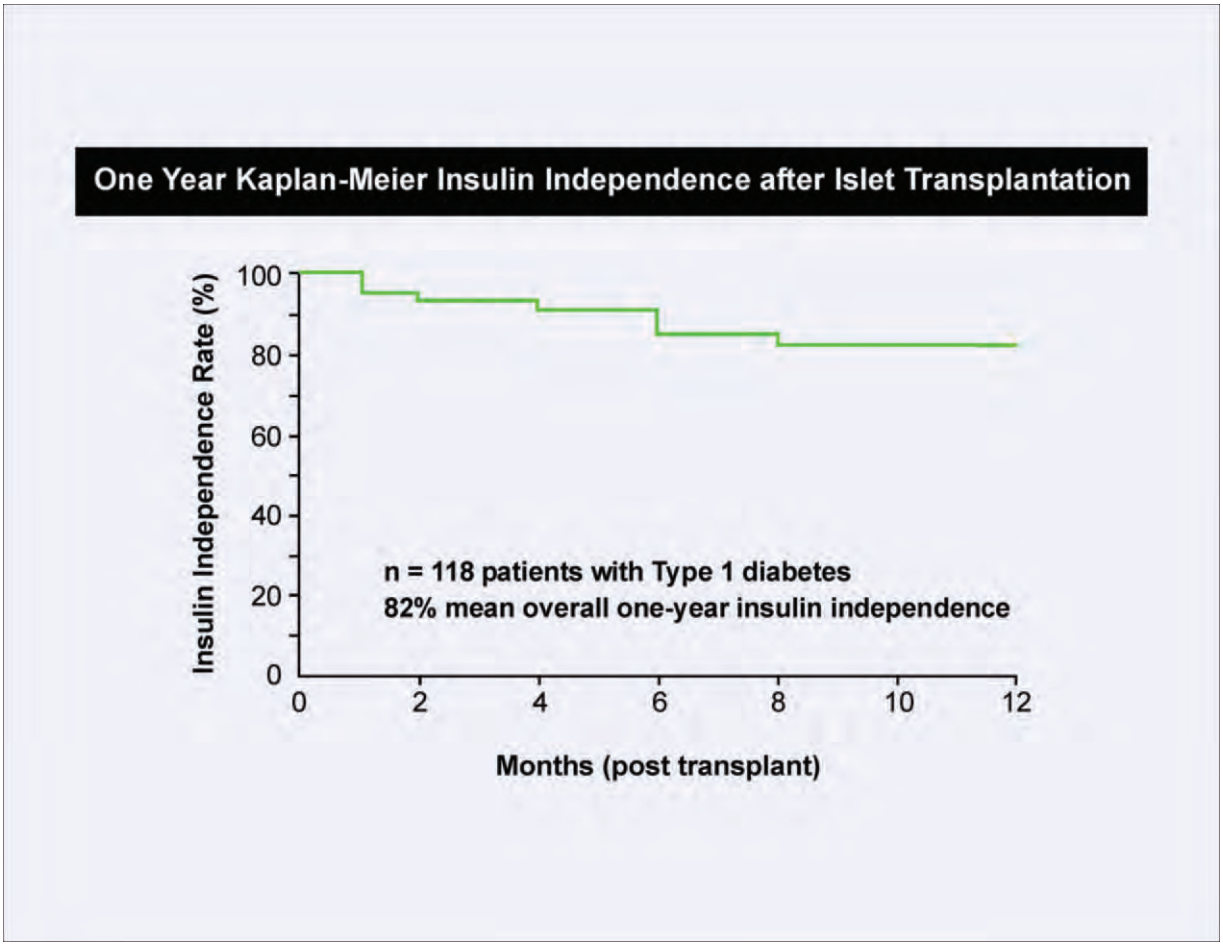

Figure 97–4. Islet transplantation survival curves. The first year of islet transplantation continues to be impressive at the three most active North American institutions, with a recent combined analysis showing 82% of a total 118 recipients in Edmonton, Miami, and Minnesota were insulin-free at 1 year.

functional islet transplant can be justified against the real and potential risks of lifelong immunosuppression and continued insulin dependence.

CHALLENGES AND EMERGING OPPORTUNITIES

The decline in insulin independence rates observed in long-term follow-up using the *Edmonton protocol* is a major challenge but also a unique opportunity to better define and understand the biology involved in promoting and sustaining islet survival (Fig. 97–5). Results from an in-depth study of factors likely influencing islet mass decay, using serial islet graft biopsies, and serologic analysis of donor sensitization, cytokine gene activity (granzyme B), and changes in autoantibody status will collectively provide valuable information. Possibilities for islet mass deterioration include chronic allograft rejection, undiagnosed acute rejection, recurrent autoimmunity, local islet toxicity from immunosuppressive drugs, or failure of islet regeneration secondary to the antiproliferative properties of sirolimus.[31]

Supply and Demand

The discrepancy between the number of potential organ donors and the potential need for islet replacement therapy is addressed only by more radical approaches. Data from the United Network for Organ Sharing (UNOS) currently indicates that only 23.8% of the potential 6182 available U.S. multiorgan donors were procured or used for pancreas or islet transplantation. This could be more effectively addressed by improved legislation and by education of the multiorgan retrieval teams. Another strategy is to develop acceptance of xenografts, where there is potential of an unlimited number of donors.

Living Donor Islet Transplantation

Living donor islet transplantation provides "near-perfect" partial grafts for islet transplantation and trials have begun in Kyoto, Japan. Avoidance of exposure to pro-inflammatory cytokines, immediate graft processing without cold ischemia, and the low anticipated tissue

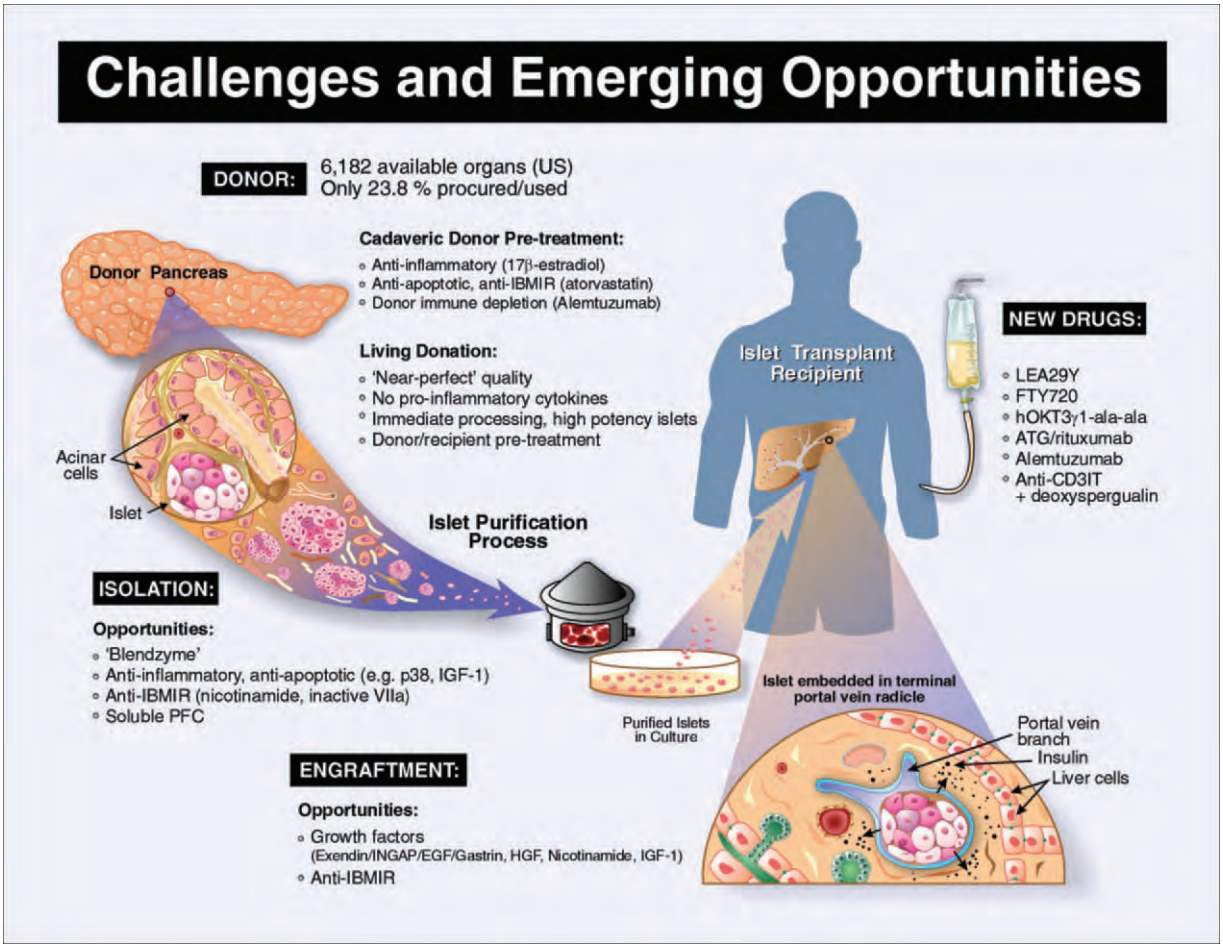

Figure 97–5. Challenges and emerging opportunities in islet transplantation. Opportunities lie ahead for development of successful living donor islet transplantation, improved isolation and engraftment, islet proliferation in vitro and in the recipient, and newer immunosuppressants with fewer side effects.

digest volume from a distal third pancreatectomy will likely eliminate the need for islet purification—all of which will substantially enhance the potency of the final islet preparation. The use of laparoscopic surgery in the donor will enhance palatability for the approach. The potential risk of diabetes in the donor could be substantially reduced by avoidance of obese donors, by confirming a normal intravenous glucose tolerance test in the donor, and by accepting only donors with negative islet autoantibody profiles. The surgical risk of pancreatic fistula in the donor is small but manageable.

Alloimmune and Autoimmune Drugs

A number of exciting, emerging compounds with distinct mechanisms of action will shortly be entering pilot clinical islet transplant trials. These agents provide an opportunity to develop more "islet-friendly" approaches with fewer non-immune-related side effects. Emerging opportunities include the following:

1. LEA29Y, a potent costimulatory signal blocker, is highly effective in promoting islet survival in primate trials and will be evaluated in Emory and Edmonton.[32]
2. FTY720, the lymphocyte homing agent, has proven to be highly effective in controlling autoimmunity in NOD mice and in promoting marginal mass islet transplants in primates. Clinical testing will depend on further safety testing from phase II trials in renal transplantation.[33,34]
3. The combination of antithymocyte globulin (ATG) and rituxumab (anti-CD20) has been shown by Naji et al. to induce tolerance in primates, and will be explored shortly at the University of Pennsylvania.
4. The non–Fc-binding hOKT3-γ1-ala-ala antibody developed by Bluestone et al. has been effective in abrogating autoimmunity in new-onset diabetes, and has facilitated single-donor islet transplant success in ongoing trials at the University of Minnesota.[25,35]
5. The T-cell-depleting antibody alemtuzumab (Campath-1H) has shown promise in clinical solid organ transplantation and is currently being evaluated in Edmonton and in Miami.
6. A potent, diphtheria-conjugated anti-CD3 immunotoxin combined with deoxyspergualin has

provided remarkable results with robust tolerance induced and sustained for more than 5 years in a series of monkeys treated by Thomas and colleagues at the University of Alabama.[36]

If these agents can provide equal or greater protection against both alloimmunity and autoimmunity, and if the safety profiles prove to be superior to current therapies, the face of islet transplantation will likely be further transformed in the coming few years.

Islet Protection and Regeneration

Opportunities to pretreat the donor with anti-inflammatory and antiapoptotic compounds such as 17β-estradiol or atorvastatin could potentially mitigate the negative impact of islet damage induced by brain injury–derived pro-inflammatory cytokines.[37,38] Immune depletion of donor passenger lymphocytes by donor pretreatment with agents such as alemtuzumab may also enhance islet survival after transplantation by reducing immune sensitization.

The opportunity to augment the islet mass of the donor both in the months before and in the recovery phase after surgery, during islet culture, and subsequently in the islet recipient using combination growth factors (including GLP-1, exendin-4, EGF, gastrin, INGAP, or hepatocyte growth factor), could further minimize the potential risk of diabetes in the donor, and could substantially enhance the rate of single-donor islet transplant success in the recipient.[39-43] Integration with the antithrombotic (immediate blood-mediated inflammatory response) strategies developed by Korsgren using nicotinamide, inactivated factor VIIa or low-molecular-weight dextran sulfate during islet culture or in the recipient post-transplant to inhibit islet tissue factor expression, will further considerably enhance the success of the living donor approach.[44,45]

SUMMARY

Phenomenal progress has occurred in the field of clinical islet transplantation in the most recent 4 years, with high 1-year rates of insulin independence and high 5-year rates of persistent C-peptide secretion. Loss of insulin independence over time still remains a concern with current protocols. Although the antirejection drugs available today have had an acceptable safety profile in islet transplantation, the drug-related and dose-limiting side effects have proved to be a challenge in some patients. Remarkable opportunities lie ahead for development of successful living donor islet transplantation; improved engraftment; islet proliferation in vitro and in the recipient; and newer, more "islet-friendly" immunosuppressants with minimal nonimmune side effects. Given these opportunities, islet transplantation will be within reach for many more patients with type 1 diabetes, including children, and will not be restricted to the most unstable patients as it is today.

ACKNOWLEDGMENT

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Chapter

98

Unusual Pancreatic Tumors

E. Ramsay Camp · Eric P. Tamm · Henry F. Gomez · Huamin Wang · Douglas B. Evans

BACKGROUND

Adenocarcinoma of the pancreas represents approximately 80% of all tumors identified in the pancreas. Pancreatic adenocarcinoma is associated with a highly reproducible constellation of signs, symptoms, and radiographic findings that minimizes (but does not eliminate) diagnostic uncertainty. This chapter addresses the less common tumors identified in the pancreas and periampullary region and reviews their natural history including presentation, diagnosis, and treatment.

Unlike pancreatic adenocarcinoma, the less common pancreatic tumors are often asymptomatic or occasionally associated with vague signs and symptoms that can create a diagnostic dilemma. The frequency with which computed tomography (CT) is used for a variety of abdominal complaints has increased the identification of incidental pancreatic pathology; all physicians, especially surgeons, need to be aware of the differential diagnosis of such incidental pancreatic cysts, neoplasms, and inflammatory mass-like abnormalities. A focused history and physical examination is important to assist in determining the etiology of a pancreatic mass. For example, a history of acute pancreatitis, alcohol abuse, or chronic abdominal pain makes chronic pancreatitis a likely diagnosis; the absence of these symptoms in a young woman may suggest a pseudopapillary tumor. The use of contemporary CT techniques, endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS) has greatly improved our ability to differentiate pancreatic adenocarcinoma from other causes of obstructive jaundice, yet no combination of preoperative studies can definitively exclude a malignant neoplasm in the setting of an abrupt cutoff of the bile duct in its intrapancreatic portion. Therefore, in the absence of choledocholithiasis or the smooth tapering stricture associated with chronic pancreatitis, biliary obstruction is most often caused by adenocarcinoma of the pancreas, distal bile duct, or ampulla of Vater.

Diagnostic Imaging

The development of multislice or multidetector CT (MDCT) allows imaging of the entire pancreas during peak contrast enhancement. In addition, scan data can be processed to display images in three-dimensional and multiplanar formats. Helical CT performed with contrast enhancement and a thin-section technique can accurately assess the relationship of the low-density tumor to the celiac axis, superior mesenteric artery (SMA), and superior mesenteric-portal vein (SMPV) confluence. For MDCT scanning at our institution, patients receive 1000 ml of water or a 2% barium sulfate suspension (Readi-CAT) to opacify the stomach and small bowel. Noncontrast-enhanced CT scans are then obtained through the liver and pancreas at a slice thickness of 5 mm contiguous, to localize the pancreas. Intravenous contrast enhancement is achieved with nonionic contrast material (300 to 320 mg of iodine per milliliter) administered by an automatic injector at a rate of 3 to 5 ml/sec for a total of 150 ml. At least two phases of contrast-enhanced helical scanning are performed. The first (arterial) phase begins 25 seconds after contrast injection and is performed during a 20-second breathhold, with imaging done from the diaphragm through the horizontal portion of the duodenum at a slice thickness of 2.5-mm contiguous, reconstructed to 1.25-mm-slice thickness for multiplanar reconstructions. Imaging during this first phase includes the pancreas at 35 to 45 seconds after contrast injection, which, at this rate of contrast injection, optimizes the difference in density between the pancreas and tumor (pancreatic parenchymal phase). The second (venous) phase, which is done to look for metastases in the liver and abdomen, begins 55 seconds after the start of intravenous contrast injection and covers the entire liver and upper abdomen at a 2.5-mm-slice thickness, which is then reconstructed to a 1.25-mm-slice thickness.

If a low-density mass is not identified by CT, patients with suspected pancreatic cancer should undergo upper

endoscopy and EUS. Endoscopic evaluation may discover an ampullary tumor or related pathology, and EUS may define a mass in the pancreas or distal bile duct not seen on CT. When possible, upper endoscopy, EUS, and ERCP should always be performed after CT, because if endoscopy (ERCP or EUS-guided biopsy)-induced pancreatitis occurs, it may interfere with accurate assessment of the extent of disease. At the time of ERCP, a malignant obstruction of the intrapancreatic portion of the common bile duct is characterized by an abrupt cutoff, or irregular stenosis, of the common bile duct (the double-duct sign), which indicates the proximal obstruction of the common bile and pancreatic ducts. A typical malignant obstruction can often be differentiated from choledocholithiasis and the long, smooth, tapering bile duct stricture seen in chronic pancreatitis. We routinely place endoscopic stents to prevent cholangitis in patients with extrahepatic biliary obstruction who undergo diagnostic ERCP.

EUS-guided fine-needle aspiration (FNA) is currently the procedure of choice for obtaining a cytologic diagnosis of a tumor in the pancreas or periampullary region. FNA is not necessary if the biopsy results will not influence the resulting treatment plan. *Negative results from EUS-guided FNA should not be considered definite proof that a malignancy does not exist.* In a patient who presents with extrahepatic biliary obstruction, a malignant-appearing stricture of the intrapancreatic portion of the common bile duct, and no history of recurrent pancreatitis or alcohol abuse, the absence of a mass on CT or EUS images should not be grounds for ruling out a carcinoma of the pancreas or bile duct. Instead, the results of EUS, with or without FNA, should be considered in the context of the clinical picture and as a complement to CT and ERCP findings. FNA biopsy should only be performed if a mass is identified; there is no place for blind biopsy of the pancreas.

UNUSUAL PANCREATIC TUMORS

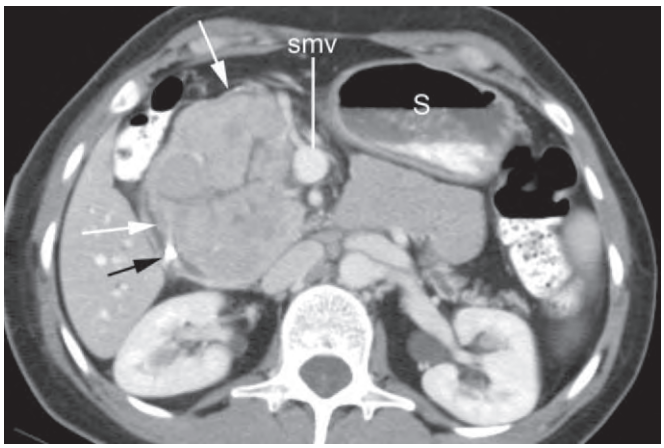
Acinar Cell Carcinoma

Illustrative Case A 42-year-old woman presented to her local physician with jaundice and intense pruritus. Ultrasonography of the gallbladder was performed and suggested a large mass in the region of the porta hepatis or pancreatic head that measured approximately 5 cm in diameter. CT of the abdomen demonstrated a large lobulated mass in the head of her pancreas that extended to the porta hepatis. The patient underwent endoscopic biliary decompression and was then referred to our institution for further care. MDCT revealed an 8-cm heterogeneous mass replacing the region of the pancreatic head and duodenal sweep (Fig. 98–1A). No evidence of vascular invasion or metastasis was identified. Because of its large size, the original diagnostic considerations, based on clinical presentation and imaging, were a neuroendocrine tumor, pseudopapillary tumor, or possibly an exophytic leiomyosarcoma.

An EUS-FNA biopsy was obtained to exclude a gastrointestinal stromal tumor, due to the availability of protocol-based targeted therapy (Gleevec) for these tumors. The biopsy revealed tumor cells that were immunohistochemically strongly positive for trypsin and negative for chromogranin and synaptophysin, consistent with an acinar cell carcinoma. Following the biopsy, the patient underwent a pylorus-preserving pancreaticoduodenectomy. An 8-cm well-circumscribed mass was identified in the head of the pancreas. The cut surface of the mass was soft and lobulated with lobules separated by thin fibrous bands and areas of necrosis and hemorrhage. Microscopically, the tumor showed predominantly acinar growth pattern with focal glandular and solid areas (see Fig. 98–1B to E). The tumor cells had moderate eosinophilic granular cytoplasm and relatively uniform nuclei with small nucleoli (see Fig. 98–1B). Consistent with the immunohistochemical results from the FNA biopsy, the tumor cells were positive for cytokeratin and trypsin but negative for synaptophysin and chromogranin (see Figs. 98–1D and E). These findings supported the diagnosis of acinar cell carcinoma. No vascular invasion was identified, and margins of resection and all regional lymph nodes were histologically negative for malignancy.

Acinar cell carcinoma accounts for approximately 1% of all pancreatic cancers. These rare tumors have the unique ability to produce pancreatic enzymes and can also be identified by specific histologic features.[1] These tumors generally occur in patients in the 5th to 7th decades of life with a slight male predominance. Similar to other solid pancreatic tumors, acinar cell carcinomas commonly present with vague symptoms of abdominal pain and bloating. They are found in the head of the pancreas in approximately one half of reported cases, often leading to obstructive jaundice and elevated liver enzymes. Acinar cell carcinoma may be associated with elevated lipase production, which is thought to be responsible for systemic manifestations such as polyarthralgias, subcutaneous fat necrosis, and an erythema nodosum–like rash and peripheral eosinophilia. The two most common histologic patterns of acinar cell carcinomas are acinar and solid patterns with delicate vessels coursing through the tumor. Less commonly, the tumor may show glandular or trabecular growth patterns. The glands are often large with irregular lumens as a result of dilated acini. Periodic acid–Schiff–positive, diastase-resistant cytoplasmic granules are commonly present in the tumor cells (see Fig. 98–1C). The tumor lacks the desmoplastic stroma commonly seen in ductal adenocarcinomas.

Acinar cell carcinomas usually exhibit an aggressive biologic behavior, similar to ductal adenocarcinoma of the pancreas. In the largest reported single institution series, from Memorial Sloan-Kettering Cancer Center, metastases were identified at the time of diagnosis in 19 (49%) of 39 patients; the most common site of distant disease was the liver.[1] Surgical resection remains the best therapy for patients with localized acinar cell carcinomas that have no evidence of extrapancreatic metastatic spread. In the report from Memorial, 18 patients underwent potentially curative resection with 2 patients receiving neoadjuvant therapy.[1] Of the resected patients, 72% eventually recurred. Chemotherapy was given to 18



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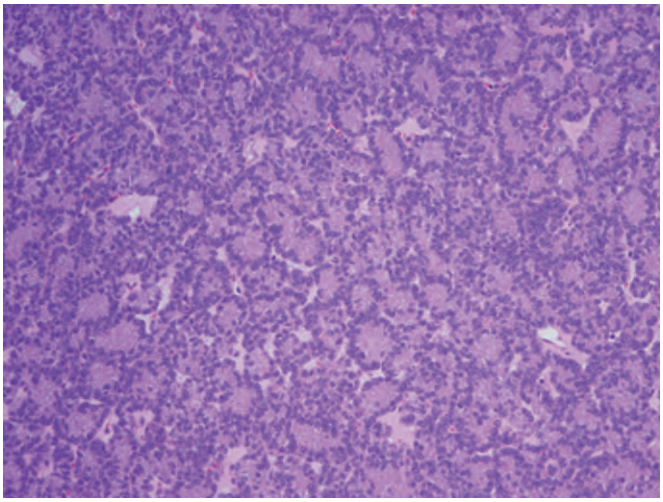

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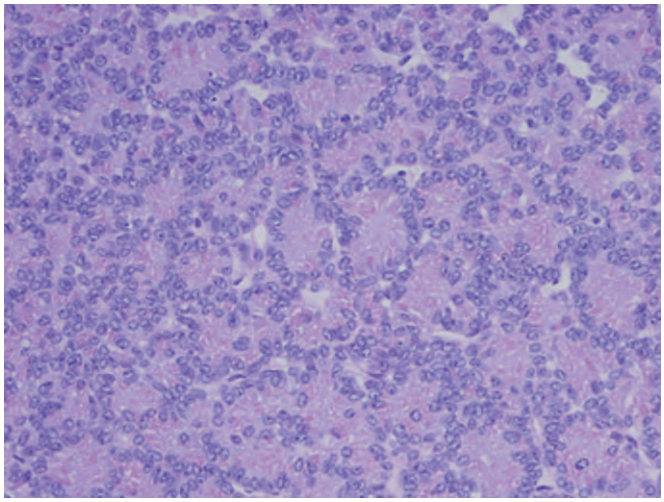

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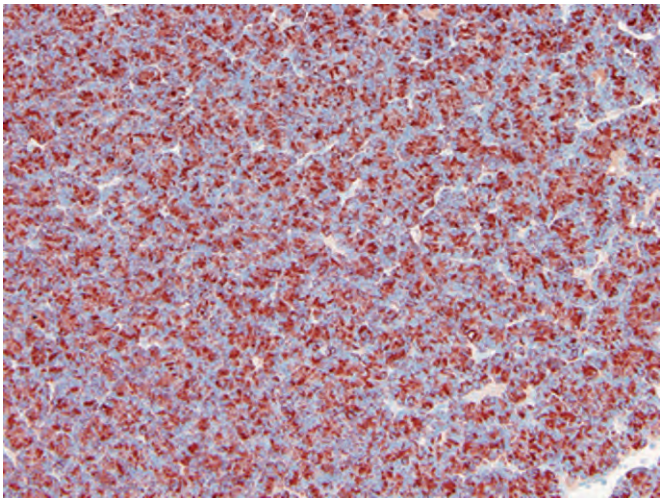

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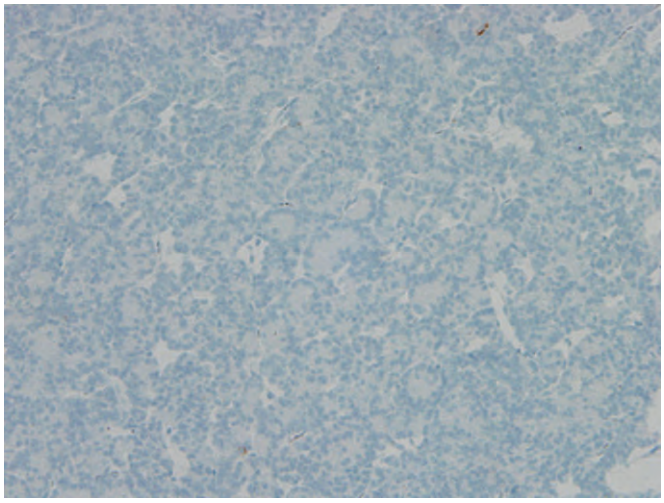


E

Figure 98–1. **A,** Contrast-enhanced CT of a 42-year-old woman with acinar cell carcinoma *(white arrows)* of the pancreatic head abutting the superior mesenteric vein (smv). The *black arrow* indicates common bile duct stent; S, stomach. **B** to **E,** Representative photomicrographs of the acinar cell carcinoma: **B,** a hematoxylin-eosin–stained section with acinar pattern; **C,** periodic acid–Schiff with diastase stain demonstrated eosinophilic intracytoplasmic granules in tumor cells; immunohistochemical stains demonstrated that the tumor cells were strongly positive for trypsin (**D,** red staining) but negative for neuroendocrine markers such as synaptophysin (**E,** original magnification ×100).

patients, including 22 different treatment regimens. The median overall survival for all patients was 19 months, which is similar to that typically seen in patients with ductal adenocarcinoma. The patients who underwent successful surgical resection had a median survival of 36 months.

Solid Pseudopapillary Tumor of the Pancreas (Papillary Cystic Solid tumors)

Illustrative Case An otherwise healthy 58-year-old woman presented to her local physician with worsening right upper quadrant pain over a 3-month period. On further questioning, she admitted having similar painful episodes for more than 20 years. The pain radiated to her back and was aggravated by eating solid food, yet she denied nausea, vomiting, or changes in her bowel habits. Initial physical examination and laboratory analysis were unremarkable. She was begun on omeprazole (Prilosec) without resolution of her symptoms. Further evaluation with an abdominal ultrasound demonstrated common bile duct dilation and an abnormally increased hepatic echo texture consistent with underlying fatty infiltration. A CT scan of the abdomen was performed that demonstrated a 6.5-cm calcified mass in the pancreatic head that was felt to be hypodense in the arterial phase. The mass appeared inseparable from the superior mesenteric vein (SMV). Because of this, the patient was referred to M. D. Anderson Cancer Center for further evaluation, where a MDCT confirmed the findings of the original CT (Fig. 98–2A).

A pylorus-preserving pancreaticoduodenectomy was performed and final pathology revealed a 5.0 × 5.0 × 3.9 cm well-circumscribed tumor mass covered by a thin, fibrous capsule. The cut surface of the tumor was soft, heterogeneous with areas of hemorrhage and cystic degeneration. Microscopically, the tumor was cellular and composed of pseudopapillae covered by multiple layers of tumor cells (see Fig. 98–2B). Areas of hemorrhage, degenerative changes, and focal collections of foamy histiocytes were present. Other areas of the tumor revealed a thick fibrovascular core with myxoid changes. At high power, nuclear grooves were present in some of the tumor cells (see Fig. 98–2C). The tumor cells were strongly positive for beta-catenin, progesterone receptor, vimentin, and CD10 (see Figs. 98–2D and E). The proliferation rate was low as assessed by immunohistochemistry for Ki-67/MIB-1. These findings supported the diagnosis of a solid pseudopapillary tumor (SPT) of the pancreas.

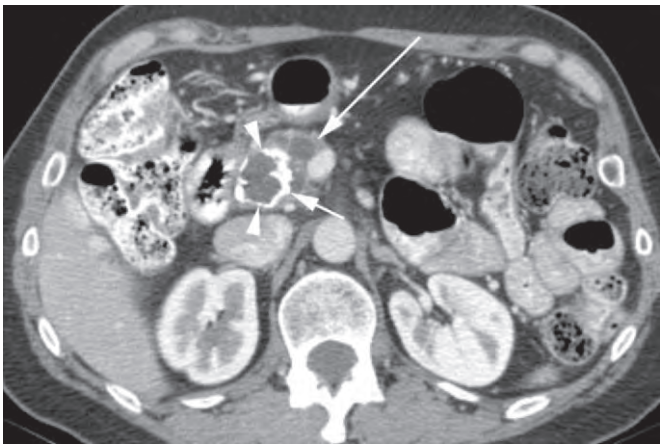
SPTs are rare, accounting for less than 1% of all pancreatic tumors and characteristically occur in young women. The female-to-male ratio has been reported as high as 10:1 with an increased incidence noted in the 3rd decade of life. The presenting signs and symptoms are nonspecific and are generally related to the large size of the tumors at diagnosis. Often, SPTs are greater than 8 to 10 cm in diameter and occur with equal frequency in the head, body, and tail of the pancreas. On CT scan, SPTs appear well circumscribed with a thick capsule and contain varying degrees of hypodensity representing hemorrhage and necrosis. Calcifications may be observed in the capsule or within tumors.

The diagnosis of SPTs is based on the presence of typical histologic characteristics such as foamy macrophages, cholesterol clefts, nuclear grooves, and aggregates of hyaline globules. The histologic appearance of SPTs includes variable degrees of degenerative changes because the cavities observed within SPTs do not represent true "cysts" but are regions of necrosis and degeneration. SPTs can mimic the histologic appearance of neuroendocrine tumors but lack the nuclear features of neuroendocrine tumors and lack the immunohistochemical expression of neuroendocrine markers such as chromogranin and synaptophysin. Although SPTs may possess features commonly associated with more aggressive behavior such as increased mitotic rate, nuclear pleomorphism, and vascular invasion, no pathologic criteria have been shown to correlate with a worse prognosis.

Even though SPTs are often quite large at diagnosis, they usually demonstrate a relatively indolent biologic behavior and rarely metastasize to distant organs.[2] Metastases are discovered at the time of diagnosis in only 10% to 15% of cases. Due to the low metastatic potential and indolent growth, complete resection is curative in most patients. The approach to patients with locally advanced (unresectable) SPTs is unclear; combination chemotherapy incorporating agents used in ductal adenocarcinoma and phase I-II investigational trials represent reasonable alternatives.

Pancreatic Lymphoma (Non-Hodgkin's Lymphoma)

Illustrative Case An otherwise healthy 53-year-old man presented to his family physician with new onset of fatigue associated with a 20-pound weight gain, nausea, vomiting, and intense pain under his left rib cage. Initial diagnostic studies consisted of an ultrasound of the gallbladder, intravenous pyelogram, and plain films of the abdomen that were nondiagnostic. A CT scan of the abdomen was believed to be consistent with pancreatitis. The patient was placed on a histamine receptor antagonist and noted mild symptomatic improvement; however, a few months later he developed recurrent left rib cage pain, nausea, and jaundice. At this point, a diagnostic CT scan revealed a mass in the head of the pancreas. He was then referred to our institution, where an MDCT scan revealed a 5-cm well-circumscribed enhancing mass in the head of the pancreas with possible adherence to the SMV (Fig. 98–3A). ERCP demonstrated a long-segment stricture of the distal common bile duct and a stricture of the pancreatic duct. The patient underwent percutaneous FNA biopsy of the pancreatic mass that revealed necrotic tissue and inflammatory cells. Due to the high suspicion of malignancy, he was taken to surgery and a pancreaticoduodenectomy was performed; this required vascular resection of the SMV with an interposition vein graft. Final pathology revealed diffuse, large, noncleaved B-cell lymphoma with sclerosis involving the head of the pancreas, peripancreatic adipose tissue, and duodenal



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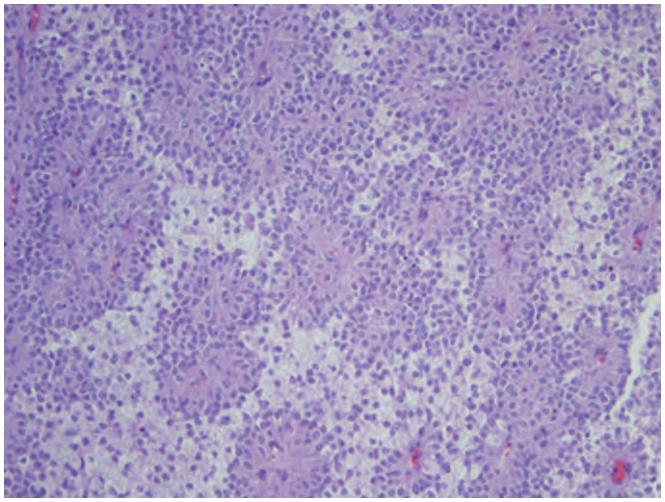

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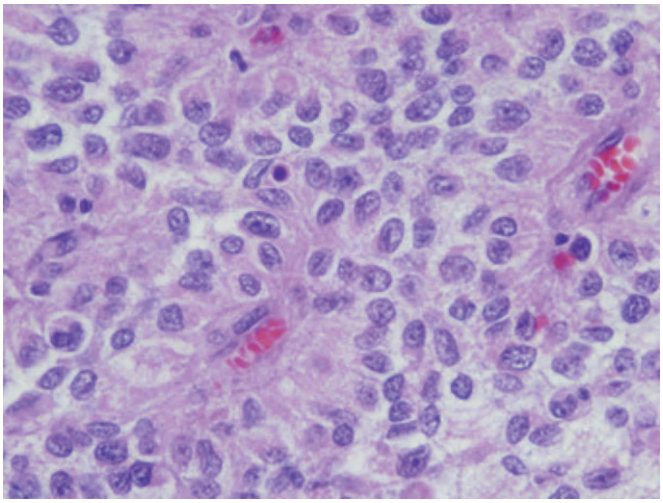

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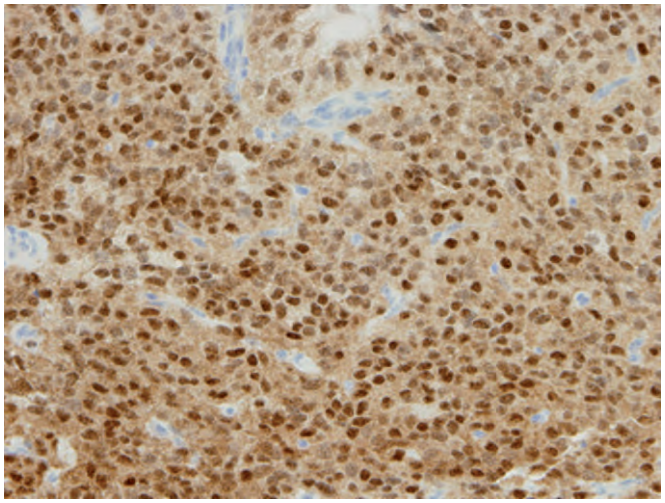

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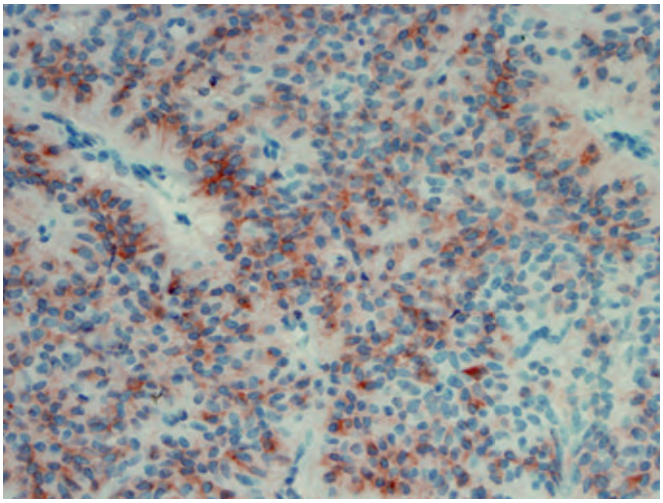

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Figure 98–2. **A,** Contrast-enhanced CT images of a 58-year-old woman with a solid pseudopapillary tumor of the pancreas *(white arrow)* obstructing the pancreatic duct *(long white arrow)*. Dense calcifications are seen *(white arrowheads)*, which are uncommon. **B** to **E,** Representative photomicrographs of the solid pseudopapillary tumor of the pancreas: **B,** the hematoxylin-eosin section showed pseudopapillary formation and focal collections of histiocytes (original magnification ×100); **C,** nuclear grooves in tumor cells (original magnification ×400); and the tumor cells were strongly positive for beta-catenin (**D** [brown nuclear staining]) and CD10 (**E** [red cytoplasmic staining]) by immunohistochemistry (original magnification ×100).

wall. Following recovery from surgery, the patient was treated with chemotherapy and external-beam radiation therapy.

Non-Hodgkin's lymphoma arises in extranodal tissue in up to 40% of reported cases, although primary pancreatic tumors are exceedingly rare. In a review of the medical literature as of 2005, only 165 cases of pancreatic lymphoma were identified.[3] The clinical presentation of patients with pancreatic lymphoma is often nonspecific, consisting of weight loss, nausea, vomiting,

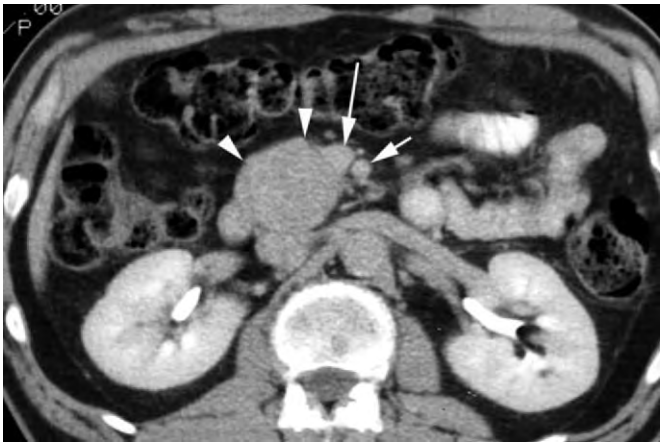


Figure 98–3. Axial contrast-enhanced CT scan shows a pancreatic head mass *(white arrowheads)* identified on surgical pathology as lymphoma. The *long white arrow* indicates the superior mesenteric vein and the *short white arrow* points out the superior mesenteric artery.

and abdominal pain. B-type lymphoma symptoms such as fever and night sweats may be present. CT images can suggest the diagnosis of pancreatic lymphoma by the presence of a bulky pancreatic mass with surrounding lymphadenopathy. CT evidence of a bulky pancreatic mass in the absence of weight loss, back pain, and extrahepatic biliary obstruction (normal bilirubin associated with an elevated lactate dehydrogenase) should cause one to consider lymphoma in the differential diagnosis.

Treatment of pancreatic lymphoma traditionally has involved cytotoxic chemotherapy. The most common chemotherapy regimens include cyclophosphamide, doxorubicin (Adriamycin), vincristine, and prednisone (CHOP). Complete remission can be expected with multidrug chemotherapy in 60% to 80% of patients with early-stage non-Hodgkin's lymphoma.[4] However, recurrence is more common in patients older than 60 years of age. More recently, rituximab (a chimeric murine/human monoclonal antibody directed against the CD20 antigen found on lymphocytes) has been combined with CHOP, resulting in improved response rates and long-term survival for patients with diffuse large B-cell lymphomas.[5]

A retrospective review from our institution evaluated the characteristics of 11 patients diagnosed with pancreatic lymphoma over a 15-year period.[6] Nine of the 11 patients presented with a mass greater than 5 cm. Five of 6 patients that underwent FNA biopsy had the diagnosis established correctly. Three of 11 patients underwent surgical resection for presumed pancreatic endocrine or exocrine carcinoma. All patients received four to six cycles of combination chemotherapy after the diagnosis was established. Following chemotherapy, external-beam irradiation was administered to 7 of the 8 patients who did not undergo pancreatectomy; 5 of these 8 patients had complete radiographic responses. Two of the eight patients had minimal response to chemotherapy and died of disease at 12 and 16 months after diagnosis. Although the three patients who underwent surgical resection achieved a complete response and were disease-free at the time of the review, similar results may have been achieved with systemic chemotherapy. In contrast, a recent report from Johns Hopkins University suggested that surgical resection may have a role in the treatment of early pancreatic lymphoma.[3] Three patients with early-stage pancreatic lymphoma underwent pancreaticoduodenectomy for suspected periampullary adenocarcinoma and were disease-free at 5-year follow-up. This anecdotal experience suggests that pancreatic resection may be associated with a therapeutic benefit in an occasional patient found to have lymphoma who underwent initial operation due to the concern over a possible periampullary or pancreatic adenocarcinoma.

Lymphoplasmacytic Sclerosing Pancreatitis

Illustrative Case A 66-year-old woman underwent an ultrasound of the abdomen for follow-up of a benign renal cyst and was found to have a 5.2 × 4.8 cm mass arising in the tail of the pancreas. This pancreatic mass had not been seen on the previous examination performed 3 years earlier. She denied any history of pancreatitis, alcohol use, gallstone disease, hyperlipidemia, or any other risk factors for pancreatitis. A MDCT scan of the abdomen demonstrated a low-density mass lesion that appeared to be arising from the body and tail of the pancreas (Fig. 98–4A). The splenic vein was occluded by the mass, and the presumed tumor extended to the origin of the splenic artery. EUS-guided FNA biopsy revealed benign epithelial cells with no evidence of carcinoma. She therefore underwent a CT-guided FNA biopsy along with a CT-guided core-needle biopsy. Again, fibrosis and chronic inflammation were present with no evidence of carcinoma. IgG subclass 4 serum levels were within normal limits. Because malignancy could not be excluded, she underwent a subtotal distal pancreatectomy and splenectomy. A 6.0 × 4.0 × 3.5 cm ill-defined mass lesion was identified in the pancreas on pathologic examination. The cut surface of the mass was firm with no necrosis. Sections from this lesion showed dense periductal lymphoplasmacytic infiltrates and periductal fibrosis, involving predominantly the medium-size and large interlobular ducts (see Figs. 98–4B and C) consistent with lymphoplasmacytic sclerosing pancreatitis (LPSP). Focal venulitis (perivascular inflammation with vascular damage) was also present (see Fig. 98–4D). No invasive carcinoma was identified.

LPSP is a unique form of pancreatitis that can clinically and radiographically mimic infiltrating pancreatic ductal adenocarcinoma.[7] Patients with LPSP may present with obstructive jaundice, weight loss, and nonspecific abdominal pain. LPSP has been associated with various autoimmune diseases such as ulcerative colitis and Sjögren's syndrome as well as with primary sclerosing cholangitis. However, many patients with LPSP have no history of, or symptoms consistent with, an autoimmune disorder. Patients with LPSP often have elevated levels of serum immunoglobulin G subclass 4.

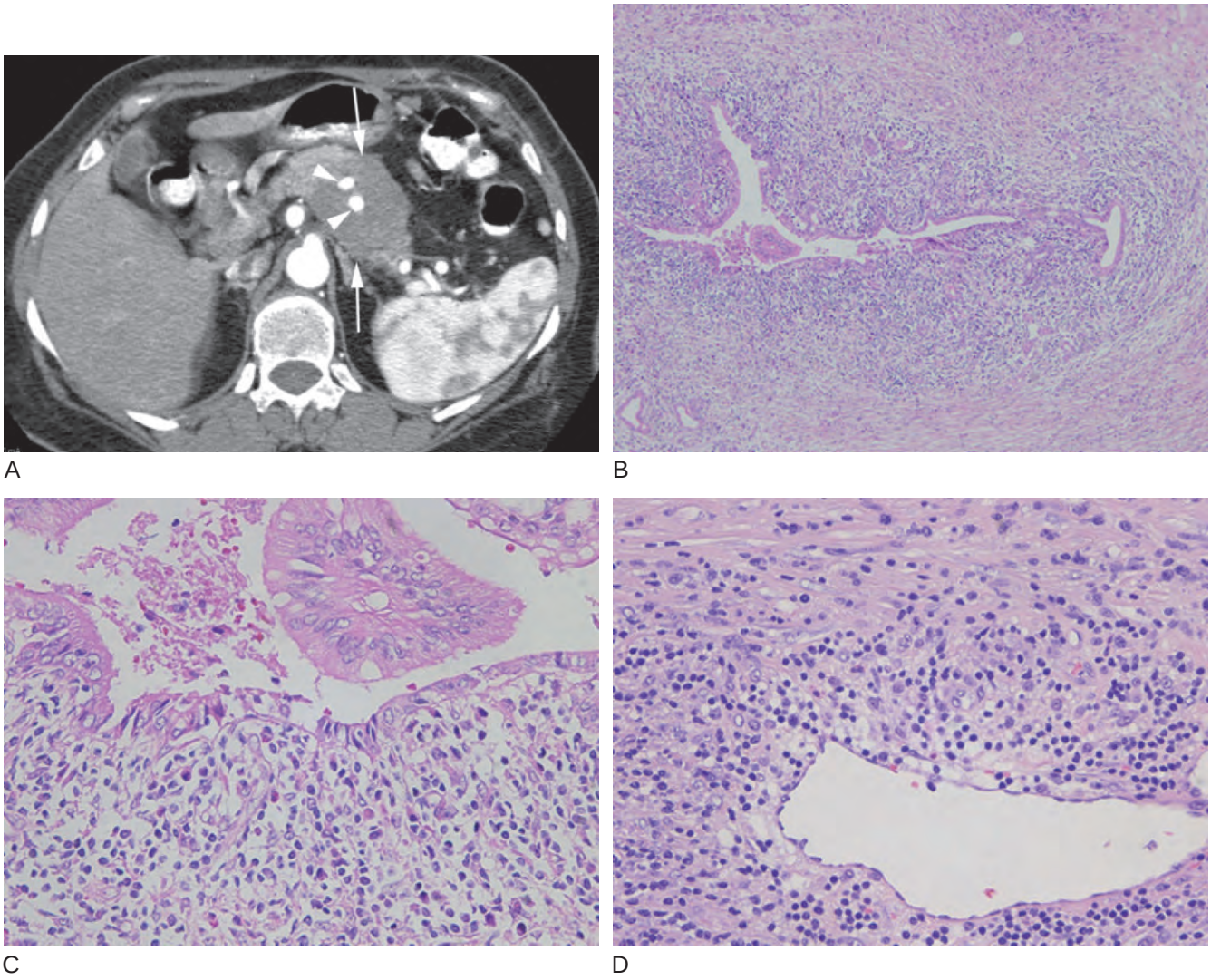
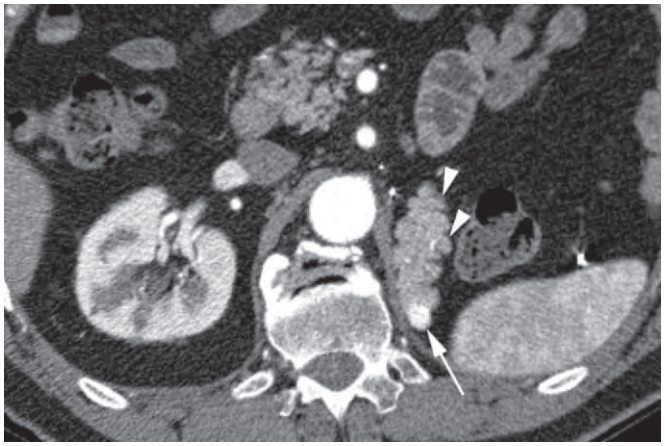


Figure 98–4. Axial contrast-enhanced CT scan shows a mass like process in the pancreatic body and tail *(white arrows)* engulfing the splenic artery *(white arrowheads)*. **B** to **D,** Representative micrographs of lymphoplasmacytic sclerosing pancreatitis: **B** and **C,** hematoxylin-eosin (H&E) sections show dense periductal lymphoplasmacytic infiltrates and periductal fibrosis involving an interlobular pancreatic duct (**B,** original magnification ×40; **C,** original magnification ×200); **D,** H&E section shows venulitis with a lymphoplasmacytic infiltrate (original magnification ×100).

Although the clinical presentation can be confused with ductal adenocarcinoma, the histologic appearance is quite distinct. LPSP is characterized by an intense inflammatory cell infiltrate consisting of lymphocytes and plasma cells within the pancreas concentrated around the pancreatic duct and ductules. Although many patients with LPSP associated with a focal mass will have surgery due to the concern over an underlying adenocarcinoma, this disease entity may respond to steroids if the diagnosis can be made preoperatively. Following pancreatic resection for LPSP, patients warrant close follow-up due to the possibility of recurrent symptoms, which may occur in up to one third of patients.[7]

Metastatic Tumors to the Pancreas

Illustrative Case A 73-year-old physician with a history of renal cell carcinoma, status post left radical nephrectomy 20 years ago, was found on CT imaging to have a 1-cm hypervascular, contrast-enhancing lesion in the pancreatic tail, suspicious for metastatic renal cell carcinoma (Fig. 98–5A). The patient was asymptomatic at the time of diagnosis yet due to the known predisposition for renal cell carcinoma to spread to the pancreas, he underwent a spleen-preserving distal pancreatectomy. Pathologic evaluation revealed a 1.3-cm well-circumscribed tumor in the pancreas. The cut surface of the mass was yellow-tan and variegated with areas of hemorrhage and



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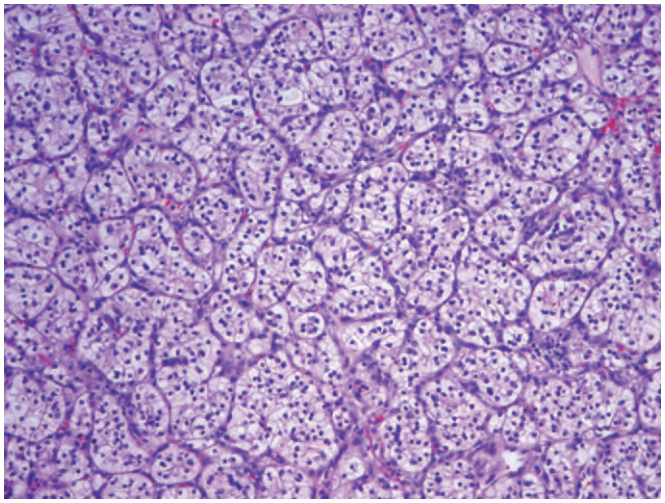

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Figure 98–5. **A,** Contrast-enhanced CT image of a 73-year-old man with a history of renal cell carcinoma demonstrating an intensely enhancing nodule *(white arrow)* compatible with metastatic renal cell carcinoma within the pancreatic tail *(white arrowheads)* that had fallen back into the left nephrectomy bed. **B,** Representative photomicrograph of metastatic renal cell carcinoma (hematoxylin-eosin stain, original magnification ×100).

necrosis. Microscopically, the tumor was composed of a solid growth of clear cells, which formed nests of different sizes separated by delicate sinusoidal-like blood vessels (see Fig. 98–5B). The tumor cells were positive on immunohistochemical staining for cytokeratin and vimentin and negative for chromogranin and synaptophysin. The histologic features and immunohistochemical staining results were consistent with metastatic renal cell carcinoma.

Although most patients who present with evidence of metastasis to the pancreas have diffuse intra-abdominal disease, 2% of patients with metastases to the pancreas will have isolated lesions. Renal cell carcinoma and malignant melanoma are the two most common tumors that can result in intraparenchymal pancreatic metastases. Tumors of the breast, lung, and gastrointestinal tract (especially adenocarcinoma of the right colon) may be associated with metastatic adenopathy in the porta hepatis and peripancreatic region that may mimic a pancreatic mass; intraparenchymal pancreatic metastases from these histologies are rare. Isolated adenopathy to the region of the pancreatic head may be difficult to differentiate from a primary pancreatic tumor if high-quality cross-sectional imaging is not performed.

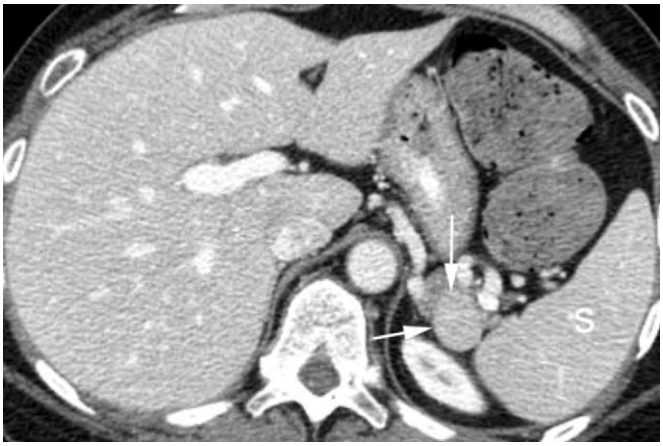

Figure 98–6. Contrast-enhanced CT image of a 49-year-old woman with an incidentally noted mass in the pancreatic tail consistent with an accessory spleen (*white arrows*). The diagnosis is further supported by the similarity of appearance of the pancreatic nodule to the adjacent spleen (S).

Renal cell carcinoma deserves special mention because it is the most common tumor to metastasize to the pancreas and such metastases may occur many years after initial nephrectomy because of the highly variable natural history of patients with renal cell carcinoma. Approximately one third of isolated pancreatic metastases from renal cell carcinoma occur 10 or more years after initial treatment of the primary cancer.[8] Most patients with metastatic renal cell carcinoma are asymptomatic and identified only by surveillance follow-up imaging. The classic features of a renal cell carcinoma metastasis are hypervascularity and high attenuation on the arterial phase of CT images (as shown in Fig. 98–5A). Patients with successfully resected isolated metastases from renal cell carcinoma have 5-year survival rates of 60% to 80% compared with patients with unresectable disease who have 1-year survival rates of less than 50%.

The differential diagnosis of a hypervascular mass in the pancreas includes neuroendocrine carcinoma (sporadic or familial [as part of multiple endocrine neoplasia type I or von Hippel–Lindau syndrome]), metastatic renal cell carcinoma, and accessory splenic tissue. As seen in Figure 98–6, this 49-year-old woman was referred to our institution with a presumed pancreatic tumor. This was an incidental finding on CT images obtained for further evaluation of intermittent, poorly localized, mild abdomen pain. Previous surgical consultation had suggested pancreatic resection be performed. MDCT at our institution (see Fig. 98–6) was consistent with an

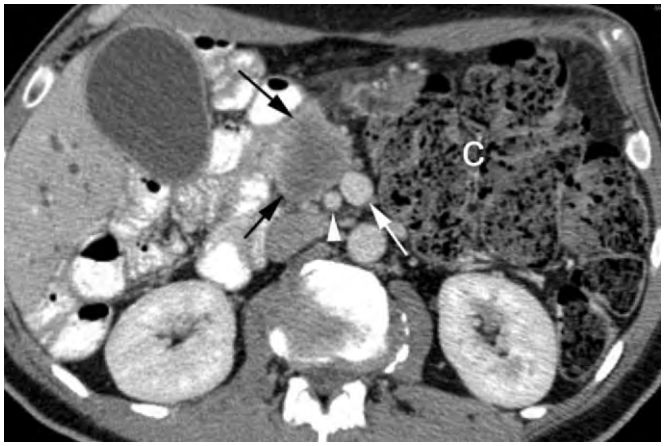

Figure 98–7. Contrast-enhanced CT image of a 53-year-old man with pancreatic cancer demonstrating a pancreatic tumor *(black arrows)* abutting the superior mesenteric vein *(white arrow)* and separated from the superior mesenteric artery *(white arrowhead)* by an intact fat plane. This patient has malrotation of the bowel; complete nonrotation of the midgut with nonrotation of both the duodenojejunal limb and the cecocolic limb. The superior mesenteric vein is located to the patient's left of the superior mesenteric artery. Note that the colon (C) is located in the left side of the abdomen consistent with malrotation.

accessory spleen in the pancreatic tail; the diagnosis was supported by the similarity in appearance to the adjacent spleen.

Finally, the relationship of the SMV and the SMA to the pancreatic head and uncinate process is a critically important relationship for the surgeon to understand if he or she plans to perform pancreatic surgery.[9,10] In fact, this tumor-vessel relationship should be one of the first things that the surgeon examines when assessing resectability of a primary pancreatic neoplasm on CT images. We recently evaluated a 53-year-old man with pancreatic cancer in whom the tumor-vessel relationship was unusual. As seen in the CT image illustrated in Figure 98–7, the pancreatic tumor is abutting the SMV, which is located to the right (patient's left) of the SMA. This is opposite to the normal relationship of the SMV and SMA; normally, the SMV is anterior and lateral (to the patient's right) to the SMA (the SMA is deep [posterior] and medial to the SMV). This patient has complete malrotation, accounting for the altered relationship of the mesenteric vessels. Note that the colon is located in the left side of the abdomen, also consistent with malrotation.

ACKNOWLEDGMENT

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Part

2

Biliary Tract

Chapter

99

Anatomy, Embryology, Anomalies, and Physiology

Henry A. Pitt ▪ Thomas R. Gadacz

The anatomy of the biliary tract is intimately associated with both the liver and the pancreas. Thus, an understanding of biliary anatomy must include these adjacent organs as well as their embryology. Similarly, anomalies of the biliary tract and the associated vasculature are common and result from arrested or abnormal development during embryonic growth. Biliary physiology also is closely associated with the liver where bile is formed as well as with the pancreas as the sphincter of Oddi regulates the flow of both bile and pancreatic juice. Thus, for a complete picture of the anatomy, embryology, and physiology of the biliary tract, the reader is referred to corresponding chapters in the sections on the liver and the pancreas.

ANATOMY AND EMBRYOLOGY

The first step in understanding the anatomy of the biliary tract is a review of the embryology of the liver, biliary tract, and pancreas. At the 4th week in the development of the human embryo, a projection appears in the ventral wall of the primitive midgut. At this 3-mm stage, three buds can be recognized. The cranial bud develops into two lobes of the liver, whereas the caudal bud becomes the gallbladder and extrahepatic biliary tree (Fig. 99–1). The ventral pancreas, which eventually becomes the pancreatic head and uncinate process, also develops from the caudal bud. The third primitive bud develops from the dorsal surface of the midgut to become the anlage of the remainder of the pancreatic head as well as the neck, body, and tail of the pancreas.[1] At the 5-mm stage the primitive gallbladder and common bile duct have appeared.

At the 7-mm stage (see Fig. 99–1) the liver and hepatic ducts have formed, and the gallbladder, the cystic duct, and the ventral pancreas have arisen from the common duct. At this stage the stomach has begun to form, and the ventral pancreas has developed from the dorsal mesogastrium. By the 12-mm stage, the ventral pancreatic bud has rotated 180 degrees clockwise around the duodenum. This rotation causes fusion of the ventral and dorsal buds to form the complete pancreas by the 6th or 7th week of gestation. Within another week, a completely open lumen has formed in the gallbladder, bile ducts, and pancreatic ducts. By the 12th week of fetal life, the liver begins to secrete bile and the pancreas secretes fluid that flows via the extrahepatic biliary tree and pancreatic ducts, respectively, into the duodenum.

Intrahepatic Ducts

The anatomy of the biliary tract can be divided into various segments, including the intrahepatic ducts, the extrahepatic ducts, the gallbladder and cystic duct, and the sphincter of Oddi. The anatomy of the intrahepatic ducts is intimately associated with the anatomy of the liver. The lobar and segmental anatomy of the liver is

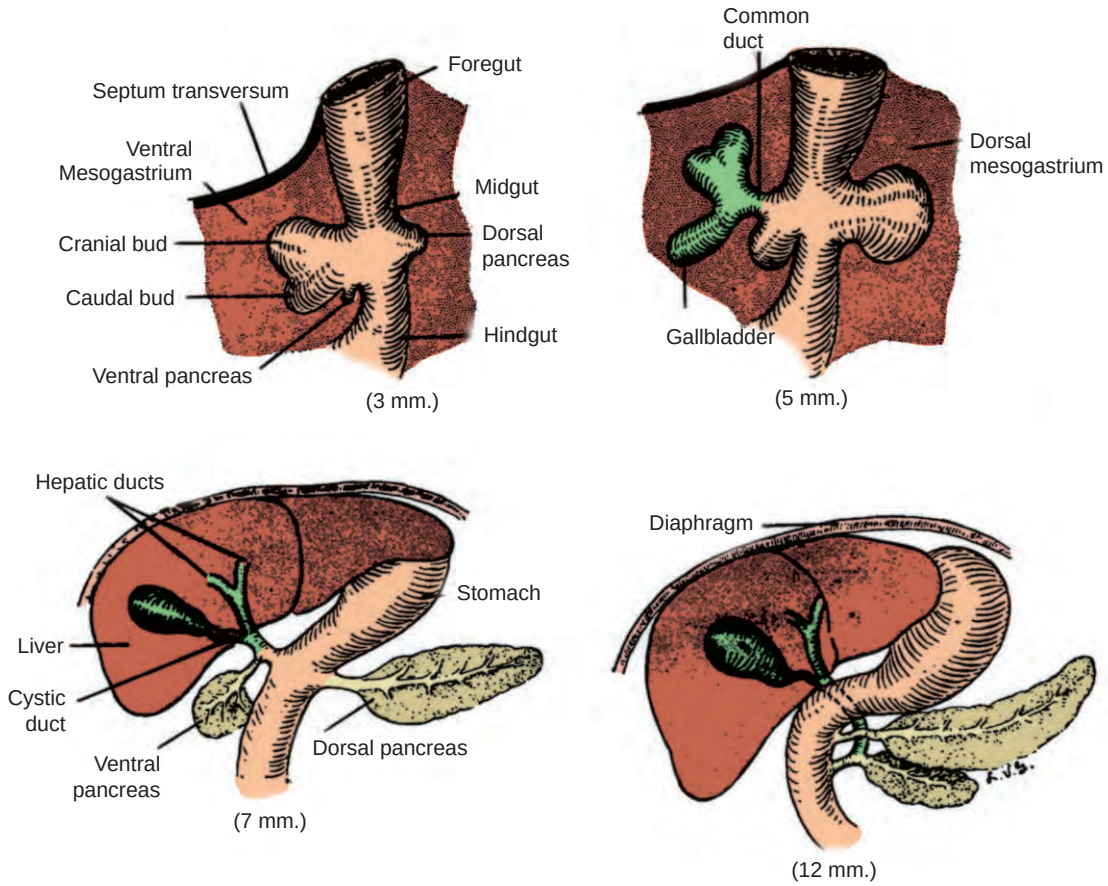

Figure 99–1. Embryonic development of the extrahepatic biliary tract and pancreas. (From Linder HH: Embryology and anatomy of the biliary tree. In Way LW, Pellegrini CA [eds]: Surgery of the Gallbladder and Bile Ducts. Philadelphia, WB Saunders, 1987, p 4.)

determined by the sequential branching of the portal vein, hepatic artery, and biliary tree as they enter the parenchyma at the hilum. All three of these structures follow roughly parallel courses and bifurcate just before entering the liver. This major bifurcation divides the liver into left and right lobes. According to Couinaud's classification, the caudate lobe is segment I; segments II to IV are on the left; and segments V to VIII are on the right (Fig. 99–2).

The biliary drainage of the right and left liver is into the right and left hepatic ducts, respectively. The left hepatic duct is formed within the umbilical fissure from the union of the three segmental ducts draining the left side of the liver (segments II through IV). The left hepatic duct crosses the base of segment IV (medial segment of the left lobe) in a horizontal direction to join the right hepatic duct and form the common hepatic duct. The right hepatic duct drains segments V through VIII and is formed from the union of the right posterior and right anterior segmental ducts. The right posterior segmental duct is formed by the confluence of ducts draining segments VI and VII. The posterior segmental duct initially courses in a nearly horizontal direction before descending in a more vertical direction to join the anterior segmental duct. The right anterior segmental duct is formed by the union of the ducts draining segments V and VIII. The biliary drainage of the caudate lobe (segment I) is variable.[2] In approximately 80% of the individuals, the caudate lobe drains into both the right and left hepatic ducts. In 15% of cases, the caudate lobe drains only into the left hepatic duct, and in the remaining 5% of cases, the caudate is drained exclusively by the right hepatic duct.[3]

Extrahepatic Ducts

Most patients have a bifurcation where the right and left hepatic ducts join to form the common hepatic duct. This junction may occur as a wide or an acute angle, or the two hepatic ducts may run parallel to each other before joining. In some patients, three hepatic ducts join to form the common hepatic duct. Usually, the hepatic ducts meet just outside of the liver parenchyma, with the cystic duct entering 2 to 3 cm distally. Occasionally, the two hepatic ducts do not unite until after the cystic duct has joined the right hepatic duct. The common hepatic duct extends for a variable length from the junction of the right and left hepatic ducts to the entrance of the cystic duct into the gallbladder (Fig. 99–3).

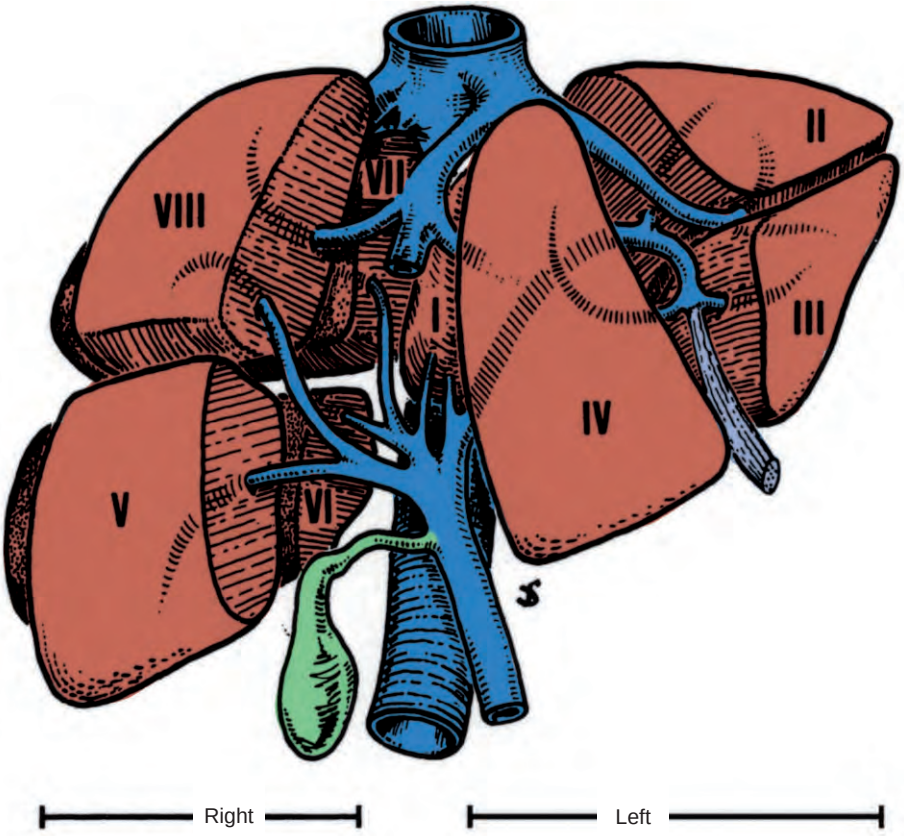

Figure 99–2. Segmental biliary drainage of the liver. (From Smadja C, Blumgart LH: The biliary tract and the anatomy of biliary exposure. In Blumgart LH [ed]: Surgery of the Liver and Biliary Tract. Edinburgh, Churchill Livingstone, 1988, p 11.)

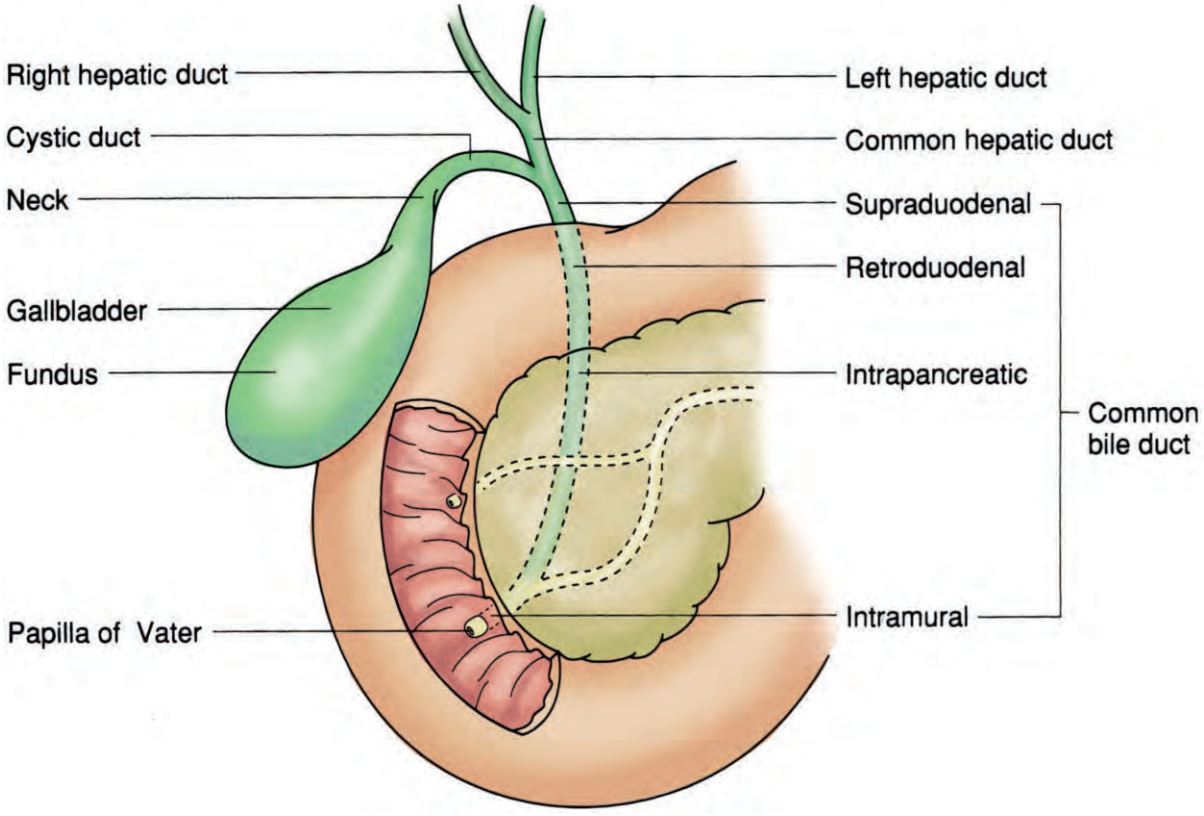

Figure 99–3. Anatomic divisions of the gallbladder and extrahepatic biliary tree. (From Gadacz TR: Biliary anatomy and physiology. In Greenfield LJ, Mulholland MW, Oldham KT [eds]: Surgery: Scientific Principles and Practice. Philadelphia, JB Lippincott, 1993, p 931.)

The common bile duct is formed by the union of the cystic and common hepatic ducts. The common bile duct is approximately 8 cm in length, but, like the hepatic duct, it varies in length according to the point of union of the cystic duct and the common hepatic duct. The normal diameter of the common bile duct ranges from 4 to 9 mm. The common bile duct is considered enlarged if the duct diameter exceeds 10 mm. The upper third, or supraduodenal portion, of the common bile duct courses downward in the free edge of the lesser omentum, anterior to the portal vein and to the right of the proper hepatic artery. The middle third, or retroduodenal portion, of the common bile duct passes behind the first portion of the duodenum, lateral to the portal vein and anterior to the inferior vena cava. The lower third, or intrapancreatic portion, of the common bile duct traverses the posterior aspect of the pancreas in a tunnel or groove to enter the second portion of the duodenum, where it is usually joined by the pancreatic duct. The intramural or intraduodenal portion of the common bile duct passes obliquely through the duodenal wall to enter the duodenum at the papilla of Vater.

The relationship between the lower common bile duct and pancreatic duct is variable: (1) the two structures may rarely unite outside the duodenal wall to form a long common channel; (2) the bile duct and pancreatic duct usually join within the duodenal wall to form a short common channel; or (3) the two structures may rarely enter the duodenum independently through separate orifices. The lower portion of the common bile duct and the terminal portion of the pancreatic duct are enveloped and regulated by a complex sphincter, the sphincter of Oddi.

The extrahepatic bile ducts contain a columnar mucosa surrounded by a connective tissue layer. The surface is relatively flat, with basal nuclei and an absent or small nucleolus. The lamina propria consists of collagen, elastic fibers, and vessels. Occasional lymphocytes are found, and pancreatic acini and ducts may be seen in the wall of the intrapancreatic portion of the distal common bile duct. Muscle fibers in the bile duct are sparse and discontinuous. The muscle fibers that are present are usually longitudinal, although occasional circular fibers are observed. The distal common bile duct begins to develop a more substantial muscle layer in the intraduodenal portion of the duct, which becomes prominent at the sphincter of Oddi, where distinct bundles of longitudinal and circular fibers are clearly identified.

Gallbladder and Cystic Duct

The gallbladder is a pear-shaped organ that lies on the inferior surface of the liver at the junction of the left and right hepatic lobes between Couinaud's segments IV and V (Fig. 99–4).[5] The gallbladder varies from 7 to 10 cm in length and from 2.5 to 3.5 cm in width. The gallbladder's volume varies considerably, being large during fasting states and small after eating. A moderately distended gallbladder has a capacity of 50 to 60 ml of bile but may become much larger with certain pathologic states. The gallbladder has been divided into four areas: the fundus, body, infundibulum, and neck. Hartmann's pouch is an asymmetrical bulge of the infundibulum that lies close to the gallbladder's neck. The neck points in a cephalad and dorsal direction to join the cystic duct.

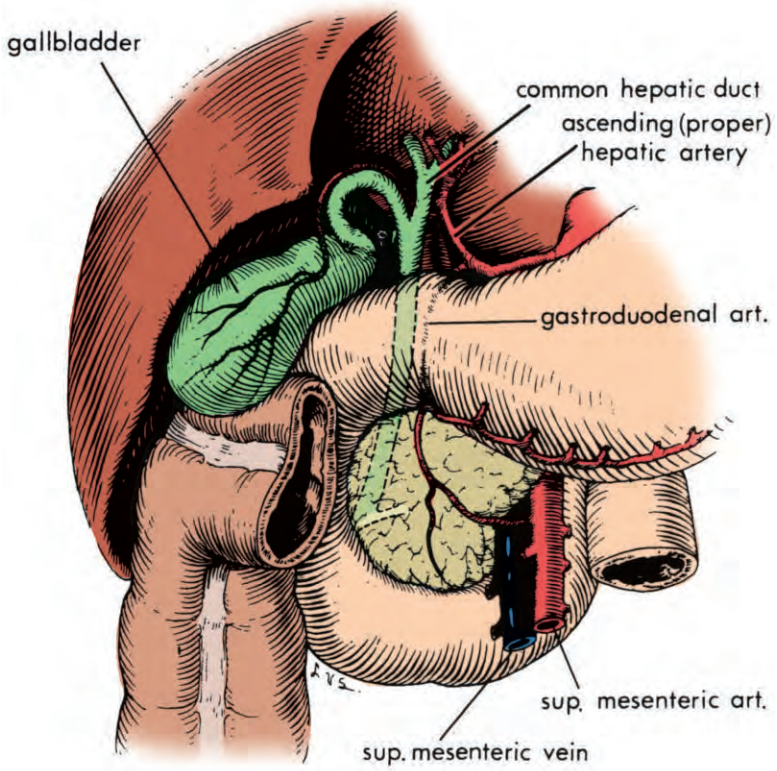

Figure 99–4. Anatomic relationships of the gallbladder. (From Linder HH: Embryology and anatomy of the biliary tree. In Way LW, Pellegrini CA [eds]: Surgery of the Gallbladder and Bile Ducts. Philadelphia, WB Saunders, 1987, p 8.)

The gallbladder wall consists of five layers. The innermost layer is the epithelium, and the other layers are the lamina propria, smooth muscle, perimuscular subserosal connective tissue, and serosa. The gallbladder has no muscularis mucosa or submucosa. Most cells in the mucosa are columnar cells, and their main function is absorption. These cells are aligned in a single row, with slightly eosinophilic cytoplasm, apical vacuoles, and basal or central nuclei.

The lamina propria contains nerve fibers, vessels, lymphatics, elastic fibers, loose connective tissue, and occasional mast cells and macrophages. The muscle layer is a loose arrangement of circular, longitudinal, and oblique fibers without well-developed layers. Ganglia are found between smooth muscle bundles. The subserosa is composed of a loose arrangement of fibroblasts, elastic and collagen fibers, vessels, nerves, lymphatics, and adipocytes.

Rokitansky-Aschoff sinuses are invaginations of epithelium into the lamina propria, muscle, and subserosal connective tissue. These sinuses are present in about 40% of normal gallbladders and are present in abundance in almost all inflamed gallbladders. The ducts of Luschka are tiny bile ducts found around the muscle layer on the hepatic side of the gallbladder. They are found in about 10% of normal gallbladders and have no relation to the Rokitansky-Aschoff sinuses or to cholecystitis.

The cystic duct arises from the gallbladder and joins the common hepatic duct to form the common bile duct (see Fig. 99–3). The length of the cystic duct is variable, averaging between 2 and 4 cm. The cystic duct usually courses downward in the hepatoduodenal ligament to join the lateral aspect of the supraduodenal portion of the common hepatic duct at an acute angle.[4] Occasionally, the cystic duct may join the right hepatic duct, or it may extend downward to join the retroduodenal duct. In addition, the cystic duct may join the common hepatic duct at a right angle, may run parallel to the common hepatic duct, or may enter the common hepatic duct dorsally, on its left side, behind the duodenum, or, rarely, may enter the duodenum directly. The cystic duct contains a variable number of mucosal folds, similar to those found in the neck of the gallbladder. Although referred to as valves of Heister, these spiral folds do not have a valvular function. Variations in the length and course of the cystic duct and its point of union with the common hepatic duct are common.

In 1891, Calot described a triangular anatomic region formed by the common hepatic duct medially, the cystic duct laterally, and the cystic artery superiorly.[6] Calot's triangle is considered by most to comprise the triangular area with an upper boundary formed by the inferior margin of the right lobe of the liver, rather than the cystic artery (Fig. 99–5).[7,8] A thorough appreciation of the anatomy of Calot's triangle is essential during performance of a cholecystectomy because numerous important structures pass through this area. In most instances, the cystic artery arises as a branch of the right hepatic artery within the hepatocystic triangle. A replaced or aberrant right hepatic artery arising from the superior mesenteric artery usually courses through the medial aspect of the triangle, posterior to the cystic duct.

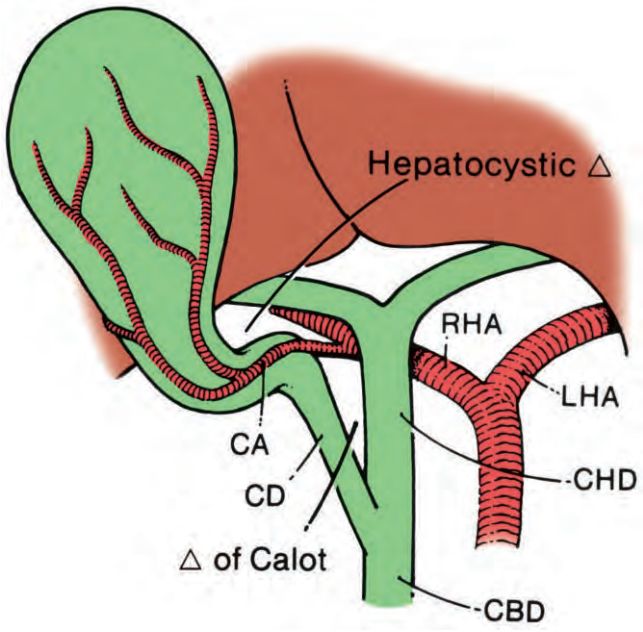

Figure 99–5. The triangle (Δ) of Calot and the hepatocystic triangle. The two triangles differ in their upper boundaries. The upper boundary of Calot's triangle is the cystic artery (CA), whereas that of the hepatocystic triangle is the inferior margin of the liver. CBD, common bile duct; CD, cystic duct; CHD, common hepatic duct; LHA, left hepatic artery; RHA, right hepatic artery. (From Skandalakis JE, Gray SW, Rowe JS Jr: Biliary tract. In Skandalakis JE, Gray SW [eds]: Anatomical Complications in General Surgery. New York, McGraw-Hill, 1983, p 31.)

Aberrant or accessory hepatic ducts also may pass through Calot's triangle before joining the cystic duct or common hepatic duct. During performance of a cholecystectomy, clear visualization of the hepatocystic triangle is essential with accurate identification of all structures within this triangle.

Sphincter of Oddi

The entire sphincteric system of the distal bile duct and the pancreatic duct is commonly referred to as the *sphincter of Oddi*. This term is imprecise because the sphincter is subdivided into several sections and contains both circular and longitudinal fibers. The sphincter mechanism functions independently from the surrounding duodenal musculature and has separate sphincters for the distal bile duct, the pancreatic duct, and the ampulla. In more than 90% of the population, the common channel, where the biliary and pancreatic ducts join, is less than 1.0 cm in length and lies within the ampulla. In the rare situation in which the common channel is longer than 1.0 cm or the biliary and pancreatic ducts open separately into the duodenum, pathologic biliary or pancreatic problems are likely to develop. The entire sphincter mechanism is actually composed of four sphincters

Figure 99–6. Human choledochoduodenal junction at the terminal portion of the common bile duct and pancreatic ducts. (From Boyden EA: The anatomy of the choledochoduodenal junction in man. Surg Gynecol Obstet 104:646, 1957.)

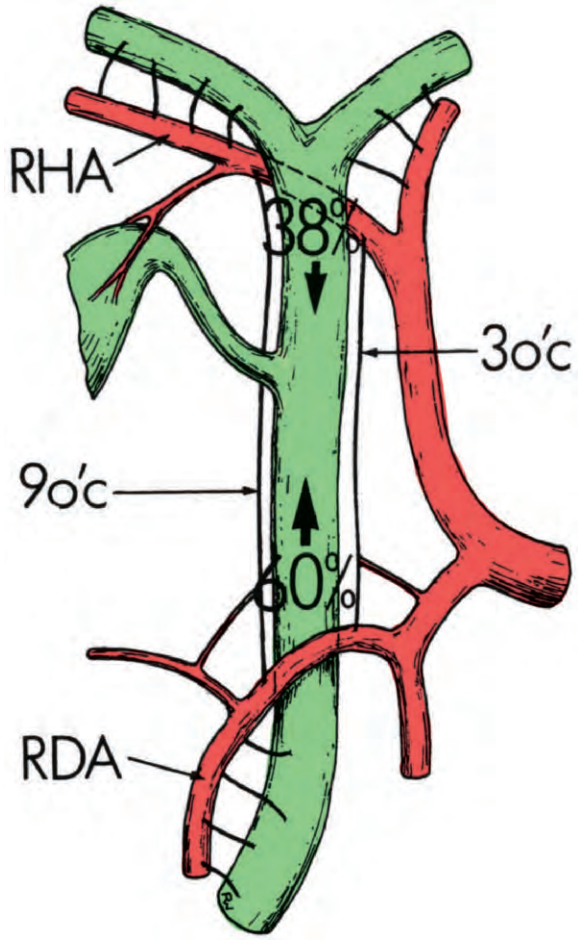

Figure 99–7. Arterial blood supply of the extrahepatic biliary tree. The proximal or hilar ducts and the retropancreatic bile duct receive a rich blood supply. The supraduodenal bile duct supply is axial and tenuous, with 60% from below and 38% from above. The small axial vessels (3 o'clock [3o'c] and 9 o'clock [9o'c] arteries) are vulnerable and easily damaged. RDA, retroduodenal artery; RHA, right hepatic artery. (From Terblanche J, Allison HF, Northover JMA: An ischemic basis for biliary strictures. Surgery 94:56, 1983.)

containing both circular and longitudinal smooth muscle fibers (Fig. 99–6). The four sphincters are the superior and inferior sphincter choledochus, the sphincter pancreaticus, and the sphincter of the ampulla.[9]

Vascular

The blood supply to the right and left hepatic ducts and upper portion of the common hepatic duct is from the cystic artery and the right and left hepatic arteries. The supraduodenal bile duct is supplied by arterial branches from the right hepatic, cystic, posterior superior pancreaticoduodenal, and retroduodenal arteries. The axial blood supply of the supraduodenal bile duct has been emphasized by Terblanche and colleagues (Fig. 99–7).[10] The most important arteries to the supraduodenal bile duct run parallel to the duct at the 3- and 9-o'clock positions. Approximately 60% of the blood supply to the supraduodenal bile duct originates inferiorly from the pancreaticoduodenal and retroduodenal arteries, whereas 38% of the blood supply originates superiorly from the right hepatic artery and cystic duct artery. Injury to this important axial blood supply may result in the formation of an ischemic ductal stricture. Only 2% of the arterial blood supply to the supraduodenal bile duct is segmental (nonaxial). These small segmental arterial branches arise directly from the proper hepatic artery as it ascends in the hepatoduodenal ligament, adjacent to the common bile duct. The blood supply to the retro-

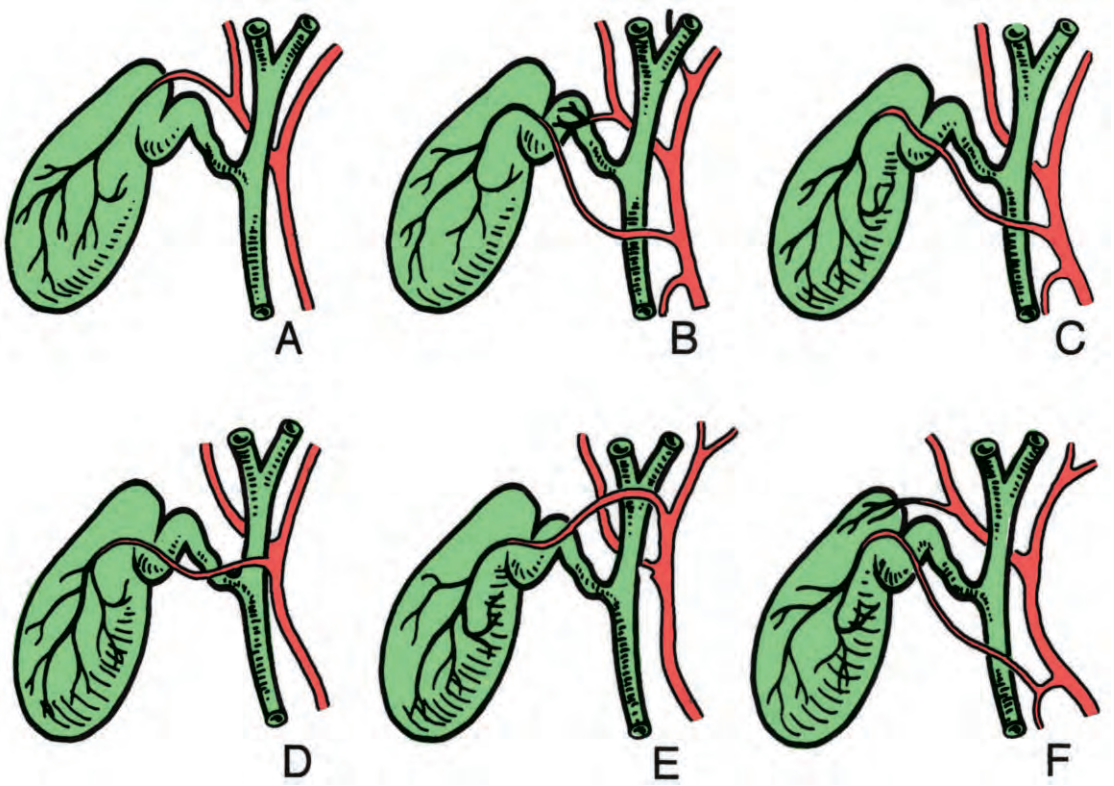

Figure 99–8. Cystic artery and its variations. **A,** Usual origin and course of the cystic artery. **B,** Double cystic artery. **C,** Cystic artery crossing anterior to main bile duct. **D,** Cystic artery originating from the right branch of the hepatic artery and crossing the common hepatic duct anteriorly. **E,** Cystic artery originating from the left branch of the hepatic artery. **F,** Cystic artery originating from the gastroduodenal artery. (**A-F,** From Smadja C, Blumgart LH: The biliary tract and the anatomy of biliary exposure. In Blumgart LH [ed]: Surgery of the Liver and Biliary Tract. Edinburgh, Churchill Livingstone, 1988, p 16.)

duodenal and intrapancreatic bile duct is from the retroduodenal and pancreaticoduodenal arteries.

The cystic artery usually arises as a single branch from the right hepatic artery within Calot's triangle (Fig. 99–8).[11,12] Infrequently, the cystic artery may arise from the left hepatic, common hepatic, gastroduodenal, or superior mesenteric artery.[13] When the cystic artery arises from the right hepatic artery, it usually courses parallel, adjacent, and medial to the cystic duct. This relation is far from constant, however; and if the artery arises from the proximal right hepatic artery or from the common hepatic artery, it may lie close to the hepatic duct, which may be injured when the artery is ligated.

As it crosses Calot's triangle, the cystic artery often supplies the cystic duct with one or more small arterial branches. Near the gallbladder, the cystic artery usually divides into a superficial branch and a deep branch. The superficial branch of the cystic artery courses along the anterior surface of the gallbladder, whereas the deep branch passes between the gallbladder and liver within the cystic fossa.

The right hepatic artery passes posterior to the common hepatic duct as it ascends to the liver in 85% of individuals and anterior to the common hepatic duct in the remaining 15%. In approximately 15% of individuals, a replaced or aberrant right hepatic artery originates from the superior mesenteric artery and courses through the medial aspect of Calot's triangle, posterior to the cystic duct.

The venous drainage from the hepatic ducts and hepatic surface of the gallbladder is through small vessels that empty into branches of the hepatic veins within the liver. A small venous trunk ascending parallel to the portal vein receives veins draining the gallbladder and bile duct before entering the liver, separate from the portal vein.[3] Venous drainage of the lower portion of the bile duct is directly into the portal vein.

Lymphatic Drainage

Lymphatic vessels from the hepatic ducts and upper common bile duct drain into the hepatic lymph nodes, a chain of lymph nodes that follows the course of the hepatic artery to drain into the celiac lymph nodes. Lymph from the lower bile duct drains into the lower hepatic nodes as well as the upper pancreatic lymph nodes. Lymphatic vessels from the gallbladder and cystic

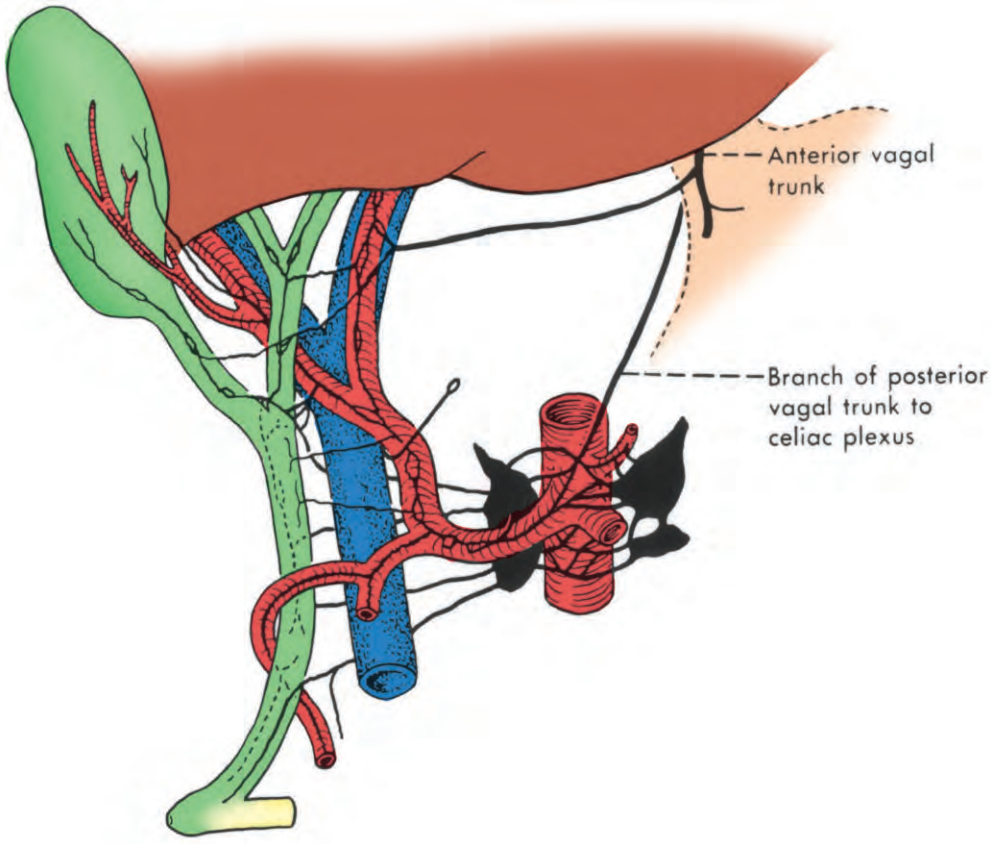

Figure 99–9. Nerve supply to the extrahepatic bile tree. (From Linder HH: Embryology and anatomy of the biliary tree. In Way LW, Pellegrini CA [eds]: Surgery of the Gallbladder and Bile Ducts. Philadelphia, WB Saunders, 1987, p 21.)

duct drain primarily into the hepatic nodes by way of the cystic duct node, a constant lymph node located at the junction of the cystic duct and common hepatic duct. Lymphatic vessels from the hepatic surface of the gallbladder may also communicate with lymphatic vessels within the liver.

Neural Innervation

The gallbladder and biliary tree receive sympathetic and parasympathetic nerve fibers that are derived from the celiac plexus and course along the hepatic artery (Fig. 99–9). The left (anterior) vagal trunk branches into hepatic and gastric components. The hepatic branch supplies fibers to the gallbladder, bile duct, and liver. Sympathetic fibers originating from the 5th to the 9th thoracic segments pass through the greater splanchnic nerves to the celiac ganglion. Postganglionic sympathetic fibers travel along the hepatic artery to innervate the gallbladder, bile duct, and liver. Visceral afferent nerve fibers from the liver, gallbladder, and bile duct travel with sympathetic afferent fibers through the greater splanchnic nerves to enter the dorsal roots of the 5th through 9th thoracic segments. Sensory fibers from the right phrenic nerve also innervate the gallbladder, presumably through the communications between the phrenic plexus and the celiac plexus. This innervation may explain the phenomenon of referred shoulder pain in patients with gallbladder disease.

ANOMALIES

Biliary Ducts

The anatomy of the extrahepatic biliary tree is highly variable. A thorough knowledge of this variable anatomy is important because failure to recognize the frequent anatomic variations may result in significant ductal injury. Anomalies of the extrahepatic biliary tree may involve the hepatic ducts, common bile duct, or cystic duct.

Hepatic Ducts In 57% to 68% of patients, the right anterior and right posterior intrahepatic ducts join, and the right hepatic duct unites with the left hepatic duct to form the common hepatic duct (Fig. 99–10).[2,14,15] Three other common variations are recognized. In 12% to 18% of patients, the right anterior, right posterior, and left hepatic ducts unite to form the common hepatic duct. In 8% to 20% of patients, the right posterior and left hepatic ducts join to form the common hepatic duct, and the right anterior duct joins below the union. In 4% to 7% of patients, the right posterior duct joins the common hepatic duct below the union of the right anterior and the left hepatic ducts. In 1.5% to 3% of patients, the cystic duct joins at the union of all the ducts or with one of the right hepatic ducts.

Accessory hepatic ducts may emerge from the liver to join the right hepatic duct, common hepatic duct, cystic duct, common bile duct, or gallbladder (Fig. 99–11).

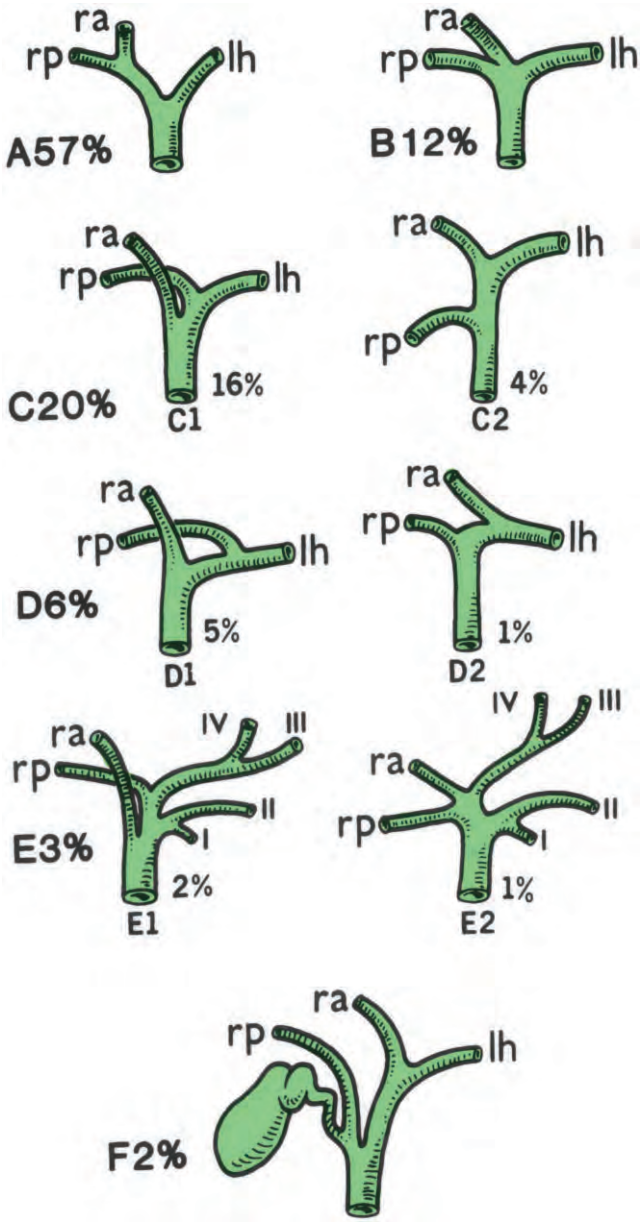

Figure 99–10. **A** to **F,** Variations in hepatic ducts and hepatic duct bifurcation. lh, left hepatic duct; ra, right anterior segmental duct; rp, right posterior segmental duct. The Roman numerals I to IV refer to hepatic segmental ducts. (**A-F,** From Smadja C, Blumgart LH: The biliary tract and the anatomy of biliary exposure. In Blumgart LH [ed]: Surgery of the Liver and Biliary Tract. Edinburgh, Churchill Livingstone, 1988, p 17.)

These ducts are present in approximately 10% of individuals. Although accessory hepatic ducts may approach the size of a normal cystic duct, they are often delicate, thin structures that may easily be overlooked. Accessory hepatic ducts often course through Calot's triangle and may be injured during dissection in this area. Cholecystohepatic ducts are small biliary ducts that emerge from the liver to enter the hepatic surface of the gallbladder directly.[16] If a cholecystohepatic duct is discovered during dissection of the gallbladder from the cystic fossa, it should be ligated to avoid a postoperative bile leak.

Common Bile Duct Malpositions or duplications of the common bile duct are rare anomalies. However, recognition of their presence is extremely important to prevent serious injury to the common bile duct during operations on the biliary tract or stomach. Several variations of common bile duct malposition and duplication have been described: (1) a single duct opening into the pylorus or antrum; (2) a single duct opening into the gastric fundus; (3) a single duct entering the duodenum independently of the pancreatic duct; (4) two separate ducts entering the duodenum; (5) a bifurcating duct, with one branch entering the duodenum and the other branch entering the stomach; (6) a bifurcating duct with both branches entering the duodenum; and (7) a septate common bile duct, with two openings of the single duct into the duodenum. The mere presence of these anomalies does not produce symptoms, and their clinical importance rests solely on their recognition and on the avoidance of injury during an operation.

Cystic Duct In 1976, Benson and Page described five ductal anomalies of clinical significance to the surgeon during performance of a cholecystectomy.[11] Of these five anomalies, three involve abnormalities in the length, course, or insertion of the cystic duct into the common hepatic duct (see Fig. 99–11). The cystic duct may run parallel to the common hepatic duct for a variable distance, or it may spiral anterior or posterior to the common hepatic duct to form a left-sided union. Parallel cystic ducts occur in 15% of individuals, whereas spiral cystic ducts are found in approximately 8%. The parallel or spiral cystic duct may be normal in length or may course downward in the hepatoduodenal ligament for a considerable distance before forming a low union with the common hepatic duct. In both situations, the cystic duct is usually closely adhered to the common hepatic duct by a sheath of connective tissue.

The cystic duct may join the right hepatic duct or a right segmental duct. Less often, the cystic duct, right hepatic duct, and left hepatic duct may join at the same level to form a trifurcation. In these situations, the right hepatic duct may easily be mistaken for the cystic duct and may be inadvertently ligated and divided. Occasionally, the gallbladder may join the common hepatic duct with a short or virtually nonexistent cystic duct. During ligation of a short cystic duct, care must be taken not to compromise the lumen of the common bile duct.

Gallbladder

Some apparent anomalies are acquired, but most result from arrested or abnormal development at some stage of embryonic growth. These anomalies vary in their clinical significance: Some are only medical curiosities and require no attempt at correction, whereas others require surgical intervention. The gallbladder anomalies may be divided into three groups based on formation, number, and position (Box 99–1).

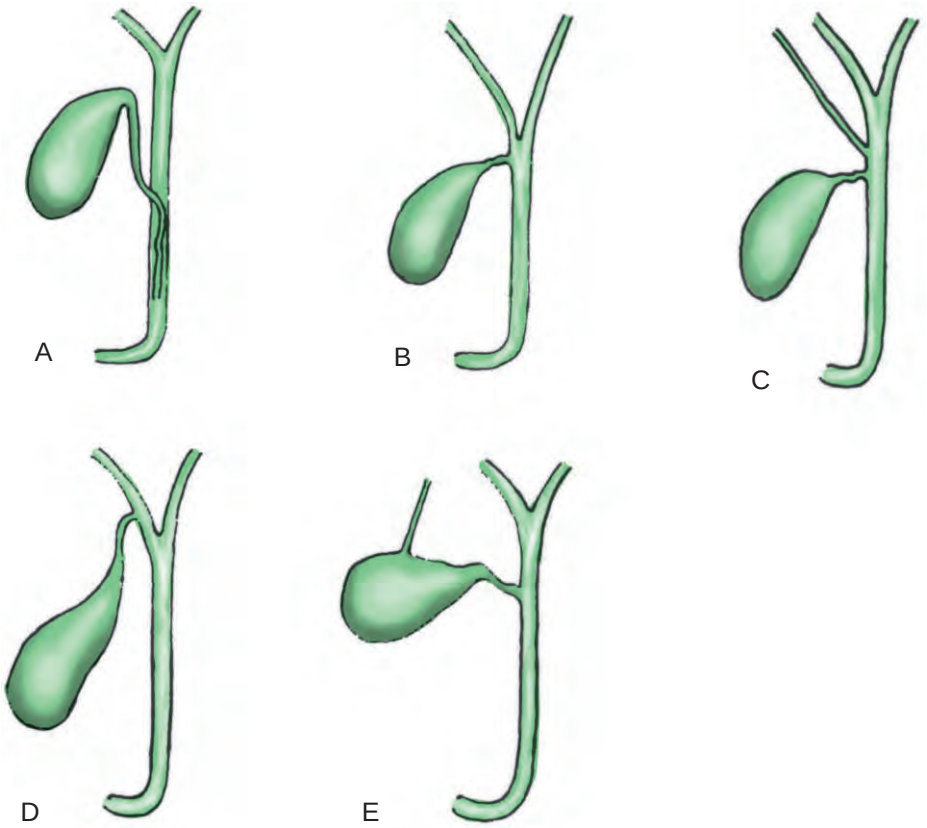

Figure 99–11. Duct anomalies. **A,** Long cystic duct with low fusion with common hepatic duct. **B,** Abnormally high fusion of cystic duct with common hepatic duct (trifurcation). **C,** Accessory hepatic duct. **D,** Cystic duct entering right hepatic duct. **E,** Cholecystohepatic duct. (**A-E,** From Benson EA, Page RE: A practical reappraisal of the anatomy of the extrahepatic bile ducts and arteries. Br J Surg 63:854, 1976.)

Box 99–1 Anomalies of the Gallbladder

Formation

- Phrygian cap
- Bilobed gallbladder
- Hourglass gallbladder
- Diverticulum of the gallbladder
- Rudimentary gallbladder

Number

- Absence of the gallbladder (agenesis)
- Duplication of the gallbladder

Position

- Floating gallbladder
- Intrahepatic gallbladder
- Left-sided gallbladder
- Transverse gallbladder
- Retrodisplaced gallbladder

Phrygian Cap This anomaly of formation is the most common of the gallbladder (Fig. 99–12A). Phrygian cap occurs in individuals of all ages and more commonly in women. Boyden found that this anomaly was present as confirmed by oral cholecystography in 18% of patients with a functioning gallbladder.[9] The phrygian cap deformity is created by an infolding of a septum between the body and the fundus. The gallbladder functions normally, and this anomaly is not an indication for cholecystectomy.

Bilobed Gallbladder This rare anomaly of formation consists of a completely divided gallbladder drained by a common cystic duct (Fig. 99–13A). Bilobed gallbladder occurs in two forms: (1) a type that has the outward appearance of a single gallbladder but is divided internally by a longitudinal fibrous septum; and (2) a type that has the outward appearance of two separate gallbladders that are fused at the neck. A bilobed gallbladder has no clinical significance and does not require excision unless it becomes symptomatic.

Hourglass Gallbladder Alterations in the contour of the gallbladder may result in a dumbbell or hourglass form (see Fig. 99–13B). These anomalies are not rare and can be congenital or acquired. In children, this anomaly is congenital and does not require removal. In adults, this abnormality usually results from chronic cholecystitis and should be removed.

Diverticulum of the Gallbladder Congenital diverticula of the gallbladder are rare, being found in only 25 of 29,701 gallbladders removed surgically at the Mayo Clinic (see Fig. 99–13C).[17] Diverticula may occur in any part of the gallbladder and may vary greatly in size from 0.5 to 9 cm in diameter. These diverticula are clinically

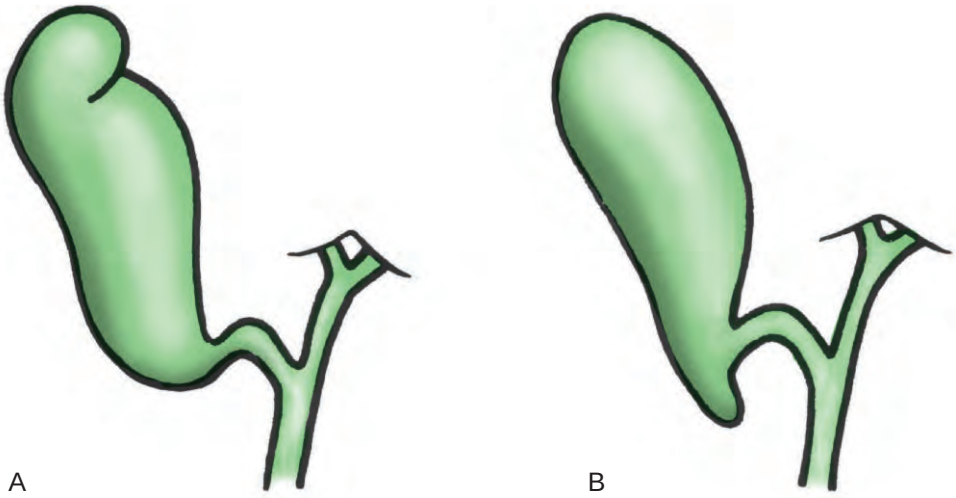

Figure 99–12. Deformations of the gallbladder. **A,** Phrygian cap deformity. **B,** Hartmann's pouch of the infundibulum. (From Gray SW, Skandalakis JE: Embryology for Surgeons. Philadelphia, WB Saunders, 1972, p 254.)

insignificant unless they become the site of disease, in which case they may contain stones, become acutely inflamed, or even perforate. Hartmann's pouch is an acquired diverticulum of the infundibulum or neck of the gallbladder (see Fig. 99–12B). This pouch projects from the convexity of the gallbladder neck and may be closely adherent to the common bile duct.[3] Hartmann's pouch is associated with pathologic conditions of the gallbladder, especially those involving prolonged obstruction to gallbladder emptying.[18]

Rudimentary Gallbladder This condition consists of a small nubbin at the end of the cystic duct. When found in infants and children, a rudimentary gallbladder is believed to be due to congenital hypoplasia and usually requires no treatment. In an elderly person, this situation may be the result of fibrosis from cholecystitis and may require removal.

Absence of the Gallbladder (Agenesis) More than 200 cases of absence of the gallbladder have been reported. Most cases are associated with other biliary abnormalities, and most of the patients die before 6 months of age. One publication reviewed 185 cases of gallbladder agenesis. In this series, 70 (38%) were completely absent, 60 (32%) were rudimentary, and 55 (30%) were a fibrous structure.[19]

Duplication This anomaly occurs in approximately 1 in 4000 persons. A true duplicated gallbladder has two separate cavities, each drained by its own cystic duct and sometimes supplied by its own cystic artery (Fig. 99–14). Duplication occurs as one of two varieties: (1) the more common ductular type, in which each gallbladder has its own cystic duct that empties independently into the same or different parts of the extrahepatic biliary tree; and (2) a type in which the two ducts gradually merge into a common cystic duct before emptying into the common bile duct. The gallbladder itself may be seen as two distinct organs at variable distances apart or may outwardly have the appearance of a single organ. Each cavity may function normally or become diseased independently of the other. Duplication of the gallbladder is clinically unimportant and generally requires no treatment.

Rarely, a gallbladder may be found in an abnormal location. This type of gallbladder requires no treatment unless it causes symptoms. Five different conditions are recognized: floating, intrahepatic, left-sided, transverse, and retrodisplaced.

Floating Gallbladder A floating gallbladder has been reported to occur in approximately 5% of persons. In this condition, the gallbladder is completely surrounded by peritoneum and is attached to the undersurface of the cystic fossa by the peritoneal reflection from the liver. This attachment may extend the entire length of the gallbladder, or it may include only the cystic duct, thus leaving the gallbladder unsupported and ptosed (Fig. 99–15A and B). This condition usually occurs in women older than 60 years of age. Such a gallbladder not only is subject to the same pathologic changes as a normally placed gallbladder but also may undergo torsion around its pedicle. Torsion of the gallbladder usually occurs in persons 60 to 80 years of age, but it has also been reported to occur in young children. When torsion of the gallbladder occurs, an abrupt onset of symptoms may include acute right upper quadrant abdominal pain, nausea, and vomiting. Torsion of the gallbladder requires operative detorsion and removal of the gallbladder, which may be infarcted as a result of occlusion of its blood vessels.

Intrahepatic Gallbladder The gallbladder is usually intrahepatic during its embryologic period and becomes extrahepatic later in its development. An intrahepatic gallbladder is one that is partially or completely embedded within the substance of the liver (see Fig. 99–15C). The condition may be suspected if the cholecystogram or ultrasound reveals a gallbladder in an unusually high location. In adults, approximately 60% of intrahepatic gallbladders are associated with gallstones. Most intrahepatic gallbladders are only partially embedded within the hepatic parenchyma, and they can usually be easily identified at the time of cholecystectomy. Those that are

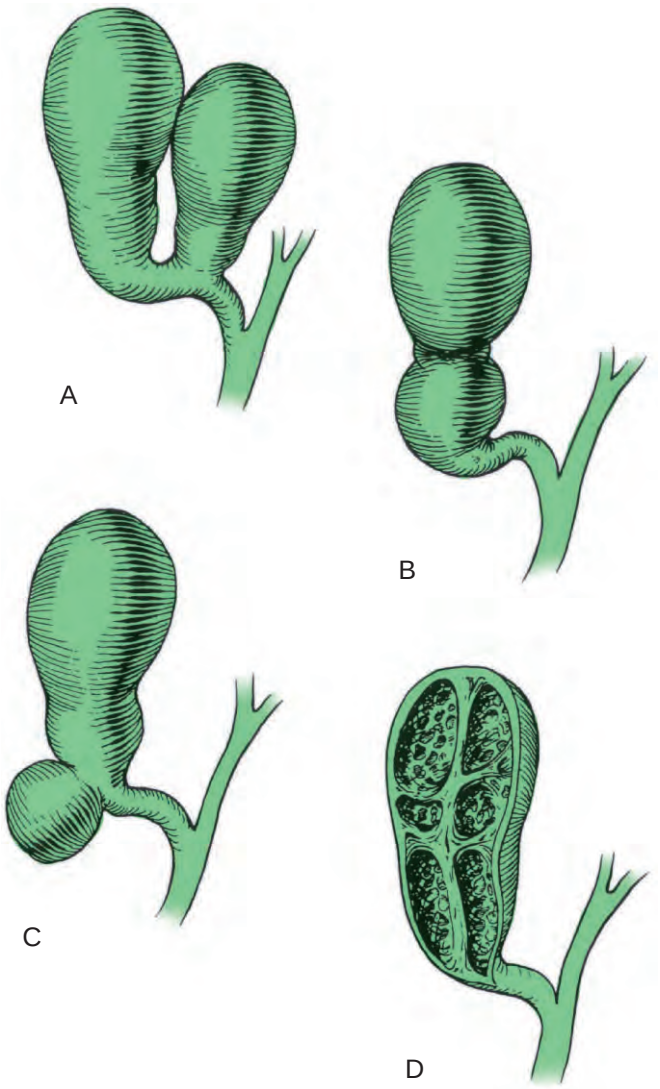

Figure 99–13. Anomalies of the gallbladder. **A,** Bilobed gallbladder. **B,** Hourglass gallbladder. **C,** Congenital diverticulum of the infundibulum. **D,** Septate gallbladder. (**A-D,** From Linder HH: Embryology and anatomy of the biliary tree. In Way LW, Pellegrini CA [eds]: Surgery of the Gallbladder and Bile Ducts. Philadelphia, WB Saunders, 1987, p 5.)

completely buried within the liver may be a challenge to remove. A completely embedded gallbladder is best approached by first identifying the cystic duct where it joins the common hepatic duct and then following the cystic duct back to the gallbladder.

Left-Sided Gallbladder The two types of left-sided gallbladders are (1) left-sided gallbladder associated with situs inversus, in which the heart and abdominal viscera are transposed from their usual position; and (2) the type in which the gallbladder alone is transposed. Both types of left-sided gallbladders are rare. The malpositioned gallbladder is usually located on the undersurface of the left lobe of the liver. In most instances, the cystic duct joins the common hepatic duct in the usual location, but it may occasionally join the left hepatic duct.

Transverse Gallbladder In this rare anomaly, the gallbladder is positioned horizontally in the transverse fissure of the liver. In these cases, the gallbladder is usually deeply embedded within the liver parenchyma.

Retrodisplaced Gallbladder Retrodisplacement of the gallbladder is a condition in which the organ is not situated in the gallbladder fossa but is bound to another portion of the liver or freely suspended from the liver with the fundus extending posteriorly. The retrodisplaced gallbladder may be partially or completely located within the retroperitoneum. This type of gallbladder may be difficult to expose and excise. If the gallbladder is located retroperitoneally, dividing the peritoneum overlying it will facilitate its removal.

Vascular

Variations in the arterial supply of the extrahepatic biliary tree are more common than variations in the ductal anatomy. Anatomic variations of the hepatic and cystic arteries are present in approximately 50% of individuals.[3,11,20] Based on their anatomic dissections, Benson and Page described three surgically important variations in the arterial anatomy (Fig. 99–16).[11] An accessory or double cystic artery occurs in approximately 15% to 20% of individuals.[11,21] These arteries usually arise from the right hepatic artery within Calot's triangle. Triple cystic arteries are unusual and occur in less than 1% of individuals. During dissection of Calot's triangle, care should be taken to exclude the presence of an accessory cystic artery.

In 5% to 15% of individuals, the right hepatic artery courses through Calot's triangle in close proximity to the cystic duct before turning upward to enter the hilum of the liver.[11,20] In this location, the cystic artery arises from the convex aspect of the angled or humped portion of the hepatic artery. This "caterpillar hump" right hepatic artery may easily be mistaken for the cystic artery and may be inadvertently ligated during performance of a cholecystectomy. The cystic artery that arises from the caterpillar hump is typically short and may easily be avulsed from the hepatic artery if excessive traction is applied to the gallbladder.[11]

The cystic artery may occasionally pass anterior to the common bile duct or common hepatic duct.[12] In this location, the cystic artery, rather than the cystic duct, is usually the first structure encountered during dissection of the lower border of Calot's triangle.[21,22] These arteries usually require ligation and division early in the dissection during a cholecystectomy, to provide adequate exposure of the cystic duct.

PHYSIOLOGY

Bile Production

Bile Formation The formation of bile by the hepatocyte serves two purposes. Bile represents the route of excretion for certain organic solutes, such as bilirubin and cholesterol, and it facilitates intestinal absorption of

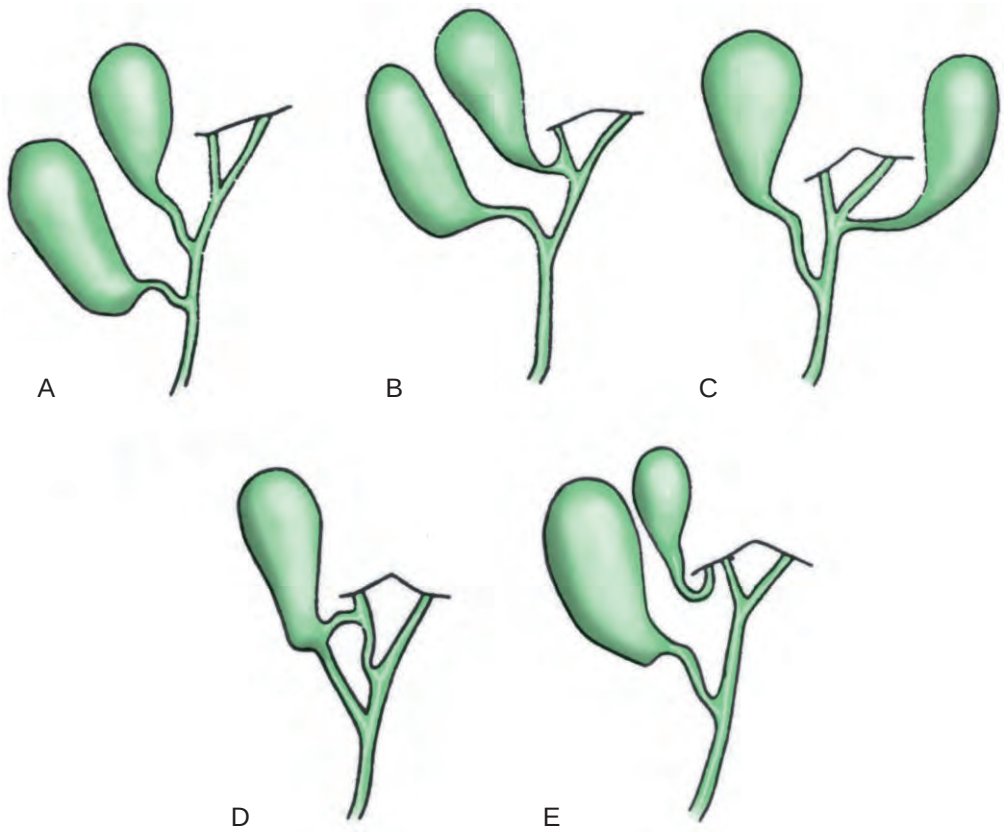

Figure 99–14. **A** to **E,** Duplication of the gallbladder. (**A-E,** From Glassman JA: A short practical review of surgical anatomy of the biliary tract. In Glassman JA [ed]: Biliary Tract Surgery: Tactics and Techniques. New York, Macmillan, 1989, p 18.)

lipids and fat-soluble vitamins. Bile secretion results from the active transport of solutes into the canaliculus followed by the passive flow of water. Water constitutes about 85% of the volume of bile.

The major organic solutes in bile are bilirubin, bile salts, phospholipids, and cholesterol. Bilirubin, the breakdown product of spent red blood cells, is conjugated with glucuronic acid by the hepatic enzyme glucuronyl transferase and is excreted actively into the adjacent canaliculus. Normally, a large reserve exists to handle excess bilirubin production, which might exist in hemolytic states. Bile salts are steroid molecules synthesized by the hepatocyte. The primary bile salts in humans, cholic and chenodeoxycholic acid, account for more than 80% of those produced. The primary bile salts, which are then conjugated with either taurine or glycine, can undergo bacterial alteration in the intestine to form the secondary bile salts, deoxycholate and lithocholate. The purpose of bile salts is to solubilize lipids and facilitate their absorption. Phospholipids are synthesized in the liver in conjunction with bile salt synthesis. Lecithin is the primary phospholipid in human bile, constituting more than 95% of its total. The final major solute of bile is cholesterol, which is also produced primarily by the liver with little contribution from dietary sources.

The normal volume of bile secreted daily by the liver is 500 to 1000 ml. Bile flow depends on neurogenic, humoral, and chemical control. Vagal stimulation increases bile secretion. Splanchnic stimulation causes vasoconstriction with decreased hepatic blood flow and, thus, diminished bile secretion. Gastrointestinal hormones including secretin, cholecystokinin, gastrin, and glucagon all increase bile flow, primarily by increasing water and electrolyte secretion. This action probably occurs at a site distal to the hepatocyte. Finally, the most important factor in regulating the volume of bile flow is the rate of bile salt synthesis by the hepatocyte. This rate is regulated by the return of bile salts to the liver by the enterohepatic circulation.

Cholesterol Saturation Cholesterol is highly nonpolar and insoluble in water; thus, it is insoluble in bile. The key to maintaining cholesterol in solution is the formation of micelles, a bile salt–phospholipid-cholesterol complex. Bile salts are amphipathic compounds containing both a hydrophilic and hydrophobic portion. In aqueous solutions, bile salts are oriented with the hydrophilic portion outward. Phospholipids are incorporated into the micellar structure, allowing cholesterol to be added to the hydrophobic central portion of the micelle. In this way, cholesterol can be maintained in solution in an aqueous medium. The concept of mixed micelles as the only cholesterol carrier has been challenged by the demonstration that much of the biliary cholesterol exists in a vesicular form. Structurally, these vesicles are made up of lipid bilayers of cholesterol and phospholipids. In their simplest and smallest form, the vesicles are unilamellar, but an aggregation may take place, leading to multilamellar vesicles. Present theory suggests that in states of excess cholesterol production, these large vesicles may also exceed their capability to

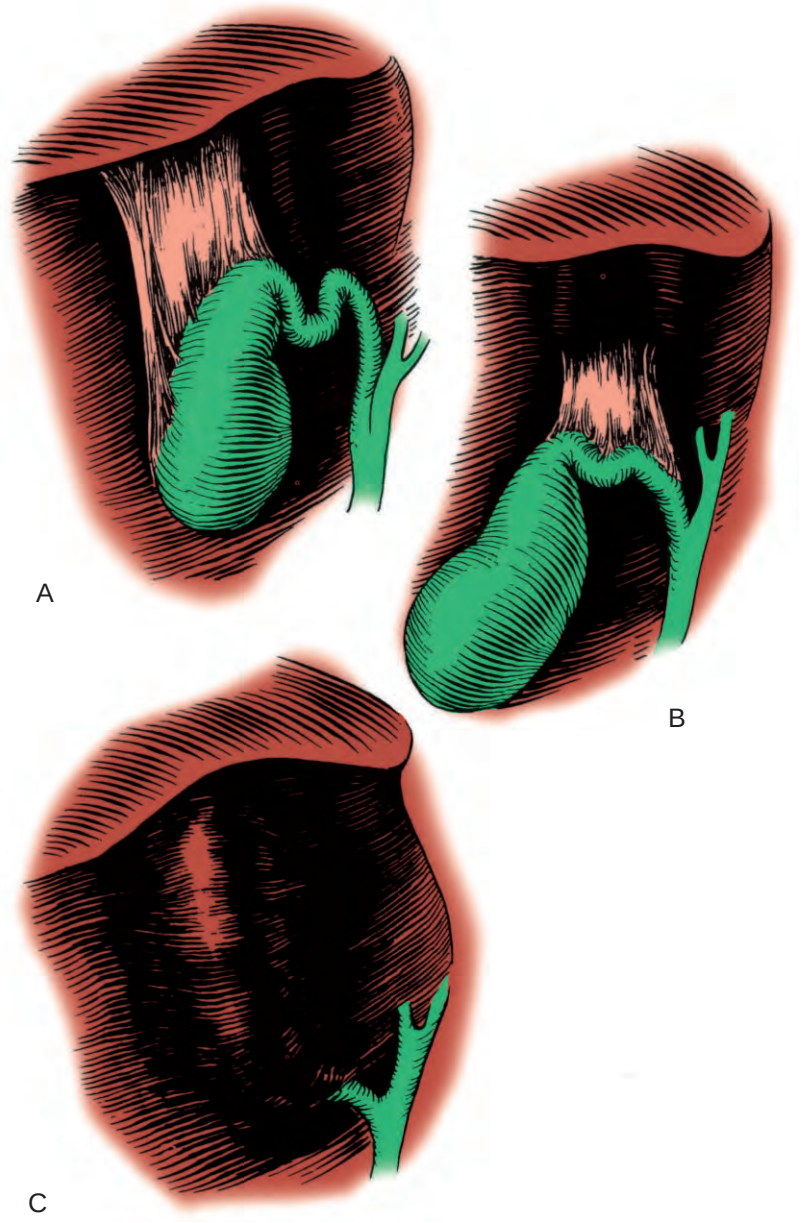

Figure 99–15. Anomalies of gallbladder position. **A,** Floating gallbladder with mesentery. **B,** Cystic duct with mesentery. **C,** Intrahepatic gallbladder. (**A-C,** From Linder HH: Embryology and anatomy of the biliary tree. In Way LW, Pellegrini CA [eds]: Surgery of the Gallbladder and Bile Ducts. Philadelphia, WB Saunders, 1987, p 5.)

transport cholesterol, and crystal precipitation may occur (Fig. 99–17).

Cholesterol solubility depends on the relative concentration of cholesterol, bile salts, and phospholipids.[23] By plotting the percentages of each component on triangular coordinates, the micellar zone in which cholesterol is completely soluble can be demonstrated (Fig. 99–18). In a solution composed of 10% solutes similar to bile, the area under the curve represents the concentration at which cholesterol is maintained in solution. In the area above the curve, bile is supersaturated with cholesterol, and precipitation of cholesterol crystals can occur.

A mathematical model of cholesterol solubility has been developed and is influenced by the relative concentrations of lipid components and the total lipid composition.[24] A numerical value, known as the *cholesterol saturation* (or lithogenic) *index,* is derived that expresses the relative degrees of cholesterol saturation. When the cholesterol saturation index is greater than 1.0, the solution is supersaturated with cholesterol. Changes in the relative concentrations of bile salts, cholesterol, or phospholipids alter the capacity of micelles, thus changing the solution's cholesterol saturation index (see Fig. 99–18).

Enterohepatic Circulation Bile salts are synthesized and conjugated in the liver, secreted into bile, stored temporarily in the gallbladder, passed from the gallbladder into the duodenum, absorbed throughout the small intestine but especially in the ileum, and returned to the liver via the portal vein. This cycling of bile acids between the liver and the intestine is referred to as the *enterohepatic circulation* (Fig. 99–19). The total amount of bile acids in the enterohepatic circulation is defined as the circulating bile pool. In this highly efficient system, nearly 95% of bile salts are reabsorbed. Thus, of the total bile salt pool of 2 to 4 g, which recycles through the

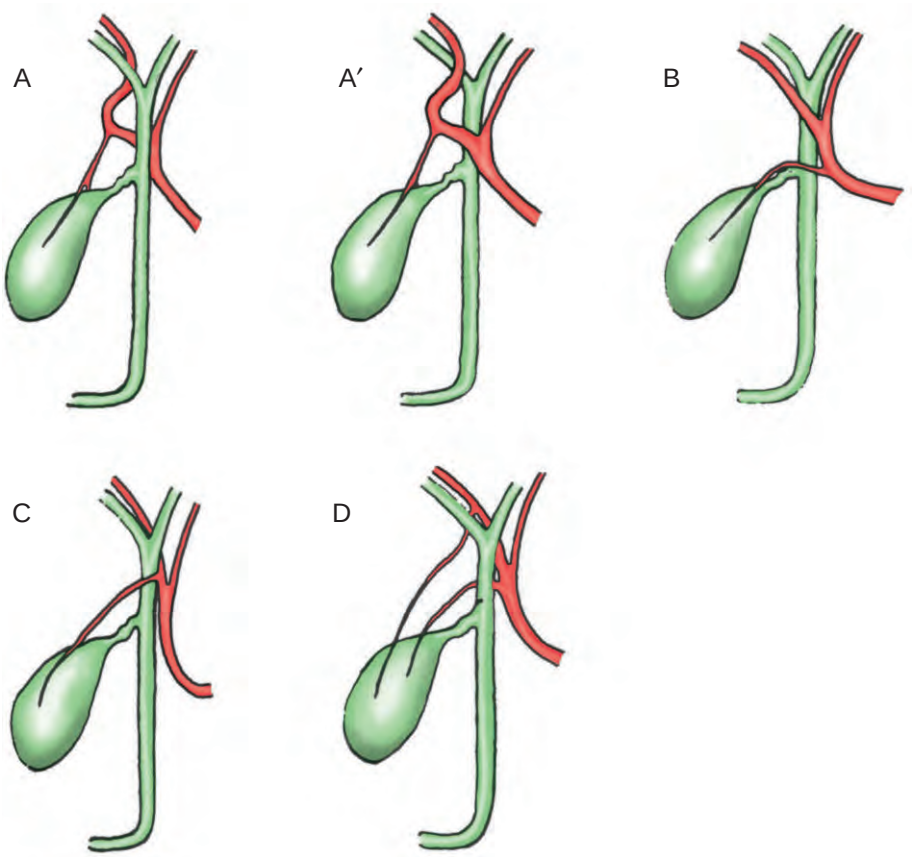

Figure 99–16. Vascular anomalies. **A, A′**, "Caterpillar hump" right hepatic artery. **B,** Right hepatic artery anterior to common hepatic (or common bile) duct. **C,** Cystic artery anterior to common hepatic (or common bile) duct. **D,** Accessory cystic artery. (**A-D,** From Benson EA, Page RE: A practical reappraisal of the anatomy of the extrahepatic bile ducts and arteries. Br J Surg 63:854, 1976.)

enterohepatic cycle 6 to 10 times daily, only about 600 mg of bile salt is actually excreted into the colon. Bacterial action in the colon on the two primary bile salts, cholate and chenodeoxycholate, results in the formation of the secondary bile salts, deoxycholate and lithocholate. Although some deoxycholate is reabsorbed passively by the colon, the remainder is lost in fecal waste.

The enterohepatic circulation provides an important negative feedback system on bile salt synthesis. Should the recirculation be interrupted by resection of the terminal ileum, or by primary ileal disease, abnormally large losses of bile salts can occur. This situation increases bile salt production to maintain a normal bile salt pool. Similarly, if bile salts are lost by an external biliary fistula, increased bile salt synthesis is necessary. However, except for those unusual circumstances in which excessive losses occur, bile salt synthesis matches losses, maintaining a constant bile salt pool size. During fasting approximately 90% of the bile acid pool is sequestered in the gallbladder.

Bilirubin Metabolism Heme, released at the time of degradation of senescent erythrocytes by the reticuloendothelial system, is the source of approximately 80% to 85% of the bilirubin produced daily. The remaining 15% to 20% is derived largely from the breakdown of hepatic hemoproteins.[25] Both enzymatic and nonenzymatic pathways for the formation of bilirubin have been proposed. Although both may be important physiologically, the microsomal enzyme heme oxygenase, found in high concentration throughout the liver, spleen, and bone marrow, plays a major role in the initial conversion of heme to biliverdin. Biliverdin is then reduced to bilirubin by the cytosolic enzyme biliverdin reductase in an NADH-dependent reaction before being released into the circulation. In this "unconjugated" form, bilirubin has a very low solubility. Bilirubin is bound avidly to plasma proteins, primarily albumin, before uptake and further processing by the liver. The liver is the sole organ capable of removing the albumin-bilirubin complex from the circulation and esterifying the potentially toxic bilirubin to water-soluble, nontoxic monoconjugated and deconjugated derivatives. Conjugated bilirubin is then excreted into the duodenum.

Bile Flow

The bile ducts, gallbladder, and sphincter of Oddi act in concert to modify, store, and regulate the flow of bile. Approximately 600 to 750 ml of bile is produced daily. During its passage through the bile ductules, canalicular bile is modified by the absorption and secretion of electrolytes and water. The gastrointestinal hormone, secretin, increases bile flow primarily by increasing the active secretion of chloride-rich fluid by the bile ducts. Bile ductular secretion is also stimulated by other hormones such as cholecystokinin and gastrin. The bile duct epithelium is also capable of water and electrolyte absorption, which may be of primary importance in the

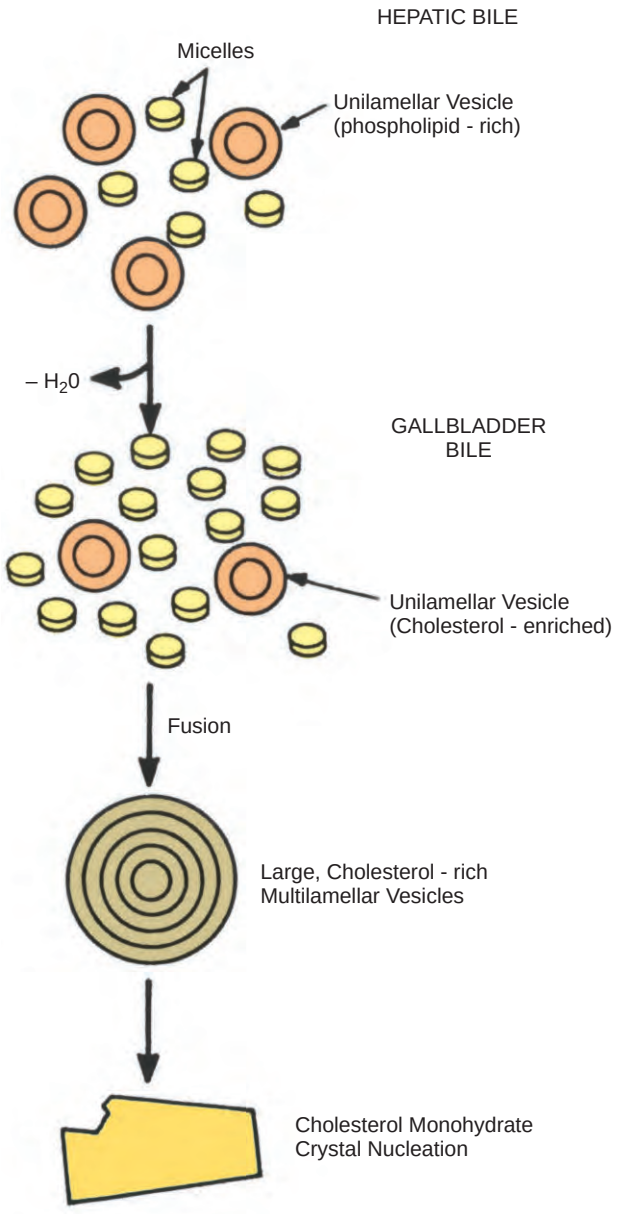

Figure 99–17. Concentration of bile leads to net transfer of phospholipids and cholesterol from vesicles to micelles. Phospholipids are transferred more efficiently than cholesterol, leading to cholesterol enrichment of the remaining (remodeled) vesicles. Aggregation of these cholesterol-rich vesicles forms multilamellar liquid crystals of cholesterol monohydrate. (From Vessey DA: Metabolism of drugs and toxins by the human liver. In Zakin D, Boyer TD [eds]: Hepatology: A Textbook of Liver Disease, 2nd ed. Philadelphia: WB Saunders, 1990, p 1492.)

storage of bile during fasting in patients who have previously undergone cholecystectomy. The main functions of the gallbladder are to concentrate and store hepatic bile during the fasting state and deliver bile into the duodenum in response to a meal. The usual capacity of the human gallbladder is about 40 to 50 ml. Only a small fraction of the 600 to 750 ml of bile produced each day would be stored were it not for its remarkable absorptive capacity. The gallbladder mucosa has the greatest absorptive capacity per unit of any structure in the body.

Table 99–1 Composition of Hepatic and Gallbladder Bile

Characteristics*	Hepatic Bile	Gallbladder Bile
Na	160	270
K	5	10
Cl	90	15
HCO_3	45	10
Ca	4	25
Mg	2	4
Bilirubin	1.5	15
Protein	150	200
Bile acids	50	150
Phospholipids	8	40
Cholesterol	4	18
Total solutes	—	125
pH	7.8	7.2

*All determinations are milliequivalents per liter, except for pH.

Bile Composition

Bile is usually concentrated 5-fold to 10-fold by the absorption of water and electrolytes leading to a marked change in bile composition (Table 99–1).[26] Active sodium chloride transport by the gallbladder epithelium is the driving force for the concentration of bile. Water is passively absorbed in response to the osmotic force generated by solute absorption. The concentration of bile may affect the solubilities of two important components of gallstones: cholesterol and calcium. Although the gallbladder mucosa does absorb calcium, this process is not nearly as efficient as for sodium or water, leading to a greater relative increase in calcium concentration. As the gallbladder bile becomes concentrated, several changes occur in the capacity of bile to solubilize cholesterol. The solubility in the micellar fraction is increased, but the stability of phospholipids-cholesterol vesicles is greatly decreased. Because cholesterol crystal precipitation occurs preferentially by vesicular rather than micellar mechanisms, the net effect of concentrating bile is an increased tendency to form cholesterol crystals.[26]

Gallbladder Function

The main function of the gallbladder is to concentrate and store hepatic bile during the fasting state, thus allowing for its coordinated release in response to a meal. To serve this overall function, the gallbladder has absorptive, secretory, and motor capabilities. As a result of active absorption, the gallbladder stores concentrated bile that

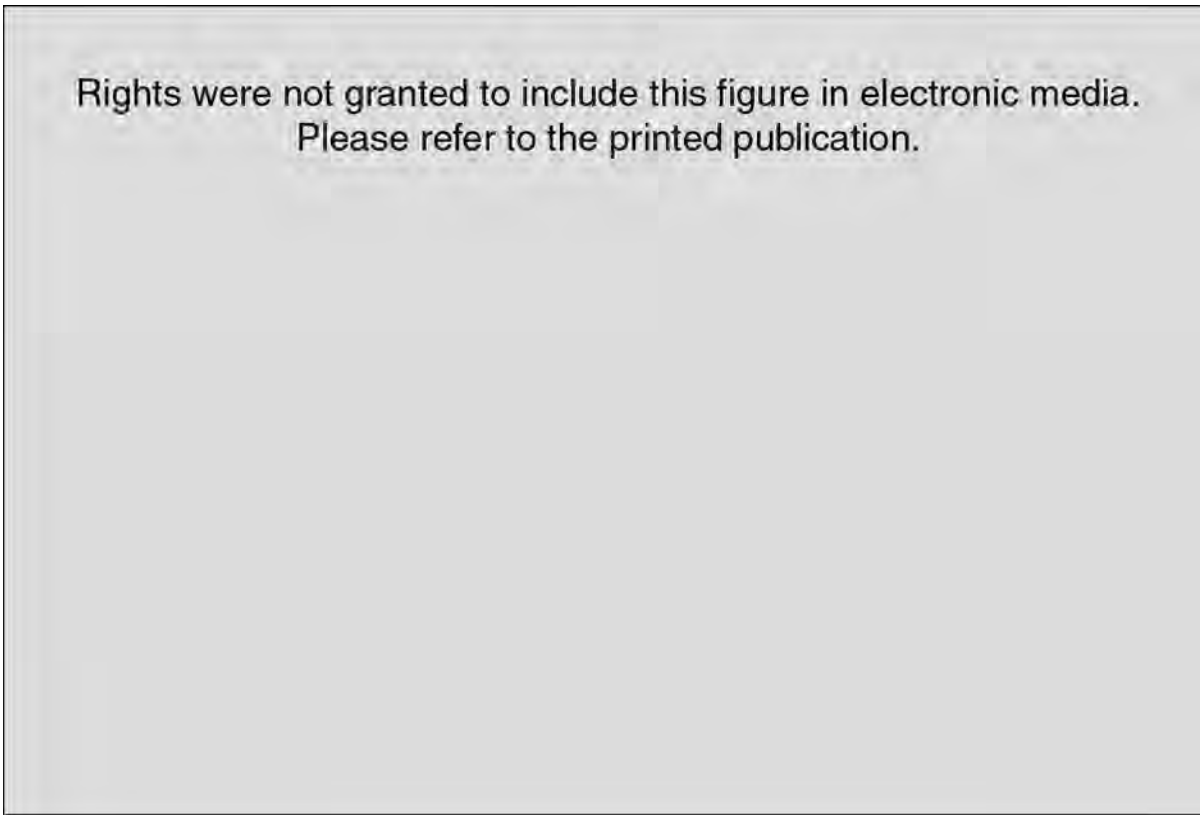

Figure 99–18. Interrelationships of bile salts, lecithin, and cholesterol. The graph is a plan taken from a tetrahedron at 90% water concentration. The tetrahedral plot is used to record the relationships of the four major constituents of bile: water, bile salts, lecithin, and cholesterol. The triangular coordinates can be divided into four zones, representing the physical state of the solutes in bile: crystals of cholesterol plus liquid (A); cholesterol crystals plus cholesterol liquid crystals plus liquid (B); liquid crystals plus liquid (C); and the micellar zone in which cholesterol is in water solution through the formation of cholesterol-lecithin-bile salt micelles (D). The solid line is the 10% solute line. (From Admirand WH, Small DM: The physicochemical basis of cholesterol gallstone formation in man. J Clin Invest 47:1043, 1968.)

re-enters the distal bile duct and is secreted into the duodenum in response to a meal. In addition to absorption and concentration, the gallbladder's mucosa actively secretes glycoproteins and hydrogen ions. Secretion of mucus glycoproteins occurs primarily from the glands of the gallbladder neck and cystic duct. The resultant mucin gel is believed to constitute an important part of the unstirred layer (diffusion-resistant barrier) that separates the gallbladder cell membrane from the luminal bile.[30,31] This mucus barrier may be very important in protecting the gallbladder epithelium form the strong detergent effect of the highly concentrated bile salts found in the gallbladder. However, considerable evidence also suggests that mucin glycoproteins play a role as a pronucleating agent for cholesterol crystallization. The transport of hydrogen ions by the gallbladder epithelium leads to a decrease in gallbladder bile pH through a sodium-exchange mechanism. Acidification of bile promotes calcium solubility, thereby preventing its precipitation as calcium salts. The gallbladder's normal acidification process lowers the pH of entering hepatic bile from 7.5 to 7.8 down to 7.1 to 7.3.[26,27]

Absorption The gallbladder's mucosa has the greatest absorptive capacity per unit of any structure in the body. Bile is usually concentrated fivefold by the absorption of water and electrolytes. Active Na-Cl transport by the gallbladder epithelium is the driving force for the concentration of bile (Fig. 99–20). Water is passively absorbed in response to the osmotic force generated by solute absorption. The concentration of bile may affect both calcium and cholesterol solubilities. The concentration of calcium in gallbladder bile, which is an important factor in gallstone pathogenesis, is influenced by serum calcium, hepatic bile calcium, gallbladder water absorption, and the concentration of organic substances such as bile salts in gallbladder bile.[28] Although the gallbladder mucosa does absorb calcium, this process is not nearly as efficient as for sodium or water.

As the gallbladder bile becomes concentrated, several changes occur in the bile's capacity to solubilize cholesterol. The solubility in the micellar fraction is increased, but the stability of phospholipids-cholesterol vesicles is greatly decreased. Because cholesterol crystal precipitation occurs preferentially by vesicular rather than

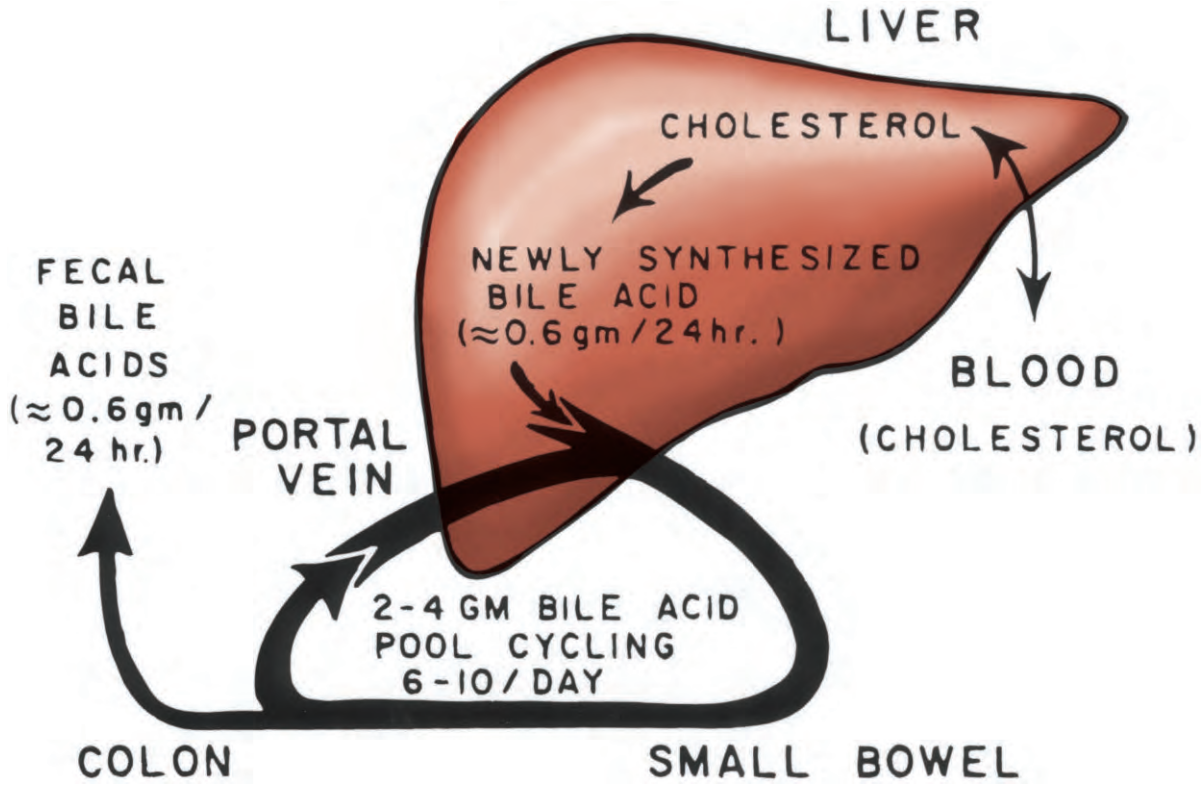

Figure 99–19. Enterohepatic circulation of bile salts. Cholesterol is taken up from plasma by the liver. Bile acids are synthesized at a rate of 0.6 g/24 hours and are excreted through the biliary system into the small bowel. Most of the bile salts are reabsorbed in the terminal ileum and are returned to the liver to be extracted and re-extracted. (Modified from Dietschy JM: The biology of bile acids. Arch Intern Med 130:472-474, 1972.)

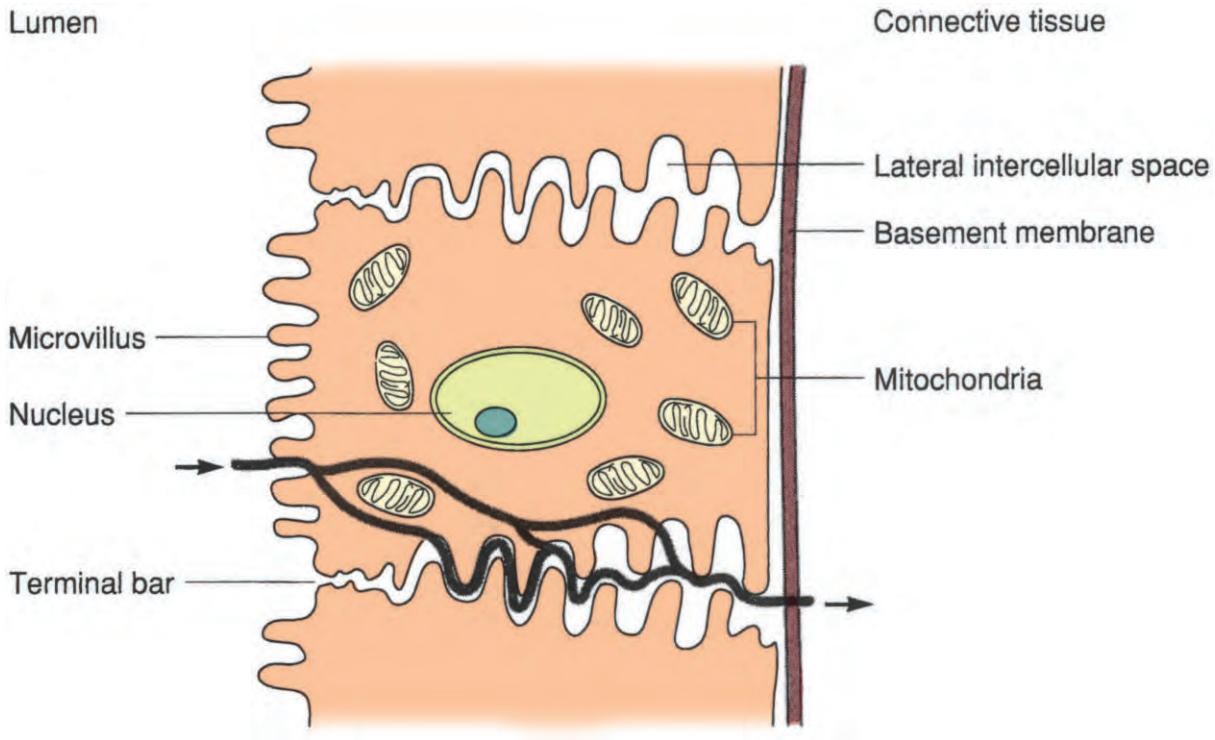

Figure 99–20. Cellular mechanisms of gallbladder mucosal absorption. The *arrows* indicate the route of water flow across the cell membrane and into the intercellular spaces. Sodium chloride is pumped into the intercellular space, and the result is a hypertonic environment. As water is transported into the space, the space distends and an isotonic solution enters the connective tissue space. (From Gadacz TR: Biliary anatomy and physiology. In Greenfield LJ, Mulholland MW, Oldham KT [eds]: Surgery: Scientific Principles and Practice. Philadelphia, JB Lippincott, 1993, p 935.)

micellar mechanisms, the net effect of concentrating bile is an increased tendency to nucleate cholesterol.[29] Absorption of organic compounds also occurs; lipid solubility is the major determinant of movement across the gallbladder mucosa. However, the absorption of bilirubin, cholesterol, phospholipids, and bile salts is minimal compared with that of water. Thus, these organic compounds are significantly concentrated by the normal absorptive process that occurs in the gallbladder. Unconjugated bile salts are absorbed more readily than conjugated bile salts and may actually damage the gallbladder's mucosa, causing a nonselective increase in absorption of other solutes. Thus, increased absorption of unconjugated bile salts, caused by bacterial deconjugation or mucosal inflammation, may impair cholesterol solubility and therefore promote cholesterol gallstone formation.

Secretion The gallbladder's epithelial cells secrete at least two important products into its lumen: glycoproteins and hydrogen ions. Prostaglandins play an important role as stimulants of gallbladder mucin secretion. Furthermore, mucin glycoproteins are key pronucleating agents for cholesterol crystallization.

The acidification of bile occurs by the transport of hydrogen ions by the gallbladder epithelium, probably through a sodium-exchange mechanism. Acidification of bile promotes calcium solubility, thereby preventing its precipitation as calcium salts. The gallbladder's normal acidification process lowers the pH of gallbladder bile, which normally varies from approximately 7.1 to 7.3. Compared with gallbladder bile, the bile secreted by the liver is slightly alkaline, pH 7.5 to 7.8, so that excess losses of hepatic bile may cause metabolic acidosis.

Motility Gallbladder filling is facilitated by tonic contraction of the ampullary sphincter, which maintains a constant pressure in the common bile duct (10 to 15 mm Hg). However, the gallbladder does not simply fill passively and continuously during fasting. Rather, periods of filling are punctuated by brief periods of partial emptying (10% to 15% of its volume) of concentrated gallbladder bile which are coordinated with each passage through the duodenum of phase III of the migrating myoelectric complex (MMC). This process is mediated, at least in part, by the hormone motilin.[32-34] Following a meal, the release of stored bile from the gallbladder requires a coordinated motor response of gallbladder contraction and sphincter of Oddi relaxation. One of the main stimuli to gallbladder emptying is the hormone, cholecystokinin, which is released from the duodenal mucosa in response to a meal. When stimulated by eating, the gallbladder empties 50% to 70% of its contents within 30 to 40 minutes. Gallbladder refilling then occurs gradually over the next 60 to 90 minutes. Many other hormonal and neural pathways are also necessary for the coordinated action of the gallbladder and sphincter of Oddi. Defects in gallbladder motility, which increase the residence time of bile in the gallbladder, play a central role in the pathogenesis of gallstones.[26]

Sphincter of Oddi

The human sphincter of Oddi is a complex structure that is functionally independent from the duodenal musculature. Endoscopic manometric studies have demonstrated that the human sphincter of Oddi creates a high-pressure zone between the bile duct and the duodenum (Fig. 99–21). The sphincter regulates the flow of bile and pancreatic juice into the duodenum and also prevents the regurgitation of duodenal contents into the biliary tract. These functions are achieved by keeping pressure within the bile and pancreatic ducts higher than duodenal pressure.[35] The sphincter of Oddi also has high-pressure phasic contractions, which may play a role in preventing the regurgitation of duodenal contents into the biliary tract.

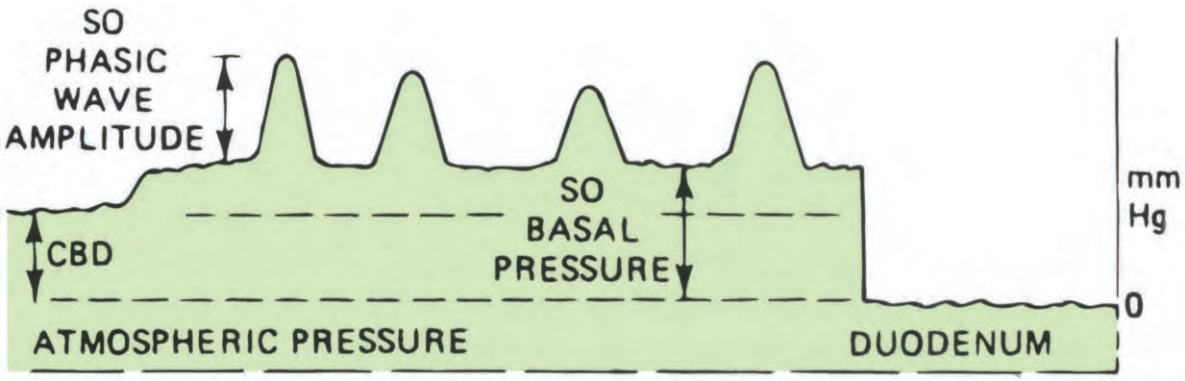

Figure 99–21. Sphincter of Oddi (SO) manometric pressure profile obtained by catheter pull-through from the common bile duct (CBD) into the duodenum. The CBD pressure and SO basal pressure are both referenced to duodenal pressure. SO phasic-wave amplitude was measured from basal SO pressure. The CBD-to-duodenal pressure gradient is indicated by the parallel broken lines. (From Geenen JE, Toouli J, Hogan WJ, et al: Endoscopic sphincterotomy: Follow-up evaluation of effects on the sphincter of Oddi. Gastroenterology 87:754-758, 1984.)

Both neural and hormonal factors influence the sphincter of Oddi. In humans, sphincter of Oddi pressure and phasic wave activity diminish in response to cholecystokinin. Thus, sphincter pressure relaxes after a meal, allowing the passive flow of bile into the duodenum. During fasting, high-pressure phasic contractions of the sphincter of Oddi persist though all phases of the MMC. However, recent animal studies suggest that sphincter of Oddi phasic waves do vary to some degree in concert with the MMC. Thus, sphincter of Oddi activity is undoubtedly coordinated with the partial gallbladder emptying and increases in bile flow that occur during phase III of the MMC. This activity may be a preventive mechanism against the accumulation of biliary crystals during fasting.[26]

Neurally mediated reflexes link the sphincter of Oddi with the gallbladder and stomach to coordinate the flow of bile and pancreatic juice into the duodenum. The cholecysto–sphincter of Oddi reflex allows the human sphincter to relax as the gallbladder contracts.[36] Similarly, antral distention causes both gallbladder contraction and sphincter relaxation.[37]

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Chapter

100

Imaging and Intervention in the Biliary System

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The purpose of this chapter is to familiarize the reader with imaging and intervention in the biliary system. Optimal management of patients with benign or malignant biliary disease requires a multidisciplinary approach frequently involving the primary care physician, surgeon, gastroenterologist, and interventional radiologist. A patient presenting with obstructive jaundice is evaluated clinically, and subsequent work-up and therapy may include diagnostic imaging and, in specific instances, biliary interventions. On completion of the chapter, the reader should have an understanding of (1) the noninvasive imaging techniques used in the management of patients with biliary disease and (2) the minimally invasive percutaneous techniques used to treat patients with biliary obstruction or injury.

We provide an overview of the role of imaging in patients with biliary disease to include the use of ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine. Regarding MRI, attention is directed toward the increasing role of magnetic resonance cholangiopancreatography (MRCP).

Following the imaging section, percutaneous techniques for management of patients with benign and malignant biliary disease are reviewed.

GENERAL APPROACH TO THE PATIENT WITH OBSTRUCTIVE JAUNDICE

A patient presenting with signs and symptoms of obstructive jaundice undergoes clinical evaluation and a diagnostic work-up. Included in the latter are laboratory data (i.e., blood studies) and imaging. The goals of imaging include the following:

1. Confirmation of the presence of obstructive jaundice using cross-sectional imaging (i.e., US, CT, or MRI)
2. Precisely defining biliary anatomy to determine the severity and the level of obstruction, using the techniques of MRCP (noninvasive); percutaneous transhepatic cholangiography (PTC or PTHC) and percutaneous biliary drainage (PBD or PTBD) (invasive); and endoscopic retrograde cholangiopancreatography (ERCP) (invasive)
3. Image-based assistance in the staging of malignant disease
4. Image-based guidance for possible nonsurgical therapy

IMAGING MODALITIES FOR THE BILIARY SYSTEM

Ultrasonography

US is a relatively inexpensive, noninvasive imaging modality used to confirm the presence of biliary ductal dilation (Fig. 100–1). US, when performed correctly, may provide considerable information to assist the internist, surgeon, gastroenterologist, or interventional radiologist in the management of patients with hepatobiliary disease.

Though operator dependent, US is generally readily available in most medical institutions caring for patients with biliary disease. The normal gallbladder is an anechoic (fluid-filled) oval structure.[1] The position of the gallbladder fundus is variable; however, the gallbladder neck has a fixed relationship with the main interlobar fissure of the liver. The wall of the gallbladder is a thin, smooth, echogenic line that should not exceed 3 mm. The gallbladder wall may appear abnormally thickened in the nonfasting state. Pathologic gallbladder wall thickening may be secondary to cholecystitis, hepatitis, hepatic failure, congestive heart failure, renal failure, neoplasm, or human immunodeficiency virus.

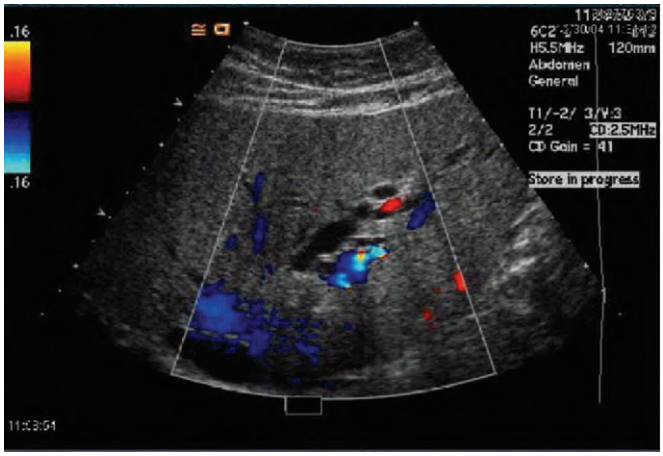

Figure 100–1. Color-flow Doppler image from a right upper quadrant ultrasonographic scan confirming intrahepatic biliary ductal dilation. The image shows dilated intrahepatic ducts adjacent to blood vessels (the latter demonstrating Doppler flow [color]). This adult patient presented with jaundice, weight loss, and fatigue. The patient had a hilar mass (not shown).

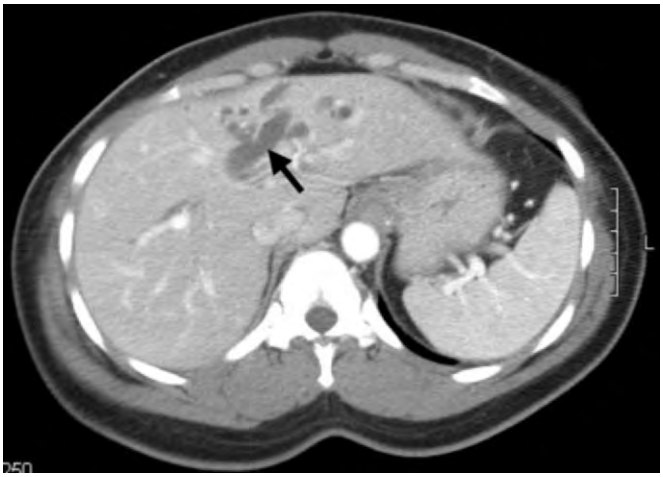

Figure 100–2. A 34-year-old woman with prior episodes of fevers, chills, elevated white blood cell count, and abnormal liver function tests. Axial helical CT scan of the abdomen with intravenous contrast shows intrahepatic biliary ductal dilation *(arrow),* especially in the left lobe of the liver. (The patient has intrahepatic cholelithiasis [see also Figs. 100–6 to 100–8]).

The common hepatic duct is easily visualized in the porta hepatis as it crosses the undivided right portal vein. In most cases, the hepatic artery passes between the common hepatic duct and portal vein; however, in 10% to 15% of patients, the hepatic artery is located anterior to the common hepatic duct. The joining of the cystic duct with the common hepatic duct forms the common bile duct. The cystic duct is generally located posterior to the common hepatic duct and may travel a variable distance before joining the common hepatic duct. Within the hepatoduodenal ligament, the common bile duct is anterior and lateral to the portal vein. As the common bile duct travels caudally to the second portion of the duodenum, it assumes a more posterior position.[1,2] On US, the normal diameter of the extrahepatic bile ducts may range from 4 to 8 mm.[3] The size of the extrahepatic bile ducts may increase slightly with increasing patient age, after cholecystectomy, or bile duct surgery, or after endoscopic manipulation of the duct. The maximum upper limit of normal in the extrahepatic biliary tree after cholecystectomy is 10 mm. However, it is generally accepted that a duct that measures 6 mm or greater in symptomatic patients warrants further investigation.[4]

Intrahepatic bile ducts can be considered normal if they are less than 40% of the diameter of the accompanying portal vein or if they are 2 mm or less in diameter.[2] Intrahepatic biliary dilation may appear as an alteration in the normal anatomic relationships in the portal triads and a confluence of tubular structures near the hilum of the liver. The appearance of peripheral intrahepatic duct dilation has been called the *parallel channel sign*.[5] Color-flow Doppler US is useful in this setting to confirm the presence of biliary dilation. Using color-flow Doppler US, one may differentiate between vessels and dilated biliary ducts. US accurately predicts the level of biliary obstruction in the majority of cases (92%), but it is less accurate in suggesting the correct cause (71%).[6]

There are many causes of biliary obstruction. These include stones, neoplasms, inflammatory disease, and congenital causes (rare). Newer noninvasive techniques include the use of tissue harmonic imaging to improve visualization of the bile ducts.[7] US coupled with the use of CT or MRCP to determine extent of disease assists the interventional radiologist, gastroenterologist, or surgeon in planning therapy.

Computed Tomography

In many institutions, the initial noninvasive imaging modality of choice for patients with suspected biliary obstruction is CT, specifically helical CT scanning (Fig. 100–2). The latter provides rapid imaging. The disadvantages include (1) the requirement for intravenous contrast administration (not always possible in patients with renal dysfunction), (2) the use of ionizing radiation, and (3) additional cost as compared to US.

CT scanning is less "operator dependent" than US. Thus, it is reproducible and studies are easily compared. It is therefore important for follow-up after biliary surgical or interventional procedures. When correctly performed, CT provides valuable information not only of the intrahepatic and extrahepatic bile ducts but also of structures outside the biliary system (e.g., liver parenchyma, adjacent lymph nodes, the presence of choledocholithiasis, neoplasms).

To optimize biliary tract imaging with helical CT, a 3- to 5-mm collimated scan (pitch 1:1) should be performed from the porta hepatis through the pancreatic head during the portal venous phase of contrast enhancement.[8] Overlapping axial reconstructions of the

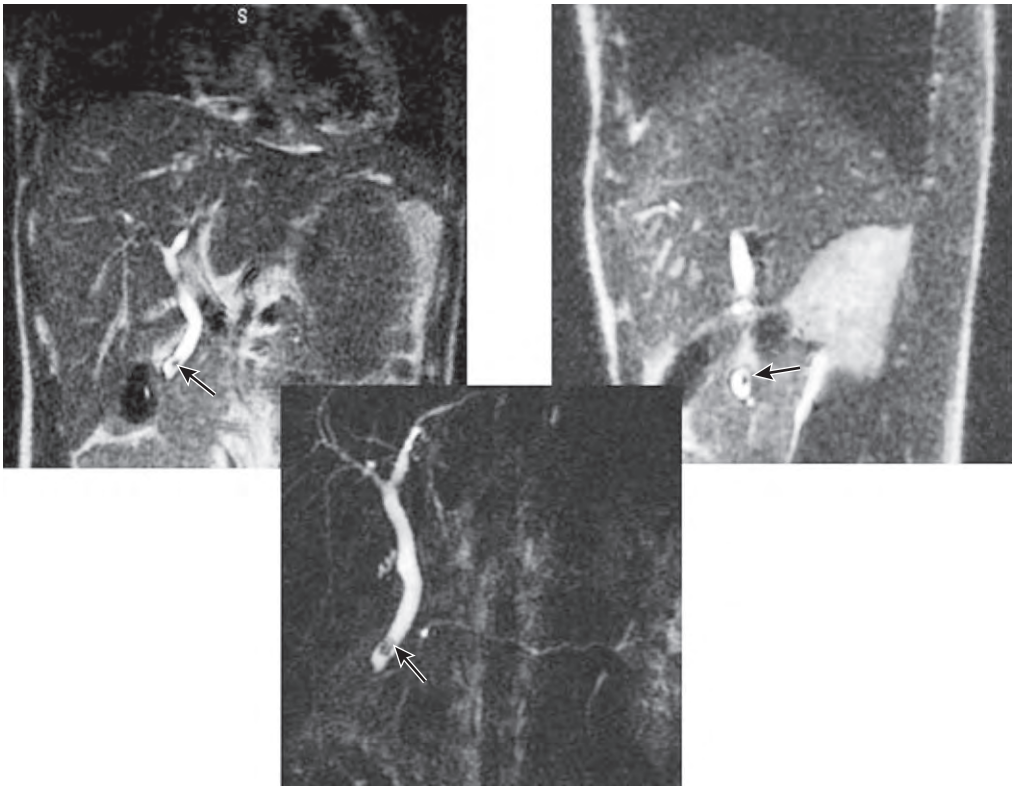

Figure 100–3. Composite image of an adult patient with a distal common bile duct stone *(arrow).* Magnetic resonance cholangiopancreatography uses heavily T2-weighted multiplanar imaging and provides a noninvasive means of defining biliary anatomy. (Courtesy of Michael C. Hill, MB, George Washington University Medical Center, Washington, D.C.).

helical acquisition can aid interpretation. The extrahepatic bile duct is typically visualized throughout its entire course in the hepatoduodenal ligament as a water-density tubular structure. At the level of the pancreatic head, the distal common bile duct has a round or oval configuration. Although normal intrahepatic bile ducts can occasionally be seen with current CT technology, it usually is not difficult to differentiate normal intrahepatic bile ducts from true dilated ducts. Normal intrahepatic ducts should be less than 2 mm and not confluent.[8]

Multidetector CT technology shortens acquisition time. This has the advantage of allowing single breath-hold imaging, which is important when scanning pediatric or critically ill patients. Multidetector CT also allows the ability to obtain a three-dimensional data set, which enables image reconstruction for CT angiography and cholangiography.[1]

Magnetic Resonance Imaging

Perhaps the most significant contribution in the use of noninvasive imaging for management of patients with suspected biliary disease is MRI. MRCP has played an increasing role in the evaluation of such patients (Fig. 100–3). In fact, accurately performed MRCP has, in many institutions, replaced conventional ERCP or PTC (or PTHC).

Though more expensive than US or CT, MRCP is considered an accurate, noninvasive technique for evaluation of the biliary tract. MRCP uses heavily T2-weighted sequences to show bile ducts as high-signal-intensity structures. Many MRI techniques (i.e., pulse sequences) have been described to generate high-resolution images.[9-14] MRCP may be useful in the evaluation of congenital disorders and benign and malignant biliary obstruction and for patients with failed or incomplete ERCP or PTC.[13,15] This is a valuable noninvasive means to visualize the biliary tree before therapeutic intervention or surgery.[1]

Nuclear Medicine

A suspected traumatic injury to the biliary system may be confirmed using nuclear medicine scintigraphy (e.g., ^{99m}Tc- DISIDA scan). Confirmation of the presence of a biliary leak mobilizes the multidisciplinary team to rapidly manage the patient. In addition to confirming the presence of bile duct injury (i.e., leak), the technique may also prove useful in confirming the presence of gallbladder disease (Fig. 100–4), biliary obstruction, and so forth.

BILIARY INTERVENTIONS

Role of the Interventional Radiologist

As mentioned earlier, the interventional radiologist is frequently involved at multiple levels in the work-up of patients with biliary disease. A summary may include the following:

1. Precisely defining biliary anatomy to determine the severity and level of obstruction using percutaneous techniques (i.e., PTC or PTHC)

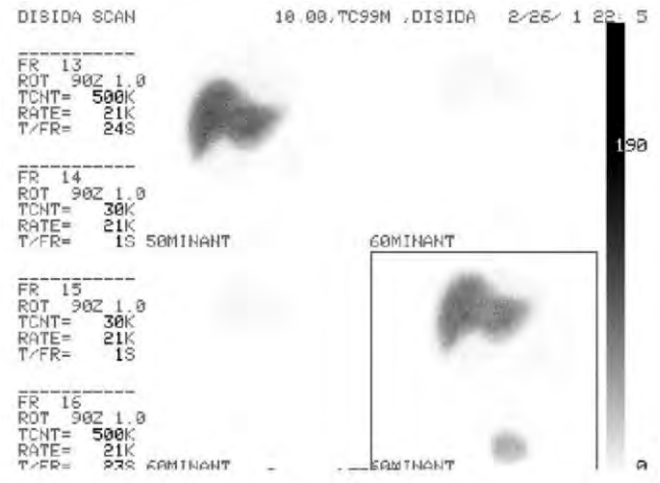

Figure 100–4. Nuclear medicine scintigraphy (DISIDA scan) confirming presence of cystic duct and common bile duct obstruction. There is no radiotracer in the gallbladder or bowel at 60 minutes after injection. There is a small amount of radiotracer in the bladder on the 60-minute image.

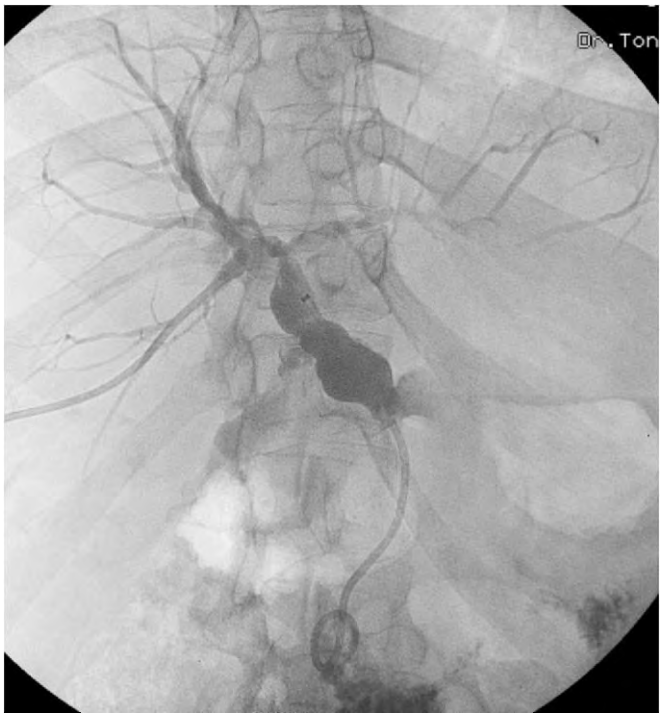

Figure 100–5. Right anterior oblique digital spot film after right mid-axillary percutaneous transhepatic biliary drainage (PBD or PTBD). This elderly woman presented with a clinical picture of obstructive jaundice and was found to have unresectable pancreatic carcinoma. This cholangiogram documents placement of a multi-side-hole biliary drainage catheter that is seen coursing from the peripheral right biliary ducts (intrahepatic ducts) to the duodenum.

2. Drainage of obstructed bile ducts (i.e., PTB or PTHB) (Fig. 100–5)
3. Obtaining tissue and/or bile to confirm a suspected diagnosis (i.e., percutaneous biopsy and/or bile sampling for cytopathology)
4. Percutaneous management of benign biliary strictures in those patients who are not good surgical candidates due to other comorbid disease (e.g., advanced cardiopulmonary disease)
5. Percutaneous management of patients with retained intrahepatic or extrahepatic biliary stones in those patients who cannot undergo ERCP (e.g. patients who have undergone biliary reconstructive surgery such as a Roux-en-Y loop or have stones located beyond the reach of the endoscope) (Figs. 100–6 to 100–8)
6. Palliative measures for patients with biliary malignancy to include deployment of biliary endoprostheses (Figs. 100–9 and 100–10)
7. Confirming the presence of a biliary leak or gallbladder obstruction using radionuclide hepatobiliary scintigraphy

In many institutions, after initial clinical, laboratory, and imaging evaluations, ERCP is generally the first minimally invasive procedure performed in patients with known biliary disease. This is especially true for patients with nondilated biliary ducts (e.g., patients with a suspected bile duct injury such as a leak after surgery or with sclerosing cholangitis).

In general, ERCP should be used in patients when the following conditions apply:

1. Intrahepatic bile ducts are nondilated.
2. The patient has an absolute contraindication to PTC/PBD (i.e., a coagulopathy that cannot be corrected).
3. The patient has a relative contraindication to PTC/PBD (i.e., ascites, polycystic liver disease).

PTC (often followed by PBD) should be performed when the following conditions apply:

1. When ERCP fails and the patient is symptomatic (e.g., obstruction with sepsis)
2. When the patient has had a prior biliary-enteric anastomosis (such surgical biliary reconstructions frequently prevent successful cannulation of the ampulla during ERCP)
3. If surgical resection of a tumor at the biliary confluence, is planned—PBD (often bilateral) is performed to relieve symptoms (i.e., to drain obstructed and potentially infected bile). In some centers, it is thought that the presurgical placement of percutaneously placed biliary drainage catheter(s) facilitates intraoperative biliary reconstruction and aids in the surgical creation of a biliary-enteric anastomosis(es).
4. In those patients who are not surgical candidates and who have known malignant tumors at the biliary confluence, bilateral PTC/PBD will allow palliative endoprosthesis placement.[16-29] The endo-

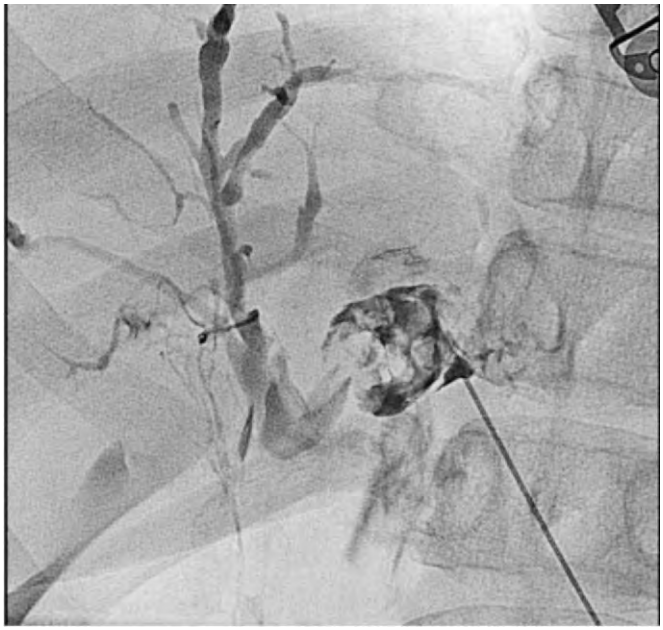

Figure 100–6. Digital spot film obtained during initial left percutaneous transhepatic cholangiogram (PTC) (subxiphoid approach). The skinny needle (21-gauge Trocar needle) partially opacifies a markedly dilated left biliary system that is filled with numerous stones. There is reflux of contrast into the right-sided bile ducts. These ducts are irregular in caliber and "pruned" (i.e., demonstrate a reduced branching pattern). Such findings are consistent with sclerosing cholangitis, in this case due to numerous episodes of sepsis (cholangitis) associated with the intrahepatic stones (same patient as shown in Fig. 100–2).

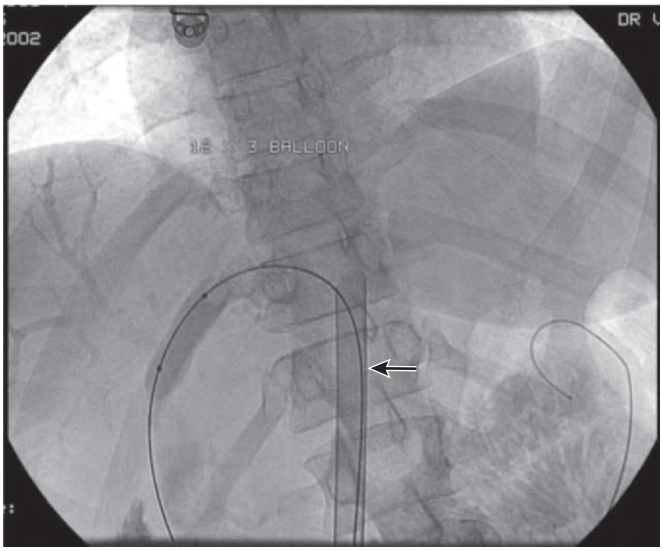

Figure 100–7. Digital spot film obtained during fluoroscopically guided left biliary duct stone removal (same patient as in Figs. 100–2 and 100–6). After outpatient sequential left biliary drainage catheter up-sizings, a large sheath has been placed into the left biliary system *(arrow)* to facilitate placement of stone baskets and to remove stone fragments. A 12-mm-diameter balloon has been inflated to dilate a left central (hilar) stricture. This stricture was biopsied and found to be benign on pathologic analysis. The stricture was believed to contribute to left biliary duct stone formation. This patient had a remote history of a cholecystectomy.

scopist may not be able to successfully relieve obstruction from malignant tumors located at the biliary confluence. An endoprosthesis placed during endoscopy is frequently deployed into either the right or the left biliary duct. If both sides are not stented, this may result in inadequate biliary drainage (see "Percutaneous Image-Guided Therapy of Malignant Biliary Disease").

Percutaneous techniques are especially well suited for patients with biliary bifurcation (i.e., hilar) or intrahepatic lesions and in those patients with prior surgical failures (e.g., anastomotic strictures at the site of a prior biliary-enteric surgical reconstruction). As mentioned earlier, ERCP may prove inadequate when biliary strictures are located in the hilum. In fact, ERCP may lead to emergency PTC/PBD due to "instrumentation" in the clinical setting of inadequate biliary drainage. This is due to the inability of the endoscopic stent to reach the upper level of the biliary obstruction. Such patients, with high-grade obstruction and subsequent unsuccessful bile duct manipulation, may require emergent percutaneous transhepatic drainage or surgery due to sepsis.

Technique of PTC/PBD and Dilation of Benign Biliary Strictures

The technique of PTC and PBD is well described.[30-32] Access to the biliary system may be achieved under cross-sectional imaging or fluoroscopic guidance. We prefer fluoroscopy. Briefly, after informed consent, conscious sedation, and intravenous antibiotics, biliary anatomy is defined from either a right (mid axillary) or a left (subxiphoid) approach (see Fig. 100–6). A second needle may be used to select the appropriate duct for percutaneous biliary drainage. Generally an 8- to 10-French locked multi-side-hole catheter is placed at the initial biliary drainage procedure. Depending on the location and nature of the biliary lesion (e.g., benign hilar stricture), the patient is brought back to the interventional suite and balloon cholangioplasty is performed. In general, cholangioplasty of the distal common bile duct is achieved with a 10- to 12-mm-diameter balloon; a hilar stricture with an 8- to 10-mm-diameter balloon. Similar sized balloons (e.g., 10 mm diameter) are used for a benign stricture at a biliary-enteric anastomosis (e.g., a Roux-en-Y choledochoenterostomy anastomosis). Following balloon dilation, upsizing to a larger caliber external/internal biliary drainage catheter is generally believed to be the most appropriate therapy. At our institution, soft Silastic biliary tubes (e.g., 16-French) are often used. The drainage catheters are sutured to the

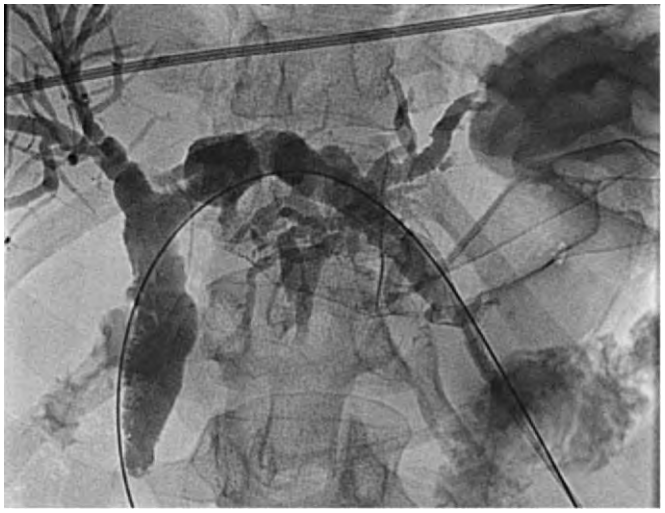

Figure 100–8. Completion cholangiogram after outpatient left biliary stone extraction procedures (same patient as in Figs. 100–2, 100–6, and 100–7). Using both fluoroscopic and endoscopic guidance, the patient's left biliary system was rendered stone free. The left central hilar biliary stricture (benign) was dilated (see Fig. 100–7) and stented with a large-caliber 16-French Silastic external/internal biliary drainage catheter (not shown). This final "over-the-wire" cholangiogram was performed after stenting the stricture for 3 months. Contrast rapidly flowed across the previously dilated and stented central left biliary stricture and opacifies the right biliary system, common hepatic, and common bile ducts. The duodenum is also opacified, indicating no ampullary obstruction. This patient's tube was removed, and the patient remains asymptomatic at 2-year follow-up.

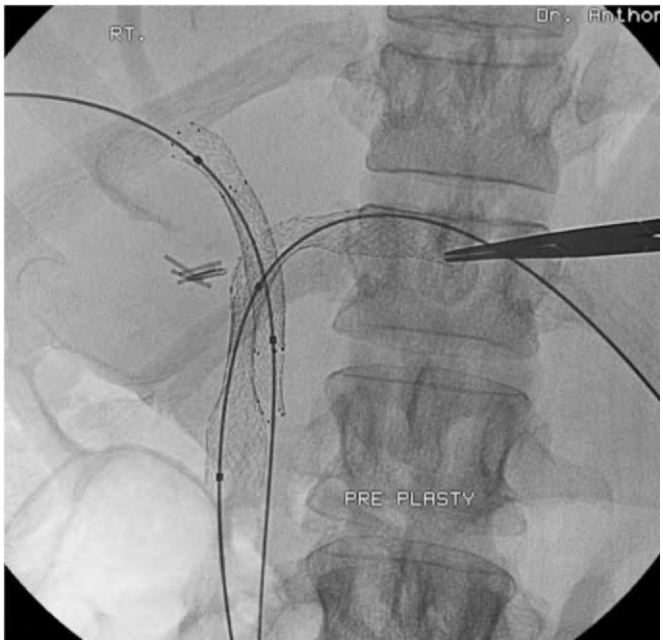

Figure 100–9. Digital spot film in a 65-year-old woman with unresectable biliary malignancy (end-stage hilar cholangiocarcinoma). Overlapping bilateral self-expanding stents (biliary endoprostheses) have been placed from the right and left percutaneous biliary access sites (Zilver stents). This image was obtained prior to gentle balloon dilation of the stents and bilateral guidewire removals. Use of biliary endoprostheses for palliation frees a patient from the encumbrance of external/internal biliary drainage catheters.

skin entry site. Patients flush their tubes with 10 ml of normal saline once or twice daily. Should intrahepatic strictures be found, the appropriate duct must be chosen for percutaneous access such that the stricture is negotiated (i.e., crossed) and balloon dilation is performed (see Fig. 100–7) followed by external/internal biliary stenting.

Should a patient fail a course of balloon dilation and stenting (i.e., failure of a clinical trial in which the biliary drainage catheter is pulled above the stricture), or should the patient fail a graduated infusion "stress" test across the stricture (i.e., a biliary manometric perfusion test), a retrial of balloon dilatation and stenting is an option. Dialogue with the patient, gastroenterologist, and surgeon is critical to formulate an appropriate treatment plan. Should the patient be deemed a poor surgical candidate, the patient may have to be maintained with permanent internal/external biliary drainage catheters changed every 2 to 3 months on an outpatient basis.

For benign biliary strictures, metallic stents should not be used because (1) such devices generally will occlude in 6 to 12 months and (2) the metallic struts of the stent become incorporated into the bile duct epithelium and, should future surgery be required, additional

Figure 100–10. Photograph of a self-expanding covered biliary endoprosthesis (Viabil). (Courtesy of W. L. Gore and Associates, Flagstaff, AZ.)

nondiseased bile duct may be sacrificed, complicating the originally planned biliary reconstructive surgery. At our institution, external/internal biliary stenting is the norm for percutaneous management of patients with benign biliary strictures. As mentioned earlier, catheters are routinely changed on an outpatient basis at 2- to 3-month intervals. In general, bile duct injury requires a lengthy healing process. Although controversial, it is not unusual for patients, after biliary enteric reconstructive surgery, to be stented for 6 months to a year with large-caliber Silastic stents. On completion of the stenting interval, successful completion of a clinical trial and/or biliary manometric perfusion test is required prior to stent removal.

Rarely, benign biliary strictures may undergo metallic stenting. This might be in the setting of a patient who cannot psychologically tolerate internal/external biliary drainage catheters, patients with short life expectancies due to other comorbid conditions despite the benign biliary process, and the occasional patient who cannot undergo surgery. For example, a patient with a liver transplant and a focal stricture at a choledochocholedochostomy anastomosis might, if no surgical option exists, be a candidate for a short-segment metallic biliary endoprosthesis (stent).

Recent anecdotal reports indicate that covered biliary stents may be used to treat benign biliary strictures.[33] Such stents may be later successfully removed without apparent damage to bile duct epithelium. However, human data are limited, and the use of covered stents as a biliary endoprostheses in patients with benign biliary disease is under ongoing clinical investigation.

Percutaneous Management of Biliary Stones

In general, biliary stones are associated with infected bile. Thus, complete removal of stones is essential to render the patient "stone free" and to prevent further episodes of cholangitis. Often, biliary stones are associated with underlying biliary strictures. Extrahepatic biliary stones may be treated by the endoscopist. Treatment may consist of a sphincterotomy followed by endoscopic stone removal using baskets, balloons, and so forth. Intrahepatic stones present a particular challenge to the endoscopist, surgeon, and interventional radiologist. The multidisciplinary approach is necessary for optimal patient management. This may consist of an ERCP with sphincterotomy and removal of distal common bile and common hepatic duct stones. Following this, percutaneous access may be necessary from the right (mid axillary) and/or left (subxiphoid) approach. With appropriate biliary drainage catheter up-sizing, fluoroscopically directed interventions may be performed to remove intrahepatic stones. These include balloon dilation of strictures and removal of stones with stone baskets and grasping forceps. This is followed by stenting with an external/internal biliary drainage catheter. If necessary, stone removal procedures are repeated until the patient is "stone free." Such procedures may be performed on an outpatient basis (see Figs. 100–2 and 100–6 to 100–8).

The increase in use of fiberoptic transhepatic or trans T-tube cholangioscopy by interventional radiologists has changed management of patients with retained intrahepatic biliary stones.[34-36] Such a technique generally necessitates the use of larger cholangioscopes (e.g., 15- to 16-French) and requires tube up-sizing to 18- to 20-French prior to stone removal.

The advantages of percutaneous cholangioscopy include (1) the use of electrohydraulic lithotripsy under direct vision to fragment large stones, (2) the ability to negotiate eccentric biliary strictures under direct vision when fluoroscopically guided attempts have failed, (3) the ability to biopsy suspicious lesions seen during biliary interventions (i.e., to biopsy suspected malignant biliary lesions), (4) a reduction in radiation both to the patient and health care personnel in the interventional suite, and (5) the procedure (i.e., percutaneous cholangioscopy) may be performed generally on an outpatient basis.

Disadvantages of cholangioscopy include (1) the general lack of familiarity of radiologists with the use of a fiberoptic scope; (2) considerable cost for initial purchase of equipment (unless it can be borrowed from other services such as urology); (3) the need for a different type of recording system than that found in a conventional interventional suite (i.e., videotape, digital endoscopic images); and (4) a requirement for purchase or loan of an energy source for electrohydraulic lithotripsy. The equipment cost and lack of training are generally reasons why the use of cholangiography for biliary interventions has not received widespread acceptance in the interventional radiology community.

When using fluoroscopy, biliary calculi, once captured in a stone basket, are generally "swept" forward into the bowel. Theoretical risks of pulling stones through a transhepatic tract include tract trauma and the potential risk of stone fragments being "lost" and becoming a "nidus" of infection in the transhepatic tract of the liver. The use of a large percutaneously placed transhepatic sheath may facilitate stone removal by this route (see Fig. 100–7). At our institution, the preference is to perform percutaneous cholangioscopy with electric hydraulic lithotripsy followed by the use of soft latex occlusion balloons to sweep stone fragments into the bowel. To facilitate passage of stone fragments through the ampulla and into the bowel without stone impaction, percutaneous cholangioplasty is first performed generally with a 10- to 12-mm-diameter balloon prior to moving stones forward into the gastrointestinal tract.

Percutaneous Image-Guided Therapy of Malignant Biliary Disease

Patients with malignant biliary obstruction may benefit from the use of either (1) plastic, (2) open mesh (i.e., bare metal or uncovered), or (3) covered biliary endoprostheses. With time, the bare metal endoprostheses have gained in popularity. Most investigators think that bare metal biliary endoprostheses are advantageous for the following reasons:

1. The bare metal biliary stents (endoprostheses) used for palliation of malignant biliary obstruction are generally placed through a smaller percutaneous transhepatic tract than a plastic endoprosthesis.
2. There is controversy in the medical literature, but it is generally thought that bare metal biliary endoprostheses have better long-term patency than plastic endoprostheses.
3. Metallic endoprostheses may be placed in a single-step procedure (i.e., PTC followed by PBD and endoprostheses placement) in those patients deemed nonsurgical candidates.

Disadvantages of bare metal or open mesh metallic endoprostheses include the following:

1. Their considerable cost (at least 10 to 12 times that of plastic endoprostheses)
2. They generally cannot be easily removed except through a surgical resection.
3. Bare metal endoprostheses occlude, repeat percutaneous or endoscopic drainage is required.

The following is a partial listing of metallic endoprostheses commercially available in the United States (those approved for palliation of malignant biliary obstruction by the US Food and Drug Administration are included):

1. Self-expanding bare metal (open mesh or uncovered) stents. Examples include (a) Gianturco Z-stent (Cook Inc., Bloomington, IN); (b) Zilver stent (Cook Inc., Bloomington, IN); (c) Luminexx Biliary Stent (Bard Peripheral Vascular, Tempe, AZ); (d) Protégé GPS (EV3, Plymouth, MN); (e) Smart Stent (Cordis Endovascular, Warren, NJ); (f) Symphony (Boston Scientific, Natick, MA); and (g) Wallstent (Boston Scientific, Meditech, Natick, MA).
2. Balloon-expandable bare metal (open mesh or uncovered) stents. Examples include (a) Express Biliary LD (Boston Scientific, Natick, MA); (b) Omni Flex Biliary (Angio Dynamics, Inc., Queensbury, NY); (c) Palmaz and Palmaz Genesis (Cordis Corporation, Miami, FL); and (d) Vista Flex (Angio Dynamics, Inc., Queensbury, NY).
3. Self-expanding covered biliary stent. An example is Viabil (W.L. Gore and Associates, Flagstaff, AZ) (see Fig. 100–10).

In general, open-mesh (i.e., uncovered) metallic endoprostheses require a 7- to 9-French access, whereas the less expensive but larger caliber plastic endoprostheses generally require a 10- to 14-French transhepatic tract. In the case of placement of a plastic endoprosthesis, tract dilation may be associated with considerable patient discomfort and risk of hemobilia.

If no hemobilia is noted after PTC/PBD, the metallic endoprosthesis may be placed in a single step, thus offsetting the increased cost of the device. In contrast, plastic endoprosthesis placement from a percutaneous transhepatic approach includes multiple steps (i.e., PTC/PBD), tube tract maturation, tract dilation, and endoprosthesis placement. Multiple steps add to the overall cost and to the potential patient discomfort and risk.

Given the limitations of bare metal and plastic endoprostheses in patients with malignant obstruction of the biliary system, the application of covered stents for improving long-term patency is being actively studied in clinical trials. These stents are self-expanding, covered with prosthetic material, and have both anchoring "fins" and holes, the latter placed to prevent obstruction of the cystic duct in the case of distal common bile duct obstruction or at the biliary bifurcation for hilar obstruction. Such devices require a larger transhepatic tract and are considerably more expensive than uncovered metallic stents.

In a multicenter study by Schoder et al, 42 patients with malignant biliary obstruction were treated by using an ePTFE-FEP-covered biliary endoprosthesis. In this series, patients had obstruction of the common bile duct, common hepatic duct, and hilar confluence. Unilateral ($n = 38$) or bilateral ($n = 4$) drainage was accomplished using covered endoprostheses with anchoring fins. To avoid branch duct blockage, endoprostheses with drainage holes at the proximal end were available. Procedure- and device-related complications were recorded. Successful deployment, correct positioning, and patency of the device were achieved in all patients. Procedure-related complications occurred in 2 (5%) patients. Thirty-day mortality rate was 20% (8 of 42 patients), and median survival time was 146 days. Laboratory values decreased significantly after the procedure ($P < 0.001$). Recurrent obstructive jaundice occurred in 6 patients (15%). Primary patency rates at 3, 6, and 12 months were 90%, 76%, and 76%, respectively. Calculation of the composite end point of death or obstruction revealed a median patency duration of 138 days. No endoprosthesis migration was observed. Branch duct obstruction was observed in 4 patients (10%). Postmortem examination of one stent revealed a widely patent endoprosthesis with intact covering.[28]

In another clinical study by Miyayama et al, 62 patients with malignant biliary obstruction distal to the hilar confluence were treated with a covered stent (group 1, $n = 22$), a bare metal stent with large interstices (i.e., Z stent), (group 2, $n = 19$) and a bare metal stent with smaller interstices (i.e., mesh), (group 3, $n = 21$). Patency rates of each group were compared. Early stent revision was required after 3 days in 18% (4/22) of group 1, 26% (5/19) of group 2, and 0% (0/21) of group 3. The 10-, 20-, and 40-week primary patency rates were 77%, 77%, and 59% (group 1); 42%, 25%, and 8% (group 2); and 76%, 71%, and 55% (group 3), respectively. Primary patency rates of groups 1 and 3 were significantly higher than those of group 2 ($P < 0.05$), and there was no statistically significant difference between those of group 1 and group 3. The 10-, 20-, and 40-week assisted primary (secondary) patency rates were 96%, 96%, and 96% (group 1); 68%, 49%, and 39% (group 2); and 86%, 74%, and 58% (group 3), respectively. Assisted primary patency (secondary) rates of group 1 were significantly higher than those of groups 2 and 3 ($P < 0.01$ and $P <$

0.05, respectively). The authors conclude that their study suggests the primary patency rate of the covered stents is equal to that of mesh stents and that covered stent patency may be improved further to possibly avoid the need for early revision.[29]

The advantages of palliative percutaneous placement of an endoprosthesis in the setting of unresectable malignant distal biliary obstruction include (1) restoration of bile flow into the duodenum with its associated improved physiologic and metabolic effects, and (2) conversion of an external/internal biliary drainage catheter (stent) into a "self-contained" intraductal device eliminating the external component of the tube and the daily care required for an external/internal biliary drainage catheter. The endoprosthesis offers the patient the advantage of enhanced quality of life (i.e., the patient is no longer burdened with a catheter that requires maintenance such as dressing changes, flushing of the tube once or twice daily, elimination of potential bile leakage and infection at the catheter skin entry site, and routine periodic catheter exchanges).

The disadvantages of an endoprosthesis (plastic or bare metal) for palliation include (1) premature endoprosthesis occlusion with the associated complications (e.g. recurrent jaundice, possible sepsis), (2) possible dislodgement of the device, and (3) increased cost of the metallic device (offset by a reduced hospitalization time). A bare metal biliary endoprosthesis (stent) in place for weeks or months cannot be exchanged either endoscopically or transhepatically. Should premature occlusion occur or should the patient outlive the patency of the stent, a repeat percutaneous biliary drainage is necessary with placement of either a new endoprosthesis inside the old one, or an external/internal biliary drainage catheter. A second option is attempted endoscopic placement of an endoprosthesis through the occluded metallic stent. If tumor "overgrowth" has occurred, the site of obstruction may be beyond the reach of the endoscopic cannula.

There is recent experimental work on other novel biliary endoprosthesis designs. One is a flexible, open mesh (uncovered) coil-like stent, potentially a removable device for use in patients with benign biliary disease (e.g., strictures). However, extensive clinical data on its use in humans are lacking.

Benign Biliary Disease (Iatrogenic or Traumatic Injuries of the Biliary System)

The clinical results of percutaneous (nonsurgical) management of patients with biliary tract injuries have also received considerable attention in the medical literature. Bile duct injuries occur in 0.3% to 0.6% and 0.06% to 0.21% of laparoscopic and conventional cholecystectomy procedures respectively. In general, the role of the interventional radiologist in the management of patients with biliary leaks includes (1) defining biliary anatomy prior to definitive surgical biliary reconstruction, and (2) diverting bile externally in those patients with complete obstruction of the extrahepatic biliary system (e.g. due to inadvertent clipping of the common hepatic or common bile duct), or in those patients who have sustained complete duct transection with free spillage of bile into the subhepatic space. In the clinical setting where there is free spillage of bile into the abdomen, external diversion coupled with percutaneous biloma drainage may set the stage for surgical reconstruction and allow clinical stabilization of the patient. In the setting of iatrogenic or post-traumatic ductal injury, a focal stricture may be treated solely with percutaneous methods. However, the role of the interventional radiologist is generally to prepare the patient for eventual biliary reconstructive surgery. Trerotola and colleagues reported a series of 13 patients who had undergone laparoscopic cholecystectomy and had experienced a ductal injury.[37] Six patients (46%) had postoperative bilomas or bile leaks. Of these, two (33%) were managed by percutaneous means alone, thus avoiding a second operation. vanSonnenberg and colleagues reported on management of 21 patients with laparoscopic cholecystectomy injuries, 11 of which consisted of bilomas or bile leaks. Seven of these patients were treated percutaneously and without further surgical intervention.[38]

Complications of PTC/PBD and Biliary Interventions

The incidence of major complications associated with percutaneous biliary drainage is 4.6% to 25%, and the incidence of procedure related deaths is 0% to 5.6%.[23-27] Major complications include hemobilia requiring blood transfusion and cholangitis associated with hypotension. Hemobilia, a recognized complication of PTC/PBD, occurs in 2.6% to 9.6% of cases.[27,30] Although bleeding is the most common cause of serious procedure-related morbidity, it is rarely a cause of death in patients undergoing percutaneous transhepatic biliary interventions.

Should a patient develop hemobilia, a cholangiogram is initially performed to assess whether the vascular system opacifies. During cholangiography, should injected contrast opacify only the venous system (e.g., hepatic vein or portal vein), tube repositioning or up-sizing is generally all that is required to tamponade the bleeding site. It is important to first check that the proximal most (i.e., most peripheral) side-hole is intraductal (i.e., not outside and in the transhepatic tube tract). If the proximal side-hole is outside the biliary system, the last side-hole may serve as a site of "egress" for venous blood should a vein have been inadvertently transgressed during initial placement of the tube. Biliary drainage catheter up-sizing may be tried next if venous bleeding (oozing) persists despite catheter side-hole repositioning.

Infrequently, should a major central portal venous branch be injured, repeat biliary drainage at a different site with embolization of the original transhepatic tube tract using embolic spring coils, Gelfoam, or both may be necessary.

If, during a biliary catheter exchange, pulsatile bright red blood is seen, an arterial injury must be suspected. The nonsurgical treatment of patients with arterial

hemobilia is transcatheter embolotherapy of the injured hepatic arterial branch. Such arterial injuries may occasionally be life threatening. Patients are consented for an emergency hepatic arteriogram and embolization. The hepatic arteriogram is performed with the biliary drainage catheter briefly pulled out over a guidewire to maximize the chance of identifying the injured vessel. Once the site of bleeding is identified (e.g., pseudoaneurysm of the hepatic artery, fistula between hepatic artery and a bile duct), the arterial catheter is advanced distal to the site of injury and spring coils or other suitable embolic material is deployed to occlude the segment of vessel injured during PBD. It is important to begin embolization distal (peripheral) to the site of injury and then to continue embolization proximal to the site. This technique "bridges," "isolates," or "traps" the segment of injured vessel preventing recurrent bleeding due to collateral hepatic arterial blood flow. The injured arterial branch is functionally "double ligated."

Another complication of PTC/PBD is biliary infection. Fevers and chills may occur in 5% to 26% of patients undergoing biliary drainage. Four percent to 12% of patients develop frank septicemia. Cholangitis may occur in as many as 50% with long-term drainage.[27,30] Occasionally, complications of PTC/PBD include inadvertent puncture of other structures such as the transverse colon, especially in subxiphoid or left biliary drainage procedures. With adequate review of previously obtained cross-sectional imaging studies and appropriate use of US and fluoroscopic monitoring during PBD, such injuries can generally be avoided during left-sided percutaneous biliary drainage procedures.

Of the patients undergoing biliary drainage procedures reported in the literature, the presence of malignant biliary obstruction and the high complication rate is generally attributed to the fact that these patients are more debilitated than those presenting with biliary obstruction due to benign biliary strictures. A review by Yee and Ho combine the results of six groups of investigators (702 patients) and report major complication rates of 8% and death in 2%. In this retrospective review, 609 (87%) of the 702 patients had malignant biliary obstruction.[27]

CONCLUSION

In recent years, the imaging and interventional procedures used in the management of patients with biliary obstruction have evolved rapidly. The interventional radiologist provides minimally invasive, image-guided therapeutic options for management of patients with benign or malignant biliary disease. Percutaneous biliary interventions performed for malignant biliary disease may be palliative or, if the patient's malignant disease is deemed resectable, may set the stage for surgery. Similarly, for benign biliary disease, such percutaneous interventions may be definitive treatment or prepare the patient for surgical reconstruction with creation of a Roux-en-Y loop. Percutaneous biliary access provides a means for adjunctive biliary interventions whether that be stricture dilation, stone removal, access for bile cytology or biopsy, intraductal brachytherapy, or placement of an endoprosthesis.[39-42] The use of plastic or metallic biliary endoprostheses for patients with malignant biliary obstruction provides the means to eliminate the physical and psychological encumbrances of an external appliance needing daily maintenance. In patients with benign disease, percutaneous biliary interventions provide a minimally invasive therapeutic option, but long-term success is not as good as that reported in the surgical literature. Of benign biliary strictures managed percutaneously, the best results are generally believed to be in the clinical setting where balloon dilatation is performed at a biliary enteric anastomosis. Such anastomotic strictures may occur after biliary reconstructive surgery. Long-term patency in such patients ranges between 60% and 70% as compared to 80% to 90% in the surgical literature.[43]

Use of covered biliary stents for improving long-term endoprosthesis patency is a relatively recent development in patient management. It is hoped that the information presented in this chapter provides the multidisciplinary health care team caring for such patients with a comprehensive overview of imaging and percutaneous interventional options available to patients with biliary disease.

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Chapter

101

Operative Management of Cholecystitis and Cholelithiasis

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Cholelithiasis is a common disease throughout the Western world. Gallstones can be found in 10% to 20% of the western population at some stage of life. In both sexes the prevalence increases with age; however, overall gallstones are nearly twice as common in females than in males. Obesity and family history are also significant risk factors. Most gallstones are asymptomatic, and only 1% to 2% develop biliary symptoms necessitating intervention, either surgical or endoscopic. The spectrum of symptomatic cholelithiasis ranges from biliary colic to acute and chronic complications. Complications of cholelithiasis include cholecystitis, common bile duct obstruction/impingement (Mirrizzi's syndrome), pancreatitis, cholangitis, and rarely gallbladder cancer. The most common of these is cholecystitis. Approximately 65% of patients with acute cholecystitis have some element of chronic cholecystitis, which is characterized by fibrosis and inflammatory infiltrate of the gallbladder wall.[1] Regardless of the cause, almost all cases of symptomatic or complicated cholelithiasis are treated by a cholecystectomy—surgical removal of the gallbladder.

The widespread popularity and acceptance of laparoscopy and minimally invasive surgery are exemplified by the laparoscopic cholecystectomy, making it one of the most commonly performed procedures today. Although the advantages of laparoscopic cholecystectomy are acknowledged, its limitations and unique complications should also be kept in mind. There is a significantly higher incidence of bile duct injuries in laparoscopic cholecystectomy (0.2% to 0.8%) compared to open cholecystectomy (0.1% to 0.25%).[2-7] Previous abdominal operations may create technical difficulties with trocar placement, exposure, and visualization during laparoscopy. Furthermore, conversion to an open cholecystectomy should not be considered a complication, but rather, a reflection of sound surgical judgment in difficult cases. The rate of conversion in the United States is 5% to 10%.[8-11] The laparoscopic cholecystectomy and its related procedures are discussed in detail. In this chapter, the focus is on the indications for operative management for cholelithiasis and cholecystitis and the open technique for cholecystectomy. The indications for an open cholecystectomy are shown in Box 101–1.

ASYMPTOMATIC CHOLELITHIASIS

The large number of people who harbor gallstones but do not require a cholecystectomy makes the management of asymptomatic cholelithiasis challenging. Although cholecystectomy for symptomatic cholelithiasis is standard practice, the naturally history of asymptomatic gallstones is not well defined and therefore a standard treatment path does not exist. At present, prophylactic cholecystectomy is not recommended for most people with asymptomatic cholelithiasis. However, there are certain instances when a prophylactic cholecystectomy for silent gallstones may be warranted (Box 101–2). Certain transplant recipients or immunocompromised patients may benefit from early intervention. It has been shown that heart and lung transplant recipients develop gallbladder-related disease at a higher rate than the general population and may require an emergent operation associated with a significantly higher mortality rate than the general population.[12,13] In contrast, renal transplant recipients do not seem to have a higher rate of gallstone formation and associated complications.[14] It is not clear why this relationship exists, but one possible explanation may have to do with the duration of cyclosporine use in the heart/lung transplant patients and its affects on bile formation. Many heart/lung transplant recipients continue to use cyclosporine as

Box 101–1 Indications and Relative Indications for an Open Cholecystectomy

- Severe cholecystitis (relative)
- Inability to delineate anatomy during laparoscopic cholecystectomy
- Emphysematous gallbladder (relative)
- Suspicion for gallbladder cancer
- Perforation of gallbladder/abscess
- Fistulization of gallbladder gallstone ileus (relative)
- Cholangitis (relative)
- Multiple past abdominal procedures (relative)
- Pregnancy (relative)
- Cirrhosis/portal hypertension (relative)
- Blood dyscrasias (relative)
- Contraindication for laparoscopy

Box 101–2 Relative Indications for Prophylactic Cholecystectomy

- Cardiac transplant recipients
- Lung transplant recipients
- Chronic total parenteral nutrition requirement
- Recipients of biliopancreatic diversion (bariatric patients)
- Family history of gallbladder cancer and asymptomatic stones
- Children with hemoglobinopathy (sickle cell, thalassemia, spherocytosis)
- Cholelithiasis encountered during elective abdominal procedures

maintenance immunotherapy for 2 years or more. Chronic cyclosporine use (>2 years) has been associated with the prevalence of gallstones. In contrast, maintenance immunosuppressive regimens for renal transplant recipients have been transitioned away from nephrotoxic calcineurin inhibitors such as cyclosporine in favor of newer less nephrotoxic agents such as sirolimus. Thus, prospective heart and lung transplant recipients may benefit from prophylactic cholecystectomy prior to their transplant.

Another subset of patients who may benefit from prophylactic cholecystectomy are those requiring chronic total parenteral nutrition (TPN). Prolonged TPN use and gallbladder stone and sludge formation has been established, and the number of these patients that progress to symptoms and require a cholecystectomy is higher than the general population who have asymptomatic gallstones.[15]

Incidental cholecystectomy during an operation for another reason may also be beneficial provided that it can be done without added morbidity. There is an increased risk of developing symptoms from gallstones after major abdominal procedures, although the cause of this is not clear. Nearly one third of asymptomatic patients develop symptoms related to their gallbladder within 1 year of elective abdominal surgery. Studies on colorectal, vascular, bariatric, and the elderly (age >70 year) populations support the use of incidental cholecystectomy in preventing the exaggerated gallstone morbidity seen in patients with previous abdominal surgery.[16,17] Special consideration to patient condition, need for lengthening of the incision or additional trocar placement, and potential for introducing infection in a clean field all must be weighed before performing an incidental cholecystectomy for asymptomatic stones. For example, placement of a prosthetic graft would be a relative contraindication to an incidental cholecystectomy. The incidental cholecystectomy also removes the risk and related morbidity of cholecystitis in the immediate postoperative period.

Other cases in which a prophylactic cholecystectomy may be prudent is in the patients who have certain hemoglobinopathies, such as hereditary spherocytosis, thalassemia, and sickle cell disease. Patients who have a family history of gallbladder cancer or calcification of the gallbladder wall should also undergo a cholecystectomy for asymptomatic cholelithiasis. In most cases, these can be done laparoscopically.

CHOLECYSTITIS

Acute cholecystitis results from obstruction of the cystic duct, usually secondary to a gallstone. Local inflammatory responses may also result in edema and inflammation of the gallbladder. Nearly 90% to 95% of cases of cholecystitis are calculous in origin. Acalculous cholecystitis accounts for the remaining 5% to 10% of the cases and is more common in critically ill trauma, burn, and sepsis patients and individuals with cardiac, diabetic, and acquired immunodeficiency syndrome conditions. Patients who are on TPN, postpartum, taking steroids or narcotics, or have received transfusions are also more likely to have the acalculous variant. Acalculous cholecystitis has a higher incidence of gangrene, emphysematous infection, perforation, and mortality. These patients usually require an emergent intervention, either a percutaneous cholecystostomy tube to decompress the gallbladder or cholecystectomy.

Stagnation of bile and resultant infection from an impacted gallstone was once thought to be the main pathophysiology in the development of cholecystitis. However, studies investigating bile cultures have shown that only 15% to 30% of patients undergoing cholecystectomy for cholecystitis have positive bile cultures.[18] This indicates that inflammation of the gallbladder is not simply an infectious process but rather a multifactorial series of events that are initiated by gallstone obstruction of the cystic duct. A well-described "ball-valve" mechanism has been attributed to the characteristic pain. Ini-

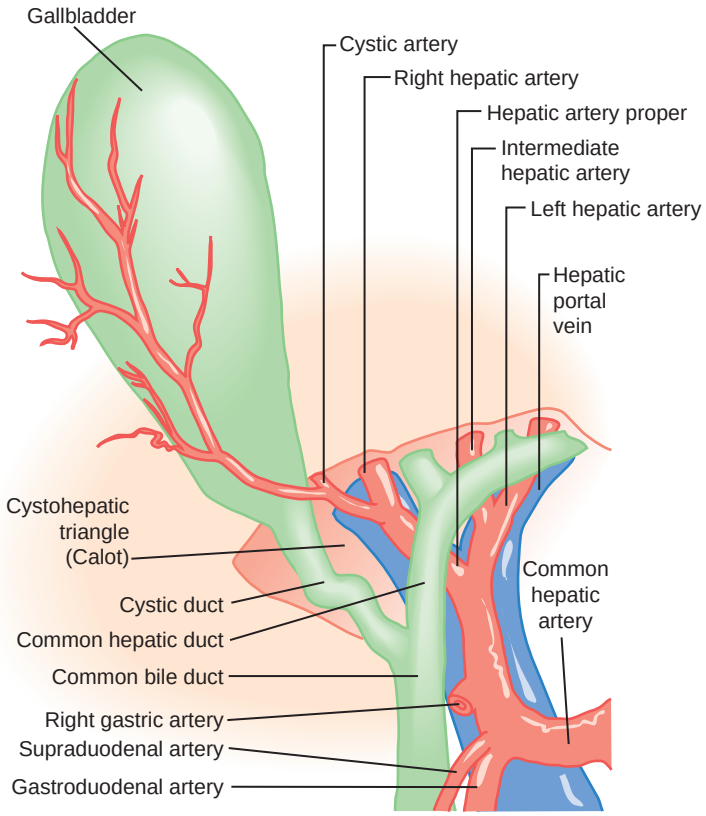

Figure 101–1. The most common anatomy of the gallbladder and relevant adjacent structures. The surgeon must also be familiar with the variations in ductal and arterial anatomy that can be encountered during a cholecystectomy.

tially, a gallstone impacts at the neck of the gallbladder leading to obstruction and wall edema. This leads to the formation of lysolecithin, a mucosal toxin. Prostaglandin synthesis increases and amplifies the inflammatory response. The edema and inflammation can then result in the lifting of the gallbladder wall away from the stone, thereby disimpacting the stone and effecting drainage through the cystic duct. In most patients this series of events plays through and conservative management is effective. In some patients, however, disimpaction does not occur, and this results in continued cystic duct obstruction and leads to venous congestion, gallbladder ischemia, biliary stasis, and a systemic inflammatory response that necessitates operative intervention.

The timing of cholecystectomy during acute cholecystitis has been debated. In the current laparoscopic era, it has been demonstrated that an earlier intervention is beneficial. In a recent prospective, randomized study comparing early cholecystectomy (within 72 hours of admission) to delayed cholecystectomy, there were no significant differences in morbidity or mortality, but there was a significantly prolonged hospital stay (11 vs. 6 days) and recovery period (19 vs. 12 days) in the delayed group.[19] In other prospective studies, early laparoscopic cholecystectomy resulted in decreased rates of conversion to open cholecystectomy, decreased length of hospital stay, and decreased overall morbidity.[20,21] Hence, early surgical intervention for acute cholecystitis has medical, economic, and social benefits that make it the recommended approach.

Cholecystitis in pregnancy presents a challenge to both the obstetrician and surgeon. Preterm labor is a significant risk in these patients and close interaction between the obstetrician and surgeon is crucial. A trial of conservative management using intravenous fluids, antibiotics, and tocolytics may be therapeutic in up to 50% of the cases. The remainder require a cholecystectomy. The effects of laparoscopy on the fetus continue to be ascertained and as such an open cholecystectomy remains a safe, viable option in this subset of patients.

ANATOMIC CONSIDERATIONS FOR CHOLECYSTECTOMY

Successful surgical removal of the gallbladder requires knowledge of normal anatomy as well as the anatomic variants associated with the liver, gallbladder, bile duct, and the arterial supply to them. Iatrogenic injuries often result from unidentified anatomic anomalies. All important structures must be identified before dividing or ligating any structure (Fig. 101–1). Vital structures include the hepatoduodenal ligament and its contents, cystic duct, common hepatic duct, common bile duct, cystic artery, and right hepatic artery. The cholecystectomy triangle, also known as *Calot's triangle,* is formed by cystic duct, common hepatic duct, and the inferior edge of the liver. It is important to identify this triangle and its related structures during any cholecystectomy (open or laparoscopic). Commonly, the right hepatic artery is located posterior to the common hepatic duct, and the origination of the cystic artery from the right hepatic artery is within the triangle of Calot. Occasionally the cystic artery may arise from the gastroduodenal artery. The cystic duct

and common duct junction is variable. The cystic duct may be long, short, or nearly nonexistent. It may run adherent to the common bile duct in a parallel course. The cystic duct may join the right or left side of the common bile duct, or it may connect to the right hepatic duct. In inflammatory states such as Mirizzi's syndrome, the cystic duct may be unrecognizably contracted.

In difficult cases where the ductal anatomy is not certain, the use of an intraoperative cholangiogram is often helpful. Routine versus selective intraoperative cholangiography is still a matter of debate, especially in laparoscopic approaches. An intraoperative cholangiogram can provide ductal anatomy, demonstrate unidentified stones in the biliary system, and identify disease in the intrahepatic or extrahepatic biliary tree. Although intraoperative cholangiography does not prevent bile duct injury, it can help to limit the severity of injury by early identification and influence the success of repair and outcomes.[22-24] In some instances the biliary injury can be repaired at the initial operative setting. Hence, the intraoperative cholangiogram can be an important adjunct to cholecystectomy.

OPEN CHOLECYSTECTOMY TECHNIQUE

The location of the gallbladder on the posterior surface of the liver combined with the liver's residence beneath the ribs makes exposure a key aspect in the successful performance of a cholecystectomy. The right subcostal incision (8 to 12 cm) provides good, direct access to the liver, gallbladder and the extrahepatic biliary tree and is the standard incision. The limitation of this incision is in providing exposure to lower abdominal organs. In cases where the costal angle is narrow or access to the entire abdominal cavity is preferred, a midline incision may offer better exposure as it can be easily extended superiorly or inferiorly. The disfiguring Holman's incision, which combines a right subcostal with an upper midline, or the paramedian incision is now rarely used.

Retraction of the right costal margin is best accomplished with the aid of a retraction system that is fixed to the operating table. This provides steady retraction, spares a hand, and limits the need for additional assistants. The patient is placed in a reverse Trendelenburg position to help bring the liver down from under the costal margin and moist gauze packs may be placed behind the right hepatic lobe to bring the liver forward. Division of the falciform ligament, and using it as a handle to lift the liver up, provides additional exposure. Alternatively, a retractor to lift the inferior aspect of the liver up may be used taking care not to tear the liver capsule. Moist packs are used to pack away adjacent structures and a wide hand-held or fixed retractor can be used to hold them in place. An orogastric or nasogastric tube is used for decompressing the stomach and enhancing exposure. Dense inflammatory adhesions to the colon or duodenum are often encountered and must be dissected free. Dissection in all instances should be performed close to the gallbladder wall. The presence of cholecystenteric fistulas must also be kept in mind.

The gallbladder fundus is grasped with a clamp for traction. A distended gallbladder may be difficult to grasp and may be aspirated to facilitate manipulation. During states of inflammation caused by cystic duct obstruction the absorptive capacity of the gallbladder mucosa is impaired by the mucosal toxin lysolecithin. As a result there is net secretion into the gallbladder with no outlet. This produces hydrops of the gallbladder and its characteristic whitish/clear gallbladder aspirate.

At this stage of the operation, the surgeon has two methods available to remove the gallbladder. Cholecystectomy from the neck toward the fundus can be used for straightforward cases in which there is minimal inflammation and adhesions, and the components of the cholecystectomy (Calot's) triangle are easily identifiable. This is also the method used in laparoscopic cholecystectomy. When there is significant inflammation and adhesions that impede safe, adequate visualization of the triangle components, the safest method is cholecystectomy from the fundus toward the cystic duct.

Neck-Toward-Fundus Approach

The operation commences with incising the peritoneal undersurface of the gallbladder and extending to the anterior aspect of the hepatoduodenal ligament (Figs. 101–2 and 101–3). Another clamp may be placed on the

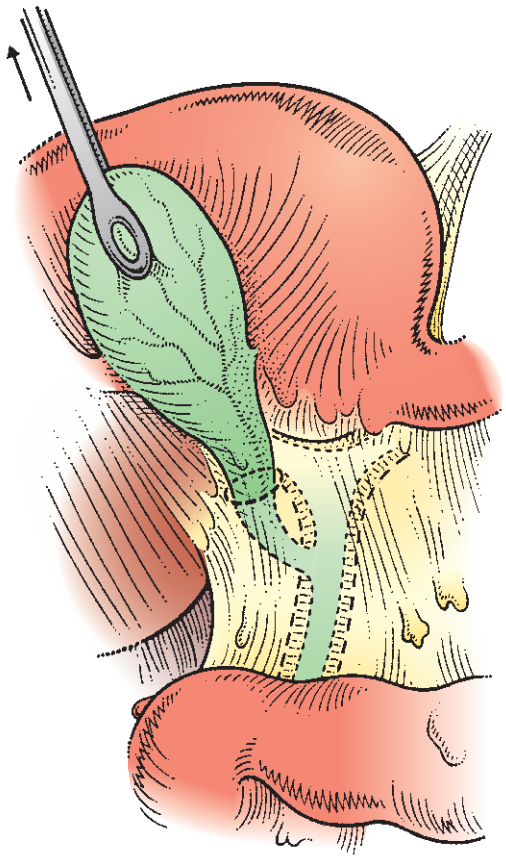

Figure 101–2. Cholecystectomy commences with adequate exposure of the gallbladder, grasping the fundus with a clamp to provide traction.

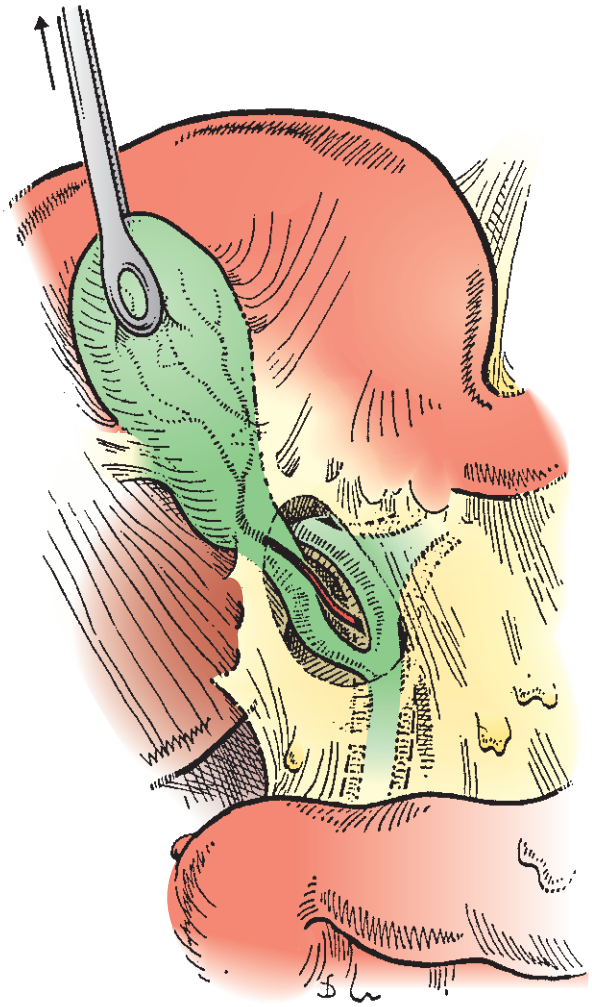

Figure 101–3. Neck-toward-fundus approach. Incising the peritoneum overlying the hepatoduodenal ligament will expose Calot's triangle.

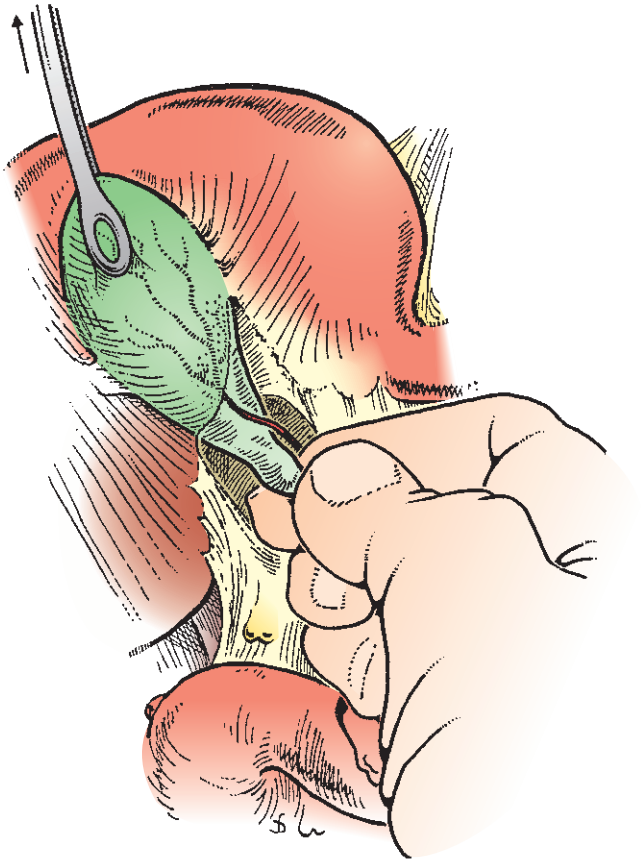

Figure 101–4. Digital palpation of the portal structures can identify stones in the cystic duct. The stones are gently milked back into the gallbladder.

infundibulum of the gallbladder and lateral and anterior traction applied to straighten the cystic duct away from the common bile duct. Too much traction may result in tenting of the common bile duct and mistakenly identifying it as the junction of the common bile duct and cystic duct. Blunt dissection of the triangle is performed to identify the cystic duct and its junction with the gallbladder and the common bile duct. The surgeon can then palpate the duct and identify stones and milk them back up into the gallbladder (Fig. 101–4). At this point an intraoperative cholangiogram may be performed if there is a suspicion for a common bile duct stone (Fig. 101–5). The common bile duct should be opened and explored if a stone is palpable within it or detected on cholangiogram. The cystic duct is sharply transected between clamps as close to the gallbladder as feasible to prevent injury to the common bile duct. The cystic duct stump is tied and reinforced with a clip. The length of the cystic duct stump, once thought to be related to post cholecystectomy syndrome, is not critical. It is far more important that the common bile duct not be injured.

The cystic artery usually lies superior to the cystic duct. The artery is dissected back to the gallbladder for confirmation. Once the cystic artery has been isolated and distinguished from a right hepatic artery, it is sharply divided between clamps and ligated. The proximal stump may be suture ligated or a clip may be applied for reinforcement.

Once the cystic artery and cystic duct have been divided, the neck of the gallbladder should be free and dissection of the gallbladder from its hepatic fossa begins. Continuous upward traction on the neck of the gallbladder facilitates exposure of the investing peritoneum around the gallbladder and the alveolar tissue between the gallbladder and the liver. The gallbladder is freed from its fossa by a combination of sharp, blunt, and electrocautery dissection. This continues all the way up to the fundus until the gallbladder is free (Fig. 101–6). Occasionally there may be aberrant bile duct branches from the right hepatic or common hepatic ducts communicating directly with the cystic fossa, the so-called ducts of Luschka. These may be clipped and divided. In cases of postoperative bile leak, these ducts often cease draining spontaneously.[25,26] The gallbladder bed and cystic artery are inspected for hemostasis.

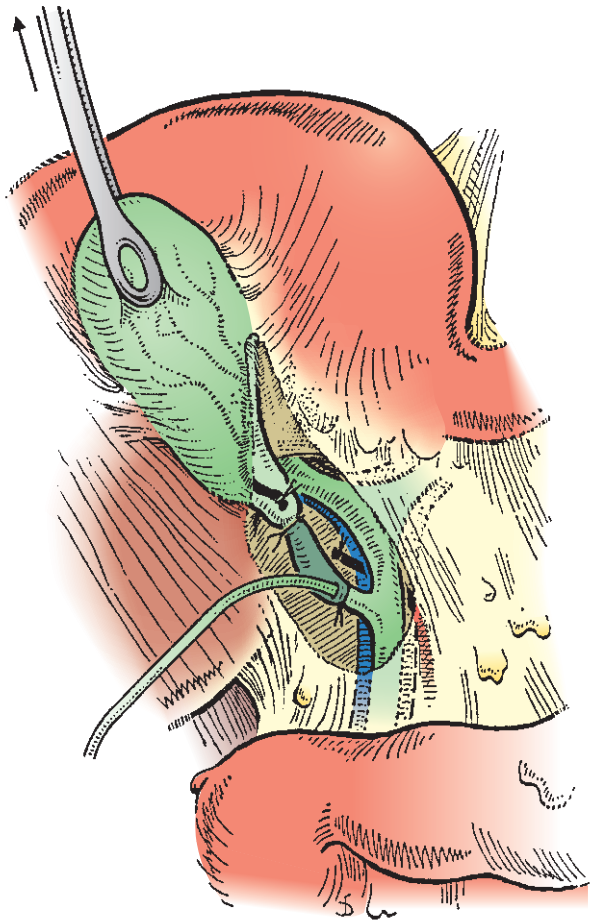

Figure 101–5. Intraoperative cholangiogram can be performed to identify anatomy or if a common bile duct stone is suspected. (Optionally, the cystic artery may be divided prior to cholangiogram if it has been identified.)

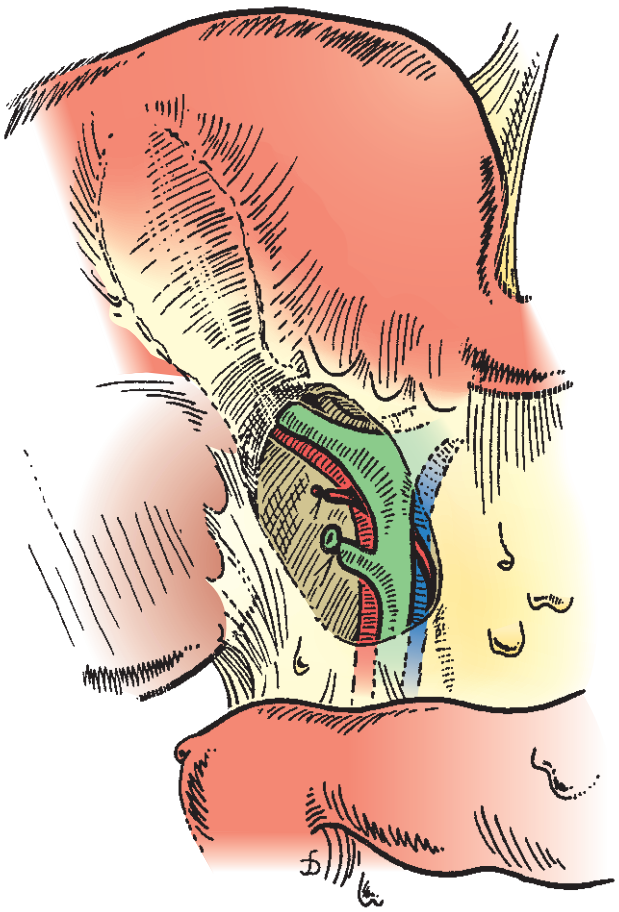

Figure 101–6. View of the gallbladder fossa on completion of the cholecystectomy with intact cystic artery and cystic duct stumps.

Fundus-Down Approach

The fundus-down method is a safe way of performing a cholecystectomy and is especially useful in the cases of cholecystitis where the neck of the gallbladder, cystic duct, cystic artery, and the hepatoduodenal ligament are obscured by inflammation and adhesions. Dissection of the fundus initially, releasing the gallbladder from the liver, and subsequent identification of ductal and vascular structures can reduce the rate of inadvertent injury by revealing planes of dissection away from the most densely adherent inflamed portions.

An incision is made in the gallbladder serosa at the tip of the fundus near the liver edge. A subserosal plane is developed between the gallbladder and the liver on each side (Fig. 101–7). The fundus is grasped with a clamp, and downward traction is applied as the gallbladder is taken out of the fossa by sharp and blunt dissection. Another clamp on the gallbladder can be used to manipulate the gallbladder laterally and medially during the dissection (Fig. 101–8). With inflammation and edema, this plane is easily dissected sharply.

It is best not to aspirate the contents of the gallbladder since it is easier to identify the wall of the gallbladder when it is full and helps define the plane of dissection. However, if it interferes with grasping or visualization, it may aspirated as described earlier. A useful maneuver in dissecting a collapsed gallbladder is to place a finger inside the gallbladder and use it as a guide for the gallbladder wall.

When the infundibulum and neck is reached, the cystic artery will be encountered entering the gallbladder wall (Fig. 101–9). The cystic artery is sharply divided between clamps and ligated close to the gallbladder. Light traction on the gallbladder and skeletonization of the infundibulum will reveal the cystic duct. The cystic duct, common bile duct, and common hepatic duct should be identified. The cystic duct is then clamped close to the gallbladder and then sharply divided between two clamps and ligated. The gallbladder is removed from the field. The cystic duct stump may further be suture ligated or reinforced with clip. The gallbladder fossa and cystic artery stump are inspected for hemostasis.

The use of a closed suction drain is only indicated if the surgeon is concerned about identifying or control-

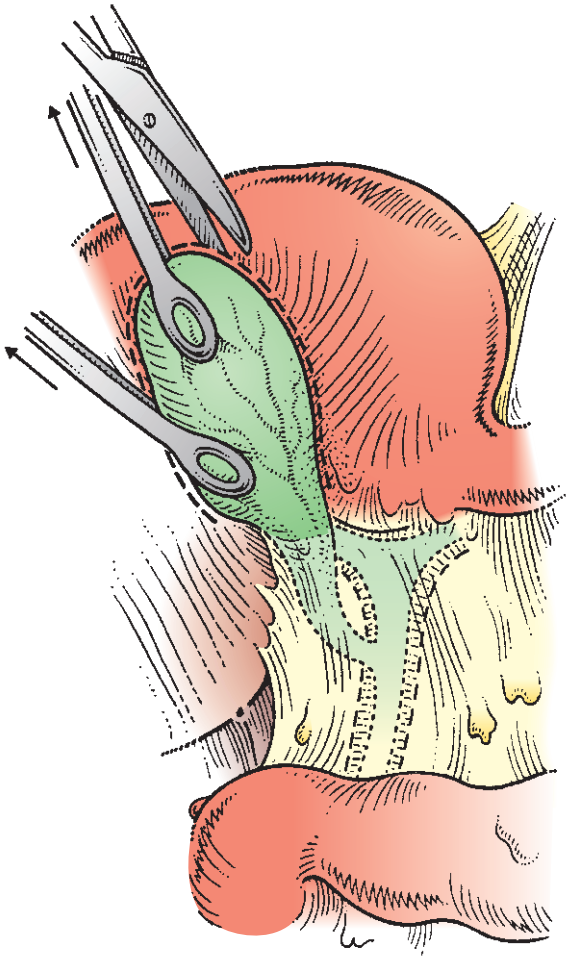

Figure 101–7. Fundus-toward-neck approach. The peritoneum over the gallbladder, close to the liver edge at the tip of the fundus, is incised.

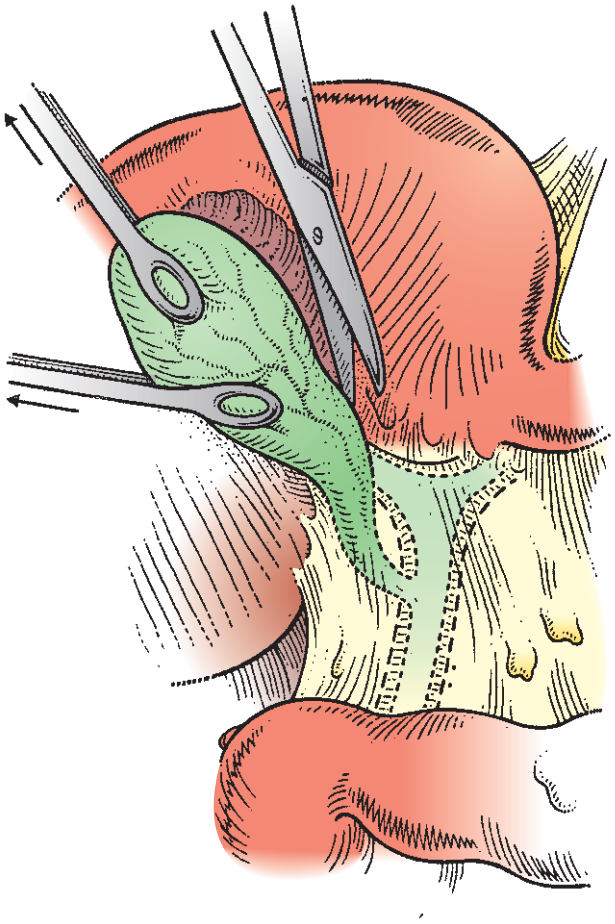

Figure 101–8. A plane is developed between the liver and the gallbladder wall. The second clamp can facilitate maneuvering of the gallbladder laterally and medially. In cases of acute inflammation, the surgeon can take advantage of the edema commonly found in this plane. The plane is most easily created by sharp dissection, but electrocautery may also be used.

ling a bile leak. The drain is placed in the gallbladder fossa and brought out through a separate lateral stab incision. The drain is removed when the output is low and nonbilious. The abdominal incision is closed in one or two layers using a monofilament absorbable suture. The skin can almost always be closed primarily except in cases of the most infected gallbladder fossa.

MINICHOLECYSTECTOMY

Minicholecystectomy was first described by Dubois and Barthelot in 1982. It was initially applied to compare its effectiveness with the then rapidly advancing laparoscopic cholecystectomy. With the patient in reverse Trendelenburg position, a transverse 5-cm incision is made just lateral to the midline in the right upper quadrant and extended as necessary. The cholecystectomy is performed in a fundus-to-neck fashion. This is in comparison to the 8- to 12-cm incision that cuts the majority of the rectus muscle in the traditional open cholecystectomy. The procedure is safe and effective and in certain emergent settings an acceptable alternative to conventional open cholecystectomy. Conditions in which laparoscopic equipment is not available or if conversion from laparoscopy is warranted may merit consideration for this technique.

PARTIAL CHOLECYSTECTOMY

On rare emergent situations a cholecystectomy may become hazardous due to inability to identify most of the gallbladder and the triangle of Calot, excessive bleeding (portal hypertension, cirrhosis), or patient instability. In these circumstances, the less desirable partial cholecystectomy may be performed. The fundus of the gallbladder is opened and the contents evacuated. The surgeon places a finger in the cavity and uses it as a guide to remove the entire anterior wall of the gallbladder above the cystic duct (Fig. 101–10). Impacted stones in the cystic duct should be removed. The posterior wall of the

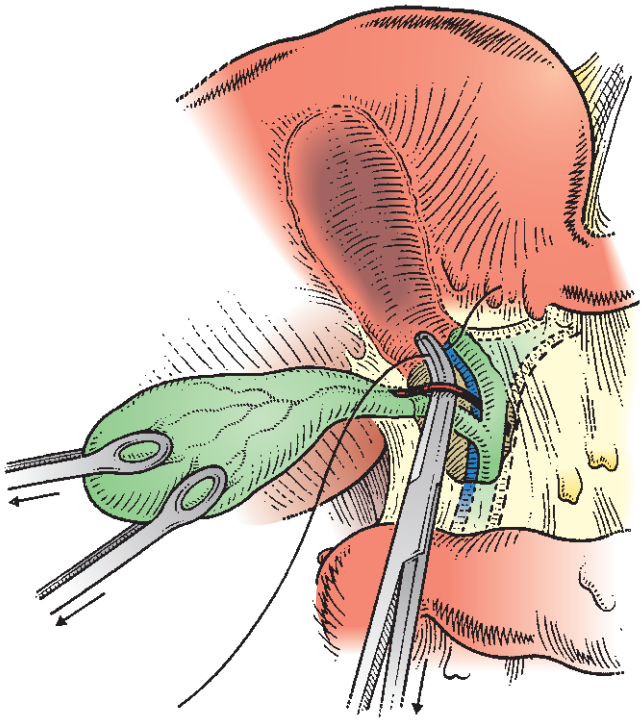

Figure 101–9. During this dissection toward the gallbladder neck, the first structure encountered will be the cystic artery as it enters the gallbladder. It is appropriately ligated and divided.

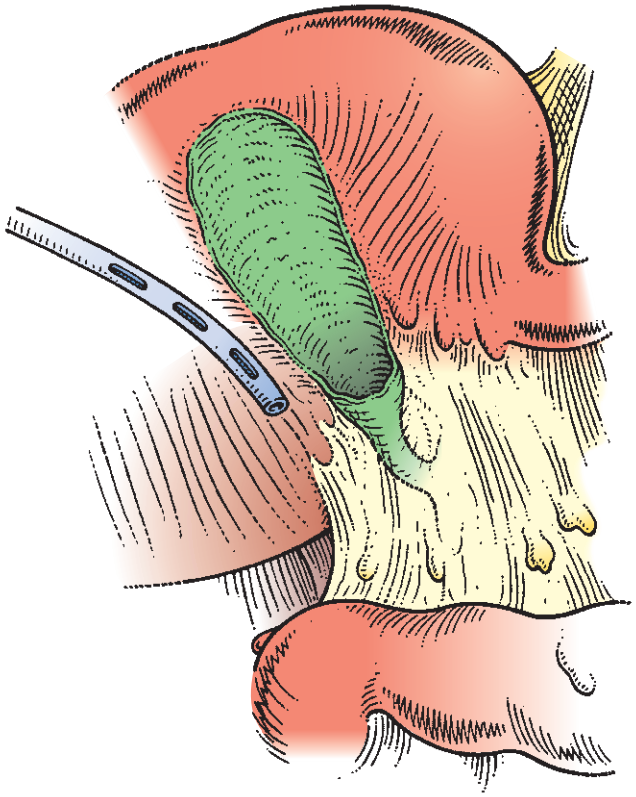

Figure 101–11. Partial cholecystectomy. The anterior portion of the gallbladder is excised, leaving the posterior wall intact within the cystic plate and the infundibulum. The cystic duct, if clearly identifiable, may be closed by suture ligation being mindful of the common bile duct. The gallbladder mucosa is removed with a curette or cauterized. A closed suction drain is placed.

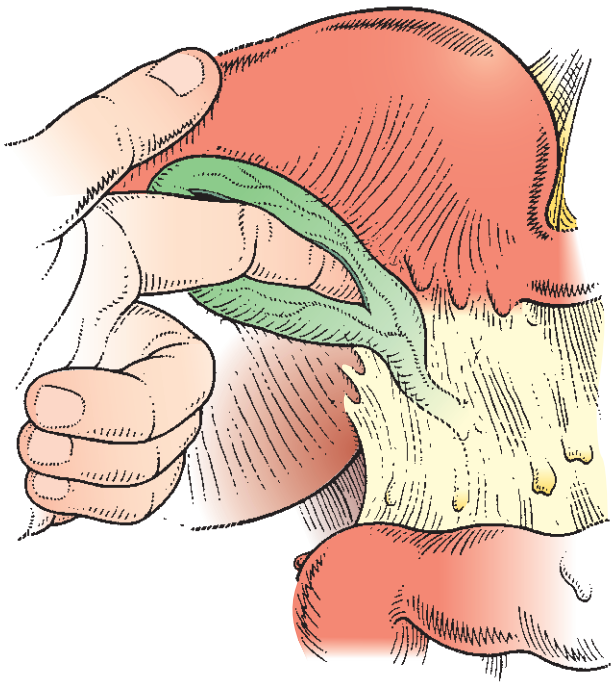

Figure 101–10. Partial cholecystectomy. The gallbladder has been opened and its contents evacuated. A finger may be used to inspect the cystic duct origination.

gallbladder that is in contact with the liver is left in place and its mucosa is removed with a curette or scored with electrocautery (Fig. 101–11). The cystic duct is ligated only if it is clearly identified. Blind stitching of possible cystic duct orifice can result in common bile duct injury. Alternatively, the cystic duct is left without further intervention and will seal, provided there is no distal common bile duct obstruction. An endoscopically placed stent across the cystic duct may also be placed after patient stabilization. The area is drained using a closed suction device. Drainage of bile usually ceases spontaneously. If drainage persists, a reoperation may be necessary, although this is quite uncommon.

CHOLECYSTOSTOMY

In high-risk surgical patients with acute cholecystitis, such as those in the intensive care unit or extensive cardiopulmonary disease, the mortality rates for an emergent operation can be as high as 46%.[27-30] For patients who are poor candidates for a cholecystectomy, the cholecystostomy tube is an effective treatment option. This can be accomplished either percutaneously or via a

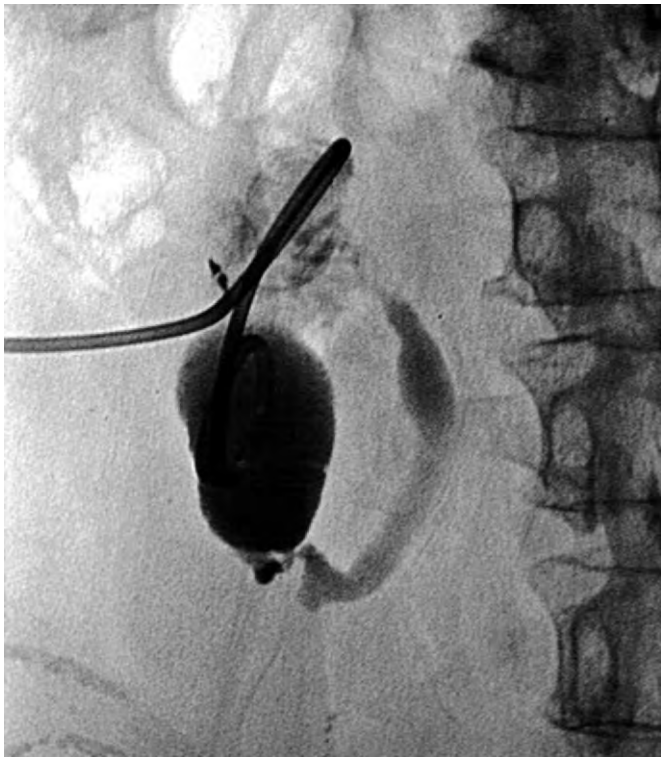

Figure 101–12. Percutaneous cholecystostomy tube is placed under fluoroscopy for acute cholecystitis. Note that there is a large intraluminal filling defect in the common bile duct, consistent with a calculus.

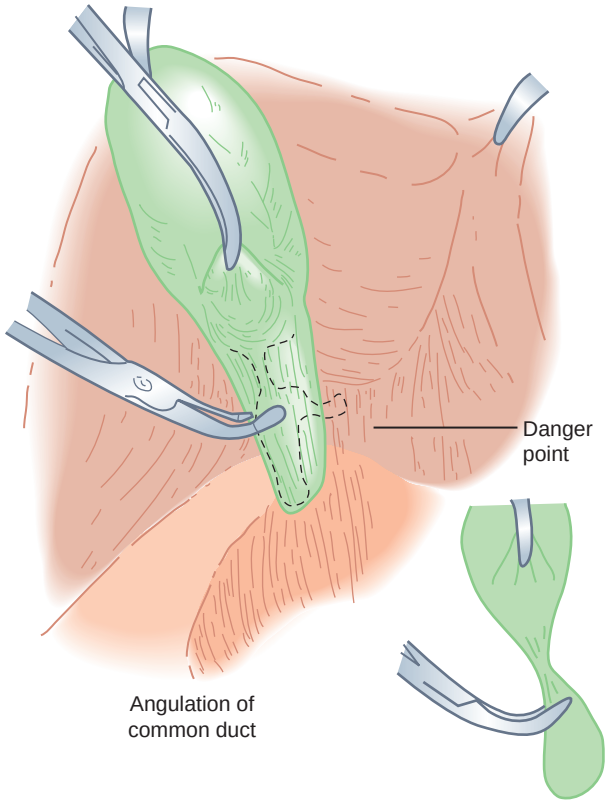

Figure 101–13. A common cause for common bile duct injury. Excessive traction on the gallbladder results in tenting of the common bile duct. This can lead to angulation of the cystic duct–common bile duct junction and erroneous clamping.

small subcostal incision under local anesthesia. It allows immediate decompression of the inflamed gallbladder and can serve as a temporizing measure or as a definitive treatment (Fig. 101–12). The percutaneous cholecystostomy is the preferred route and can even be done under ultrasound guidance in patients who are not stable to travel out of the intensive care setting. If the percutaneous method is not readily available, a small right subcostal incision permitting visualization of the fundus is made. The gallbladder is emptied as much as possible, a Malecot-type or similar catheter is placed in the gallbladder secured with a pursestring suture and exteriorized. Cholecystography is performed through the tube after resolution of cholecystitis. If there is free flow of contrast into the duodenum via a patent cystic duct and common duct, and there are no stones, the tube may be removed and cholecystectomy is not necessarily needed. Patients with gallstones who recover from their acute illness and are fit for surgery should undergo an elective cholecystectomy. In a recent retrospective analysis from our institution, 36 of 45 patients who underwent percutaneous cholecystostomy improved clinically within 5 days. Nine patients died within 30 days of the procedure, and only one death was attributable to gallbladder sepsis.[30] Thus, cholecystostomy is an easy, safe option with a low complication and high success rate for high-risk patients with acute cholecystitis.

MORBIDITY AND MORTALITY

The morbidity rate for an open cholecystectomy ranges from 5% to 20% when all complications are reported, including problems associated with any operation such as ileus, electrolyte abnormalities, atelectasis/pneumonia, and urinary retention.[31-33] The overall mortality rate from an open cholecystectomy is 0.1% to 0.5%.[31-33] Aside from the usual complications associated with any surgical procedure, the most significant complication from a cholecystectomy is a bile duct injury. The incidence of bile duct injury in open cholecystectomy is between 0.1% and 0.2%.[31,34,35] The anatomic variations of the cystic, hepatic ducts and arteries are common enough to warrant no clamping, transection, or ligation until all critical structures have been properly identified. Injury to the hepatic duct or common bile duct often results by mistaking them for the cystic duct. Excessive traction can result in clamping of the hepatic or common duct (Fig. 101–13). If identification of the ductal anatomy is difficult, a cholangiogram should be performed to identify the relationships of the ducts. If an injury has occurred, repair is best if it can be done safely at the time of the original operation. Primary repair can be performed over a T-tube if the defect is small (<1 cm) and there is

no crush or burn injury or, alternatively, a Roux-en-Y reconstruction can be performed for larger defects.

Vascular injury to the right hepatic artery occurs when it is mistaken for the cystic artery. This can lead to future biliary strictures and cholangitis and significant morbidity. In rare instances inadvertent ligation of the right hepatic artery has been fatal. The variations of the hepatic artery and cystic artery confluences and the possibility of accessory arteries mandate proper identification prior to clamping.

Bile leaks occur in less than 1% of the cases and are most commonly from cystic duct stump, accessory duct, or intrahepatic bile duct. They are usually self-limiting and cease drainage in 1 to 2 weeks. If there is failure to close in a reasonable period, a contrast study via a percutaneous cholangiogram or endoscopic retrograde cholangiogram may be diagnostic and therapeutic.[36] During endoscopic retrograde cholangiopancreatography (ERCP), a stent or sphincterotomy may sufficiently relieve the elevated bile duct pressure that is maintaining patency of the leak or fistula and allow for sealing.

In a small subset of patients, new abdominal complaints arise after cholecystectomy that are of an unclear cause despite an extensive work-up. This has been commonly referred to as the *postcholecystectomy syndrome*. Proposed etiologies for this syndrome include papillary stenosis and sphincter of Oddi dysfunction. Biliary manometry, magnetic resonance cholangiopancreatography, ERCP, and ultrasonography may help establish the diagnosis.

Length of stay for an open cholecystectomy is on average 2 to 3 days for an uncomplicated case. Although laparoscopic cholecystectomy has largely supplanted the open variant, there will always remain a role for the open cholecystectomy and its usefulness should not be overlooked.

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Chapter

102

Laparoscopic Management of Common Bile Duct Stones

Edward H. Phillips · Gregg K. Nishi

The incidence of choledocholithiasis in patients undergoing cholecystectomy varies with age, ranging from 6% in patients younger than 80 years of age to 33% in patients older than 80 years.[1] It is estimated that 5% to 12% of patients with choledocholithiasis may be completely asymptomatic, with normal liver function tests.[2-5] Most common bile duct (CBD) stones originate from the gallbladder, and only a small percentage of patients develop CBD stones de novo. Choledocholithiasis is diagnosed at cholecystectomy under two scenarios: (1) intraoperative cholangiograms performed on patients with a high suspicion of CBD stones based on history and liver function tests; and (2) intraoperative cholangiograms performed on patients as part of a protocol for routine cholangiography. The management of choledocholithiasis has been controversial and continues to evolve.

Prior to the adoption of laparoscopic cholecystectomy as the surgical treatment for patients with symptomatic cholelithiasis, the treatment of CBD calculi was relatively straightforward. Patients suspected of harboring CBD stones underwent surgery with intraoperative cholangiography. If CBD calculi were discovered, the bile duct was opened and the stones retrieved. The introduction of therapeutic laparoscopy altered the surgical approach to patients undergoing cholecystectomy. Preoperative diagnostic endoscopic retrograde cholangiography (ERC) became the standard for patients suspected of having choledocholithiasis to avoid converting to open CBD exploration (CBDE). Postoperative endoscopic sphincterotomy (ES) became the preferred approach to treat common duct stones encountered at surgery or discovered afterward. In some communities, ERC/ES increased 243%.[6]

In an effort to treat patients with common duct stones in one session and avoid the potential complications of ES (especially in younger patients with small-diameter CBDs), several laparoscopic techniques of transcystic CBDE (LTCBDE) evolved. As skill in laparoscopic suturing was acquired, laparoscopic choledochotomy was increasingly performed. Various techniques of LTCBDE developed, including lavage; trolling with wire baskets or biliary balloon catheters; the technique of cystic duct dilation; biliary endoscopy; stone retrieval with wire baskets under direct vision; and antegrade sphincterotomy, lithotripsy, and catheter placement.

LTCBDE OR CHOLEDOCHOTOMY

Indications for LTCBDE or choledochotomy include filling or equivocal defects on cholangiography, stone size less than 9 mm for LTCBDE, fewer than eight stones for LTCBDE, possible tumor, and favorable cystic duct. Contraindications to LTCBDE include stones larger than 1 cm; stones proximal to the cystic duct entrance into the CBD; small, friable cystic duct; and 10 or more stones. Indications for choledochotomy include filling defects in a bile duct larger than 6 mm in diameter but are also based on the expertise of the surgeon (Table 102–1).

CHOLEDOCHOSCOPY

Choledochoscopic transcystic CBDE requires dilation of the cystic duct in nearly all cases. To facilitate instrumentation, the cystic duct should be bluntly dissected to or near its junction with the common duct. A new incision in the cystic duct should be made approximately 1.5 cm from the common duct. A hydrophilic guidewire should be placed inside a balloon-dilating catheter and inserted into the bile duct. If there is any resistance or question regarding its location, radiographic or fluoroscopic confirmation must be obtained. A dilating balloon catheter with an outer diameter the size of the largest stone but smaller than the inner diameter of the common duct is chosen to dilate the cystic duct (Fig. 102–1). Ureteral bougies can be used for dilation but are not as successful.

Table 102–1 LTCBDE Versus Lap Choledochotomy

Variables	LTCBDE	Lap Choledochotomy
Skill	Endoscopy	Lap suturing
Stones		
Number	<8	Any number
Size	<9 mm	Any size
Location	Distal to cystic duct	Entire duct
CBD diameter	Any	>6 mm
Drain	Optional	Suggested
Contraindication	Friable cystic duct	Small-diameter CBD
	Intrahepatic stones	
	Multiple, large stones	
Advantages	No T-tube	Quick
	Shorter hospital stay	T-tube for postoperative access
Disadvantages	Equipment intensive	Lap suturing
	New skill required	T-tube

CBD, common bile duct; Lap, laparoscopic; LTCBDE, laparoscopic transcystic common bile duct exploration.

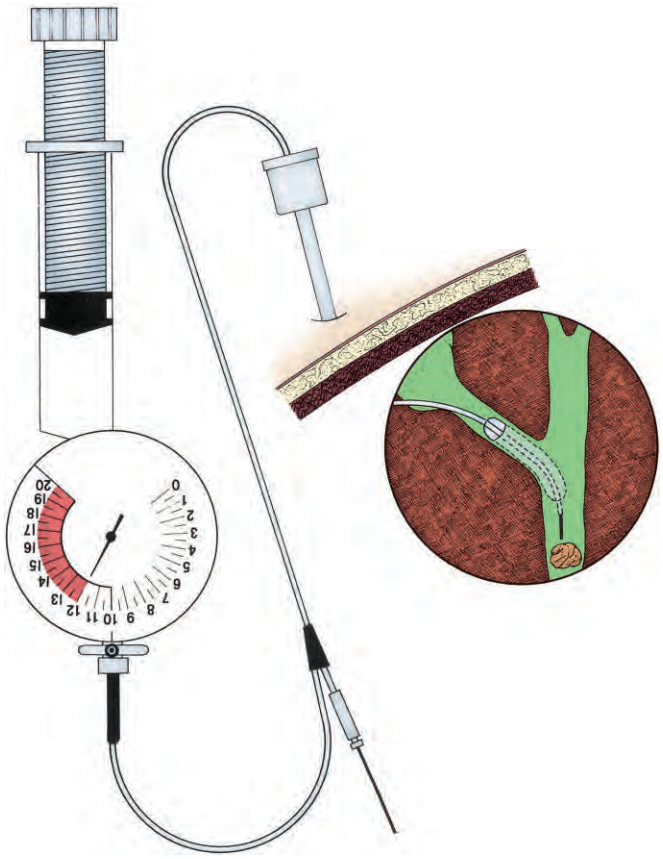

Figure 102–1. Balloon catheter attached to a LeVeen syringe during dilation of the cystic duct.

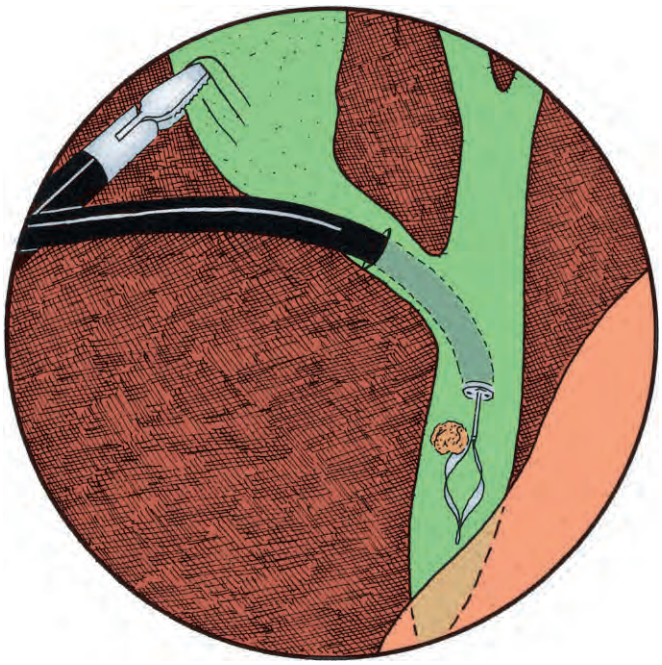

Figure 102–2. Advancing wire basket through a choledochoscope for stone entrapment.

After careful dilation of the cystic duct, a bidirectional flexible choledochoscope is introduced into the cystic duct and manipulated down the CBD while warm irrigation is employed. When the first stone is identified, a straight 4-wire 2.4-French Segura basket is inserted down the working channel, passed just beyond the stone, opened, withdrawn, and closed, capturing the stone (Fig. 102–2). The stone and basket assemblage are then pulled up to the tip of the scope and withdrawn in unison (Fig. 102–3). Choledochoscopy is continued until no stones are identified and the ampulla can be seen, not necessarily transgressed. An effort is made to pass the scope up into intrahepatic bile ducts, though this can be performed only about 10% of the time. A

Table 102–2 Results Comparing LTCBDE with Choledochoscopy

Authors, Year	Number	Choledochoscopy, %	Success, %	Retained Stones, %	Morbidity, %
Stoker, 1995[7]	33	100	97	NA	10
Roush and Traverso, 1995[8]	32	0	59	NA	0
Rojas-Ortega et al., 2003[9]	40	100	94	NA	8.8
DePaula et al., 1993[10]	107	34	84	NA	6
Petelin, 1991[11]	186	67	96	NA	10
Petelin, 2003[12]	269	68	97	10	9
Phillips et al., 1994[13]	178	91	97	4	4
Riciardi et al., 2003[14]	270	NA	98	3	9.5

LTCBDE, laparoscopic transcystic common bile duct exploration; NA, not available.

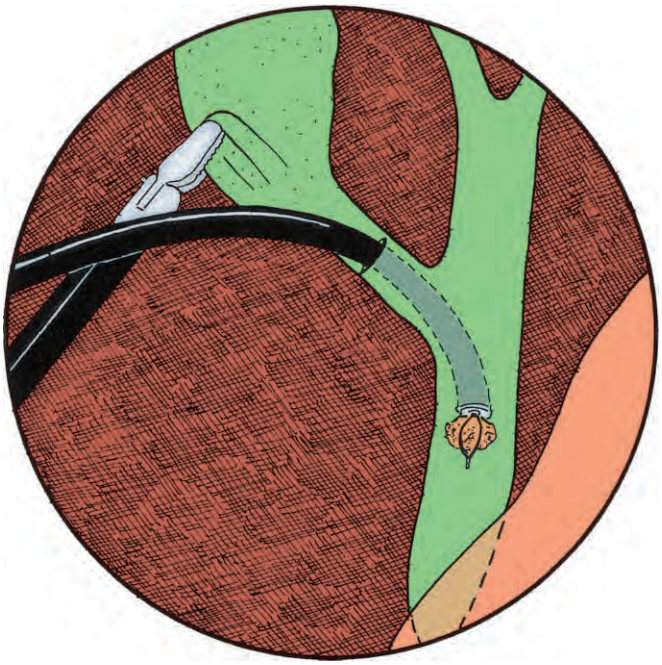

Figure 102–3. Retrieval of the choledochoscope simultaneously with the stone.

completion cholangiogram is always obtained. Results of studies comparing the two approaches are shown in Table 102–2.[7-14]

FLUOROSCOPIC WIRE BASKET STONE RETRIEVAL

Fluoroscopic wire basket stone retrieval is feasible and only requires fluoroscopy and wire baskets. This technique is less expensive than choledochoscopy and is successful approximately 60% of the time. Special spiral wire baskets with flexible leaders must be used to avoid injury to the CBD. The basket is placed into the common duct via the cystic duct. Hypaque is injected through the catheter. The catheter is advanced under fluoroscopic guidance into the lower common duct or duodenum. Then it is opened and pulled back until the stone is captured. The advantage of not having to dilate the cystic duct is offset by the problem of extracting the wire basket with the stone entrapped in it through the nondilated cystic duct. Ureteral bougies or a dilating balloon should be used to dilate the cystic duct when needed. With this technique, a significantly increased amount of fluoroscopy is used. The surgeon must apply the fluoroscopy judiciously and ensure that the total "on" time of fluoroscopy does not exceed 5 minutes.

Though it is not as successful as choledochoscopy techniques, it is a useful technique. Rhodes et al.[15] used a Dormia basket to retrieve stones in 79 selected patients with a 96% success rate. DePaula et al.[16] performed this technique in 70 (65%) of 107 transcystic explorations. The success rate of this experience was not stated, but they did report an 84% success rate for all transcystic techniques. Lezoche and Paganini[17] reported a 97% success rate using the fluoro-basket technique in 77 patients and choledochotomy in 39 patients.

BILIARY BALLOON CATHETER

Biliary balloon catheter stone retrieval is occasionally helpful, especially in cases with a dilated cystic duct. A biliary balloon catheter can be passed blindly or under fluoroscopic control via the cystic duct into the duodenum. The balloon is inflated and then the catheter is gently withdrawn, modulating the pressure on the balloon. The drawback to this technique is the potential to pull the stone into the common hepatic duct, out of reach of an endoscope.[18]

AMPULLARY BALLOON DILATION

Ampullary balloon dilation is a controversial technique. It can be employed when the cystic duct is extremely small and an endoscope cannot be inserted. Glucagon, 1 mg, is administered intravenously. A balloon-dilating

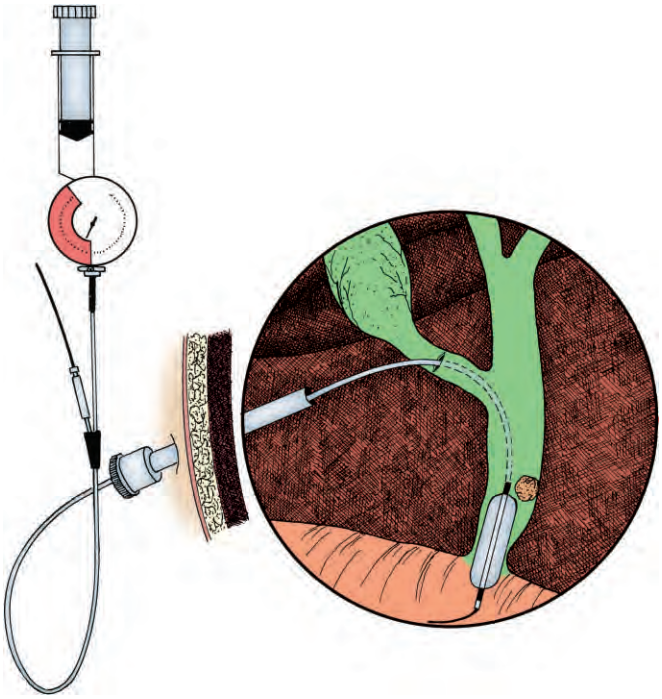

Figure 102–4. Balloon dilation of the papilla.

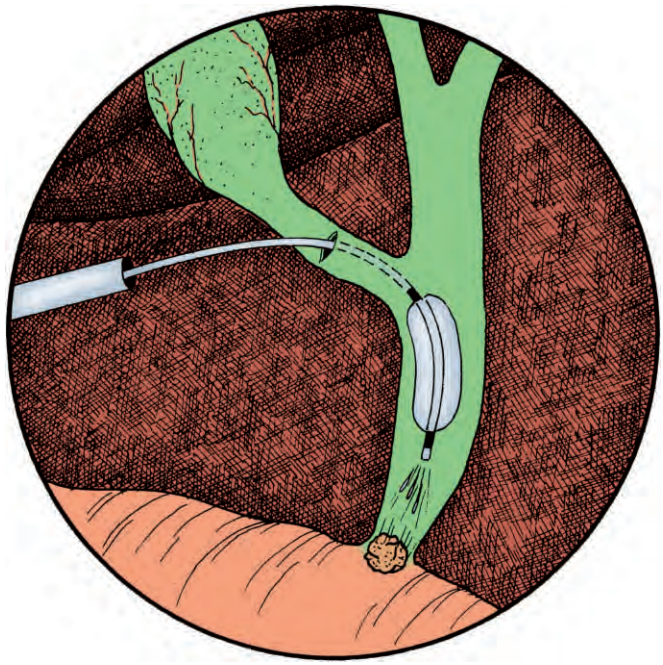

Figure 102–5. Flushing of the common bile duct.

catheter is chosen of the proper outer diameter based on the inner diameter of the common duct. A hydrophilic guidewire is inserted in the lumen of the catheter and the assemblage is inserted via the subcostal trocar. The guidewire is advanced into the duodenum via the cystic duct under fluoroscopic control. The balloon catheter is then advanced until the balloon radiopaque markers on each side of the balloon span the sphincter (Fig. 102–4). The balloon is inflated to the manufacturer's recommended pressure (12 mm Hg) with a LeVeen syringe attached to a pressure gauge. Hypaque (25%) is used to inflate the balloon so that the balloon is visible on fluoroscopy. The balloon is left inflated for 3 minutes and then deflated and withdrawn. A large-bore catheter or the dilating balloon catheter itself is placed in the cystic duct and warm saline is used to forcibly flush the CBD, using a pump or a high-flow irrigator (Fig. 102–5). A completion cholangiogram is mandatory.[19] This technique is highly successful with stones 5 mm or smaller in diameter, but postoperative hyperamylasemia occurs in approximately 25% of patients, and serious pancreatitis can occur. This should be considered when the only alternative is ES.

CYSTIC DUCT CATHETER TECHNIQUE

A cystic duct catheter technique has been reported by Fitzgibbons et al.[20] A ureteral catheter is inserted through the cystic duct into the duodenum. The catheter is used to perform postoperative cholangiography. If stones are still present, guidewire-assisted retrograde ES is performed.

ANTEGRADE SPHINCTEROTOMY

Antegrade sphincterotomy can be performed via the cystic duct. DePaulo,[10] Curet,[21] and their colleagues have employed this technique in a small number of patients with good results. A gastroscope must be inserted via the mouth to observe the papillotome orientation. This may be a safe way to achieve a drainage procedure laparoscopically, but it is equipment intensive.

LAPAROSCOPIC CHOLEDOCHOTOMY

Laparoscopic choledochotomy is an excellent approach to the CBD. It is indicated when the CBD diameter is larger than 6 mm, in cases when calculi are larger than 1 cm, when there are multiple calculi, or when lithotripsy is required for impacted calculi. It is contraindicated in small ducts because of the risk of stricture secondary to otomy closure. The advantage of a choledochotomy over the transcystic approach is that calculi can easily be irrigated out of the CBD and an endoscope can be inserted up into the intrahepatic ducts. CBDEs, especially for solitary large stones, can be performed without a choledochoscope by milking or irrigating the CBD stone into the otomy. Also, a larger diameter (3.3 mm) choledochoscope with a larger working channel (2.4 mm) can be used. The larger working channel accommodates larger and less delicate wire baskets. Another advantage of choledochotomy is that a T-tube is placed that decompresses the duct and provides access for postoperative cholangiography and retrieval of retained calculi. The disadvantages of choledochotomy

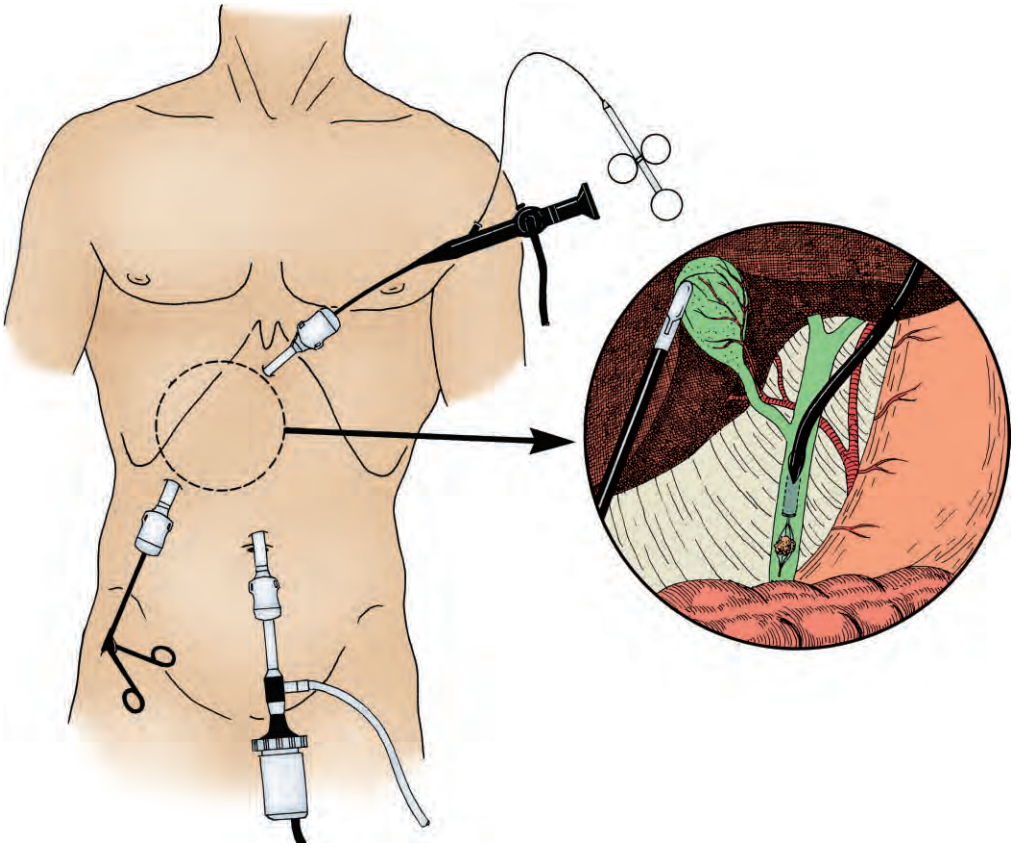

Figure 102–6. Retrieving the stone via choledochotomy.

are that a T-tube is required, and considerable laparoscopic suturing skill is needed to close the choledochotomy (see Table 102–1).

The duct exploration is performed before the gallbladder is removed so that the gallbladder can be used to elevate the liver and apply tension to the cystic duct/CBD. The anterior wall of the CBD is dissected bluntly. The choledochotomy is placed in the anterior wall below the junction of the cystic duct (Fig. 102–6). Two stay sutures can be placed in the CBD and its anterior wall tented to facilitate an incision. The choledochotomy should be made only as long as the diameter of the largest calculus to minimize the suturing required for closure. A biliary balloon catheter or wire basket or both can be used to remove calculi via the choledochoscope or even along side it.

After the exploration and if a drainage procedure is not indicated, a latex T-tube (10- to 14-French) is placed in the common duct (Fig. 102–7). The entire T-tube is placed into the abdominal cavity and the T portion is situated in the CBD. A suture is placed immediately below the tube while it is pushed cephalad (Fig. 102–8). The next suture should be placed at the other end of the choledochotomy. The two sutures are lifted to facilitate closure of the choledochotomy. The addition of another right lower quadrant trocar facilitates suturing and handling of the T-tube. The choledochotomy is closed with interrupted sutures of Vicryl lubricated with mineral oil. The long end of the T-tube is brought through the abdominal wall and completion cholangiography is performed. Results with laparoscopic choledochotomy have been excellent (Table 102–3).[10,12,13,22-29]

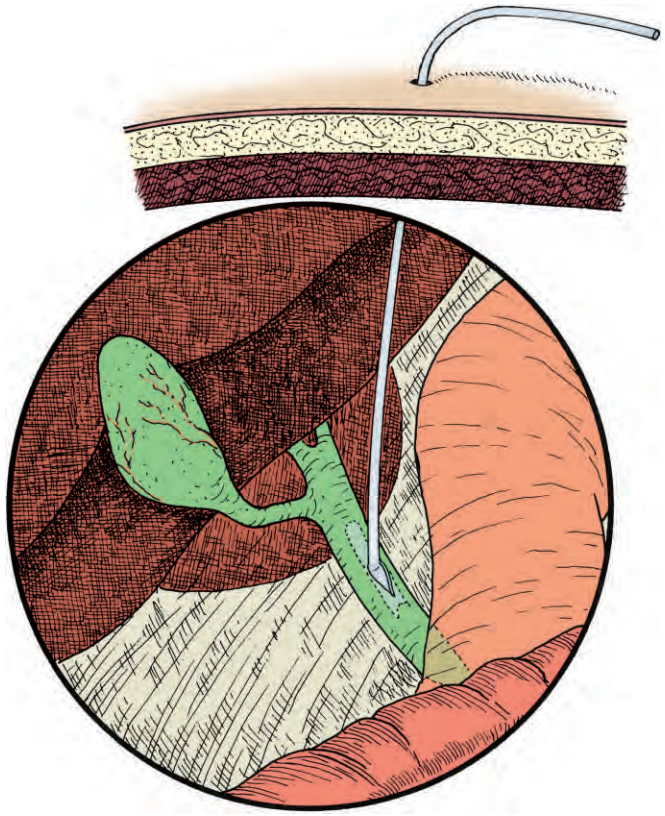

Figure 102–7. A T-tube is placed into the choledochotomy after stone removal and brought out through a subcostal trocar site.

Table 102–3 Results of Laparoscopic Choledochotomy Studies

Authors, Year	Number	Success, %	Retained Stones, %	Morbidity, %
Croce et al., 1996[22]	33	97	4	9
Franklin et al., 1994[23]	80	NA	2	5
Cuschieri et al., 1999[24]	43	NA	2	7
DePaulo et al., 1993[10]	12	100	8	17
Phillips et al., 1994[13]	18	95	17	17
Huang et al., 1996[25]	40	88	5	18
Petelin, 2003[12]	57	NA	NA	9
Millat et al., 1997[26]	92	NA	4	13
Decker et al., 2003[27]	100	100	0	11
Lien et al., 2005[28]	82	NA	17	4
Dorman et al., 1998[29]	148	96.6	2	5

NA, not available.

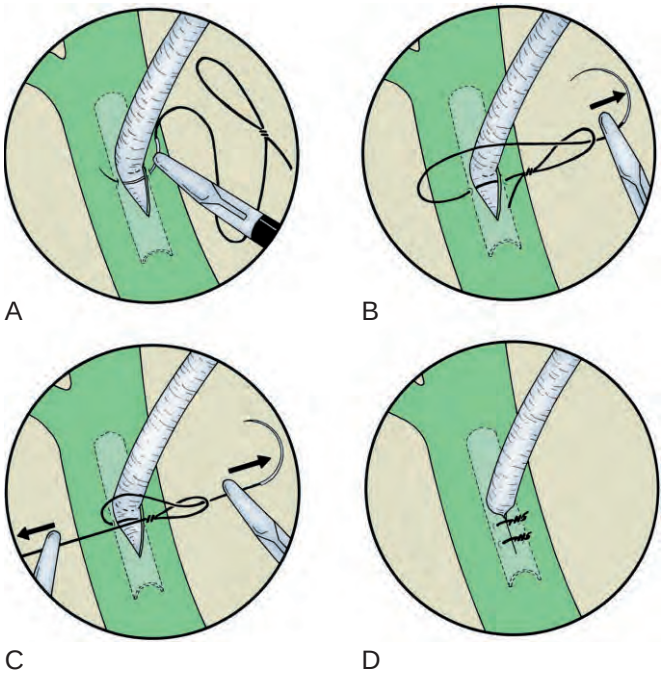

Figure 102–8. **A** to **D,** A T-tube is sutured in place.

Several authors have advocated primary closure of the CBD without the use of T-tubes during laparoscopic choledochotomies with comparable results in selected groups of patients. Noted advantages of this technique include decreased morbidity from external biliary drainage (as high as 15%), and shorter length of hospital stay. After closure of the CBD, a combination of methylene blue dye and Hypaque contrast can be injected through a transcystic cholangiogram catheter to assess for leakage or excessive narrowing of the CBD closure.[27]

Another alternative technique to CBD closure over T-tube and primary CBD closure is laparoscopic placement of an endobiliary stent with primary closure of the choledochotomy.[30] The stent, typically 10 French, is advanced into the duodenum until the proximal end is positioned distal to the lower edge of the choledochotomy. A transcystic cholangiogram can then be used to confirm placement and patency of the biliary system.

Procedure-related complications are shown in Table 102–4. Most complications are detected at surgery by direct vision or on completion cholangiogram. Careful attention to technique can avoid most problems.

DISCUSSION

A recent prospective, multicenter study of ES in 1494 patients showed a procedure-related morbidity of 7.4% when ES was performed in conjunction with laparoscopic cholecystectomy, procedure-related mortality of 0.5%, and total mortality of 2.2%.[31] Therapeutic recommendations for patients undergoing laparoscopic cholecystectomy with suspected CBD stones should consider these more inclusive morbidity figures. They should also reflect the delayed risk of stricture. These risks may exceed those of open CBDE in younger patients, especially with small-diameter common ducts, but are similar to laparoscopic CBDE in patients older than 65 years of age. Some reports indicate that open CBDE has almost no mortality in patients younger than 60 years but 4.3% mortality in those older than 60 years.[32]

The experiences with LTCBDE of our group,[33] De Paula,[16] and Petelin[11] show that the approach is applicable in more than 85% of cases and is successful in 85% to 95% of cases. Complications do occur (6% major and 12% minor), but these also include complications associated with laparoscopic cholecystectomy. There were only two LTCBDE procedure-related complications in our series of 188 LTCBDEs, no mortality in patients younger than 65 years of age, and one death (<1%) in a patient older than 65 years. The outcomes with either ES or open CBDE show that patients younger than 65 years have improved outcomes with LTCBDE. Those older than 65 years have comparable outcomes with ES plus laparoscopic cholecystectomy and laparoscopic CBDE but only require a single procedure with laparoscopic CBDE. The long-term results of LTCBDE for our group

Table 102–4 Potential Procedure-Related Morbidity

Condition	Technique	Treatment
Cystic duct avulsion	LTCBDE	Suture with or without cystic duct tube
Cystic duct leak	LTCBDE	Percutaneous drainage and transampullary stent
Bile leak	Otomy	
Entrapped basket and stone in CBD	LTCBDE	Cut wire (slide out), choledochotomy
Intimal disruption/tear	LTCBDE	T-tube or stent
	Otomy	Possible suture repair
Bile duct puncture (wire basket, balloon, guidewire, scope)	LTCBDE	T-tube or stent
	Otomy	Percutaneous drainage if biloma
Retained stone	LTCBDE	ES
	Otomy	T-tube tract retrieval

CBD, common bile duct; ES, endoscopic sphincterotomy; LTCBDE, laparoscopic transcystic common bile duct exploration.

and others have been excellent with no evidence of CBD strictures and rare occurrence of retained CBD stones at up to 72 months postoperatively.[14,33,34]

Choledochoscopy via the cystic duct appears to be the most effective (90%) and safest approach to the common duct. Nevertheless, it is possible to employ fluoroscopic basket retrieval in many cases (60%). Even irrigation and trolling with a biliary balloon catheter will be effective in some cases. Ampullary balloon dilation should be performed when the only alternative is ES. Antegrade sphincterotomy should be reserved for the 5% to 10% of complex cases that require a drainage procedure. Lithotripsy, either with electrohydraulic or laser energy, is best employed via a choledochotomy because of the resultant debris. Leaving a catheter in the cystic duct or a transampullary biliary stent will ensure successful postoperative sphincterotomy. With the tube in place, it is virtually assured that CBD stones can be removed postoperatively with guidewire-assisted ES, chemical dissolution, or tube tract extraction techniques without a second operation. Consequently, reliance on preoperative ERC is no longer needed except in cases for which it has proven efficacy, including suspicion of malignancy, worsening pancreatitis, severe cholangitis, or patients unfit for surgery. Further technologic advances will facilitate the application and adoption of laparoscopic approaches to the common duct, which should become the primary strategy in most patients.

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Chapter

103

Endoscopic Retrograde Cholangiopancreatography in the Evaluation and Management of Hepatobiliary and Pancreatic Disease

Stuart Sherman · James L. Watkins · Lee McHenry · Evan L. Fogel · Glen A. Lehman

Endoscopic cannulation of the major papilla with imaging of the pancreatic duct and biliary tree (endoscopic retrograde cholangiopancreatography [ERCP]) was first successfully accomplished with an end-viewing duodenoscope and reported in 1968.[1] The subsequent development of side-viewing endoscopes with a catheter-deflecting elevator greatly facilitated the technique. Diagnostic studies were supplemented by the first endoscopic sphincterotomies in 1973.[2,3] Techniques of biliary stone extraction, nasobiliary tube (NBT) placement, and biliary stent placement soon followed. These developments permitted less invasive diagnostic and therapeutic maneuvers in the pancreatic and bile duct that were previously limited to open surgical and percutaneous techniques. Although these procedures are more technically demanding than most other gastrointestinal endoscopic techniques, they are now being widely applied and are the method of choice for many clinical problems involving the pancreatic duct and the hepatobiliary system.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Indications

The role for diagnostic ERCP alone is diminishing as other less invasive/noninvasive imaging techniques (e.g., endoscopic ultrasound [EUS], magnetic resonance cholangiopancreatography [MRCP]) become more widely used.[4] ERCP is indicated in clinical settings in which there is significant suspicion of an obstructing, inflammatory, or neoplastic pancreaticobiliary lesion that if detected or ruled out, would alter clinical management. A general classification of indications is listed in Box 103–1.

Preparation

Preparation for ERCP involves assembly of a skilled team that includes a physician or physicians, nursing personnel, and a radiology technician. A quality fluoroscopic unit is needed. A wide variety of catheters, guidewires, stone extraction balloons and baskets, sphincterotomes, stents, drainage catheters, lithotripters, and tissue-sampling devices should be available.

Patient preparation includes an updated history and physical examination and a recent complete blood count, serum liver chemistry panel, serum amylase or lipase (or both), coagulation studies, and noninvasive imaging of the upper part of the abdomen with abdominal ultrasonography, computed tomography (CT), or magnetic resonance imaging/MRCP, depending on the clinical situation.[5,6] Special risk factors such as anticoagulant therapy, bleeding disorders, prosthetic heart valves,

Box 103–1 Indications for Endoscopic Retrograde Cholangiopancreatography

Suspected Biliary Ductal Disorder

- Jaundice or cholestasis of suspected obstructive origin
- Acute cholangitis
- Gallstone pancreatitis
- Clarification of biliary lesion seen on other imaging tests
- Biliary fistula

Suspected Pancreatic Ductal Disorder

- Pancreatic cancer
- Mucinous or cystic neoplasm
- Unexplained recurrent pancreatitis
- Chronic pancreatitis with unrelenting pain
- Clarification of pancreatic lesion detected on other imaging tests
- Ascites or pleural effusion of suspected pancreatic origin
- Pancreatic pseudocyst or fistula

To Direct Endoscopic Therapy

- Sphincterotomy
- Biliary drainage
- Pancreatic drainage

To Direct Endoscopic Tissue/Fluid Sampling

- Biopsy, brush, fine-needle aspiration
- Bile/pancreatic juice collection

Preoperative Ductal Mapping

- Malignant tumors
- Benign strictures
- Chronic pancreatitis
- Pancreatic pseudocysts and ductal disruptions
- Mucinous or cystic tumors of the pancreas

To Perform Manometry

- Sphincter of Oddi
- Ductal

and allergies must be addressed. If possible, aspirin and nonsteroidal anti-inflammatory drugs should be avoided for 7 days before the procedure.

Informed consent for ERCP must be obtained. It is both legally and ethically necessary to apprise the patient and family of the risks, benefits, and alternatives of ERCP. Table 103–1 lists the potential complications of diagnostic and therapeutic ERCP and their relative frequency. Although legal standards continue to evolve, we recommend that patients not only be informed of the frequency of potential complications but also be told that a severe complication may possibly result in a prolonged hospital stay, intensive care unit (ICU) monitoring, or open surgery and may very rarely result in permanent disability or death. Complication rates vary according to patient and procedure risk factors, as well as the disease process being evaluated and treated.[7] Patients with uncomplicated biliary stones, malignancy, or chronic pancreatitis have lower complication rates, whereas patients with recurrent pancreatitis and sphincter of Oddi dysfunction have twofold to threefold higher complication rates. Procedure techniques associated with higher complication rates include repeated cannulation attempts, repeated pancreatic duct injections, pancreatic parenchymal acinarization, and precut sphincterotomy. Attention to details of the technique and patient selection can minimize but not eliminate complications. Early recognition plus treatment of complications helps limit morbidity.

ERCP can be performed with fiberoptic or video chip instruments, which have similar performance characteristics. Video systems have the advantage of television monitor viewing by all persons in the endoscopy suite. Such systems offer better teaching capabilities and allow better coordination between the endoscopist and nursing assistants. For Billroth II patients, we generally start with a standard side-viewing duodenoscope, but an end-viewing endoscope is occasionally needed. In patients with a long Roux-en-Y gastroenterostomy, a 220-cm enteroscope will reach the site of pancreatic or bile duct drainage in approximately half the patients.[8] The lack of a catheter-deflecting elevator and limited compatible accessories make end-viewing endoscopy difficult in these settings.

Technique

The patient is positioned in a prone to slightly left lateral decubitus position on a fluoroscopic table. Intravenous access and monitoring equipment for blood pressure, pulse, and pulse oximetry are needed. Electrocardiographic monitoring is desirable for patients with angina or a history of a cardiac arrhythmia. Sedation and analgesia are achieved by slow intravenous administration of common agents such as diazepam (10 to 40 mg), midazolam (1 to 5 mg), or meperidine (25 to 150 mg). Droperidol (2.5 to 5.0 mg) is a common supplement or alternative, particularly for alcoholics or persons taking narcotics or benzodiazepines.[9] However, recent concerns about QT interval prolongation has limited the use of droperidol for conscious sedation. Although propofol

Table 103–1 Approximate Frequencies of Complications After Endoscopic Retrograde Cholangiopancreatography and Sphincterotomy (%)

	Average-Risk Patients		High-Risk Patients*	
Complication	*ERCP*	*Sphincterotomy*	*ERCP*	*Sphincterotomy*
Pancreatitis	3	5	8	12
Bleeding	0.2	1.5	0.4	3.5
Perforation	0.1	0.8	0.3	1.5
Infection	0.1	0.5	2	2
Sedation reaction or cardiopulmonary	0.5	0.5	2	2
Total†	3.9‡	8.3‡	12.7‡	21‡

*Certain patient characteristics and technical aspects of the procedure increase the risk for complications, including suspected sphincter of Oddi dysfunction, recurrent pancreatitis, difficult cannulation, precut sphincterotomy, coagulopathy, renal dialysis, cirrhosis, and advanced cardiopulmonary disease.

†Some patients have more than one complication.

‡Approximate severity of complications: mild, 70%; moderate, 20%; and severe, 10%.

may offer better procedure tolerance and a much shorter recovery time than standard sedation does, the complication rate when administered by endoscopists and not anesthesiologists has not been well studied.[10,11] A topical pharyngeal anesthetic spray is desirable. An antiperistaltic drug (e.g., glucagon or atropine) to inhibit duodenal motility is commonly needed.

Initially, a brief endoscopic examination of the esophagus, stomach, duodenum, and major duodenal papilla is performed. The finding of a large ulcer or neoplasm may cancel the need for ERCP. Other findings such as varices, a pseudocyst pressing on the gut wall, or edema of the medial wall of the duodenum help quantitate or localize disease processes. The major papilla is usually located on the medial aspect of the mid-descending duodenum. Before attempts at cannulation, fluoroscopic visualization (or filming) of the field of interest should be performed to look for calcifications, masses, and old contrast material. The major papilla is then cannulated, usually with a 5-French-diameter plastic catheter. Orientation of the catheter tip toward the 11- to 12-o'clock position will more likely permit entrance into bile duct; orientation of the catheter toward the 3- to 5-o'clock position will more likely permit entrance into the pancreatic duct. Cannulation may be accomplished by gentle impaction of the catheter tip in the papillary orifice. Deep cannulation (greater than 1-cm penetration of the catheter into the duct) more securely establishes an intraductal position, which allows contrast injection, fluid aspiration, patient position changes, and endoscope position changes without loss of access to the duct.

Standard contrast media (e.g., meglumine diatrizoate) at a 50% to 60% (full-strength) concentration is used for pancreatography, whereas a 25% to 30% (half-strength) concentration is recommended for cholangiography. Biliary stricture detail is better defined with full-strength contrast, however. Nonionic and lower-osmolality contrast media, which are more expensive, offer no safety advantage. Injection of contrast media is done with continuous fluoroscopic monitoring. The extent of ductal filling should be correlated with the clinical need to know the ductal anatomy. Complete pancreatography involves filling of the main duct and side branches to the tail. High-resolution fluoroscopy is required to see such detail. In settings in which there is excess overlying gas or obesity, underfilling of the pancreatic duct is recommended to avoid acinarization (instillation of contrast media into the pancreatic parenchyma). For a very dilated duct, initial aspiration of fluid will allow better contrast visualization without overdistention of the duct. Complete cholangiography requires filling of the peripheral intrahepatic radicles. The left lobe is more dependent in the prone position and fills preferentially. Right lobe filling may require tilting the patient's head down 15 to 20 degrees on the fluoroscopy table, more forceful injection (a balloon occlusion catheter is helpful), or turning the patient to the supine position. Contrast media mixes slowly with gallbladder bile, and final films are best taken in the supine position after withdrawal of the endoscope (and additional time for mixing with gallbladder contents). Occasionally, delayed gallbladder films taken 4 to 12 hours after completion of the procedure allow the passage of intraluminal gas and give better diagnostic film quality. In settings of tight biliary strictures, limited contrast filling upstream should be done until catheter access above the stricture is achieved. Similarly, limited pseudocyst filling should be done unless immediate drainage is certain. Several views of each ductal position are recommended in both the limited-filling and more completely filled state.

Sphincter of Oddi manometry (SOM) is usually performed at the time of ERCP. All drugs that relax (e.g., anticholinergics, nitrates, calcium channel blockers, glucagon) or stimulate (e.g., certain narcotics, cholinergic agents) should be avoided for at least 8 to 12 hours

before SOM and during the manometric session. SOM is performed with a low-compliance infusion pump system and a 5-French catheter.

Endoscopic sphincterotomy (ES) of the bile duct is commonly performed before removing bile duct stones or placing a biliary stent. A pull-type (traction) sphincterotome is advanced into the bile duct and its position confirmed with fluoroscopy. The sphincterotome is pulled back until 5 to 7 mm of cutting wire is passed into the papillary orifice. The instrument is bowed to apply gentle tension in the 11- to 12-o'clock direction. Cautery current at 40 to 60 W is applied in bursts of less than 1 second to stepwise cut 80% to 90% of the intramural portion of the bile duct. Although blended current is most commonly used, pure cut current may be associated with a lower incidence of pancreatitis without increasing the rate of sphincterotomy-induced bleeding.[12] Many endoscopists are now using a microprocessor-controlled electrosurgical generator (Endocut by Erbe).[13] Adequacy of the sphincterotomy is judged by pulling a bowed sphincterotome through the incised sphincter. Small papillae and papillae associated with diverticula may require smaller cuts. Minor bleeding may occur but usually stops spontaneously. Bleeding that limits the endoscopic view should be controlled by hydrostatic balloon tamponade, bipolar cautery, or epinephrine injection. Pancreatic sphincterotomy is performed in a similar fashion as biliary sphincterotomy (once access to the pancreatic duct is obtained with the sphincterotome), except that the direction of the cut is usually made in the 1- to 2-o'clock position. Some authorities advocate performing pancreatic sphincterotomy after placing a 3- to 4-French, 6- to 8-cm-long, unflanged polyethylene stent into the pancreatic duct and then cutting over the stent with a needle knife.

Precut sphincterotomy involves cutting the papilla to gain deep intraductal access to the biliary tree. This technique should be limited to experienced endoscopists and used when there is high clinical suspicion of obstructive pathology (e.g., a jaundiced patient with a dilated bile duct on ultrasound) after standard techniques fail. Precutting can be achieved by impaction of a short-nosed, pull-type sphincterotome into the papillary orifice with sequential shallow cephalad cuts until the biliary orifice is identified. Similar sequential shallow cuts can be made with a needle knife. We prefer to place a 3- to 4-French, 6- to 8-cm-long, unflanged polyethylene stent into the pancreatic duct first, if possible, and use the stent to guide needle knife cutting.

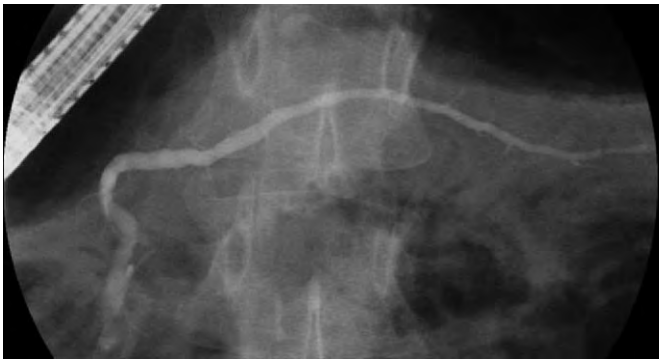


Figure 103–1. A normal pancreatogram obtained by placing a catheter in the duct of Wirsung. Note the gradual tapering of the main pancreatic duct and the delicate side branches.

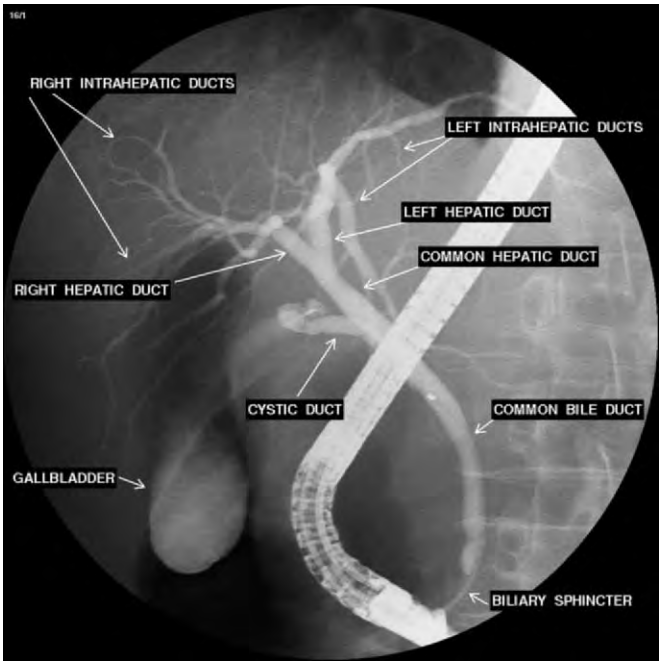


Figure 103–2. The normal common bile duct becomes the common hepatic duct proximal to the insertion of the cystic duct. The common hepatic duct bifurcates into the right and left hepatic ducts. The cystic duct has a spiral shape because of the valves of Heister and connects the gallbladder to the bile duct.

Radiology

Figure 103–1 shows a normal pancreatogram. The contour of the main duct is typically S shaped, but numerous other configurations are common and normal. The upper limits of normal for main duct diameter are 5 mm in the head, 4 mm in the body, and 2 mm in the tail. Side branches are delicate with terminal branching. The accessory duct extends from the genu at the junction of the head and body of the main duct to the minor papilla. The minor papilla has a patent orifice in approximately 85% of patients. Pancreas divisum is discussed later.

A normal cholangiogram is shown in Figure 103–2. The upper limit of normal diameter for the common bile duct is 10 mm. The cystic duct commonly joins the common duct approximately halfway from the hilum to the papilla, but this junction may be quite variable. The intrahepatic radicles have a tree-like branch pattern with marked variation in distribution.

Cannulation Success Rates

The papilla is readily identified by experienced endoscopists in nearly all patients with normal anatomy. Difficulty finding the papilla may arise in patients with large papillary tumors, duodenal stenosis, or edematous folds caused by acute pancreatitis, as well as in patients whose papilla is located inside a diverticulum. In patients with a Billroth II gastrojejunostomy, the success rate should be greater than 80% when the procedure is performed by an expert. Initial cannulation success rates with ductography vary from 80% to 98%, depending on operator experience, anatomy, and disease state. Cannulation is easiest in patients with biliary stones but more difficult in patients with periampullary neoplasms, sphincter of Oddi dysfunction, and chronic pancreatitis with obstructing stones. In experienced centers, cannulation success rates exceed 95%, even in difficult cases when a previous attempt at cannulation failed.[14] Such high success rates require supplemental use of precut sphincterotomy and minor papilla cannulation in 10% to 25% of cases.

Complications of Endoscopic Retrograde Cholangiopancreatography/Sphincterotomy

Complications of ERCP/ES are undesirable outcomes related to some portion of the procedure or sedation required for the procedure. Unsuccessful cannulation, stent placement, or stone removal and making an incorrect diagnosis are failures of the procedure but are not generally included as complications. Table 103–1 lists the more common complications of diagnostic and therapeutic ERCP. Since 1991, a more uniform classification of ERCP complications and their severity has been developed.[15]

BILE DUCT STONES

The introduction of ES by Classen and Kawai[2,3] in 1974 initiated a change in the management of bile duct stones. Before that time, laparotomy with common bile duct exploration was the main therapeutic recourse for patients with choledocholithiasis. With improvements in equipment and accessories, growth in number and skill of biliary endoscopists, and the introduction of laparoscopic cholecystectomy, the clinical settings in which endoscopic management is applied to common duct stones has been broadened considerably.

Methods of Stone Extraction

Standard (Basket and Balloon Catheters)

After identification of a common duct stone, a sphincterotomy is usually performed. The length of the cut is dictated by the length of the endoscopically visible intramural bile duct and the size of the stone. Balloon catheters are most useful for extracting one or more relatively small stones (<10 mm) in a nondilated duct. They are not as effective for extracting larger stones or small stones in a markedly dilated bile duct because the balloon will often slide past the stone. A major advantage of a stone retrieval balloon (versus a basket) is that it cannot become impacted, although the stone can.

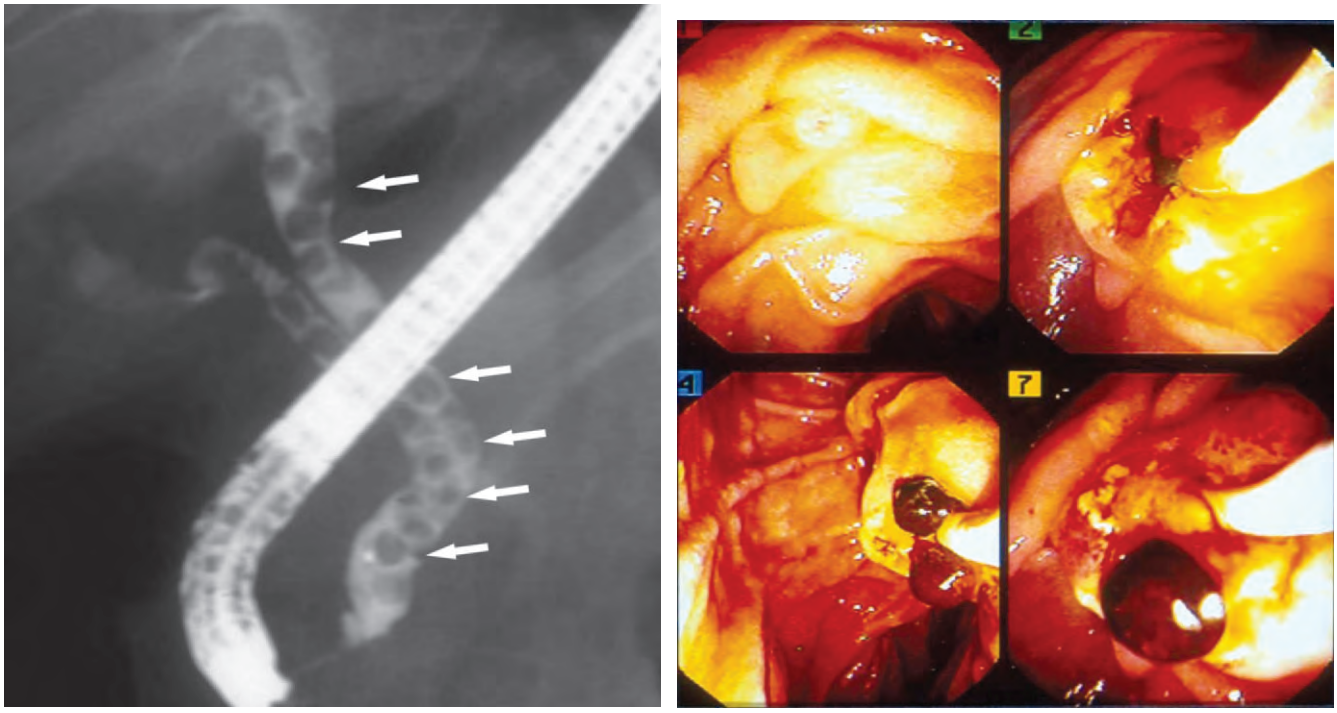
Catheters with balloons that inflate to 8 to 18 mm are commercially available. The catheter is advanced through the sphincterotomy into the bile duct proximal to the stone under fluoroscopic guidance. The balloon is then inflated to the diameter of the duct, and gentle traction is applied to deliver the stone through the sphincterotomy (Fig. 103–3). Passage of the balloon catheter over a guidewire is often helpful to allow frequent easy catheter passage through the sphincterotomy without trauma, to position the balloon proximal to the stone without pushing the stone proximally, and to avoid repeated cystic duct entry.

Stone retrieval baskets with different configurations, length/width, types of wire, and number of wires are commercially available. Settings in which a basket may be preferred over a balloon include larger stones (>10 mm), intrahepatic stones, smaller stones in a dilated duct, and stones that are larger than the downstream duct (e.g., stone proximal to a stricture). The basket is advanced through the sphincterotomy and partially or fully opened alongside or above the stone while taking care to not push the stone up the duct. The basket is then moved to and fro with the stone adjacent to the widest portion of the basket. Once captured, the stone is removed with gentle traction. Usually, there is resistance at the sphincterotomy orifice. By deflecting the scope tip down and applying extra force in the correct axis, stone removal is often successful. Vigorous pulling on the endoscope is sometimes necessary but has the potential to produce a duodenal tear.

In experienced centers, common duct stones can be successfully removed in 80% to 90% of patients after sphincterotomy with standard baskets and balloon catheters.[16] Difficulty clearing or failure to clear the common duct of stones may occur for a variety of reasons. In most cases, stone size is the major determinant of success. In one series,[17] stones less than 10 mm in diameter (n = 21) were all removed successfully, whereas only 3 of 25 (12%) larger than 15 mm were cleared by extraction with balloons and baskets. Stones greater than 15 mm are generally considered to be large; equally important, however, are stone factors, such as number, consistency, shape, and location, and ductal factors, such as contour, diameter at the level of and distal to the stone, and the presence of coexisting pathology such as a stricture or tumor.

Lithotripsy Techniques

A variety of lithotripsy techniques (mechanical, electrohydraulic, laser, and extracorporeal shock wave lithotripsy [ESWL]) and dissolution therapies have been used to facilitate the retrieval of stones not removable by standard methods.[18,19] The simplest endoscopic adjunct for the management of common duct stones that have failed to be removed by conventional baskets and balloons is the mechanical lithotripter or crushing basket. It is a safe, effective, low-cost procedure that can be



A B

Figure 103–3. **A,** Numerous bile duct stones present in the entire common duct *(arrows).* Note stones also in the cystic duct. **B,** Stones removed after biliary sphincterotomy. *Top left,* normal papilla. *Top right,* completed biliary sphincterotomy. *Bottom left* and *bottom right,* stones being removed with a stone retrieval balloon.

performed at the time of the initial ERCP. With this technique the stone is captured in a strong wire basket that has been advanced through a metal sheath. Longitudinal traction is then applied by turning a crank handle to withdraw the basket into the metal sheath, which results in stone fragmentation or wire breakage. In experienced centers, mechanical lithotripsy allows for the removal of more than 85% to 90% of difficult bile duct stones that are refractory to standard extraction techniques.[20,21] Failure of mechanical lithotripsy is typically due to an inability to engage the stone within the basket and rarely to insufficient shearing power to fragment the stone.

Lithotripsy techniques using ESWL or intracorporeal (laser or electrohydraulic) modalities are acceptable adjuncts to standard endoscopic management when attempting bile duct clearance.[22] The choice between these methods or surgery largely depends on availability because they are usually concentrated in tertiary centers. Intracorporeal lithotripsy can be achieved by producing a shock wave directly on the surface of the stone with either a flexible electrohydraulic probe or a flexible quartz fiber to deliver light from a laser. Both techniques require a fluid medium that is delivered coaxially along the probe or through an NBT. Because of the risk for bile duct injury (electrohydraulic methods have a greater risk for injury than the pulsed dye laser does), intracorporeal lithotripsy is usually performed under direct endoscopic control via the mother-baby endoscope system. In this technique, a small-caliber endoscope (baby scope) is advanced through the working channel of the duodenoscope (mother scope) into the bile duct. The laser fiber or electrohydraulic probe is advanced through the working channel of the baby scope, and apposition with the stone is ensured under direct vision. Laser lithotripsy has become possible under fluoroscopic guidance with the development of a device (smart laser) that can identify bile duct stones by analyzing backscattered light, with the pulse interrupted in the event of tissue contact.[23] Complete duct clearance rates with intracorporeal lithotripsy techniques range from 80% to 90%.[24-27] The main advantages of electrohydraulic lithotripsy over laser technology are its low cost and portability; however, the potential risk for bile duct injury is greater.

ESWL is used to treat bile duct stones in a fashion similar to renal and gallbladder applications. Most centers use machines that require fluoroscopy to target the stones and rely on injection of contrast material through an NBT,[28] but some centers have reported good visualization of the stone in 90% of patients with ultrasound imaging.[22] Complete stone clearance can be expected in approximately 80% of patients, but a number of ESWL and endoscopic sessions are generally required.[22,28,29]

Dissolution Therapy

Contact dissolution of biliary stones has been attempted by perfusing the bile duct with solvents administered via

an indwelling NBT, percutaneous transhepatic catheter, cholecystostomy tube, or T-tube. The results with these agents (monooctanoin and methy-*tert*-butyl ether) have been disappointing because of incomplete stone dissolution and the potential for complications from these solvents.[30,31] As a result of their low efficacy and high morbidity, contact dissolution has not assumed an important role in patients with refractory bile duct stones.

Stents and Nasobiliary Tubes

When stone extraction is incomplete or has failed, biliary drainage should be established to prevent stone impaction and cholangitis. In most situations, this therapy serves as a temporizing measure that allows for improvement in the patient's clinical condition pending repeat attempts at stone removal. The stent (or NBT) is placed so that one limb is above the stone and the other is in the duodenum (in the case of an NBT, the end of the tube is brought out the patient's nose and connected to a drainage bag) (Fig. 103–4). Most authorities recommend double-pigtail stents, although favorable experience is reported with straight 10-French stents.[32,33] NBTs allow for repeat contrast injection without the need for another ERCP to visualize the biliary tree. However, they are often poorly tolerated and frequently dislodged by a confused/uncooperative patient, and out-of-hospital tube management is not optimal. Endoprostheses are better tolerated, but migration or occlusion may occur and lead to recurrent symptoms of biliary obstruction and cholangitis.

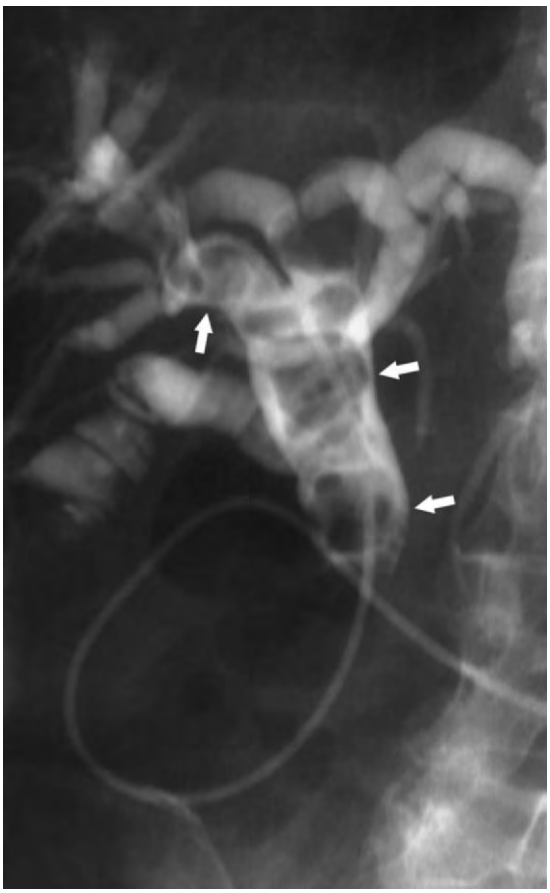


Figure 103–4. A nasobiliary tube has been placed to provide temporary biliary drainage in this patient with multiple large bile duct stones *(arrows).*

Biliary stenting not only serves to drain the bile duct but may also aid in mechanically fragmenting the stone and thereby facilitating subsequent attempts at endoscopic removal.[34] The addition of oral dissolution therapy may also soften and reduce the size of the stone and thus aid endoscopic removal. In a study by Johnson and colleagues,[35] 9 of 10 patients (90%) with nonextractable stones treated with ursodeoxycholic acid plus stenting had clearance of their bile duct after a mean of 2.7 follow-up procedures, in contrast to 0 of 12 patients (0%; $P < .01$) treated with stenting alone and a mean of 5.3 follow-up procedures.

Long-term internal stenting was believed to be a good palliative measure in elderly and high-risk patients with nonextractable bile duct stones. In several reports, the rate of late complications (primarily cholangitis) was 12% to 15%.[32] Enthusiasm for this approach has been tempered by the results of a study conducted by Bergman and associates,[33] who reported 34 complications in 23 of 58 patients (40%) stented for a median of 36 months (range, 1 to 117 months). There were nine (16%) biliary-related deaths occurring at a median of 42 months. The rate of late complications was shown to increase proportionally with time (16% at 1 year and 50% at 4 years). They advised that permanent stenting be restricted to patients unfit for elective surgical, endoscopic, or percutaneous treatment and in patients with a short life expectancy. This recommendation was supported by the results of a randomized study of endoprosthesis insertion versus standard duct clearance techniques in a group of high-risk patients with symptomatic stones.[36] DePalma and Catanzano[37] retrospectively compared the results of endoscopic biliary stenting ($n = 31$) with those of surgery ($n = 37$) in 68 patients older than 70 years with failed endoscopic bile duct clearance. Although early complications were significantly less frequent in the stented group (12.9% versus 29.7%; $P < .0005$), complications (35.5% versus 8.1%; $P < .001$) and biliary mortality (9.6% versus 0%) during long-term follow-up were significantly more common in the stented group.

Endoscopic Balloon Dilation of the Biliary Sphincter for Stone Removal

Because of the significant risks and unknown long-term effects of sphincter ablation, some authorities have suggested that small common duct stones be removed after papillary balloon dilation. The main theoretical advantages of not cutting the sphincter are that acute complications might be less frequent and that by preserving sphincter function, long-term complications (a particular concern in younger patients undergoing laparoscopic cholecystectomy) may be avoided. Bergman and colleagues[38] reported 36 biliary tract complications in 22

patients (among 93 patients) monitored for a mean of 15 years after sphincterotomy and stone removal. The same group[39] later found that after biliary sphincterotomy the function of the biliary sphincter was permanently lost, with associated bacterial colonization, the presence of cytotoxic components in the bile, and chronic inflammation of the biliary ductal mucosa. In contrast, manometric studies have suggested recovery of sphincter function within a few weeks of balloon dilation of the sphincter.[40]

In this technique the papilla is dilated with an 8- to 10-mm hydrostatic balloon. After dilation, the stones are removed via stone retrieval balloons, baskets, or mechanical lithotripsy.[41,42] Initial reluctance to use this technique arose because of concern regarding a high risk for postprocedural pancreatitis and cholangitis. A meta-analysis of eight randomized trials that compared balloon dilation with ES showed that the initial success of duct clearance was higher with ES (80% versus 70%) but that overall success did not differ significantly between the two groups (97% versus 94%) because of rescue ES when balloon dilation failed.[43] Mechanical lithotripsy was used more frequently with balloon dilation (21% versus 15%). Overall complications were similar in the two groups (10.5% versus 10.3%). The bleeding rate was higher in the ES group (2% versus 0%; $P = .001$), whereas pancreatitis occurred more frequently in the balloon dilation group (7.4% versus 4.3%; $P = .05$). Results from a more recently published randomized trial, not included in the meta-analysis, demonstrated equivalent success rates for balloon dilation and ES (98% versus 93%), but significantly higher 30-day morbidity (18% versus 3.3%) for balloon dilation, including severe pancreatitis in 5.1% (versus 0% after ES) and higher mortality (1.7% versus 0%).[44] In another randomized study comparing the two techniques, the frequency of recurrent bile duct stones and cholecystitis at 1 year was similar.[45] Moreover, 1 year after balloon dilation, common bile duct pressure, sphincter of Oddi basal and peak pressure, and sphincter of Oddi contraction frequency were significantly lower than predilation values. These results suggest that balloon dilation should probably not be used routinely but should be reserved for patients at high risk for complications of sphincterotomy, such as those with uncorrectable coagulopathy and cirrhosis.[46,47]

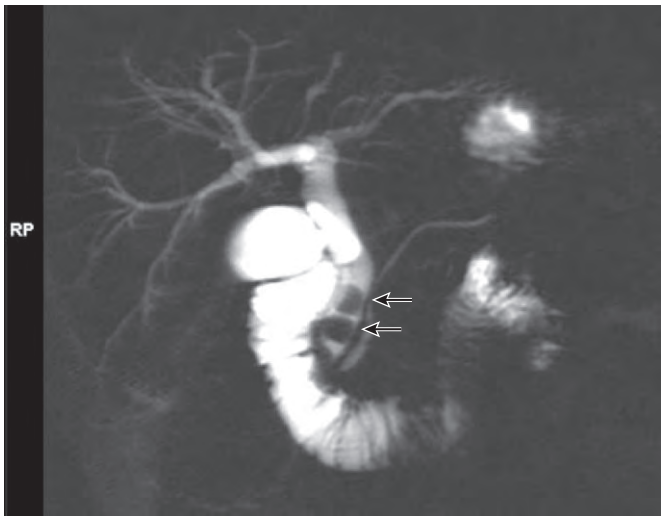
Interface of ERCP and Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy has become the standard, accepted, and preferred technique for the treatment of gallbladder stones because it is associated with less postoperative pain, reduced hospitalization time, shorter convalescence, and better cosmetic results than open cholecystectomy is. However, laparoscopic management of common duct stones is much more complex than cholecystectomy alone, advanced surgical skills and sophisticated instrumentation are required, and it is not widely available. Thus, ERCP plays an integral role in the treatment of common duct stones in the laparoscopic cholecystectomy era. The timing and need for ERCP in relation to laparoscopic cholecystectomy are dependent on the likelihood of stones being present (low, medium, and high), the skill of the endoscopist, and the ability of the laparoscopist to perform common duct exploration.[48] There appears to be little value of routine ERCP before laparoscopic cholecystectomy in patients with a low likelihood of having bile duct stones. When comparing the low yield of detecting clinically important anatomic variants and unsuspected bile duct stones with the generally accepted 3% to 7% ERCP complication rate, the routine use of ERCP before cholecystectomy cannot be justified.[49] Patients judged to have a high likelihood of harboring duct stones are likely to benefit from preoperative ERCP and stone extraction (if stones are present).[48] Patients in the medium-risk group create a diagnostic and therapeutic dilemma whose resolution depends on the skills of the endoscopist and laparoscopist at each particular center. EUS, MRCP, and spiral CT cholangiography have high sensitivity and specificity for stone detection; however, these imaging modalities are operator dependent and not universally available[5,6,50-53] (Fig. 103–5). The value of these noninvasive and less invasive techniques in the evaluation of patients at medium risk for bile duct stones needs further study.

Ultimately, a laparoscopic procedure that treats both cholelithiasis and choledocholithiasis in a single setting would be the best approach in the majority of patients. This strategy appears to be cost-effective and associated with a shorter hospital stay than with a two-stage procedure (preoperative ERCP with sphincterotomy followed by laparoscopic cholecystectomy).[54,55] When these laparoscopic skills become widely disseminated, the use of ERCP will be relegated to its well-established role in the open cholecystectomy era, specifically, the treatment of acute cholangitis, severe gallstone pancreatitis, retained common duct stones, and complications of biliary surgery.

Acute Gallstone Pancreatitis

In Western countries, gallstone disease is the leading cause of acute pancreatitis and accounts for 34% to 54% of cases.[56] Most patients with acute gallstone pancreatitis (AGP) have a mild attack and can be treated conservatively. However, the case fatality rate in severe pancreatitis remains unacceptably high, approaching 10%. In the open cholecystectomy era, urgent surgical intervention for severe AGP did not gain general acceptance because of the increased morbidity and mortality associated with this approach.[57] Coincident with these surgical reports were uncontrolled endoscopic series reporting the efficacy and safety of ERCP and ES in the setting of AGP.[58] Although the results were encouraging, the studies varied in their criteria for patient selection and timing of ES in relation to the acute attack (many were performed in the recovery phase, when surgery is also safe). These early series prompted the three randomized controlled trials[59-61] that now serve as the basis for the endoscopic treatment of AGP. The therapeutic principle for ES in AGP is simply removal of the obstructing calculus and reestablishment of bile and pancreatic juice flow.



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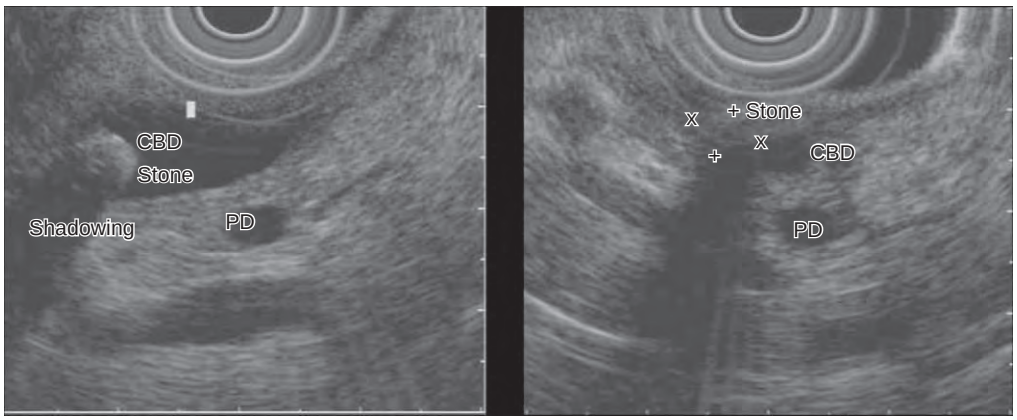


B

Figure 103–5. **A,** Magnetic resonance cholangiopancreatography demonstrating bile duct stones *(arrows).* **B,** Endoscopic ultrasound showing bile duct stones with acoustic shadowing. CBD, common bile duct; PD, pancreatic duct.

In a randomized prospective controlled trial from the United Kingdom, 121 patients with AGP either received conventional therapy (i.e., gut rest, analgesics, intravenous fluids, and antibiotics) or underwent urgent (within 72 hours after admission) ERCP with ES and stone extraction (if stones were present in the common bile duct at the time of ERCP).[59] Patients were stratified by the predicted severity of their attacks with the modified Glasgow system. Choledocholithiasis was found in 25% of patients with predicted mild attacks and 63% with predicted severe attacks. The four important findings were that (1) ERCP could be safely performed in the setting of gallstone pancreatitis, (2) there was a significant reduction in major complications in patients who underwent urgent ERCP and ES, (3) the reduction in morbidity was apparent only in patients with predicted severe attacks (61% versus 24%; $P = .007$), and (4) there was a significant reduction in hospital stay for those with severe attacks treated by urgent ERCP and ES (median of 9.5 versus 17 days, $P = .03$). The mortality rate was improved, but the difference was not statistically significant.

A second randomized controlled study was performed by the department of surgery at the University of Hong Kong.[60] One hundred ninety-five patients with acute pancreatitis were randomized to early ERCP (within 24 hours of admission) or conservative therapy. Although the methodology, patient selection, and assessment of the severity of the acute pancreatitis used in this study differed from that in the United Kingdom study, the results in the subgroup of patients with gallstone pancreatitis ($n = 127$) were quite similar. Patients with mild pancreatitis had similar morbidity and mortality regardless of the therapy. In contrast, patients with predicted severe attacks who underwent endoscopic therapy had a lower complication rate (54% versus 13%; $P = .003$) and a lower mortality rate (18% versus 3%; $P = .07$) than did patients treated conservatively.

The third study[61] was a prospective multicenter randomized controlled study from Germany in which 238 patients with AGP and no evidence of severe biliary obstruction (severe biliary obstruction defined as a bilirubin concentration >5 mg/dl) were randomized to ERCP with ES and stone extraction or conservative therapy

within 72 hours of symptom onset. This study attempted to address the major criticism of the United Kingdom and Hong Kong studies: the need to exclude patients with concomitant cholangitis because these patients are known to benefit from ERCP. The two treatment groups did not differ significantly in mortality (11% versus 6% overall mortality, 8% versus 4% AGP mortality, ERCP versus conservative therapy) or overall complications (46% versus 51%, ERCP versus conservative therapy) regardless of the predicted severity of the pancreatitis. However, respiratory failure was more frequent in the ERCP group (12% versus 5%; $P = .03$), and jaundice was more frequent in patients who received conservative treatment (11% versus 1%; $P = .02$).

Although all three studies concluded that there was no difference in outcomes for patients with mild pancreatitis treated conservatively or by ERCP, only the study from Germany suggested that early ERCP was of no benefit in patients with severe gallstone pancreatitis. Even though ERCP is clearly indicated in patients with AGP complicated by cholangitis or biliary obstruction, its role in the setting of severe AGP alone warrants further investigation. A meta-analysis[62] of these three published studies and an abstracted randomized study[63] revealed a statistically significant reduction in morbidity from 38% to 25% and mortality from 9% to 5% in the ERCP/ES group versus the conservatively treated group. A subgroup analysis based on the severity of pancreatitis was not reported in this meta-analysis. The role of EUS and MRCP in detecting bile duct stones and triaging patients with stones to ERCP is evolving. In one series of 100 AGP patients, EUS was found to be more sensitive than transcutaneous ultrasound in detecting cholelithiasis (100% versus 84%; $P < .005$) and had a sensitivity, specificity, and accuracy of 97%, 98%, and 98%, respectively, for detecting choledocholithiasis.[64] In another series of 32 patients with gallstone pancreatitis, the sensitivity, specificity, and overall accuracy of MRCP detection of bile duct stones was 80%, 83%, and 81%, respectively. Stones missed by MRCP were smaller than 6 mm in diameter.[65] Because small stones commonly cause AGP, MRCP will probably have lower sensitivity in this setting than in the overall population of patients with bile duct stones.

Sphincterotomy has been shown to prevent recurrent episodes of AGP and is an alternative to surgery in high-risk patients.[66] If sphincterotomy is not performed, early cholecystectomy is mandatory to prevent recurrent pancreatitis.[67]

Acute Cholangitis

Cholangitis is a potentially life-threatening disease that results from bacterial infection of obstructed bile. Systemic toxicity occurs when intraductal pressure is sufficiently elevated to cause reflux of bacteria or endotoxin into blood.[68] Thus, obstruction plays a key role by both increasing intraductal pressure and promoting bacterial overgrowth as a result of bile stasis. The most common cause of acute cholangitis is choledocholithiasis, which occurs in approximately 80% to 90% of unselected cases.[68] Therapy for cholangitis must be individualized because of the spectrum of severity of illness. Antibiotic therapy should be initiated promptly. Analysis of bile and stone cultures indicates that *Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Enterococcus* spp., and *Streptococcus* spp. are the most commonly isolated bacteria.[69] The antibiotic selected should preferably penetrate an obstructed biliary tree.[69] The majority of patients will respond to conservative management, thereby allowing for a more elective approach to biliary decompression.[70] Urgent decompression is indicated if improvement is not seen within a few hours of initial resuscitation.[71] The latter group will invariably have a fatal outcome if conservative treatment is continued.

Options for bile duct decompression include surgical, percutaneous, and endoscopic methods. Endoscopic intervention is now accepted as definitive therapy for acute cholangitis. The advantages of ERCP are that it can delineate the cause of obstruction, facilitate sampling of bile for culture, and decompress the biliary tree in a relatively short time with low morbidity. Biliary decompression is the goal of therapy and can be complete (e.g., stone removal) or temporary (e.g., placement of a stent without stone removal), pending more definitive management (to allow stabilization of an unstable patient). The endoscopic procedure consists of sphincterotomy with stone extraction or biliary drainage with an NBT or endoprosthesis.

Ideally, the patient should be stabilized or made as stable as possible before performing ERCP. Patients with respiratory compromise can have their ERCP performed while on ventilatory assistance. Although the procedure is best performed in a dedicated fluoroscopy room, unstable patients should undergo ERCP in the ICU. A mobile fluoroscopy unit can be used, but reports indicate that ductal decompression can be performed without fluoroscopic assistance in an ICU.[72] Because intrabiliary pressure is increased in acute cholangitis, contrast injection should be limited to reduce further systemic seeding of bacteria. Enough contrast should be injected to define the anatomy and the cause of obstruction. Alternatively, the bile duct should be aspirated completely of infected bile before injection of contrast. Aspirated bile should be cultured. In a stable patient, definitive therapy can be performed. In an unstable patient, the length of the procedure should be limited. In such cases a stent or NBT should be placed, and once the patient is stabilized, more definitive therapy can be performed.

The high morbidity and mortality associated with surgical and percutaneous therapy for acute cholangitis prompted evaluation of the safety and utility of endoscopic management.[73,74] In a retrospective analysis, Leese and colleagues[75] reported on 71 patients with stone-related cholangitis treated by early decompression either surgically ($n = 28$) or by ES ($n = 43$). Early surgery was associated with significantly higher 30-day mortality (21% versus 5%) and morbidity (57% versus 8%) than sphincterotomy was. The endoscopic group was significantly older than the surgical group and had more

medical risk factors, but there were no significant differences in the severity of cholangitis. Leung and colleagues[70] reported their experience in a retrospective analysis of 105 patients with acute calculous cholangitis who did not respond to conservative management and underwent urgent endoscopic decompression at a mean of 1.5 days after admission. Thirty-nine percent of patients had coexisting medical problems, 85% had Charcot's triad, and 40% were in shock at the time of admission. Endoscopic drainage was successful in 102 patients (97%). Ninety-seven percent of patients responded with striking improvement in abdominal pain, and 93% had resolution of fever within 3 days. The overall 30-day mortality was 5%. Among those in shock, 2 of 4 drained after 72 hours died, as compared with 3 of 38 drained before 72 hours. There were no deaths in the group without shock, irrespective of the timing of drainage. The mortality of 5% compares favorably with that of urgent surgical intervention, in which mortality has been reported to be greater than 40% in some series.[76] The ERCP complication rate was 5% and was limited to five post-sphincterotomy bleeding episodes managed by endoscopic techniques. The safety and efficacy of endoscopic therapy were corroborated in a large retrospective study of 947 patients with cholangitis secondary to stones ($n = 898$) or stricture ($n = 49$).[77] In a randomized prospective study, Lai and colleagues compared the safety and efficacy of biliary decompression by surgical and endoscopic techniques in 82 patients with severe cholangitis as a result of stones.[78] Patients treated with laparotomy and common bile duct exploration had significantly higher morbidity (64% versus 34%) and mortality (32% versus 10%) than those treated with endoscopic therapy. These and other studies clearly demonstrate the efficacy and safety of biliary decompression either as definitive therapy or as a temporizing measure pending more definitive intervention once the patient is stabilized.

BILIARY DRAINAGE PROCEDURES

Benign Biliary Strictures

Postoperative

Postoperative strictures of the extrahepatic bile duct occur after 0.25% to 1% of cholecystectomies.[79] Most such lesions are manifested as abnormal liver test results, obstructive jaundice, and cholangitis within 2 to 3 months postoperatively, although a much more delayed response may occur. In contrast, when the common duct has been completely occluded with a clip, progressive jaundice will become obvious early in the postoperative period.

The cholangiogram commonly shows a short, smooth narrowing near the cystic duct stump and surgical clips with proximal duct dilation (Fig. 103–6). Strictures greater than 2 cm in length, those with clips placed securely across the duct, or those associated with resected segments of duct require operative management. Irrespective of the site or pathogenesis of the stricture, the primary aim of endoscopy is to pass a guidewire through the stricture to permit passage of dilators (balloon or catheter) and stents. Sphincterotomy before stricture manipulation permits greater instrument maneuverability. The preferred treatment of short, simple strictures is balloon dilation to 6 to 10 mm with ultimate placement of two to three 10-French plastic stents across the stricture and extending into the duodenum. The stricture is

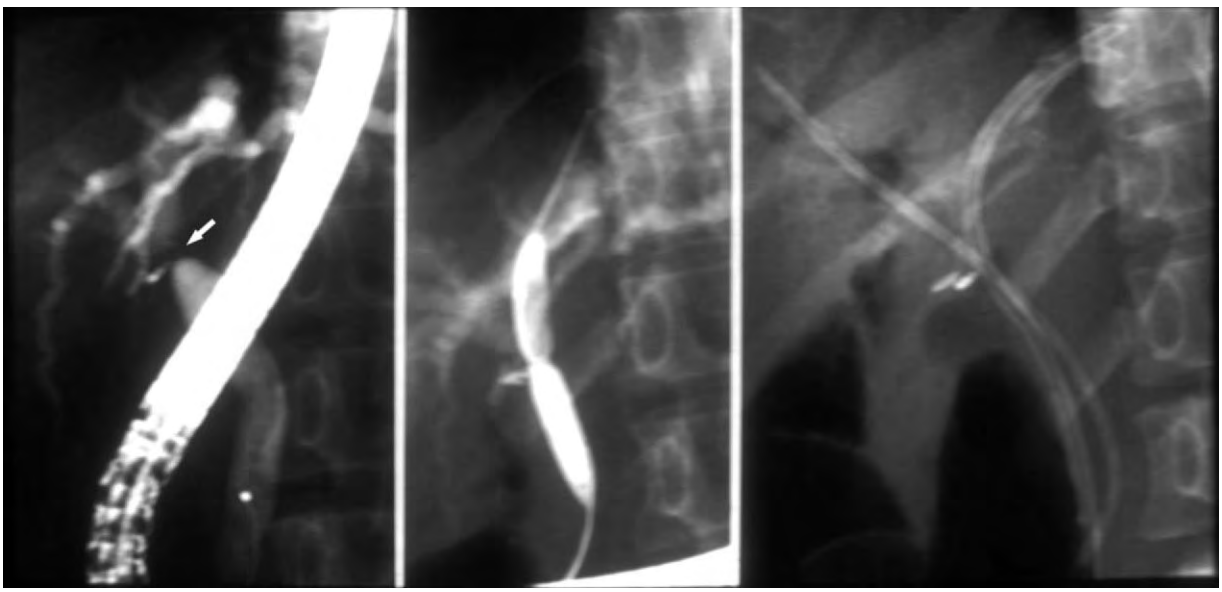


Figure 103–6. This patient was evaluated for obstructive jaundice 2 months after laparoscopic cholecystectomy. The cholangiogram shows a common duct stricture *(arrow; left).* Note the clips in the region of the common duct. The stricture was then dilated with a balloon-dilating catheter *(middle).* Two biliary stents were placed to bridge the stricture *(right).*

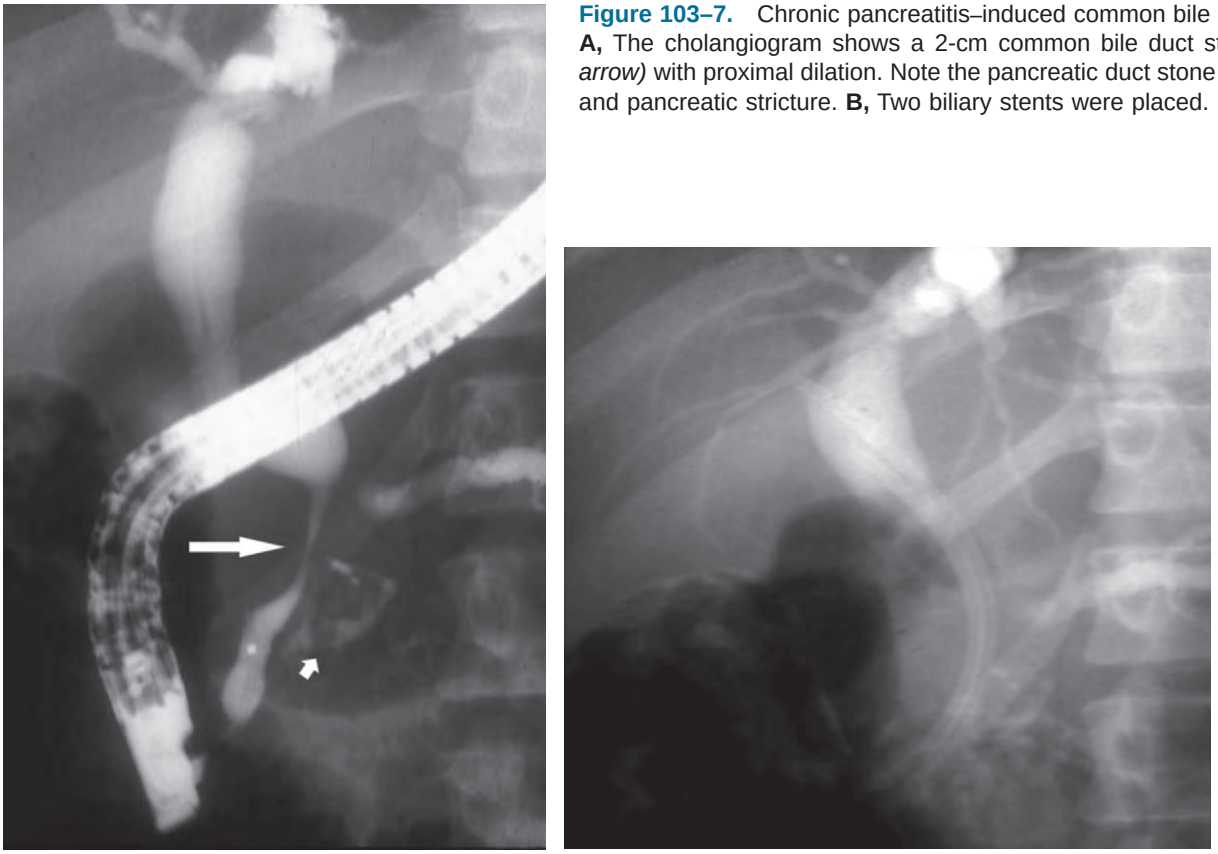
redilated and stents are exchanged at 3- to 4-month intervals for 8 to 12 months until the stricture profile is nearly as open as the downstream adjacent duct. The goals of treatment are to render the patient free of symptoms and to achieve sustained normalization of liver test results after the stents are permanently removed. Because strictures can recur many years after therapy, the long-term outcome after endoscopic intervention is of critical concern. In three uncontrolled endoscopic studies,[80-82] a good to excellent result was achieved in 70% to 80% of patients monitored for an average of 4 years. Assessment of good to excellent outcomes was based on resolution of symptoms and normalization or significant improvement in biochemical test results and radiographic findings. Two long-term follow-up studies of endoscopic stenting of biliary strictures were recently reported.[83,84] Bergman and colleagues[83] reported late complications (median follow-up of 9.1 years) in 34% of 44 patients undergoing biliary stenting with two 10-French stents for a maximum of 1 year. Re-stenosis at the site of the original stricture occurred in 20% of patients. Costamagna and colleagues[84] undertook a more aggressive endoscopic approach. Each patient received as many large-diameter stents as necessary (based on stricture tightness and bile duct diameter) to eliminate the stricture. Stents were exchanged electively at 3-month intervals and were removed after complete resolution of the stricture. There were no symptomatic recurrent biliary strictures in the 40 patients completing the stenting protocol during a 49-month follow-up period. In a nonrandomized study, Davids and colleagues[85] compared the outcome of 35 patients treated surgically (biliary-enteric anastomosis) and 66 patients managed by endoscopic balloon dilation and stenting (stents changed every 3 months for 1 year). The mean follow-up interval for the surgically and endoscopically treated patients was 50 and 42 months, respectively. Eighty-three percent of patients in both groups attained good to excellent results. The total morbidity rates (surgery, 26%; endoscopy, 35%) and stricture recurrence rates (17% for both groups) were similar for the two groups. The long-term outcome after endoscopic biliary stenting of postoperative biliary strictures has been shown to be superior to that after stenting of biliary strictures in the setting of chronic pancreatitis.[86] Collectively, these data support the use of endoscopic therapy in patients with postoperative biliary strictures. Surgically fit patients who fail initial endoscopic therapy or have recurrent strictures are best managed by a bilioenteric bypass. Although metal expandable stents offer prolonged patency in comparison to plastic stents, their use for treating benign postoperative biliary strictures should be discouraged. Dumonceau et al.[87] reported mucosal hyperplasia and Wallstent occlusion in all six patients who underwent this therapy.

Endoscopic techniques have been used to treat biliary strictures complicating orthotopic liver transplantation.[88] Such strictures are often treated in a fashion similar to strictures occurring after other biliary tract surgeries. Anastomotic strictures appear to be more responsive to endoscopic therapy than do strictures occurring at nonanastomotic sites.[88]

Distal Common Bile Duct Strictures Secondary to Chronic Pancreatitis

Intrapancreatic common bile duct strictures have been reported to occur in 3% to 46% of patients with chronic pancreatitis (Fig. 103–7). Deviere and colleagues[89] were the first to report the use of biliary stenting in patients with common bile duct obstruction and significant cholestasis (alkaline phosphatase greater than two times the upper limits of normal) secondary to chronic pancreatitis. Nineteen of the 25 patients had jaundice, and 7 had cholangitis. The patients were treated with ES followed by insertion of one or two 10-French biliary stents placed across the stricture. The stents were changed when clinical or ultrasonographic evidence of blockage was present. Cholestasis, hyperbilirubinemia, and cholangitis resolved in all patients after stent placement. The late follow-up (mean, 14 months; range, 4 to 72 months) on 22 patients was much less satisfactory. One patient died 1 month after treatment as a result of acute cholecystitis and postsurgical complications, whereas a second died 10 months after stenting as a result of sepsis that was believed to be caused by stent blockage or dislodgment. Stent migration occurred in 10 patients and stent blockage in 8 and resulted in cholestasis with or without jaundice (n = 12), cholangitis (n = 4), or no symptoms (n = 2). These patients were treated by stent replacement or surgery, or both (n = 7). Ten patients continued to have a stent in place (mean follow-up, 8 months) and remained asymptomatic. Only three patients required no further stents because of resolution of their biliary stricture. Other authors have also reported a low stricture resolution rate ranging from 11% to 32% (Table 103–2).[90-95] The salient point of these studies was that biliary drainage via a plastic biliary stent is an effective therapy for resolving cholangitis or jaundice in patients with chronic pancreatitis and a biliary stricture. However, the long-term efficacy of this treatment is much less satisfactory because stricture resolution rarely occurs. The results of nearly all studies stand in distinct contrast to those of Vitale et al.,[93] who reported that 20 of 25 patients undergoing plastic biliary stenting for a median period of 13.3 months remained stent-free without stricture recurrence during a 32-month follow-up interval. Catalano and colleagues have demonstrated better outcomes for multiple stents than for a single stent.[96]

Because of the disappointing results with plastic stents and concern for the high morbidity associated with surgically performed biliary drainage procedures in alcoholic (frequently debilitated) patients, the group from Brussels evaluated the use of uncoated expandable metal stents for this indication.[97] Twenty patients were treated with a 34-mm-long metal stent that becomes 10 mm in diameter when fully expanded. The short length of the stent was chosen so that surgical bypass (e.g., choledochoduodenostomy) would still be possible if necessary. Cholestasis (n = 20), jaundice (n = 7), and cholangitis (n = 3) resolved in all patients. Eighteen patients had no further biliary problems during a follow-up period of 33 months (range, 24 to 42 months). Epithelial hyperplasia within the stent developed in two patients (10%) and



A B

Figure 103–7. Chronic pancreatitis–induced common bile duct stricture. **A,** The cholangiogram shows a 2-cm common bile duct stricture *(large arrow)* with proximal dilation. Note the pancreatic duct stone *(small arrow)* and pancreatic stricture. **B,** Two biliary stents were placed.

Table 103–2 Summary of Selected Series Evaluating the Efficacy of Endoscopic Biliary Polyethylene Stent Insertion for the Treatment of Chronic Pancreatitis–Induced Common Bile Duct Strictures

Investigator	*N*	Technical Success (%)	Stricture Resolution (%)	Stent Dysfunction (%)		Follow-up (mo)
				Clogging	*Migration*	
Deviere et al.[89]	25	100	3 (12%)	32	40	14
Barthet et al.[90]	19	100	2 (11%)	0	5	18
Smits et al.[91]	58	100	16 (28%)	62	7	49
Kiehne et al.[92]	14	100	2 (16%)	36	NM	NM
Vitale et al.[93]	25	100	20 (80%)	12	8	32
Farnbacher et al.[94]	31	100	10 (32%)	29	23	24
Eikhoff et al.[95]	39	100	12 (31%)	33	10	58

NM, not mentioned.

resulted in recurrent cholestasis in one and jaundice in the other. These patients were treated endoscopically with standard plastic stents, with one of these patients ultimately requiring surgical drainage. The authors concluded that this therapy could be an effective alternative to surgical biliary diversion but that longer follow-up and controlled trials will be necessary to confirm these results. We suspect that all the metal stents would ultimately occlude. In a series of 14 patients treated with partially covered metal stents (0.5-cm-long uncovered metal meshes at both ends), stent dysfunction developed in 7 (50%) during a median follow-up of 22 months. Stent patency was 100% at 12 months, 40% at 24 months, and 37.5% at 30 months.[98]

The studies just presented and others indicate that plastic biliary stents are a useful alternative to surgery for short-term treatment of chronic pancreatitis–induced common bile duct strictures complicated by cholestasis, jaundice, and cholangitis. This therapy should also be considered for high-risk surgical patients. However, because the long-term efficacy of this treatment is much less satisfactory, operative intervention appears to be a better long-term solution for this problem in average-risk patients. More data on the long-term outcome, preferably in controlled trials, are necessary before expandable stents can be advocated for this indication.

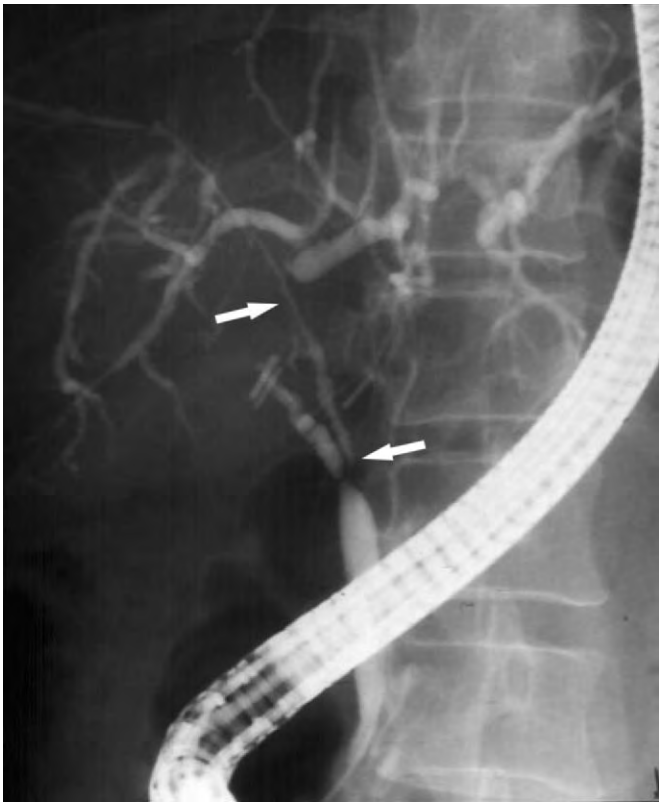


Figure 103–8. This patient has primary sclerosing cholangitis involving the extrahepatic and intrahepatic ducts. There is a long, high-grade stricture involving the common hepatic duct *(arrows)* and the right and left hepatic ducts, as well as narrowings/irregularities of the intrahepatic ducts.

Primary Sclerosing Cholangitis

Cholangiographic imaging is the gold standard for diagnosing primary sclerosing cholangitis (PSC), although conditions that mimic PSC must be excluded. In a variant, small duct PSC, the cholangiogram is normal.[99] Both percutaneous transhepatic cholangiography (PTC) and ERCP can be used to show the characteristic changes associated with PSC. The choice between PTC and ERCP depends on local and regional expertise and availability. However, when available, ERCP is the preferred modality because (1) the often small fibrotic ducts of patients with PSC may be difficult to puncture via the percutaneous route; (2) ERCP has a better safety profile; and (3) the pancreatic duct and cystic duct, which may be involved in up to 20% of patients with PSC, can be examined at ERCP. PTC is reserved for ERCP failures and patients with altered anatomy. The role of MRCP and spiral CT cholangiography in the diagnosis of PSC awaits further study.[100]

The classic cholangiographic features in PSC are diffuse multifocal strictures of the intrahepatic and extrahepatic bile ducts (Fig. 103–8).[101] These strictures are usually short, with intervening normal or dilated segments giving a beaded appearance. Other frequent findings on cholangiography include pseudodiverticula, mural irregularities, and biliary stones and sludge.[102,103]

The rationale for endoscopic intervention is based on the hypothesis that progressive liver disease and deterioration of liver function may be aggravated or accelerated by backpressure from dominant strictures and stones or debris when present. It is further hypothesized that relief of obstruction may halt, delay, or even reverse progression to cirrhosis and liver failure.[104] Because no medical therapy has definitively proved effective for PSC, a trial of endoscopic therapy in symptomatic patients seems reasonable. Indications for considering endoscopic management of PSC are treatment of jaundice or pruritus and symptomatic cholangitis, deteriorating serum hepatic chemical profile, and when concern for bile duct cancer is high, tissue sampling. The most favorable candidates for therapy are patients with a dominant extrahepatic stricture with or without stones and limited or no intrahepatic involvement. Such ideal anatomy is uncommon.

When performing ERCP in the setting of PSC, therapeutic skills are mandatory because of the serious risk for infection. Not uncommonly, contrast media will take the path of least resistance and enter the cystic duct and gallbladder; intrahepatic filling is therefore limited. Preferably, a balloon catheter is then manipulated above the cystic duct takeoff, and higher-pressure injection of the intrahepatic radicles is performed with the balloon inflated. Moreover, because the risk for post-ERCP cholangitis in patients with PSC may be as high as 20% to 30% after diagnostic and therapeutic procedures (particularly in those in whom obstructed segments are not decompressed), antibiotic prophylaxis has been advocated.

All therapeutic procedures aim at improving bile flow. Endoscopic techniques that may be used to achieve this goal are ES, stone/sludge removal, stricture dilation with balloons and catheters, placement of stents and NBTs (with or without instillation of corticosteroids and saline lavage), and combinations of therapy. Endoscopic stricture dilation and stenting have been reported in PSC patients since the early 1980s. The techniques have been standardized. The goals of endoscopic intervention in patients with PSC are to relieve jaundice and pruritus, treat cholangitis, and theoretically, delay the onset of biliary cirrhosis and thus buy time before liver transplantation. Interpretation of the reported results of endoscopic therapy is difficult because there are no randomized controlled trials, therapies are not uniform, treated patients have variable anatomy, the definition of success varies, studies are generally small, the course of untreated PSC is variable, and there is no long-term follow-up.

Johnson and associates[105] reported their results of endoscopic dilation in 35 symptomatic PSC patients (29 with cholangitis and 6 with jaundice alone). Patients were treated by dilation (balloon or catheter) with or without biliary stenting. During a mean follow-up period of 24 months, there was a significant reduction in the frequency of hospitalization for cholangitis, bilirubin, and stricture score. Cholangitis occurred shortly after treatment in six patients; five of the six had a biliary stent placed. As a result, these authors recommended avoiding biliary stents in patients with PSC.

Lee and associates[106] retrospectively reviewed the records of 85 PSC patients who underwent 175 ERCP procedures (75 diagnostic and 100 therapeutic). Endoscopic therapy was associated with a 15% major complication rate (7% pancreatitis and 8% cholangitis). Clinical follow-up (median of 31 months) was obtained in 50 of 53 patients who underwent 85 therapeutic procedures. Twenty-eight patients improved clinically, whereas 21 felt the same and 1 felt worse. Serum liver chemistry results obtained within 3 months of the endoscopic intervention were significantly improved in comparison to pretreatment values. Overall, 41 of 53 patients (77%) had improvement in their clinical symptoms, liver function test results, or cholangiograms.

Van Milligen de Wit and colleagues[107] reported the results of stent therapy in 25 patients with PSC and dominant extrahepatic strictures. Stents were exchanged or removed electively at 2- to 3-month intervals or because of symptoms attributable to stent clogging. Endoscopic therapy was technically successful in 21 patients (84%). In these 21 patients, the results of all serum biochemical liver tests improved significantly within 6 months of stent therapy. During a median follow-up of 29 months (2 to 120 months) after stent removal, 12 patients (57%) remained asymptomatic with stable biochemical liver test results and 4 (19%) had clinical and biochemical relapse of disease that responded favorably to repeat endoscopic therapy. Early procedure-related complications occurred in 14% of the procedures. The value of short-term endoscopic stenting (mean, 11 days; range, 1 to 23 days) for 32 patients with dominant strictures was reported by Ponsioen and colleagues.[108] Cholestatic symptoms improved in 83%, and there were statistically significant reductions in abdominal pain, fatigue, and pruritus. Serum liver chemistry results were significantly improved. Eighty percent of patients were free of reinterventions at 1 year and 60% at 3 years. Procedure-related complications occurred in 15%, but there were no episodes of cholangitis. The authors advocated this technique because it was efficacious and overcame the complications associated with stent occlusion. Kaya and colleagues reported that stenting after balloon dilation (median stenting interval of about 4.5 months) of dominant strictures provides no additional benefit and is associated with more complications than balloon dilation alone is.[109] Baluyut and colleagues[110] found that repeated endoscopic treatment to maintain bile duct patency was associated with a significantly higher observed 5-year survival rate than predicted by the Mayo Clinic survival model.

Cholangiocarcinoma is a dreaded complication of PSC that occurs in 9% to 15% of patients.[99] The risk appears to be greatest in patients with long-standing ulcerative colitis and cirrhosis. Surprisingly, recent studies suggest that there may be an inverse relationship between the duration of PSC and the risk for cholangiocarcinoma.[111,112] Sudden worsening of jaundice should raise the possibility of the development of cholangiocarcinoma. Cholangiographic findings that suggest malignant transformation include markedly dilated ducts of the ductal segments proximal to a stricture, the presence of a polypoid mass, and progressive stricture formation.[102] Comparison with previous ERCP results is essential to signal the presence of complicating cholangiocarcinoma because with PSC uncomplicated by malignancy, the cholangiographic appearance frequently remains static for years.[102] Unfortunately, early diagnosis of cancer is difficult because we lack a sensitive, specific serologic marker and bile duct tissue sampling is relatively insensitive. However, tissue sampling of any suspicious lesion at ERCP is indicated.

Although the utility of ERCP in helping make the diagnosis of PSC is clear, its therapeutic efficacy in improving the course of the disease appears highly likely but has not definitively been established. Clearly, symptomatic patients with dominant extrahepatic strictures are the best candidates for therapy.

Biliary Fistulas

Biliary fistulas most commonly occur as a complication of cholecystectomy, common bile duct exploration, or inadvertent operative injury of the bile duct or as a consequence of a local infection. Rarely, biliary fistulas result from long-standing untreated biliary tract disease. With more widespread use of laparoscopic cholecystectomy, the incidence of bile duct injury, including biliary fistulas, has increased.[113,114] Bile leakage from the cystic duct remnant is among the most common injuries reported as a complication of laparoscopic cholecystectomy. The most common cause of cystic duct leaks involves imprecise application of clips on the duct or their subsequent dislodgment during the procedure.[115,116] Biliary fistulas may also arise from the intrahepatic ducts and common

duct. The duct of Luschka, if present, is quite vulnerable to transection during cholecystectomy.[117] Clearly, distal obstruction from a stone, stricture, or papillary stenosis increases ductal pressure proximally and may promote and maintain the biliary fistula.

Postoperative bile duct leaks are usually manifested within a week after surgery.[116,118,119] In a series of 62 patients with postcholecystectomy leaks, initial symptoms included abdominal pain in 89%, abdominal tenderness in 81%, fever in 74%, nausea and vomiting in 43%, and jaundice in 43%.[119] Only 2% had a clinically detectable mass or ascites. Biochemical testing is usually nonspecific with variable elevations in serum hepatic chemistry values and the white blood cell count.

A high index of suspicion for bile duct injuries after laparoscopic cholecystectomy should be maintained in any patient who fails to follow a smooth, uneventful postoperative course. Patients with suspected biliary fistulas often undergo abdominal ultrasonography or CT to look for evidence of a biloma, as well as a hepatobiliary iminodiacetic acid (HIDA) scan to diagnose the leak.[48] However, direct cholangiography (most often by ERCP) is the most sensitive test to detect a biliary fistula.[119]

Treatment options for biliary leaks include percutaneously or endoscopically placed biliary drains or stents and surgical drainage and repair of the leak. Patients with large bilomas should undergo percutaneous drainage of the fluid collection (unless surgery is performed). Endoscopic therapy has been shown to be definitive therapy in this setting with low morbidity. Patients with leaks from the cystic duct, duct of Luschka, and T-tube tract are optimal candidates for endoscopic treatment. However, patients with injuries of the common bile duct, common hepatic duct, and intrahepatic ducts can also be managed by endoscopic techniques.

The primary goal of endoscopic therapy is to decrease the pressure gradient between the bile duct and duodenum and thereby allow drainage of bile along the path of least resistance and away from the site of leakage (to permit the defect to seal). This objective can be accomplished with biliary sphincterotomy alone, stenting alone, an NBT alone, or any combination thereof.[48,114,118-126] Kaffes and colleagues[125] performed ES alone ($n = 18$), bile duct stenting alone ($n = 40$), or ES plus stenting ($n = 31$) in 89 patients, with leaks arising in 80 from the cystic duct stump ($n = 48$), duct of Luschka ($n = 15$), T-tube tract ($n = 7$), common duct ($n = 5$), an intrahepatic duct ($n = 4$), and an uncertain site ($n = 1$). The biliary fistula closure rate was 95%, and significantly more patients in the sphincterotomy-alone group required surgery to control leaks than in the other groups (22% versus 0%; $P = .001$). Sandha et al.[126] recommended a systematic approach to bile duct fistulas based on their experience in 207 patients. Low-grade leaks (leak identified only after intrahepatic opacification) resolved in 91% with sphincterotomy alone (along with bile duct stone removal when present), and 100% of high-grade leaks (leak observed before intrahepatic opacification) resolved with stenting with or without ES (and stone extraction when present). Patients with clinically evident leaks not identified on cholangiography may have a disconnected duct. Kalacyi and colleagues showed that MRCP may be helpful in identifying the upstream bile duct and the site of injury.[127]

Experience with NBTs to treat biliary leaks is limited, but data available from several investigators have been favorable.[128] Because most fistulas seal in a few days, NBT placement is a reasonable option. Advantages of an NBT include the ability to monitor closure of the leak with repeat cholangiography, the possibility of applying maximum decompression with suction, and easy removal of the tubes without the need for a second endoscopic procedure. However, the risk of infection when improperly cared for, poor patient acceptance and discomfort, and potential electrolyte disturbances from external drainage have been cited as potential disadvantages of this approach.[48] Biliary stents are a very effective therapy for resolving biliary leaks. The observation from several uncontrolled studies that patients treated with stents alone experience equally good outcomes as patients treated with a combination of stents and sphincterotomy suggests that sphincterotomy can be avoided in patients with otherwise unobstructed ducts.[123,124] Therapeutic efficacy for 7-French stents has been high. However, Foutch and colleagues[124] reported a 22% failure rate with 7-French stents; these fistulas resolved by upsizing the stent to 10 French. Larger-caliber stents are certainly preferred when a concomitant stricture is present. In most reported series, stents were inserted with the proximal end positioned above the leak site.[123,124] It is assumed that the stent can partially mechanically occlude the leak site, thus favoring more rapid closure. However, Bjorkman and colleagues[122] reported a 100% fistula closure rate in 15 patients after placing one short (2 to 3 cm) 10-French stent with the stent tip distal to the leak site. The results of this study confirm the importance of eliminating the transpapillary pressure gradient. Most studies that monitor drain output or reassess the fistula by repeat cholangiography report rapid closure of the fistula in most cases with cessation of bile extravasation in 1 to 7 days.[128] The precise time when the fistula site is permanently closed is difficult to determine from reported series, however.

The available data suggest that biliary fistulas are likely to heal regardless of the therapy used to decrease the pressure gradient in the direction of the duodenum. Randomized studies comparing sphincterotomy, internal stents, and NBTs will be necessary to determine which of these therapies is the safest, most reliable, and most cost-effective management option. Biliary fistulas associated with bile duct strictures will require long-term stenting, preferably with large-bore stents (10- and 11.5-French stents).

Malignant Bile Duct Obstruction

A variety of palliative options can be offered to a patient with malignant obstructive jaundice, including surgical, percutaneous, endoscopic, and medical therapy (chemotherapy and radiation therapy). Certainly, a surgically fit patient with a resectable tumor after staging should be offered the option of surgical resection for

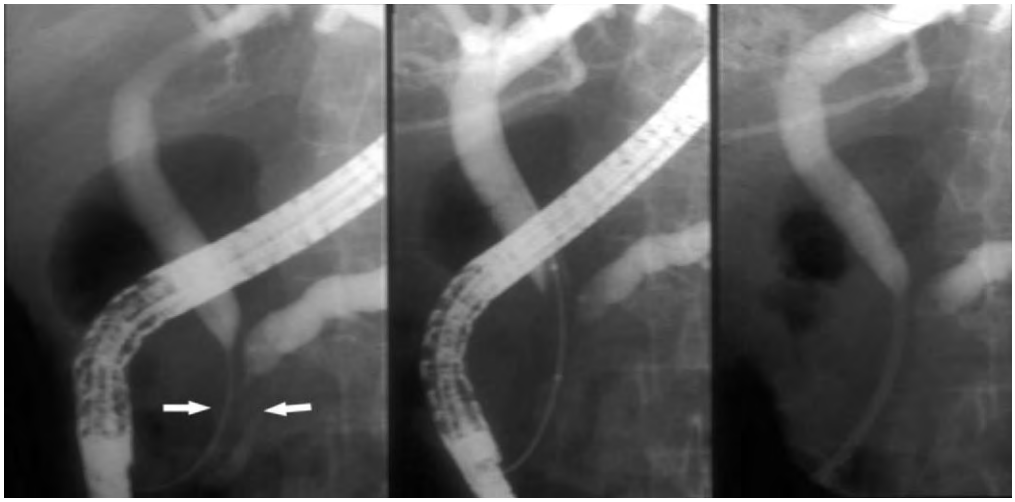


Figure 103–9. This patient has pancreas cancer. Endoscopic retrograde cholangiopancreatography *(left)* demonstrates a classic double-duct sign with strictures of both the common bile duct *(left arrow)* and the pancreatic duct *(right arrow)* in the pancreas head with upstream ductal dilation. The stricture was then dilated *(middle)* and a biliary stent was placed *(right).*

cure. In a high-risk patient or one with an unresectable tumor, endoscopic placement of polyethylene stents has become a widely accepted method of management (Fig. 103–9).[129] Soehendra and Rejinders-Frederix[130] first described endoscopic biliary stenting in 1980. Since then, many advances in stent technology have been made. Despite these developments, stent patency remains a major problem, with 10-French stents becoming occluded after 3 to 6 months.[131,132] The problem with stent occlusion has been studied intensively, but attempts at altering bile composition with choleretic agents, reducing bacterial load with antimicrobial agents, changing the stent material, or influencing mucin production with aspirin have failed to prolong stent patency.[133-135] Because deposition of sludge (leading to stent occlusion) may depend on the flow rate through the stent, a change in stent diameter may influence the process of stent clogging. Theoretically, a small increase in stent diameter may result in an appreciable increase in flow. The limiting factor for insertion of larger plastic biliary stents is the size of the instrumentation channel of the duodenoscope. With presently available endoscopes, plastic stents up to 12 French can be placed. The question of whether bigger is better still cannot be definitively answered for plastic stents. In some studies, stent patency was significantly longer for large-diameter plastic stents than for small-diameter ones.[136] Others have found no prolongation of stent patency and more complications when larger stents are used.[137] The divergent results of these studies may be explained by study design, patient selection criteria, and sample size.

There is considerable debate about whether patients with strictures involving the bifurcation require ductal decompression of both the right and left intrahepatic systems.[129] Advocates of a single stent argue that ductal decompression of one lobe improves symptoms of cholestasis and allows jaundice to resolve.[138] Proponents of decompressing both sides of the liver point to the 30% to 40% incidence of cholangitis, increased mortality, and death from sepsis when only one lobe is drained.[139] Our approach to hilar strictures is as follows: once a guidewire is advanced into an intrahepatic duct, bile is aspirated to limit systemic seeding of any resident bacteria when contrast is injected. Only enough contrast should be injected to define the stricture anatomy. If a good stentable duct is identified, that lobe is drained. When draining only one lobe of the liver, it is imperative to limit contrast injection to the lobe to be drained and avoid manipulation of the other lobe. The other lobe should be stented if cholangitis develops or symptoms of cholestasis persist. Two recent studies support this approach.[140-142] De Palma and colleagues randomized 157 consecutive patients with malignant hilar obstruction to undergo unilateral or bilateral hepatic duct drainage.[141] In the intention-to-treat analysis, unilateral drainage was associated with significantly higher rates of successful drainage and lower early complication rates (primarily because of lower rates of cholangitis). Thirty-day morality, late complications, and median survival were similar for the two groups. MRCP can help in selecting the liver lobe to be drained, thus avoiding injection of contrast medium into the contralateral lobe.[143] Freeman and Overby used MRCP and CT to guide unilateral metal stent placement in 35 patients with no episodes of cholangitis.[144]

The success rate of plastic stent insertion is about 90%, and it is higher with distal than with proximal tumors.[145] If endoscopic stent placement fails, percutaneous drainage or a combined endoscopic radiologic procedure (rendezvous procedure) can be performed. If contrast was injected into the biliary tree, such therapy should be performed urgently to prevent cholangitis. In a surgically fit patient, particularly if duodenal obstruction is present, surgical bypass is a reasonable option. Relief of symptoms can be expected in nearly all patients

after successful deployment of a plastic stent. Stenting not only resolves jaundice and pruritus but is also associated with improvement in quality of life.[146-148]

Early postprocedure complications, which have been reported in 10% to 20% of patients in most studies, are related to the sphincterotomy or to insertion of the stent itself. The most frequent early complication is cholangitis, which is reported to occur in as many as 10% to 15% of patients and is probably due to the introduction of bacteria during the procedure into the stagnant bile proximal to the stricture.[15,149] The risk for cholangitis is higher if incomplete drainage is achieved.

The main late complication of biliary stenting is cholangitis as a result of stent occlusion. Stents placed for hilar obstruction appear to occlude faster than stents placed for more distal obstructing lesions.[145,150] Patients with symptomatic stent occlusion will require stent change and possibly hospitalization for treatment of cholangitis. As a result, some authorities have advocated prophylactic stent changes in the hope of avoiding cholangitis. Sherman and colleagues have demonstrated that nearly 50% of patients undergoing stenting with 10- or 11.5-French plastic biliary stents die before stent occlusion.[150] Thus, patients with a short life expectancy would be subjected to unnecessary procedures if prophylactic stent changes were performed. Using computer modeling, Tarnasky and associates[151] suggested that indicated stent exchanges are more cost-effective than prophylactic stent change at any interval. Prat and colleagues[152] reported that symptom-free survival was longer in patients undergoing planned stent exchange every 3 months but that planned stent exchange offered no cost advantage over stent exchange for symptomatic occlusion. The preliminary results of a randomized trial comparing scheduled stent change every 4 months with symptomatic stent change revealed no difference in the number of ERCP procedures per patient, number of stents per patient, mortality rate, need for metal stenting, frequency of surgery, mean stent survival, frequency of cholangitis, and time to death.[153]

One of the major advances in stent technology was development of the metal expandable stent. Expandable metal stents may offer improved biliary drainage with prolonged patency rates because of their large diameter and small surface area. Several types of expandable metal stents are available that are characterized by different insertion devices, methods of deployment, radial forces, and metal composition. To date, most experience has been gained with the Wallstent. This stent is easily inserted over a well-positioned guidewire and is successfully deployed in more than 95% of cases. The Wallstent is mounted on a 7.5-French delivery device and shortens and expands to 8 to 10 mm as it is deployed. Five prospective, randomized trials[154-158] (four endoscopic and one percutaneous) have shown that a metal expandable biliary stent occludes less frequently and less rapidly than do conventional 10- and 11.5-French plastic stents. This translated into a reduction in hospitalization requirements (for cholangitis and stent change) and an overall cost savings for the metal stents. Because metal stents are more costly initially and approximately half the patients in most plastic stent series will need a second stent, identification of patients who are likely to outlive their first plastic stent (and warrant a metal stent) is a major challenge for the managing physician. In the Amsterdam study,[154] the stent patency curves of Wallstents and plastic stents ran parallel during the first 3 months after stent insertion. After that time the curves diverged in favor of the Wallstent. Therefore, based on data from this study, the authors recommended that only patients with a life expectancy of more than 3 months be potential candidates for the use of an expandable metal stent. An additional indication for the use of metal stents is in the small group of patient who suffer rapid and repeated obstruction of plastic stents. These patients have not been well studied and can, at present, not be identified at the initial stenting session. Studies comparing endoscopically placed metal stents with plastic stents for malignant hilar obstruction have not been performed. However, using MRCP and CT targeting, metal stents can be successfully placed with long patency rates and infrequent episodes of cholangitis.[159]

When palliation is the goal of therapy for patients with malignant bile duct obstruction, how does endoscopic decompression compare with percutaneous and surgical drainage procedures? In a randomized study comparing percutaneous with endoscopic drainage,[160] endoscopic stenting was associated with more frequent successful drainage (81% versus 61%, $P < .05$), a lower complication rate (19% versus 67%, $P < .05$), and lower 30-day mortality (15% versus 33%, $P < .05$). Median survival was similar for the two groups (23 versus 16 weeks). Three prospective, randomized trials[161-163] have compared endoscopic and surgical drainage for malignant distal biliary obstruction. Endoscopic stenting and surgery were equally effective palliative treatments, with endoscopic treatment having a lower early complication rate and mortality, but a higher risk for late complications such as stent blockage and gastric outlet obstruction. None of these studies demonstrated a difference in survival rates between treatment groups.

Tissue Sampling at ERCP

ERCP frequently provides the first opportunity to obtain a histologic or cytologic specimen from an unexplained biliary or pancreatic stricture. A variety of tissue-sampling techniques are available to the endoscopist at the time of ERCP, including bile and pancreatic juice cytology, brush cytology, intraductal forceps biopsy, intraductal fine-needle aspiration, stent cytology, and juice and tissue evaluation for aneuploidy, tumor markers (e.g., carcinoembryonic antigen [CEA], CA 19-9), p53 immunoreactivity, and K-*ras* oncogene mutations.[164]

Brush cytology is the most commonly applied method of tissue sampling and the most extensively studied. Although the technical success rate is high (90% to 95%), most studies demonstrate cancer detection rates in the 20% to 60% range.[165-170] The sensitivity of bile duct brush cytology is higher for cholangiocarcinoma than for pancreatic cancer.[164] Sawada and colleagues[171] have shown that brushing the pancreatic duct may increase the diagnostic yield of brush cytology (versus brushing the bile duct) in pancreatic cancer. However, pancreatic

cancers often disrupt the duct and prevent passage of the brush through the tumor in more than 25% of patients. In an attempt to improve on the sensitivity of brush cytology, other methods have been used more recently. Howell et al. originated use of the ERCP endoscopic needle aspiration (ENA) technique and reported 62% sensitivity for detection of cancer from biliary samplings in patients with biliary strictures (including 53% in pancreatic cancer and 80% in cholangiocarcinoma).[172] These impressive results for ENA were not found in subsequent reports,[169,173] where the sensitivity ranged from 26% to 30%.

Endobiliary forceps biopsy allows examination of tissue specimens below the bile duct epithelium. The results of six selected studies have shown improved cancer detection rates in comparison to cytologic techniques, with a cancer detection rate of 56% in 502 patients.[164,174]

Although it would be preferable to have one technique that would have a cancer detection rate similar to that seen with biopsy of upper gastrointestinal and colonic neoplasms, this goal has not been reached in the pancreaticobiliary tree. Investigators have therefore evaluated the added sensitivity of combining a number of tissue-sampling techniques. Jailwala and colleagues[169] reported their results of the cumulative sensitivity of triple tissue sampling at one ERCP session with brush cytology, fine-needle aspiration, and forceps biopsy in 104 patients with malignant bile duct obstruction. Tissue sampling sensitivity varied according to the type of cancer; the highest yield was seen in patients with ampullary cancer. The combination of techniques was superior to individual methods, with the addition of a second or third technique increasing cancer sensitivity rates in most instances.

It is clear that the cancer detection sensitivity of these standard techniques individually is suboptimal. Methods to improve this sensitivity are therefore being evaluated. Preliminary studies suggest that the yield may be increased by evaluating aspirated fluid and tissue for aneuploidy[175] and tumor markers such as CEA and CA 19-9. Recent investigation has suggested that evaluation of tissue or fluid for K-*ras* mutations is more accurate than cytology in the diagnosis of pancreatic cancer.[176-178] However, some authors[177] have identified K-*ras* mutations in patients with chronic pancreatitis, thus reducing the specificity of this test. Further study is warranted to determine the role of these new techniques in the assessment of pancreatic and biliary strictures.

Sump Syndrome

Sump syndrome is an infrequent complication of side-to-side choledochoduodenostomy. Some degree of stenosis of the surgical anastomosis is usually present. Cholangitis, pain, and pancreatitis may occur as food, stones, or other debris accumulates in the common bile duct in the bypassed segment. The reported median time interval between surgery and the appearance of symptoms was 5 years and between surgery and the diagnosis of sump syndrome was 6 years. ES with removal of the debris has been shown to be effective treatment.[179,180] Although it may be possible to extract debris and stones via the choledochoduodenostomy, thereby obviating the need for sphincterotomy, this approach puts the patient at risk for recurrent symptoms.

Choledochal Cysts and Anomalous Pancreaticobiliary Union

Choledochal cysts are uncommon anomalies of the biliary tree that are manifested as cystic dilation of the intrahepatic or extrahepatic ducts (or both).[181,182] These cysts are most often classified by the scheme proposed by Todani and associates.[182] Type I cysts, which involve only the extrahepatic biliary tree, are the most common form and account for 80% to 90% of all choledochal cysts.[183] In this form of the anomaly, the cystic duct generally enters the choledochal cyst, and the right and left hepatic ducts and the intrahepatic ducts are normal in size. Type II cysts are extrapancreatic bile duct diverticula and make up 2% of reported cases.[184] Type III cysts, which account for 1.4% to 5% of cases, are choledochoceles and most often involve only the intraduodenal part of the common bile duct, but occasionally the intrapancreatic portion.[185] Type IV cysts are subdivided into type IV A, or multiple intrahepatic and extrahepatic cysts, and type IV B, or multiple extrahepatic cysts. Type IV A cysts account for approximately 19% of reported cases, whereas type IV B cysts are much less common.[186] Finally, a type V cyst, or Caroli's disease, consists of either single or multiple intrahepatic cysts. This form of cystic disease within the liver communicates with the biliary system, as opposed to fibrocystic disease, in which cysts filled with bile do not.[187]

An anomalous pancreaticobiliary union is considered to be present when the common channel is longer than 15 mm. In this situation, the pancreatic duct and bile duct junction is outside the duodenal wall and proximal to the sphincter of Oddi, thus promoting reflux of pancreatic juice into the biliary tree. Reflux of pancreatic juice has been postulated to be involved in the pathogenesis of carcinoma, which occurs in 2.5% to 17% of patients with choledochal cysts.[188-192]

Surgery is the recommended treatment for most patients with choledochal cysts.[192-195] Cholangiography is the gold standard for diagnosing choledochal cysts. Although ERCP and PTC are invasive, they can thoroughly assess the cyst anatomy, site of biliary origin, extent of intrahepatic and extrahepatic disease, associated biliary tract anomalies, and complications (e.g., bile duct strictures, stones); in addition, they shed light on possible therapeutic intervention, either definitive or temporizing pending surgery. ERCP is often the preferred modality because it provides detailed evaluation of the pancreatic duct and the pancreaticobiliary union and is very useful in the diagnosis of type III choledochal cysts (choledochocele). MRCP can also delineate the anatomy noninvasively.

ERCP has become the procedure of choice to evaluate and treat most patients with type III choledochal cysts.[196] Patients with choledochoceles will commonly

have biliary symptoms (biliary colic, cholestatic jaundice, jaundice) or unexplained pancreatitis prompting evaluation by ERCP. The endoscopic features of a choledochocele include the following: the intramural segment of the common bile duct protrudes into the duodenum in continuity with an enlarged papilla, the papilla is soft and smooth, ballooning of the papilla is noted with contrast injection, on contrast injection a cyst-filled structure is apparent on fluoroscopy and in continuity with the common bile duct, and no impacted stone is present. Several small series have reported the utility of endoscopic cyst unroofing and sphincterotomy for both pancreatic and biliary indications.[196-201] Ladas and associates[196] identified 15 symptomatic choledochocele patients among 1019 (1.5%) referred for ERCP. Twelve patients were treated by endoscopic therapy. During long-term follow-up (mean, 26 months; range, 4 to 56 months), 10 of 12 patients were asymptomatic with normal liver test results. One patient had a mild episode of cholangitis, and carcinoma developed in the choledochocele in another. This unusually high frequency of choledochoceles may represent overdiagnosis because several of these patients appeared to have only bile duct and ampulla of Vater dilation associated with ductal stones (not true choledochoceles). Although the risk for cancer in these patients is uncertain, it appears appropriate to recommend long-term follow-up in patients treated by endoscopic therapy alone. How this follow-up should be pursued remains to be clarified. Elton and colleagues[200] described a variant of a choledochocele that they called a dilated common channel syndrome. These patients have enlarged common pancreaticobiliary channels that were thought to have developed because of papillary stenosis. Among 77 patients treated by unroofing and sphincterotomy, 77% had complete and long-lasting resolution of symptoms.

Management of anomalous pancreaticobiliary union in the absence of a choledochal cyst is unclear. Because of the high risk for gallbladder cancer, prophylactic cholecystectomy has been recommended by some.[191] In one series of 15 patients with an anomalous pancreaticobiliary union (7 had choledochal cysts) and recurrent pancreatitis or abdominal pain (or both) treated by ES, 13 had resolution or a reduction in the frequency of pancreatitis and pain.[202] Ng and colleagues[203] similarly reported resolution of pain and pancreatitis in 5 of 6 patients with a long common channel after endoscopic therapy. Whether patients with anomalous junctions without choledochal cysts treated by sphincterotomy need surveillance for cancer cannot be answered at the current time.

PANCREATIC DRAINAGE PROCEDURES

Chronic Pancreatitis

Pancreatic duct pressure is generally increased in patients with chronic pancreatitis regardless of the etiology and whether the main pancreatic duct is dilated.[204] The aim of endoscopic therapy (and decompressive surgical therapy) for patients with chronic pancreatitis and pain or clinical episodes of acute pancreatitis (or both) is to alleviate the obstruction to outflow of exocrine juice. Certain pathologic alterations of the pancreatic duct, bile duct, or sphincter lend themselves to endoscopic therapy. The techniques (e.g., sphincterotomy, dilation, stenting) and instruments (e.g., sphincterotome, dilating balloon, pancreatic stent) used to treat biliary tract disease have been adapted for use in the pancreatic duct.

Data in this area are often difficult to interpret because of heterogeneous populations with one or more pathologic processes being treated (e.g., pancreatic duct stones, strictures, pseudocysts) and because of the multiple therapies being performed in a given patient (e.g., stricture dilation, stone extraction, bile or pancreatic duct ES). No controlled studies have been reported to date.

Pancreatic Strictures

Benign strictures of the main pancreatic duct may be a complication of a previous embedded stone or a consequence of acute inflammatory changes around the main pancreatic duct.[205] In Cremer and colleagues' large referral population, only 10% of patients had a stricture without associated calcified pancreatic stones.[205] Pancreatic duct strictures can be treated by stent therapy. If stents larger than 7 French are to be used, patients often require both pancreatic and bile duct sphincterotomy followed by stricture dilation. For optimal results, the therapy must address both the pancreatic duct stricture and duct stones. The best candidates for stenting are those with a distal stricture (in the pancreatic head) and upstream dilation.

The technique for placing a stent in the pancreatic duct is similar to that used for inserting a biliary stent. A guidewire must be maneuvered upstream to the narrowing. Hydrophilic flexible-tip wires are especially helpful. The pancreatic stent is advanced over the wire through the stricture with a pusher tube. Most pancreatic stents are just standard biliary stents with extra side holes at approximately 1-cm intervals to permit better side branch juice flow. In general, the size of stent should not exceed the size of the normal downstream duct. Therefore, 4- to 7-French stents are commonly used in small ducts, whereas 10- to 11.5-French stents can be used in patients with advanced chronic pancreatitis and grossly dilated ducts. Pancreatic sphincterotomy (major or minor papilla, or both) is often performed before (or after) placing a pancreatic stent.[206-208] This procedure is done with a standard pull-type sphincterotome or by using a needle knife to incise the sphincter over a previously placed stent. Some authorities favor performing biliary sphincterotomy before pancreatic sphincterotomy because of the high incidence of bile duct obstruction and cholangitis, as reported by one group, if this is not done.[209] Such complications were not found by others and have been infrequent in our experience.[206,207,210] Performing biliary sphincterotomy first, however, can expose the pancreaticobiliary septum and allow the length of the cut to be gauged more accurately.

Wilcox summarized the results of pancreatic duct stent placement, usually with ancillary procedures.[205,211-216] Among the 1500 patients treated in 15 series, benefit was seen in 31% to 100% of patients during a follow-up interval of 8 to 72 months. The greatest benefit was achieved in patients with dominant strictures and dilated ducts.[217] Like surgical decompressive procedures, it appears that the response attenuates over time. Quantification of the degree of improvement is often poorly defined. Partial or complete symptom improvement after stenting suggests that intraductal hypertension was an etiologic factor. Continued symptom relief after stent removal indicates adequate dilation of the narrowing. Differentiation of these two types of improvement is, unfortunately, not clarified in some reports. In the largest published study, 1018 patients with chronic pancreatitis were monitored prospectively for a mean of 4.9 years after endoscopic intervention.[218] At follow-up, 60% of patients had completed endotherapy, 16% were still undergoing endoscopic treatments, and 24% had undergone surgery. Complete (69%) or partial (19%) technical success of endoscopic therapy was achieved in 88%. All patients had pain initially, but only 34% had pain at follow-up ($P < .0001$); a significant reduction in pain (no or weak pain) was achieved in 85%. Rates of pain relief were similar in patients with dominant strictures in the head or body (or both), pancreatic stones in the head or body (or both), a combination of stones and strictures, and complex pathology. Dite and colleagues[219] reported the results of a randomized study comparing surgical and endoscopic treatment in 72 patients with a dilated pancreatic duct and stones, strictures, or both. An additional 68 patients who refused randomization and opted for endoscopic therapy ($n = 28$) or surgery ($n = 40$) were included in the total results. At 1 year after the intervention, 92% of patients in each group had complete or partial pain relief. After 5 years, rates were 65% for endotherapy patients and 86% for surgical patients (complete resolution, 14% versus 37%, respectively, $P = .002$; partial relief, 51% versus 49%, P = NS). Weight gain was similarly common in the two groups at 1 year (66% versus 60%, respectively), but significantly more patients had gained weight in the surgical group (52%) than in the endotherapy group (27%) by 5 years. Outcomes in the randomized group were similar to those in the total group. Despite the many methodologic problems associated with this study, the data suggest that surgical outcomes are more durable. In a long-term outcome study, 100 patients with severe chronic pancreatitis and pancreatic duct strictures were treated with plastic pancreatic stents (median duration of 23 months) and monitored for 69 months from study entry, including a median period of 27 months after stent removal.[220] The stents were exchanged when recurrent pain developed and removed when defined clinical and endoscopic parameters were met. After stent removal, 30 patients (30%) required re-stenting within the first year of follow-up, whereas in 70 (70%) patients, pain control was adequate during that period. By the end of the follow-up period, 38 patients required re-stenting and 4 ultimately underwent pancreaticojejunostomy. Pancreas divisum was the only factor significantly associated with a higher risk for re-stenting.

It appears that complete stricture resolution is not mandatory for improvement in symptoms, which implies that luminal patency was sufficient or other therapies performed along with the stenting contributed to the benefit. Because the stricture persists in many patients, Cremer and colleagues evaluated the expandable metal stent (18 French in diameter, 23 mm in length) in 29 patients.[221] After 6 months, mucosal hyperplasia resulted in stent occlusion in most patients.

Pancreatic Ductal Stones

It has been postulated that increased intraductal pressure proximal (upstream) to an obstructed focus within the pancreatic duct, as with pancreatic duct stones, is one of the potential mechanisms responsible for attacks of acute pancreatitis or exacerbations of chronic abdominal pain in patients with chronic pancreatitis. Reports indicating that endoscopic (with or without ESWL) or surgical removal of pancreatic calculi results in improvement in symptoms support this notion.[209,222-230] In one series,[225] 32 patients with pancreatic duct stones underwent attempted endoscopic removal. Of these patients, 72% had complete or partial stone removal and 68% improved after endoscopic therapy. Symptomatic improvement was most evident in the group of patients with chronic relapsing pancreatitis (versus those with chronic continuous pain alone; 83% versus 46%). Factors favoring complete stone removal included (1) three or fewer stones, (2) stones confined to the head or body of the pancreas (or both), (3) absence of a downstream stricture, (4) stone diameter less than 10 mm, and (5) absence of impacted stones. After successful stone removal, 25% of patients demonstrated regression of the ductographic changes of chronic pancreatitis and 42% had a decrease in diameter of the main pancreatic duct. The only complication from therapy was mild pancreatitis in 8%. These data suggest that removal of pancreatic duct stones may result in symptomatic improvement. Longer follow-up will be necessary to determine the stone recurrence rate and whether endoscopic success results in long-standing clinical improvement. It is apparent from this and other studies that the success rate for complete stone extraction from the pancreatic duct by endoscopic techniques alone is significantly inferior to that seen in the bile duct. The problem of delivering a large stone, an impacted stone, or a stone upstream to a stricture can be overcome by reducing the stone's size by either dissolution or fragmentation. No chemical agents have been found to effectively dissolve stones.

ESWL can be used to facilitate fragmentation and stone removal when endoscopic therapy alone fails or as a primary therapy.[209,222,227-232] Thus, this procedure is complementary to endoscopic techniques and improves the success of nonsurgical ductal decompression. This technique is a widely available alternative that has been performed since 1987 and for which substantial clinical experience has accumulated. There have more than 18 published reports totaling more than 700 patients who were treated with ESWL.[233] Patients with obstructing prepapillary concrements and upstream ductal dilation appear to be the best candidates for ESWL. In the largest

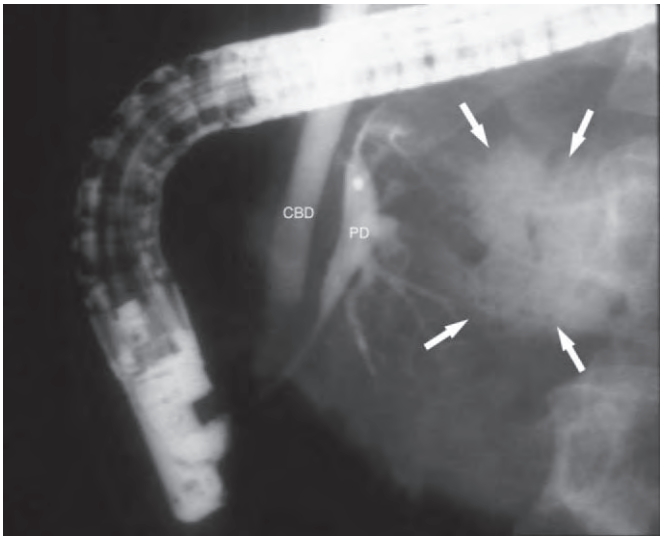
reported series,[209] 123 patients with main pancreatic duct stones and proximal dilation were treated with the electromagnetic lithotripter, usually before pancreatic duct sphincterotomy. Stones were successfully fragmented in 99% and resulted in a decrease in duct dilation in 90%. The main pancreatic duct was completely cleared of all stones in 59%. Eighty-five percent of patients noted improvement in pain during a mean follow-up of 14 months. However, 41% of patients had a clinical relapse as a result of stone migration into the main pancreatic duct, a progressive stricture, or stent occlusion. Complications in series using ESWL were mostly minor and primarily related to the endoscopic procedure. A meta-analysis of 16 studies published between 1989 and 2002 that included 588 patients showed that ESWL had a significant impact on reduction of pancreatic stone burden and improvement in pain.[234] Brand and colleagues[235] showed that the global quality of life was improved in 68% of patients undergoing ESWL. Overall, the endoscopist is encouraged to remove pancreatic duct stones in symptomatic patients when the stones are located in the main duct (in the head or body, or both) and are thus readily accessible. The currently available data suggest that the clinical outcome after successful endoscopic removal is similar to the surgical outcome, but with lower morbidity and mortality.[236] Long-term follow-up studies have shown that ESWL combined with ERCP may avoid the need for surgery in approximately two thirds of patients on an intention-to-treat basis.[237] However, to date, no comparative trials have been conducted in patients with pancreatic stones alone.

Pancreatic Pseudocysts and Fistulas

Pancreatic pseudocysts are defined as encapsulated collections (without an epithelial lining) of pancreatic juice, either pure or containing necrotic debris or blood (or both), that are situated either outside or within the limits of the pancreas from which they arise.[238] A pancreatic pseudocyst develops as a consequence of acute pancreatitis, chronic pancreatitis, or pancreatic trauma.[239] The optimal pseudocyst candidate for endoscopic drainage has a single mature cyst without pancreatic necrosis, residual adjacent inflammation, or portal hypertension. More complex patients are generally best managed by a multidisciplinary approach with input from surgery, medicine, and interventional radiology.

Two endoscopic approaches can be used, depending on whether the cyst communicates with the pancreatic duct.[212,240-249] Cysts communicating with the ductal system can be drained by a transpapillary approach (Fig. 103–10). The proximal tip of the prosthesis has generally been placed in the cystic cavity, but it can be placed upstream at the site of disruption. A pancreatic duct sphincterotomy may be required.

Noncommunicating pseudocysts can be treated by direct cystoenterostomy via the stomach (endoscopic cystogastrostomy) or duodenum (endoscopic cystoduodenostomy). The aim of therapy is to create a communication between the cystic cavity and the gastric or duodenal lumen. Two prerequisites should be fulfilled



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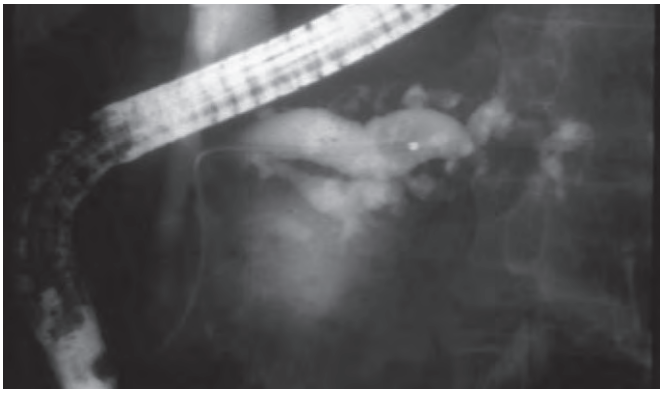
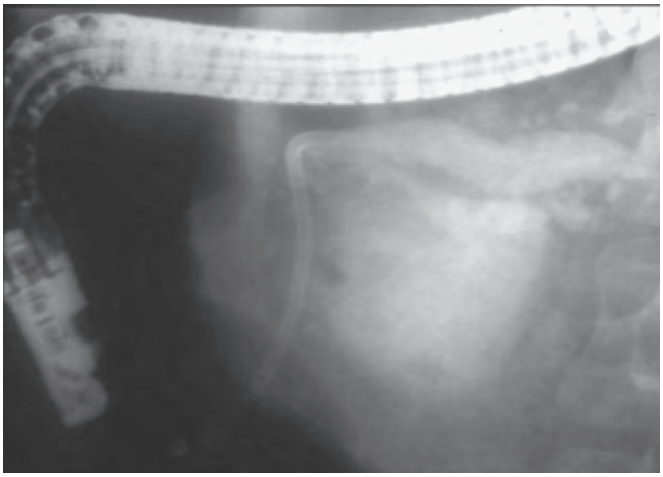


B



C

Figure 103–10. Chronic pancreatitis with a 5-cm communicating pseudocyst. **A,** The pancreatogram demonstrates a leak from the neck of the pancreatic duct that is filling a pseudocyst cavity *(arrows).* CBD, common bile duct; PD, pancreatic duct. **B,** The upstream duct is accessed and demonstrates marked dilation of the main duct and side branches. **C,** A pancreatic stent was placed to bridge the site of disruption.

Table 103–3 Results of Endoscopic Management of Pseudocysts

Author	Technical Success	Method of Pseudocyst Decompression			Complications	Death
		Transpapillary	*Cystogastrostomy*	*Cystoduodenostomy*		
Binmoeller[240]	47/53*	31	6	10	6	0
Catalano[241]	17/21	17	0	0	1	0
Cremer[242]	32/33	0	11	21	3	0
Kozarek[244]	12/14	12	0	0	5	0
Barthet[245]	58/67	26	1	31	9	1
Smits[246]	31/37*	16	8	7	6	0
Howell[247]	100/108	37	38	25	25	0
Baron[248]	82/95	NM	NM	NM	17	0
Grimm[249]	14/16	5	1	8	5	1
Total	*393/444 (89%)*	*144*†	*65*†	*102*†	*77 (17%)*	*2 (0.5%)*

NM, not mentioned.
*Combination therapy in several patients.
†Does not include numbers from Baron et al.

before attempting this treatment: bulging because of the cyst should be obvious during upper endoscopy, and the distance between the cyst and the lumen should not exceed 1 cm.[238] This distance can usually be assessed by CT, ultrasound, or endosonography, but when the compression is visible, usually the distance from the cyst to the lumen is less than 1 cm. In addition, the cyst wall should be mature. A double- or triple-lumen, beveled-tip needle knife is used to burrow a hole (usually with blended current) into the cyst cavity. A cystoenterotome is commercially available.[250] Many authorities advocate needle localization to identify a safe entry site before diathermic puncture.[251] The complication rate of this procedure may also be reduced by using the Seldinger technique without electrocautery.[252] A guidewire is advanced into the cyst and looped 360 degrees to secure positioning. Puncture should be performed perpendicular to the cyst wall, and thus a duodenoscope is preferred. The newly created tract is then balloon-dilated to 8 to 10 mm. Vigorous flow of pseudocyst fluid into the gut lumen generally occurs, and this fluid must be aspirated to maintain the endoscopic view. Two or more double-pigtail stents are then placed to bridge the cyst and the intestinal lumen. When significant debris or necrotic tissue is present, use of a nasocystic drain should be considered to allow for lavage of the cyst cavity. It is appropriate to maintain the patient with nothing by mouth (NPO) and administer broad-spectrum antibiotics intravenously for 1 to 3 days if the cyst is larger than 6 cm or contains debris. Diabetics, patients with debris in the cyst, and immunosuppressed patients may need a longer NPO interval because oral intake permits food and a greater concentration of bacteria to enter the residual cyst. Pseudocyst size is monitored by ultrasonography or CT at 4- to 6-week intervals. After resolution (usually in 1 to 2 months), the stents are endoscopically removed and follow-up pancreatography is performed. Pseudocysts resolve after endotherapy in approximately 80% to 90% of patients, with the complication rate ranging from 4% to 20%. The pseudocyst recurs in 10% to 20% of endoscopically managed patients, especially those with duct cutoff on the pancreatogram. Table 103–3 shows the results of endoscopic management from large centers. EUS has been used increasingly for the evaluation and treatment of pancreatic fluid collections. This endoscopic procedure can (1) determine whether there is significant solid debris within a collection, (2) differentiate between a pseudocyst and other noninflammatory cystic lesions, (3) guide transmural drainage, and (4) be used to perform drainage of the pseudocyst. Because a visible luminal bulge is not required for direct EUS pseudocyst drainage, the number of potential patients available for endoscopic therapy has increased.[253]

These excellent results certainly support the use of endoscopic therapy in appropriate candidates. When compared with other endoscopic techniques, this procedure has a relatively high bleeding and perforation rate. Bleeding complications are decreased by use of a hydrostatic balloon (not sphincterotome) to enlarge the tract orifice or by initial puncture with a needle catheter instead of the needle knife. Nevertheless, the overall complication rate probably compares favorably with surgical series. Coordination with the surgeon is necessary when performing this procedure.

Pancreatic duct disruptions or leaks occur as a result of acute or chronic pancreatitis, trauma, or surgical injury and can produce pancreatic ascites, pseudocyst formation, pleural effusions, and cutaneous fistulas. Pancreatic leaks and fistulas can be successfully treated with transpapillary stents. Telford and colleagues[254] reported that 25 of 43 (58%) disruptions resolved with pancreatic stenting, with no recurrence during a 2-year follow-up interval. Bridging the disruption was found on multivariate analysis to be predictive of a successful outcome.[254,255] Endoscopic injection of tissue glue has also been used to close pancreatic fistulas.[256]

Endoscopic therapy has been used to treat sterile organized necrosis in symptomatic patients.[248] The procedure is more technically difficult, carries a higher rate of complications, has a lower cure rate, and tends to be performed in more severely ill patients than those with pseudocysts.

PANCREAS DIVISUM

Pancreas divisum, the most common congenital variant of pancreatic ductal anatomy, occurs when the ductal systems of the dorsal and ventral pancreatic ducts fail to fuse during the second month of gestation. With nonunion of the ducts, the major portion of pancreatic exocrine juice drains into the duodenum via the dorsal duct and minor papilla. It has been proposed that a relative obstruction to pancreatic exocrine juice flow through the minor papilla could result in pancreatic pain or acute pancreatitis (or both) in a subpopulation of patients with pancreas divisum.[257] Endoscopic attempts to decompress the dorsal duct in symptomatic patients with pancreas divisum have been performed primarily by dilation, stent insertion, minor papilla sphincterotomy, or any combination of these techniques.[258-260] Lans and colleagues[258] reported their results of a randomized controlled trial of long-term (12 months) stenting of the minor papilla in patients with recurrent pancreatitis (n = 19). Follow-up continued for at least 12 months after stent removal. Stented patients had fewer hospitalizations and episodes of pancreatitis ($P < .05$) and were more frequently judged to be improved (90% versus 11% for controls, $P < .05$). Although the symptomatic improvement after this therapy has been encouraging, multiple stent changes are generally required and the risk for stent-related complications is considerable. Ertan[259] reported that stent-induced ductal changes developed in 21 of 25 patients (84%) with pancreas divisum after stenting periods of 6 to 9 months.

A more permanent enlargement of the minor papilla orifice is possible with sphincterotomy. Lehman and colleagues[260] attempted to evaluate the efficacy of minor papilla ES for patients with pancreas divisum (N = 52) and disabling pancreatic-type pain (n = 24), idiopathic acute recurrent pancreatitis (n = 17), or chronic pancreatitis (n = 11). A short 4- to 7-French stent was placed in the minor papilla and a 3- to 6-mm sphincterotomy was performed over the stent, with the stent used as a guide for cutting and a bridge to prevent edema-induced closure of the cut. The stent was then removed in approximately 2 weeks. The mean duration of symptoms was 5.1 years, and follow-up averaged 1.7 years, with all patients being observed for at least 6 months after therapy. Although 76.5% of the acute recurrent pancreatitis group improved after therapy, only 26% of the chronic pain group (P = .002) and 27% of the chronic pancreatitis group (P = .01) benefited. Similarly, when compared with the chronic pain and chronic pancreatitis groups, the acute recurrent pancreatitis group had a significant reduction in mean pain score and number of hospital days per month required for severe pain or pancreatitis (or both). These discordant results in responsiveness to therapy for the acute recurrent pancreatitis group versus the chronic pancreatitis and chronic pain groups were noted in several surgical series evaluating dorsal duct decompression[261,262] and other endoscopic series.[263,264] Pancreatitis complicating therapy occurred in 13% but, in general, was mild and managed conservatively. Stent-induced dorsal duct changes occurred in 50%. Heyries and colleagues reported that 22 of 24 patients (92%) had no further episodes of pancreatitis during a median follow-up period of 39 months (range, 24 to 105 months) after minor papilla sphincterotomy in 8 and dorsal duct stenting for a median time of 8 months in 16 patients.[265] When summarizing eight published studies that evaluated the efficacy of minor papilla therapy in 127 patients, no further attacks occurred in 81% monitored for a mean of 27 months after the intervention.[266] The results of these studies suggest that patients with pancreas divisum and acute recurrent pancreatitis are good candidates for endoscopic therapy whereas patients with chronic pancreatitis or chronic pain alone (or both) do not appear to do as well.

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Chapter

104

Biliary Tract Tumors

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BENIGN GALLBLADDER TUMORS

Benign tumors of the gallbladder are relatively common. With increased use of improving ultrasonographic techniques, there is accumulating experience with the management of these often asymptomatic lesions. Up to 5% of patients undergoing abdominal sonography may be found to harbor gallbladder polyps.[1] Benign gallbladder tumors can be broadly categorized as epithelial (adenomas), mesenchymal (fibromas, lipomas, hemangiomas), or as pseudotumors (cholesterol polyps, inflammatory polyps, adenomyomas). Most gallbladder cancers do not arise from precursor adenomas. Cholesterol polyps are the most common of the benign tumors. Adenomyomas are extensions of Rokitansky-Aschoff sinuses through the muscular layer of the gallbladder wall; they can appear polypoid or infiltrative in morphology and can be associated with biliary colic–like symptoms.

The likelihood of malignancy in gallbladder polyps is higher with increasing polyp size and decreasing polyp number. A review of 182 cases of resected gallbladder polyps identified only 13 cases of malignancy; likelihood of malignancy in this series was associated with patient age older than 50 years and solitary polyps larger than 1 cm.[2] In a similar review of 134 cases, 6 malignancies were identified and noted to be associated with fewer than 3 polyps.[3]

The management of gallbladder polyps is dictated by the presence of symptoms or their likelihood of harboring occult malignancy. Any patient with symptoms referable to gallbladder polyps should undergo cholecystectomy. In addition, patients with suspicious polyps (size >1 cm, number <3, sessile lesions, or those with sonographic evidence of mucosal invasion) should undergo cholecystectomy. Cholecystectomy performed for patients with suspicious polyps should be performed via an open approach to minimize the likelihood of tumor spillage. Furthermore, intraoperative frozen section analysis of the resected gallbladder specimen must be performed, because confirmation of malignancy may dictate the performance of an extended oncologic resection. Patients who do not undergo surgical therapy deserve close radiographic follow-up with serial sonograms performed at 6-month intervals to identify any rapid interval size progression that may indicate the presence of malignancy.

GALLBLADDER CANCER

Cancer of the gallbladder is the most common biliary malignancy and is the fifth most common gastrointestinal cancer. In the United States, it has an incidence of approximately 1.2 per 100,000 and is the cause of about 2800 deaths yearly.[4] Owing to its aggressive nature (manifested by its propensity toward nodal metastases, direct hepatic invasion, and seeding of peritoneal surfaces), it is usually diagnosed at an advanced stage, resulting in an overall median survival of less than 6 months.[5] These dismal biologic characteristics have historically fostered a cynical nihilism among clinicians caring for patients afflicted with this malignancy. However, recent advances in our understanding of its tumor biology, accompanied by significant progress in diagnostic and surgical extirpative techniques, have motivated a fresh new approach to this once universally fatal disease, providing the possibility of cure to a subset of patients presenting with gallbladder cancer.

Epidemiology

The prevalence of gallbladder cancer appears to be highest in South America, intermediate in Europe, and lower in the United States and the United Kingdom. In the United States, Native Americans, patients in urban areas, and those of lower socioeconomic status appear to be affected more commonly. Epidemiologic analysis of this disease identifies those processes promoting chronic gallbladder irritation and inflammation as risk factors for the onset of gallbladder cancer.[6,7] As such, a history of biliary disease, age, female gender, obesity, high carbohydrate diet, ethanol abuse, and tobacco abuse (all of which are associated with calculous biliary disease) have

been shown to be associated with a higher risk of developing gallbladder cancer.[8,9] Indeed, 79% to 98% of patients diagnosed with gallbladder cancer possess a personal history of gallstone disease (usually large, symptomatic, cholesterol stones). Mirizzi's syndrome, characterized by chronic gallbladder irritation from an impacted stone, has been associated with an increased risk of gallbladder cancer. The presence of an abnormal pancreaticobiliary duct junction, thought to promote chronic biliary inflammation, has been associated with both choledochal cyst disease as well as gallbladder cancer.[10] The incidence of gallbladder cancer in the so-called porcelain gallbladder, presumably resulting from chronic inflammation and calcification of the gallbladder wall, has been estimated to be as high as 61%; however, recent analyses suggest that the figure is more likely between 7% and 25%.[11,12]

The exact nature of the relationship between chronic inflammation and gallbladder tumorigenesis is unclear. It has been estimated that only 0.3% to 3% of patients with gallstones develop gallbladder cancer, rendering the theoretical benefit of prophylactic cholecystectomy nil (with the potential exception of those with porcelain gallbladder). Introduction of cholesterol stones into normal gallbladders does not experimentally induce gallbladder cancer in animal models; however, the presence of stones does appear to facilitate the ability of teratogens to induce gallbladder cancer.[13]

Anatomy

The anatomic relationships of the gallbladder to surrounding structures dictate the surgical strategies that must be employed in its treatment. The gallbladder fossa, in which lie the fundus and body of the gallbladder, rests beneath the junction of hepatic segments IVB and V. As a result, the likelihood of direct hepatic invasion of gallbladder cancer typically mandates anatomic resection of these segments. The infundibulum of the gallbladder lies adjacent to the right portal pedicle within the porta hepatis; as a result, tumors arising in the infundibulum commonly require a right trisegmentectomy for complete surgical resection.

The thin gallbladder wall comprises an inner mucosa, a thin lamina propria, and a single muscularis layer (unlike the two muscle layers that line most hollow viscera). The serosa of the gallbladder is typically opened during a standard cholecystectomy, and the avascular subserosal layer is the used as the surgical plane of dissection; the ability of tumor to microscopically invade well beyond the serosa explains the high prevalence of positive resection margins after standard cholecystectomy for gallbladder cancer.

The lymphatic drainage of the gallbladder has been well characterized. The pattern of lymphatic flow appears to be directed initially to the cystic and pericholedochal lymph nodes; then to the posterior pancreaticoduodenal, periportal, and common hepatic artery nodes within the hepatoduodenal ligament; and subsequently to the celiac, interaortocaval, and superior mesenteric artery nodes. There does not appear to be any ascending drainage into the hilum of the liver. For this reason, meticulous lymphadenectomy within the hepatoduodenal ligament is a critical component of surgical strategy in the management of gallbladder cancer. Unfortunately, the observed potential of direct drainage from the pericholedochal nodes into the interaortocaval nodes explains the difficulty of completely encompassing the extent of lymphatic involvement after surgical resection.[14]

Pathology

Approximately 60% of gallbladder cancers arise in the fundus, with 30% arising from the body and 10% from the neck.[15] Although it is likely that gallbladder cancer may follow the pathogenetic sequence of mucosal dysplasia to carcinoma in situ to invasive cancer, it is unlikely that most gallbladder cancers arise from precursor adenomas.

Gallbladder cancers have been categorized as infiltrative, nodular, combined nodular-infiltrative, papillary, and combined papillary-infiltrative.[16] Infiltrative tumors, which are the most common, initially appear as an indurative thickening of the gallbladder wall, spreading into the subserosal plane that is typically violated during routine cholecystectomy. Nodular tumors invade into adjacent pericholecystic structures early, but unlike infiltrative cancers, induce sharply defined borders that can facilitate curative resection. Papillary tumors tend to grow in a polypoid fashion, often filling into the lumen of the gallbladder with minimal wall invasion; as such, these tumors tend to be associated with more a favorable prognosis.

Microscopically, adenocarcinoma is the most common histologic subtype seen with gallbladder malignancies. Other histologic subtypes that have been reported include adenosquamous carcinoma, oat cell carcinoma, sarcoma, carcinoid, lymphoma and melanoma.[15] Histologic grading for gallbladder cancer, which has been recognized as a significant prognostic variable, is categorized from G1 (well-differentiated) to G4 (undifferentiated); patients most commonly present with G3 (poorly differentiated) tumors.[17]

The propensity of gallbladder cancer to penetrate beyond the single muscle layer of the gallbladder wall results in a high likelihood of tumor penetration into the liver, peritoneal cavity, and lymphovascular spaces at the time of diagnosis. Review of the literature suggests that only 10% of cases are confined to the gallbladder wall at diagnosis; 59% involve direct hepatic invasion, 45% demonstrate lymph node metastases, and 20% present with distant extrahepatic metastases.[18] The most common site of extra-abdominal spread is the lungs, although pulmonary metastases are rare in the absence of extensive intraperitoneal disease.

Diagnosis

Patients with gallbladder cancer may experience complaints that mimic those of benign biliary colic. Symptoms of persistent pain, weight loss, anorexia, jaundice,

and a palpable right upper quadrant mass are typically indicative of advanced disease that is not amenable to surgical resection. In fact, in a recent review of the Memorial Sloan-Kettering Cancer Center (MSKCC) experience, 95% of patients presenting with jaundice were ultimately noted to harbor unresectable disease.[19]

Tumor markers provide limited assistance with diagnosis. In the presence of appropriate symptomatology, carcinoembryonic antigen (CEA) elevations greater than 4 ng/ml have been shown to predict gallbladder cancer with 50% sensitivity and 93% specificity.[20] Similarly, elevations of CA 19-9 greater than 20 U/ml are 79.4% sensitive and 79.2% specific.[21]

Radiographic findings on ultrasonography include the presence of a polypoid gallbladder mass (seen in 27% of gallbladder cancer cases) or an invasive gallbladder-based lesion (seen in 50% of cases); other sonographic findings consistent with gallbladder cancer include the presence of discontinuous gallbladder mucosa, echogenic mucosa, or submucosal echolucency.[22] Computed tomographic (CT) findings seen in patients with gallbladder cancer include a mass filling the gallbladder lumen in 42% of cases, a polypoid mass in 26%, a mass in the region of the gallbladder fossa without a distinctly recognizable gallbladder in 26%, and diffuse wall thickening in 6% (Fig. 104–1).[23] More experience is being collected with the use of magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), which provide an especially accurate means of identifying small hepatic metastases and involvement of the common bile duct.

Despite the high frequency of nodal involvement, definitive preoperative identification of lymph node metastases remains challenging. Enlarged benign inflammatory lymph nodes are commonly encountered at the time of laparotomy. Although the CT finding of ring-like or heterogeneous enhancement of a greater than 10-mm lymph node has been associated with lymph node metastases with 89% accuracy, only 38% of nodal metastases are preoperatively identified by CT scanning.[24] Endoscopic ultrasonography may be useful for assessing peripancreatic and periportal adenopathy. Fluorodeoxyglucose positron emission tomography (PET) is employed to identify distant metastases that may contraindicate surgical therapy.

The potential for tumor cells to implant within needle tracts limits the usefulness of percutaneous core biopsy for diagnosis. Percutaneous fine-needle aspiration is associated with a lower incidence of needle tract seeding while providing satisfactory diagnostic accuracy and can be employed in cases of surgically unresectable disease where a definitive tissue diagnosis may direct nonoperative therapy.[25] Cytologic analysis of bile samples collected either percutaneously or endoscopically is associated with suboptimal sensitivities of 50% to 73%.[25,26]

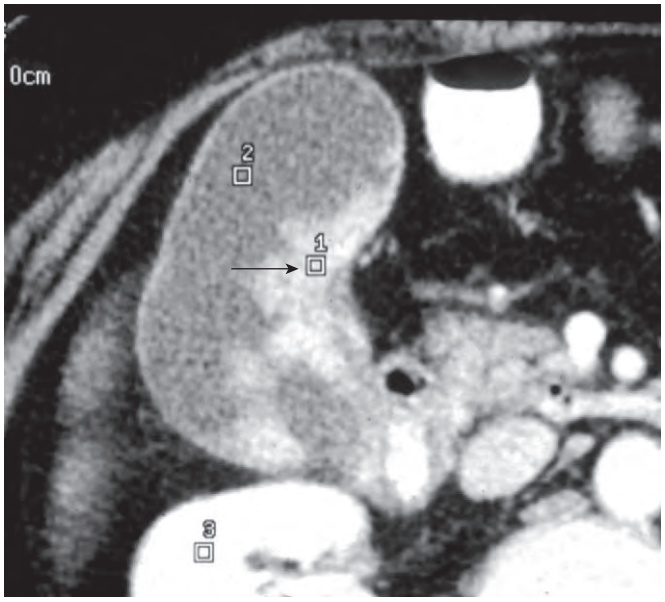

Figure 104–1. Appearance of gallbladder cancer on CT scan. Note the extensive sessile polypoid lesion within the lumen of the gallbladder wall.

Staging

The most accurate predictor of outcome is tumor stage. The major staging systems that have been proposed include the modified Nevin classification system,[27] the Japanese Society of Biliary Surgery classification system,[28] and the American Joint Committee on Cancer (AJCC)/International Union Against Cancer TNM staging system (Table 104–1A-C). With changes and improvements in surgical therapy, the impact of various staging criteria has changed. For example, the AJCC system has typically categorized patients with T4 tumors as having unresectable stage IV disease. With the increased implementation of modern hepatic resection techniques, we have observed that curative resection may be possible for patients with T4 gallbladder cancer. For this reason, we have proposed a modification of the AJCC staging system in which patients with T4 N0 M0 disease are placed in the stage IIIB category (see Table 104–1D).[29] In this manner, recommended surgical therapy is specifically dictated by the stage of disease present (see later).

Surgery

The standard template on which all operations for gallbladder cancer should be based is the extended cholecystectomy. This consists of cholecystectomy with en bloc resection of segments IVB and V and lymphadenectomy of the cystic, pericholedochal, periportal, and posterior pancreaticoduodenal lymph nodes residing in the hepatoduodenal ligament, as well as local interaortocaval lymph nodes (Fig. 104–2). Knowledge of a patient's tumor stage and familiarity with the general biologic proclivities of gallbladder cancer permit the surgeon to specifically tailor surgical therapy to the individual oncologic needs of each patient. For example, the lymphadenectomy can often be performed by simply skeletonizing the porta hepatis. However, in cases of prior dissection, where scar formation in the porta

Table 104–1 Gallbladder Cancer Staging Systems

Stage/TNM	Criteria
A. Modified Nevin System*	
Stage I	In situ carcinoma
Stage II	Mucosal or muscular invasion
Stage III	Transmural hepatic invasion
Stage IV	Lymph node involvement
Stage V	Distant metastases
B. Japanese Society of Biliary Surgery System†	
Stage I	Confined to gallbladder wall
Stage II	Minimal hepatic or bile duct invasion
	Lymph node involvement within hepatoduodenal ligament
Stage III	Major hepatic or bile duct invasion, N2 disease
	Lymph node involvement beyond hepatoduodenal ligament
Stage IV	Distant metastases
C. AJCC System‡	
T1	Mucosal or muscular invasion
T2	Transmural invasion
T3	<2 cm hepatic invasion
T4	>2 cm hepatic invasion
N0	No lymph node involvement
N1	Lymph node involvement within hepatoduodenal ligament
N2	Lymph node involvement beyond hepatoduodenal ligament
M0	No distant metastases
M1	Distant metastases
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1-3 N1 M0
Stage IVA	T4 N0-1 M0
Stage IVB	Tx N2 M0
	Tx Nx M1
D. Proposed Modified System§	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage IIIA	T3 N0 M0
Stage IIIB	T4 N0 M0
	Tx N1 M0
Stage IV	Tx N2 M0
	Tx Nx M1

*Data from Nevin JE, Moran TJ, Kay S, King R: Carcinoma of the gallbladder: Staging, treatment, and prognosis. Cancer 37:141-148, 1976; Donohue JH, Nagorney DM, Grant CS, et al: Carcinoma of the gallbladder. Does radical resection improve outcome? Arch Surg 125:237-241, 1990.

†Data from Onoyama H, Yamamoto M, Tseng A, et al: Extended cholecystectomy for carcinoma of the gallbladder. World J Surg 19:758-763, 1995.

‡Data from Bartlett DL, Fong Y, Fortner JG, et al: Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg 224:639-646, 1996.

§Data from Bartlett DL, Fong Y, Fortner JG, et al: Long-term results after resection for gallbladder cancer: Implications for staging and management. Ann Surg 224:639-646, 1996.

AJCC, American Joint Committee on Cancer; T, tumor; N, node; M, metastasis.

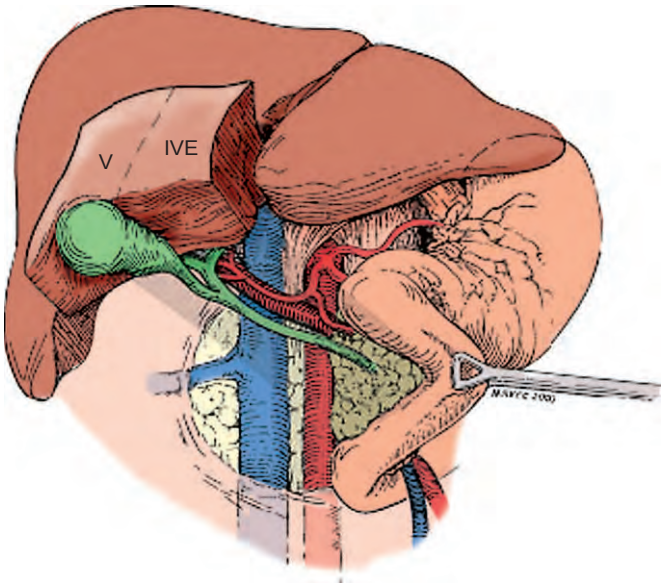

Figure 104–2. Portal lymphadenectomy and radical cholecystectomy with en bloc segment IVB/V hepatic resection for gallbladder cancer. (From Bartlett DL, Fong Y: Gallbladder cancer. In Blumgart LH, Fong Y, Jarnagin WR [eds]: Hepatobiliary Cancer: A Volume in the American Cancer Society Atlas of Clinical Oncology Series. Hamilton, Ontario, BC Decker, 2001, p 216.)

hepatis may blur the distinction between tumor and postoperative change, or in patients with infundibular tumors extending into the region of the common bile duct, or in obese patients, resection of the extrahepatic biliary system with Roux-en-Y hepaticojejunostomy reconstruction may be necessary to complete the lymphadenectomy with negative margins.

Analysis of the MSKCC experience demonstrated that only 25% of patients presenting with gallbladder cancer harbored disease ultimately amenable to curative resection. Among those patients who underwent curative resection, a median survival of 26 months and a 5-year actuarial survival of 38% were observed. Factors predictive of poor survival were advanced T stage and N stage.[30]

Staging laparoscopy has been advocated as a means of identifying patients with unresectable gallbladder carcinoma. Among 44 patients submitted for staging laparoscopy in the absence of preoperative evidence of unresectability at MSKCC, 21 patients were found to have evidence of distant metastatic disease at the time of laparoscopy. Among the 23 patients without laparoscopic evidence of metastatic disease, 15 were ultimately found to harbor unresectable disease due to distant metastases, distant nodal involvement, or locally advanced tumors at the time of laparotomy (producing an accuracy of 42%).[31]

Stage I Disease

The setting in which the surgeon is most likely to encounter stage I gallbladder cancer is after routine cholecystectomy for benign stone disease, when pathologic analysis of the resected gallbladder identifies cancer within the muscular layer of the gallbladder wall. As stated earlier, the plane of dissection used during a typical cholecystectomy is along the subserosal plane, which should not violate a T1 tumor. The likelihood of N1 disease is vanishingly small for patients with T1 tumors.[32] For this reason, simple cholecystectomy should be curative for patients with pathologically confirmed stage I disease.[33-36] A notable exception to this is the situation in which the cystic duct margin remains positive, in which case re-resection to negative margins is imperative. On occasion, this may necessitate common bile duct excision with re-establishment of biliary-enteric continuity. A review of 89 patients with stage I gallbladder cancer identified only two patients who recurred after simple cholecystectomy; both had a positive cystic duct margin.[33]

Stage II Disease

The subserosal plane of dissection employed in the standard cholecystectomy is likely to violate T2 tumors; indeed, patients with T2 tumors resected by simple cholecystectomy have a 40% to 50% likelihood of margin positivity.[29,32] Furthermore, approximately one half of patients with T2 tumors harbor nodal metastases. For these reasons, extended cholecystectomy with portal lymphadenectomy is the procedure of choice for patients with stage II disease. The importance of performing an extended cholecystectomy with negative margins is underscored by the observation that patients with stage II disease may enjoy 5-year survival rates of 70% to 90% after extended cholecystectomy as compared to 20% to 40% after simple cholecystectomy alone (with no 5-year survivors noted among those with positive resection margins).[33,36]

Stage III Disease

Performance of an extended cholecystectomy for patients with stage III disease has resulted in 5-year survival rates of 44% to 67%.[28,29,37] Occasionally, tumors localized to the infundibulum of the gallbladder can present unique surgical challenges, as extensive tumor within the region of the adjacent right portal pedicle may necessitate removal of the right hepatic lobe in addition to resection of segment IVA, typically in the form of an extended right hepatectomy (right trisegmentectomy).

Stage IV Disease

Extended cholecystectomy has yielded 5-year survival rates of up to 33% among patients with stage IVA disease.[29] Unfortunately, no long-term survival is seen among patients with stage IVB disease. This suggests that involvement of N2 nodes outside of the hepatoduodenal ligament and distant metastases are indicative of a uniquely more aggressive tumor biology than that seen in bulky T4 tumors extending more than 2 cm into the hepatic parenchyma or in those with nodal disease confined to the hepatoduodenal ligament. This

dichotomous outcome among patients with AJCC stage IV tumors has motivated the recommendation to categorize patients with T4 N0-1 M0 gallbladder cancer as having stage IIIB disease.

In practice, the surgeon is often confronted with gallbladder cancer that is diagnosed incidentally after a routine simple cholecystectomy. As outlined earlier, such patients who are found to harbor T1 tumors do not require repeat resection, provided that all margins of resection (with particular attention paid to the cystic duct margin) are negative. The high likelihood of positive margins and occult nodal metastases among patients with T2 and larger tumor mandates repeat resection in the form of an extended cholecystectomy. The primary challenge confronting the surgeon at this point is the ability to achieve a curative resection. A review of the MSKCC experience with gallbladder cancer patients referred for further surgical therapy after prior laparoscopic cholecystectomy demonstrated that 22 of 42 patients were noted to have unresectable disease at the time of second laparotomy.[38] Laparoscopy trocar site scars are typically excised, although this is done more for staging purposes to identify M1 disease than for any potential therapeutic benefit. In the scenario where the diagnosis of gallbladder cancer is unexpectedly made at the time of laparoscopy, the operating surgeon should either convert to an open exploration for possible extended cholecystectomy or abort the procedure with subsequent re-exploration or referral. A comparison of gallbladder patients presenting for initial definitive operation to those presenting for a second definitive operation identified no adverse survival effect associated with having undergone a prior noncurative exploration.[30]

Adjuvant Therapy

Gallbladder cancer unfortunately exhibits poor chemosensitivity, and its proclivity toward diffuse peritoneal spread limits the applicability of radiation therapy. Uncontrolled studies investigating the use of adjuvant chemotherapy and radiation have provided mixed outcomes with no consistent benefit.[39,40] One phase III trial examining the efficacy of 5-fluorouracil (FU)/mitomycin as adjuvant therapy for various pancreaticobiliary malignancies demonstrated a measurable improvement in 5-year overall survival (26.0% vs. 14.4%) and 5-year disease-free survival (20.3% vs. 11.6%) for patients with gallbladder cancer treated with adjuvant chemotherapy ($n = 69$) versus those treated with surgical resection alone ($n = 43$).[41] Notably, no such survival benefit was observed among patients with pancreatic cancer, cholangiocarcinoma, or ampullary carcinoma in this series.[41] Meta-analysis of studies employing palliative and adjuvant radiation therapy for patients with gallbladder cancer suggests a small benefit in survival for those treated with radiotherapy.[42] One report observed a 5-year survival of 64% among a cohort of 21 gallbladder cancer patients treated with concurrent 5-FU and 54 Gy of external-beam radiation therapy (EBRT) after resection, suggesting that the use of adjuvant chemoradiation may potentiate the therapeutic benefit of surgical treatment.[43] Unfortunately, there have been no large randomized trials from which recommendations regarding the routine use of adjuvant chemotherapy and/or radiation therapy for gallbladder cancer can be definitively made. In practice, however, most patients with positive resection margins or nodal metastases are usually offered adjuvant therapy without definitive proof of demonstrable efficacy.

Palliation

Because of the extremely high likelihood of surgical unresectability, comprehensive care for patients with gallbladder cancer must include an armamentarium of palliative procedures. Unfortunately, the median survival of patients with unresectable gallbladder cancer is typically only 2 to 4 months (with a 1-year survival <5%).[35] Therefore, effective palliation should be accompanied by minimal risk of morbidity. Surgical palliation in the form of a segment III biliary bypass provides a relatively simple means of durable biliary decompression due to its distance from the gallbladder and hepatic hilum.[44] However, percutaneous biliary drainage may provide a more reasonable method of palliation when the expected duration of survival is brief. Whenever feasible, port site recurrences after prior laparoscopic cholecystectomy should be resected to prevent the pain and local cutaneous complications associated with necrotic abdominal wall wounds. Palliative chemotherapy has not shown a consistent benefit[45]; palliative radiation therapy may provide minimal prolongation of median survival.[42]

Practical Management of Gallbladder Cancer

There are four characteristic scenarios in which clinicians are most often confronted with gallbladder cancer: (1) the preoperatively diagnosed radiographically suspicious gallbladder polyp; (2) the incidentally diagnosed gallbladder cancer encountered postoperatively after routine laparoscopic cholecystectomy; (3) gallbladder cancer presenting as a large gallbladder mass; and (4) gallbladder cancer presenting with obstructive jaundice.

Preoperatively Diagnosed Radiographically Suspicious Gallbladder Polyp These polyps are most often encountered after abdominal sonography, typically performed to evaluate symptoms of biliary colic. Sonographic findings that raise the suspicion of possible malignancy include size greater than 1 cm, polyp number less than 3, sessile polyps, and polyps with evidence of possible gallbladder mucosal invasion. Prior to operative intervention, diagnostic evaluation should be completed with MRCP and PET. MRCP imaging can delineate the biliary anatomy, identify biliary tumor involvement, and identify small intrahepatic metastases. PET imaging serves to rule out the possibility of distant metastases that may render operative intervention futile. In the absence of unresectable or metastatic disease, operative intervention should be undertaken in the form of an open cholecystectomy to minimize the likelihood of tumor dissemination resulting from inadvertent bile spillage.

Rather than opening the serosa of the gallbladder, the plane of dissection during cholecystectomy is along the cystic plate of the liver, to avoid violation of the gallbladder subserosa. Intraoperative frozen section is then performed to confirm the presence of gallbladder cancer. In practice, should the frozen section confirm the presence of a T1 tumor, simple cholecystectomy would suffice (assuming a negative cystic duct margin), given the low likelihood of nodal metastases. In practice, however, definitive demonstration of a T1 tumor is difficult to confirm by frozen section analysis. Therefore, the pathologic confirmation of malignancy alone is generally sufficient to warrant performance of an extended cholecystectomy, with en bloc resection of hepatic segments IVB and V (to encompass the gallbladder fossa) and portal lymphadenectomy (most commonly with resection of the common bile duct).

Gallbladder Cancer Diagnosed Incidentally After Laparoscopic Cholecystectomy Most gallbladder cancers diagnosed incidentally after routine cholecystectomy are early-stage tumors. Depending on particular operative and pathologic variables, repeat resection is often warranted for these patients. The decision-making process begins with careful pathologic analysis of the resected gallbladder. The low likelihood of nodal and distant metastases and the absence of tumor at the subserosal cholecystectomy dissection plane among T1 tumors obviates any need for further surgical therapy after routine cholecystectomy. Two critical exceptions to this rule would be the presence of intraoperative bile spillage and cystic duct margin positivity. The well-characterized propensity of gallbladder cancer to seed the peritoneal cavity considerably raises the possibility of peritoneal dissemination after inadvertent bile spillage. The presence of tumor cells at the cystic duct resection margin warrants repeat resection of the cystic duct and/or common bile duct to pathologically confirmed negative margins.

Repeat operative intervention must therefore be entertained when pathologic analysis identifies T2 or greater disease or if intraoperative bile spillage has occurred. Preoperative imaging studies should include MRCP and PET imaging to delineate the relevant biliary anatomy and pathology and to rule out metastatic disease. If these studies do not identify unresectability, extended cholecystectomy with hepatic segment IVB and V resection and portal lymphadenectomy is performed. The presence of peritoneal dissemination negates any potential benefit for resective therapy. A careful search for occult distant disease is particularly important when the previous laparoscopic cholecystectomy was complicated by bile spillage. Because of the documented ability of disseminated gallbladder cancer to seed laparoscopic incisional sites, trocar scars are routinely widely excised. As stated, this is primarily a staging maneuver, as identification of tumor infiltration in these areas portends the development of peritoneal metastases.

Gallbladder Cancer Presenting as a Gallbladder Mass In the situation where the suspicion of gallbladder cancer arises from the radiographic observation of a large mass emanating from the gallbladder, it is imperative to determine resectability. Again, this is best accomplished by MRCP and PET imaging. If resectability is confirmed for these locally advanced lesions, effective extirpation will usually require a right trisegmentectomy with portal lymphadenectomy, extrahepatic biliary resection, and hepaticojejunostomy, due to the likelihood of local hilar tumor involvement.

Gallbladder Cancer Presenting with Obstructive Jaundice As stated earlier, the presence of jaundice has been shown to independently predict a poor likelihood of resectability and long-term survival. In fact, management of this cohort of patients usually centers around palliation. Candidacy for operative intervention can be made on the basis of MRCP and PET imaging. When faced with radiographic evidence of unresectability or other contraindications to surgical treatment, percutaneous external biliary drainage offers a minimally invasive and effective means of palliation. In the limited subset of jaundiced patients demonstrating resectable disease, operative exploration may be undertaken. If operative findings confirm resectability, right trisegmentectomy and portal lymphadenectomy with extrahepatic biliary resection and hepaticojejunostomy offers the most likely means of complete extirpation.

Surgical Technique for Gallbladder Cancer

Surgical therapy is reserved for the subset of patients who demonstrate no evidence of unresectability on preoperative imaging. With the exception of those patients who have undergone cholecystectomy with a pathologic-confirmed T1 tumor not extending to the cholecystectomy margins, patients are offered an extended cholecystectomy with portal lymphadenectomy and partial hepatectomy.

The operative strategy begins with deliberate abdominal exploration through a bilateral subcostal or right transverse incision with a vertical extension to the xiphoid process. If no evidence of technically unresectable disease, distant disease, or N2 nodal metastases is identified, the lymphadenectomy is begun by mobilizing the duodenal sweep with an extensive Kocher maneuver. The retroduodenal lymphatic tissue is harvested, with care taken to include aortocaval and superior mesenteric nodes. The portal lymphatic tissue may be skeletonized off of the extrahepatic biliary system, but in cases of prior hilar dissection, tumor extension into the bile duct, or in obese patients, comprehensive portal lymphadenectomy may require excision of the extrahepatic bile ducts. In this scenario, the supraduodenal bile duct is divided, then elevated with its surrounding lymphatic tissue off of the underlying portal vein and hepatic artery with dissection proceeding toward the hepatic hilus.

At the hilus, the hilar plate is lowered by incising Glisson's capsule along the base of segment IVB. A determination is made at this point regarding the extent of hepatic resection that will be necessary for complete tumor extirpation. For patients with extensive invasion into the porta hepatis, a right hepatic lobectomy or

trisegmentectomy may be necessary. If the bile duct has been divided, a right hepatectomy or trisegmentectomy will require division of the left hepatic duct; otherwise, the common hepatic duct is divided below its bifurcation.

In the absence of significant tumor extension into the porta hepatis, an anatomic resection of segments IVB and V is performed. Prior to hepatectomy, care is taken to maintain a low central venous pressure, and the patient is placed into a moderate Trendelenburg position to minimize the risk of air embolism. Inflow control to segment IVB can be obtained by dissection in the region of the umbilical fissure, where the vessels to IVB can be identified and ligated to minimize intraoperative hemorrhage. Control of the segment V vessels is achieved after parenchymal transection; care must be exercised to avoid inadvertent injury to the adjacent right anterior sectoral branches or to the segment VIII vessels. In addition, the middle hepatic vein draining segments IVB and V runs between segments IV and VIII, and is divided after parenchymal transection. Inflow and outflow control and accurate segmental resection are facilitated by the use of intraoperative ultrasonography, which can identify the anatomy and course of the relevant vessels. In cases where extrahepatic bile duct excision has been performed, a retrocolic Roux-en-Y hepaticojejunostomy is constructed to re-establish biliary-enteric continuity. Finally, for patients who have previously undergone laparoscopic cholecystectomy, the surrounding skin and fascia of the laparoscopic port sites are excised and submitted for pathologic analysis.

BENIGN BILIARY TUMORS

Benign tumors of the biliary tract are exceedingly rare but can manifest symptoms not dissimilar from those resulting from malignant causes. The most common benign tumors are papillomas and adenomas. Less common benign tumors include granular cell myoblastomas, neural tumors, endocrine tumors, and leiomyomas. Because they are found most frequently in the region of the ampulla of Vater or along the common bile duct, benign biliary tumors typically present with jaundice that is slowly progressive or intermittent in nature. Optimal treatment includes local excision with removal of a portion of the duct wall from which they originate because local recurrences have been reported after subtotal resection.[46]

Bile duct adenomas are benign intrahepatic tumors that are typically found incidentally at the time of laparoscopy or laparotomy. They often appear as well-demarcated white subcapsular lesions ranging from several millimeters to 1 or 2 cm in size. Histologically, they are characterized by numerous well-differentiated bile duct–like structures surrounded by a fibrous stroma. They generally present without associated symptoms and have not been definitively shown to be precancerous in nature.[47]

Biliary cystadenomas are unusual benign tumors often characterized by a multiloculated cystic appearance. Most cystadenomas are mucinous in nature; such mucinous cystadenomas may be associated with pancreatic mucinous cystic neoplasms and are often associated with an ovarian-like stroma in females. Far less common are the serous cystadenomas. The occasional presence of dysplasia suggests the possibility that these tumors may harbor the potential for malignant transformation into biliary cystadenocarcinomas.[48]

Several noteworthy benign conditions must be considered in the differential diagnosis of obstructing biliary tract lesions. Primary sclerosing cholangitis is an idiopathic, premalignant disorder characterized by progressive biliary tract fibrosis whose cholangiographic appearance can mimic that of malignant biliary disease. Untreated, it can ultimately progress to cholestatic liver failure and cholangiocarcinoma. Mirizzi's syndrome is an unusual benign condition resulting from a chronically impacted stone in the neck of the gallbladder that, over time, induces sufficient pericholecystic inflammation to obstruct the adjacent proximal common bile duct.[49] Finally, another unusual benign process that can produce biliary tract obstruction is benign idiopathic focal stenosis, or the so-called malignant masquerade. Because of its propensity to involve the confluence of the hepatic ducts, this benign fibroproliferative disorder is often indistinguishable from cholangiocarcinoma without extensive surgical intervention.[50]

CHOLANGIOCARCINOMA

Cholangiocarcinoma is an uncommon cancer, accounting for only 2% of all reported malignancies. Its incidence in the United States has been estimated at 1 to 2 per 100,000.[4] It may arise anywhere along the entire length of the biliary system; 40% to 60% develop in the hilum (hereafter referred to as hilar cholangiocarcinomas), 20% to 30% in the distal lower biliary tract (distal cholangiocarcinomas), 10% arise intrahepatically (the so-called peripheral or intrahepatic cholangiocarcinomas), and less than 10% develop in a diffuse or multifocal fashion.[51,52] The anatomic differences between these subtypes result in disparate clinical presentations and demand unique surgical resective strategies. As is the case with gallbladder cancer, most patients afflicted with cholangiocarcinoma present with disease that is no longer amenable to surgical resection; as a result, most patients die within 6 to 12 months of diagnosis from hepatic insufficiency or cholangitis. However, also like gallbladder cancer, improvements in diagnosis and surgical technique have recently given rise to new optimism in its management.

Epidemiology

In the United States, cholangiocarcinoma is more common among Native Americans and Japanese Americans. Most patients are diagnosed after the age of 65 years, with a peak incidence occurring during the 8th decade of life.[4] Unlike gallbladder cancer, men appear to be afflicted by cholangiocarcinoma slightly more frequently than women. Known risk factors include primary sclerosing cholangitis (8% incidence observed over 5 years in a longitudinal Swedish observation study,[53]

choledochal cyst disease (15% to 20% incidence among patients not treated with resectional therapy before 20 years of age),[54,55] hepatolithiasis (up to 10% incidence among patients with chronic primary duct stones),[56] prior operative transduodenal sphincteroplasty (7.4% incidence measured over 18 years after the procedure),[57] chronic biliary parasitic infestation, and numerous teratogens, including Thorotrast, asbestos, dioxin, and nitrosamines.

Pathology

Intrahepatic Cholangiocarcinoma

On gross examination, intrahepatic cholangiocarcinomas appear as scirrhous primary hepatic lesions with a nonencapsulated infiltrative pattern of growth that produces poorly defined tumor margins. Their most common histologic type is poorly differentiated adenocarcinoma; as a result, they are not uncommonly misdiagnosed as metastatic adenocarcinomas. Indeed, it is quite likely that many hepatic tumors classified as metastatic adenocarcinoma of unknown primary in the past were truly intrahepatic cholangiocarcinomas. Variants with focal areas of papillary carcinoma, signet ring cells, squamous cells, mucoepidermoid cells, and spindle cells have been described.

Hilar and Extrahepatic Cholangiocarcinoma

Extrahepatic hilar and distal cholangiocarcinomas are categorized into three macroscopic subtypes: sclerosing (the most common subtype, usually hilar in location, characterized by circumferential duct thickening with periductal fibrosis and inflammation), nodular (firm tumors extending irregularly into the duct lumen, occasionally growing in a nodular-sclerosing pattern), and papillary (soft and friable tumors typically projecting into the duct lumen in a pedunculated fashion, usually distal in location, and associated with higher resectability and favorable outcomes).[58] Their pattern of growth is insidiously longitudinal, with tumor cells often extending both proximally and distally beneath normal ductal epithelium.[59] This pattern of growth mandates careful microscopic attention to margins at the time of surgical extirpation to ensure complete tumor resection. Another pathologic feature of cholangiocarcinoma is the exuberant desmoplastic reaction that often accompanies these tumors. Histologic analysis of these tumors occasionally identifies only small foci of malignant cells within densely fibrotic stroma. This characteristic can render the analysis of needle biopsy specimens challenging and highly susceptible to sampling error.

The tendency of extrahepatic cholangiocarcinoma to occlude biliary ducts and to invade portal venous branches often results in hepatic atrophy. Gradually progressive segmental or lobar atrophy in the setting of cholangiocarcinoma is indicative of chronic biliary obstruction; comparatively rapid parenchymal atrophy is typically the result of portal obstruction.[60] Distant metastases are not uncommon, and perineural and lymphovascular spread are often observed, with up to one third of patients presenting with nodal metastases.

Presentation

Symptoms associated with intrahepatic cholangiocarcinomas are nonspecific, including malaise and abdominal pain. Unlike hilar and distal cholangiocarcinomas, a few patients develop jaundice. Hilar and distal cholangiocarcinomas can present with nonspecific symptoms of pain, anorexia, and weight loss. Distal cholangiocarcinoma can be clinically indistinguishable from other periampullary neoplasms. Pruritus is a common symptom for patients with extrahepatic cholangiocarcinoma, and it typically precedes clinically apparent jaundice. It is jaundice or the presence of abnormal liver enzymes that often prompts medical attention. It is helpful to note, however, that although most patients with hilar and distal cholangiocarcinoma ultimately develop jaundice, segmental or incomplete lobar obstruction can produce considerable hepatic atrophy without frank jaundice.

Some of the more nonspecific presenting symptoms of cholangiocarcinoma can closely resemble those associated with benign gallstone disease, and malignant biliary disease can in fact coexist with benign calculous disease. The level of hyperbilirubinemia can be informative in the distinction between benign and malignant biliary obstruction; benign causes of obstructive jaundice typically produce bilirubin levels ranging from 2 to 4 mg/dl (rarely >15 mg/dl), whereas biliary obstruction from cholangiocarcinoma usually results in serum bilirubin levels greater than 10 mg/dl (with a mean level ≈ 18 mg/dl).[61] On occasion, intraluminal growth of papillary cholangiocarcinomas (more common among distal tumors) can induce a physiologic ball-valve effect that produces intermittent symptoms of obstructive jaundice.

Although a 30% rate of bactibilia has been observed among patients with extrahepatic cholangiocarcinoma, clinically evident cholangitis is unusual as a presenting symptom. The noteworthy variance from this observation comes from patients who undergo biliary instrumentation (either percutaneously or endoscopically), who uniformly develop bactibilia and not uncommonly develop manifestations of cholangitis.[62]

Diagnosis

Cholangiocarcinomas in general are often accompanied by elevations in CA 19-9. Levels of CA 19-9 higher than 100 U/ml have been shown to correspond with the presence of cholangiocarcinoma with a sensitivity of 89% and a specificity of 86%.[63]

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinomas appear as avascular masses on standard imaging techniques and can appear similar to other primary and metastatic hepatic malignancies (Fig. 104–3). Ultrasonography, CT, and MRI techniques are useful in defining the anatomic relation-

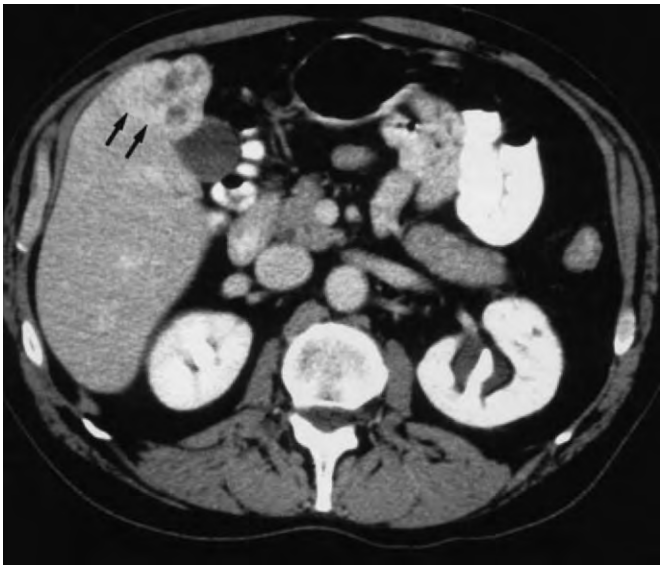

Figure 104–3. CT appearance of large intrahepatic cholangiocarcinoma. (From Koea J, Fong Y: Primary hepatic malignancies. In Blumgart LH, Fong Y, Jarnagin WR [eds]: Hepatobiliary Cancer: A Volume in the American Cancer Society Atlas of Clinical Oncology Series. Hamilton, Ontario, BC Decker, 2001, p 59.)

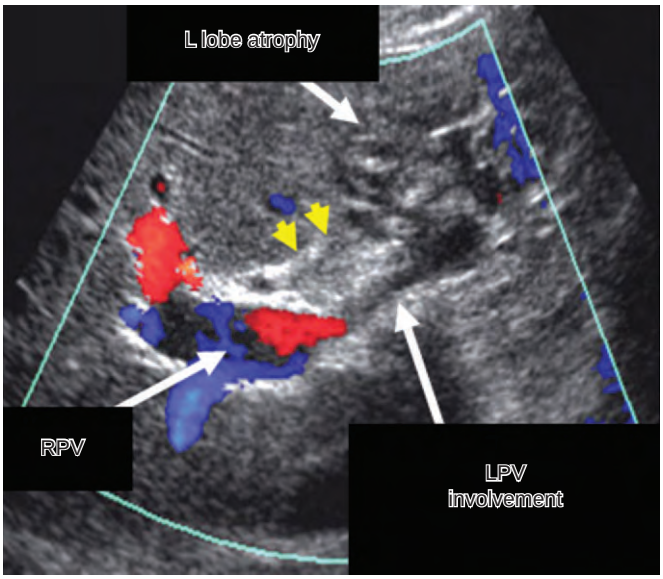

Figure 104–4. Ultrasound duplex image of hilar cholangiocarcinoma with lobar atrophy *(upper white arrow).* The *lower white arrows* indicate left portal vein (LPV) and right portal vein (RPV) involvement; the *yellow arrowheads* indicate the tumor.

ships between the tumor and adjacent vascular and biliary systems.

Hilar Cholangiocarcinoma

Duplex ultrasonography and MRCP are the principal radiographic techniques used to image hilar cholangiocarcinoma. In experienced hands, duplex ultrasonography can provide data regarding extent of biliary ductal, periductal, and vascular involvement with a sensitivity and specificity matching or exceeding that of CT angiography (Fig. 104–4).[64,65] MRCP provides an accurate assessment of biliary ductal anatomy and can evaluate distal or proximal ductal systems that are excluded by the tumor and therefore not imaged by percutaneous or endoscopic cholangiography. MRCP also avoids the biliary instrumentation (and potential infectious complications) associated with invasive cholangiography.[66,67] The finding of hepatic parenchymal atrophy is indicative of biliary and/or portal venous obstruction from tumor. It is also an indication that partial hepatectomy of the atrophic segment or lobe may be necessary for complete extirpation of disease (Fig. 104–5).

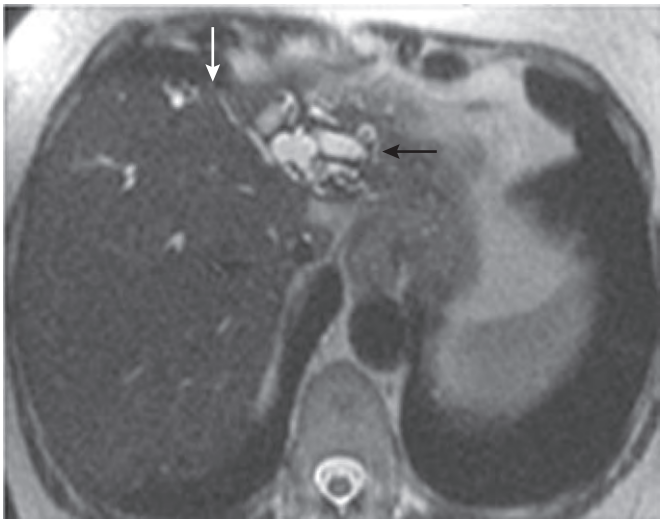

Figure 104–5. MRI appearance of hilar cholangiocarcinoma with lobar atrophy. Note the crowded, dilated ducts *(black arrow)* denoting the presence of small, hypoperfused left hepatic lobe (demarcated by the *white arrow*).

Distal Cholangiocarcinoma

Owing to its proximity to the duodenum, the radiographic evaluation of distal cholangiocarcinoma more commonly employs endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound technology. Although the primary lesions are often too small to be visible on cross-sectional imaging, CT is useful to evaluate the extent of metastatic disease. Endoscopic brushings and biliary cytology are associated with very low sensitivity in diagnosis[68]; this, combined with their typical inaccessibility to percutaneous biopsy techniques, often requires that therapeutic intervention be undertaken for extrahepatic cholangiocarcinoma in the absence of a definitive tissue diagnosis.

Table 104–2 AJCC Staging of Extrahepatic Bile Ducts

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct histology
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)
T4	Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

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Box 104–1 **Criteria for Unresectability of Cholangiocarcinoma**

- Medical contraindication to surgical intervention
- Advanced cirrhosis/portal hypertension
- Bilateral second-order biliary involvement
- Main portal vein involvement
- Lobar atrophy with contralateral second-order biliary radicle involvement
- Lobar atrophy with contralateral portal vein involvement
- N2 nodal involvement
- Distant metastases

Data from Burke EC, Jarnagin WR, Hochwald SN, et al: Hilar cholangiocarcinoma: Patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg 228:385-394, 1998.

Staging

The two major conventional staging systems for cholangiocarcinoma are the Bismuth-Corlette system[69] and the AJCC TNM system (Table 104–2). The Bismuth-Corlette system is an anatomically based, surgically oriented system that is not too predictive of patient outcome. The AJCC system is a pathologic-driven system that also correlates poorly with surgical resectability and patient outcome. Any attempt to enhance treatment and outcome predictability with a revised staging system must consider the determinants of surgical resectability and outcome.

In the absence of effective chemotherapy or radiation therapy, surgical resection remains the mainstay of treatment for cholangiocarcinoma. Within this context, the ability to effect a margin-negative R0 complete resection is the best predictor of improved patient survival. A recent trend in which partial hepatectomy has been increasingly used in the surgical management of extrahepatic cholangiocarcinoma has largely accounted for increasing rates of R0 resection and improved survival outcomes.[70-73]

The criteria for surgical unresectability of extrahepatic cholangiocarcinoma are listed in Box 104–1.[73] As discussed previously, the presence of hepatic segmental or lobar atrophy is indicative of biliary and/or portal venous obstruction and likely requires resection of the atrophic segment or lobe for complete tumor removal. Therefore, the observation of portal venous or biliary obstruction contralateral to an atrophic lobe is suggestive of bilobar tumor involvement that would not be amenable to surgical resection. Based on these criteria for tumor unresectability, we have previously proposed a clinical preoperative staging system that has been shown to be predictive of both tumor resectability and patient survival outcome (Table 104–3).[73]

Surgery

The goal of surgical therapy for cholangiocarcinoma is complete R0 resection. Complete resection has consistently proved to correlate well with survival.

Intrahepatic Cholangiocarcinoma

Techniques of anatomic hepatic resection for intrahepatic cholangiocarcinoma follow those employed for other hepatic malignancies. A review of the MSKCC experience with 53 patients undergoing operative intervention for intrahepatic cholangiocarcinomas demonstrated a resectability rate of 62%.[74] Patients with disease amenable to surgical resection exhibited a median survival of 37.4 months and a 3-year actuarial survival of 55%; predictors of poor survival were vascular invasion, positive resection margins, and multiple tumors.[74]

Table 104–3 Proposed Preoperative Tumor Staging System for Cholangiocarcinoma

T Stage	Type of Biliary Involvement	Presence of Ipsilateral Lobar Atrophy	Presence of Ipsilateral Portal Vein Involvement	Presence of Main Portal Vein Involvement	Resectability, %
1	Hilus and/or unilateral bile duct	No	No	No	48
2	Hilus and/or unilateral bile duct	Yes	No	No	43
3	Hilus and/or unilateral bile duct	Yes/No	Yes	No	25
4	Bilateral second-order radicles	Yes/No	Yes/No	Yes	0

Data from Burke EC, Jarnagin WR, Hochwald SN, et al: Hilar cholangiocarcinoma: Pattern of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg 228:385-394, 1998.

Median disease-free survival for this cohort of patients was 19.4 months with a 3-year disease-free survival of 22%; predictors of recurrence were multiple tumors, tumor size, and vascular invasion.[74]

Hilar Cholangiocarcinoma

A prospective evaluation of the ability of staging laparoscopy to identify patients with unresectable disease demonstrated that 14 of 56 patients with hilar cholangiocarcinoma undergoing exploratory laparoscopy at MSKCC were found to have laparoscopic evidence of unresectable disease; of the remaining 42 patients who then underwent laparotomy with curative intent, an additional 19 patients were found to have unresectable tumors for reasons not appreciated laparoscopically (resulting in an accuracy for staging laparoscopy of 42%).[74]

Because of its propensity for longitudinal ductal spread, partial hepatectomy is often necessary in addition to extrahepatic bile duct excision for complete resection of extrahepatic cholangiocarcinoma. As stated previously, review of the relevant literature suggests that the rate of negative margin resection closely approximates the frequency with which partial hepatectomy is performed. The proximity of the caudate lobe to the hepatic hilus often mandates concomitant caudate lobectomy for hilar tumors; this is particularly evident for left-sided hilar tumors, as the major caudate lobe ducts drain into the left hepatic duct.[75] The MSKCC institutional experience with hilar cholangiocarcinomas showed that only 50% of patients undergoing surgical intervention harbored resectable disease.[76] This number of patients with resectable disease represented only 36% of all patients evaluated at MSKCC with the diagnosis of hilar cholangiocarcinoma.[76] Patients undergoing resection exhibited an overall median survival of 35 months; predictors of improved survival were well-differentiated tumors, negative resection margin, and the performance of a concomitant hepatic resection. The importance of obtaining negative resection margins is underscored by the observation that patients with histologically positive margins of resection demonstrated survival outcomes indistinguishable from those with locally advanced tumors undergoing operative exploration without attempted resection. It appears that the performance of partial hepatectomy at the time of resection of hilar cholangiocarcinoma is critical for optimizing outcome. Indeed, the 5-year actuarial survival among those patients undergoing partial hepatectomy was 37%, compared to 0% for those treated with bile duct excision alone.[76] Even within the cohort of patients who underwent complete R0 resection, the performance of partial hepatectomy conferred a statistically significant survival advantage on multivariate analysis.[76]

Distal Cholangiocarcinoma

Most distal cholangiocarcinomas require pancreaticoduodenectomy for complete resection. A review of the MSKCC experience with distal cholangiocarcinomas demonstrated that only 13% of these tumors could be removed with bile duct excision alone.[77] As mentioned previously, distal cholangiocarcinomas are often clinically indistinguishable from other periampullary neoplasms, including pancreatic adenocarcinoma. However, distal cholangiocarcinomas appear to exhibit less lymphovascular invasion, lower margin positivity, higher resectability, and correspondingly better survival as compared to pancreatic ductal adenocarcinoma.[77-79] When compared between equivalent stages and resections, there do not appear to be any meaningful survival differences between hilar and distal cholangiocarcinomas.[80]

Orthotopic Liver Transplantation

Orthotopic liver transplantation for cholangiocarcinoma, often done for patients with underlying primary sclerosing cholangitis, has traditionally been associated with suboptimal survival outcomes. Three-year survival

rates observed for patients treated with allotransplantation for intrahepatic and hilar cholangiocarcinoma have ranged between 0 and 36%.[81] Recently, the Mayo Clinic has demonstrated promising results among a select cohort of patients undergoing neoadjuvant chemoradiation followed by cadaveric or living-donor liver transplantation. In this clinical protocol, eligibility is reserved for patients with confirmed cholangiocarcinoma who are believed to have technically unresectable disease and no evidence of extrahepatic metastases. Neoadjuvant therapy begins with an initial period of external beam radiation therapy (EBRT) with intravenous 5-FU, followed by transcatheter iridium-based brachytherapy, then subsequent maintenance therapy with oral capecitabine. After completion of their neoadjuvant radiotherapy, all patients undergo a staging laparotomy to confirm absence of extrahepatic disease. In their experience, 29% of patients completing neoadjuvant chemoradiation were found to harbor extrahepatic disease, nullifying their continued candidacy for transplantation. In a recent update of this experience, among 56 patients initiating therapy under this protocol, 28 ultimately went on to undergo liver transplantation. Among this subset of patients, after a mean follow-up duration of 43 months, 1- and 5-year actuarial survival has been 88% and 82%, respectively.[82] These novel observations suggest that a highly selected subset of patients with unresectable but nonmetastatic cholangiocarcinoma may experience a considerable survival benefit after orthotopic liver transplantation.

Adjuvant Therapy

As is the case with gallbladder cancer, there have not been sufficiently large or controlled trials rigorously examining the efficacy of adjuvant chemotherapy or radiation therapy for patients undergoing resection of cholangiocarcinoma to dictate general treatment guidelines. A phase III trial examining the effect of 5-FU and mitomycin C on 139 patients with cholangiocarcinoma demonstrated no survival benefit over surgical resection alone.[40]

Palliation

Palliation in the setting of unresectable cholangiocarcinoma is usually directed toward the control of refractory malignant jaundice. Palliation of jaundice is generally indicated for cases of cholangitis, intractable pruritus, or for patients in whom maximization of hepatic function is necessary prior to initiation of chemotherapy. Several important principles guide the manner in which biliary decompression is attempted. First, it is worthy to note that jaundice is typically not relieved until more than one third of functional liver mass is effectively decompressed.[52] Because of the propensity of advanced cholangiocarcinoma to obstruct and isolate multiple hepatic segments or lobes, this may necessitate separate drainage of more than one biliary ductal system. Second, decompression of an atrophic segment or lobe does not control jaundice. Third, it is possible for jaundice to develop in the absence of biliary obstruction. Portal venous obstruction or thrombosis from cholangiocarcinoma can produce rapid hepatic atrophy and dysfunction; jaundice in such patients is not relieved by biliary decompression.[52]

Selection of the optimal method of biliary decompression requires a careful balance between the expected duration of treatment benefit and the anticipated length of patient survival, as well as between the potential for treatment-related morbidity and patient quality of life. Operative bypass options, which include hepaticojejunostomy for hilar cholangiocarcinoma or choledochoenterostomy for distal cholangiocarcinoma, are generally associated with high durability of patency, but at the cost of high potential morbidity, mortality, and recovery time. As such, operative biliary bypass is generally reserved for patients in whom unresectability and present or impending biliary obstruction is recognized at the time of attempted surgical resection or for patients whose expected survival exceeds 6 months. Operative bypass to the segment III ducts is particularly appealing in the setting of unresectable hilar cholangiocarcinoma due to its distance from the hepatic hilus and demonstrates an 80% patency rate at 1 year; bypass to the right anterior or posterior sectoral duct can also be performed.[83] For others, percutaneously or endoscopically placed self-expanding biliary Wallstents may be preferable. Percutaneous biliary drainage is generally preferred for patients with hilar cholangiocarcinoma, whose tumors can be difficult to traverse with endoscopically placed stents. Bile duct occlusion from distal cholangiocarcinoma is ideally treated with endobiliary stenting, which can demonstrate 1-year patency rates of up to 89%.[84] Typical duration of patency for permanent metallic Wallstents (8 to 10 months) doubles that of temporary plastic endobiliary stents (4 to 5 months).[85] There is some evidence that intraluminal brachytherapy with iridium-based radiation may prolong patency by delaying ingrowth of tumor into the lumen of the stent. However, the palliative use of intraluminal radiotherapy, even when employed in conjunction with EBRT, has not consistently shown a measurable survival benefit over that seen with biliary decompression alone.[86]

Practical Management of Cholangiocarcinoma

Intrahepatic Cholangiocarcinoma

The presentation of intrahepatic cholangiocarcinoma is not dissimilar to that of other intrahepatic malignancies, and it is often difficult to distinguish cholangiocarcinoma in this setting from other histologic tumor types. The finding of an intrahepatic mass prompts an extensive diagnostic work-up that can, in large part, be directed by relevant findings from the patient's history and physical examination. For example, a history of colon cancer or hepatitis might direct the diagnostic evaluation toward hepatic colorectal metastases or hepatocellular carcinoma, respectively. Otherwise, evaluation begins with measurement of tumor markers including CEA, alpha-fetoprotein, and CA 19-9, as well as viral hepatitis serolo-

gies. Colonoscopic evaluation can identify the possible presence of a primary colorectal adenocarcinoma.

Operative planning then begins with staging CT imaging of the chest, abdomen, and pelvis, including triphasic liver imaging. MRI can also be used to delineate the extent and anatomic relationships of the intrahepatic disease. If these imaging studies do not indicate the presence of unresectable disease, surgical extirpation of intrahepatic cholangiocarcinoma employs standard anatomic hepatectomy techniques employed for other liver tumors.

Hilar Cholangiocarcinoma

As stated previously, hilar cholangiocarcinoma most often presents with the clinical finding of jaundice. MRCP and duplex sonography are most effective in the assessment of relevant anatomy and determination of surgical resectability. Patients presenting with acute renal insufficiency or cholangitis, those with unresectable disease, or patients with medical comorbidities that preclude operative intervention, may best be suited with early biliary decompression. Effective relief of jaundice often requires drainage of multiple segments of the biliary tree, which are best identified by sonography and MRCP. Percutaneous drainage generally provides the most effective means of decompression in hilar cholangiocarcinoma; external drains may subsequently be converted to internal stents and drains in a subset of patients. As outlined previously, surgical resectability is determined by the presence of portal venous involvement, biliary radicle involvement, and lobar atrophy. Those patients who are found to harbor resectable disease should undergo operative exploration; complete extirpation requires extrahepatic bile duct excision with partial hepatectomy and hepaticojejunostomy.

Distal Cholangiocarcinoma

The typical presentation of distal cholangiocarcinoma is characterized by jaundice, with radiographic evidence of distal biliary obstruction. As stated earlier, the ability to distinguish these tumors from other periampullary neoplasms can be challenging. The initial radiographic assessment should employ CT and MR imaging to identify a discrete mass lesion and to determine resectability based on the relationship of the lesion to the adjacent superior mesenteric vein/portal vein confluence and superior mesenteric artery. In the absence of a radiographically demonstrable tumor, ERCP or endoscopic ultrasonography may be helpful in delineating a lesion in the region of the distal bile duct. Although unusual, patients presenting with liver insufficiency or cholangitis may benefit from early biliary decompression. For patients with resectable disease, this is best performed with temporary endobiliary stenting. Permanent metallic Wallstents provide more durable biliary decompression for patients with technically unresectable disease. Patients with radiographic evidence of resectable distal cholangiocarcinoma are offered surgical exploration with the intention of performing pancreaticoduodenectomy.

Surgical Technique for Hilar Cholangiocarcinoma

The technique of resection for intrahepatic cholangiocarcinoma follows standard procedures of hepatic resection (Fig. 104–6). Similarly, surgical extirpation of distal cholangiocarcinoma is performed by pancreaticoduodenectomy. In the following section, we review the basic technique of surgical management of hilar cholangiocarcinoma.

If preoperative imaging demonstrates no clear evidence of unresectability, operative intervention is undertaken. In selected cases, this may be begun with an initial laparoscopic inspection. Alternatively, abdominal exploration through a bilateral subcostal or right transverse incision with a midline extension to the xiphoid process is commenced. Careful visual and manual inspection is performed to identify evidence of distant or N2 nodal metastases that would preclude resection. The ligamentum teres is divided, ligated, and elevated to permit careful inspection of the liver for previously unidentified intrahepatic lesions. The lesser omentum is opened to permit careful inspection of the caudate lobe, and a Kocher maneuver is performed to inspect the retroduodenal lymph nodes. Should evidence of unresectable disease be encountered at this point, the surgical strategy turns to one of palliation of biliary obstruction by operative biliary-enteric bypass or nonoperative drainage.

If tumor resectability is confirmed, preparations are begun for possible partial hepatectomy. Low central venous pressure is maintained to minimize blood loss during hepatic parenchymal transection, and the patient is placed in a moderate Trendelenburg position for prevention of air embolism. The supraduodenal bile duct is divided and a cholecystectomy is performed to begin mobilization and inspection of the extrahepatic biliary system. The bile duct is then dissected free from the underlying portal vein and hepatic artery in an ascending fashion toward the hepatic hilus; direct tumor invasion into the portal vein may preclude resection unless a segmental portal vein resection and reconstruction can be performed with restoration of sufficient portal venous blood flow to the liver. The left hepatic duct is exposed by dividing the bridge of hepatic tissue that typically joins the bases of segments IVB and III, and the hilar plate is lowered by incising Glisson's capsule along the base of segment IVB. By exposing the hepatic hilus in this fashion, the need for partial hepatectomy may be determined. If evidence of unilateral second-order biliary radicle involvement or ipsilateral portal vein involvement is detected, partial hepatectomy of the involved lobe is mandated to maximize the likelihood of complete R0 resection. However, in the limited number of cases in which second-order biliary radicles are not involved and vascular involvement is absent, segmental extrahepatic bile duct excision may be sufficient.

When segmental bile duct excision can be performed, the right and left bile ducts are divided well above the proximal extent of visible tumor. In certain cases, this may require division of the bile ducts above the level of a sectoral bifurcation, resulting in more than two duct

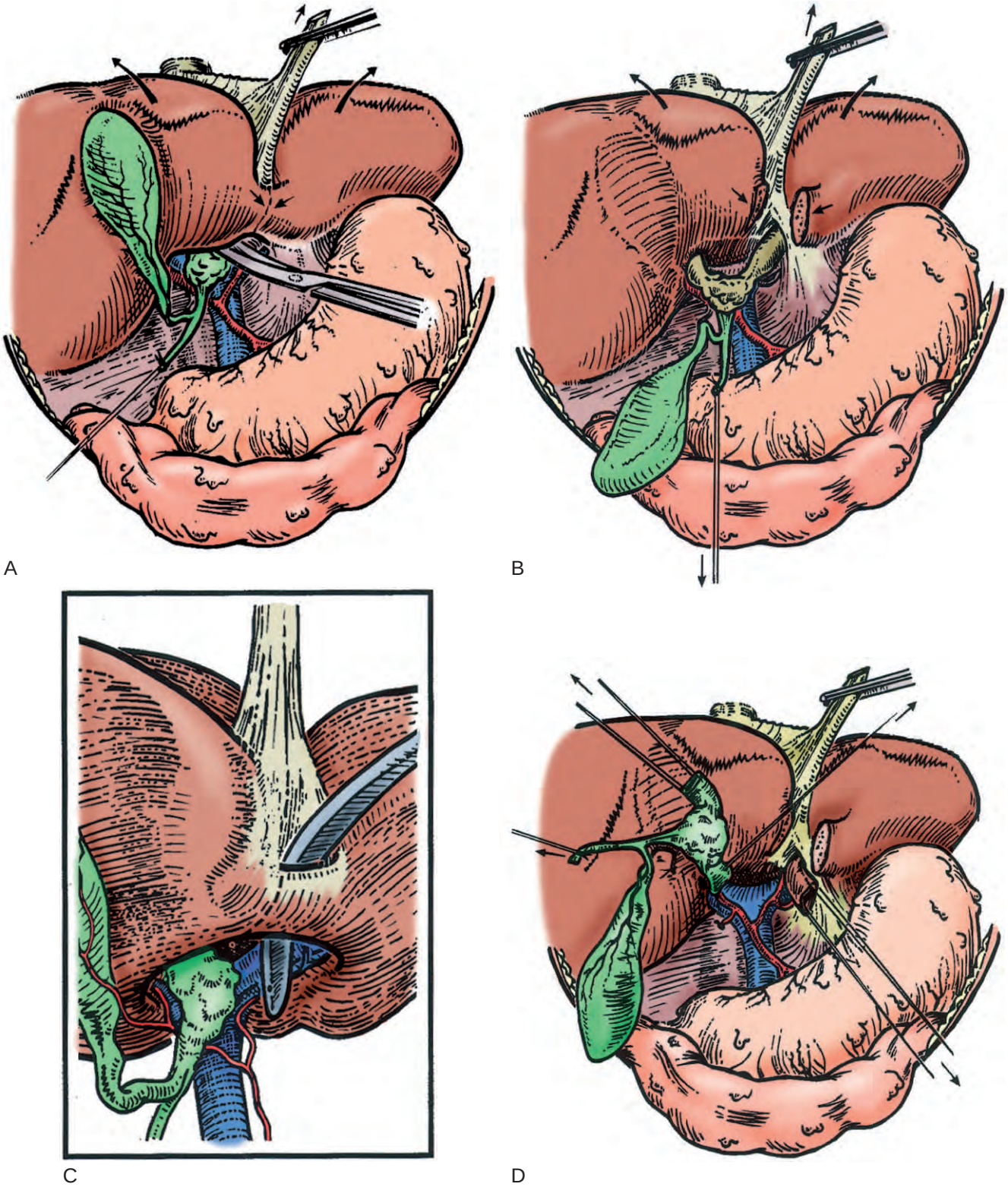
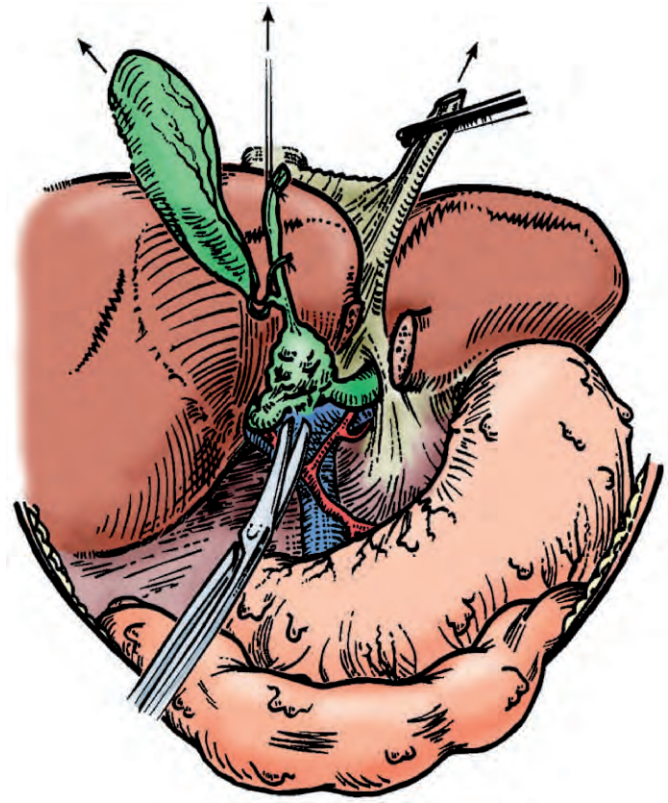


Figure 104–6. **A** to **F,** Resection of hilar cholangiocarcinoma with partial hepatectomy. (**A-F,** From Jarnagin WR, Saldinger PF, Blumgart LH: Cancer of the bile ducts: The hepatic ducts and common bile duct. In Blumgart LH, Fong Y [eds]: Surgery of the Liver and Biliary Tract. London, WB Saunders, 2000, pp 1033-1035.) *Continued*



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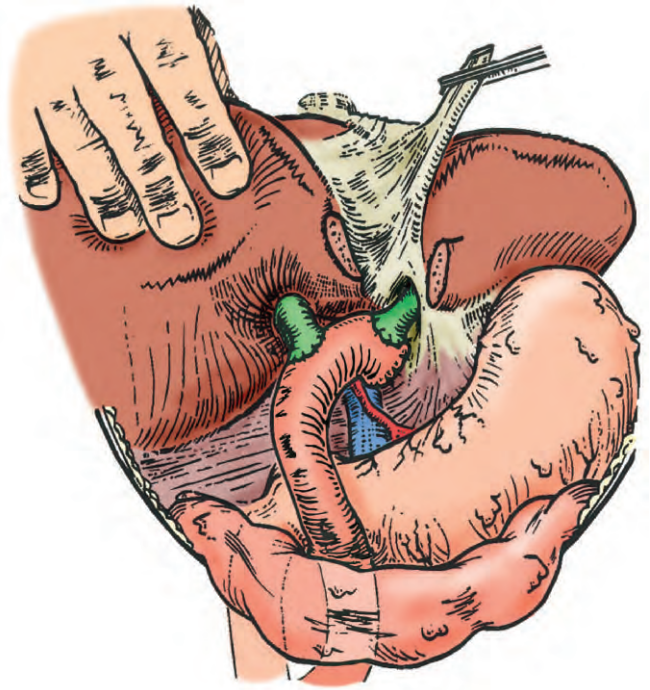

F

Figure 104–6, cont'd.

orifices. Biliary-enteric continuity is then re-established by construction of a retrocolic Roux-en-Y hepaticojejunostomy. Whenever possible, separated ipsilateral sectoral ducts are first sutured into close proximity with one another so that they may be used as a single functional duct unit when constructing the hepaticojejunostomy. Alternatively, separated sectoral ducts can be sequentially anastomosed into a single enterotomy site. To accomplish this, a row of anterior sutures is first placed along the separated ducts. A posterior row is then placed along the ducts and the jejunotomy and serially tied to bring the back wall of the separated ducts into direct apposition against the back wall of the jejunum. The preplaced anterior row of sutures can then be placed along the anterior wall of the jejunum.

In the more common situation in which partial hepatectomy is deemed to be necessary for complete resection, the liver is mobilized by dividing its peritoneal and diaphragmatic attachments. For patients with left-sided tumors, careful inspection of the caudate lobe is necessary, because involvement of the usually left-sided caudate ducts may require en bloc caudate lobectomy. The hepatic artery and portal vein to the involved lobe or segment are divided, as is the draining hepatic vein. Hepatic parenchymal transection is then performed to complete the resection, and construction of a Roux-en-Y hepaticojejunostomy to the contralateral duct or ducts is performed as described earlier. External drains are routinely placed in the vicinity of the biliary-enteric anastomoses.

OTHER MALIGNANT BILIARY TUMORS

Mixed Hepatocellular and Cholangiocarcinoma

Limited experience exists with the management of this distinct primary hepatic malignancy. These intrahepatic tumors possess histologic features of both hepatocellular carcinoma and cholangiocarcinoma. Demographics of patients with these mixed tumors appear to be more similar to those with pure intrahepatic cholangiocarcinoma than to hepatocellular carcinoma. Furthermore, the survival outcomes of patients undergoing surgical resection of these mixed tumors appear to more closely parallel those of patients treated for cholangiocarcinoma.[74,87]

Biliary Cystadenocarcinoma

Biliary cystadenocarcinomas are rare malignancies that are typically intrahepatic. The presence of an associated ovarian-like stroma in female patients appears to signify a favorable prognosis, and these lesions may arise from preexisting biliary cystadenomas.[47]

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Chapter

105

External Biliary Fistula

Itzhak Avital · Leslie H. Blumgart

A biliary fistula is an abnormal, persistent discharge of bile. The term *uncontrolled fistula* denotes fistula with intraperitoneal leakage and collection of bile. *Controlled fistula* denotes a fistula with drainage to the exterior but without significant intraperitoneal collection.

Biliary fistulas may be intentionally created by the surgeon, as for example in the creation of a cholecystostomy or a choledochostomy. These fistulas are of significance only when they continue to discharge bile unexpectedly.

Almost all clinically significant biliary fistulas follow some type of surgical procedure. Persistent biliary discharge is the result of some unrecognized disease in the bile ducts, an unexpected complication, or a surgical error.

The initial management of these lesions demands a team approach consisting of an experienced interventional radiologist, an endoscopist, and a surgeon.[1]

ETIOLOGY AND PREVENTION

When grouping the causes of biliary fistulas, it is useful to classify them according to the type of previous intervention performed. The following procedures are the more commonly associated surgical antecedents of fistulas.

Fistula Following Cholecystostomy

Cholecystostomy is now infrequently performed. A persistent biliary fistula from the biliary system after cholecystostomy is usually due to distal biliary tract obstruction, as either a result of a retained bile duct stone or an unrecognized malignancy.

Fistula Following Open Cholecystectomy

The occurrence of unexpected biliary fistula after cholecystectomy almost always indicates operative injury to a major bile duct. Such fistulation may arise from damage to the common bile duct or to an anomalous sectoral right hepatic duct. Bile duct injury is recognized at the time of cholecystectomy in only a few patients. In about 25% to 40% of patients with unrecognized bile duct injury, the injury becomes apparent only when the presence of a controlled or an uncontrolled biliary fistula is recognized or if biliary stricture develops.[2] Inadequately ligated or sloughed ligatures on the cystic duct are responsible for biliary fistula in rare instances, and for this reason transfixion suturing of the cystic stump is recommended. However, the presence of an unrecognized significant distal obstruction may be followed by a blowout of the cystic duct stump, resulting in a biliary fistula or bile peritonitis.

Cholecystectomy is sometimes performed under difficult circumstances, as in the presence of a gangrenous gallbladder associated with fibrosis and inflammation in the region of the triangle of Calot. In these instances, proper identification of the cystic stump may not be possible and the patient is left with a temporary biliary fistula. The presence of a type II Mirizzi's syndrome with a cholecystocholedochal fistula may pose significant technical difficulties, and specific surgical techniques have been devised to deal with this situation.[3] In instances where the anatomy is not clear, it is better not to attempt direct repair of the defect in the common bile duct because this may result in further damage or stricture formation. Rather, end the procedure with adequate drainage expecting a future controlled fistula.

In all these difficult instances, it is imperative to exclude the presence of a distal obstruction to biliary-enteric bile flow. Under these circumstances, most fistulas close spontaneously following conservative treatment.

Fistula Following Common Duct Exploration

Replaced by laparoscopic and endoscopic techniques, the classic open common duct exploration is now less frequently performed.[4] However, a biliary fistula after open or laparoscopic exploration of the common bile duct or a biliary fistula persisting after removal of a T-tube is almost always due to a residual bile duct gallstone. Therefore, it is essential to perform cholangiography and rule

out the presence of retained stones before removal of a T-tube or a biliary stent placed at exploration.

Less commonly, an overlooked malignant distal obstruction is the causative factor.

Fistula Following Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy is currently the standard procedure for symptomatic cholelithiasis and cholecystitis and is performed even in instances of gangrenous cholecystitis. However, it is also associated with an increased incidence of bile duct injuries, including fistula, which may rise to 1.3% and as high as 5.5%.[5] Under these difficult circumstances, the procedure should be performed or supervised by an experienced surgeon, and a high conversion rate, of up to 40% in instances of gangrenous cholecystitis, should be expected.[6]

The operative treatment of Mirizzi's syndrome now includes a laparoscopic option. However, it is our belief that once the presence of Mirizzi's syndrome, and particularly type II, is suspected or realized, safety demands that the laparoscopic procedure be converted to an open one.[7]

Small amounts of bile leakage may occur occasionally in the immediate postoperative period after inadvertent damage to a subvesical duct, which is present in normal subjects in 20% to 50% of cases.[8] Removal of an intrahepatic gallbladder may also be followed by a transient biliary leak caused by damage to tiny bile ducts in the liver around the gallbladder fossa.

Biliary fistula following laparoscopic cholecystectomy may occur as a result of injury to the extrahepatic biliary tree, or it may originate from the cystic duct stump.[9] A leak from the cystic duct stump may occur from burn injury or pressure necrosis of a metal clip. However, in most instances, it occurs from distal bile duct obstruction caused by a retained stone and results in a build-up of pressure and a resultant blow-out of the cystic stump. It is therefore important to differentiate those patients at risk of having choledocholithiasis. Patients having deranged liver function tests and/or dilated bile ducts on ultrasound should undergo endoscopic cholangiography prior to cholecystectomy. Sphincterotomy and stone extraction should be performed if choledocholithiasis is established.

Most ductal injuries are not recognized during the initial laparoscopic cholecystectomy or even in the immediate postoperative period.[9] The resulting uncontrolled biliary fistula becomes evident within days or sometimes even weeks after the operation—with the clinical presentation of abdominal pain, fever, and jaundice and demonstration of an intra-abdominal fluid collection that produces bile on puncture.

Compared to open cholecystectomy, laparoscopic cholecystectomy is associated with an increased rate of bile duct injuries.[10] Such injuries are common to most reported series of laparoscopic cholecystectomy and may reach an incidence as high as 0.9%. Reviews by Strasberg and Vecchio encompassing more than 100,000 patients from multiple hospitals found the incidence of major bile duct injuries to be around 0.5%, and this incidence has reached a steady-state.[11-14]

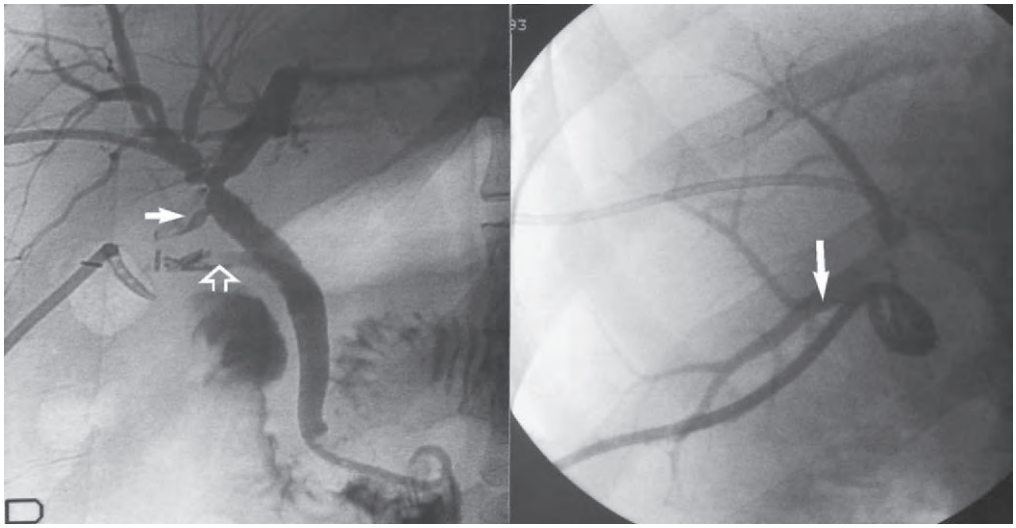
The most usual injury is caused by misidentification of the common duct for the cystic duct, resulting in complete transection of the common duct and often including a portion of the biliary tree. A traction injury results from inadvertent lateral traction of the gallbladder and "tenting" of the cystic duct–common duct junction. In this instance, the common bile duct may be occluded by the clip intended for the cystic duct or a portion of the common bile duct may be removed between clips.

An unrecognized anomalous biliary system, such as a cystic duct emptying directly into the right hepatic duct or a low-inserted right hepatic sectoral duct, may result in similar damage (Fig. 105–1).[10] Other less common mechanisms include thermal injury due to excessive use of the cautery and the application of excessive clips to control bleeding in the triangle of Calot.

The role of intraoperative cholangiography in the prevention of bile duct injuries remains controversial. However, a large study investigating 1,570,361 Medicare patients undergoing cholecystectomy concluded that not using intraoperative cholangiography was associated with a 50% to 70% increase in the risk of bile duct injury.[14] Intraoperative cholangiography may supply information regarding the presence of unsuspected choledocholithiasis and unexpected anomalous anatomy, and its routine use is recommended by several authors.[15,16] Nonetheless, the evidence that it may prevent major bile duct injury is not conclusive.[17] Indeed, the use of operative cholangiography has not increased and, in a recent review of 40 series of laparoscopic cholecystectomy in the United States, intraoperative cholangiography was performed in only 40% of cases.[18] We use operative cholangiography selectively, such as when ductal anatomic variations/anomalies or bile duct injuries are suspected. It should be stressed that operative cholangiography cannot replace meticulous technique and cannot be relied on to prevent biliary injuries.

Fistula Following Biliary-Intestinal Anastomosis

A major biliary fistula following biliary-intestinal anastomosis, though uncommon, does occasionally occur. Anastomoses created well below the hilus, as with choledochoduodenostomy or choledochojejunostomy for example, are rarely associated with fistulas, whereas biliary fistula following hilar hepaticojejunostomy is more common.[19] When fistulas do occur, a technical error such as suture line disruption or failure to incorporate a significant bile duct within the anastomosis must be suspected. Failure of the surgeon to appreciate ductal anatomy is most likely to occur in the hilar region, where the mode of confluence of the right and left ducts and caudate lobe ducts is extremely variable. In these instances, the fistula becomes evident immediately after surgery. Meticulous technique with mucosa-to-mucosa anastomosis obviates most such leakage.



A B

Figure 105–1. Injury to the right sectoral hepatic duct at laparoscopic cholecystectomy. **A,** Percutaneous transhepatic cholangiography. Note the remnant of the duct draining into the common bile duct *(arrow)* and cystic stump *(open arrow).* Note, too, the low entry of this duct into the common bile duct. **B,** Tube fistulography. The biliary ductal system of the cut sectoral duct is outlined *(arrow).* (**A** and **B,** From Czerniak A: External biliary fistula. In Blumgart LH, Fong Y [eds]: Surgery of the Liver and Biliary Tract, 3rd ed. Philadelphia, WB Saunders, 2000, p 937.)

Alternatively, suture line disruption may also be caused by local factors such as abscess or ischemic necrosis of the bile duct or bowel wall. Such fistulas may become evident days after surgery. It is important to ascertain whether the fistula is purely biliary or whether it also contains duodenal and/or pancreatic juice.

Biliary Fistula After Liver Injury

Biliary fistulation may occur in association with damage to the liver (Fig. 105–2) as well as the bile ducts, or it may follow sequestration and infection of areas of liver necrosis. Blunt or penetrating grade III or IV liver trauma may be complicated by biloma and biliary fistula in around 5% of instances.[20] Emergency partial hepatectomy for major liver trauma may result in an injury to the bile ducts at the confluence with an early biliary leak and, subsequently, a biliary stricture.[21] Complete transection of the common bile duct requires immediate hepaticojejunostomy, whereas lacerations of the main biliary channel may be sutured after placement of a T-tube.

A persistent biliary fistula may occur from a segment of the liver that is isolated by the injury. Management of this situation is difficult, particularly when the fistula is associated with a distal stricture. In rare circumstances, the fistula can be identified at operation and oversewn. Alternatively, a well-developed fibrous fistulous tract may be anastomosed to a jejunal loop or to the gallbladder.[22]

Biliary Fistula After Liver Surgery

Liver resection carried out for tumor may be followed by biliary fistula, which may result from inadequate control of the bile ducts at the cut liver surface or failure to

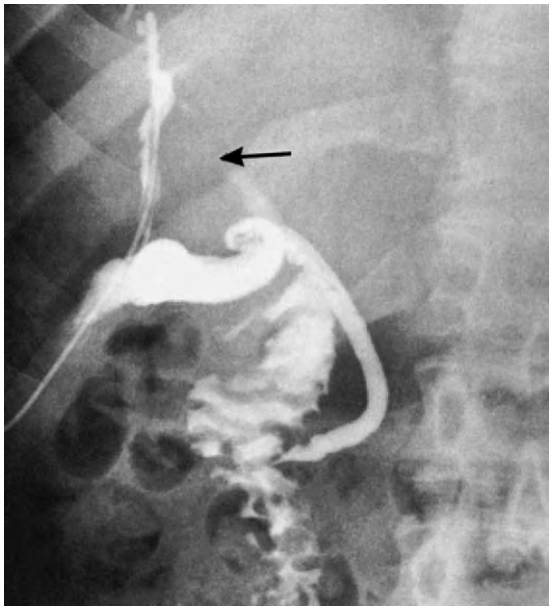


Figure 105–2. External biliary fistula following blunt injury to the right lobe of the liver and subsequent drainage of a large right intrahepatic hematoma. The injury was associated with damage to the right hepatic duct and subsequent intrahepatic stricture *(arrow).* Following external drainage, a high-output biliary fistula developed. The tubogram illustrated was obtained after anastomosis of the fistulous tract issuing from the liver to the adjacent mobilized gallbladder. Note that the cavity within the liver has collapsed and the gallbladder fills and subsequently outlines the common bile duct. The tube was removed, and postoperative recovery was uneventful. (From Czerniak A: External biliary fistula. In Blumgart LH, Fong Y [eds]: Surgery of the Liver and Biliary Tract, 3rd ed. Philadelphia, WB Saunders, 2000, p 940.)

secure the bile ducts at the hilus. This is more likely following right hepatectomy where the anatomy of the right sectoral hepatic ducts is variable. Extended left hepatic lobectomy has also been associated with biliary fistula.[23]

Operative injury to the biliary tract that is likely to result in fistulation is more common following resection of lesions involving the hilar structures. It is also more likely to occur after resection of lesions involving the caudate lobe ducts, since the anatomy of these ducts is variable in the hilar region. Resection of hilar cholangiocarcinoma, using major hepatic resections, combined with biliary-enteric reconstruction may be complicated by a biliary fistula originating usually either from caudate lobe ducts or from the biliary-enteric anastomosis.

Hepatic cryotherapy or the harmonic scalpel, which may be used either for ablation of deep intrahepatic lesions or at the cut liver surface, respectively, may be complicated by biliary fistula.[24] It may be prudent to leave a drain in situ following this procedure.

Hydatid Disease of the Liver

Hydatid disease of the liver is associated with biliary involvement in around 10% of instances.[25] A live, expanding cyst results in compression and stretching of adjacent liver tissue, including the bile ducts. It may then erode into a stretched bile duct with the establishment of continuity between the cyst cavity and the biliary system. Hydatid material may enter into the biliary tree or, conversely, bile may leak into the cyst.

Biliary fistula develops after operation for hydatid disease in three situations. First, a communication between the cyst cavity and the biliary system is missed at operation and is not directly secured. Unless a distal obstruction is present, these fistulas usually close spontaneously.

Second, and rarely, the presence of hydatid material within the biliary tract produces biliary ductal obstruction (Fig. 105–3), resulting in a persistent biliary fistula that is only relieved once the hydatid material passes or is removed. This is achieved either by exploration of the common bile duct with or without a bypass procedure or by endoscopic methods.[26,27] Assessment of the biliary tree, preferably by endoscopic cholangiography or magnetic resonance cholangiopancreatography (MRCP), should therefore be performed prior to surgery in patients with a history of jaundice or cholangitis or in the presence of a large cyst located centrally and abutting the hilar structures. Once a cystobiliary communication is demonstrated, the biliary system should be cleared of all debris and cyst remnants, and endoscopic sphincterotomy should be performed prior to surgical intervention.[28] Percutaneous treatment of hydatid cysts is associated with a 10% incidence of biliary fistula. Such fistulas usually close spontaneously once biliary distal obstruction, when present, is relieved.[29]

Third and finally, although liver resection is not the preferred method of treatment for liver hydatid disease, it is occasionally performed for this condition. Such patients are prone to all the complications of liver resections carried out for other reasons.

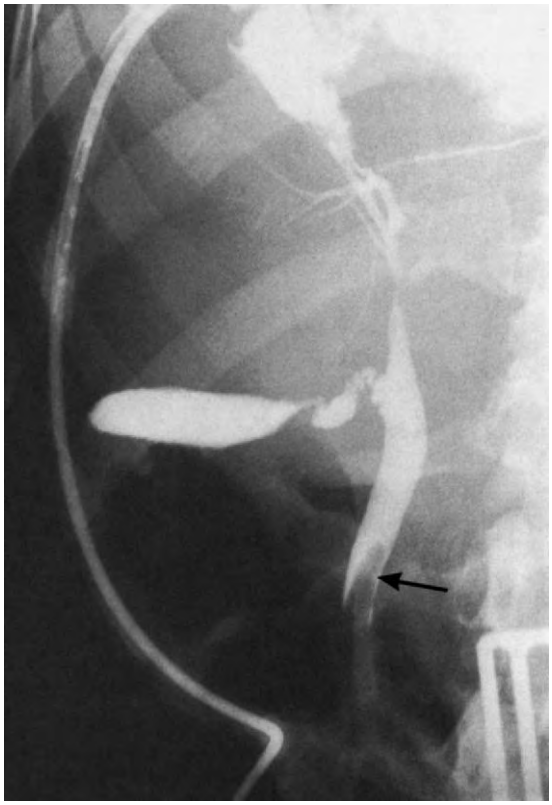


Figure 105–3. Fistulography obtained after excision of a right hepatic hydatid cyst. Note the persistent fistula consequent on retained hydatid material in the common bile duct and surgical removal of the retained hydatid material *(arrow)*. Subsequently, the fistula rapidly closed. (From Czerniak A: External biliary fistula. In Blumgart LH, Fong Y [eds]: Surgery of the Liver and Biliary Tract, 3rd ed. Philadelphia, WB Saunders, 2000, p 942.)

Biliary Fistula After Liver Transplantation

Biliary leak and fistula are a continuing source of morbidity and mortality following liver transplantation. Pathogenesis is usually related to technical and vascular considerations and, in particular, to hepatic artery thrombosis.[30]

Biliary Fistula After Gastrectomy

Injury to the bile duct may occur during gastrectomy and is more common in Billroth II gastrectomy, particularly when the pyloric region or the first part of the duodenum is grossly distorted and inflamed.[31] Such an injury becomes apparent either as a biliary fistula or at a later stage with the development of a stricture.

Biliary Fistula After Invasive Radiologic Procedures

Biliary leak and fistulas may follow most invasive radiologic procedures on the hepatobiliary system. The

creation of a transjugular intrahepatic portosystemic stent-shunt may be complicated by biliary-venous fistulas, especially when a large-caliber intrahepatic bile duct is transected. The resulting biliary leak plays an important role in the stenosis and occlusion of the portosystemic shunt.[32]

CLINICAL PRESENTATION

The clinical presentation of a biliary fistula may be of an excessive, abnormal biliary drainage from the drain site/wound or, alternatively, a localized or generalized peritonitis resulting from an intra-abdominal collection of bile. Once a diagnosis of biliary fistula has been established, it is most important to clinically assess the adequacy of bile drainage.

In controlled fistulas, there is adequate external biliary drainage with no signs of localized or generalized peritonitis; the adverse pathophysiologic features associated with cholestasis are not present.

In an uncontrolled biliary fistula, there is inadequate biliary drainage resulting in an intra-abdominal bilious collection. Since the bile is usually or soon becomes infected, the presentation is mostly of either a subphrenic or subhepatic abscess or generalized peritonitis. The situation may further be complicated by cholangitis with or without intrahepatic abscess and septicemia demanding urgent treatment. It must be stressed that in some patients with sterile bile, huge volumes may accumulate within the peritoneal cavity with minimal clinical findings apart from a distended abdomen (Fig. 105–4).

Therefore, it is important to observe patients with laparoscopic cholecystectomy at 24 hours after the operation, at which time the liver function tests are checked. A high index of suspicion is important because minimal abdominal symptoms and slightly deranged liver function tests may be the only indicators of biliary damage.

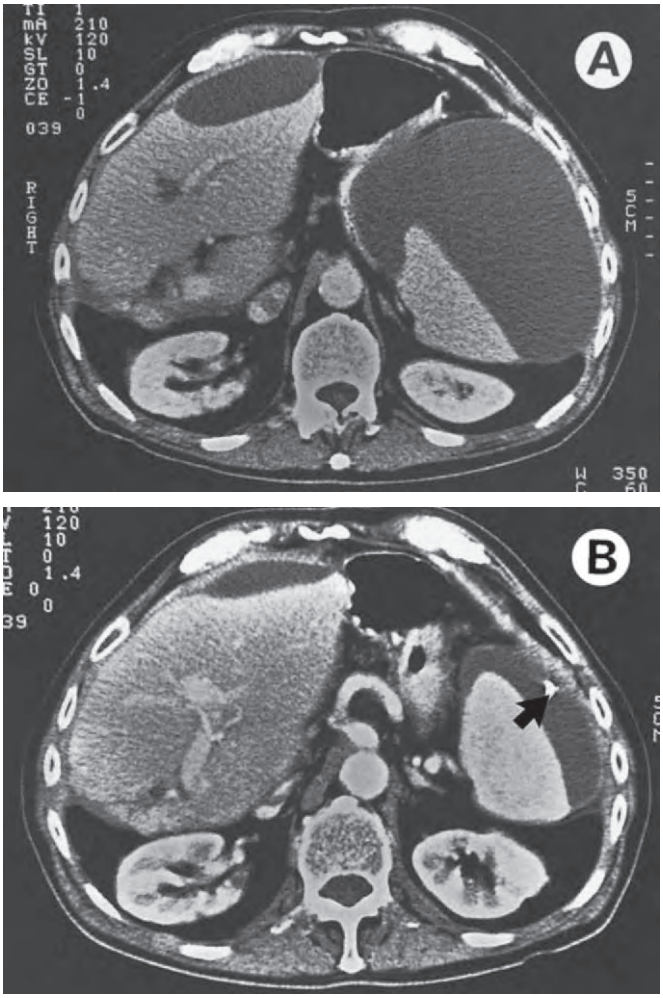


Figure 105–4. **A,** Huge asymptomatic biloma 3 weeks after partial hepatectomy for hepatocellular cancer. The patient complained of abdominal distention only. **B,** CT-guided puncture and drainage *(arrow)* converted the uncontrolled fistula into a controlled one. The fistula closed spontaneously after 17 days. (**A** and **B,** From Czerniak A: External biliary fistula. In Blumgart LH, Fong Y [eds]: Surgery of the Liver and Biliary Tract, 3rd ed. Philadelphia, WB Saunders, 2000, p 943.)

PATHOPHYSIOLOGIC CONSEQUENCES OF EXTERNAL BILIARY FISTULA

The important pathophysiologic effects of an external biliary fistula depend on the volume of bile drained daily, the length of time the fistula has been present, and the degree to which bile is diverted from the gastrointestinal tract. Consequences of biliary fistula are mainly due to depletion of electrolytes and fluid, to the absence of bile from the gut, and to the possibility of ascending exogenously acquired biliary infection. The important practical considerations are that the volume of bile secreted daily by the liver is on the order of 1000 ml and that the electrolyte composition of bile is equal to that of blood.

Total biliary loss for short periods of up to 3 weeks may not result in a serious depletion of electrolytes and fluid since the body is able to compensate for this loss. Long-term total external biliary fistula results in fluid and electrolyte disturbances if replacement therapy is not instituted. Sodium loss is usually in excess of chloride loss, leading to metabolic acidosis. The serum potassium level is initially lowered, but the accompanying fluid loss may lead to a decrease in plasma volume, low-output renal failure, and hyperkaliemia.[33] Absence of bile from the gastrointestinal tract causes interference in the absorption of fat-soluble vitamins A, D, and K. Clinically, patients with an external biliary fistula (in the short term) feel unwell, weak and lethargic. In advanced and neglected cases, caloric and protein malnutrition results in gradual weight loss, while the electrolyte changes may result in stupor and vasomotor collapse.

DIAGNOSTIC PROCEDURES AND INITIAL TREATMENT

The presence of a biliary fistula may first become apparent at reoperation. More commonly and particularly

after laparoscopic cholecystectomy, the biliary fistula becomes apparent at endoscopic cholangiography or following percutaneous drainage of a perihepatic collection.

Reoperation is usually done for peritonitis or for drainage of an intra-abdominal collection. Such collections may be a complication from previous surgery on the hepatobiliary system, the pancreas or, rarely, the stomach or duodenum. They may also follow a spontaneously occurring pathologic process such as hemorrhagic pancreatitis or rupture of a liver cyst. Once the presence of an uncontrolled biliary fistula has been realized, initial management demands conversion of the fistula into a controlled one, usually by means of tube drainage. No attempt at definitive repair should be made at this early stage since the involved bile duct(s) are collapsed and friable and are usually embedded within a severe local inflammatory reaction. Moreover, it is virtually impossible to expose healthy bile ducts for any form of long-lasting definitive repair, and such an attempt, which is bound to fail, will render further operation more difficult.[34]

The early demonstration of an uncontrolled biliary fistula, within 24 to 48 hours of laparoscopic cholecystectomy, together with a transected or completely occluded common bile duct is an indication for early surgical intervention. Decision regarding definitive repair is based on operative findings. Rarely, removal of a misplaced clip intended for the cystic stump and causing complete obstruction of the common bile duct is all that is necessary.

Alternatively, percutaneous computed tomography (CT) or ultrasound-guided drainage of a subphrenic or infrahepatic fluid collection may be followed by the establishment of an external biliary fistula. It is then most important to ensure adequate drainage and that the fistula is indeed controlled. Biliary drainage is ideally carried out using a sealed-drainage bag system.[35] Initially, drainage should be under a low-pressure, closed-suction system, which is valuable in reducing the cavity of the intra-abdominal bile collection or abscess to a fistula track. Improvement of the clinical picture—together with repeat ultrasound or CT studies—should eventually demonstrate proper positioning of the drain and no residual collection or abscess. Technetium 99m disofenin (HIDA) scintigraphy and tubography are helpful in this respect.

Once the fistula is controlled, conservative treatment should be instituted, the patient nourished, deficits of electrolytes and vitamins (mostly vitamin K) corrected, and infection treated. It is important to know whether the biliary fistula contains bile only or whether it also contains duodenal, pancreatic, or intestinal juice. When the latter is present, appropriate measures to protect the skin should be taken. Parenteral nutrition is an essential element in the management of duodenal and pancreatic fistulas, since total prohibition of oral intake is important in allowing healing to occur. It has been shown that treatment with somatostatin can significantly reduce bile secretion.[36] Following the establishment of a controlled fistula, various radiologic investigations are then performed with the aim of assessing the following:

- Origin of the fistula
- Location and extent of the injury to the extrahepatic biliary system
- Adequacy of drainage
- Presence of biliary-enteric bile flow

The anatomy of the entire intrahepatic and extrahepatic biliary tree should be demonstrated, and this is achieved by a variety of radiologic studies.

Tube cholangiography should be performed routinely prior to removal of a cholecystostomy, choledochostomy tubes, or tubal drainage across biliary-enteric anastomoses. Removal of such a tube in the presence of a distal stricture or a retained bile duct stone invariably results in a persistent biliary fistula.

Fistulography is a simple and effective means of finding out whether biliary drainage is adequate and whether a fistulous cavity has indeed converted to a fistulous track. The site and underlying cause of the biliary fistula can also be clearly demonstrated by fistulography.

Percutaneous transhepatic cholangiography (PTC) is used when the findings of fistulography are equivocal and when the intrahepatic biliary tract, the right system in particular, is not fully demonstrated. Iatrogenic damage to a right sectoral hepatic duct is an example of this problem and PTC is the only diagnostic modality to yield accurate definition.

MRCP is an accurate diagnostic technique in the identification of postoperative bile duct injuries. This technique allows rapid exploration both above and below the level of injury (an advantage not available by endoscopic retrograde cholangiography [ERC] or PTC) and allows accurate classification of these injuries, which is of utmost importance for the treatment planning. A recent prospective study by Ragozzino et al. demonstrated the unique ability to virtually explore the biliary tree noninvasively in cases of biliary injury.[37] In particular, MRCP allows exact definition of the level and length of the biliary injury. Additionally, MRCP detects the presence of subhepatic collections, demonstrating the site of leakage, and delineates the anatomic variants. Mangafodipir trisodium is a magnetic resonance hepatobiliary contrast agent and can add a dynamic and functional dimension to MRCP.[38]

ERC is a most useful diagnostic and therapeutic tool in instances where there is a continuity of the extrahepatic biliary system, particularly following laparoscopic cholecystectomy and in liver transplanted patients.[39,40] The value of ERC is limited in fistulation arising at the hilus and resulting from iatrogenic bile duct injury.

HIDA scintigraphy is a useful noninvasive method of evaluating liver function and bile secretion.[41] Although it may not supply accurate anatomical details, it can obtain information regarding the presence of a fistula, its origin (liver or extrahepatic biliary system), and the adequacy of drainage (controlled or uncontrolled).

TREATMENT

The principles of management of a postoperative biliary fistula are essentially the same regardless of the initial

surgical procedure. These principles are modified slightly according to the initial surgical procedure and to the individual patient. Endoscopic cholangiography and endoscopic techniques now play an integral and indispensable part in the management of biliary fistula. The individual treatment plan should therefore be made and agreed on jointly by all members of the team involved in the treatment of the patient.

As stated previously, it is important to establish a controlled fistula. This can be achieved initially by ultrasonography or CT-guided drainage of the abscess or collection. Operation is indicated when nonoperative measures are unsuitable—such as in diffuse bile peritonitis, a septic patient with an intra-abdominal abscess too large to be drained by the percutaneous route, or the presence of necrotic material and debris within the abscess. Early surgery is also indicated when percutaneous drainage has failed. It must be stressed again that, during the operation, one should not be tempted to attempt primary repair at this stage, but rather to establish good drainage only. Occasionally, drainage of large amounts of bile with significant fluid and electrolyte loss may necessitate early operation. In these circumstances, the external fistula may be converted to an internal fistulojejunostomy using a mobilized and approximated Roux-en-Y jejunal loop.[22]

It is critical to identify the presence or absence of biliary-enteric bile flow. This differentiates a total biliary fistula from a partial fistula with some residual biliary-enteric continuity. This also significantly influences subsequent management since in the first case operation is usually unavoidable, whereas in the latter case the nonoperative approach may be successful. Occasionally, a total biliary fistula closes spontaneously when an internal fistula develops between the divided upper duct and the gut.[42]

When biliary-enteric continuity is present and there is no obstruction to bile flow distal to the origin of the fistula, a prolonged period of conservative treatment is indicated because spontaneous closure of the fistula is usual. The mainstay of this conservative treatment is the adequate and timely application of endoscopic techniques. Fistula closure may be facilitated by temporary placement of a stent across the fistulous opening in the bile duct, thus excluding bile flow through the fistula. This method may be attempted in instances where there is an intact common bile duct above the fistula origin and the defect in the bile duct is not too large. It may be particularly helpful in instances of cystic stump fistula and may facilitate early closure. Stenting may be achieved by endoscopic placement of an endoprosthesis or a nasobiliary tube with its tip above the origin of the fistula. When a short period of stenting is anticipated, nasobiliary intubation is preferred because (1) it allows follow-up cholangiography; (2) damage to the papilla is minimal; and (3) a second endoscopic procedure is avoided. Using this method, some fistulas close within 2 weeks.[43] In most instances, a biliary endoprosthesis is used and is left in place, usually for several weeks, until fistula closure. Closure is verified by HIDA scan prior to removal of the stent. Some surgeons recommend endoscopic sphincterotomy alone with the intention of reducing the pressure gradient between the biliary system and the duodenum.[44] However, this is unnecessary because the fistula closes in any event if no distal obstruction is present. Sphincterotomy may also be associated with short- and long-term septic and obstructive complications and should be avoided unless specifically indicated (e.g., in patients with a papillary stricture.) It has also been shown that stenting is more effective than sphincterotomy alone in the resolution of biliary fistulas.[45]

Once an obstruction distal to the fistula has been diagnosed, it should be dealt with because the fistula will not close spontaneously. Obstruction is usually caused by a retained stone or a stricture. The former is usually removed by endoscopic means; the latter can be relieved using balloon dilation applied either endoscopically or by interventional radiology following PTC. The patient is then treated conservatively and expectantly, either for fistula closure or for restricture, which, once it occurs, is then treated operatively. Thus, fistula closure can be facilitated by temporary stenting if the location and the size of the defect in the bile duct are suitable. The use of temporary stenting is limited in high, complex, hilar fistulas combined with stricture(s), particularly those with separation of a right and left ductal system. Some surgeons place an endoprosthesis across the stricture and leave it for many months with periodic replacements.[44] This is not only unnecessary but may also be harmful, resulting in obstruction and septic complications. The endoprosthesis, if placed, should be removed when the fistula has closed.

Management of biliary fistula following laparoscopic cholecystectomy follows the same principles. Since early recognition of biliary fistula or bile duct damage significantly affects treatment, a high index of suspicion is important. Initial evaluation includes abdominal ultrasound and HIDA scan to rule out the presence of an abnormal collection and establish the presence of free biliary-enteric bile flow. Abnormal findings at either study calls for an endoscopic cholangiography. Treatment of biliary fistula with or without biliary enteric continuity follows the guidelines outlined.

A biliary fistula associated with malignant distal obstruction is treated with reoperation and surgical excision of the neoplasm or the creation of an appropriate biliary-enteric bypass. Following closure of the fistula, patients are followed carefully with regular liver function tests and HIDA scan to detect early signs of the development of a biliary stricture. This may take months or years and is especially likely to occur in instances where a stricture has already been present or when the fistula was associated with an injury to a major bile duct.[2]

The proposed plan may involve relatively prolonged management, but it improves the chances of a successful and long-lasting bile duct repair, particularly in instances following injury at cholecystectomy. In this situation, early and untimely surgical attempts at definitive repair carry a high risk of biliary leak and anastomotic stricture.

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Chapter

106

Biliary Atresia, Biliary Hypoplasia, and Choledochal Cyst

Stephen Dunn

Biliary atresia is a disease characterized by progressive obliterative destruction of intrahepatic and extrahepatic biliary structures.[1] It is the most common cause of direct hyperbilirubinemia in infancy and must be quickly and effectively differentiated from the numerous other causes of jaundice.[2] Early surgical intervention and appropriate postoperative medical management are necessary to prolong native liver function.[3] Ultimately, liver transplantation is required in most cases. However, the combination of early surgical intervention and hepatic transplantation has transformed the prognosis in this disease characterized as fatal in the 1960s to one in which the great majority survive with an excellent quality of life.[4,5] Choledochal cyst is a congenital dilation of the intrahepatic and/or extrahepatic biliary tree that can cause obstructive jaundice and cholangitis and may result in cholangiocarcinoma. It is commonly recognized now on antenatal ultrasound imaging, and early intervention is curative.[6] Biliary hypoplasia is the liver biopsy finding of a paucity of interlobular bile ducts and is most common as a component of Alagille's syndrome.[7,8] Many of these patients may have serious cardiac anomalies as well as growth deficiency and decreased renal function. Progressive biliary cirrhosis may occur in the syndromic and nonsyndromic varieties, requiring hepatic transplantation.

DIAGNOSIS

Jaundice is common in newborns and is secondary to immature hepatic enzyme activity resulting in indirect hyperbilirubinemia. Jaundice persisting beyond the age of 2 weeks should be evaluated by fractionated bilirubin determination. Diagnostic evaluation should be initiated promptly if the direct bilirubin fraction is greater than 20% of the total.[9] Infection, especially when caused by gram-negative bacteria, may cause jaundice. Serologic testing for congenital infection, Pi typing for α_1-antytrypsin deficiency, sweat testing or genetic studies for cystic fibrosis, tests to exclude galactosemia, and tests for defects of oxidative enzyme and amino acid metabolism are included in this evaluation.[1,2] Ultrasound examination of the abdomen should be obtained early in the evaluation.[10] In biliary atresia, the gallbladder is normally shrunken, and no common bile duct is visible. A "triangle cord sign" found on ultrasound has a predictive accuracy of 95%.[11] Hepatobiliary scintigraphy with technetium 99m disofenin (HIDA) with 3 to 5 days of preimaging phenobarbital administration demonstrates no intestinal excretion initially or at 24 hours.[12] Percutaneous liver biopsy is helpful. Typical histology demonstrates intracanalicular cholestasis with proliferation of bile ducts.[9] Findings compatible with neonatal hepatitis, periportal fibrosis, and giant cell formation also may be present.

In the absence of a definitive diagnosis excluding biliary atresia, operative cholangiography must be performed and, if possible, before the age of 60 days. The patient must be prepared for definitive hepatoportoenterostomy at that time.

Choledochal cyst may be discovered on antenatal ultrasound. The cyst is subhepatic and is observed at a mean of 26.9 weeks' gestation.[13] Ultrasound is a useful method of diagnostic imaging in older children presenting with the diagnostic triad of jaundice, abdominal mass, and fever. Confirmation of the ultrasound finding may be done by HIDA testing or computed tomography with intravenous contrast. Hepatic function test results may vary depending on the degree of biliary obstruction, presence of cholangitis, and age at presentation. Pancreatitis may be a common finding at presentation and

is postulated to be due to an anomalous common channel at the outflow of the biliary and pancreatic ducts.[14] This finding may be relatively common, although it has not been prominent in the cases diagnosed during the neonatal period. The pancreaticobiliary abnormality probably underlies the etiology of cystic dilation of the biliary tree and injury of the biliary epithelium. Reflux of pancreatic enzymes into the biliary tree may result in injury.[15] Hepatic fibrosis or cirrhosis may be seen in the newborn and is associated with complete obstruction of the biliary tree. Surgical intervention is beneficial in these cases.

Biliary hypoplasia is diagnosed by the findings on liver biopsy and operative cholangiography. A diminished number of interlobular bile ducts and the cholangiography findings of small intrahepatic and extrahepatic biliary structures with the presence of bile in the gallbladder at exploration are typical. The syndromic form of this disease described by Alagille includes several other important findings. These include butterfly-like vertebral arch defects, the ophthalmologic finding of posterior embryotoxon, peculiar facies, and cardiac anomalies, of which the most common is branch pulmonary artery stenosis. Renal tubular abnormalities may also be present on ultrasound. Recent work has identified the abnormal gene, *JAGGED1*.[7] Testing for this abnormality is now available.

ETIOLOGY

The cause of biliary atresia remains enigmatic. Although approximately 10% of cases occur in the context of other associated anomalies suggesting a genetic basis, most occur randomly or sporadically, which is consistent with an infectious cause.[1] Animal models of biliary injury have been developed with reovirus and rotovirus as the infectious agent.[16] These agents have not been definitively implicated in biliary atresia in humans. It is suggested that exposure of antigen on biliary epithelium secondary to the consequences of infection leads to an autoimmune-type process. This hypothesis is speculative but is supported by the investigations of the inflammatory process found in biliary atresia. Of particular interest in the sporadic cases is the not-uncommon history that an affected newborn had pigmented stools initially. This history suggests the progressive nature of the biliary injury and is one of the intriguing aspects of this disease. The most common presentation of the syndromic variety of biliary atresia is within the context of heterotaxia now known as *left isomerism*. In these cases, the associated anomalies may include polysplenia; malrotation; situs inversus; interrupted inferior vena cava with azygous continuation; preduodenal portal vein; and cardiac anomalies, including heterotaxia or more severe lesions.[17]

The cause of choledochal cyst is speculative.[18] Malformation of the confluence of the biliary and pancreatic ducts with reflux of the pancreatic enzymes into the biliary tree leading to cystic degeneration is suggested.[19] Cholangiography has demonstrated this common channel in many patients with choledochal cysts. However, the common channel is not found in all cases and may be found in patients without choledochal cyst.[6] Familial association of choledochal cyst is rare but does occur.[20] There is also an association of choledochal cyst and biliary atresia. In these cases, cystic dilation of the common bile duct is associated with fibrous obliteration of the proximal hepatic duct. This suggests a common cause may result in either of these diseases.

The genetic abnormality underlying Alagille's syndrome has been discovered during the past decade. Studies of *JAGGED1* expression patterns have shown that the associated abnormalities of Alagille's syndrome are not coincidental but related to abnormalities of this gene.[7] The cause of sporadic biliary hypoplasia is not known.

CLASSIFICATION

Ohi and colleagues[27] created an effective classification scheme for the biliary abnormalities found in biliary atresia (Fig. 106–1). This scheme allows each case to be designated by the operative findings. Although this classification is important for proper case description, no correlation has been found that associates the various categories with etiology, treatment, or prognosis. The most common findings at operation are atresia at the porta hepatis (type III) with a fibrous common bile duct (subtype b) and a fibrous mass at the hepatic radicles (subgroup ν). When biliary atresia was first classified, terms such as *correctable* and *uncorrectable* forms were used. These terms are misleading, as Kasai and Suzuki described their surgical procedure for the "uncorrectable" form of the disease.[21] Most patients have the uncorrectable form of the disease and are still excellent candidates for surgical therapy with a high expectation of benefit if surgery is performed prior to 60 days of age. Nevertheless, as many as 10% of all patients never achieve bile drainage due to the damage of the intrahepatic biliary tree, and these cases are correctly identified as uncorrectable. At present, we have no way to identify these cases for whom hepatoportoenterostomy will have no merit.

Choledochal cyst abnormalities are classified according to location of the cystic dilation of the intrahepatic and extrahepatic structures and gallbladder. The classification scheme of Tonadi, which is a modification of the Alonzo-Lej classification, has been widely accepted.[22] The most common type is type I, which represents 85% of cases (Fig. 106–2). The association of type V with hepatic fibrosis and the syndrome of polycystic kidney disease is significant. Also known as *Caroli's disease,* this form may be associated with a benign course or may include progressive liver disease with portal hypertension.[23] Careful follow-up is required in these cases.

OPERATIVE MANAGEMENT

Biliary Atresia

The operation for biliary atresia begins as a diagnostic procedure with a small incision to inspect the gallblad-

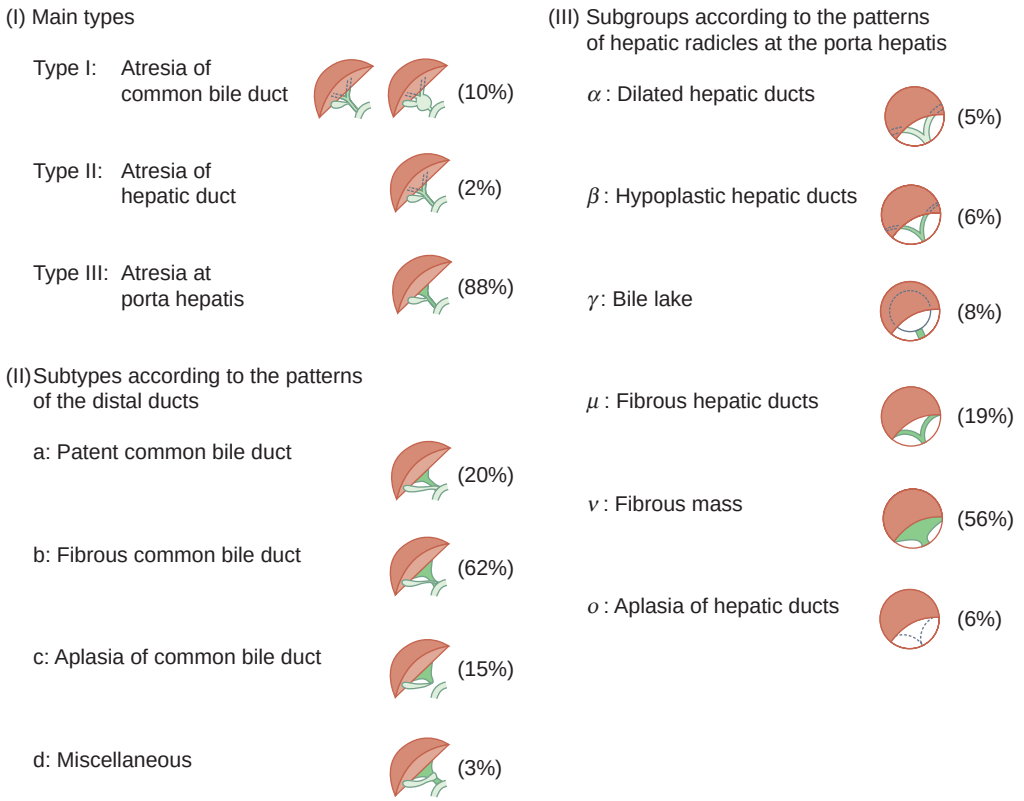

Figure 106–1. Morphologic classification of biliary atresia based on macroscopic and cholangiographic findings. (From Ohi R, Nio M: The jaundiced infant: Biliary atresia and other obstructions. In O'Neill JA, Rowe MI, Grosfeld JA, et al [eds]: Pediatric Surgery, 5th ed. St. Louis, Mosby, 1998, p 1466.)

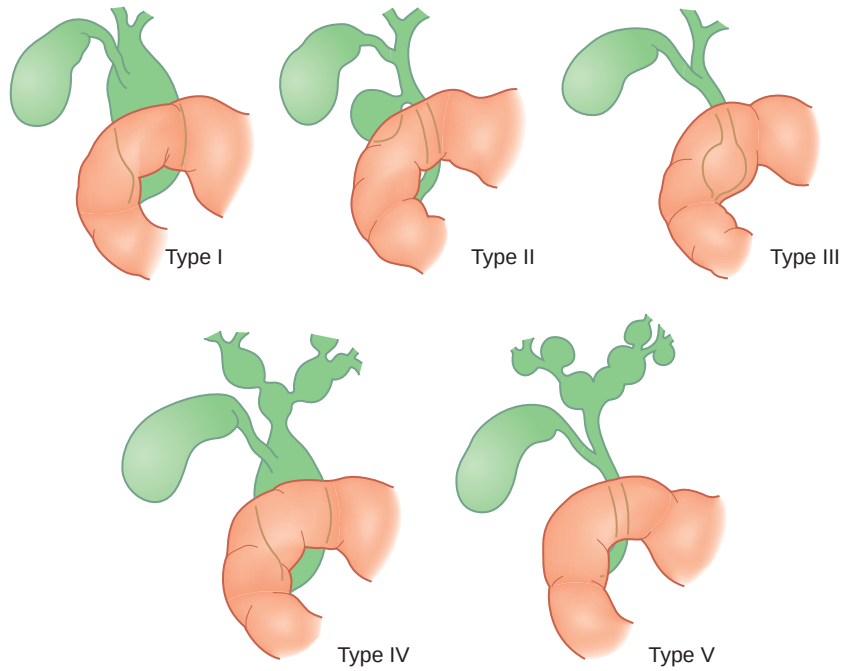

Figure 106–2. The five general forms of choledochal cyst that can be found on cholangiography. (From Taylor LA, Ross AJ: Abdominal masses. In Walker AW, Durie PR, Hamilton JR, et al [eds]: Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management. Philadelphia, BC Decker, 1991, p 134.)

der and biliary tree. In the presence of a small, shrunken, or scarred gallbladder that may contain a small amount of clear fluid, further investigation is not needed. The incision is lengthened to facilitate portal dissection. If the gallbladder is of normal caliber, cholangiography is performed through the dome of the gallbladder. Flow into the duodenum may be encountered, necessitating external pressure to the distal common bile duct to facilitate flow into the proximal ductal structures. If these structures cannot be seen, dissection of the porta is required. Presence of a fibrous extrahepatic biliary tree and, in some cases, its disruption or absence is consistent with biliary atresia. Portal dissection is facilitated by division of the fibrous remnant of the extrahepatic biliary tree near the duodenum. The fibrous remnant is then lifted off of the portal vein and separated from the hepatic artery branches. Care must be taken not to injure these vessels. The target of the dissection is the fibrous cone of tissue just anterior to the bifurcation of the right and left branches of the portal vein. Removal of the fibrous remnant between the point of entry of the portal vein branches and the hepatic parenchyma is the goal and is the highest safe point for dissection. Gentle traction on the portal vein branches has been advocated to facilitate this dissection. Small vessels from the main portal vein to the biliary plate need to be carefully ligated with fine suture to achieve an adequate dissection (Fig. 106–3).

Reconstruction of bile drainage is through a hepaticojejunostomy. A Roux-en-Y limb of jejunum is formed by dividing the proximal jejunum approximately 10 cm from the ligament of Trietz. The distal end is passed through the transverse mesocolon to the area of the porta hepatis. The anastomosis of the proximal jejunum is to the side of the distal jejunum approximately 40 cm from the initial point of jejunal division. The portal reconstruction is performed using an anastomosis of the side of the Roux limb of the jejunum a few centimeters from the blind end to the tissue surrounding the biliary plate. This is usually performed with fine absorbable sutures, especially on the back or inside row with a single layer where the suture knots necessarily are on the inside of the anastomosis. The anastomosis should incorporate the entire biliary plate.

At the completion of the hepaticojejunostomy, the retrocolic tunnel and the mesenteric defects are repaired. A single, closed-suction drain is placed posterior to the anastomosis, exiting through the side of the infant. A needle biopsy of the liver is always obtained at the time of operation to document the degree of hepatic fibrosis. Biliary diversion or formation of one-way valves in the Roux limb have not measurably altered the progression of this disease to biliary cirrhosis, although the incidence of cholangitis may be decreased. Heterotaxia findings may complicate the operative procedure. Placement of the initial incision should be guided by ultrasound location of the porta or palpation of the liver under general anesthesia. Malrotation may be found associated with the syndrome and may make retrocolic placement of the Roux limb impossible. Abnormalities of hepatic arterial supply and the presence of a preduodenal portal vein should be anticipated and recognized during portal dissection. Placement of the hepaticojejunostomy is guided by identification of the portal vein bifurcation.

Choledochal Cyst

The indication for operative intervention is the finding of the choledochal cyst. Antenatal diagnosis has led to the dilemma of the timing of operative intervention. Immediate intervention post delivery is not warranted because it does not appear to improve the benefit of later cyst excision. However, excessive delay also is not warranted because hepatic injury from cholestasis or cholangitis will be the result. Surgery during the first few weeks or months of life can be done safely by experienced surgeons and is probably the best approach. Preoperative intervention with hepatic drainage may be necessary in older patients who have cholangitis. In most cases, treatment with broad-spectrum antibiotics with good biliary penetration is effective. Surgery within a few days after the patient resolves the acute symptoms of cholangitis is usually possible. The incision should provide adequate visualization. Many children who present with this condition later in life may have quite massive dilation of the choledochal cyst dissecting posteriorly to the duodenum and pancreas. Cholangiography should be performed prior to dissection specifically to visualize the pancreatic duct location and to identify biliary anatomy. In neonates, the choledochal cyst may not communicate with the hepatic ducts. It should be assumed that these patients have biliary atresia. The choledochal cyst should be excised and the portal dissection completed with drainage by hepatoportoenterostomy. The dissection of the choledochal cyst may be complicated by pericholedochal inflammation, edema, or portal hypertension. The goal of dissection is complete removal of the cyst up to the level of noninflamed biliary ducts, even if they are dilated. The dissection is facilitated by circumferential dissection at a level where the cyst is narrower, with division of the cyst. Care should be taken not to injure the portal vein, which is usually posterior and medial to the cyst. A dissection plane that leaves a portion of the back wall of the cyst intact while the abnormal mucosal lining is removed has been advocated when necessary. The biliary connection to the common channel of the bile and pancreatic duct should be oversewn when present without narrowing the pancreatic duct. Proximal dissection of the choledochal cyst should proceed to the level of normal-appearing duct epithelium and may require dissection onto right or left hepatic duct branches. Reconstruction is by hepaticojejunostomy using a Roux-en-Y limb of jejunum. A closed suction drain is placed posterior to the anastomosis. Perioperative antibiotics should continue until there are no signs of bile leak or infection. In one report long-term follow-up did not reveal cholangiocarcinoma in remnant abnormal ducts after primary choledochal cyst excision. Subsequent choledochojejunal stricture with symptoms of cholangitis and stone formation may occur but is relatively uncommon.[24]

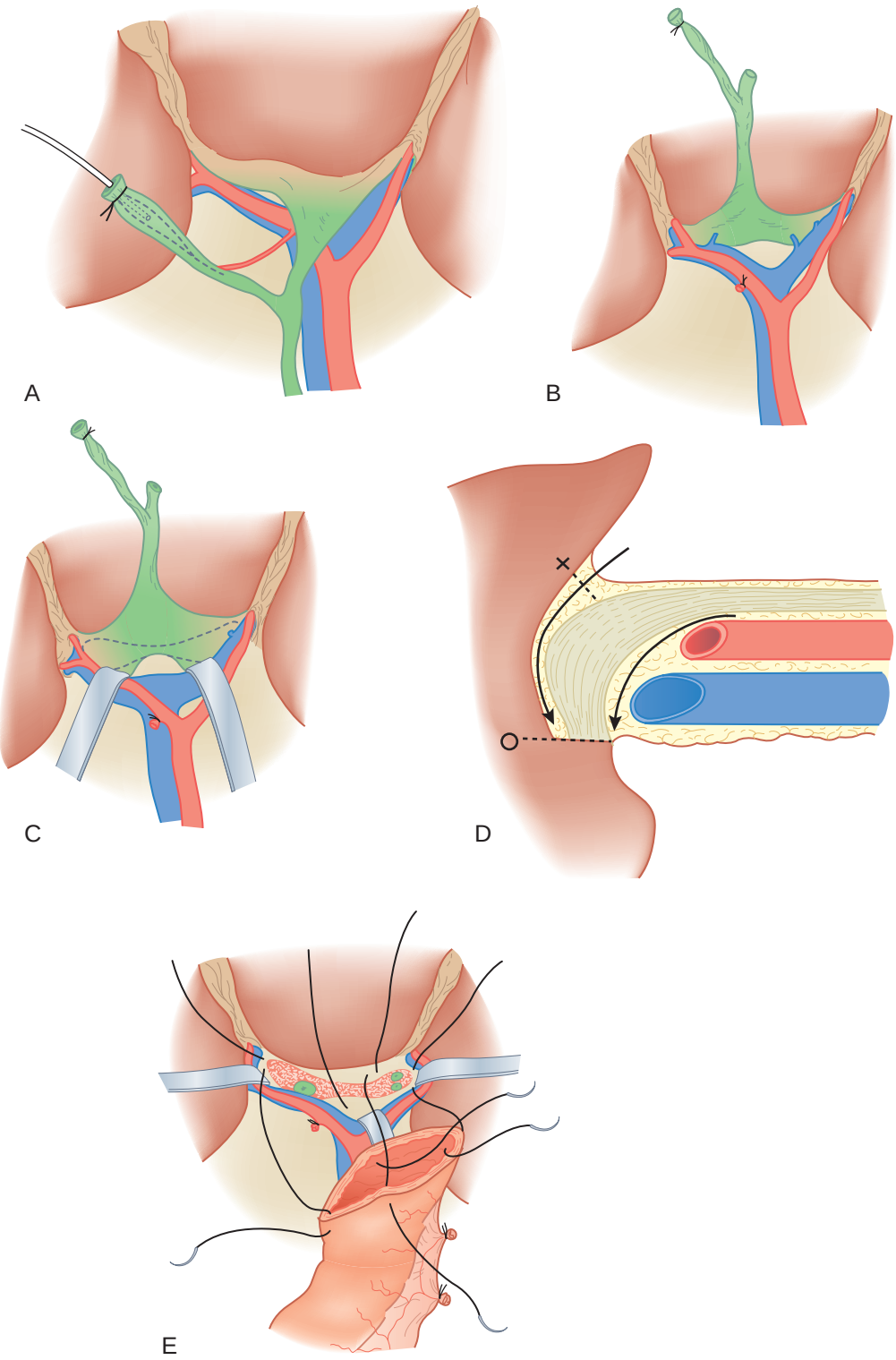

Figure 106–3. Sequential depiction of the dissection and reconstruction of the porta hepatis during operation for hepatoportoenterostomy: **A,** Demonstrates the usual finding at exploration with fibrosis of the extrahepatic biliary tree; **B,** demonstrates the dissection of the fibrous duct off of the portal vein and hepatic artery; **C** and **D,** demonstrate the level of transection of the fibrous remnant of the bile duct; and **E,** demonstrates the reconstruction of the porta in progress. (**A-E,** From Ohi R, Nio M: The jaundiced infant: Biliary atresia and other obstructions. In O'Neill JA, Rowe MI, Grosfeld JA, et al [eds]: Pediatric Surgery, 5th ed. St. Louis, Mosby, 1998, pp 1470-1471.)

Table 106–1 Medical Regimen to Prevent Cholangitis[25]

Drug or Regimen	Dose	Duration
Methylprednisolone	Taper 10, 8, 6, 5, 4, 3, to 2 mg/kg/day	7 days
Oral prednisone	2 mg/kg/day	8-12 wk after intravenous antibiotics stopped
Antibiotics		
Piperacillin/tazobactim	300 mg/kg/day	8-12 wk
Gentamicin	5 mg/kg/day	8-12 wk
Oral trimethoprim/sulfathiazole	5 mg/kg/bid	Indefinite after intravenous antibiotics stopped
Ursodeoxycholic acid	10 mg/kg/bid	Indefinite

POSTOPERATIVE MANAGEMENT

Biliary Atresia

Bile flow is achieved in most infants who receive surgery prior to 60 days of life. Bile flow may be slow at first and not reach normal proportions for several months. A medical regimen of corticosteroids, ursodeoxycholic acid, and prophylactic antibiotics to prevent cholangitis appears to enhance and sustain bile flow. A recently recommended regimen is included in Table 106–1.[25]

Recurrence of jaundice implies cholangitis. Liver biopsy may be helpful in diagnosis, although presumptive treatment is standard practice. Systemic antibiotics and increased corticosteroids may result in improved bile flow. At one time, repeat operation was advocated for infants who had drained bile initially and subsequently become jaundiced. This treatment is no longer advocated because it has not had a high rate of success. Infants whose jaundice does not clear or with recurrent jaundice should be referred for early evaluation for liver transplantation. The average length of survival in those infants whose total bilirubin did not decrease below 5 mg/dl after hepatoportoenterostomy was 18 months.[26] Prevention of malnutrition secondary to fat and fat-soluble vitamin malabsorption avoids unnecessary liver dysfunction, poor growth, bone disease, and coagulopathy.

Choledochal Cyst

Excellent bile flow with normal hepatic function is the best deterrent to recurrent cholangitis. Oral antibiotic prophylaxis may be used in the first few weeks or months following operation as well as ursodeoxycholic acid, but these are probably unnecessary as long-term treatment. Annual follow-up with ultrasound evaluation of the liver and liver function tests may be useful as late recurrence of biliary obstruction, stone formation, and cholangitis may occur. These studies become less interesting after a few years of follow-up when the patient has developed no signs or symptoms of biliary tract disease.

OUTCOMES

Biliary Atresia

Perioperative mortality is approximately 1.5% after hepatoportoenterostomy.[27] Most infants clear their jaundice if operated on prior to age 60 days. Approximately 35% of children may do well over time with their native liver. However, clearance of jaundice is not curative and may recur. Progression of liver disease to frank cirrhosis may occur over a number of years. Recurrent bouts of cholangitis accelerate the progression of liver disease. Almost one third of patients have only modest or no improvement in the jaundice after hepatoportoenterostomy. Liver disease progression in these infants is rapid. Liver transplantation is the next line of therapy for the jaundiced child and for those with the sequelae of progressive liver disease.[28]

Choledochal Cyst

Generally, outcomes are excellent with a low operative mortality except in the smallest infants.[28] Late recurrence of cholangitis or stone formation may be found, requiring further operative therapy. Cholangiocarcinoma is extremely rare in those treated with cyst excision.[24]

LIVER TRANSPLANTATION

Biliary atresia is the most common indication for liver transplantation in children.[5] Most children with biliary atresia require transplantation at some time in their lives due to the progression of liver disease. Transplantation may be required in infancy because of the inability to obtain bile drainage with hepatoportoenterostomy or at the time of initial diagnosis if end-stage liver disease is present. Indications for transplantation are persistent cholangitis, gastrointestinal bleeding from esophageal varices, uncontrolled ascites, and declining synthetic function. Most challenging for the child facing liver transplantation is the inadequacy of the donor organ pool. Segmental transplantation from cadaveric or live donors

can meet this need but is neither universally practiced nor possible without the cooperation of adult transplant surgeons. Numerous ideal adult donor organs are not split (i.e., separated) into two useable donor grafts suitable for both a child and an adult. Deaths while on the waiting list may be as high as 10% in the youngest age group. Liver transplantation, whether prior to or after hepatoportoenterostomy, is straightforward, although technically challenging. Biliary drainage is by choledochojejunostomy to a Roux-en-Y limb of jejunum. Hepatic artery and portal vein anastomosis are facilitated by operating loupes or microscope. Patient and graft survival rates are excellent. More than 90% of children are alive at 1 year, and of those, most are alive at 10 years.[29]

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Chapter

107

Cystic Disorders of the Bile Ducts

Tadahiro Takada · Hisami Ando

CLASSIFICATION OF CYSTIC DISORDERS OF THE BILE DUCTS

In 1959, Alonso-Lej[1] first classified extrahepatic bile duct cysts into the following three types: type I is congenital cystic dilation of the common bile duct (choledochal cyst) where the intrahepatic tree is usually normal; type II is congenital diverticulum of the common bile duct and is extremely rare; type III is choledochocele, a cystic dilation of the distal segment of the common bile duct protruding into the duodenal lumen. Alonso-Lej's classification, however, did not include intrahepatic bile duct cysts or pancreaticobiliary maljunction, the abnormal union between the pancreatic and common bile duct. Todani[2,3] refined the classification of bile duct cysts into five types (see Fig. 106–2) and included the concept of pancreaticobiliary maljunction. Type IV-A is a choledochal cyst complicated with intrahepatic duct dilatation. Type V is single or multiple intrahepatic duct dilations. The frequencies of the types of bile duct cyst are type I, 73%; type IV-A, 24%; type III, 1.1%; type V, 1.1%; and type II, 0.4% of patients.[4]

CHOLEDOCHAL CYST (TYPES I AND IV-A)

General Description of Choledochal Cyst

The first authentic case of choledochal cyst was reported by Douglas in 1852.[5] Choledochal cysts have generally been considered a rarity, but recently the number of cases reported in the literature has steadily increased. The incidence of choledochal cysts in Western countries is 1 in 100,000 to 190,000 live births.[6] A marked prevalence has been seen in the Japanese population.[7] The preponderance of female patients is well known, with the female-to-male ratio being 3 or 4 to 1.[7,8] Choledochal cysts may be found at any age, but more than two thirds of cases are diagnosed in children younger than 10 years of age, and some cases are diagnosed prenatally by ultrasound examinations as early as the 15th week of gestation.[9]

Choledochal cysts are characterized by localized dilatation of the common bile duct and are associated with pancreaticobiliary maljunction (Fig. 107–1). Pancreaticobiliary maljunction, which was first noted by Kozumi and Kodama[10] in an autopsy case with choledochal cyst in 1916, is a congenital anomaly defined as a union of the pancreatic and biliary ducts. This initial observation did not attract attention for many years. However, since Babbitt[11] reported the anomaly in 1969, the concept has been accepted widely.[12] Pancreaticobiliary maljunction is thought to develop as a misarrangement of the embryonic connections in the pancreaticobiliary ductal system, with the terminal bile duct joined to the second branch of the ventral pancreas.[13] As a consequence, the pancreaticobiliary junction is located outside the duodenal wall, where the normal sphincter does not work (Fig. 107–2). This permits reflux of pancreatic juice into the biliary tree and destruction of the bile duct wall. Diagnostic criteria for pancreaticobiliary maljunction by radiography are that (1) the pancreatic duct and choledochus connect with an obviously long common channel or (2) the ducts unite in an apparently anomalous form.[14]

Choledochal cysts have been subdivided into those exhibiting cystic, cylindrical, or fusiform dilation of the common bile duct but with no difference in symptoms, signs, complications, or surgical care among the types. Many theories have been proposed to explain the origin of bile duct dilation and can be divided into two groups: (1) that due to an obstructive factor localized at the junction of the choledochus with the duodenum as an abnormal angularity or congenital stenosis of the terminal common bile duct and (2) that due to a condition originating in the common bile duct proper. However, the mechanism of bile duct dilation remains uncertain.

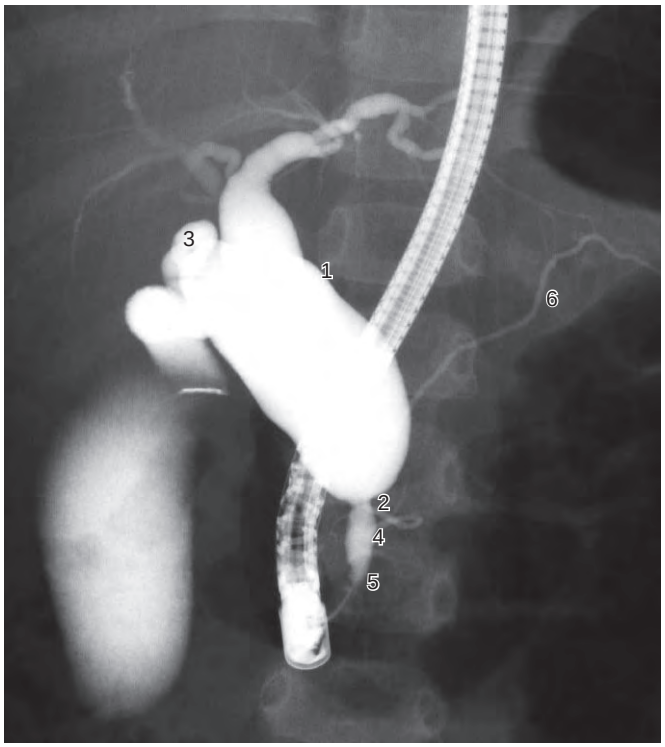


Figure 107–1. Endoscopic retrograde cholangiopancreatography provides characteristic images of choledochal cysts: (1) cystic dilatation confined to the common bile duct, (2) stenoses at the lower portion of the cyst, (3) dilated cystic duct, (4) abnormal junction of the pancreatic and bile ducts away from the papilla, (5) dilated common channel, and (6) normal dorsal pancreatic duct.

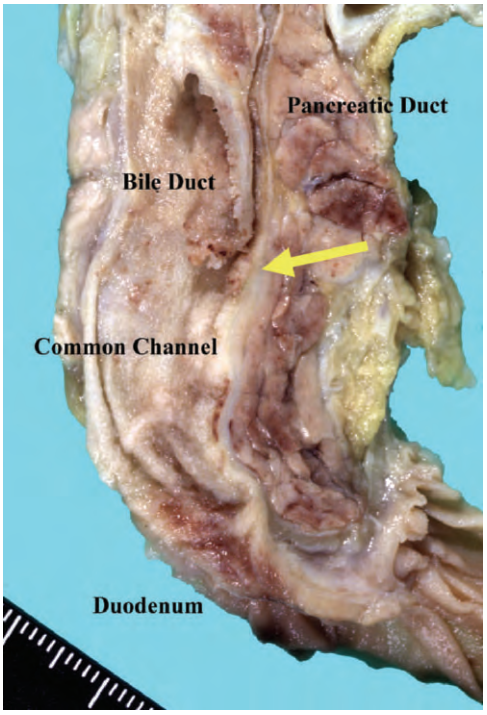


Figure 107–2. Gross dissection shows the long common channel and pancreaticobiliary junction *(arrow)* in the extraduodenal region.

The cyst wall is usually 1 to 2 mm thick and composed mainly of a fibromuscular layer. This layer is made up of dense connective tissue that is fibrocollagenous and sometimes contains smooth muscles and elastic elements. The epithelium is sometimes lacking, but columnar epithelium is identified by gently manipulating the cyst during surgery. On rare occasion, ectopic pancreatic tissue may be found in the cyst wall.

Symptoms and Signs

Patients with choledochal cysts including type IV-A, most often present with nonspecific symptoms, and half of the patients appear asymptomatic, particularly adults. In children, the major clinical symptoms are recurrent abdominal pain (81.8%) that may occur repeatedly for several days, nausea and vomiting (65.5%), mild jaundice (43.6%), an abdominal mass (29.0%), and fever (29.0%). The simultaneous occurrence of symptoms may be explained by the disturbance in bile and pancreatic secretory flow caused by a protein plug, which resolves spontaneously, in the common channel.[15] The classic triad of abdominal pain, jaundice, and abdominal mass occurs in less than 10% of patients.

Diagnosis

There are no specific laboratory tests to identify a choledochal cyst. Patients with choledochal cysts sometimes temporarily show abnormal data for serum bilirubin levels, serum amylase, and serum transaminases.

The noninvasiveness and accuracy of ultrasonography support its use as the initial investigative procedure. Ultrasonography shows the dilated common bile duct. Biliary sludge or stones within the cyst also can be identified in some cases. Focal thickening of the cyst wall raises the suspicion of carcinoma.

Endoscopic retrograde cholangiopancreatography (ERCP) gives an excellent visualization of the cyst, duct anatomy, and pancreaticobiliary maljunction. This examination is important to avoid intraoperative injury of the pancreatic duct and to recognize protein plugs within the common channel. However, ERCP is invasive and associated with a small risk of complications such as iatrogenic pancreatitis and must be performed under general anesthesia in children.

Magnetic resonance cholangiopancreatography (MRCP) provides a noninvasive method, one that is particularly advantageous in patients with postoperative choledochocystectomy and may be an efficacious alternative to ERCP.[16] However, MRCP can be hindered by the technical difficulty of children holding their breath.[17]

Computed tomography (CT) combined with intravenous cholangiography is useful for the demonstration of a cyst or postoperative evaluation for intrahepatic bile

ducts and bilioenteric anastomoses. Helical CT cholangiography is useful for identifying the anastomotic site of hepaticojejunostomy and hepatic ductal stenosis in postoperative follow-up.[17]

Complications

Cholelithiasis

Cholelithiasis is the most frequent complication associated with choledochal cysts. The prevalence of intracystic stones ranges from 11.2% in children to 41.1% in adults, with the stone site being cholecystlithiasis in 11.1%, choledocholithiasis in 20.6%, and hepatolithiasis in 6.5% of cases.[18]

Pancreatitis

The association of pancreatitis with choledochal cysts is well recognized. Clinical pancreatitis is present in nearly 30% of patients.[8] The pattern of pancreatitis can be acute, relapsing, or mild and may be caused by protein plug impaction within the common channel, where the plug acts like a ball-valve, producing a transient and abrupt elevation in the intraluminal pressure in both the bile and pancreatic ducts (Fig. 107–3).[15]

Spontaneous Perforation of the Bile Duct

Spontaneous perforation of the bile duct is a relatively rare complication of choledochal cysts and has been found in 26 (1.8%) of 1433 patients with choledochal cysts reported in the Japanese literature.[7] Most patients are children, with 60% being younger than 1 year of age. Perforation of the bile duct occurs as a small, punched-out hole, and although found mainly in the anterior aspect, can be found in any part of the cyst. In many cases, cholangiography reveals the presence of protein plugs.[19] Clinical symptoms and signs are abdominal distention, pain, nausea, vomiting, fever, jaundice, and light-colored stool. Preoperative laboratory investigations show elevated serum bilirubin levels, serum amylase, and transaminases. Preoperative diagnosis is based on the examination of samples of biliary fluid obtained by paracentesis and ultrasonic evidence of dilation of the common bile duct.

Carcinoma

The association of carcinoma with choledochal cysts was first reported in 1944.[20] Tumors may develop anywhere within the bile ducts, but more than one half occur within the cyst itself. The incidence of hepatobiliary malignancies associated with choledochal cysts ranges from 3.2% to 39.4%.[7,21,22] The incidence of cholangiocarcinoma with choledochal cysts is approximately 10 to 20 times greater than the incidence of bile duct carcinoma in the general population and is related to age.[23] The youngest reported patient with primary adenocarcinoma complicated with choledochal cyst was a 12-year-old girl.[24] The pancreaticobiliary maljunction results in free reflux of pancreatic juice into the bile duct and inflammatory changes in the epithelium of the bile duct and may be a key factor in the pathogenesis of malignant changes in cysts.[25]

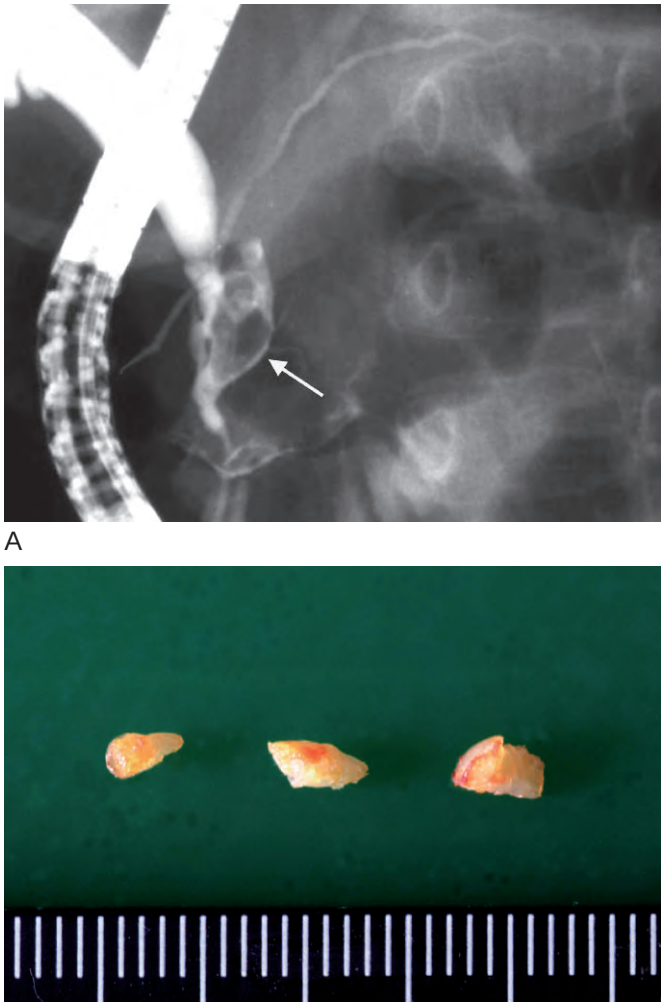


Figure 107–3. **A,** Protein plugs present at the common channel *(arrow).* **B,** The plugs consist mainly of protein, and most are soluble.

Surgical Management

General Treatment Before Operation

Historically, internal drainage by cyst-enterostomy was performed as the standard operation for choledochal cysts. However, internal drainage, particularly cystduodenostomy increased the frequency of cholangitis, biliary stones, and the risk of malignant changes in the retained cyst or gallbladder.[26,27] The mean age of the affected patients was approximately a decade younger than the mean age of patients who develop malignancy in an unoperated cyst.[26] The definitive treatment of choledochal cysts is to excise the whole extrahepatic bile duct and perform Roux-en-Y hepaticojejunostomy to separate

the bile and pancreatic ducts to prevent free reflux of pancreatic juice into the bile duct. This also removes the common site of the carcinoma.

In patients with biliary infection or jaundice, non peroral, drip infusion therapy and broad-spectrum antibiotics are recommended. In patients whose infection or jaundice fails to resolve with conservative therapy, percutaneous or endoscopic biliary drainage should be performed, and the infection or jaundice should be controlled prior to the definitive operation. In patients with spontaneous perforation of the bile duct, emergency treatment is to improve the patient's condition and treat the biliary peritonitis by means of T-tube drainage, followed by delayed surgery once the inflammation has subsided and after the anomalous anatomy has been clarified as safe for the procedure.[19]

Operative Technique

First, the gallbladder is mobilized. Intubated choledochoscopy is recommended to exclude retained ductal stones and to biopsy the abnormal epithelium to exclude malignancy. A thin tube is then intubated through the cystic duct for bile aspiration and intraoperative cholangiography, which is required to confirm the orientation of the pancreatic duct and check for protein plugs in the common channel or stenoses of the intrahepatic bile ducts. Dissection of the intrapancreatic cyst proceeds on the outer plane of the epicholedochal plexus, where only loose fibrous tissue exists, so as to leave the plexus with the cyst wall.[28] Further dissection should reveal that the narrow distal segment connecting the cyst and the main pancreatic duct is located not at the bottom of the cyst, but almost always to the right and ventral to the cyst (Fig. 107–4). Attention must be directed to the main pancreatic duct just ventral to the cyst. The distal narrow segment is ligated carefully with absorbable suture to prevent narrowing of the pancreatic duct. For patients with protein plugs stuck in the common channel, irrigation with saline solution through a thin tube placed in the common channel or removal using a blunt spoon through the narrow segment is recommended.[29]

Next, the cyst is mobilized proximally to the common hepatic duct. The hepatic duct near the bifurcation is transversely incised for confirmation of the stenoses at the orifice of the left and right hepatic ducts. If no stenosis is present at the bile ducts, the proximal cyst is transected and the cyst removed. In patients with Todani's type IV-A, stenoses are frequently found at the orifice of the left and right hepatic ducts (Fig. 107–5). There are two different types of stenosis: membranous and septal (Fig. 107–6).[30] When found, stenoses can be corrected by incising the hepatic ducts laterally to obtain a large anastomosis[31] or by resection.[32] Biliary reconstruction is accomplished by a 45-cm retrocolic Roux-en-Y hepaticojejunostomy.

Postoperative Complications

Early complications can include anastomotic leakage, postoperative bleeding, acute pancreatitis, ileus, gastrointestinal bleeding, and pancreatic fistula. Late complications are cholangitis, intrahepatic lithiasis, and pancreatic stones. Recurrent cholangitis from anastomotic strictures occurs in 10% to 25% of patients.[3,33] The incidence of hepatolithiasis, usually occurring in Todani's type IV-A, has been reported in as many as 2.7% to 10.7% of cases after long-term follow-up.[31,34] Although some cases do have a stricture of the anastomosis, in many other cases, especially type IV-A, calculi occur by residual stenoses near the confluence of the left and right hepatic duct.[32]

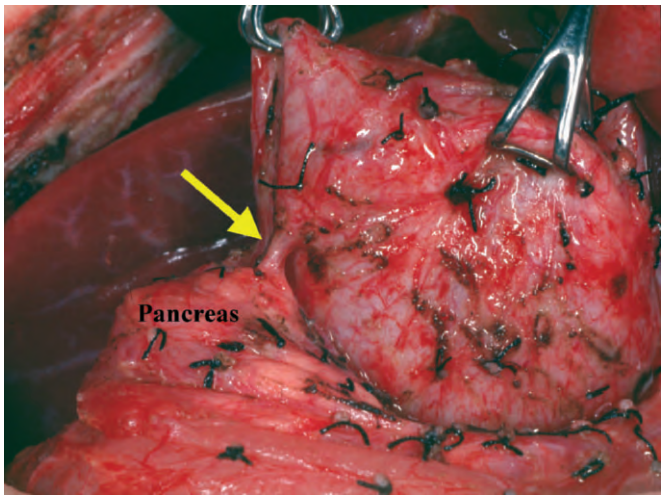


Figure 107–4. Operation for choledochal cyst shows the narrow segment *(arrow)* connecting the cyst and the main pancreatic duct, which is located not at the bottom of the cyst but almost always to the right and ventral to the cyst.

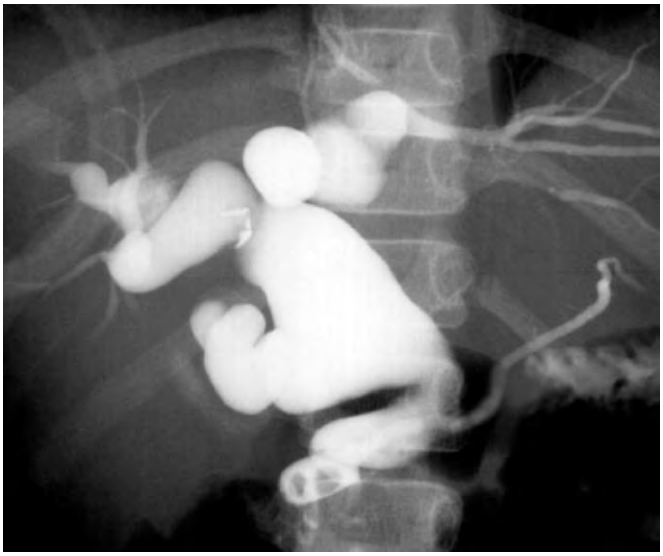
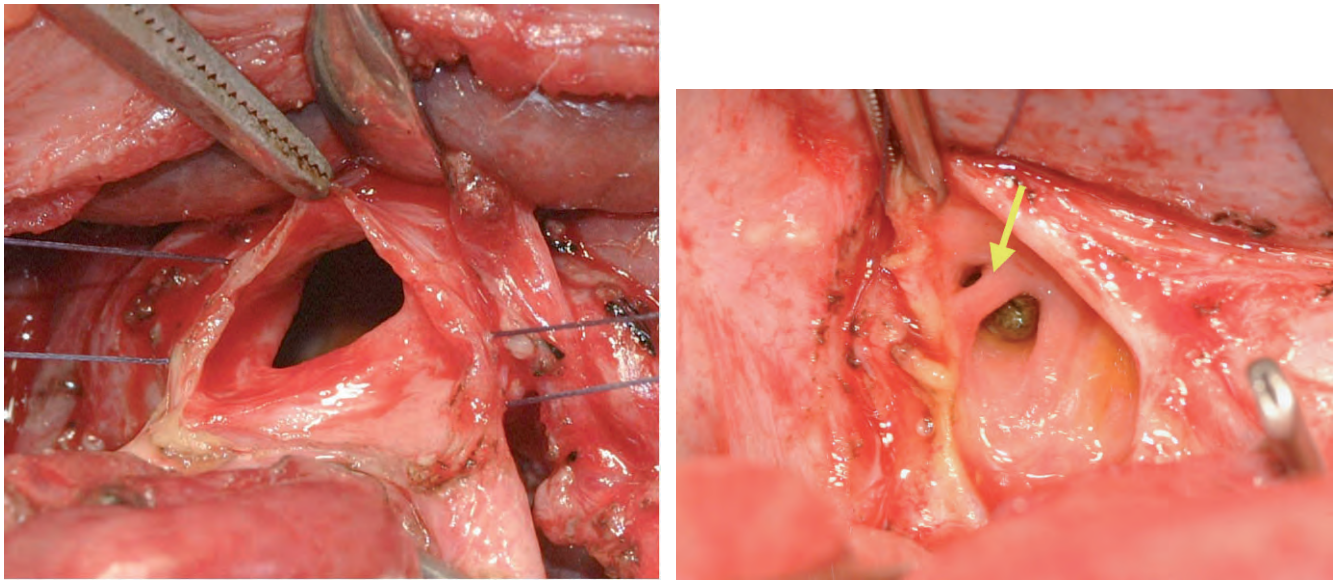


Figure 107–5. Endoscopic retrograde cholangiopancreatography shows the type IV-A choledochal cyst. Characteristics of this type are remarkable dilation of the intrahepatic bile ducts and stenoses at the hepatic hilum.



A B

Figure 107–6. Two types of stenoses at the right hepatic duct are shown. **A,** The membranous stenosis is characterized by the presence of a thin wall. **B,** The septal stenosis *(arrow)* is characterized by a slender column of tissue.

Cyst excision has been recognized as the definitive operation for choledochal cyst; however, reports of bile duct cancer after cyst excision are gradually increasing.[7,21,35] Watanabe et al.[21] reported 23 patients with bile duct cancer developing after cyst excision. Indeed malignant changes may occur before cyst excision or cyst enterostomy and may advance after cyst excision. Long-term follow-up is important, even after complete cyst excision.

DIVERTICULUM (TYPE II)

Type II diverticulum arises laterally from the wall of the common bile duct (Fig. 107–7). However, experience with this type is limited.[36] In this type, the weakness factor is limited to one small area of the side of the wall. The treatment of choice is simple cyst excision, a procedure that can be performed laparoscopically. Type II diverticulum is not usually associated with pancreaticobiliary maljunction.

CHOLEDOCHOCELE (TYPE III)

Choledochocele is a rare abnormality of cystic or diverticular dilation of the terminal intramural portion of the common bile duct, first described by Wheeler in 1940.[37] The term *choledochocele* was introduced by Wheeler, who saw the analogy with congenital ureterocele. The first classification of choledochocele was proposed by Scholz et al. in 1976[38] and has been classified by various authors according to this type. There are two different types of the internal cyst wall component. One is lined by duodenal mucosa and the other lined by bile duct mucosa. The former type suggests that choledochocele is a congenital

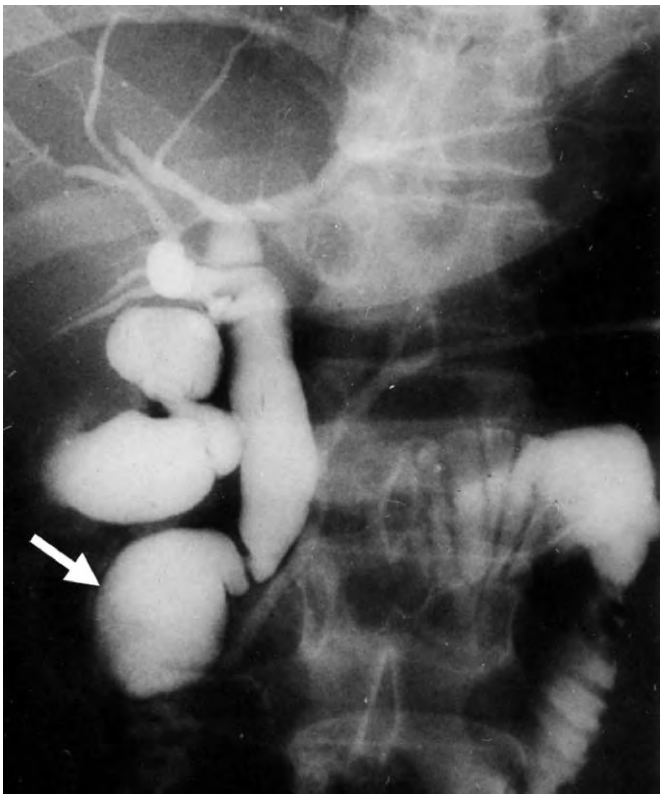


Figure 107–7. Endoscopic retrograde cholangiopancreatography shows type II biliary cyst, which is a saccular diverticulum of the common bile duct *(arrow).*

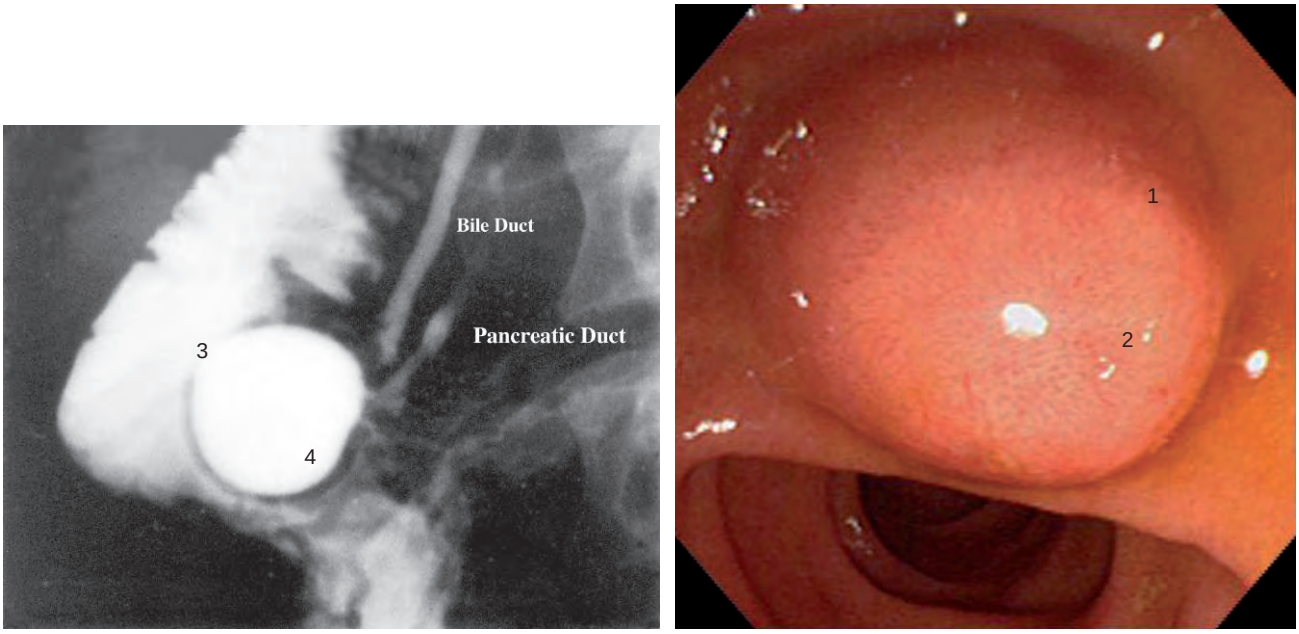


Figure 107–8. Endoscopic retrograde cholangiopancreatography **(A)** and endoscopy **(B)** shows characteristic images of choledochocele: (1) an intramural segment of the common bile duct protruding into the duodenum in continuation with an enlarged papilla with a spherical shape; (2) soft overlying mucosa with a smooth appearance; (3) ballooning of the papilla during contrast injection; and (4) a rather spherical, cystlike, contrast-filled structure in continuity with the terminal common bile duct.

duodenal duplication arising near the main duodenal papilla, which communicates with the common bile duct.[39] The latter type suggests a diverticular enlargement of the terminal portion of the common bile duct.[38] In the latter type, papillary stenosis or congenital or acquired dysfunction of the sphincter of Oddi may cause obstruction of bile flow, resulting in increased pressure within the distal bile duct, which could then evaginate into the duodenum.[40] However, the etiology remains unclear.

Choledochocele can be diagnosed by duodenoscopic or cholangiographic findings, with a cystic dilation of the distal segment of the common bile duct protruding into the duodenal lumen (Fig. 107–8).[41] However, the criterion does not specify the size of the cele. Despite the widely recognized view that other biliary cysts are truly congenital, some choledochoceles appear to be acquired. Some authors have stated that an arbitrary 1-cm dividing line may be used to differentiate between a choledochocele and a dilated common channel or normal variants.[42,43] Choledochocele usually shows a normal junction but is associated with pancreaticobiliary maljunction in rare cases. Patient age ranged from 1 to 89 years (median, 40 years), and there was no sex predominance.[39] Patients of choledochocele clinically present intermittent episodes of upper abdominal pain accompanied by nausea and vomiting, obstructive jaundice, cholangitis, or recurrent acute pancreatitis.[38,39,43] Associated lithiasis occurs in about 20% of cases, but the risk of malignant changes is extremely low.[39]

Although surgical excision of the duodenal luminal portion of the cyst wall has been performed, endoscopic papillotomy has been increasingly chosen as treatment for this type. Asymptomatic choledochoceles, incidentally identified during ERCP examinations, are probably best left alone and observed.[39]

CAROLI'S DISEASE (TYPE V)

In 1958, Caroli described a disease entity characterized by (1) segmental cystic dilation of the intrahepatic ducts; (2) increased incidence of biliary lithiasis, cholangitis, and abscesses; (3) absence of cirrhosis and portal hypertension; and (4) association of renal tubular ectasia or similar renal cystic disease. Still later, Caroli[44] recognized two entities: a "simple" type and a "periportal fibrosis" type. The so-called pure type, originally described in 1958, is a rare congenital abnormality, and the more common type is associated with congenital hepatic fibrosis, which is present in childhood.[45] However, as a term, *Caroli's disease* has been applied broadly to describe some patients with segmentally ectatic appearance of the intrahepatic bile ducts, identical to that seen in intrahepatic involvement of the choledochal cyst.

Caroli's disease is generally considered autosomal recessive, but there are some cases of autosomal dominant inheritance.[46] The male-to-female ratio is 3 to 2, and age at diagnosis ranges between 1 and 60 years (median, 25 years).[46] Symptoms include cholangitis (64%), portal hypertension (22%), and abdominal pain in the right upper quadrant (18%).[46,47] The dilated ducts connect with the main duct and are liable to become infected and contain stones.

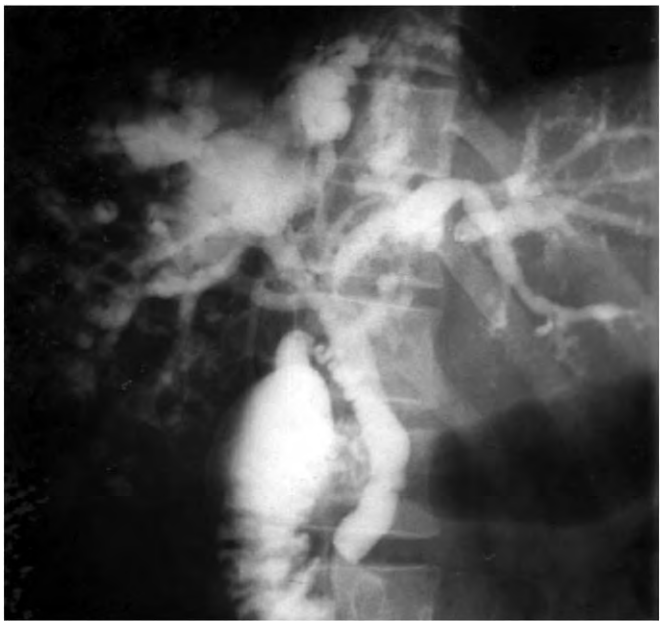


Figure 107–9. Endoscopic retrograde cholangiopancreatography shows Caroli's disease, with multiple communicating sacculi of the intrahepatic biliary tree. The sacculi are large and are distributed within the right lobe.

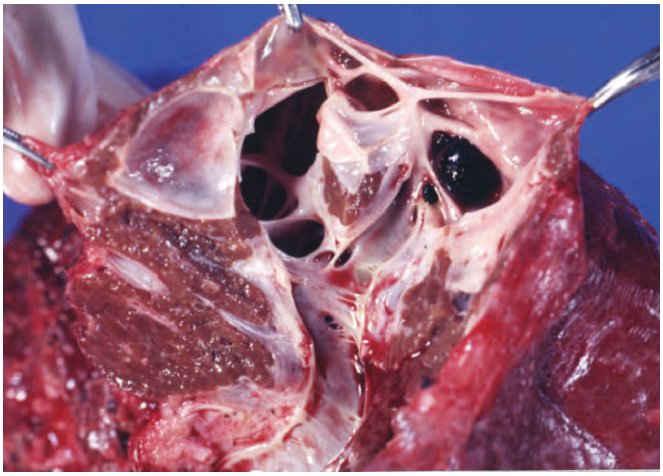


Figure 107–10. Gross pathology sections of the liver in Caroli's disease show multiple saccular dilations of the intrahepatic bile ducts and black-pigmented calcium bilirubinate stones. Septum-like fibrovascular bundles are seen on the walls of the cut sacculi.

Caroli's disease can be diagnosed by cholangiographic findings of a multiple saccular appearance of intrahepatic bile ducts (Fig. 107–9).[48] Sonography and CT have been shown to be useful in detecting saccular dilatation of the intrahepatic bile ducts. The sacculi may vary greatly in size and distribution within the liver.[45] CT scans of the liver show tiny dots with strong contrast enhancement within the dilated intrahepatic bile ducts or the "central dot sign," which corresponds to intraluminal portal radicles surrounded by the dilated intrahepatic bile ducts (Fig. 107–10).[45,49]

The long-term prognosis for patients with Caroli's disease is quite poor, with a marked predisposition to septicemia, liver abscess, resultant hepatic failure, or portal hypertension.[47] Cholangiocarcinoma has been reported in about 7% of patients.[47,48] The therapeutic management of Caroli's disease is difficult, whether using conservative medical management or surgical interventions. Liver transplantation should be considered if the patient's condition deteriorates.[50]

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Chapter

108

Primary Sclerosing Cholangitis

Konstantinos N. Lazaridis · Gregory J. Gores

Primary sclerosing cholangitis (PSC) is an idiopathic, chronic, cholestatic liver disease characterized by diffuse inflammation and fibrosis of the bile ducts.[1,2] PSC is ultimately progressive, leading to obliteration of the biliary tree, and subsequent to biliary cirrhosis.[1,2] The disease has been diagnosed more frequently in the past 3 decades because of routine liver biochemistry testing in clinical practice and widespread availability of endoscopic retrograde cholangiopancreatography (ERCP). To date, the etiology of PSC remains unknown and effective medical therapy is not currently available. Patients with PSC have shortened life expectancy. Orthotopic liver transplantation (OLT) extends the life of patients with advanced-stage PSC.

EPIDEMIOLOGY

PSC affects young males more than females.[1,2] The mean age of diagnosis is the late 30s. In the United States, population-based studies have estimated an age-adjusted incidence for PSC to be 1.25 and 0.54 per 100,000 men and women, respectively.[3] Moreover, the calculated prevalence of PSC was 20.9 per 100,000 men and 6.3 per 100,000 women.[3] PSC is strongly associated with inflammatory bowel disease (IBD). Of interest, about 75% of patients of northern European–origin with PSC suffer from IBD (chronic ulcerative colitis [CUC] being more common [~90%] than Crohn's disease).[2]

PSC is associated with lack of smoking. In one study, the incidence of current smoking was 19% in patients with PSC compared with 38% of controls.[4] In another study, 4.9% of PSC patients were reported to smoke compared with 26.1% of controls. The odds of having PSC in current smokers or former and current smokers compared with never-smokers were 0.13 and 0.41, respectively, regardless of the presence or absence of IBD.[5] Studies have also reported that prior appendectomy may delay the onset of PSC but does not affect either the prevalence or severity of the latter.[6]

CLINICAL PRESENTATION

The clinical presentation of PSC is heterogeneous and varies widely depending on the disease stage at the time of diagnosis. Most commonly, asymptomatic individuals come to medical attention because of abnormal liver biochemistries following routine screening. Symptomatic patients present with symptoms and signs of cholestasis and complications of end-stage liver disease. The symptoms may include fatigue, pruritus, right upper quadrant pain, weight loss, and manifestations related to portal hypertension (i.e., ascites, gastrointestinal bleed from esophageal varices). Symptoms of bacterial cholangitis are less common, except if the patient has dominant biliary strictures and/or biliary stones. The physical examination of symptomatic patients may reveal jaundice, hepatomegaly, splenomegaly, skin excoriations, ascites, and peripheral edema.

A frequent clinical scenario is a patient with CUC who presents with a cholestatic pattern of liver enzymes. PSC can affect any age group, including children.[7] Children may present with an overlap syndrome of PSC and autoimmune hepatitis (AIH), which can be as high as 35% according to a recent study.[8]

DIAGNOSIS

The diagnosis of PSC is made based on (1) characteristic cholangiographic abnormalities of the biliary tree; (2) clinical and biochemical evidence of ductal cholestasis (i.e., elevated serum alkaline phosphatase of at least 6 months' duration); and (3) exclusion of secondary sclerosing cholangitis (Box 108–1). Currently, the most frequent clinical presentation is an asymptomatic patient with persistently increased levels of alkaline phosphatase noted on routine serum biochemical testing.

Liver biopsy is not always required to make the diagnosis. In a study of 79 patients with established PSC

Box 108–1 Causes of Secondary Sclerosing Cholangitis

- Choledocholithiasis (in the absence of PSC)
- Biliary trauma/ischemia
- Chemicals/drugs (i.e., 5-fluorouracil)
- AIDS-associated cholangiopathy
- Bile duct neoplasm (in the absence of PSC)
- Congenital bile duct abnormalities (i.e., Caroli's disease)
- Idiopathic adulthood ductopenia
- Amyloidosis

AIDS, acquired immunodeficiency syndrome; PSC, primary sclerosing cholangitis.

Box 108–2 Differential Diagnosis of Primary Sclerosing Cholangitis

- Primary biliary cirrhosis
- Drug-induced cholestasis
- Cholestasis associated with autoimmune hepatitis or alcoholic liver disease
- Bile duct carcinoma (i.e., cholangiocarcinoma)
- Extrahepatic obstruction
- Secondary sclerosing cholangitis
- Histiocytosis X
- Hyper-IgM syndrome
- Autoimmune pancreatitis with involvement of bile ducts

by cholangiography, liver biopsy did not affect the management in most patients.[9] The role of liver biopsy in PSC is to (1) exclude other causes of cholestatic liver disease; (2) diagnose small duct PSC; and (3) define the PSC stage, which may have prognostic value. Small duct PSC is a variant of PSC that accounts for approximately 5% of disease occurrences.[10] The patient presents with a cholestatic pattern of liver enzymes but normal cholangiography and liver biopsy reveals evidence of PSC. Small duct PSC has better long-term prognosis compared with classic PSC. However, a portion of patients with small duct PSC can progress to classic PSC over time.[10]

In most patients, the history, clinical presentation, serum biochemical profile, and cholangiography distinguish PSC from other causes of chronic cholestatic liver disease. Box 108–2 lists the differential diagnosis of PSC.

BIOCHEMICAL AND SEROLOGIC ABNORMALITIES

In patients with PSC, serum alkaline phosphatase level usually is elevated three or four times the upper limit of normal. A normal alkaline phosphatase, however, does not rule out PSC since normal levels have been reported in patients with cholangiographic evidence of disease.[11] PSC patients often have mildly increased aminotransferases (<3 times the upper limit of normal).[1,2,12]

Serum bilirubin is usually normal. Bilirubin levels markedly rise as PSC progresses to end-stage liver disease (i.e., biliary cirrhosis). An abrupt, sustained rise of bilirubin may herald the presence of dominant biliary stricture and bile duct stone or the development of cholangiocarcinoma. Serum copper and ceruloplasmin levels as well as hepatic and urinary copper values are often abnormal. The copper increase is because of prolonged cholestasis. Of note, hepatic copper levels in PSC can be elevated to the same range seen in Wilson's disease and primary biliary cirrhosis (PBC).[12]

None of the autoantibodies detected in PSC is pathognomonic. The prevalence of antineutrophil cytoplasmic antibodies, anticardiolipin antibodies, and antinuclear antibodies is 84%, 66%, and 53%, respectively.[13] Autoantibody testing may be helpful to identify those PSC patients with concurrent AIH. However, antibody titers are not important in following PSC activity. Antimitochondrial and antismooth muscle antibodies are rare in patients with PSC. Approximately one fourth of patients have hypergammaglobulinemia with elevated immunoglobulin M levels.[1,2,12]

IMAGING STUDIES

To diagnose a patient with PSC, cholangiography is required. Among imaging modalities, ERCP is the gold standard approach to evaluate the bile ducts. The classic cholangiographic findings of PSC include multifocal stricturing and beading throughout the biliary tree (Fig. 108–1). Strictures are often diffusely distributed with intervening segments of dilated ducts (i.e., ectasia). The cholangiographic findings usually involve both the intrahepatic and extrahepatic bile ducts. Strictures can vary from 1 to 2 mm to several centimeters in length. About 30% to 40% of PSC patients may have mural irregularities producing a shaggy appearance; these lesions may vary from a fine brush border to frank nodularity.[14] Pseudodiverticula (i.e., tiny diverticulum-like outpouchings) of the extrahepatic bile ducts are nearly pathognomonic for PSC.[14] In approximately 20% of PSC patients, only the intrahepatic and proximal extrahepatic bile ducts are involved, and as many as 15% of PSC patients have involvement of the gallbladder and cystic duct. Moreover, approximately 5% of patients have small duct PSC (i.e., normal cholangiogram but liver disease detectable on biochemical testing and histology).[10] ERCP should be performed in all patients with suspicion for PSC to define the extent of disease, identify benign dominant strictures for endoscopic therapy, and allow brushings for cytology studies to exclude cholangiocarcinoma.

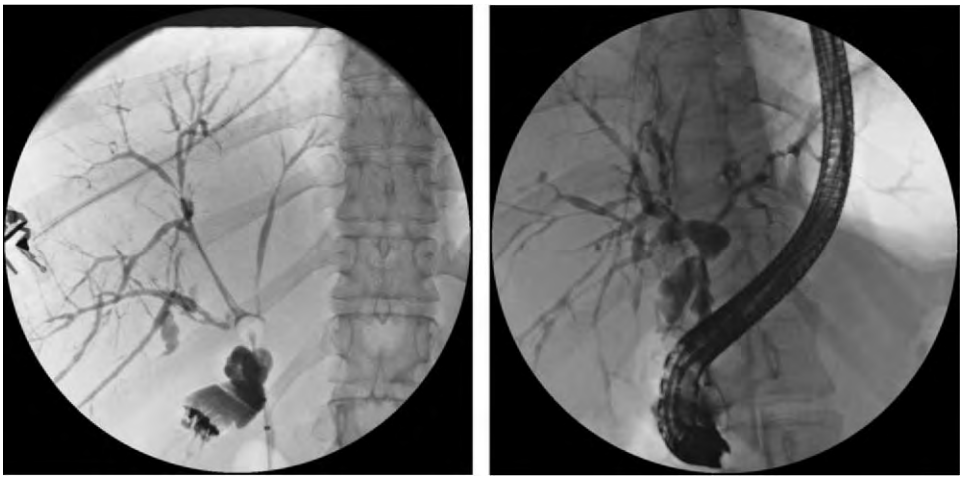

Figure 108–1. Endoscopic retrograde cholangiopancreatography images depicting typical cholangiographic findings of primary sclerosing cholangitis.

Magnetic resonance cholangiography (MRC) has shown promise as a noninvasive substitute of ERCP for the diagnosis of PSC. In a recent study of 73 patients with clinically suspected biliary disease, the sensitivity and specificity of MRC for diagnosing PSC were 82% and 98%, respectively.[15] These authors reported that MRC had diagnostic accuracy comparable to ERCP leading to reduced cost when used as the initial approach to diagnose PSC. In another study, MRC was better than ERCP to identify peripheral biliary strictures.[16] In PSC patients, MRC could be used as a noninvasive imaging method for the detection of cholangiocarcinoma. In the future, MRC will likely replace diagnostic ERCP. However, at the present ERCP is more sensitive than MRC and permits biliary cytology and biopsy studies as well as therapeutic intervention (i.e., biliary dilation/stenting).

Currently, percutaneous cholangiography (PTC) is used less frequently to image the bile ducts in patients with suspected PSC. PTC is an alternative approach to access the biliary tree when ERCP is not technically possible. Abdominal ultrasonography is valuable to evaluate the bile ducts for dilation and/or stones, and liver parenchyma for cirrhosis. Computed tomography (CT) can reveal morphologic features of liver cirrhosis. Atrophy of the left lateral segments and hypertrophy of the caudate lobe may differentiate cirrhosis associated with PSC from that seen in other causes of chronic liver disease.[17,18] CT can also complement cholangiography in evaluating for malignancy given its ability to detect peripheral, intrahepatic cholangiocarcinoma and metastatic spread within the hepatic parenchyma or the abdomen.[19] Perihilar lymphadenopathy is common in PSC, and this finding alone cannot be taken as evidence of malignancy or metastasis.

PATHOLOGY

PSC can affect any portion of the biliary tree. Rarely, PSC may be limited to the small intrahepatic ducts (i.e., small duct PSC).[15] Liver biopsy specimens from PSC patients show portal tract inflammation and sclerosis. Affected bile ducts are surrounded by a cuff of lightly inflamed sheets of fibrous tissue leading to fibrotic layers and may form the nearly pathognomonic "onion skin" appearance. Afflicted biliary ducts eventually become atrophied and are replaced by rounded cords of scars.

In addition to PSC, other causes of fibro-obliterative cholangitis include PBC, mechanical obstruction of large bile ducts, ductopenic rejection following liver transplantation, and biliary damage after intra-arterial infusion of 5-fluorouracil. Involvement of both the large intrahepatic and extrahepatic ducts usually distinguishes PSC from PBC. Granulomas, once thought to be associated with PBC, may be seen in approximately 4% of biopsies from PSC patients.

Canalicular cholestasis is nonspecific to PSC and can occur with any cause of biliary obstruction. As PSC progresses, however, the histopathologic changes of chronic cholestasis spill into the hepatic parenchyma.[20] To this end, the liver histology PSC grading system is based on the stage of parenchymal changes. For example, in stage 1 (portal stage), there is edema, inflammation, and ductal proliferation. In stage 2 (periportal stage), periportal fibrosis and inflammation are noted. Stage 3 (septal stage) is defined by septal fibrosis or bridging necrosis. Finally, stage 4 (cirrhotic stage) is characterized by biliary cirrhosis (Table 108–1). Unfortunately, histologic changes can be markedly varied from segment to segment of the liver at any given point in time. Histologic staging was formerly used as an independent predictor of PSC natural history. However, in the revised Mayo PSC risk survival model, histologic stage is not required.[21]

ETIOPATHOGENESIS

At present, the exact pathogenesis of PSC is elusive. The consensus working hypothesis postulates that PSC develops in a genetically predisposed individual following exposure(s) to a biliary insult that causes persistent immune-mediated inflammation leading over time to progressive destruction of bile ducts, cholestasis, and cirrhosis. Current proposed etiologies encompass both genetic elements and environmental exposures, thus

Table 108–1 Primary Sclerosing Cholangitis Staging

Stage	Description
Portal (stage 1)	Portal edema, inflammation, ductal proliferation; abnormalities do not extend beyond the limiting plate
Periportal (stage 2)	Periportal fibrosis, inflammation with or without ductular proliferation; piecemeal necrosis may be present
Septal (stage 3)	Septal fibrosis or bridging necrosis can be identified
Cirrhotic (stage 4)	Biliary cirrhosis

underscoring the host-environment interaction in the development of PSC. Moreover, it is now widely accepted that biliary epithelia (i.e., the cells that line the bile ducts) are the target cells of PSC.

The strong association of PSC with IBD has drawn much attention to the potential role of the inflamed colon in causing the former. The hypothesis suggests that inflammation of the colon may increase permeability to various intraluminal products (i.e., bacteria, toxins) that ultimately lead to liver disease. Bacteria have been considered but not conclusively shown to have a pathogenetic role in PSC development.[22,23]

Using animal models of PSC, researchers demonstrated that bacterial chemotactic peptides can lead to portal inflammation and histologic changes of PSC.[24,25] Nevertheless, in a pilot study of pentoxifylline, a tumor necrosis factor (TNF) inhibitor, no beneficial effect on symptoms or liver biochemistry was reported in PSC patients.[26] Moreover, PSC can develop in approximately 25% of patients who have no evidence of IBD despite aggressive endoscopic screening. The lack of association between the seriousness of colonic disease and the likelihood of development and severity of PSC also strengthens the argument that CUC may not directly cause PSC. Finally, failure of proctocolectomy to modify the natural history of PSC disputes against a direct causative role of CUC in PSC.[27] Viral agents and other microorganisms have been postulated as instigating the development of PSC. At present, there is no strong evidence to implicate microorganisms as a cause of PSC.

On the other hand, genetic variation likely contributes to PSC predisposition. To this extent, reports of affected PSC families support the notion of genetic inclination to develop the disease.[28,29] Moreover, various HLA associations have been reported with PSC. The HLA B8, DR3, DR2, and haplotype A1, B8, and DR3 are associated with the disease.[30-33] Additional associations of PSC with DRB3*0101, DRB1*0301, DQA1*0501, DQB1*0201 and DRB1*1301, DQA1*0103 and DQB1*0603 have been reported.[33] Polymorphisms in the TNF-α receptor have been described as a possible genetic link to PSC. Possession of the TNF2 allele, a G to A substitution, at position -308 in the TNF-α gene, has been associated with susceptibility to PSC.[34] In another study, a functional variant of stromelysin (i.e., matrix metalloproteinase 3) may also influence PSC susceptibility and disease progression.[35] Moreover, variations in the *MICA* gene (major histocompatibility complex class I related [*MIC*] gene family) have a role in PSC predisposition. Independent of other HLA haplotypes, the MICA 002 allele appears to significantly reduce the risk of PSC, whereas the MICA 008 allele increases the risk of developing PSC.[36] Recently, the CCR5-δ-32 mutation, characterized by a 32-base pair deletion in the *CCR5* gene of T cells, has been associated with susceptibility to PSC development and severity.[37]

Immune-mediated damage of cholangiocytes is likely to contribute to PSC pathogenesis. Theoretically, certain HLA molecules and haplotypes may contribute to this event by eliciting an immune response against antigenic epitopes present on biliary epithelia. Enhanced expression of MCH class II antigens (i.e., HLA DR) on cholangiocytes in early-stage PSC has drawn suspicion toward their role in disease pathogenesis. However, aberrant expression of HLA DR is apparent in PBC and extrahepatic biliary obstruction, suggesting that this observation is an epiphenomenon rather an implicit PSC cause.[38,39] Other proposed mechanisms of immunomediated pathogenesis in PSC include (1) diminished clearance of circulating immune complexes; (2) complement activation; and (3) sharing of specific epitope(s) between human colonic and biliary epithelial cells.[40-42] Interactions of intracellular adhesion molecule (ICAM)-1 present on biliary epithelia with its cognate ligand on T cells (i.e., leukocyte function-associated antigen [LFA]-1) may be important in PSC development. In fact, genetic polymorphisms of ICAM-1 have been implicated in susceptibility to PSC. For example, homozygote status of the E469E allele for ICAM-1 has been associated with protection against PSC.[43] Enhanced expression of ICAM-1 on proliferating cholangiocytes and increased serum levels of ICAM-1 have been reported in PSC patients.

ASSOCIATED DISEASES

PSC is strongly associated with IBD most commonly CUC. A minority of patients with PSC may also present or develop features of AIH. In addition, a variety of diseases have been reported to weakly associate with PSC (Box 108–3). Because most of these associations represent case reports, their significance is questionable.

Inflammatory Bowel Disease

IBD is seen in approximately 70% of patients with PSC.[1,2,12] CUC accounts for 85% to 90% of those patients and Crohn's disease is responsible for the remaining.[44] Patients with PSC and Crohn's disease may have milder hepatic disease than patients with PSC and CUC.[45] Usually, the diagnosis of IBD is established about 8 to 10

Box 108–3 Diseases Associated with Primary Sclerosing Cholangitis

- Chronic ulcerative colitis
- Crohn's disease
- Autoimmune hepatitis
- Chronic pancreatitis
- Sicca syndrome
- Hypereosinophilia
- Riedel's thyroiditis
- Celiac disease
- Autoimmune hemolytic anemia
- Sarcoidosis
- Glomerulonephritis
- Retroperitoneal fibrosis
- Systemic sclerosis

years before the diagnosis of PSC, although cases of IBD occurring years after the diagnosis of PSC have also been reported.[44] Conventional treatment of IBD does not alter the course of PSC, and severity of the former does not affect the disease seriousness of the latter. Proctocolectomy, the most aggressive treatment for CUC, has had no effect on the natural history of PSC.[27]

Colitis is usually milder in patients with both CUC and PSC compared with CUC patients alone. However, PSC is an indepedent risk factor in the development of colorectal dysplasia and carcinoma in the setting of CUC. In a Swedish study, patients with both CUC and PSC have an increased risk of colonic dysplasia compared with patients only suffering from CUC.[46] In fact, the absolute cumulative risk of developing colorectal dysplasia/carcinoma in patients with both PSC and CUC was 9%, 31%, and 50% after 10, 20, and 25 years of PSC duration, respectively.[46] On the contrary, patients with CUC alone had 2%, 5%, and 10% absolute cumulative risk to develop colorectal dysplasia/carcinoma following 10, 20, and 25 years' history of CUC, respectively.[46] In a U.S. study, patients with both PSC and CUC were five times more likely to develop colonic dysplasia compared to patients with CUC alone.[47] In another study, patients with concurrent CUC and PSC had 16% cumulative risk of colon cancer 10 years after the diagnosis of the liver disease.[48] Nonetheless, it remains unknown whether these observations reflect the fact that patients with PSC have milder pancolonic disease that remained undetected for a longer period. Conversely, a retrospective case control study found similar prevalence of PSC in patients with both CUC and colorectal carcinoma compared with those who had CUC but no neoplasia (carcinoma or dysplasia).[49] Because in patients with both PSC and CUC systematic colon screening and early detection improves survival, annual colonoscopy with surveillance biopsies is recommended. Yearly surveillance by colonoscopy is also suggested for PSC patients without evidence of IBD.

PSC patients with CUC have increased risk of colorectal dysplasia and neoplasia after OLT.[50] The increased neoplastic potential is of concern in PSC patients following OLT, particularly because of the required life-long immunosuppression. Thus, in PSC patients who undergo OLT, annual colonoscopy with surveillance biopsies is recommended.

Autoimmune Hepatitis

PSC can coexist with AIH.[51] These patients typically fulfill definite criteria for both diseases and have elevated serum alkaline phosphatase and aminotransferases, increased IgG, and antinuclear and/or antismooth muscle antibodies. Liver biopsy shows moderate to severe interface hepatitis with or without biliary destruction. Aminotransferase levels are higher than what one would expect for classic PSC. Patients with overlap syndrome may show improvement of AIH with immunosuppressive therapy. Indeed, patients who present with AIH and do not respond entirely to immunosuppressant therapy should be suspected of having concurrent PSC.

NATURAL HISTORY

PSC is an insidious and progressive disease that ultimately leads to end-stage liver disease. Patients with early-stage PSC are virtually asymptomatic. Advanced-stage PSC is described by chronic cholestasis and complications of end-stage liver disease. The median survival from the time of diagnosis is about 12 years if OLT is not available. Asymptomatic PSC patients have decreased survival compared with matched controls. In a study of 45 PSC patients who were asymptomatic at the time of diagnosis, 34 patients (76%) progressed and 14 patients (31%) developed hepatic failure that resulted in death or referral for OLT (mean follow-up of 6.25 years).[52]

The progressive natural history and associated complications of PSC warrant close medical management. To this end, prognostic PSC models have been developed to predict survival and identify the ideal timing for OLT. The revised Mayo PSC natural history model uses five independent, reproducible parameters to estimate the survival of PSC patients. These variables include age, bilirubin, albumin, aspartate aminotransferase, and history of variceal bleeding.[21]

Small duct PSC has a more favorable long-term prognosis compared with classic PSC. Nevertheless, small duct PSC can progress to classic PSC in a small number of patients.[10] Children with PSC have also progressive disease, with a median survival of 12.7 years despite medical therapy.[8]

COMPLICATIONS

Complications of PSC are divided into two categories: (1) PSC associated and (2) non-PSC associated. Complications of the first group include cholelithiasis, choledo-

cholithiasis, gallbladder polyps, dominant biliary strictures with or without recurrent bacterial cholangitis, cholangiocarcinoma, and peristomal varices in PSC patients who had undergone proctocolectomy and ileostomy for CUC. Complications of the second group are secondary to chronic cholestasis (i.e., pruritus, steatorrhea, fat-soluble vitamin deficiency, hepatic osteodystrophy) and to the development of end-stage liver disease (i.e., cirrhosis, portal hypertension, ascites).

PSC-ASSOCIATED COMPLICATIONS

Cholelithiasis, Choledocholithiasis, and Gallbladder Polyps

From 25% to 30% of PSC patients have or will develop calculi in the gallbladder or bile ducts during the course of the disease. In a study of 121 patients with PSC, 32 patients (26%) had gallstones, half of which were pigment stones and 18 patients (15%) had PSC involving the gallbladder.[53] PSC patients can also present with an unusual, but not specific, form of acalculous cholecystitis characterized by a diffuse lymphoplasmacytic infiltrate.[54] Gallbladder polyps in patients with PSC require special consideration. In a recent study of 102 PSC patients, 14 patients (13.7%) had an intraluminal gallbladder mass, of which 8 lesions (57%) were found to be adenocarcinomas.[55] Therefore, in patients with PSC the presence of gallbladder polyps is an indication for cholecystectomy.

Intrahepatic calculi are present in approximately 8% of PSC patients.[56] Biliary calculi can serve as a nidus for the development of bacterial cholangitis in these patients, although the latter is less common in the absence of dominant biliary strictures or prior bile duct surgery. Following diagnosis of bacterial cholangitis, ERCP is required to remove possible bile duct calculi and/or to dilate biliary strictures allowing satisfactory bile drainage. Nevertheless, bacterial cholangitis can occur in PSC patients after ERCP. To prevent this complication, we suggest prophylactic coverage with intravenous antibiotics prior to and oral ciprofloxacin for 10 days following ERCP.

Dominant Biliary Strictures

Up to 45% of PSC patients have or will develop dominant biliary strictures. These lesions present with increase of jaundice, pruritus, right upper quadrant pain, and bacterial cholangitis. ERCP is required to assess the biliary strictures, rule out the possibility of cholangiocarcinoma, and allow therapeutic dilation with or without biliary stenting to relieve cholestasis. A prospective study of 12 symptomatic PSC patients with major ductal strictures treated with repeated balloon dilation and nasobiliary catheter perfusion showed sustained improvement in 8 patients following an average of three treatment sessions (mean follow-up of 23 months).[57] A retrospective study of 25 PSC patients with symptomatic dominant strictures reported that endoscopic stenting was technically successful in 21 patients (84%) and was associated with significant improvement of liver tests. Moreover, 12 (57%) of the 21 PSC patients remained asymptomatic with stable liver biochemistries, while 4 patients (19%) had clinical and biochemical relapse over a median follow-up of 29 months. All 4 patients with relapse did respond positively to additional endoscopic therapy.[58] The same authors reported 16 symptomatic PSC patients treated with short-term biliary stent placement (median duration of 9 days); 13 patients (81%) remained symptom-free and without biochemical evidence of cholestasis after a median follow-up of 19 months.[59] Despite these findings, it is uncertain if dominant biliary strictures are directly accountable for cholestasis in PSC patients. In a recent retrospective study of 125 patients with PSC, alkaline phosphatase and bilirubin levels were not significantly different between the 56 patients with and the 69 patients without dominant strictures 2 and 12 months after cholangiography.[60]

Cholangiocarcinoma

The most threatening complication of PSC is the development of cholangiocarcinoma, which occurs in 8% to 15% of PSC patients.[2,12] In a recent study of 161 PSC patients, approximately 7% developed cholangiocarcinoma during a mean follow-up of 11.5 years.[61] In patients with PSC the estimated annual incidence of cholangiocarcinoma is about 1%.[62] In one study, the cumulative risk of developing biliary duct malignancy was 11.2% at 10 years after diagnosis of PSC.[63]

Patients with PSC who develop cholangiocarcinoma have poor survival. In a retrospective study of 30 patients with PSC, median survival was only 5 months following the diagnosis of cholangiocarcinoma. Additionally, at the time of cholangiocarcinoma diagnosis, 19 (63%) of 30 patients had metastatic disease, and 8 (47%) of 17 patients although believed to have localized malignancy were found to have abdominal metastases during surgical exploration. Moreover, metastasis or local cholangiocarcinoma extension prevented curative tumor resection in all but one patient who was free of malignancy more than 2 years later. For those PSC patients who acquired cholangiocarcinoma, palliative therapies including resection, chemotherapy, and radiation therapy do not improve survival.[62,64]

Cholangiocarcinoma remains unrecognized in many PSC patients until it is too advanced to cure because of its insidious nature. In fact, many of the signs and symptoms associated with cholangiocarcinoma development are typical of PSC itself, making early detection of the former highly challenging.[62] The suspicion for cholangiocarcinoma should be high when a PSC patient reports rapidly progressive jaundice, weight loss, or abdominal discomfort. In a retrospective study, when PSC patients who developed cholangiocarcinoma were compared with those who did not, no clinical or bio-

chemical features were found that could herald the onset of biliary cancer in the year prior to diagnosis of the malignancy.[65] In PSC patients, risk factors for developing cholangiocarcinoma include age, liver histologic stage, concurrent CUC,[64] smoking,[65] and history of variceal bleeding.[61]

In patients with PSC, dysplasia of the biliary epithelium is likely a cholangiocarcinoma precursor. In a study from the United Kingdom, biliary dysplasia was detected in 20% of liver biopsies derived from 26 PSC patients with concurrent and subsequent cholangiocarcinoma, but not in a single case of 60 PSC patients without biliary malignancy during a follow-up period of 2 years.[66] From the same study, recognition of biliary dysplasia by three independent pathologists showed moderate reproducibility suggesting dysplasia as a feasible indicator of present or prospect biliary malignancy.[66] Similarly, colonic dysplasia appears to be a risk factor for developing cholangiocarcinoma in PSC, and the risk is significantly increased in patients with both PSC and CUC.[46] Thus, detection of dysplasia in either bile ducts or colon warrants vigilant surveillance and may deserve consideration for OLT in particular situations.

At this time, early detection of cholangiocarcinoma, and thus hope for cure, is hindered because of the low sensitivity and specificity of standard diagnostic tests. Sclerosing cholangiocarcinoma of the large bile ducts, presents as biliary stricture and is best detectable by ERCP or PTC.[62] To this end, cholangiographic features suggestive of cholangiocarcinoma have been described, but accurate distinction between benign and malignant biliary stricture is often impossible. In fact, about 10% of malignant appearing biliary strictures are ultimately benign.[67] Biliary brush cytology and biopsy obtained during ERCP are 30% to 40% sensitive for securing the diagnosis of cholangiocarcinoma.[62] Novel tests for early detection of cholangiocarcinoma include digitized image analysis (DIA) and fluorescence in situ hybridization (FISH). These tests are performed on bile duct cytology specimens. In a study of 100 patients undergoing routine ERCP, DIA was found to be more sensitive (39.3% vs. 17.9%, $P = 0.014$) but less specific (77.3% vs. 97.7%) than routine cytology for detection of malignant strictures.[68] In addition, DIA was accurate in 56%, a value comparable to the accuracy of cytology (53%).[68] In another recent study for detection of malignant biliary strictures, the sensitivity of FISH (34%) was better compared with the sensitivity of standard cytology (15%, $P < 0.01$); moreover, the specificity of FISH and cytology were 91% and 98%, respectively ($P = 0.06$).[69] Therefore, we recommend obtaining biliary brushings from PSC patients during ERCP to carry out DIA and FISH, because these new tests can improve the detection rate of cholangiocarcinoma.

Carbohydrate antigen (CA) 19-9 is a serum marker for pancreatobiliary malignancies. In PSC patients a serum level greater than 100 U/ml is 75% sensitive and 80% specific for diagnosing cholangiocarcinoma in the absence of bacterial cholangitis.[70] However, elevated CA 19-9 can be seen in patients with pancreatic malignancies and bacterial cholangitis and in active smokers. In patients with PSC, we recommend periodic CA 19-9 testing; a sustained rise should draw attention for possible development of cholangiocarcinoma. To date, we need dependable molecular markers to detect cholangiocarcinoma early at a hopefully curable stage.

Endoscopic ultrasound is better than CT and magnetic resonance imaging to evaluate regional lymph nodes for possible cholangiocarcinoma metastasis including the option to biopsy questionable lesions.[62] Positron emission tomography (PET) is another promising tool for detection of cholangiocarcinoma in PSC. In one study, PET was 100% accurate to identify small cholangiocarcinomas arising in the setting of PSC compared with controls.[71] More studies are needed to fully assess the capacity of PET for detection of cholangiocarcinoma in PSC.

NON–PSC-ASSOCIATED COMPLICATIONS

PSC patients may complain of fatigue and pruritus. The etiology of fatigue is unknown, and, more important, it can affect the quality of life. In patients with PSC, pruritus can be debilitating, but its mechanism is not well defined. Endogenous opioids and retention of additional unknown factors usually excreted in the bile may contribute in the development of pruritus.[72] Overall the intensity of pruritus does not parallel with the severity of disease. Pruritus may lessen as PSC progresses.

Patients with PSC may also suffer from steatorrhea and ensuing deficiencies of fat-soluble vitamins. In a pretransplant group of PSC patients, deficiencies of vitamins A, D, and E were present in 82%, 57%, and 43% of patients, respectively.[73] In patients with PSC and steatorrhea, consideration should be given to rule out celiac sprue or chronic pancreatitis since either entity can coexist with PSC and both conditions are treatable causes of fat malabsorption. Metabolic bone disease is also common in PSC. Osteopenic bone disease can be severe in advanced-stage PSC, with 50% of patients having a bone mineral density below the fracture threshold.[74] Although most PSC patients are males, bone biopsies revealed findings consistent with osteoporosis rather than osteomalacia.[74]

Patients with PSC suffer from complications of portal hypertension just as patients with other etiologies of liver cirrhosis. In a study of 283 patients with PSC, 102 patients (36%) had esophageal varices, including 57 (56%) of 102 patients deemed to have moderate to large varices.[75] In the same study, platelet count, albumin level, and advanced histologic disease were independent predictors of esophageal varices. Esophageal varices are usually managed with endoscopic banding. If these measures are ineffective, a shunting procedure (i.e., transjugular intrahepatic portosystemic shunt) can be performed, but hopefully as a bridge to OLT. Patients with advanced-stage PSC develop ascites, spontaneous bacterial peritonitis, and encephalopathy. Treatment of these complications is similar as in other causes of end-stage liver disease. Liver transplantation should be considered as the ultimate therapy for persistent complications.

MEDICAL APPROACH TO THERAPY

To date, there is no specific medical therapy for PSC. Medical management should converge on the treatment of complications. Clinical trials directed at treating the underlying hepatobiliary disease are currently in progress.

PSC-Associated Complications

Cholelithiasis, Choledocholithiasis, and Gallbladder Polyps

Symptomatic gallbladder disease in patients with early-stage PSC should be treated with cholecystectomy. In an asymptomatic PSC patient, presence of an intraluminal gallbladder mass that cannot be attributed to gallstones requires cholecystectomy. As discussed previously, in a study of PSC patients who underwent cholecystectomy, 13.7% of patients were found to have gallbladder mass, more than half of which were adenocarcinomas.[55]

Following diagnosis of choledocholithiasis, the therapeutic intervention of choice is ERCP. During this procedure, endoscopic sphincterectomy is performed with removal of biliary stones and dilation of possible strictures. Temporary biliary stent placement is recommended, but final decisions should be made based on completeness of stone extraction and the location and nature of biliary strictures.

Dominant Biliary Strictures and Recurrent Bacterial Cholangitis

Dominant biliary strictures should be evaluated by ERCP or PTC to ensure comprehensive imaging of the biliary tree and to permit biliary brushings as well as biopsies of the affected areas to exclude cholangiocarcinoma. The main goal is to exclude that a biliary stricture represents cholangiocarcinoma or is otherwise a benign lesion.

The therapeutic management of dominant bile duct strictures includes the combination of biliary dilation and stenting interventions. The preferred approach of intervention (i.e., ERCP vs. PTC) depends on biliary stricture characteristics (i.e., region, length), and experience with the procedures. Most bile duct strictures are amenable to endoscopic cholangioplasty followed by biliary stenting. PTC is useful for cholangioplasty of biliary strictures that affect intrahepatic ducts and cases of unsuccessful endoscopic attempts to enter the biliary tree (i.e., patients with history of Roux-en-Y gastrojejunostomy).

PSC patients with frequent episodes of bacterial cholangitis should have cholangiography to evaluate the patency of the bile ducts. If strictures are present, they have to be treated endoscopically or percutaneously. In patients with PSC, recurrent bacterial cholangitis is not always the result of dominant biliary strictures. Edema, inflammatory exudation, and intraluminal debris can result in temporary stenosis of bile ducts leading to obliteration and subsequent recurrent bacterial cholangitis. To this end, temporary intranasal biliary tubes and biliary lavage has been used to flush out potential irritants, keeping the biliary ducts patent. Patients with relapsing episodes of bacterial cholangitis should be given ciprofloxacin orally as prophylaxis to prevent recurrent events.

Table 108–2 Medications for Treatment of Pruritus

Medication	Dosage
Cholestyramine*	4 g tid or qid PO
Phenobarbital	120-160 mg/day PO
Ursodeoxycholic acid	15-20 mg/kg/day PO
Hydroxyzine	25 mg tid or qid PO
Rifampin	150-300 mg bid PO
Naltrexone	50 mg/day PO

*Should be given 2 hr before or after other medications.
PO, orally.

Non–PSC-Associated Complications

Pruritus

Patients with PSC frequently complain of intense pruritus. This distressing symptom can be treated using various medical therapies (Table 108–2).[76] Cholestyramine is a nonabsorbable resin that decreases the intestinal absorption of bile acids and alleviates pruritus. Phenobarbital has been used in conjunction with cholestyramine to treat PSC patients with nocturnal pruritus. Ursodeoxycholic acid (UDCA, ursodiol), a hydrophilic bile acid that likely replaces hydrophobic, toxic bile acids from the bile pool, may also improve pruritus in PSC patients. Antihistamines such as hydroxyzine and diphenhydramine can be used as supplements to cholestyramine or UDCA, particularly for nocturnal pruritus because of their sedative properties. Rifampin may also alleviate pruritus, though its potential side effects (i.e., drug-induced hepatitis) make it a second-line agent for this upsetting symptom. In patients with PSC, opiate antagonists like naloxone, nalmefene, and naltrexone have been used to treat pruritus.

Steatorrhea, Fat-Soluble Vitamin Deficiency, and Hepatic Osteodystrophy

Prolonged cholestasis causes decreased intestinal bile acid concentration. Therefore, patients with advanced-stage PSC may develop fat malabsorption and steatorrhea. PSC patients who develop steatorrhea, however, should first be evaluated for other coexisting causes of steatorrhea, including celiac sprue and pancreatic insufficiency. Steatorrhea due to intraluminal bile acid deficiency may improve by dietary changes such as lowering daily fat intake and substituting medium-chain triglycerides for long-chain ones.

Table 108–3 Vitamin Replacement Therapy for Primary Sclerosing Cholangitis

Vitamin	Dosage
A	25,000-50,000 units two or three times per wk PO
D	25,000-50,000 units two or three times per wk PO
E	100 units bid PO
K	5 mg/day PO

PO, orally.

Fat-soluble vitamin (i.e., A, D, E, K) deficiencies are treated by simple oral replacement (Table 108–3). Special consideration must be given to advanced-stage PSC patients who have moderate to severe osteopenia. Calcium supplements, replenishment with vitamin D, and use of estrogens all have had therapeutic value. PSC patients deficient in vitamin K have prolonged prothrombin times that usually improve with oral vitamin K supplementation.

Decompensated Cirrhosis and Portal Hypertension

Complications of decompensated cirrhosis and portal hypertension should be managed expectantly as in other end-stage liver diseases. As PSC progresses, the complications of end-stage liver disease turn out to be intractable and liver transplantation becomes the only effective cure.

Hepatobiliary Disease

Multiple medical therapies have been evaluated for the treatment of PSC including D-penicillamine, cyclosporine, azathioprine, budesonide, silymarin, pentoxifylline, colchicine, and UDCA; however, none thus far has proven to be effective.

A randomized, controlled study of 105 PSC patients treated with standard-dose UDCA (13 to 15 mg/kg body weight/day) did not report any clinical benefit in the treatment group compared with controls (median follow-up of 2.2 years). However, two independent pilot studies of PSC patients treated with high-dose UDCA have demonstrated promise. A small, double-blind, placebo-controlled study from the United Kingdom, reported that 13 PSC patients who received high-dose (20 mg/kg body weight/day) UDCA had significant improvement in liver biochemistries, cholangiographic appearance, and reduction of liver fibrosis compared with 13 PSC patients taking placebo.[77] A U.S. study of 30 PSC patients treated with high-dose UDCA (25 to 30 mg/kg body weight/day) for 12 months reported improvement of the Mayo PSC risk score at the end of therapy. The observed changes were translated into a significantly better than expected survival at 4 years in the high-dose UDCA group compared with a historic placebo group.[78] To further evaluate these promising results, a multicenter, randomized placebo-controlled trial of long-term, high-dose UDCA is underway. High-dose UDCA shows promise; however, at present, UDCA treatment for PSC patients is encouraged only in the context of therapeutic trials.

Beyond treating the underlying liver disease, UDCA has also been shown to affect the frequency of colonic dysplasia or cancer in patients with PSC and CUC. In a cross-sectional study of 59 patients with both PSC and CUC who were undergoing chronic dysplasia surveillance endoscopy, UDCA use was correlated with decreased prevalence of colonic dysplasia.[79] In a retrospective analysis of a randomized, placebo-controlled trial of 52 patients with concurrent PSC and CUC, use of UDCA resulted in a reduced relative risk (relative risk, 0.26; confidence interval, 95%: 0.06-0.92; $P = 0.049$) for developing colorectal dysplasia or cancer.[80] Additional prospective, randomized placebo-controlled studies are needed to verify the postulated chemopreventive effect of UDCA in patients with PSC and CUC.

SURGICAL APPROACH TO THERAPY

In the past 4 decades, the surgical approach to PSC has evolved tremendously. Once operative cholangiography along with choledochotomy and biopsy were performed to diagnose PSC; the need for these procedures was obviated by the advent of ERCP and PTC. In the present era of transplant medicine, palliative biliary reconstruction has largely been replaced by OLT.

Reconstructive Biliary Surgery

The early surgical approaches to treat PSC advocated prolonged T-tube drainage and use of steroids. Wood and Cuschieri[81] suggested that T-tube drainage and lavage might actually reverse the disease process. Attempting to improve on the palliation of simple T-tube drainage and to alter the PSC course, Pitt et al. advocated a more aggressive surgical approach employing biliary-enteric anastomosis[82]; indeed, they reported the outcome of 22 PSC patients managed with surgery between 1974 and 1980. In these series, 17 of the 22 PSC patients underwent choledochoenteric anastomosis and 13 patients had a good or excellent outcome following surgery.[82]

In 1988, Cameron et al. reported the Johns Hopkins experience with PSC patients who underwent extended biliary resection in combination with stenting and biliary-enteric anastomosis.[83] This procedure involved excision of the ductal bifurcation and extrahepatic biliary tree, dilation of the intrahepatic ducts, insertion of Silastic transhepatic biliary stents, and bilateral hepaticojejunostomies. In that report, 2 (40%) of 5 PSC patients with cirrhosis died following the operation; conversely, only 1 (3.9%) of 26 PSC patients with liver fibrosis died after the operative procedure. The 1-, 3-, 5-year actuarial survival rates for PSC patients with cirrhosis and hepatic fibrosis were 20%, 20%, 20%, and 92%, 87%, 71%,

respectively.[83] The authors recommended that patients with PSC and cirrhosis should be referred for consideration of OLT; however, PSC patients with significant extrahepatic disease and no evidence of cirrhosis should be considered for biliary reconstructive surgery.[83]

In the past 2 decades, biliary reconstructive surgery for PSC has become less common because endoscopic techniques for bile duct dilation and stenting as well as the outcome of OLT have improved. Nevertheless, biliary-enteric anastomosis may still be indicated in noncirrhotic patients with significant but localized extrahepatic disease. However, the reported association of precedent biliary-enteric drainage surgery for benign disease with subsequent development of cholangiocarcinoma causes skepticism to the proposition for biliary reconstructive surgery in PSC.[84] In addition there is hesitation of bile duct reconstructive surgery in PSC patients after several medical centers reported increased difficulty performing OLT in patients who had previous biliary surgery. In our practice, we refer PSC patients with dominant biliary strictures for endoscopic dilation given the high degree of success attained by this procedure, its relative ease, and low morbidity/mortality compared with biliary surgery. We would recommend biliary reconstructive surgery only for those few PSC patients who have extrahepatic strictures not amenable to endoscopic treatment, are not candidates for OLT, and have no cirrhosis.

Orthotopic Liver Transplantation

OLT remains the most effective treatment for PSC. At our institution, the 1- and 5-year survival rates for PSC patients following OLT are 95% and 86%, respectively. These rates compare favorably with results of OLT for other chronic liver diseases. Risk factors that adversely affect the outcome of patients who undergo OLT for PSC are divided into those that influence the general OLT outcome and the ones specific for PSC.[85] The former include stay in the intensive care unit or being on life support prior to OLT, age older than 65 years, poor nutritional status, Child–Pugh class C, and renal failure requiring dialysis prior to or after OLT. These factors are also predictive of increased blood loss, prolonged intensive care unit stay, and major postoperative complications. Risk factors specific for PSC include disease severity, previous biliary or shunt surgery, coexistent cholangiocarcinoma, and presence of IBD. Using the Mayo PSC natural history model as the measure of disease severity, actual survival following transplantation was improved with OLT for all stages of disease.[86] Thus, earlier OLT has been advocated for patients with PSC, because this approach would improve patient outcome and resource utilization.

Controversy exists on the impact of prior biliary surgery on subsequent OLT for PSC. There is little doubt that prior biliary surgery increases the technical difficulty of OLT, but it is unknown if this event affects survival. In a combined series of 216 patients from the University of Pittsburgh and the Mayo Clinic, prior biliary tract surgery and/or surgery for portal hypertension was associated with less favorable survival after OLT, but this event did not reach statistical significance.[86] In a study from the University of California at San Francisco, increased operative time and blood loss, but not mortality, were found in PSC patients with history of prior colectomy or biliary surgery.[87] These reports suggest that prior biliary tract surgery increases the technical difficulty of OLT for PSC and is associated with a trend toward slightly increased mortality even when performed at large transplant centers.

Following OLT for PSC, these patients develop unique complications. Increased rates of biliary strictures have been noted; however, not all of these cases represent PSC recurrence as other factors may also cause biliary stricturing, including ischemia related to chronic rejection or possible chronic low-grade bacterial cholangitis resulting from the Roux-en-Y anastomosis, which is performed much more frequently in PSC patients. However, a study from the University of Pittsburgh found a significantly increased incidence of biliary strictures in allografts of patients transplanted for PSC versus patients who also underwent OLT and choledochojejunostomy for other non-PSC causes of end-stage liver disease.[88] Because cholangiographic, clinical, and biochemical criteria for recurrent disease have not been widely accepted, there is no consensus regarding the incidence of recurrent PSC in liver allografts. Nevertheless, careful analysis of a registry of transplanted PSC patients at our institution concluded that 20% of patients developed recurrent disease based on characteristic cholangiographic and histologic features.[89] Several transplant centers have reported an increased incidence of rejection in patients transplanted for PSC.[90] Acute and chronic ductopenic rejection can be severe and steroid resistant, often leading to graft loss.[87] In a study of 100 consecutive PSC patients transplanted at Baylor University Medical Center, chronic rejection and disease recurrence occurred in 13% and 16% of patients, respectively, following OLT. These events had adversely affected both graft and patient survival, markedly so in those patients with chronic rejection.[91] Five-year graft survival rates were 33% and 65% for patients with chronic rejection and disease recurrence, respectively, as compared to 76% for patients free of chronic rejection or recurrence. The authors postulated that chronic rejection and disease recurrence following OLT for PSC are two distinct entities as evidenced by the difference in outcome; therefore, these causes should be managed accordingly.[91]

Because many patients with PSC have concurrent CUC, there was concern that life-long immunosuppression after OLT may increase the risk of colorectal carcinoma in such cases. In a study of 108 patients with PSC and concomitant IBD who underwent OLT, Loftus et al. reported a fourfold increase in colon carcinoma in the group that did not have a prior colectomy compared to the expected colon cancer in a group with comparable (pre-OLT) duration of IBD.[92] This finding however was not statistically significant and did not affect patient survival.[92] Goss et al. also reported that post-transplant colectomy for dysplasia-carcinoma or symptomatic colitis does not affect PSC patient survival.[93] Given the lack of impact on patient survival, we do not recommend prophylactic proctocolectomy in PSC patients with IBD who undergo OLT. Nonetheless, the high risk of colonic neoplasia in

transplanted PSC patients warrants annual surveillance colonoscopy with biopsies.

Cholangiocarcinoma

In patients with PSC who develop cholangiocarcinoma, curative therapy for the latter is disappointing. In general, cholangiocarcinoma is regarded as a contraindication for OLT given the reported poor outcome of patients who received transplants to treat this tumor in the past. However, incidental cholangiocarcinoma defined as lesions less than 1 cm in diameter discovered at the time of pathologic sectioning of explanted liver have a much better prognosis. In a study of 127 transplanted PSC patients, 10 (8%) were found to have incidental cholangiocarcinoma, but they enjoyed a 5-year actuarial survival rate of 83%, which is comparable to survival rates of OLT patients without incidental cholangiocarcinoma.[93] Because our ability to detect small cholangiocarcinomas preoperatively will improve, we need to reevaluate the surgical management of these tumors in PSC patients. For example, selected liver transplant centers have shown promising outcome of patients with hilar cholangiocarcinoma (5-year actuarial survival rate of ~80%)[94] using radiation therapy, chemotherapy, and abdominal exploration prior to OLT.

Proctocolectomy

In patients with CUC, development of PSC affects the management of the former. Overall, we recommend proctocolectomy only for indications pertinent to CUC, these being medical failure to control severe symptoms or presence of colon dysplasia. Nevertheless, the decision to perform Brooke ileostomy versus ileal pouch–anal anastomosis (IPAA) is greatly influenced by the presence of PSC. In a retrospective study of 72 patients with PSC and CUC treated with either Brooke ileostomy ($N = 32$) or IPAA ($N = 40$), 8 (26%) of 32 patients who underwent ileostomy developed peristomal varices and subsequent bleeding; however, none of the 40 patients who underwent IPAA developed perianastomotic varices or perineal bleeding.[95] Of interest, the cumulative risk of pouchitis at 10 years after IPAA was 61% for patients with PSC and CUC compared with 36% for patients with CUC alone.[96] Therefore, patients with PSC have increased risk of pouchitis if treated for CUC with IPAA. In our practice, for PSC patients who need proctocolectomy, we recommend IPAA and not Brooke ileostomy, because treating the pouchitis is simpler than managing bleeding peristomal varices.

CONCLUSION

PSC is a chronic, cholestatic liver disease of unknown cause affecting mainly young men. The disease is characterized by a progressive, fibrous obliteration of the bile ducts resulting in biliary cirrhosis and ultimately liver failure. PSC is strongly associated with CUC. During the course of the illness, patients with PSC develop disease-specific and nonspecific complications. Medical management is challenging and requires a team approach of hepatologists, gastroenterologists, radiologists, and surgeons. At present, we lack an effective medical therapy to treat the primary disease. Nonetheless, OLT is the ultimate choice of treatment. More basic and translational research studies are required to better understand the pathogenesis of PSC before we can apply more effective therapies.

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Chapter

109

Operative Management of Strictures and Benign Obstructive Disorders of the Bile Duct

Keith D. Lillemoe · Charles J. Yeo · Henry A. Pitt

Strictures and other benign obstructive disorders of the bile ducts represent a heterogeneous group of conditions, largely with similar clinical manifestations, that often require challenging surgical approaches. The many causes of benign obstruction of the bile ducts are listed in Box 109–1. Although numerous technologic developments have improved diagnosis and management, bile duct strictures remain a significant clinical problem. If these strictures or benign obstructive disorders are unrecognized or managed improperly, life-threatening complications such as cholangitis, biliary cirrhosis, portal hypertension, and end-stage liver disease can result. To avoid these complications, virtually every patient with a bile duct stricture or a benign obstructive disorder of the bile duct should undergo evaluation and treatment with the goal of relieving the obstruction to biliary flow.

Most biliary strictures occur after primary operations on the gallbladder or biliary tree. With the introduction of laparoscopic cholecystectomy in the 1990s, bile duct injuries and associated strictures have been seen with an increased frequency. This chapter focuses on postoperative bile duct strictures and primary sclerosing cholangitis (PSC). Many of the other causes of strictures and benign obstructive disorders of the bile ducts listed in Box 109–1 are discussed in other chapters in this volume.

POSTOPERATIVE BILE DUCT STRICTURES

Pathogenesis

The majority of benign bile duct strictures are the result of operations that involve the right upper quadrant of the abdomen. More than 80% of strictures occur after injury to the bile ducts following cholecystectomy. Cholecystectomy is the most frequently performed abdominal operation in the United States, with more than 700,000 operations performed annually. Before the widespread use of laparoscopic cholecystectomy, major bile duct injuries were relatively infrequent, occurring in approximately 2 of 1000 open cholecystectomies.[1,2] It appears that the rate of bile duct injury has more than doubled since the introduction of laparoscopic cholecystectomy.[2,3] It is likely that the exact incidence of bile duct injury is unknown, because many cases go unreported in the literature. However, a wide range in the incidence of injury after laparoscopic cholecystectomy can be found in reported series, with the most accurate data from surveys that encompass thousands of patients. The reported incidence of *major* bile duct injuries ranges from 0.3% to 0.8%, with the incidence of bile leaks or other *minor* injuries ranging from 0.3% to 0.55%.[2-5] Based on a 1995 analysis and collective review by Strasberg et al.,[2] the overall rate of reported major bile duct injury was 0.52%, whereas the rate of minor injury was 0.33%.

Since the introduction of laparoscopic cholecystectomy into clinical practice, the rate of bile duct injury appears to have risen to a higher level and remains largely stable.[5] Although the reported incidence of bile duct injury in many single institutions remains quite low, the overall population-wide incidence appears to have reached a steady state. In a review compiled with a Danish laparoscopic cholecystectomy database, which included the results of all procedures performed in that country, the incidence of major bile duct injury was 0.7%.[4] Minor bile duct leaks for reasons other than a major bile duct injury occurred in 2% of patients. No change in the annual incidence of such bile duct injuries

Box 109–1 Causes of Biliary Strictures and Benign Obstructive Bile Duct Disorders

Postoperative Strictures

Injuries at primary biliary operations
- Laparoscopic cholecystectomy
- Open cholecystectomy
- Common bile duct exploration
- Prior stricture repair procedure

Injuries at other operative procedures
- Gastrectomy
- Duodenal ulcer procedures
- Hepatic resection
- Liver transplantation
- Pancreatic procedures
- Portacaval shunt

Stricture at a biliary-enteric anastomosis

Strictures Related to Endoscopic or Percutaneous Biliary Manipulations

Blunt or Penetrating Trauma

Strictures Due to Inflammatory Conditions

Chronic pancreatitis
Cholelithiasis and choledocholithiasis
Mirizzi's syndrome
Primary sclerosing cholangitis
Duodenal ulcer
Duodenal diverticulum
Crohn's disease
Sphincter of Oddi stenosis
Viral infections
Toxic drugs
Radiation fibrosis
Subhepatic abscess
Parasitic infestations

Benign Bile Duct Tumors

Congenital Conditions

Choledochal cyst
Caroli's disease
Congenital stricture, webs
Biliary atresia

occurred between 1991 and 1994. Comparable results have been reported from the United States and Australia, demonstrating no significant reduction in the incidence of laparoscopic bile duct injuries since the early 1990s. It appears that further refinements in laparoscopic cholecystectomy technique will be necessary to return this rate to the lower rate observed with open cholecystectomy.

A number of factors have been associated with the occurrence of bile duct injuries. Factors pertaining to the local operative environment around the gallbladder can increase the difficulty of the procedure and increase the risk of injury. For example, such factors as chronic inflammation, patient obesity, fat in the periportal area, poor exposure, and bleeding that obscures the operative field all appear to increase the risk of bile duct injury. Further, increasing patient age, male gender, a long period of symptoms before cholecystectomy, and an increasing number of painful attacks all appear to be associated with increased difficulty of laparoscopic cholecystectomy. The risk of bile duct injury is also higher in patients with complicated gallstone disease compared with patients with chronic cholecystitis or symptomatic cholelithiasis. In addition, when laparoscopic cholecystectomy is performed for acute cholecystitis, there appears to be an increased need for conversion to an open procedure (29% vs. 8%) and an increased risk of bile duct injury (1.3 vs. 0.6%) compared with cases performed for all other indications.

There is no doubt that specific problems encountered at the time of cholecystectomy may be associated with an increased risk of bile duct injury. Bleeding from the cystic or hepatic arteries can lead to bile duct injury during attempts to gain hemostasis. The overzealous application of suture ligatures or Ligaclips to periductal areas at either open or laparoscopic cholecystectomy can result in bile duct injury. Further, failure to recognize congenital anatomic abnormalities of the bile ducts, such as insertion of an aberrant right hepatic duct into the cystic duct or a long common wall between the cystic duct and the common bile duct, can also lead to injury (Fig. 109–1).

Intraoperatively, a number of technical factors appear to be associated with an increase in the risk of bile duct injury. The *classic laparoscopic injury* occurs when the cystic duct and common bile duct are brought into alignment during the dissection and the common bile duct is mistaken for the cystic duct, being dissected, clipped, and divided (Fig. 109–2).[6] This can occur when excessive cephalad retraction on the gallbladder fundus tents or retracts the common bile duct to the patient's right side. In this injury, after the common bile duct has been divided, the common hepatic duct is subsequently divided a variable distance from the hepatic hilus, often with injury to the right hepatic artery. Other intraoperative factors that may contribute to bile duct injury include poor clip placement on the cystic duct, injudicious use of electrocautery, dissection too deep into the liver parenchyma, and failure to distinguish between the cystic duct and the common hepatic or common bile duct.

Routine operative cholangiography has been recommended to decrease or prevent biliary injuries, but no conclusive data support this viewpoint. Cholangiography can define the biliary anatomy, identify injuries, and limit the ductal damage and allow the diagnosis and treatment to be instituted at the time of injury, thus avoiding complications that occur when injuries present in the postoperative period.[7,8] Furthermore, several large

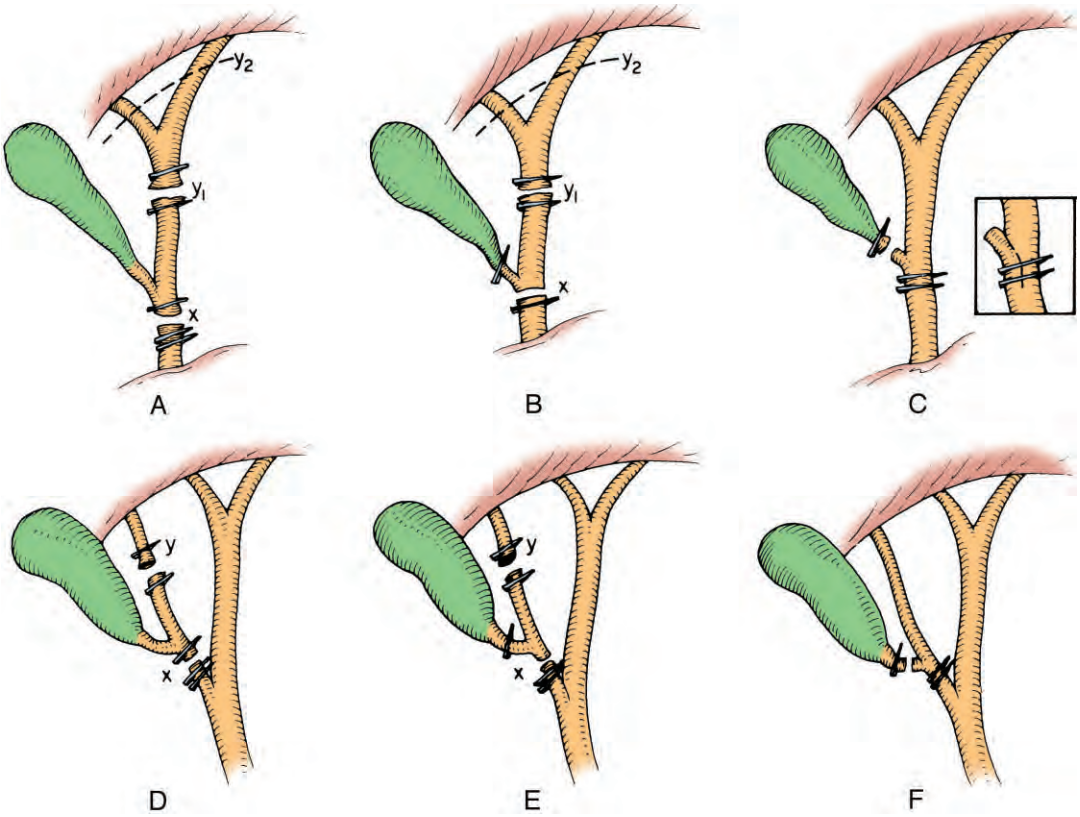

Figure 109–1. Various patterns of biliary tract injury. **A,** Classic injury. **B** and **C,** Variants of the classic injury. **D** to **F,** Different injuries resulting from the cystic duct originating from an aberrant right hepatic duct. (From Strasberg SM, Hertl M, Soper NJ: An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 180:101, 1995.)

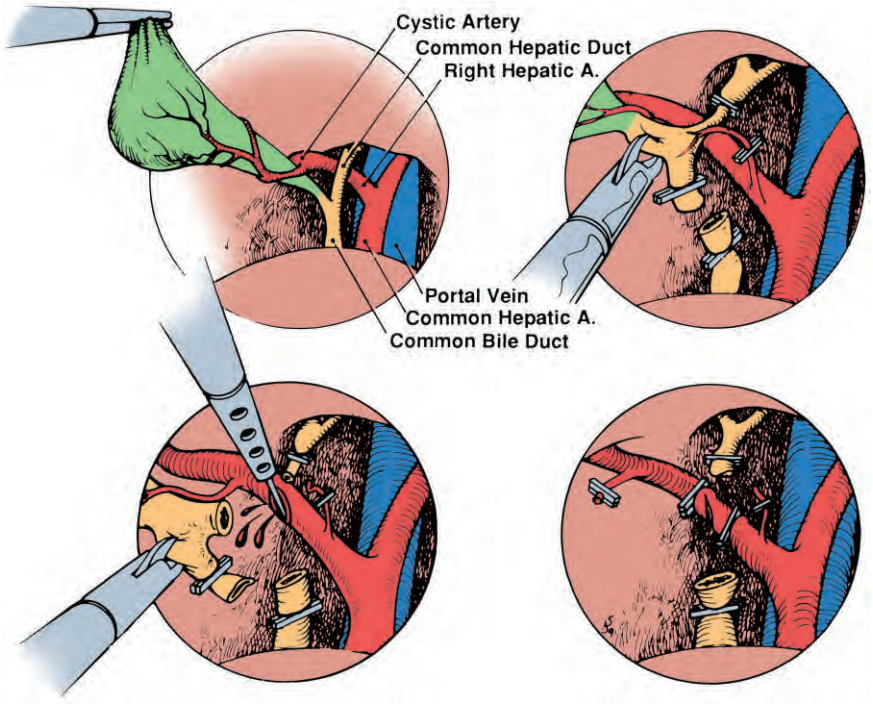

Figure 109–2. The classic laparoscopic cholecystectomy injury. *Top left,* Normal anatomy. *Top right,* Misidentification of the common duct for the cystic duct leads to division of the common duct. In many cases, the common hepatic duct will not be clipped but rather will be divided by scissors or cautery. *Bottom left,* Injury to right hepatic artery occurring during bile duct injury. *Bottom right,* A combined injury to common hepatic duct, common bile duct, and right hepatic artery. (From Davidoff AM, Pappas TN, Murray EA, et al: Mechanisms of major biliary injury during laparoscopic cholecystectomy. Ann Surg 215:196, 1992.)

population-based studies have shown that the risk of common bile duct injury is decreased with the use of intraoperative cholangiography. Flum and colleagues analyzed the results of more than 1,570,000 cholecystectomies performed in Medicare patients by more than 40,000 surgeons.[9] More than 75% of these procedures were classified as laparoscopic cholecystectomy. Bile duct injury occurred in 0.5% of patients. If cholangiography was not performed, the incidence of injury was 0.58%. The use of cholangiography significantly reduced the incidence of injury (0.39%). Similarly, intraoperative cholangiography had a protective effect against bile duct injury in a series from Australia.[3] In this study intraoperative cholangiography was associated with a significant 50% reduction in the risk of bile duct injury. Whether or not cholangiography is performed, careful exposure of the structures in the triangle of Calot and clear definition of the gallbladder–cystic duct junction before the division of any structures appear to be the best techniques to limit bile duct injuries during laparoscopic cholecystectomy (Fig. 109–3).[2]

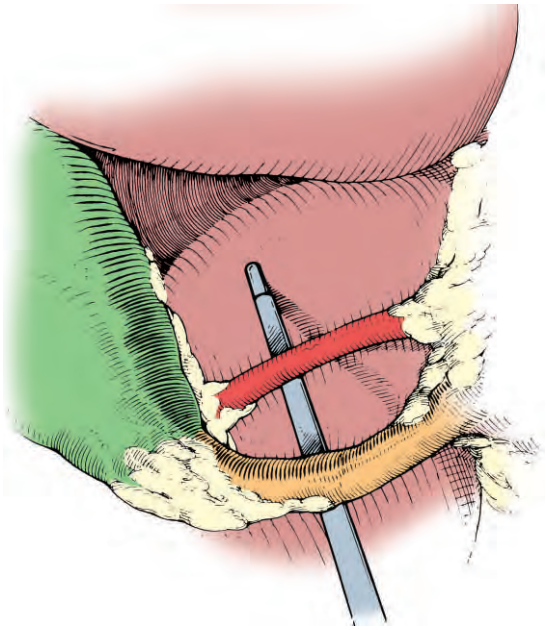

Figure 109–3. The critical view needed to avoid bile duct injury. Here, the triangle of Calot has been dissected free of all tissue except the cystic duct and cystic artery. A laparoscopic instrument is shown dorsal to the cystic duct and artery. (From Strasberg SM, Hertl M, Soper NJ: An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 180:101, 1995.)

There are clearly factors related to the surgeon performing laparoscopic cholecystectomy that can be associated with increased risk with bile duct injury. The "learning curve" for the procedure was well recognized early after the initial reports.[10] Although this factor remains clearly present, it does not alone explain the overall increased risk of bile duct injury that has persisted as we now approach the second decade of this procedure. Whether the operation was learned during the course of residency training or after completion of residency also appears to be a factor.[8] Finally, in recent years, there has been a growing understanding of surgeon cognitive factors associated with bile duct injury during laparoscopic cholecystectomy. An analysis examining 252 biliary injuries during laparoscopic cholecystectomy using human error factor and cognitive science techniques found that 97% of injuries were due to visual perceptual illusion or inadequate visualization.[11] Further work by that group has determined a major explanation for surgeons' frequent inability to recognize bile duct injury. Bile duct injuries appear to be associated with confirmation bias, which is a propensity to see cues to confirm a belief and to discount cues that might discount the belief. Although cognitive factors, training, and experience are important for the understanding of the issues associated with bile duct injuries, surgeons must continue to have the appropriate corrective mechanisms in place to minimize the chance of these injuries, including knowledge of anatomy, typical mechanisms of injury, and appropriate level of suspicion and logic.

In some cases, ischemia of the bile duct may contribute to the occurrence of a postoperative bile duct stricture. Unnecessary dissection around the bile duct during cholecystectomy or during a bile duct anastomosis may injure the major arteries of the bile duct that run in the 3- and 9-o'clock positions. A further factor that may contribute to the formation of biliary strictures is an intense connective tissue response with fibrosis and scarring that can occur after bile duct dissection. Experimental studies of bile duct ligation in a canine model have demonstrated immediate and sustained elevation of bile duct pressure and progressive increase in bile duct diameter. Histologic changes at 1 month after such canine bile duct ligation have shown that the bile duct wall is thickened, with a reduction in mucosal folds and loss of surface microvilli. Biochemical analyses of this connective tissue response have shown that collagen synthesis and its associated features are increased within 2 weeks in the obstructed bile duct. Moreover, a marked local inflammatory response can develop in tissue adjacent to bile leakage, which commonly accompanies many bile duct injuries. This inflammatory response set up by bile leakage may be intensified in the face of infection and can lead to fibrosis and scarring in the periductal tissues.

The location of a bile duct stricture appears to be of primary importance in dictating management and predicting outcome. Bismuth developed a classification of bile duct strictures based on the anatomic pattern of involvement (Fig. 109–4). In general, the higher the location of the stricture, the more difficult is the repair and the greater is the recurrence rate.

Although most postoperative bile duct strictures occur after cholecystectomy and operations on the extrahepatic biliary tree, bile duct injury can also occur during other operative procedures. Injury may occur during gastrectomy, various duodenal ulcer operations, liver resection and transplantation, pancreatic procedures, and

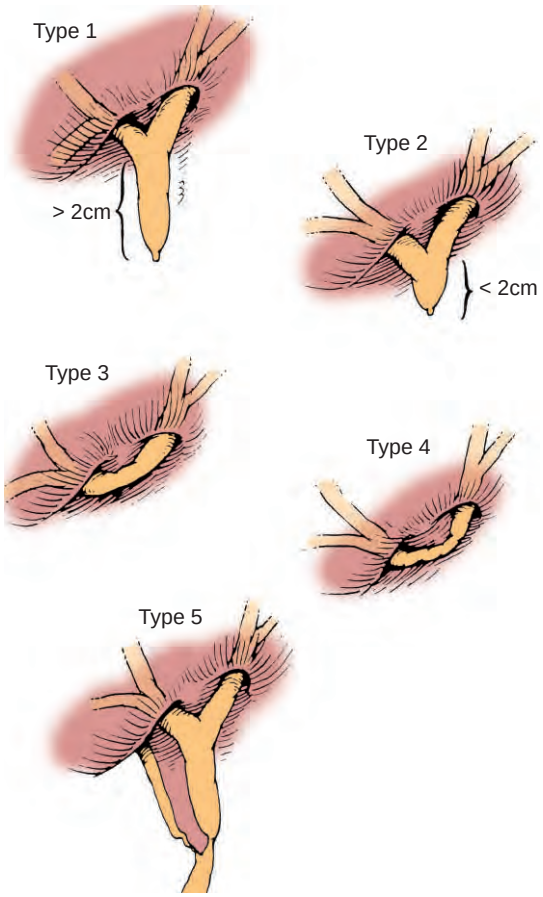

Figure 109–4. Classification of bile duct strictures based on the level of the stricture in relation to the confluence of the hepatic ducts. Types 3, 4, and 5 are typically considered complex injuries. (From Bismuth H: Postoperative strictures of the bile ducts. In Blumgart LH [ed]: The Biliary Tract. Clinical Surgery International Series, Vol 5. Edinburgh, Churchill Livingstone, 1983, pp 209-218.)

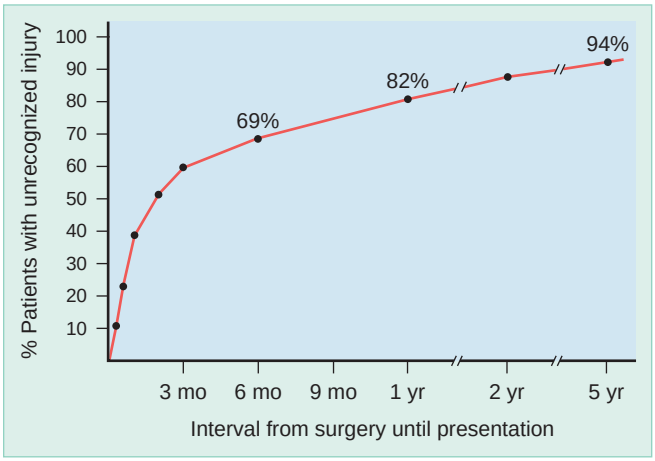

Figure 109–5. Graph from the open cholecystectomy bile duct injury era, depicting the cumulative percentage of patients with bile duct strictures developing symptoms with respect to the time interval from the operative injury. (From Pitt HA, Miyamoto T, Parapatis SK, et al: Factors influencing outcome in patients with postoperative biliary strictures. Am J Surg 144:14, 1982.)

portacaval shunting. Injuries that occur during gastrectomy typically involve a failure to recognize the location of the extrahepatic biliary tree at the time of transection of the first portion of the duodenum. The anatomy of this area may be abnormal due to tumor involvement or due to complicated duodenal ulcer disease. Various pancreatic procedures, such as pancreaticoduodenectomy, pancreatic pseudocyst drainage, duodenum-sparing pancreatic head resection, or extended distal pancreatectomy, may be attended by bile duct injury due to the intrapancreatic location of the common bile duct en route to the ampulla of Vater.

Clinical Presentation

Most patients with postoperative bile duct stricture present early after their initial operation. After open cholecystectomy, only about 10% of patients with postoperative strictures are detected within the first week. However, 69% are diagnosed within the first 6 months, and 82% are diagnosed within the first year after surgery (Fig. 109–5). In most series reporting bile duct injuries after laparoscopic cholecystectomy, the injury is usually recognized either during the laparoscopic cholecystectomy or, more commonly, in the early postoperative period.

There are two different modes of presentation of patients who are recognized to have early postoperative bile duct injuries. One group of patients presents with leakage of bile from the injured biliary tree. Such patients may present with bilious drainage from operatively placed drains or through the wound, or patients without drains may present with free leakage of bile into the peritoneal cavity. Such bile leakage can loculate as a biloma or can cause abdominal distention from biliary ascites or bile peritonitis. In these patients, jaundice may not be evident. The second group of patients presents with jaundice, scleral icterus, and elevations of liver function tests, particularly serum total bilirubin and alkaline phosphatase. It is imperative that patients who undergo laparoscopic cholecystectomy and fail to improve within a few days of the operative procedure be evaluated for the possibility of a bile duct injury. Most patients who undergo uncomplicated laparoscopic cholecystectomy have little or no pain on the first to second postoperative days, require little in the way of analgesics, and can resume near-normal activities by the third to fifth postoperative days. Patients with persistent postlaparoscopic cholecystectomy nausea, vomiting, abdominal distention, and declining activity level should be suspected of harboring a bile leak or extrahepatic biliary injury until these entities are ruled out.

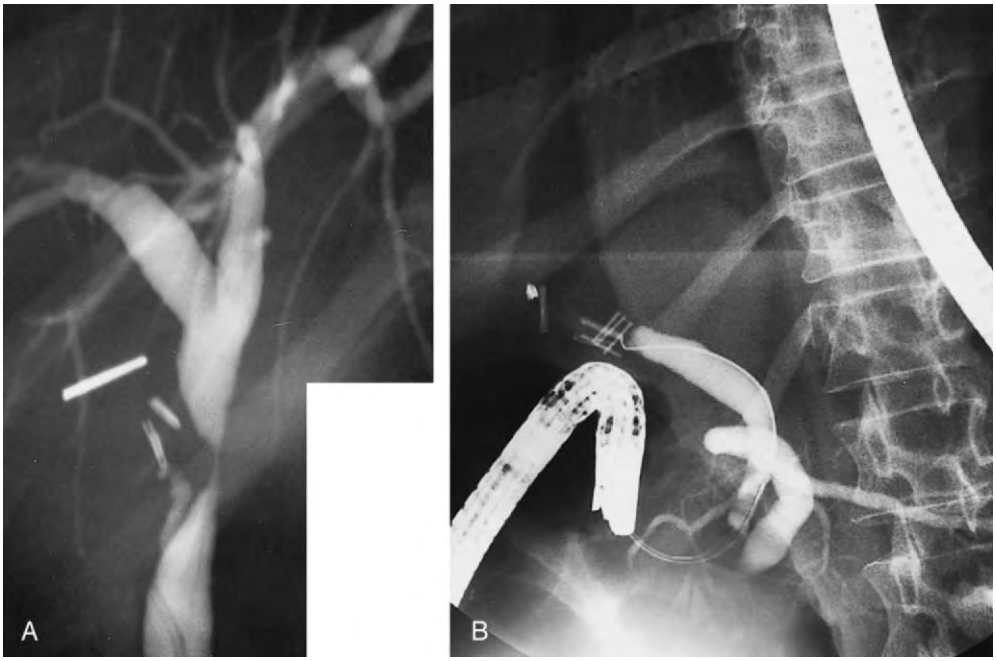

Figure 109–6. **A,** An endoscopic retrograde cholangiopancreatogram from a patient with elevated liver function tests 4 years after open cholecystectomy. Note the extensive narrowing of the bile duct below the bifurcation and the surgical clips close to the strictured area. **B,** A cholangiopancreatogram from a patient with a total transection of the common bile duct during laparoscopic cholecystectomy. Note the multiple clips across the common bile duct and the abrupt termination of the column of contrast medium at the site of the clips.

Laboratory Investigations

Most patients with postoperative bile duct strictures have evidence of abnormal liver function tests. The serum bilirubin level is typically elevated, may fluctuate, and may occasionally even be normal. In patients with bile leakage, the bilirubin may be normal or only minimally elevated (because of the lack of true biliary obstruction); however, mild bilirubin elevation may be seen due to absorption from the peritoneal cavity. Often, the serum alkaline phosphatase is elevated, as a marker of biliary epithelial injury. In contrast, the levels of alanine aminotransferase and aspartate aminotransferase may be normal or only minimally elevated, except during episodes of cholangitis. Patients with postoperative bile duct strictures who present months to years after the initial operation typically have elevated liver function tests but also may show evidence of cholangitis. Such patients may have intermittent fever, leukocytosis, or an elevated erythrocyte sedimentation rate. Occasionally, patients with markedly delayed diagnoses may present with advanced biliary cirrhosis and laboratory findings of diminished hepatic synthetic activity (e.g., hypoalbuminemia and prolonged prothrombin time).

Radiologic Imaging

Both transcutaneous abdominal ultrasonography and computed tomography can be used to evaluate patients with postoperative biliary injury. These studies may define biliary leaks (bilomas or ascites), can identify intrahepatic and extrahepatic biliary dilatation, and can be used to assess the entire abdomen for other intra-abdominal collections. These studies can be used in the initial postoperative period or if the patient presents after a delay.

In patients suspected of having early postoperative bile duct injury, there is a role for radionuclide technetium-HIDA (hepatobiliary iminodiacetic acid) scanning, which can be used either to assess for biliary leakage or to document a complete biliary obstruction. In patients with suspected early injuries, such a nuclear medicine scan is a reasonable early approach to identifying biliary leakage or biliary obstruction. Further, in patients with postoperative bile leaks to operatively placed drains, the injection of water-soluble contrast medium through the drainage tract (sinography) may define the source of leakage, as well as the anatomy of the biliary tree.

In most circumstances, formal evaluation and imaging of the biliary tree should be performed via cholangiography. Three different techniques exist: (1) percutaneous transhepatic cholangiography (PTC), (2) endoscopic retrograde cholangiography (ERC), and (3) magnetic resonance cholangiopancreatography (MRCP). ERC appears to be particularly useful in cases of cystic duct stump leaks and partial injuries to the extrahepatic biliary tree (Fig. 109–6), because it can define the entire extrahepatic biliary anatomy and allow the placement of an endoprosthesis, which may allow

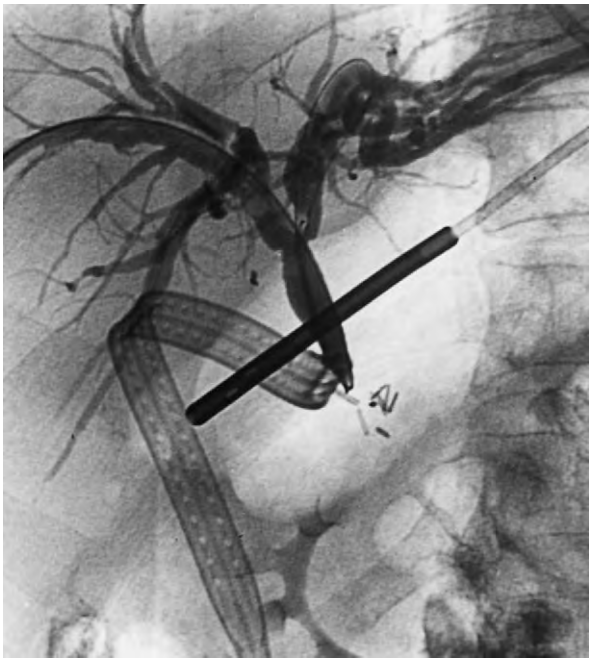

Figure 109–7. A percutaneous transhepatic cholangiogram from a patient with a complete transection of the common hepatic duct, which ends close to several surgical clips. A surgical drain is in place, as well as a duodenal feeding tube (which crosses obliquely over the common hepatic duct).

healing of the biliary leak. PTC is generally more valuable when an assessment of the proximal or intrahepatic biliary tree is necessary above the injury site (Fig. 109–7). PTC can be followed by the placement of a percutaneous transhepatic biliary drainage catheter, which can decompress the biliary tree, treat cholangitis, and control a bile leak. These catheters can also be of assistance in the repair of difficult high bile duct strictures. Further, they provide access to the biliary tree for nonoperative dilation.

The development of MRCP has also provided a noninvasive technique that provides excellent delineation of biliary anatomy. The quality of these images have led some surgeons to advocate this technique as the initial step in evaluation of patients with suspected bile duct injuries and can eliminate the need for diagnostic ERC. If performed as an initial noninvasive technique, MRCP can define major bile duct transection in which ERC will be of no value versus a cystic duct leak in which ERC can lead to therapeutic stent placement.

SURGICAL MANAGEMENT OF POSTOPERATIVE BILE DUCT STRICTURES

The appropriate management of postoperative biliary tract injuries is dependent on the time at which the injury is diagnosed after the operation and the type, extent, and level of the injury. The goal of any surgical repair of the biliary tract is to establish bile flow into the proximal gastrointestinal tract, preventing the short- and long-term complications of cholangitis, sludge or stone formation, restricture, intra-abdominal fluid collection or abscess, and biliary cirrhosis. The greatest opportunity to achieve this goal comes with the performance of a tension-free, mucosa-to-mucosa repair using a segment of noninjured proximal bile duct.

Immediate Repair of Intraoperative Bile Duct Injury

The initial appropriate management of a bile duct injury (recognized at the time of the index operation) can avoid the development of a bile duct stricture and its multiple sequelae. Unfortunately, recognition of such a bile duct injury is not common during either open or laparoscopic cholecystectomy.[12-18] Unexpected bile leakage observed during surgery or the suspicion of "aberrant ductal anatomy" should raise concern for a biliary injury. If such a biliary injury is suspected, it is imperative that the surgeon define the biliary anatomy via cholangiography, avoiding dissection that may further injure or devascularize the bile duct. In most cases, the conversion from a laparoscopic cholecystectomy to an open procedure facilitates identification of the biliary anatomy and allows repair. If an injury is confirmed cholangiographically and the surgeon is not experienced in performing complex biliary reconstructions, then the patient should be referred to a specialized hepatobiliary unit. The placement of a small red rubber catheter into an injured or a transected proximal bile duct allows opacification of the biliary tract postoperatively and may assist with future attempts at the placement of a percutaneous transhepatic catheter. Furthermore, a closed-suction drain should be left in the subhepatic space to drain any extravasating bile.

If a segmental or accessory bile duct less than 2 to 3 mm in diameter has been injured and cholangiography demonstrates that the disrupted or injured ductal system does not communicate with a major ductal system or drain a large portion of the hepatic parenchyma, then simple ligation of the injured segmental or accessory duct is adequate. However, if the injured duct is 3 to 4 mm or larger, it may drain multiple hepatic segments or the entire right or left lobe. This should be defined via intraoperative cholangiography. Ducts that drain multiple hepatic segments require operative repair.

If the bile duct injury involves either the common hepatic duct or the common bile duct, the repair is best carried out at the time of injury recognition. The aims of any repair should be to maintain ductal length, to not sacrifice tissue, and to create a repair that will not result in postoperative bile leakage or stricturing. Partial transections of the biliary duct (i.e., usually involving less than a 180-degree circumference of the biliary tree) may be primarily closed over a T-tube. The duct is repaired with interrupted sutures, and the T-tube is brought out the duct via a separate choledochotomy (Fig. 109–8).

If the injury to the bile duct involves more than a 180-degree circumference or is a complete transection of the

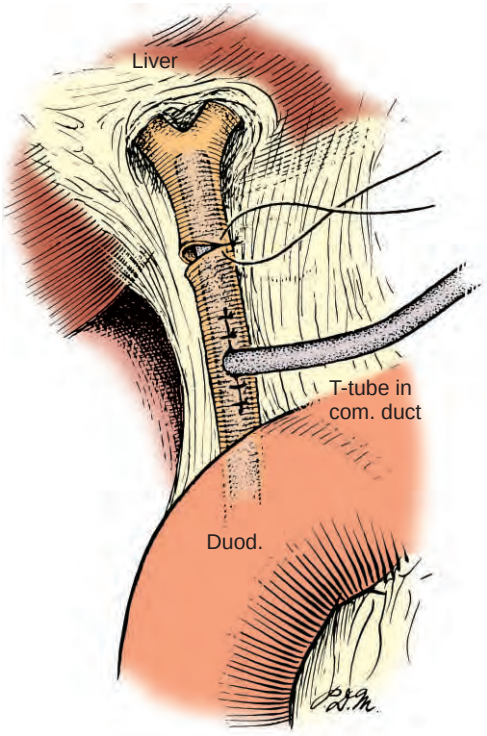

Figure 109–8. Primary end-to-end repair of a bile duct injury over a T-tube. In general, this technique is used for partial transections of the bile duct, when there has been no associated loss of ductal length. Note that the T-tube does not exit at the site of injury.

bile duct or if the injured segment of the bile duct is less than 1 cm in length, it may be possible to oppose the two ends of the duct without tension, performing an end-to-end anastomosis with the placement of a T-tube through a separate choledochotomy either above or below the anastomosis. Such end-to-end ductal repairs, however, are rarely achieved without some tension, even with additional mobilization of the duodenum via a Kocher maneuver. In fact, a restricture rate approaching 100% has been reported for such end-to-end repairs of laparoscopic bile duct injuries,[19] leaving open to question whether such a repair should ever be performed.

Most ductal transections, particularly high transections or those associated with significant loss of length of the biliary tree, should be repaired with a tension-free biliary-enteric anastomosis via a Roux-en-Y jejunal limb. In these circumstances, the distal bile duct should be oversewn, and the proximal bile duct should be débrided of injured tissue and anastomosed in an end-to-side manner to the Roux-en-Y jejunal limb (Fig. 109–9). The use of a Roux-en-Y jejunal limb is preferable to direct anastomosis to the duodenum via choledochoduodenostomy or hepaticoduodenostomy, because when the duodenum is used an anastomotic leak results in a duodenal fistula.

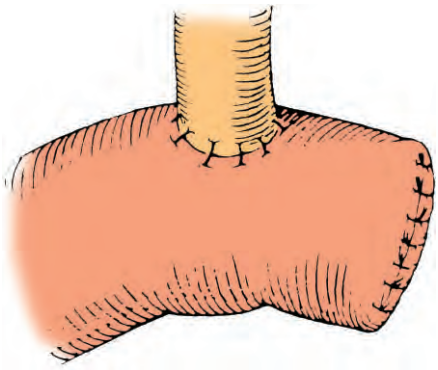

Figure 109–9. A completed Roux-en-Y hepaticojejunostomy. The anastomosis is typically performed with interrupted sutures, in a single layer. The Roux limb is usually 40 to 60 cm long.

Elective Repair of Postoperative Injuries or Strictures

The elective repair of established strictures or injuries depends primarily on the timing and presentation. Patients who have presented with sepsis require control of the sepsis with broad-spectrum antibiotics, percutaneous or endoscopic biliary drainage, and percutaneous or operative drainage of biliary collections. Once biliary drainage has been achieved and sepsis is controlled, attention should be paid to correcting fluid and electrolyte abnormalities, anemia, and possible nutritional deficits. The principles associated with successful surgical repair of an established biliary stricture or injury include (1) definition of the biliary anatomy, (2) exposure of healthy proximal bile ducts that provide drainage of the entire liver, (3) use of a suitable segment of intestine that can be brought to the area without tension (most frequently, a Roux-en-Y jejunal limb), and (4) creation of a direct biliary-enteric mucosa-to-mucosa anastomosis. In many circumstances, preoperatively placed percutaneous transhepatic stents can be useful technical aids to identify the proximal hepatic ducts, particularly with more proximal strictures.[20,21] Many surgeons do not use percutaneous transhepatic stents, particularly in patients with relatively low bile duct strictures. Such patients may undergo repair without preoperative percutaneous stenting or may be preoperatively stented by an endoprosthesis. There remains some controversy regarding the use of transanastomotic stents after bile duct stricture repair. Many surgeons use the preoperatively placed percutaneous transhepatic catheters, exchange them intraoperatively for Silastic transhepatic stents, and leave the anastomosis stented on a long-term basis. Other surgeons never or rarely use transanastomotic stenting.

The operative technique for biliary reconstruction with preoperatively placed percutaneous transhepatic catheters and transhepatic Silastic stents is shown in Figures 109–10 to 109–12. The actual operative procedure requires dissection of the porta hepatis, often with

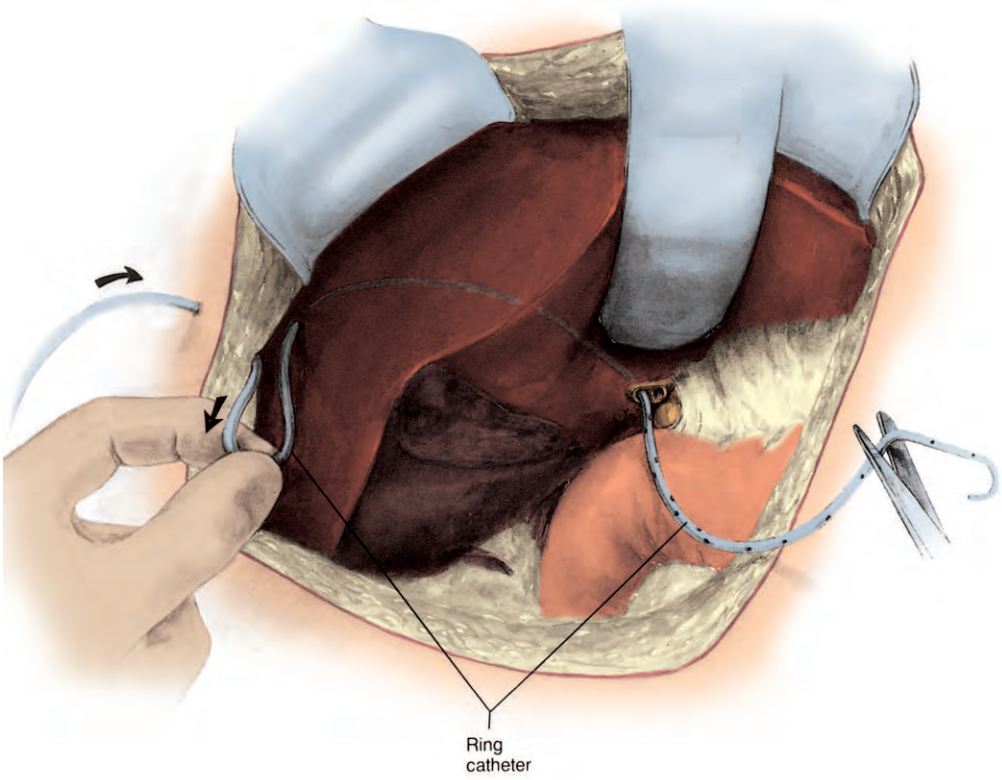

Figure 109–10. Repair of common hepatic duct stricture with transhepatic Ring catheter exiting at the bifurcation. The stricture has been resected, and the distal biliary tree is oversewn. The hepaticojejunal anastomosis can then be performed over the Ring catheter, or the Ring catheter can be exchanged for a Silastic transhepatic stent. (From Cameron JL: Atlas of Surgery, Vol 1. Toronto, BC Decker, 1990, p 43.)

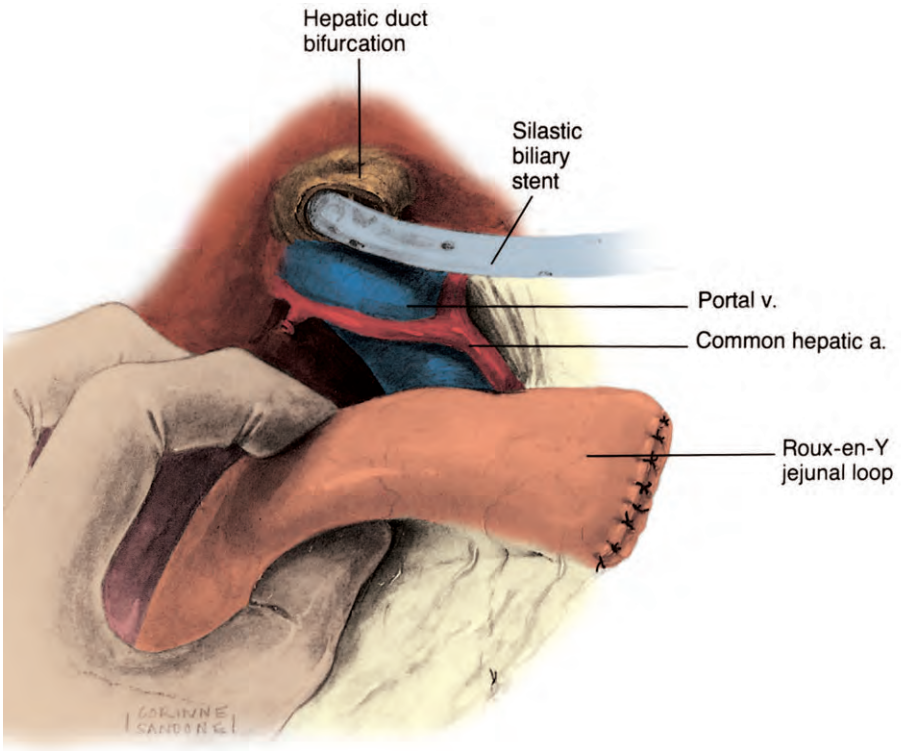

Figure 109–11. The Silastic transhepatic stent shown exiting the biliary tree, with the Roux-en-Y jejunal limb prepared for the hepaticojejunostomy. (From Cameron JL: Atlas of Surgery, Vol 1. Toronto, BC Decker, 1990, p 53.)

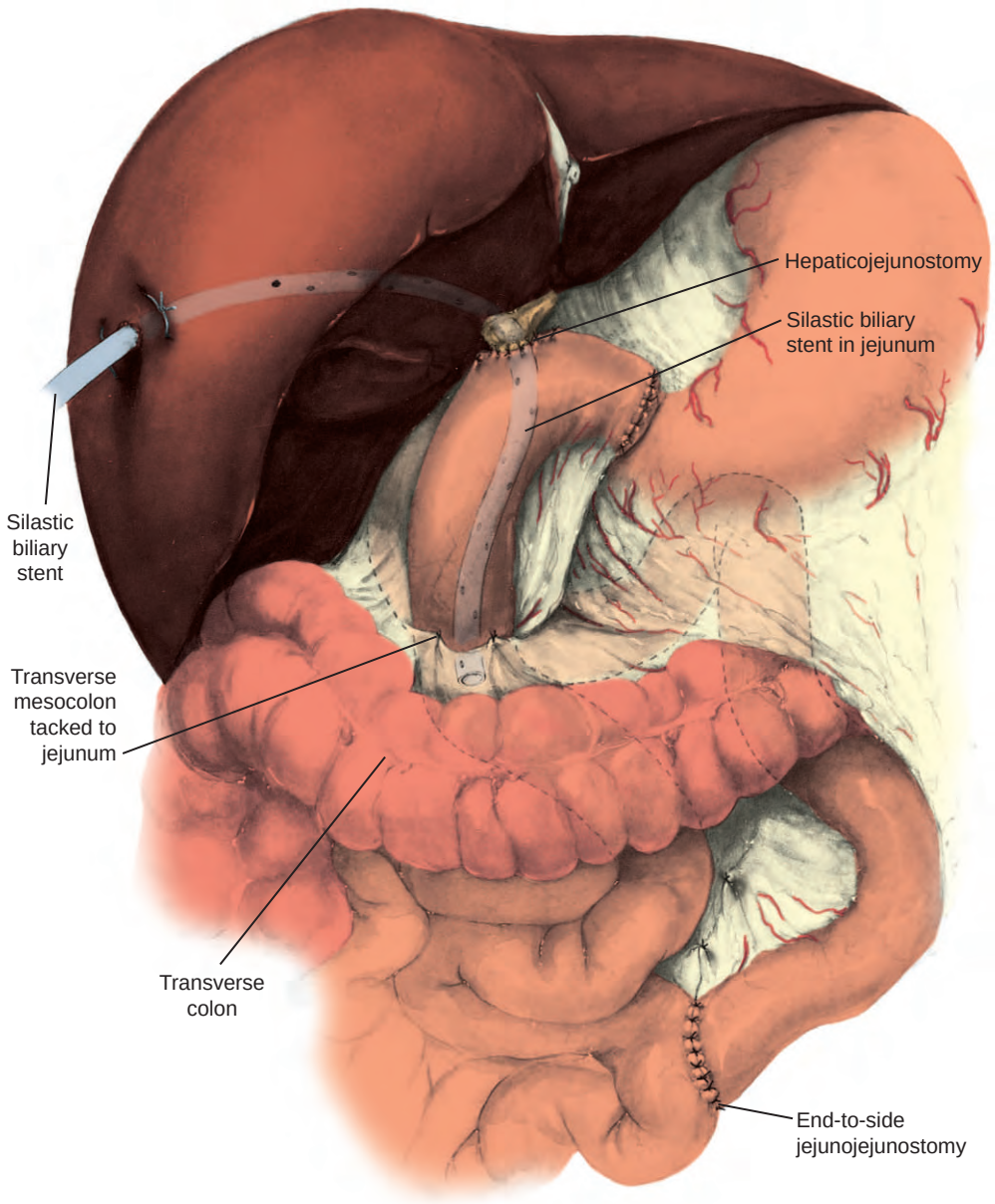

Figure 109–12. Completed repair showing the Silastic biliary stent traversing the liver and the hepaticojejunostomy. The Roux-en-Y jejunal limb has been brought to the hepatic hilum in retrocolic position. (From Cameron JL: Atlas of Surgery, Vol 1. Toronto, BC Decker, 1990, p 57.)

clearance of previous adhesions between the duodenum and hepatic flexure of the colon to the subhepatic space and gallbladder fossa. The identification of the proximal biliary segment above the stricture can be difficult and may be aided by the presence of a transhepatic biliary catheter. In most cases, the bile duct stricture will be resected, extending the resection proximally to a normal bile duct. The bile duct proximal to the stricture should be carefully dissected circumferentially in a cephalad direction for a distance of approximately 5 mm. Excessive proximal dissection should be avoided to prevent vascular compromise of this segment of duct, which will be used for the anastomosis. The distal biliary tree, if it is in continuity with the duodenum, is oversewn. The anastomosis can then be created as a standard end-to-side Roux-en-Y hepaticojejunostomy or choledochojejunostomy, typically using one layer of suture material. If the anastomosis is particularly high in the hilum or if a good mucosa-to-mucosa anastomosis cannot be performed, then the surgeon may choose to exchange the percutaneous transhepatic catheters for transhepatic Silastic stents. These Silastic stents are approximately 70 cm

long, ranging in size from 12 to 22 French. The multiple side holes present along 40% of the length of the stent are left to reside within the intrahepatic biliary tree and the portion of the Roux-en-Y jejunal limb that is used for the biliary anastomosis. The end of the stent without the side holes is brought through the hepatic parenchyma and out through a stab wound in the upper anterior abdomen.

Postoperative Complications and Death

Commensurate with the overall improvements in preoperative care, operative techniques, and postoperative management, there has been an improvement in immediate postoperative outcomes of the repair of bile duct strictures and injuries. In 1982, a review article evaluated 38 series published to that date, reporting on 7643 procedures in more than 5000 patients. In this review, the overall operative mortality rate was 8.6%.[22]

More recently with improved technology and a multidisciplinary approach, as well as improved surgical experience, the incidence of operative mortality has decreased markedly. A recent series of 200 consecutive patients managed at the Johns Hopkins Hospital reported three deaths in patients who did not undergo an attempt to repair who were referred with sepsis secondary to an uncontrolled biliary leak for a mortality of 1.5%.[18] Definitive surgical reconstruction was performed in 175 patients with a perioperative mortality of only 1.7% In this series the timing of repair, the mode of presentation, the previous attempts at repair, and the level of injury did not influence outcome. Chronic liver disease can be an important factor for operative mortality and morbidity, with advanced biliary cirrhosis and portal hypertension leading to mortality rates approaching 30%. Fortunately in the modern era, such advanced disease is uncommon.

In most series postoperative morbidity rates are in the range of 20% to 40%. In the recent Johns Hopkins series, complications occurred in 41% of patients. Most complications, however, were minor and could be managed with either interventional radiology techniques or conservative management. No patient required reoperation for postoperative complications. The median length of stay in this series was 8 days. Typical complications that are specific to the repair of bile duct strictures include anastomotic leaks, cholangitis, and hepatic insufficiency from preexisting biliary cirrhosis. Transhepatic stenting may also be attended by hemobilia, bile leaks from hepatotomy sites, and stent occlusion leading to cholangitis.

Long-Term Results

It appears that excellent long-term results can be achieved in roughly 80% to 90% of patients who undergo repair of bile duct strictures (Table 109–1). The definition of success requires that patients have no symptoms, jaundice, or cholangitis. Without a doubt, the length of follow-up is important, because although 80% of recurrent bile duct strictures present within 5 years of repair, 5% of recurrent strictures present more than 12 years after repair (Fig. 109–13).

It appears that in the era before laparoscopic cholecystectomy, reasonable long-term results were best obtained in centers specializing in hepatobiliary surgery. Questions have arisen as to whether the excellent results of bile duct stricture repair after open cholecystectomy could be directly transferred to patients sustaining laparoscopic bile duct injuries. The observation was made that some patients undergoing laparoscopic cholecystectomy and primary repair by the primary laparoscopic surgeon appeared to have a less favorable outcome. A report by Stewart and Way[19] reviewed 85 patients who had undergone a total of 112 biliary repairs. It appeared that four factors determined the success or failure of treatment in this series: (1) performance of preoperative cholangiography, (2) choice of surgical repair, (3) details of the operative repair, and (4) experience of the surgeon performing the repair. The importance of preoperative cholangiography for delineation of

Table 109–1 Selected Results of Surgical Repair of Bile Duct Strictures

Authors, Year	No. of Patients	Success Rate, %	Follow-up, Months
Pellegrini et al., 1984[36]	60	78	102
Genest et al., 1986[37]	105	82	60
Innes et al., 1988[38]	22	95	72
Pitt et al., 1989[24]	25	88	57
David et al., 1993[26]	35	83	50
Chapman et al., 1995[39]	104	76	86
McDonald et al., 1995[40]	72	87	<60
Tocchi et al., 1996[41]	84	83	108
Lillemoe et al., 2000[17]	156	91	58

Table 109–2 Repair of Laparoscopic Cholecystectomy Bile Duct Injuries: Results of Selected Series

Authors, Year	No. of Patients	Recognized at Laparoscopic Cholecystectomy, %	Bismuth Types 3 to 5*	Success Rate†, %
Walsh et al., 1998[13]	34	33	80	91
Bauer et al., 1998[14]	32	31	24	83
Lillemoe et al., 1997[12]	52	8	53	92
Mirza et al., 1997[15]	27	22	33	81
Nealon et al., 1996[42]	23	70	26	100

*See text for explanation of Bismuth type.
†Success rate is defined as when the patient is asymptomatic or has mild symptoms not requiring further invasive diagnostic or therapeutic procedures.

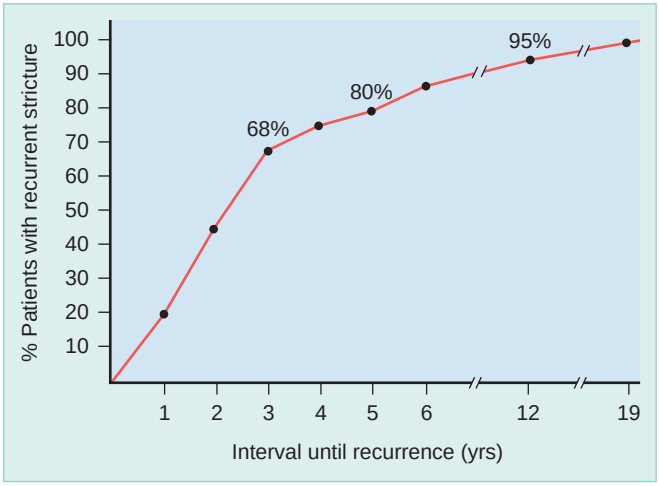

Figure 109–13. Cumulative percentage of recurrent strictures with respect to the time interval from the initial repair. (From Pitt HA, Miyamoto T, Parapatis SK, et al: Factors influencing outcome in patients with postoperative biliary strictures. Am J Surg 144:14, 1982.)

biliary anatomy was clearly defined: 96% of procedures in which cholangiograms were not obtained before surgery were unsuccessful, and 69% of repairs were not successful when the cholangiographic data were incomplete. In contrast, the initial repair was successful in 84% of patients when cholangiographic data were complete. The type of repair was important in determining outcome; primary end-to-end ductal repair over a T-tube was unsuccessful in all patients in whom a complete transection of the bile duct had taken place. Attempts at repair by the primary surgeon were successful in only 17% of cases. Further, in cases in which the first repair was performed by an experienced biliary surgeon, a 94% success rate was obtained. Results of several series reporting repair of laparoscopic bile duct injuries are given in Table 109–2.

The management was reported of 156 patients with bile duct injuries or strictures treated at the Johns Hopkins Hospital during the decade of the 1990s.[17] Data were collected prospectively on all patients, and follow-up was obtained via medical record review or telephone interview. The mean age of the patients was 43 years, and 77% were female. One hundred forty-five of these patients (93%) had their original surgery at an outside institution, with the original surgical procedure being laparoscopic cholecystectomy in 72%, open cholecystectomy in 21%, and other abdominal surgery or trauma in 3%. In total, 60 patients (41%) had undergone previous attempts at surgical repair before referral. The median time interval between injury and referral to Johns Hopkins Hospital was 3 months. Patients referred with laparoscopic cholecystectomy were more likely to have a biliary leak (37% vs. 13%) and less likely to have cholangitis (23% vs. 61%) than were other patients.

Among all 156 patients, the level of biliary obstruction was classified as Bismuth 1 in 5%, Bismuth 2 in 40%, Bismuth 3 in 30%, Bismuth 4 in 16%, and Bismuth 5 in 5%. Of note, patients whose initial injury occurred during laparoscopic cholecystectomy had a significantly higher percentage of complex injuries (63%), whereas only 41% of patients undergoing open cholecystectomy sustained such complex injuries (Fig. 109–14). Regarding outcomes, there was only one death in the postoperative period, for a perioperative mortality rate of 0.6%. The overall outcome with surgical reconstruction was excellent in 71% and good in 20%, yielding an overall success rate of 91%. There were 13 failures (9%) after surgical reconstruction. These failures were analyzed with respect to the presence of previous repair, symptoms, level of obstruction, number of stents, length of stenting, and interval to referral. There were no significant differences in outcome with respect to any of these factors. The only factor that seemed to influence outcome was the type of initial operation. The overall success rate associated with injury during laparoscopic cholecystectomy was 94%, significantly better than the success rates observed in patients referred after open

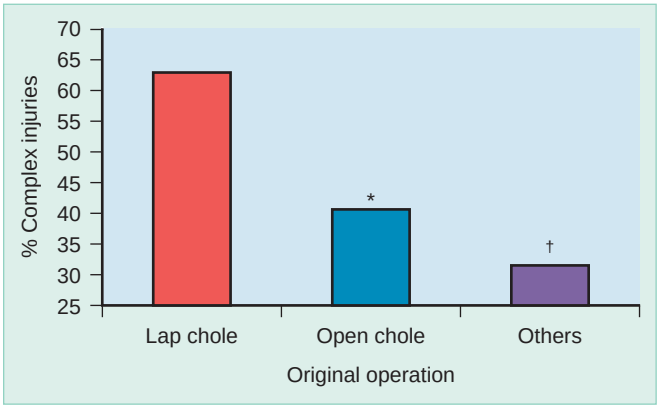

Figure 109–14. Complex bile duct injuries observed after laparoscopic cholecystectomy (63% were complex), open cholecystectomy (41%), or other operations (32%). *Complex injuries* were defined as Bismuth 3, 4, or 5 injuries. Patients undergoing laparoscopic cholecystectomy had a significantly higher percentage of complex injuries compared with those undergoing open cholecystectomy (*$P < 0.05$) or other procedures (†$P < 0.001$). chole, cholecystectomy; lap, laparoscopic. (From Lillemoe KD, Melton GB, Cameron JL, et al: Postoperative bile duct strictures: Management and outcome in the 1990s. Ann Surg 232:430, 2000.)

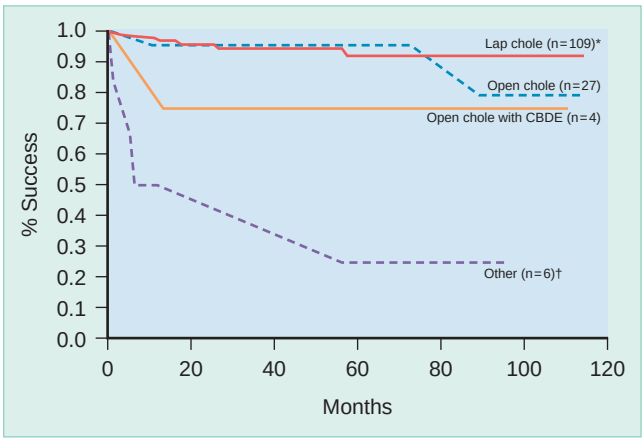

Figure 109–15. Actuarial success of surgical repair in patients undergoing bile duct repair. The success rate for patients undergoing repair after laparoscopic cholecystectomy was significantly better (*$P < 0.05$) than that for all other original operations. CBDE, common bile duct exploration; chole, cholecystectomy; lap, laparoscopic. (From Lillemoe KD, Melton GB, Cameron JL, et al: Postoperative bile duct strictures: Management and outcome in the 1990s. Ann Surg 232:430, 2000.)

cholecystectomy (80%) and other operations (Fig. 109–15).

Despite the overall high level of success in the surgical management of bile duct injuries associated with laparoscopic cholecystectomy, there is an impression that patients may have an impaired quality of life even after successful repair of their bile duct injury. Quality of life assessments after laparoscopic cholecystectomy–associated bile duct injury have been addressed in several recent reports. These results have generally reported either comparable or mildly diminished quality of life when compared to matched controls. In one such study, patients following successful surgical repair reported quality of life scores comparable to controls in the physical and social domains of a standardized health-related quality of life assessment.[23] Only in the psychological domain were patients following bile duct injury repair found to have significantly worse scores when compared to controls. Patients who reported pursuing a lawsuit following their injury had significantly worse quality of life scores in domains when compared to those who did not entertain legal action.

COMPARATIVE DATA BETWEEN SURGICAL REPAIR AND NONSURGICAL MANAGEMENT

Unfortunately, there are no prospective, randomized trials that compare operative with nonsurgical management of postoperative bile duct strictures. Few centers have large experiences with both operative and nonoperative management, and the management techniques have changed. However, two retrospective comparative studies exist that provide important information.

The first study, a retrospective review of the results at the Johns Hopkins Hospital by Pitt et al[24] between 1979 and 1987, compared percutaneous balloon dilation with surgery in 43 patients with benign postoperative bile duct strictures. Twenty-five patients underwent surgical repair with postoperative transhepatic stenting for a mean of 13 months, and 20 patients underwent percutaneous balloon dilation for a mean of four times, with transhepatic stenting for a mean of 13 months. Three patients were managed with both surgery and balloon dilation. The two groups were similar with respect to multiple demographic and clinical parameters. No deaths occurred in either group. Procedure-related complications occurred in 20% of the surgical patients and in 35% of the patients undergoing balloon dilation. A successful outcome was achieved in 89% of the surgical patients and in only 52% of the balloon dilation patients. To compare further the differences between the two approaches, total hospital stay and total procedural costs were determined. Although the initial hospitalization was longer for patients managed surgically, total hospital stay did not differ significantly between the two groups when rehospitalizations for further dilation, complications, or recurrences were considered. Cost data paralleled hospitalization data and did not differ significantly between the groups. A recent report from Johns Hopkins showed a 58% success rate with a mean follow-up of 76 months in 51 patients with bile duct strictures after laparoscopic cholecystectomy managed with percutaneous balloon dilation.[25]

A second comparative study from the Netherlands evaluated endoscopic versus surgical treatment of benign bile duct strictures.[26] Thirty-five patients were treated

surgically, and 66 were treated via endoscopic stenting. Surgical therapy consisted of Roux-en-Y hepaticojejunostomy, whereas endoscopic therapy consisted of the placement of an endoprosthesis that was exchanged every third month. Early complications occurred more frequently in the surgically treated group (26% vs. 8% for endoscopy); however, the only procedure-related death occurred in a patient who developed severe pancreatitis after the placement of an endoprosthesis. The total complication rates were similar at 26% for surgical patients and 35% for endoscopic patients. After surgery, excellent results were observed in 83% of patients, with 6 patients (17%) developing a recurrent stricture at a mean of 40 months after the initial operation. After endoscopic stenting, excellent results were obtained in 72% of patients, with 18% of patients developing restricture at a mean of 3 months after stent removal. These Dutch investigators concluded that endoscopic stenting should be considered as the initial approach to management in suitable patients in the hope of avoiding operative repair. Of note, the long-term follow-up information regarding outcomes in these patients was not reported.

PRIMARY SCLEROSING CHOLANGITIS

PSC is a chronic cholestatic liver disease of unknown cause. The disease is characterized by ongoing inflammation, destruction, and fibrosis of intrahepatic and extrahepatic bile ducts. PSC, although only about 1% as common as alcoholic liver disease, is a not uncommon indication for liver transplantation in adults in the United States. The disease progresses silently but relentlessly, and in most patients it leads to cirrhosis, portal hypertension, and liver failure.[27]

At presentation, 70% of patients with PSC are male, with a mean age of 39 years. Approximately 75% of all patients with PSC have inflammatory bowel disease, with 87% having ulcerative colitis and 13% having Crohn's disease (Table 109–3). The prevalence of PSC is approximately 3 cases per 100,000. Other diseases associated with PSC are also listed in Table 109–3. PSC is discussed in detail in Chapter 108.

Pathology

Four histologic stages of PSC have been identified. The initial lesion, stage I, is characterized by degeneration of epithelial cells in the bile duct and infiltration of the bile duct by lymphocytes and occasionally neutrophils. In stage II, the lesion is more widespread, with fibrosis and inflammation infiltrating the periportal parenchyma. As the disease progresses to stage III, portal-to-portal fibrous septa develop, and bile ducts may disappear and undergo severe degenerative changes. Stage IV is the end stage, characterized by frank cirrhosis. Macroscopically, thickening and induration of the common bile duct can be seen at laparotomy. The liver may appear normal in early stages, but as the condition progresses, the liver becomes coarsely nodular and stained with bile.

Table 109–3 Diseases Associated with Sclerosing Cholangitis

Disease	Frequency, %
Inflammatory bowel disease	75
Ulcerative colitis	50-65
Crohn's disease	3-10
Pancreatitis	10-25
Diabetes mellitus	5-10

Pathogenesis

The cause of PSC is unknown. A number of theories have been proposed on the cause of recurrent damage to the biliary ducts, including chronic portal bacteremia, toxic bile acid metabolites produced by enteric flora, chronic viral infections, ischemic vascular damage, toxins produced directly by enteric bacteria, and genetic abnormalities of immunoregulation.

The known association between PSC and ulcerative colitis has led numerous researchers to postulate that chronic portal bacteremia might cause chronic biliary tract infection, portal fibrosis, and, ultimately, PSC. Other researchers have suggested that PSC results from toxic bile acid metabolites generated from gut flora. Although some of these toxic metabolites are hepatotoxic in animals, no major abnormalities in the composition and concentration of bile acids have been found in patients with PSC or chronic inflammatory bowel disease. Another possible cause of PSC has been postulated to be toxic proinflammatory agents resulting from bacterial products. Although some experimental evidence exists to support this theory, there is no correlation between the severity of ulcerative colitis and that of PSC. Moreover, PSC may develop years before the onset of colitis or years after patients have had total colectomies. Unquestionably, genetic and immunologic factors appear to play a role in PSC, although the relationships are not clear. There is clearly a relationship between PSC and HLA-B8, -DR3, -DR2, and -DR4. The first two HLA types are associated with autoimmune diseases, whereas in patients with HLA-DR4, the course of PSC tends to be accelerated. In addition, there are measurable immunologic abnormalities in patients with PSC, such as hypergammaglobulinemia, perinuclear antineutrophil cytoplasmic antibodies, circulating immune complexes, increased metabolism of the complement system, and others. It is unknown, however, whether these immunologic abnormalities are primary events or are the result of the underlying hepatic disease.

Diagnosis

The diagnosis of PSC is based on characteristic changes in the intrahepatic and extrahepatic biliary tree, combined with the exclusion of disorders that cause secondary sclerosing cholangitis. Entities that may cause secondary sclerosing cholangitis include chronic bacte-

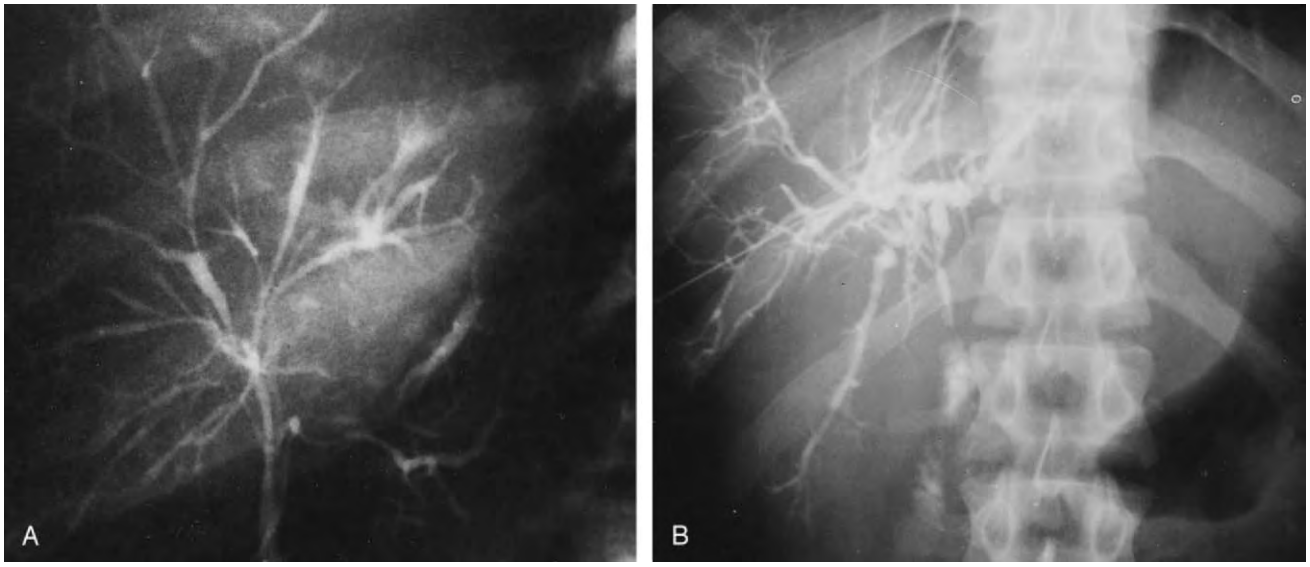

Figure 109–16. An endoscopic retrograde cholangiopancreatogram **(A)** and a percutaneous transhepatic cholangiogram **(B)** in two patients with primary sclerosing cholangitis. Note the multiple intrahepatic bile duct strictures and small peripheral bile ducts.

rial cholangitis in patients with bile duct stricture or choledocholithiasis; infectious cholangiopathy associated with acquired immunodeficiency syndrome; previous biliary surgery; congenital biliary abnormalities; ischemic cholangiopathy secondary to intra-arterial floxuridine (FUDR); hepatic allograft rejection; graft-versus-host disease in bone marrow transplantation, various collagen vascular diseases; histiocytosis X; sarcoidosis; and mast cell cholangiopathy.

Laboratory tests in patients with PSC usually show a cholestatic pattern, with most patients having elevations in serum alkaline phosphatase, increases in the aminotransferases, and normal serum albumin early in the disease. Bilirubin levels gradually increase as the disease progresses. Hypergammaglobulinemia is found in about 30% of patients, and increased immunoglobulin M levels are seen in up to half of all patients. Autoantibodies are less frequently seen in PSC than in autoimmune chronic active hepatitis or primary biliary cirrhosis.

Imaging of the biliary tract is essential to make the diagnosis of PSC. Endoscopic retrograde cholangiopancreatography is the method of choice, whereas MRCP may gain increasing importance. Percutaneous cholangiography is technically more difficult in patients with PSC because the intrahepatic ducts are often attenuated, fibrotic, or reduced in number. The characteristic radiologic findings of PSC include multifocal strictures and dilations, usually involving both the intrahepatic and extrahepatic biliary tree (Fig. 109–16).

Clinical Presentation

Most patients with PSC are initially asymptomatic and are identified on the basis of abnormal liver function tests, as discussed. Although asymptomatic, some patients may present with surprisingly advanced disease, as assessed both histologically and radiographically. Symptoms such as pruritus, fatigue, jaundice, and weight loss typically mark advanced disease. In about 10% of patients, fever, night sweats, chills, and pain in the right upper quadrant are present at the time of diagnosis. Blood cultures are rarely positive. It is not known whether these cholangitis-like episodes are caused by bacterial infections in areas near strictured and transiently occluded bile ducts or whether they are simply part of the underlying inflammatory process.

Natural History

Most patients with PSC are asymptomatic at the time of diagnosis and eventually develop symptoms. Cirrhosis, portal hypertension, and liver failure typically follow. In one study, the median length of survival from the time of diagnosis was 12 years. Patients who are symptomatic at diagnosis have shorter survival times than those who are diagnosed at an asymptomatic stage. Multivariate analyses have been used to identify prognostic variables and develop models that predict the progression of PSC. Variables that adversely affect survival include increasing age at diagnosis, increasing serum bilirubin and hemoglobin levels, worsening hepatic histology, the presence of splenomegaly, and elevated serum alkaline phosphatase level.

Treatment

A variety of immunosuppressive, antifibrotic, and anti-inflammatory agents have been used to treat PSC. To date, no drug has been shown to improve the natural history of the disease. In a disease with a known tendency

to exacerbations and remissions, anecdotal reports of drug therapy success must be looked at cautiously. Of the various drugs used to treat PSC, only a few have been evaluated in randomized, controlled trials. Drugs that have been studied include corticosteroids, penicillamine, ursodiol, azathioprine, methotrexate, and colchicine. There is little enthusiasm for corticosteroid therapy in PSC. Penicillamine has been evaluated in a double-blind, prospective trial and had no beneficial effect on symptoms, disease progression, or survival. Further, 21% of the patients had major side effects from the drug. Ursodiol has been associated with a clear improvement in the results of liver function tests, with therapy leading to a twofold to threefold increase in the serum bile acid concentration. In a prospective, randomized, double-blind, placebo-controlled trial, there was improvement in liver function tests and liver histology in those patients receiving ursodiol, but there was no difference in patient survival or in referral for liver transplantation.[28]

Three classes of drugs are useful in treating symptoms of sclerosing cholangitis. First, pruritus can be a problematic symptom for many patients. Pruritus can be treated with cholestyramine, a bile acid–binding resin that can be effective presumably because the true pruritogenic agent is excreted in the bile. Second, steatorrhea and malabsorption of fat-soluble vitamins may occur late in the course of PSC and can be treated with fat-soluble vitamin supplementation. Third, patients may have intermittent episodes of cholangitis, necessitating the use of antibiotic therapy. Prophylactic antibiotics such as amoxicillin, ciprofloxacin, or trimethoprim-sulfamethoxazole are often used for recurrent episodes of cholangitis.

Nonoperative Dilation Therapy

It appears that dominant strictures of the extrahepatic biliary tree may cause or exacerbate symptoms. Such strictures occur in 15% to 20% of patients with PSC and have been treated via endoscopic balloon dilation, endoscopic stenting, or percutaneous transhepatic approaches. Such treatment has relieved symptoms of jaundice, pruritus, and fever in some patients and improved liver function tests. At present, there are no controlled trials that evaluate such nonoperative therapy, but there appears to be little risk and some potential benefit from this approach.

Operative Management

The operative approach to patients with symptomatic PSC has evolved. In the 1980s and 1990s, several centers reported good results in patients with dominant hilar strictures treated via extrahepatic biliary resection or bypass.[29-31] One report of such an approach compares 50 patients managed with hepatic bifurcation resection and long-term transhepatic stenting with 54 patients treated nonoperatively, 28 patients treated medically, and 21 patients treated via liver transplantation; this experience reviews a total of 146 cases from 1980 to 1994 at the Johns Hopkins Hospital.[32] In noncirrhotic patients, the serum bilirubin level was significantly reduced from preoperative levels up to 3 years after bifurcation resection but was not reduced after endoscopic or percutaneous management (Fig. 109–17). For such noncirrhotic patients, overall 5-year survival rate was 85% after bifurcation resection compared with 59% after nonoperative dilation with or without stenting. However, for cirrhotic patients, survival after liver transplantation was longer than that after resection or nonoperative dilation with or without stenting. None of the 50 surgically resected patients developed cholangiocarcinoma during a mean follow-up of 62 months.

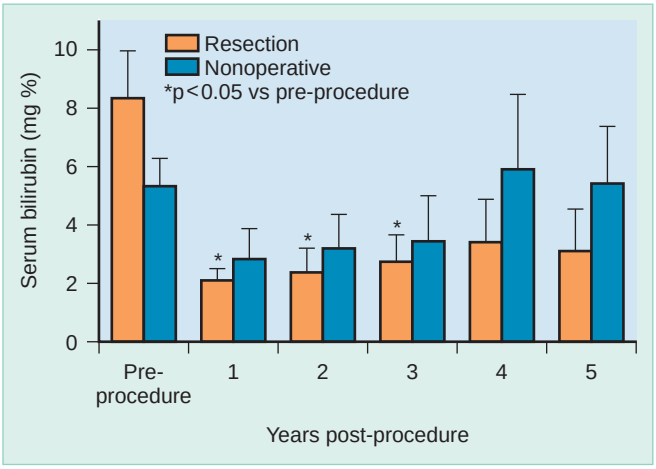

Figure 109–17. Serum bilirubin levels of patients with primary sclerosing cholangitis after bifurcation resection and nonoperative biliary drainage. The bilirubin levels were significantly lower at 1, 2, and 3 years after resection but not after nonoperative management compared with preoperative levels. (From Ahrendt SA, Pitt HA, Kalloo AN, et al: Primary sclerosing cholangitis: Resect, dilate, or transplant? Ann Surg 227:412, 1998.)

The issue of cholangiocarcinoma in PSC deserves special attention. Cholangiocarcinoma develops in approximately 10% to 15% of PSC patients followed for 5 years and in about 30% of patients followed for 10 or more years. Unfortunately, none of the current diagnostic techniques are 100% accurate for detecting cholangiocarcinoma. One study investigated the accuracy of serum levels of the tumor markers CEA and CA 19-9, showing that an index of the two serum tumor markers (using the formula CA 19-9 + CEA × 40) gave an accuracy of 86% for the diagnosis of cholangiocarcinoma, with a specificity of 100% and a positive predictive value of 100%. The cutoff value used for this analysis was 400.[33]

Overall, the role of bile duct bifurcation resection and stenting has diminished with the growing success of liver transplantation. Considerable data now support the use of liver transplantation in patients with advanced PSC, particularly in those patients with underlying cirrhosis. PSC has become one of the most common indications for liver transplantation in the United States. A report from Pittsburgh documenting the largest single-institution experience with liver transplantation notes that PSC was an indication for transplantation in 8% of the 4000

patients reported.[34] Survival rates after liver transplantation approximate 85%, 70%, and 60% at 1, 5, and 10 years, representing an improvement over earlier results. These results underscore the previous calculations that used a simulated control technique to compare the actual survival of 216 adult patients with the diagnosis of advanced PSC who underwent liver transplantation with the expected survival estimated by the Mayo PSC natural history model.[35] Using this mathematical modeling, the Kaplan-Meier survival probability was higher 6 months after transplantation than the Mayo model and remained significantly higher up to 5 years after transplantation. At all risk stratifications, transplantation significantly improved survival. This mathematical model, performed in an era of poorer liver transplantation survival than is seen today, supports the application of liver transplantation to patients with PSC.

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Chapter

110

Management of Common Bile Duct Stones

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The optimal treatment of choledocholithiasis is controversial. Many methods for treating common bile duct (CBD) stones have been reported, and the appropriate therapy depends on the patient's condition and the relative local expertise in laparoscopy, endoscopy, and interventional radiology. Before the age of laparoscopy, patients with choledocholithiasis required a laparotomy CBD exploration and T-tube placement. Laparoscopic CBD exploration (LCBDE) is now routinely performed with transcystic and transcholedochal techniques. Endoscopic retrograde cholangiography with or without sphincterotomy (ERC/ES) is commonly performed by endoscopists. Interventional radiologists may dislodge or disintegrate stones by percutaneous transhepatic cholangiography techniques. One of the main determining factors of who performs these procedures is if choledocholithiasis is detected before, during, or after cholecystectomy. In this chapter, we review the various techniques available to clear the CBD of stones, focusing on LCBDE. We propose an algorithm that assumes an advanced laparoscopic surgeon with excellent endoscopic and radiologic support (Fig. 110–1) and takes into account the ability to clear the CBD in the safest and most cost-effective manner.

DETECTION OF COMMON DUCT STONES

The most common clinical presentations for patients with choledocholithiasis are cholecystitis, pancreatitis, biliary colic, cholangitis, and jaundice. Cholangitis is most predictive, with some studies showing 100% specificity.[1] However, none of the other more common clinical presentations are predictive. A recent study by Tranter and Thompson[1] demonstrated a 14.2% incidence of choledocholithiasis in 1000 consecutive laparoscopic cholecystectomies (LC) with routine intraoperative cholangiogram. Patients presenting with cholecystitis, biliary colic, pancreatitis, and jaundice were found to have common duct stones 7%, 16%, 20%, and 45% of the time, respectively.

Transabdominal ultrasound is the most common imaging modality used in evaluating patients with biliary symptoms. Compared to its high accuracy in diagnosing cholelithiasis and cholecystitis, transabdominal ultrasound only has 50% to 80% sensitivity in detecting common duct stones, depending mostly on the presence of CBD dilation.[2,3] Some studies have shown that if sonographic CBD dilation is combined with age older than 55 years and abnormal liver enzymes, choledocholithiasis can be predicted up to 95% of the time.[4]

For those patients in which choledocholithiasis is suspected, more definite tests may be performed. ERC is highly specific in diagnosing common duct stones and may be therapeutic with sphincterotomy and duct clearance. However, this procedure is invasive and associated with significant morbidity. A recent prospective study of 1177 consecutive ERC demonstrated a 30-day morbidity rate of 15.9% with procedure related mortality at 1%.[5] Also, up to 61% of patients undergoing ERC will be found not to have common duct stones and will have undergone an unnecessary invasive test.[6,7]

Recently, endoscopic ultrasound (EUS) and magnetic resonance technology have been used to diagnose choledocholithiasis. To decrease unnecessary ERC/ES, some centers now routinely perform EUS prior to ERC. A recent study showed the sensitivity and specificity of EUS to be 98% and 99%, respectively.[8] Additionally, magnetic resonance imaging has shown promise as a noninvasive alternative to diagnose choledocholithiasis, with a recent study showing a positive predictive value of 95%.[9] MRCP is quite expensive though and does not have the therapeutic possibilities of ERC.

PREOPERATIVE ENDOSCOPIC THERAPY

ERC plays an important role in the early treatment of common duct stones for elderly or debilitated patients

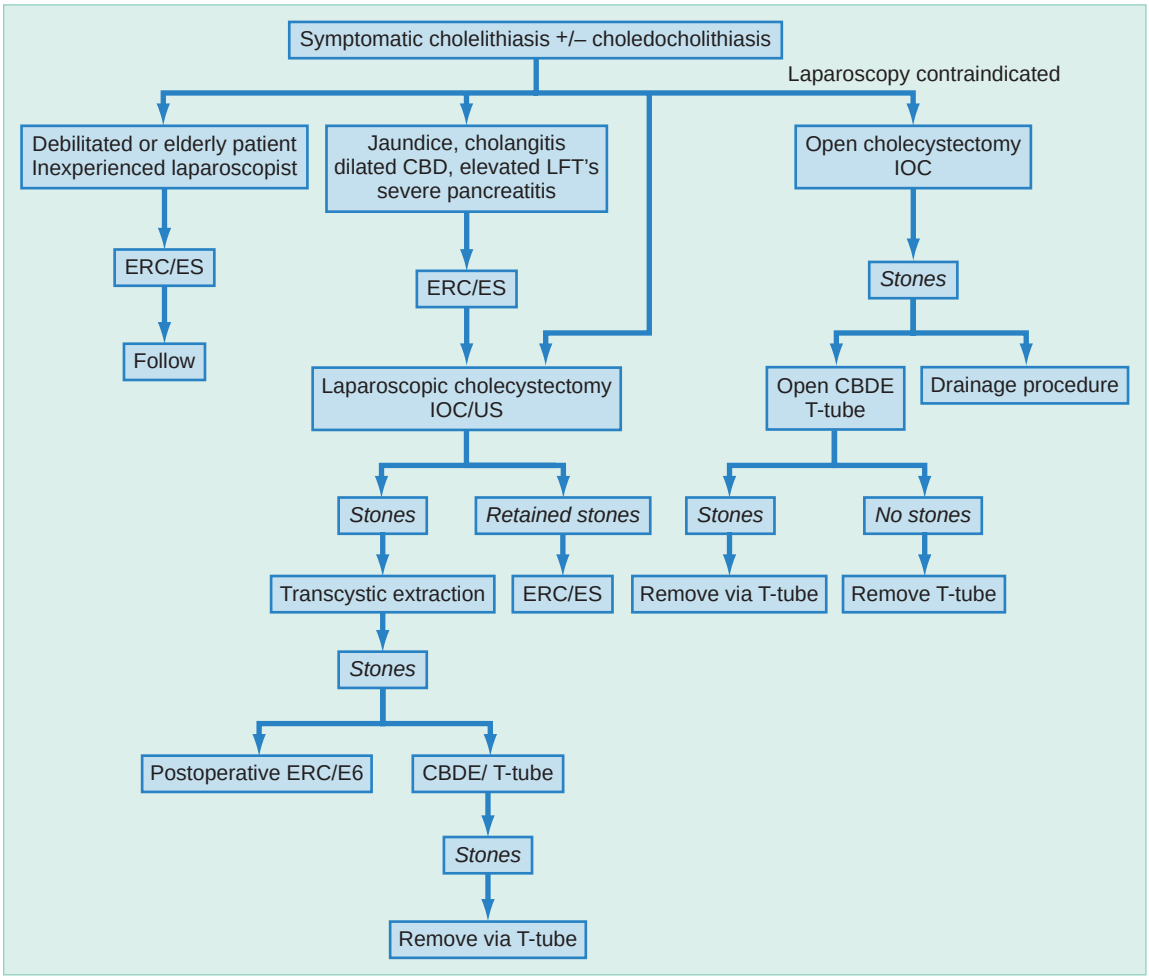

Figure 110–1. Management algorithm for treatment of common bile duct (CBD) stones. This approach assumes that the laparoscopist is experienced in transcystic techniques and that ERC/ES is at least 90% successful at CBD stone clearance. CBDE, common bile duct exploration; ERC, endoscopic retrograde cholangiography; ES, endoscopic sphincterotomy; LFT, liver function test; IOC, intraoperative cholangiography; US, laparoscopic ultrasonography. (From Jones DB, Soper NJ: The current management of common bile duct stones. Adv Surg 29:271, 1996.)

and in patients that present with jaundice, cholangitis, or severe pancreatitis. For patients who may not tolerate an operation, performing ERC/ES and leaving the gallbladder in situ is a good alternative to cholecystectomy, because recent studies have demonstrated that 75% to 84% of patients remain symptom free with up to 70-month follow-up.[10,11] Other studies have demonstrated a decreased mortality for patients undergoing ERC versus surgical drainage for cholangitis and severe pancreatitis.[12-14] The use of routine preoperative ERC for suspected choledocholithiasis, however, is not warranted because recent studies demonstrate that up to 61% of patients with suspected common duct stones undergo an unnecessary ERC with its associated morbidity.[6] Additionally, the European Association of Endoscopic Surgery prospective, randomized trial comparing two-stage versus single-stage management, demonstrated equivalent success rates for LCBDE versus preoperative ERC/ES followed by LC, with a significantly reduced hospital stay for LCBDE.[15] Tai et al. showed that LCBDE had a 100% success rate in salvaging failed preoperative ERC/ES.[16]

Much of the morbidity associated with ERC/ES is associated with the sphincterotomy. Endoscopic papillary dilation has been suggested as an alternative; however, a recent multicenter, controlled, randomized study demonstrated that endoscopic balloon dilation resulted in a higher rate of pancreatitis compared with sphincterotomy and recommended that it should be avoided in routine practice.[17] A recent meta-analysis suggested that dilation should be the preferred method for endoscopic removal of common duct stones in patients with coagulopathy.[18]

INTRAOPERATIVE DIAGNOSIS AND TREATMENT

For patients undergoing LC, the CBD should be imaged if choledocholithiasis is suspected or if the biliary

anatomy is unclear. This can be achieved by intraoperative cholangiography (IOC) or laparoscopic ultrasonography (LUS). Prior to either procedure, a clip is applied high on the cystic duct at its junction with the gallbladder to prevent stones migrating down the duct. To perform IOC, the cystic duct is partially transected and "milked," moving stones away from the CBD and out the ductotomy. A cholangiography catheter is inserted into the cystic duct and secured in place with a clip, grasping jaws, or balloon fixation. Cholangiography is now routinely performed with real-time fluoroscopy while injecting 5 to 10 ml of water-soluble contrast medium. The following characteristics should be ascertained: (1) the length of cystic duct and location of its junction with the CBD; (2) the size of the CBD; (3) the presence of intraluminal filling defects; (4) the free flow of contrast into the duodenum; and (5) the anatomy of the extrahepatic and intrahepatic biliary tree.

Evaluation of the CBD by LUS is an alternative to IOC, even though most surgeons do not have experience with this technique. A recent prospective study showed that LUS had greater sensitivity and equal specificity compared with IOC for detecting CBD stones.[19] LUS has better resolution than transabdominal ultrasonography, and in experienced hands, LUS appears to be as accurate as cholangiography for demonstrating choledocholithiasis and can be performed more rapidly.[20,21] In a prospective, multicenter trial with 209 LC patients, the time to perform LUS (7 ± 3 minutes) was significantly less than that of IOC (13 ± 6 minutes).[20] The study also showed that LUS was more sensitive for detecting stones but that IOC was better in delineating intrahepatic anatomy and defining anatomical anomalies of the ductal system. The authors concluded that the two methods of duct imaging were complementary.

LAPAROSCOPIC COMMON BILE DUCT EXPLORATION

When CBD stones are found, laparoscopic CBD exploration can take place via the cystic duct (transcystic technique) or by directly incising and opening the CBD with stone retrieval (laparoscopic choledochotomy). In the transcystic duct approach, small stones can often be flushed through the ampulla into the duodenum. Intravenous glucagon (1 to 2 mg) may be used to relax the sphincter of Oddi, followed by vigorous flushing of 100 to 200 ml of saline. When these methods fail, a helical stone basket can be passed over a guidewire through the cystic duct and into the CBD to extract stones under fluoroscopic guidance. If attempts at transcystic basket extraction fail, a choledochoscope (≤10 French) should be tried next to remove the stones under direct vision. If the CBD stone is larger than the lumen of the cystic duct, the cystic duct should first be balloon dilated to a maximum of 8-mm diameter but never larger than the internal diameter of the CBD.[22] The choledochoscope is then passed into the peritoneal cavity through the midaxillary port, using a sheath to prevent damage to the scope by the port's valve. The choledochoscope is then inserted through the cystic duct into the CBD under direct vision. Continuously infusing saline through the biopsy channel helps dilate the lumen of the duct facilitating visualization. The tip of a Segura-type stone basket is advanced via the working channel of the scope beyond the stone and opened. As the basket is pulled backward and rotated, the stone is ensnared (Fig. 110–2).[23] A completion cholangiogram or ultrasound should always be performed to conclusively demonstrate clearance of the duct. Because of tissue edema secondary to ductal dilation and manipulation, the cystic duct stump is ligated (rather than clipped) for added security.

Successful transcystic duct clearance has been reported in 80% to 98% of patients in recent series.[15,24,25] Complications, such as infection and pancreatitis, have been reported in 5% to 10% of patients with a mortality rate of 0 to 2%. The duration of hospitalization following an uncomplicated transcystic duct stone extraction is the same as that for LC alone, averaging 1 to 2 days. The main advantage of the transcystic approach is that it avoids choledochotomy. Poor candidates for transcystic extraction techniques are those with large or multiple CBD stones, those with stones in the proximal ductal system, and those with small or tortuous cystic ducts.

Other novel transcystic approaches include balloon dilation of the sphincter of Oddi and antegrade sphincterotomy. Carroll et al. reported successful clearance of CBD stones in 17 (85%) of 20 patients by balloon dilation; however, even in this small series, three patients (15%) experienced mild postoperative pancreatitis.[26] This method should be avoided in patients with preexisting pancreatitis, biliary dyskinesia, or anatomic sphincter anomalies. A sphincterotome may be inserted via the cystic duct and its tip placed just through the ampulla of Vater into the duodenum. A duodenoscope is passed transorally and used to allow proper positioning of the sphincterotome before applying current to perform a sphincterotomy. DePaula and associates have reported the performance of transcystic antegrade sphincterotomy at the time of LC in 22 patients, and all had successful stone clearance without complications; the procedure added only 17 minutes to the operation.[27]

If the transcystic approach fails, we recommend laparoscopic choledochotomy. Indications for this procedure are multiple or large stones or those positioned within the proximal bile ducts in patients with a CBD diameter larger than 8 to 10 mm.[28,29] Stay sutures are usually placed on either side of the midline of the anterior CBD wall to allow anterior traction on the duct. A longitudinal choledochotomy is made on the distal CBD, of adequate length to allow easy placement of a choledochoscope and removal of the largest stone.

After the stones are removed under endoscopic visualization, the ductotomy is usually closed either primarily or over an appropriately sized T-tube. Some centers have used transcystic tubes (C-tubes) or antegrade stenting with choledochorrhaphy for CBD drainage.[29,30] Common duct closure is accomplished with fine absorbable sutures using intracorporeal suturing techniques, and if a T-tube or C-tube is used, it is exteriorized through the lateral port site. Recent studies have demonstrated comparable results regardless of the technique of

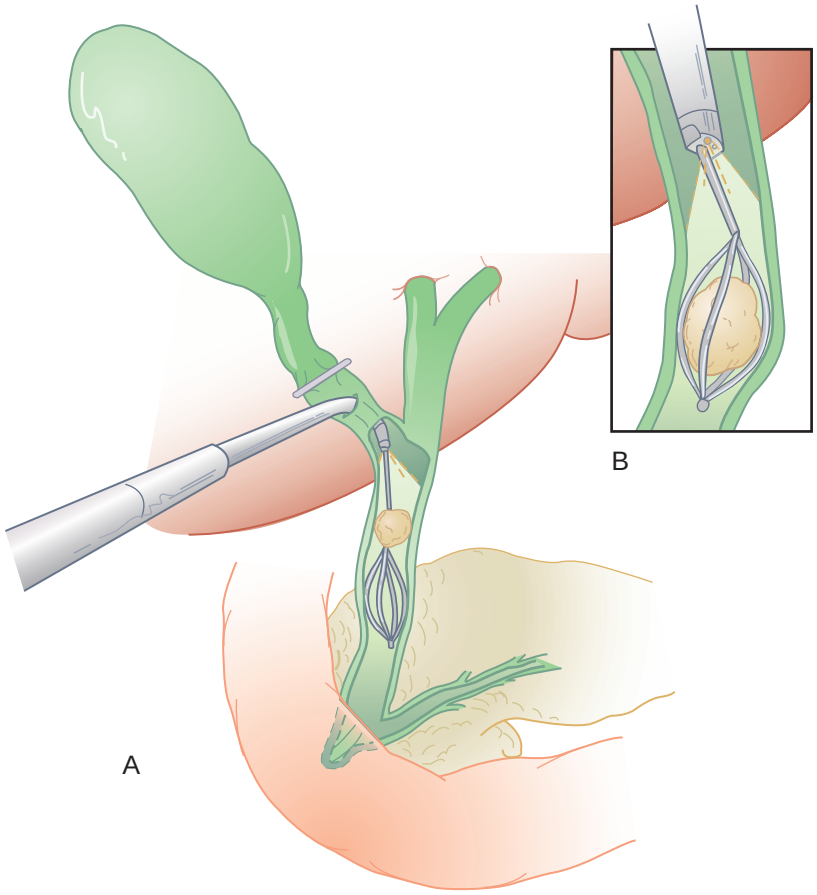

Figure 110–2. Transcystic choledochoscopy. **A,** The flexible choledochoscope is passed into the common bile duct through the cystic duct. Under direct vision the basket is advanced distal to the stone and opened. **B,** As the basket is withdrawn through the working channel of the choledochoscope, the stone is ensnared. The basket, stone, and choledochoscope are then removed as a unit. (From Jones DB, Soper NJ: The current management of common bile duct stones. Adv Surg 29:271, 1996.)

duct closure.[31] Others have shown decreased complications with primary closure compared with T-tube use.[29,32]

The patient is generally discharged 2 to 4 days postoperatively. If a T-tube is used, a final cholangiogram is performed 14 to 21 days postoperatively with removal of the tube if no abnormalities are noted. Retained stones demonstrated by T-tube cholangiography may be effectively removed percutaneously after allowing maturation of the T-tube tract. Percutaneous extraction is successful in more than 95% of patients with retained stones,[33] otherwise postoperative ERC will be required.

Overall, laparoscopic choledochotomy is successful in 84% to 94% of patients with a minor morbidity rate of 4% to 16% and a mortality rate of 0 to 2%.[15,24,25] Potential complications of this technique include CBD laceration, bile leak, sewn-in T-tubes, and stricture formation.[28] Many surgeons have not mastered laparoscopic suturing and feel uncomfortable closing the choledochotomy for fear of a resultant stricture; however, no biliary strictures were identified in two recently published studies of more than 500 patients undergoing LCBDE with a mean follow-up of more than 3 years.[34,35]

Recently, some centers have explored intraoperative ERC as an alternative to CBD exploration. Enochsson et al. reported that the technique was safe with 93.5% duct clearance; however, it added 1 hour of operative time compared with LC alone.[36] In another study, intraoperative ERC was as effective as LCBDE in duct clearance (~90%), but morbidity was doubled and hospital costs were significantly increased.[37] Intraoperative ERC also relies on preoperative coordination with a skilled endoscopist if the surgeon is not trained in ERC. Positioning in the operating room also makes the technique more difficult than in the endoscopy suite.

The possibility of finding CBD stones at the time of LC and potential treatment plans must be discussed with the patient prior to the operation. Many surgeons routinely leave CBD stones in place during LC for planned postoperative endoscopic removal. Additionally, a recent prospective study reported that more than 50% of clinically silent CBD stones passed spontaneously within 6 weeks.[38] Neither the number of stones nor stone size was predictive of spontaneous stone passage. The authors suggested a short-term expectant management approach for patients with clinically silent choledocholithiasis.

POSTOPERATIVE ENDOSCOPIC THERAPY

Postoperative ERC/ES should be considered when (1) LCBDE fails to clear the duct; (2) the surgeon is inexperienced in LCBDE; (3) retained stones are discovered postoperatively; (4) a patient's comorbidities make a prolonged operation risky; and (5) the CBD is small and prone to postoperative stricture. Multiple studies have

shown that the incidence of retained CBD stones after LC is approximately 2.5%.[35,39] Regardless of the reason, postoperative ERC/ES maintains the goals of minimally invasive surgery with a rapid return to full activity. However, relying on postoperative ERC/ES subjects the patient to an additional procedure with its associated morbidity and possibly a second operation if endoscopic stone extraction fails. In a recent study by Rhodes et al., 80 patients discovered to have choledocholithiasis at the time of LC were randomized to have LCBDE versus postoperative ERCP.[40] Clearance of the duct was 100% for LCBDE and 93% for ERC, with a significantly decreased hospital stay for patients undergoing LCBDE. Other studies have shown that even in experienced hands, endoscopic sphincterotomy has an overall failure rate for stone clearance of 4% to 18%.[41] Because of the uncertainty of postoperative ERC, it may be reasonable to insert a catheter through the cystic duct into the CBD at the time of LC when CBD stones are discovered. Leaving a transcystic catheter in the CBD may increase postoperative ERC success by allowing a guidewire to be passed into the duodenum, thereby ensuring cannulation of the duct.[42]

Ultimately, the overall skill and comfort level of available surgeons and endoscopists determine the algorithm used to treat patients with choledocholithiasis. Open CBDE (OCBDE) should always be considered a viable option.

OPEN COMMON BILE DUCT EXPLORATION

OCBDE should be considered the default position, not a "failure," if LCBDE and/or postoperative ERC are unsuccessful. The most common reason to convert to OCBDE is an impacted stone at the ampulla of Vater, and these cases require a transduodenal exploration. OCBDE should also be considered as the initial procedure of choice if patients present with dilated CBD or multiple CBD stones. This entails performing either a choledochoenterostomy or a sphincterotomy ("-plasty"). Studies have shown overall similar results with either of the two operations. Therefore, surgeon experience should dictate which one is performed.[43] Some authors, though, have suggested choledochoenterostomy for CBD greater than 2 cm in diameter to create a large opening between the bile duct and intestine.

Sphincterotomy and Sphincteroplasty

Sphincterotomy consists of incising the distal part of the sphincter musculature for a distance of approximately 1 cm. This incision should not extend beyond the outer wall of the duodenum. A sphincteroplasty requires complete division of the sphincter muscle. This creates a patulous, wide opening that is followed by suture approximation of the wall of the duodenum to the wall of the CBD.

After a choledochotomy is made as previously described, a catheter or dilator is passed distally and left in place to serve as a guide. A generous Kocher maneuver is then performed, after which a longitudinal anterior duodenotomy is made at the level of the ampulla, which can be palpated. The dilator is then used to bring the ampulla into the operative field, being careful not to perforate the duct. For sphincterotomy, the ampulla is then incised sufficiently along the anterosuperior side (opposite the pancreatic duct orifice) to permit removal of the impacted calculus.

For sphincteroplasty, the ampulla and distal CBD are divided for a distance of 1.5 to 2 cm directed anteromedially. The sphincter is usually divided sequentially between small clamps, with sequential suture approximation of the duodenal and bile duct mucosa. This is done using fine interrupted absorbable suture. The duodenum is closed transversely and the choledochotomy is managed as previously described.

Choledochoenterostomies

The most common choledochoenterostomy is the side-to-side choledochoduodenostomy, usually in the setting of a dilated CBD with multiple stones. A generous Kocher maneuver is performed and the distal CBD is exposed. A 2- to 3-cm longitudinal choledochotomy is made close to the lateral border of the duodenum along with a similar-sized longitudinal duodenotomy at the corresponding location. A "diamond-shaped" anastomosis is made with interrupted absorbable sutures. One potential complication from this is the "sump syndrome" caused by food or other debris caught in the distal CBD. This complication is rare (~1%) and can be managed with ERC/ES.[44,45] Other authors have suggested end-to-side choledochoduodenostomy as well as choledochojejunostomy as alternatives,[46] although endoscopic biliary access following these operations is technically challenging.

CONCLUSION

There are many ways to treat patients with choledocholithiasis. The algorithm proposed is only a guideline, and ultimate treatment will depend on physician experience and available resources.

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Part

3

Liver

Chapter

111

Anatomy and Physiology of the Liver

Ernesto P. Molmenti · Arnold Radtke · George C. Sotiropoulos · Massimo Malagó

Events such as repairs of surgical hepatobiliary injuries, the advent of liver transplantation, advanced resections, and interventional radiology techniques led to a radical change in the interpretation of surgical functional hepatic anatomy. Subsequently, live-donor and deceased donor segmental liver transplantation made it a necessity.[1-6] Lasala and Molmenti described this reinvention of hepatic anatomy as derived from an anatomic-physiologic inside-out approach, as opposed to the purely topographic outside-in view of the classics (Fig. 111–1).[2]

An important conceptual remark is that human anatomy is classified and classifiable, but in cases such as delicate resections or live liver donors, there are tools to outline the "individual anatomy" of the subject undergoing surgery. Although we believe that this chapter provides the basic concepts of anatomy, we would also like to remark that such rules do not always apply.

MODERN ANATOMIC APPROACH TO LIVER SURGERY

The liver is a single organ that can be functionally regarded as two hemilivers. The parenchyma can be further subdivided into several regions sharing common arterial, portal, and biliary supply and venous drainage. The portal and venous systems delimit these regions that are named sectors and segments, respectively (Figs. 111–2 to 111–5). The liver has a rather constant anatomic pattern, the knowledge of which allows for a safe surgical approach. Nevertheless there are some anatomic irregularities, and in particular instances exact knowledge of the anatomy specific to the individual patient being examined or operated on is necessary (live donors, left extended or central hepatectomies, caudate lobe masses). In these cases a computed three-dimensional reconstruction of each anatomic detail is possible following an accurate computed tomographic or magnetic resonance imaging contrast scan. Several software packages are currently available that allow for the mapping of the individual anatomy as well as for the calculation of volumes corresponding to the whole liver, liver sectors, and segments.* Our results demonstrate the reliability of virtual three-dimensional reconstructions based on standard anatomic landmarks for both surgical planning and graft volume calculations (Fig. 111–6).[13] For standard liver surgery, the operating surgeon should be familiar with the basic anatomic pattern of the liver and the most frequent variations that have been described.

*Hepavision, MeVis-Germany, Hitachi-Japan, Hepavis-Slovenia, Université de Starsbourg-France.

A B

Figure 111–1. **A** and **B,** Classic depictions of the liver anatomy. (**A** and **B,** From Bourgery JM, Jacob NH: Traité Complet de L'anatomie de L'homme. In Delaunay CA [Éd]: Tome Cinquième. Paris, 1839. [Private collection of Ernesto P. Molmenti, MD, PhD, MBA.])

EMBRYOLOGY OF THE LIVER

The liver primordium, also known as *diverticulum hepatis* or *liver bud,* arises from endoderm in the 3rd-4th week of embryologic development and invades the septum transversum, vitelline (omphalomesenteric) veins, and umbilical veins. Its connection to the embryologic duodenum (foregut) will eventually become the bile duct.[7,8] Embryologically, the liver receives blood from both portal and umbilical veins, themselves connected by the left portal vein.[9,10] Although the primitive portal veins arise from the caudal part of the vitelline veins, the primitive hepatic veins arise from the cranial part of the vitelline veins.[7,11] In humans and many other mammals, the inferior vena cava (IVC), ductus venosus, and umbilical vein are initially surrounded by liver parenchyma and become extrahepatic only in later stages of embryologic development.[10] The arteries develop in conjunction with the bile ducts at a later period than the veins. On the right side, arteries and bile ducts follow the trajectory of the portal venous branches. On the left side, although arterial and biliary branching follows a symmetrical pattern similar to that of the right side, the portal vein branches do not.[11] During early stages of development, there are three hepatic arteries: (1) a left hepatic artery arising from the left gastric artery, (2) a middle hepatic artery arising from the celiac trunk, and (3) a right hepatic artery arising from the superior mesenteric artery. Although in most cases the middle artery is the only one that persists, variations in regression and origin of these three early arteries account for the so-called accessory and replaced variants.[10] A complete ductal system is present by the 10th week of intrauterine life.[8,10] The mesoderm of the septum between liver and abdominal wall develops into the *falciform ligament.* The surface of the developing liver in contact with the diaphragm is devoid of peritoneum, and the so-called bare area is a reminder of such association.[7,8] By the 10th week, the liver is involved in hematopoietic function, an activity that diminishes markedly during the 8th and 9th months of gestation.[7] By the 12th week, the liver is already producing bile.[7] However, hepatocytes only attain single-cell plate configuration by the age of 5 years.[12]

Several events take place at birth. The *ductus venosus,* which optimized venous return from the placenta to the fetus by connecting the left umbilical and common hepatic vein, closes and becomes the *ligamentum venosus.* Also at birth, the *extrahepatic* umbilical vein closes and becomes the ligamentum teres.[11]

True anomalies of the liver are relatively infrequent. Prolongations of liver tissue from either the right (Riedel's lobe) or left lobes usually present as incidental abdominal masses. In other instances, hepatic tissue connected by an isthmus to the liver is found in the chest. Small accessory collections of tissue attached to the liver by a pedicle are also occasionally encountered.[8]

HEPATIC DIVISIONS

Several nomenclatures and topographic divisions have been proposed. According to Couinaud, the right and left hemilivers are supplied by first-order branches. Sectors are supplied by second-order branches. Segments are supplied by third-order branches. Subsegments are supplied by fourth-order or other branches.[10] Segments are numbered in a counterclockwise fashion, from I to VIII.[10] A main portal fissure, a right portal fissure, and a left portal fissure are grossly or conceptually defined, since they may not always be anatomically present.[10,11] Left and right paramedian sectors are adjacent to the main portal fissure. Left and right lateral sectors are located on the outer side of the corresponding paramedian ones (see Figs. 111–2 to 111–5).[10] During

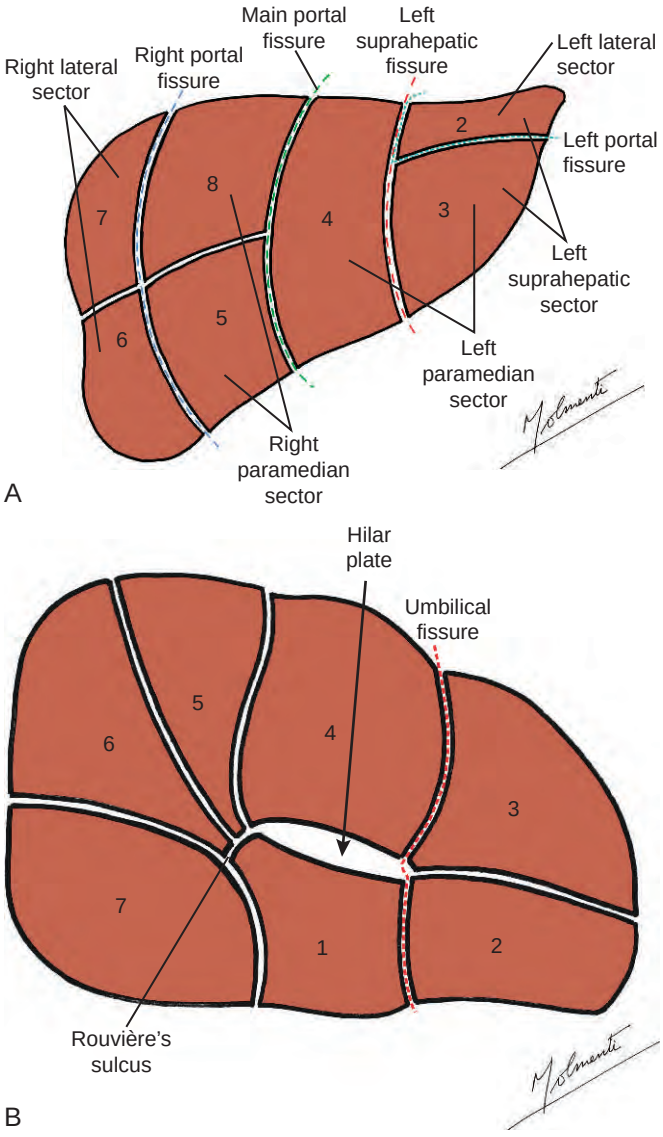


Figure 111–2. **A** and **B,** Schematic representation of the liver anatomy. The hepatic segments have been numbered, and the major structures have been labeled.

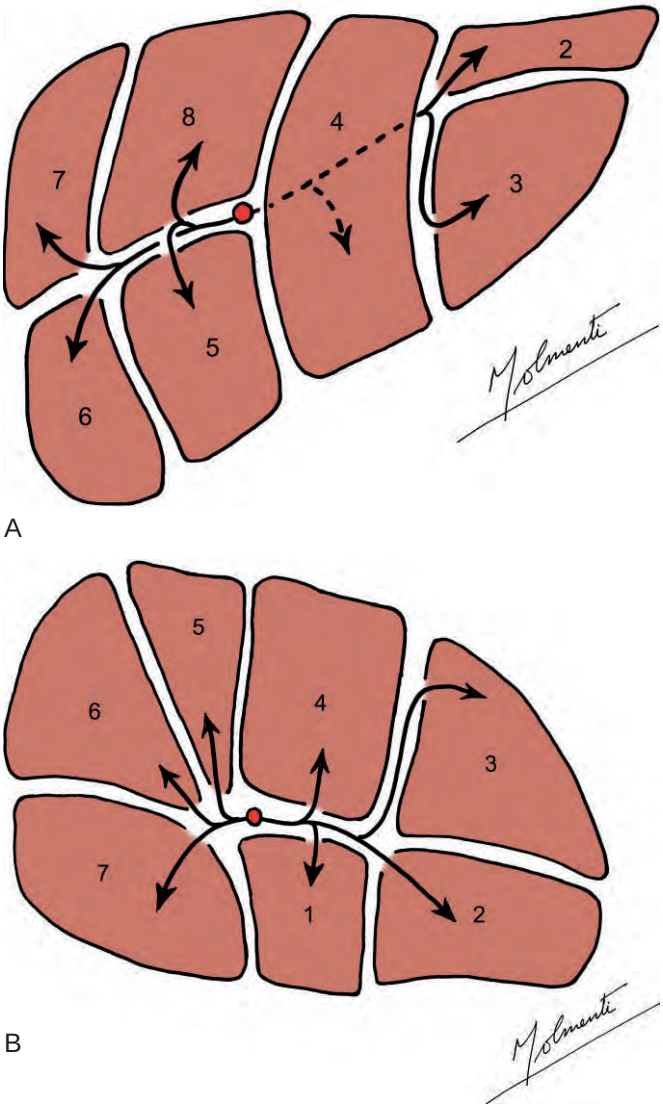


Figure 111–3. **A** and **B,** Schematic representation of the arteriobiliary liver anatomy.

our discussion, we follow this nomenclature with some modifications.[10,11]

VASCULOBILIARY SHEATHS

Couinaud referred to the vasculobiliary sheaths that envelop the portal elements as "the most important structure of liver anatomy."[10,14] They seem to have been described initially by Walaeus in 1640 and thus some have used the terms *walaean pedicles* or *walaean sheaths.*[10,15] Glisson published his description of the liver "tunic" in 1642, and Laennec did so in 1803.[10,16,17] The elements of the *portal pedicle* (hepatic artery, portal vein, bile ducts, nerves, and lymphatics) are surrounded throughout their trajectory to the parenchymal plates by connective tissue. Not so the hepatic veins.[10,18] The *hilar plate* is located over the left and right pedicles, and the portal division, on the hilum of the liver.[10,18] The *umbilical plate* is found in continuity with the hilar plate and the round ligament, covering the left paramedian pedicle in its upper surface.[10] According to Couinaud and others, dissection of the hilar plate allows for the detachment of the hilar contents.[1,2,10,18] Exposure of the umbilical plate is the gateway to the segmental and sectoral pedicles of the left liver. Since dissection at the level of the plates can lead to complications, an approach to the sheaths is recommended.[10] This strategy has been applied by Lazorthes et al. in the so-called suprahilar approach for anatomic hepatectomies and segmentectomies.[19] Sheaths originate at the right edge of the hilum, at the umbilical plate, and at the posterior margin of the hilar plate. From these sites they will reach the right liver, the left liver, and the caudate area, respectively.[10,18] In cases of narrow hila or hila of difficult access, consideration should be given to dividing the anterior portion of the

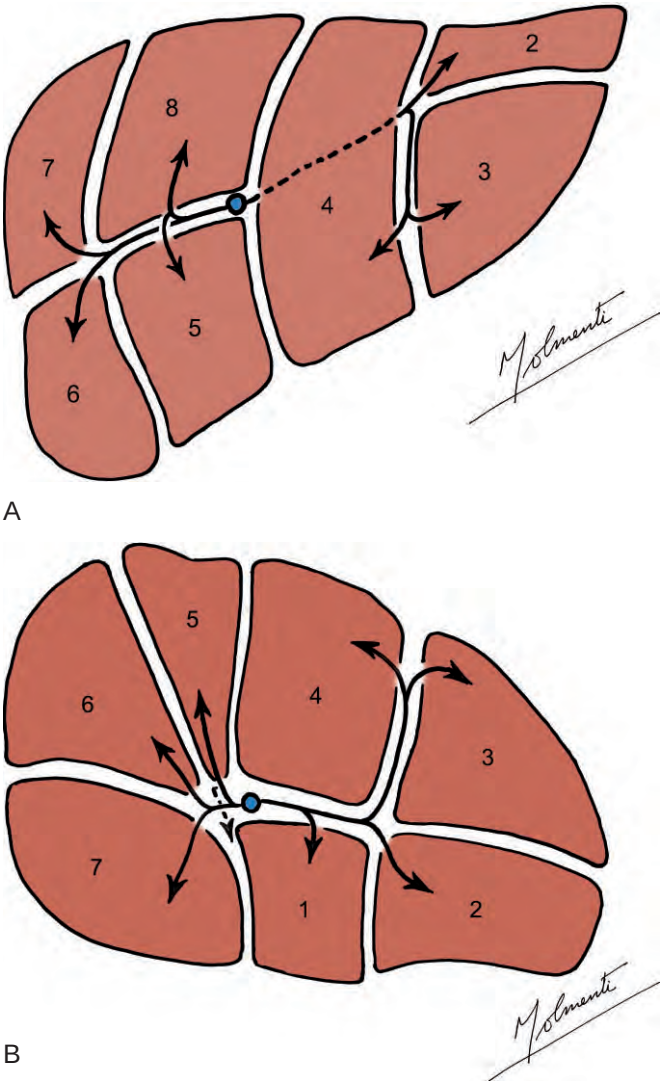


Figure 111–4. **A** and **B,** Schematic representation of the portal venous liver anatomy.

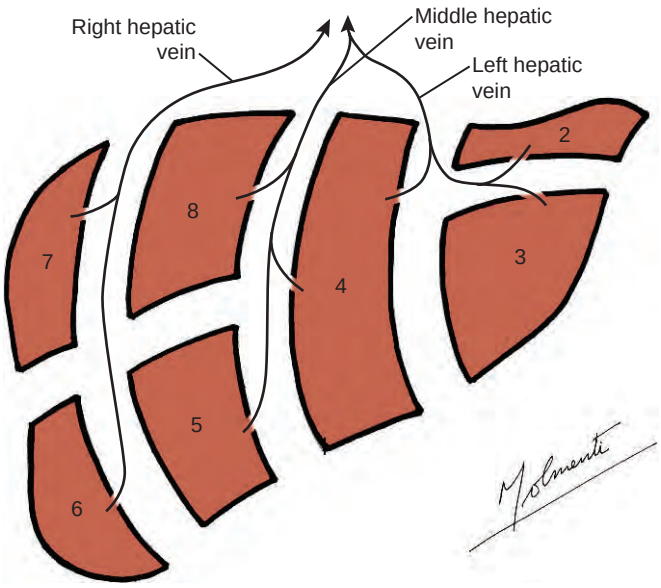


Figure 111–5. Schematic representation of the hepatic venous liver anatomy.

main portal fissure. This maneuver does not damage any structures of significance and allows better exposure of the hilar elements.[10]

Couinaud recognized the following three types of approaches to a portal pedicle[10]:

1. Intrafascial—dissection within the sheath, where the elements are identified
2. Extrafascial—dissection around the pedicle sheath
3. Extrafascial and transfissural—dissection of the sheaths at their origin from the hilar and umbilical plates (considered the safest approach, especially for second- and third-order branches)

ARTERIAL AND BILIARY SYSTEMS

According to Couinaud and Houssin, the most frequent arterial and biliary configurations, accounting for almost 90% of cases in their series, are the following[20]:

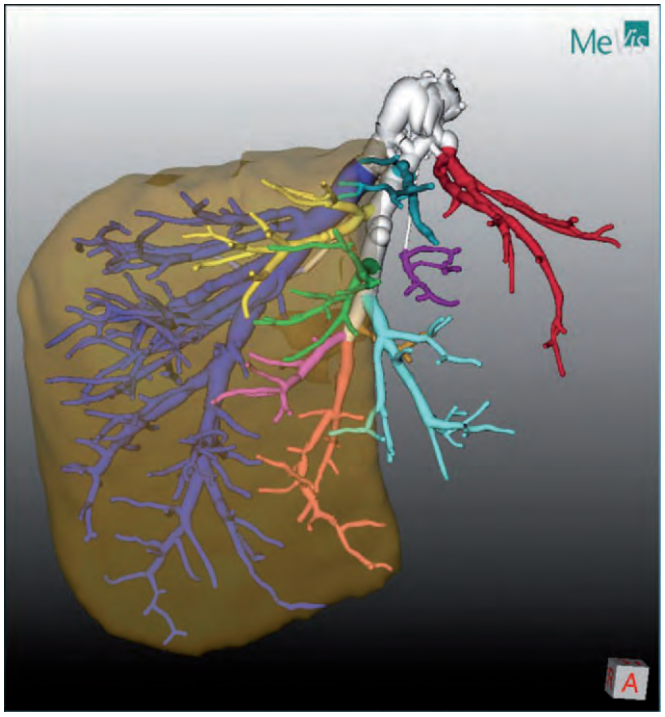
- A unique artery and bile duct on right and left (24%)
- Two right bile ducts (17%)
- Two left arteries (26%)
- Two right ducts and two left arteries (22%)

Bile ducts are usually located above the portal branches, and arteries below the corresponding veins.[18] The bile ducts derive their blood supply preponderantly from arterial branches.[10,12] Preliminary results from our observations in live-donor liver transplantation, however, would point to some differences in the classically accepted (see Fig. 111–3) anatomic similarities among arteries and bile ducts.

Hepatic Arteries

Molmenti et al. noted that "the occurrence of (arterial) variants that differ from the usual pattern is both surprisingly common and unpredictable."[21] Such findings are especially relevant not only in liver transplantation but in all types of hepatobiliary surgery.[1,2,4,21,22] When addressing arterial polymorphism and nomenclature, it is essential to keep in mind the embryologic reality that the liver has a tripartite arterial supply during developmental life. Although all these structures may not be patent in adulthood, vestigial remnants such as fibrous bands will always be encountered by the hand and sight of gifted surgeons.

The *common hepatic artery* originates from the celiac trunk in more than 80% of cases. In 5% of instances, there is a *replaced common hepatic artery*, most frequently arising from the superior mesenteric artery. In approximately 10% of cases, there is an *absent common hepatic artery*. In such instances, the right and left hepatic arteries originate independently.[21]



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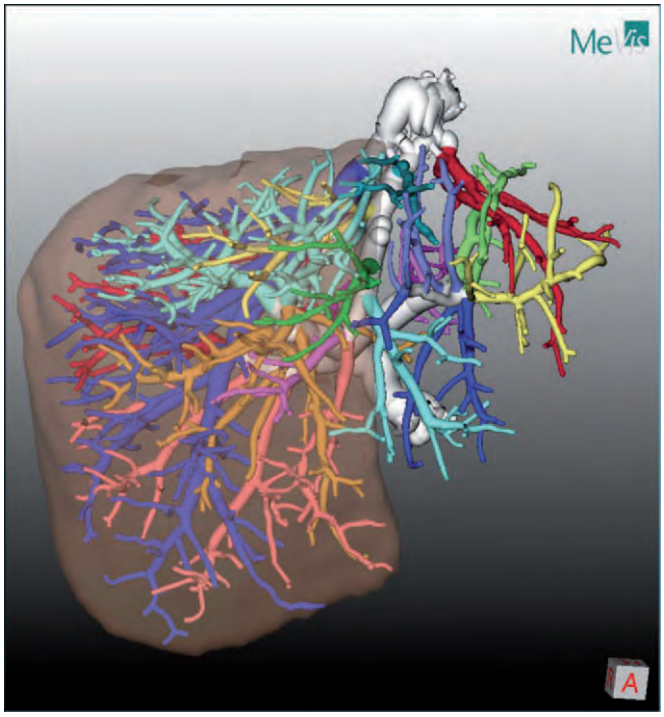

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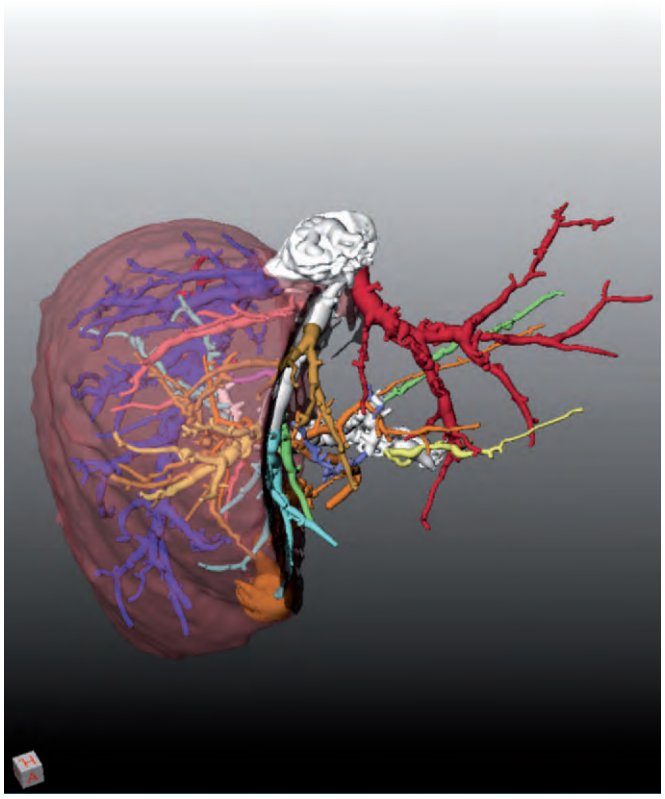


C

Figure 111–6. Virtual three-dimensional reconstruction of the liver anatomy by means of Hepavision, MeVis-Germany software. The right lobe has been reconstructed in a virtual fashion, together with the hepatic veins **(A)**, hepatic veins and portal veins **(B)**, and hepatic veins and biliary system **(C)**.

The *right hepatic artery* originates from the proper hepatic artery in more than 80% of cases. In approximately 15% to 20% of cases, there is a *replaced right hepatic artery* that arises in most instances from the superior mesenteric artery. In slightly more than 5% of individuals, there is an *accessory right hepatic artery* that may arise from the superior mesenteric artery. The right hepatic artery crosses underneath the common hepatic duct in 65% of cases, anterior to it in approximately 10% of cases, and underneath the common bile duct in approximately 10% of cases.[21,22]

The *left hepatic artery* arises from the hepatic artery proper in more than 80% of instances. In about 15% to 20% of cases, there is a *replaced left hepatic artery* that most frequently may arise from the left gastric artery, celiac axis, or replaced common hepatic artery. An *accessory left hepatic artery* may be seen in up to 35% of individuals.[21] Finding such vessels is of help during surgical interventions. Replaced and accessory left hepatic arteries can usually be detected by palpation of the gastrohepatic ligament. Replaced and accessory right hepatic arteries can be identified by palpating the posterior right portion of the hepatoduodenal ligament, with one finger inserted into the foramen of Winslow. The most frequent left-sided arterial distribution is a common trunk formed by the arteries of segments III and IV, which is joined by the artery of segment II. When the latter enters the former near the left-right bifurcation, the left hepatic artery is short. When the entrance occurs at the bifurcation or at the hepatic artery proper, there is a duplication of the left hepatic artery.[20] The hepatic artery is rarely involved by severe atherosclerotic changes, even in elderly individuals.[6]

Hepatic Ducts

The *left hepatic duct* drains segments II to IV. It is formed by the junction of ducts from segments II and III into a common trunk that is subsequently joined by the duct from segment IV (see Fig. 111–3). Duct IV usually joins at the umbilical fissure, or somewhat to its right. In most cases, the left hepatic duct lies in the most superior location of the left portal pedicle. The most frequent left biliary distribution is a common trunk from segments II and III that is joined by that of segment IV. In cases where duct IV joins late, it may form the upper edge of the left portal pedicle.[10,18,20] In a very small number of cases, the ducts from the left paramedian sector (segments III and IV) may themselves form a trunk, which is joined by the duct of the left lateral sector (segment II) and the caudate lobe (segment I), or the duct from segment IV enters the confluence of the other ducts or the common duct itself. Such variations may lead to the finding of a short left hepatic duct (≈17% of cases) or a double left hepatic duct (≈12% of cases).[10] The left duct has a classic configuration in almost 70% of cases.[18] Biliary drainage may be achieved by performing a bilioenteric anastomosis to the left hepatic duct at the hilum or to ducts III or IV by accessing them at the umbilical fissure (Hepp-Couinaud operation).[23] Variations in anatomic patterns should be kept in mind.[10,18]

The *right hepatic duct* is present in slightly more than 50% of cases (see Fig. 111–3). It is harder to reach than its left counterpart, is usually short, and may even be missing in cases of an early second-degree bi-trifurcation (or division). It drains segments V to VIII. The duct draining segments VI and VII has a horizontal trajectory. The duct draining segments V and VIII has a vertical course.[10,18]

The caudate lobe has its own bile drainage.[18]

The *confluence of the hepatic ducts* is observed in front of the portal bifurcation in 57% of cases, in front of the left portal vein in 37% of cases, and in front of the right portal vein in 6% of cases. Isolated segmental or subsegmental bile ducts, usually arising from segments I, IV, and V,[10] can lead to biliary fistulas after interventions in the hilar region. The confluence of the right and left hepatic ducts is described as following a normal configuration in approximately 70% of cases. Other possible configurations and their approximate incidences include trifurcation with left, paramedian and lateral right ducts (10%), right sectoral duct merging into the common bile duct (20%), and right sectoral duct joining the left duct (5%).[18]

PORTAL VEIN AND PORTAL VEIN ANOMALIES

The left portal, left paramedian, left lateral, and right paramedian veins are constant structures within the liver architecture.[10] The absence of the bifurcation of the portal vein can be an extremely dangerous situation. In such cases, the portal vein follows a curvilinear trajectory within the liver, arching from right to left, and giving off collateral branches along the way until it reaches the caudate lobe. Ligation of the presumed right portal vein branch leads to complete interruption of portal blood into the liver.[10,24,25] The classically accepted portal venous branching is illustrated in Figure 111–4.

HILUM, PLATES, FISSURES, AND OTHER STRUCTURES

Couinaud reminded us that "*hilum* meant in Latin a tiny black point seen in beans" and that anatomists in antiquity referred to that region as *porta hepatis*, or gateway of the liver.[10] It contains the bifurcation of the portal elements, with the short right and the long left branches. In approximately 23% of cases, the right portal vein is not present but rather is replaced by two sectoral branches. In 47% of cases, the right hepatic duct is not present as such.[10]

The location of the *main portal fissure,* described by Rex, may vary (see Fig. 111–2). It is identified by the posterior extremity of the cystic plate, and in cases of normal right portal vein anatomy tends to be located to the right of the portal vein, less frequently at the site of the bifurcation of the portal vein, or even less frequently to its left. In cases of right portal vein variants, the fissure is almost always at the level of the bifurcation or at the left portal vein. Its topographic location on the liver is not outlined by superficial markings in humans and can be traced

from the gallbladder fossa to the left anterior surface of the IVC. Furthermore, it has been noted that when the main portal fissure lies on the left, the biliary confluence is located in more than 70% of cases in front of the left portal vein.[10,26,27]

The *hilar plate* (see Fig. 111–2) is detached from the liver parenchyma by dissecting in between the left portal pedicle and liver tissue. The left hepatic duct is the structure located in the superior aspect of the portal elements. No major vessels or biliary ducts are encountered in this pathway. Only in the posterior region are there branches to the caudate lobe.[2,10,18,23,28]

The *umbilical fissure and plate* (see Fig. 111–2) is the site of origin of segmental and sectoral pedicles to the left liver. Its anatomic landmarks are the falciform ligament and the left longitudinal sulcus. The left paramedian pedicle and the umbilical plate can be identified by following the round ligament in continuity with the left portal vein. No walaean pedicles cross the umbilical fissure.[10] This structure divides the left lobe from the rest of the liver and is a landmark point for the evaluation and performance of left lobectomies and trisectorectomies (trisegmentectomies in the classic diction).[29]

The *sulcus of Rouvière* is an irregular fissure in continuity with the right hilum (see Fig. 111–2). It represents the extrahepatic anatomic landmark of the right fissure, usually buried in liver parenchyma. Following this structure leads to the pedicles of segments V and VI and further deeply and posteriorly to the pedicles of segments VII and VIII. The maneuver of isolating these structures is advantageous in the difficult procedures of right sectorectomy (segments VI-VII resection) or left trisectorectomy (trisegmentectomy) (segments I-II-III-IV-V-VIII resection).

The right paramedian portal pedicle is, according to Couinaud, "one of the most constant vessels of the liver."[10]

The *parabiliary venous system* of Couinaud is an accessory venous system with collateral branches to the duodenum, pancreas, and stomach, located within the hilar plate. It is associated with liver parenchyma, especially in the caudate and quadrate lobes, as well as with cystic veins. It may act as a collateral pathway in cases of portal hypertension and may serve as a connection between the right and left livers.[10]

The *cystic vein(s)* usually drain into the right portal vein but may also drain into the right liver, the left liver, and/or enter the parabiliary venous system.[10,12]

In 20% to 50% of cases, *small ducts* that are not part of a portal pedicle and do not communicate with the gallbladder are encountered in the cystic fossa. These ducts, described by Luschka, represent part of the "vasa aberrantia." They are different from the *cystohepatic ducts*, true biliary ducts that traverse from liver tissue to the gallbladder.[10,30]

HEPATIC, SUPRARENAL, AND PHRENIC VEINS

There are three main hepatic veins that drain into the IVC (see Fig. 111–5): the right hepatic vein (RHV), the middle hepatic vein (MHV), and the left hepatic vein (LHV). Accessory, inferior, right inferior, right middle, or dorsal hepatic veins drain directly into the IVC.[31] The MHV and LHV show a relative lack of anatomic diversity, whereas the RHV exhibits multiple variants.[32]

Right Hepatic Vein

In most cases, the RHV is single; rarely, it is double. In more than 50% of cases, it has no tributaries within 1 cm of its entrance into the IVC. In such cases, it is possible to potentially ligate it prior to parenchymal transections. In the other variants, attempts to ligate it may lead to profuse bleeding and potentially air emboli in cases where injuries occur.[18,31]

Middle Hepatic Vein

The MHV travels in the liver parenchyma along the main portal fissure (Cantlie's line). In approximately 85% of cases, the MHV and the LHV join in a common trunk prior to their entrance into the IVC. There are five most frequent venous confluence patterns when a length of approximately 1 cm from the IVC is considered (percentiles are approximate numbers)[31]:

- No venous branches (10% of cases)
- Bifurcation (40% of cases)
- Trifurcation (25% of cases)
- Quadrifurcation (5% of cases)
- Independent MHV and LHV (15% of cases)

Left Hepatic Vein

The LHV has two main tributaries, which usually converge more than 2 cm away from the common trunk's entrance (MHV and LHV) into the IVC.[31] The confluence of the LHV and the MHV represents the posterior part of the sulcus venosus. A posterior vein usually follows the posterior margin of the left lobe.[10] The LHV has a wide variety of branching patterns. However, all principal branches are within the territory limited by the left portal fissure (fissure that separates segments II and III).[10]

Inferior Hepatic Veins

There are multiple inferior hepatic veins (IHVs) that drain directly into the IVC. According to their location, they can be classified as posterior, posterolateral, posteroinferior, and caudate. Posteroinferior veins were observed in 95% of cases. The veins of the caudate lobe usually range in number from one to four.[31]

Right Suprarenal Vein

There are four frequent suprarenal venous configurations, as follows[31]:

- Single vein flows directly into the IVC, on the right side (75% of cases)
- Single vein merges together with a dorsal hepatic vein prior to entering the IVC (22% of cases)
- Single vein flows into the confluence of the right renal vein and the IVC (1% of cases)
- Two veins (2% of cases)

Phrenic Veins

There are one to five phrenic veins observed. Their confluence into the IVC or hepatic veins was observed with the following frequency patterns (approximate percentages)[31]:

- Supradiaphragmatic IVC, right anterior wall (25% of cases)
- Infradiaphragmatic IVC, right anterior wall (90% of cases)
- Retrohepatic IVC, right posterior wall (50% of cases)
- Supradiaphragmatic IVC, left anterior wall (5% of cases)
- Infradiaphragmatic IVC, left anterior wall (35% of cases)
- Common trunk of MHV and LHV (30% of cases)

ANATOMIC APPROACHES TO HEPATIC RESECTIONS (ACCORDING TO COUINAUD) (see Figs. 111–2 to 111–5)

Posterior Liver (Dorsal Liver, Sector I)

Couinaud[10] proposed a posterior or dorsal liver that he designated as *sector I*. This area encompasses right and left dorsal segments. The left dorsal segment, also called *segment II*, is the liver parenchyma also known as *caudate lobe*, *spigelian lobe* (or lobe of Spieghel), or *segment I*. The right dorsal segment, also called *segment Ir*, is the remainder of the liver parenchyma ventral to the IVC, inferior to the right superior and middle hepatic veins, and posterior to the right pedicle.[10] Others view the caudate lobe as "embracing" the IVC and contacting segment VII in approximately half of all cases.[18] Its pathologic involvement may be associated with invasion of the IVC.[4]

Portal vein branches originate from the left portal vein, from the portal bifurcation, from the right portal vein, and from the parabiliary system. There is an artery and bile duct accompanying each vein within the walaean sheaths. Efferent veins drain into the retrohepatic IVC, and hepatic veins.[10]

When attempting to resect part or all of the posterior liver, the sector can be divided into three. The area in front of the IVC, in between the left and middle hepatic veins, can be reached anteriorly by removing segment IV. The area in between the middle and right superior hepatic veins can be reached anteriorly by removing segment VIII (a difficult task!). The area below the right superior hepatic vein can be reached anterolaterally by resecting segment VII.[10] Alternatively, a completely posterior approach to the dorsal or paracaval liver can be used after detachment of the liver from the IVC. Caution should be paid to the posterior aspect of the hilum.

Left Hemiliver (Segments II, III, IV, ± I)

Segment II makes up the left posterior angle, whereas segment III constitutes the left anterior angle of the liver. The left lateral sector encompasses segment II, whereas the left paramedian sector is made up by segments III and IV.[2]

Removal of the left liver along the main portal fissure entails ligation and transection of the left portal pedicle, LHV, and left-sided tributaries of the MHV. The caudate lobe is usually not included when performing a left hepatectomy. The left posterior dissection, dividing the left liver from segment I, is limited by the sulcus of Arantius. Approximately 40% of the functional liver mass is represented by the left hemiliver.[4,10,18,33] Preoperative imaging studies provide a road map, especially useful when anatomic variations are present. The hilar plate is identified and dissected, ligating and transecting any branches to segment IV. The left portal pedicle is encircled and tied, providing a vascular demarcation of the territory to be resected along the main portal fissure. The left hemiliver is mobilized by transecting its ligaments. As dissection is carried out through the liver parenchyma toward the LHV, collaterals are tied or clipped. A venous branch from segment IV may be encountered posteriorly. The LHV is identified, tied, and transected.[4,10,18]

Potential complications based on liver anatomy include walaean sheaths, variations in hepatic vein topography, portal branches that supply the right liver but arise in the left portal vein or traverse close to it, bile ducts that drain the right liver but end in the left hepatic duct or traverse close to it, and vice versa.[10]

Left Lobe (Segments II and III)

Access to and knowledge of the *umbilical plate* provides the gateway to left liver surgery. As outlined by Couinaud, the *left portal fissure* separates segments II and III and constitutes the plane where all the main branches of the LHV lie. This fissure should not be confused with the *umbilical (left suprahepatic) fissure*, that runs on the lateral edge of segment IV.[10] Second-order portal branches supply segment II, while third-order ones supply segment III. A large posterior branch of the LHV follows the posterior edge of segment II. Resection of segments II or III individually entails dissection by careful identification of pedicles, preservation of veins, and guidance by means of color demarcation.[4,10] The ligamentum teres (round ligament) joins the terminal part of the left portal vein. In this region, the bile duct lies above while the artery lies anterior and below the left portal vein. The surgical approach always entails the identification of the artery, followed by dissection and division of the most posterior segment III branches of the portal vein, and finally by the

identification of the bile duct. In cases where biliary obstruction must be resolved, the bile duct of segment III can be accessed on the left of the ligamentum teres, and a biliary-enteric anastomosis constructed.[2,18,23]

Segment IV

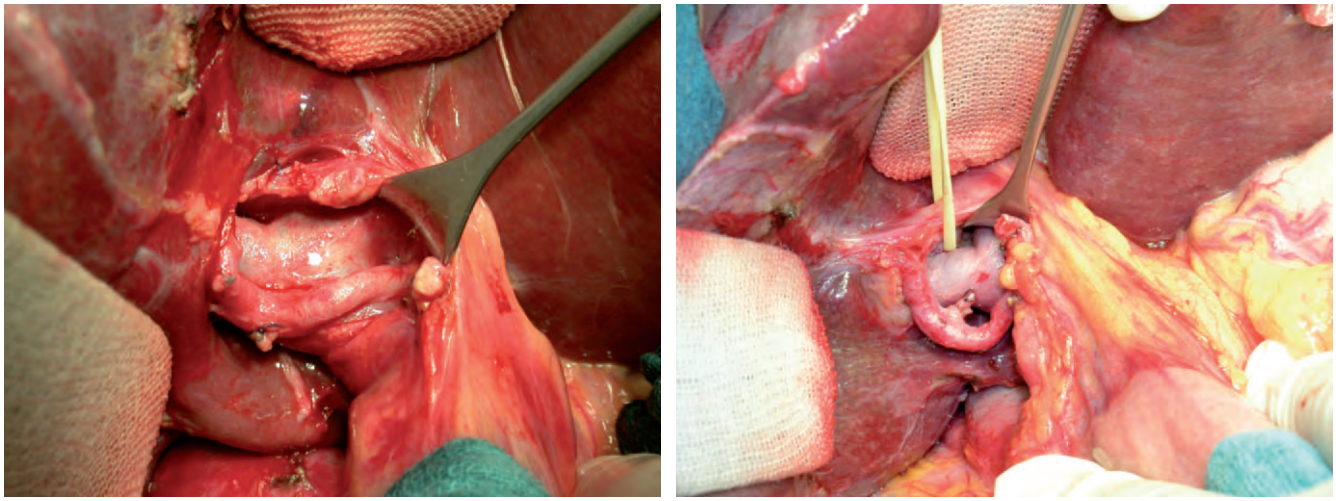
Segment IV can be resected without altering the integrity of the remaining liver mass.[4] Third-order portal branches supply this segment. Resection entails in all cases access to the umbilical fissure, with subsequent ligation and transection of all sheaths arising from the left portal branch and entering segment IV. The liver is divided along the left border of the MHV, allowing for its preservation. However, when necessary it can also be resected.[4,10] If specific cases where pathologic findings demand it, segment IV can be removed in continuity with segments II, III, V, VIII ± I.

Right Hemiliver (Segments V, VI, VII, and VIII)

Segment V constitutes the right border of the gallbladder bed. Segment VI makes the right anterior angle of the liver and is occasionally delimited by the sulcus of Rouvière to the right, while segment VII configures the right posterior angle. Segment VIII is not visible from the inferior surface of the liver.[2] Anatomic variations in portal and hepatic venous configurations are much more frequent in the right than in the left liver.[10] In 1888, Rex described the main portal and the right portal fissures. The *main portal fissure* extends from the anterior-left surface of the IVC to the cystic fossa. The MHV runs within it. In cases where the fissure is at the level of the right portal vein, there is a very low incidence of right portal vein anatomic variants. When the portal vein anatomy shows no variants, the convergence of the right and left hepatic ducts is usually located in front of the bifurcation of the portal vein. In cases of absent right portal vein, the convergence is in front of the left portal vein. The *right portal fissure* has a posterior edge at the RHV but is otherwise devoid of topographic anatomic landmarks. The right superior hepatic vein runs within it.[10,26]

There are several intraoperative ways to outline hepatic territories. Such maneuvers are especially useful in cases of anatomic distortions caused by tumors. Isolating the right (Fig. 111–7) or left branches of the portal vein and hepatic artery and clamping them temporarily (*right* or *left Pringle maneuver*) leads to a color demarcation of the right or left hemilivers, respectively. In the *Malagó maneuver*, developed by one of us (M.M.), the territory of the right hemiliver drained by the MHV is delineated. This maneuver entails the temporary clamping of the right branch of the portal vein, the right branch of the hepatic artery, and subsequently the RHV. Temporary nonperfusion of the area of the liver supplied by the right portal system is achieved and physically demarcated by a darkened color of the liver parenchyma. When the clamp on the right hepatic artery is released, the arterial perfusion will revascularize the right lobe of the liver. However, by maintaining the RHV clamped, its territory will remain demarcated, and only the parenchyma of the right liver drained by the middle hepatic vein will regain its color. The Malagó maneuver is especially useful in right liver resections in live-donor liver transplantation.

Segmental pedicles on the right, as opposed to what is encountered on the left liver, arise within the liver parenchyma. As such, the gateway to right liver surgery is the right hilar extremity. The right pedicle is short (see Fig. 111–7), and sometimes the division of the portal



A B

Figure 111–7. Surgical dissection of the right portal pedicle. **A,** The right hepatic artery and right portal vein have been dissected. **B,** The right hepatic duct was subsequently isolated and circled with a rubber band.

pedicle is so early that it replaces the pedicle itself. The right portal vein is estimated to be missing in slightly more than 20% of cases.[10] Anatomically, the right paramedian portal sheath has an oblique configuration, entering the liver parenchyma from the right area of the hilum. The right paramedian portal vein is a constant structure. The right lateral portal sheath can be found parallel to the inferior surface of the liver.[10,18]

The right hepatic duct is believed to be absent in almost 50% of cases, with variations of trifurcation or right segmental biliary drainage emptying into the left-sided biliary ducts in the majority of the remaining cases.[10,34]

Drainage of the right liver (see Fig. 111–5) is by means of the right and middle hepatic veins. The MHV drains segment V on its left side by means of the anterior branches and segment VIII by means of its posterior branches. Couinaud made a distinction between superior, middle, and inferior right hepatic veins and noted their high anatomic variability. Small drainage veins originating in segments VII and VIII can be found to enter the IVC independently.[10]

Couinaud related that "the facility and safety of right hepatectomy depends on the length of the right portal pedicle." Broelsch stated that "control of the afferent and efferent vessels is of vital importance." Ease of access to the right pedicle may be encountered by accessing the sulcus of Rouvière, which prolongs the right edge of the hilum, or by addressing its lateral and paramedian pedicles.[4,10,35,36] Small branches that originate from the right portal vein may go toward the precaval parenchyma, segment VII, or the caudate process.[10] Mobilization of the right lobe is of vital importance. Hepatic veins can be approached by rotating the right lobe medially or from the transected parenchyma at the main portal fissure. Approximately 60% of the functional liver mass is represented by the right hemiliver.[4,10]

Right Paramedian Sector (Segments V and VIII)

The right paramedian sector is of variable extent. It is limited by the main portal fissure, the right portal fissure, and the dorsal liver. In approximately 75% of cases, interruption of its pedicle has no associated anatomic complications. In the remainder of cases, variants that may lead to surgical challenges include the origin of branches to segments VI or VII, duplication of its usual branches, and absence of the portal vein bifurcation. In most cases in which the main portal fissure is to the right of the portal vein at the level of the hilum, there are no anatomic variants. As suggested by Couinaud, control of the paramedian portal pedicle should be preferably attained via an extrafascial approach at the level of the hilum as it ascends into the liver parenchyma. Variations in branching of the portal distribution manifest as changes in the pattern of color demarcation after occlusion of inflow. When resecting this sector, the RHV (if not atrophic) should be preserved.[10,18] The right paramedian sector can be resected in continuity with segments IV, VI, and VII.[10]

Right Lateral Sector (Segments VI and VII)

The right lateral sector is located lateral to the right portal fissure. On gross inspection, the right margin of the liver is part of the right lateral sector. The plane of the right portal fissure is along the RHV. The RHV, however, may be unusually small in approximately 25% of cases. Couinaud described the fissure as a "very large" fissure, with an oblique orientation, that encompasses "the whole width of the right liver." When performing a resection of the right lateral sector, the portal pedicle can be identified on the right edge of the hilum, usually 2 cm to the right of the main portal fissure. The right lateral pedicle follows a course parallel to the liver surface. Anatomic variations that can be encountered include branches to the right lateral sector originating from the right paramedian sector and duplication of the pedicle of the latter. In more than 80% of cases where the main portal fissure is located to the right of the portal vein, there are no anatomic variations on the right side. The right inferior and middle veins are always part of the right lateral sector. Transection of the hepatic parenchyma is along the line of color demarcation after the pedicle is occluded.[10,18]

Resection of the right lateral sector can be performed together with segments V and VIII.[10]

Segments V and VI

When performing an anatomic resection, the pedicles are controlled in an extrafascial way. Segment V is supplied by portal branches arising from the anterior aspect of the right paramedian bundle. Branches to segment VI arise from the anterior aspect of the right lateral pedicle. Occasionally, there is a single pedicle for segment VI. Venous drainage of segment V is into the MHV, while that of segment VI is into the right hepatic vein. Resection is guided by the coloration changes associated with vascular occlusion.[10]

Segment VII

The border between segments VII and VIII is the right portal fissure. Segment VII has the peculiarity of being supplied by a single portal pedicle, known as *Rex's ramus arcuatus*. This pedicle originates from the right lateral portal bundle, distal and posterior to the branches for segment VI. Occasionally, such as in cases of right portal trifurcation, it may arise on its own. Venous drainage is usually into the right hepatic vein. When resecting this segment, it is recommended to expose the IVC and right hepatic vein.[10]

Segment VIII

Segment VIII is supplied by posterior branches of the right paramedian portal bundle. Its venous drainage is mostly via the middle hepatic vein.[10]

LYMPHATICS

The lymphatic system of the liver is not yet fully understood. Lymphatic channels are encountered in the portal tract and collect lymph that may originate in the spaces of Disse. Lymphatics travel together with other elements of the portal bundle to the hilum of the liver, eventually reaching the aortic lymph nodes and the thoracic duct. Lymphatic vessels also travel with the hepatic veins, along the IVC, and subsequently into the thoracic region. There are also superficial lymphatics within the capsule of the liver.[12,37]

NERVES

The liver receives both sympathetic and parasympathetic innervation. Sympathetic supply is via the celiac plexus. Stimulation leads to increases in glucose and lactate. Parasympathetic innervation is via the vagus nerve. Stimulation leads to glycogen synthesis, decreased glucose release, and gallbladder contraction.[12,37,38]

MICROSCOPIC STRUCTURE

Given the surgical nature of our chapter, we describe here only the basic aspects of the hepatic microscopic structure. The hexagonal lobule, the portal lobule, and the acinus have been described as hepatic functional units by Kiernan, Mall, and Rapaport, respectively.[37] This anatomic-physiologic configuration is associated with topographic variations in hepatocyte metabolic activity, exposure to toxic substances, and oxygen concentrations.[12] It is estimated that the liver has approximately 100 billion hepatocytes that make up 80% of hepatic cells. Hepatocytes are polyhedral in shape and arranged in one-cell-thick plates lining the sinusoids. Hepatocytes have a basolateral (sinusoidal, vascular) domain, a canalicular (apical, biliary) domain, and a lateral domain.[37] The basolateral (vascular, sinusoidal) domain is located toward the sinusoids and space of Disse. The corresponding hepatocytic membrane is lined with microvilli and is a zone of active transport between blood and the hepatocyte. It is responsible in part for maintaining the liver pH around 7.2.[37] The canalicular membrane contains active transport systems and is also responsible in part for maintaining the liver pH around 7.2. This domain contains multiple enzymes with active sites directed toward the exterior of the cell. Bile canaliculi, 1 to 2 μm in diameter, located in between the canalicular domains of hepatocytes, merge into canals of Herring, which in turn drain into bile ductules lined by cholangiocytes. These in turn lead to ducts of larger size and eventually form the common bile duct.[37] The lateral domain separates the former two domains and contains junctional complexes.[37] The perisinusoidal space of Disse is a site where fluids can move freely given the absence of basement membranes in both hepatocytes and sinusoid-lining cells. There are four types of cells in the sinusoids: hepatic sinusoidal endothelial cells, Kupffer cells, lymphocytes, and stellate (Ito) cells. The latter store vitamin A and would contribute to the pathogenesis of cirrhosis.[12,37]

Large and septal bile ducts express blood group antigens.[12] Chronic rejection, toxin reactions, graft-versus-host disease, and other afflictions involve mostly ducts smaller than 0.1 mm.[12]

HEPATIC BLOOD FLOW AND METABOLISM

The liver weighs approximately 1800 g in men and 1400 g in women. It receives approximately 1500 ml of blood per minute, 30% from the hepatic artery and the remaining 70% from the portal vein. There are 25 to 30 ml of blood per 100 g of liver under normal conditions, but that volume may reach up to 60 ml/100 g in cases of congestion. Blood flow also varies as a result of other physiologic conditions, such as ingestion of a meal. Portal blood flow is most sensitive to protein meals. Carbohydrate intake has a moderate effect on increases in portal flow. The influence of lipids is thought to be of minimal importance.[12,37]

The liver is the main site of protein and amino acid metabolism. More than 90% of circulating plasma proteins come from the liver. The liver receives dietary amino acids via the portal circulation. Their availability is limited by hepatocyte membrane transport activity. Hepatocytes are also able to endocytose large proteins and other macromolecules. Nonessential amino acids are synthesized in the liver from pathways based on pyruvate, α-ketoglutarate, and oxaloacetate (from the Krebs' cycle). Amino acid catabolism occurs mostly in the liver. Those that are not destined to become hepatocytic or plasma proteins are degraded into pyruvate, acetyl CoA, or members of the tricarboxylic acid cycle intermediaries. The nitrogen from the amino groups is excreted as urea in the urine after being processed by the urea cycle.[37,39]

The liver produces fatty acids from excess sugar. Fatty acids are stored intracellularly mainly as triglycerides. Oxidation of fatty acids in the liver produces ketone bodies.[37] The liver is intimately involved in lipoprotein physiology. It is the site of production of very-low-density lipoprotein (VLDL) and a great part of plasma high-density lipoprotein.[40] Austin Flint was the first to describe hypercholesterolemia in liver disease. Incidentally, he is also credited by some as being the first to report the hepatorenal syndrome.[40,41]

The liver must provide for its own physiologic needs as well as for those of other organs. This is best exemplified when addressing hepatic physiology during fed, postabsorptive, and fasting states.[42] In the *prandial state,* most of the glucose during fed states is converted in the liver to glycogen via three-carbon fragments. The liver can store up to a maximum of 65 g of glycogen for each kilogram of liver tissue. Excess glucose can be directed in a variety of ways. An important such way is the synthesis of fatty acids. Fatty acids are sterified and transported as VLDL to adipocytes.[42] In the *postprandial state,* hepatic glycogen is broken down into glucose mainly at the brain and red blood cells. Adipocytes release fatty

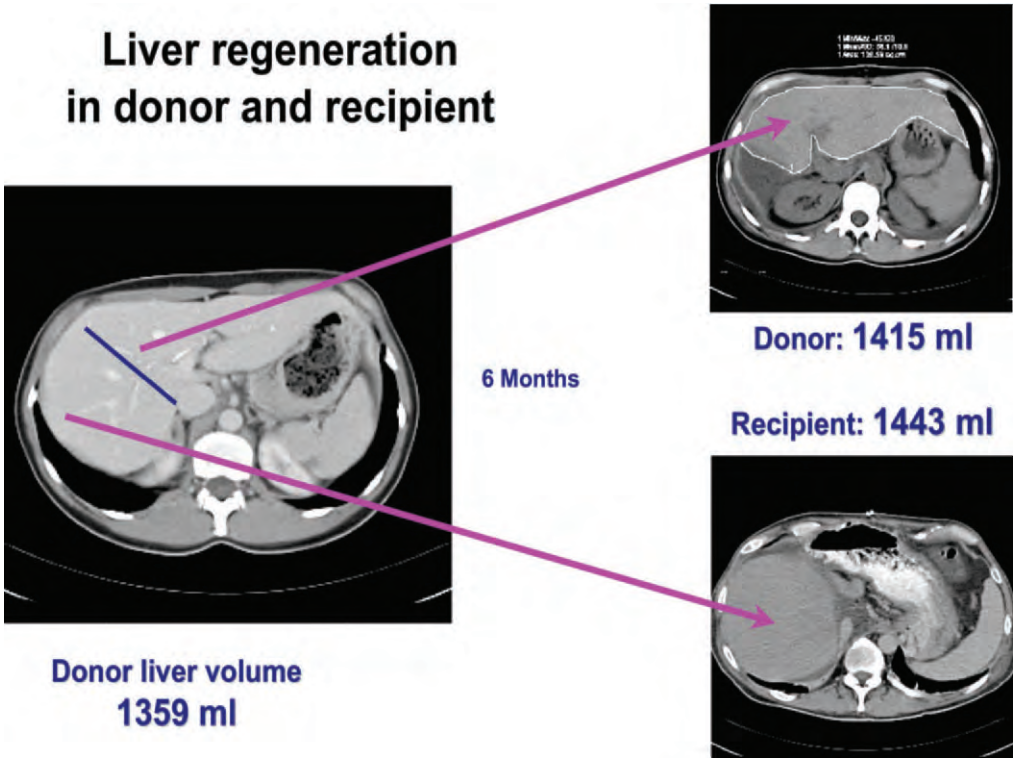


Figure 111–8. CT imaging of a live liver donor prior to resection (*left*) and the subsequent regrowth of remnant and allograft hemilivers in donor and recipient, respectively.

acids that act as an energy source for most tissues.[42] In the *fasting state,* glycogen depletion is encountered within 48 hours. Glucose for the brain and red blood cells is produced by means of gluconeogenesis. Gluconeogenesis reaches its peak rate at 24 to 48 hours. In the liver, glycerol rather than fatty acids provides the carbon source for gluconeogenesis. During prolonged starvation, glucose utilization by the brain decreases and ketone bodies generated by the liver become the major source of energy.[42]

LIVER REGROWTH (REGENERATION)

The liver constitutes the major detoxifying site in the human body and, as such, is prone to significant injury. Loss of liver mass by injury or resection seems to be the inciting event for liver regrowth. Already in Greek mythology, the titan Prometheus is described as exhibiting cyclical hepatic regrowth during his punishment for having provided fire to humans.

The liver seems to adapt to the metabolic needs of each individual by reducing or increasing its mass and function. This has been observed in "large for size" liver transplantation in children when a transplanted liver mass greater than needed will shrink by apoptosis. Conversely and most frequently after removal, functional inactivation (ligature or embolization) of large amounts of parenchyma, or after "small for size" transplantation, there is a hyperplastic-trophic response, leading to an increase of liver mass. This finding has been described as consisting of cytokine-dependent and cytokine-independent pathways.[43] This process has become clearly evident in live-donor liver transplantation, where hepatic regrowth is observed in both donor and recipient. Although the liver does not recover its original anatomic morphology with right and left lobes, the volume increases surprisingly quickly up to the point where it is able to accommodate the physiologic needs of the host (Fig. 111–8).[3,44] Mean residual volume increased by 88% within 10 days after right hepatectomies in cases of live liver donors.[44] The response, however, varies according to the situation. Hepatocyte injury is associated with a greater inflammatory response than posthepatectomy regeneration. In cirrhosis, although there is regrowth, excessive amounts of collagen are also produced leading to injury rather than a salutary response.[43] It is estimated that hepatocytes have a life span of approximately 1 year, and that in healthy individuals, 1 of every 1000 hepatocytes is replicating at any given point.[45]

BILE FORMATION

Bile consists of an aqueous solution of salts, electrolytes, amino acids, proteins, lipids, vitamins, steroids, toxins, drugs, and heavy metals.[46] It is formed based on an osmotic filtration and the transport of substances that lead to the development of such osmotic gradient. Its function involves absorption and digestion of dietary substances, cholesterol excretion, and the elimination of toxic substances.[46]

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Chapter

112

Approach to the Patient with Abnormal Hepatic Laboratory Tests

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The commonly used laboratory tests to detect liver diseases are often referred to as *liver function tests* (LFTs). However, this terminology is misleading in that many of the tests routinely obtained in the evaluation of liver disease are not true measures of hepatic synthetic function but are indicators of hepatocellular or biliary tract injury. Furthermore, these tests may be normal in patients with advanced liver disease or abnormal in individuals with a normally functioning liver. Although these tests are crucial in the evaluation of patients with suspected liver disease, abnormalities are occasionally seen when asymptomatic individuals donate blood, apply for life insurance, or undergo routine screening. It has been estimated that liver chemistry abnormalities occur in approximately 4% of apparently healthy individuals since the normal limits of laboratory tests are determined by two standard deviations above and below the mean. Therefore, by definition, 2.5% of individuals tested will have a value above the upper limit of normal for any given test. An extensive work-up for most of these patients would not be warranted. However, it is equally important to avoid assuming that minor abnormalities do not indicate serious underlying liver disease. Consequently, the physician encountering abnormal liver tests must carefully assess the need for further evaluation based on the each patient's clinical scenario, including data from the physical examination, coexisting diseases, and current medical therapies.

There are few, if any, prospective controlled trials that define the optimal approach to the evaluation of patients with abnormal liver tests. In one study of almost 20,000 presumably healthy military recruits, an elevation in alanine aminotransferase (ALT) concentration greater than 2.25 standard deviations above the mean was detected in 99 subjects (0.5%).[1] In only 12 of these individuals was a specific cause identified, such as viral hepatitis, autoimmune hepatitis, and cholelithiasis. In the remainder, no specific diagnosis was made. In a study of 1124 patients referred specifically for evaluation of abnormal liver enzymes, the diagnosis was made noninvasively in 1043 patients. Of the remaining 81 patients whose diagnosis could not be inferred noninvasively, subsequent liver biopsy demonstrated steatosis in 84%.[2] Although it is difficult to extrapolate data from these studies to individual patients, these observations suggest that a specific diagnosis can be made in most asymptomatic patients with abnormal liver enzymes by using laboratory testing. Most of the remaining patients will have steatosis, either from alcohol or nonalcoholic fatty liver disease (NAFLD).

A careful history is essential in the effective evaluation of patients with abnormal liver enzymes. When possible, it is important to determine the time of onset of abnormalities. For example, finding elevated liver enzymes shortly after the start of a new medication may establish the diagnosis without further investigation. Other important historical information includes exposure to blood or blood products, illicit drug use, tattoos, alcohol consumption, or intimate contact with individuals at risk for hepatitis. A travel history and questions concerning occupational exposures may also be helpful.

The physical examination is an important component of the evaluation of abnormal liver enzymes. For example, a thorough skin examination may detect cutaneous stigmata of chronic liver disease, such as spider angiomata, palmar erythema, and dilated abdominal veins. Similarly, on abdominal examination, detecting an enlarged spleen implies advanced liver disease with portal hypertension, or a prominent left hepatic lobe may suggest cirrhosis. The physical examination can be unreliable in detecting small amounts of ascites, and ultrasonography may be required for documentation.

Some diseases have cardinal physical examination findings as well, such as the bronze skin of hemochromatosis or the Kayser-Fleischer rings of Wilson's disease. Thus, clues from the history and physical examination may help determine the sequence in which tests should be ordered.

At most centers, the standard "hepatic profile" includes total bilirubin (occasionally fractionated), aspartate aminotransferase (AST), ALT, alkaline phosphatase, total protein, and albumin levels. Of these tests, only two truly assess hepatic function. The bilirubin concentration measures the liver's ability to take up, conjugate, and excrete bilirubin into the biliary canaliculus. The albumin concentration reflects the liver's synthetic capacity. Instead of focusing on individual laboratory values, it is most helpful to look at patterns of laboratory abnormalities. Using this system, hepatic diseases have traditionally been classified as "hepatocellular" when the aminotransferases predominate and "cholestatic" when there is a disproportionate elevation in the alkaline phosphatase concentration. Though useful, this simplistic approach may be limited in circumstances where there are overlapping patterns. In addition, the term *cholestatic* may be inappropriate for "infiltrative" disorders of the liver that may cause a significant elevation in the alkaline phosphatase levels with a normal bilirubin level.

The following sections present guidelines for the initial assessment of patients with varying patterns of hepatic enzyme abnormalities.

ASSESSMENT OF PATIENTS WITH PREDOMINANT ELEVATIONS OF THE AMINOTRANSFERASES

The aminotransferases are a class of enzymes that catalyze the transfer of amino groups to ketoacids to form amino acids. Because of their abundance in hepatocytes, they are sensitive measures of hepatic injury. AST was formerly referred to as *serum glutamate oxaloacetate transaminase* (SGOT) and the term *ALT* has replaced *serum glutamate pyruvate transaminase* (SGPT). These enzymes are present within hepatocytes but differ in location. ALT is localized to the cytosol, whereas AST is present in both the cytosol and the mitochondria. Consequently, the pattern of enzyme release is determined by the liver cell component affected by the particular disorder. Additionally, the "normal" amounts of both aminotransferases detected in the blood may be affected by sex and body mass, though most reported ranges do not account for these differences.[3]

There are many potential pitfalls in the evaluation of abnormal liver enzymes. Some medications such as erythromycin estolate or para-aminosalicylate may affect the aminotransferase assays, leading to spurious elevations in the absence of liver disease.[4] In addition, significant quantities of AST are present in nonhepatic tissues including skeletal muscle, heart muscle, kidney, brain, pancreas, lung, leukocytes, and erythrocytes. Although most ALT is found in the liver, small quantities can also be found in other tissues.[5,6] Consequently, elevations in the aminotransferases, particularly AST, may be seen in nonhepatic disorders such as rhabdomyolysis, polymyositis, or hemolysis. Rarely, elevations in the AST and ALT concentrations may be encountered in endocrinopathies such as hypothyroidism, hyperthyroidism, and Addison's disease.[7] Although the reasons for these abnormalities have not yet been determined, they seem to resolve once the underlying disease is treated. Elevations in the aminotransferase levels have also been reported in patients with celiac disease and returned to normal on a gluten-free diet.[8,9]

The degree of aminotransferase elevation is a poor indicator of the degree of liver cell injury since necrosis is not required for their release. For instance, patients with fatal acute alcoholic hepatitis may have minimal aminotransferase elevations, whereas uncomplicated acute viral hepatitis may cause enzyme elevations in the thousands.

While the degree of aminotransferase elevation is of limited prognostic value, it may be helpful in establishing the etiology of the hepatic injury (Box 112–1). Very high levels (>3000 IU/L) are seen in acute viral hepatitis, toxic or drug-induced liver disease, ischemic liver injury and, rarely, autoimmune hepatitis and Wilson's disease. Transient marked elevations in the AST and ALT concentrations may be seen on occasion with choledo-

Box 112–1 Approach to the Patient with Abnormal Aminotransferases

Mild (<500 IU/L)

- Nonalcoholic fatty liver disease
- Chronic viral hepatitis
- Alcoholic hepatitis
- Obstruction
- Infiltration
- Nonhepatic sources (e.g., hemolysis, myositis)
- Hemochromatosis
- Acute fatty liver of pregnancy

Moderate (500-1000 IU/L)

- Autoimmune hepatitis
- Wilson's disease
- Viral hepatitis
- Medications

Marked (>5000 IU/L)

- Hepatotoxic
- Ischemia
- Acute viral hepatitis

cholithiasis. The highest elevations (>10,000 IU/L) are detected in individuals with hepatic ischemia and acetaminophen hepatotoxicity. In both of these settings, the AST will initially predominate but will "cross" with the ALT once the injury is terminated and recovery ensues. This phenomenon reflects differences in the rates of clearance of the aminotransferases because AST has a shorter half-life than ALT. A rapid fall in the AST and ALT concentrations in the setting of a rising bilirubin or increasing prothrombin time suggests fulminant hepatitis.

In most patients, mild to moderate elevation of the aminotransferases (less than five times the upper limit of normal) is encountered. Before concluding that the patient has liver disease, the tests should be repeated, preferably within 2 weeks. If the abnormalities persist, then it is highly likely the patient has some form of hepatic injury that should be investigated further.

A careful history of use of both prescription and nonprescription medications, including herbal preparations, is essential. Correlating hepatic enzyme elevations with the introduction or change in medication dosage may be all that is required to establish a diagnosis, especially if eliminating the potentially hepatotoxic agent is followed by a fall in the enzymes within a few weeks. Rechallenge with the medication is usually not recommended unless there is no substitute for the offending agent and it is absolutely medically necessary.

If there is no circumstantial evidence of hepatotoxicity, then the following disorders should be considered: alcoholic liver disease, NAFLD, autoimmune hepatitis, hemochromatosis, Wilson's disease, and alpha$_1$-antitrypsin deficiency.

ALCOHOLIC LIVER DISEASE

Consumption of large amounts of alcohol can directly result in liver damage or exacerbate other disorders such as hepatitis C or hemochromatosis. A number of questionnaires are available to assess the amount of alcohol a patient is consuming and thus to estimate its clinical effects.[10] No safe level of alcohol consumption has been established for all individuals, but there is little evidence that ingestion of less than 50 g of alcohol per day in the absence of comorbid conditions such as hepatitis C or obesity results in any significant liver injury. The pattern of enzyme elevation may be helpful in establishing the diagnosis of alcoholic liver disease. Alcoholic hepatitis is associated with an increased AST/ALT ratio greater than 2:l. In most cases the AST is less than 400 IU/dl and the ALT concentration is often normal. The low concentration of ALT reflects a deficiency in pyridoxal phosphate, a necessary cofactor for the activity of ALT.[11] Superimposed hepatic injury from hepatotoxic agents such as acetaminophen may cause much higher enzyme levels but the AST/ALT ratio usually remains intact.[12]

Before concluding that a patient with an AST/ALT ration has alcoholic liver disease, other causes of selective AST elevation should be considered. As previously mentioned, muscle diseases or hemolysis may contribute to the AST elevation. In addition, patients with hepatitis C who have progressed to cirrhosis have higher AST than ALT, but the ratio is usually less than 2.[13]

Additional laboratory observations may help establish the diagnosis of alcoholic liver disease. Patients who consume large quantities of alcohol often have an elevated mean corpuscular volume even after correcting for folate or vitamin B_{12} deficiency and have a disproportionate elevation in the gamma-glutamyl transferase concentration.

VIRAL HEPATITIS

Chronic viral hepatitis is a common cause of moderate aminotransferase elevations, particularly in asymptomatic individuals. In most patients the ALT predominates except in those patients with hepatitis C who have progressed to cirrhosis. Approximately 2% of the population has been infected with hepatitis C, making it one of the most common causes of chronic liver disease and the most frequent indication for liver transplantation. It is important to question patients regarding risk factors for transmission, although 30% of patients report no history of transfusion, intravenous or intranasal drug use, tattoo placement, body piercing, or exposure to an individual with hepatitis. The diagnosis of chronic hepatitis C is established by a positive hepatitis C virus (HCV) antibody test and a positive polymerase chain reaction (PCR) for HCV RNA. A quantitative measure of HCV RNA can assess the level of viremia by reverse transcription PCR or branched DNA assays. Determining the HCV genotype may be helpful in determining the duration and response rate to therapy. There is no consensus regarding the need for liver biopsy in patients with hepatitis C. Finding little or no fibrosis on histologic examination of the liver may raise the threshold for treatment, especially in individuals with coexisting disorders such as depression since the antiviral therapies can worsen psychiatric disease. Panels of laboratory abnormalities have been devised to predict the degree of inflammation and fibrosis on biopsy.[14,15] Although these tests appear to accurately predict mild and advanced disease, intermediate grades of injury are difficult to assess without histology, and biopsy sampling error may also be a factor that limits accurate prognostic assessment.

Although hepatitis B is a common cause of chronic liver disease in the world, it is less prevalent in the United States. Risk factors for the acquisition of hepatitis B are similar to those for hepatitis C, although vertical transmission and sexual transmission appear to be more efficient than for hepatitis C. Detecting the hepatitis B surface antigen establishes the diagnosis of chronic hepatitis B. Measuring the HBV DNA level and ALT level is helpful in determining which patients should receive antiviral therapy.

NONALCOHOLIC FATTY LIVER DISEASE

Recent studies have suggested that steatosis in the absence of significant alcohol consumption is the most common cause of chronic elevations in the aminotrans-

ferases. A variety of terms are used to describe this disorder, including *nonalcoholic fatty liver disease* and *nonalcoholic steatohepatitis*. The former is probably preferable since recent studies have suggested that it may be difficult to assess reliably the extent of inflammation and fibrosis even with liver biopsy in patients with steatosis.[16]

Although many patients with NAFLD have obesity, glucose intolerance, or hyperlipidemia, hepatic steatosis has been increasingly recognized in individuals with none of these risk factors.[17] Several studies have shown that this disorder is responsible for most hepatic enzyme abnormalities once viral hepatitis, autoimmune, metabolic, drug-induced, and alcoholic liver disease have been excluded. At present there is no way to confirm the diagnosis of hepatic steatosis through laboratory tests. Imaging studies may show changes suggestive of fatty infiltration, but considerable variations are found among individual interpreters. Weight loss, glycemic control, and correction of hyperlipidemia are recommended when obesity, diabetes mellitus, and/or dyslipidemia are present, though it has been difficult to prove that these therapeutic interventions alter the natural history of NAFLD. The addition of vitamin E, ursodeoxycholic acid, folic acid, and oral hypoglycemic agents such as metformin are currently under investigation.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is an important disorder to consider in the differential of abnormal hepatic enzymes since immunosuppressive therapy has been shown to dramatically affect the outcome of the disease. It occurs most often in young to middle-aged women. Although most patients are asymptomatic when the disease is diagnosed, some patients, particularly older women, may present with symptoms of acute hepatitis. Patients with autoimmune hepatitis usually have a polyclonal increase in immunoglobulins with the IgG fraction predominating. Most have a positive antinuclear antibody and smooth muscle (anti-actin) antibody.[18] Prompt diagnosis is essential because significant fibrosis may develop rapidly in untreated patients. A liver biopsy is helpful in establishing the diagnosis and determining the degree of fibrosis. The inflammatory infiltrate often contains numerous plasma cells and can be more extensive than suspected based on the patient's clinical presentation and degree of aminotransferase elevations. Patients are treated with immunosuppression using corticosteroids with or without azathioprine.

HEMOCHROMATOSIS AND WILSON'S DISEASE

Hereditary hemochromatosis is a common genetic disorder causing elevated hepatic enzymes. It is inherited as an autosomal recessive trait with an increased prevalence among those of northern European descent. Calculating transferrin saturation is the most effective screening test for hemochromatosis. A transferrin saturation greater than 45% should be investigated further.[19] A serum ferritin greater than 400 ng/dl in men and 300 ng/dl in women provides additional evidence of clinically significant iron overload. Most patients with genetic hemochromatosis can be diagnosed through the use of genetic analysis, with the genes *C282Y* and *H63D* being the most commonly associated with genetic hemochromatosis.[20] Detecting homozygosity for the *C282Y* mutation establishes the diagnosis. The *H63D* gene probably represents a polymorphism, since most patients who are homozygous for this gene do not show manifestations of genetic hemochromatosis.

There is no consensus about the need for liver biopsy in patients who have genetic hemochromatosis. Material obtained from a biopsy can be assessed for iron content with calculation of a hepatic iron index (hepatic iron content divided by the patient's age), with an index greater than 1.9 providing compelling evidence of hemochromatosis even if genetic testing is negative. In addition, the degree of fibrosis can be assessed. However, many believe that this information is not essential in homozygous patients to begin treatment with phlebotomy. A biopsy should be performed when there are potentially comorbid conditions that may require additional or alternative therapeutic interventions such as hepatitis C, obesity, or significant alcohol consumption.

Wilson's disease is a rare inherited disorder than may cause abnormal hepatic enzymes. Wilson's disease should be considered in patients younger than 45 years of age who have unexplained elevations in the ALT. Finding a low serum ceruloplasmin warrants additional investigation including a 24-hour urine collection for quantitation of copper excretion. In patients with a high index of suspicion, a formal ophthalmic examination should be obtained to look for Kayser-Fleischer rings. If these tests suggest copper overload, a liver biopsy with quantitation of hepatic copper should be performed. Hepatic copper greater than 250 µg per gram of liver suggests Wilson's disease and the patient should be treated with chelating agents such as penicillamine.[21]

APPROACH TO THE PATIENT WITH ELEVATED SERUM BILIRUBIN

Bilirubin is a metabolite of the degradation of the heme moiety that is released predominantly from senescent red blood cells. About 30% of serum bilirubin is derived from heme-containing cytochromes or myoglobin. After its initial release into the blood, bilirubin is bound to albumin and thus is not filtered through the kidney glomeruli and does not appear in the urine. It is then taken up by the hepatocytes and conjugated with glucuronic acid to form monoglucuronides and diglucuronides. Conjugated bilirubin is then actively transported across the canalicular membrane into the bile.

Jaundice can develop from alterations in any step in bilirubin metabolism. Because the energy-requiring step in bilirubin metabolism is canalicular transport, most hepatic diseases cause a conjugated (or direct) hyper-

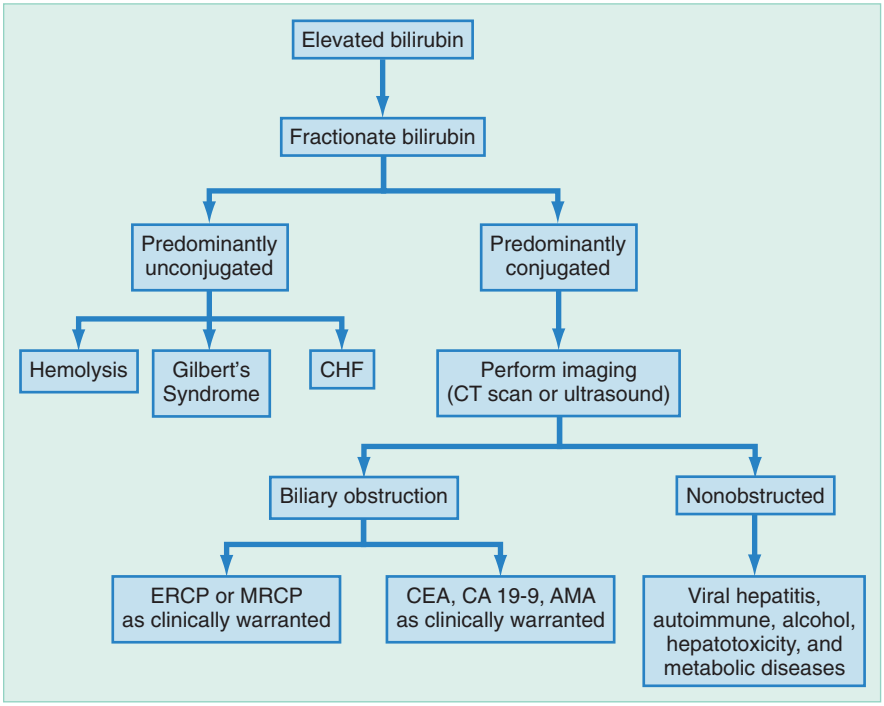

Figure 112–1. Outline of the evaluation of hyperbilirubinemia. AMA, antimitochondrial antibody; CEA, carcinoembryonic antigen; CHF, congestive heart failure; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

bilirubinemia, and, conversely, most causes of indirect hyperbilirubinemia are not related to hepatic dysfunction (Fig. 112–1).

Unconjugated or indirect hyperbilirubinemia develops from overproduction or ineffective uptake of bilirubin from the blood. The enzymes responsible for bilirubin metabolism are inducible and are capable of handling approximately six times the normal production of bilirubin before it begins to accumulate in the blood. Formation of large hematomas or hemolysis can cause increases in indirect bilirubin, but rarely does the serum bilirubin rise above 5 mg/dl. Evidence supporting hemolysis would include an elevated reticulocyte count, low haptoglobin concentration, and an elevation in lactate dehydrogenase level. As outlined earlier, hemolysis can also cause mild increases in AST.[22] Also, mild increases in unconjugated bilirubin can be seen in patients with congestive heart failure and after portosystemic shunts.

Gilbert's syndrome is a common disorder of bilirubin metabolism that affects about 5% of the population and is inherited as an autosomal dominant trait. The term *syndrome* is a misnomer because Gilbert's should probably be considered a normal variant in bilirubin metabolism rather than a disease. It results from a polymorphism in the gene encoding the enzyme responsible for bilirubin conjugation.[23] Consequently, mild degrees of unconjugated hyperbilirubinemia (with bilirubin levels typically more than 2 mg/dl but rarely higher than 6 mg/dl) are seen, particularly during periods of fasting or systemic illnesses. This becomes important in the patient with Gilbert's syndrome who develops acute cholecystitis, because concomitant hyperbilirubinemia is often a result of the fasting state (in preparation for surgery) rather than biliary obstruction from choledocholithiasis. This phenomenon highlights the need to check a fractionated bilirubin any time a bilirubin elevation is detected. Patients with Gilbert's syndrome should be reassured and advised that brief periods of jaundice may occur sporadically.

APPROACH TO THE PATIENT WITH ELEVATED ALKALINE PHOSPHATASE

Conjugated, or direct, hyperbilirubinemia can be caused by disorders affecting the hepatocytes or the biliary tract anywhere from the canalicular membrane to the sphincter of Oddi. When conjugated hyperbilirubinemia is seen in the setting of a predominant aminotransferase elevation, injury from a drug, toxin, virus, or metabolic disorder is likely. When bilirubin accumulates because of injury to the bile ducts, there is usually a concomitant rise in the alkaline phosphatase concentration. Alkaline phosphatase is an enzyme localized to the sinusoidal membrane of the hepatocyte and the microvilli of the biliary canaliculi. The elevation in serum alkaline phosphatase in hepatobiliary diseases appears to result from an increase in the de novo synthesis in the liver followed by release into the blood in the hepatic sinusoids. Retention of bile salts may be responsible for the induction of alkaline phosphatase synthesis and may also promote its release across the hepatocyte plasma membrane. The normal values for alkaline phosphatase vary based on demographic factors. Individuals older than 60 years of age tend to have higher values than younger adults. In subjects younger than 50 years, the alkaline phosphatase activity is higher in men than in women, whereas in adults older than 60 years, enzyme activity in women is higher than in men.[24]

Alkaline phosphatase is not isolated to the liver and is found in the intestine, bone, and placenta. Assays using heat fractionation or gel fractionation can isolate the individual fractions, thus identifying the specific source, but are seldom used clinically. Instead, measurement of gamma-glutamyl transpeptidase (GGT) is used as a surrogate marker for hepatic alkaline phosphatase as it is not found in these other tissues. Unfortunately, the usefulness of GGT is limited by its lack of specificity. A number of disorders affecting the heart, kidneys, and lungs, as well as many medications and alcohol, can elevate the serum GGT concentration in the absence of liver disease.

If an elevation in serum alkaline phosphatase is found to be of hepatic origin, the first step is to exclude obstruction of the biliary tract. The most commonly used modality to detect extrahepatic biliary obstruction is ultrasonography. If the extrahepatic ducts are dilated, magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) can define the abnormality more precisely. MRCP is increasingly considered the diagnostic test of choice for choledocholithiasis given high sensitivity and lower risk profile.[25] In addition to providing important diagnostic information, ERCP may afford the opportunity to relieve the obstruction by performing a sphincterotomy with removal of a biliary calculus or placement of a stent; however, there is controversy about whether ERCP should be performed prior to cholecystectomy.[26]

When an elevation in the alkaline phosphatase concentration is detected in the absence of hyperbilirubinemia, a disorder causing partial obstruction of the biliary tree or affecting the hepatocyte-canalicular membrane or septal or interlobular bile ducts should be considered. Primary sclerosing cholangitis (PSC) should be suspected in individuals with inflammatory bowel disease. PSC is a radiographic diagnosis based on irregularities in the caliber of the right hepatic duct, left hepatic duct, or the common bile duct. A disorder similar to PSC, known as *human immunodeficiency virus (HIV) cholangiopathy,* is seen in HIV-infected patients as a complication of opportunistic infections of the biliary tract by *Cryptosporidium* or *Cytomegalovirus*.[27]

If imaging studies show a normal biliary tree in the setting of an elevated alkaline phosphatase, then intrahepatic disorders are likely present. Infiltration of the liver by granulomata, tumor, or fat and on occasion congestion of the liver from heart failure can cause elevations in hepatic alkaline phosphatase. Appropriate imaging studies can often detect evidence of tumor invasion or steatosis of the liver. Finding tender hepatomegaly with jugular venous distention suggests congestive heart failure. A liver biopsy is required to confirm the presence of hepatic granulomata.

A hepatotoxic reaction to a drug or toxin may cause an elevated alkaline phosphatase with or without jaundice. Such drugs include trimethoprim-sulfamethoxazole, ampicillin, erythromycin, anabolic steroids, chlorpromazine, and estrogens. Patients with sepsis and those receiving hyperalimentation may occasionally develop intrahepatic cholestasis.[28] Modest elevations in alkaline phosphatase and bilirubin have also been seen in patients with a variety of malignancies in the absence of liver involvement, presumably as a result of paraneoplastic syndromes (e.g., Stauffer's syndrome).[29]

Primary biliary cirrhosis (PBC) should always be considered in the differential diagnosis of a persistently elevated alkaline phosphatase concentration, particularly in middle-aged women. Presumably an autoimmune disorder, PBC is associated with the detection of antimitochondrial antibodies directed toward the pyruvate dehydrogenase enzyme complex on the inner membrane of the mitochondria of the bile duct epithelium. Finding an antimitochondrial antibody is virtually diagnostic of PBC, and a liver biopsy is usually not necessary to confirm the diagnosis unless there are other disorders that could be causing coexisting hepatic injury such as obesity, alcohol, or certain drugs.[30]

OTHER LABORATORY TESTS USED IN THE ASSESSMENT OF LIVER DISEASES

The prothrombin time measures several of the coagulation factors synthesized in the liver and is helpful in assessing synthetic capacity of the liver. The half-life of factor VII, an important component of the prothrombin time assay, is approximately 6 hours. Consequently, the prothrombin time is particularly useful in the evaluation of patients with acute liver injury such as viral hepatitis or toxic liver injuries. It is also a component of the Child-Pugh score for chronic liver disease and the Model of End-Stage Liver Disease (MELD) score used to assess candidacy for liver transplantation.* Prolongation of the prothrombin time can also result from vitamin K deficiency. Traditionally, adequacy of vitamin K stores is assessed by measuring the prothrombin time after parenteral vitamin K administration. Within 24 hours after 1 mg of vitamin K is given subcutaneously, the prothrombin time should fall by 30%. Consumptive coagulopathies may also cause an abnormal prothrombin time when hepatic synthesis is adequate. Simultaneously measuring a factor VIII level (synthesized by vascular endothelium) may help distinguish hepatic failure from disseminated intravascular coagulation; factor VIII levels may be inordinately high in cirrhotic patients, while other coagulation factor levels are decreased.[31] A normal or increased factor VIII level in the setting of an abnormal prothrombin time suggests hepatic failure, whereas equal suppression of both implies an underlying coagulopathy.

Albumin is a protein synthesized exclusively by the liver and is another important constituent of the assessment of patients with liver disease. The half-life of albumin is usually 19 to 21 days and therefore is often used to assess hepatic protein synthesis in chronic liver diseases. It is also a component of the Child-Pugh classification. Unfortunately, extrahepatic factors can affect the albumin concentration. The expanded plasma volume that often complicates cirrhosis may falsely lower

*MELD score = 10(0.957 Ln[serum creatinine] + 0.378 Ln[total bilirubin] + 1.12 Ln[INR] + 0.643.

the albumin concentration, and malnutrition or malabsorption may result in inadequate substrates for protein synthesis despite normal synthetic capacity. Also, albumin levels decrease in the setting of systemic inflammation (as a so-called negative acute-phase reactant) as a result of increased catabolism as well as decreased synthesis.[32]

PERCUTANEOUS LIVER BIOPSY IN THE DIAGNOSIS OF LIVER DISEASE

As previously discussed, performing a liver biopsy can be helpful in establishing the diagnosis and prognosis in a variety of settings where elevated hepatic enzymes are encountered. It is not possible to describe global indications for liver biopsy. Each patient must be assessed for the relative benefit of histologic information compared with the potential risk of performing the procedure. When a biopsy if performed, it is essential to obtain adequate tissue samples for histologic examination, especially when attempting to confirm the presence of cirrhosis. For many diseases like steatohepatitis, sampling error is a major problem. One recent study showed that different stages of disease were seen when the same liver was sampled in different locations.[12]

Most liver biopsies are performed safely in outpatient facilities, though complications requiring hospitalization have been reported in up to 4% of patients. Severe complications—defined as death, severe hemorrhage, pneumothorax, or bile peritonitis—occur in 0.1% to 0.3% with a mortality rate of 9/100,000.

A liver biopsy should not be attempted in an uncooperative patient or when a vascular lesion has been identified. It may be difficult to identify an appropriate site for biopsy in a patient with ascites or a right pleural effusion. Because of the risk of bleeding, a biopsy should not be attempted in patients with a significant coagulopathy. There are no published guidelines for a "safe" coagulation profile, although, in general, biopsies are not performed if the prothrombin time exceeds the control value by 3 seconds or the platelet count is less than 60,000/dl.

With increasing frequency, liver biopsies are performed using ultrasound guidance. When a biopsy attempts to sample focal hepatic defects, guidance with computed tomography or ultrasound should be used. Ultrasound guidance is also helpful when ascites is present or when obesity makes it difficult to accurately locate the liver on physical examination. At many centers even "routine" liver biopsies are now performed under ultrasonographic guidance, and several studies suggest that this technique can reduce the risk of several potential complications.[33]

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Chapter

113

Perioperative Management and Nutrition in Patients with Liver and Biliary Tract Disease

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Diseases of the liver and biliary tract can alter the normal physiology of other organ systems in ways that range from subtle to profound. There are special concerns and considerations that must be acknowledged when contemplating surgical intervention in such patients. All phases of patient care, including preoperative, intraoperative, and postoperative management, can be affected. This chapter focuses on perioperative issues in patients with various degrees of dysfunction as a result of primary liver disease and the consequences of biliary obstruction. Because candidates for liver transplantation are addressed elsewhere, this discussion relates primarily to patients with hepatobiliary malignancy.

PATHOPHYSIOLOGY OF CIRRHOSIS AND OBSTRUCTIVE JAUNDICE

The suffering of Prometheus in classical Greek mythology illustrates our long-standing appreciation for the unique regenerative capacity of the liver. Unfortunately, this process does not always restore the normal anatomic structure of the organ. In general, liver disease is defined by some degree of hepatocyte injury and necrosis. Regardless of the etiology, fibrosis is a consequence of hepatocellular necrosis. Hepatic fibrosis exists on a continuum, and extensive fibrosis with nodule formation defines cirrhosis. Normally, both hepatic arterial and portal blood flow perfuses the sinusoids, with a zonal distribution of hepatocytes relative to the nutrient- and oxygen-rich blood supply. Single plates of sinusoids are arranged in lobules with a central hepatic vein and portal triads at the periphery. In contrast, regenerating nodules lack this normal elegant framework, with only a single blood supply derived from the hepatic artery. The portal venule is unable to penetrate the collagen rim around this distorted architecture. As a consequence, this nodular format is no longer as well suited for perfusion and single-pass uptake from the gastrointestinal (GI) tract. In addition, even normal areas of hepatocytes suffer from the increased resistance to portal flow. This increased resistance results in the development of collateral pathways for portal venous flow around the liver and thus the clinical aspects of portal hypertension.

Pathology at any point between the hepatocyte and the duodenum may give rise to cholestasis.[1] A cholestatic liver is enlarged, green, and rounded, and patients with cholestasis as a result of biliary obstruction are at risk for changes similar to those seen in early cirrhosis. Indeed, in its extreme chronic form, biliary obstruction can lead to secondary biliary cirrhosis. Although the mechanisms are more complex than is appropriate for this discussion, cholestasis itself does lead to hepatic dysfunction, and simple relief of obstructive jaundice does not immediately obviate the risk for ongoing impairment. Another long-standing association exists between cholestasis and postoperative renal failure, although the mechanisms remain somewhat elusive.[2] Coagulopathy arising from both hepatocellular synthetic dysfunction and malabsorption of vitamin K–dependent coagulation factors is also a significant concern in patients with jaundice. As we shall see, cholestasis alone can have profound effects on many other organ systems, including the

Table 113–1 Occult Hepatic Disease: Potential Causes

Category	Entity	Action/Associations
Infectious	HBV ± delta	History and serology
	HCV	
Metabolic	Fatty liver disease	History/lab screen (see Table 113–3)
	Iron overload	History/specific testing
	Others	
Toxic	Alcohol	History/screen
	Drugs	Amiodarone
	Environmental	Methotrexate
Structural	Cholestasis	Stone or tumor
	Hepatic venous outflow	Budd-Chiari syndrome
		Heart failure
		Pericardial disease
Immune mediated	Primary sclerosing cholangitis	Inflammatory bowel disease/colorectal tumor
	Primary biliary cirrhosis	Cholangiocarcinoma
	Autoimmune	
Others	Granulomatous disease	
	Cryptogenic	

immune response, central nervous system function, and the GI tract.

PREOPERATIVE CONSIDERATIONS

General Assessment and Preoperative Preparation

A successful outcome for any surgery is predicated on the patient's ability to tolerate and recover from the stress of the procedure. Although there are many objective criteria on which to base such an assessment, the subjective judgment of an experienced clinician remains paramount. The relevant details of a thorough history include any personal or family accounts of liver disease. No matter how distant, a previous diagnosis of hepatitis or jaundice may elicit the need for further specific laboratory testing. Even in the absence of a previous diagnosis, questions regarding the risk for acquiring hepatitis, such as past intravenous drug use, tattoos, or blood transfusion, should be routine. Such questioning may elucidate one or more potential causes of occult hepatic disease (Table 113–1). Also of particular relevance is any history of recent weight loss, exercise intolerance, shortness of breath, smoking, GI bleeding, easy bruising, previous surgery, or delayed healing. In addition to a good general physical evaluation, a focused examination should uncover evidence of liver disease (Table 113–2). Specifically, one should look for evidence of temporal wasting, scleral icterus, jugular venous distention, supraclavicular adenopathy, diminished breath sounds at the lung bases, gynecomastia, spider angiomas, palmar erythema, splenomegaly, a firm liver edge, peripheral edema, and asterixis.

Table 113–2 Clinical Examination: Evidence of Liver Disease

Skin	Jaundice
	Spider angiomas
	Dupuytren's contracture
Head	Scleral icterus
	Temporal wasting
Chest	Gynecomastia
Lungs	Right base effusion
Abdomen	Caput medusae
	Fluid wave
	Palpable spleen
	Shrunken liver
	Enlarged liver
	Cardiovascular hum
Extremities	Edema
Neurologic	Asterixis

Basic laboratory tests are necessary, including those that are part of a complete blood count, as well as a comprehensive metabolic panel and a coagulation profile (Table 113–3). Frequently in elective circumstances, abnormalities may be able to be corrected before surgery. Even more important may be the clues provided by identified abnormalities with regard to the extent of underlying disease.

In any liver or biliary surgery, the potential need for intraoperative transfusion should be anticipated. Depending on timing, anemia may be treated simply by correcting basic deficiencies such as iron, folic acid, or

Table 113–3 Laboratory Testing

Metabolic panel	Sodium	Hyponatremia associated with ascites
	Potassium	Hypokalemia associated with urinary excretion
	BUN/creatinine	Hepatorenal dysfunction
	AST/ALT	Assess ongoing cellular injury
		ETOH: increased ratio
	Alkaline phosphatase	Mass or obstruction
	GGT	Acute ETOH associated
	Total/direct bilirubin	Assess nature of cholestasis
Coagulation	INR	Synthetic dysfunction
		Vitamin K deficiency
Blood count	Hemoglobin	Anemia
	MCV/MCHC	Nature of anemia
	Platelets	Evidence of portal hypertension

ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; ETOH, ethanol; GGT, γ-glutamyltransferase; INR, international normalized ratio; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

vitamin B_{12}. If time does not permit, it is generally prudent to transfuse packed red blood cells to achieve a hematocrit of at least 30%. If anemia is absent and a delay is acceptable, autologous blood donation may be an option. Autologous donation has been associated with an improved prognosis in patients with cirrhosis who are undergoing resection of hepatocellular carcinoma.[3] Although there is less evidence with autologous transfusion, the use of banked blood has long been controversial from the standpoint of immune function versus recurrence of malignancy.[4,5] A more modern alternative for the correction of preoperative anemia is the use of weekly or even daily erythropoietin injections in conjunction with repletion of iron stores.[6-8] This strategy is obviously preferred in patients who subscribe to the Jehovah's Witness faith.

The other parameters of a complete blood count are not to be ignored. Mean corpuscular volume and mean corpuscular hemoglobin concentration may be clues to the nature of an existing anemia or raise suspicion regarding associated diseases or behavior. Perhaps the most relevant is the platelet count. Thrombocytopenia correlates well with diminished hepatocellular function and portal hypertension.[9] Although hypersplenism can be associated with a reduction in any of the formed blood elements, a low platelet count is most common. Indeed, it is not uncommon for patients with occult liver disease and cirrhosis to be referred first to a hematologist for evaluation, including a bone marrow biopsy, before an accurate diagnosis is made. Any degree of thrombocytopenia should be considered a hint to possible underlying portal hypertension.

Abnormalities in electrolytes and intravascular volume are common in patients with liver or biliary tract disease. Patients may have a dilutional hyponatremia with peripheral edema and third-space fluid accumulation compounded by hypoalbuminemia. Hypokalemia may also result from increased urinary excretion, even in the presence of a potassium-sparing diuretic such as spironolactone. Hyponatremia should be corrected with appropriate fluid restriction, whereas either supplemental oral or intravenous potassium can correct hypokalemia. Because diminished renal function is so often associated with liver disease, scrutiny should be given to serum blood urea nitrogen and creatinine, but consideration also should be given to urine electrolytes and even assessment of 24-hour creatinine clearance.

Coagulation testing should include a partial thromboplastin time, a prothrombin time, and an international normalized ratio (INR). An additional assessment of fibrinolytic activity requires measuring fibrin degradation products and fibrinogen. With any identified abnormalities, a more informed discussion regarding risks could take place with the patient and family, in addition to allowing better care from the anesthesiologist.

Finally, basic general tests, as well as those that are more specific, should be used to assess the function of the heart and lungs. Clearly, an electrocardiogram (ECG) is indicated in anyone with previous heart disease, anyone older than 40 years, or anyone older than 35 if a major procedure is being contemplated. If the patient's history, physical examination, or ECG suggests the need, further cardiac evaluation may be required. For older patients undergoing major hepatic surgery, a cardiac stress test is always indicated. In a high-risk patient, cardiac catheterization may be necessary. Although the presence of a malignancy may pressure some to proceed directly to surgery, an intraoperative death is clearly of benefit no one. Formal pulmonary function tests can be performed when the history or clinical findings warrant or when a pulmonologist is required. Often, a trip up a nearby set of stairs will provide good clinical insight. In those with significant pulmonary risk factors, including smoking, chronic cough, or shortness of breath, room-air blood gas analysis may be very helpful. A preoperative visit with an anesthesiologist is routine at many centers and is often quite helpful in avoiding last-minute issues on the day of surgery.

Hepatic Functional Reserve

A simple test to judge hepatic functional reserve is still awaiting discovery. Many different methods have been used throughout the history of hepatic resection in an effort to determine the adequacy of the postoperative remnant liver. This is often not a concern with a healthy liver or with smaller resections. However, when a major trisegmentectomy is required or underlying liver disease is present, functional reserve becomes extremely important to avoid a lingering hepatic failure and death.[10] In the field of liver transplantation, the term *small-for-size* syndrome is the accepted terminology and describes the similar consequences of an allograft of inadequate volume.[11,12] Nevertheless, a number of different testing modalities have been investigated. One such test, which is still clinically available, uses indocyanine green (ICG), a high first-pass metabolized drug that is excreted into bile. The rate of ICG clearance can be correlated with hepatic blood flow and hepatocyte function. Biliary ICG excretion correlates with a decreased hepatic adenosine triphosphate (ATP) concentration, which may reflect a decrease in regenerative ability after resection.[13] Results are typically measured as the percentage of ICG retained after 15 minutes. The clinical utility of the ICG test remains questionable. Over the years a number of other tests have been used, including nuclear imaging of asialoglycoprotein receptor, determination of the hippurate ratio, the aminopyrine breath test, the caffeine clearance test, galactose elimination capacity, arterial ketone body ratio, monoethylglycinexylidide, trimethadione, and single-photon emission computed tomography.[14] The search for tests that accurately assess hepatic function and reserve continues. In the meanwhile, the current best and most commonly used method is volumetric analysis with axial imaging. The volume of the remnant tissue can be estimated and a clinical decision made accordingly. It has been suggested that resection of less than 60% of nontumorous liver is acceptable and resection of greater than 60% of noncirrhotic liver may require another approach such as portal vein embolization to increase the size of the remnant liver parenchyma.[14,15] One study reported that hepatic dysfunction develops in 90% of patients if less than 25% of normal liver remains after trisegmentectomy for colorectal hepatic metastases.[16] A significant incidence of morbidity and mortality was found in this group, although the sensitivity was reported as low. It must be appreciated that volume assessments are most appropriate only when there is no underlying parenchymal disease. Any degree of fibrosis, inflammation, or fatty infiltration will effectively diminish function of the remnant liver. In patients with frank cirrhosis, even a small segmental resection may result in hepatic failure.

Nutritional Status

Poor nutritional status is associated with a diminished immune response; an increased susceptibility to infection, poor wound healing, and risk for further organ dysfunction; and suboptimal outcomes in general. Although nutritional status is extremely important, the number of different methods for its assessment suggests that none are ideal. As usual, the patient's history and physical examination are most relevant. Signs and symptoms of wasting are important to note. Establishing a baseline for the patient's premorbid state is essential. An individual with normal weight may recount significant weight loss from a baseline of obesity. Patients or family members may recall a very muscular physique in an individual who now appears normal. Temporal and thenar wasting may be missed if not specifically pursued. Overt cachexia is certainly not uncommon in patients with cirrhosis or malignancy.

More formal methods of nutritional assessment include measurement of albumin, triceps skin fold thickness, visceral proteins, and the total lymphocyte count, as well as indirect calorimetry. Some are cumbersome or limited by cost and accessibility. Many are no better than the judgment of an experienced clinician.[17] Predicting an individual's ability to heal an anastomosis, susceptibility to sepsis, and ability to recover from sepsis can be used to assess postoperative risk. Characteristics of patients at risk include (1) serum albumin less than 3.0 g/dl, (2) weight loss of 10% to 15% over a period of 3 to 4 months, (3) serum transferrin level less than 200 mg/dl, (4) anergy to injected skin antigens, (5) functional impairment for ordinary tasks, or (6) lack of ability to carry out functional tests such as hand dynamometry to normal capacity.[18] In a prospective cross-sectional study, Padillo et al. evaluated the specific assessment of patients with benign and malignant biliary obstructive diseases. They identified protein-calorie malnutrition in 82% of patients with obstructive jaundice as a result of either benign or malignant causes. In this study it was clear that the duration of jaundice correlated with worsening malnutrition. Not surprisingly, patients with malignancy were more likely to have moderate or severe malnutrition than were those with benign obstruction.[19,20]

Many other investigations have also shown that nutritional status can be a predictor of morbidity in patients undergoing major surgical procedures. In a large Veterans Affairs study it was shown that the albumin level alone was the best predictor of morbidity.[21] In still another study of patients undergoing esophageal, gastric, colon, or pancreatic surgery, preoperative albumin levels below 3.25 g/dl correlated with higher morbidity.[22] Indeed, levels of preoperative albumin correlated inversely with complications, length of stay, postoperative stay, intensive care unit (ICU) stay, mortality, and resumption of oral intake. Although patients undergoing pancreatic and esophageal resections had increased morbidity when compared with those undergoing colon surgery, there was still significant difference at all albumin levels. These authors suggest that many prospective studies either under-appreciate or under-recognize patients with hypoalbuminemia and thus skew the reported results.

Intervention in Nutritional Status

Nutritional supplementation with both enteral and parenteral formulas has improved outcomes in many

surgical patients in the past 3 decades. Since the early 1990s there has been a significant body of literature addressing the indications, methods, and end points of nutritional supplementation for surgical patients. More recently, the role of enteral nutrition has been recognized as an important factor in the outcome of surgical, trauma, and burn patients.[18,23] Total parenteral nutrition (TPN) is useful when the gut cannot be used, and although it has a proven record of usefulness, the enteral route remains preferred. TPN was evaluated in the Veterans Affairs Cooperative Study and shown to improve outcomes in severely malnourished patients.[21] However, a period of 2 weeks was required to obtain nutritional enhancement. Mildly malnourished patients did show improvement in surgical outcome but had significant increases in non–catheter-related nosocomial infections, which negated the benefit. In general, TPN administered before surgery has been studied repeatedly and found to increase rather than decrease surgical risks.[24]

It is tempting to believe that when instructed, patients will be able to successfully improve their nutritional status. Unfortunately, in those with cirrhosis or protein and calorie malnutrition resulting from obstructive jaundice, such an outcome is extremely unlikely. Although a delay in surgery in an effort to improve nutrition is defensible, it must be tempered with likelihood of success. In jaundiced patients, it has been shown that decompression of the biliary tree can stimulate appetite and caloric intake. Regrettably, this has not been well correlated with outcomes.

Early enteral nutrition is now accepted practice in both trauma and burn patients because it prevents the normally ensuing hypercatabolic state.[25] Both animal and human studies have shown that enteral nutrition prevents small bowel disuse atrophy and subsequent bacterial translocation, septic complications, and multisystem organ failure.[26-29] It is now appreciated that although some bacterial translocation may be normal, clearance of these bacteria is what determines the clinical consequence. Unfortunately, patients with cirrhosis and biliary obstruction are clearly compromised in this capacity. Animal studies are yielding insight into the exact mechanisms of such observations.[30,31]

To date, most studies have concluded that the enteral route is always preferable for both preoperative and postoperative nutrition when feasible. TPN can be reserved for circumstance in which the GI tract is truly unavailable. In addition to a lower rate of overall complications, the enteral route is cheaper and easier to manage. This leaves us with the basic philosophy, "if the gut works, use it."

BILIARY TRACT DISEASE

Biliary disease runs the spectrum of the common gallbladder disease treated by most general surgeons to complex problems related to stones, fistulas, and neoplasms such as cholangiocarcinoma cared for at specialty centers. Patients with obstructive jaundice are inherently at risk for hepatocellular injury and postoperative liver failure, as noted earlier. Simple relief of obstruction does not guarantee timely complete recovery or normalization of serum bilirubin levels. Because patients undergoing procedures for biliary decompression require some degree of sedation or anesthesia (or both), subsequent fluid shifts, electrolyte abnormalities, hemorrhage, bile peritonitis, sepsis, or decompensation must be anticipated.[32]

Many centers advocate surgical intervention without any prior biliary decompression or instrumentation.[33] Indeed, evidence exists to indicate a higher likelihood of contamination of bile in patients who are instrumented before surgery.[34] Frequently, such an approach precludes a definitive preoperative tissue diagnosis. A multidisciplinary approach to such patients is optimal in that opinions from the endoscopist, interventional radiologist, and surgeons can be evaluated before treatment decisions are made. Both retrospective and prospective randomized studies have shown not only no improvement in morbidity or mortality but rather an increase in infectious complications.[35,36] The biliary tract is sterile under most circumstances before endoscopic or percutaneous manipulation. When the biliary tract is instrumented, a fluoroquinolone and possibly a cephalosporin active against enterococcus (e.g., ceftriaxone) can be administered before intervention.[37]

There are circumstances in which patients do undergo endoscopic retrograde cholangiopancreatography with stenting as the preferred management. Obviously, in cases in which the patient is judged by the surgeon to be unfit for surgery, decompression and nutritional supplementation should be undertaken to improve the candidacy for subsequent resection. Biliary decompression alone did not necessarily improve hepatic function or outcome, but it has shown improvement when coupled with either enteral or parenteral nutrition.[35,38] Recent studies investigating the treatment of pancreatic cancer address the use of neoadjuvant chemoradiation. Inherently, these patients require biliary decompression to complete their medical treatment, before restaging and possible surgical exploration. The specifics of this approach are beyond the scope of this discussion.

In preparation for surgical exploration, any correctable factors should be addressed, including electrolytes with supplements. Anemia can be corrected, again with either blood transfusion if necessary or recombinant erythropoietin as discussed earlier. Hemostatic abnormalities should also be corrected with weekly or every-other-day injections of vitamin K as time permits. In addition, blood and blood products should be immediately available during the surgical procedure, as with any major abdominal operation.

Gut preparation should be undertaken preoperatively, especially in patients taking H_2 blockers or proton pump inhibitors, because these medications can lead to a hypochlorhydric state. In this situation the usual gastric acidity cannot maintain sterility of the upper GI tract. Furthermore, there are occasions when en bloc resection will require colon resection with anastomosis, and this should be done in one operation. Any standard bowel preparation should suffice (GoLYTELY, lactulose, Fleet Phospho-Soda), at the discretion of the operating surgeon.

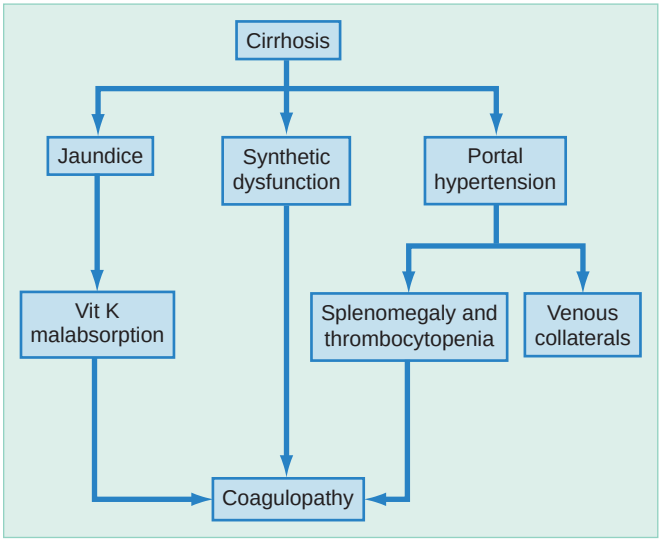

Figure 113–1. Schematic showing the interrelationship of multiple physiologic disturbances occurring in patients with portal hypertension and cirrhosis.

CIRRHOSIS

The complexity of a cirrhotic patient cannot be taken lightly. Patients have multiple underlying and overlapping medical issues that complicate surgical care. It is difficult to picture how each organ system relates to the others because it takes place on multiple levels at all times and must be considered as a whole by the liver surgeon. The diagram in Figure 113–1 indicates the organ system interaction that occurs in chronic liver disease. Although it is difficult to separate out each portion as it relates to operating on a patient with cirrhosis, we will attempt to individually review these areas while keeping in mind the continuous interaction that occurs.

Hemodynamics

Perhaps the most pervasive physiologic changes associated with cirrhosis are those affecting hemodynamics. Similar to those seen in sepsis, these changes can affect each of the other organ systems. Chronic liver disease leads to generalized vasodilation with reduced systemic vascular resistance (SVR) and a hyperdynamic state. In addition to reduced SVR, a host of attendant changes can be found, including increased peripheral blood flow, reduced arteriovenous oxygen difference, decreased effective blood volume with reduced cortical renal blood flow, and activation of the renin-angiotensin axis with sodium and water retention contributing to ascites formation. This makes the use of a pulmonary artery catheter for fluid resuscitation necessary in patients with a distorted difference in right and left heart pressure from ascites or other variables. Patients with cirrhosis are generally observed to have elevated cardiac output, tachycardia, and low blood pressure. Many of the common physical findings seen in cirrhotic patients, such as palmar erythema and cutaneous spider angiomas, are also explained by these vascular changes.

Volume loading has been used since the 1970s in an attempt to counteract the hypotension caused by both acute and chronic liver disease. By improving mean arterial pressure with colloid volume loading, investigators demonstrated the importance of low SVR in cirrhotic patients.[39] Of additional importance is the impaired oxygen supply that results. In a study of patients with fulminant hepatic failure, lower SVR measurements and lower oxygen extraction ratios portended a worse prognosis, more often resulting in death.[40] Although this does not necessarily describe a patient with chronic liver disease, acute decompensation also occurs and may become more relevant in a postoperative liver patient who decompensates and requires intervention.

Although a definitive method to improve the hemodynamics of chronic liver disease has yet to be described, it may be important to attempt to improve oxygen delivery. Some evidence suggests that using *N*-acetylcysteine can improve oxygen delivery, oxygen extraction, and cardiac output. This may improve the activity of the nitric oxide–soluble cyclic guanylate monophosphate enzyme system and potentially decrease the rate of other organ failure.[41,42] Conflicting data also exist.[43] Eventually, the use of inotropes may be required, but the development of hypotension in the face of adequate filling pressure is associated with a poor prognosis.

Cardiopulmonary

Cardiac disease is present in many patients with chronic liver disease. Although many patients have other medical problems associated with cirrhosis, it is difficult to quantify the degree of cardiac disease that results from portal hypertension. Right heart pressure is elevated because of the hemodynamic disturbances just described and can lead to progressive heart failure or valvular problems. Recently, the effect of portal hypertension on cardiac function was evaluated in four groups of patients, including normal controls, patients with noncirrhotic portal fibrosis (portal hypertension without liver dysfunction), and cirrhotics with and without ascites.[44] Cardiac function was evaluated by echocardiography. Additional measurements of plasma rennin activity and aldosterone levels were performed. Diastolic function as assessed by the ratio between the E wave and the A wave (E/A ratio) was significantly lower in patients with noncirrhotic portal fibrosis (median, 1.3) than in normal controls (median, 1.52). However, even lower values were observed in cirrhotics without ascites (median, 1.05) and with ascites (median, 0.94). There was a significant correlation between plasma aldosterone levels and the E/A ratio in cirrhotics. This finding supports the concept that portal hypertension is an important factor in the development of cardiac dysfunction.

Cirrhosis can be associated with reduced arterial oxygen saturation. The hepatopulmonary syndrome and portopulmonary hypertension are each related to the hyperdynamics of cirrhosis. Portopulmonary

Table 113–4 Laboratory Methods to Control Variceal Bleeding

Medical	Mechanical	Endoscopic	Radiologic	Surgical
Vasopressin	Sengstaken-Blakemore tube	Band ligation	TIPS	Portocaval shunt End to side Side to side
Octreotide	Minnesota tube	Sclerotherapy		Mesocaval shunt H-graft
β-Blockers				Splenorenal shunt Esophageal transection

TIPS, transjugular intrahepatic portosystemic shunt.

hypertension affects only about 2% of patients with severe liver disease. The associated pulmonary arterial changes are identical to those seen in patients with primary idiopathic pulmonary hypertension. If suggested by echocardiography, right heart catheterization is always indicated. The finding of a mean pulmonary arterial pressure (MPAP) higher than 25 mm Hg is diagnostic, whereas a MPAP higher than 35 mm Hg (PVR >240 dynes/sec/cm^5) is associated with an increased risk for death. Treatment consists of prostacyclins, nitric oxide, or other vasoactive agents. Hepatopulmonary syndrome is another rare entity defined by the triad of chronic hypoxemia (PaO_2 <60 mm Hg), pulmonary vascular dilation, and severe chronic liver disease. Demonstration of a large pulmonary shunt on ventilation-perfusion scanning or echocardiography is necessary.

Portal Hypertension

The most clinically relevant aspect of cirrhosis is portal hypertension. Complications of portal hypertension are well described and consist mainly of variceal bleeding, particularly from the esophagus (Table 113–4). These thin-walled vessels allow blood flow around the diseased liver and are formed from the resultant pressure increase. Approximately 90% of such episodes are successfully treated with endoscopic or pharmacologic interventions (or both). When indicated, an experienced interventional radiologist can place transjugular intrahepatic portal systemic shunts (TIPS) to allow a decrease in portal pressure when medical and endoscopic therapies have been exhausted or are unavailable. Surgical shunts remain appropriate in the nonacute setting, when the most prominent feature of disease is bleeding in an otherwise well-compensated patient. TIPS may be contraindicated by significant hepatic encephalopathy or bilirubin levels elevated much over 3.0 mg/dl, in which case progressive liver failure may ensue without shunt reversal.

Endoscopic therapy for acutely bleeding varices should not be delegated to an inexperienced endoscopist. Multiple approaches have been used, each with a significant risk. Unfortunately, in an acutely bleeding cirrhotic, there is little time to plan options, and interventions at the surgeon's disposal should be immediately implemented. Options for endoscopic therapy include banding, which should be followed by reexamination at approximately 1 week for possible rebanding. Sclerotherapy is another option that risks esophageal perforation or injury, but it has been successful. If endoscopy is not available, balloon compression with a Sengstaken-Blakemore or other balloon device is a mechanical measure that can be used until medical therapy can be implemented successfully. Patients are generally intubated before passage of these tubes because they are uncomfortable, may compromise the oral airway, and may increase the risk for aspiration. All of these measures are temporizing until portal hypertension can be corrected by liver transplantation.

Pharmacologic therapy is the primary modality for controlling GI bleeding in a patient with chronic liver disease. Although portal hypertensive patients are at risk for gastric and duodenal ulceration, standard methods as used for any critically ill patient are implemented. Antacids, H_2 blockers, and proton pump inhibitors are the mainstay of therapy and should be administered at the time of admission. For acute variceal hemorrhage, intravenous octreotide is considered first-line therapy. Additionally, a vasopressin drip can be administered at 0.4 U/min in the acute setting for at least 48 hours with or without nitrates.[45-47] In the long-term management of portal hypertensive gastroesophageal varices, β-blockers are the mainstay of therapy.

Ascites/Gastrointestinal Disease

The pathophysiology of the development of ascites is a complex and interrelated mechanism that is beyond the scope of this discussion. Briefly, it is a consequence of both portal hypertension and hypoalbuminemia, along with a component of salt and water retention. Serum albumin is usually less than 30 g/dl, and the associated renal excretion of sodium is less than 10 mmol/24 hr. Management generally entails potassium-sparing diuretics to control the third spacing and attempt to create an ascites-free peritoneal cavity before any operation. Additionally, ascites can be controlled with serial paracentesis and can be done in large volumes if necessary.

This issue can be complicated by a diuresis-induced renal impairment that can progress to the dreaded hepatorenal syndrome, as discussed in the next section. Again, the interrelated difficulties of multiple organ systems become apparent here. If fluid status becomes an issue in the postoperative period, we support the use of a pulmonary artery catheter to improve management.

Associated GI diseases may also be involved in a cirrhotic patient. Specifically, inflammatory bowel disease is strongly associated with primary sclerosing cholangitis (PSC). Patients with PSC have a 75% prevalence of ulcerative colitis (UC), whereas the converse is true in only 5%. PSC may also be associated with colonic Crohn's disease. In patients with both PSC and UC, the risk for colonic malignancy may be greater than that in those with UC alone and is an indication for vigilant screening colonoscopy both before and after transplantation.

Renal Dysfunction

In the absence of other identifiable pathology, the development of severe renal dysfunction in the presence of end-stage liver failure defines the hepatorenal syndrome. Although the etiology remains uncertain, it is probably related to the hemodynamic changes noted earlier. Because it is largely a functional problem, normal renal function can usually be expected to return when liver function is restored after transplantation. However, in long-standing hepatorenal dysfunction, normalization may not occur and may be unpredictable. Hepatorenal syndrome has been subdivided into type I and type II based on the pace of functional loss. Patients with type I hepatorenal syndrome experience rapidly progressive deterioration in kidney function with a doubling of the initial serum creatinine value in a period of less than 14 days. Such patients have 90% mortality within 90 days. Those with type II syndrome have less rapid progression and fare better as a group. In either case, patients often require hemodialysis.

Metabolic Abnormalities

Fluid and electrolyte balance becomes increasingly difficult for a cirrhotic patient. The changes noted earlier also contribute, with hypoalbuminemia resulting in intravascular depletion with associated third spacing of fluids. Additionally, cirrhotic patients have increased levels of aldosterone and antidiuretic hormone, which causes the resultant salt and water retention. Therefore, it is important to choose appropriate diuretic therapy for each patient. Although some variation exists, in general, a combination of furosemide and spironolactone is the usual treatment. Furthermore, because of a propensity to cause encephalopathy, thiazide diuretics should be avoided.

Renal function also plays a part in this scenario. Renal perfusion can be affected because of decreased peripheral perfusion pressure and a perceived decrease in intravascular volume. This activates the renin-angiotensin system and the resultant cascade. It therefore becomes very important to monitor renal function and electrolytes during diuretic therapy and adjust for changes in blood urea nitrogen and creatinine.

Hepatic Encephalopathy

The clinical findings of hepatic encephalopathy can range from subtle personality changes and sleep disturbance to frank coma. Careful questioning of the patient or family member can elicit a suggestive history. This condition can be acutely exacerbated by infection or a large GI protein load, either dietary or from bleeding. With proper management, even in the most severe circumstance, the mental status changes are temporary and reversible. The mechanisms underlying hepatic encephalopathy appear to be related to the accumulation of unmetabolized ammonia as a result of poor hepatic function and portal-systemic shunting. Other factors may also contribute to encephalopathy, including the production of false neurotransmitters, activation of γ-aminobutyric acid receptors, altered cerebral metabolism, and disturbed sodium potassium ATPase activity, to name a few.[48] When unrecognized, the confusion of hepatic encephalopathy is often treated with benzodiazepines, which unfortunately exacerbates and greatly prolongs the symptoms.

Coagulopathy

Among the many problems associated with liver disease, the most potentially life-threatening is acute bleeding. Figure 113–1 provides an overview of the factors that can contribute. One aspect of the coagulopathy associated with liver disease is related to diminished synthetic capacity. Factors II, VII, IX, and X are synthesized in normal liver, and as chronic liver disease progresses, one of the identifiers of severity is prolongation of the INR or prothrombin time. Whether related to parenchymal dysfunction or obstruction, cholestasis further contributes by inhibiting absorption of vitamin K, on which many clotting factors depend. Thrombocytopenia is also associated with chronic liver disease and is a result of portal hypertension and hypersplenism. The degree of thrombocytopenia appears to roughly correlate with the severity of portal hypertension and cirrhosis. The manifestations of hypersplenism may be improved by the placement of a TIPS device. TIPS placement, however, can present significant inherent risks.[49,50]

Treatment of coagulopathy in patients with liver and biliary tract disease is dictated by the underlying pathology. Parenteral vitamin K replacement corrects coagulopathy related to biliary obstruction, bacterial overgrowth, or malnutrition. Vitamin K is less effective for coagulopathy caused by severe parenchymal liver injury. Transfusion of fresh frozen plasma (FFP) is the typical treatment of significant coagulopathy in patients with liver disease and active bleeding. Transfusion of FFP also reverses the moderate to severe coagulopathy of cirrhosis before invasive procedures. It is important to realize that more FFP may be required in patients with chronic liver disease than in those with coagulopathy from unrelated causes.[51] Cryoprecipitate can also be

useful for severe coagulopathy with hypofibrinogenemia, especially when avoidance of volume overload is desired. Platelet transfusions, pooled or single donor, are useful in thrombocytopenic patients before performing invasive procedures or in the presence of significant bleeding, especially when the platelet count is below 50,000/ml. The use of recombinant factor VIIa and thrombopoietin therapy for correction of coagulopathy and thrombocytopenia, respectively, in patients with cirrhosis is currently under investigation. Therapy with prothrombin complex concentrates, 1-deamino-8-*d*-arginine vasopressin, and antithrombin III concentrates for the management of coagulopathy caused by liver disease is being studied, but such treatment is not standard therapy at this time.[52]

Infectious Diseases

Infectious complications associated with liver disease are well described. For pretransplant and post-transplant patients, these issues are of constant concern to the liver surgeon as a potential cause of morbidity and mortality. The cause of the infectious risk is probably multifactorial and related to impaired protein synthesis, malnutrition, and enteric bacterial translocation as discussed earlier. In addition to pneumonia, urinary tract infection, and sepsis, spontaneous bacterial peritonitis (SBP) is a significant risk in patients with ascites. In cases of suspected SBP, broad-spectrum antibiotics should be started without delay. Improvement in nutritional status and control of complications may serve to decrease infectious incidents, but this is easier said than done. Cholangitis is obviously a major concern in patients with biliary obstruction.

INTRAOPERATIVE CONSIDERATIONS

Anesthesia Considerations

In addition to the altered hemodynamics, coagulopathy, and other systemic effects of liver disease, the hepatic metabolism of many routinely used drugs further challenges the anesthesia management of such patients. The half-life of drugs cleared by the liver can be significantly prolonged and can thus alter dosage, duration of action, and lipid solubility. Ascites or edema present in cirrhotics can also result in a larger volume of distribution. On the other hand, in patients with a history of chronic alcohol use, an increased capacity for enzymatic metabolism may result in larger drug requirements during surgery. Because hepatic impairment also leads to decreased serum albumin concentrations, drugs that are usually protein bound may be present at increased plasma concentrations and give rise to an exaggerated response.

Surgical manipulation of the liver significantly increases the hepatic oxygen extraction ratio in connection with splanchnic vasoconstriction.[53] However, portal blood flow can be preserved despite a 20% to 60% reduction in blood pressure, provided that the cardiac index is maintained during sodium nitroprusside hypotension.[54] Therefore, a well-planned anesthetic that includes the aforementioned considerations and makes use of the now accepted low central venous pressure (LCVP) technique will allow the greatest success. LCVP anesthesia is designed to avoid vena cava distention and facilitate hepatic mobilization and dissection of the retrohepatic cava and hepatic veins.[55,56] This is a different outlook from crystalloid fluid loading in the preresection phase. The goal in the loading method is to account for expected blood loss by dilutional bleeding. On the contrary, this technique can lead to more blood loss by distending the cava and making venous repair more difficult. Blood loss greater than 5 L has been associated with excess mortality.[57] Consequently, if central venous pressure is lowered from 15 to 3 mm Hg, caval blood loss from an injury can be theoretically reduced by a factor of 5. This pressure decrease requires fluid restriction until the resection is completed. Therefore, minimal preoperative fluid is given, and small boluses are used to maintain blood pressure. This strategy requires the close availability of a rapid infusion system to provide emergency fluid and blood infusion. Although a low intraoperative urine volume may result, this is not necessarily associated with an increased incidence of postoperative renal failure.[56] The need for effective communication between the surgeon and anesthesiologist cannot be overemphasized. Communication alone can make the difference between success and failure during major hepatic resection.

Anesthesiologists experienced in the care of patients with liver disease have extensive knowledge of several important medication issues. Inhalational agents such as isoflurane and desflurane have been studied extensively and been found to be safe in patients with liver disease. They both undergo negligible hepatic metabolism and result in no free radical formation.[58] Hepatic blood flow and the hepatic artery buffer response are maintained better with isoflurane than with any other volatile anesthetic.[59] In contrast, halothane and other halogenated hydrocarbons must be avoided. Although halothane is a good general anesthetic for most patients, the entity of halothane hepatitis may occur from even one exposure.[60] Multiple exposures can result in fulminant hepatic failure. Although the exact cause remains unclear, hypoxic, metabolic, or immunologic mechanisms are likely.[61-63]

The use of local anesthesia should be encouraged, especially for small procedures. Amide-linked local anesthetics do undergo hepatic metabolism and should be used with caution. Regional anesthesia is an excellent adjunct, and continuous epidural catheter placement can enhance pain control in the intraoperative and postoperative period. The problem with the widespread use of regional anesthesia in this population is hemostatic impairment, which is a contraindication to spinal or epidural puncture.

Operative Considerations in Patients with Liver and Biliary Disease

Although preparation for surgery is the key to success, some special intraoperative factors must be considered,

as well as the basic tenets of abdominal surgery. Adequate exposure is critical, and proper consideration must be given to the type and extent of the incision. Extension of the incision should be performed whenever safety requires. A dependable self-retaining retractor system is essential.

The use of intraoperative ultrasound should always be considered and planned in advance. A working knowledge of the application of ultrasound is now standard of care in liver surgery and is obviously required for certain techniques such as radiofrequency ablation. In addition, using ultrasound to navigate both anatomic and nonanatomic resections allows identification of vessels before causing bleeding. This can be particularly helpful in nonanatomic resection and in cases in which a Pringle maneuver is not used. If the patient may be a transplant candidate in the future, a minimal dissection approach should be used. In addition, portal dissection should be avoided if possible when considering shunt procedures to keep from making the future transplant procedure more difficult or dangerous. This is unlikely to affect metastatic colorectal patients but certainly pertains to patients with hepatocellular carcinoma.

Methods to control blood loss deserve mention and can be used when indicated. The use of total vascular occlusion for some major liver resections may be feasible but should be discussed well in advance with the anesthesiologist. For those familiar with its use, venovenous bypass may be a useful adjunct in extreme circumstances, especially in patients with large tumors involving the vena cava. The most common method used to limit blood loss during liver resection is either intermittent or continuous clamping of the portal triad (Pringle maneuver). Use of this technique is limited by the degree of underlying parenchymal disease. A normal liver may tolerate up to a total cumulative clamping time of 1 hour, but a diseased liver will tolerate much less.

Hepatic parenchymal transection can be performed by many different methods. To date, no randomized trials have shown one method to be superior to another. Each has different benefits with regard to speed of transection versus control of blood loss. Available techniques include electrocautery, the Cavitron ultrasonic aspirator (CUSA), endovascular staplers, and newer devices such as the floating ball cautery and water jet device.

The use of tubes and drains after liver and biliary surgery will differ from one institution to another. If drains are used, the closed suction varieties are preferred and are removed within 3 to 7 days, depending on the procedure performed, the character and volume of the drainage fluid, and the surgeon's preference. Frequently after hepatic resection, for example, if the fluid is not bilious or bloody by postoperative day 3, the drain is removed regardless of volume. In contrast, after pancreaticoduodenectomy, a single drain may be left to drain both the biliary and pancreatic anastomosis and is removed when the patient is eating and the output appears normal. Some authors prefer to place both gastrostomy and jejunostomy tubes after all pancreaticoduodenectomies. In malnourished patients, a nasogastrojejunostomy tube can be placed at the time of surgery through the gastrojejunal anastomosis and feeding commenced almost immediately.

Wound closure can be performed by any standard method—running or interrupted. Special consideration should be given to patients with ascites or those at risk for its development.

POSTOPERATIVE MANAGEMENT

Advances in anesthesia, surgical technique, and postoperative intensive care have lowered the morbidity and mortality associated with major liver resection to an acceptable level. Jarnagin et al. reported on the outcomes of 1803 patients undergoing liver resection at a single institution. In this study the overall operative mortality was 3.1%. The authors found a progressive increase in blood loss as the number of segments resected increased. The perioperative morbidity was 45%, with 19% experiencing multiple complications. Among those experiencing complications, infections occurred in 41%. The most common complications were liver or biliary related (or both), although pulmonary complications were nearly as common.[10]

In general, patients are observed in a surgical ICU postoperatively and transferred to a specialized liver ward when stable. Hemodynamic monitoring is performed with at minimum a central venous catheter for infusion and measurement of central venous pressure and an arterial line for monitoring blood pressure. The use of pulmonary artery catheters depends on the case. Low-volume intravenous fluid hydration is used to maintain adequate blood pressure and urine output. Bolus fluids are given as necessary with a combination of crystalloid, albumin, and blood products. Laboratory values, oxygenation, and urine output are monitored closely to look for early complications. Patients undergoing biliary and pancreatic resection may have multiple anastomoses for which closed suction drains are generally placed to monitor for problems.

Some unique issues related to major hepatic resection should be discussed. Drug metabolism and anesthetic clearance may be altered by resection. Coagulation levels need to be followed closely in the first 48 to 72 hours and patients monitored for bleeding problems. Vitamin K is given routinely during the hepatic regeneration phase. Phosphorus replacement must be undertaken diligently because life-threatening hypophosphatemia (phosphorus <1.0 mg/dl) has been reported after liver resection.[64] Hypophosphatemia is associated with reversible cardiac dysfunction, hypoventilation, and impaired immunity. Pomposelli and Burns reported the incidence of hypophosphatemia after elective right hepatic lobectomy for living donor adult liver transplantation (LDALT) and the associated complication rate and surgical outcome of living liver donors.[65] This was done to determine the efficacy of prospective treatment with phosphate repletion as part of TPN. Hypophosphatemia developed in all donors without replacement and resulted in either a life-threatening (phosphorus <1.0 mg/dl) state in 70% or a severely depleted (phosphorus, 1.5 to 1.1 mg/dl) state in 30%. With more aggressive phosphate repletion,

life-threatening (phosphorus <1.0 mg/dl) hypophosphatemia developed in only 8% and severe (phosphorus, 1.1 to 1.5 mg/dl) hypophosphatemia in 30%. The results of this study suggest that hypophosphatemia is a universal event after LDALT; it can probably be extrapolated to any major hepatic resection and should be aggressively treated.[64] Liver regeneration involves rapid cell division as early as 24 to 72 hours after resection. This is an ATP-dependent process that probably depletes the remaining stores after resection. For this reason, KPO_4 supplementation is undertaken in the immediate postoperative period as an infusion or frequent replacement.

Other standard postoperative activities should be performed, such as pain control with narcotic injection or patient-controlled analgesia. This is discontinued when the patient can tolerate an oral diet and pain medication. Perioperative antibiotics are continued in uninfected patients for 24 to 48 hours only.

Because the incidence of morbidity reported by large studies, as discussed earlier, is not negligible, monitoring for complications is imperative. Particularly in patients with chronic liver disease, any of the progressive problems may worsen after surgery: jaundice, ascites, encephalopathy, infection, and GI bleeding. The cause should be sought and treated as quickly as possible.

SUMMARY

Success in performing major liver and biliary resection has improved over recent decades, mainly as a result of better perioperative management. Care of this special group of patients requires a working knowledge of the intricate relationship of many pathophysiologic mechanisms resulting from chronic liver disease and cirrhosis. Experienced teams of surgeons and anesthesiologists have also made great advances in hepatic resection and blood loss control techniques. By combining a comprehensive preoperative work-up with safe intraoperative techniques and diligent postoperative care, successful results can be obtained in patients requiring major resection. This has led to better overall care of complex patients with liver and biliary disease.

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Chapter

114

Hepatic Cyst Disease

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Hepatic cysts are encountered in clinical practice with increasing frequency due to advances in cross-sectional imaging. The most common cystic hepatic lesions in Western countries are developmental in origin, followed by neoplastic cysts. Worldwide, cystic lesions caused by hepatic infection with *Echinococcus granulosus* predominate. Treatment is dictated by underlying cause, anatomic features, and symptomatic presentation.

SOLITARY HEPATIC CYSTS

Solitary hepatic cysts are noted frequently during laparotomy when near the liver surface, but earlier surgical and autopsy series have underestimated the true incidence of liver cysts. An early report, based on the demonstration of liver cysts at autopsy, noted 28 hepatic cysts in 20,000 examinations, a calculated incidence of 0.14%.[1] Other early reports quoted similarly low incidences of 0.17% and 0.53%.[2,3] The increased use of abdominal ultrasound examination for a variety of indications has generated additional information and a higher incidence for hepatic cysts. In a European study of 1695 patients referred for abdominal and pelvic ultrasound examinations, an overall incidence of 2.5% was recorded.[4] In a second European study of 26,000 patients undergoing upper abdominal ultrasound, 1235 cysts were identified, for an incidence of 4.75%.[5] In both of these studies, the incidence of hepatic cysts increased with age, with more than 92% of cysts identified in patients older than 40 years of age.[5] Hepatic cysts are more common in women, with a 1:1.5 male-to-female ratio, and are more frequently symptomatic in women than in men.

Simple hepatic cysts are characterized histologically by a simple cuboidal epithelium. The surrounding stroma is hypocellular and fibrous. The ability to derive epithelial cell cultures from hepatic cysts suggests that these structures derive from biliary origin.[6] Current understanding suggests that biliary cysts originate from biliary microhamartomas or peribiliary glands that lose their connection with the bile ducts.

Most simple hepatic cysts are discovered incidentally; approximately 85% of patients are asymptomatic. The most common symptom attributed to simple hepatic cysts are abdominal pain or distention due to mass effect. Early satiety, nausea, or vomiting are noted in a minority of symptomatic patients. Symptoms have been recorded in patients and young adults but are increasingly frequent in the 4th to 6th decades, corresponding to cyst enlargement. Physical examination may demonstrate an abdominal mass or hepatomegaly, but these findings are both infrequent and nonspecific.

Ultrasound, computed tomographic (CT) scan, and increasingly, magnetic resonance (MR) imaging studies are used to anatomically define and classify cystic hepatic lesions. Improvements in cross-sectional imaging techniques during the past decade have greatly enhanced delineation of intrahepatic anatomy. In fact, imaging studies are the means by which many of these lesions are currently discovered. The morphologic distinctions between simple cysts and neoplastic or infectious lesions are paramount as the first diagnostic step.

Because ultrasonography is inexpensive, noninvasive, and informative, this should be the preferred initial test for evaluation of cystic hepatic lesions. Ultrasonography is the most accurate imaging method for diagnosis of hepatic cysts, with a sensitivity and specificity greater than 90%.[7] On ultrasonography, simple hepatic cysts appear as anechoic masses with smooth margins and imperceptibly thin walls (Fig. 114–1). Because of differential reflection of ultrasound waves by the cyst fluid and the cyst wall, back wall enhancement may be noted. Ultrasound is highly reliable in distinguishing between solid and cystic lesions of the liver. The ultrasonographic determination of a simple cyst is based on the absence of intracystic septations; the presence of internal septa suggests the diagnosis of a neoplastic cyst. In recent series, a lack of internal septations was 100% predictive of simple hepatic cyst.[8]

Although ultrasonography can reliably distinguish between solid and cystic liver lesions, CT scans are superior in demonstrating the location and spatial

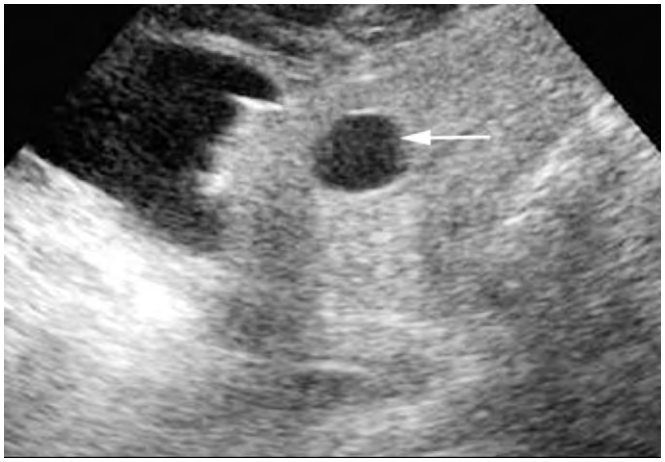


Figure 114–1. Simple hepatic cyst. Transverse ultrasound image of the left lobe shows an anechoic cyst *(arrow)* with smooth imperceptible walls and increased through transmission.

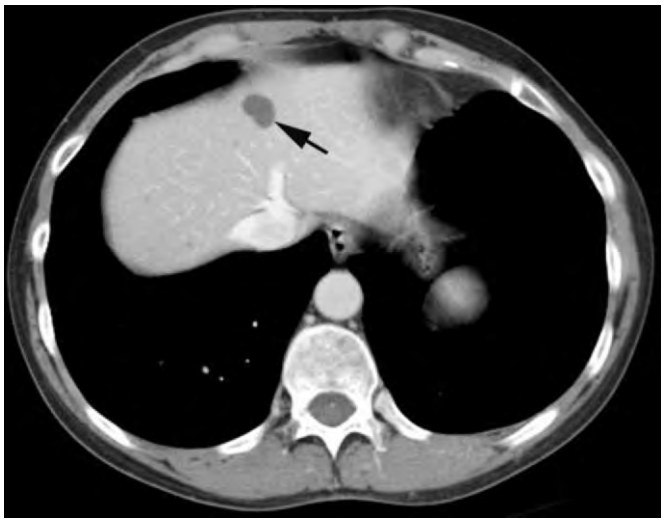


Figure 114–2. Simple hepatic cyst. Transverse contrast-enhanced CT image shows a simple cyst *(arrow)* in the left lobe of the liver. The cyst has water attenuation and imperceptible walls and does enhance with contrast.

relationships of hepatic lesions necessary for surgical planning. CT scans should be performed to optimize imaging of the cyst and surrounding blood vessels, bile ducts, and hollow organs. Both oral and intravenous contrast should be administered. CT protocols are used that time scanning relative to contrast infusion to initiate imaging during maximum hepatic contrast enhancement. On CT images, simple cysts are nonenhancing, water-density (0-10 Hounsfield units) lesions with smooth imperceptible walls (Figs. 114–2 and 114–3).[9] Liver cysts less than 1 cm in size may be difficulty to distinguish from solid lesions due to partial volume averaging with adjacent liver. In such cases, MR imaging can be used for

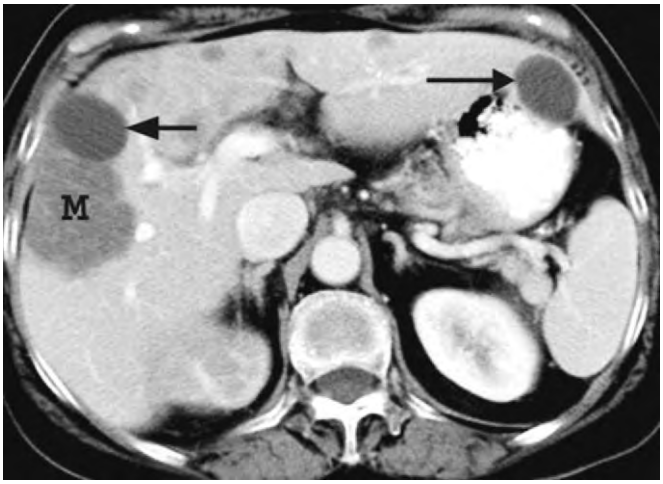


Figure 114–3. Two simple hepatic cysts and a liver metastasis. Transverse contrast-enhanced CT image shows two simple hepatic cysts *(arrows)* with water attenuation in the right and left lobes of the liver. The cysts are unenhanced and have imperceptible walls. Compare to the enhanced metastasis (M) adjacent to the cyst in the right lobe. Note several other small metastatic lesions in the liver.

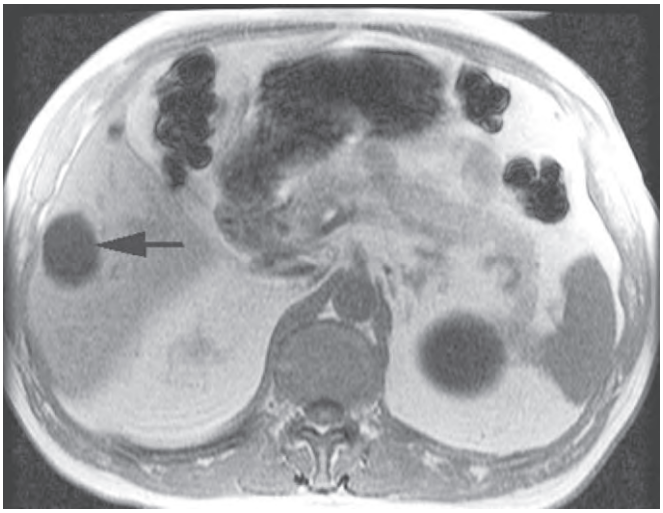
characterization.[10] Simple cysts do not demonstrate loculations or septae; their presence should suggest neoplasia. Simple cysts do not contain irregular walls, papillary mural projections, or intracystic debris.

MR imaging provides information similar to that of CT scanning. When viewed on MR imaging, simple hepatic cysts have homogeneous very low signal intensity relative to surrounding liver parenchyma on T1-weighted images, homogeneous very high signal intensity on T2-weighted images, and no enhancement after administration of gadolinium chelates (Fig. 114–4).[9,11] MR imaging is particularly useful for characterization of small (≤2 cm) cysts that can be indeterminate on CT (Fig. 114–5).[19] If intracystic hemorrhage has occurred, the lesion will appear hyperintense on both T1- and T2-weighted images, usually with a fluid-fluid level (Fig. 114–6).[11] Internal cyst structure, in the form of septations, papillary nodules, and debris are well demonstrated with MR imaging techniques.

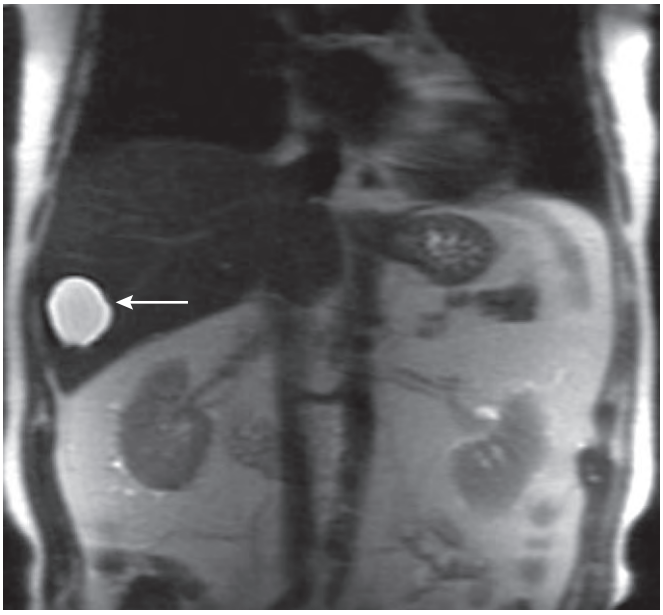
With advances in cross-sectional imaging techniques, other radiologic modalities have decreased in utility. Angiography demonstrates that the mass is avascular, with displacement of surrounding vessels. Nuclear scintiscans demonstrate a "cold" mass.

Laboratory evaluation should be directed by preexisting comorbidities, physical findings, and age. In most series of simple hepatic cyst, no abnormality of any laboratory measurement is noted. Echinococcal serology should be obtained to exclude infectious causes.

The treatment of simple hepatic cysts is predicated on the presence of symptoms. When simple hepatic cysts are discovered incidentally by imaging studies or at laparotomy, and the patient is determined to be asymptomatic, conservative treatment is appropriate. When



A



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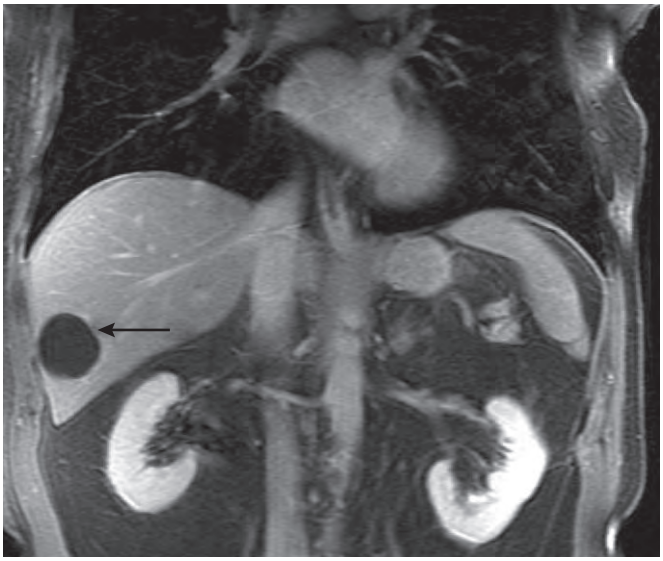


C

Figure 114–4. Simple hepatic cyst on MR imaging. Transverse T1-weighted **(A)** and coronal T2-weighted **(B)** images of the liver show a well-defined mass *(arrows)* with low signal intensity on T1-weighted imaging and very high signal intensity on T2-weighted imaging. The mass *(arrow)* does not enhance on the coronal postgadolinium image **(C).**

this approach is followed, 80% to 95% of patients will remain asymptomatic.

When symptoms are attributed to the cyst, treatment of hepatic cysts is indicated. Percutaneous aspiration using ultrasound guidance is not effective; this simple approach is associated with a recurrence rate of 100%.[12] Attempts at permanent ablation via percutaneous means have also involved the instillation of sclerosants after cyst aspiration. In a study of 30 hepatic cysts treated with 95% ethanol after aspiration, the recurrence rate was 17%.[13] Reports of sclerosants have involved small numbers of patients and relatively short periods of follow-up. These methods have been largely supplanted by laparoscopically guided treatment, which in addition to relatively low operative trauma offers the advantage of cyst wall biopsy.

Most investigators advocate surgical treatment of symptomatic hepatic cysts. At the time of operation, the cyst is visualized as a blue-domed structure protruding from the surface of the liver. The cyst should be inspected visually and by intraoperative ultrasonography to demonstrate its extent and to confirm its relationship to biliary and vascular structures. Color Doppler examination is useful in identifying vascular structures. The cyst should then be aspirated and fluid sent for Gram stain, bacterial culture, and cytologic examination. A biopsy of the cyst wall should be sent for intraoperative examination to exclude neoplasia. The lining of the cyst cavity must be inspected; papillary projections should undergo biopsy.

Solitary nonparasitic cysts may be treated by fenestration. The wall of the cyst is excised to within 2 cm of the liver parenchyma. Hemostasis of the edges is obtained with electrocautery. The remaining cyst cavity is left intact to drain into the peritoneal cavity. In rare cases in which aspiration of cyst fluid is bilious, implying communication with the biliary ductal system, drainage may be affected by Roux-en-Y cystojejunostomy. In this circumstance, the cyst lining should be inspected and identified biliary communications suture ligated.

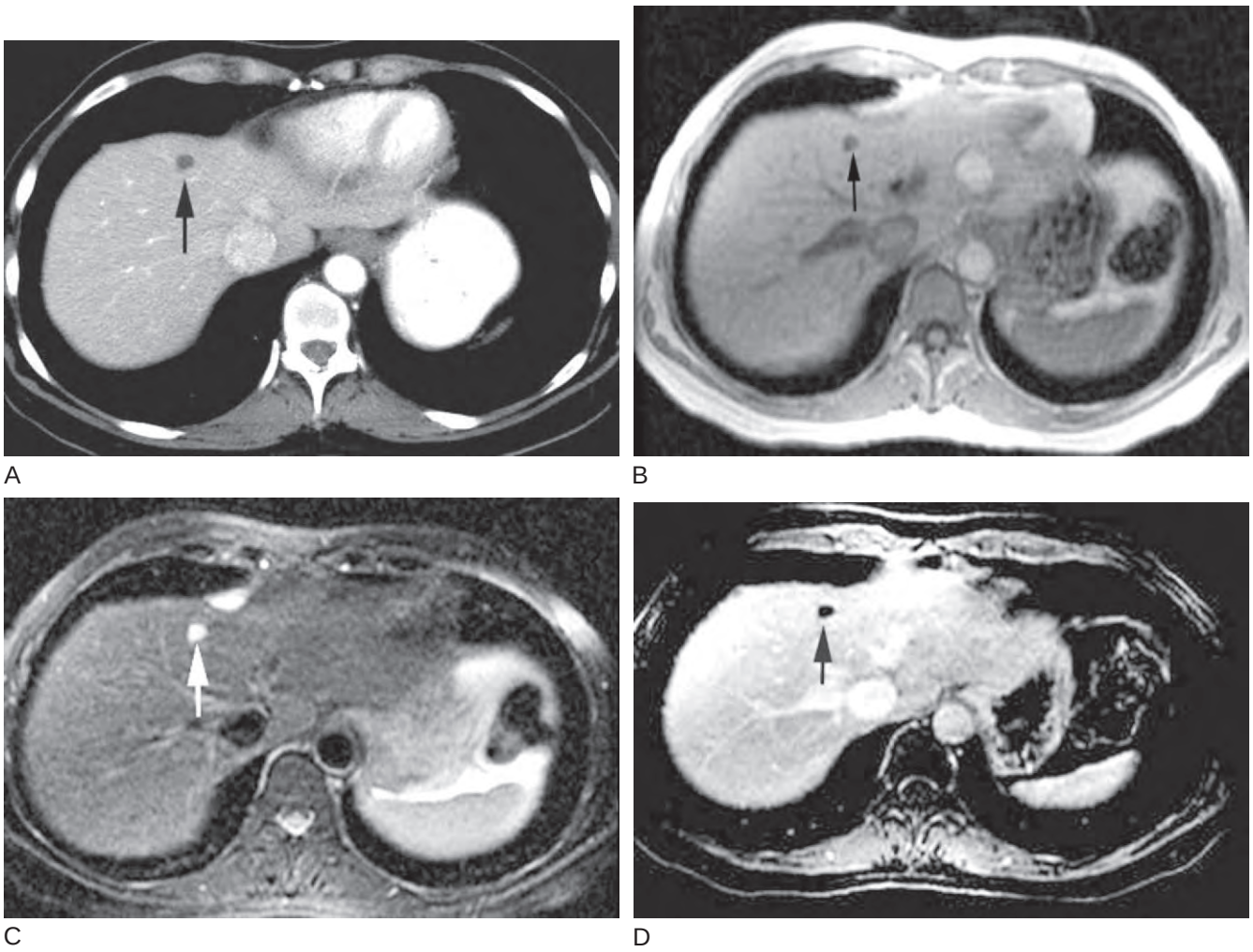


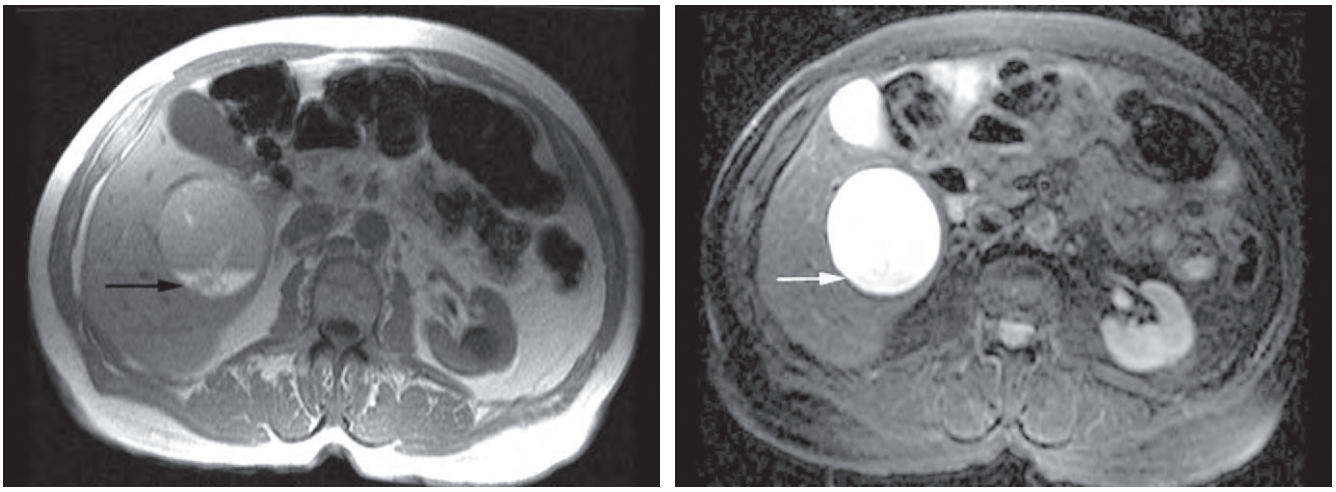
Figure 114–5. A small incidentally detected simple cyst on CT and MR imaging in a patient with no history of malignancy or chronic liver disease. Transverse contrast-enhanced CT image **(A)** shows a 1-cm hypodense mass in the medial segment of the left lobe *(arrow).* The mass is too small to be accurately characterized. Transverse T1-weighted **(B)** and T2-weighted **(C)** images of the liver show the mass *(arrows)* to be hypointense relative to liver on T1-weighted imaging and markedly hyperintense on T2-weighted imaging. The mass *(arrow)* does not enhance on the transverse gadolinium-enhanced image **(D)**.

Multiple surgical investigators have reported surgical treatment of solitary hepatic cysts with good results.[14] Overall, cyst fenestration is associated with recurrence rates of 0 to 20% and mortality of 0 to 5%. Morbidity rates are also correspondingly low.

Hepatic lobectomy has been reported for treatment of simple hepatic cysts. Recurrence rates after hepatic resection approximate 0%, but a procedure of this magnitude is seldom required. Hepatic resection may occasionally be appropriate for recurrent cysts or for those with biliary communication.

Laparoscopic resection has been increasingly used for treatment of symptomatic hepatic cysts. Successful laparoscopic treatment requires adequate visualization of liver structures. The technique is best used with lesions in the anterolateral segments II to VI of the Couinaud classification. Centrally located lesions or cysts in the posterior aspects of segments VI, VII, and IVa are more difficult to access. The patient is positioned in lithotomy, with the surgeon standing between the legs. Assistants stand at the sides. A 30-degree laparoscope is placed at the umbilicus. Two ports surround the umbilicus in a triangulated fashion. A subxiphoid retractor is used for introduction of a fan retractor or suction device. The cyst wall is excised with scissors; hemostasis may be obtained with electrocautery or a variety of laparoscopically applied devices.

Laparoscopy provides excellent visualization of the upper abdomen. Success rates, defined as lack of symptomatic cyst recurrence, have exceeded 90% in several series.[15] Postoperative complications approximate 10%, with mortality approaching 0%. Because of the excellent recurrence rates and decreased postoperative pain, laparoscopic cyst resection should be considered the preferred procedure for simple hepatic cysts.[16]



A B

Figure 114–6. Hemorrhage within a simple cyst. Transverse T1-weighted **(A)** and T2-weighted **(B)** MR images show a high attenuation content of the cyst on T1-weighted and T2-weighted imaging with layering high T1-weighted and low T2-weighted signal intensity material *(arrows)* in the dependent portion of the cyst indicating the presence of hemorrhagic products (methemoglobin).

POLYCYSTIC LIVER DISEASE

Polycystic liver disease is a benign condition that occurs in close association with polycystic kidney disease, which is inherited as an autosomal dominant disorder. In affected individuals, hepatic cysts become increasingly prevalent with age. Hepatic cysts are present in 25% of cases by age 30 and in 80% by 60 years.

Autosomal dominant polycystic kidney disease is caused by defects in two genes, *PKD1* and *PKD2*.[17,18] In murine models, cysts do not form in heterozygous pkd +/− or pkd +/− knockout mice. In contrast, severe cystic disease is observed in homozygotes or heterozygotes with a hypermutable normal allele.[19] These observations, coupled with the age dependence of human hepatic cyst formation, suggests that many human cases may arise as a germline mutation in one *PDK1* or *PDK2* gene coupled with a somatic mutation in the remaining normal allele. In support of this mechanism, most hepatic cysts are clonal in origin and have somatic mutations in the normal allele with loss of heterozygosity.[20] Hepatic cysts are believed to originate from biliary epithelial cells.

Hepatic cyst formation is influenced by the endocrine environment. Polycystic liver disease is more common in females with polycystic kidney disease. Greater numbers of cysts develop in women that have experienced pregnancy or have received exogenous hormones. In one study, exposure of patients with polycystic kidney disease to Premarin caused a 7% increase in liver cyst size over a period of 1 year relative to untreated controls.[21]

Renal function and hepatic cyst load are correlated: Patients with the greatest renal cyst load and the greatest reduction in renal function have the most extensive hepatic cyst disease.[22]

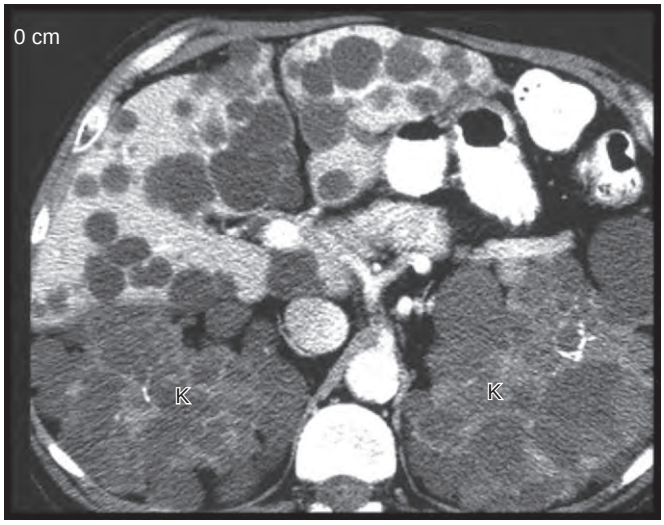
Most patients with adult polycystic liver disease are asymptomatic, despite multiple cysts and gross distortion of liver shape. Liver failure has not been observed in these patients. Complications attributable to polycystic liver disease are rare, occurring in fewer than 5% of affected individuals. Reported complications include cyst infection or rupture, portal hypertension with ascites or variceal bleeding, and hepatic venous outflow obstruction secondary to cyst compression.

Although remarkably well tolerated by most patients, hepatic enlargement does cause symptoms in some patients. Abdominal pain and distention, early satiety and vomiting, respiratory embarrassment, and lower extremity edema may occur. Although such problems are not life threatening, they be debilitating and result in a poor quality of life.

Most patients with polycystic liver disease can be treated conservatively. Operative therapy should be considered only if it can both significantly reduce cyst-caused hepatomegaly and provide long-term relief of symptoms. The form of therapy that achieves these goals is uncertain; no prospective trials are available and the surgical literature does not provide consensus. In this regard, a classification of liver cysts by Gigot et al. is useful in comparing treatments.[23]

- Type 1: 10 or fewer large cysts (>10 cm) with large areas of noninvolved liver parenchyma on CT scan
- Type 2: diffuse involvement of liver parenchyma by medium-sized cysts but with large areas of noncystic parenchyma on CT scan
- Type 3: massive and diffuse involvement of liver parenchyma with only a few areas of normal live substance between cysts (Fig. 114–7).

Cyst aspiration followed by instillation of a sclerosing agent such as alcohol has been proposed when a small number of dominant cysts are believed to cause symptoms. This approach is limited by the ability to treat only a small number of cysts per session and by the potential



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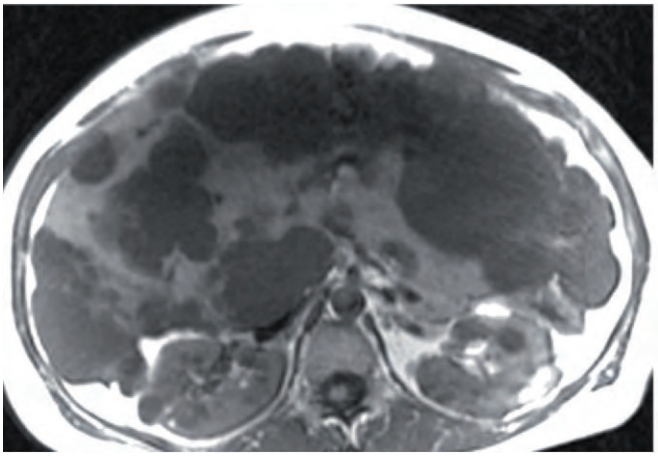

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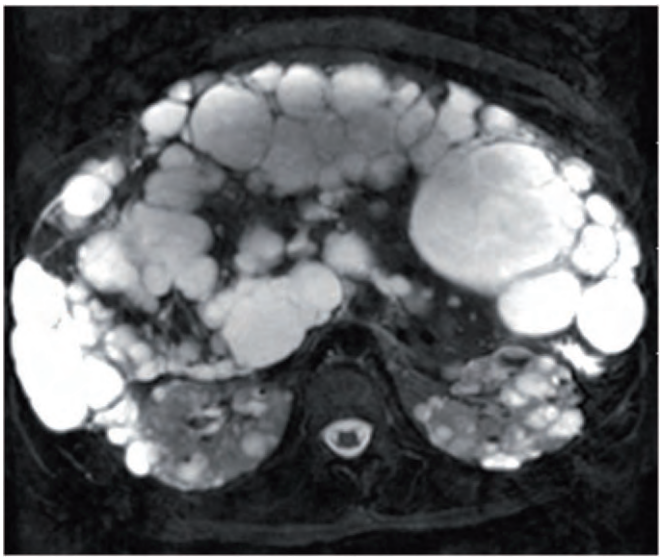


C

Figure 114–7. Hepatic cysts in two patients with autosomal dominant polycystic kidney disease. **A,** Transverse contrast-enhanced CT image shows numerous nonenhancing cysts in the liver and kidneys (K). Transverse T1-weighted **(B)** and T2-weighted **(C)** images of the liver showing numerous simple hepatic and renal cysts with homogeneous low T1- and high T2-weighted signal intensity.

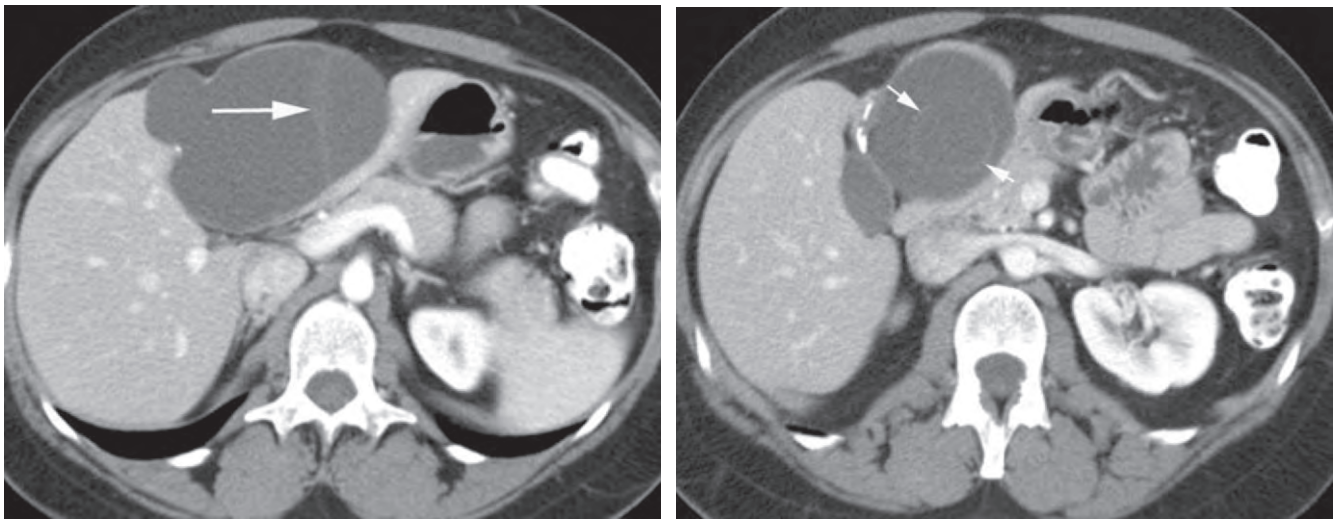
for alcohol extravasation. Experience is limited and recurrence rates are variable, ranging from 30% to 100%.[24]

Cyst fenestration, or deroofing, has been reported by multiple surgical investigators.[25] This procedure allows cyst contents to drain into the peritoneal cavity and reduces the overall size of the liver. Both open and laparoscopic approaches have been reported. Cysts in the right posterior segments and in Couinaud segments VI, VII, and VIII are difficult to expose laparoscopically. Deeply situated cysts have been drained through more superficial cysts by penetrating the intervening liver parenchyma. Failure to appreciate intrahepatic veins and portal radicles within the thinned parenchyma may lead to injury and is a major technical complication.

Cyst fenestration is most applicable to type 1 polycystic liver disease patients. In properly selected type 1 patients, a recurrence rate of 11% at 30 months has been reported.[25] For patients with type 2 or 3 disease, recurrence rates of 72% were noted. The most common postoperative complication is ascites formation, occurring when cyst fluid secretion exceeds the clearance capacity of the peritoneum.

A combination of partial hepatic resection and fenestration has been reported in multiple surgical series. Combined resection and fenestration allows treatment of deep-seated cysts that are difficult to access. This combined approach has the lowest recurrence rate but carries substantial risk. Postoperative ascites, bleeding, and biliary leak are the most frequent complications.

Liver transplantation has been reported in several series, totaling fewer than 50 patients.[26] Candidates for liver transplantation are those with type 3 disease who have failed other palliative measures. Patients with concomitant renal failure should be considered for combined renal and hepatic transplantation. It seems ironic that these patients with typically normal liver function must accept the effects of permanent immune suppression as treatment for a benign disease.



A B

Figure 114–8. Biliary cystadenoma. **A** and **B,** Transverse contrast-enhanced CT images show a cystic mass in the left lobe containing thin enhancing septa *(arrows).*

CYSTIC NEOPLASMS

Cystic neoplasms, which include biliary cystadenomas and cystadenocarcinomas, are rare lesions, comprising 5% of intrahepatic cysts. Neoplastic hepatic cysts are believed to be derived from bile duct origin. The cause of these tumors is unknown.

Cystadenomas are encountered almost exclusively in women (>90%). The sexual distribution of cystadenocarcinomas is more nearly equal.[27] A marked ethnic or racial predominance has not been identified, although the relative rarity of the tumors limits this information. In spite of the predominance of cystadenomas in women, an association with oral contraception use has not been noted. The mean age of diagnosis is 45 years.

Most patients present with a history of abdominal pain or mass, and the diagnosis is suggested by ultrasonography, CT, or MR imaging. A neoplastic cause of hepatic cyst disease is strongly suggested by demonstration of internal septations (Fig. 114–8) or multiloculation or by papillary projections from the wall of the cyst.[28] On MR imaging, the cyst content may have variable signal intensity on T1- and T2-weighted imaging depending on the presence of hemorrhage, protein content, or solid components (Fig. 114–9).[9,11] Although invasion of surrounding structures suggests malignancy, this finding is unusual, and imaging studies cannot usually differentiate benign and malignant neoplastic cysts.

The distinction of biliary cystadenomas and cystadenocarcinomas is made histologically.[29] Cystadenomas are lined by a simple columnar epithelium resembling bile duct epithelium. In most cases, the stroma underlying the epithelium is distinctive, resembling ovarian stroma. The subjacent liver parenchyma demonstrates compression atrophy, creating a pseudocapsule separating the cystadenoma and the native tissue. Cystadenocarcinomas are also multiloculated. Loculated tumors may be lined by both benign and malignant epithelium, implying progression from benign adenoma to carcinoma. The malignant epithelium is multilayered and demonstrates numerous papillary projections. Absence or invasion of the underlying basement membrane is associated with involvement of the adjacent fibrous stroma.

The treatment of neoplastic hepatic cysts is surgical.[30] The neoplastic nature of the lesion must be recognized preoperatively because attempts to treat with unroofing or fenestration are uniformly associated with recurrence.[31] Biliary cystadenomas have been treated with both formal hepatic resection and enucleation. Enucleation requires complete removal of the cyst with a rim of surrounding liver parenchyma. This procedure has been recommended for large or centrally located cystadenomas. A number of small series have reported successful treatment of cystadenomas via enucleation with low recurrence rates.[32,33] Formal resection has the advantage of complete removal and dissection of biliary and vascular structures. Resection is the only appropriate treatment for cystadenocarcinomas.

ECHINOCOCCAL CYSTS

Hepatic infection with *E. granulosus* is a major public health problem worldwide and a common cause of cystic lesions of the liver in endemic areas. Transcontinental travel and immigration make recognition of echinococcal liver cysts important in Western countries as well. Human infection occurs following oral intake of the cestode eggs. Within the upper gastrointestinal tract, the oncospheres are released, attach to, and then penetrate the intestinal wall and enter the portal venous system. Hematogenous dissemination occurs to the liver, although other organs may also be infected, including lung (20%) and kidney, brain, and bone (20%).

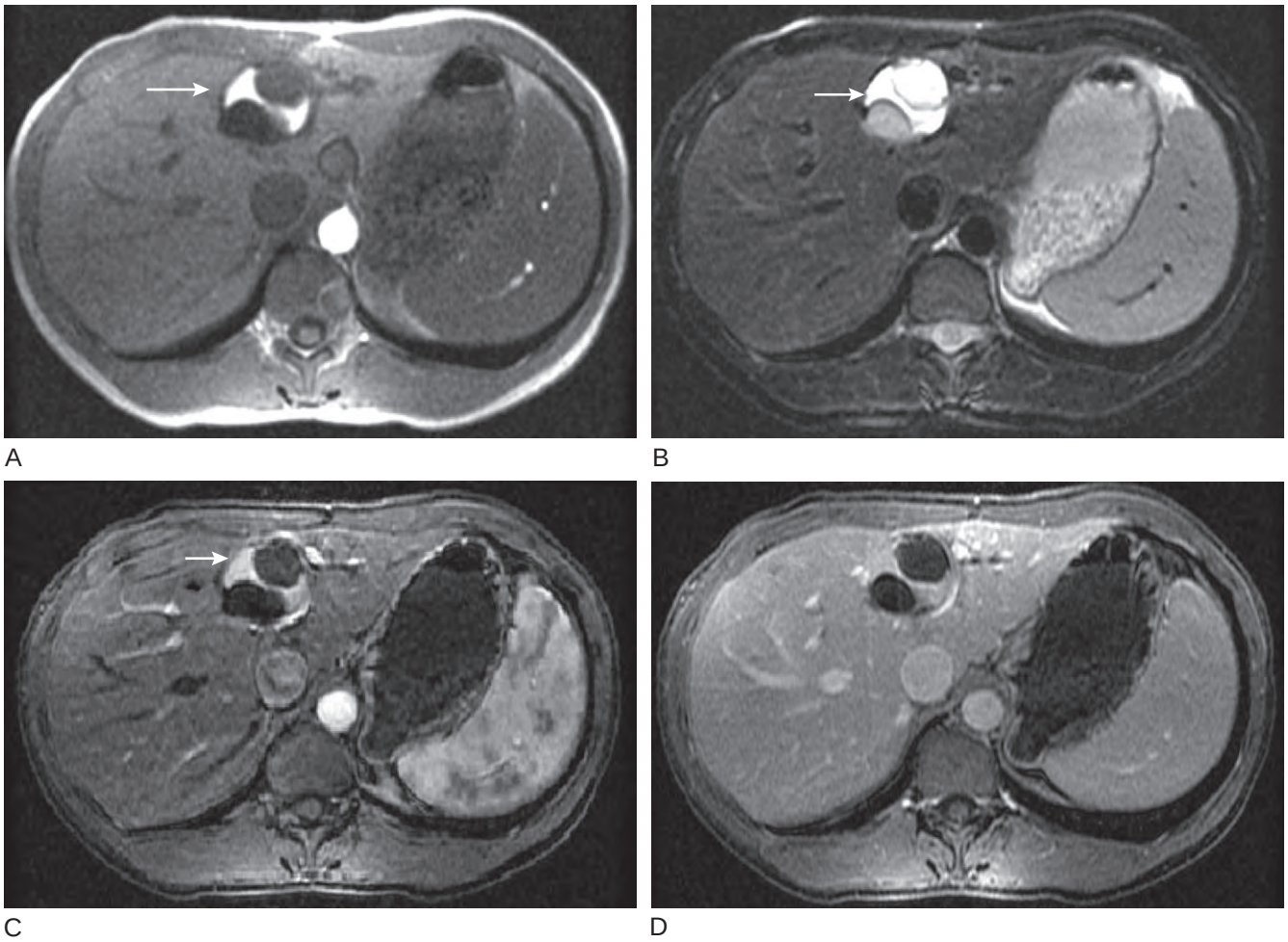


Figure 114–9. Hepatobiliary mucinous cystadenoma with ovarian stroma. Transverse T1-weighted **(A)** and T2-weighted **(B)** images of the liver show a complex multilocular mass in the left lobe *(arrows).* The mucinous content of the mass has mixed high and low signal intensity on T1-weighted imaging and high and intermediate signal intensity on T2-weighted imaging, respectively. The mass *(arrows)* does not enhance on early **(C)** or delayed **(D)** postgadolinium imaging.

Following tissue lodgment, cestode proliferation occurs in the form of a slowly enlarging cyst. In 80% of affected individuals, a solitary cyst occurs in one organ.

Cyst expansion is slowly progressive, estimated at 1 to 30 mm yearly.[34] With time, multiple daughter cysts may form within a single larger cyst. The slow cyst growth causes compression atrophy of the adjacent liver. Host reaction incites the formation of a fibrous surrounding capsule, termed a *pericyst.*

Symptoms may be caused by compression or displacement of adjacent organs or structures or by biliary obstruction by parasites. Most commonly, symptoms are neither dramatic nor pathognomonic. Malaise, weight loss, and chronic wasting are common. Spontaneous rupture, with release of infected material into the peritoneum, can cause anaphylaxis but is rare.

The diagnosis of echinococcal infection is confirmed by serologic demonstration of an antibody response. Sensitivity and specificity both approximate 90%.[35] Children may have a low antibody response, and false-positive reactions may occur in individuals infected with other helminthic organisms.

Ultrasonography is an appropriate first-line diagnostic test for patients with echinococcal disease. Ultrasonography confirms the number and location of cysts. Echinococcal cysts can be distinguished from simple cysts by the presence of internal structure from daughter cysts and their contained parasites. In Western countries, ultrasonography has a specificity of 90%.[36]

Ultrasonography is equivalent to CT for diagnosis of hydatid disease of the liver but is not adequate in planning surgical therapy. CT scanning is superior in demonstrating the size and depth of cysts, the presence of daughter cysts, and extrahepatic involvement (Fig. 114–10).[37] MR imaging provides excellent structural detail of hydatid cysts and is superior to CT scanning in demonstrating alteration of the hepatic venous system.

Although most patients with hydatid disease are asymptomatic, diagnosis should prompt therapy to halt progression of infection and to prevent complications.

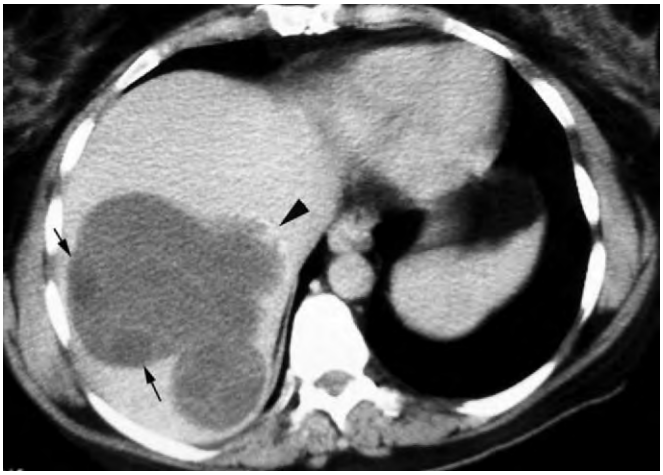


Figure 114–10. Hydatid cyst. Transverse nonenhanced CT image shows a cystic mass containing several daughter cysts *(arrows)* and peripheral calcification *(arrowhead).*

Potential complications include secondary hematogenous dissemination, rupture into adjacent organs or structures, intraperitoneal dissemination, anaphylactic reaction, and penetration of the biliary tree with obstructive jaundice.

Patients who are candidates for surgical therapy of hepatic echinococcal disease have been treated preoperatively with antihelminthic agents. Mebendazole and albendazole have been mainstays of treatment. Both drugs act as parasitostatic agents rather than parasiticides, implying that they cannot cure hydatid cysts in the absence of surgical evacuation. The major side effects include alterations in liver enzymes and bone marrow suppression. Severe reactions are unusual. Treatment with these agents is contraindicated in early pregnancy.

The World Health Organization (WHO) lists the following indications for operative treatment of hydatid cysts of the liver: large cysts with multiple daughter cysts, single superficially located cysts in danger of intraperitoneal rupture, infected cysts, cysts communicating with the biliary tree, and cysts communicating with the lung.[38] The principles of hydatid surgery are well established and include complete elimination of the parasite, avoidance of intraoperative spillage, and preservation of normal hepatic tissue. The details of operative treatment are still debated because randomized, controlled trials are lacking, which is surprising given the worldwide importance of helminthic diseases.

A plethora of operative procedures have been described for treatment of hydatid liver cysts. The major point of controversy involves treatment of the pericyst. Radical operations remove the infected cyst, pericyst, and a margin of normal surrounding liver tissue. More conservative treatments seek to sterilize and then evacuate cyst contents, leaving the noninfectious pericyst intact. Many investigators have argued that liver resection represents overtreatment of this benign disease.

Meta-analyses of reported series suggests that radical and conservative approaches have similar mortality rates (1.2% to 2%).[39] With either approach, morbidity is high (12% to 23%), including wound and intraperitoneal infection, hemorrhage, biliary fistula, and pulmonary complications. Recurrent helminthic infection ranges from 2% to 10%.[39]

Operative goals are fourfold: (1) inactivating infectious cyst contents (scolices and the germinative membrane); (2) preventing spillage of cyst contents; (3) evacuating all viable elements; and (4) managing the residual cavity. In spite of long-established surgical practice, WHO does not endorse any scolicidal agents for the intraoperative killing of helminths.[38] No agent is both effective and safe. Ethanol (70% to 95%), hypertonic saline (15% to 20%), and certrimide solution (5%) have been widely used at acceptably low risk.

Prior to instillation of scolicidal agents into the cyst cavity, the area immediately adjacent to the cyst should be excluded from the peritoneal cavity by disinfectant-soaked pads to reduce the risk of contamination (see Fig. 114–10). In viable cysts, the pressure may reach 75 cm H_2O, and aspiration of a small amount of fluid to reduce pressure should be performed prior to cyst opening.[40] In cases of spillage of scolices, the WHO recommends postoperative treatment with albendazole (1 month) or mebendazole (3 months) to reduce the risk of subsequent intraperitoneal recurrence.

After total evacuation of infected contents, there are several options for dealing with the residual intrahepatic cavity. The cyst edges may be sutured to prevent bleeding. The cavity may be left open to the peritoneum, leaving the pericyst intact. Omentoplasty fills the cavity with pedicled omentum and has been associated with fewer postoperative complications than external drainage in two prospective studies.[41,42] Efforts to obliterate the cavity by coapting the walls with sutures risk injury to hepatic veins and bile ducts.

Laparoscopic treatment of hepatic hydatid cysts has been reported.[43,44] Advantages include shortened length of stay, lessened pain, and reduced incidence of wound complications. Major disadvantages center on prevention of intraperitoneal spillage and difficulty in aspiration of thick gelatinous cyst contents. Technical advances have been reported that may overcome these problems, but the relative infrequency of the disease in Western countries will likely limit their adaptation in these locales.

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Chapter

115

Liver Abscess

L. Christopher DeRosier · Cheri M. Canon · Selwyn M. Vickers

Liver abscess formation is a rare occurrence whose classification, diagnosis, etiology, and treatment have changed from earlier descriptions. Despite these changes, hepatic abscesses still carry significant morbidity and mortality and continue to challenge the clinician with diagnostic and therapeutic dilemmas. Traditionally, there are two major classifications of hepatic abscess: those of bacterial origin and those caused by *Entamoeba histolytica*. However, with the increase in patients with acquired immunodeficiency syndrome and other types of immunosuppression, the reporting of fungal and mycobacterial abscesses is increasing.

Ocshner and colleagues reported in 1938 that amebic liver abscesses were three times more common than pyogenic liver abscesses in Charity Hospital in New Orleans.[1] Improvements in public sanitation and hygiene led to a decrease in cases of amebiasis and amebic abscess. As international travel has become more common, American medical centers are observing a new increase in amebic abscesses as travel and immigration from regions where *E. histolytica* infections are endemic increases. Currently, pyogenic abscesses make up the majority of hepatic abscesses in most series in the Western literature. Improving imaging techniques have aided the clinician in the diagnosis of hepatic abscesses and have subsequently become important treatment tools, decreasing the number of cases treated with surgical intervention. Furthermore, the demographics of the hepatic abscess have changed. Ocshner and colleagues' report and other earlier descriptions identified young males with intra-abdominal infections with secondary pylephlebitis as those most at risk for a pyogenic abscess. However, with improving antibiotic and diagnostic technologies, the peak incidence has shifted to the 5th and 6th decades of life, with the predisposing hepatobiliary disorders being the most common cause.

PYOGENIC HEPATIC ABSCESSES

Demographics

There have been several studies in the past 60 or 70 years (Table 115–1) demonstrating a mild increase in the incidence of pyogenic hepatic abscesses. The first of these was that of Ochsner and associates in 1938. In their review, hepatic abscesses were found in 8 of 100,000 admissions to Charity Hospital in New Orleans.[1] The Johns Hopkins Hospital experience was described in two papers and stated an incidence of 13 of 100,000 admissions from 1952 to 1972 and 20 of 100,000 from 1973 to 1993.[2,3] The data from Duke University demonstrated a similar increase (11.5 of 100,000 hospital admissions from 1970 to 1978 and 22 of 100,000 from 1979 to 1986).[4] Several other studies have documented rates similar to those above (see Table 115–1).[5-8] Explanations for this increase include advances in diagnostic accuracy with improvements in imaging modalities, as well as increasing association with the rising incidence and aggressive treatment of hepatobiliary disorders.[2,8]

In Oschner and colleagues' 1938 review of 877 cases (47 from the New Orleans series, 830 collected from the literature of the time), the peak incidence of pyogenic liver abscesses occurred in the 3rd to 4th decades.[1] Recent publications describe an older population. A review of 171 cases from two hospitals in New York City found a mean age of 56.4 years.[9] Furthermore, a review of 69 patients from a U.K. hospital demonstrated a mean age of 64 years.[6] There have been roughly 17 studies over the past 50 years with average ages in the 5th to 6th decades of life.[10] This change in age distribution probably reflects the changing etiology of pyogenic hepatic abscesses. With the advent of antibiotics, sequelae of intra-abdominal infections such as appendicitis are

Table 115–1 Selected Series of Pyogenic Hepatic Abscesses

Author, Year	Location	No. of Cases	Time Period	Age, yr	Male-to-Female Ratio	Incidence	Mortality Rate, %
Oschner et al., 1938[1]	New Orleans	47	1928-1937	30-39 (mean)	2.35:1.0	47/540,776 admissions	72.3
Pitt and Zuidema, 1975[3]	Baltimore	80	1952-1972	60 (mean)	1.0:1.0	13/100,000 admissions	65
Branum et al., 1990[4]	Durham	73	1970-1986	53 (median)	1.1:1.0	*1970-1978:* 11.5/100,000 *1979-1986:* 22/100,000	19
Seeto and Rockey, 1996[7]	San Francisco	142	1979-1994	51 (median)	1.3:1.0	22/100,000 admissions	11
Huang et al., 1996[2]	Baltimore	153	1973-1993	55.5 (mean)	1.3:1.0	20/100,000 admissions	31
Alvarez et al., 2001[5,8]	Spain	133	1985-1997	58.1-64.9 (mean)	1.6 : 1.0	Not reported	14
Mohsen et al., 2002[6]	United Kingdom	65	1988-1999	64 (median)	1.3:1.0	18.5/100,000	12.3
Wong et al., 2002[15]	Hong Kong	80	1991-2001	63.4 (mean)	1.67:1.0	Not reported	6

better managed; therefore, the development of hepatic abscesses in patients with intra-abdominal infections has been greatly decreased. However, as the population ages, biliary disorders become more common, and hepatic abscesses, although not a common occurrence, are sequelae of these disorders and their treatment; hence the increase in this age distribution.

Early reports of pyogenic hepatic abscesses described a large male preponderance and explained this occurrence by citing the increased incidence of etiologic agents at that time (e.g., appendicitis) in males.[1] More recent studies show only a slight increase in males if any at all (see Table 115–1). Once again, this change is likely due to changing etiologic factors. There have not been any studies that document a preponderance of hepatic abscesses in members of different races in the same geographic population. The difference between African American and white patients in the New Orleans data was 47.6% and 52.3% of patients admitted for pyogenic hepatic abscesses, respectively, and this has held true in current literature as well.[1]

Etiology and Pathogenesis

The underlying etiologies of pyogenic hepatic abscesses have changed just as the demographics have, and it is likely that these changes are related. Oschner and colleagues' 1938 paper reviewed 575 cases from their institution and current literature and found 37.2% were secondary to appendicitis, although the authors did raise questions about the accuracy of this number.[1]

More recent studies evaluating etiologies have identified hepatobiliary disorders as the major identifiable cause of hepatic abscesses (Table 115–2). Despite these changes, the clinician must be cognizant that hepatic abscesses may be the sequelae of multiple disease processes and that identification of the primary disease process, when possible, can have significant impact on both treatment and outcome. There are five major identifiable routes of hepatic invasion, with cryptogenic hepatic abscess being a sixth category.

Of all identifiable sources of pyogenic hepatic abscesses, *biliary disorders* has emerged as the most common. Examples include abscesses occurring in the setting of an obstructing cholangiocarcinoma and associated ascending cholangitis. In these cases, obstruction of the extrahepatic biliary system, from either calculi or malignancy, provides an ideal setting for ascending cholangitis. Furthermore, the use of stents in these complicated cases also increases the risk of biliary infections and subsequently the risk of associated hepatic abscess. The majority of large series published over the past 20 years cited biliary disorders as the most common identifiable source of the hepatic abscesses (see Table 115–2). Johns Hopkins hospital has published their hepatic abscess series in two periods (1952 to 1972 [$n = 80$] and 1973 to 1993 [$n = 153$]).[2,3] In these papers, a biliary cause was the most common (51% and 60%, respectively). In the latter data set, hilar cholangiocarcinomas were the most frequent underlying cause, with 22% of patients having a bile duct malignancy.[2,3] The authors of the latter series suggested an important consideration that reflects current management of hepatobiliary diseases, in that the use of large-bore Silastic transhepatic stents can be associated with abscess formation. Furthermore, the organisms associated with these infections are often more resistant and may require a different spectrum of

Table 115–2 Etiology of Pyogenic Hepatic Abscess

Author, Year	No. of Cases	Cryptogenic, %	Hepatobiliary, %	Portal, %	Hepatic Artery, %	Other, %
Oschner et al., 1938[1]	47	60	6	19	N/A	15
Pitt and Zuidema, 1975[3]	80	20	51	15	1	<10†
Branum et al., 1990[4]	73	27	31.4	18.2	10	14‡
Huang et al., 1996[2]	153	16	60	<10	10	<10†
Seeto and Rockey, 1996[7,*]	142	40	37	11	N/A	12*
Alvarez et al., 2001[5,8]	133	26	25§	13	2	33¶
Mohsen et al., 2002[6]	65	24 (18 uninvestigated)	28	48	N/A	N/A
Wong et al., 2002[15]	80	Not reported	61	Not reported	1.25	Not reported

*Includes direct extension, abdominal trauma, and chronic granulomatous disease.
†Trauma.
‡Trauma, other solid tumors, direct extension, Crohn's disease.
§Includes seven patients with recent hepatic surgery.
¶Trauma, direct extension.
N/A, not available.

antibiotic and antifungal therapy.[2] Prior biliary procedures and operations can predispose to hepatic abscess formation, illustrating the importance of thorough examination of the reconstructed biliary anatomy for appropriate correction of not only the hepatic abscess but the etiologic factor as well.[11]

Hematogenous spread from other intra-abdominal infections, although not the highest percentage, still remains an important avenue of infection. Diverticulitis, perforated carcinomas, and perforated ulcers have replaced appendicitis as common sources for this type of infection. The clinician must be suspicious of these disease processes, both in diagnosis and treatment, because the underlying disorders could govern the decision for surgical abscess drainage versus percutaneous therapy.

Any type of systemic bacteremic infection has the potential to seed the liver and subsequently form an abscess. Common etiologies include endocarditis, intravenous drug abuse, and other infectious processes that can produce bacteremia.

The incidence of liver abscess following transarterial embolization or radiofrequency ablation (RFA) procedures of hepatic malignancies is low, ranging from 0 to 3.3%. However, the diagnosis of hepatic abscess in the post-treatment setting can be difficult because current imaging modalities do not always differentiate between postembolization changes and abscess. Therefore, the clinician must be suspicious of hepatic abscesses as a source of prolonged fever so as not to overlook the diagnosis. Two large Taiwanese studies describe an incidence of 0.27% (7 abscesses in 2581 procedures) and 1.1% (5 of 452 patients).[12,13] In agreement with these results, a study of 91 RFA procedures in 84 patients at the John Wayne Cancer Center found two postprocedure hepatic abscesses.[14]

Intra-abdominal infectious processes can involve the liver and lead to abscess formation. This can be from gastric or colonic perforation or from perinephric or subphrenic abscesses. Identifying these contiguous infections becomes important in planning treatment of the liver and primary abscess, both in terms of type of drainage therapy and antibiotic choices. Furthermore, liver abscesses can follow penetrating trauma. The patient's clinical history guides the clinician in this diagnosis. This is a rare occurrence that can occur with direct seeding of the liver parenchyma with bacteria accompanying a penetrating injury or when a perihepatic hematoma becomes infected.

In many cases, a predisposing condition cannot be identified. The series from Duke describes 25% of abscesses without an identifiable source.[4] Similar findings were found in a collection of Spanish patients with cryptogenic abscesses described as 25.5%.[5,8] Although there are no definitive studies, host factors that can weaken the immune system are thought to predispose to abscess formation (e.g. cirrhosis, diabetes, or malignancy).

Risk Factors

Hepatobiliary disorders, as mentioned previously, are present in a large number of patients with hepatic abscesses. Furthermore, patients with associated hepatobiliary malignancy might have an increased risk due to physical obstruction and resistance to bacterial infections. These patients frequently have biliary stents placed to relieve obstruction, which can predispose to infection. Most series note an association of not only hepatobiliary malignancy and hepatic abscess but solid organ and hematologic malignancy as well. The Johns Hopkins data

Table 115–3 Presenting Symptoms and Signs in Pyogenic Hepatic Abscess

Author, Year	No. of Cases	Fever, %	Abdominal Pain, %	Nausea/ Vomiting, %	Weight Loss, %	Diarrhea, %	Jaundice, %	Hepatomegaly, %
Pitt and Zuidema, 1975[3]	80	92	74	N/A	51	23	54	48
Branum et al., 1990[4]	73	75	55	27	29	8	23	38
Huang et al., 1996[2]	153	89	55	N/A	43	10	50	35
Seeto and Rockey, 1996[7]	142	79	55	30/37	28	20	22	28
Alvarez et al., 2001[5,8]	133	92	69	29	42	N/A	21	24
Mohsen et al., 2002[6]	65	67	67	41	35	23	14	30
Wong et al., 2002[15]	80	99	35	N/A	10	N/A	14	18

N/A, not available.

demonstrated a substantial increase in associated hepatobiliary malignancies from 23% (1952-1972) to 42% (1973-1993).[2] Branum et al. noted an underlying malignancy in 20 (27%) of their 73 patients.[4] Multiple studies have found the presence of malignancy to increase mortality rate when controlling for other variables associated with hepatic abscesses.[5,8,15]

Cirrhosis has also been identified as a predisposing factor as in a Danish study of 22,764 patients with cirrhosis, of which 665 patients had a hepatic abscess producing an age-adjusted risk 15-fold higher than the background population.[16] Diabetes has been cited in numerous studies from across the globe as a possible predisposing factor. Spanish studies report 13% of patients with abscesses having diabetes similar to a New York study demonstrating 15.2% of patients with diabetes mellitus.[5,8,9] Most striking is a publication from Taiwan in which 75% of patients with liver abscesses secondary to *Klebsiella pneumoniae* were diabetic.[17]

Presenting Symptoms and Signs

The diagnosis of hepatic abscess based on history and physical examination findings can be challenging. The disease can occur in association with many other intra-abdominal processes that can divert attention away from the hepatic abscess. The classic presentation triad of right upper quadrant pain, fever or chills, and generalized malaise is rarely completely present.[4] Constitutional symptoms such as fever, malaise, weight loss, and fatigue are more common (Table 115–3). The most commonly cited presenting symptom is fever, which is present in 61% to 92% of patients. Right upper quadrant pain is also a frequent complaint present in 35% to 72% of patients.[2-6,8,9,15] There is no clear agreement across series regarding percentages of other signs at presentation. Patients can present with hepatomegaly, jaundice, or right upper quadrant tenderness.

The duration of symptoms has also varied widely in most case series.[10] For example, Seeto and Rockey cited a mean duration of symptoms prior to admission of 26 days with a range of 1 to 300 days, whereas Alvarez et al. described a mean duration of symptoms of 9.1 days for patients with multiple lesions and 7.2 days for patients with solitary lesions.[5,7] The underlying disease process probably influences the duration of symptoms leading to the patient seeking medical attention.

Laboratory Analysis

Patients presenting with hepatic abscesses have nonspecific laboratory abnormalities on routine admission laboratory studies; most patients have some abnormality in liver function studies (Table 115–4). The most consistent liver function abnormality across series is an elevation of alkaline phosphatase, up to 80% to 90% of patients in some studies. Clearly the cause of the hepatic abscess can alter the presenting laboratory studies. Many of the laboratory values including leukocytosis and hypoalbuminemia signify that this process, although confined to the liver, can produce changes consistent with systemic disease. Branum et al. commented that no single test or combination of tests was more predictive of outcome or significantly correlated with the size or number of abscesses, complications, or length of hospitalization.[4] There have been studies that have identified marked leukocytosis or profound hypoalbuminemia in association with increased mortality rate.[2,15]

Table 115–4 Laboratory Findings in Pyogenic Hepatic Abscesses

Author, Year	Leukocytosis, %	Elevated Alkaline Phosphatase Level, %	Hypoalbuminemia, %	Hyperbilirubinemia, %	ALT, %	AST, %	Anemia, %
Pitt and Zuidema, 1975[3]	69	90	62	68	82	90	N/A
Branum et al., 1990[4]	68	78	N/A	36	N/A	57	67
Huang et al., 1996[2]	77	70	71	49	67	64	N/A
Seeto and Rockey, 1996[7]	64	80	>67	N/A*	69†	57†	75
Alvarez et al., 2001[5,8]	65	56	50	23	N/A	41	56
Mohsen et al., 2002[6]	88	64	N/A	36	67	49	*Male:* 74 *Female:* 47
Wong et al., 2002[15]	84	73	94	48	50-63	N/A	76

*Exact numbers not provided, but was present in most patients with biliary tract disease and hepatic abscess.
†Specific to patients with biliary tract and hepatic abscess.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; N/A, not available.

Anatomic Considerations

The location of the liver abscess becomes important in making therapeutic decisions because abscesses in the right lobe are more amendable to percutaneous drainage, whereas those in the left lobe are more problematic to treat with image-guided drainage.[4] The location of liver abscesses appears to be rather consistent across most large series in that most solitary pyogenic abscesses are located in the right lobe (Table 115–5). Several authors have hypothesized that this finding is due to a greater amount of blood flow to the right side of the liver and that there is preferential drainage of the superior mesenteric vein to the right lobe.

Several series also differentiate between single and multiple abscesses with conclusions drawn about each. The presence of a solitary abscess versus a multiple abscesses has been linked to the cause of the liver abscess, although data to support this are not convincing. Malignant obstructions of the extrahepatic biliary system or bacteremic conditions are thought to predispose to development of multiple abscesses because both the right and left lobes are equally exposed to the offending pathogen. Alvarez et al. found that multiple abscesses were more likely to occur in patients with a biliary origin; however, they could not identify any clinical findings that predicted the presence of multiple or single abscesses.[5,8] Branum et al. found that the incidence of single and multiple abscesses did not vary among different etiologic categories but that solitary abscesses were more likely to be polymicrobial.[4] Multiple abscesses have been associated with an increased severity of disease and with an increase in both mortality and morbidity (e.g., higher incidence of pleural effusions, acute renal failure and respiratory failure).[18] The increased morbidity and mortality associated with multiple abscesses are likely related to the severity of the underlying disease (septicemia or malignant biliary obstruction) as well as the infectious burden in the liver.

Microbiology

There are many case series of hepatic abscesses in the literature, from many different regions of the world; therefore, it is difficult to make generalizations regarding bacterial flora responsible for pyogenic hepatic abscesses. Furthermore, there are many confounding factors in these series in terms of collecting microbiology data because many patients receive antibiotic therapy prior to culture (especially abscess culture). Furthermore, culture techniques and quality differ based on facility, and microbiology culture technology has evolved considerably since the early 20th century. This was illustrated by Sabbaj et al. in 1972 when, using strict anaerobic culture techniques, they determined that 45% of cultures obtained from hepatic abscesses in their series were anaerobic, a finding much higher than any prior studies at the time.[19] This illustrates the care and attention that must be employed while culturing abscesses to identify anaerobic pathogens.

Despite these problems, it does appear that certain pathogens are more likely to be found in patients with pyogenic hepatic abscesses. *Escherichia coli* and *K. pneumoniae* are the common aerobic gram negative isolates. *K. pneumoniae* is extremely prevalent in liver abscesses in Asian countries as well as in predominantly Asian populations in the Western world for unclear reasons. Diabetes was present in the majority (67.5%) of these patients in the Taiwanese study.[9,17] Streptococcal species and *Staphylococcus aureus* have also been isolated at increased frequency in hepatic abscesses. Improving anaerobic culture techniques have led to the recognition of anaerobic and microaerophilic organisms present in

Table 115–5 Anatomic Characteristics of Hepatic Abscesses

Author, Year	Solitary Abscess, %	Multiple Abscesses, %	Right Lobe, %	Left Lobe, %	Bilateral Lobes, %
Oschner et al., 1938[1]	54.5	45.5	68.1	2.2	27.2
Pitt and Zuidema, 1975[3]	40	60	38	14	49
Branum et al., 1990[4]	59	41	70	N/A	N/A
Huang et al., 1996[2]	52	48	63	14	22
Seeto and Rockey, 1996[7]*	61	39	58	19	19
Alvarez et al., 2001[58]	73	27	71	16	13
Mohsen et al., 2002[6]	58	42	66	8	26
Wong et al., 2002[15]	80	20	Majority of solitary abscesses	—	Majority of multiple abscesses

*In this study, 4% of abscesses were in caudate lobe.
N/A, not available.

liver abscesses. In the Johns Hopkins series, there was a significant increase in anaerobic isolates, from the 1952-1972 period to 1973-1993.[2] A 2003 study from the Cleveland Clinic identified *Streptococcus milleri,* a microaerophilic or anaerobic collection of streptococcal bacteria, (present in 41% of solitary abscesses) and anaerobic gram-negative bacilli as the most common pathogens isolated.[20] The recognition of anaerobic organisms is consistent in more recent studies, with *Bacteroides* species commonly isolated.[10] These findings have led many to believe that abscesses previously thought to be "sterile" or cryptogenic have been caused by anaerobic organisms that were not identified.

The offending pathogen can correspond to the route of infection with enteric gram-negative pathogens infecting the liver in those abscesses arising from biliary sources or *S. aureus* infecting the liver in patients with hematogenous sources of hepatic abscess. Furthermore, the Johns Hopkins series found an increase in *K. pneumoniae, Streptococcus,* and *Pseudomonas,* with an increasing resistance pattern. The increased resistance is thought to be in part related to the increasing use of indwelling biliary stents with recurrent episodes of cholangitis treated with antibiotics.[2]

Studies over the past several decades have found varying rates of monomicrobial and polymicrobial infections. Reports range from 33% to 50% of hepatic abscess cultures yielding polymicrobial infections, with a lower rate of polymicrobial blood culture isolates.[6-9] There is conflicting data about whether monomicrobial infections or polymicrobial infections cause solitary or multiple hepatic abscesses. The Duke series found that solitary abscesses were more likely than multiple abscesses to be polymicrobial (63% vs. 30%), whereas Mohsen et al. did not find any difference in the causative bacterial agent in patients with single and multiple abscesses.[4,6] Therefore, the clinician should be mindful that a pyogenic hepatic abscess could contain multiple species of bacteria, and antibiotic choices should reflect this until definitive culture results can be obtained.

Liver abscesses are potentially fatal if drainage and appropriate antimicrobial therapy are not instituted. Frequently, antibiotic therapy will be instituted prior to definitive abscess culture therefore accurate knowledge of possible pathogens is necessary. Common pathogens have been previously discussed; however, the use of blood cultures as well as Gram stain of liver abscess aspirates can provide useful information prior to actual abscess culture data. Chemaly et al. evaluated the predictive value of abscess Gram stain and associated blood cultures from 38 patients treated at the Cleveland Clinic from 1995 to 2000. All patients evaluated were subjected to the same culture protocols. Fifty percent of blood cultures were positive, with 44% of these being polymicrobial. Blood cultures under-represented types of bacteria present in the liver abscess compared to the liver abscess culture. The discrepancy in temporally associated blood culture with abscess culture results is attributed to prior antibiotic use affecting organism recovery from the blood. The authors advocated including antibiotic coverage for common pathogens even in situations when these organisms are absent from blood culture data, especially when abscess culture information is unavailable. Gram stain detected bacteria in 31 (79%) of 39 cases with the sensitivity and specificity for gram-positive cocci of 90% and 100%, respectively, and 52% and 94% for gram-negative bacilli, respectively. In this study anaerobic gram-negative bacilli and *S. milleri* were the most commonly isolated pathogens from the liver abscess, and *S. milleri* was also the most isolated pathogen from blood cultures. The authors state the possibility that this reflects improvement in culture techniques as opposed to changes in the disease process, but further studies would be needed to substantiate this assumption. In summary, blood cultures and Gram stain are tests that can guide appropriate therapy until liver abscess culture is available.[20]

Diagnosis

Branum et al. found that in 88% of patients the diagnosis of hepatic abscess was made using a combination of clinical suspicion, physical examination findings, laboratory values, and various imaging modalities.[4] As discussed earlier, history and laboratory findings are rarely specific for liver abscesses and therefore imaging becomes a critical aid in diagnosis and subsequent treatment. The main differential diagnostic considerations of hepatic abscesses are benign or malignant focal liver lesions that possess ring enhancement, including metastatic disease, hepatocellular carcinoma, and lymphoma. The distinction from cystic metastatic disease or chemotherapy-treated metastatic disease with central necrosis may be even more challenging to differentiate.[21] There are several different imaging modalities that have been used in diagnosing hepatic abscesses.

Roentgenographic Findings

Chest radiographs are frequently ordered on hepatic abscess patients in evaluation of fever or other systemic findings. Nonspecific abnormalities are found in roughly 50% of cases.[7,22] In a study of 142 patients in San Francisco, 49% of radiographs had abnormal findings consistent with subdiaphragmatic disorders: atelectasis (21%), elevated right hemidiaphragm (20%), pleural effusion (18%), and pneumonia (10%).[7] Radiographs of the abdomen can also demonstrate signs of an abscess with either hepatomegaly or an air-fluid level within the liver. Obviously aerobilia outside of the postprocedure period provides a diagnosis of cholangitis. The absence of these findings does not by any means rule out hepatic abscess.

Cholangiography

Cholangiography (Fig. 115–1), either endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography (PTC), has proven useful in the evaluation of the patient with liver abscesses. As ascending cholangitis continues to increase as an inciting agent in liver abscesses, these diagnostic procedures allow definition of anatomy and possibly identification of the inciting condition. Furthermore, PTC can be used to decompress the biliary system in cases of obstruction-related ascending cholangitis. Catheter-based therapy similar to PTC has developed into one of the main drainage modality for hepatic abscesses, especially when there is biliary communication of the abscess. These procedures must be used with caution in that both are capable of increasing intrabiliary pressure, acutely worsening the patient's clinical condition.

Ultrasound

The ease and relatively low cost associated with ultrasound has made these studies useful in both the evaluation and therapy of hepatic abscesses. These studies are able to identify lesions as small as 2 cm, and in contrast to isotope scanning, do not require ionizing radiation

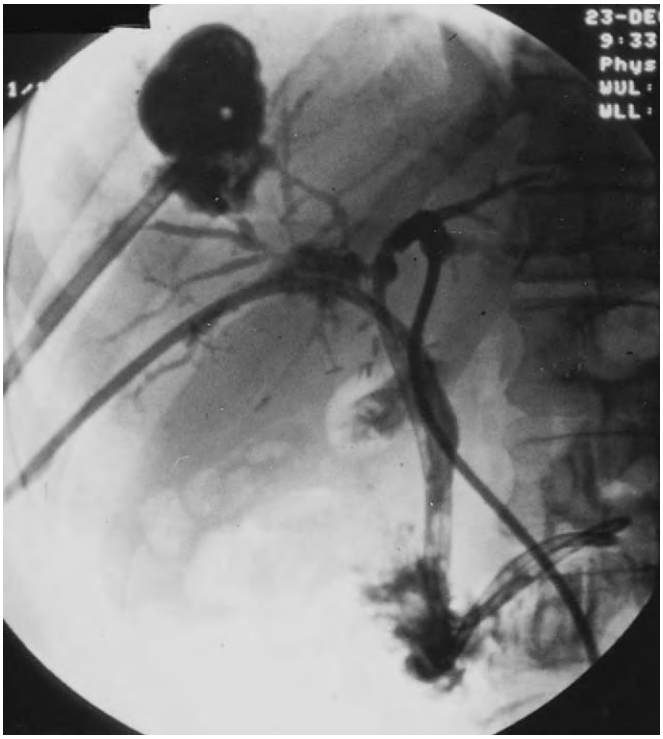


Figure 115–1. Cholangiogram demonstrating a perihilar cholangiocarcinoma as well as an abscess near the dome of the right lobe of the liver.

and can differentiate between fluid-filled and solid lesions. The lesion is a hypoechoic round lesion with an echogenic wall, acoustic enhancement, and internal debris.[23] Recent studies describe a sensitivity ranging from 83% to 95%.[2,6,8,15] There have been three potential drawbacks of ultrasound identified. First, ultrasound does not always visualize the liver dome, thereby failing to identify abscesses in this region. Second, multiple microscopic abscesses, such as those seen with ascending cholangitis, may not be appreciated by ultrasound. Third, fatty infiltration may increase the echogenicity of the liver, thus decreasing the sensitivity. Nevertheless, ultrasound studies remains useful in the evaluation and treatment of hepatic abscesses.

Computed Tomography

Computed tomographic (CT) scanning has the added advantage of being able to detect intrahepatic lesions as small as 0.5 cm and image the entire abdomen. On CT (Figs. 115–2 and 115–3), pyogenic abscesses are classified as either microabscesses (<2 cm) or macroabscesses (>2 cm). Microabscesses appear as multiple, small, low-density lesions throughout the liver. If contrast medium is administered, there will often be peripheral ring enhancement. CT examination of a pyogenic abscess shows a hypodense cystic lesion with thick segmental wall enhancement and surrounding low-density edema. Classically, there can be adjacent "daughter" abscesses clustering around the central larger abscess. This may

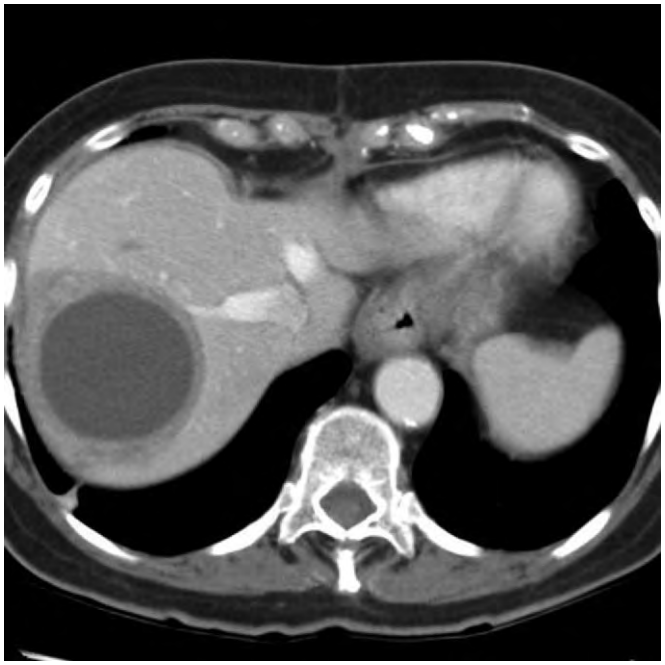


Figure 115–2. Contrast-enhanced CT through the liver reveals a unilocular low-density mass near the dome representing a pyogenic abscess. Note the peripheral enhancing rim, which is relatively narrow.

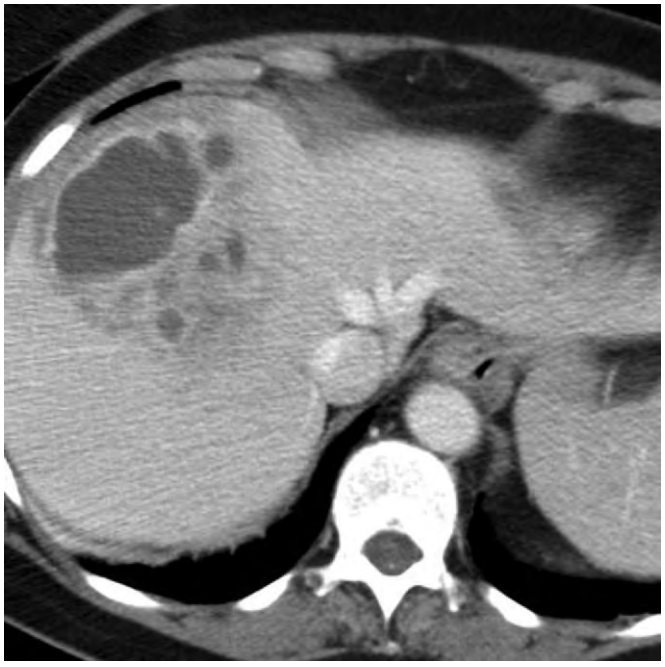


Figure 115–3. Contrast-enhanced CT through the liver reveals the "cluster" appearance of a pyogenic hepatic abscess with several smaller peripheral abscesses that have coalesced.

represent coalescence of multiple smaller abscesses. This "cluster sign" is suggestive of a bacterial cause.[24] Furthermore, a target appearance with ringlike enhancement of the periphery can also be observed in pyogenic abscesses.[25] The transition zone between the low-density central portion of the abscess and the enhancing rim is typically narrow, a feature than can help differentiate from a necrotic metastasis.[26] The sensitivity of CT scanning in the evaluation of hepatic abscesses has been studied and is superior to that of liver scanning and ultrasound. Recent studies document a sensitivity of 93% to 100%.[2,6,8,24,27,28] CT scan has become the imaging modality of choice in the evaluation of hepatic abscesses; furthermore, its role as a therapeutic modality in the case of CT-guided biopsy is becoming well established. CT scans do have some difficulty distinguishing hepatic abscesses between cystic diseases of the liver as well as necrotic tumors.

Magnetic Resonance Imaging

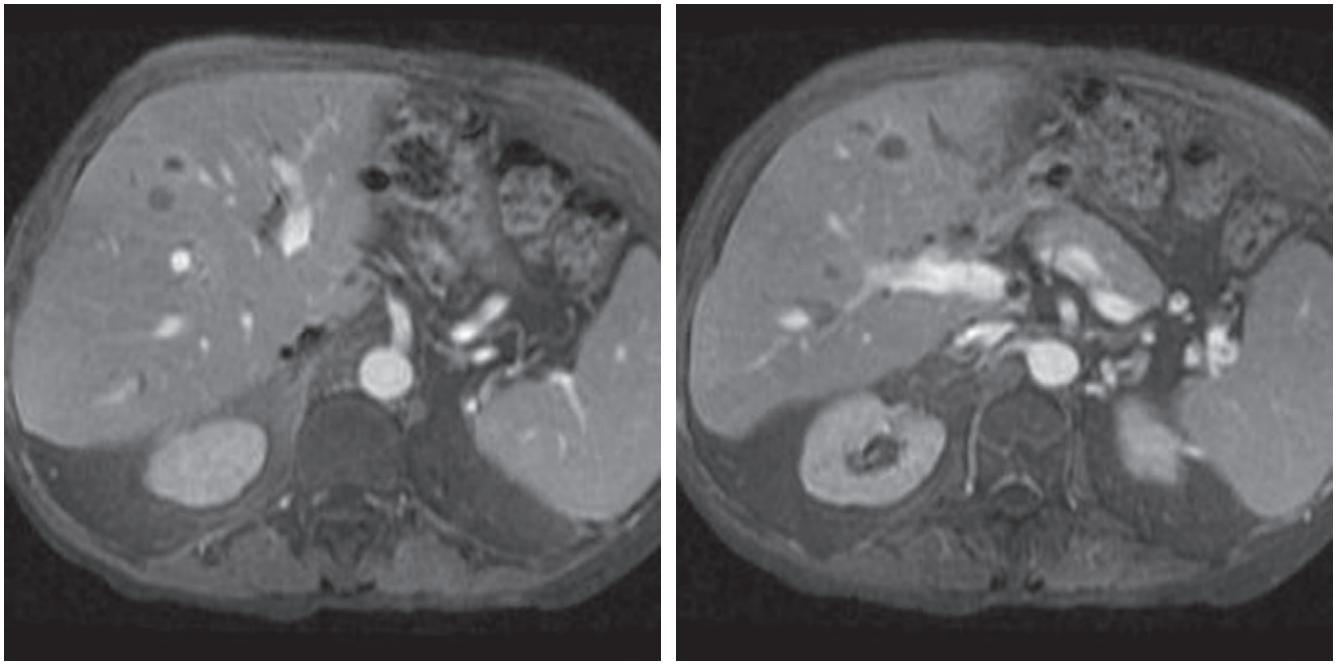
Magnetic resonance (MR) imaging technology is rapidly improving. MR imaging offers several advantages in that it can evaluate blood vessel anatomy of the liver without the intravenous contrast of a CT scan and that it can better characterize hepatic lesions when compared to CT. Currently, the role of MR imaging should be in patients where the diagnosis remains in question, because MR imaging can distinguish liver abscesses from other liver lesions such as cystic or necrotic tumors. MR imaging has also been used for diagnosis, but the high cost, length of study, and lack of easy access for drainage have limited the usefulness of this type of imaging in the management of these patients (Fig. 115–4).[2] A retrospective review of MR imaging of 20 patients with a total of 53 abscesses, with parameters similar to that of the described literature, found that 48 of 53 abscesses were hypointense on T1-weighted images and hyperintense on T2-weighted images, which is consistent with published data.[21] Characteristics present with the administration of gadolinium and with the use of different MR imaging modalities (e.g., T1- and T2-weighted imaging) can be helpful in differentiating abscesses from other focal liver lesions.[21,29]

Other Imaging

Liver scanning using sulfur colloid or gallium citrate scans was the first tool that physicians had to rapidly detect hepatic abscesses with good sensitivity. However, with the development of ultrasound and CT, liver scanning as well as arteriography has almost been completely replaced.

Management

In the preantibiotic era, bacterial liver abscesses were associated with intra-abdominal infection such as appendicitis. In these cases open surgical drainage with intervention for the causative intra-abdominal disorder was the only opportunity for cure. Accordingly, in this era,



A B

Figure 115–4. **A** and **B,** Gadolinium-enhanced T1-weighted MR imaging through the liver reveals multiple low-signal lesions with a thin peripheral ring of enhancement in this patient with multiple pyogenic microabscesses.

the disease carried a very high mortality rate as quoted in Oschner and colleagues' paper from 1938 with a nonoperative mortality rate of 100%. Furthermore in cases where operation was performed, the mortality rate was greater than 50%.[1] With the advent of antibiotics, the principles of management became surgical drainage of the abscess with antibiotic therapy. However, with the evolution of ultrasound and CT-guided procedures, more centers have moved therapy away from open surgical procedures to percutaneous drainage techniques, either aspiration or catheter drainage.

Antibiotic Therapy

Once the diagnosis of hepatic abscess is suspected, antibiotics and appropriate resuscitation should be initiated. As mentioned earlier, blood cultures, although not completely accurate in revealing organisms present in the abscess material, should be obtained as soon as possible. At this time *Entamoeba histolytica* serology should also be obtained to assist in differentiating the two major types of hepatic abscess because amebic abscesses frequently do not require drainage. Once abscess material is obtained, the Gram stain should be aggressively sought because it has a high rate of identification of gram-positive organisms and a reasonably high rate of identification of gram-negative ones. Therapy should not be delayed while waiting on blood or abscess culture results. In choosing antibiotic therapy, knowledge of common organisms is helpful. The most common organisms were discussed earlier and should be treated with the selected antibiotic regimen. Furthermore, an idea of the cause of the abscess is helpful because abscesses of biliary cause commonly yield enteric gram-negative pathogens, whereas colonic disorders (e.g., from diverticulitis) yield anaerobic pathogens.[10] In previous years, suggested regimens included three-drug therapy with a penicillin, an aminoglycoside, and metronidazole. With the emergence of many resistant bacteria, antimicrobials such as imipenem, piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam have been recommended. The addition of metronidazole treats *Bacteroides* as well as other anaerobic bacteria. Also, metronidazole is the treatment of choice in patients with amebic hepatic abscesses. In patients where the nephrotoxic potential of aminoglycosides does not justify their administration, a third-generation cephalosporin may be substituted, although *Enterococcus* will not be treated as effectively.

Duration of antibiotic therapy and route of admission are also an important factor and should be individualized to the patient based on the number of abscesses, underlying condition, toxicity of the antibiotic regimen, and clinical response. Treatment should be initiated parenterally, and some authors recommend continuing this for 2 to 3 weeks prior to converting to an oral regimen to complete a 4- to 6-week course.[10] Mohsen et al. administered broad-spectrum antibiotics for a mean of 37 days regardless of type of drainage procedure. Twelve patients received medical therapy alone, with a success rate of 58.4%.[6] There have been other groups advocating medical management of pyogenic abscesses. There have been small groups of patients treated successfully with antibiotics alone, such as the 9 of 10 patients in a 1982 publication by Herbert et al.[30] However, with the ease and

availability of drainage techniques, the decision to use medical therapy alone must be strongly justified.

Drainage Procedures

Most patients require some form of abscess drainage whether it is surgical, percutaneous, or closed aspiration. There have been many different studies evaluating and comparing these methods. As the anatomic location of the abscess, concurrent and causative disorders, and patients' general condition can govern therapeutic drainage decisions, generalized comparisons between percutaneous drainage (aspiration or catheter drainage) and surgical drainage must be made carefully. For example, the patient with a nonloculated abscess in the posterior right lobe would be perfectly suited for a percutaneous procedure, whereas the patient with a left lobe lesion and a diverticular abscess would be better suited for an open procedure. Comparing the two methods of drainage in these patients is not applicable. As such, an emerging principle of management, especially in light of association with hepatobiliary disorders, is a search for underlying intra-abdominal and hepatobiliary disorders. Therefore, data comparing percutaneous drainage and surgical drainage must be interpreted carefully, and each individual case must be scrutinized to determine the most appropriate method. Regardless of treatment method, drainage substantially improves mortality rates; however, as a consequence of this, morbidity rates will increase.[4] Also important in analyzing various treatment methods is the knowledge that death is consistently related to a patient's underlying disease and general medical condition, not to the type of intervention chosen for that patient.[4]

Closed Aspiration and Percutaneous Catheter Drainage

The first description of closed aspiration in 1953 by McFadzean and colleagues reported successful management of 14 patients with pyogenic hepatic abscesses treated with closed-needle aspiration and intracavitary antibiotics.[31] An Italian study of 115 patients with 147 abscesses with a mean diameter of 6.8 cm were treated with ultrasound-guided percutaneous needle aspiration repeated every 3 to 7 days as needed along with standard parenteral antibiotics. A total of 301 aspirations were performed (2.2 per patient), with single aspiration sufficient in 50% of cases. Cure (normalization of clinical, laboratory, and imaging parameters) was achieved in 113 patients (98.3%). The authors also stated that the patients had less discomfort and costs were lower with this method. This series' patient population had only 13% of abscesses associated with biliary malignancies, although 20 patients in the series (31.3%) had some form of immunosuppression.[32] The authors used these explanations to justify their success rate being greater than those of other series describing a 64% cure rate, with a significantly longer amount of time to resolution.[33] Furthermore, many series consider reaccumulation of abscess and repeat treatment a treatment failure and would report these results in a different light. This underscores an important point, that the appropriate therapy for hepatic abscesses must be selected based on careful evaluation of the patient, not solely on published results.

Percutaneous catheter drainage is also a method employed by many institutions, in which a pigtail catheter or similar device is advanced into the abscess cavity using some form of image guidance. A 2003 prospective, randomized trial from Hong Kong randomized 64 patients with hepatic abscesses to treatment with intermittent needle aspiration or percutaneous continuous catheter drainage. Both groups received the same pretreatment antibiotic regimen. No statistically significant difference was seen in the main procedure outcome measures between the two groups. The authors of this study cited the ease of the aspiration procedure, the ability to drain multiple abscesses in one setting, and the decreased costs when compared to percutaneous catheter drainage to justify closed aspiration as first-line therapy for pyogenic hepatic abscesses.[34] To determine the actual advantage and reach statistical significance, a larger trial would be required. However, in appropriately selected patients, such as those not requiring operative intervention for other coexisting problems, percutaneous methods are safe and usually effective treatments as long as careful attention is paid to detecting patients worsening clinically or failing to improve with nonsurgical therapy.

In patients with indwelling biliary stents who develop an abscess, treatment options include systemic antibiotic and stent change with or without percutaneous drainage. If the abscess clearly communicates with the biliary tree on cholangiography, stent change may be adequate. If no communication exists, if the tract is small, or if the patient's condition remains septic, abscess drainage is required.

Percutaneous treatments, although effective, do have morbidity associated with them, defined as reaccumulation of the abscess with repeat or surgical drainage as well as prolonged ileus, small bowel obstruction, pleural effusions, and recurrent abscesses. The morbidity rate of the Duke series patients treated with percutaneous drainage was 71% (48% following open surgical intervention) when morbidity is defined as just described. The literature quotes a similar morbidity rate using these criteria of 40% to 60%.[4]

Surgical Drainage

The role of surgical therapy in the treatment of hepatic abscesses has changed greatly with the development of percutaneous and aspiration techniques; however, surgery still plays a vital role in the comprehensive treatment of hepatic abscesses. This is illustrated in a series from Bertel et al. in which 61% of patients with hepatic abscesses required an additional procedure at time of operation to treat the causative condition.[35] Huang et al. made the important point that percutaneous and surgical drainage are not considered competitive but rather complementary techniques.[2]

In the preantibiotic era, an extraperitoneal approach was used to drain the abscess to avoid contamination of

the pleural or peritoneal cavity. The current operation of choice for most surgeons is a transperitoneal exploration with drainage of all hepatic collections and correction of the causative intra-abdominal disorders. Through a midline incision or extended subcostal incision, after thorough exploration of the abdomen and repair of associated abdominal disorders, the area of the liver containing the abscess is isolated from the rest of the abdomen with laparotomy towels. Adjuncts to identifying the abscess include needle aspiration, which yields appropriate culture material, as well as intraoperative ultrasound. The aspirated material should be placed directly into appropriate culture vials to maximize identification of anaerobic bacteria. Once the abscess cavity has been identified, a tract is gently made through the hepatic parenchyma to have the abscess drain in a dependent fashion. A suction catheter is then inserted into the abscess cavity to remove the purulence and minimize spillage into the abdomen. After complete aspiration of the abscess contents, the tract is enlarged and the abscess cavity explored to ensure adequate drainage of any loculated pockets. At this time biopsies of the abscess wall should be obtained to rule out tumor with necrosis and infection as well as examination for trophozoites of *E. histolytica* present in amebic abscesses. A drainage catheter is placed into the abscess cavity is such a manner that all abscess pockets may be drained; multiple catheters can be used if necessary. These catheters are brought out through separate stab incisions; they can be used for drainage, irrigation, or contrast studies to evaluate closure of the abscess space. These drains can be progressively removed over the course of 2 to 3 weeks. An omental pedicle can also be placed in the abscess cavity to provide blood supply. Reaccumulation of the abscess should prompt re-evaluation of the patient's abdomen for unidentified disorders.

Infrequently, patients with long-standing biliary obstruction confined to one hepatic lobe who have undergone multiple biliary drainage procedures present with a hepatic abscess. Hepatic resection may be the only alternative for this rare group of patients. The largest series of hepatic resection for pyogenic abscess is that from Balasegaram, who performed 21 resections with 3 deaths.[36]

Outcome

Mortality rates have improved greatly since Oschner and colleagues' series, where overall mortality was 77%.[1] Mortality rates vary from series to series for hepatic abscesses and can be influenced by many factors. Mortality rates in recent studies range from 2.5% to 19%,[4-6,8,9,15,17] but these numbers can be misleading. In the study by Mohsen et al., the overall mortality rate was 12.3%; however, if there was an associated biliary disorder, there was a 33% mortality rate.[9] The series from Duke described an overall 19% mortality rate, with a mortality rate for patients with an underlying malignancy of 35%.[4] The data from Johns Hopkins showed a decrease in mortality rate from 65% to 31% comparing the 1952-1972 period with the 1973-1993 period.[2] Differences in mortality rates between series are possibly due to differences in the percentage of multiple abscesses, abscesses of biliary origin, underlying malignancy, or abscesses secondary to generalized septicemia, all of which would carry a higher mortality rate.

Prognostic Factors

Several studies have attempted to identify prognostic factors; however, these are inconsistent between studies and generally follow common knowledge of hepatobiliary disorders in that patients with elevated prothrombin times, elevated creatinine, decreased hemoglobin, or poor baseline pulmonary function, for example, have worse outcomes. A Taiwanese study found on multivariate analysis that marked leukocytosis greater than 20,000, albumin lower than 2.5 g/dl, and the presence of pleural effusions were independent risk factors for predicting mortality.[37] The Johns Hopkins series found that multiple abscesses, an associated malignant disease, jaundice, hypoalbuminemia, leukocytosis, bacteremia, or a significant complication were associated with an increased mortality.[2]

In summary, hepatic abscesses are rare conditions that can have a myriad of presentations and pathologic associations. The key to successful treatment is prompt recognition of patients at risk for hepatic abscess and rapid initiation not only of specific treatment for the abscess but also of correction of underlying disorders to prevent further abscess formation and clinical deterioration.

AMEBIC HEPATIC ABSCESSES

Amebic liver abscesses are the most common extraintestinal manifestation of amebiasis. Amebiasis is a relatively common parasitic infection caused by the protozoan *E. histolytica*. The World Health Organization (WHO) reported in 1980 that up to 12% of the world population could be infested with *E. histolytica*.[38] Furthermore, out of the large number of infested individuals, 50 million will become symptomatic.[39,40] This organism is the second leading cause of parasite-related death in the world, second to malaria. *E. histolytica* is a 10- to 40-μm organism, capable of invading nearly every tissue of the human body.[41] Unlike pyogenic hepatic abscesses, amebic abscesses have a strong geographic distribution and male preponderance. This section discusses the incidence, demographics, and pathogenesis of amebic abscesses, as well as patient presentation, diagnosis, treatment, and potential complications. Furthermore, differences between pyogenic and amebic abscesses are highlighted because treatment for these two entities also differs.

Incidence

Amebiasis is a global disease, with highest incidence in tropical and subtropical climates. Amebic infestation is endemic between parallels 40° North and 30° South with the highest incidences in Mexico, India, East and South

Africa, and portions of Central and South America.[41] Furthermore, incidence is increased in areas with higher poverty levels, presumably a direct reflection of poor sanitation, public health, and hygiene.

For years, patients were found to have an amebic infection on serology or stool studies yet did not demonstrate symptoms of amebic infection. Studies have revealed the existence of a second amebic species, *Entamoeba dispar,* which is now thought to be responsible for most asymptomatic infections in certain areas.[42] For purposes here, all discussion of amebic abscess refers to *E. histolytica.*

The incidence of amebic abscess in the United States and other industrialized countries is low compared to the rest of the world. However, with increased travel between countries, the presence of human immunodeficiency virus, and the influx of immigrants to the United States from other countries, the incidence is increasing, especially in the southern United States. For example, a 1987 study from Los Angeles County Hospital of 144 patients with hepatic abscesses, 96 were amebic. This is in contrast to the traditional distribution of the United States; however, 98% of the patients were Hispanic and 95% were born in Latin America.[43] Homosexual men are also at increased risk: A review over 20 years found an increased incidence of amebic infestation in homosexual men above the general population.[44] Despite the high incidence of amebiasis, hepatic abscesses are found in roughly 1% of patients with amebiasis.[39]

Demographics

The age and sex distribution of amebic hepatic abscesses are different than those of pyogenic abscesses. In contrast to pyogenic abscesses, the large majority of patients with amebic abscesses are young men. A recent comprehensive review of literature studying amebic hepatic abscesses described a male-to-female ratio of 10:1.[42] The average patient affected by amebic abscesses is between 20 and 40 years of age.[39] The reasons for the great male preponderance are not clear, although several theories have been postulated: heavy alcohol consumption in men, hormonal effects in premenopausal women, and a possible protective effect of iron deficiency anemia in menstruating women.[42]

There have not been any racial predispositions isolated for amebic abscesses. The preponderance of amebic abscesses tends to be linked to geographic distribution and travel to endemic areas.

Etiology and Pathogenesis

Infection with *E. histolytica* begins with ingestion of the quadrinucleate cyst. This typically occurs with ingestion of food or water contaminated with fecal material. Obviously, public health and hygiene standards govern infection rates, and breakdown of these systems can lead to outbreaks of disease. In the Republic of Georgia, an outbreak of amebiasis, with subsequent increase in hepatic liver abscesses that may have affected 84,000 to 225,000 people, was attributed to contamination of the municipal water system.[45] This underscores the low incidence of amebic liver abscess in developed countries.

The cyst is resistant to the acidic pH of the stomach, and once in the small intestine excystation occurs in the setting of alkaline or neutral pH, releasing the trophozoite form of the parasite. The trophozoites then pass to the large intestine and, using lectin-carbohydrate interaction, adhere to the colonic mucosa.[46] Infectious cysts can reform in the colon and are then excreted in the stool to further perpetuate the spread of the organism. Once in the colon, the trophozoite either causes invasive disease when it penetrates through the colonic mucous layer or can live in the mucous layer without tissue invasion or symptoms. Invasion is mediated by direct cell killing of host epithelial cells and other immune cells. There is a direct amebic-cell interaction that has been shown to trigger apoptosis in the host cells. *E. histolytica* also has been found to secrete a protein that may also contribute to host cell lysis and amebic invasion through colonic tissue.[47-49] The cellular invasion extends to the submucosa, then extends laterally, creating the classic flask-shaped ulceration. At this stage, the disease can be confused with inflammatory bowel disease. Distinction is important because those patients with amebiasis who receive corticosteroids have an increase in severity of disease and a raised incidence of perforation and liver abscess.[49] Of note, the cecum and ascending colon are frequently the site of amebic infestation.

Hepatic spread is thought to occur by hematogenous routes through the portal vein or, less frequently, through direct extension. The liver is the most common extraintestinal site of amebiasis, although other organs can be affected. Animal studies have shown that within 3 hours of embolization of trophozoites to the portal circulation, hepatic sinusoids contain ameba surrounded by neutrophils. This is thought to produce small areas of infarction in the hepatic parenchyma because 24 hours later lysed neutrophils are seen in the setting of hepatic necrosis. It is postulated that neutrophil lysis and subsequent release of cytotoxic chemicals leads to the extensive surrounding necrosis. Roughly 1 week later there is extensive necrosis with scant inflammation.[50] It is likely that the large hepatic amebic abscesses found in autopsy studies and in the patient with amebic abscess are the result of coalescing multiple small abscesses with associated necrosis.

The liver abscess is a well-circumscribed area where the parenchyma has been replaced by necrotic tissue.[41] The abscess itself contains acellular fluid that is usually dark reddish brown, classically described as "anchovy paste." Trophozoites are notoriously absent from the fluid of the abscess, which is composed of the products of necrosis of the hepatocytes and cellular debris. Trophozoites reside in the necrotic tissue surrounding the abscess along with connective tissue and inflammatory cells.[42]

Location and Number of Abscesses

At autopsy the average size of an amebic abscess is 5 to 15 cm in diameter, and most occur in the right lobe.[41]

Table 115–6 Selected Signs and Symptoms in Series Comparing Pyogenic and Amebic Hepatic Abscesses*

	Conter et al., 1986[53] (University of California, Los Angeles): Data Period 1968-1983		Barnes et al., 1987[43] (University of Southern California, Los Angeles): Data Period 1979-1985		Lodhi et al., 2004[51] (Karachi, Pakistan): Data Period 1988-1998	
Study Descriptors	*Pyogenic Abscess*	*Amebic Abscess*	*Pyogenic Abscess*	*Amebic Abscess*	*Pyogenic Abscess*	*Amebic Abscess*
No. of cases	42	40	48	96	106	471
Age, yr	46.5 (mean)	37.6 (mean)	44 (mean)	28 (mean)	51 (mean)	40 (mean)
Male-to-female ratio	2.5:1.0	3.4:1.0	1.4:1.0	18.2:1.0	2.9:1.0	6.1:1.0
Symptoms						
Fever, %	88	93	77	87	48	67
Abdominal pain, %	64	93	66	90 ($P < 0.001$)	N/A	N/A
Diarrhea, %	12	60 ($P < 0.005$)	32	35	22	30
Symptom duration, %	N/A	N/A	63 < 14 days 37 > 14 days	86 < 14 days 14 > 14 days	N/A	N/A
Nausea/vomiting, %	31	50	62/43	85/32	N/A	N/A
Signs						
Abdominal tenderness, %	50	75	42	67	77	87
Jaundice, %	36	5	22	10	43	32
Shock/sepsis, %	26	0	N/A	N/A	N/A	N/A
Hepatomegaly, %	26	53	18	25	67	74

*Listed *P* value indicates significant difference between pyogenic and amebic abscesses in that specific study.
N/A, not available.

Consistent with published series, a large review of 3785 cases revealed only 14.6% of cases confined to the left lobe alone, with 12.4% bilateral.[42] A review of 577 cases of liver abscesses revealed 471 amebic abscesses, of which 73% were in the right lobe alone.[51] The right-sided preponderance has been explained by the right lobe receiving a majority of superior mesenteric vein flow, draining the cecum and ascending colon.

Most amebic abscesses are solitary lesions. In the study just cited, 348 of 451 amebic liver abscesses were solitary.[51] Other published reports described a slightly smaller preponderance of solitary lesions. A review of 3347 published cases from the literature demonstrated 37.7% of liver abscesses were multiple.[42]

Patient Presentation

Most patients with amebiasis are asymptomatic and clear their infection without any sign of disease. However, 4% to 10% of patients with amebiasis develop colitis within 1 year.[49] The onset of colitis is typically a gradual process, developing over several weeks. Symptoms can range from small-volume mucoid stools to profuse bloody diarrhea and toxic megacolon with systemic effects.

Although some studies describe the association of gastrointestinal symptoms (e.g., diarrhea) and amebic abscesses, there are other studies that have failed to demonstrate an association (Table 115–6).[42,49,50] One large review of 1420 cases from the literature reported coexisting diarrhea in 23% of cases.[42] The point to be made is that the clinician should not exclude amebic hepatic abscess based on the absence of intestinal signs of amebic disease and that the presence of intestinal symptoms such as diarrhea can be a clue to the presence of amebic liver abscess in the appropriate patient.

In nonendemic areas, patients describe travel to endemic areas in the preceding 2 to 5 months, and 95% of these patients will present within 5 months of travel.[52] The duration of symptoms associated with amebic hepatic abscesses varies from acute onset to that of a more insidious course, with the majority of patients presenting with an illness of less than 1 month. The majority of patients in a 96-patient review from Los Angeles presented with less than 2 weeks of symptoms, and only 14% of patients reported feeling ill for more than 2 weeks.[43] Several studies have described a longer prepresentation illness with pyogenic hepatic abscesses compared to amebic abscesses.

The most common presenting symptom in the majority of series is right upper quadrant pain and fever (see Table 115–6). The patient can experience pleuritic and right scapular pain if the diaphragmatic surface of the liver is involved with or in close approximation to the abscess. Tender hepatomegaly is also a common presenting factor, present in 62% of 1539 cases from the

Table 115–7 Selected Laboratory Parameters in Series Comparing Pyogenic and Amebic Hepatic Abscesses*

Laboratory Parameter	Conter et al., 1986[53] (University of California, Los Angeles): Data Period 1968-1983		Barnes et al., 1987[43] (University of Southern California, Los Angeles): Data Period 1979-1985		Lodhi et al., 2004[51] (Karachi, Pakistan): Data Period 1988-1998	
	Pyogenic Abscess	*Amebic Abscess*	*Pyogenic Abscess*	*Amebic Abscess*	*Pyogenic Abscess*	*Amebic Abscess*
Amebic serology, % positive	0	95	4	94	33	72
Mean alkaline phosphate or % with elevation	319 IU	198 IU	50% > 220 U/L	35% > 220 U/L	236 IU	211 IU
Mean total bilirubin or % elevated	4.1 mg/dl	0.9 mg/dl	15%	2% ($P < 0.005$)	2.4 mg/dl	1.9 mg/dl
Albumin level or % with hypoalbuminemia	2.7 g/dl	2.9 g/dl	50%	16%	2.1 g/dl	2.4 g/dl
WBC × 10^3/mm^3 or % elevation > 10^3/mm^3	13.4	13.5	91%	92%	18.9	19.1

*Listed *P* value indicates difference between pyogenic and amebic hepatic abscesses.
WBC, white blood cell.

literature, and has been described as being twice as common in amebic abscesses compared with the pyogenic type.[42,53] Other signs and symptoms include anorexia, fatigue, abdominal pain, fever, jaundice, and diarrhea (see Table 115–6). In terms of differentiating amebic from pyogenic abscess based on history, signs, and symptoms, tender hepatomegaly, a relatively short course of illness, and travel to an endemic area in a young male all are factors that make the diagnosis of amebic abscess more likely, whereas in an older patient with sequelae of hepatobiliary disease, a pyogenic cause is more likely. These distinctions are rarely clear enough to forego further diagnostic studies, and fortunately there are beneficial diagnostic modalities available to aid in this distinction (Table 115–7).

Diagnosis

There are multiple laboratory abnormalities that have been described in the literature; however, none of these are specific to amebic liver abscesses. Most patients demonstrate some degree of leukocytosis without eosinophilia. There have been varying reports of trends in liver transaminases, although most reviews have reported mild elevations, if any. Alkaline phosphatase was elevated in 76% of 589 cases from the literature.[42] There have been descriptions of elevated aspartate aminotransaminase (AST) with normal alkaline phosphatase in acute amebic hepatic abscesses, with normal AST and elevated alkaline phosphatase in chronic infection. Jaundice also occurs with a low frequency and, when present, has been linked to a more severe disease course.

Stool studies have also been employed with varying success in the diagnosis of amebic abscess, with the thought that the observation of ameba in the stool could help confirm an amebic cause of a hepatic abscess. Multiple collections (at least 3) of fresh specimens and a trained technician capable of distinguishing trophozoites from fecal leucocytes are required. Furthermore, the test can be complicated by barium, laxatives, antibiotics, and soap enemas, and only 10% to 40% of patients with amebic liver abscesses have ameba visible on microscopic stool examination.[41] This low rate could be due to confounding variables of the test as mentioned earlier rather than a low rate of patients passing amebic organisms in their stool. The most efficient method of obtaining samples is with a scraping or biopsy of rectal mucosa during sigmoidoscopy. Furthermore, with the recognition that *E. dispar* frequently is present in asymptomatic individuals and that it is microscopically indistinguishable from *E. histolytica,* the role of stool examination comes under further question. There are other tests, such as enzyme-linked immunosorbent assay (ELISA), that can identify *E. histolytica* antigens in the stool and can differentiate between *E. dispar* and *E. histolytica.* Stool polymerase chain reaction is also being developed; however, both studies require further refinement and are difficult to use as screening and or diagnostic tools in endemic areas.[49]

With the difficulties in establishing diagnosis based on stool studies, there have been several serologic studies developed to aid in diagnosis. Amebic serology is both a highly sensitive and specific test in identifying patients with amebic infection, thus aiding in the differentiation between pyogenic and amebic hepatic abscess. These tests identify circulating ameba-specific antibodies. Tests

that provide antibody titers provide positive confirmation of current or past infection. Currently ELISA for detection of the galactose-inhibitable adherence protein in serum and feces and indirect hemagglutination (IHA) tests appear to be the most reliable and sensitive serologic tests, both with sensitivity and specificity greater than 95%.[54] These antibodies are present roughly 7 days after the onset of symptoms. Furthermore, there are specific monoclonal antibody-based tests against *E. histolytica* that allows differentiation between invasive and noninvasive parasites.[41] The downfall of these ELISA and IHA studies is that patients remain positive for years following infection. Counterimmunoelectrophoresis and gel diffusion tests can identify patients infected within the past 6 to 12 months and are useful in endemic areas or in evaluating the patient from areas where *E. histolytica* is endemic.[55,56]

Imaging

Roentgenographic Findings

Roentgenographic studies are common in the initial evaluation of the patient with amebic liver abscesses. Focal elevation of the right hemidiaphragm occurs in 59% of patients with a hepatic abscess. This elevation usually is accompanied by a small pleural effusion and pneumonitis or atelectasis of the lower lobe with diminished excursion of the right hemidiaphragm. Once the patient has developed clinical symptoms of chest disease, the area of localized edema at the lung base will become an irregular area that obscures the hemidiaphragm and the costophrenic angle. From this stage pneumonia can ensue with subsequent abscess or empyema formation.[41]

Abdominal films can be helpful in evaluating colonic manifestations of amebiasis by identifying thumbprinting of the colon or, in more severe cases, megacolon or perforation. Hepatomegaly will be seen in most cases of amebic liver abscess. Gas within the abscess cavity signifies rupture into hollow viscous, secondary bacterial infection, or prior percutaneous intervention.[41]

Liver Scanning

Liver scans have demonstrated excellent sensitivity (>90%) in identifying amebic liver abscesses. However, as with pyogenic abscesses, the role of liver scanning has been replaced with ultrasound and CT scan.

Ultrasound

Ultrasound has emerged as a tremendously useful tool in the diagnosis of amebic liver abscess. Ultrasound characteristics can vary based on the stage of the lesion. When the lesion is in its early stages, there will be greater echogenicity than the adjacent parenchyma. Once necrosis has developed the abscess core will become echolucent with a posterior acoustic enhancement. Correct diagnosis of amebic liver abscess based on ultrasound findings alone can be difficult. A South African review of 425 ultrasound studies of normal and diseased livers demonstrated an 81% accuracy rate in diagnosing amebic liver abscesses. Overlap between ultrasound features of amebic liver abscesses, hepatocellular carcinomas, and metastatic carcinomas complicated the correct diagnosis of amebic liver abscesses in these cases.[57] Sonography can determine the number, size, and location of abscesses and can be used as a guide for percutaneous aspiration. Ultrasound is a noninvasive, rapid, relatively inexpensive, and reproducible tool, ideal for the diagnosis and follow-up of patients with amebic abscesses.

Computed Tomography

The major advantage CT scanning has over ultrasound is the ability to detect small lesions, although most amebic lesions are large enough to be seen on ultrasound, and image adjacent structures.[41] A retrospective review of 23 patients with amebic abscesses were reviewed, finding extrahepatic abnormalities in 9 patients as a direct result of extension or local reaction (pleural effusion) of the abscess.[58] The ease and accuracy of ultrasound, combined with the sensitivity of physical examination, patient history, and amebic serology in the diagnosis of amebic abscess, places CT scan as a second-line diagnostic modality reserved for cases in which ultrasound is not diagnostic.

Magnetic Resonance Imaging

MR imaging is a powerful tool in characterizing, detecting, and monitoring the evolution and regression of focal hepatic lesions. There are characteristic changes on T1- and T2-weighted images that develop based on the stage of the abscess. The hypointensity of the abscess wall on T1-weighted images and the hyperintensity on T2-weighted images might correspond to areas of thrombosis with inflammation discussed in the pathogenesis section of this chapter.[41] A study from Mexico examined the MR imaging scans of 17 patients with 29 amebic abscesses, both before and after treatment. With successful treatment, concentric rings corresponding to an inner margin of inflamed granulation tissue, the next ring corresponding to bands of type I collagen, and the outer margin of atrophic and/or mildly inflamed liver tissue became prominent on T1- and T2-weighted images. T2-weighted images showed rapid resolution of the perifocal hepatic edema.[59] Despite these findings and pathologic correlations, pyogenic abscesses, hematomas, and necrotic neoplasms may have similar characteristics, and MR imaging should not supersede ultrasound or CT in the diagnosis.[41,60]

Complications

The most common complications of amebic liver abscess are those arising from rupture of the abscess into surrounding organs or anatomical spaces. Abscesses near or involving the diaphragmatic surface of the liver can induce inflammatory reactions of the diaphragm, pleura, pericardium, or lungs. Furthermore, gastrointestinal

symptoms can be common, with some series reporting as many as 20% of amebic abscess patients with gastrointestinal complications.[61] These complications include rupture/extension of the abscess into the peritoneum producing peritonitis, paralytic ileus, abdominal pain with distention, and rupture into adjacent small or large intestine. Concurrent colonic manifestations of intestinal amebiasis must not be overlooked because fulminant colitis, toxic megacolon, and colonic perforation all can occur in the setting of hepatic abscess. Rupture into the peritoneal cavity has been described in 2% to 30% of patients, although the true incidence is probably toward the lower end of this range.[27,36] When peritoneal rupture is encountered, laparotomy should be performed with drainage of the liver abscess in addition to the administrations of amebicidal agents. Obviously rupture into the peritoneum or into the gastrointestinal tract increases morbidity and mortality in this patient population.

Pleuropulmonary Complications

Extension of disease into the chest is a relatively common complication, with many patients developing right-sided atelectasis and pleural effusions. These effusions are normally a reactive process and are sterile, not requiring treatment in addition to the abscess itself. However, the presence of pleuritic pain, cough, or respiratory distress suggests rupture of the abscess through the diaphragm and leads to the formation of an amebic empyema or pulmonary abscess requiring additional treatment. The abscess may erode into a bronchus, which induces a productive cough in which the contents of the abscess are expectorated. Pulmonary complications of all types have been described in 7% to 20% of patients with amebic liver abscesses.[49] There are several possible routes of pulmonary infection, including direct hematogenous spread via vertebral vessels or middle or inferior rectal veins to the right heart and inhalational amebiasis. Both of these conditions are rare, with the majority of cases a result of spread from a hepatic abscess.[62] Chest radiograph findings are nonspecific but include elevation of the right hemidiaphragm in 50% of cases.[62] A series of 501 cases of amebic liver abscess with thoracic complications from Mexico City were reviewed from 1961 to 1979, with 326 patients having rupture into the chest. Rupture into the pleural cavity can be accompanied with rapidly progressive respiratory distress and sepsis. The overall mortality for thoracic complications in the Mexico City series was 8.3%.[63] Obviously empyema and lung abscess must be treated surgically in addition to amebicidal agents. Some authors advocate an open decortication of amebic abscesses because the fibrous connective tissue can be dense enough to complicate thoracoscopic surgical techniques.

Rupture into the Pericardium

Abscess rupture into the pericardium is a rare but serious complication of amebic abscesses, occurring in 1.3% to 2% of cases with mortality rates from 30% to 60%.[27,36,62,63] Most cases of pericardial rupture result from left-sided or more centrally located hepatic abscesses. These cases are not necessarily instantly fatal, and patients who have had rupture into the pericardium can have examination findings as subtle as a pericardial rub with muffled heart tones to cardiac tamponade. Management of patients with cardiac complications of hepatic abscess must include prompt recognition of cardiac complications and the presence of hepatic abscess, close hemodynamic monitoring, administration of tissue amebicidal agents, and adequate pericardial drainage.

Other Complications

There are other conditions that can occur with hepatic abscesses, including hemobilia (0.7%); complications of liver failure (2.5% to 3.1% of cases), because abscesses can grow quite large and replace and destroy a large amount of hepatic parenchyma; and secondary bacterial infections with resultant septicemia.[27,36,64] Isolated cases of metastatic brain abscess have also been reported and have been uniformly fatal.

Treatment

The mainstay of treatment of uncomplicated amebic hepatic abscesses remains amebicidal drugs. Management of complications has been discussed previously. Controversy still exists over the need for aspiration with either closed or percutaneous catheter drainage. Surgical drainage is now reserved for complicated cases or cases that have failed prior, less-invasive therapy.

Medical Therapy

Metronidazole has emerged as the drug of choice for amebic hepatic abscesses. Other nitroimidazole derivatives (tinidazole or ornidazole) are also effective but are currently unavailable in the United States. Prior to the introduction of metronidazole in 1966, the mainstay of therapy was chloroquine and emetine, although this therapy failed to eradicate intestinal infestation. The response of most patients with amebic liver abscesses to metronidazole is profound, with most patients demonstrating improvement in symptoms in 72 to 96 hours. The current recommendations for treatment are metronidazole 750 mg three times a day for 5 to 10 days;[42,49] this treats intestinal amebiasis. However, a luminal agent such as paromomycin (30 mg/kg three times a day for 5 to 7 days), iodoquinol (650 mg orally three times a day for 20 days), or diloxanide furoate (500 mg orally three times a day for 10 days) should also be used to eradicate intestinal colonization.[49] A prospective study of 178 patients with 203 amebic liver abscesses treated with metronidazole alone were evaluated in a South African tertiary referral hospital: 150 of these patients were managed successfully with drug therapy alone, with those demonstrating clinical deterioration or no improvement (persistence of pain) after 48 to 72 hours then receiving percutaneous ultrasound-guided aspiration. The authors concluded that conservative medical management of uncomplicated liver abscesses is safe, with patients who fail medical therapy progressing to aspiration.[65] At least

two more randomized, controlled trials did not identify a statistically significant benefit of aspiration and medical therapy over medical therapy alone.[66,67] Although these studies clearly point out that medical management alone is a safe initial management of these patients, many authors acknowledge a role for abscess drainage. These indications include persistence of symptoms or clinical deterioration with medical management, concern of impending rupture based on size or location, suspicion of bacterial superinfection or pyogenic abscess, or the presence of a large abscess with more than 250 ml of fluid aspirated. As serologic testing has improved, aspiration of contents is becoming less necessary in aiding in the differentiation between pyogenic hepatic abscesses.

Percutaneous Drainage

The role of percutaneous drainage is minimal in amebic hepatic abscesses. Many authors have cited concerns over catheters increasing the risk of bacterial superinfection. Furthermore, the thick viscous material characteristic of amebic abscesses is difficult to drain through standard catheters. An Italian study treated 31 patients with percutaneous drainage with intralesional nitroimidazole therapy and reported improvements in clinical response, with faster resolution, fewer relapses, and less residual hepatic scarring than with medical therapy alone or open surgical drainage combined with medical therapy.[68] Given the potential for infection, and multiple other studies advocating medical management, percutaneous catheter drainage is not warranted in uncomplicated amebic liver abscess.

Surgical Drainage

As mentioned previously, most patients with uncomplicated amebic liver abscesses can be managed successfully with medical management, reserving surgical intervention for those patients with certain complications. Most authors agree that patients with peritoneal rupture and associated peritonitis require surgical treatment. Debate remains over the best management of thoracic complications. Obviously empyema requires operative intervention, but as mentioned earlier, amebic pericarditis can be managed with needle aspiration of both the pericardium and liver abscess.[27]

Surgical intervention as primary therapy of amebic hepatic abscesses is a rare occurrence. Surgical series that have been published report varying numbers of patients requiring operation, which can be explained in part by differences in opinion regarding indications for operation. The practice of most authors is to reserve surgical intervention for those patients failing less invasive management, patients with complications of amebic hepatic abscess, and those patients with large left-sided abscesses not amenable to catheter-based drainage that are posing a risk of rupture into the pericardium.

Once the decision has been made to drain the abscess surgically, there are specific principles that must be utilized. Through a subcostal or midline incision the liver is thoroughly examined, with care taken not to disrupt the abscess. The abscess should be carefully drained through closed suction, and the cavity should be irrigated with sterile saline. Care must be taken when dividing septa within the abscess as these can be blood vessels or biliary radicles whose disruption can lead to hemorrhage or postoperative biliary leaks. Following drainage, the abscess cavity may be irrigated with 65 mg of emetine hydrochloride in 100 ml of sterile saline for 3 to 5 minutes. Drains may be used as needed.[69]

Outcome and Prognostic Factors

The survival rate in patients with amebic liver abscesses is much better than that of pyogenic hepatic abscesses. The 1986 paper by Conter and colleagues had 29 of 40 patients treated with antiamebicidal medications alone, 3 of 40 patients treated with aspiration therapy, 1 patient treated with catheter drainage, and 6 patients treated with surgical therapy for concerns of impending rupture or other conditions. All patients with amebic abscesses in this series survived.[53] Similar findings were found in a review of 96 patients with amebic abscesses in which no mortality was attributed to the abscess. In this series all but two patients were managed with antiamebics alone.[43] There have been other studies that have found more significant mortality, as in a 1996 prospective study where 135 patients with amebic abscesses were treated with 10 days of metronidazole therapy. Aspiration was used if patients did not respond clinically or were found to be at risk for impending rupture. In this series 24 patients did not survive, for a mortality rate of 18%.[70] Clearly this disease can have complications associated with the abscess itself and concurrent amebic disease, which can explain differences in mortality rates. An extensive review of 3530 cases from the literature found an overall mortality rate in uncomplicated cases of 5.9%.[42]

There have been several patient factors that have been associated with poor outcomes. A 1996 prospective cohort study from India treated patients with metronidazole with or without surgical drainage based on response to medical therapy. This study found an 18% mortality rate, with several factors found to be independent predictors of mortality. These factors (significant in logistic regression analysis) were a bilirubin level greater than 3.5 mg/dl, encephalopathy, volume of abscess cavity greater than 500 ml, albumin less than 2.0 g/dl, and the number of abscesses.[70] It is obvious that patients who experience complications, such as rupture into the peritoneal cavity, will have a worse outcome.

In summary, patients presenting with amebic abscesses can have positive results with medical treatment alone. Drainage procedures should be reserved for those patients who do not respond to medical therapy, whose abscess appears to have a high likelihood of rupture, or those whose diagnosis is in question. Surgical procedures are used for patients who fail these management approaches or experience complications of the abscess, such as peritoneal rupture or empyema. Essential to therapy of amebic abscesses is prompt recognition of the disease process, which in endemic areas is done quite well. However, in areas where amebic abscesses and

amebiasis is a rare occurrence, inclusion of amebic disease in the differential diagnosis of patients with signs and symptoms consistent with the disease is essential.

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Chapter

116

Management of Hepatobiliary Trauma

Cuthbert O. Simpkins · Atta Nawabi · Gazi B. Zibari

In the past decade, the benefit of nonoperative management of liver injuries in a hemodynamically stable patient has become clear. The efficacy of packing for severe bleeding from the liver has also been clearly demonstrated. Controversy remains between surgeons who would observe after packs are removed and those who would débride necrotic liver tissue with nonanatomic or anatomic resection. Strong acknowledges the success of the nonoperative approach but warns against the pendulum swinging too far toward not resecting liver when it is advisable to do so.[1] The primary cause of mortality from hepatobiliary trauma continues to be uncontrollable bleeding and prolonged hemorrhagic shock. Successful management of hepatobiliary trauma requires comprehension of the anatomic basis of critical technical maneuvers, in addition to a well-conceived approach.

MOBILIZATION OF THE LIVER

The liver is fixed in position in the abdomen by the falciform, coronary, triangular, and gastrohepatic ligaments (Fig. 116–1). The falciform ligament attaches the liver to the diaphragm and the anterior abdominal wall. The triangular ligaments attach the right and left boundaries of the liver to the diaphragm. The coronary ligaments are bifurcations of the triangular ligaments. These ligaments attach the liver to the diaphragm and have anterior and posterior components. The area between these components is the "bare" area of the liver. The gastrohepatic ligament is an extension of peritoneum between the stomach and liver. The liver may be mobilized by dividing these ligaments.

Continued division of the falciform, triangular, and coronary ligaments reveals the hepatic veins. On the right, division of the dorsal ligament provides additional access to the veins from the caudate lobe that drain into the inferior vena cava (Fig. 116–2). Similarly, the left side is mobilized by division of the left triangular ligament, with division of the caudate-caval ligament providing additional access to the hepatic venous connections to the vena cava (Fig. 116–3).

BILIARY SYSTEM

The hepatic ducts and the proximal and middle thirds of the common duct are supplied by branches of the cystic artery. The middle third is also supplied by branches of the right hepatic and superior pancreaticoduodenal arteries. The distal third is likewise supplied by the same branches. The general distribution of the blood supply of the common bile duct is at 3 and 9 o'clock (Fig. 116–4). This anatomy should be considered when repairing the bile duct or creating a biliary-enteric anastomosis (or both).

MECHANISM OF LIVER INJURY

At the Louisiana State University Health Sciences Center from 1993 through 2003 there were 378 cases of liver trauma. Of these cases, 77% were due to blunt trauma and 27% were due to penetrating trauma. Of the penetrating injuries 77% were due to guns and 23% were due to knives. Blunt trauma was caused primarily (74%) by motor vehicle collisions.[2] The liver is well protected by the rib cage and thoracoabdominal musculature. In blunt trauma, the elasticity of the arterial tree provides some protection for these vessels. In contrast, the systemic and portal hepatic veins, as well as the biliary system, have only thin adventitia. Therefore, most liver injury bleeding is venous, not arterial. Such bleeding can be voluminous. Nonetheless, because most liver bleeding is venous and therefore low pressure, tamponade is readily performed. The liver parenchyma is easily disrupted. Glisson's capsule is thin and has little elasticity. It provides a tenuous barrier for containment of intraparenchymal bleeding, as with a subcapsular hematoma.

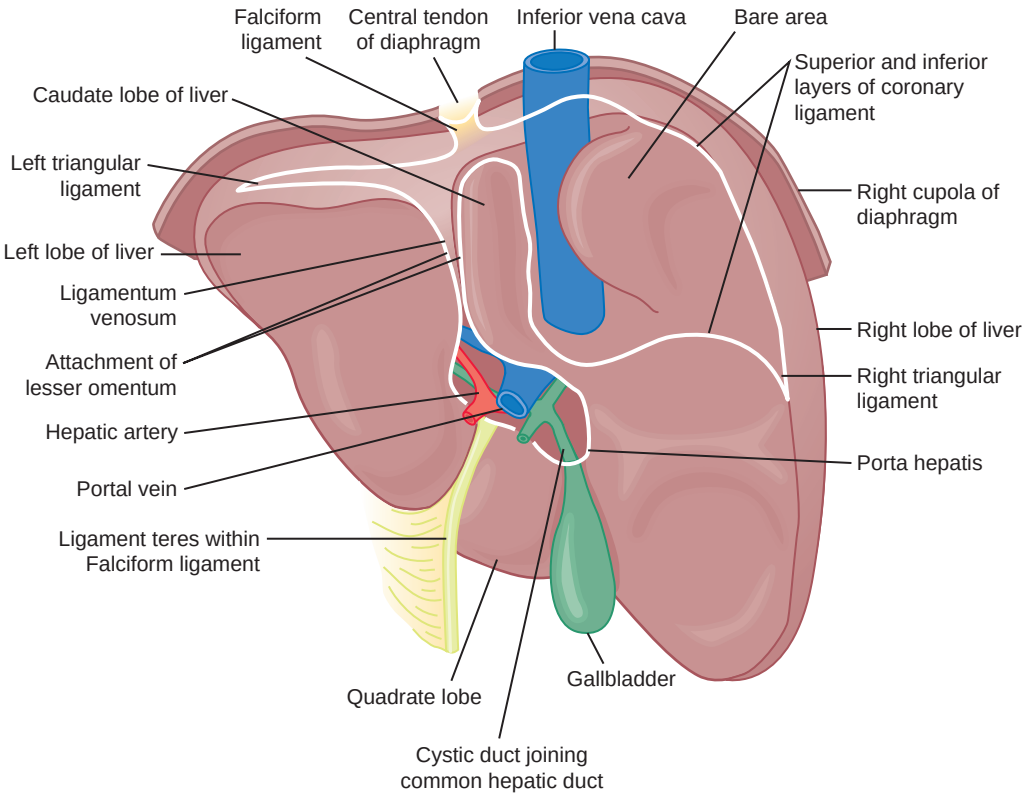


Figure 116–1. Posterior surface of the liver showing its ligamentous attachments. (From Snell RS: Atlas of Clinical Anatomy. Boston, Little, Brown, 1978, with permission.)

In blunt trauma, a variety of forces can cause injury to the liver. In an accident involving rapid deceleration, such as a motor vehicle collision or a fall, the relatively massive liver continues to move while motion of the torso has stopped. This causes tension at the hepatic attachments. Parenchyma and the hepatic veins may be torn from the vena cava. The result ranges from pericaval hematoma to torrential bleeding. Shear forces at the interface between the liver and its attachments to the abdominal wall, such as the coronary or triangular ligaments, may cause superficial or deep excavations of the liver parenchyma, which also may or may not bleed. In addition, direct compression force may be applied by, for example, a steering wheel against the liver. This type of force could result in impaction of the ribs into the liver with rupture of Glisson's capsule and the soft liver parenchyma. The term *bear claw defect* is used when the imprint of the ribs can be seen on the traumatized liver.[3] Contusion of the dome of the right lobe of the liver may occur as a result of compression of the right hemidiaphragm against it. Injuries to the extrahepatic biliary system are less frequent than injuries to the liver, primarily because of the small surface area as well as the fibrous covering surrounding the portal triad.

Penetrating injury to the liver or extrahepatic biliary system usually results from knives or bullets, but it may also be caused by interventional radiologic procedures.[4] A knife creates a wound that is limited to its path, whereas a bullet creates a cavity. The extent of damage done by a bullet depends on its pathway, velocity, yaw, and design.

CLASSIFICATION OF LIVER INJURY

The standard classification of liver injuries was developed by Moore et al.[5] (Table 116–1). Mirvis and colleagues[6] also developed a useful system (Table 116–2).

DIAGNOSTIC APPROACH: PENETRATING TRAUMA

Stable patients with penetrating abdominal injuries and no signs of peritonitis may be evaluated by computed tomography (CT). If the CT scan is negative, the patient may be observed. If, for example, CT reveals that a bullet is embedded in the lateral portion of the right lobe of the liver, the patient is hemodynamically stable, and the path of the bullet makes involvement of any other viscus unlikely, observation is justified. If the bullet is medial enough to make injury to the gallbladder, portal triad structures, or other viscera probable, exploration is performed. Hemodynamically unstable patients should be assessed rapidly. A focused assessment with sonography for trauma (FAST) will confirm the presence of intra-abdominal fluid. A false-negative ultrasound finding could result from evacuation of blood through a

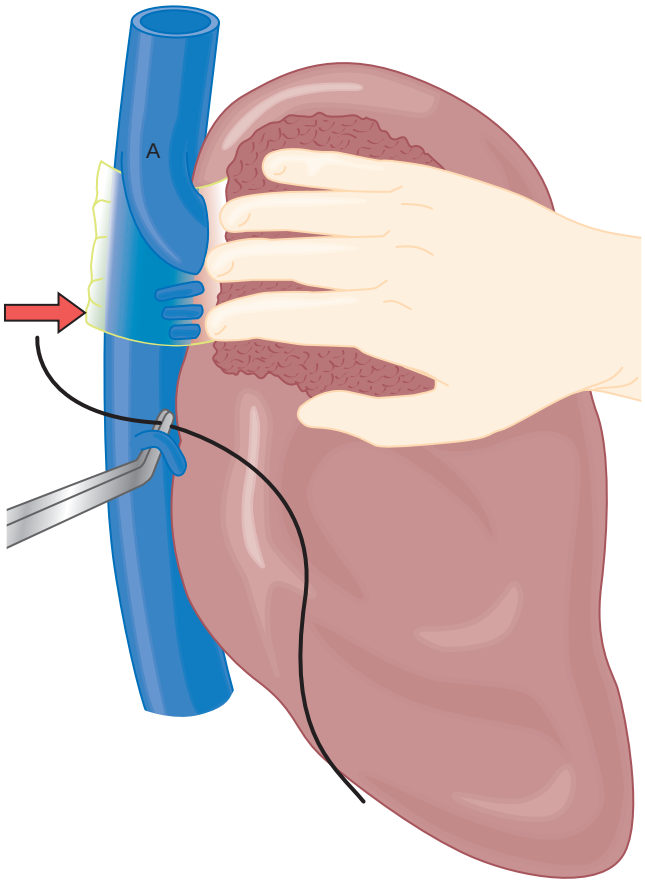
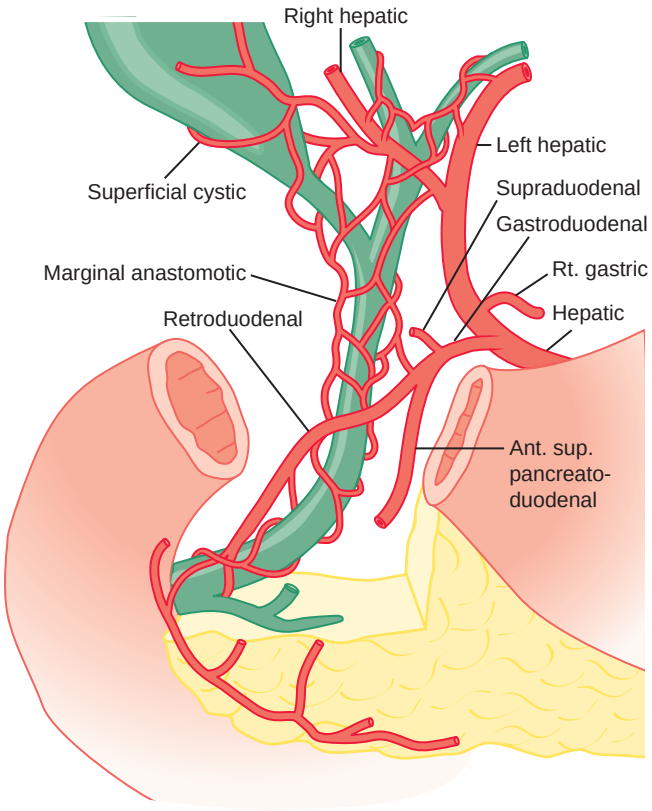


Figure 116–2. Exposure of the right hepatic vein (A). After division of the right triangular and coronary ligaments, the dorsal ligament (*arrow*) must also be divided for full exposure. Further exposure to the caudate lobe is achieved by division of the short veins from the caudate lobe to the vena cava. (From Liau KH, Blumgart LH DeMatteo RP: Segment-oriented approach to liver resection. Surg Clin North Am 84:543-561, 2004.)



Blood supply of the common bile duct

Figure 116–4. Blood supply of the common bile duct showing the origin and general distribution of the periductal vasculature. (From Parke WW, Michels NA, Ghosh GM: Blood supply of the common bile duct. Surg Gynecol Obstet [now J Am Coll Surg] 117:47-55, 1963.)

Figure 116–3. *Left,* Full mobilization of the left lobe of the liver after division of the left triangular ligaments. After rotating the left lateral segment to the right, the caudate–caval ligament (D) is divided to exposing the short retrohepatic venous branches to the inferior vena cava. A, portal inflow pedicle; B, left hepatic vein; C, caudate lobe; E, main portal vein. *Right,* Division of caudate–caval veins. (From Liau KH, Blumgart LH, DeMatteo RP: Segment-oriented approach to liver resection. Surg Clin North Am 84:549, 2004.)

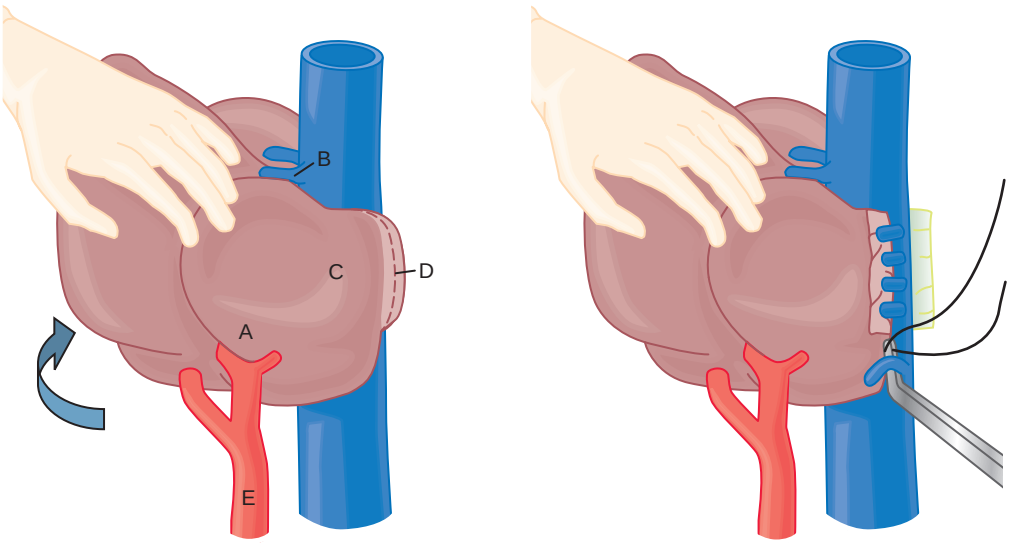


Table 116–1 Classification of Liver Injury (Moore)

Grade*		
I	Hematoma	Subcapsular, <10% of surface area
	Laceration	Capsular tear, <1 cm in parenchymal depth
II	Hematoma	Subcapsular, 10%-50% of surface area
		Intraparenchymal, <10 cm in diameter
	Laceration	1-3 cm in parenchymal depth, <10 cm in length
III	Hematoma	Subcapsular, >50% of surface area or expanding; ruptured subcapsular or parenchymal hematoma
		Intraparenchymal, hematoma >10 cm or expanding
	Laceration	>3 cm in parenchymal depth
IV	Laceration	Parenchymal disruption involving 25%-75% of the hepatic lobe or 1-3 Couinaud's segments in a single lobe
V	Laceration	Parenchymal disruption involving >75% of the hepatic lobe or >3 Couinaud's segments within a single lobe
	Vascular	Juxtahepatic venous injuries, i.e., retrohepatic vena cava/central major hepatic veins
VI	Vascular	Hepatic avulsion

*Advance one grade for multiple injuries, up to grade III.

Table 116–2 Classification of Liver Injury (Mirvis)

Grade	
I	Capsular avulsion, superficial laceration(s) less than 1 cm deep, subcapsular hematoma less than 1 cm in maximum thickness, periportal blood tracking only
II	Laceration(s) 1-3 cm deep, central-subcapsular hematoma(s) 1-3 cm in diameter
III	Laceration greater than 3 cm deep, central-subcapsular hematoma(s) greater than 3 cm in diameter
IV	Massive central-subcapsular hematoma greater than 10 cm, lobar tissue destruction (maceration) or devascularization
V	Bilobar tissue destruction (maceration) or devascularization

diaphragmatic defect into the thorax. If ultrasound is not available, the presence of intra-abdominal bleeding can be confirmed by diagnostic peritoneal lavage. Aspiration of gross blood justifies a decision to explore.

Exploration requires transporting the patient to the operating room (OR). Any unstable patient should be intubated. If one thinks about intubation, it should be done. Unless the OR is in the immediate vicinity, the patient should have a minimum blood pressure of 70 systolic and preferably 90 systolic before transfer to the OR. This should be accomplished by whatever means necessary, including rapid infusion of crystalloid and blood and administration of pressors. If these measures fail, the patient should be rushed to the operating room if it can be accomplished in 5 minutes. If more than 5 minutes is required, the aorta must be cross-clamped.

If the pathway of the penetrating weapon in a stable patient is such that a diaphragmatic injury is highly probable but there is no sign of diaphragmatic injury on the chest radiograph or CT scan, one option would be to laparoscopically examine and repair the diaphragm later when the patient is recovering.

BLUNT LIVER INJURY

After blunt trauma, hemodynamically stable patients may be observed once the CT scan shows that there is no extravasation of contrast, pseudoaneurysm, or laceration involving main hepatic veins (Fig. 116–5). We observe these patients in the hospital for 1 week. In a consensus meeting of the Eastern Association for the Surgery of Trauma (EAST),[7] it was determined that bed rest during this period is not necessary. In addition, the consensus of this group[7] was that as long as the patient is improving, there is no need for a repeat CT scan during the initial admission to the hospital. The EAST consensus group found that for grades I through V there is no relationship between the grade of liver injury and the need for operative management. In the event of hemodynamic instability, bleeding must be stopped by angiographic or surgical means.

Poletti et al. studied the indications for performing angiography in patients with lacerations caused by blunt trauma to the liver. They used the Mirvis classification (see Table 116–2) to describe the degree of injury to the liver.[6] In this study angiography was performed when extravasation of contrast or the presence of a pseudoaneurysm was demonstrated on CT. In the absence of extravasation or a pseudoaneurysm, they recommended

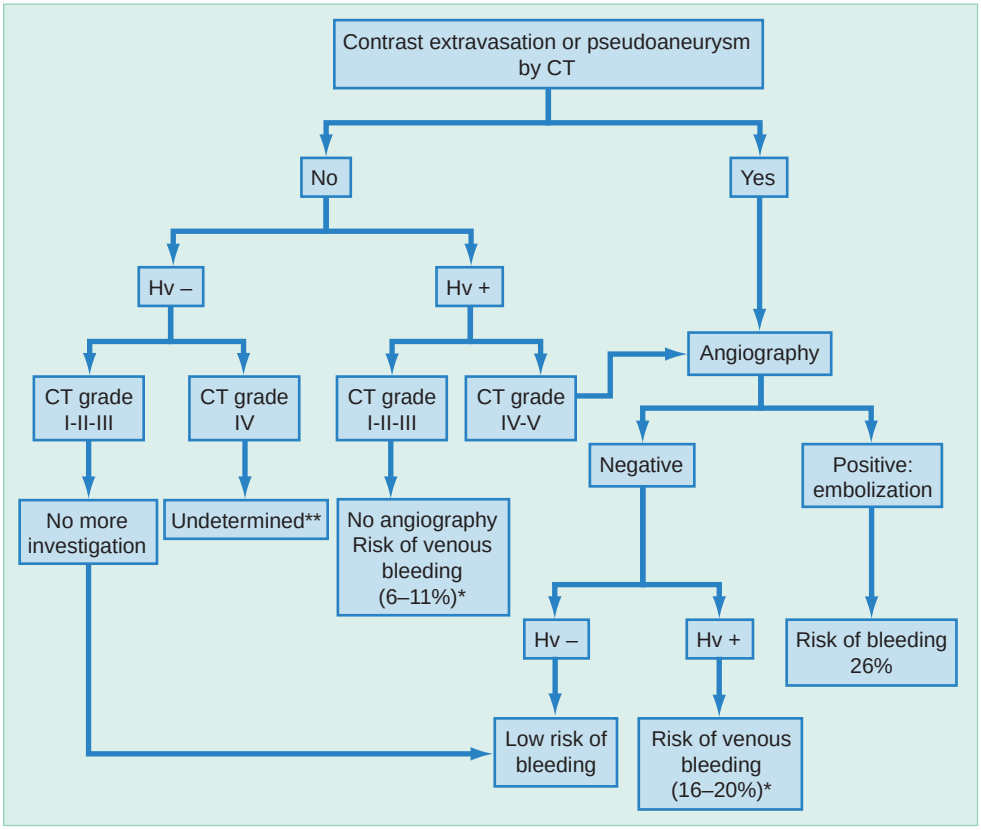


Figure 116–5. Decision algorithm for arteriography of liver lacerations. CT, computed tomography; Hv +, hepatic vein involvement; Hv –, no hepatic vein involvement. *Percentages were determined from the 72 patients in this study. **Only four patients were in this category and therefore the group was too small to determine statistical significance; none of these four patients rebled. (From Poletti, Mirvis SE, Shanmuganathan K, et al: CT criteria for management of blunt liver trauma: Correlation with angiographic and surgical findings. Radiology 216:418-427, 2000.)

angiography for a grade IV or V liver laceration involving a hepatic vein. They found a 6% to 11% incidence of bleeding in their study when grade I to III liver laceration involved a hepatic vein and therefore did not recommend angiography for these patients. Their decision algorithm for performing angiography is shown in Figure 116–5. Percentages are patients who bled after management recommended by this algorithm, probably from a venous source.

Operative management is required if the patient is hemodynamically unstable, if embolization fails to stop the bleeding, or when there is another injury that requires operative intervention.

INJURY TO THE BILIARY SYSTEM

Injury to the biliary system may not be initially detected because physical findings are typically absent until the process is in a late stage. The incidence of biliary injuries accompanying blunt liver trauma is 4% to 5%.[8,9] There is a significant potential to miss this injury on initial work-up because of a lack of sensitivity of CT scans or other modalities such as diagnostic peritoneal lavage. Even with initial laparotomy the incidence of missed bile duct injury is 12%.[10] The area of the bile duct most commonly injured in blunt trauma is at the superior portion of the pancreas posterior to the duodenum. Other areas of relative fixation that tend to be injured are the origin of the left hepatic duct and the bifurcation of the hepatic ducts.[11] In blunt trauma or proximity penetrating trauma, a Kocher maneuver is advisable. However, injury to the intrapancreatic portion of the common bile duct has also been reported. In this case the injury may not be apparent, even with a Kocher maneuver, and may not exhibit bile staining. Such injuries may be detected intraoperatively with a cholangiogram performed through the gallbladder.[12] When missed, bile duct injuries may take an insidious course that may span weeks, as described by Zollinger et al.[13] An intense chemical peritonitis leading to septic shock may develop in patients in whom a significantly large leak is diagnosed late. Therefore, it is important to diagnose bile duct injury early. Bile duct injury may be suspected in patients with increased serum bilirubin, a rising white cell count, or unexplained signs of sepsis. A hydroxyiminodiacetic acid (HIDA) scan is a sensitive test.[14] If positive, endoscopic retrograde cholangiopancreatography (ERCP) or transhepatic cholangiography should be performed to localize the leak.

Gallbladder Injuries

CT findings consistent with injury to the gallbladder are fluid around the gallbladder or in the subserosal area, wall thickening, a poorly defined or irregular wall contour, fluid within the lumen, contrast enhancement of the gallbladder wall or mucosa, medial displacement, a mass effect on the duodenum, and a free intraluminal mucosal flap.[15]

OPERATIVE MANAGEMENT

According to Longmire, the liver is a "hostile" organ because it welcomes malignant cells so warmly, because it bleeds so copiously, and because it is often the first organ injured in blunt abdominal trauma.[16] In trauma patients, who are often physiologically and hemodynamically compromised, a liver injury that requires surgery is especially daunting. The fundamental objectives of operative management are to stop the bleeding; maintain tissue perfusion intraoperatively; prevent or correct acidosis, coagulopathy, and hypothermia; and miss no injuries. If laparotomy is being carried out for a reason other than an injury to the liver and the liver is not bleeding, it is best to leave it alone.

A midline incision affords access, as well as the option of extension into a mediastinotomy if needed. Sufficient and reliable intravascular lines for rapid fluid administration should be in place. A cell saver should be in the room and ready to operate. All OR personnel should have on appropriate barrier protection. Two suctions should be ready. The room should be warm and fluid should be administered through a fluid warmer. Anesthetic agents that may precipitate a rapid drop in blood pressure, such as propofol, are not advisable in this setting. A midline fascial incision should be made quickly without initially going though the peritoneum. The anesthesiologist should be prepared for large blood loss and a drop in pressure when the peritoneum is entered. Once the peritoneal layer is opened, blood should be quickly evacuated and packs placed in the right upper quadrant. The other three quadrants are then packed. With the bleeding controlled, the anesthesiologist is given time to resuscitate the patient before removing the packs. In the interim, any bowel spillage is controlled. The packs are removed from the lower quadrants and then from the left upper quadrant. If the spleen is lacerated, it is resected. Packs are then removed from the right upper quadrant. If there is a liver laceration that can be controlled by manual compression, such compression should be maintained for 20 minutes. It may be helpful to mobilize the liver by releasing it from its attachments. During this period a blood sample should be sent for a prothrombin time, partial thromboplastin time, and platelet count, and any coagulopathy should be quickly corrected. Intravascular volume should be corrected and the patient should be warmed. If the bleeding stops, no further treatment is needed and the abdomen should be closed. If the bleeding cannot be controlled with compression alone, a Pringle maneuver should be performed. If this stops the bleeding, bleeding points in the laceration can be identified by intermittently clamping and releasing the portal triad. Ligation of these vessels may be done with 3-0 or 4-0 silk or with hemostatic clips. How long the Pringle maneuver can be maintained is in dispute. In elective situations 1 hour has been shown to be tolerated. In patients in shock, however, the time during which a Pringle maneuver can be tolerated may be shortened because of the presence of ischemia. Some surgeons intermittently release the clamp from the portal triad to minimize any ischemic effects. At any rate, 30 minutes of portal triad clamping appears to be well tolerated.[3]

If control is not achieved with compression or a Pringle maneuver, the bleeding is coming from either an aberrant hepatic artery or the hepatic veins. The aberrant vessel might be in the lesser omentum and controlled there if found. Deeply placed liver sutures can be used to close the laceration. These sutures should be properly placed so that they encompass the full depth of the wound. Leaving dead space increases the possibility of development of an abscess or biloma. This may be avoided by mobilizing the omentum and placing it into the laceration, followed by closure of the laceration with 0 chromic catgut suture on a large curved needle. Liver sutures should not be tied too tightly to avoid pulling them through the parenchyma or causing necrosis. With the right lobe mobilized, added hemostasis can be provided by compression of the right hepatic vein.

When the aforementioned measures are not successful, the liver should be packed. This decision should be made as quickly as possible. Laparotomy pads are rolled and the packs are placed so that the liver laceration is closed (Fig. 116–6). Placement of packs inside the laceration should not be done because it might extend the laceration. However, in patients with massive bleeding, the packs may have to be placed in the laceration.

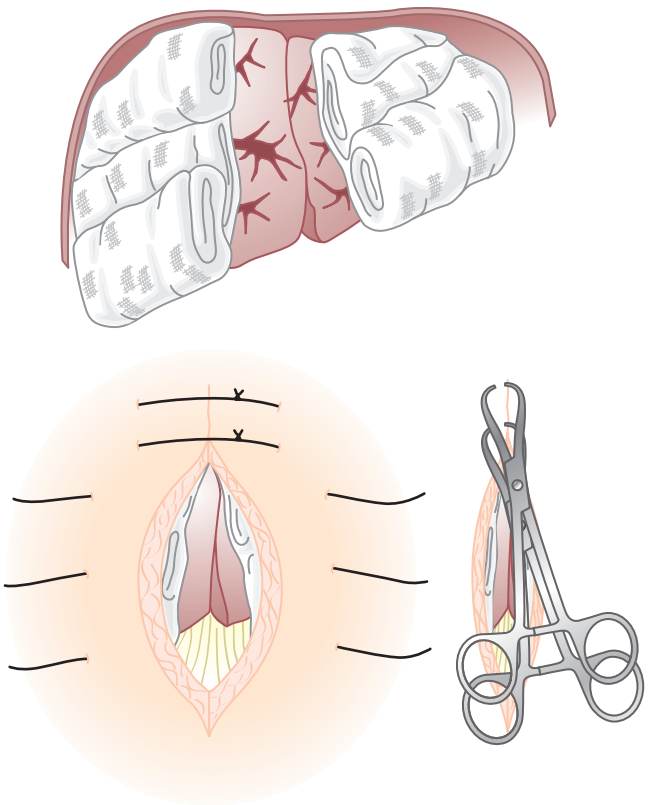


Figure 116–6. Placement of liver packs over a laceration of the right lobe while avoiding insertion of the lap pads into the incision. (From Donovan AJ: Trauma Surgery. St Louis, CV Mosby, 1994, p 127.)

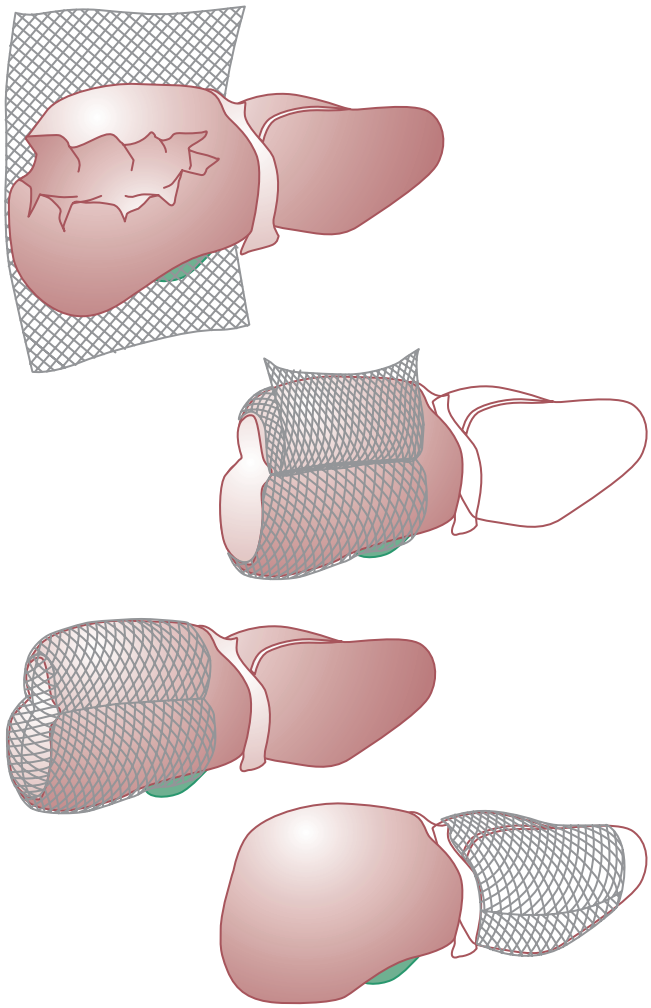


Figure 116–7. Absorbable mesh is wrapped around the mobilized liver and sutured to provide the tension necessary for a tamponade effect. (From Parks RW, Chrysos E, Diamond T: Management of liver trauma. Br J Surg 86:1121-1135, 1999.)

Figure 116–8. Balloon made from a red rubber catheter and a Penrose drain to tamponade bleeding in a bleeding tract. (From Fabian TC, Bee TK: Liver and biliary tract trauma. In Moore EE, Feliciano DV, Mattox RL [eds]: Trauma, 5th ed. New York, McGraw-Hill, 2004, pp 637-662.)

Adequate mobilization of the liver may enable placement of packs around rather than in the laceration. Nonetheless, it must never be forgotten that the first priority is to stop the bleeding and stabilize the patient. Care should be taken to minimize compression of the vena cava. Abdominal compartment syndrome can be avoided by temporary abdominal closure. The packs should be removed as soon as optimal intravascular perfusion is achieved and hypothermia, coagulopathy, and acidosis are corrected. Leaving the packs in for more than 48 hours markedly increases the probability of local infection and sepsis.

Wrapping the liver with absorbable mesh may be an alternative to packing (Fig. 116–7), except for lacerations involving the retrohepatic vena cava. The mesh is placed around the mobilized liver, and tension on the liver is created by suturing the mesh around it. An advantage of mesh wrap is that there is no need for a second operation to remove it, as is required with packs. When there is continued bleeding from a long bullet tract, a Penrose drain may be tied to the distal and proximal ends of a red rubber catheter to which additional holes have been added. This may be inserted into the tract and inflated with contrast to tamponade the bleeding (Fig. 116–8).

When the liver is avulsed from the hepatic veins or vena cava, hemostasis may not be achieved with packing or any of the other aforementioned measures. This situation must be recognized quickly so that a decision to isolate the liver can be made and the time that the patient is unstable is minimized. The Shrock shunt, which entails placing an endotracheal or chest tube through the right atrium to the vena cava just above the renal vessels, has lost favor because it is more difficult to perform than other methods and has not been demonstrated to be superior. We favor exclusion by clamping the vena cava. To do this the supradiaphragmatic vena cava is approached via a sternotomy. The infradiaphragmatic vena cava is approached by performing a Kocher maneuver to expose the vena cava superior to the renal vein. Vascular clamps or tourniquets are placed on both ends of the vena cava and on the porta hepatitis (Fig. 116–9). It is important for the anesthesiologist to rapidly replenish intravascular volume during this time through access located above the cross-clamped vena cava, such

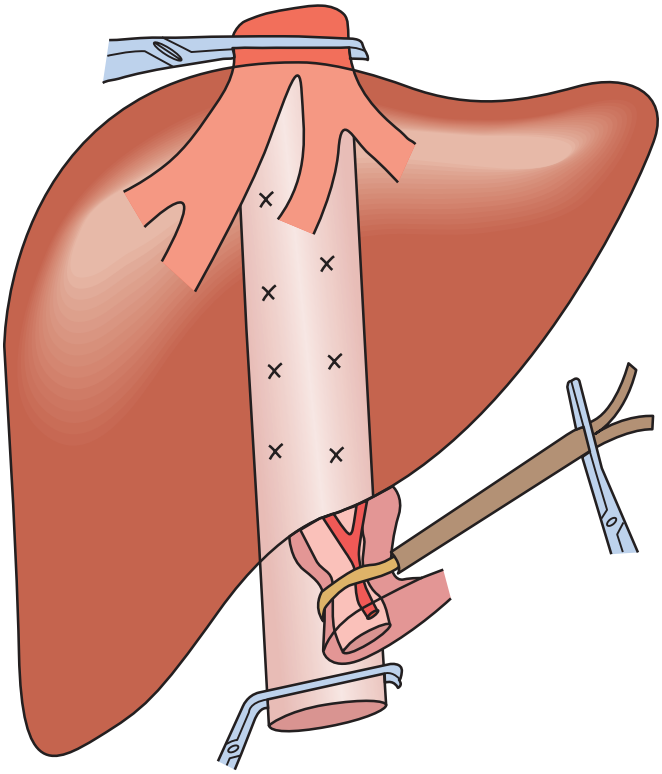


Figure 116–9. Vascular isolation of the liver. (From Abdalla EK, Noun R, Belghiti J: Hepatic vascular occlusion: Which technique? Surg Clin North Am 84:563-585, 2004.)

as the internal jugular or subclavian vein, so that the heart is not empty while the liver is isolated. Otherwise, ventricular fibrillation will ensue. The aorta is clamped if there is bleeding from the aorta or one of its branches. If possible it is best to avoid the severe hypoperfusion that occurs when the aorta is cross-clamped. However, to perfuse the brain and coronary arteries, the aortic cross-clamp might be needed until the anesthesiologist can catch up with the volume as the bleeding is controlled. With the liver totally isolated, the venous source of bleeding can be addressed.

Débridement

Whenever the patient is sufficiently stable, either during the initial or subsequent operation, necrotic tissue and debris should be removed. Leaving necrotic tissue increases the incidence of abscesses, sepsis, bilomas, and fistulas. Debris may consist of clothing, shotgun pellets, wadding, or necrotic liver. A necrotic liver may be débrided by nonanatomic or anatomic resection. In nonanatomic resection, parenchyma is removed with a combination of techniques, including the placement of deep liver sutures parallel to the direction of incision, crush clamping, and finger fracture. Raw surface hemostasis can be obtained with argon beam coagulation, Surgicel, fibrin glue, or other hemostatic materials.

Unstable patients may require nonanatomic resection to control bleeding. In such cases, removal of bleeding liver is a completion resection. When débridement is best served by anatomic resection, a surgeon with experience performing liver resection may be needed, which in most institutions would be a hepatobiliary or liver transplant surgeon. For lacerations of the right lobe, the right hepatic vein can be isolated by continuing the medial dissection of the right triangular ligament and the right anterior and posterior coronary ligaments. The vein can be isolated and ligated in its extrahepatic segment. The portal triad is dissected to isolate and ligate the right portal vein and artery. Once vascular control is achieved, an incision is made to the right of the line between the gallbladder fossa and the left side of the inferior vena cava. The capsule is incised with cautery and the parenchyma is divided.

Resection of the left segments is performed by dividing the left triangular and coronary ligaments, as well as the falciform ligament. The left hepatic vein branches that drain these segments (II and III) are ligated, followed by parenchymal dissection as mentioned earlier. A formal left hepatectomy would include segment IV, as well as III and II. Vascular control of this lobe is achieved by dividing the left hepatic vein at a point where it is separate from the middle hepatic vein. Branches of the left hepatic vein to segment IV are ligated separately. The left portal vein and left hepatic artery are dissected out and ligated. After vascular control is attained, the capsule is divided along a line of vascular demarcation and the parenchyma divided.

The extent of surgery that is performed is dictated by the state of the patient. If coagulopathy, acidosis, hypothermia, and poor perfusion are advanced, it is best to simply pack, resuscitate the patient, and return at a later time to perform additional procedures as necessary. At times it is not possible to completely stop the bleeding by operative means. In such cases the patient might benefit from postoperative angiography.

Biliary Trauma

Biliary tract injuries are unusual. Of 10,500 consecutive trauma admissions reported by Dawson et al., only 1 was due to an injury to the bile duct.[17] Bile drainage may not be noted in the porta hepatis. Therefore, a routine Kocher maneuver is recommended. An intraoperative cholangiogram will decrease the probability of missing this injury. If bile injury is detected, it should be fixed, except in a damage control setting, in which case drainage must suffice. It is important to fix the damaged duct before local inflammation and sepsis develop. In more stable circumstances, after débridement the decision becomes whether to primarily close the duct over a T-tube or perform a biliary-enteric anastomosis with a Roux-en-Y limb. It is critical to preserve the ductal blood supply at 3 and 9 o'clock around the duct. If 50% or more of the duct diameter is transected, success is greater with a duct-to-enteric rather than a primary anastomosis.[3] One of the problems in traumatic biliary injuries is the small size of the duct. The duct orifice can

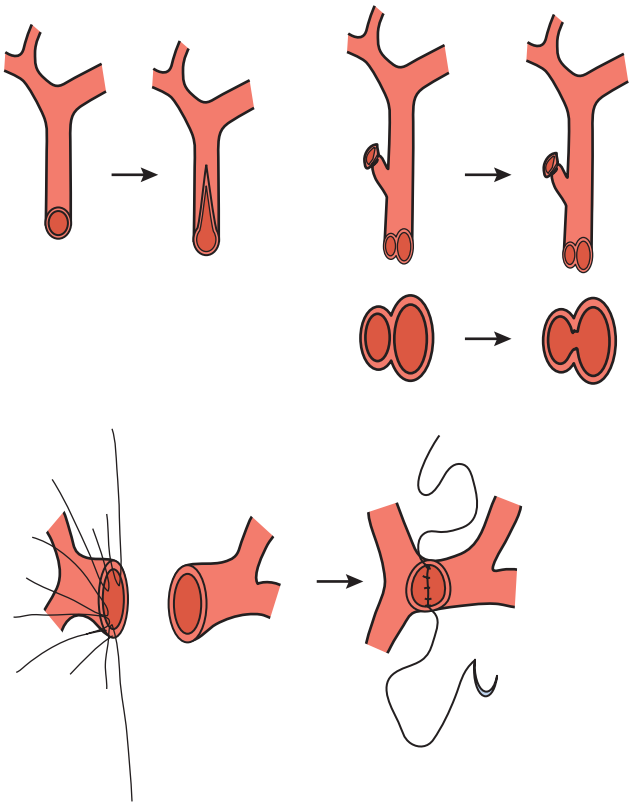


Figure 116–10. Various techniques for enlarging a small bile duct. (From Taylor BR, Lange B: Biliary Tract Procedures in ACS Surgery: Principles and Practice. WebMD Corporation, 2002, p 738.)

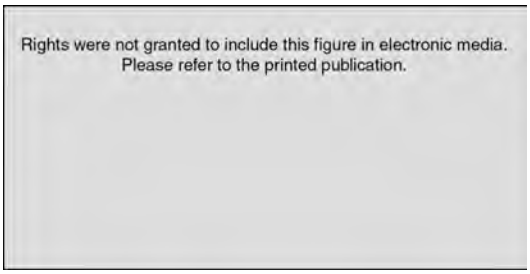


Figure 116–11. Anastomosis between the left hepatic duct and a Roux-en-Y limb (From Thal ER, Weigelt JA, Carrico CJ: Operative Trauma Management. New York, McGraw-Hill, 2002, p 267.)

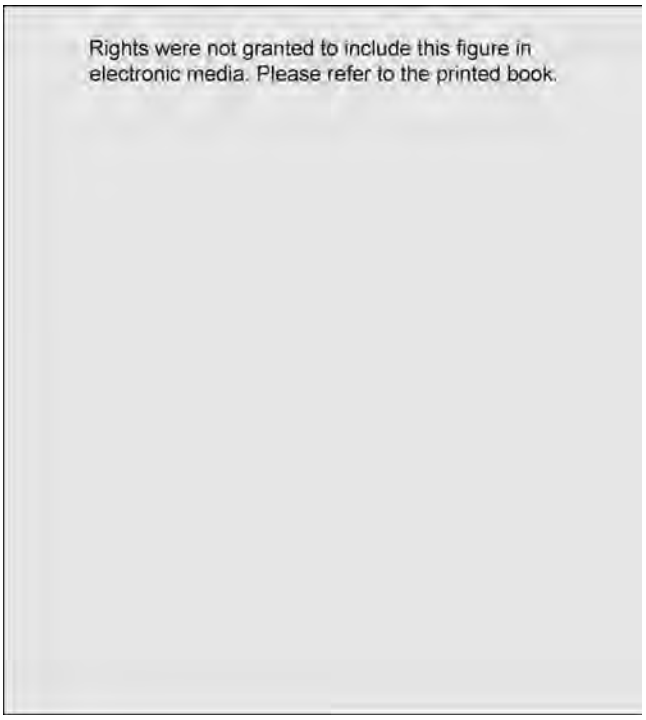


Figure 116–12. Anastomosis of the dome of the gallbladder to ensure bile drainage when the common bile duct is small. (From Donovan AJ: Trauma Surgery. St Louis, CV Mosby, 1994, p 97.)

be enlarged by methods shown in Figure 116–10. Anastomosis of the left hepatic duct to a Roux-en-Y limb is shown in Figure 116–11. Another technique is to anastomose the dome of the gallbladder to the Roux-en-Y limb, in addition to the duct-enteric anastomosis (Fig. 116–12). Before doing this the patency of the cystic duct can be ascertained by injecting contrast into the gallbladder. Leaving a stent fashioned from a pediatric nasogastric tube in the biliary duct anastomosis and bringing it out through a transjejunal or transhepatic route to the skin will help ensure patency (Fig. 116–13). A simpler method is to stent the anastomosis with a T-tube.

Gallbladder Injury

Cholecystectomy should be performed for most injuries to the gallbladder. A repair of a gallbladder laceration is likely to leak. An alternative to cholecystectomy in a damage control mode is placement of drains or a cholecystostomy tube with drainage.

Total Hepatic Resection

Unfortunately, in a few patients the liver damage is extraordinary and control of bleeding is not possible unless a total hepatectomy is performed. In these cases an end-to-side portocaval shunt is constructed to maintain intestinal blood flow. A liver transplant is then performed when a donor is available.[18]

NEW DEVELOPMENTS

Hemostasis Coagulation factors are typically replaced with fresh frozen plasma (FFP). The recently available factor VIIa corrects the coagulopathy almost as soon as it is administered intravenously and without the 30- to 45-minute delay required for FFP to be obtained.[19] Hemostasis may also be achieved with a new modified

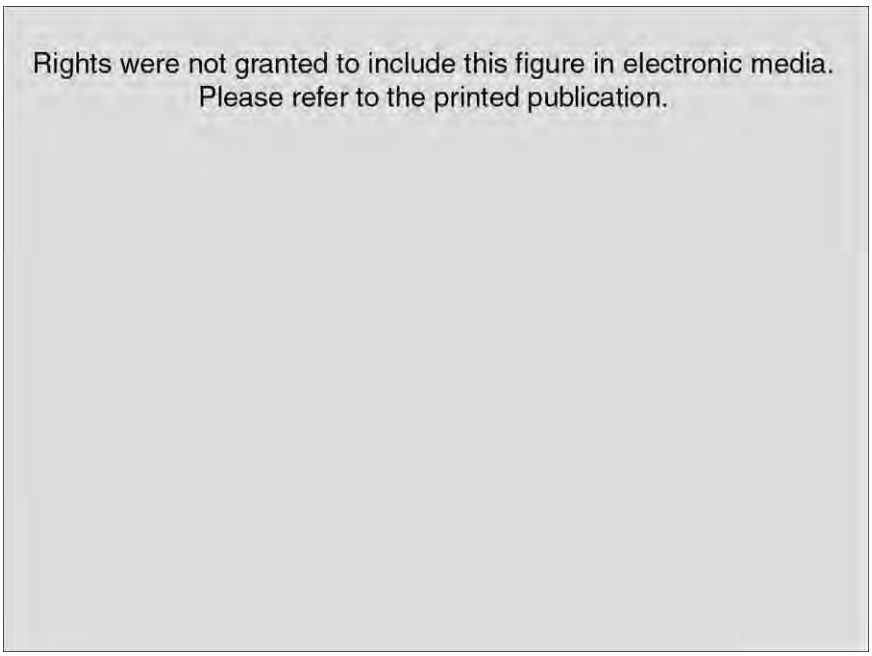


Figure 116–13. Anastomosis of a Roux-en-Y limb to the common bile duct and the insertion of a stent. (From Thal ER, Weigelt JA, Carrico CJ: Operative Trauma Management. New York, McGraw-Hill, 2002, p 267.)

rapid deployment hemostat bandage, which is effective even in patients with profound acidosis and hypothermia.[20]

Diagnosis Sharif et al. advocate the routine performance of a technetium scan in all patients with major blunt liver trauma. They concluded that routine scanning prevents sepsis and other complications that they encountered in patients whom they had not scanned routinely.[21]

Shock In cases of prolonged shock with loss of responsiveness to catecholamines, the vasculature may still respond to the intravenous administration of 40 IU of vasopressin.[22]

Technique Repairs of technically difficult biliary duct injuries have been performed with Gore-Tex grafts by Besozzi et al.[23]

CONCLUSION

Significant progress has been made over the past 15 years in the management of liver trauma. Nonetheless, there is still work to be done. Continued investigation of methods for detection of complications during nonoperative management, coupled with early definitive treatment, will result in a further reduction in morbidity. Research will lead to discoveries of methods for extending the time before irreversible shock develops, often exemplified by a patient who has a cardiac rhythm but is unresponsive to fluids or pressors. Optimistically, research now in progress will result in dramatically increasing the time before irreversible shock occurs. Current work is promising.

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Chapter

117

Diagnostic Operations of the Liver and Techniques of Hepatic Resection

Richard D. Schulick

LIVER BIOPSY

Percutaneous and Transjugular Liver Biopsy

It is often necessary to obtain liver tissue for either gross or microscopic examination to aid in diagnosis and treatment planning. Liver biopsy was originally described by Ehrlich in 1883 to determine glycogen stores in patients with diabetes.[1] There are multiple approaches for performing liver biopsy, including percutaneous, transjugular, laparoscopic, and open techniques. If the liver abnormality is relatively diffuse, then a percutaneous biopsy without image guidance can be contemplated. Image-guided percutaneous biopsies are required for focal lesions. When performed by experienced physicians, percutaneous hollow-needle liver biopsy is safe and reliable and can provide a cylindrical core of tissue, generally with good preservation of hepatic architecture and minimal artifact.

When a percutaneous biopsy is contraindicated, for example in the presence of significant ascites or with coagulopathy, a transjugular biopsy can be performed. A transjugular biopsy allows also the measurement of intrahepatic portal pressures. However, transjugular biopsies are often smaller and more fragmented than core biopsies, making pathologic assessment more difficult. Additionally, transjugular biopsy techniques cannot be used for small focal lesions, because of the inability to accurately place the needle.

If multiple percutaneous attempts have failed to obtain adequate material, if there is suspicion that a liver lesion is highly vascularized and prone to bleeding, if there is a need to obtain tissue from multiple sites, or if it is otherwise preferable to biopsy the liver under direct vision, then either laparoscopic or open liver biopsy may be used.

Laparoscopy and Biopsy

Laparoscopic examination of the liver is performed using standard laparoscopic equipment along with laparoscopic ultrasound probes. Laparoscopic examination consists of visual inspection, "palpation" using the instrumentation, and tissue biopsy. In general, fine-needle aspiration should be avoided during laparoscopy because of the superior results of core biopsies and the ability to directly address bleeding problems resultant from the more aggressive core biopsies. Superficial lesions can be directly biopsied under visualization using cupped biopsy forceps, and deeper lesions can be biopsied percutaneously under laparoscopic ultrasound guidance.

There has developed a great deal of interest in the role of laparoscopy in hepatobiliary malignancies to identify disease that is unresectable, thus avoiding unnecessary laparotomy. Hepatobiliary malignancies are associated with particularly high rates of unresectability, and although preoperative imaging is improving, it is relatively insensitive for small liver lesions, peritoneal disease, and sometimes even vascular invasion.

Patients with extrahepatic cholangiocarcinomas or gallbladder cancer often present with unresectable disease. Even with state-of-the-art preoperative imaging, they are often found to have occult metastatic disease at the time of exploration. In a series from Memorial Sloan-Kettering Cancer Center (MSKCC), the yield of laparoscopy for occult unresectable disease in gallbladder cancer was approximately 50%.[2] Even in patients whose gallbladder cancer had been incidentally identified after recent laparoscopic cholecystectomy, the yield of relaparoscoping the patient was about 20%. In the same study, the yield of staging laparoscopy for hilar cholangiocarcinomas was about 25%. For gallbladder

and hilar cholangiocarcinomas, the yield of staging laparoscopy and ultrasonography is relatively high and the value of surgical palliation is relatively low and therefore staging laparoscopy should be considered.

Because hepatocellular carcinoma rarely presents with peritoneal dissemination, the potential value of laparoscopy and ultrasonography should be its ability to identify additional liver lesions and the assessment of cirrhosis. Again, in the study from MSKCC the use of laparoscopy and ultrasound was able to avoid unnecessary laparotomy in 29% of patients who had cirrhosis or stage IVA disease.[2] However, if the patients had neither of these factors, then in only 5% of the patients did laparoscopy and ultrasonography avoid unnecessary laparotomy. In another series from Hong Kong, laparoscopy and ultrasonography was performed in 91 patients taken to the operating room for planned curative resection of liver tumors.[3] Laparoscopy and ultrasonography correctly identified 15 of 24 patients whose tumors subsequently proved unresectable. Of the 15 patients identified to have contraindications to resection, 11 had bilateral metastases, 6 had severe cirrhosis or inadequate liver remnant, 2 had main portal vein tumor thrombus, 1 had inferior vena cava (IVC) thrombus, and 1 had peritoneal metastases (some had multiple findings). Of the 9 patients with unresectable disease not detected by laparoscopy and ultrasonography, 3 had main portal vein tumor thrombus, 3 had involvement of adjacent organs, 2 had bilateral metastases, 1 had inadequate liver remnant, and 1 had IVC thrombus. Staging laparoscopy and ultrasonography is more likely to benefit patients with hepatocellular carcinoma who have cirrhosis and central lesions.

In one of the largest studies in 103 patients on the use of staging laparoscopy and ultrasonography for resection of colorectal metastases to the liver, only 14% of patients overall had unresectable disease identified, and only 10% were spared laparotomy.[4] An additional 8% of patients had unresectable disease missed by laparoscopy. The authors concluded that staging laparoscopy and ultrasound should be used selectively in patients at highest risk of having unresectable disease.

Open Liver Biopsy and Examination

An open liver biopsy can be performed through a limited right subcostal incision. The incision should be placed over the inferior edge of the liver but should be at least 3 cm below the costal margin to allow for adequate fascial closure. The liver can be examined both visually and by palpation, but care should be taken to not disturb any portosystemic collateral vessels. If these friable vessels are disrupted, or if the hepatic capsule is ruptured during examination, a major abdominal operation may be required to gain control. Visual inspection for gross evidence of cirrhosis, nodularity, abnormal color or texture, or neoplasm may be revealing. A laparoscopic ultrasound probe can be used through a small incision, or if the incision is large enough, the regular probe may be used. A wedge biopsy can be obtained using a No. 15 scalpel and removing a specimen measuring about 1 cm at its base. A core-needle biopsy can be obtained through the same site, directed deeper into the liver parenchyma but away from the porta hepatis. If significant bleeding is expected, hemostatic 2-0 chromic catgut or Vicryl mattress sutures can be placed in an interlock V shape outside the biopsy site prior to biopsy. Once the biopsies are taken, the base of the biopsy site is treated with the argon beam coagulator for hemostasis. The fascia should be closed with running permanent suture if ascites is anticipated. Similarly, the skin should be closed with a running long-lasting suture if ascites is anticipated.

INCISIONS FOR LIVER OPERATIONS

Subcostal Approach

Most hepatectomies can be accomplished via a right subcostal incision made 3 to 4 cm below the right costal margin with an upper midline extension in a supine patient. The right rectus abdominis muscle is completely divided, as are the medial portions of the external oblique, internal oblique, and transversus abdominis muscles. Depending on the exposure required, the incision can be made up to and beyond the midaxillary line between the costal margin and the iliac bone. This incision exposes the anterior and inferior surfaces of the right and left liver and provides good access to the porta hepatis. For exposure to the dome of the liver, a midline extension over and above the xiphoid is performed and the xiphoid removed. For even more exposure, the incision can be extended under the left subcostal area (Figs. 117–1 and 117–2). With this full incision, the surgeon has excellent exposure to the entire upper abdomen, including the liver as well as the retrohepatic and suprahepatic IVC. Because of the appearance when closed, this incision is often referred to as the *Mercedes incision*.

In extreme circumstances, a median sternotomy or right thoracotomy through the costal margin can even further increase access and exposure.

Midline Approach

The midline incision is sometimes used in thin patients, when a pelvic procedure such as low anterior resection is being performed at the same time, or if the hepatic resection will be limited to the left half of the liver. The patient is positioned supine. It does not generally afford good access to the retrohepatic vena cava, the right hepatic vein, or the right posterior sector of the liver until the liver is completely mobilized off the diaphragm and retroperitoneum. It is commonly used in exploration for trauma where hepatic injury may be found. If greater exposure is required, a median sternotomy or right thoracotomy through the costal margin can be performed.

Right Thoracoabdominal Approach

The thoracoabdominal incision is sometimes used in patients with large bulky lesions involving the right dome or right posterior sector of the liver. It gives the best

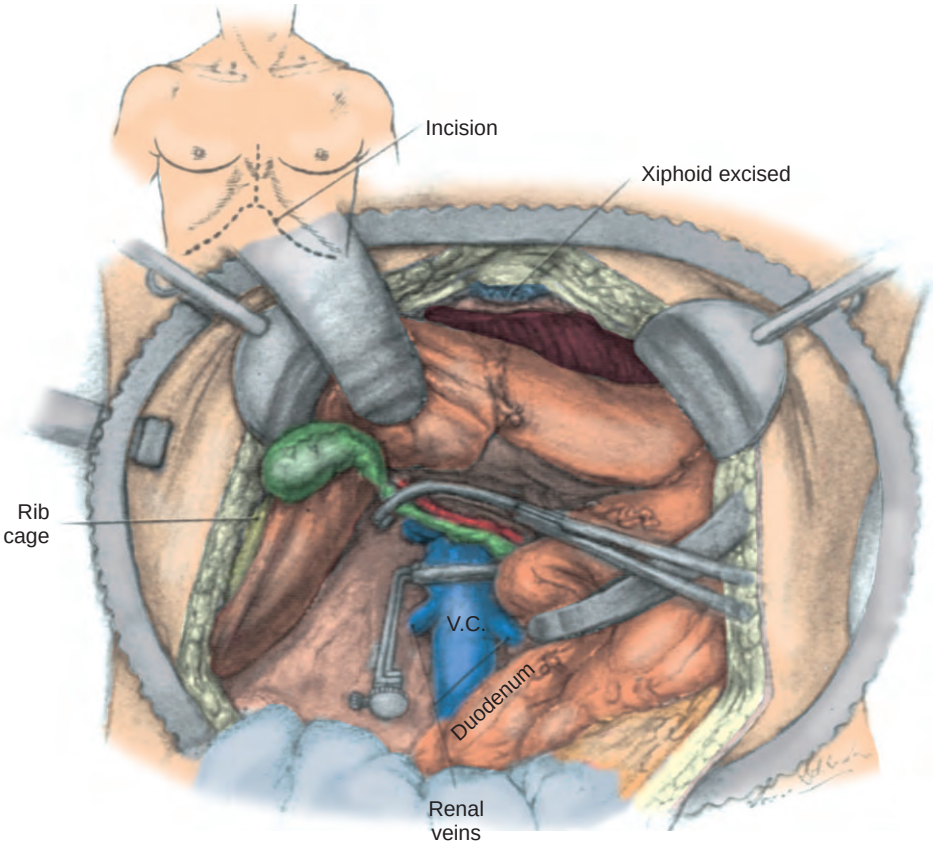

Figure 117–1. Bilateral subcostal incision with a short midline extension. This is a versatile incision appropriate for most major hepatic resections and portosystemic shunts. VC, vena cava.

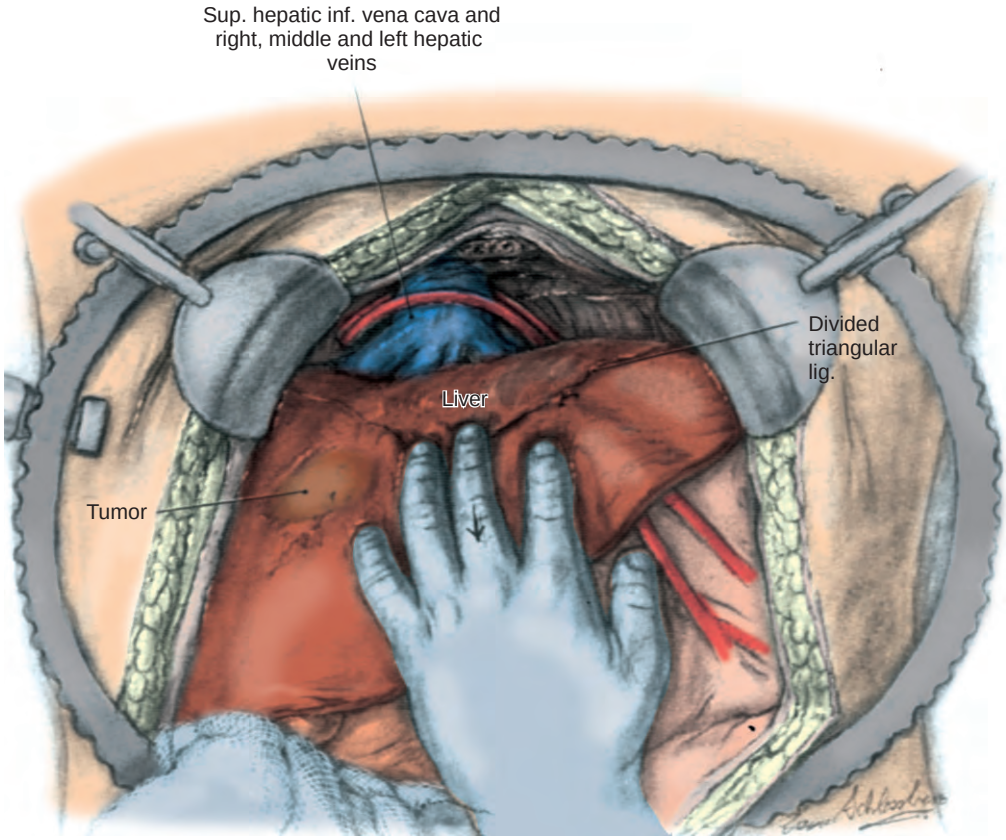

Figure 117–2. "Mercedes sign" incision. Excision of the xiphoid process and downward traction on the liver provide excellent exposure of the hepatic veins and suprahepatic inferior vena cava (Sup. hepatic inf. vena cava).

access to the suprahepatic and retrohepatic vena cava as well as the right hepatic vein. Additionally, it is sometimes used in instances of significant right diaphragmatic involvement. The patient is positioned on a bean bag with the chest in a lateral position but the hips at 45 degrees. The incision is made from the umbilicus to the right costal margin, and depending on the location of the lesion, the 7th, 8th, or even 9th rib interspace is opened. If keeping the right lung unventilated will help, then a double-lumen endotracheal tube should be used. The diaphragm should be incised circumferentially to avoid the neurovascular bundle supplying it. Care should be taken to leave 3 to 4 cm of diaphragm on the rib cage to allow for later closure.

MORPHOLOGIC AND FUNCTIONAL ANATOMY

It is important that the surgeon performing a hepatectomy intimately understands the anatomy of the liver. The reader is strongly encouraged to review Chapter 111 detailing the anatomy of the liver. However, a brief review and overview are re-presented to clarify this topic. The description and definition of the anatomic divisions of the liver have been revised and written about numerous times in the past 100 years.[5-12] At present, there is still confusion between the various hepatic anatomic nomenclatures in the literature. Based only on morphologic criteria and surface anatomy, the liver can be divided into right and left halves by forming a plane through the gallbladder fossa (Cantlie's line) and the IVC (Fig. 117–3). This plane approximates the true division between the right and left halves using the more strict definition of a plane through the middle hepatic vein and IVC, but the middle hepatic vein is not obvious by direct inspection of the surface. Further subdivisions of the right half of the liver into a right anterior section and a right posterior section are not possible based only on surface anatomy. The left half of the liver can be further subdivided into a left medial section and left lateral section based on the umbilical fissure and falciform ligament. The caudate of the liver is identified as lying posterior to the gastrohepatic ligament and emanating from a process of liver situated posterior to the main portal pedicle and anterior to the IVC.

The most widely accepted nomenclature of liver anatomy is based on Couinaud's description of the eight discrete anatomic segments of the liver (Fig. 117–4).[10] The eight segments of a liver can be determined using surface anatomy, the location of the three main hepatic veins, the location of the portal pedicle bifurcation, and the location of the umbilical fissure and falciform ligament. The right and left halves of the liver are delineated by a plane through the middle hepatic vein and IVC. Segments II, III, and IV lie to the left of this plane and form the left half of the liver. Segments V, VI, VII, and VIII lie to the right of this plane and form the right half of the liver. Segment I, or the caudate, is morphologically distinct from the two halves of the liver and emanates from a process of liver lying posterior to the portal pedicle and anterior to the IVC. Whereas the right and left halves of the liver derive blood supply from the corresponding right and left portal veins and hepatic arteries, respectively, segment I derives blood supply from both. Additionally, the right half of the liver has venous drainage mostly through the right and middle hepatic veins, and the left half of the liver has drainage mostly through the left and middle hepatic veins. Segment I, however, drains directly via small branches into the IVC.

The right half of the liver can be further subdivided using a plane through the right hepatic vein and the IVC. The liver anterior to this plane forms the right anterior sector of the liver, and liver posterior to this plane forms

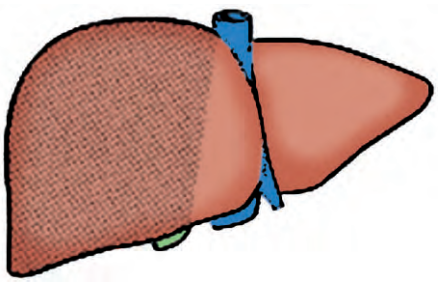

Figure 117–3. The liver can be divided into right and left halves by forming a plane through the gallbladder fossa (Cantlie's line) and inferior vena cava. (From Blumgart LH, Fong Y: Surgery of the Liver and Biliary Tract: Selected Operative Procedures. CD-ROM, 3rd ed. London, Harcourt, 2000.)

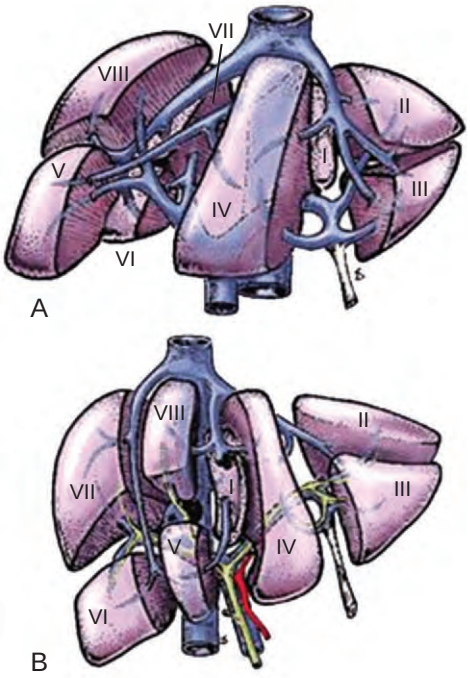

Figure 117–4. Couinaud's eight anatomic segments of the liver: anterior **(A)** and posterior **(B)** views. (**A** and **B,** From Blumgart LH, Fong Y: Surgery of the Liver and Biliary Tract: Selected Operative Procedures. CD-ROM, 3rd ed. London, Harcourt, 2000.)

the right posterior sector. The right anterior sector of the liver comprises segment V (caudal to the portal bifurcation) and segment VIII (cephalad to the portal bifurcation). The right posterior sector of the liver comprises segment VI (caudal to the portal bifurcation) and segment VII (cephalad to the portal bifurcation).

The left half of the liver can be further subdivided using a plane through the umbilical fissure and falciform ligament. Liver medial to this plane forms the left medial section of the liver or segment IV, and liver lateral to this plane forms the left lateral section of the liver. The left lateral section of the liver is further subdivided into segment II (closer to segment I) and segment III (closer to segment IV), which are supplied by separate portal pedicles from the umbilical fissure

PREOPERATIVE EVALUATION OF HEPATIC RESERVE

When a surgical resection is planned, the future remnant liver should be sufficient and healthy enough to regenerate and sustain the patient long term. Up to 70% to 75% of the hepatic volume may be resected with good recovery in patients with relatively normal hepatic parenchyma (without active hepatitis, cirrhosis, or metabolic defects), as long as the remnant liver has adequate portal venous and hepatic arterial inflow, adequate hepatic venous outflow, and adequate biliary drainage. Different groups have used various strategies to try to predict hepatic reserve, including the following:

- Child-Pugh score that assesses synthetic ability (albumin, prothrombin time, and ascites), bile excretory function (total bilirubin), and metabolic function (changes in mental status from ammonia retention) (Table 117–1)[13]
- Volumetric measurements of the liver and predicted liver remnant after resection based on three-dimensional reconstructions from computed tomographic scan and magnetic resonance imaging[14]
- Clearance of galactose or organic anionic dyes, such as indocyanine green[15-17]
- Tests of microsomal function, such as caffeine clearance,[18] lidocaine clearance,[19] or aminopyrine breath tests[20,21]

None of these tests or strategies has demonstrated better ability to predict outcome than another. Many hepatobiliary centers in the United States rely simply on the Child-Pugh score and the prediction of adequate liver remnant volume after resection. In select circumstances it may be of benefit to perform portal vein embolization to the right or left half of the liver in the hopes of obtaining compensatory hypertrophy of the other side prior to resection.[22,23] This is especially useful when the predicted liver remnant after resection is small or if the patient has an underlying hepatic dysfunction that may not allow the remnant to fully regenerate and sustain the patient long term. The disadvantage of portal vein embolization includes the need to wait 4 to 6 weeks prior to resection to allow the compensatory hypertrophy to occur. Additionally, the surgeon must commit to taking out one or the other side without the benefit of intraoperative evaluation.

Table 117–1 Child-Pugh Classification*

	Score		
Parameter	*1*	*2*	*3*
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Ascites	Absent	Moderate	Severe
Encephalopathy	Absent	Moderate	Severe
Prothrombin time			
Seconds prolonged	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

*The Child-Pugh classification:
Grade A = 5-6 points
Grade B = 7-9 points
Grade C = 10-15 points
INR, international normalized ratio.

ONCOLOGIC CONSIDERATIONS IN HEPATIC RESECTION

The decision of whether and when to operate is as important as the technical details of successfully performing a hepatectomy. In making these decisions it is important to consider the diagnosis. For example, a solitary liver lesion presenting in an elderly patient with a rising carcinoembryonic antigen level and a recent history of a resected colon cancer should be approached and treated differently from a young woman with a solitary lesion with radiologic characteristics of a focal nodular hyperplasia. It is also important to consider the biology of the tumor within the patient. An extreme example of this are two patients where the first re-presents with a solitary hepatic colorectal cancer metastasis 4 years after resection of the primary and the second who presents with 12 synchronous lesions in the liver at the time of diagnosis of the primary. The former patient is much more likely to benefit from surgical resection than the latter patient.

It is also important to consider if the goal of resection is curative or palliative. Patients with neuroendocrine tumor metastatic to the liver may be debulked of disease, but the disease is rarely totally eradicated. If the tumor is functional and difficult to control medically, then there may be significant benefit to debulking. Even if the tumor is not functional there is some evidence that surgical debulking of liver metastases in carefully selected patients may benefit long-term survival.[24,25] It is important to exclude other distant extrahepatic disease with a reasonable number of preoperative tests. For example, prior to performing hepatic resection for colorectal cancer metastases, it is often helpful to obtain a positron emission tomographic scan to exclude extrahepatic

metastases.[26,27] For patients with neuroendocrine tumors metastatic to the liver, it is often helpful to obtain an octreotide scan to survey for extent of disease.[28] These tests allow better selection of patients most likely to benefit from hepatic resection.

The comorbid status of the patient is also important. Extended hepatic resections with or without biliary reconstruction can exert a toll on even very fit patients. It is important to identify patients who may have difficulties with hepatic regeneration such as those with a history of hepatitis, cirrhosis, or metabolic disorders. Patients with suspected cardiopulmonary disease should undergo appropriate preoperative evaluation and treatment prior to hepatic resection. Finally, other effective treatments and the optimal sequence of treatments should be considered. For example, in the treatment of hepatocellular carcinoma the possibilities include liver transplantation, liver resection, liver ablation (radiofrequency, cryotherapy, or ethanol), embolization, and systemic chemotherapies. A patient with poor hepatic reserve due to chronic liver disease and a single small hepatocellular carcinoma may be best treated with liver transplantation, whereas a patient with normal liver parenchyma and a resectable lesion may be best treated with liver resection. Additionally, some patients may best be treated with ablative techniques, especially if they have extremely small lesions that are easily approached percutaneously. Some patients are treated with a combination of these modalities. For example, some patients will first be treated with ethanol ablation and embolization prior to liver transplantation or resection for hepatocellular carcinoma.

INTRAOPERATIVE ASSESSMENT

Incisions for hepatic resections usually involve a right subcostal incision. Significant exposure can be obtained with a trifurcated incision as previously discussed. However, in most cases, all that is needed is an extended right subcostal incision with a vertical extension to the base of the xiphoid. The xiphoid may be resected for better exposure. For bulky lesions on the left or if the left half of the liver extends significantly to the left upper quadrant, a left subcostal component can be added. In rare circumstances, especially for lesions high on the dome, an intercostal extension or even median sternotomy may improve exposure. This is especially true for lesions involving the hepatic vein and IVC confluences.

Several versions of self-retaining costal margin retractors or ringed retractors are available that provide good access to the subdiaphragmatic surface. For complete intraoperative ultrasonography and for major resections, mobilization of the liver is required. The round ligament is divided and the falciform ligament divided close to the liver parenchyma. The right and left triangular ligaments are then divided to expose the bare areas of the liver. During exposure of the bare areas of the liver, care should be taken to not enter the right or left chest through the ligamentous portions of the diaphragm as this will cause excessive bellowing of the diaphragm and poor exposure until a chest tube is placed on that side. Additionally, the right and left phrenic veins are very superficial on the hemidiaphragms and are prone to injury. The right colon can be mobilized out of the field by dividing Gerota's fascia over the right kidney and pulling the hepatic flexure inferiorly. To completely assess the caudate lobe, the overlying lesser omentum should be divided. Care should be taken to not inadvertently divide a replaced or accessory left hepatic artery running in this plane. After mobilization, a thorough bimanual examination should be performed and intraoperative ultrasonography used.

Hepatic ultrasonography can be quite useful in identifying lesions within the hepatic parenchyma, and at most centers intraoperative ultrasonography is used routinely to assess the anatomy of the pedicles (portal vein, hepatic artery, bile duct), the hepatic veins, and the hepatic parenchyma. It is both useful to further identify and characterize lesions within the hepatic parenchyma and to delineate their relationships within the eight anatomic segments of the liver. Additionally, it is often helpful to delineate proximity of lesions to major vascular structures and to survey for abnormal anatomy in planning a resection. With radiofrequency ablation more commonly employed, ultrasound has become indispensable in directing its use.

Using the ultrasound probe, the main portal pedicle is identified within the hepatoduodenal ligament. It is followed cephalad to the portal bifurcation into the main right and left pedicles. The portal pedicles are invested with Glisson's capsule and have a very echogenic covering to them in contrast to hepatic vein branches. The main right portal pedicle is followed toward the right, where it gives off an anterior and posterior branch (Fig. 117–5). The right anterior branch gives off separate pedicles to segment V (caudal) and to segment VIII (cephalad). The right posterior branch gives off separate pedicles to segment VI (caudal) and to segment VII (cephalad). The main left pedicle is usually much longer and courses intact to the base of the umbilical fissure before branching into various segmental pedicles. At the

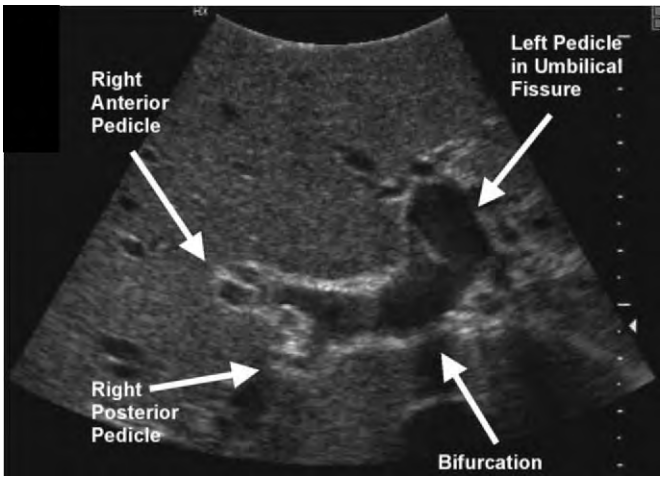

Figure 117–5. Intraoperative ultrasound image of bifurcation of the main portal pedicle into the right and left branches.

base of the umbilical fissure the main left pedicle courses anteriorly toward the round ligament and gives off a pedicle to segment IV medially and pedicles to segments II and III laterally. Next, if the bare areas around the junction of the hepatic veins and IVC have been well mobilized, the hepatic veins can easily be visualized using intraoperative ultrasonography (Fig. 117–6). As described previously, usually a larger right hepatic vein can be delineated and smaller left and middle hepatic veins joining into a common trunk before emptying into the IVC are seen. Commonly, an umbilical hepatic vein branch can be identified coursing between the middle and left hepatic veins and running under the falciform ligament. Not uncommonly, significant accessory right hepatic veins can be seen emptying from the posterior surface of the right liver directly into the IVC as it courses posterior to the liver. The identification of these accessory right hepatic veins is quite important for both vascular control and preservation of outflow from the liver. Finally, the hepatic parenchyma is systematically scanned to identify lesions within the liver. It is sometimes useful to adjust the ultrasound settings on a known lesion defined preoperatively to maximize the echogenicity in the hopes of identifying other occult lesions not identified preoperatively.

GENERAL MANEUVERS FOR HEPATECTOMY

The porta hepatis can be dissected to identify the main bifurcations of the hepatic artery, bile duct, and portal vein and to allow individual ligation of these. Ligation of the hepatic artery and portal vein to one side causes the liver parenchyma to demarcate between the right and left liver. Greater exposure of the cephalad aspect of the hepatic hilum and exposure of a high or intraparenchymal bifurcation of portal triad structures may be aided by lowering the hilar plate (Fig. 117–7) and dividing Glisson's capsule at the most inferior border of segment IV.

Control of the inflow hepatic artery and portal vein branches to a specific anatomic section of the liver may also be obtained by pedicle ligations in which small hepatotomies are made around the main right pedicle, main left pedicle, right anterior pedicle, or right posterior pedicle after identification with ultrasound (Fig. 117–8).[29] The pedicle of interest can be dissected out bluntly with a right angle or by finger fracture. The pedicle should be test clamped atraumatically to confirm that it does indeed supply the area of liver of interest. If the proper pedicle is clamped, the appropriate portion of the liver (i.e., right half, left half, right anterior section, or right posterior section) should demarcate. Once confirmed, it can be divided. Alternatively, the specific inflow pedicles can be divided as they are encountered during parenchymal transection. With this technique, hemorrhage can be minimized by intermittent portal inflow occlusion accomplished by atraumatically clamping the main portal triad within the hepatoduodenal ligament (Pringle's maneuver).

Outflow control of the hepatic veins can be obtained at differing time points depending on the situation. If there is a sufficient length of extraparenchymal hepatic vein, often it is easier to divide the hepatic vein early and prior to parenchymal transection (but after inflow

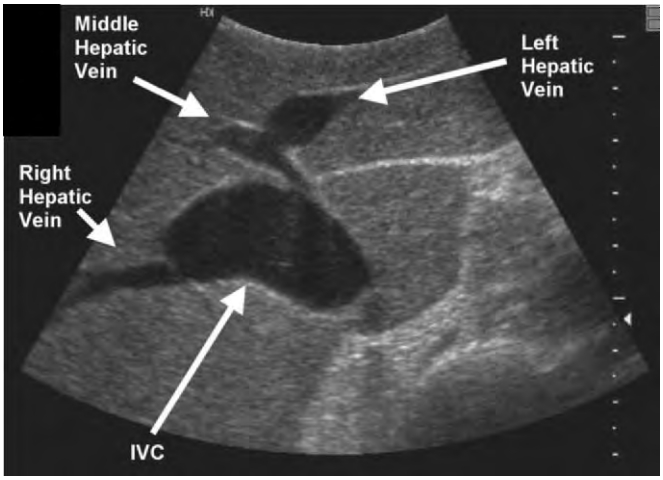

Figure 117–6. Intraoperative ultrasound image of the three main hepatic veins. The left and middle hepatic veins often join together before emptying into the inferior vena cava (IVC).

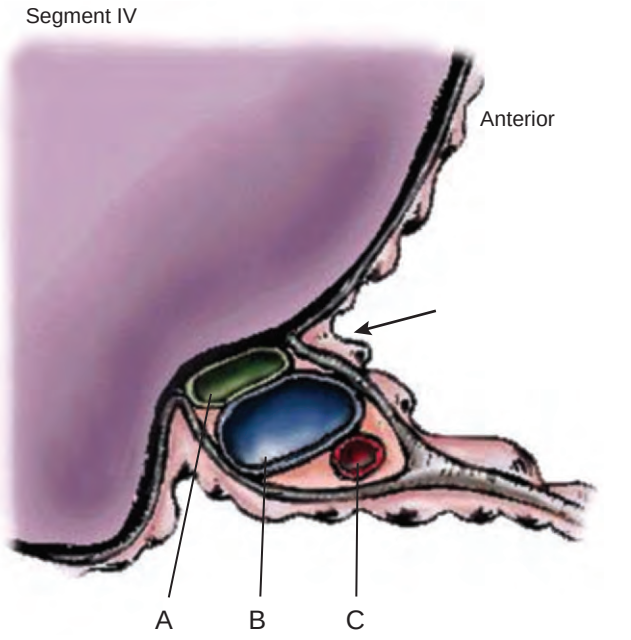

Figure 117–7. The hilar plate of the liver can be "lowered" by dividing Glisson's capsule at the lowest edge of segment IV. This maneuver gains access to the most cephalad portion of the bifurcation of the porta hepatis. A, B, and C are the left hepatic duct, portal vein, and hepatic artery, respectively. (Adapted from Blumgart LH, Fong Y: Surgery of the Liver and Biliary Tract: Selected Operative Procedures. CD-ROM, 3rd ed. London, Harcourt, 2000.)

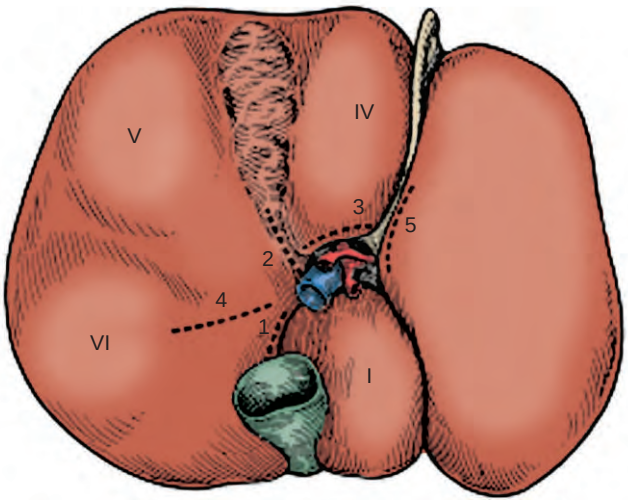

Figure 117–8. Sites for intraparenchymal portal pedicle ligation. Incisions at 1 and 2 allow isolation of the main right pedicle. Incisions at 1 and 4 allow isolation of the right posterior pedicle. Incisions at 2 and 4 allow isolation of the right anterior pedicle. Incisions at 3 and 5 allow isolation of the left pedicle. (From Fong Y, Blumgart LH: Useful stapling techniques in liver surgery. J Am Coll Surg 185:93-100, 1997.)

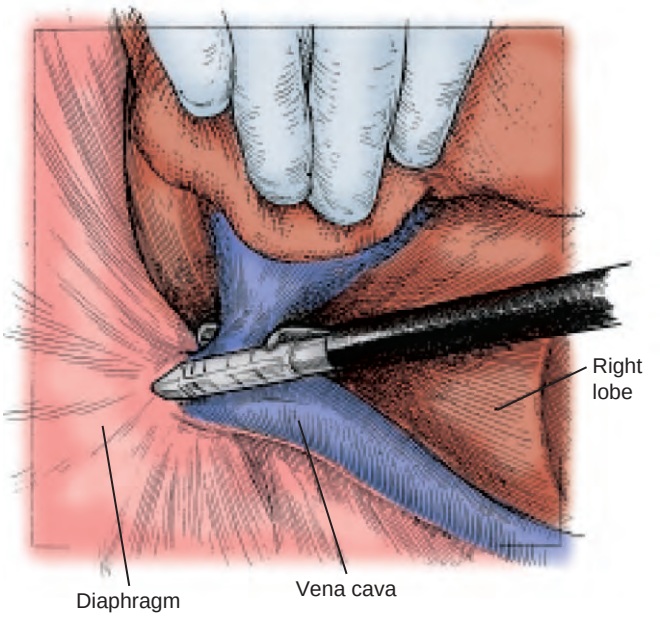

Figure 117–9. The right hepatic vein can be divided with the aid of an endoscopic stapling device with a vascular load. (From Fong Y, Blumgart LH: Useful stapling techniques in liver surgery. J Am Coll Surg 185:93-100, 1997.)

control). If the extraparenchymal portion of the hepatic vein is short (or absent), it may be easier and safer to divide the hepatic vein or veins within the hepatic parenchyma after most of the parenchymal transection has been performed. The use of endoscopic vascular stapling devices has made the ligation of hepatic veins whether extraparenchymally or intraparenchymally much quicker and safer (Fig. 117–9).[29] Another technique used to minimize blood loss is a low central venous pressure technique where the central venous pressure of the patient is kept low (<5 mm Hg) until after parenchymal transection.[30] Once the parenchymal transection is complete and the bleeding is controlled, the patient is made euvolemic. This minimizes the bleeding coming from the hepatic vein branches.

MAJOR HEPATECTOMIES

To develop a uniform nomenclature understood by all, the American and International Hepato Pancreato Biliary Association (AHPBA and IHPBA, respectively) have adopted the Brisbane 2000 terminology of hepatic anatomy and resections.[31] Right hepatectomy or right hemihepatectomy involves the resection of segments V through VIII; left hepatectomy or hemihepatectomy involves the resection of segments II through IV. Either of these resections may or may not include resection of segment I, which should be stipulated. Extended right hepatectomy involves the resection of segments IV through VIII; extended left hepatectomy involves the resection of segments II through V plus VIII. Again, either of these extended resections may or may not include resection of segment I, which should be stipulated.

Right anterior sectionectomy includes segments V and VIII. Right posterior sectionectomy includes segments VI and VII. Left medial sectionectomy removes segment IV. Left lateral sectionectomy includes segments II and III. A segmentectomy involves the resection of a single segment, and a bisegmentectomy involves the resection of two contiguous segments.

The steps involved in major hepatectomies include optimal exposure, vascular inflow control, vascular outflow control, and parenchymal transection. Vascular inflow control may be obtained by directly ligating the main right or left branches of the hepatic artery and portal vein in the hilum and/or by intermittent 10- to 20-minute intervals of a Pringle maneuver with 3 minutes in between to re-establish blood flow. I prefer to encircle the hepatoduodenal ligament twice with a $^1/_4$-inch Penrose drain that is tightened and clamped for a Pringle maneuver. Alternatively, pedicle ligations can be performed as described previously, or the pedicles can be controlled as they are encountered during parenchymal transection. I prefer to obtain vascular inflow by ligating the appropriate vessels in the hilum or by pedicle ligations and to supplement this with intermittent Pringle maneuvers as necessary during parenchymal transection for hemihepatectomies. Vascular outflow to the right or left liver can be obtained by exposing and ligating the hepatic veins as previously described or by ligating the vessels intraparenchymally during transection of the liver tissue.

Parenchymal transection can be performed using a multitude of techniques from finger fracture, using a Kelly clamp to fracture, Cavatron ultrasonic surgical

aspirator (CUSA), harmonic scalpel, stapling devices, electrocautery devices with or without saline perfusion, and high-pressure water jets. The superiority of any one of these techniques has not been established, and all are used. With these techniques, individual blood vessels and bile ducts are cauterized, clipped, or sutured in rapid succession as they are encountered. Constant re-evaluation of the direction of transection is important both to not injure vital structures to the remnant liver and to maintain a negative margin. After parenchymal transection and removal of the specimen, the raw surface of the liver is carefully inspected for bleeding and bile leakage, which can then be controlled by suture ligation and argon beam coagulation. New formulations of fibrin glues are constantly being developed to aid in hemostasis and prevention of biliary leak. Whether they are indeed a cost-effective way of controlling bleeding and maintaining hemostasis has yet to be determined.[32-34] I prefer to place closed-suction drains near resected liver surfaces to monitor and drain unrecognized postoperative bile leaks, but some centers do not routinely place drains and their routine use is controversial.[35,36]

Right Hepatectomy with Hilar Dissection

A right hepatectomy can usually be accomplished through a right subcostal incision with upper midline extension and involves resection of segments V, VI, VII, and VIII. If greater exposure toward the left is required, a trifurcated incision can be used. The hepatic flexure of the colon is mobilized caudad. The round ligament and falciform ligament are divided. The right bare area of the liver is exposed by dividing the right triangular ligament. The right inferior liver edge is mobilized out of the retroperitoneum. This dissection reveals the upper pole of the right kidney, right adrenal gland, and suprahepatic IVC. The liver is then rotated to the left, and the subhepatic IVC is dissected by controlling the small venous branches draining directly from the liver. There is often an IVC ligament that extends from the right liver and around the right side of the IVC just caudad to the right hepatic vein. This can often be controlled with an endoscopic stapler with a vascular load after it is dissected out. At this point the right hepatic vein can be identified and dissected out, whereupon a vessel loop can be placed around it. If dissection of the right hepatic vein is not safe at this time, it can be controlled later after parenchymal transection.

A cholecystectomy is then performed. The hepatic artery bifurcation is localized. The right hepatic artery is ligated. The common hepatic duct is then dissected and mobilized anteriorly and to the left to expose the portal vein (Fig. 117–10). Dissection is then carried out into the hilum of the liver to expose the bifurcation of the portal vein. The right portal vein is circumferentially dissected (Fig. 117–11). Care should be taken to make sure that the left portal vein takeoff is clear of the dissection and that small branches draining the caudate are sufficiently controlled and divided. The right portal vein can be divided with ties with a reinforcing suture ligature on the stump or with an endoscopic stapler with a vascular load. Hilar dissection is then completed by identifying and isolating the right hepatic duct, which is next ligated and divided.

The liver is then rotated to the left and the previously isolated right hepatic vein is divided between vascular clamps or an endoscopic stapler with a vascular load. If vascular clamps are used, the caval stump is closed with a running 4-0 Prolene suture and the specimen side simply suture-ligated. Several minutes after the right hepatic artery and portal vein are ligated, the right liver should become devascularized and turn dusky. Glisson's capsule is then scored with the electrocautery device starting at the level of the divided right hepatic vein to the gallbladder fossa on the anterior surface. If preservation of the middle hepatic vein is intended, then the line of transection should be moved slightly lateral. If the intention is to take the middle hepatic vein, then the line of transection should be moved medially. Intraoperative ultrasound can be used to carefully map this out. On the posterior surface of the liver the liver is scored along the liver over the right lateral border of the IVC toward the portal bifurcation. Parenchymal transection is then performed by any of the previously described techniques. Intermittent portal inflow clamping, as described previously, can be used to help decrease blood loss if this is a problem during parenchymal transection. During parenchymal transection vascular and biliary structures are controlled by the appropriate combination of clips, sutures, suture ligatures, and stapling devices. Once the parenchyma is transected, the specimen can be removed.

Left Hepatectomy with Hilar Dissection

A left hepatectomy can also be accomplished through a right subcostal incision with an upper midline extension and involves resection of segments II, III, and IV. For large bulky tumors on the left or if the left liver extends significantly laterally, a left subcostal component may be needed to trifurcate the incision. Alternatively, a midline incision can be used, but this may limit exposure to the right liver should unexpected findings be encountered during exploration. The round ligament and falciform ligament are divided. The left bare area is next exposed by dissecting the left triangular ligament. Usually the left hepatic vein and middle hepatic vein join together within the parenchyma of the liver before emptying into the IVC, which precludes extrahepatic dissection of this vessel without taking the middle hepatic vein. If it is separate and dissectible, a vessel loop is encircled around it. A cholecystectomy is performed. The lesser omentum is divided to fully expose the margins of the hepatoduodenal ligament. Care should be taken to note a replaced or accessory left hepatic artery running in this location. The proper hepatic artery is identified and dissected above the bifurcation of the right and left branches. The left hepatic artery is then divided.

The common hepatic duct is next exposed, and the left hepatic duct is divided above the bifurcation. The left portal vein can then be identified at the base of segment IV and traced to the hilus of the liver. It is circumferentially dissected and can be ligated or controlled with an

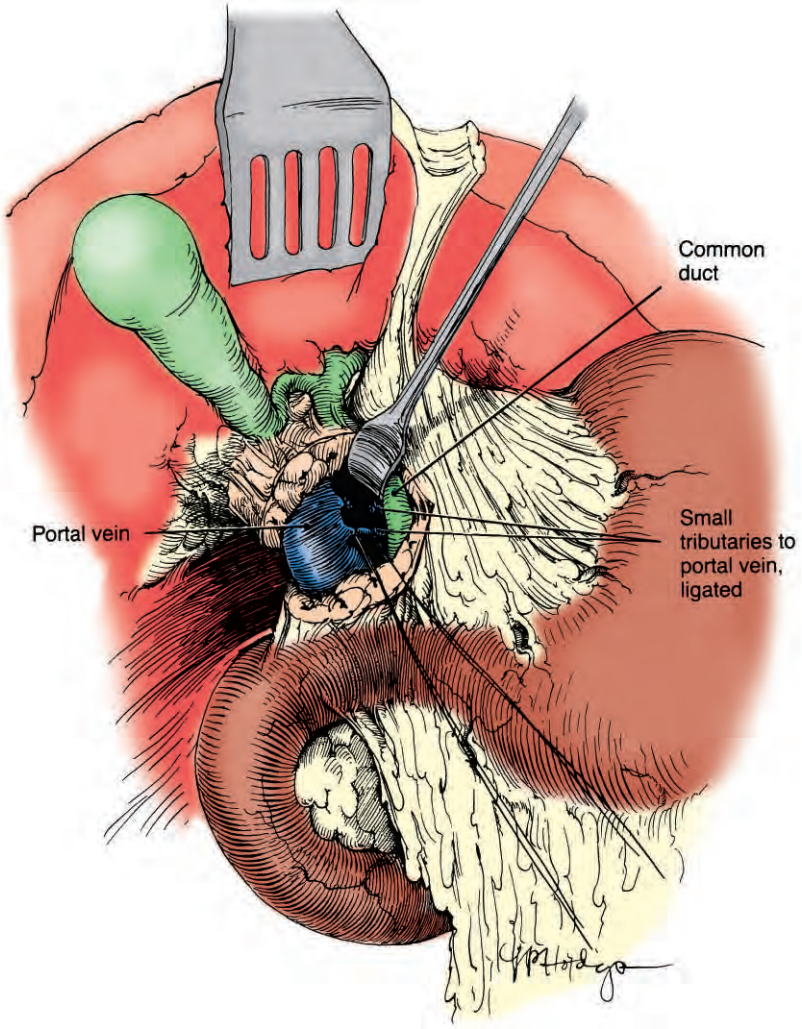

Figure 117–10. Right hepatectomy. Initial exposure of the portal vein before hilar ligation of its right branch is shown. The area to be dissected, closer to the hilus of the liver than shown, has no branches. (From Nora PE: Operative Surgery: Principles and Techniques. Philadelphia, Lea & Febiger, 1980, p 647.)

endoscopic stapler with a vascular load. The left liver should become devascularized and turn dusky. If the left hepatic vein was previously successfully dissected then it can be divided with either ligatures or an endoscopic stapler with a vascular load. The anterior surface of the liver is then scored with the electrocautery device from the left hepatic vein (or stump) to the top of the gallbladder fossa. The posterior surface of the liver is then scored with the electrocautery device from the top of the gallbladder fossa to the portal bifurcation. If preservation of the middle hepatic vein is intended, then the line of transection should be moved slightly to the left; if the intention is to take the middle hepatic vein, then the line of transection should be moved to the right. Intraoperative ultrasound can be used to carefully map this out. Parenchymal transection is then performed by any of the previously described techniques. Intermittent portal inflow clamping as described previously can be used to help decrease blood loss if this is a problem during parenchymal transection. During parenchymal transection, vascular and biliary structures are controlled by the appropriate combination of clips, sutures, suture ligatures, and stapling devices. Once the parenchyma is transected, the specimen can be removed (Fig. 117–12). If the caudate must also be removed to provide adequate tumor clearance, it can be mobilized off the IVC by sequentially dividing the short veins that directly drain into the IVC.

Left Lateral Sectionectomy

Left lateral sectionectomy can usually be performed through an upper midline incision and involves resection of segments II and III of the liver. If unexpected findings in the right liver are discovered during exploration, however, a midline incision may be limiting. Alternatively, a bilateral subcostal incision can be used. The round ligament and falciform ligament are divided. The bridge of liver parenchyma between segments III and IV over the round ligament is divided either with electrocautery or with an endoscopic stapler with a vascular load. The left bare area is next exposed by dissecting the left triangular ligament.

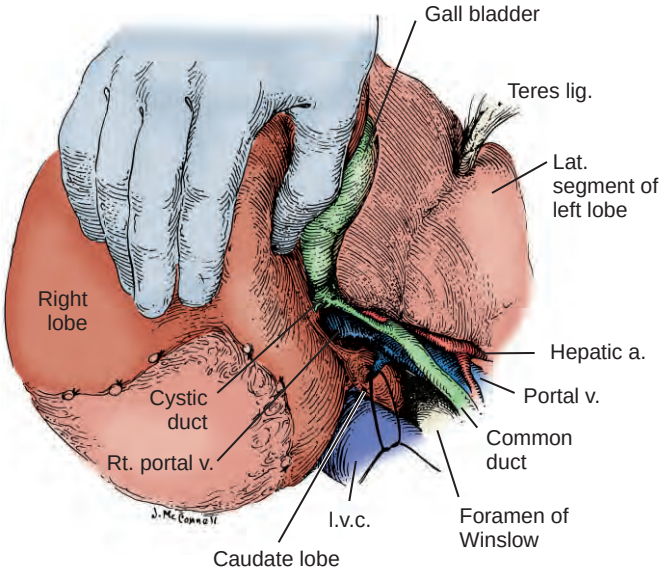

Figure 117–11. Right hepatectomy: Exposure of the right branch of the portal vein from the posterior approach. The liver has been retracted anteriorly and to the left. The looped ligature is around a branch to the caudate lobe. Ivc, inferior vena cava. (From Starzl TE, Bell RH, Baert RW: Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 141:429, 1975.)

For resection of tumor, the surface of the liver is then scored 1 cm to the left of the falciform ligament and to the left of the umbilical fissure (provided that the margin is adequate). This preserves the blood supply and biliary drainage to segment IV of the remnant liver. For donor hepatectomy, the anterior surface of the liver is scored 1 cm to the right of the falciform ligament and to the right of the umbilical fissure. This preserves the blood supply and biliary drainage to segments II and III of the donor liver. Parenchymal transection is then performed by any of the previously described techniques. Intermittent portal inflow clamping is usually not required for left lateral sectionectomy. As the main portal pedicles to the segments are encountered within the parenchyma, they are controlled with clamps, divided, and ligated or stapled with an endoscopic stapler with a vascular load. The left hepatic vein can then be finally controlled within the hepatic parenchyma either with ligatures or a stapler.

Extended Right and Left Hepatectomies

Extended right and left hepatectomies are perhaps the most difficult and complicated types of liver resections and are covered in classic manuscripts.[37-39] The initial maneuvers for the extended right hepatectomy are similar to right hepatectomy. The cystic artery and duct are ligated and divided, but the gallbladder can be left attached to the specimen as segments IV, V, VI, VII, and VIII are to be resected in continuity. The portal structures are dissected and divided as before. The right hepatic vein is controlled and divided, if possible, as before. Because the line of parenchymal transection is just to the right of the umbilical fissure and falciform ligament, the feedback structures to segment IV must be controlled. The bridge of liver parenchyma between segments III and IV is divided. The liver parenchyma is scored with the electrocautery device along the plane of transection. Parenchymal transection is then performed by any of the previously described techniques. As the main portal pedicles to segment IV are encountered within the parenchyma, they are controlled with clamps, divided, and ligated or stapled with an endoscopic stapler with a vascular load. This dissection is carried to the base of the umbilical fissure (Fig. 117–13). Parenchymal transection is continued posteriorly ligating the middle hepatic vein and/or its branches. Great care is taken to preserve the left hepatic vein (Fig. 117–14). Intermittent portal inflow clamping as described previously can be used to help decrease blood loss if this is a problem during parenchymal transection. The caudate is either preserved or resected with the specimen. Because of the risk of torsion of the liver remnant, it should be attached back to the falciform ligament.

The initial maneuvers for an extended left hepatectomy are similar to left hepatectomy. The cystic artery and duct are ligated and divided, but the gallbladder can be left attached to the specimen as segments II, III, IV, V, and VIII are to be resected in continuity. The right triangular ligament, in addition to the left, is also divided. The portal structures are dissected and divided as before. The left hepatic vein (with the middle hepatic veins) is controlled and divided, if possible, as before. The difficulty with extended left hepatectomy is performing the parenchymal transection to preserve the right posterior pedicle and the right hepatic vein while taking the right anterior sector of the liver (segments V and VIII). Intraoperative ultrasound is useful in locating and protecting these structures. Intermittent portal inflow clamping as described previously is usually required because of the magnitude of parenchymal transection and difficulty in early control of the right anterior pedicle. Parenchymal transection is then performed by any of the previously described techniques (Figs. 117–15 and 117–16).

SEGMENTAL RESECTIONS

To maximize functional reserve, (multi)segmental or subsegmental (or nonanatomic) hepatectomies can be performed. For example, left lateral sectionectomy (segments II and III), central hepatectomy to remove the right anterior section (segments V and VIII) and left medial section (segment IV), right posterior sectionectomy (segments VI and VII), or caudate resection (segment I) are examples in which one, two, or three contiguous segments are removed to eradicate tumors within those regions of the liver. These resections are often done with intermittent Pringle's maneuver until the specific pedicles supplying these areas are controlled.

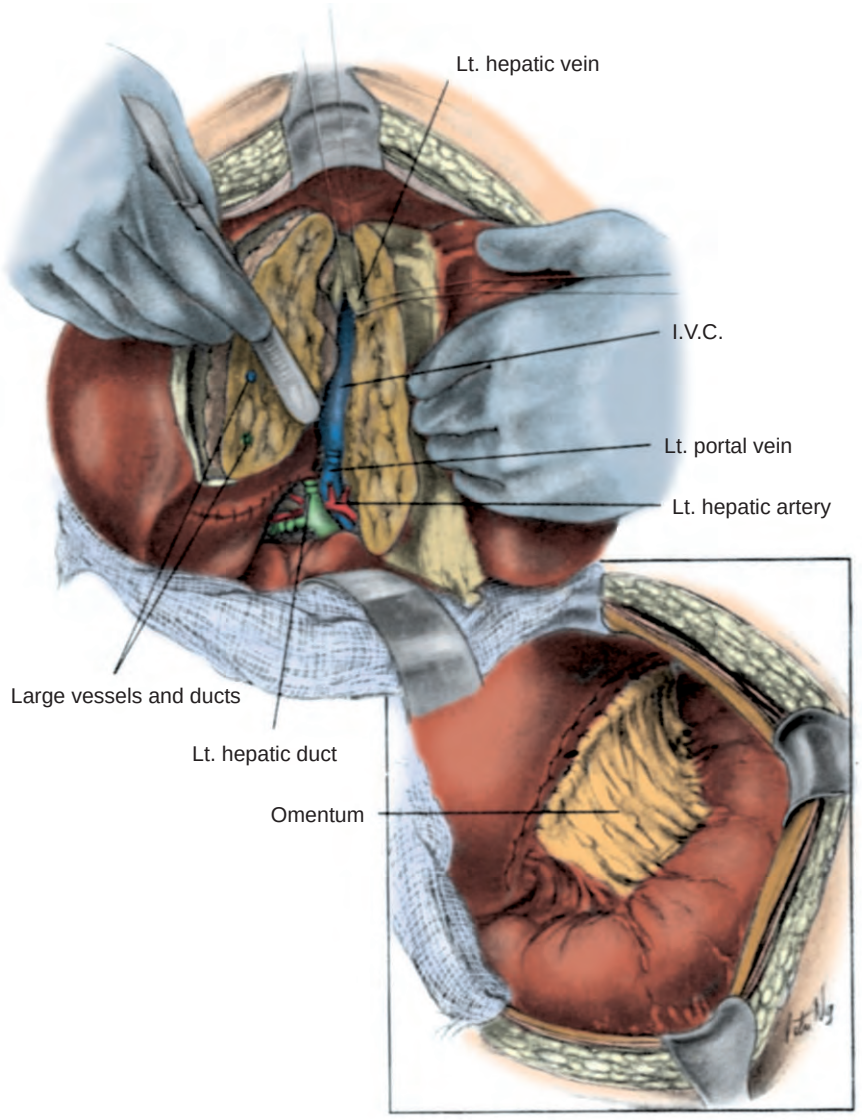

Figure 117–12. Left hepatectomy. The hilar structures have been dissected and ligated, and the parenchymal transection is complete. In this case, the left hepatic vein has been left for last. This also depicts a resection that includes the caudate lobe. IVC, inferior vena cava. (From Schwartz SI: Surgical Diseases of the Liver. New York, McGraw-Hill, 1964, p 254.)

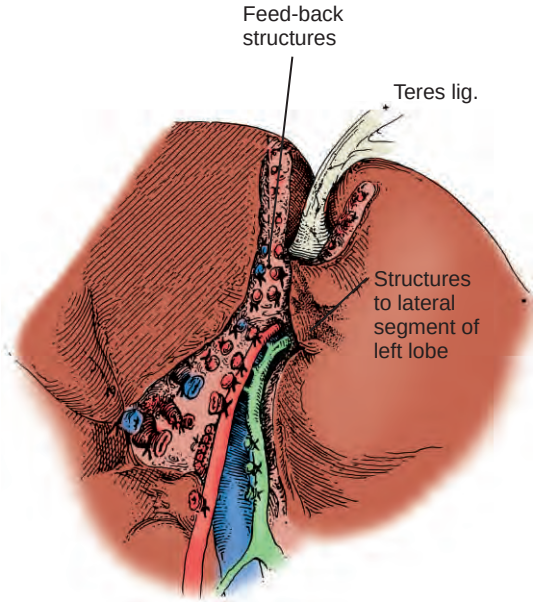

Figure 117–13. Right extended hepatectomy. Control of the feedback vessels to segment IV. Blunt dissection in liver substance just to the right of the umbilical fissure exposes these vessels. Each vascular and biliary structure is ligated individually to complete devascularization of segment IV. (From Starzl TE, Bell RH, Baert RW: Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 141:429, 1975.)

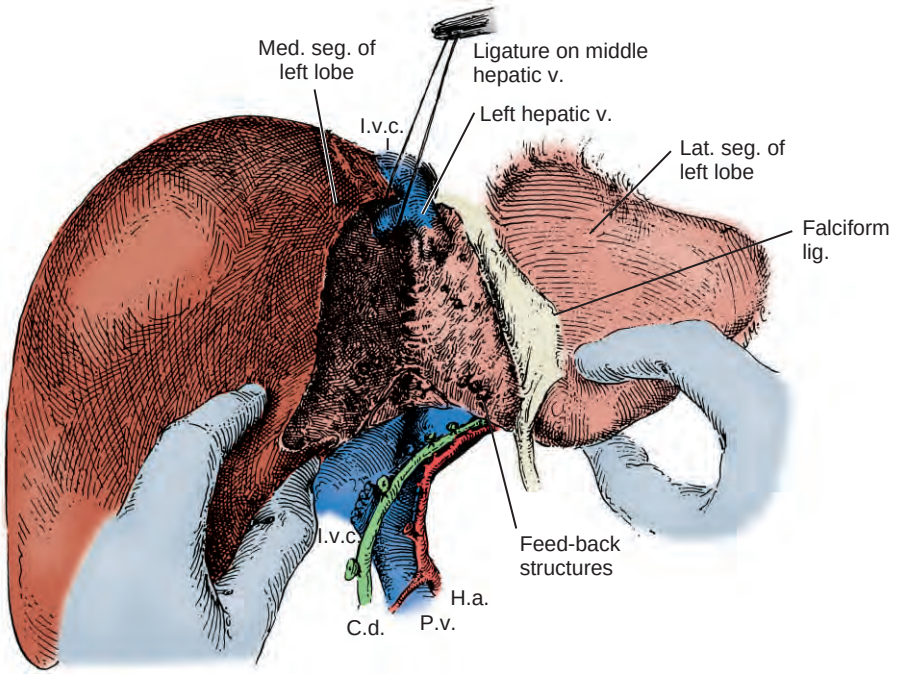

Figure 117–14. Right extended hepatectomy. Parenchymal transection is nearly complete. The main trunk of the middle hepatic vein is exposed, with a ligature around it. At this juncture, the caudate still may be left in situ. Cd, common duct; Ha, hepatic artery; Ivc, inferior vena cava; Pv, portal vein. (From Starzl TE, Bell RH, Baert RW: Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 141:429, 1975.)

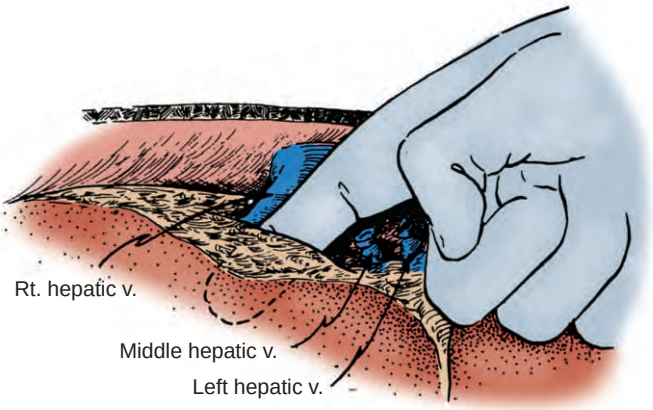

Figure 117–15. Left extended hepatectomy: superior-to-inferior dissection between the right anterior sector and right posterior sector. The dissecting finger is kept anterior to the right hepatic vein. The left and middle hepatic veins have been ligated or sutured. (From Starzl TE, Iwatsuki S, Shaw BW Jr, et al: Left hepatic trisegmentectomy. Surg Gynecol Obstet 155:25, 1982.)

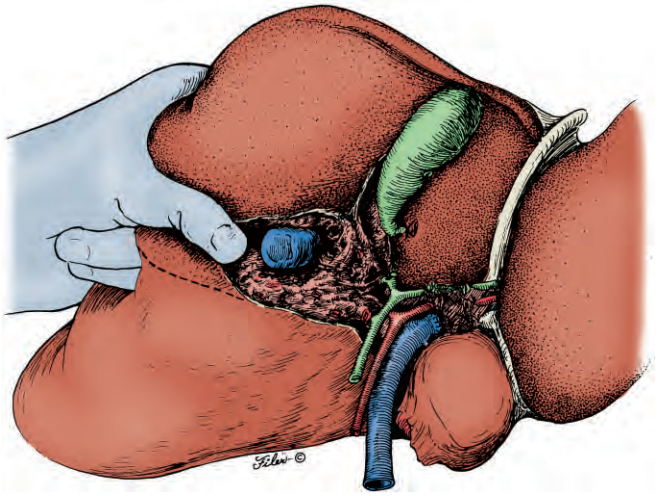

Figure 117–16. Left extended hepatectomy. Further development of the plane between the anterior and posterior sectors of the right liver. (From Starzl TE, Iwatsuki S, Shaw BW Jr, et al: Left hepatic trisegmentectomy. Surg Gynecol Obstet 155:25, 1982.)

WEDGE RESECTIONS

When a simple wedge resection of the liver is appropriate, the area to be resected is isolated between two interlocking mattress sutures of heavy absorbable material (Fig. 117–17). The two mattress sutures are placed in the form of a V intersecting at the apex. After the wedge resection is performed the mattress sutures can be tied to each other to approximate the two opposing raw liver surfaces.

POSTOPERATIVE MANAGEMENT

The resection of a large portion of liver results in metabolic derangements that should be anticipated and treated. Jaundice is not uncommon and is secondary to loss of hepatic parenchyma and to effects from blood transfusion if used. Hyperbilirubinemia usually peaks 3 to 4 days postoperatively and then begins to resolve as the liver remnant recovers and regenerates. Serum transaminase elevations are expected but generally plateau at less than 1000 units/L and are not usually ominous in the absence of severe prolongation in INR, decreased fibrinogen, hepatic encephalopathy, acidosis, and elevated serum ammonia levels. Hypophosphatemia and hypokalemia are common after liver resection, and these electrolytes should be monitored closely and repleted. Hypoglycemia is sometimes observed after massive liver resection, as is hypoalbuminemia.

Coagulopathies are often noted after hepatic resection, due to a combination of blood loss, dilution of clotting factors, blood product transfusion, and inadequate liver function. Vitamin K is administered commonly to patients after liver resection, although a patient with a prolonged prothrombin time often does not respond to this therapy if the primary cause is liver failure. Patients with coagulopathy and ongoing bleeding may require support with blood, plasma, cryoprecipitate, and platelets as appropriate.

Most surgeons use parenteral antibiotics prior to incision and for one or two doses intraoperatively and/or postoperatively. In general, diets can be advanced relatively quickly once patients can tolerate liquids. Patients may need to be salt restricted if fluid retention is significant. Some patients benefit from diuresis after the acute postoperative period.

POSTOPERATIVE COMPLICATIONS

Postoperative complication rates vary greatly depending on what population of patients is being studied. For example, mortality and morbidity following donor hepatectomy are appropriately very low, whereas, those following liver resection in patients with cirrhosis are high. The degree of hepatic resection as well as whether the biliary tree requires reconstruction or not also will affect morbidity and mortality.

Mortality rates following liver resection in many modern series are now less than 5%. Not uncommon complications following liver resection are bile leak, intra-abdominal abscess, bleeding, pneumonia, and cardiac complications.

SUMMARY

It is important for surgeons performing liver resections to be familiar with normal anatomy as well as the specific anatomic variations for each patient. Patient selection is paramount, so that those most likely to benefit can be appropriately taken to the operating room. The indications for performing a liver resection are myriad and cover many primary and secondary conditions of the liver. An operative plan should be formulated based on preoperative imaging and intraoperative findings after visualization, examination, and intraoperative ultrasound where appropriate. A strategy of resection including inflow vascular control, outflow vascular control, and

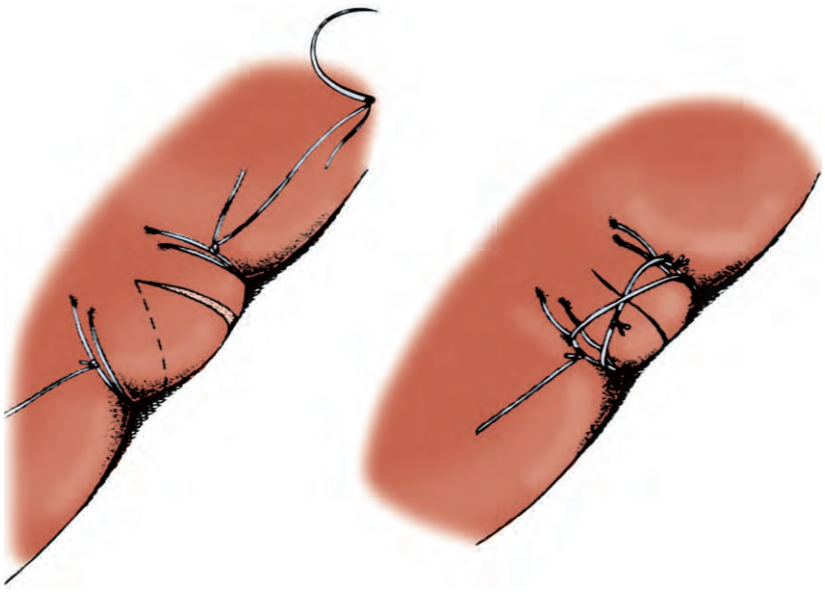

Figure 117–17. Wedge biopsy of the free margin of the liver. The two mattress sutures of heavy absorbable material actually should be placed as a V and should intersect at the apex, not run parallel as shown. (From Grewe HE, Kremer K: Atlas of Surgical Operations, Vol. 2. Philadelphia, WB Saunders, 1980, p 321.)

parenchymal transection should be formulated that will remove the lesion(s) with appropriate margins but that will leave the patient with an adequate liver remnant that has good vascular inflow, vascular outflow, and biliary drainage.

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Chapter

118

Hepatic Transplantation

Steven D. Colquhoun · Nicholas N. Nissen · Andrew S. Klein

In 1984 the National Institutes of Health (NIH) convened a consensus development conference to evaluate the existing state of the art of liver transplantation. Results of the procedure had improved dramatically since the first human liver transplants performed by Starzl in 1963. A number of quantum advances had overcome most of the technical aspects of the procedure. With the improved immunosuppression afforded by the availability of cyclosporine in 1979, the balance had clearly shifted in favor of acceptable outcomes. The NIH panel concluded "that liver transplantation is a therapeutic modality for end-stage liver disease that deserves broader application."[1] With this endorsement, broader application indeed occurred with some enthusiasm. In the United States alone, the availability of liver transplantation spread swiftly from just a single center to eventually more than 120 programs nationwide. Most importantly, liver transplantation was firmly established as the standard of care for selected patients with end-stage cirrhosis. Patients who would have succumbed to their disease a few years earlier now completely recovered and once again enjoyed normal and productive lives.

In the years intervening to the present, surgical techniques have continued to evolve along with a better understanding of disease processes, immunosuppression, prophylaxis against infection, and the general sophistication of patient management, both before and after transplantation. With these advances, outcomes have also continuously improved, with current national statistics for 1-year patient survival rates in the range of 90% and 3-year survival rates greater than 70%.[2] Although in the earlier days of liver transplantation the goal was simply survival, in the current era the focus has shifted to quality of life and other long-term issues facing transplant recipients.

As succinctly stated by T.S. Eliot, "Success is relative." Ironically, improved results, expanded indications, and wider availability of expertise have all led to what is undoubtedly the single greatest challenge facing the field of liver transplantation yet: the extreme shortage of suitable organs for transplantation. In the span of a few short years, the number of patients awaiting liver transplantation increased almost exponentially. In the 5 years between 1996 and 2001, the number of patients waiting for liver transplants nationwide increased from just over 7000 to more than 18,000 (Fig. 118–1). In the same interval and despite efforts to improve organ donation, the number of deceased donor organs did not keep pace, with an increase from about 4500 to just over 5000 each year. Not surprisingly, there was a corresponding increase in deaths in potential recipients waiting for organs.[2] These frustrating facts have led to a number of strategies for increasing the number of available organs, including improved nationwide donor awareness campaigns, division of deceased donor organs to provide allografts to two recipients, the acceptance of increasingly "marginal" or "extended criteria" deceased donors, the use of "non–heart-beating" donors, and finally, the general acceptance of adult-to-adult living donor liver transplantation.

In this chapter, many of the clinically relevant details of liver transplantation are discussed, including the current challenges and opportunities faced by those in the field.

EPIDEMIOLOGY

Chronic end-stage cirrhotic liver disease is the most frequent indication for orthotopic liver transplantation (OLT). In the United States, the overall incidence of cirrhosis of any etiology is in the range of 70 per 100,000, with rates higher for men than for women (95 versus 50 per 100,000). Currently in the United States, 6 million individuals are estimated to have cirrhosis. Viral hepatitis, cholestatic liver disease, and alcoholic and fatty liver disease are some of the more common causes of end-stage liver failure (Table 118–1).

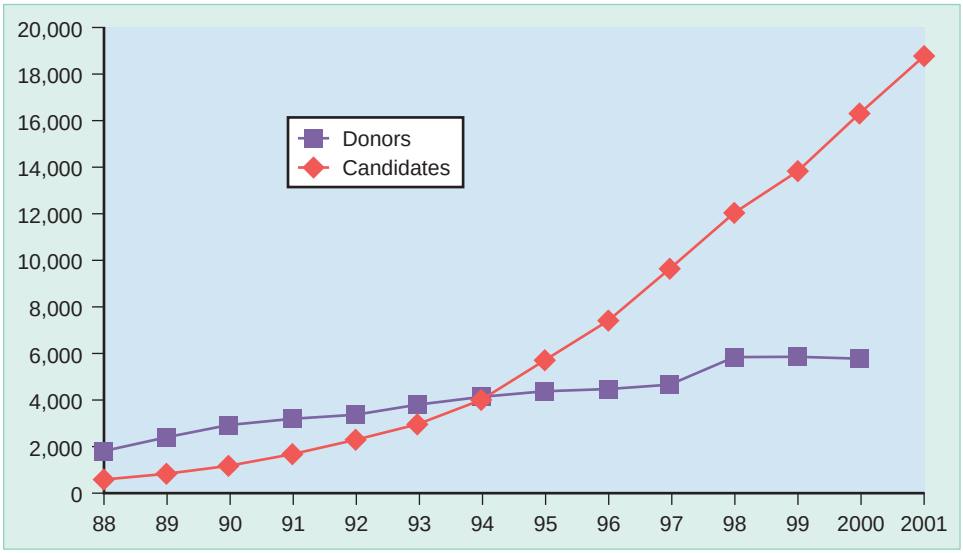

Figure 118–1. Annual number of candidates waiting for liver transplantation versus available deceased donor organs.

Table 118–1 Chronic End-Stage Liver Disease: Causes

Category	Disease	Frequency
Hepatitis	(Hepatitis A)	Never chronic
	Hepatitis B	10% to 15%
	Hepatitis C	40%
Noncholestatic	Laënnec's cirrhosis	
	Cryptogenic cirrhosis	
	Autoimmune hepatitis	
Cholestatic	Primary sclerosing cholangitis	
	Primary biliary cirrhosis	
Metabolic	Hemochromatosis	
	Wilson's disease	
	α_1-Antitrypsin deficiency	
Malignancies	Hepatocellular carcinoma	Adults
	Hepatoblastoma	Children
	Cholangiocarcinoma	Investigational
	Carcinoid/ neuroendocrine	Rare
	Hemangioendothelioma	Rare
	Hemangiosarcoma	
Atresia:	Biliary atresia	50% children
Others	Budd-Chiari syndrome	Rare
	Cystic fibrosis	
	Congenital hepatic fibrosis	
	Benign tumors	

Causes of End-Stage Liver Disease

Hepatitis C Cirrhosis from hepatitis C virus (HCV) remains the most common indication for liver transplantation in the United States, and it accounts for roughly 40% of the activity at most centers.[2] HCV is a parenterally transmitted RNA virus with no DNA intermediates. The HCV genome was elucidated in 1989, and screening of blood products began shortly thereafter. Acute HCV infections are usually subclinical with no icteric phase. The disease becomes chronic in the majority of those infected, with cirrhosis developing between 1 and 2 decades later. The interval to cirrhosis is greatly accelerated by heavy alcohol consumption.[3] In the United States, 1% to 2% of the population is infected with HCV—from blood transfusions before 1990, intravenous drug use, or other parenteral routes such as tattoos. Despite blood product screening and efforts at greater public awareness and because of the prolonged course of the disease, hepatitis C is predicted to be an increasing problem for at least another decade.

Hepatitis B Hepatitis B virus (HBV) is a DNA virus endemic in many countries of the Pacific Rim. Although effective vaccines have been available for over 20 years, hepatitis B continues to be a major worldwide health problem, especially because of its vertical transmission. HBV-related liver disease currently accounts for up to 15% of transplant activity at most centers. Reinfection after transplantation was a major issue in the early days of transplantation; however, with improved prophylactic strategies using HBV immune globulin injections and the more recent availability of effective antiviral agents, allograft reinfection is no longer a major problem.[4]

Cholestatic Diseases Collectively, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are referred to as the cholestatic liver diseases. Although both are idiopathic, each has a genetic/autoimmune element, and overlap syndromes with autoimmune

hepatitis can occur. Together, they account for upward of 25% of transplant activity at most centers.[2]

Ninety percent of patients with PBC are female with an average age of 50 years, and not uncommonly, familial clustering is noted. Pruritus is the most common initial symptom, whereas the diagnostic hallmark is the presence of antimitochondrial antibodies, which are present in virtually 100% of those with the disease.[5]

Men are twice as likely as women to be afflicted with PSC, with onset of the disease in men generally occurring between 25 and 45 years of age. Many cases are discovered incidentally on routine blood tests with the finding of elevated serum alkaline phosphatase. Patients with symptoms are equally likely to have either pruritus or jaundice. In the proper clinical context, the diagnosis is confirmed by the presence of irregular stricturing and beading of the intrahepatic biliary tree on endoscopic retrograde cholangiography. As discussed in some detail later, there is a strong association between PSC and inflammatory bowel disease. Much more worrisome in patients with PSC is the 15% to 30% overall associated risk for the development of cholangiocarcinoma.[6] Unfortunately, as yet there is no reliable method for predicting or detecting this malignancy in its early stages. Ironically, demonstrable disease is considered a relative contraindication for transplantation because of generally dismal outcomes. However, those who undergo transplantation and are found to have incidental disease actually fare comparatively well, and experimental protocols using pretransplant exploration and aggressive combination chemotherapy and radiotherapy have shown promise.[7]

Alcoholic Liver Disease Alcoholic liver disease ranks as one of the most common causes of death in the United States and the second most common indication for liver transplantation in adults.[8] Interestingly, cirrhosis develops in only 10% to 15% of alcoholics. Nevertheless, it has been roughly determined that much more than 80 g of alcohol per day for more than 5 years will put most individuals at risk. As already noted, alcohol and HCV or HBV infection seem to act synergistically. Liver injury from alcohol can be manifested across a spectrum from acute alcoholic hepatitis to fatty changes and ultimately to cirrhosis and hepatocellular carcinoma (HCC). Most transplant centers maintain strict abstinence guidelines for determining candidacy when alcohol is the cause of the liver failure. Most often a 6-month period of sobriety is required to allow demonstration of insight and compliance. A second very practical reason for adequate abstinence is to exclude those who will recover sufficiently in the absence of alcohol to the point of no longer meeting transplant criteria.

Unresectable Hepatocellular Carcinoma HCC is one of the most common malignancies worldwide; it ranks eighth among all cancers while accounting for approximately 90% of those that are primary to the liver. The incidence of HCC in endemic regions of Asia and Africa can be as high as 150 cases per 100,000. Although much lower rates, in the range of 1 to 5 cases per 100,000, are found in Western Europe and the United States, the incidence is rising. In the United States the incidence of HCC is currently estimated to be 8500 to 11,500 new cases per year.[9,10]

Even though environmental toxins pose a major risk in some parts of the world, in general, the incidence of HCC is primarily related to the prevalence of cirrhosis from chronic viral hepatitis B and C, with a relative risk several hundredfold greater than in those not infected. In fact, cirrhosis per se is a premalignant condition, regardless of etiology. Although cirrhosis remains the common denominator, the DNA intermediates in the replicative cycle of HBV may be directly carcinogenic, even in the absence of cirrhosis.

Unusual Tumors From an early experience with dismal outcomes, most metastatic tumors to the liver have since been considered absolute contraindications to transplantation. A few exceptions do exist. Acceptable outcomes have been described in patients with metastatic carcinoid tumors, but patients who receive transplants for other unresectable neuroendocrine tumors have not generally fared well. Anecdotal reports of good outcomes have been reported for primary hepatic angiosarcoma, as well as biliary cystadenocarcinoma. Hepatic epithelioid hemangioendothelioma has also been treated by OLT with reasonable outcomes. Usually, the tradeoff in outcome is unclear between traditional therapies for an otherwise slowly progressive tumor versus the potential for rapid progression of occult residual disease under the influence of post-transplant immunosuppression. A small number of symptomatic and otherwise unresectable benign tumors or those with the potential for malignant degeneration, such as adenomas, have also been treated by transplantation.[11]

Other Causes A number of other disorders that can also lead to liver failure and the need for transplantation do exist, but they are beyond the scope of this discussion. Metabolic abnormalities of iron and copper underlie the disorders of hemochromatosis and Wilson's disease, respectively. As outlined in Table 118–1, other entities include autoimmune hepatitis, α_1-antitrypsin deficiency, nonalcoholic fatty liver disease, and Budd-Chiari syndrome. In addition, there are a host of other disorders that occur in the pediatric population, the most common of which is biliary atresia.

EVALUATION PROCESS

In the entire field of medicine there is unlikely to be another area in which the word *team* more aptly applies. Organ transplantation in general and liver transplantation in particular are so complex that they are possible only through the coordinated efforts of many individuals with special expertise working in concert. The patient's first encounter through the evaluation process is illustrative of this principle. The three goals of evaluation are to (1) confirm the presence of end-stage liver disease and the indications for transplantation, (2) exclude contraindications, and (3) initiate patient and family education regarding the transplantation process.

Table 118–2 Acute Liver Failure: Causes

Toxic	Infectious	Metabolic	Cardiovascular
Drugs or chemicals	Viral hepatitis	Wilson's disease	Acute Budd-Chiari syndrome
Acetaminophen	Yellow fever	Acute fatty liver of pregnancy	Portal vein thrombosis
Halothane	Q fever	Reye's syndrome	"Shock" liver
Isoniazid	Other viruses	Other inborn errors	Heat stroke
Valproate			
Amanita phalloides			

To that end, each patient is seen by a core group of individuals composed of a transplant hepatologist, a transplant surgeon, a psychiatrist, a social worker, and a nursing coordinator. Additional cardiology, pulmonology, nephrology, neurology, anesthesiology, infectious disease, and nutrition consultations are obtained as indicated. Each of the consultants has acknowledged experience in working with liver failure patients and understands the special concerns and challenges presented by liver disease and transplantation. In the evaluation of healthy volunteer candidates for living donation, a physician independent of the recipient's transplant team acts as a dispassionate advocate for the donor. Increasingly, transplant programs are also engaging regular interactions with hospital ethicists to ensure the appropriateness of details related to living donation and other aspects of transplantation discussed later.[12]

TRANSPLANT CANDIDACY

Although the basic indications for determining liver transplant candidacy have changed little from the earliest days, there has been a continuous evolution and ongoing effort to better define these indications as they apply to organ allocation. There has been a determined progression away from the subjective toward the objective and away from the empirical in favor of evidence-based processes. There are three relevant and interrelated areas of candidacy, including indications and contraindications for the procedure and prioritization of candidates in the context of a limited supply of deceased donor organs.

Indications for Transplantation

Chronic Disease The basic clinical indications for liver transplant candidacy in patients with chronic disease have remained relatively constant over the past 2 decades and include the following:

1. Progressive hyperbilirubinemia
2. Portal hypertension as evidenced by signs of gastrointestinal bleeding (usually from esophageal or gastric varices)
3. Hypersplenism with thrombocytopenia
4. Disabling symptoms of portosystemic or hepatic encephalopathy
5. Synthetic dysfunction as reflected by diminished fibrinogen, cholesterol, and albumin, but most often assessed by the prothrombin time or international normalized ratio (INR)

A more subjective criterion includes general wasting or a "failure-to-thrive" condition, which can certainly afflict patients with the constellation of problems associated with end-stage liver disease. As noted earlier, a final common indication is otherwise unresectable HCC. The vast majority of patients with this tumor have underlying cirrhosis, which even if clinically well compensated, nevertheless precludes major hepatic resection.

Acute Disease Patients with acute (fulminant) liver failure have a more exaggerated clinical manifestation. In such circumstances there is a prominent defining role for encephalopathy, which in contrast to the chronic setting, can progress to cerebral edema with herniation. In the acute more than the chronic setting, jaundice parallels the degree of hepatocyte injury. Toxic exposure, such as to acetaminophen, acute hepatitis, or metabolic conditions such as acute Wilson's disease account for the majority of cases in which a diagnosis can be established (Table 118–2). Other rarer conditions, such as acute Budd-Chiari syndrome or an idiosyncratic drug reaction, can also occur, and in some instances, no apparent etiology can be identified. There are two standard definitions of fulminant liver failure, and both require the absence of any preexisting chronic liver disease. The first includes the clinical manifestation of encephalopathy 8 weeks or less after the onset of symptoms, and the second is based on the development of encephalopathy 2 weeks or less after the onset of clinical jaundice. Another method to categorize such patients is to assess the time from clinical jaundice to the development of encephalopathy, as seen in Table 118–3. Interestingly, a worse clinical prognosis is associated with a longer interval between the development of jaundice and encephalopathy.

Contraindications

Contraindications to liver transplantation can be relative or absolute, but in either case the list continues to dwindle. Extremes of age, for example, were once limitations that have since broadened dramatically. More recently, human immunodeficiency virus disease was considered an absolute contraindication, but this too is

being revisited. More so than for other organs, candidacy for liver transplantation places equal weight on the medical and the psychosocial condition of the patient. With the shortage of organs juxtaposed against a history of misreported media events, celebrity transplants, publicly misunderstood issues of substance abuse, and government oversight, transplant centers take such issues extremely seriously.

In general, contraindications are comorbid conditions that would preclude an operative procedure of such magnitude. The hemodynamic changes that can occur during liver transplantation may be extreme and can stress any or all of the major organ systems. Candidates undergoing outpatient evaluation for chronic conditions must be considered in this light and appropriate tests and consultations obtained (Table 118–4).

Severe cardiac and pulmonary conditions are the most frequently identified medical contraindications. Although advanced age per se is uncommonly cited as a contraindication, it is rare for most programs to consider candidates aged much beyond the mid-70s. Many centers do adhere to programmatically agreed-on age thresholds. More important than age is the overall condition of a potential recipient. This assessment can be difficult in that liver failure has dramatic systemic effects that may lead to severe deconditioning. An inexperienced clinician might find many transplant candidates to be "too sick." However, on careful consideration, many of the patient's organ dysfunctions can frequently be attributed directly to the liver disorder, with the expectation that they will be reversed by the liver transplant.

The shortage of organs and the methodology of the organ allocation algorithm, which provides priority to the "sickest first," makes it is increasingly common that patients undergoing OLT are extremely ill, often hospitalized or in an intensive care unit. For such patients with decompensated chronic disease or those with fulminant liver failure, other more specific, acute criteria are applicable (Tables 118–5 and 118–6). Patients must have adequate hemodynamics and be maintained on no more than a single pressor agent. Those on a ventilator should not have oxygen requirements exceeding an Fio_2 of 50%. As noted earlier, cerebral edema can develop in patients with acute liver failure. In such circumstances, if cerebral perfusion pressure has been inadequate, an acceptable outcome is unlikely and use of an organ is unwarranted. Infectious issues, such as active pneumonia or other systemic processes, can also be acute contraindications. Occasionally, severe psychiatric or extreme social conditions may also present at least relative contraindications. In the event of acetaminophen overdose, for example, multiple previous suicide attempts despite adequate psychiatric therapy could be a contraindication. Similarly, patients with a history of liver failure related to substance abuse but without an adequate period of abstinence or

Table 118–3 Acute Liver Failure: Definitions

Jaundice to Encephalopathy	Days
Hyperacute	≤7
Acute	8 to 28
Subacute	29 to 60

Table 118–4 Preoperative Assessment

Laboratory Tests	Imaging	Consultations
CMP	CXR	Surgery
CBC	ECG	Hepatology
INR/prothrombin time	PFT with ABG	Psychiatry
Hepatitis serology	Axial imaging	Nursing
Iron	Doppler US	Social work
AMA, ANA	PPD/*Candida*/mumps/tetanus	Nutrition
CMV	Mammogram >45 years	Cardiology PRN
EBV	Echocardiogram >45 years	Pulmonology PRN
$TSH/T_3/T_4$	Chest CT if tumor	Nephrology PRN
HIV	Bone scan if tumor >stage II	Infectious diseases PRN
CEA/AFP		
U/A		
Type and screen		
VDRL		

ABG, arterial blood gases; AFP, α-fetoprotein; AMA, antimitochondrial antibody; ANA, antinuclear antibody; CBC, complete blood count; CEA, carcinoembryonic antigen; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CT, computed tomography; CXR, chest x-ray; EBV, Epstein-Barr virus; ECG, electrocardiogram; HIV, human immunodeficiency virus; INR, international normalized ratio; PFT, pulmonary function tests; PPD, purified protein derivative; PRN, as needed; T_3, triiodothyronine; T_4, levothyroxine; TSH, thyroid-stimulating hormone; U/A, urinalysis; US, ultrasound; VDRL, Venereal Disease Research Laboratory.

Table 118–5 Contraindications: Acute

Organ System	Observation	Contraindication
Cardiac	CAD risks	Recent MI
	Unstable hemodynamics	Inadequate CO
		>1 Pressor required
Pulmonary	Pneumonia	Active/progressive
	ARDS	PEEP ≥10 mm Hg
	Ventilator dependency	FiO_2 ≥50%
Neurologic	Altered mental status	Recent/acute CVA
	Acute encephalopathy/cerebral edema	Herniation or CPP ≤50
	Seizures	Uncontrolled activity
Infectious disease	Chronic condition	Untreated TB or similar
	Acute infection	Untreated or progressive
Renal	Azotemia	
	Hyperkalemia	Inadequate renal replacement therapy
	Acidosis	
	Hypervolemia	
Psychiatric*	Substance abuse	Inadequate abstinence period
	Suicide attempt(s)	Repeated despite therapy
	Schizophrenia or bipolar disorder (refractory)	Jeopardy to follow-up care
Social*	Inadequate support	Jeopardy to follow-up care

*Relative.
ARDS, adult respiratory distress syndrome; CAD, coronary artery disease; CO, cardiac output; CPP, cerebral perfusion pressure; CVA, cerebrovascular accident; MI, myocardial infarction; PEEP, positive end-expiratory pressure; TB, tuberculosis.

Table 118–6 Contraindications: Severe Chronic

Organ System	Contraindication*
Cardiac	CAD
	Valvular disease
	Cardiomyopathy
Pulmonary	COPD
	Pulmonary HTN
	Hepatopulmonary syndrome
	Pulmonary fibrosis
Infectious Diseases	HIV
	Untreated TB
	Syphilis
	Other
Psychiatric	Jeopardy to follow-up care
Social	Inadequate transportation
	Inadequate communication
	Homeless
	Inadequate support in general

*Relative/evolving.
CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HTN, hypertension; TB, tuberculosis.

Table 118–7 Preexisting Malignancy: Risk for Post-transplant Recurrence

Low (0%-10%)	Intermediate (11%-25%)	High (>25%)
Renal cell	Lymphoma	Breast
Uterine	Wilms'	Bladder
Testicular	Prostate	Renal cell (large)
Uterine cervix	Colon	Sarcoma
Papillary thyroid	Melanoma	Myeloma

patients with no evidence of social support may also be denied candidacy.

One final, but extremely important potential contraindication to transplantation is any previous history of extrahepatic malignancy in the candidate. Early in the experience of organ transplantation it was learned that immunosuppression might have profound effects on the growth of a malignancy, including subclinical residual tumor. Many common cancers may recur, even years after definitive treatment, and despite modern imaging technology, in many cases only the passage of time can be the determinant of cure. The histologic cell type, the stage and grade of the tumor, and the interval between treatment and transplantation are factors considered in the selection process. Based on the propensity to recur after transplantation, various tumor cell types have been categorized as low (0% to 10%), intermediate (11% to 25%) or high (>25%) risk (Table 118–7). For the majority of the more commonly occurring malignancies, a 2- to 5-year waiting period is generally required.[13] Most

Table 118–8 Child-Turcotte-Pugh Scoring

	1 Point	2 Points	3 Points
Encephalopathy	None	Stage 1 or 2	Stage 3 or 4
Bilirubin (noncholestatic disease)	<2	2 to 3	>3
Bilirubin (cholestatic disease)	<4	4 to 10	>10
Albumin	>3.5	3.5 to 2.8	<2.8
Ascites	None	Moderate	Severe
International normalized ratio/(prolongation of prothrombin time)	<1.7 (4 sec)	1.7 (4 sec) to 2.3 (6 sec)	>2.3 (6 sec)

programs avoid transplantation in patients with a history of histologically aggressive tumors. Of those that do recur after transplantation, the majority become evident within 2 years of transplantation.

Allocation

In the earliest days of organ transplantation there were no systems in place to facilitate the placement of available donor organs to appropriate recipients. In the mid-1960s, center-to-center phone calls for matching donated kidneys with potential recipients evolved into essentially two confederations of transplant centers: one in the eastern part of the United States and one in the west. By the early 1970s, the use of a computerized database to track patient information was implemented in the east, and with further refinements in 1977 it was named the "United Network of Organ Sharing" (UNOS). As of 1984, UNOS had evolved into a nationwide transplant candidate registry and was incorporated as a private, nonprofit organization. Finally, in 1986, UNOS was awarded a federal contract by the Department of Health and Human Services to establish the Organ Procurement and Transplant Network (OPTN).[14]

In an ongoing effort to balance utility with equity and optimize outcomes, the algorithms for allocating livers have been under constant revision. To minimize ischemia times, organs have always been used locally first, followed by regional and then national placement. Unlike the past, patients with acute conditions are currently prioritized above those with chronic disease and now also take precedence regionally over local primacy.[2] Originally, time on the waiting list weighed heavily in determining priority. This practice has since essentially been eliminated and replaced by greater emphasis on the philosophy of the "sickest first." Until relatively recently, the Child-Turcotte-Pugh system (Table 118–8) was used to prioritize patients. Unfortunately, not only did this scheme suffer from excessively subjective criteria, but it also inadequately partitioned patients into only one of four categories, thereby failing to account for a vast spectrum of disease severity. Other criteria, such as a patient's need for hospitalization, also proved to be too arbitrary to fairly assess need. Under government pressure to decrease the disparity in waiting times between regions, the Model for End-stage Liver Disease (MELD) was introduced in February 2002. Despite its development for another purpose, the MELD system was shown to be predictive of death on the waiting list, had the advantage of using only objective criteria (Table 118–9), and allowed much better differentiation between patients according to the severity of disease.[15] The more discrete data offered by MELD have also facilitated statistical analyses that have provided additional insight, such as the risk-benefit threshold of illness versus transplantation. The PELD (Pediatric End-Stage Liver Disease) provides a similar objective system for children. The current liver allocation scheme is outlined in Tables 118–9 and 118–10. In summary, patients can be placed on the UNOS transplant waiting list with a minimum MELD score of 6, organs are offered first to patients above the "minimum transplant" MELD score of 15, and

Table 118–9 Model for End-Stage Liver Disease: Formula

$$\begin{aligned}\text{MELD score} = {} & 0.957 \times \log(\text{creatinine, mg/dl}) \\ + {} & 0.378 \times \log(\text{bilirubin, mg/dl}) \\ + {} & 1.120 \times \log(\text{international normalized ratio}) \\ + {} & 0.643\end{aligned}$$

Multiply score × 10 and round to the nearest whole number. Laboratory test results less than 1.0 are set to 1.0.

Table 118–10 Pediatric End-Stage Liver Disease: Formula

$$\begin{aligned}\text{PELD score} = {} & 0.480 \times \log(\text{bilirubin, mg/dl}) \\ + {} & 1.857 \times \log(\text{international normalized ratio}) \\ + {} & 0.687 \times \log(\text{albumin, g/dl}) \\ + {} & 0.436 \text{ if patient } <1 \text{ year of age} \\ + {} & 0.667 \text{ if growth failure } (\leq 2 \text{ SD})\end{aligned}$$

Multiply score × 10 and round to the nearest whole number. Laboratory test results less than 1.0 are set to 1.0.

Table 118–11 UNOS Hepatocellular TNM/Staging

T1	Single nodule <1.9 cm	Stage I
T2	Single nodule 2.0-5.0 cm or up to three nodules, all <3.0 cm	Stage II
T3	Single nodule >5.0 cm or up to three nodules, one >3.0 cm	Stage III
T4a	Four or more nodules	Stage IVA
T4b	Any of the above with portal vein involvement on imaging	Stage IVA2
	Any N1 or M1	Stage IVB

UNOS, United Network of Organ Sharing.

the maximum score rests at 40. With exceptions, organs are offered within blood groups only.

Despite the significant improvements offered by the MELD system, allocation remains imperfect.[16] It has been estimated that up to 10% of patients have conditions that are underappraised. The best example of such a deficiency is HCC. Because cirrhosis of any etiology may predispose to the development of HCC, such tumors are present or eventually develop in many patients (Table 118–11). Even in those who are well compensated, only about 15% are amenable to liver resection because of issues of tumor size and location in the context of underlying cirrhosis and portal hypertension. Because allocation schemes have been designed to assess the degree of liver failure, patients with HCC were thus disadvantaged. With introduction of the MELD system, HCC patients were acknowledged and additional MELD points granted. Currently, automatic increases in MELD points are given every 3 months based on a defined statistical likelihood of receiving an organ over the ensuing 3 months. This increase is in effect until transplantation occurs or the tumor stage has progressed beyond acceptable limits. With adjustments, this system has worked well for tumor patients. However, there is a relatively long list of conditions and circumstances that are increasingly recognized to be "missed" by the MELD system and may also benefit from a similar system of granting additional points (Table 118–12). Discussions regarding such changes are ongoing, but complete resolution of these issues seems unlikely in the near future. Currently, additional MELD points may be granted to specific patients with special considerations through an appeals process to a "jury of peers" provided by the UNOS Regional Review Board (RRB). At present, no unusual primary or metastatic tumors are given special consideration for additional or automatic MELD points, except within the RRB process. The search for the *Holy Grail* of the perfect allocation system continues.[17]

Associated Conditions and Special Considerations

Patients with end-stage liver disease often have significant associated conditions affecting other organ systems.

Table 118–12 Potential MELD Exceptions

Diagnosis	Problem
Ascites	Failed/contraindicated TIPS
	Frequent large-volume paracentesis
Encephalopathy	Repeated hospitalization
	Refractory to therapy
Budd-Chiari syndrome	Chronic
	TIPS shunt failed/not feasible
Cholangiocarcinoma	Confined to the proximal ducts
	Small size
Cystic fibrosis	Cirrhosis alone
	With lung transplant
Hepatopulmonary syndrome	PaO_2 <60 mm Hg at rest
Portopulmonary hypertension	MPAP >35 mm Hg
Oxalosis	With/without renal transplant
Polycystic disease	Malnutrition
	With/without renal disease
Pruritus (intractable)	Cholestatic diseases
Primary sclerosing cholangitis	Recurrent cholangitis
	Repeated hospitalization/sepsis
Small-for-size syndrome	Inadequate volume
	Living donor organ
	Split deceased donor organ
Unusual tumors	Carcinoid/NET
	Sarcoma
	Epithelioid hemangioendothelioma
	Other
Refractory GI hemorrhage	Failed conservative measures
	Failed/contraindicated TIPS
Hereditary hemorrhagic telangiectasia	High-output failure
	Portal hypertension
	Biliary stricture
Familial amyloidotic polyneuropathy	With/without combined cardiac transplant

GI, gastrointestinal; MELD, Model for End-Stage Liver Disease; MPAP, mean pulmonary artery pressure; NET, neuroendocrine tumor; TIPS, transjugular intrahepatic portosystemic shunt.

Those that are more common, surprising, or sinister are briefly mentioned here by organ system. An understanding of these conditions can be critical to the management of severe cirrhosis and maintenance of transplant candidacy.

Hemodynamics

Perhaps the most pervasive physiologic changes associated with cirrhosis are those affecting hemodynamics,

which in turn can affect each of the organ systems.[18] Cirrhosis leads to generalized vasodilation and a hyperdynamic state. In addition to reduced systemic vascular resistance, a host of attendant changes can be found, including increased peripheral blood flow, reduced arteriovenous oxygen difference, decreased effective blood volume with reduced renal cortical blood flow, and activation of the renin-angiotensin axis with sodium and water retention contributing to the formation of ascites. Patients with cirrhosis are generally observed to have elevated cardiac output, tachycardia, and low blood pressure. As cirrhosis progresses, patients with a history of hypertension no longer require antihypertensive medications. Many of the common physical findings seen in cirrhotic patients, such as palmar erythema and cutaneous spider angiomas, are also explained by these vascular changes.

Heart

Iron overload states, such as that seen with genetic hemochromatosis, can lead to cardiac iron deposition. Although overt abnormalities may be discovered with echocardiography, patients afflicted are at risk for conduction abnormalities, severe dysrhythmias, and right heart failure, especially during the considerable stress of surgery. Magnetic resonance imaging can detect cardiac iron overload, and cardiac catheterization is usually required to determine transplant candidacy. In some circumstances, patients have been considered for simultaneous dual-organ transplantation. As a group, those with either primary or secondary iron overload fare worse with transplantation than do those without.[19]

Lung

Up to a third of patients with cirrhosis may be found to have reduced arterial oxygen saturation, and a number of conditions common to cirrhosis may affect pulmonary function (Box 118–1). Two of the most serious conditions are portopulmonary hypertension and hepatopulmonary syndrome. Both are probably related to the hyperdynamic state of cirrhosis.[20] Although the etiology of portopulmonary hypertension is unclear and the incidence is low, 2% of patients with severe liver disease are at risk for the development of pulmonary arterial changes indistinguishable from those seen in primary idiopathic pulmonary hypertension. If suspected on the basis of echocardiography, right heart catheterization must be performed. Mean pulmonary arterial pressure (MPAP) higher than 25 mm Hg defines the disease, whereas a value greater than 35 mm Hg (pulmonary vascular resistance >240 dynes/sec/cm^5) is considered the threshold for an increased risk for death. Treatment with prostacyclins, nitric oxide, or similarly active agents can be used in an attempt to lower MPAP and facilitate safe OLT.

Hepatopulmonary syndrome is another uncommon entity defined by the triad of (1) chronic hypoxemia (PaO_2 <60 mm Hg) and (2) pulmonary vascular dilation as seen on examinations such as angiography or bubble echocardiography, both in the context of (3) severe underlying chronic liver disease. This syndrome is a progressive condition that can be reversed after transplantation. Some patients with advanced disease are clearly in jeopardy for death at surgery, but for those with acceptable risk, current UNOS regulations do provide additional points to facilitate transplantation within a 3-month period.[2]

Box 118–1 Pulmonary Issues in Cirrhosis

- Hepatopulmonary syndrome
- Pulmonary hypertension
- Pleural effusions
- Raised hemidiaphragm
- Basal atelectasis
- Ventilation-perfusion mismatch

Gastrointestinal

Portal hypertensive bleeding is a well-known complication of cirrhosis, and about 90% of such episodes can be successfully treated with endoscopic or pharmacologic interventions (or both). When indicated, an experienced interventional radiologist can place a transjugular intrahepatic portal systemic shunt (TIPS).[21] Surgical shunts remain appropriate in the nonacute setting when the most prominent feature of disease is bleeding in an otherwise well-compensated patient. TIPS may be contraindicated by significant hepatic encephalopathy or bilirubin levels elevated much over 3.0 mg/dl, in which case progressive liver failure may ensue without shunt reversal.

Inflammatory bowel disease is strongly associated with PSC.[6] Patients with PSC have a 75% prevalence of ulcerative colitis (UC), whereas the converse is true in only 5%. PSC may also be associated with colonic Crohn's disease. In those with PSC and UC, the risk for colonic malignancy may be greater than in those with UC alone and is an indication for vigilant screening colonoscopy, both before and after transplantation.

Bone

Hepatic osteodystrophy can be a complication of end-stage liver disease, especially in patients with cholestatic conditions. Steroid treatment before or after transplantation can also exacerbate this problem. Consequences include bone pain, fractures, and vertebral collapse.[18] Aggressive calcium replacement and hormonal therapy are usually indicated.

Kidney

In the absence of other identifiable pathology, the development of severe renal dysfunction in the presence of end-stage liver failure defines the hepatorenal

Box 118–2 Stages of Encephalopathy

Stage	Clinical Findings
I	Irritability, altered sleep cycles
II	Disorientation, asterixis
III	Confusion, somnolence
IV	Coma

syndrome.[22] Although the etiology remains uncertain, it is probably related to the hemodynamic changes noted earlier. Because it is largely a functional problem, the renal failure can be expected to resolve after liver transplantation. However, in patients with long-standing hepatorenal dysfunction, normalization may be unpredictable. Hepatorenal syndrome has been subdivided into type I and type II based on the pace of functional loss. Patients with type I hepatorenal syndrome experience rapidly progressive deterioration, with a doubling of the initial serum creatinine in a period of less than 14 days. Such patients have 90% mortality within 90 days. Those with type II syndrome have less rapid progression and fare better as a group. In either case, patients often require hemodialysis. When renal dysfunction is severe and of a long-standing nature, consideration must be given to combined liver and kidney transplantation. Because one of the parameters for the MELD calculation is serum creatinine, such patients are favored, and nationwide, an increasing number of patients are undergoing dialysis at the time of transplantation, as well as simultaneous renal transplantation.

Brain

Hepatic encephalopathy is a neuropsychiatric condition associated with severe liver disease.[23] It can have manifestations that affect the spectrum of neurologic function, from changes in personality and intellect to altered levels of consciousness (Box 118–2). Although it can complicate either chronic cirrhosis or acute liver failure, there are distinct clinical differences between the two conditions. In chronic disease, symptoms of encephalopathy may wax and wane with dietary indiscretion, poor compliance with medications, gastrointestinal bleeding, or infection. In the worst scenario, stage IV coma may require endotracheal intubation for airway protection. However, with proper management, the mental status changes are temporary and reversible, even in the most severe circumstance. On the other hand, encephalopathy associated with *acute* liver failure may likewise lead to coma, but unlike its counterpart, it is also associated with cerebral edema and acute brainstem herniation. Optimal management of acute hepatic encephalopathy may require intracranial pressure monitoring, which is never necessary in the chronic setting.

Infectious Diseases

Cholangitis can be a significant pretransplant issue, especially in patients with biliary strictures, such as those with PSC or other rarer congenital or acquired conditions. Such patients may require repeated endoscopic balloon dilatation or stenting of prominent strictures. Occasionally, the administration of chronic rotating antibiotics may be necessary. Repeated hospitalization, episodes of biliary sepsis with positive blood cultures, and associated hypotension may be factors considered for requesting additional MELD points.

Skin

Intractable pruritus is occasionally seen in patients with cholestatic liver disease. Curiously, the symptoms do not correlate well with the level of cholestasis, and the exact etiology remains unclear. A variety of treatment options can be used, but none with predictable results. Such options include ursodeoxycholic acid, cholestyramine, rifampin, opioid receptor antagonists such as naloxone, or serotonin receptor agonists such as ondansetron.[18] Some patients may be driven to the point of considering suicide, and despite the fact that liver transplantation provides definitive relief, additional MELD points are rarely considered appropriate. Small-vessel vasculitis and cryoglobulinemia, as manifested by palpable cutaneous purpura, may develop in patients with chronic HCV–related cirrhosis. In addition to those mentioned here and earlier, a number of other skin changes can be associated with specific liver diseases.

ADULT-TO-ADULT LIVING DONOR TRANSPLANTATION

The first living donor liver transplants were performed from adults to children in the late 1980s, but the evolution to adult-to-adult living donor liver transplantation in the United States has been much more recent. Only after the shortage of organs reached a critical threshold was consideration given to performing such a procedure on healthy volunteers because it poses substantial perioperative and long-term risks. Many ethical issues continue to be raised, including the age, relationship to the recipient, and the social circumstances of potential donors.[12] The advantages of this procedure are primarily twofold. First, transplantation can be timed to intervene before a recipient becomes severely decompensated, thereby minimizing the risk for certain complications, avoiding repeated hospitalization, and even minimizing cost. Second, the quality of the allograft should be optimal with minimal cold ischemia time and without the physiologic insults often suffered by deceased donors. On the other hand, the relatively smaller volume and the increased technical anastomotic challenges presented by partial grafts create a new set of potential recipient problems. Add to that the most paramount concern of donor health, and the advantages of living versus deceased donors become less distinct. Indeed, recent data from the Scientific Registry of Transplant Recipients

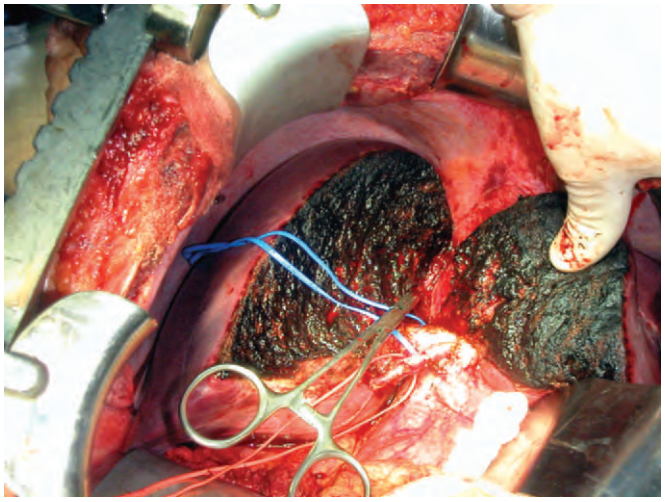

Figure 118–2. The magnitude of the living donor procedure is evident in this intraoperative photograph. The blue tape surrounds the vascular pedicle while a vascular clamp has been temporarily placed on a segment VIII hepatic vein.

(SRTR) have shown inferior outcomes for right lobe allografts than for whole organs from deceased donors.[24] The magnitude of this surgery and its potential impact on the donor are evident when viewing an intraoperative photograph (Fig. 118–2).

One of the greatest concerns regarding adult-to-adult living donor transplantation is the adequacy of the liver volume provided by a partial allograft. A pattern of graft failure is now recognized and referred to as the *small-for-size syndrome* (SFS).[25,26] This condition can occur when the actual or functional volume of an allograft is inadequate for the recipient. As a general rule, the liver is approximately 2% to 3% of body weight in healthy individuals, but there is considerable individual variability. An SFS graft is now generally accepted to have a graft-to-recipient weight ratio of less than 0.8%, or less than 30% to 50% of the standard estimated liver volume required by the recipient. Factors such as fatty change, donor age, duration of ischemia, and adequacy of venous drainage can contribute to a functionally diminished graft volume. Severe cholestasis, ongoing coagulopathy, and ascites are all prominent features of SFS syndrome. Although recovery is possible, outcomes are unpredictable and survival without retransplantation may be uncertain. Sepsis and multiorgan failure can follow, and retransplantation must often be performed within a narrow window of time. Because recipients of living donor organs have otherwise not drawn from the "pool" of deceased donors organs, RRBs generally grant additional points when necessary to ensure timely retransplantation in such circumstances.

The first report from the Adult-to-Adult Living Donor Liver Transplant Cohort Study (A2ALL) has recently been published.[27] This is the first multicenter prospective study of this procedure. Early results indicate a 1-year graft survival rate of 81%, with 13.2% of the grafts failing within 90 days. Biliary complications were most common, with 30% occurring early and 11% late. Graft failure was notably greater in transplant programs with less experience. The role of this procedure in the armamentarium of liver transplant surgeons is still in evolution.

TRANSPLANT PROCEDURE

Total Native Hepatectomy

Because of the location of the liver in the right upper quadrant, a number of different incisions have been used to gain adequate access for the transplant procedure. One of the more commonly used is a bilateral subcostal incision with an upward midline extension to the xyphoid process, euphemistically referred to as the "Mercedes Benz" incision. Often the xyphoid process is removed, both to increase exposure and to prevent laceration of the graft during manipulation. All ligamentous attachments to the liver are divided with cautery. The hepatoduodenal ligament is opened and the hepatic artery and bile duct are divided close to the liver so that maximal length is left with the recipient. The gastrohepatic ligament is divided and the suprahepatic and infrahepatic segments of the vena cava are isolated. If a standard orthotopic approach is used, the infrahepatic and suprahepatic vena cava will be clamped, and the intrahepatic portion will be resected with the native liver. If a "piggyback" approach is used, the liver is separated from the intrahepatic cava by dividing all penetrating hepatic veins up to the level of the main hepatic vein orifices and then leaving the native cava in situ. In some cases the portal vein is temporarily connected to the cava to maintain portal decompression during the anhepatic phase. The infrahepatic cava on the allograft is then oversewn, and the suprahepatic cava is anastomosed to the confluence of the native hepatic veins.[28] The choice of standard versus piggyback technique is largely one of familiarity. The standard approach allows more rapid hepatectomy but requires an additional infrahepatic anastomosis.

Venovenous Bypass

Venovenous bypass is a technique in which blood is rerouted from the clamped splanchnic and lower extremity venous circulation to the right heart via a nonheparinized centrifugal pump circuit. The decision to use venovenous bypass must be made before dividing the portal vein during total hepatectomy. The use of bypass is a matter of preference and patient selection. Once considered a major technical advance in liver transplantation, some transplant programs routinely use venovenous bypass, whereas in others it is virtually never implemented.[29] A third approach is selective use in cases in which the recipient demonstrates hemodynamic compromise during test clamping of the portal vein and infrahepatic vena cava. Another factor considered when using bypass is the size of the allograft versus the recipient's abdominal space. On occasion, bypass may be required to minimize edematous enlargement of the intestines, which might otherwise leave inadequate room

for a relatively large allograft, or when unmanageable portal hypertensive bleeding is present.

If a decision to use venovenous bypass is made, cannulas are placed above and below the diaphragm to bypass the occluded inferior vena cava and maintain cardiac filling during clamping. Hepatectomy using the piggyback technique may allow continuous flow in the vena cava without complete occlusion by clamping at the level of the hepatic veins. However, partial compromise of flow with this technique may still be associated with a significant decrease in venous return. Bypass cannulas may be placed by either a cut-down or percutaneous technique. In the former, the cannulation sites are usually the saphenous vein and axillary veins, whereas in the latter, the femoral and jugular or cephalic veins are used. Flow rates of 1 to 1.5 L/min can be achieved without difficulty with a simple centrifugal pump. Portal vein inflow is easily added to the inflow circuit by using an additional cannula if portal vein decompression is needed. In cases in which cannulation of the portal vein is difficult or dangerous, such as during retransplantation, portal decompression can be accomplished by cannulation of the inferior mesenteric vein. A heat exchanger is often safely added to the circuit to reduce ambient heat loss in the extracorporeal tubing.[30]

Back Table Preparation of the Donor Organ

Before implantation, the donor organ is prepared in a saline ice slush "back table" basin to minimize rewarming. All extraneous peritoneal and diaphragmatic tissue is excised, and any open veins are ligated. If the piggyback technique is to be used, the infrahepatic cava on the allograft must be oversewn. When high-potassium preservative solutions are used, a small cannula is placed in the donor portal vein to allow irrigation during implantation before reperfusion. Aberrant arterial anatomy is managed by reconstructing the vessels to provide a single inflow to all arteries.[31] It is paramount that all vessels be preserved to prevent segmental biliary ischemic changes or graft dysfunction.[32] Most aberrant left hepatic arteries do not need reconstruction because the left gastric artery from which they arise is preserved with the donor celiac trunk. The standard approach to reconstructing an accessory right hepatic artery is to create an anastomosis to either the gastroduodenal or the splenic artery or, to avoid smaller branches, to simply anastomose the superior mesenteric artery trunk to that of the celiac.

Implantation

Implantation of the donor organ must be accomplished quickly and efficiently to minimize warm ischemic time, which is calculated as the time that the organ is out of ice but not yet reperfused with blood. The first anastomosis is between the suprahepatic cava of the allograft and either the recipient cava or the native hepatic vein confluence if the piggyback technique is used. The second anastomosis is an end-to-end infrahepatic anastomosis if indicated. Both are usually performed with running nonabsorbable suture. If flushing of the preservative solution from the allograft is required, it is usually performed during the infrahepatic caval anastomosis. The third step is an end-to-end anastomosis between the donor and recipient portal veins. This is also performed with running suture, with care taken to avoid excessive redundancy, which could predispose to kinking and thrombosis. A growth factor roughly half the circumference of the portal vein is generally included in the anastomosis to prevent a purse-string compromise of the vessel's caliber. Before portal reperfusion the vein is vented to eliminate any clots that may have formed during clamping. If the hepatic arterial anastomosis can be completed quickly, some prefer to proceed to this anastomosis before reperfusion. This is typically a running anastomosis between the celiac trunk of the donor and the common hepatic artery of the recipient and is also given a growth factor. If the recipient artery is prepared in advance, this anastomosis can usually be completed in 5 to 10 minutes. However, if it appears that the arterial anastomosis will be difficult or more prolonged for any reason, it may be better to reperfuse the organ with portal blood flow only. In an effort to minimize the duration of warm ischemia, most transplant programs routinely reperfuse with portal flow alone and then perform delayed hepatic arterial reconstruction. The tradeoff between the additional warm ischemic time when performing the arterial anastomosis first versus the compromise of portal-only perfusion is a matter of debate and personal preference.

Reperfusion Syndrome

With reintroduction of blood flow to the allograft, significant hypotension or cardiac dysrhythmia (or both) can occur, which is collectively termed "reperfusion syndrome."[33] Such changes can occur across a spectrum from very mild and transient bradycardia and peaked T waves to cardiac failure and asystole. Sudden exposure of the heart to cold hyperkalemic fluid and the milieu of cytokines released from the organ are the probable causes. An ominous sign is escalating pulmonary artery pressure associated with falling systolic blood pressure, which often signals right heart failure. This scenario is more common in recipients with preexisting pulmonary hypertension, diastolic dysfunction, or any other condition leading to fixed cardiac output.

The 30-minute period immediately after perfusion distinguishes an experienced liver transplant anesthesiologist, who must contend with massive volume shifts, bleeding, severe acidosis and hyperkalemia, pulmonary hypertension, heart failure, and arrhythmias.

Biliary Reconstruction

After reperfusion of the graft when hemostasis has been achieved, attention can be turned to biliary reconstruction. The donor gallbladder is removed, after which the donor and recipient bile ducts are trimmed to

appropriate length as demonstrated by healthy bleeding from periductular vessels. Most often, an end-to-end anastomosis between the donor and recipient ducts is fashioned with interrupted absorbable suture. In the past, T-tubes were used commonly but were associated with a number of biliary complications.[34] Most programs now avoid the use of T-tubes except in unusual circumstances, such as concern over distal drainage because of stones or pancreatitis. In the event of a severe discrepancy in donor/recipient duct size, retransplantation, or compromised health of a recipient duct, as in the case of PSC, a Roux-en-Y reconstruction is performed.

INTRAOPERATIVE PROBLEM SOLVING

Portal Vein Thrombosis

Preoperative assessment of portal vein patency is vital to planning the transplant procedure. Patients with preexisting portal vein thrombosis (PVT) can be expected to have higher blood product requirements and more postoperative complications. When preoperative PVT is present, several management options exist. Most acute and chronic thrombi can be removed with eversion end-venectomy and restoration of portal venous inflow. If the lumen is obliterated or the occlusion extends substantially into the superior mesenteric vein, this technique may not be sufficient, and consideration should be given to use of an interposition venous graft. Iliac veins from the deceased donor must always be obtained at the time of organ procurement for just this purpose. An inability to identify a vessel with adequate portal flow to reperfuse the allograft is a rare, but potentially catastrophic occurrence. In such circumstances, flow from the inferior vena cava can be diverted to the allograft with a cava-portal anastomosis, which includes restricting flow in the proximal inferior vena cava. In a few cases such portacaval hemitranspositions have been reported to result in survival.[35] This technique leaves patients with portal hypertension, and they are often plagued by persistent ascites and a risk for gastrointestinal bleeding.

Hepatic Artery Failure

During preparation of the recipient hepatic artery, the dissection is usually carried back to at least the common hepatic artery to allow for an anastomosis of adequate size. If inflow at this level is inadequate, it may be necessary to create alternative hepatic arterial inflow. Donor iliac artery can be used to fashion a conduit from the infrarenal aorta to the donor hepatic artery. Alternatively, a conduit of donor iliac artery can be originated at the supraceliac aorta. Clamping the aorta at this level, however, has been associated with lumbar ischemia and paralysis. In some cases, hepatic artery flow has been found to be compromised by the recipient arcuate ligament, which is most often associated with significant respiratory variation in arterial flow. Dramatic improvement can be achieved with release of the celiac axis from this ligament at its origin at the aorta.

Split Grafts

The increasing shortage of deceased donor organs has led to a number of methods to expand the donor organ pool. One such option is that of dividing a healthy donor liver into two portions for use in two recipients. Most often, the left lateral segment is divided for use in a child, whereas the remaining right trisegment is used for an appropriately sized adult. On rare occasion an organ may be of adequate size and quality to split into true right and left portions that could potentially be used in two small adults. Depending on the nature of the split, the piggyback technique may be required. Extra effort must be made to ensure adequate recipient vessels for proper vascular reconstruction. Because a split graft carries the additional risk of bile leakage from the cut edge, a T-tube or internal stent in the case of hepaticojejunostomy may provide optimal decompression of the biliary tree. Patient selection is perhaps the most important aspect of split liver transplantation. The process of dividing an otherwise excellent allograft effectively compromises its function to the level of an "extended criteria" graft. Severely ill recipients are not likely to do well with split-liver transplants because of the risk for SFS syndrome, portal hyperperfusion, bile leak, and vascular complications.[36]

Graft Function and Primary Nonfunction

Assessment of graft function involves the use of clinical signs, laboratory analysis, and a certain amount of intuition. In the ideal scenario, the graft shows a healthy perfusion pattern and starts producing bile within 30 minutes of reperfusion. The organ should be soft, and hemostasis and hypothermia should improve rapidly. Acidosis should resolve over the next 12 to 24 hours, and hemodynamics, mental status, and urine output should improve. Hypoprothrombinemia should correct within 24 to 48 hours, and the peak elevation in aspartate transaminase (AST) should be unimpressive.

When a transplanted organ shows signs of dysfunction in the first several hours or days after transplantation, several factors must be considered. Vascular and other technical complications are discussed later. In the absence of any technical complications, severe graft dysfunction within 7 days is termed "primary nonfunction" (PNF).[37] This poorly defined condition is a diagnosis of exclusion and can occur across a spectrum from mild to catastrophic. Although most grafts do show at least partial function, the signs and symptoms of a truly nonfunctional graft may be easy to recognize. After reperfusion some grafts may appear hyperemic, "blebbed," and firm, and some may even fracture with manipulation. Recipient acidosis, persistent vasodilation, renal failure, coagulopathy, and even cerebral edema may occur. AST levels are usually greater than 5000 IU/ml. By definition, the end result of PNF is either retransplantation or recipient death. Rarely, in extreme circumstances, before a replacement organ can be identified, removal of the nonfunctional graft and creation of a temporary portacaval shunt may allow a patient to stabilize. Other manipulations, such as plasmapheresis or the use of experimental

artificial devices, have been attempted with varying degrees of success.[38] Because of the risk for rapid deterioration and death from PNF, UNOS guidelines allow for these patients to be listed at the highest priority level (status 1).

Most graft dysfunction is not as severe as true PNF. Less severe graft dysfunction is typically manifested as failure of the INR to correct, persistently climbing bilirubin, and moderate elevations in AST (3000 to 5000). Graft dysfunction of this sort is often accompanied by ileus, renal insufficiency, and if a T-tube is present, poor bile output. Some of these grafts may recover, provided that other major complications such as infection do not destabilize the patient. In other cases, graft dysfunction leads to a cascade of events resulting in multiorgan dysfunction and "failure to thrive," which may ultimately culminate in sepsis and death. It is up to the transplant team to weigh the risks associated with hopeful waiting for improved function versus retransplantation. Although early retransplantation can be technically straightforward, it is not to be taken lightly because it removes a donor organ from the pool and is clearly associated with increased morbidity and mortality. Even though the etiology of PNF is unknown, many associations do exist. Clearly, an important component of minimizing the consequences of PNF is proper matching of graft and recipient. A severely ill patient may offer an inhospitable environment for a marginal graft, thereby leading to a poor outcome.

EARLY COMPLICATIONS

Hepatic Artery Thrombosis

Hepatic artery thrombosis (HAT) occurs in 2% to 10% of liver transplants and is often associated with a suboptimal result.[39] Because the hepatic artery is the sole blood supply to the biliary tree, HAT results in biliary ischemia, which can have various manifestations, depending on the interval since transplantation. HAT within the first 1 to 2 weeks after transplantation, before anastomotic healing is secure, often leads to breakdown of the biliary anastomosis and bile leakage, hepatic necrosis, and intrahepatic abscess. Occasionally, in a liver heavily reliant on hepatic arterial flow, HAT will result in a picture of graft failure similar to PNF. HAT occurring more than 30 days after transplantation is typically manifested as a mild elevation in liver test results or as biliary stricture or hepatic abscess.

The diagnosis of HAT should be considered in patients with unexplained changes in liver tests or if biliary complications are identified. Doppler ultrasound can be useful, but it is very operator dependent. Definitive diagnosis of HAT requires either surgical exploration or angiography. If HAT is detected within several hours, there may be value in operative hepatic artery thrombectomy and revascularization. Biliary damage occurs quickly, however, and most patients with established HAT are best served by timely retransplantation.[40,41]

The mechanism by which HAT occurs is not always clear. Small donor arteries and the need for revision of the arterial anastomosis are risk factors for HAT, thus supporting the contention that technical factors play a great role. Other risk factors suggested by some studies, which are less intuitive, include an HCV-positive recipient, cytomegalovirus infection, and transplantation of a female donor organ into a male recipient.[39,42] HAT may also occur more frequently in patients with conditions causing postoperative peritonitis, such as pancreatitis or bacterial peritonitis.

In the past, UNOS guidelines allowed patients with HAT diagnosed within 7 days of transplantation to be listed at the highest priority (status 1). In recent years it has become increasingly appreciated that HAT is rarely associated with PNF-like organ dysfunction.[43] For this reason, current UNOS guidelines allow for HAT that occurs within 7 days of transplantation to receive a MELD score of 40, unless PNF criteria are met.

Portal Vein Thrombosis

Fortunately, PVT is exceptionally uncommon after liver transplantation and occurs in only about 1% of cases or less.[44] Because the portal vein provides the majority of oxygen delivery to the parenchyma, PVT is a reliably devastating event. Graft loss and patient death are common. Occasionally, thrombectomy may be possible if PVT is detected early. The main risk factor for PVT is the need for thrombectomy at the time of liver transplantation.

Biliary Complications

Complications related to the biliary tree occur in up to 15% of deceased donor liver transplant patients, with the reported incidence often greater than 30% in recipients of living donor transplants.[45,46] The most frequent complication is the development of biliary strictures, which usually occur at the site of the biliary anastomosis. Strictures at this level can often be managed with endoscopic or percutaneous interventional radiology techniques, but occasionally, surgical revision with hepaticojejunostomy is required. Intrahepatic strictures and those that are remote from the anastomosis generally reflect a more diffusely diseased biliary tree. HAT and recurrent PSC should be excluded. Other factors such as the use of extended criteria grafts, long ischemic times during transplantation, cytomegalovirus infection, and primary choledocholithiasis should also be considered. Many grafts with intrahepatic strictures can be temporized with aggressive and repeated percutaneous or endoscopic interventions, but some will require repeat transplantation because of recurrent cholangitis or secondary biliary cirrhosis.

Bile leaks typically occur within the first 1 to 2 weeks after transplantation and usually reflect either technical error or HAT. If the bile leak is of a large volume or is associated with peritonitis, surgical repair should be attempted promptly. A skilled endoscopist or radiologist can often manage smaller-volume leaks by stenting the anastomosis and decompressing the biliary tree.[47]

LATE COMPLICATIONS

Late complications of liver transplantation can be divided into those caused by rejection, those caused by immunosuppressant medications, and those caused by recurrent liver disease.[48]

Rejection

The number of drugs available for preventing rejection, as well as knowledge regarding mechanisms of action, optimal combinations, and timing of administration, continues to advance rapidly.[49] Acute cellular rejection occurs with a reported incidence of 10% to 40% in the first 6 months after liver transplantation. Typically, an episode of rejection is asymptomatic and the diagnosis is suspected on the basis of abnormal liver test results and is confirmed by liver biopsy. Treatment options include simply increasing the maintenance immunosuppression in mild cases and initiating a steroid pulse in those that are more severe. Rare cases of refractory rejection may require the use of a monoclonal or polyclonal antilymphocyte antibody, although this has become exceedingly rare in the past decade. Even though acute rejection itself does not appear to have an impact on long-term graft function, diseases such as hepatitis B and C may be associated with greater risk for recurrence in those with demonstrated rejection. This is thought to be the result of the intense period of immunosuppression used to treat rejection, which in turn allows more aggressive return of viral hepatitis. Chronic rejection is a poorly understood entity often referred to as "vanishing bile duct syndrome." This condition is characterized by a cholestatic pattern typically occurring several years after transplantation and is diagnosed by finding a paucity of bile ducts on liver biopsy. There is no effective therapy, and some of these patients may benefit from retransplantation.

Complications of Immunosuppressive Medications

Infection

Not surprisingly, immunosuppression puts individuals at increased risk for infection. The nature of that risk depends on a number of parameters, including the interval since transplantation, the intensity of immunosuppression, preexisting exposure to certain infectious agents, the age of the recipient, and the nature and extent of other comorbid conditions (Table 118–13). The risk for bacterial infection is greatest in the first few weeks after transplantation, as with any other surgical patient. Fungal infections are also a risk in the first 1 to 2 months and are largely related to the patient's overall state of deconditioning.[50] Patients who have been hospitalized immediately before transplantation, have been treated with broad-spectrum antibiotics, are malnourished, or have received steroids are at increased risk for postoperative fungal infections. High-risk donor/recipient cytomegalovirus exposure history can also predispose to infection or reactivation with that agent.[51] Three to 4 months after transplantation, *Pneumocystis*, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus all become a concern. Because of their impaired cellular-mediated immunity, transplant patients remain at higher than normal risk for viral and fungal infections for life. Prophylactic antibiotics are always given after transplantation, although the exact agent and duration vary between programs. An example of the success of prophylaxis is in the treatment of cytomegalovirus. This agent was once a common cause of morbidity and death after liver transplantation but now occurs at an incidence of less than 5%.

Malignancy

Although the exact mechanisms are still incompletely understood, immunity and malignancy are clearly at odds, and suppression of immunity favors malignancy. Transplant immunosuppression places recipients at increased risk for certain types of de novo malignancy, and a threefold to fourfold increased incidence of cancer as compared with age-matched controls is expected. The largest increases are in skin cancer in sun-exposed areas. Although the incidence of other primary neoplasms, such as those of the breast and colon, are not increased in solid organ recipients, when present, they tend to demonstrate more aggressive behavior than would otherwise be expected in a nonimmunosuppressed individual. Transplant recipients in general must be considered to

Table 118–13 Immunosuppression Profiles

Agent	Use	Toxicity	Typical Duration
Cyclosporine	Primary immunosuppressant	Nephrotoxicity, neurotoxicity, hyperkalemia	Lifelong
Tacrolimus	Primary immunosuppressant	Nephrotoxicity, neurotoxicity, hyperkalemia	Lifelong
Mycophenolate	Used as an adjunct to the primary agent	Diarrhea, leukopenia	As needed
OKT3	Induction	Cytokine storm, pulmonary edema	5 days
Interleukin-2 receptor antibodies	Induction		2 weeks

be at high risk for malignancy and should undergo all of the recommended screening tests with vigilance.

Cardiovascular Side Effects

Cardiovascular disease has become one of the leading causes of long-term morbidity in liver transplant survivors.[52] Several factors probably contribute to this morbidity, including the increasing frequency of older and obese transplant recipients and medication-related dyslipidemia and diabetes.

RESULTS

Disease Recurrence

Recurrence of underlying liver disease is a common cause of long-term morbidity and mortality in liver transplant recipients. Because of its prevalence as an indication for transplantation, its propensity to reinfect the new allograft, and our relatively ineffectual ability to treat it in the post-transplant setting, recurrence of hepatitis C is the single greatest problem facing liver transplant physicians and their patients.[53] In patients with HCV, graft reinfection is virtually guaranteed, but the clinical consequences are most often minor for at least 5 years. An unfortunate unpredictable subgroup will manifest early aggressive recurrence, often leading to graft failure within the first year. The mainstay of treatment at present is interferon-based viral suppression. When and how to treat post-transplant hepatitis C is currently a matter of intense interest and activity. In the absence of new effective treatments, many patients can be expected to again progress to advanced liver disease within 10 years. Clearly, more effective HCV treatment strategies will represent a major advance in the field of liver transplantation.

Other diseases can also recur after transplantation. In the past, recurrence of hepatitis B was universal, with dismal outcomes. Attentive adherence to present antiviral therapies has essentially eliminated this problem. PBC, PSC, and autoimmune hepatitis are all diseases that do recur with varying incidence.

FUTURE ASPECTS OF LIVER TRANSPLANTATION

Organ Shortage

As stated earlier, the greatest crisis facing the field of liver transplantation remains the donor organ shortage. The best option for any recipient, especially those who are quite ill, is to receive a whole-organ allograft from a stable deceased donor. Many efforts to expand the pool of available organs have been aimed at marginal, or "extended criteria," organs (Box 118–3), including organs from suboptimal circumstances, such as older or less stable donors, non–heart-beating donors, or those with comorbid conditions such as significant steatosis. It should also be appreciated that "split" allografts, including those from living donors, represent a form of "extended criteria" grafts that are in many ways inferior to a whole organ. The most significant advances will probably be those that successfully increase rates of organ donation, such as registries and implied consent laws. The ultimate answer remains more successful prevention or treatment of diseases that lead to transplantation.

Box 118–3 Deceased Donor Extended Criteria

- Steatosis
- Hepatitis B core antibody positive
- Hepatitis C positive
- Age >65 years
- Non–heart-beating donor

Future Directions

In the immediate future the field of liver transplantation will continue to be dominated by a search for effective treatment of hepatitis C and for solutions to the donor organ shortage. Clearly, these two are related, and perhaps the single greatest potential advance in this field would be the development of more effective treatment of hepatitis C. Another approach that would both decrease transplant organ demand and increase organ longevity would be the development of antifibrotic agents that slow or halt the progression of hepatic fibrosis, thereby having an impact on most chronic liver diseases. The fields of stem cell research and xenotransplantation also hold promise as potential additional treatment options for liver failure either as cellular or whole-organ replacements. Finally, as the number of donors and recipients affected by living donor liver transplantation grows, their long-term surveillance will continue to shape the role played by this operation.

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Chapter

119

Fulminant Hepatic Failure and Bioartificial Liver Support

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Acute liver failure (ALF) is a devastating condition.[1] Fulminant hepatic failure (FHF) is the most severe form of ALF and is distinguished by the rapid development of hepatic encephalopathy (<8 weeks from symptom presentation).[2,3] Up to 72% of all FHF cases are due to acute viral hepatitis, and, in most instances, hepatic failure is a result of massive hepatocyte necrosis.[4] Despite improvements in our understanding of the disease and advances in critical care, medical management alone can achieve only a 10% to 50% survival rate.[5,6] Orthotopic liver transplantation (OLT) has greatly improved survival to 60% to 90%,[5,7-9] but many FHF patients are not transplanted primarily due to limited organ availability.[4] Furthermore, the donor organ deficit is increasing as indications for liver transplantation are broadened.[10] Even as new modalities such as living-related liver transplantation become widely accepted, it is unlikely that the projected additional supply of organs will meet increasing demand. Additionally, many patients with hepatic failure do not qualify for transplantation because of metastatic cancer, concomitant infection, active alcoholism, drug abuse, or concurrent medical problems. Still others do not recover after OLT because of irreversible brain damage caused by preoperative hepatic encephalopathy with elevated intracranial pressure (ICP).

The liver has a remarkable regenerative capacity, and some patients with ALF, especially those with toxic insult and viral hepatitis, have the potential for spontaneous recovery. The likelihood of significant hepatic regeneration increases if short-term metabolic and physiologic support can be provided. An artificial liver support system could serve as a "bridge" to either OLT or recovery of the native liver. The development of such a system is a major challenge. Owing to the complexity of the liver and our poor understanding of the pathogenesis of hepatic failure, it is difficult to design an effective liver support system. Since the leading cause of death in FHF is massive cerebral edema, an artificial liver should be able to either arrest or reverse cerebral edema and intracranial hypertension. Additional desirable beneficial effects should include improvement of hemodynamic parameters and correction of coagulopathy and other metabolic and physiologic derangements.

ACUTE LIVER FAILURE

The classic definition of ALF by Trey and Davidson is based on encephalopathy developing within 8 weeks from the onset of illness[2]; it recognizes that clinical findings and prognosis vary depending on the interval between the onset of jaundice and development of encephalopathy. Bernuau and associates[11] defined FHF as ALF complicated by encephalopathy occurring within 2 weeks after the onset of jaundice. The term subfulminant hepatic failure (SHF) was introduced to describe ALF complicated by encephalopathy developing 2 to 12 weeks after the onset of jaundice.[11] Despite the various definitions and classifications of ALF, common to all of them is lack of preexisting liver disease. The term FHF is used in the following section to refer to ALF of various etiologies according to the definition of Trey and Davidson.

Etiology

The etiology of FHF falls in one of four groups: (1) viral, (2) drug induced, (3) toxin induced, and (4) miscellaneous. A multicenter study demonstrated that acetaminophen toxicity was the main cause of FHF (20%) followed by FHF of indeterminate cause (15%).[12]

Viral Hepatitis

The incidence of FHF and SHF in hepatitis A viral (HAV) infection is low; it occurs in less than 0.01% of cases.[11] Young patients with HAV infection rarely develop FHF, and survival with medical therapy is relatively high (40% to 60%). Relapse of HAV occurs in 10% of patients, usually within 2 to 3 months after initial clinical improvement. Relapse is recognized by an increase in serum transaminases and bilirubin with reappearance of the virus in the stool. If encephalopathy occurs during this period, the outcome is poor.[13]

Hepatitis B viral (HBV) infection is the most common cause of viral-induced FHF.[12,14,15] As is the case in HAV infection, HBV infection results more commonly in FHF than SHF. Hepatitis B surface antigen (HBsAg) and HBV DNA may be absent in some cases of FHF secondary to HBV infection.[15] The survival rate in patients positive for HBsAg on presentation (17%) is much lower than that of patients who are HBsAg negative (47%).[11] Clearance of HBsAg and HBV DNA results in better survival rates as well as decreased incidence of recurrence after emergency liver transplantation.[16] Hepatitis D virus (HDV or delta agent) is a defective virus that utilizes the HBsAg as the envelope protein. HDV RNA is detected in only 10% of patients with fulminant hepatitis D.[17] HDV can occur either as a coinfection with HBV or as a superinfection in patients with prior HBV.[18] Among patients with FHF, HDV coinfection is more common than superinfection; however, HDV superinfection is associated with higher mortality and more often predisposes to chronic liver disease than does HDV coinfection.[19]

Indeterminate

Previously, FHF of indeterminate cause was attributed to non-A, non-B viral hepatitis. The extent of the contribution of HCV infection to the indeterminate group is unclear. In contrast to hepatitis A and B virus infections, SHF is more common than FHF in hepatitis C patients. Despite the availability of advanced serologic testing, there are still many cases of FHF and SHF with indeterminate cause.[20,21]

Drug-Induced Hepatotoxicity

Drug toxicity accounts for 35% of all cases of FHF and SHF and usually runs a subfulminant course.[12] Drug ingestion results in liver injury in less than 1% of patients, with 20% of those patients developing FHF or SHF. The risk of either FHF or SHF increases with an increase in total drug dose, simultaneous ingestion of other drugs that induce or inhibit hepatic enzymes, and continuation of drug administration after the onset of liver disease.[11] Acetaminophen toxicity is the most common cause of drug-induced ALF. Acetaminophen-induced FHF is usually associated with better prognosis than FHF caused by nonacetaminophen drugs such as isoniazid, psychotropic drugs, antihistamines and nonsteroidal anti-inflammatory drugs.[22] Halothane-induced FHF occurs within 2 weeks of general anesthesia and is associated with a high mortality.[23]

Toxins

Mushroom poisoning and exposure to industrial hydrocarbons are implicated in many cases of toxic liver injury. In mushroom poisoning, the active agents are heat stable and are not destroyed by cooking. Liver damage from mushroom toxins is delayed and is usually preceded by several days of vomiting and diarrhea. Mushroom toxicity is associated with up to 22% mortality in one series.[24] Emergency liver transplantation can be successful.[25] Industrial hydrocarbons, such as carbon tetrachloride and trichloroethylene, are rare causes of FHF. In third-world countries, aflatoxin and herbal medicines have been implicated as causes of FHF.

Wilson's Disease

Wilson's disease may present as FHF or SHF with intravascular hemolysis and renal failure.[26,27] Family history of liver and neurologic disease, Kayser-Fleischer rings, and low serum ceruloplasmin levels help establish the diagnosis. Acute, decompensated Wilson's disease is associated with high mortality, and emergency liver transplantation is indicated.[28]

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy is a rare cause of FHF with a high mortality rate for both mother and infant. Delivery of the fetus results in regression of hepatic microvascular steatosis and abnormal liver function tests for the mother. The risk of FHF is increased with misdiagnosis and continuation of pregnancy. Liver transplantation has been successfully performed.[29]

Treatment Strategies

Standard Medical Therapy

Medical management of FHF has to be multidisciplinary because of the complexity of the disease and its rapid progression to multiple organ failure.[30] Hemodynamic and respiratory support and prevention and treatment of cerebral edema are the major goals of therapy. Patients with severe FHF are managed in an intensive care unit. General measures are instituted with invasive monitoring, including placement of a pulmonary artery catheter for cardiovascular pressure and mixed oxygen measurements, arterial line, continuous pulse oximetry, urinary catheter, and nasogastric tube placement. Patients in stage III/IV encephalopathy with brainstem dysfunction are placed on ventilatory support and have an ICP monitor installed at the bedside for ICP and cerebral perfusion pressure (CPP) monitoring. The head of the bed is elevated, noise in the room is kept at a minimum, and lighting is sparingly used to avoid agitating the patient. Vital signs, neurologic assessment, intravenous input, and body fluid output are recorded hourly. In patients with neurologic dysfunction, a head computed tomographic scan is obtained. Liver function tests, coagulation tests, complete blood cell count, serum electrolytes, ammonia, lactate, blood urea nitrogen, and creatinine

levels are determined at regular time intervals. Arterial gases are determined serially. Standard medical therapy includes hyperventilation and administration of mannitol and lactulose. Supportive measures are initiated to correct electrolyte (e.g., hypocalcemia, hypophosphatemia, and hypokalemia) and acid-base (e.g., lactic acidemia) imbalances; hypoglycemia; and respiratory, coagulation, and hemodynamic abnormalities.

Management of elevated ICP involves use of hyperventilation and mannitol infusion. Patients are usually sedated with a short-acting agent such as fentanyl in small boluses prior to any procedure, nasotracheal suction, venipuncture, or line placement. Mechanical hyperventilation lowers ICP by lowering carbon dioxide pressure to 25 to 30 mmHg. This maximizes cerebral vascular constriction and reduces blood flow. This vascular effect progressively diminishes after 6 hours of therapy, though clinical response may be apparent for days. Mannitol infusion has up to an 80% response rate in patients without renal failure. Serum osmolality should be measured frequently and maintained at 300 to 320 mOsm. Mannitol should be withheld if osmolality is 320 mOsm or higher, if renal failure occurs, or if oliguria and rising serum osmolality develop simultaneously. Repeated administration of mannitol may reverse the osmotic gradient. Thus mannitol should be discontinued if the ICP does not respond after the first few boluses. Patients who fail to respond to conventional therapy could be placed in barbiturate coma. In our experience, however, we find the barbiturate effect on ICP to be transient and unpredictable.

Fluid management in FHF requires maintenance of euvolemia to avoid fluid overload, pulmonary edema, and dehydration. Extreme fluid shifts should be avoided—the presence of cerebral edema and intracranial hypertension requires careful fluid administration to avoid expansion of the intravascular space and exacerbation of cerebral edema. Renal dialysis and filtration are used, as needed.[30] Infection poses a serious threat to AHF patients both by placing them at risk for sepsis and by being a contraindication to liver transplantation. Although prophylactic antibiotic administration is not advocated without suspicion of active infection, the threshold for starting antibiotics should be low, because the usual clinical presentation with fever and leukocytosis may be absent in 30% of FHF patients.[31]

Bleeding is a frequent complication of FHF. Plasma activity of all clotting factors synthesized by the liver (II, V, VII, IX, and X) is depressed in FHF. Factor II, with a half-life of 2 hours, is the first to be depleted and also the first to be repleted during recovery. Prothrombin time (PT) is invariably prolonged, reflecting a generalized clotting factor deficiency, and is used as one of the criteria for determining the likelihood of spontaneous recovery. We use fresh frozen plasma (FFP) infusion as needed to partially correct coagulopathy, especially in patients with an ICP monitor in place or patients actively bleeding. At some centers, FFP transfusion is withheld and the PT is followed carefully. However, intracranial bleeding with its neurologic sequelae is a devastating complication of coagulopathy in FHF. Thrombocytopenia and abnormalities of platelet function are frequently encountered in FHF. We transfuse platelets either for thrombocytopenia (platelet count <50,000/mm^3) or in actively bleeding patients.

Liver Transplantation

Investigators at King's College Hospital in London have compiled prognostic criteria predictive of poor outcome following medical therapy and hence the need for emergency liver transplantation.[32] Underlying cause was found to be the single most important variable predicting outcome. Patients were divided into two groups based on either acetaminophen toxicity or all other causes. Other significant variables included age, degree of encephalopathy, serum pH, PT, admission serum creatinine, and bilirubin. Patients who met those criteria in either group had a 95% chance of dying with medical therapy alone and were identified as candidates for emergency liver transplantation. In another study, plasma factor V level and age were found to be independent predictors of survival.[33] The criteria for liver transplantation were the presence of hepatic encephalopathy (stage 3 or 4) associated with either (1) a factor V level less than 20% of normal in patients less than 30 years of age or (2) a factor V level less than 30% of normal in patients older than 30 years of age. We use the King's College criteria on admission as guidelines to predict outcome with medical therapy. Once the initial assessment is completed, the decision for an emergency evaluation for liver transplantation is completed within 12 to 24 hours. Additionally, an extensive neurologic evaluation is undertaken to rule out irreversible brain damage due to intracranial hypertension.

LIVER SUPPORT SYSTEMS

Use of artificial liver support systems has been proposed as a means of treating patients with ALF. This is based on the assumption that such systems can provide temporary support until the liver recovers or until an organ becomes available for transplantation. The complexity of the liver is so great, and the number of physiologic, biochemical and metabolic functions it performs so large, that no realistic method of permanent liver replacement exists short of liver transplantation. Most currently studied liver support therapies are therefore aimed toward providing temporary support.

The major limitation to the provision of effective liver support is lack of clear understanding of the etiology of ALF and the mechanism of development of encephalopathy, hepatic coma, and cerebral edema. Various toxic factors have been implicated; as a result, detoxification therapies were introduced to remove either a broad range of suspect molecules or specific toxins. It would appear that in ALF, the goal would be to remove toxins responsible for the development of cerebral edema. However, it is unknown whether toxins cause the syndrome. It is possible that a specific metabolic imbalance or absence of protective factor(s) synthesized or processed by the liver are responsible. In this case, detoxification therapy will not be effective. Also, it is

difficult to predict whether removal of a specific toxin will have a positive or negative effect. For example, plasma interleukin (IL)-6 levels are elevated in patients with severe ALF. IL-6 can have toxic effects on hepatocytes and other cells. However, it is also a potent stimulus of liver regeneration and its absence may impair the liver's ability to regenerate. If the therapeutic goal is liver cytoprotection, then IL-6 should be removed; if on the other hand the goal is stimulation of liver regeneration, it should not be removed. The complexity of the situation increases when one realizes that some of these compounds have inhibitory or stimulatory effects depending on their plasma and tissue levels.

Some argue that a major therapeutic goal in ALF should simply be provision of additional liver mass. After all, replacing the diseased liver with a healthy one is effective. However, auxiliary liver transplantation, which provides a substantial increase in liver mass, has not emerged as a successful therapy in ALF. Similarly, in experimental animals with ALF, treatment with a small number of cells in a liver support system resulted in profound changes in the native liver's regenerative response pattern as well as reduction in serum levels of transforming growth factor-β, a potent inhibitor of liver regeneration.[34]

The findings from the basic research and clinical studies are indeed confusing and often conflicting. In this backdrop, investigators are attempting to design rational liver support systems. There is lack of clear therapeutic objectives. Therapeutic options are based on detoxification, provision of missing synthetic functions, provision of cytoprotective factors, provision of factors that induce liver differentiation, administration of liver mitogens to promote regeneration, and various combinations of the above. There is a need for a concerted effort to carry out further basic, as well as clinical, research to better understand the pathophysiology of liver failure. This in turn will allow development of appropriately targeted therapies.

The Need for Liver Support Systems

There is a shortage of available organs for transplantation. In recent years, indications for liver transplantation have been expanded. Patients with small hepatocellular carcinoma are being transplanted. The age range for recipients has been expanded at both ends of the spectrum. Patients with more than one failing organ are being offered liver and heart, liver and kidney, or a cluster of organs. The number of patients listed for transplantation has increased. In addition, there has been an increase in the number of patients dying while waiting for a transplant. Increased need for organs may result in marginal organ transplantation with suboptimal results, high retransplantation rates, and additional demands on the donor organ pool. There is a need for provision of temporary liver support in severe ALF until either the liver regenerates and recovers or an organ becomes available for transplantation. The potential impact of an effective, focused, and well thought-out liver support treatment strategy could be significant improvement in patient survival with or without transplantation.

Box 119–1 Liver Support Systems

Nonbiologic Systems

- Plasma exchange
- Hemodialysis
- Hemofiltration
- Sorption therapy
  - Nonspecific (i.e., charcoal hemoperfusion)
  - Specific (i.e., resin)
  - Combined-system therapy (i.e., hemodialysis/hemoperfusion)

Biologic Systems

- Human "hepatocyte lines" (i.e., tumor derived)
- Porcine hepatocytes (fresh, cryopreserved)

Current Technologies

Liver support approaches traditionally have involved two broad categories: use of nonbiologic and biologic systems. A list of system types is shown in Box 119–1.

Nonbiologic Systems

Plasma Exchange The aim of plasma exchange in ALF is removal of the patient's plasma and replacement with normal plasma to reduce the level of circulating toxins and to provide deficient essential factors (e.g., clotting factors). Initial uncontrolled trials achieved only transient biochemical and neurologic improvements but demonstrated no effect on patient survival.[35-40] Kondrup et al.[41] investigated the effect of repeated, high-volume plasma exchange in FHF patients and reported some beneficial results that need to be confirmed in a prospective, controlled trial. Plasma exchange is currently being used primarily to correct severe coagulopathy.

Hemodialysis It is based on diffusive removal of small-molecular-weight (MW) toxins. In early studies with hemodialysis utilizing low-MW cut-off membranes (i.e., cellulose, cuprophane), lowering of blood ammonia was associated with only transient improvement in the level of consciousness.[42-48] The results of hemodialysis utilizing poly-acrylonitrile membrane permitting passage of substances with MW as large as 15 kDa seem promising. However, prospective, controlled trials have not been carried out. Stange et al.[49] introduced the Molecular Adsorbent Recycling System (MARS) that utilizes a "tight" membrane impregnated with albumin; this facilitates rapid and efficient transport of albumin-bound substances such as bilirubin. Albumin in the dialysate is "regenerated" during continuous recirculation in a closed-loop system through adsorbents. Initial results in patients with ALF were encouraging; however, controlled clinical trials are needed to establish if the technology has any therapeutic value. The MARS system has been

shown to improve early survival in a subgroup of patients with hepatorenal syndrome in a prospective, controlled, randomized study.[50]

Hemofiltration Denis et al.[51] introduced this method in which putative neurotoxins, including "middle" protein-bound molecules, freely pass across a hollow-fiber wall to treat patients with liver failure. Studies by Matsubara,[52] and Yoshiba,[53] and their colleagues, in patients with ALF, reported promising results. However, prospective, controlled trials have not been carried out.

Charcoal Hemoperfusion Since the initial pioneering work of Yatzidis,[54] charcoal hemoperfusion has been the most thoroughly tested sorption therapy for liver failure. Earlier, nearly all investigators signaled improvement in the patients' neurologic status and reported survival rates higher than those seen following hemodialysis.[55,56] A later, controlled clinical trial reported less favorable outcomes with charcoal hemoperfusion.[57] An interesting system combining hemodialysis with sorption therapy has been introduced by Ash et al.[58] This is a single-access device utilizing a parallel plate and a cellulose membrane dialyzer in which a patient's blood is circulated against a proprietary mixture of finely powdered charcoal, cation-exchangers, electrolytes, macromolecular wetting agents, and other chemicals. The charcoal is very finely powdered, and its adsorptive surface area is so large that toxins can be removed from the blood over long periods without saturation. From preliminary clinical studies it appears that the system has significant capacity to remove drugs and small toxins but has no beneficial effects on the clinical course of ALF. Large-scale, appropriately controlled, prospective multicenter trials with this system have not been carried out.

Resin Hemoperfusion Hemofiltration using cationic resins was introduced for the treatment of hepatic coma by Schechter et al.[59] Resins (neutral, cationic, anionic) efficiently remove from plasma protein-bound, nondialyzable compounds (i.e., bilirubin, bile acids, barbiturates). Unfortunately, resins are equally efficient in adsorbing clotting factors and other molecules and can cause hypotension, thrombocytopenia, leukopenia, and bleeding. In general, the ability of resin hemoperfusion to reverse hepatic encephalopathy has not been demonstrated. It could, however, have potential value as a component of more complex detoxification systems or devices utilizing other approaches (i.e., plasma exchange, biologic devices).

Biologic Systems

The concept of bioartificial liver (BAL) support system was introduced by Sorrentino in 1956[60]; he demonstrated that fresh liver tissue homogenates could metabolize ketone bodies, barbiturates, salicylic acid, and ammonia. Subsequently, Reuber hepatoma cells placed in the extrafiber space of a hollow-fiber cartridge were shown to conjugate bilirubin.[61] Using a similar bioreactor and isolated human hepatocytes, Hager et al.[62,63] demonstrated ureagenesis, protein synthesis, and drug metabolism. Eiseman et al.[64] and Olumide et al.[65] carried out a series of studies in which hepatocytes were placed in several devices, including a centrifuge, a dialyzer, and a perfusion chamber. These investigators introduced two important concepts: (1) use of plasma separation, and (2) placement of liver cells in a chamber within a high-flow plasma recirculation loop. Uchino et al.[66] also utilized high-flow plasma recirculation; in their device liver cells were cultured on collagen-coated glass plates. However, neither Eiseman nor Uchino tested their systems clinically.

More recently, advances in hepatocyte isolation and culture techniques, improved understanding of hepatocyte/matrix interactions, availability of new biomaterials, and improved hollow-fiber technology resulted in the development of a new generation of liver assist devices utilizing intact functional hepatocytes. Some of these BAL systems are currently being tested clinically.

The first clinical report of use of a liver support system utilizing isolated hepatocytes is that of Matsumura,[67] who converted a dialyzer to an "artificial liver" by adding a cryopreserved rabbit liver cell suspension to the dialysis chamber. In addition, he replaced the usual cuprophane membrane with a cellulose membrane permeable to middle-range molecules but not proteins. Although some favorable biochemical effects were noted (i.e., a reduction in serum bilirubin), there was no effect on outcome and no further use of this system was reported.

Sussman et al.[68,69] developed an extracorporeal liver assist device (ELAD) utilizing whole blood perfusion through a conventional hollow-fiber bioreactor loaded with a cell line (C3A) derived from human hepatoblastoma (HepG2). In the initial group of patients, no significant effect on disease outcome was noted. In patients with ALF, treatment with ELAD had no effect on clinical outcome when compared to patients receiving standard therapy.

Several other systems are currently in various stages of laboratory and clinical testing.[70-83] These systems have several elements in common: liver cells (xenogeneic or human), bioreactors of varying designs and an extracorporeal circulation system for plasma or blood incorporating oxygenators, temperature control mechanisms, and pumps. One system that stands out because its design more closely resembles normal liver architecture is that of Gerlach et al.[84,85] They developed a Modular Extracorporeal Liver System (MELS) based on a multicompartment bioreactor in which four interwoven hollow-fiber capillary systems carry out independent functions: medium inflow, cell oxygenation/carbon dioxide removal, and medium outflow. Self-assembled aggregates of mixed porcine liver cell populations remain in close proximity to inflow, outflow, and oxygenation membranes. The bioreactor can accommodate up to 650 g of hepatocytes. In vitro, the MELS system maintained hepatocyte-specific functions for longer than 2 months. The results of animal studies were encouraging, and eight patients with ALF were successfully bridged to transplantation. The main difficulty with the MELS system is that it is a complex system that must be maintained in a "standby mode" and used within a 2- to 3-week period. A multicenter, controlled, prospective clinical trial needs to be carried out to determine the

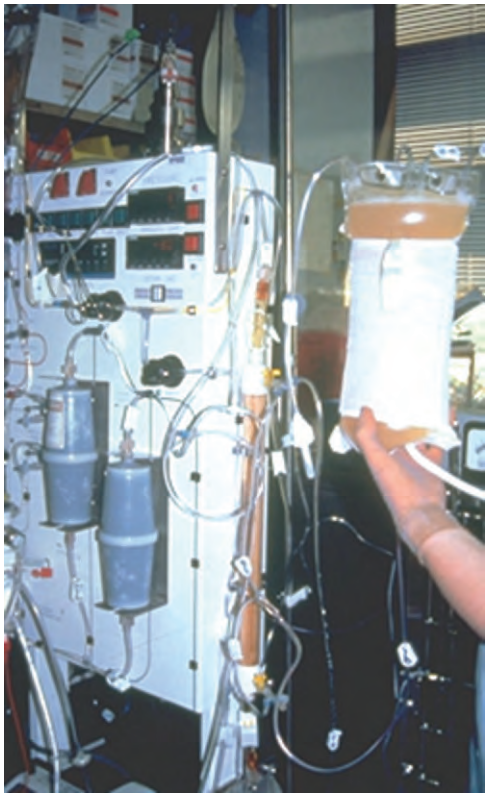

Figure 119–1. Thawed, cryopreserved porcine hepatocytes suspended in Ringer's lactate solution are being loaded into a hollow-fiber bioreactor in the bioartificial liver circuit.

feasibility of the technology in the field and the efficacy of the system.

Our group has led the development of a BAL that has been tested in pilot and phase I clinical trials (HepatAssist System; Circe Biomedical, Inc., Lexington, MA).[86-93] This is the first true hybrid BAL where the function of a hepatocyte bioreactor was supplemented by a column filled with activated cellulose-coated charcoal (Adsorba 300C; Gambro BCT). Plasma was removed from patients using a plasma separator (Spectra, COBE, Gambro BCT) and recirculated in a loop consisting of a reservoir, a charcoal column, an oxygenator, a heater, and a hollow-fiber bioreactor. The extra-fiber space of the bioreactor was filled with 7 billion to 9 billion cryopreserved porcine hepatocytes. Cryopreserved cells were thawed and rinsed and were placed in the devices just prior to clinical use (Fig. 119–1). An attachment surface was provided by the incorporation of collagen-coated dextran microcarriers. The microcarriers enhanced distribution of the cells amidst the fibers. It is worth noting that by placing the charcoal column before the hepatocyte bioreactor in the plasma circuit, porcine hepatocytes were likely to be "protected" from possible toxic effects of FHF plasma. We tested the BAL extensively in vitro and in vivo in animals and in patients. Patients were admitted to a dedicated liver support unit. Invasive hemodynamic monitoring (peripheral arterial catheter and pulmonary artery catheter) was instituted after blood product administration to partially correct coagulopathy. All patients received standard medical care and, additionally, BAL treatments (one to five) each lasting 6 to 7 hours. Patients with signs of intracranial hypertension had an ICP monitor placed at the bedside (subdural) for ICP and CPP monitoring. Patients were intubated endotracheally when in stage 4 encephalopathy and were placed on ventilator support. BAL treatments were well tolerated, and no technical problems were identified during BAL therapy. A total of 32 patients were treated with the BAL (29 FHF and 3 primary nonfunction patients post-transplant); 84% of the patients survived with or without transplantation. Patients experienced remarkable neurologic improvement with reversal of the decerebrate state after BAL treatments; posturing, anisocoria, sluggish pupil reactivity were lessened, and patients became more responsive to external stimuli. Brainstem function improved, and there was significant reduction in ICP with a concomitant increase in CPP. Other effects of BAL treatment included a decrease in ammonia, transaminases, and bilirubin levels and a significant increase in the ratio of branched chain to aromatic amino acids.

BAL: Prospective, Randomized Clinical Trial Based on the findings just discussed and observations, the safety and efficacy of the BAL were evaluated in a prospective, randomized, controlled, multicenter trial in patients with severe ALF.[93] A total of 171 patients (86 control and 85 BAL) were enrolled in the trial. Patients with FHF/SHF and primary nonfunction following liver transplantation were included. Data were analyzed with and without accounting for the following confounding factors: liver transplantation, time to transplant, disease etiology, disease severity, and treatment site. For the entire patient population, survival at 30 days was 71% for BAL versus 62% for control ($P = 0.26$). After exclusion of primary nonfunction patients, survival was 73% for BAL versus 59% for control ($n = 147$; $P = 0.12$). When survival was analyzed accounting for confounding factors, in the entire patient population, there was no difference between the two groups (risk ratio [RR] = 0.67; $P = 0.13$). However, survival in FHF/SHF patients was significantly higher in the BAL compared to the control group (RR = 0.56; $P = 0.048$). This is the first prospective, randomized, controlled trial of an extracorporeal liver support system, demonstrating safety and improved survival in patients with FHF/SHF.

The Future of Liver Support

Technology currently used to construct a liver support system will undergo multiple refinements based on the resolution of a number of practical and theoretical considerations. Future prospects and limitations for liver support technology development are summarized in Box 119–2.

A number of goals need to be achieved to ensure further progress in the field of artificial liver support. These include the following:

Box 119–2 **Liver Support Systems: Future Prospects and Limitations**

Nonbiologic Systems

No large, controlled, randomized clinical trial

Lack of understanding of mechanism of action

Biologic Systems

Human hepatocytes

- Large-scale use of human organs for hepatocyte harvest is impractical
- Hepatocyte cryopreservation remains a challenge
- Stem cell use to develop hepatocyte lines is promising, but the technology needs to be further developed

Porcine hepatocytes

- Probably best cell for use in biologic systems in the immediate future
- Use is limited by risk of retroviral transmission from animals to humans

- Development of primary normal human hepatocyte lines expressing high levels of liver-specific functions. Currently, no highly differentiated human hepatocyte line is available for liver support therapy.
- Ability to expand fetal or adult liver stem cells and subsequently induce their differentiation should allow their use in liver support systems. Renewed interest in stem cell technology development may lead to availability of novel liver cell populations for clinical use.
- Improved understanding of the xenogeneic immune response in humans and development of strategies to manipulate it, as well as establishment of transgenic animal colonies for hepatocyte harvest, may result in the establishment of a stable source of cells for BAL use.
- Enhancement of differentiated hepatocyte functions in liver support systems by utilizing new types of matrix, growth factors, and culture techniques.
- Determination of the optimal hepatocyte mass is needed in liver support systems to provide adequate metabolic support.
- Improvement of hepatocyte cryopreservation technology is essential for transporting cells and allowing their widespread use.
- Development of more efficient bioreactor designs.
- Development of novel modular systems to meet specific clinical needs.
- Improvement in the methods of plasma separation, allowing longer and safer treatments.
- Development of novel, safer anticoagulants to allow effective whole blood perfusion.

This chapter summarizes significant advances made in the past 50 years in the area of artificial liver support for the treatment of ALF patients. With improved understanding of the pathophysiology of ALF and further technical innovations in the areas outlined earlier, the goal of provision of effective and practical liver support therapy can become a reality.

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Chapter

120

Vascular Diseases of the Liver

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The topic *vascular diseases of the liver* encompasses an array of disparate clinicopathologic entities with the common thread that they specifically affect the hepatic vasculature. Furthermore, they can be arbitrarily classified into those that involve the hepatic arterial blood supply, those that involve the portal vein, and those that involve the hepatic veins. Most hepatic vascular lesions are uncommon, making their diagnosis and management a challenge. In this chapter, disorders of the hepatic artery and hepatic veins are presented. Disorders of the portal venous system, specifically portal hypertension and portal vein thrombosis, are addressed as a separate topic in Chapter 125.

HEPATIC ARTERY DISORDERS

Aneurysms of the Hepatic Artery

Hepatic artery aneurysms are rare, comprising about 10% to 20% of all visceral aneurysms. True aneurysms may be the result of systemic diseases including atherosclerosis or vasculitides such as polyarteritis nodosa (PAN).[1] They most commonly are solitary, involve the extrahepatic portion of the artery, and are 3 to 4 cm in diameter at the time of presentation.[2] The clinical presentation varies considerably. Some are discovered incidentally by noninvasive imaging studies (Fig. 120–1). Others present with rupture into the peritoneal cavity or biliary tree. Rupture is associated with a high mortality rate.[2]

Pseudoaneurysms of the hepatic artery can result from hepatic trauma or procedure-related injury to the artery. Mycotic pseudoaneurysms, resulting from bacterial endocarditis[3] or following liver transplantation,[4] have also been reported. Pain, fever or other signs of infection, and hemorrhage are the most common findings at presentation, but some are asymptomatic and are discovered incidentally. Hemobilia following laparoscopic cholecystectomy,[5] liver biopsy, or interventional radiologic procedures can result from rupture of a pseudoaneurysm into the biliary tree.

The diagnosis may be suspected based on the presentation but is confirmed by Doppler ultrasonography, intravenous contrast-enhanced computed tomography (CT), or magnetic resonance (MR) imaging. Angiography can be diagnostic, and with the aid of interventional radiologic techniques, can be therapeutic as well.[6]

The treatment of hepatic artery aneurysms depends on their cause, size, location, and patient condition. The high incidence of eventual complications, especially hemorrhage, warrants the consideration of treating all of these lesions, even those that are asymptomatic or are discovered incidentally.[2] The underlying condition needs to be addressed, and adequate resuscitation is required for patients presenting with intraperitoneal or gastrointestinal hemorrhage.

Aneurysms of the extrahepatic portion of the artery are classically managed surgically. Those affecting the common hepatic artery may be ligated proximally and distally if adequate collateral circulation to the liver is afforded by the gastroduodenal artery via the pancreaticoduodenal arcade. Those originating distal to the gastroduodenal artery, affecting the proper hepatic artery, can be treated by resection and revascularization of the liver. An anastomotic aneurysm of the hepatic artery following liver transplantation is a serious complication. The usual treatment is revascularization of the liver with resection of the pseudoaneurysm. In an emergency, ligation of the artery proximally and distally may be the only option. Urgent retransplantation may be necessary. Of note, as interventional radiological techniques have developed, cases of extrahepatic aneurysms treated by percutaneous transarterial catheter embolization or endovascular stent placement have been reported.[7,8]

Intrahepatic aneurysms can be managed by percutaneous transarterial catheter embolization (Fig. 120–2). This approach is especially useful if the lesions are multiple as seen in cases of polyarteritis nodosa.[9] The risk of significant hepatic ischemia is minimized if there is adequate portal venous blood flow and the affected artery branch is distal within the liver. Solitary posttraumatic intrahepatic pseudoaneurysms, confined to a hepatic segment or lobe, may be treated by hepatic

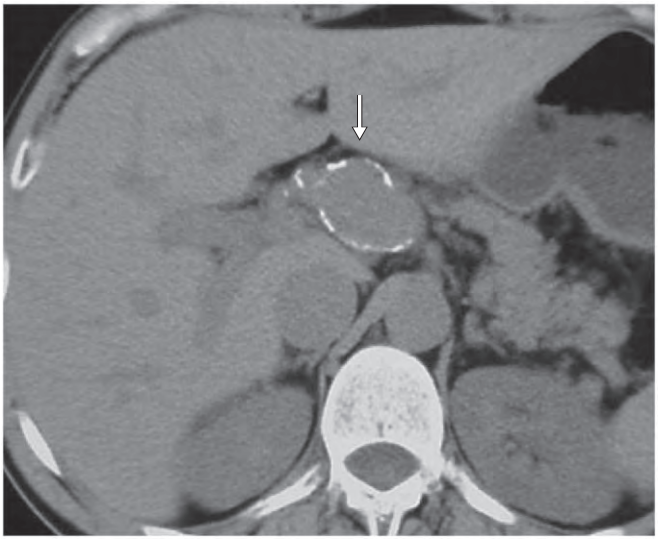
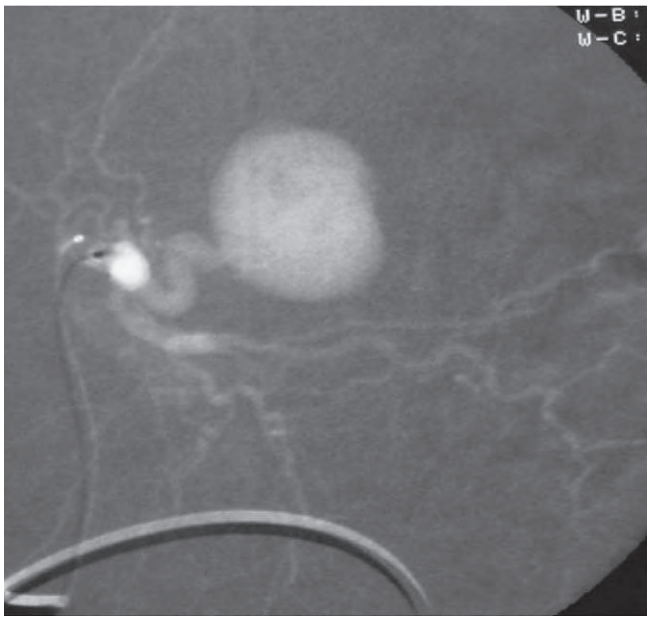
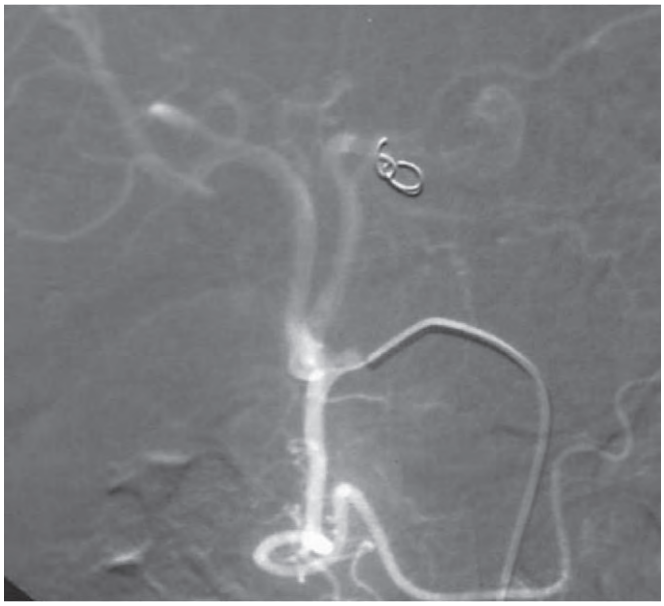


Figure 120–1. CT demonstration of a large, solitary, calcified hepatic artery aneurysm *(arrow).*



A



B

Figure 120–2. **A** and **B,** Transarterial catheter embolization of a traumatic pseudoaneurysm of the left hepatic artery.

resection if an interventional radiologic approach is not possible.[10]

Hepatic Artery Injury

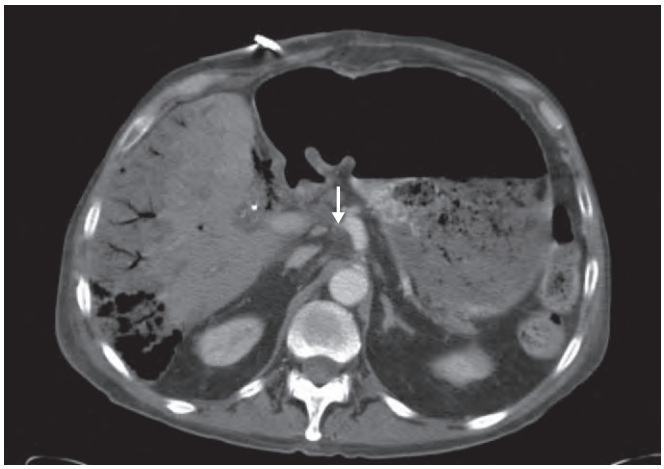
Traumatic injury of the hepatic artery is uncommon. Penetrating injuries to the portal triad outnumber blunt injuries and associated injuries are the rule. The diagnosis is made at the time of laparotomy or postmortem. Portal triad injuries carry a high mortality rate due to exsanguinating hemorrhage or refractory shock. Successful treatment requires control of bleeding, aggressive resuscitation, and temporization of other injuries. Treatment options for the injured artery include ligation or primary repair. Better survival has been reported with hepatic artery ligation over repair.[11]

Iatrogenic injury of the hepatic artery is an uncommon but potentially devastating complication of laparoscopic cholecystectomy. At least one fifth of cholecystectomy related bile duct injuries have an associated hepatic artery injury.[12] The addition of an injury to the artery portends a higher complication rate after biliary reconstruction and a greater risk of mortality.[13] The injury is rarely recognized at the time of surgery, even if the biliary injury is identified and corrected immediately. In the patient presenting with bile duct strictures after cholecystectomy, the presence of a concomitant arterial injury is suspected based on the severity of the bile duct injury and a report of difficulty gaining hemostasis during the cholecystectomy. Angiography can demonstrate the interrupted vessel, but this study is not necessary if it will not alter patient management.

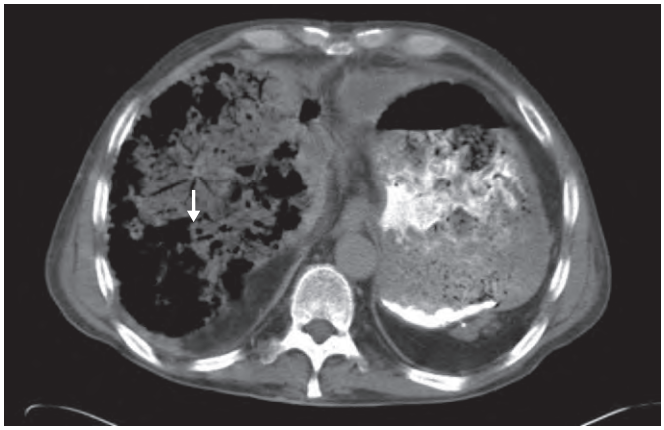
The treatment of these injuries is usually directed toward repairing the bile duct, either primarily or by Roux-en-Y hepaticojejunostomy. Arterial reconstruction is seldom indicated or performed.[12] Rarely, an injury to the right hepatic artery results in acute necrosis of the right hepatic lobe or right-sided intrahepatic strictures and cholangitis, both amenable to hepatic resection.[14]

Hepatic Artery Thrombosis

Hepatic artery thrombosis is the most dreaded vascular complication following liver transplantation. With an incidence of 2% to 8% of cases, it has a high associated morbidity and mortality. Pediatric cases and cases requiring more complex arterial reconstruction are at increased risk for the development of this complica-



A



B

Figure 120–3. CT scan images of hepatic artery thrombosis after liver transplantation. **A,** The *arrow* marks the thrombus in the hepatic artery. **B,** The *arrow* denotes the gangrenous liver allograft.

tion.[15,16] When it occurs early, within the first month following transplantation, it usually results in acute graft necrosis necessitating urgent retransplantation (Fig. 120–3). Protocol surveillance of the hepatic artery using Doppler ultrasound may detect early or impending thrombosis allowing for immediate revascularization and potential graft salvage.[17]

Late hepatic artery thrombosis is less well understood than early thrombosis and has a wider spectrum of presentation. Some patients are asymptomatic and the diagnosis is discovered incidentally. For others, biliary tract complications including stricture formation, bile leak, cholangitis, and hepatic biloma/abscess are the consequence. Cholangitis can be managed by percutaneous or endoscopic catheter decompression of the biliary tree. Infected bilomas are treated by percutaneous drainage and antibiotics. Attempts at biliary reconstruction or hepatic artery revascularization are rarely successful.[18] Although some asymptomatic patients will do well, most patients with late hepatic artery thrombosis will eventually require retransplantation.

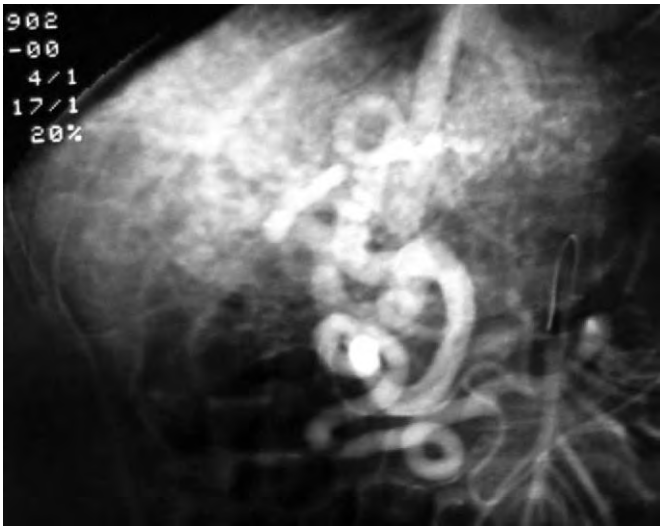


Figure 120–4. This angiogram of a patient with hereditary hemorrhagic telangiectasia with liver involvement depicts an enlarged, tortuous hepatic artery with shunting to the hepatic veins.

Hepatic Arterioportal and Arteriovenous Shunts

Aberrant connections between the hepatic artery and either portal or hepatic venous branches are seen in a variety of diseases and are of variable clinical significance. These shunts can result from blunt or penetrating trauma, iatrogenic injury to the liver, benign and malignant hepatic neoplasms, or hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease). Iatrogenic causes include core liver biopsy, hepatic resection, and radiofrequency tumor ablation.[19] Hepatocellular carcinoma can produce a vascular fistula by eroding into a vein branch and tumors like cavernous hemangioma, focal nodular hyperplasia, and infantile hepatic hemangioendothelioma can develop abnormal shunts. Hereditary hemorrhagic telangiectasia is an autosomal dominant disorder characterized by microscopic and macroscopic arteriovenous malformations with rare but well-described liver involvement (Fig. 120–4).[20]

The pathophysiologic and clinical impact of these shunts depend on their type and hemodynamic magnitude. A large shunt from the high-pressure hepatic artery to the low-pressure portal vein can lead to the development of portal hypertension and its consequences, particularly variceal hemorrhage.[21] Additionally, the increase in portal venous blood flow can cause fibrous tissue proliferation and nodule formation within the liver. A large shunt from the hepatic artery to the hepatic venous system can have two main effects. First, this shunt siphons oxygenated blood away from the hepatic parenchyma and biliary tree. Hepatic necrosis and/or ischemic biliary injury can result. Second, this arteriovenous shunt can provoke a hyperdynamic response eventually leading to high-output cardiac failure. This is typically seen in infantile hepatic hemangioendothelioma.[22]

The treatment of arterioportal and arteriovenous shunts is dependent on the size, location, and cause of the shunt. Small, focal, hemodynamically insignificant shunts may be found incidentally on radiologic images studies and may not require specific treatment. Shunts that are confined to one lobe or segment of the liver, such as those related to a hepatic tumor, may be amenable to resection. Those shunts resulting from trauma or iatrogenic injury affecting the extrahepatic hepatic artery and portal vein may be treated by surgical interruption of the fistula and primary repair of the vessels. As interventional radiologic techniques have improved, more shunts have been treated by percutaneous transarterial catheter embolization.[22,23] Finally, those patients presenting with multifocal or diffuse intrahepatic arteriovenous shunts, as seen in infantile hemangioendothelioma and hereditary hemorrhagic telangiectasia, may be best treated with liver transplantation.[24,25]

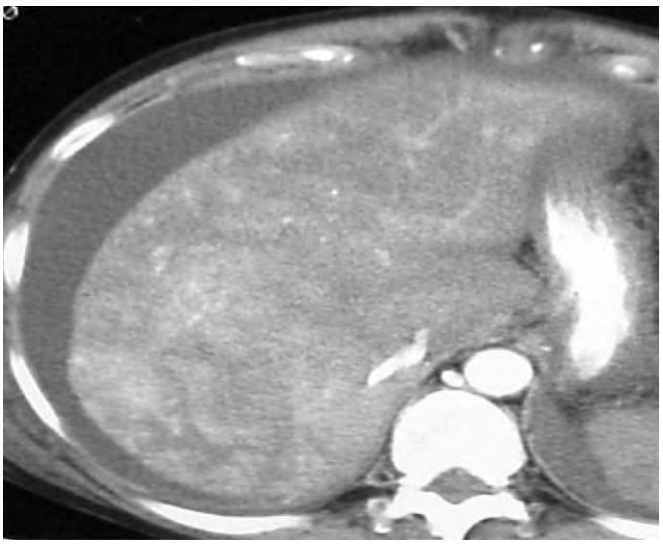


Figure 120–5. CT image of a patient with Budd-Chiari syndrome characterized by heterogeneously appearing hepatic parenchyma, caudate lobe enlargement, ascites, and no visualization of the hepatic veins.

HEPATIC VEIN DISORDERS

Budd-Chiari Syndrome

Budd-Chiari syndrome can result from an array of disorders and has a variable clinical presentation. The common denominator in the pathogenesis of this syndrome is hepatic venous outflow obstruction resulting in a clinical picture characterized by abdominal pain, hepatomegaly, and ascites.

The list of disorders that can cause the syndrome includes various inherited and acquired hypercoagulable states, tumor invasion of the hepatic outflow tract typically by liver, adrenal, or renal malignancies,[26] iatrogenic outflow obstruction following liver surgery or transplantation, vascular webs, and trauma. Myeloproliferative disorders, especially polycythemia vera, are the most common cause.[27]

Hepatic vein occlusion results in increased sinusoidal pressure and decreased sinusoidal blood flow. Hepatic congestion can cause liver enlargement and abdominal pain. Diminished sinusoidal blood flow is thought to be important in the pathogenic progression of fibrosis and regenerative nodule formation to cirrhosis. Portal hypertension contributes to ascites formation and the development of varices. Concomitant portal vein thrombosis is present in approximately 20% of cases.[28] Because the venous outflow for the caudate lobe is separate from the major hepatic veins, compensatory hypertrophy of this hepatic segment is common. The enlarged caudate lobe can extrinsically compress the adjacent inferior vena cava (IVC) producing a pressure gradient across it.

The clinical presentation of patients with Budd-Chiari syndrome varies depending on the extent and acuity of the obstruction to the hepatic venous outflow. Sudden-onset, complete hepatic vein thrombosis may on occasion present as fulminant liver failure. If the onset is gradual and/or the degree of obstruction is incomplete, there is the opportunity for the development of venous collaterals. The degree to which these collaterals decompress the portal venous system impacts the clinical manifestations of the syndrome. Some patients develop liver enlargement and intractable ascites with relatively preserved hepatic function, whereas others develop cirrhosis with hepatic decompensation.[27]

The diagnosis of Budd-Chiari syndrome should be considered in any patient with hepatomegaly and ascites. Laboratory investigation of liver function may reveal abnormalities, but these tests are nonspecific. Doppler ultrasonography is excellent for visualizing the hepatic vasculature revealing the level and extent of the obstruction of the hepatic outflow.[29] It is also useful for evaluating the retrohepatic vena cava and the portal vein. CT and MR imaging may reveal obliterated hepatic veins, heterogeneously perfused hepatic parenchyma and areas of necrosis, hepatomegaly, caudate lobe hypertrophy, narrowing of the retrohepatic vena cava, and ascites (Fig. 120–5). When the underlying cause is tumor invasion of the hepatic veins these imaging studies are important for determining the local extent of the disease. Hepatic venography is often not needed for establishing a diagnosis but may be useful for direct measurement of a pressure gradient across a narrowed IVC or stenotic hepatic outflow tract. Interventional radiologic techniques including transluminal angioplasty, vein stenting, and transjugular intrahepatic portosystemic shunt (TIPS) placement may be employed therapeutically at the time of hepatic venography.[30]

The treatment of Budd-Chiari syndrome must be individualized to the patient and is enhanced by a multidisciplinary team approach.[27] The principles of treatment include addressing the underlying cause, decreasing hepatic sinusoidal pressure and congestion, and preserving liver function. Once the diagnosis is established, a liver biopsy may be needed to determine the extent of hepatic fibrosis and cirrhosis. Because the hepatic parenchyma may not be uniformly affected, bilobar biopsies have been advocated to avoid sampling error.[28] Liver

biopsy is unnecessary in cases where it is clear that the liver can not be salvaged such as those with fulminant liver failure or decompensated cirrhosis.

A variety of medical therapies, interventional radiologic techniques, and surgical procedures are available for the patient with Budd-Chiari syndrome. The best therapy or combination of therapies depends on the patient's individual anatomic and physiologic condition as much as the expertise and bias of the team caring for the patient. Medical therapies include thrombolysis, anticoagulation, and pharmacologic treatment of ascites and portal hypertension. Interventional radiologic techniques that have been developed include percutaneous transluminal angioplasty with or without stent placement and TIPS. Surgical procedures include a variety of portosystemic shunts and liver transplantation.

Thrombolysis has been attempted for acute hepatic vein thrombosis anecdotally and with limited success.[31] Its best place in therapy may be as a prelude to a more definitive procedure such as a TIPS or a surgical shunt. Vein angioplasty with or without stent placement also has been tried in selected cases. It is indicated for short segment stenoses of a hepatic vein or veins, hepatic venous outflow tract stenosis following liver transplantation,[32] or IVC webs. Angioplasty with stenting of the retrohepatic IVC has been performed in conjunction with surgical portosystemic shunting when a pressure gradient exists across this segment of the IVC from caudate lobe compression.[33]

Physiologically, a TIPS is a central portosystemic shunt. It is indicated in the patient with Budd-Chiari syndrome and chronic, well-compensated liver disease to relieve portal hypertension and treat intractable ascites. Some patients that have presented with acute liver failure have been treated with TIPS with excellent long-term survival.[30] For patients with fulminant liver failure or decompensated cirrhosis, the procedure has a high incidence of complications.[34] The disadvantages of the TIPS procedure are that its placement may be technically difficult especially if the ostia of the hepatic veins are occluded, and it often needs revision over time. The introduction of covered stents may decrease the need for subsequent intervention.[35]

Surgical intervention remains the gold standard for the definitive treatment of Budd-Chiari syndrome. However, there is no consensus as to the best procedure for the disease. The decision between TIPS or a surgical shunt and which shunt depends largely on the experience of the treatment team. For those patients with chronic, symptomatic Budd-Chiari syndrome, a variety of surgical shunts are available to decompress the portal venous system and preserve liver function. Survival following these procedures is determined primarily by the rate of progression of the liver disease and the long-term patency of the shunt.

If the IVC is widely patent, a mesocaval shunt, a central splenorenal shunt, and a side-to-side portocaval shunt are the available options. Mesocaval and splenorenal shunts are employed most commonly. Mesocaval shunts require an interposition graft of synthetic material or autologous vein between the superior mesenteric vein and the infrahepatic IVC. If the graft thromboses, the superior mesenteric vein will probably not be available should liver transplant eventually become necessary. A direct, side-to-side splenorenal shunt preserves the hepatic hilum and does not require a vein graft. Although side-to-side portocaval shunts have a high reported high-patency rate,[36] hypertrophy of the caudate lobe can make direct shunting impossible. Also, dissection of the hepatic hilum can make subsequent liver transplantation difficult. Finally, portal vein thrombosis is an obvious contraindication for the procedure.

The long-term patency of these surgical shunts depends on the presence of a pressure gradient between a high-pressure, portal venous system and a low-pressure, infrahepatic IVC. If the retrohepatic vena cava is stenotic or thrombosed, this pressure gradient may be insufficient. In this situation, the retrohepatic vena cava may be stented prior to the surgical shunt.[33] Another procedure developed to address this situation is a mesoatrial shunt[37] or one of its variations.

Most would agree that liver transplantation is the procedure of choice for the patient with fulminant liver failure or decompensated cirrhosis related to the syndrome.[28] The shortage of available organs for transplant and the need for immunosuppression after transplant are the main reasons for reserving this option for those patients with liver failure. Depending on the underlying cause, liver replacement may correct the hypercoagulable state providing a phenotypic cure. For the rest, long-term anticoagulation is essential after transplantation to avoid recurrence of the syndrome. Regardless of the treatment, TIPS, surgical shunt, or liver transplantation, the eventual outcome depends largely on the ability to control the underlying disorder.

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Chapter

121

Drug-Induced Liver Disease

Anurag Maheshwari • Rudra Rai

Drug-induced hepatotoxicity is a frequent cause of liver injury.[1-4] It is the most frequent reason for withdrawal from the market of an approved drug and accounts for one third to one half of the cases of acute liver failure in this country.[5] It can mimic both acute and chronic forms of liver disease and often represents an important diagnostic and therapeutic challenge for the treating physician. Although more than 1000 drugs are thought to have the potential to cause hepatotoxicity, only a handful have caused acute liver failure with resultant death or liver transplantation.[2,4]

EPIDEMIOLOGY

Drug-induced hepatotoxicity for most agents is relatively rare with the incidence ranging from 1 to 10 per 100,000 persons exposed.[1-5] It is higher for some agents such as isoniazid (INH) that can cause some form of liver injury in up to 2% of the exposed population. In general drugs that cause liver injury can be divided into two categories: (1) those that cause dose-dependent toxicity such as acetaminophen or tetracycline and (2) the vast majority of others that cause idiosyncratic reactions. For the former group, factors such as dose, blood level, and duration of intake play an important role in determining toxicity. For the latter group host factors such as age, gender, concomitant diseases, and other drug exposure are important factors.[6-8]

Age Hepatic drug reactions are more common in the elderly and much less frequent among children. The exceptions include valproic acid, where hepatotoxicity is frequently seen among children younger than 3 years of age. Salicylic acid–induced Reye's syndrome is also exclusively seen in children.

Gender Women seem to be particularly predisposed to drug-induced hepatotoxicity, and a recent study noted that women comprised 76% of all transplant recipients for acute liver failure caused by drugs.[9]

Past Drug History Cross-reactivity to related agents in cases of drug-induced liver injury are uncommon but have been reported, particularly with erythromycin-related compounds.

Concomitant Drugs Recipients of polypharmacy are more likely to experience liver toxicity due to various mechanisms including enhanced cytochrome P450[7] metabolism that results in accumulation of the toxic metabolite, or delayed biliary excretion. Chronic alcohol ingestion can increase the severity of liver injury from certain agents such as acetaminophen and INH.[10-13]

Concomitant Illnesses In general, preexisting liver disease[14] including cirrhosis is not a predisposition to adverse hepatic reactions with some exceptions. Human immunodeficiency virus (HIV) infection increases the risk of sulfonamide toxicity,[15-17] and renal transplantation is a risk factor for azathioprine-induced vascular injury.

PATHOPHYSIOLOGY

The liver is the site of first-pass metabolism and is highly exposed to drugs that are absorbed from the gastrointestinal tract. Drugs tend to be lipophilic compounds that are not readily excreted in bile or urine, so one of the functions of drug metabolism in the liver is its conversion to a hydrophilic substrate.[5,9,18-26] Drug metabolism in the liver is divided into three series of pathways: Phase 1 metabolism alters the parent molecule, phase 2 produces a conjugate of the drug or its metabolite, and phase 3 metabolism comprises energy-dependent pathways for excretion of the conjugate from the hepatocyte.

Phase 1 Phase 1 pathways include oxidation, reduction, and hydrolytic reactions. Most reactions are catalyzed by microsomal drug oxidases that act by way of the cytochrome P450 system. Reduced NADPH in the cytosol acts as cofactor. A typical example is the production of *N*-acetyl-*p*-benzoquinone imine (NAPQI) from acetaminophen mediated by the CYP2E1 pathway. Enzyme

inducers include barbiturates, alcohol, anticonvulsants, rifampin, inhaled anesthetics, and oral hypoglycemic agents. Enzyme induction has implications for metabolism of other drugs and mechanisms for drug-induced liver injury.

Phase 2 These reactions involve the conjugation of the parent drug or its metabolite with a small endogenous molecule. The conjugates are highly water soluble and readily excreted in bile or urine. Conjugation is dependent on cofactors such as glucuronic acid and can be impaired by their depletion.

Phase 3 This involves the active excretion of drug and drug metabolites into bile or sinusoids and involves energy-dependent pathways mediated by the adenosine triphosphate (ATP) binding cassette transport proteins. This system is located at the biliary pole of the hepatocyte and can be saturated, with implications for drug accumulation and cholestatic drug-induced liver injury.

MECHANISMS OF LIVER INJURY

Various mechanisms of drug-induced injury, as follows, have been identified that involve the hepatocyte,[5] and the manner in which the intracellular organelles are affected defines the pattern of disease:

1. Disruption of calcium homeostasis can result in actin disruption and loss of ionic gradient, which results in cell swelling and rupture.
2. Covalent binding of drug to the cytochrome P450 system involving high-energy reactions can lead to the formation of nonfunctioning adducts. Such covalent binding may inactivate key enzymes in the cell; the protein-drug adducts may serve as immune targets inducing the formation of antibodies, or they can evoke a direct cytolytic T-cell response.
3. Oxidative stress in the liver can produce reactive oxygen species that disrupt mitochondrial DNA and microsomal electron transport systems. This results in the disruption of fatty acid metabolism and energy production with ensuing anaerobic metabolism and can result in lactic acidosis as well as microvesicular steatosis.
4. Drugs that affect transport proteins at the canalicular membrane can interrupt bile flow. Interruption of transport pumps such as multidrug resistance–associated protein 3 (MRP-3) prevents the excretion of bilirubin, resulting in intracellular cholestasis causing secondary injury to the hepatocytes.
5. Other cells within the liver may be targets of injury or serve as modulators of injury. Activation of Kupffer cells may release reactive oxygen species and cytokines that amplify the injury to hepatocytes. Injury to hepatic sinusoidal endothelium can result in drug-induced vascular injury and the development of veno-occlusive disease. Activation of hepatic stellate cells by methotrexate or vitamin A can result in increased matrix deposition with resultant fibrosis and cirrhosis.

Drugs can be divided into dose-dependent hepatotoxins or dose-independent (idiosyncratic) hepatotoxins. Dose-dependent hepatotoxins require activation to a toxic metabolite and interference with the function of intracellular organelle such as the mitochondria or canalicular biliary secretion. Liver injury caused by these drugs occurs after a short latent period is characterized by zonal necrosis and can be reproduced in other species. In contrast, idiosyncratic reactions cause a wide variety of histologic changes, exhibit a variable latent period to onset of injury, and cannot be reliably reproduced. Idiosyncratic hepatotoxicity is thought to occur by two major mechanisms: metabolic idiosyncrasy or immunoallergy. Metabolic idiosyncrasy is the susceptibility of rare individuals to a drug, which in conventional doses is usually safe. This susceptibility may be the result of genetic or acquired differences in drug metabolism or excretion. Immunoallergy indicates immune-mediated injury in response to the formation of adducts or hapten molecules, which may result from the interaction between the drug metabolite and the cell proteins or cytochrome P450 enzyme.

DIAGNOSIS AND TREATMENT OF DRUG-INDUCED LIVER DISEASE

Almost any drug has the potential for hepatotoxicity and should be suspected when considering the diagnosis.[5,28-43] Clinicians must have a high index of suspicion, and the history should include the dose, route, duration, and concomitant administration of all drugs (Table 121–1). Particular interest should be paid to the use of alternative and complementary medications because that history is not easily forthcoming. The onset of injury is usually within 5 to 90 days of exposure to the drug. A positive dechallenge is defined as a drop in serum transaminases by 50% within days or weeks of cessation of the offending drug. Although a deliberate rechallenge is logistically and ethically impossible, an inadvertent rechallenge may give valuable evidence of a drug's hepatotoxicity. Other causes of liver disease such as viral hepatitis, autoimmune liver disease, or biliary obstruction must be excluded, and in difficult cases a liver biopsy may be useful. Though not universally recommended in all cases of drug-induced liver injury, certain findings such as steatosis, granulomas, zonal hepatic necrosis, bile duct lesions, and mixed hepatocellular necrosis with cholestasis may point toward a drug reaction. The treatment of drug-induced liver disease obviously includes cessation of the offending drug, and continuation of therapy after development of hepatotoxicity is a predictor of poor outcome. There is no role for glucocorticoids, though few reports have indicated benefit in cases of chronic hepatitis with autoimmune features. Ursodeoxycholic acid and cholestyramine may be useful for the treatment of pruritus in cases of cholestasis, along with supportive care for liver failure. Resolution of liver damage can take weeks to months after cessation of offending drug, though immediate improvement is the norm.

Table 121–1 Classification of Drug-Induced Liver Injury Based on Histologic Damage

Histologic Damage	Histologic Features	Commonly Associated Drugs
Zone 3 necrosis	Hepatocellular necrosis in zone 3 (region of lowest sinusoidal O_2 tension)	Amanita mushroom, CCl_4, acetaminophen
Zone 1 necrosis	Periportal hepatocellular necrosis	Yellow phosphorous
Mitochondrial cytopathies	Steatosis, occasional cholestasis with focal hepatocellular cell death	Valproate, HAART, tetracyclines
Steatohepatitis	NASH, fibrosis, and cirrhosis	Amiodarone, tamoxifen, methotrexate, perhexiline
Acute hepatitis	Acute hepatocellular necrosis, occasional plasma cells, submassive to massive necrosis	Nitrofurantoin, phenytoin, methyldopa, disulfiram, sulfonamides, isoniazid, ketoconazole, troglitazone
Chronic hepatitis	Spotty hepatocellular necrosis, occasional plasma cells, bridging fibrosis	Nitrofurantoin, methyldopa, diclofenac, minocycline, isoniazid, dantrolene
Canalicular cholestasis	Cholestasis without associated hepatitis	Synthetic estrogens, androgens, cyclosporine
Hepatocanalicular cholestasis	Cholestasis with associated hepatitis and inflammation	Chlorpromazine, clavulanic acid, dextropropoxyphene, erythromycin
Veno-occlusive disease	Zone 3 inflammation and fibrosis with intimal edema and sclerosis	Cyclophosphamide, busulfan, carmustine, etoposide, azathioprine, total-body irradiation, Jamaican bush tea, comfrey
Nodular regenerative hyperplasia	Endothelialitis of hepatic arterioles and portal venules	Chemotherapeutic agents, especially alkylating agents
Noncirrhotic portal hypertension	Portal venular sclerosis with periportal fibrosis	Arsenic, vitamin A, methotrexate, vinyl chloride
Peliosis hepatitis	Blood-filled cavities without endothelial lining	Androgens, azathioprine, tamoxifen, estrogens, vitamin A
Hepatic adenoma	Single or multiple adenomas	Estrogens, anabolic steroids, danazol
Hepatocellular carcinoma	Overlap with adenoma	Long-term estrogen use (>8 yr)
Angiosarcoma	Malignant transformation of endothelium	Androgenic metabolic steroids, vinyl chloride, arsenic salts, thorium and copper salts

HAART, highly active antiretroviral therapy; NASH, nonalcoholic steatohepatitis.

CONDITIONS ASSOCIATED WITH DRUG-INDUCED LIVER DAMAGE

Hepatocellular Zone 3 Necrosis

Liver injury observed in zone 3 is caused by dose-dependent hepatotoxins such as acetaminophen, carbon tetrachloride, amanita mushrooms, and salicylates. Injury is rarely due to the drug itself, and a toxic metabolite is usually responsible. The cytochrome P450 enzymes produce electrophilic drug metabolites. These metabolites then bind covalently to liver molecules that are essential to the life of a hepatocyte and necrosis occurs. In addition, exhaustion of intracellular substances (e.g., glutathione) capable of conjugating the toxic metabolite contributes to further damage. Histologically, damage is greatest in zone 3 where the cytochrome P450 enzymes are present in highest concentration and sinusoidal oxygen tension is the lowest. Hepatic necrosis is dose dependent and marked elevations in serum transaminases are seen. Enzyme induction enhances drug toxicity as evidenced by chronic alcohol ingestion that induces the CYP2E1 enzyme, which is important in generating toxic metabolites of acetaminophen. As a result, as little as 4 g can cause serious liver toxicity in chronic alcoholics. Rats pretreated with phenobarbital show increased zone 3 necrosis following carbon tetrachloride ingestion, and cimetidine can modify the hepatotoxicity of acetaminophen by inhibition of the cytochrome P450 system.

Carbon Tetrachloride Ingestion of this toxic solvent may be accidental or suicidal. It is used in dry-cleaning liquids and fire extinguishers. Liver injury is induced by a toxic metabolite and its production depends on the cytochrome P450 oxygenase enzyme. This enzyme can be induced by prior alcohol and barbiturates intake and may potentiate toxicity. Clinical features include vomiting, abdominal pain, and diarrhea followed by jaundice. In severe cases, acute renal failure overshadows the liver toxicity and death is usual. If the patient survives, there seems to be no evidence for chronic liver damage in humans. Acute poisoning is treated by a high-carbohydrate diet in addition to supportive therapy for hepatic and renal failure. Prompt administration of acetylcysteine may help minimize hepatic damage.

Amanita Mushrooms Ingestion of a single Amanita mushroom can cause acute liver failure, and the syndrome is common in Western Europe where mushroom hunting is more popular than in the United States. Clinical features include nausea, cramping, abdominal pain, and watery diarrhea. This can last for 3 to 5 days and is usually followed by massive hepatorenal and nervous system necrosis. Spontaneous recovery can occur, though patients usually require liver transplantation. Silymarin has been used as an antidote for the mushroom toxin phalloidin.

Acetaminophen Liver toxicity is caused by the toxic metabolite, NAPQI. This metabolite is generated by the CYP2E1 enzyme and is inactivated by glutathione. Cell damage follows the depletion of glutathione, and enzyme induction by alcohol or drugs such as INH or anticonvulsants increases toxicity. As a result, as little as 4 to 8 g/day may produce liver damage in an alcoholic patient, whereas a minimum of 8 to 10 g is necessary to produce hepatic necrosis in adults. Clinical features include nausea and emesis soon after ingestion followed by an apparent period of recovery for 48 hours. Thereafter the patient deteriorates and develops jaundice and significant elevations of serum transaminases are seen. Renal failure follows in as many as one third of cases, and hypoglycemia is a prominent feature late in the disease. The Kings College criteria for fulminant hepatic failure identifies those with a poor prognosis that usually require transplantation, although spontaneous recovery is the norm without late sequelae. Specific treatment of acetaminophen overdose includes the use of *N*-acetylcysteine (NAC), which should be given as early as possible after ingestion.[44,45] Guidelines for its use are based on a nomogram plotting serum acetaminophen levels against time from ingestion. Although maximum benefit is achieved when NAC is given within 16 hours of ingestion, its use is recommended for all patients with evidence of significant liver injury irrespective of time from ingestion. The mechanism of action is the replenishment of glutathione reserves in the hepatocyte.[46] Fulminant hepatic failure requires liver transplantation, though its necessity is diminishing with time.[2,5,47]

Hepatocellular Zone 1 Necrosis

Yellow Phosphorus About 50 to 60 g may be a lethal dose and ingestion is usually suicidal or accidental. Necrosis is predominantly in zone 1 (periportal areas) and patients develop jaundice 2 to 4 days after ingestion. There is no specific antidote, and fulminant hepatic failure often develops with mortality rates as high as 50%. No late sequelae have been described.

Mitochondrial Cytopathies

Some drugs predominantly inhibit mitochondrial function causing lactic acidosis and hypoglycemia. β-Oxidation of fatty acids in the mitochondria is associated with microvesicular steatosis.

Valproic Acid Younger patients are more susceptible to valproic acid–associated liver damage, which can be severe and sometimes fatal. More than two thirds of reported cases have been younger than 10 years of age. Males are particularly affected and clinical presentation occurs between 2 and 12 months of onset of therapy. Sodium valproate or its metabolites interfere with mitochondrial function and the susceptibility may be genetic. Some reports have suggested that patients with severe reactions to valproate may have inborn deficiencies of urea cycle enzymes. Liver biopsy usually demonstrates microvesicular steatosis with hepatocellular necrosis in zone 3, and electron microscopy shows mitochondrial destruction.

Tetracyclines Large intravenous doses have been associated with hepatic failure, particularly in pregnant women. It has also been associated with acute fatty liver of pregnancy and therefore should be avoided during pregnancy.

Highly Active Antiretroviral Therapy The frequency of hepatic injury with combination therapy is estimated to be 10% or more. Whether concomitant hepatitis C infection increases the risk of drug-induced toxicity is unclear. All nucleoside and nucleotide analogues can inhibit mitochondrial DNA polymerase causing cell death. Although zidovudine and didanosine are the most commonly reported hepatotoxins, all drugs in this category can cause liver injury with the exception of lamivudine. Several cases of fulminant liver failure associated with didanosine have been reported, and the clinical course is characterized by severe metabolic acidosis with multiorgan failure leading to death. Drug combinations seem more likely to result in hepatotoxicity compared to monotherapy. Among the protease inhibitors, indinavir and ritonavir have been most commonly reported to cause liver injury. The pattern of injury is usually mixed with prominent steatosis, associated with cholestasis and focal hepatic injury. Recovery from protease inhibitor associated liver injury is slower when compared to other antiretroviral drugs.

Steatohepatitis, Fibrosis, and Cirrhosis

Nonalcoholic steatohepatitis (NASH) can produce focal liver injury, Mallory's hyaline, and inflammation with fibrosis.

Amiodarone Amiodarone can cause a variety of adverse effects with abnormal liver tests seen in 15% to 50% of treated patients. There are rare cases of acute liver failure, though the typical lesion is steatohepatitis. Cirrhosis may develop in rare cases, and progression of disease may occur after drug discontinuation due to prolonged storage of the drug in the liver. Liver disease is usually detected a year after beginning therapy, and symptoms may range from asymptomatic elevations of liver function tests (LFTs) to jaundice with features of cirrhosis. Serial LFT monitoring is recommended in all patients treated with this drug.

Tamoxifen The development of steatosis in women administered tamoxifen correlates with other risk factors for NASH such as obesity and insulin resistance. Tamoxifen may play a synergistic role with other risk factors to produce NASH. Although steatosis is the most commonly reported form of liver injury, it has been associated with cholestasis, acute hepatitis, peliosis hepatis, and fulminant hepatic failure. Although most cases of abnormal LFTs improve after cessation of tamoxifen, underlying NASH or metastatic breast cancer may be the cause in other cases. Monitoring for patients on tamoxifen should include periodic LFT determinations with yearly imaging tests.

Methotrexate Methotrexate causes dose-dependent liver injury resulting in fibrosis and cirrhosis. Risk factors for methotrexate-induced fibrosis include total dose, alcohol intake, and preexisting liver disease. Cirrhosis can be complicated by the development of hepatocellular cancer. Serum transaminases correlate poorly with the degree of fibrosis but should be monitored routinely because elevations may indicate the need for a liver biopsy. It is now recommended that liver biopsy be performed after 4 g of cumulative dose or 2 years of therapy, and strict avoidance of alcohol should be emphasized. There have been reports of liver transplantation for severe methotrexate-associated liver injury.

Other Drugs Other drugs associated with the development of steatosis include perhexiline, synthetic estrogens in large doses, calcium channel blockers, and methyldopa. Perhexiline has now been withdrawn from the market, and the association with other drugs may be anecdotal and related to other risk factors for NASH such as diabetes, obesity, and hyperlipidemia.

Acute Hepatitis

The reaction is characterized by acute cell death and associated inflammation.[48-53] Severe forms of acute hepatitis can cause fulminant hepatic failure. Acute hepatitis is the most commonly reported drug reaction. The reaction is usually immunoallergic, though some drugs cause reactions by metabolic idiosyncrasy and lack typical features of the immunoallergic reaction. The immunoallergic reaction occurs more commonly in women and usually presents with prodromal symptoms after a latent period of 2 to 10 weeks. Eosinophilia is a common feature, and extrahepatic manifestations such as rash and lymphadenopathy are also seen. Autoantibodies may be detected in the serum and improvement after discontinuation of the drug is prompt. In contrast, the idiosyncratic reaction lacks the classic prodromal symptoms and extrahepatic manifestations and eosinophilia is rarely observed. Other drugs (e.g., alcohol, rifampin) may exacerbate the reaction, and improvement after drug discontinuation is variable.

Immunoallergy

Nitrofurantoin This drug can cause liver toxicity ranging from acute hepatitis to chronic hepatitis, cholestasis, granulomatous hepatitis, and cirrhosis. The frequency of liver damage increases with age and is more common in women. Chronicity usually depends on the duration of drug ingestion. Early symptoms are frequently nonspecific (e.g., fever, weight loss, and anorexia) and are followed by more specific symptoms of liver disease such as jaundice, pruritus, and high-colored urine. Patients with chronic hepatitis may show signs such as spider angiomata, splenomegaly, and ascites. Autoantibodies are frequently noted, as is an increase in serum globulins. Eosinophilia may also be present in one third of cases. Recovery is rapid after drug discontinuation, and systemic steroids have not proven useful even in cases of chronic hepatitis associated with autoimmune features.

Methyldopa The clinical features of hepatotoxicity are similar to those noted with nitrofurantoin. Hepatic damage can range from acute hepatitis, cholestasis, chronic hepatitis, and cirrhosis.

Phenytoin Drug toxicity occurs in equal frequency among children and adults. The systemic features of immunoallergy such as fever, rash, eosinophilia, and lymphadenopathy are common. A familial enzyme defect in the metabolism of phenytoin has been identified, suggesting that not all reactions are immunoallergic. The mortality rate is high among patients with jaundice. The most common reaction associated with phenytoin is related to microsomal induction with elevated gamma-glutamyl transpeptidase and alkaline phosphatase levels in a large proportion of cases.

Sulfonamides Hepatotoxicity usually occurs as part of the broader serum sickness (Stevens-Johnson syndrome) reaction due to the sulfa moiety. Reactions may be severe and have caused death due to hepatic failure. Patients infected with HIV have a higher predilection for sulfa toxicity. Hepatotoxicity due to Bactrim is frequently due to trimethoprim, which causes a cholestatic picture.

Minocycline Tetracycline can rarely cause acute hepatitis, and minocycline has been associated with the development of drug-induced autoimmune hepatitis.

Disulfiram A drug used to treat alcoholism itself is associated with acute hepatitis that can be fatal and has required liver transplantation.

Etretinate This is a synthetic retinoid used for dermatologic conditions that has been associated with abnormal LFTs in up to one fourth of cases. A few cases of severe acute hepatitis have been reported mostly in older women. LFTs may improve with dose reduction implying dose-dependent toxicity, but the compound has a long half-life, necessitating periodic monitoring of alanine aminotransferase (ALT) levels.

Zafirlukast This leukotriene antagonist used in the treatment of asthma has been associated with rare cases of acute liver failure and patients treated with it should have periodic monitoring of ALT levels.

Metabolic Idiosyncrasy

Isoniazid (INH) Ten percent to 36% of persons taking INH develop asymptomatic elevations of LFTs in the first 8 weeks that resolve spontaneously. Acute hepatitis is seen in up to 2% of individuals, with the highest risk for women older than 50 years of age and those on combination drug regimens using rifampin and pyrazinamide. Chronic excessive alcohol intake and acetaminophen use also increases the risk of toxicity, as may concomitant illnesses such as malnutrition and chronic hepatitis B and C. Clinical symptoms include nonspecific anorexia and weight loss preceding jaundice 8 to 12 weeks after starting therapy. Although the hepatitis resolves rapidly on stopping the drug, prognosis is poorer for those with high bilirubin levels. The severity of reaction is higher in cases of continued ingestion after development of symptoms and has required transplantation on occasion. Rechallenge has not been proved to cause recurrent hepatitis especially with slow reintroduction of the drug. Biweekly or monthly monitoring of LFT during therapy has been advocated to monitor for hepatotoxicity. Rifampin and pyrazinamide have both been associated with hepatotoxicity, though most often in combination with INH.

Antifungals Ketoconazole is associated with increased LFTs in up to 17% of patients treated for onychomycosis. Symptomatic hepatitis is rare and seen more frequently in older women. LFTs improve rapidly after drug discontinuation, though rare cases requiring transplantation have been reported. Terbinafine has been reported to cause prolonged cholestasis occurring 4 to 6 weeks after starting therapy. Periodic monitoring of LFTs during therapy is recommended. Fluconazole and itraconazole have also rarely been associated with hepatotoxicity, though the frequency is much lower than that seen with ketoconazole.

Troglitazone This drug seemed free of hepatotoxicity in early clinical trials, but postmarketing data found significant cases of fatal hepatotoxicity. The mechanism of injury seems to be metabolic idiosyncrasy, though immunologic injury may play a role in some cases, and cross-reaction with rosiglitazone has been observed. There is no clear relationship of toxicity to dose or timing. Nor has screening by ALT monitoring always proven useful in preventing the development of acute hepatitis. Mortality is higher in older patients and several cases requiring liver transplantation have been reported. The drug was withdrawn from the U.S. market in March 2000.

Chronic Hepatitis

Although the true definition of chronicity is persistence of inflammation more than 6 months after its onset, in cases of drug-induced hepatitis, clinical and biochemical evidence of liver injury associated with histologic changes of fibrosis confirms the diagnosis of drug-induced chronic hepatitis.[48-53] There are two distinct clinical pictures associated with this form of drug toxicity. The first scenario resembles acute hepatitis that either persists longer or is delayed in recognition without signs or symptoms of chronic liver disease. The second syndrome resembles autoimmune hepatitis in serologic and histologic features. The management of both syndromes consists of drug withdrawal and supportive care, though glucocorticoids have shown to benefit those with autoimmune features. The drugs most commonly associated with chronic hepatitis include nitrofurantoin, methyldopa, diclofenac, minocycline, INH, dantrolene, and etretinate. Indeed, a large number of patients thought to have chronic drug-induced hepatitis in the past were found to have chronic hepatitis C, and the evidence for causality is not always convincing.

Cholestasis

Drugs can cause cholestasis with or without concomitant hepatitis. Clinical and biochemical features resemble many hepatobiliary conditions, and imaging is often necessary to exclude biliary obstruction. A liver biopsy is often helpful in the diagnostic algorithm and histologic features of acute hepatitis with cholestasis are highly suggestive of a drug reaction. Clinical features include pruritus, jaundice, and dark-colored urine. Glucocorticoids have no role in management, and resolution of jaundice may take a few weeks after discontinuation of the drug. Cholestyramine and ursodeoxycholic acid are first-line therapies for pruritus, though phenobarbital, antihistamines, rifampin, phototherapy, plasmapheresis, and naloxone all have been attempted with variable success.

Canalicular Cholestasis

Cholestasis without associated hepatitis is caused by the retention of bile within the biliary canaliculi. This represents a primary disturbance in biliary flow and susceptibility may be related to genetic variations in biliary transporters. Various androgens and estrogens are the typical causative agent. The cause is usually, though not always, a C-17 alkylated testosterone, and the reaction is dose dependent and reversible. Cyclosporine also inhibits ATP-dependent bile salt transport. Hyperbilirubinemia is common with features of cholestasis. The reaction is frequently mild and reverses rapidly with dose reduction.

Hepatocanalicular Cholestasis

The histologic picture of cholestasis predominates but is associated with hepatocellular features including cell death and inflammation. There is considerable overlap with drug-induced hepatitis, and the immunodestructive injury focuses on the bile ducts. The acute reaction may resolve in 3 months, but cases of protracted cholestasis have been reported, some requiring liver transplantation due to progressive ductopenia.

Chlorpromazine Up to 2% of patients taking the drug may develop cholestatic hepatitis. There is no relationship to dose, and the onset is usually within 4 weeks of starting therapy. Female predominance suggests an

autoimmune cause. Patients present with pruritus preceding jaundice in a syndrome that resembles acute viral hepatitis. Recovery is usual with discontinuation, though a few cases of prolonged cholestasis with ductopenia requiring transplantation have been reported.

Amoxicillin/Clavulanic Acid Clavulanic acid is the hepatotoxic agent because liver injury due to amoxicillin is rare. Cholestasis is noted predominantly in older men on long-term therapy and may evolve into prolonged cholestasis with vanishing bile duct syndrome. Recovery after drug discontinuation is usual.

Dextropropoxyphene This is an opioid analgesic that can cause cholestatic hepatitis associated with injury to the bile ducts. The onset of symptoms is within 2 weeks of the first dose and consists of abdominal pain as the presenting sign. This can be followed by recurrent jaundice and rigors mimicking structural biliary disease. Biliary imaging is usually normal and LFTs improve within a couple of months after stopping the drug.

Erythromycin Hepatotoxicity seems more common with the estolate salt of the drug and is associated with fever, jaundice and pruritus. Eosinophilia may be observed suggesting autoimmune disease. The predominant histologic feature is cholestasis with acidophil bodies, and recurrent jaundice may be noted with distant administration of other erythromycin derivatives.

Vascular Toxicity

Veno-occlusive Disease (VOD)

The terminal hepatic venules and the small zone 3 hepatic veins are sensitive to endothelial damage by alkylating agents that cause intimal edema and subsequent collagen deposition. This can result in hepatic venous outflow tract obstruction, and patients present with painful hepatomegaly, jaundice, and ascites. Veno-occlusive disease is particularly associated with the use of anticancer drugs such as cyclophosphamide, busulfan, carmustine, etoposide, and azathioprine, and total-body irradiation. Recipients of allogeneic bone marrow transplantation are frequently afflicted and the onset is usually 2 to 10 weeks after therapy. Occasional cases may recover, though prognosis is generally poor with death due to liver failure a few weeks later. The condition was first described in association with Jamaican bush teas (that contain pyrrolizidine alkaloids) and later with comfrey as well.

Nodular Regenerative Hyperplasia

The condition is characterized by the development of regenerating nodules in the absence of fibrosis. The underlying lesion seems to be endothelial damage to the terminal hepatic arterioles and portal venules with the resulting ischemia inducing regenerative changes. The drugs implicated are similar to those implicated in the development of veno-occlusive disease and the two conditions frequently overlap. The clinical features are those of portal hypertension with esophageal varices. The overall prognosis is better than with veno-occlusive disease and complete reversal may occur with cessation of the offending drug.

Noncirrhotic Portal Hypertension

Noncirrhotic portal hypertension caused by drugs is usually the result of obstruction to portal blood flow. This is usually caused by sclerosis of the portal vein branches and is associated with a variable degree of periportal fibrosis. Agents associated with this condition include arsenic, vitamin A, methotrexate, and vinyl chloride. Clinical features of portal hypertension including splenomegaly, esophageal varices, and thrombocytopenia predominate. Angiosarcoma may be an occasional complication and has been reported with the use of arsenic and vinyl chloride.

Peliosis Hepatis

Peliosis hepatis refers to blood-filled cavities without endothelial lining. The lesions vary from a few millimeters to several centimeters. The disruption of normal sinusoidal architecture is the underlying disease. Peliosis hepatis has been associated with androgens, azathioprine, tamoxifen, estrogens, and possibly vitamin A. The condition has also complicated danazol therapy and is rarely suspected before surgery or liver biopsy. Rare cases of shock and abdominal pain due to rupture have been reported. Helical computed tomography or magnetic resonance imaging that can identify the lesion should be used to investigate unexplained hepatomegaly in a patient taking an implicated drug.

Hepatic Tumors

Hepatic Adenoma

High-dose estrogens in oral contraceptive pills as well as anabolic steroids have been implicated in the genesis of hepatic adenomas. Danazol, a synthetic steroid used for the treatment of hereditary angioedema, has been associated with the development of hepatic adenomas. Although regression of smaller lesions after withdrawal of steroids has been noted, resection may be necessary for larger or symptomatic lesions. Transition to hepatocellular cancer has been documented, and recurrence rate is high with pregnancy or continued steroid use.

Focal Nodular Hyperplasia

Although commonly observed in women in their reproductive years, the association between FNH and exogenous sex hormones is unproven. Estrogen has shown to have a trophic effect on established lesions, and larger lesions should undergo resection especially if associated with symptoms.

Hepatocellular Carcinoma

The risk of hepatocellular carcinoma in patients on long-term (>8 years) estrogen use is higher, but estrogen-

related hepatocellular carcinoma is rare as compared to other causative etiologies such viral hepatitis. There have been cases reported of concomitant adenoma and carcinoma in the same liver and recurrence rate of estrogen-induced tumors is high.

Angiosarcoma

Angiosarcoma is a rare liver tumor associated with androgenic metabolic steroids, vinyl chloride, arsenic salts, and thorium and copper salts. Cases are diagnosed 2 to 3 decades after exposure to toxic agents and periodic hepatic imaging is indicated among patients with chronic liver disease and high levels of exposure.

Alternative Remedies, Recreational Drugs, and Environmental Agents

Numerous other medicinal and nonmedicinal compounds including vitamins, herbal remedies, environmental agents, and recreational drugs can cause various forms of hepatotoxicity. The increasing popularity of alternative medicines has led to many reports of associated toxicity. In most cases, the hepatotoxin is not readily apparent and many preparations contain more than one ingredient that may be the culprit. The spectrum of toxicity ranges from acute hepatitis, chronic hepatitis with cirrhosis, cholestasis, and vascular injury. Chinese herbal teas and other mixed preparations can cause a host of toxic reactions, and patient self-reporting may be unreliable to establish temporal relationships. Recreational drugs such as ecstasy and cocaine have been associated with hepatotoxicity severe enough to require liver transplantation. Hypervitaminosis A is now more commonly recognized as secondary to self-medication of large doses of vitamin A over prolonged periods. The pathologic spectrum of liver disease due to vitamin A toxicity can range from abnormal LFTs, stellate cell hyperplasia, noncirrhotic portal hypertension, cirrhosis, and rare cases of peliosis hepatis. The prognosis is poorer in cases with established cirrhosis and portal hypertension, and patients with chronic liver diseases should be cautioned against vitamin A supplementation.

CONCLUSION

Clinical trials are often inadequate in identifying a drug's potential for liver injury, and this may be evident only after the drug has been approved for public use.[5,54,55] Although several drugs cause asymptomatic transient elevations of LFTs, the safety of such a reaction is questionable. LFTs should be monitored 3 to 4 weeks after commencing therapy with any drug that has the potential to cause liver toxicity. Continued administration of the offending drug after development of liver toxicity is the most common cause of poor outcome necessitating early recognition of the syndrome. The increasing use of complementary medications has raised awareness of their potential for liver toxicity among the medical community, though the lay public must also be cautioned about the dangers of unregulated nonproprietary preparations. Practitioners are encouraged to report suspected drug reactions because under-reporting is common and improved reporting may help early recognition of drug toxicity.

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Chapter

122

Benign Hepatic Neoplasms

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Widespread use of imaging modalities (especially ultrasound) has led to a more frequent discovery of incidental hepatic lesions. Correct evaluation is crucial for these lesions because management depends on exact diagnosis and the differentiation from malignant processes. Even benign lesions can cause considerable anxiety for patients, and this has to be taken into account when designing the management strategy. Life-long follow-up of a young patient might be more distressing and costly than definitive resection. Such resections are good indications for laparoscopy if the location is suitable (i.e., the lesion is in the lateral and anterior segments). However, the reduced morbidity of laparoscopic resections should not lead to an expansion of operative indications. Generally, an aggressive surgical approach is warranted when there is any suspicion of malignancy. Clinically the most important benign lesions are hemangioma, focal nodular hyperplasia (FNH), and hepatic adenoma, but a variety of rarer lesions have been described.

HEMANGIOMA

Hemangiomas are the most common benign neoplasm of the liver. The prevalence is around 5% to 10% of the population, although one autopsy study explicitly searching for hepatic lesions suggested a prevalence as high as 20%.[1] Hepatic hemangiomas are usually small and incidentally discovered during abdominal imaging procedures for unrelated causes, but they can become quite large. Lesions larger than 5 cm have been arbitrarily termed *giant hemangiomas*. Patients presenting for evaluation of hepatic hemangioma are predominantly female (2:1 to 4:1) and often in the 5th and 6th decade of life. Hemangioma are most often located in the right hemiliver[2] and solitary in 60% to 80% of cases. If more than one lesion is present, these are mostly located in the same hepatic lobe.[3,4]

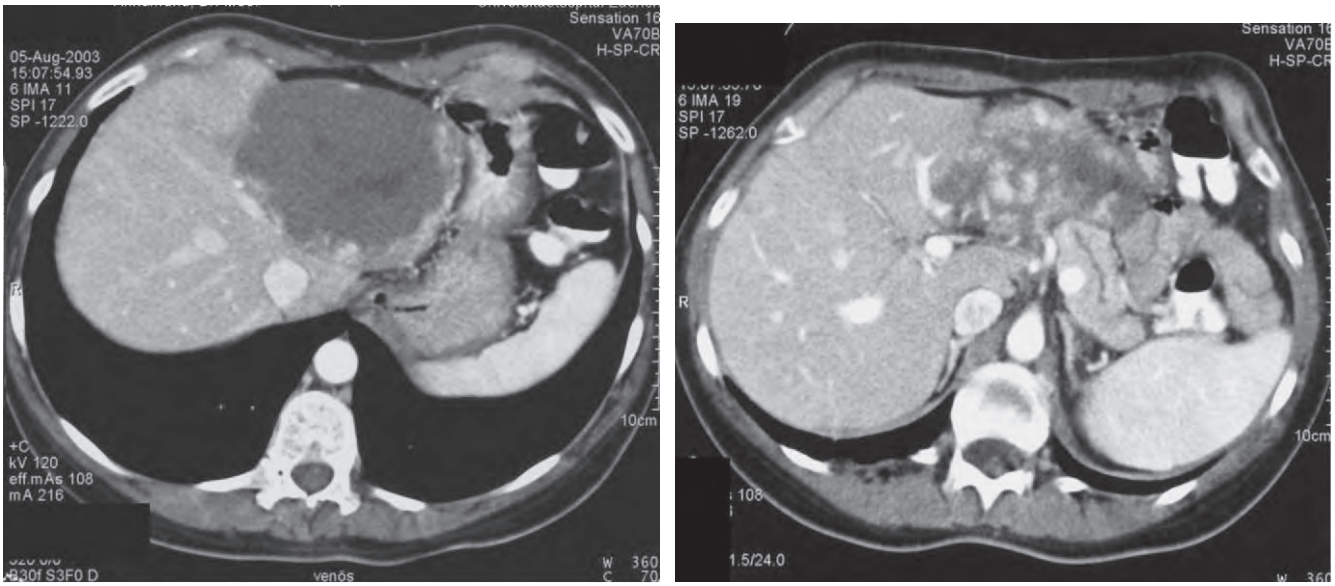
Macroscopically hemangiomas are dark purple, well-demarcated, soft, and compressible lesions. Histologically they consist of dilated vascular spaces lined by endothelium and separated by connective tissue, totally lacking biliary or portal structures. By immunohistochemistry the endothelium displays vascular as opposed to sinusoidal differentiation.[5] Large tumors can have central thromboses, necroses, or dystrophic calcifications.

Etiology

The cause of hepatic hemangioma is mostly unknown, but they are considered to be vascular malformations of congenital origin. Enlargement occurs by ectasia rather than hypertrophy or hyperplasia. As there is a predilection for females, and enlargement of existing hemangioma has been reported during pregnancy, there might be a relationship with female hormonal factors such as estrogen and progesterone exposure. This effect is not too pronounced in newer studies.[2,6] Kasabach-Merrit syndrome was originally described as purpura associated with thrombocytopenia and "capillary hemangioma." Newer analyses have identified these tumors as tufted angioma or kaposiform hemangioendothelioma rather than typical hemangioma.[7]

Diagnosis

Most patients are asymptomatic, and the lesion is an incidental finding on an imaging study performed for unrelated reasons. If symptoms are present, right upper quadrant pain and discomfort are the most frequent. However, unspecific abdominal symptoms and hepatic hemangioma are both common conditions; therefore, the likelihood of a coincidence is high. Often these symptoms have been found unrelated to the hemangioma itself.[8] Young women are more likely to complain of symptoms. Very large hemangiomas can cause symptoms due to their size, such as early satiety by gastric compression, biliary stasis, or vascular obstruction.[9] Rapid onset of symptoms is a sign of bleeding or thrombosis. Rupture is an extremely rare complication, even in very large hemangiomas or during pregnancy.[10] Liver



A B

Figure 122–1. Contrast-enhanced CT of large hemangioma in the left hemi-liver displaying hypoattenuation on early scans **(A)** and centripetal filling on delayed images **(B).**

function tests and tumor markers (carcinoembryonic antigen, alpha-fetoprotein) are usually normal.[11]

Hemangiomas can often be unequivocally identified by imaging studies due to typical features. Ultrasonography displays a well-defined hyperechoic lesion, although larger lesions are often more complicated due to calcifications, thromboses, or hemorrhage. In a fatty liver the lesion might actually appear hypoechoic compared to the surrounding parenchyma. Typical findings by contrast-enhanced ultrasonography are rapid peripheral globular-nodular enhancement, followed by centripetal filling of the lesion.[12] Native computed tomography (CT) scanning shows a well-demarcated hypodense mass. After intravenous contrast application a peripheral nodular enhancement is evident, followed by centripetal filling over minutes (Fig. 122–1). Late images show the lesion as isodense or hyperdense to surrounding tissue. Small hemangioma (<3 cm) can lack the characteristic filling pattern, and it can be difficult to discriminate it from hypervascular malignant tumors.[13] The best imaging modality for detection and characterization of hemangioma is magnetic resonance imaging (MRI).[14] Typical findings are hypointensity on T1-weighted sequences and hyperintensity on T2-weighted sequences. Contrast enhancement with gadolinium leads to centripetal filling similar to CT. Scintigraphy with technetium 99m pertechnetate–labeled erythrocytes documents gradual accumulation of red blood cells inside the hepatic lesion.[15] Although the specificity is extremely high and can be further improved by using single-photon emission CT, the technique is cumbersome and rarely used today. Hepatic angiography can be helpful because hemangiomas present a characteristic "cotton wool" appearance, yet it is rarely necessary. Percutaneous biopsy has a low diagnostic yield[16] and carries the risk of bleeding complications. Therefore, biopsies are contraindicated when there is a suspicion of hemangioma.

Treatment

Complications of hepatic hemangiomas are extremely rare,[17] and malignant transformation has never been reported. Therefore, most patients can be followed without any therapeutic intervention.[18] One series followed 97% of 249 patients with liver hemangioma conservatively for up to 14 years without adverse events or morphologic changes of the lesions.[4] Patients without risk factors for hepatic malignancy and typical features of hemangioma on ultrasound do not need to undergo further imaging studies and can be followed safely. Only 1 in 213 patients managed by such a strategy developed a neuroendocrine metastasis misdiagnosed by ultrasound.[19] It is prudent to follow up patients with clear hemangioma once or twice in 6-month intervals and then refrain from further imaging. Women should neither discontinue oral contraception nor refrain from pregnancy.

Surgical intervention is necessary in only a small subset of patients.[8] The most common therapeutic indications are symptomatic lesions, unclear dignity, and growth. Large superficial hemangiomas in physically active individuals are often considered for surgery due to the perceived danger of rupture, although there is no evidence to support this approach.

Surgical interventions include resection or enucleation. Enucleation is possible due to a pseudocapsule of compressed hepatic parenchyma between the hemangioma and the surrounding tissue.[20] This technique spares hepatic parenchyma and does not transect any

biliary structures.[21] Overall these advantages are minor, and we prefer standard liver resection for hemangioma. Occasionally giant hemangiomas can be technically challenging to resect, and special techniques such as total vascular exclusion must be employed. Recurrence after enucleation or resection requiring reoperation is extremely rare.[22] However, small residual hemangioma are not uncommon at the resection margin after extended resections for very large lesions.

Arterial embolization[23] or radiation therapy[24] of hepatic hemangiomas is a rarely used therapeutic possibility. These can be useful in patients who are inoperable for technical or medical reasons. Liver transplantation is an exceptional treatment modality described for symptomatic but unresectable hemangioma.[25]

FOCAL NODULAR HYPERPLASIA

FNH, the second most common benign hepatic tumor, is more prevalent in women (about 8:1) and presents in the 3rd to 5th decades of life.[26] Lesions are usually small and solitary in 80% of cases. Macroscopically, FNH appears as a light brown, well-circumscribed lobulated tumor. It lacks a capsule and has a central scar around a prominent arterial vessel with fibrous septa radiating outward. Histology reveals morphologically normal hepatocytes arranged in thickened plates. FNH contains Kupffer cells and hepatocyte-derived biliary ductules at the interface between fibrous bands and nodules but lacks actual bile ducts. Atypical or nonclassic forms of FNH exist, constituting as much as 20% in series of resected cases: telangiectatic FNH, mixed hyperplastic and adenomatous form, and FNH with cytological atypia.[26]

Etiology

The pathogenesis of FNH is controversial. Originally FNH was considered a neoplasm, a hamartoma, or a hyperplastic regenerative response to ischemia. Currently FNH is thought to develop as a dysplastic response to malformed vascular structures. This theory is strengthened by an association of FNH with other vascular malformations such as hemangioma,[27] hereditary hemorrhagic telangiectasia[28] and Klippel-Trénaunay syndrome,[29] as well as the case of identically located FNH in identical twins.[30] Hepatocytes within FNH have been described as polyclonal in some studies, further supporting a non-neoplastic origin.[31] A possible association with female hormonal factors is derived from the predominant occurrence in women of child-bearing age. However, no influence of oral contraception on the size, number, or natural history of FNH could be shown in a study with 216 women.[32]

Diagnosis

The most important management aspect with FNH is to differentiate it from other focal hepatic lesions, especially from hepatic adenoma and fibrolamellar carcinoma, both of which require surgical resection. FNH is asymptomatic in most cases, yet in surgical series one fourth to more than one half of patients are symptomatic.[26] Complications such as rupture, bleeding or malignant transformation do not occur. Clinical findings and laboratory test results are usually normal. Although ultrasound is often the initial diagnostic evaluation, the diagnosis of FNH cannot be confidently made for lack of specific signs. FNH can appear hyperechoic, isoechoic, or hypoechoic in conventional ultrasound. Contrast-enhanced ultrasound seems to be more useful due to unique portal and arterial perfusion patterns within FNH.[33] Native CT displays an isodense or hypodense lobulated tumor. After contrast application FNH becomes hyperattenuating in the arterial phase, sparing the central scar.[34] The scar may show some enhancement on portal or later phases, when the remainder of the lesion has already returned to baseline attenuation. By MRI FNH is typically isointense or hypointense on T1-weighted images and isointense or hyperintense on T2-weighted images, with the central scar being hyperintense in T2.[35] The pattern after contrast application is equal to CT imaging: rapid hyperintensity sparing the central scar, which shows increased signal intensity in later acquisitions (Fig. 122–2). The presence of Kupffer cells in FNH leads to an uptake of superparamagnetic iron oxide (SPIO) contrast agents, distinguishing it from adenoma in MRI. The same effect can be used by scintigraphy with 99m-technetium–sulfur-colloid. Angiography demonstrates a "spoked wheel" appearance but is usually not indicated for diagnosis. We do not advocate biopsy due to its low diagnostic yield.

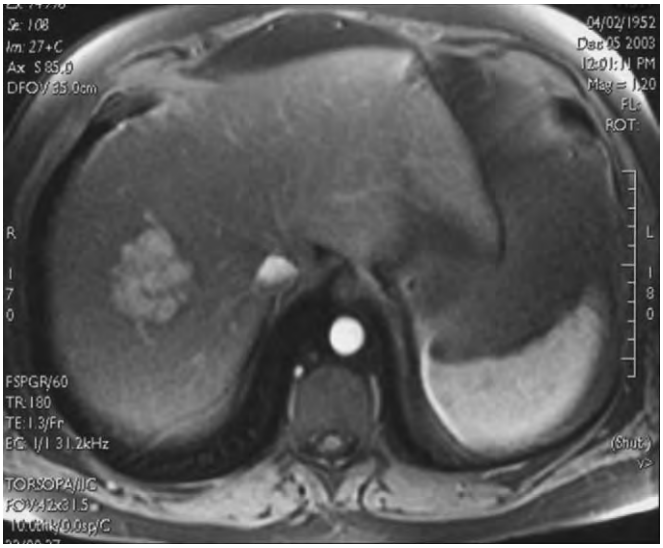


Figure 122–2. Dynamic contrast-enhanced MRI of focal nodular hyperplasia presenting as a hypervascular lesion with a central scar.

Treatment

FNH has a benign and stable natural history and therefore should be treated conservatively. When a diagnosis

has been achieved, follow-up imaging should be performed after 6 to 12 months. If the lesion remains stable and asymptomatic, no further imaging is required. If symptoms can be confidently linked to FNH, or if the benignity of the lesion is in doubt, resection is indicated. This can be performed laparoscopically or openly by partial hepatectomy.

HEPATIC ADENOMA

Hepatic adenoma, or hepatocellular adenoma, is a rare benign hepatic neoplasm. It typically affects young women, with around 80% of tumors being solitary. The incidence rose after the introduction of oral contraceptives in the 1960s, and long-term contraceptive use has been associated with a 30-fold increase of the incidence in epidemiologic studies.[36] As newer formulations use lower doses of estrogen and progesterone, the incidence seems to be declining again. *Adenomatosis* refers to the presence of more than 10 hepatic adenomas and represents a distinct disease entity because there is no relationship with hormone exposure.[37]

Macroscopically, adenoma is a well-circumscribed mass with a pseudocapsule of compressed hepatic parenchyma. The cut surface is inhomogeneous, displaying areas of yellow-brown lipid-rich tissue, as well as hemorrhage, necrosis, and calcifications. Histologically, adenoma is composed of large lipid and glycogen-containing hepatocytes arranged in plates, separated by dilated sinusoids that are fed by arterial perfusion. In contrast with FNH, adenoma contains few or no Kupffer cells and no bile ductules.

Etiology

The best-described factor favoring the development of hepatic adenoma is exposure to steroid hormones, although the molecular mechanisms have not been elucidated.[38] Two thirds of adenomas express estrogen and progesterone receptors,[39] and enlargement or even rupture has been reported during pregnancy. An increased risk of hepatic adenoma has also been noted with the use of androgen preparations, such as in aplastic anemia, hypogonadism, hypopituitarism, and other disorders.[40] Illicit use by body builders has also been reported to lead adenoma formation.[41] Other predisposing conditions are type I and III glycogen storage disease, where adenoma predominantly affects males.[42]

Diagnosis

About half of adenomas are discovered incidentally during imaging procedures for unrelated conditions.[18] The larger the tumor, the more likely it will be symptomatic by right upper quadrant or epigastric pain. Clinical examination is normal. Acute onset of pain is related to rupture or bleeding, which can lead to dramatic manifestations of acute abdomen and shock. Adenomatosis is more often symptomatic and has a higher tendency for bleeding complications.[37]

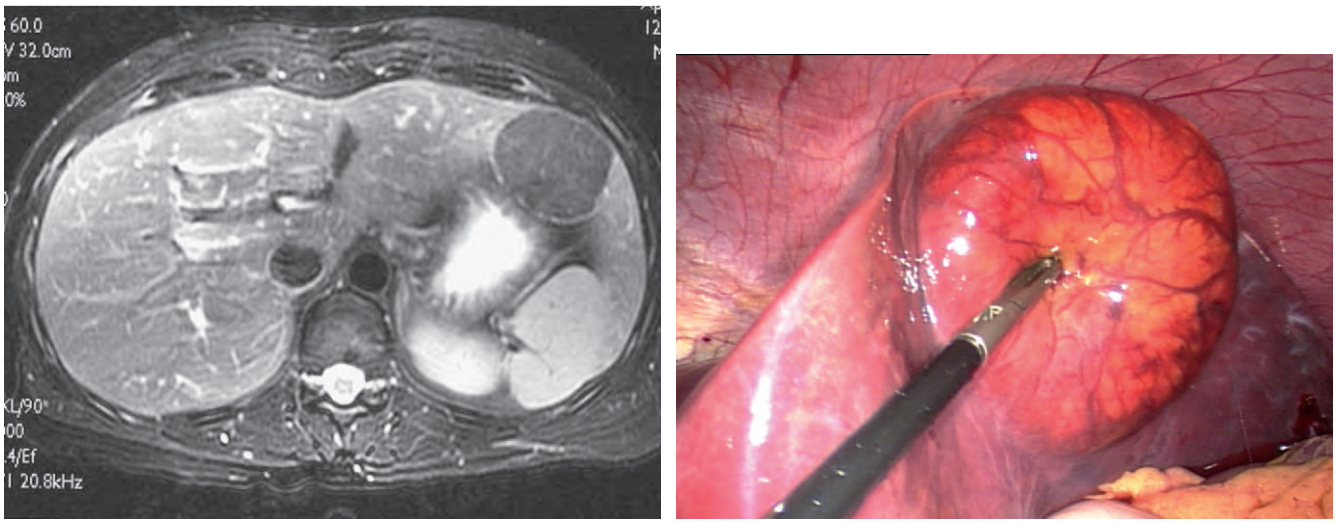
The initial evaluation is often done by ultrasound, yet this modality does not permit final diagnosis. The adenoma appears hyperechoic with hypoechoic and cystic areas, as well as occasional calcifications. In contrast with FNH, CT scanning shows a heterogeneous, mostly hypodense mass, interspersed with hyperdense regions of hemorrhage and hypodense areas of necrosis.[43] Contrast application leads to a rapid enhancement in the arterial phase, which is often pronounced at the margin due to peripheral vascularization and then proceeds centripetally. MRI shows a similarly heterogeneous lesion, which is predominantly hyperintense in both T1- and T2-weighted sequences but can also be hypointense (Fig. 122–3A). Dynamic contrast-enhanced sequences display rapid arterial enhancement. As adenoma contains none or few Kupffer cells, special imaging techniques such as MRI with superparamagnetic iron oxide (SPIO) contrast or 99m-technetium–sulfur-colloid scanning can be used to distinguish it from FNH. MRI imaging with gadobenate dimeglumine can also differentiate between adenoma and FNH because its uptake and excretion are reduced in adenoma, rendering the lesion hypointense on delayed scans. Laboratory analyses including tumor markers are usually normal. Biopsy has a low diagnostic yield,[18] especially if diagnostic uncertainty exists after several imaging modalities, and it carries a risk of bleeding.

Treatment

Hepatic adenoma has a different natural history from FNH, since it poses the risk of rupture and bleeding. Furthermore, there is a small risk of malignant transformation into hepatocellular carcinoma.[44] For these reasons we advocate surgical resection of all hepatic adenomas, as well as cases of diagnostic uncertainty. Others have a proposed a less aggressive approach for asymptomatic adenoma by discontinuing contraceptive therapy and following patients with serial imaging and alpha-fetoprotein determinations.[45] Radiofrequency ablation is a possibility, but follow-up data are lacking.[46] However, the standard of care is surgical resection, which can be achieved by the open approach or by laparoscopy (see Fig. 122–3B). Adenomatosis associated with glycogen storage disease can be an indication for liver transplantation, especially due to the high risk of malignant transformation.[47]

OTHER BENIGN TUMORS

A variety of rare benign tumors have been described to occur in the liver. In contrast to hepatocellular tumors, the benign variant of a biliary tumor is exceedingly rare. Bile duct adenoma is usually asymptomatic, but obstructive jaundice can be the presenting symptom depending on location and size.[48] As the diagnosis is rarely accurate preoperatively, and bile duct adenoma is considered a premalignant lesion, management should consist of surgical resection with clear margins. Biliary hamartomas (von Meyenburg complexes) are more common benign malformations of the biliary tract. The only relevance of



A B

Figure 122–3. **A,** Hepatic adenoma in the left lateral segment presenting as a T2-weighted hypointense encapsulated lesion. **B,** Laparoscopic view of the adenoma depicted in **A.**

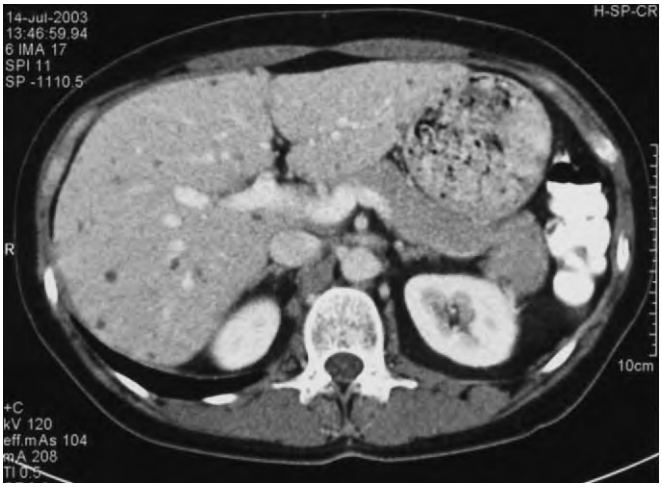


Figure 122–4. Contrast-enhanced CT scan of multiple biliary hamartomas (von Meyenburg complexes) evident as multiple cystic lesions.

these small lesions (<1 cm) consisting of cystic spaces and fibrous stroma is to distinguish them from metastases (Fig. 122–4). The diagnosis can be made by high-frequency ultrasound or by MRI.[49]

Angiomyolipomas are tumors derived from perivascular epithelioid cells, which are associated with tuberous sclerosis and mostly occur in the kidney. Hepatic angiomyolipomas are rarely diagnosed correctly by imaging procedures. They are a premalignant lesion and should be resected.[50]

Peliosis hepatis refers to a vascular disorder that can appear as a tumor.[51] It is associated with the use of steroid hormones, malignancy, transplantation, and chronic inflammation. Histology reveals multiple blood-filled cysts of different sizes. The natural history is not known, but rupture has been reported, and this lesion should probably be resected.

Other primary tumors described in the liver include solitary fibrous tumors, schwannoma, lipoma, leiomyoma, teratoma, and lymphangioma.

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Chapter

123

Hepatocellular Carcinoma

Elika Kashef ▪ Francis Yao ▪ John P. Roberts

EPIDEMIOLOGY AND ETIOLOGY

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and the fifth most common cancer in the world.[1] More common among men, the incidence of HCC in the United States has doubled since 1975, from 1.4 to 3 per 100,000 (Fig. 123–1).[2] The incidence of HCC in Asia and Africa, however, remains up to 15 times higher than that in the United States.[3]

There are clear associations between hepatitis B and C viruses and the development of HCC.[4] The geographic variation in both incidence and the etiology of HCC is predominantly related to these viruses. Hepatitis B has a higher prevalence in Asia and Africa, whereas hepatitis C is more prevalent in western countries and Japan.[3,5] The etiology of HCC in Japan, for example, is 70% related to hepatitis C, 20% to hepatitis B, and 10% to other causes such as alcohol, alfatoxins, and hemochromatosis.[5] A recent paper by Tanaka et al.[6] stated that the hepatitis C virus first appeared in Japan in 1882 and began to spread by 1930. It reached the United States in 1910 and has spread rapidly since 1960. This time frame may explain the recent rise in HCC incidence in the United States because the time interval between exposure to hepatitis C and development of HCC has been reported to be as long as 28 years.[7] The increased incidence of HCC in the United States has been attributed to the increased incidence of hepatitis C because the incidence of HCC as a result of hepatitis B, alcohol, and idiopathic cirrhosis has remained stable. It is estimated that 50 million to 80 million people are infected with hepatitis C virus worldwide, creating a substantial reservoir of patients at risk for HCC.

RISK FACTORS

The risk factors for HCC are listed in Box 123–1.

PATHOLOGY

In the United States, Western Europe, and Japan, 80% to 90% of HCCs occur in patients with cirrhosis.[8] The highest incidence of HCC in the cirrhotic liver occurs in patients infected with hepatitis B and C, but a lower incidence of HCC is also found in patients with nearly any cause of cirrhosis.

Hepatitis B and C cause chronic viral infections of the liver and result in hepatic inflammation. After exposure to hepatitis C, 20% to 25% of patients develop cirrhosis or hepatic decompensation, and, of this group, 20% to 25% develop HCC.[9]

Hepatitis B, a DNA virus, integrates itself into hepatocyte DNA and is thought to increase the rate of oncogene transcription. Hepatitis C, an RNA virus, does not incorporate into DNA of the hepatocytes. Its relationship with HCC is thought to be through chronic inflammation leading to cirrhosis, which has a strong association with HCC.[10] After cirrhosis develops, hepatitis C virus continues to replicate, which sustains inflammation and a rapid cell turnover, resulting in mutation and dysplastic changes that lead to neoplastic growth.[11]

The cirrhotic liver consists of regenerative nodules surrounded by fibrosis. It appears that there is a progression from regenerative nodules to dysplasia and then to HCC (Fig. 123–2).[12] The dysplastic nodules generally range from 1 to 2 cm and contain areas of dysplasia or carcinoma in situ. Although not all HCCs arise in livers where there are dysplastic nodules, it appears that a high percentage of patients (~85%) with end-stage liver disease and HCC will be found to have dysplastic nodules.[13,14]

The effect of this pathogenesis on the cirrhotic liver is to make the entire liver at risk of dysplasia and subsequent HCC. This "field effect" is responsible for the high rate of recurrence after resection of HCC.

A clinically important feature of HCC is its propensity to derive its blood supply from the hepatic artery. There appears to be a progression of the degree of arterial perfusion corresponding to the progression of dysplasia. Dysplastic nodules appear not to have a substantial arterial supply, whereas even small lesions of HCC appear to have a substantial arterial supply.[15] The clinical relevance of this finding has to do with the radiologic appearance of HCC versus regenerative nodules. HCC usually is characterized by being hyperdense on the arterial phase of

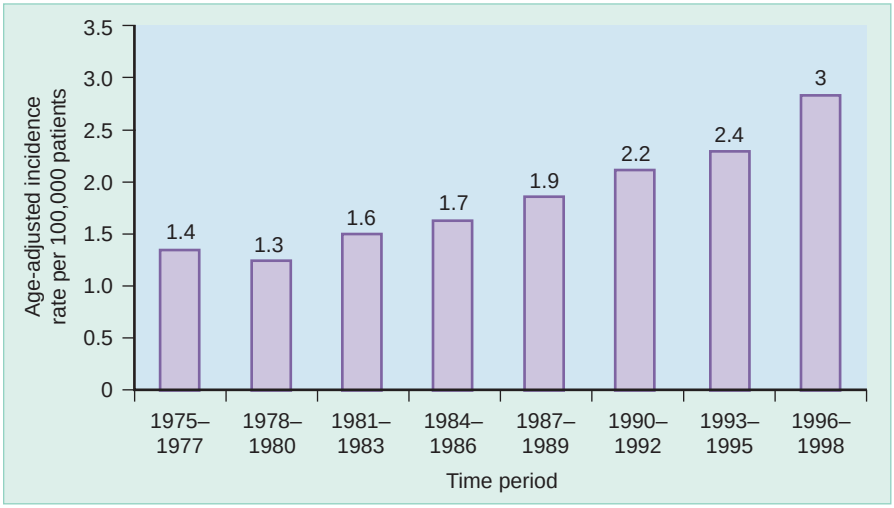


Figure 123–1. The overall age-adjusted incidence rates for hepatocellular carcinoma for consecutive 3-year periods between 1975 and 1998. (From El-Serag HB, Davila JA, Peterson NJ, et al: The continuing increase in the incidence of hepatocellular carcinoma in the United States: An update. Ann Intern Med 139:10, 2003.)

Box 123–1 Risk Factors for Hepatocellular Carcinoma

Alcoholic liver disease ← cirrhosis
Aflatoxins
α_1-Antitrypsin deficiency
Anabolic steroids
Hemochromatosis
Hepatitis B virus
Hepatitis C virus
Oral contraceptive pill

Figure 123–2. Pathologic specimen showing multiple HCC *(white arrows)* and dysplastic nodules *(black arrows).* The hepatocellular carcinoma in the upper right corner had been treated with alcohol ablation.

contrast imaging, meaning that they have more arterial perfusion, whereas regenerative nodules do not enhance on the arterial phase, suggesting more similar arterial perfusion to the background liver.[16] The arterial perfusion of HCC also allows for treatment of the lesions via embolization of the feeding artery.

Another characteristic of HCC involving the blood supply to the liver is its propensity to invade the portal vein. The risk of portal vein invasion appears to correlate with tumor size and differentiation.[17] The outcome of patients with portal venous invasion is worse than that of patients whose tumor does not invade the portal vein.

CLINICAL PRESENTATION

Because of the known risk factors for HCC, there is usually a history of viral hepatitis, alcohol or drug abuse, metabolic disorders, or past history of HCC. Many patients have a history of complications of cirrhosis.

HCC can present in varying ways: as a finding during ultrasonographic screening for patients at risk for HCC, right upper quadrant pain, abdominal mass, weight loss, anorexia, or symptoms of cirrhosis such as the new onset of ascites. A patient with known cirrhosis who develops any of these symptoms should be suspected of having developed HCC. The finding of small liver lesions during the radiologic evaluation for liver transplantation is now a common presentation, particularly in patients with hepatitis C.

Physical examination can reveal jaundice, ascites, cachexia, splenomegaly, or hepatomegaly or it may be normal. Owing to the strong association between cirrhosis and HCC, examination can reveal more subtle stigmata of liver disease such as spider angiomata.[18]

Laboratory Investigation

Blood tests can reveal abnormal liver function tests and liver enzymes. A common finding is thrombocytopenia,

which commonly occurs early in patients with cirrhosis. Viral serologies such as hepatitis B surface antigen and hepatitis C antibody tests should be obtained.

Alpha-fetoprotein, which is a globulin produced in the first trimester of pregnancy, can be elevated in patients with HCC. However, this is not a specific test because levels are also elevated in patients with liver cirrhosis who do not have HCC,[18] and in patients with other tumors, such as germ cell tumors. The value of alpha-fetoprotein in screening protocols for HCC has been questioned, and its best use is probably as a confirmatory test in patients with cirrhosis and a liver mass.[19] In children with hepatoblastoma, the alpha-fetoprotein is frequently elevated to levels 1000 to 10,000 times normal.

Biopsy

The value of biopsy is questionable in patients with risk factors for HCC and a mass larger than 2 cm with radiologic characteristics of HCC. The likelihood of these patients having HCC is quite high, and a negative biopsy has a substantial chance of being a false negative. Bleeding after biopsy and seeding along the needle track are significant risks.[20] Liver biopsy has greater value in HCC occurring in patients without risk factors for HCC and where the imaging studies are unclear.

Imaging

Imaging in HCC is important to both diagnose HCC and rule out bilobar disease and vascular invasion, thus determining the ability to resect the lesion.[21] Because HCC most commonly occurs in the cirrhotic liver, imaging may provide other clues regarding the ability of the patient to undergo liver resection, such as evidence of portal hypertension.

The nodular nature of cirrhosis makes imaging difficult. In the noncirrhotic liver, HCC nodules stand out against a homogeneous background, whereas in the cirrhotic liver, an HCC nodule is another nodule in a sea of regenerative or dysplastic cirrhotic nodules (see Fig. 123–2). The probability that a lesion found on imaging is HCC increases with the size and arterial phase enhancement of the lesion.

A recent consensus conference on HCC suggested that its diagnosis in the cirrhotic liver can be assumed if two different imaging modalities demonstrate a focal lesion greater than 2 cm with arterial hypervascularization.[22] The finding of a hypervascular lesion greater than 2 cm combined with an alpha-fetoprotein level of greater than 400 ng/ml was also considered to be diagnostic for HCC. The basis of this conclusion was that regenerative nodules are rarely greater than 2 cm and are not hypervascular. The consensus conference also concluded that the sensitivity and specificity of imaging techniques in lesions smaller than 2 cm are poor.

A major issue regarding imaging is the sensitivity and specificity of the various techniques. Sensitivity and specificity are usually best assessed by preoperative radiologic examination of the liver and then meticulous pathologic examination of the specimen removed at resection or transplantation. Based on these types of studies, the sensitivity of radiologic imaging studies for determination of a lesion is about 60%. In a recent review of the literature, Fung et al.[23] found that there was little evidence to support one imaging modality over another in cirrhotic patients with HCC, although a recent paper suggested the superiority of magnetic resonance imaging (MRI) to computed tomography (CT) scanning.[14] Further research is necessary to establish the superiority of one technique over others. Currently, it is probably best to think of these studies as complementary.

The relatively poor sensitivity of imaging of HCC in the cirrhotic liver suggests that accurate staging of patients with HCC is difficult because current radiologic techniques do not provide accurate information regarding the presence of other HCC lesions in the liver. The failure of accurate staging is probably partly responsible for the high recurrence rate of HCC following resection.

Ultrasonography

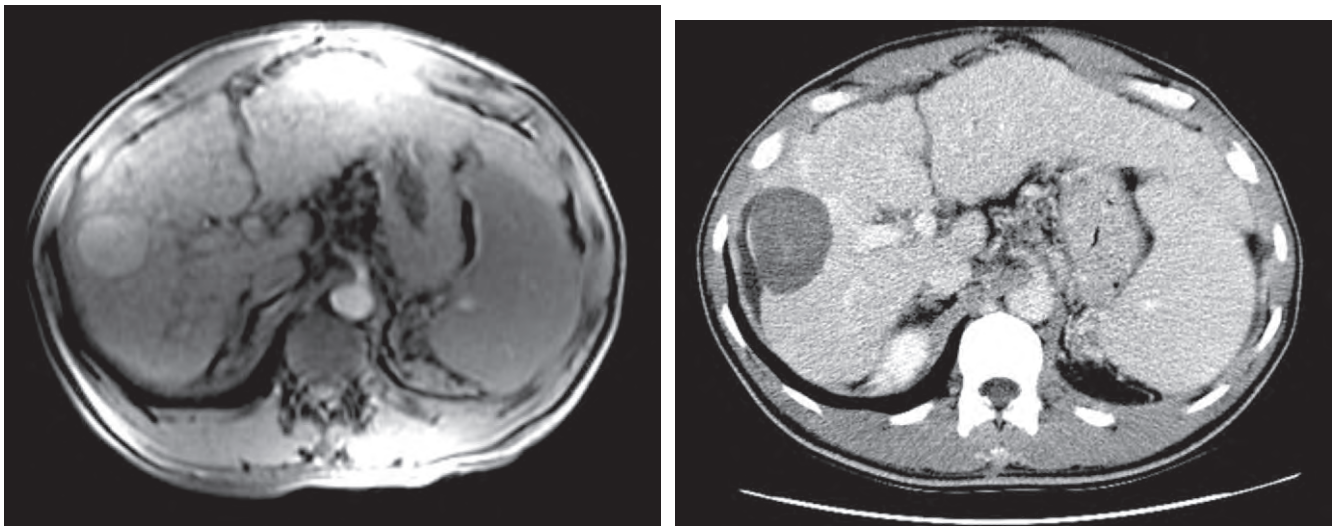
The primary use for ultrasonography is in screening populations for HCC.[24] The value of doing so is primarily related to the low cost. For populations in which the incidence of HCC may be quite high, such as patients awaiting liver transplantation, ultrasound may be less useful.[25] The finding of a lesion less than 1 cm on ultrasound should result in frequent follow-up monitoring of the lesion. The finding of a lesion greater than 2 cm should be confirmed with another imaging modality. There is no consensus of opinion regarding what to do with lesions between 1 and 2 cm.

Ultrasound cannot differentiate between benign and malignant lesions but can differentiate between solid and cystic nodules, and it can be used to guide needle biopsies. The use of contrast agents containing microbubbles may increase the value of ultrasound in distinguishing between liver masses.[26] The role of ultrasound in the management of HCC for directing the use of ablative techniques are discussed later.

Computed Tomography

In the early stages of HCC, the tumor appears as a hyperattenuating lesion. This is due to angiogenesis and the rich vasculature of the tumor, and, unlike normal liver parenchyma, its blood supply is predominantly from hepatic artery. Because of this, helical CT scanning with arterial, portal, and hepatic venous phase provides more information than conventional CT scanning. This is important because of the vasculature of the lesion and its variable attenuation during different phases of scanning.[27] By using higher doses of contrast, "double arterial-phase imaging"—where images are taken early and late during the arterial phase—can be performed to reduce false-positive rates.[28]

The sensitivity of CT scanning has been purported to increase with iodized oil (lipiodol) injected intravenously. Lipiodol is an iodized ethyl ester of fatty acid from poppy seed oil.[29] It has a specific affinity for HCC, which is believed to be via uptake by the cell types and reticuloendothelial system or lipid capturing by microvessels. The lesion retains the oil, and follow-up



A B

Figure 123–3. Hepatocellular carcinoma before (**A,** MRI) and after (**B,** CT scan) radiofrequency ablation.

images are taken 2 to 4 weeks after injection. The best reported sensitivity of lipiodol for HCC is about 53%, which is similar to techniques using standard contrast agents.[30]

CT scanning is also used after treatment for HCC to monitor patients for recurrence. Radiofrequency ablation (RFA) leaves a large area of tissue destruction, the radiologic appearance of which varies over time (Fig. 123–3B).[31] The ablation site 3 months after ablation should be of low attenuation and should not have areas of arterial enhancement that could signify tumor recurrence. The presence of either higher attenuation or arterial enhancement should raise a concern of tumor recurrence.

Magnetic Resonance Imaging

HCC has high signal intensity on T2-weighted images and variable signal intensity on T1-weighted images. HCC tends to enhance during the arterial phase, after administration of gadolinium (see Fig. 123–3A).[32]

MRI can be used to assess the vascular dynamics of the tumor. It can assess arterial hepatic perfusion, peak portal venous perfusion, and maximum hepatic enhancement phases. Most HCCs have maximal enhancement during the arterial phase (keeping in mind that the normal liver is supplied mainly by the portal system, whereas the tumor is mainly supplied by the hepatic artery).

MRI needs less contrast volume than CT and injection time is shorter. There is also no ionizing radiation in MRI. Contrast agents used include gadolinium chelates, superparamagnetic iron oxide, and hepatocyte-directed agents (mangafodipir trisodium).

Superparamagnetic iron oxide (SPIO) is taken up by the Kupffer cells and acts as a contrast agent. Studies have shown SPIO-enhanced MRI to be more sensitive than noncontrast MRI and contrast CT. It is less invasive than CT angiography but is thought to be as informative.[33]

STAGING

Staging of HCC provides information about the degree of spread and/or metastases. The staging system can act as a prognostic tool and can be used to ascertain which patient should get which treatment modality. It is also useful in research studies, including analysis of response to therapy in clinical trials.

The most common staging systems are the following:[34-36]

- *TNM* (tumor, node, metastasis), which only assesses the tumor and not the function of the liver in the nontumorous liver. TNM is difficult to use preoperatively because it relies on histologic assessment of the liver. Currently in the United States, this staging system has been modified for use to prioritize patients with HCC for transplantation based on radiologic imaging.[36]
- *Okuda classification* (I to III) assesses both the tumor and the liver. It takes into account tumor size and liver function tests such as albumin and bilirubin levels. It does not take into account vascular invasion or whether or not the tumor is single or multiple. This is a commonly used staging system.[35]
- *Barcelona Clinic Liver Cancer* (BCLC) staging system provides information on prognosis and aids with planning treatment. It takes into account a variety of factors, including clinically relevant portal hypertension. Patients with stage A (early tumor) are suitable for all treatment modalities. Those with stage B (intermediate) or C (advanced) are more suitable for palliative care and use of new agents, which are in stage II trials. Patients with stage D (end-stage) should be treated symptomatically only.[34]

- *Cancer of the Liver Italian Program* (CLIP) includes the Child-Pugh stage, tumor extension, alpha-fetoprotein levels, and portal vein thrombosis.[35]

Less commonly used staging systems include the "French" scoring system, Chinese University Prognostic Index, and the Japanese Staging System.[34,35]

The following example shows how staging systems are used. The TNM classification is used in the United States to determine which patients with HCC have priority for receiving a liver transplant. Patients are stratified by the tumor size, the number of tumors, and the presence of vascular invasion. Patients with a single lesion between 2 and 5 cm in diameter or fewer than three lesions with no lesion greater than 3 cm are given priority for transplantation. Patients with single lesions greater than 5 cm, with more than three lesions, with fewer than three lesions where one lesion is greater than 3 cm, or with radiologic evidence of vascular invasion are given no priority for transplantation. The rationale underlying this system is based on the higher incidence of recurrence in patients with HCC who do not meet the criteria for receiving priority. Although the absolute values of these criteria have been challenged, the overall benefit of a scoring system to assign priority has not.[36]

MANAGEMENT

Management of HCC is dependent on a variety of factors, including the size and site of tumor, the extent of spread, the premorbid condition of the patient, and the function of the nontumorous liver.[37]

Management can be divided into medical therapies, ablative techniques, and resection. Because of the association of cirrhosis with most cases of HCC, along with the presence of advanced disease at the time of diagnosis, only a percentage of the affected population is suitable for intervention. Ablative techniques such as ethanol or RFA are an alternative to resection and have been used more frequently in recent years. These techniques offer the advantage of destroying the tumor while possibly sparing more functional parenchyma. Chemotherapy has also been used both locally, as part of ablative techniques, and systemically.

Chemotherapy

HCC is usually chemoresistant. However, for patients who are not suitable for surgery or interventional therapies, chemotherapy is used for palliation of symptoms.

Until recently, chemotherapy has not been proven to provide remission or improve the possibility of resecting a tumor. However, when Lau et al.[38] treated a group of patients with unresectable HCC with systemic chemotherapy/immunotherapy (cisplatin, α-interferon, doxorubicin, and 5-fluorouracil), they found that 10% of patients were able to have surgical resection after the therapy, and 1.3% had complete remission of tumor. These results need to be confirmed by other studies.

Postresection adjuvant chemotherapy has been administered in a randomized, controlled trial but was abandoned due to high complication rates.[39] There is no current class 1 evidence to support using chemotherapy to improve outcome after resection. A recent report of a randomized trial demonstrated that adjuvant chemotherapy does not improve survival after liver transplantation for HCC.[40]

Ablative Therapies

Ablative therapies have changed the management of HCC. Ablation has the advantage of destroying the tumor with potentially less normal tissue damage and less physiologic insult than resection. Ablative procedures can be repeated when lesions recur or when new lesions develop. Ablative therapies can be performed percutaneously, during open surgery, or laparoscopically.

The role of ablation versus resection of the tumor is currently unclear. The major question is that for patients who would be candidates for either ablation or resection, which one provides the best control of the tumor, with the lowest risk for morbidity and mortality? This question would best be answered in a randomized trial. Currently, it appears that the convenience of a percutaneous or laparoscopic ablation may be taking precedence over the incomplete knowledge of the relative oncologic outcomes of these ablative procedures versus resection.

There are several categories of ablative procedures, including the following:

- Transcatheter arterial embolization/chemoembolization
- Percutaneous ethanol injection
- Radiofrequency ablation
- Thermal ablation
- Cryoablation
- Other therapies[41]

Transcatheter Arterial Embolization/Chemoembolization

Transcatheter arterial embolization/chemoembolization (TAE/TACE) is a commonly utilized technique for managing unresectable HCC. It takes advantage of the fact that HCCs are usually highly vascularized lesions for which the predominant blood flow comes from the hepatic artery. The technique couples occlusion of the hepatic arterial supply to the lesion with providing local chemotherapy. The expectation is that the occlusion may increase the tumor's susceptibility to the chemotherapeutic agent.

Intra-arterial catheterization is performed under radiologic guidance. Catheterization is followed by infusion of chemotherapy mixed with lipiodol, followed by embolization by using a gelatin sponge. Chemotherapy agents such as cisplatin, doxorubicin, and mitomycin are usually used.[41]

Since tumor progression can result in patient ineligibility for liver transplantation, patients awaiting a transplant can undergo this procedure to attempt to prevent tumor progression and vascular invasion. This procedure is also used in patients who are not suitable candidate for anesthesia and/or transplantation. However, patients

with liver decompensation are not usually suitable for this technique since there is increased risk of hepatic ischemia. Use of highly selective arterial catheterization may decrease the risk of liver failure after TACE.

Results of chemoembolization on improving survival outcomes for patients with HCC have been mixed in the past.[42] A recent study by Llovet and colleagues[43] on unresectable HCC showed 3-year survival rates of 29% for embolization, 29% for chemoembolization, and 17% for symptomatic treatment only. This was the first randomized study to demonstrate better survival with the two treatments; previous studies had only demonstrated the antitumor effects. These results have been confirmed by Lo et al.[44]

Most clinicians would not propose chemoembolization in a patient where resection, RFA, or ethanol injection could be used. Although there is no class 1 evidence available, these other therapies are considered more likely to provide cure than chemoembolization. A recent retrospective analysis has suggested that the two therapies may be equivalent.[45]

A similar form of chemoembolization therapy can also be used in patients after resection. Lau and colleagues[46] performed a small randomized study comparing two groups, both of whom had partial hepatectomies for HCC. One group received a single postoperative dose of iodine 131–labeled lipiodol therapy, and one group did not. The recurrence rate was 20% lower in the lipiodol group than in the nonlipiodol group (28.5% vs. 59%), and the 3-year survival rate was 40% higher (86% vs. 46%).

There has been some hope that iodine 131–labeled lipiodol therapy may be helpful in patients with unresectable HCC, but the data are inconclusive.[47]

Percutaneous Ethanol Injection

Ethanol causes cell damage by coagulative necrosis, cell dehydration, and denaturation. It is relatively inexpensive and has few side effects. Percutaneous injection takes place under ultrasound guidance using absolute alcohol.[48] The tumor is injected and the needle is left in situ for 1 to 2 minutes and then withdrawn with negative pressure. Because this procedure can be difficult for lesions near the dome of the liver, CT- or MRI-guided injection is preferred. Injections can be given several times without the need for overnight hospitalization. As a rough guide, the number of sessions is twice the size of the lesion in centimeters.[48]

Side effects of the procedure include pain, transient fever, intoxication, portal venous system thrombosis, right pleural effusion, and hemobilia; therefore, if, during percutaneous ethanol injection (PEI) the gallbladder is becoming distended, the procedure must be terminated.[49] PEI should not be carried out in patients with bleeding tendencies or advanced cirrhosis.[48,*]

PEI has a response rate of 90% to 100% in tumors less than 2 cm and of 50% for tumors 5 cm in diameter.[1] Five-year survival rates of 48% have been reported by two different studies.[48]

After PEI, CT scans are obtained for follow-up. Because necrotic tissue does not enhance on CT, any enhancement is a sign of residual viable tissue. Alpha-fetoprotein levels are checked 2 to 3 weeks after PEI to monitor the effect of therapy.[49]

Radiofrequency Ablation

RFA consists of a high-frequency alternating current that causes agitation and frictional heat, resulting in denaturing of proteins and of the lipid bilayer of tumor cells, resulting in tissue destruction and necrosis. RFA can be performed percutaneously under ultrasound guidance, laparoscopically, or during a laparotomy. Some reports suggest this technique is as effective as PEI but requires fewer sessions and is more effective in tumors grater than 3 cm.[1]

Percutaneous RFA may be limited in lesions that are close to the right hemidiaphragm or are near extrahepatic structures such as the duodenum or colon. The use of a laparoscopic or open surgical approach offers the advantage of being able to inspect the surface of the liver and the ability to move extrahepatic structures such as the colon away from the planned ablation site.[50]

The stainless-steel insulated needle is inserted into the tumor site and the prongs are then deployed to provide heating over a larger area. The unit can generate a temperature of up to 120°C. The diameter of coagulation can range from 0.5 to 3 cm. Repeated applications of the heating can be used to treat larger tumors. There are reports that the diameter coagulated by radiofrequency is greater in bigger tumors, due to a conductive "oven effect."[51] When the needles are withdrawn, diathermy is used to prevent tumor seeding, which has been reported to occur.[1,41]

In addition, difficulties may arise due to the site of the tumor. Tumors near the dome and surface of the liver are difficult to ablate. Satellite lesions may also be present, making complete ablation in one session difficult. To ablate satellite lesions, either the patient must undergo multiple ablative sessions or multiple electrode insertions are necessary in the one session.[51] Complete ablation is also difficult for tumors near large vessels because of the perfusion of the tissue, which results in protective cooling of the tumor. The use of occlusion of the portal triad (Pringle's maneuver) may decrease the effect of the flowing blood removing heat and allow adequate heating of tumors.[52,53]

RFA can be used in patients awaiting liver transplantation.[54] It may help reduce their "dropout" rate by preventing tumor growth to sizes that would prohibit transplantation.

A disadvantage of RFA is incomplete tumor destruction. Consequently patients who undergo it must be monitored every 3 months with CT scans or MR images to detect any recurrence.

Recurrence rates after one session of radiofrequency for tumors located deep in the liver are 7.8% at 1 year, 11.0% at 2 years, and 11.0% at 3 years. For tumors near the surface of the liver for which ablation is technically

*Recommended cut-off point is prothrombin time <40% and platelet count <40,000/mm^3.

difficult, recurrence rates rise to 20.0%, 34.5%, and 50.9%, respectively.[51] Five-year survival rates range from 33% to 40% in all treated patients.[1]

Complications of RFA appear to be more frequent for open treatment than for percutaneous treatment and are even more frequent in patients with cirrhosis.[55] Depending on the tumor location and size, percutaneous or laparoscopic RFA may be appropriate. The laparoscopic approach is replacing open surgical ablations.

Microwave Thermotherapy

In radiofrequency therapy, the electrodes act as an active source of energy, whereas in microwave thermotherapy, which causes kinetic energy among molecules that converts into heat energy, the probe inserted into the tumor site acts as a transmitter of energy from an external source. Microwave therapy can be given percutaneously or laparoscopically. It is thought to penetrate tissue better than radiofrequency therapy, resulting in larger areas of necrosis and ablation. Complications include pain, fever, hematoma formation, and bleeding.[56]

Several studies have reported the efficacy of microwave ablation. A recent study reported response rates between 92% and 98%, depending on tumor size. Survival rates at 1, 2, and 3 years were 96%, 83%, and 73%, respectively, in the same study.[57]

Laser Thermotherapy

Laser thermotherapy is given by inserting fine, flexible, optic fibers into the tumor site via image-intensifier–guided percutaneous needles. These provide heat energy to cause cell breakdown and death. This ablative technique has been used mostly for secondary liver metastases. Several fiberoptic insertions are needed to induce a complete necrosis because each optic fiber allows ablation of up to only 1.6 cm. Research into ways of improving the coagulation diameter of each fiber optic is currently being carried out. Response rates range from 50% to 97.5%.[56] Complications of laser therapy are similar to those of the other ablative techniques: pain, bleeding, right pleural effusion, and fever.

Cryoablation

Cryoablation consists of freezing and thus denaturing hepatic cells. This procedure is usually carried out during open surgery, and, in tumors greater than 8 cm, requires several probe insertions. The larger the probe size, the larger the area of tissue destruction. Intraoperative ultrasound is used to locate the tumor, and liquid nitrogen is passed through the probe. After the controlled flow of nitrogen is stopped, the probe is left in situ until thawing has commenced. The nitrogen is then restarted to refreeze the tissue.

Since the purpose of ablative therapy is mainly to provide an alternative for patients who are unsuitable candidates for surgery, the fact that cryoablation requires a laparotomy is a major limitation of its use. Although cryoablation has not yet been performed percutaneously, there are designs of probes that may be used for this purpose.[56]

Complications include hypothermia, cardiac arrhythmias (especially when tumor is located near the inferior vena cava), and liver cracking.[58] Because of these complications, cryoablation is not a commonly used procedure.

Other Treatments

Acetic Acid *Acetic acid* (50% solution) penetrates through more tissues than ethanol and is able to infiltrate the tumor capsule, which ethanol is unable to do. Consequently, acetic acid injection kills tissue more evenly. A randomized trial of PEI versus acetic acid found that the local recurrence rate in the acetic acid group was lower (8% vs. 37%).[59]

Side effects of acetic acid injection include hemoglobinuria, which is self-limiting, and renal toxicity. However, the acid load from this agent does *not* cause a metabolic acidosis.

Acetic acid needs further evaluation before it can be used as an established form of treatment in HCC.

Combination Therapies Combination therapies can be used to ensure complete tumor ablation and reduce recurrence rates. Generally, single tumors are more suitable for treatment with percutaneous therapies such as PEI or RFA, whereas multiple tumors are better treated with TAE or TACE.

TACE or PEI have been combined in a number of studies, recently reviewed by Goldberg and Ahmed.[56] Several studies have demonstrated improved survival rates in patients who received this combination therapy. Survival rates were higher in patients who received this combination therapy than in those who received just TACE.

A recent small randomized trial comparing TACE versus a combination of TACE and RFA or PEI demonstrated improved local control in the combination therapy group (18% vs. 0% local recurrence).[60] The authors found that the effect of combination therapy on the prevention of recurrence seemed to reside in those patients who received PEI and not RFA, suggesting that RFA may be more effective local therapy.

Percutaneous and transarterial techniques can be used to treat or reduce the rate of tumor progression in patients with HCC. This may be of benefit in patients awaiting transplantation and may reduce the rate at which they have to drop out because of tumor progression.

Resection

If the HCC tumor is limited to one lobe and there is no extrahepatic invasion, the remaining liver is functional enough to support life, and the tumor is surgically accessible, then surgical resection should be considered.

The usually advanced nature of HCC at the time of presentation means that up to 80% to 90% of patients are not suitable for surgical resection, usually because of concurrent cirrhosis and hepatic impairment.[61] Post-

operatively, such patients are at risk of hepatic failure. Therefore, the determining factor of whether a patient is a candidate for resection is adequate hepatic function, which must be assessed preoperatively.

Several tests have been used to assess hepatic function before resection to determine the appropriate extent of hepatic resection. Indocyanine green (ICG) clearance is used in patients with normal synthetic function (bilirubin, albumin, and prothrombin time). If hepatic ICG retention is greater than 20% at 15 minutes after injection, no more than one sixth of the liver should be resected. If ICG retention is greater than 30%, then limited resection or enucleation is appropriate.[62] Makuuchi and colleagues use ICG clearance with the Child-Turcotte-Pugh (CTP) classification to determine the level of resection a patient should have.[62] The value of this test in preoperative assessment of liver function is controversial.[63]

Other tests used to assess liver function include urea nitrogen synthesis rate, galactose elimination capacity, and aminopyrine breath test. The presence of portal hypertension, a platelet count less than 100,000, and an abnormal bilirubin appears to be a risk factor for decompensation.[64]

More recently, portal vein embolization has been used to assess and minimize the risk of liver failure after resection.[65] This technique consists of accessing the portal vein percutaneously and embolizing the branch of the portal vein that supplies the lobe to be resected. In theory, portal vein embolization allows the portal blood to be diverted from the lobe to be resected and allows compensatory hypertrophy of the lobe that is to remain after resection. Significant growth of the lobe contralateral to the embolized portal branch appears to signify that a liver is capable of regeneration. Failure of growth suggests that the liver that would be left behind after resection may not be capable of regeneration.

The technique may allow for improved postoperative survival in patients with fibrosis or cirrhosis who undergo resection. Further analysis of this technique in regard to which patients are likely to benefit from it is needed.

Intraoperative ultrasonography has been used to ascertain vessel orientation, which, when combined with preoperative knowledge of the tumor and its blood supply, makes accurate resection of the tumor and its associated segments possible. Once the tumor and its associated vessels are identified, the surface markings are made on the liver using diathermy. The information gained by this technique may allow for segmental or subsegmental resections that are oncologically correct but spare as much residual liver as possible.[62]

Operative Techniques

There are probably as many ways of performing liver surgery as there are surgeons doing the operations. The appropriate technique depends on the location of the tumor, the degree of cirrhosis, and the experience of the surgeon. The principles are the prevention of blood loss and the preservation of as much functional liver as possible. It does appear that margins greater than 1 cm are adequate.[66]

Several techniques are used to minimize blood loss. These include inflow occlusion, total vascular isolation, and the use of clamps to compress the parenchyma. The intermittent inflow occlusion technique (Pringle's maneuver) is used to minimize blood loss during hepatectomies. Fifteen minutes of occlusion followed by 5 minutes of reperfusion is usually used. Another technique is total vascular isolation of the liver in which occlusion of the infrahepatic and suprahepatic vena cava is combined with occlusion of portal triad inflow. This technique can be helpful when the resection requires dividing parenchyma that is close to a major hepatic vein that cannot be sacrificed.

If the tumor is on the surface of the liver, away from major vessels and less than 3 cm in diameter, a laparoscopic partial hepatectomy may be performed. Similarly, the lateral segment of the left lobe is amenable to laparoscopic resection. Laparoscopic resection is less invasive and results in shorter postoperative hospital stays as a result of earlier patient mobilization and restoration of normal bowel function. The expectation is that as instrumentation improves and surgeons get more experience with laparoscopic resection of the liver, it will become much more common. Currently, only major centers are performing laparoscopic resection of the lateral segment of the liver.

The major issue regarding resection as the treatment for HCC is tumor recurrence in the remaining liver. The risk of recurrence is high because of the predominance of viral liver disease in patients with HCC. This risk does not appear to be just of recurrence of the resected lesion; rather, it also may be of second primary lesions. The outcome after resection indicates a high risk of further disease; commonly reported recurrence rates are 40% to 50% at 3 years.[67-69]

One potential contributing effect to the risk of recurrence is the relatively poor sensitivity of current radiologic techniques to stage the patient's tumor stage accurately.[70] Thus, patients with HCC in a cirrhotic liver can be frequently expected to have a missed second primary at the time of hepatic resection.

Transplantation

Hepatic transplantation is an effective way to remove both the carcinoma and the remaining cirrhotic liver. Overall survival and recurrence-free survival after transplantation is better than resection for selected tumor stages. The major issues regarding transplantation are the cost and the lack of organs for transplantation. In the United States, 18,000 patients await liver transplantation and the number of cadaveric donors is 5000 per year.[1] Not surprisingly then, considerable effort has been directed toward determining which patients with HCC will have excellent survival outcomes after liver transplantation.

Criteria stated by Mazzaferro and colleagues,[71] also known as the *Milan criteria,* propose transplantation for patients who have a single tumor smaller than 5 cm or fewer than three tumors, each of which are smaller than 3 cm. The results using these criteria resulted in a 5-year

survival rate of 80%, similar to that for patients who received a liver transplant but did not have HCC.[72] There has been criticism that the Milan criteria may be too strict, eliminating patients from transplantation who would have equivalent survival. Alternative criteria, known as the *University of California San Francisco (UCSF) criteria,* were proposed by Yao et al.[73] These criteria offered transplantation to patients with a single tumor less than 6.5 cm or less than three tumors, the total diameter of all being less than 8 cm and the largest tumor less than 4.5 cm. The 1-year and 5-year survival rates for these patients were 90% and 75.2%, respectively. In another set of criteria, Marsh and Dvorchik[74] noted that patients with vascular invasion of a major portal vein branch have a poor prognosis and therefore removing the diseased liver would not improve outcomes.[75] In February 2002, The United Network for Organ Sharing (UNOS) modified their criteria giving priority to patients with HCC. This has increased the number of liver transplants among patients with HCC.

While patients are on the waiting list for a liver transplant, tumor progression or even death may occur. As noted earlier, a major obstacle for patients for whom a transplant is suitable is the lengthy waiting time during which continuous tumor growth may result in them becoming unsuitable and having to drop off the waiting list. Ideally, waiting times should be less than 6 months, but because of the donor shortage, waiting times can exceed 12 months. Dropout rates for patients with HCC have been reported to be as high as 70%.[76] An obvious advantage to resection then is that this waiting period, with its risk of tumor progression, is eliminated.

The aim of adjuvant therapy is to slow down or even prevent tumor progression while patients await transplantation. Adjuvant therapy (e.g., TACE, RFA, PEI) given to patients while on the waiting list may reduce dropout rates,[77] but the results so far have been only for small groups of patients or short follow-up periods.[78] Further studies, specifically randomized trials, are necessary to determine whether these adjuvant techniques improve survival for patients on the waiting list and after transplantation.

Living donor liver transplantation (LDLT) has provided a new source of organs for transplantation. Originally, LDLT was performed in children, with an organ donated from a parent or other relative; however, adult-to-adult LDLT is now performed throughout the world.[79] The advantages of LDLT for patients with HCC include little or no time on the waiting list, thus avoiding the risk of tumor progression. Decision analyses have shown that LDLT for patients with HCC improves life expectancy and is more cost-effective than waiting on the transplant list for more than 7 months.[80] In a case-control study in the United States, the 2-year graft survival rate was 64.4% for LDLT and 73.3% for cadaveric grafts.[81] A study of LDLT in Germany[82] reported a 3-month graft survival rate of 83%. Reports published so far are of small numbers of patients with no long-term follow-up. No randomized, controlled trials have compared LDLT and cadaveric transplantation for patients with HCC.

LDLT raises a number of ethical issues that need to be dealt with on an individual basis. These include ascertaining that a donor's decision to donate part of their organ is voluntary and ensuring a clear understanding by the donor that the procedure, unlike most operations, is not being done for their own medical problem, that it is associated with complications both intraoperatively and postoperatively, and that there is uncertainty about the long-term survival of donors and the effect on their quality of life.

RESECTION VERSUS TRANSPLANTATION

Controversy continues about whether a patient with HCC should undergo resection (or possibly an ablative technique) or liver transplantation. In many parts of the world, the lack of resources available for transplantation makes this question moot. In countries that have available resources, the question is unresolved and a randomized trial comparing the outcomes is unlikely. It appears that for tumors that fit the Milan or UCSF criteria, the outcome after transplantation is better than the outcome 5 years after resection. However, while on the face of it there would appear to be little controversy regarding survival, a major issue is that the patients on the transplant waiting list have a risk of tumor progression during the waiting time. Therefore, there are competing risks of having a resection "now" versus having a transplant "later."[77] To examine this competition between risks, decision analysis models have been developed. They have shown that the outcome after transplantation is better if the waiting time is less than 6 to 12 months.[83] LDLT may be advantageous when long waiting times for cadaveric liver transplantation exist.[79,80] Controversy exists about the strategy of initially resecting patients who would be transplant candidates and having transplantation as a means of salvage if the tumor recurs.[83-85] This strategy attempts to take advantage of the fact that about 30% of patients who undergo resection or ablation will have a disease-free survival 5 years after resection. Currently, there is no way to prospectively select the patients who will survive. If patients could be followed closely after resection and salvaged by transplantation when they recurred, this 30% of patients would avoid transplantation and still survive 5 years. This presupposes that transplantation after resection (secondary transplantation) does not have a significantly different survival rate than transplantation without resection (primary transplantation) and that patients with recurrence are frequently transplant candidates. The paper by Adam et al.[84] suggested that neither of these assumptions is true. Patients undergoing secondary transplantation had a higher operative mortality (28.6% vs. 2.1%) and a lower disease-free survival (29% vs. 58%). Only 25% of the patients who recurred after initial resection were eligible for transplantation.

In our opinion, resection should be preferred to transplantation in the following groups: (1) patients without cirrhosis[86]; (2) patients whose tumors do not meet the criteria for transplantation; and (3) patients with contraindications for transplantation.

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Chapter

124

Management of Malignant Hepatic Neoplasms Other Than Hepatocellular Carcinoma

Jason K. Sicklick ▪ Michael A. Choti

The liver is a complex system of numerous cell types including hepatocytes, cholangiocytes, neuroendocrine cells, hepatic progenitors, myofibroblastic mesenchymal cells, and vascular endothelial cells. Primary malignancies of the liver have the potential to arise from any one of these cell types. Because most of the liver parenchyma is composed of hepatocytes and bile duct epithelial cells, liver tumors arising from these cell types are the most common. Hepatocellular carcinoma (HCC) comprises an estimated 80% to 90% of primary liver cancers,[1] whereas all other primary malignancies of the liver, including cholangiocarcinoma, account for the remaining 10% to 20%. Table 124–1 outlines the primary hepatic neoplasms based on the cellular phenotype of the tumors. Given the complex cellular composition of the liver, and therefore the numerous potential forms of primary malignancies, histopathology remains the standard for definitive diagnosis. This chapter focuses on the infrequent or rare, but often highly aggressive, forms of primary liver tumors other than HCC occurring in the adult population.

For all of these liver tumors, determining the potential surgical options for a patient is dependent on several factors, including patient-related factors, local/tumor-related factors, and the presence of metastatic disease. In general, the primary modality of therapy for all of these tumor types, if resectable, is liver resection. Although many of these liver tumors do not occur in the setting of cirrhosis, it is occasionally the case that underlying liver disease can limit a patient's ability to tolerate major hepatic surgery. Moreover, insufficient remnant liver volume to maintain adequate hepatic function (<20% remaining volume) limits surgical options in some patients. Finally, medical contraindications to major abdominal surgery may preclude some patients from open operative therapies where laparoscopic liver surgery may be a viable alternative.[2]

In the process of diagnosing a hepatic tumor and determining the appropriate course of therapy, it is crucial to determine the type and locoregional extent of disease. All patients being considered for resection of these primary liver tumors should undergo preoperative computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate the extent of intrahepatic disease and to exclude extrahepatic metastasis. Preoperative imaging should define the extent of disease and proximity to major biliary and vascular structures.

Based on imaging to determine locoregional lymphadenopathy as well as distant metastases, the tumor stage can be used to guide the appropriate form of treatment. Needle biopsy using either core or fine-needle aspiration can be considered in selected cases. In tumors that warrant resection regardless of the pathologic diagnosis, preoperative biopsy is not always necessary. In cases where the malignancy is not being considered for surgical therapy, biopsy is important to confirm the diagnosis prior to initiating nonextirpative therapy. Box 124–1 outlines the surgical and nonsurgical management options that may be used in the treatment of hepatic tumors.[3,4]

EPITHELIAL TUMORS

Intrahepatic Cholangiocarcinoma

Following HCC, cholangiocarcinoma is the second most common type of primary liver cancer, accounting for about 10% to 15% of malignant hepatic tumors. It is

Table 124–1 Cellular Phenotype and Primary Hepatic Neoplasms

Cellular Phenotype	Primary Hepatic Tumor
Epithelial	
Hepatocellular	Hepatocellular carcinoma (hepatoma)
Hepatic progenitor	Hepatoblastoma
Cholangiocellular	Intrahepatic cholangiocarcinoma
	Hepatic cystadenocarcinoma
Mixed	Mixed cholangiohepatocellular carcinoma
Other	Primary squamous cell carcinoma
	Adenocarcinoma of unknown primary site
Mesenchymal	
Muscular	Leiomyosarcoma
	Rhabdomyosarcoma
Fibroblastic	Fibrosarcoma
Adipose	Liposarcoma
Neural	Schwannoma
Vascular	Angiosarcoma
	Epithelioid hemangioendothelioma

Box 124–1 **Management Options and Therapies for Primary Hepatic Neoplasms**

Surgical

- Resection
  - Anatomic resection
  - Wedge resection
  - Laparoscopic liver resection (LLR)
- Orthotopic liver transplantation (OLT)

Ablation (Operative, Laparoscopic, or Percutaneous)

- Heat based[3]
  - Radiofrequency ablation (RFA)
  - Microwave ablation
  - Laser hyperthermia
- Cold based
  - Cryotherapy
- Chemical therapy
  - Percutaneous ethanol injection (PEI)

Nonoperative

- Chemotherapy
  - Systemic chemotherapy
  - Transarterial chemoembolization (TACE)
  - Hepatic artery infusion (HAI)
- Radiation therapy
  - Radioembolization

more common outside the United States with particularly higher incidences in South America, Central-Eastern Europe, Israel, and northern Japan. In the United States, cholangiocarcinoma has an incidence of 1.5 per 100,000 in males and 1.0 per 100,000 in females. It can be classified by three distinct anatomic locations: intrahepatic (or peripheral) cholangiocarcinoma, hilar/perihilar cholangiocarcinoma or Klatskin's tumor, and distal or periampullary tumors.[5] Hilar cholangiocarcinoma makes up the majority of cholangiocarcinoma, but intrahepatic cholangiocarcinoma (IHCC) is being reported with increasing frequency. It is this peripheral cholangiocarcinoma that is the focus of this section.

The histology of IHCC is largely that of adenocarcinoma. The most common classification is that proposed by the Japan Society for Liver Cancer based on macroscopic features. It can be classified as mass-forming, infiltrating, intraductal, or mixed type. Patients with IHCC often present with findings of a mass within the liver, much like patients with metastases or HCC. Patients with this disease typically present in the 6th and 7th decades of life with symptoms including generalized abdominal pain, focal right upper quadrant pain, jaundice, or symptoms of systemic disease including anorexia and weight loss.

Etiology of IHCC is not clear in most cases. In rare cases, preexisting conditions related to chronic injury and inflammation within the biliary system have been associated with IHCC, including Thorotrast exposure, ulcerative colitis, primary sclerosing cholangitis, intrahepatic cholelithiasis, and liver fluke *(Clonorchis sinensis)* infection. In addition, patients with hepatic adenoma can progress to malignancy, and some of these are IHCC.

The evaluation and staging of IHCC is based on serologic, radiologic, and histologic findings. Previous studies have demonstrated that elevated serum concentration of CA 19-9, a tumor-associated antigen, has good sensitivity and specificity for cholangiocarcinoma in patients and is a useful adjunct to the work-up of cholangiocarcinoma.[6] Radiologic evaluation is critical in the evaluation of an IHCC.[7] As with other intrahepatic malignancies, CT or MRI can identify a mass lesion within the liver. In some cases, segmental or lobar biliary ductal dilation can be seen (Fig. 124–1A). In most cases, the tumor can have the imaging characteristics of metastases, including peripheral venous enhancement and central necrosis. Yet sometimes these tumors can demonstrate arterial enhancement as seen with HCC.[8] Unlike with hilar cholangiocarcinoma, imaging and drainage of the biliary

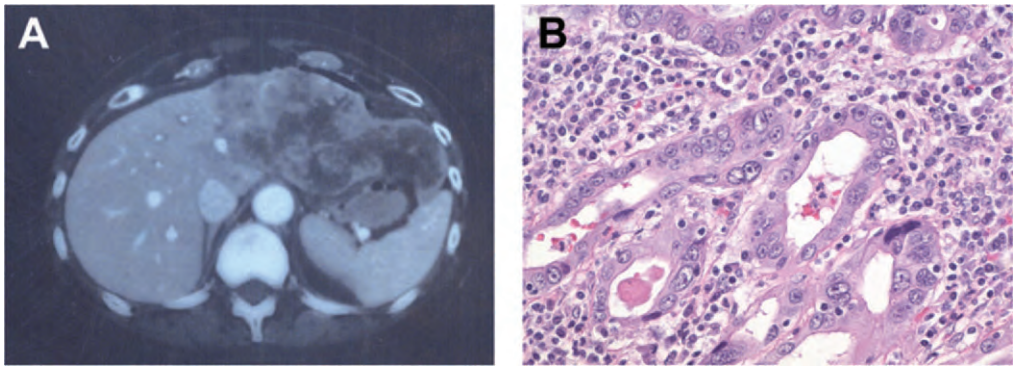

Figure 124–1. **A,** Abdominal CT scan demonstrating a large intrahepatic cholangiocarcinoma involving the left hemiliver. **B,** Photomicrograph of an intrahepatic cholangiocarcinoma: The small glandular structures with nuclei that are oval and vesicular. There is also demonstrable mucin production within the ducts. (**A** and **B,** Courtesy of M. S. Torbenson, Department of Pathology, Johns Hopkins Hospital, Baltimore.)

tree using percutaneous or endoscopic cholangiography are seldom helpful and uncommonly used.

When a biopsy of a suspicious liver tumor reveals adenocarcinoma, perhaps the most common diagnostic dilemma is differentiating IHCC from hepatic metastasis from a known or unknown site.[9] In such cases, careful history of a previous malignancy, identification of other risk factors, and scrutiny of tumor markers can be helpful. Moreover, multifocal lesions within the liver increase the likelihood that these are metastases. Staging of the chest and abdomen using CT scanning is useful to help rule out other potential primary tumors as well as metastatic disease. Colonoscopy should be considered in some cases, particularly when there is an elevation of the carcinoembryonic antigen.

Based on the characteristics of the tumor and the patient-related factors, complete resection can be performed safely in many cases. Resection is associated with long-term survival in selected patients with IHCC.[10] Unfortunately most of the symptoms of IHCC arise late in the disease's progression and therefore only about one third of patients are viable candidates at the time of presentation. In one case series from the Mayo Clinic that reviewed their management and outcomes in 61 patients with IHCC treated over 31 years, 74% of patients died of their disease.[11] Of the patients resected for cure, the survival rate at 3 years was 60%. Although the prognosis for patients with IHCC is poor, in those scenarios of complete resection with node-negative disease, long-term survival may be possible.

Similar to the management of other primary liver tumors and hepatic metastases, other local approaches can be used in the unresectable patients. Thermal ablation can used in selected cases of IHCC.[12,13] However, this approach is only useful in small tumors (<5 cm), an uncommon scenario in this disease. In addition, although ablation has been shown to play a role in other liver malignancies, there are no data of sufficient numbers that have reported long-term results with this therapy. Much like when managing HCC, transarterial chemoembolization (TACE) can be considered in cases of large unresectable IHCC, particularly if symptomatic.

In spite of the relatively high risk of recurrence following complete (R0) resection, there are no level 1 data demonstrating a benefit of postoperative adjuvant therapy in the management of IHCC.[14] Similarly, the role of systemic chemotherapy in patients with disseminated or unresectable IHCC is unclear. Orthotopic liver transplantation (OLT) should not be considered an option in patients with IHCC.[15] Although some reports from the Mayo Clinic and others have shown some promising results in selected patients with hilar cholangiocarcinoma when combined with chemoradiation therapy, this therapy should only be considered for IHCC in the context of a clinical trial.

A liver carcinoma of unknown primary site is characterized as metastatic disease to the liver and is, by definition, not of primary origin. However, the differentiation between IHCC and adenocarcinoma of unknown primary is difficult to make at diagnosis. The incidence of such carcinomas is between 0.5% and 15% of all adult tumors.[16-19] The diagnosis is often made by exclusion—in cases of adenocarcinoma it is made on biopsy when the histology is not consistent with IHCC or when it has a multifocal distribution. In most cases, when solitary, these are likely poorly differentiated IHCCs.[20] Management of liver tumors diagnosed as adenocarcinoma of unknown origin should be managed much like IHCC. Based on reported retrospective series, these tumors are less likely resectable and have overall poor prognosis.[21,22]

Mixed Cholangiohepatocellular Carcinoma

Over the past several years, evidence for the stem cell theory of cancer has grown.[23] Given that bipotential liver progenitors exist in the adult liver and have the potential to differentiate toward hepatocytic and biliary lineages, it is conceivable that these cells may give rise to tumors of heterogeneous cellularity or the mixed

cholangiohepatocellular carcinoma. Based on the concomitant cytokeratin profile consistent with a bile ductular lineage, albumin expression consistent with a hepatocytic lineage, as well as carcinoembryonic antigen and α-fetoprotein (AFP) levels, mixed cholangiohepatocellular carcinomas can be distinguished from IHCC and HCC. Like HCC, these rare tumors have been associated with chronic viral hepatitis as well as cirrhosis suggesting that chronic injury and expansion of hepatic progenitors may be earlier events in tumor progression. However, this is not always the case.[24] Histologically, although two cellular patterns are recognized, this tumor has features of both HCC as well as IHCC within one discrete mass. They can be classified into two types: (1) "collision" tumors, which demonstrate more discrete areas of domination by hepatocytic or biliary cells; and (2) "transition" tumors, which have a more uniform heterogeneity.[25,26]

Given the origin of these tumors, occasionally AFP may be mildly elevated. In light of the rarity of mixed cholangiohepatocellular carcinomas, liver resection is the preferred therapeutic option (Fig. 124–2). Despite a lack of evidence for the role of OLT, guidelines may be extrapolated from HCC, suggesting that small masses (<5 cm) may be treated with liver transplantation. Predicting outcomes (e.g., disease progression, metastasis, and prognosis) based on histopathology is difficult given the infrequency of these tumors. One group has reported an aggressive clinical course for these tumors, with 3- and 5-year overall survival rates of 30% and 18%, respectively.[24] In the case of patients undergoing resection, these survival rates are marginally improved to 38% and 24%, respectively.

Hepatic Cystadenocarcinoma

In addition to the IHCC and mixed cholangiohepatocellular carcinoma, the hepatic or biliary cystadenocarcinoma is a tumor with an epithelioid phenotype. The hepatic cystadenocarcinoma is rare, with only 113 cases reported in the literature.[27,28] The relationship between cystadenoma and cystadenocarcinoma is not clear. Unlike the benign cystadenoma, which occurs mostly in women, the incidence of cystadenocarcinoma is not biased toward one gender.[27,29] Depending on the study, 38% to 44% of cystadenocarcinomas have occurred in men with a mean age in the middle to late 50s.[27,28,30,31] Still, many believe that at least a subset of cystadenocarcinoma arises from malignant transformation of cystadenoma and in fact has been reported in some series. It is for this reason that most advocate the complete resection of the benign condition. In some cases, these tumors are associated with Caroli's disease, a form of intrahepatic bile duct ectasia.

Cystadenocarcinomas can arise from congenital liver cysts, bile ducts, and cystadenoma with mesenchymal stroma (CMS).[32] CMS typically occurs in women when a papillary adenocarcinoma invades the underlying stroma and develops in the epithelial layer. In women, malignant degeneration of CMS into a cystadenocarcinoma is slow and occurs over the course of years,[33,34] but the predisposing factors and mechanisms remain unknown. Alternatively, cystadenocarcinoma in men is not associated with CMS. It has poorer prognosis than in women even after complete excision.[35]

Hepatic cystadenocarcinoma can present with localized symptoms or from metastatic disease. In recent years, this disease has presented more often as an incidental finding on radiologic imaging such as CT, MRI, and ultrasonography. Biliary cystadenocarcinoma tends to be multilocular, but unilocular cases can occur. Cystadenocarcinoma tends to be larger than its benign counterpart, but this feature is far from diagnostic. Radiologic findings of a hepatic cystic mass with features of a thick or irregular wall, peripheral enhancement, associated mass, or papillary tumor projections into the cyst cavity should lead one to suspect cystadenocarcinoma. Histologically, this tumor is characterized by cellular pleomorphism, anaplasia, and the ability to invade adjacent organs and metastasize. Fluid from the cyst can be blood stained, clear, or bile tinged.[9,34] However, preoperative cyst aspiration is not recommended because there is a risk for peritoneal tumor seeding.[36]

The only potentially curative treatment for cystadenocarcinomas is complete removal, usually by a major liver resection with clear margins.[27] Survival rates for this

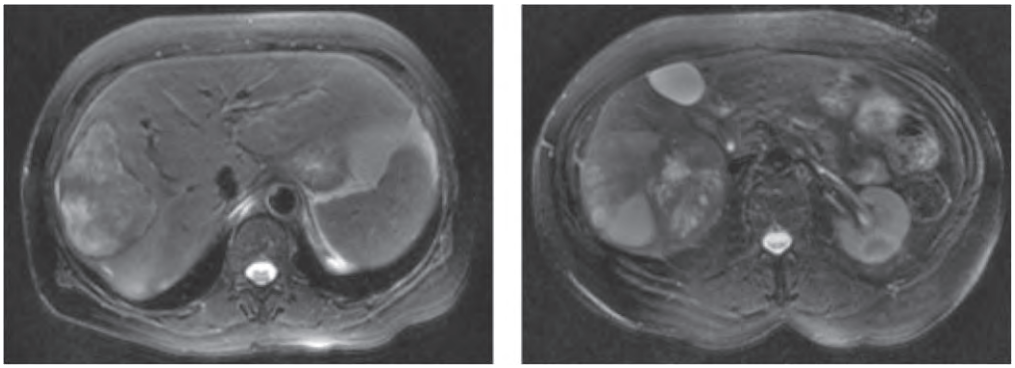

Figure 124–2. **A** and **B,** Abdominal MRI views revealing a large right liver mass. Pathologic analysis following resection demonstrated findings consistent with a mixed cholangiohepatocellular carcinoma.

disease have been reported in the range of 25% to 100% at 5 years.[27] Cystadenocarcinomas arising in women with CMS are believed to be relatively indolent, whereas those not associated with CMS, particularly in men, have a worse prognosis.[27] In addition, there are also case reports of patients being successfully managed by OLT.[15]

Primary Squamous Cell Carcinoma

The literature on primary squamous cell carcinoma of the liver is limited.[37-39] The diagnosis should be made only without evidence of a primary epidermoid malignancy from another site such as skin, oropharynx, or anus. Careful examination of the patient for such a primary site is important in any patient with squamous cell histology on biopsy or resection specimen of a liver tumor. Histologically, reports have described keratinized-type cellular features, often with benign-appearing metaplastic squamous epithelium. Treatment by partial hepatectomy has been recommended, although there are few data to determine if this provides a survival benefit.

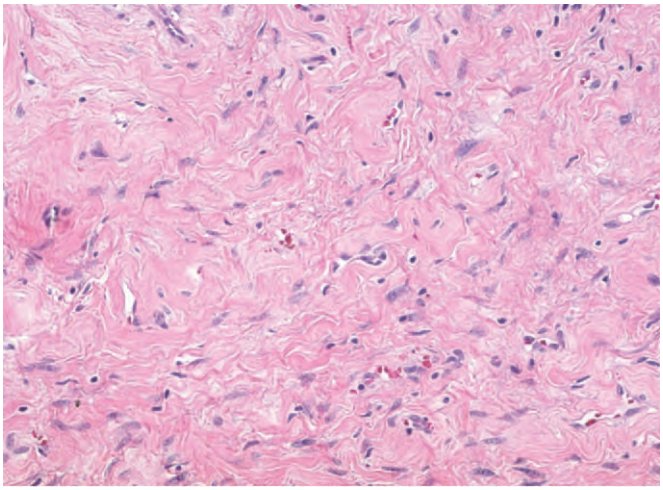

Figure 124–3. Photomicrograph of a fibrosarcoma. These tumors are characterized by spindle-like cells interspersed with collagen. (Courtesy of M. S. Torbenson, Department of Pathology, Johns Hopkins Hospital, Baltimore.)

MESENCHYMAL TUMORS

Hepatic Leiomyosarcoma, Rhabdomyosarcoma, Fibrosarcoma, and Liposarcoma

Sarcomas represent only about 2% of primary liver malignancies. Hepatic sarcomas can arise from any type of connective tissue, including smooth muscle, liver mesenchymal cells, or fatty tissue. Hepatic tumors originating from these tissues, however, are extremely infrequent and patients may present with symptoms of local or systemic disease.

Sarcomas are more often hypervascular tumors (Fig. 124–3). However, the pattern of vascularization and a lack of venous invasion can differentiate primary hepatic sarcomas from HCC, especially in noncirrhotic patients.[40] Corroboration with immunohistochemical staining for vimentin, a mesenchymal marker, without staining for epithelial markers, helps confirm the diagnosis. Again, resection appears to be the optimal treatment option when possible with small series reporting some long-term survivors. Although reasonable to consider, the role of TACE or systemic chemotherapy is unproven.

Hepatic Schwannoma

Although malignant schwannoma is the most common soft tissue sarcoma in adults, primary hepatic schwannomas are extremely rare.[41] Typically, schwannomas occur in the setting of von Recklinghausen's disease, or neurofibromatosis 1, which usually involves peripheral nerves. First identified by Young in 1975, few others have resected such tumors in the last 30 years.[42] Overall, fewer than 10 cases of malignant schwannomas of the liver have been reported in the medical literature.[22] Therefore, most data are based solely on isolated case reports where patients have developed hepatic neurofibromas that underwent malignant degeneration.[43]

Although most schwannomas are located in the extremities and trunk of patients with neurofibromatosis 1, this population is at risk for hepatic schwannomas. Based on CT scans, the tumors are well-circumscribed, hypodense masses without contrast enhancement. Angiography reveals a hypovascular liver lesion. Histologically, these tumors resemble peripheral schwannomas with moderately pleomorphic spindle cells, hyperchromatic nuclei, and mitotic figures. Immunohistochemical staining is positive for both S-100 protein and vimentin, like other sarcomas. Malignant schwannomas have been treated with surgical resection in four cases with survivors 2 years after resection.[44,45] Although chemotherapy and OLT have been attempted, patients have developed recurrent disease.[22] At this time, surgical resection is the treatment of choice for these patients.

VASCULAR TUMORS

Angiosarcoma

Hepatic angiosarcoma is the most common of the liver sarcomas but it still remains a rare (1.4 per 100 million) malignancy. These tumors tend to present in older patients during their 6th and 7th decades and is more frequent in men.[46] The etiology of this tumor has been associated with exposure to Thorotrast, vinyl chloride, vinyl fluoride monomer, arsenic, androgenic steroids such as methyltestosterone, as well as long-term use of oral contraceptives.[47] Approximately 40% of the patients have an identifiable risk factor, and 20% have coexisting cirrhosis. However, the period from exposure to disease is on the order of several decades.

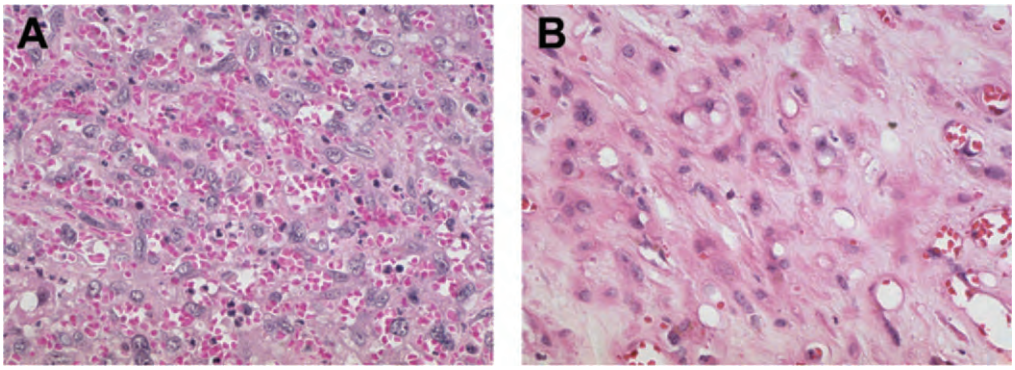

Figure 124–4. Comparison of vascular tumors of the liver. **A,** Photomicrograph of an angiosarcoma. Note the small, highly aggressive-appearing cells with disruption of the hepatic parenchymal architecture. **B,** Photomicrograph of an epithelioid hemangioendothelioma. Note the tumor cells' abundant cytoplasm. Although the tumor cells are often surrounded by sclerotic stroma with diffuse hepatic involvement, the liver architecture is preserved. (**A** and **B,** Courtesy of M. S. Torbenson, Department of Pathology, Johns Hopkins Hospital, Baltimore.)

The presenting symptoms are similar to those of most other hepatic malignancies, but spontaneous hemorrhage from the tumor may occur. There are two classic presentations of angiosarcoma. These tumors either occur as multiple nodules or as a single, large solitary tumor.[48] In the case of multiple tumors, it is often unclear if this is due to multicentric occurrence or multiple intrahepatic metastases occurring via hematogenous spread. When suspecting a vascular malignancy, it is important to differentiate angiosarcoma from another type of vascular liver tumor—epithelioid hemangioendothelioma. Operative biopsy via an open or laparoscopic approach is recommended for tissue diagnosis due to the high risk of bleeding during percutaneous procedures. Histologic appearance reveals small, highly aggressive-appearing cells that stain strongly for coagulation factor VIII (Fig. 124–4A). Unlike epithelioid hemangioendothelioma (see Fig. 124–4B), the parenchymal architecture is disturbed. Most radiologic features of angiosarcomas may be similar to those of epithelioid hemangioendothelioma, but on CT scans, angiosarcoma tends to be more focal and lacks peripheral enhancement after the administration of intravenous contrast. These distinctions are critical for determining the appropriate diagnosis.

Unlike epithelioid hemangioendothelioma, angiosarcoma is not suitable for OLT. Patients have received liver transplants for this disease either on the basis of a presumed diagnosis of epithelioid hemangioendothelioma or as an intentional therapeutic strategy. Most patients, however, have died due to rapid tumor recurrence, and no patient has survived beyond 28 months.[22] Overall, survival rates are poor for patients, with a median survival of 6 months and a 2-year survival rate of only 3%.[22] Only three patients have been reported to have survived longer than 38 months.[45,49] Although it is feasible that long-term survival can be achieved with an R0 resection of a single tumor, in more than 50% of patients, survival rates are significantly worse due to the presence of multiple unresectable tumors or metastatic disease. In addition, nonoperative management with chemotherapy remains anecdotal due to the limited number of cases. Some groups have treated with protocols such as vincristine with doxorubicin (Adriamycin) or TACE using a combination of Lipiodol, doxorubicin, and mitomycin, although success has been negligible.[49]

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma, like angiosarcoma, is a rare tumor arising from the vascular endothelium. First described in 1982,[50] these tumors are distinct from angiosarcomas. In contrast to angiosarcomas, hemangioendotheliomas tend to occur in young adults with a female predominance (67%); and unlike angiosarcoma, only 10% of these tumors occur in patients older than 6 months of age. Hemangioendothelioma has no clear association with environmental exposure but has been reported to have a possible association with oral contraceptives.[51]

The clinical presentation of epithelioid hemangioendotheliomas is variable depending on the size of the tumor. Patients may have abdominal pain, weight loss, and/or a palpable abdominal mass. Occasionally, they are found incidentally on a CT or MRI performed for other reasons. In approximately one half of cases, cutaneous hemangiomas are also present (45%). When tumors are of large size within the liver, symptomatic pulmonary vascular congestion can be seen due to tumor shunting and increased pulmonary blood flow. Moreover, patients may have signs of liver failure including ascites. Like many other tumors in the liver such as HCC and hepatoblastoma, serum AFP levels can be mildly elevated.

Radiologic evaluation can be helpful in identifying epithelioid hemangioendothelioma and distinguishing it from angiosarcoma. CT scans can show irregular hypodense lesions that may have hypervascular enhancement in the periphery following injection of intravenous

contrast. Tumor calcification is also notable in about one fifth of cases. The extent of the tumors is difficult to evaluate radiologically because they tend to be multifocal and widespread within the liver at the time of diagnosis.

Although imaging studies can distinguish these vascular tumors from other liver neoplasias as well as angiosarcoma, diagnosis is confirmed by histologic examination. These tumors stain strongly positive for coagulation factor VIII expression. The cells are typically epithelioid with abundant cytoplasm, but a dendritic cell type has also been recognized (see Fig. 124–4B). The tumor progression occurs along hepatic sinusoids and vascular invasion may occur. Although the tumor cells are surrounded by sclerotic stroma and there is often a characteristic diffuse hepatic involvement, the liver parenchymal architecture is preserved unlike with angiosarcomas.

The diffuse nature of these tumors often precludes surgical resection and, therefore, survival rates following liver resection are poor. Only a few cases have been successfully managed by this method.[22] But the results with OLT appear to be favorable. The largest single-center series in the literature described 5-year survival rates of 71% to 76%.[52,53] Others have reported survival rates of 82% at 2 years and 43% at 5 years.[54] A subset of OLT patients have undergone adjuvant chemotherapy (cisplatin/doxorubicin) with or without the addition of corticosteroids. When chemotherapy has been used in cases of unresectable disease, responses have been reported.[22] Moreover, one group has had success with OLT in the presence of extrahepatic disease with one survivor at 11 years after OLT.[52] In general, the pulmonary metastatic rate is high, and the clinical course quite variable, but like HCC and metastatic neuroendocrine tumors, OLT can be considered in patients with epithelioid hemangioendothelioma.[55,56]

SUMMARY

Although the worldwide incidence of HCC is rising, those treating patients with liver disease should be aware of the other types of primary hepatic malignancies. The most common of these, intrahepatic or peripheral cholangiocarcinoma appears to be increasing in incidence. As with HCC and liver metastases, the evaluation and staging should be done based on the potential treatment options available to the patient. When surgical resection is being considered, careful imaging of both the liver and extrahepatic sites is important to determine resectability. Although many of these diseases are rare and therapeutic decisions cannot be based on large prospective studies, hepatic resection should generally be considered when possible for most of these diseases. The role of OLT, ablation, TACE, and systemic chemotherapy is less well established. As with other diseases, it is prudent when managing these patients to do so with a multidisciplinary team involving hepatic surgeons, medical and radiation oncologists, diagnostic and interventional radiologists, and hepatologists.

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Chapter

125

Multidisciplinary Approach to the Management of Portal Hypertension

J. Michael Henderson

The management of portal hypertension has changed dramatically in the past 2 decades with improved understanding of the pathophysiology, better and more logical approaches to patient evaluation, and many new and improved treatment modalities. By definition, portal hypertension is present when the portal pressure rises above 8 mm Hg, but the wide spectrum of etiologies leading to this broad clinical syndrome mandates the need for a multidisciplinary approach to identification, evaluation, and management of these patients. The clinical manifestations of portal hypertension are variceal bleeding, ascites, liver failure and hepatic encephalopathy, hepatoma, and the hepatopulmonary syndromes (HPSs). These cover every field of medicine, with the main players in the multidisciplinary team being the following:

- Hepatologists
- Gastroenterologists/Endoscopists
- Radiologists
- Surgeons
- Pathologists
- Anesthesia/Critical Care Staff
- Nurse Clinicians/Support Team

The role of the surgeon has changed dramatically over these 2 decades in this multidisciplinary team, with the main role now being in liver transplantation as compared to a role in operative decompressive shunts for such patients 20 to 30 years ago. The goal of this chapter is to present current status of knowledge for the pathophysiology of portal hypertension, present a logical approach to the evaluation of such patients, and give an assessment of current treatment modalities and when they should be used.

HISTORY

The liver was recognized as a highly vascular organ in ancient times with writings from the ancient Egyptians, the Greeks, and the Romans.[1] However, most misunderstood the liver, its vasculature, and its physiologic role. Francis Glisson and William Harvey gave structural proof and functional demonstration of the anatomy and blood flow through the liver. It was not until microscopic examination became possible that the liver lobule with its hexagonal appearance, portal venous and hepatic arterial inflow from the periphery, and hepatic venous drainage from the center could be fully understood.

Ascites was the first clinical complication of portal hypertension to be recognized long before its pathogenesis was understood. Ascites is mentioned in the ancient text of Egypt and the Central American Mayans and acquired its name from the ancient Greeks. Gastroesophageal varices were not recognized until the mid-19th century, and even then they were believed to be a rare entity. Much confusion reigned over the next 100 years as to the pathophysiology of portal hypertension. It was recognized that there was elevated pressure in the portal venous system, but it was not recognized that this occurred secondary to cirrhosis. For a long time the so-called forward theory of portal hypertension popularized by Banti was accepted.[2] Banti believed that patients with splenomegaly, anemia, and leukopenia suffered from a splenopathy which in turn injured the liver and caused cirrhosis; this led to the term *hepatosplenopathy*. It was in the 1920s that McIndoe[3] postulated a "backward flow" theory for portal hypertension based on the primary pathology being in the liver—cirrhosis obstructing portal flow—and a build-up of portal pressure behind this obstruction.

The treatment of these conditions had focused on splenectomy, omentopexy, or other "preobstructive" operations while the forward flow theory held. Recognition that a blockage to portal flow within the liver—usually due to cirrhosis—led to portal hypertension initiated an era of decompressive operations to manage the overall syndrome. Portacaval shunt was initially performed in dogs by Nicolai Eck[4] in St. Petersburg in 1890, but it was another Russian, Pavlov,[5] who documented the risks of such portal diversion leading to progressive liver failure, inanition, and hepatic encephalopathy. However, a new era of surgery for portal hypertension started in the 1930s when it was believed that careful technique could circumvent these issues and provide a viable treatment modality with portacaval shunt. The pioneering work of Whipple[6] and his colleagues at Columbia in New York did significantly advance the field. However, they soon recognized that such shunts, while controlling bleeding and ascites, led to acceleration of liver failure with no survival advantage to their patients. This initiated the era of randomized controlled trials in portal hypertension.

Portal hypertension has evolved over the past 50 years because of the multiple randomized, controlled trials performed for all treatment modalities introduced. This was one of the earliest fields of medicine to receive such scrutiny, and as a result the progress in managing patients has been based on level 1 evidence since the 1950s. Initial trials compared surgical shunts to medical therapy in patients who had not bled and showed that mortality was increased with such intervention.[7] Subsequent studies comparing medical therapy and surgical shunts in patients following their initial variceal bleed showed no improvement in overall survival, but a change in the mode of death from variceal bleeding to liver failure.[8] These observations stimulated the investigators of that time to look for new treatment modalities.

Selective shunts were pioneered by Warren and associates[9] and Inokuchi[10] who showed that variceal decompression could be achieved while maintaining portal perfusion to the cirrhotic liver. Partial shunts were carefully studied and championed by Sarfeh and colleagues,[11] who documented that they could achieve adequate decompression of varices and maintain some portal flow. Preservation of portal flow with both selective and partial shunts resulted in lower encephalopathy and liver failure. Endoscopic therapy was initially introduced by surgeons (Johnston and Rodgers,[12] Terblanche et al.,[13] Paquet and Oberhammerk[14]) using rigid esophagoscopes but rapidly moved to flexible endoscopy in the 1980s as this technology was introduced. Sclerotherapy of varices became the realm of the gastroenterologist, but it was another surgeon (Steigmann and associates[15]) who introduced variceal banding as a further significant advance in endoscopic therapy for bleeding varices.

Even as these multiple therapeutic interventions were evolving, the pathophysiology of portal hypertension was becoming better understood.[16,17] The recognition that the perpetuation and even increase in portal pressure is mediated through splanchnic hyperemia and a hyperdynamic systemic circulation (see later) not only resurrected a component of Banti's forward flow hypothesis but also led to the introduction of pharmacologic means of reducing portal hypertension. Lebrec et al. introduced noncardioselective β blockers to ameliorate these changes and reduce portal pressure.[18] This has become one of the mainstays of managing such patients.

Technology has also contributed to radiologic decompressive shunts for portal hypertension following the lead of cardiac and peripheral vascular stents. Transjugular intrahepatic portosystemic shunts (TIPSs) were pioneered by Rosche,[19] and became widely used in the 1990s. "Minimally invasive" shunting has come of age and is clearly part of the treatment armamentarium for these patients.

Finally, the history of portal hypertension must recognize the role of liver transplantation introduced by Starzl et al.[20] and Calne and Williams[21] in 1970s and coming of age in the mid-1980s and 1990s. Their perseverance and pioneering work to resolve many of the technical issues of liver transplantation bore fruit. But it was really the immunologic advances and the introduction of powerful new immunosuppressants that gave life to liver transplantation. The clinical reality is that many patients with significant liver disease have only their complications of portal hypertension and their survival improved by liver transplantation. For the surgeon this brings the management of such patients full circle where the surgeons role is now largely in the field of liver transplantation as part of the multidisciplinary team taking care of such patients.

ANATOMY

The portal vein has complex embryologic development from the vitelline and umbilical veins.[22] The vitelline veins intercommunicate in the septum transversum, which is the site of development of liver sinusoids. The left vitelline vein forms most of the extrahepatic portal venous system, whereas the left umbilical vein plays a critical role in utero as the ductus venosus, which communicates directly from the rudimentary portovenous system to the hepatic veins, bypassing the hepatic sinusoids.

The portal vein is formed behind the neck of the pancreas by the joining of the superior mesenteric and splenic veins.[22] It is normally 10 to 20 mm in diameter, but in portal hypertension may enlarge up to 20 mm. It courses along the free edge of the gastrohepatic ligament to the liver hilus, where it divides into right and left branches (Fig. 125–1). Its feeding tributaries have some variability, with the inferior mesenteric vein entering the splenic vein in approximately two thirds of persons and superior mesenteric vein in one third. Similarly, the left gastric or coronary vein enters the portal vein in approximately two thirds and the splenic vein in one third. The latter may vary considerably in size in portal hypertension and is often one of the major veins feeding into gastroesophageal varices. The umbilical vein is remarkably constant in its communication with the left branch of the portal vein, and in portal hypertension when recanalized this may be quite large. The major changes of clinical significance are around the gastroesophageal junction in

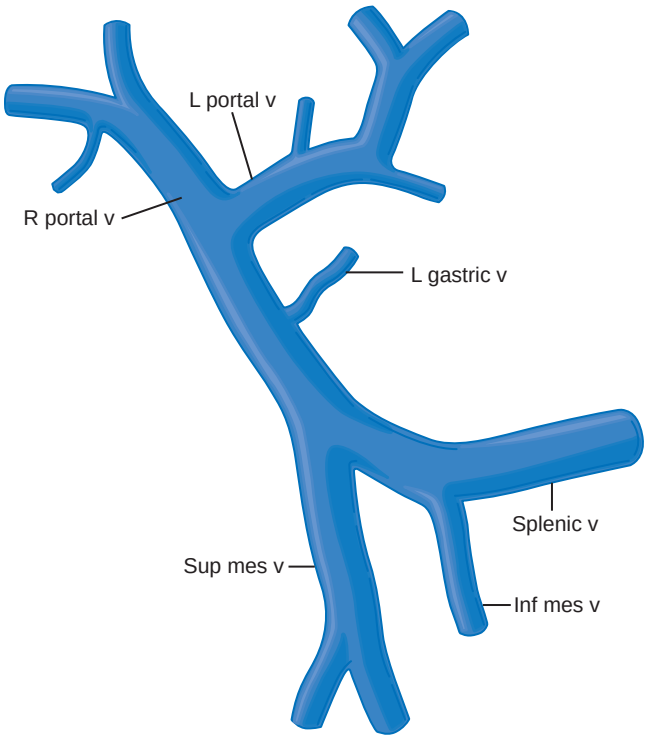

Figure 125–1. Portal venous anatomy. The portal vein is formed by the union of the superior mesenteric (Sup mes) and splenic veins behind the neck of the pancreas. The inferior mesenteric vein (Inf mes) enters the splenic vein in two thirds of patients, and the left gastric vein enters the portal vein in two thirds of patients.

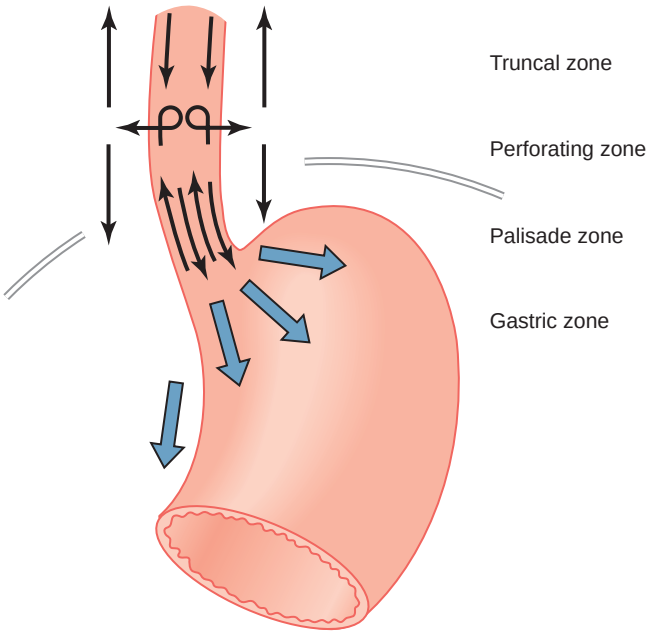

Figure 125–2. Diagrammatic representation of the venous "zones" at the gastroesophageal junction. The perforating zone is the site of highest variceal bleeding risk. Details of the zones are given in the text. (Modified from Vianna A, Hayes PC, Moscoso G, et al: Normal venous circulation of the gastroesophageal junction. A route to understanding varices. Gastroenterology 93:876-889, 1987.)

portal hypertension. Studies by Vianna and colleagues[23] using radiologic studies, corrosion casting, and morphometry have clarified the venous pathologic changes at this location in portal hypertension. These are schematically represented in Figure 125–2, where the following four zones are recognized:

1. The gastric zone extends 2 to 3 cm below the gastroesophageal junction. These veins run longitudinally in the submucosa and lamina propria to the short gastric and left gastric veins.
2. The palisade zone extends 2 to 3 cm superiorly from the gastric zone in the lower esophagus. These parallel palisades run longitudinally and correspond to the esophageal mucosal folds. There are multiple communications between these veins in the lamina propria, but there are no perforating veins in the palisade zone linking the intrinsic and extrinsic venous plexuses.
3. The perforating zone extends approximately 2 cm higher up the esophagus just superior to the palisade zone. In this zone the vessels perforate through the esophageal wall linking the internal and external veins.
4. The truncal zone extends 8 to 10 cm up the esophagus and is characterized by four or five longitudinal veins in the lamina propria. In this zone there are irregular perforating veins from the submucosa to the external esophageal venous plexuses.

Hepatic arterial anatomy is highly variable, with anomalies being of clinical importance to transplant surgeons, particularly during donor hepatectomy. The normal arterial anatomy is a common hepatic artery arising from the celiac axis that gives rise to a right and left artery just above the gastroduodenal artery. In approximately 20% of persons there is an anomalous right accessory or replaced hepatic artery arising from the superior mesenteric artery. Similarly there is an approximately 20% incidence for an accessory or replaced left hepatic artery arising from the left gastric artery. These two anomalies may coexist (Fig. 125–3).

The segmental anatomy of the liver is of importance to the surgeon in liver resection and in living donor liver transplant. The liver has eight segments, each with its own hepatic arterial and portal venous inflow and hepatic venous drainage (Fig. 125–4).[24] This allows for division in these planes with functional segments for liver remnant or for donor grafts. At a physiologic level each of these segments has smaller microscopic functional units of the liver lobules. At this level the portal vein and hepatic artery enter the periphery of hexagonal shaped liver lobules, with blood traversing the sinusoids and draining through central hepatic veins.

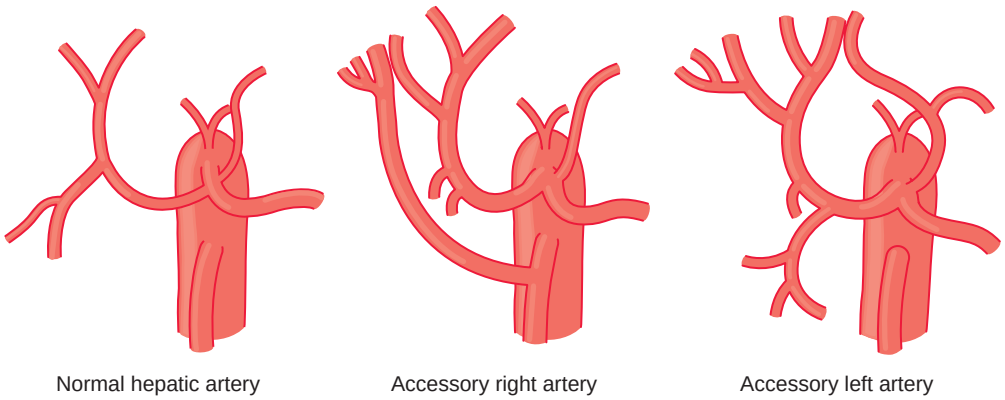

Figure 125–3. Hepatic arterial anatomy is highly variable. The most common anomalies are accessory—or replaced—right and left hepatic arteries arising from the superior mesenteric and left gastric arteries, respectively. These occur in approximately 20% of the population each; they may coexist. (From Henderson JM: Atlas of liver surgery. In Bell RH, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery: A Text and Atlas. Philadelphia, Lippincott-Raven, 1995.)

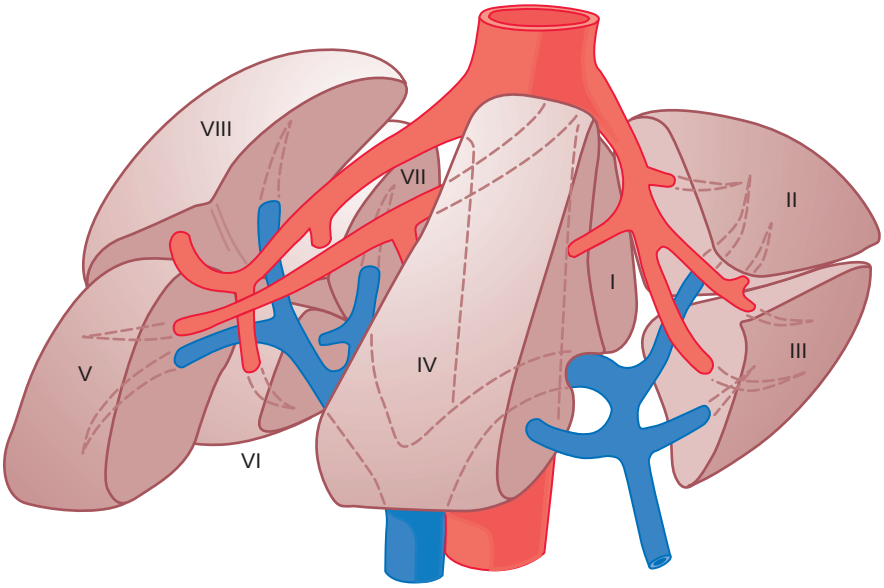

Figure 125–4. Liver segmental anatomy is based on portal inflow and hepatic venous outflow. Each of the eight segments is its own functional anatomic unit. (From Henderson JM: Atlas of liver surgery. In Bell RH, Rikkers LF, Mulholland MW [eds]: Digestive Tract Surgery: A Text and Atlas. Philadelphia, Lippincott-Raven, 1995.)

PATHOPHYSIOLOGY

Normal portal venous pressure is 5 to 8 mm Hg with the portal flow in the 1 to 1.5 L/min range. The portal vein is a passive conduit from the gut that carries blood back to the liver. Total liver blood flow is regulated by intrinsic and extrinsic mechanisms with alteration of portal venous flow having a direct reciprocal increase or decrease in hepatic arterial flow.[25] The changes in portal hypertension occur on this physiologic background. The steps in the development of the pathophysiology of portal hypertension have been carefully elucidated in the past 2 decades in animal models. Portal hypertension is present when portal pressure exceeds 8 mm Hg, but variceal bleeding rarely occurs until portal pressure exceeds 12 mm Hg. There is a well-defined sequence of events, as follows, that occurs in the pathophysiology of portal hypertension (Fig. 125–5) [16,17]:

- Obstruction to portal venous flow is usually secondary to an intrahepatic block with cirrhosis. However, the inciting event may be one of the other etiologic causes of portal hypertension.
- Functional increase in resistance occurs secondary to activated hepatic stellate cells and myofibroblasts in the fibrous septa of the sinusoid. These represent a potentially reversible component to intrahepatic resistance.
- There is an imbalanced production of vasoconstrictors such as endothelin, norepinephrine, and angiotension, with an insufficient release of hepatic vasodilators such as nitric oxide and prostaglandins.
- Splanchnic vasodilation occurs with increased splanchnic flow aggravating and contributing to the portal hypertensive syndrome. This is multifactorial with neurogenic, humoral, and local mediators.

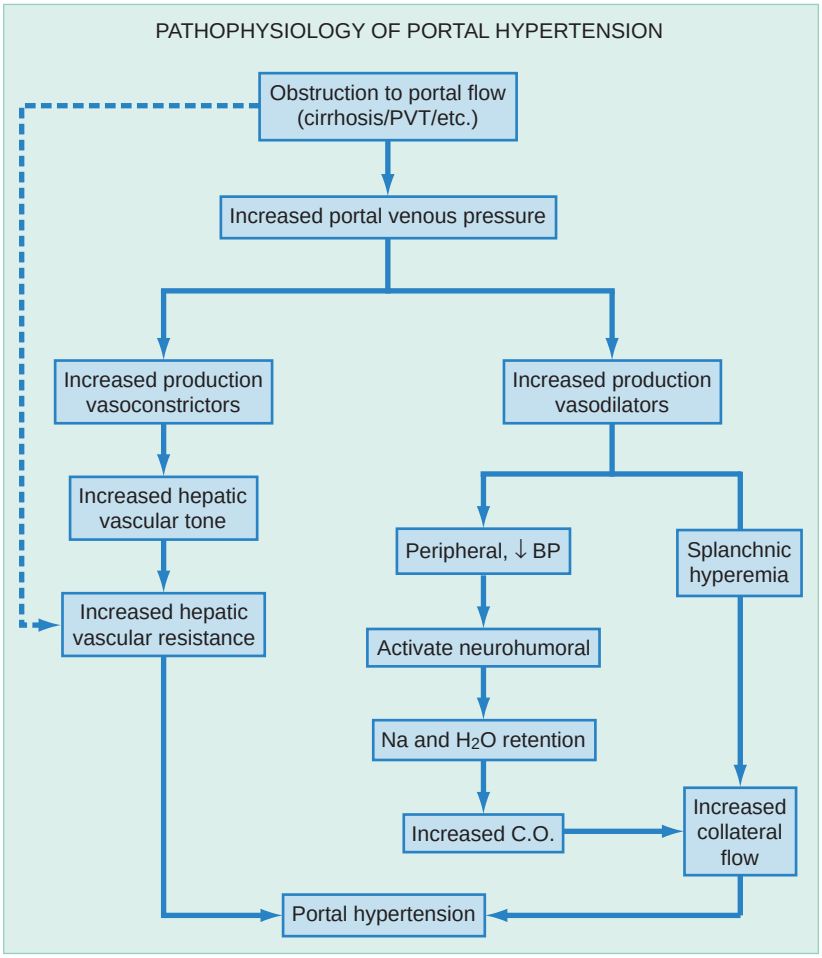

Figure 125–5. Pathophysiology of portal hypertension. Complex vascular and neurohumoral responses that affect splanchnic, renal, and peripheral vascular control are shown. BP, blood pressure; CO, cardiac output; PVT, portal vein thrombosis.

- Portosystemic collaterals develop not only at the gastroesophageal junction but the abdominal wall and retroperitoneum.
- There is an increase in plasma volume secondary to the vascular changes.
- A systemic hyperdynamic circulation develops with increased cardiac output, low total systemic vascular resistance, and further aggravation of the splanchnic hyperemia and overall hyperdynamic state.

This sequence of pathophysiologic changes in the hepatic, splanchnic, and finally systemic circulation offers an opportunity for pharmacologic manipulation and management of portal hypertension.

CLINICAL PRESENTATIONS IN PORTAL HYPERTENSION

Variceal bleeding is one of the most lethal complications of portal hypertension. An improved understanding of the natural history of varices has helped put logic into their management.[26,27] The following points apply:

- Thirty percent of patients with cirrhosis develop varices.
- Thirty percent of patients with varices bleed from varices.
- Patients with large varices are more at risk of bleeding than patients with small varices.
- Patients with variceal bleeding and well-preserved liver function have a broader range of treatment options and better outcomes than patients with variceal bleeding and poor liver function.

All patients with documented or suspected cirrhosis should have an upper endoscopy to document whether or not they have varices. Documentation of varices may lead to treatment at the following time points:

- Prophylactic therapy, prior to the initial bleed
- Management of an acute variceal bleeding episode
- Therapy to prevent a recurrent variceal bleed

The details of evaluation and management for patients are dealt with in the following discussion.

Ascites develops in patients with cirrhosis at a more advanced stage than may be the case for variceal bleeding.[28,29] Ascites is a sign of "decompensation" of the underlying liver disease. From a clinical perspective it is the responsiveness of ascites to simple treatment with salt restriction and diuretics versus refractory ascites that is

important in patient management. The diagnosis and management of ascites are discussed in later sections.

Liver failure and encephalopathy are common complications of portal hypertension, are caused by progressive liver disease, and are the most definitive markers of end-stage disease. From a clinical perspective, recurring encephalopathy or signs of liver failure are an indication for evaluation for liver transplant. If the patient is not a candidate for liver transplant, their treatment options are limited once this clinical presentation occurs.

Hepatocellular carcinoma (HCC) is an increasingly frequent complication of cirrhosis seen in patients with portal hypertension.[30] The epidemic of HCC is largely due to the increased incidence of hepatitis C, but this complication of chronic liver disease can occur with cirrhosis of any etiology. From a clinical perspective hepatoma should be looked for in all patients with a documented cirrhosis with serial scanning with ultrasound and evaluation of α-fetoprotein. If HCC is the initial presentation of the patient, it is important for the clinician to document if the rest of the liver is normal or indeed has an established cirrhosis. The management options for hepatoma are dictated by the rest of the liver as much as by the tumor itself.

The *portopulmonary syndromes* have more recently been recognized as an important component of the clinical presentation of patients with portal hypertension.[31,32] There are two broad groups of patients: (1) those with HPS that is marked by hypoxemia secondary to intrapulmonary shunting in patients with chronic liver disease, in the absence of pulmonary hypertension, and (2) patients with pulmonary hypertension and chronic underlying liver disease who have a more sinister syndrome with a poor prognosis.

ETIOLOGY OF PORTAL HYPERTENSION

The etiologies of portal hypertension are summarized in Box 125–1. Broadly, the etiologies fall into the categories of (1) prehepatic block raising portal pressure, (2) intrahepatic obstruction to portal flow, and (3) posthepatic venous outflow block.

Prehepatic portal hypertension comprises 5% to 10% of portal hypertension patients in the United States and Europe.[33] In other parts of the world such as India, this may be the etiology in a higher percentage of portal hypertension patients.[34] The importance of identifying patients with this etiology is that the liver is usually normal, which is a major factor in overall prognosis. The most common prehepatic block is portal and/or splenic vein thrombosis. Portal vein thrombosis may be associated with umbilical vein catheterization or other causes of sepsis and dehydration in infancy. In the adult patient the hypercoagulable syndromes should be sought in patients with a newly diagnosed portal or splenic vein thrombosis, with a full hematologic work-up.[35] Other etiologies include pancreatitis and pancreatic tumors, with the later portending a poor prognosis related to the cancer. Occasionally, extrinsic pressure on the portal vein from lymph nodes or other tumors can lead to portal hypertension, but this is unusual. Finally, hepatic artery–to–portal venous fistulas, usually secondary to a liver biopsy, can occur and if large can lead to portal hypertension.[22] Fistulas are diagnosed with radiologic imaging and can usually be managed with endoluminal angiographic techniques for their occlusion.

Box 125–1 Etiology of Portal Hypertension

Prehepatic
- Portal or splenic vein thrombosis
- Extrinsic portal vein compression
- Arteriovenous fistula

Intrahepatic
- Cirrhosis: multiple etiologies
- Schistosomiasis
- Congenital hepatic fibrosis
- Rare causes

Posthepatic
- Budd-Chiari syndrome
- Constrictive pericarditis

One important variant of portal hypertension is left-sided (sinistral) portal hypertension with isolated splenic vein thrombosis, a normal portal vein, and no intrahepatic block.[36] The most common causes of this are pancreatitis and carcinoma of the body and tail of the pancreas. This is increasingly recognized on computed tomographic (CT) scan with large collaterals coming from the splenic hilus up to the fundus of the stomach. From a portal hypertension perspective this is readily handled with splenectomy, but clearly an understanding of the underlying pathology is most important in prognosis.

The intrahepatic causes of portal hypertension account for 90% of the cases in the United States and Europe. Most patients with an intrahepatic block have cirrhosis, which has multiple etiologies.[37] These include alcohol, hepatitis B, hepatitis C, the cholestatic liver diseases (primary sclerosing cholangitis and primary biliary cirrhosis), hemochromatosis, and the other metabolic causes of cirrhosis. In the course of patient evaluation, full definition of the underlying disease is important for management. It is the natural history, activity, and rate of progression of the underlying liver disease that ultimately sets the prognosis.

Schistosomiasis is still an important cause of portal hypertension on a world-wide basis.[37] Still seen in the Middle and Far East and in South America, the pathologic block in schistosomiasis is fibrosis of the terminal portal venules. Although pathologically an intrahepatic block, it is presinusoidal, and lobular architecture is maintained with well-preserved liver function. However,

many patients with schistosomiasis may also have hepatitis as a concomitant disease with implications of liver function impairment.

Congenital hepatic fibrosis is a relatively rare cause of an intrahepatic block in the United States and Europe, but it is important to recognize because it is usually associated with preserved liver function.[38] However, more recently there have been reports of progression of congenital hepatic fibrosis to end-stage liver disease requiring liver transplantation. A similar entity is seen in India as noncirrhotic portal fibrosis, which is a cause for portal hypertension in that country.[39] The implication of preserved liver function is that there is a broader range of options for treatment, particularly for variceal bleeding.

The posthepatic causes of portal hypertension fall into the broad category of Budd-Chiari syndrome[40,41] and the occasional patient with a constrictive pericarditis. The common feature is hepatic venous outflow block. Classic Budd-Chiari syndrome involves thrombosis of the main hepatic veins, but other etiologies such as inferior vena caval (IVC) webs may cause this syndrome. The outflow block leads to an increase in sinusoidal pressure, centrilobular hepatocyte damage, and ultimately fibrosis, scarring, and cirrhosis. These are exceedingly rare syndromes, accounting for 1% to 2% of the cases of portal hypertension.

EVALUATION

Evaluation of patients with portal hypertension requires a multidisciplinary approach focused on the clinical presentations. All patients with cirrhosis should have some component of this evaluation, with the depth of evaluation determined by the specific presentation as outlined earlier. The essential components of such evaluation are summarized in Box 125–2.

Endoscopy plays a key role in the evaluation because varices and bleeding are the most serious complication of portal hypertension. Any patient with cirrhosis should have an endoscopy to assess for varices. The presence of varices may be the first indication that a patient does have portal hypertension. Even if the patient has not bled, this evaluation will identify some patients with moderate to large varices who should receive prophylactic therapy. Endoscopy should assess the size of the varices, their extent, and risk factors.[42] Risk factors are red color signs that indicate thin-walled varices that are at increased risk of bleeding. In addition, the gastric mucosa should be assessed for portal gastropathy, which also has risk factor grading with red color signs that indicate an increased risk of bleeding. Grading systems to classify bleeding risk for gastroesophageal varices,[43] portal hypertension gastropathy,[44] and gastric varices[45] help standardize patient populations.

Radiologic evaluation of the portal venous system is the next important step. Initially done with Doppler ultrasound,[46] this method gives imaging of the portal vein and its main tributaries as well as assessing flow patterns in the portal venous system. This is also the best method for assessing the hepatic veins both for patency and their wave-flow patterns. Ultrasound is the most useful screening modality for liver morphology, defining the cirrhotic liver, but focal lesions suggestive of HCC can also be assessed.

Further imaging of the liver and its vasculature may be done with either CT scan[47] or magnetic resonance (MR) imaging.[48] The choice is largely made by institutional preference and experience. Both provide good methods of imaging the normal and cirrhotic liver. Morphologic assessment for liver tumors, particularly with the increasing incidence of hepatoma, is increasingly accurate with these imaging modalities. Both also provide a further means to evaluate the portal venous system, with the ability to look at flow patterns with faster scanners and more sophisticated postimage processing. These have largely replaced the need for visceral angiography in this population.

Arteriography and hepatic venous studies still play some role in evaluation of these patients.[49,50] Hepatic venous pressures are measured with a balloon occlusion catheter in the hepatic vein, measuring the occluded and free hepatic vein pressures. The difference between these gives the hepatic venous pressure gradient (HVPG), which is an indirect measure of portal venous pressure akin to pulmonary artery pressure in the lungs. Increasing emphasis is being placed on the value of this measurement in the era of more sophisticated pharmacologic therapies.[50] If the HVPG can be reduced to 10 mm Hg or less, variceal bleeding will not occur.

Box 125–2 Evaluation of Patients with Portal Hypertension

Endoscopy
- Size of varices
- Extent of varices
- Risk factor, red color signs
- Portal gastropathy

Imaging
- Doppler ultrasound
- CT scan
- HVPG and imaging
- Angiography

Liver Function
- Clinical: ascites, encephalopathy, jaundice, muscle wasting
- Laboratory data
- Child's score
- MELD score

HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease.

Table 125–1 Child-Pugh Grading* of Severity of Liver Disease

Clinical and Laboratory Measurement	Patient Score for Increasing Abnormality		
	1	*2*	*3*
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	None	Mild	Moderate
Bilirubin (mg/dl)	1-2	2.1-3	≥3.1
Albumin (g/dl)	≥3.5	2.8-3.5	≤2.7
Prothrombin time (increase, seconds)	1-4	4.1-6	≥6.1

*Grade A = 5-6 points; grade B = 7-9 points; grade C = 10-15 points.

Occasionally visceral arteriography followed through to the venous phase is required for full clarification of portal hypertension. When there remains doubt after CT or MR imaging as to patency and flow patterns in the superior mesenteric, splenic, or portal veins angiography may clarify this. It also gives dynamic imaging of the flow patterns in the major tributaries and collaterals associated with portal hypertension.[49] This may be of importance to the surgeon considering intervention.

Liver function assessment is the final phase of evaluation. The components of this are clinical, laboratory data, and calculation of prognostic indices. The important parts in clinical assessment of liver function are the detection of ascites, evaluation for encephalopathy, detection of clinical jaundice, and assessment of muscle wasting. All of these clinical signs are indications of advanced liver disease.

Laboratory data that are important are those that directly assess liver status: bilirubin, albumin, prothrombin time, aspartate aminotransferase, alanine transaminase, and alkaline phosphatase. In addition, hematologic parameters (i.e., hemoglobin, platelet count, and white blood cell count) may be affected by portal hypertension. A platelet count lower than 100,000 is indicative of significant portal hypertension. A prothrombin time international normalized ratio (INR) of 1.5 indicates poor liver function. All patients should have checks made of specific liver disease markers, including hepatitis panels, antinuclear antibody, antimitochondrial antibody, and metabolic disease markers for iron, copper, and α_1-antitrypsin. Finally, hepatoma risk can be assessed with α-fetoprotein.

The prognostic indices that are used in patients with portal hypertension are the Child-Pugh score (Table 125–1),[51] and the model for end-stage liver disease (MELD) score (Box 125–3).[52] The Child-Pugh score, developed to assess prognosis of patients undergoing portal decompressive surgery, has stood the test of time for more than 50 years as a useful index of disease severity. More recently, the MELD score has come into being as a more objective way of assessing mortality risk for patients with more advanced disease. Its genesis was the need for a better method for grading disease severity for liver transplantation.

Box 125–3 **Model for End-Stage Liver Disease Score for Liver Disease Severity**

Score = 0.957 × $\log_e$ creatinine (mg/dl) + 0.378 × $\log_e$ bilirubin (mg/dl) + 1.120 $\log_e$ INR

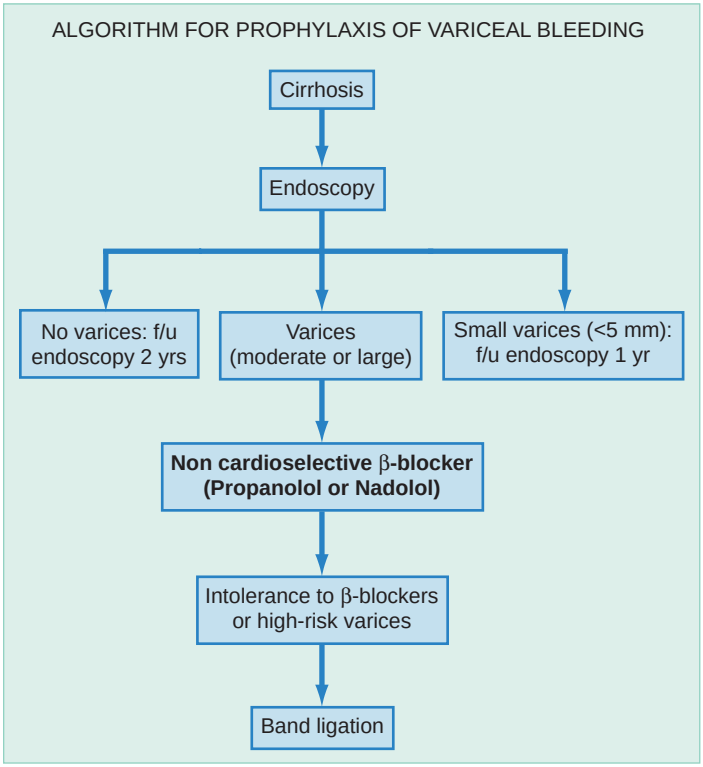

Figure 125–6. Algorithm for prophylaxis of the first variceal bleed. Diagnosis of varices is Step 1; grading of size determines the need for therapy. Moderate or large varices should be treated. f/u, follow-up.

MANAGEMENT OF VARICEAL BLEEDING

Prophylaxis of Variceal Bleeding

Figure 125–6 shows an algorithm for the investigation and management of patients with cirrhosis and varices that have not bled. The initial step, as indicated earlier, is endoscopic evaluation of all patients with cirrhosis. If they have no varices, they should have a follow-up endoscopy at 2 years. If they have small (5 mm) varices they should receive no prophylactic therapy and have a follow-up endoscopy in 1 year. If they have moderate to large varices (>5 mm) and/or red color risk factors, they

should receive prophylactic therapy. Standard prophylactic therapy to reduce the risk of an initial bleed is with a noncardioselective β blocker—propranolol or nadalol.[53] In patients who are intolerant to β blockers or who have large, high-risk varices, a course of endoscopic banding may be appropriate. Both of these approaches reduce the risk of initial bleed from 30% to approximately 15% to 18%.

Acute Variceal Bleeding

Figure 125–7 shows a management algorithm for acute variceal bleeding.[54] This falls into the following three broad steps:

1. General measures for managing the patient when it is still not certain if they are bleeding from varices
2. An endoscopic assessment and treatment
3. Those that need to be taken if patients are not controlled with endoscopic and pharmacologic therapy or rebleed through endoscopic treatment

The general measures for a suspected variceal bleed are initial pharmacologic therapy with either somatostatin or its analogue octreotide as a continuous infusion at 50 μg/hr. These drugs have virtually replaced vasopressin/nitroglycerine, although triglycyl lysine vasopressin (Terlipressin) is available and used in Europe. Patient resuscitation should be on the conservative side with under-resuscitation rather than over-resuscitation. It is better to have a patient with a slightly reduced intravascular volume rather than over-expanded volume, which increases the risk of a recurrent variceal bleed. In practical terms this means that a systolic blood pressure of 100 to 110 mm Hg is preferable to 120 to 130 mm Hg. Ideally, patients should be placed in an intensive care unit (ICU) for ongoing monitoring. A Foley catheter should be placed so that urine output can be monitored. Finally, it has been increasingly recognized that sepsis plays an important role in prognosis at this time and all patients with cirrhosis and an acute variceal bleed should receive antibiotics—a systemic cephalosporin should be given for 3 to 5 days.

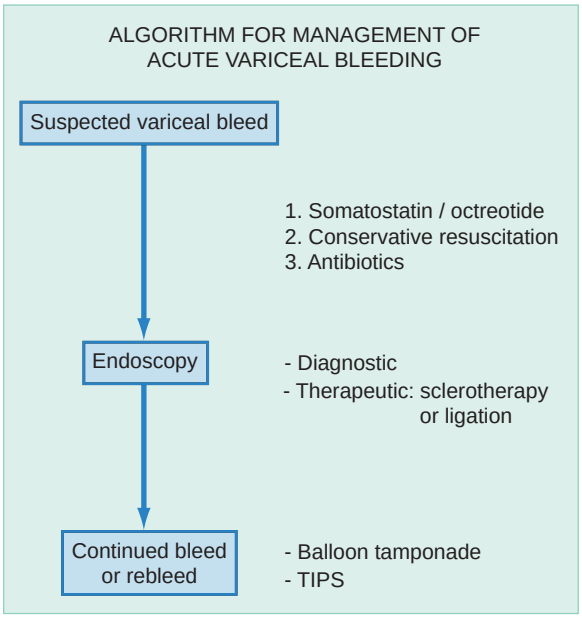

Figure 125–7. Algorithm for managing acute variceal bleeding. This falls into (1) general measures, (2) endoscopic therapy, and (3) salvage of refractory/recurrent bleeding. TIPS, transjugular intrahepatic portosystemic shunt.

Endoscopy at the time of an acute variceal bleed is initially diagnostic but, if appropriate, becomes therapeutic. Diagnostic endoscopy focuses on the presence of varices, their risk factors, and identification of an actively bleeding or a recently bleeding site. The latter are identified by a platelet plug on a varix. In addition, other sites of upper gastrointestinal bleeding such as peptic ulcer disease should be excluded. Frequently an active site is not identified, and a recently bleeding site may not be seen. In the absence of any other bleeding source, it is thus assumed that bleeding was from varices and treatment initiated. The therapeutic component of endoscopy is usually endoscopic banding of the varices. This should be aggressively undertaken with serial spiral banding of all varices around the gastroesophageal junction (Fig. 125–8). If banding is not available, direct endoscopic sclerotherapy can be completed at this time to control acute bleeding.

For the 5% to 10% of patients in whom the acute variceal bleed is not controlled, or the 10% to 15% of patients in whom there is early rebleeding after the management discussed earlier, balloon tamponade may play a role to stabilize patients prior to moving to decompression. Balloon tamponade requires a knowledgeable team and careful protocols for its use. Patients requiring balloon tamponade should have endotracheal intubation for control of their airway. The tube can either be passed through the nose or the mouth. The position of the gastric balloon in the stomach should be confirmed with a radiograph after inflating it with 25 to 30 cc of air. Once the position is confirmed, the gastric balloon is inflated to approximately 200 cc and brought up snuggly in the gastric fundus. Occasionally the esophageal balloon may need to be inflated to 40 mm Hg (monitored through a pressure cuff,) but usually this is not required. Placement of a tamponade balloon mandates a further step within 12 to 24 hours to control bleeding, which is usually done with an urgent TIPS. Once the patient is stabilized, an urgent TIPS should be done.[55] This must be viewed as similar to taking the patient to the operating room—intubation, sedation, and careful monitoring should be performed. TIPS is therefore indicated in a very small number of patients in the acute setting who do not respond to pharmacologic and endoscopic therapy.

Prevention of Recurrent Variceal Bleeding

Figure 125–9 presents an algorithm for management to prevent recurrent variceal bleeding.[54,56] Following stabilization of an acute bleeding episode, patients should undergo evaluation, as outlined earlier.

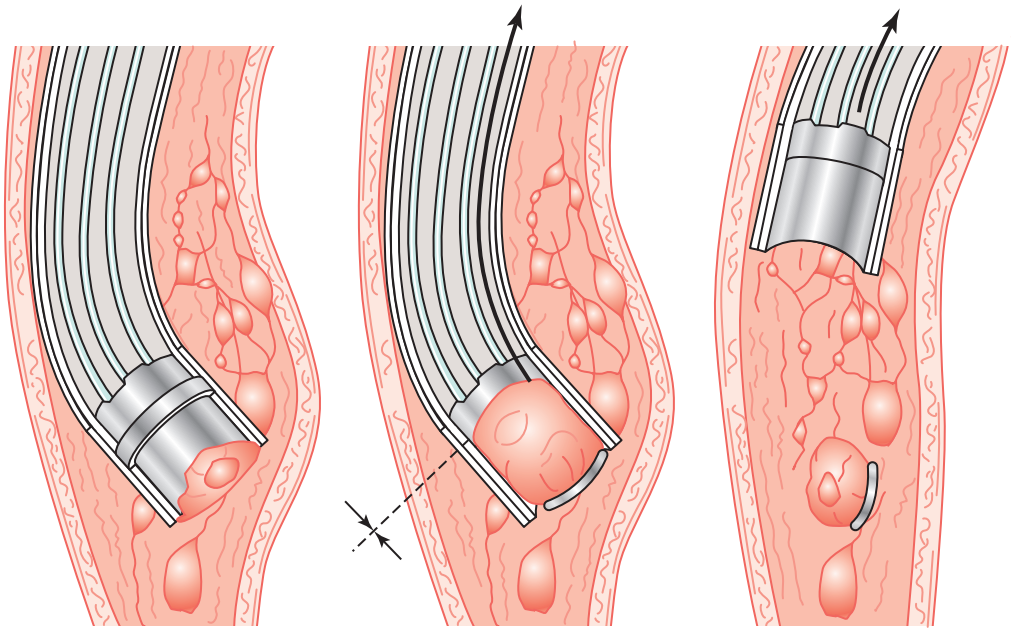

Figure 125–8. Diagnostic representation of variceal banding. The varix is sucked into the "cup" at the end of the endoscope and a tight band is fired around the base of the varix. The bands slough off in 5 to 10 days. (From Sanyal AJ, Shah VH [eds]: Portal Hypertension. Totowa, NJ, Humana Press, 2005, p 227.)

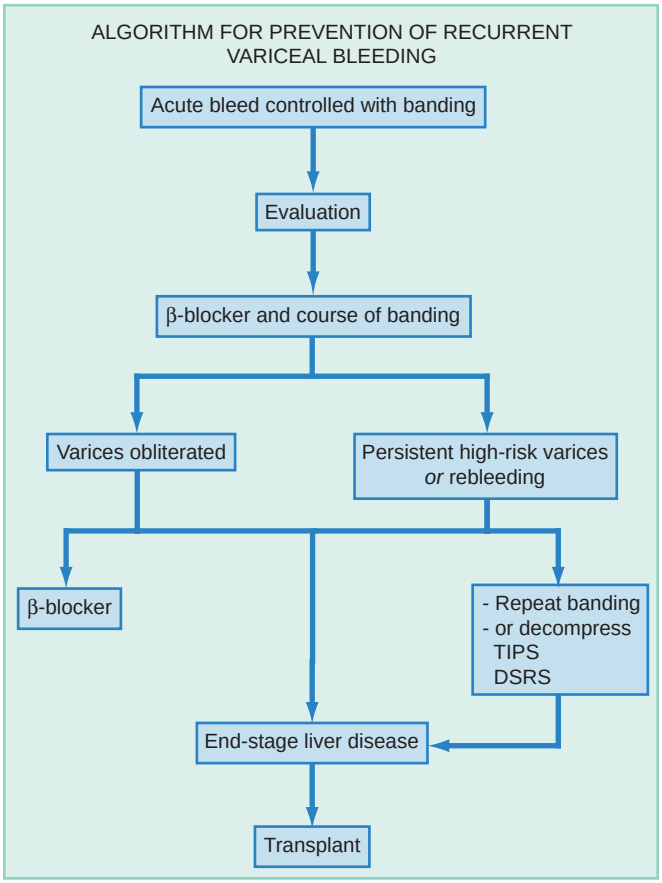

Figure 125–9. Algorithm for prevention of recurrent variceal bleeding. Primary therapy for all patients is with β blockers and banding. Secondary therapy may be variceal decompression for recurrent bleeding or transplant for advanced disease and recurrent bleeding. DSRS, distal splenorenal shunt; TIPS, transjugular intrahepatic portosystemic shunt.

Primary Therapy

The initial management to prevent recurrent bleeding should be a combination of pharmacologic and endoscopic therapy. The aggressive banding session at the time of the acute bleed should be followed in 7 to 10 days with further variceal ligation and repeat sessions until the varices are obliterated. Usually two or three sessions suffice. Banding has been shown to be better than sclerotherapy[57] with better bleeding control and fewer complications. Concurrently, the patient should be started on a noncardioselective β blocker to reduce portal hypertension. There are multiple trials of both of these modalities either on their own, compared to each other, or used in combination.[56] Both reduce the risk of further bleeding at 1 year from 70% in untreated patients to 30%. The combination may reduce the risk to closer to 20%. If the banding course obliterates the varices, the patient should continue on their β blocker indefinitely. If the banding course, in combination with pharmacologic therapy, leaves persistent high-risk varices, or there is an episode of rebleeding, further treatment decisions need to be made. Depending on the time scale over which the endoscopic therapy has been implemented, it may be reasonable to repeat an aggressive further course of banding. Decisions also depend on the patient's underlying liver disease and its prognosis. If the patient has moderate or significantly advanced liver disease and is headed for transplant, a more conservative approach bridging the patient to transplant is indicated. If, on the other hand, the patient has well-preserved liver function, stopping the bleeding becomes of paramount importance so that the liver disease is not accelerated. Such patients may be candidates for decompression.

Decompression of Varices

The current recommendations for variceal decompression are to use either TIPS or a surgical shunt. It is only approximately 10% to 15% of patients with variceal bleeding who will need this level of treatment.

TIPS

TIPS has evolved over the past decade.[58] The technical advances and the wide-spread application of TIPS by interventional radiologists with a relatively low morbidity have led to its general acceptance. This is being supported by data as indicated later. Although the initial rebleeding rates were in the 20% to 25% range, this appears to be dropping. First the technology has improved and covered stents have a lower rate of stenosis than the original uncovered stents.[59] In addition, data indicate that ongoing monitoring with reintervention for stenosis will further bring down the rebleeding rates. More recent studies have shown that rebleeding rates with TIPS have fallen to the 11% to 15% range. However, the costs of doing this in terms of reintervention rates and the dollars required for reintervention have not yet been fully assessed. TIPS has been shown to control bleeding better than endoscopic therapy, but the higher rate of encephalopathy, and no difference in survival has not led to implementation of TIPS as primary therapy to prevent rebleeding.[60,61]

The Procedure TIPS is usually placed via a right transjugular route to the right or middle hepatic vein (Fig. 125–10), but any hepatic vein can be used and the choice is dictated by liver morphology. Direct access from the IVC to the portal vein has been used in some cases of Budd-Chiari syndrome. Next, the hepatic parenchyma is traversed with a needle to puncture the portal vein; ultrasound guidance can be used, but experienced interventional radiologists can usually access the portal vein readily. It is important to enter the right or left portal vein within the liver above the bifurcation that sits outside the liver—puncture and dilation of the tract at the bifurcation can result in a major intra-abdominal bleed. A catheter is placed over a guidewire into the portal vein, pressure is measured, and a portogram contrast study performed. The transparenchymal tract is dilated and the stent(s) placed to keep the tract open. The stent is dilated to reduce the portal-to-right atrial gradient to equal 10 mm Hg. Stent placement is important: not too low into the portal vein and not too high into the suprahepatic IVC, both of which can create technical problems if subsequent transplant is needed. However, the tract must be adequately stented because the most common site for subsequent stenosis is the hepatic vein end of the stent. Covered stents require more fastidious placement to be sure the covered components do not protrude into the portal vein or IVC. Covered stents have a short uncovered segment at the end. A completion study should document patency and appropriate pressure gradient reduction (≤10 mm Hg).

Follow-up requires careful monitoring. Doppler ultrasound is adequate for screening and documenting total thrombosis. Covered stents do not transmit the Doppler signal for several days, so initial evaluation should be 3 to 4 days after the procedure. Ultrasound does not always document stenosis, which requires stent recatheterization and pressure measurement and possibly imaging. Gradients ≥12 mm Hg or stenosis greater than 50%

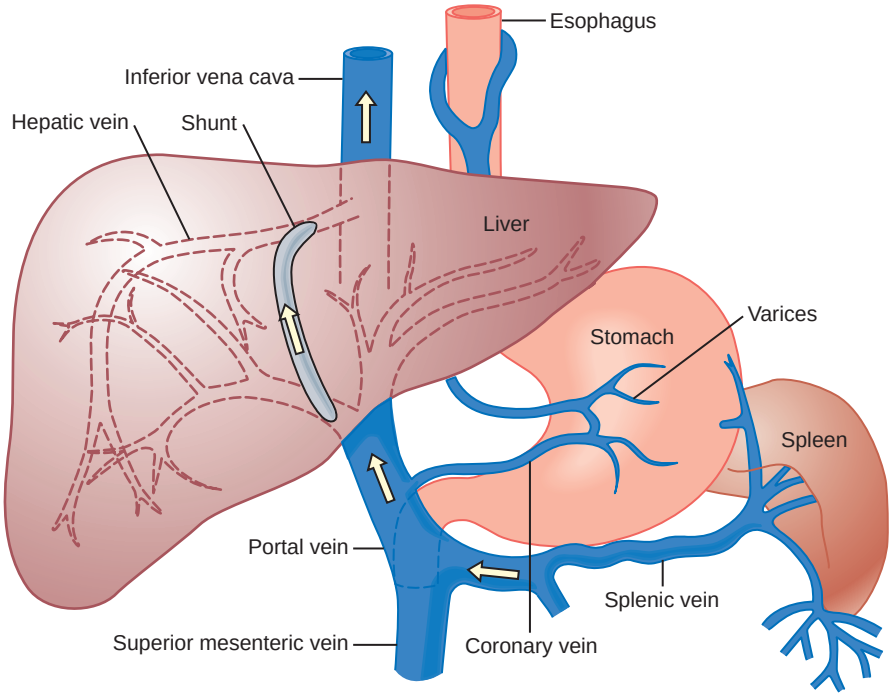

Figure 125–10. Transjugular intrahepatic portosystemic shunt (TIPS) is diagrammatically illustrated. The stent is placed between the hepatic vein and the portal vein, dilated to 10 to 12 mm, and the portal-to-right atrial pressure gradient is reduced to less than 10 mm Hg. (From Henderson JM: Portal hypertension. In Corson JD, Williamson R [eds]: Surgery. London, Mosby, 2001.)

require dilation. Additional stents may be required if the stenosis is refractory to dilation or occurs at either end of the initial stents(s). The necessary frequency of recatheterization is undefined: current indications are when Doppler ultrasound studies change—increased or decreased velocities. The study with the lowest rebleeding rate after TIPS (11%) included protocol recatheterization at yearly intervals—this may set a standard.[62]

Surgical Shunts

Surgical shunts fall into three broad categories: total,[63,64] partial,[11] and selective shunts.[9,10] There are few indications for total surgical shunts at the current time. Partial shunts have been used successfully by some groups, with rebleeding rates in the 5% to 10% range, and because some portal perfusion is preserved, encephalopathy rates are lower with partial shunts than total shunts.[65,66] Selective shunts are most commonly done with the distal splenorenal shunt (DSRS), which selectively decompresses gastroesophageal varices while maintaining portal hypertension in the splanchnic-to-portal axis, thereby maintaining portal flow. DSRS controlled bleeding better than sclerotherapy in controlled trials, with equivalent encephalopathy.[67] Several uncontrolled series of DSRS in the 1990s to early 2000s showed rebleeding rates of 5% to 6%, encephalopathy rates around 15%, and 1- and 3-year survival rates of 85% and 75%, respectively, in good-risk Child's Class A and B patients.[68-71] Selective shunts remain the most widely used surgical shunts at the present time.

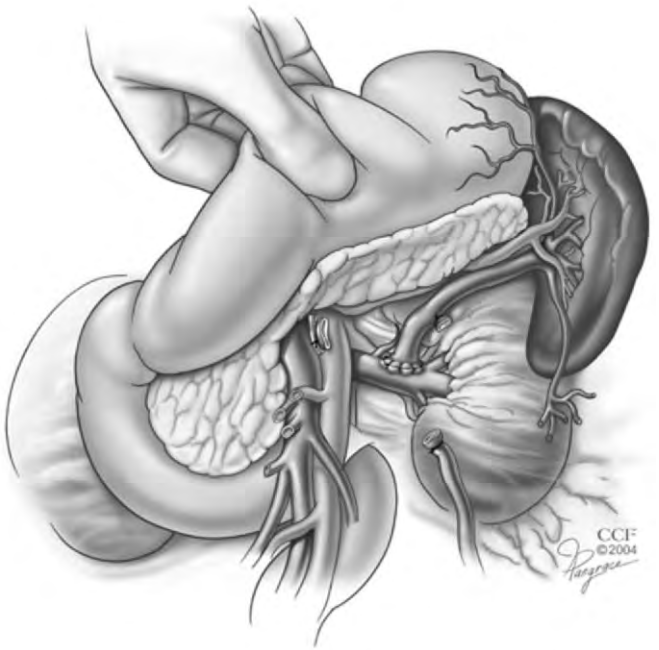

Figure 125–11. Distal splenorenal shunt selectively decompresses gastroesophageal varices through the spleen and splenic vein to the left renal vein. Portal hypertension and portal perfusion of the liver are maintained in the superior mesenteric and portal veins. (© 2004, Cleveland Clinic Foundation.)

Distal Spenorenal Shunt

The Procedure DSRS is performed through a long left subcostal incision carried across the midline to the right rectus muscle (Fig. 125–11). Exposure of the splenic and left renal veins is key. Access to the pancreas is obtained through the lesser sac, taking down the gastroepiploic vessels from the pylorus to the short gastric veins—this also serves as part of the portal/azygos disconnection. In addition the splenic flexure of the colon should be taken down from the spleen—this both improves access to the posterior surface of the pancreas and interrupts potential collaterals to the shunt. The pancreas is fully mobilized along its inferior margin from the superior mesenteric vein to the splenic hilus—it is turned cephalad to expose its posterior surface and the splenic vein. Dissection of the splenic vein from the pancreas is done from the superior mesenteric vein over sufficient distance to mobilize enough vein to come down to the left renal vein without kinking. The posteroinferior surface is cleared first, then the small draining tributaries from the pancreas are isolated and ligated. The left renal vein is then identified in the retroperitoneum—a move made easier by preoperative venographic imaging. The left renal vein is mobilized with the left adrenal vein ligated and the gonadal vein left intact. This mobilization must be sufficient to allow the vein to come up into a side-biting clamp. The splenic vein is then divided at the splenic–superior mesenteric–portal junction and brought down for end-to-side anastomosis to the renal vein. We recommend interrupted sutures to the anterior row of the anastomosis to avoid purse stringing. The shunt is opened, and the spleen can be seen to decompress. The operation is completed with further portal/azygos dissection mainly by interrupting the left gastric vein both at the portal vein and above the pancreas.

Management Perioperative and postoperative details in care are important for patients with cirrhosis having major operative procedures. The major risks are ascites, infection, and liver failure. Ascites risk is minimized by careful fluid management: minimize sodium, run the patient "dry," and use diuretics judiciously. Infection risk is minimized with appropriate perioperative antibiotic coverage and vigilance for potential postoperative infection, always a consideration in a patient with cirrhosis who is "not doing well." Liver failure risk is minimized by appropriate patient selection for the procedure.

Shunt patency should be documented in 5 to 7 days by direct shunt catheterization and pressure measurements prior to hospital discharge. Full variceal decompression takes 4 to 8 weeks, so knowing shunt status prior to discharge is important. If the shunt is working well at this time, late stenosis/thrombosis is unusual.

Follow-up Patients are discharged on a low-sodium, low-fat diet. The latter because of the risk of chylous ascites in the first 6 to 8 weeks. Medications are spironolactone (Aldactone), 100 mg/day, and an H_2 blocker for gastric

acid suppression. Blood work—liver function tests and electrolytes—should be monitored carefully for the first 2 to 3 months. Long-term follow-up is dictated by the underlying liver disease.

A National Institutes of Health–funded prospective, randomized, controlled trial has just been completed comparing TIPS and DSRS.[62] This study in Child's Class A and B patients who were refractory to endoscopic and pharmacologic therapy ran over 7 years, with a median follow-up of 42 months. The rebleeding rates were not significantly different (5.6% in the DSRS group and 11.5% in the TIPS group). Encephalopathy rates were not significantly different, with 50% of patients in each group having at least one clinical encephalopathy event by 5 years. The survival rates were not significantly different, with 85% survival at 1 year and 65% survival at 5 years. What was significantly different was the reintervention rate, which was 82% in the TIPS group and 11% in the DSRS group ($P < .001$). It was the careful surveillance, protocol recatheterizations of TIPS at annual intervals, and completeness of follow-up that contributed to the low rebleeding rate in the TIPS group. This trial was conducted with uncovered stents. A European multicenter trial compared covered and uncovered TIPS—the reintervention rate with covered stents dropped to 15% at 1 year.[59] The issue remains, however, of how to identify those patients who do have a stenosis that does require reintervention?

A trial compared TIPS to the 8-mm H-graft interposition portacaval shunt in an "all-comers" population.[66] This trial entered patients who had failed primary therapy; 50% were Child's C and 63% had alcoholic cirrhosis. At late follow-up, the rebleeding rate was significantly lower ($P < .01$) in the surgical shunt group (3%) compared to the TIPS group (17%), and fewer patients in the surgical shunt group came to transplant ($P < .01$). Mortality was not significantly different but in both groups was significantly better at 2-year follow-up than the predicted mortality by MELD score at study entry.[72]

Devascularization Procedures

Devascularization procedures have been more extensively used in Japan and Egypt than in the United States and Europe. The goal of this group of operations is to reduce variceal inflow and to have the following components:

- Splenectomy
- Esophageal devascularization—at least 7 cm
- Gastric devascularization—all the greater curvature and the upper two thirds of the lesser curvature

The advantage of these procedures is that they maintain portal hypertension and perfusion of the cirrhotic liver, provided there is no portal vein thrombosis, which occurs in up to 20%. Maintaining portal flow has been associated with lower encephalopathy rates.

The results have been better in Japan[73,74] than in the United States and Europe,[75] but good results have also been achieved in Mexico.[76] Although not widely used in good-risk cirrhotic patients who have "shuntable" veins, an indication for this operation at the present time is in patients with extensive portal venous system thrombosis and recurrent variceal bleeding—many of these patients have a normal liver.

Transplant

Finally, in preventing variceal rebleeding, it is clear that transplant has played a major role over the past 2 decades.[77] Although variceal bleeding per se is not an indication for transplant, progression of liver disease, often with variceal bleeding as a component, is an indication for transplant. Transplant is the best shunt for variceal bleeding in patients with advanced liver disease and provides excellent control of bleeding. However, not all patients with variceal bleeding are candidates for transplant, and there are not enough livers available to provide transplantation for every patient with portal hypertension and variceal bleeding. Appropriate listing criteria have been developed by the United Network for Organ Sharing (UNOS), and allocation of organs to the sickest patients has improved the overall outcome and utility of organs available for transplantation. This is a field that continues to evolve and is an area in which surgeons still play a role in the management of patients with variceal bleeding.

Summary for Variceal Bleeding

At the present time, the management of variceal bleeding falls into the following three time points:

1. Prophylaxis with pharmacologic β blockers
2. Acute bleed with pharmacologic and endoscopic therapy
3. Prevention of rebleeding with initial pharmacologic and endoscopic therapy, with decompression reserved for the 10% to 15% of patients who rebleed

Finally, liver transplantation is the treatment of choice for patients with variceal bleeding and advanced liver disease.

ASCITES

Ascites is the most common complication of cirrhosis, with approximately two thirds of patients with compensated cirrhosis developing ascites within 10 years. Once a patient with cirrhosis develops ascites, particularly as it becomes increasingly difficult to manage, there is approximately 50% mortality over the next 3 years without liver transplantation.[28,29]

Pathophysiology

Ascites develops in patients with cirrhosis because of overall hemodynamic changes, vasoconstrictor and sodium-retaining systems being triggered in the kidneys, and the accompanying renal dysfunction.[78] The pathophysiologic sequence in the development of ascites is summarized in Figure 125–12. As indicated earlier in this chapter, one of the early vascular responses to portal

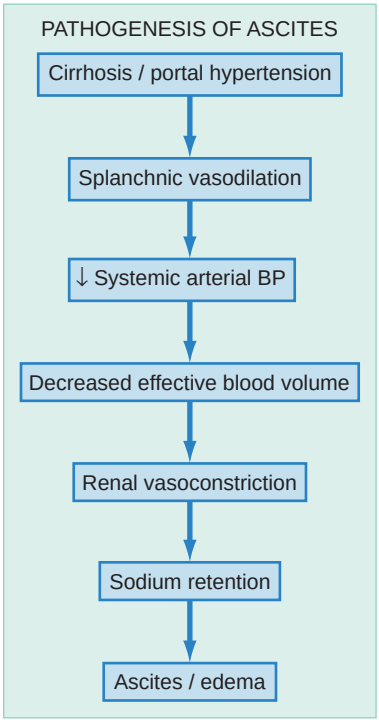

Figure 125–12. Pathogenesis of ascites. Sequential changes in local and systemic vascular beds play a major role. BP, blood pressure.

hypertension is marked arterial vasodilation of the splanchnic circulation. This in turn leads to a hyperdynamic systemic circulation, decreased systemic vascular resistance, and lowered blood pressure. This in turn activates the vasoconstrictor and antinatriuretic systems that affect the kidneys, with sodium and water retention and renal vasoconstriction.[79] The inability of the kidneys to excrete sodium is thus the first event, with water retention subsequently leading to dilutional hyponatremia. This gives the deceptive laboratory picture of low serum sodium yet high total body sodium.[80]

The secondary component of pathophysiology in the development of ascites is the hepatic sinusoidal change.[81] Cirrhosis results in high intrasinusoidal pressure and further damage to the already discontinuous endothelium of the sinusoid. This high pressure leads to excess fluid filtration through the sinusoid, and much of the ascitic fluid forms from the liver surface.

Diagnosis

Traditionally, ascites is a clinical diagnosis.[82] However, in patients with cirrhosis, ascites is increasingly recognized at evaluation imaging ultrasound and CT scan. Ascites volume as low as 100 ml can be detected on ultrasound.[83] However, it is clinical ascites that is important to the patient, and the first sign of this is often an unexpected and unanticipated weight gain. There may be associated peripheral edema.

A diagnostic paracentesis should be performed on all patients with cirrhosis when they first present with ascites.[84] This is done to characterize the ascites and to exclude the diagnosis of spontaneous bacterial peritonitis (SBP), the most lethal complication of cirrhotic ascites. The fluid (30 to 50 ml) should be sent for the following diagnostic tests:

- Appearance of the fluid
- Ascites albumin concentration (a concurrent serum albumin should be measured)[85]
- Total protein content
- White blood cell count and differential[86]
- Culture[87]

Ascites total protein level of less than 2.5 g/dl with a serum/ascites albumin gradient greater than 1.1 is highly indicative of ascites being of cirrhotic origin. In malignant ascites the total protein content is usually higher than 2.5 g/dl and the serum/ascites albumin gradient is less than 1.1. The white blood cell count is important in differentiating SBP, with a count of 500/mm^3 being diagnostic and the 250- to 500/mm^3 range being highly suspicious. Samples for culture should be placed in blood culture bottles with both aerobic and anaerobic media. The minimum amount of ascitic fluid in these bottles should be 10 ml.

Management

The management of ascites[88,89] falls into the following phases:

1. Treat the underlying liver disease
2. Take simple steps to manage ascites
3. Take major steps to manage intractable ascites

A summary of these is given in Figure 125–13.

Patients with mild to moderate ascites require dietary sodium restriction and appropriate diuretic management. Ascites is a disease of sodium retention; therefore, limiting sodium intake is important. This requires patient education on how to achieve a 2 g/day sodium diet and where they can obtain appropriate products. Water restriction is not usually required unless patients become significantly hyponatremic (serum sodium <120 mmol/L). Initial diuretic management is with an aldosterone antagonist because hyperaldosteronism is a major factor in their sodium retention. Starting with spironolactone 100 mg/day, this may be titrated up to a maximum of 400 mg/day. It takes approximately 48 to 72 hours for the effect of spironolactone to occur unlike the rapid response within hours with loop diuretics. An indication as to whether sodium reabsorption is being blocked in the tubules can be obtained from a spot sodium-to-potassium ratio in the urine. If there is more sodium than potassium being excreted, the spironolactone is probably at an adequate dosage. Some patients develop significant gynecomastia with spironolactone, and in such patients amiloride is an alternative starting at 5 mg/day and titrating up to 25 mg/day.

A loop diuretic such as furosemide may be added to the spironolactone. Furosemide has a quick onset of

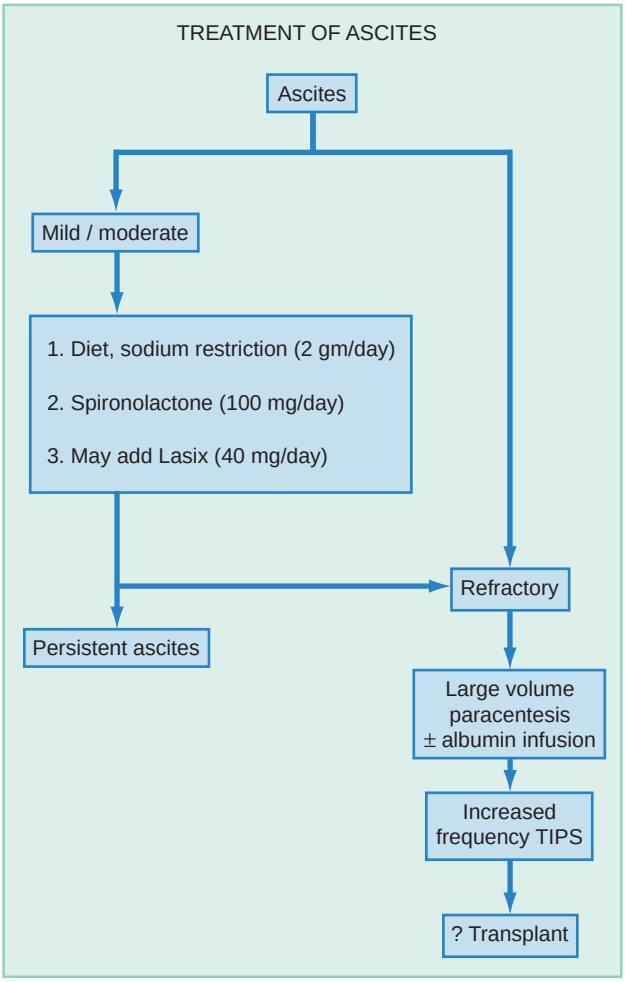

Figure 125–13. Management of ascites. Most patients are managed with diet and diuretics. Refractory ascites portends a poor prognosis and the need for more aggressive therapy. TIPS, transjugular intrahepatic portosystemic shunt.

action (within the first hour of administration) and is given only if the spironolactone is ineffective. Started at 40 mg/day, it may be increased up to 160 mg/day. Although spironolactone retains potassium, furosemide will promote potassium loss. Hence, the use of these in combination is often optimal for patients. Much has been written about the optimal combination of diet and diuretics in managing ascites—this is an art form rather than an exact science.[88]

Refractory ascites is defined as ascites that cannot be mobilized with adequate medical therapy.[90] This term really only applies to approximately 10% of patients who are unresponsive to the regimen discussed earlier. This group of patients are candidates for large-volume paracentesis, TIPS, or transplantation.

Large-volume paracentesis entails removal of 4 to 6 L of ascites at a single sitting.[88] This may or may not be associated with albumin reinfusion.[91,92] The argument for concomitant albumin infusion is that it will minimize the circulatory dysfunction associated with loss of a large volume at the time of paracentesis, but it is expensive. Although most patients have some circulatory dysfunction if they do not receive albumin, this is not considered sufficiently severe in most patients to warrant its use. This remains an ongoing controversy in this field.

The major issue with large-volume paracentesis is the frequency with which it needs to be used. A single large-volume paracentesis, or requirement to do this once a month, may be acceptable management for many patients. However, once large-volume paracentesis is required on a weekly basis, these patients have truly refractory ascites that requires further management.

The use of TIPS for refractory ascites dates from the success of total surgical portosystemic shunts in managing ascites several decades ago.[93] Lowering of intrahepatic sinusoidal pressure to less than 10 mm Hg can now be achieved with the minimally invasive TIPS compared to open surgical side-to-side total shunts. TIPS not only reduces the intrahepatic sinusoidal pressure but also contributes to improvement in the other pathophysiologic abnormalities leading to ascites.[94] The splanchnic hyperdynamic circulation is returned to the systemic circulation leading to a more effective blood volume, better maintained arterial pressure, and improved renal perfusion. Diuresis does not always occur immediately after TIPS placement, but over 1 to 2 weeks the overall improvement in systemic hemodynamics will initiate a natriuresis. Several randomized, controlled trials[95-98] have compared TIPS to repeated large-volume paracentesis and have shown an advantage with TIPS with control of ascites, although there was not a survival advantage in all trials. It is clear that TIPS is not the panacea for all ascites, a major concern being that it will accelerate liver failure and encephalopathy with the portal diversion that occurs with TIPS. Data are conflicting on this, and at the present time TIPS remains widely used for ascites. Long-term follow-up remains important, and recurrence of ascites is usually the first sign of a TIPS stenosis that requires dilation in such patients. Some caution in selecting patients is indicated, and as general guidelines TIPS has been reserved for patients younger than 65 years of age with normal cardiac and renal function, bilirubin less than 6.0, and an INR less than 2.0 and the absence of any evidence of systemic infection or SBP.

Liver transplantation is the only definitive treatment for patients with cirrhosis who develop moderate or refractory ascites. As indicated at the beginning of this section, ascites is an ominous sign for a patient with cirrhosis. Unless easily managed, ascites is a trigger for transplant evaluation. Liver transplant not only replaces the diseased liver but also totally relieves the portal hypertension and reverses the majority of the hemodynamic consequences. The goal is to perform liver transplant on these patients before they have severely impaired renal function, which will limit the options for managing immunosuppression in such patients post-transplantation. Liver transplant is the one therapy that has been clearly shown to have survival benefit in patients with cirrhosis and ascites.

Table 125–2 Pulmonary Syndromes in Liver Disease

Variables	Hepatopulmonary Syndrome	Portopulmonary Hypertension
Prevalence	8-20% of cirrhosis	3-12% of cirrhosis
Pulmonary vascular changes	Vasodilation	Vasoconstriction
Contributing factors	Liver dysfunction, portal hypertension	Portal hypertension
Place of transplant	Curative	Contraindicated

PULMONARY SYNDROMES IN LIVER DISEASE

Lung dysfunction has been recognized in some patients with liver disease for more than a century, but it is only the past 2 decades that two distinct pulmonary vascular disorders have been better understood.[31,32] HPS occurs when there is a pulmonary vascular vasodilation and hypoxemia, whereas portopulmonary hypertension (PPH) occurs when there is pulmonary vasoconstriction and increased pulmonary artery pressure. The major features of these two syndromes are summarized in Table 125–2.

Pathophysiology

Both HPS and PPH occur in the setting of cirrhosis and portal hypertension.[99] The comparative contributions of liver dysfunction and portal hypertension vary with these syndromes. HPS can occur without severe portal hypertension and has also been recognized in some patients with prehepatic and postsinusoidal blocks. PPH can occur when the degree of liver dysfunction is relatively minor in the presence of established portal hypertension.

The mechanisms for development of both disorders remains unclear. Chronic liver disease and its associated systemic hemodynamic changes probably induce changes in the pulmonary vasculature mediated by shear stress, cytokine release, and local endothelin 1 release. Local overproduction of nitric oxide in the pulmonary vasculature appears to contribute to the vasodilation of HPS. Although no clear evidence exists as to the role of cytokines and inflammatory responses in the pulmonary vasculature in PPH, these have been postulated as contributory.

Clinical Presentation

Shortness of breath is the most common presentation for either HPS or PPH.[100-102] Increased dyspnea on standing, cyanosis, and finger clubbing are often present with HPS and should lead to evaluation for this syndrome in patients with cirrhosis. Although patients with PPH may present with dyspnea, they are more likely to be asymptomatic, are not usually cyanotic, and do not develop finger clubbing but may have chest pain and syncopal episodes.

It is important to differentiate these pulmonary syndromes from other causes of dyspnea in patients with cirrhosis. Intrinsic cardiopulmonary diseases such as chronic obstructive pulmonary disease or congestive heart failure are more common than either of these syndromes. Appropriate evaluation of cardiac and other pulmonary causes needs to be made.

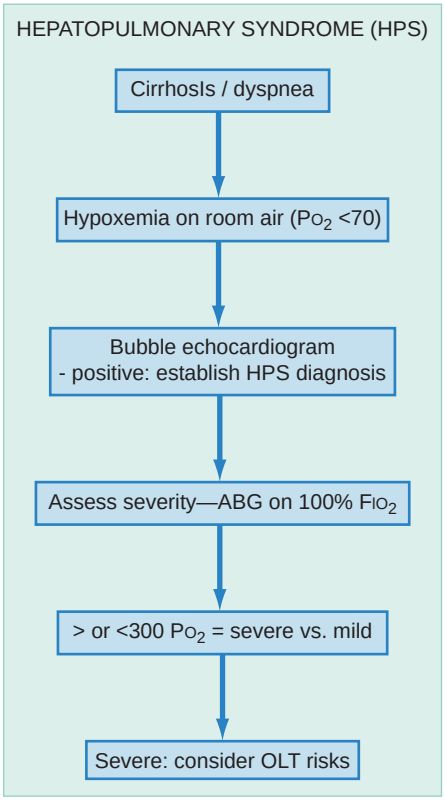

Figure 125–14. Hepatopulmonary syndrome: diagnosis and management. The sequential steps in diagnosis, with their management implications are illustrated. ABG, arterial blood gas; F_{IO_2}, fraction of inspired oxygen; OLT, orthotopic liver transplant; P_{O_2}, partial pressure of oxygen.

Hepatopulmonary Syndrome

Figure 125–14 outlines the diagnostic and management steps for this syndrome. Patients with cirrhosis and shortness of breath in whom pulmonary and cardiac disease causes of dyspnea have been excluded should be considered as potentially having HPS. If a patient is hypoxemic on room air (P_{O_2} <70 mm Hg), the next study should be a bubble-contrast echocardiogram.[103] If this is positive as judged by delayed visualization (occurring

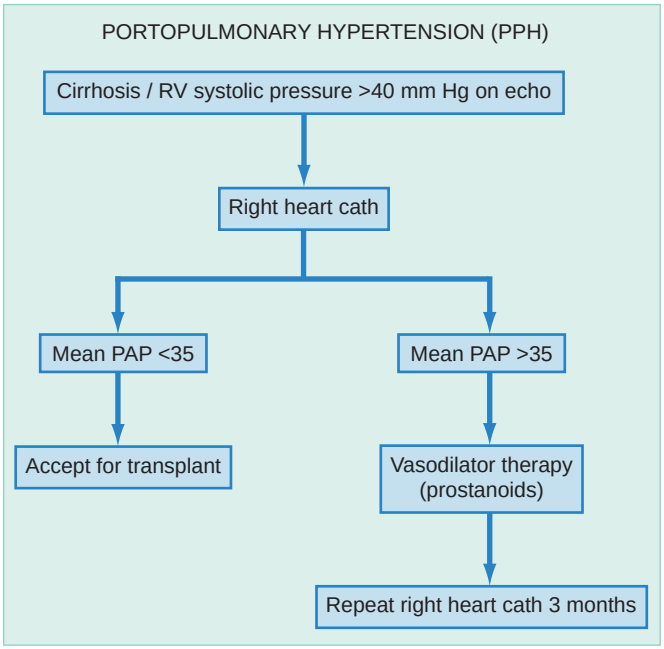

Figure 125–15. Portopulmonary hypertension: diagnosis and management. Evaluation steps and their management implications are defined. cath, catheterization; echo, echocardiogram; PAP, pulmonary artery pressure (measured in mm Hg); RV, right ventricular.

after the third heartbeat) of intravenously administered microbubbles in the left cardiac chamber, the patient has HPS. Evaluation of the severity of the syndrome can be assessed by measuring arterial oxygenation on 100% oxygen inspiration. If the patients have a P_{O_2} higher than 300 mm Hg, they have mild disease, whereas below this level they have severe disease.[104] Patients with HPS require oxygen therapy. Many other pharmacologic therapies have been tried with little effect. The only effective treatment for HPS is liver transplant, which results in resolution of the syndrome over several months. Patients with P_{O_2} less than 50 mm Hg going into liver transplant have poorer survival rates than those with P_{O_2} higher than 50 mm Hg. Currently this syndrome gives patients priority scores on the MELD system for liver transplantation to ensure timely transplant within 3 to 6 months in the United States.[105-107]

Portopulmonary Hypertension

The diagnosis of PPH (Fig. 125–15) requires documentation of elevated pulmonary arterial pressures.[108] Echocardiography is used for screening for elevated right heart pressure,[109] but when the estimate is equal to or greater than 40 mm Hg, direct pulmonary artery pressure measurements should be made with right heart catheterization. At right heart catheterization, a mean pulmonary artery pressure of greater than 25 mm Hg with a capillary wedge pressure less than 15 mm Hg confirms a diagnosis of pulmonary arterial hypertension. Mild degrees of pulmonary artery hypertension up to 35 mm Hg do not preclude liver transplantation in otherwise acceptable candidates, but pressures greater than 35 mm Hg require aggressive evaluation and treatment. At the present time pulmonary artery pressures greater than 50 mm Hg are considered an absolute contraindication to liver transplantation because of the high perioperative mortality.[110] For patients with pulmonary artery pressure greater than 35 mm Hg, prostanoid therapy should be considered, with reassessment of patients after 3 months.[111] Response to this treatment may make such patients candidates for liver transplantation.

The Multidisciplinary Team

The content of this chapter has involved many specialists to take care of the complications of portal hypertension, including the following:

- *Hepatologists* are in the front line for diagnosing and directing the management for many of the clinical presentations.
- *Endoscopists* play an important role diagnostically and in primary therapy for managing variceal bleeding. Endoscopic banding requires significant expertise.
- *Radiologists,* both imaging and interventional, play roles in diagnosis, directed biopsy, and procedural (TIPS) management of these patients.
- *Surgeons* play a major role in liver transplant but should also have a place in shunting good-risk patients with refractory variceal bleeding.
- *Pathologists* with an interest in liver pathology are important in the accurate diagnosis and staging of disease severity.
- *Critical care physicians and anesthesiologists* are vital team members when patients with portal hypertension have "acute events" and in their perioperative management. The different pathophysiology of portal hypertension can be challenging in the ICU and operating room.
- *Nephrologists, cardiologists, and pulmonologists* all play a role in the management of some of these patients, and in major centers it is important to have members of all these specialties "on the team" who understand the pathophysiologic changes of portal hypertension.

Finally, who coordinates? In a complex multidisciplinary team such as described, it is frequently the nurse clinicians or "coordinators" who help bring these specialists together. Undoubtedly it is the coordinators that patients turn to for help in navigating their way through management in this complex field.

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Part

4

Spleen

Chapter

126

Anatomy and Physiology of the Spleen

Ernesto P. Molmenti · Donald O. Christensen · Hugo V. Villar

The spleen has been associated throughout history with melancholy, laughter, discomfort, and the inability to attain optimal athletic capacity.[1] Hippocrates described the anatomy of the spleen in 421 BC. Approximately 600 years later, Galen called it an "organ of mystery" and believed that it extracted "melancholy" from blood and liver, purified it, and released it via the splenogastric vessels into the stomach. During the 17th and 18th centuries, Malpighi, Glisson, Harvey, and Morton further described the structure of the spleen. The spleen was associated with the lymphatic system by Hewson in 1777, in 1846 Virchow demonstrated that the Malpighian follicles were involved in the formation of white cells, and Ponchif in 1885 recognized that the spleen was involved in the removal of red blood cells. Quittenbaum is credited with the first removal of a spleen in 1826, although the rationale for performing it remains unclear.[2] Pean, in 1865, performed a successful splenectomy in a patient with a splenic cyst,[1] and Spencer Wells in 1887 successfully removed the spleen from a young woman with hereditary spherocytosis, achieving life-long remission of the disease. By 1921, as stated by Lord Moynihan, splenectomy was considered to be of value for hematologic diseases such as "leukaemia, pernicious anaemia, Hodgkin's disease, splenic anaemia (Banti's disease), haemolytic jaundice, Gaucher's diseases, and polycythaemia."[2]

The two main functions of the spleen are phagocytosis and the development of both humoral and cellular immunity.[3] However, the spleen is also associated with multiple nonimmunologic functions. Such functions include being the differentiation site for platelets, reticulocytes, and monocytes; the reservoir for granulocytes and erythrocytes; and the removal site for aged and deformed red blood cells.[3]

The spleen is the largest reticuloendothelial organ.[4] It consists of vascular and lymphoid tissue derived from the primitive mesoderm and is surrounded by a thin capsule. Although present in other mammals, smooth muscle cells are not a feature of the human splenic capsule.[1,4] The spleen lies underneath the 9th, 10th, and 11th ribs on the left, measures 7 to 11 cm in length, and weighs an average of 150 g, although normal weights range from 80 to 300 g. Its weight decreases with advancing age.[1,4,5] It becomes palpable underneath the left costal margin in instances where its size is at least double the normal.[1,4] The spleen receives at least 5% of the cardiac output[6] and contains 20 to 40 ml of blood.[7] Approximately 20% of the population has one or more accessory spleens, usually located within the hilar region. The incidence of accessory spleens may be as high as 30% in individuals with hematologic pathologies.[4] The spleen is covered by a fibrous capsule. Trabeculae arising from the inner aspect of the capsule divide the spleen into communicating

compartments.[3] Surrounding the arteries within the splenic parenchyma is a central area known as the *white pulp*. The larger surrounding area is known as the *red pulp*. In between red and white pulp is the marginal zone, which contains lymphatics and macrophages.[1] Externally, it is enveloped almost entirely by peritoneum, which is adherent to the splenic capsule and forms several ligaments to surrounding structures.[5] These ligaments develop collateral vessels in cases of portal hypertension.[4] Transection of these ligaments is necessary when mobilizing the spleen. The tail of the pancreas lies within 1 cm of the splenic hilum in more than 70% of cases and is in direct contact with the spleen in 30% of instances.[1,4]

EMBRYOLOGY

The splenic primordium appears during the 5th week of development as a mesodermal proliferation between the two leaves of the dorsal mesogastrium. As the stomach rotates around an anteroposterior axis, with its caudal portion moving upward and to the right and its cephalic portion moving downward and to the left, a portion of the dorsal mesogastrium eventually fuses with the peritoneum of the posterior abdominal wall. The spleen remains intraperitoneal and is connected to the kidney by the lienorenal (splenorenal) ligament and to the stomach by the gastrolienal (gastrosplenic) ligament (Fig. 126–1).[8] The splenic primordium is eventually infiltrated by lymphoid cells. Hematopoiesis is prominent in the spleen from the 3rd to the 5th months of embryonic life. By the 4th month, the red pulp structure begins to appear.[9]

BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION

The spleen receives its arterial supply from the splenic artery, the largest of the three branches of the celiac trunk. Accessory supply is from the left gastroepiploic artery.[1,5] The splenic artery lies posterior to the superior border of the body of the pancreas, forming multiple coils, and eventually divides into two or three main branches that penetrate through the hilum of the spleen (Fig. 126–2). These branches in turn divide into segmental arteries that enter along the splenic trabeculae (Fig. 126–3). There is little collateral circulation at this level, and occlusion of one of these arteries usually is associated with infarction of the corresponding region of the spleen. Segmental arteries give rise to trabecular arteries, which in turn and by means of perpendicular branches give origin to central arteries.[1,5] Veins leave the spleen via fibrous bands, or trabeculae, attached to the capsule, and coalesce to form the splenic vein. This vein, in turn, joins the superior mesenteric vein behind the neck of the pancreas to give origin to the portal vein (see Fig. 126–2). Two types of circulation have been described. The *fast flow,* which accounts for about 10% of blood flow and has a predominance of plasma, returns blood rapidly to the veins. The *slow flow,* with a predominance of erythrocytes, makes up 90% of the splenic circulation and leads to a filtration process within the fenestrated red pulp network.[1]

Lymphatic drainage follows the vasculature. Drainage is into the hilar and celiac nodes.[1,5]

The splenic nervous plexus is formed by branches of the celiac plexus, left celiac ganglion, and right vagus. It runs together with the splenic artery and is composed mainly of sympathetic fibers that reach blood vessels and nonstriated muscle of the capsule and trabeculae. Sympathetic activity seems to be associated with an increase in the "fast" circulation of the spleen. Referred pain from the spleen is frequently localized in the central epigastrium.[5]

FUNCTIONS OF THE SPLEEN

The spleen has an acidotic, hypoxic, and hypoglycemic environment and performs several erythrocyte-associated functions. Culling, or the destruction of ery-

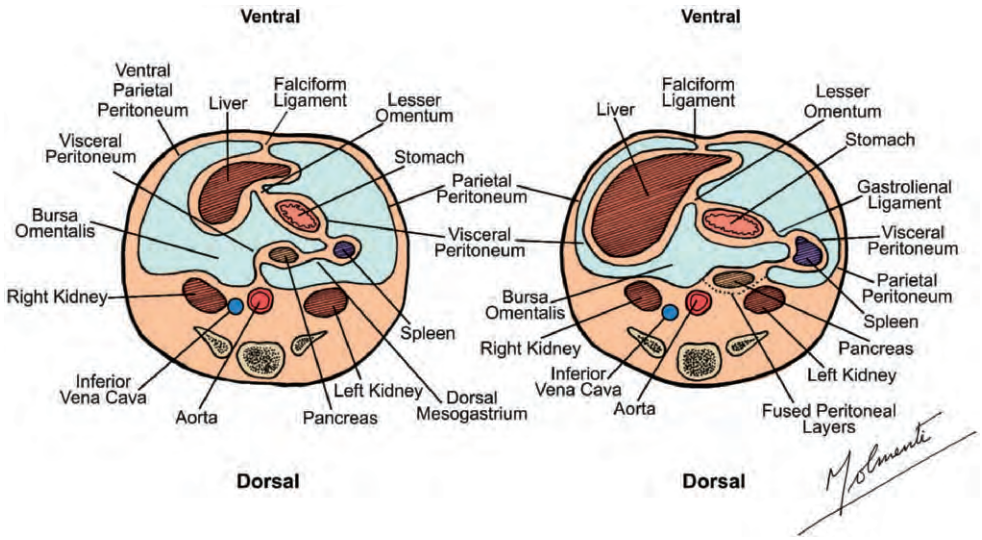


Figure 126–1. Transverse schematic sections through the region of the stomach, liver, and spleen during embryologic development. It is possible to visualize the lesser peritoneal sac, the rotation of the stomach, and the positioning of the spleen and tail of the pancreas between the two leaves of the dorsal mesogastrium. The pancreas eventually assumes a secondary retroperitoneal position.

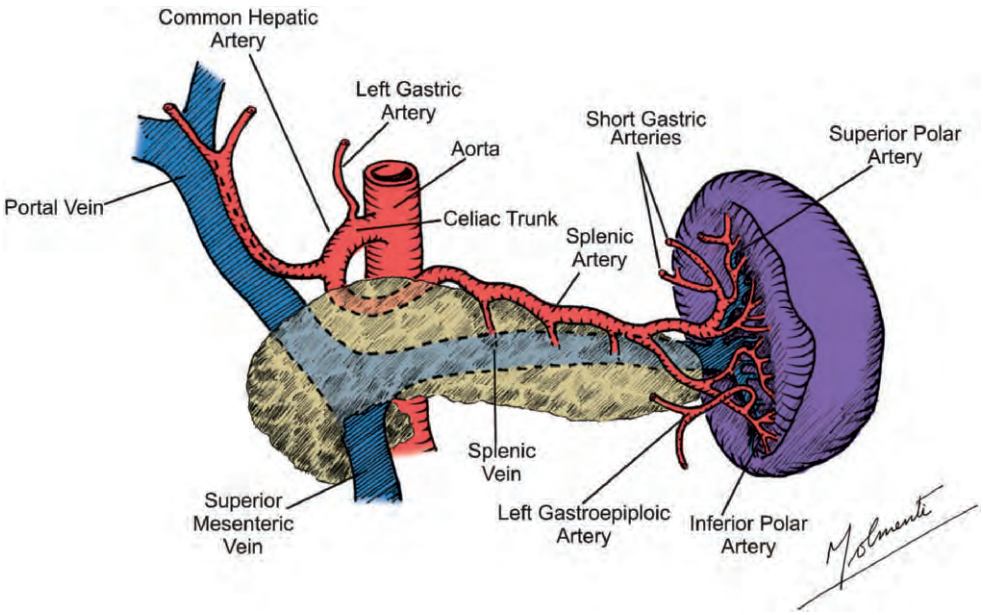


Figure 126–2. Arterial and venous supply of the spleen.

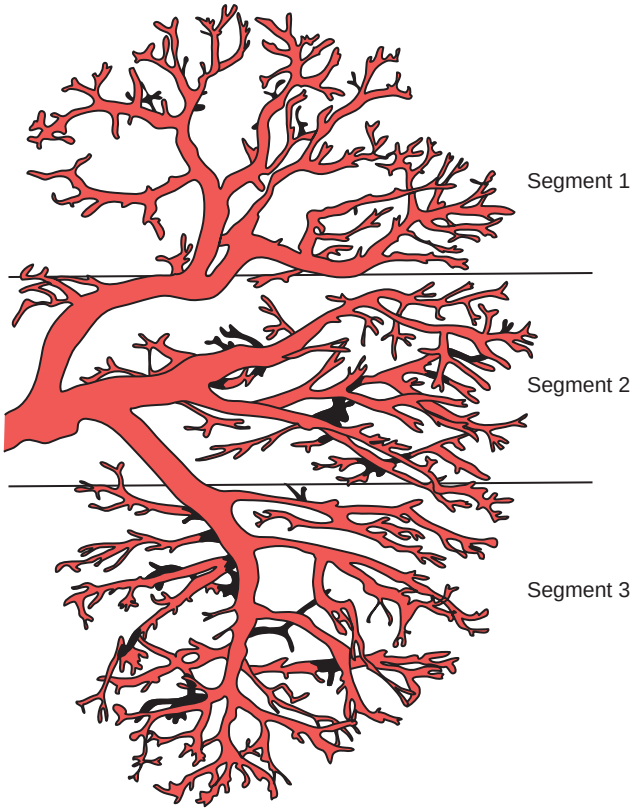


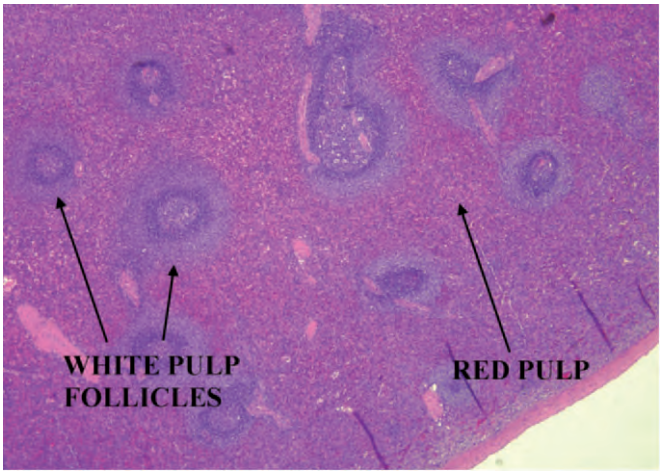
Figure 126–3. Segmental splenic arterial supply showing a division into three distinct segments. (From Morgenstern L: Splenic repair and partial splenectomy. In Nyhus LM, Baker RJ [eds]: Mastery of Surgery, 2nd ed, Vol 2. Boston, Little, Brown, 1992, p 1103.)

throcytes, is one of them. Another is pitting, or the removal, of erythrocytic inclusions. Platelets and leukocytes are not usually removed in the spleen. The spleen has a major role in the recognition of antigens, in the production of antibodies, and in the removal from the bloodstream of particles coated with antibodies. Under nonpathologic conditions, hematopoiesis is not encountered in the adult spleen.[7]

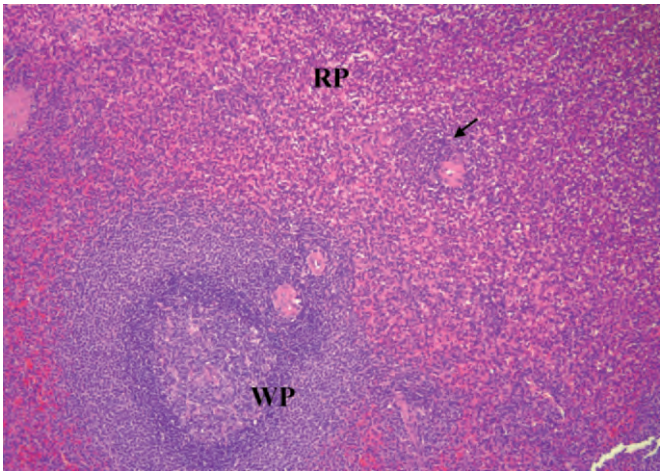
NORMAL BASIC HISTOLOGY AND IMMUNOPHENOTYPE OF THE SPLEEN

The human spleen is composed of red and white pulp (Fig. 126–4). The red pulp makes up approximately 75% of the spleen and is predominantly composed of splenic cords, capillaries, and venous sinuses, which express endothelial markers (e.g., clotting factor VIII), within loose reticular tissue. This richly vascular, specialized portion of the spleen enables it to function as a filter of blood. The white pulp, including the lymphoid follicles (mostly B lymphocytes) and the periarterial lymphoid sheath (PALS) (mostly T lymphocytes), along with the lymphoid, nonfiltering red pulp (both B and T lymphocytes), are responsible for the spleen's immunologic function. Although comprising only a minority of the overall mass, this lymphoid compartment plays an important role in the early immunologic response against blood-borne antigens and is the compartment primarily responsible for splenic involvement with lymphoproliferative disorders.[10-13]

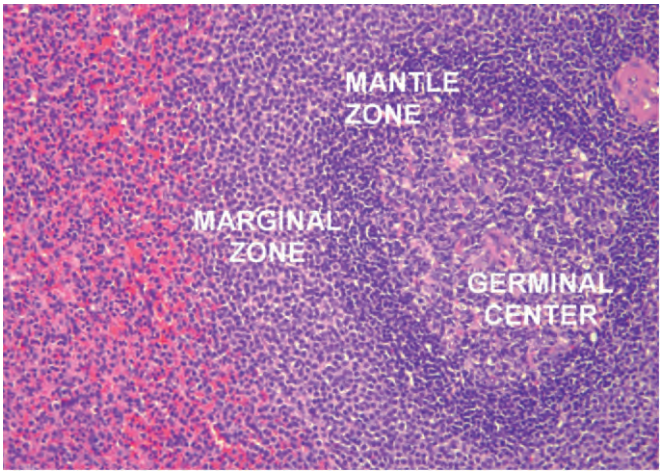
The primary follicle and secondary follicle mantle zone comprise "naïve" (nonimmunologically challenged) B lymphocytes that have small, round nuclei with condensed chromatin, inconspicuous nucleoli, and scant cytoplasm. These lymphocytes characteristically have the



A



B



C

Figure 126–4. Normal human spleen on hematoxylin-eosin staining. **A,** Low-power photomicrograph showing relationship and relative proportions of red and white pulp. **B,** Medium-power photomicrograph (*arrow* indicates periarterial lymphoid sheath). RP, red pulp; WP, white pulp (secondary follicle). **C,** High-power photomicrograph showing detailed secondary follicle architecture.

following immunophenotype (Table 126–1): surface immune globulin (sIg) positive, both sIgD and sIgM; CD5 positive; positive for pan B-cell antigens (CD19, CD20, and CD79a); CD23 positive; BCL2 positive; and BCL6 negative. These mantle zone cells undergo blast transformation and migrate to the germinal center, forming a secondary follicle. Centroblasts are large cells with vesicular nuclei, often multiple, prominent, peripheral nucleoli, with a narrow rim of basophilic cytoplasm. Changes in the immunophenotype of these cells include switching on BCL6 expression and switching off BCL2 expression. Centroblasts express CD10 and pan B-cell antigens and lack expression of sIg. Centroblasts mature into centrocytes (cleaved follicular center cells) within the germinal center. Centrocytes are medium-sized lymphocytes with irregular nuclei, inconspicuous nucleoli, and scant cytoplasm. As part of the germinal center reaction, the immune globulin variable region *(IGVR)* gene and the *BCL6* gene undergo somatic mutations. The resulting centrocytes re-express sIg, which has altered antigen affinity. Decreased affinity results in apoptosis while increased affinity results in "rescue" of the cell by antigen-mediated binding to the follicular dendritic cell processes. The rescued centrocytes re-express *BCL2*. Centrocytes switch off *BCL6* expression and mature into memory B cells, which then migrate to the marginal zone. Memory B cells (marginal zone B cells) have round to slightly irregular nuclei and a moderate amount of cytoplasm. These cells characteristically express sIgM (but not sIgD), lack CD5 and CD10, and express the pan-B cell antigens. The lymphoid follicles contain a small number of scattered CD3-positive T lymphocytes, which are predominantly CD4-positive T-helper cells.[10-13]

Peripheral to the marginal zone and abutting the red pulp is the perifollicular zone, made up of reticular tissue, capillaries, red blood cells, and leukocytes. Within this perifollicular zone, as well as within the red pulp surrounded by its own perifollicular zone, are PALSs. PALSs are composed of antigen-presenting cells and small polymorphic CD3-positive T lymphocytes (of both subsets—CD4 and CD8—with T-helper cells predominating). The lymphoid, nonfiltering red pulp contains a mixture of mature B and T lymphocytes, with a T-cell predominance. As in the PALS and peripheral blood, the CD4-positive T-helper cells outnumber the CD8-positive T cells.[10-13]

Understanding the normal lymphoid morphology and immunophenotypic distribution (see Table 126–1) within the spleen is important when discriminating between normal and pathologic states (Fig. 126–5). For example, the spleen is a frequent site of involvement with mature B-cell neoplasms—clonal proliferations of B cells, which, to some extent, reflect the stages of physiologic B-cell maturation. Classification of these neoplasms is based, in part, on this relationship between normal physiology and its neoplastic counterparts. Characterizing the departure from the physiologic state (by means of histologic, immunohistochemical, flow cytometric, cytogenetic, polymerase chain reaction, and/or fluorescent in situ hybridization analysis) can confirm the process as pathologic, demonstrate genotypic and phenotypic alterations, and identify the cell from which the

Table 126–1 Significant Cluster Designations (CD Markers) and Other Antigens: Description of Function and Clarification of Cell Type Typically Expressing the Antigen

Cluster Designation	Function	Physiologic Staining
CD3	Antigen recognition	Thymocytes, peripheral T cells, NK cells
CD4	T-cell activation	Thymocytes, mature T cells (~65%, T-helper subset), macrophages, Langerhans cells, dendritic cells, granulocytes
CD5	Signal transducer	B cells of mantle zone of spleen and lymph nodes, almost all T cells
CD8	Increases avidity of cell-to-cell interactions	Mature T cells (~35% of peripheral T cells, most cytotoxic T cells), NK cells, cortical thymocytes (70-80%)
CD10	Inactivates bioactive peptides	Pre-B cells, cortical thymocytes; follicular center cells; granulocytes; lymphohematopoietic precursors; neutrophils
CD19	Regulates B-cell development, activation, differentiation	Pre-B cells, B cells, first B-cell antigen after HLA-DR, follicular dendritic cells
CD20	Early activation of B cells	Most B cells (after CD19 and CD10 expression, before CD21/22 expression and surface immunoglobulin expression), retained on mature B cells until plasma cell development, follicular dendritic cells
CD23	Regulates IgE synthesis; B-cell growth factor	Activated mature B cells expressing IgM or IgD, monocytes/macrophages, T-cell subsets, platelets, eosinophils, Langerhans cells, follicular dendritic cells
CD45	T- and B-cell antigen receptor–mediated activation	All hematopoietic cells; stronger in lymphocytes (10% of surface area)
CD79a	Encodes Ig proteins	Early in B-cell differentiation (often positive when mature B-cell markers are negative), plasma cells
BCL2	Induces apoptosis	Mantle zone B cells, germinal center centrocytes
BCL6	Regulates transcription	Germinal center centroblasts and centrocytes

tumor originated. This information has significant implications regarding the expected course of the disease, available treatments, and overall prognosis. Similarly, as the spleen receives a significant percentage of the total cardiac output, it is not an uncommon site for hematogenously spread metastatic carcinoma. Such neoplasms differ not only in cytologic morphology from both normal and lymphomatous spleen but have reliably distinctive immunohistochemical staining patterns. Specifically, a splenic nodule from a patient with occult primary neoplasm, which stains positive for cytokeratin and negative for leukocyte common antigen (CD45) should be considered non-native splenic tissue—confirming metastatic disease. A more extensive immunohistochemical work-up could then be performed in an effort to determine the site of origin.[10-13]

SPLENIC CIRCULATION

There is an ongoing and still unresolved debate regarding whether the spleen has an open or a closed circulation (Fig. 126–6). The closed circulation concept entails continuity of the endothelium from arteries to sinuses. The open circulation theory proposes that blood empties into the marginal zone and red pulp cords, travels through the cavernous spaces, and finally re-enters the vasculature through interendothelial slits.[3]

PERIPHERAL BLOOD SMEAR AND SPLENIC FUNCTION

The peripheral blood smear is a very useful way to evaluate splenic function. The presence of Howell-Jolly bodies, or nuclear remnants removed by the spleen, indicates hyposplenism. The exception is in infants, who commonly have them. Pappenheimer bodies, or siderotic particles removed by the spleen, are also seen in cases of hyposplenism, especially in those associated with hemolysis. The presence of acanthocytes and target cells represents lack of membrane polishing by the spleen. The number of pitted cells is inversely proportional to splenic function. Pits represent vesicles containing hemoglobin, ferritin, and mitochondrial remnants. Under normal circumstances, there are less than 2% pitted cells. The number of platelets and granulocytes is increased in asplenia.[7]

IMAGING TECHNIQUES

A liver-spleen scan uses intravenous ^{99m}Tc–sulfur colloid that is taken up by macrophages at these two sites. Ultrasonography is a non-invasive, rapid, and cost-effective way that can assess splenic anatomy without imparting any radiation. Duplex ultrasonography allows for the

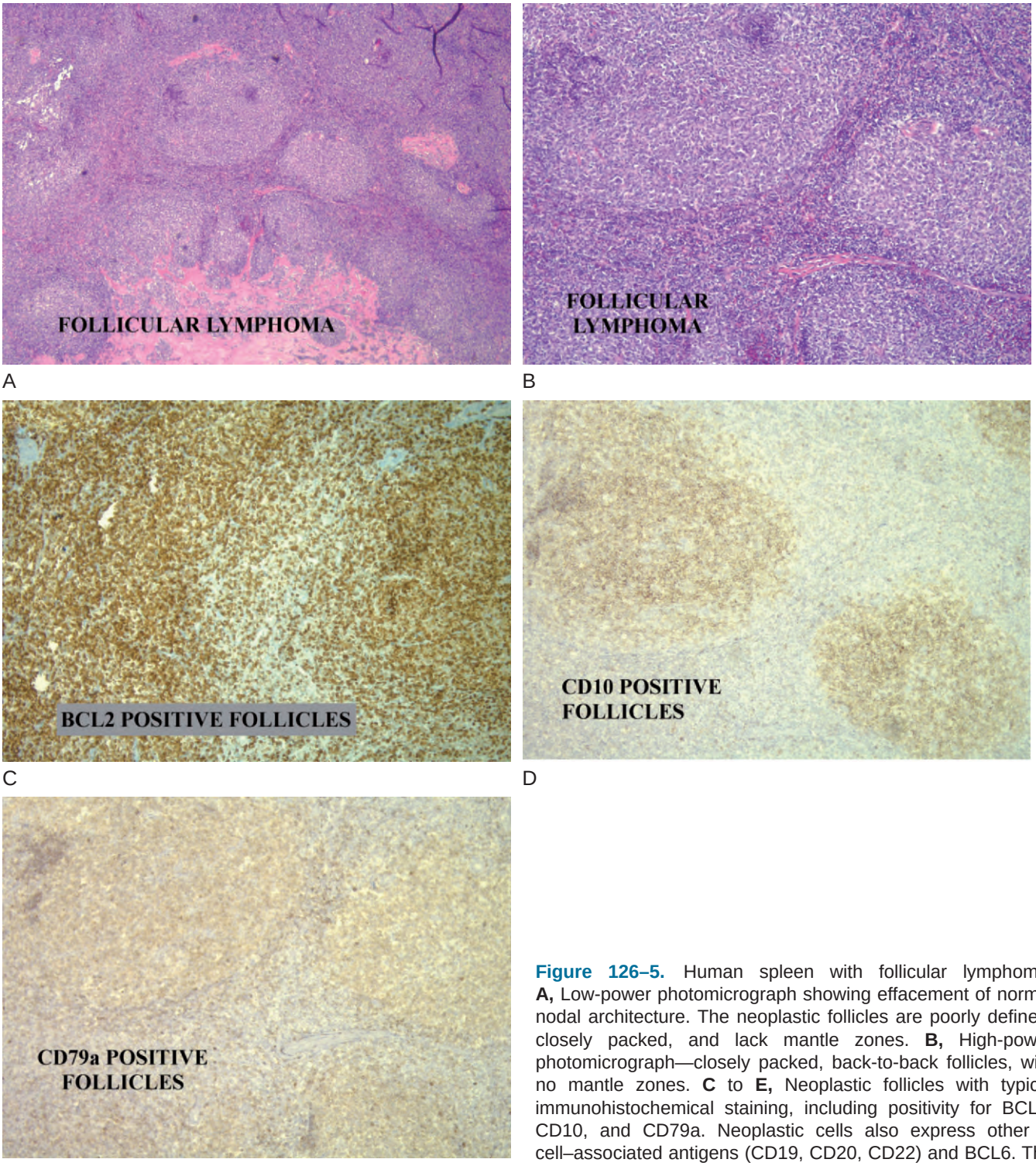


Figure 126–5. Human spleen with follicular lymphoma. **A,** Low-power photomicrograph showing effacement of normal nodal architecture. The neoplastic follicles are poorly defined, closely packed, and lack mantle zones. **B,** High-power photomicrograph—closely packed, back-to-back follicles, with no mantle zones. **C** to **E,** Neoplastic follicles with typical immunohistochemical staining, including positivity for BCL2, CD10, and CD79a. Neoplastic cells also express other B cell–associated antigens (CD19, CD20, CD22) and BCL6. The tumor cells are usually CD5 and CD43 negative.

assessment of vascular flow. Computed tomographic (CT) scanning demonstrates anatomy, volume, lesions, and some aspects of splenic function. Magnetic resonance imaging may avoid the need for angiograms, has no associated radiation, and is useful in some infections such as candidiasis.[7]

PATHOLOGIC FINDINGS

Congenital asplenia may occur in an isolated fashion or in conjunction with severe congenital cardiac disease. Administration of polysaccharide vaccine and early prescription of antibiotics is recommended in these indi-

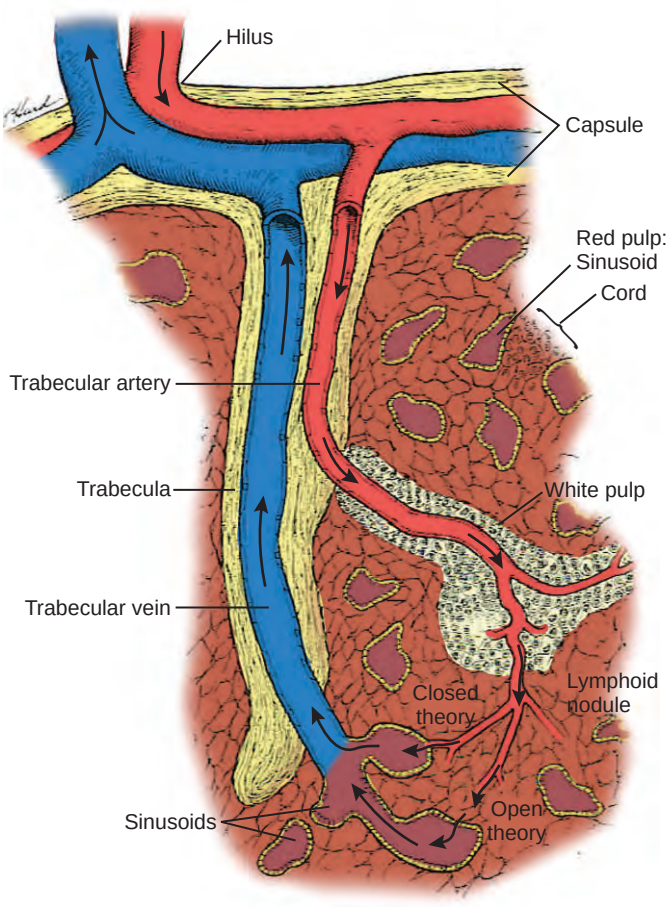


Figure 126–6. Structure of the sinusal spleen. (From the Microcirculatory Society Eugene M. Landis Award Lecture—Microcirculature of the Spleen: New Concepts, New Challenges. Microvasc Res 34:270, 1987.)

viduals to prevent an overwhelming sepsis.[7] Polysplenia is also associated with congenital defects, both of vascular and nonvascular nature. It has not been shown to be associated with an increased risk of infection.[7] In sickle cell disease, the hypoxic, hypoglycemic, and acidotic environment of the spleen is associated with erythrocyte sickling. This in turn leads to blockage of splenic blood vessels and subsequent splenic infarcts. In cases of splenic sequestration, there is massive pooling of blood secondary to occlusion of the venous drainage. In such potentially life-threatening cases, splenectomy is recommended.[7] *Hypersplenism* is a term used to define the nonimmune destruction of formed blood elements by an enlarged spleen, with or without the presence of portal hypertension. Splenectomy corrects the low cell counts in such cases.[7] Splenic hypertrophy leads to pooling of blood and the premature destruction of cells by splenic macrophages.[7] Hyposplenism associated with decreased phagocytic function and increased risk of infections is seen in rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, sarcoidosis, celiac disease, ulcerative colitis, amyloidosis, mastocytosis, combined immunodeficiency, and chronic graft-versus-host disease.[7] Radiation therapy affects splenic function. Although phagocytic cells are not usually affected by irradiation, lymphoid cells are. Corticosteroid therapy impairs the function of splenic macrophages. Intravenous IgG is also known to impair splenic function.[7] Splenomegaly of anatomic origin is rare and may be due to cysts, pseudocysts, hamartomas, hemangiomas, and peliosis. In most cases, however, splenomegaly represents the manifestation of an underlying pathology that should be diagnosed.[7]

SPLENECTOMY

The indications for splenectomy are usually clinical. The decision to proceed with this intervention should be based on specific clinical indices and parameters. Pathologies that benefit from splenectomy include some instances of trauma, idiopathic thrombocytopenic purpura, hemolytic anemias due to intrinsic erythrocyte membrane or enzyme disorders (pyruvate kinase deficiency, hereditary spherocytosis), and chronic conditions such as those seen in storage diseases (Gaucher's disease).[7] Other indications for splenectomy include left-sided (sinistral) portal hypertension.

Laparoscopic splenectomy is considered the technique of choice in cases of intractable benign hematologic disorders. Although its efficacy, morbidity, and mortality rates are comparable to those of open splenectomy, parameters such as return of intestinal function and length of stay are significantly shorter.[14,15] Its popularity is especially associated with diseases such as idiopathic thrombocytopenic purpura, hereditary spherocytosis, autoimmune hemolytic anemia, and thrombotic thrombocytopenic purpura. A series reported significant resolution of thrombocytopenia in more than 80% of patients with idiopathic thrombocytopenic purpura, improvement in hematocrit levels in 70% of patients with chronic hemolytic anemia, and a positive response in more than 90% of patients with hereditary spherocytosis.[14] Elective laparoscopic splenectomy was found to have a greater incidence of postoperative thrombosis of the portal venous system than the open technique. In such instances, diagnosis was established by contrast-enhanced CT scanning and successful treatment achieved with anticoagulation therapy.[16] Although laparoscopic splenectomy is also effective in cases of giant spleens, its usefulness has been questioned as a result of the greater morbidity rates reported in such cases.[17]

Leukocytosis is usually observed after splenectomy and may last up to a few months. It is characterized by a preponderance of granulocytes. Thrombocytosis is also encountered in most patients but is rarely associated with thrombotic events.[6] Extramedullary hematopoiesis, found in pathologies such as malignant osteoporosis in children and myelofibrosis in adults, constitutes a relative contraindication to splenectomy. In such cases, it should be determined that the patient is not dependent on splenic hematopoiesis.[7] Complications associated with splenectomy include splenic rupture, hemorrhage, postsplenectomy septicemia, subphrenic abscesses, necrosis

of the fundus of the stomach, injury to the tail of the pancreas, and atherosclerotic heart disease. The presence of remnant accessory spleens in instances of splenectomy for hematologic disorders may be associated with relapse of the underlying disease.[6] Splenosis, or the regeneration of miniscule splenic remnants in the peritoneal cavity, may be encountered in cases of traumatic rupture where splenic tissue disseminates throughout the peritoneal cavity. Its protective effect against sepsis in humans is still unclear.[7] Intraoperative diagnosis is by means of frozen section.

OVERWHELMING POSTSPLENECTOMY INFECTION

Overwhelming postsplenectomy infection (OPSI) is a life-threatening potential complication seen in asplenic individuals that gained significant acceptance in 1953 after an observation by King and Shumacker.[18] OPSI is encountered with greatest frequency within 2 years after splenectomy, in the very young, in patients with other medical complications, and in those with malignancies.[18] The risk of postsplenectomy sepsis increases according to the indications for splenectomy. Trauma, hematologic disorders, portal hypertension, Hodgkin's disease, sickle cell disease, and thalassemia represent increasing cumulative indices of sepsis, ranging from 1.5% to 25%, respectively.[7] OPSI occurs mostly in association with encapsulated organisms that require opsonization for effective phagocytosis. The most frequent such pathogens are *Neisseria meningitides, Hemophilus influenzae* type b, and *Streptococcus pneumoniae*. There are effective vaccines against all of them, and it is recommended that they be administered 3 weeks prior to splenectomy to allow for a more effective immune response.[7] Focal infections such as meningitis are more frequent in children younger than 5 years of age.[18] OPSI usually follows a rapid course, evolving into sepsis and disseminated intravascular coagulation; 80% of deaths occur within the first 48 hours. Asplenic patients who develop fever should be immediately evaluated and promptly treated with broad-spectrum intravenous antibiotics.[18]

MASSIVE SPLENOMEGALY

Massively enlarged spleens constitute a special challenge because of their size and risk of bleeding or fracture at the time of splenectomy. A generous midline incision rather than a transverse one is preferable to allow for the pivoting of the inferior pole of the spleen and the subsequent ligation and division of the enlarged and usually lengthened short gastric vessels. Opening the gastrocolic omentum allows access to the splenic artery that is subsequently ligated in continuity. The artery is approached with greater ease halfway along the superior pancreatic border. Although this maneuver will not diminish significantly the size of the spleen, it will make it softer and easier to handle and will diminish blood loss in cases of splenic fractures or tears associated with mobilization. The upper two or three short gastric vessels are hard to reach because the massive spleen blocks the view and may be safely divided after the spleen is exteriorized and the hilum divided. Division of the attachments to the colon may also facilitate safer mobilization. Division of the phrenosplenic ligament allows safe exteriorization of massively enlarged spleens and ligation under full view of the splenic artery and vein. Often the spleen is wrapping the tail of the pancreas, and "carving" the vessels into the spleen will avoid damage to the tail of the pancreas. Because of the significant weight of the spleen while still attached to the hilum, caution should be exercised to prevent the splenic vessels from tearing by unexpected traction or tilting of the spleen. Seroserosal invagination of the greater curvature of the stomach where the short gastric vessels were tied is a good way to prevent a tie from coming off and causing postoperative hemorrhage, as well as to minimize the chances of gastric necrosis and fistulas from ties placed too close to the stomach. In cases where platelet counts are below 10,000 to 50,000/μl and replacement is desired, platelet transfusions are usually given after ligation of the splenic artery.

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Chapter

127

Minimally Invasive Surgical and Image-Guided Interventional Approaches to the Spleen

Michael R. Marohn · Kimberley E. Steele · L. P. Lawler

Surgeons caring for disorders of the spleen need to be familiar with traditional "open" surgical approaches to managing splenic problems. Contemporary surgeons also need to be familiar with minimally invasive surgical and image-guided interventional approaches to splenic problems, which form the focus of this chapter's two sections.

Minimally invasive surgical approaches to the spleen were first described during the rapid expansion of laparoscopic surgery in the early 1990s. Laparoscopic splenectomy has become the procedure of choice for patients requiring elective splenectomy for spleens of normal size. Because the spleen is a fragile solid organ situated close to the colon, stomach, pancreas, and kidney, with a rich blood supply, it poses special challenges for minimally invasive surgery. As improvements in laparoscopic techniques and instrumentation evolve, even more challenging cases have become amenable to a minimally invasive surgical approach. Our section on laparoscopic splenectomy describes current indications; patient selection criteria; preoperative preparation; vaccination; operative techniques, including pitfalls and their avoidance; postoperative complications; and discussion of the pros and cons of emerging approaches to larger spleens, including preoperative embolization and the use of hand-assisted devices.

Minimally invasive vascular interventional techniques to the spleen were popularized in the 1970s and 1980s and have played an increasing role in algorithms for managing splenic problems, in parallel with the shift toward preservation of functioning splenic tissue through nonoperative management. Our section on imaged-guided interventions involving the spleen reviews techniques that should be part of the surgeon and imaged-guided interventionalist partnership tools for clinical applications, including splenic trauma, splenic artery pseudoaneurysm, hypersplenism, and drainage of splenic collections.

LAPAROSCOPIC SPLENECTOMY

First described by Delaitre and Maignien in 1991, laparoscopic splenectomy has become the procedure of choice for patients with normal-sized spleens requiring elective splenectomy. Conversion to "open" splenectomy is reported in less than 10% of cases, with splenomegaly or hemorrhage being the usual cause for conversion. Improvements in laparoscopic techniques and instrumentation have resulted in even more challenging cases becoming accessible to a laparoscopic approach. Potential benefits of a minimally invasive approach include reduced blood loss, better pain control, decreased perioperative morbidity, and shorter hospital length of stay.[1,2]

Indications: Emergency Situations

The most common indication for splenectomy overall is for management of splenic trauma, and the vast majority of these cases are performed through an "open" trauma laparotomy. The major thrust of trauma management of an injured spleen in the past 20 years, however, has been toward preservation of functional splenic tissue through nonoperative management.

The safety and efficacy of laparoscopic splenectomy is well established for benign hematologic disorders, but reports of laparoscopy for managing an injured spleen

remain uncommon, with the indications being very selective and limited and most trauma surgeons considering the minimally invasive approach contraindicated.[3] Individual cases and limited series using selective laparoscopic approaches for isolated abdominal trauma in patients with splenic injury and stable vital signs have been reported. Laparoscopy has been used to confirm the diagnosis of splenic injury, determine the degree of spleen injury, determine the need for splenectomy that may be performed laparoscopically, and selectively apply spleen-preserving techniques, including the application of electrocautery, fibrin, Gelfoam, suture repair, or the use of a hand-assisted device for early-grade splenic injuries.[4-6] No prospective randomized trials have compared selective laparoscopic approaches to splenic trauma with nonoperative management, thus making the benefit of this approach unclear. Laparoscopic surgery may, however, prove to be a safe and feasible alternative to traditional surgical approaches.

We do not advocate laparoscopy as standard of care for splenic trauma. Further experience is needed to define selection criteria for laparoscopy in trauma patients with splenic injury, just as criteria were developed for nonoperative management.[7]

Indications: Elective Situations

In the elective setting, the indications for laparoscopic splenectomy are similar to those for the "open" procedure, typically for hematologic disorders. In cases requiring splenectomy for a normal-sized spleen, laparoscopic splenectomy has become the standard of care.

The most common indication for elective splenectomy is idiopathic thrombocytopenic purpura (ITP).[8] Other indications include disorders of red blood cells, white blood cells, and platelets and malignancy. Box 127–1 summarizes indications for laparoscopic splenectomy.

Box 127–1 Indications for Laparoscopic Splenectomy

Platelet Disorders

- Idiopathic thrombocytopenic purpura
- Human immunodeficiency virus–related immune-mediated thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Evans' syndrome

Anemias/Red Blood Cell Disorders

- Autoimmune hemolytic anemia
- Hereditary spherocytosis
- Hereditary elliptocytosis
- Hereditary pyropoikilocytosis

White Blood Cell Disorders/Malignancy

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Chronic myeloid leukemia
- Chronic lymphocytic leukemia
- Hairy cell leukemia
- Myelofibrosis
- Primary splenic tumors

Miscellaneous

- Splenic abscess
- Splenic cysts
- Splenic trauma
- Sarcoidosis
- Hypersplenism—Gaucher's disease, Felty's syndrome, systemic lupus erythematosus, splenic vein thrombosis

Contraindications

Physiologic contraindications to laparoscopic splenectomy, as for all surgical procedures, include acute coagulopathic states or an inability to tolerate general anesthesia. Acute hemorrhage limits safe laparoscopic splenectomy, a major reason limiting the role of laparoscopic splenectomy in trauma. Though not an absolute contraindication, patients with portal hypertension should be approached cautiously.

Patient Selection

Spleen size is the most important factor for patient selection in determining whether to proceed with "open" versus laparoscopic splenectomy. When outcome measures of conversion rates, length of stay, and complications were compared in patients with spleens of normal size and those with splenomegaly, with 500 mg being used as a criterion for a large spleen, no statistical differences were observed in outcomes.[9] However, some authors use spleen weight greater than 1000 g as an exclusion criterion for laparoscopy because of conversion rates approaching 0% for small spleens and 60% for spleens weighing more than 1 kg.[10] Other surgeons use 2 kg as a laparoscopic exclusion criterion and cite similar outcome variables of higher conversion rates, greater blood loss, longer hospitalization, and increased morbidity with larger spleens.[11] Weight criteria, however, are difficult to assess preoperatively.

Spleen size based on computed tomography (CT) or ultrasound imaging measurements provides a more useful preoperative selection criterion. As a guideline, spleen size on ultrasound or CT scan should be less than 20 to 25 cm in the craniocaudal axis.[12-14] Larger spleens have been removed laparoscopically, but such procedures are technically challenging, require experience in managing larger spleens, and may necessitate the use of

a hand-assisted device. Spleens measuring greater than 30 cm leave little room for favorable port placement, limit working space, and often require hand-assisted laparoscopic splenectomy (HALS). Moreover, specimen removal may require either an incision comparable to the "open" technique or the use of a morcellation technique, both with their own risks, and specimen morcellation may have an adverse impact on pathologic analysis. Many surgeons believe that the maneuvers required to remove such large spleens do not warrant these procedures. Special considerations regarding laparoscopy for giant spleens are discussed later in this section.

Preoperative Considerations

Imaging

Preoperative ultrasound or CT imaging is critical for operative planning. As outlined earlier, imaging can not only help with patient selection based on spleen size but also can define useful anatomic relationships that can have an impact on the conduct of surgery, such as nestling of the spleen against the stomach, pancreas, colon, and kidney and the rich, variable blood supply of the spleen. A normal spleen measures about 11 cm in length. Moderate splenomegaly, from 11 to 20 cm, should be noted in the preoperative planning. Massive splenomegaly, greater than 20 cm in length, may alter the preoperative strategy. Preoperative imaging may also identify accessory spleens, which are reported in 10% to 29% of patients.

Though not routinely used with a normal-sized spleen, preoperative splenic artery embolization can be performed in patients with massive splenomegaly to reduce blood loss, reduce the conversion rate, and make laparoscopic splenectomy more manageable. Angiographically guided coil embolization of the proximal splenic artery limits blood flow to the hilum and, in experienced hands, can be a safe and effective way to limit blood loss when preparing for surgery on a giant spleen. If splenic artery embolization is performed, it should be done distal to the great pancreatic artery. This technique is discussed in our image-guided interventional section.

General Considerations

A broad-spectrum antibiotic covering skin flora should be administered approximately 30 minutes before skin incisions. Postoperative antibiotic prophylaxis is discussed later.

Patients being treated by splenectomy for a hematologic disorder should undergo the same preparation that they would for "open" splenectomy, which may include the administration of steroids, globulin, fresh frozen plasma, cryoprecipitate, or platelets. Blood products should be available intraoperatively, especially platelets for intraoperative transfusion in patients with severe thrombocytopenia. In such patients, prophylactic platelet transfusions are typically given only for platelet counts below 50,000 and are typically administered only after the splenic artery has been ligated.[12]

All patients require protection against deep venous thrombosis. We favor knee-high TED hose, sequential compression devices, and if tolerated, preoperative and postoperative heparin prophylaxis according to established national guidelines.

Recommendations regarding bowel preparation for splenectomy remain variable. We favor mechanical bowel preparation the day before surgery or, at a minimum, a cleansing enema the night or morning before surgery to clear the left colon of stool bulk, with the objectives of both improving the ease of intraoperative mobilization of the splenic flexure of the colon and avoiding postoperative constipation.

Immunizations Against Overwhelming Post-Splenectomy Sepsis

Patients who have undergone splenectomy are at increased lifetime risk for overwhelming post-splenectomy infection (OPSI), reported by most experts as occurring in 3% to 5% of patients. The annual incidence of OPSI is reported to be between 0.23% and 0.42%. Risk is highest in three groups:

1. Patients at the extremes of age
2. Immunocompromised patients
3. Those in whom splenectomy was preformed for a hematologic disorder

Trauma patients who require splenectomy are among the lowest-risk groups for OPSI. Cases of OPSI are emergencies, can be lethal, and require immediate parenteral antibiotics and intensive care. Intravenous immunoglobulin may play a beneficial role. OPSI carries a mortality rate of 38% to 69%. The mechanism of OPSI is thought to be decreased antigen clearance in post-splenectomy patients and decreased antigen response. *Streptococcus pneumoniae* is the most common infective agent and is recovered in 50% to 90% of isolates from OPSI patients, followed by *Haemophilus influenzae* type b (Hib), *Streptococcus* group B, *Staphylococcus aureus*, and *Escherichia coli* and coliforms. Increased susceptibility to parasites and malaria is noted in endemic areas. The hypothesized increased risk for *Neisseria meningitides* is unclear.[15]

Optimally, patients should be immunized against encapsulated organisms 14 days before surgery. Recommended immunizations include polyvalent pneumococcal, meningococcal, and *Haemophilus* vaccinations.[16] Pneumovax provides protection against 73% of OPSI-causing organisms. Data on revaccination remain unclear, but current consensus favors a Pneumovax booster every 5 to 10 years, which may be protective against all OPSI bacteria. The benefit of Hib/meningococcal/influenza vaccine is unproven, but it is recommended. For patients who do not receive recommended OPSI immunizations before surgery, we immunize patients just before hospital discharge.

Operative Technique

There is wide variation in the technique of laparoscopic splenectomy with respect to approach, patient positioning, port site placement, port size selection,

number of ports, and instrumentation for controlling splenic vessels. The two most common laparoscopic surgical approaches are the anterior and lateral approaches.

Anatomic Considerations

Laparoscopic splenectomy is not a forgiving procedure. Methodical maintenance of hemostasis, both during division and control of the splenic vasculature and as the spleen is mobilized, is key to a successful minimal access approach. The splenic parenchyma is fragile and particularly vulnerable to capsular tears and procedure-limiting bleeding. Understanding the variable splenic anatomy is essential to intraoperative management. Michels' 1942 review of 100 spleens noted that no two spleens have the same anatomy.[17] Michels divided the splenic blood supply into two types, distributed and magistral, with the distributed type being present in 70% of patients. Splenic size does not correlate with the number or distribution of splenic arteries, although the number of splenic notches and tubercles does. Splenic hilar anatomy can include numerous branches with various division levels. In addition, up to six short gastric arteries may be found in the gastrosplenic ligament arising from the fundus of the stomach. The lienorenal ligament contains hilar vessels and the tail of the pancreas. In nearly three quarters of patients, the tail of the pancreas lies within 1 cm of the spleen, and direct contact between the pancreas and spleen is noted in about a third of patients.

Getting Started—Position, Equipment, "Time-Out," and Team Orientation to the Operative Steps

Minimally invasive surgery is a high-tech environment. The surgeon should review the videoendoscopic equipment required before the procedure starts by systematically going through a checklist to ensure that all needed or potentially needed equipment is available, including video towers with high-fidelity cameras, insufflator, high-intensity light source, video capture device, preferred energy sources (harmonic scalpel, LigaSure, etc.), angled telescope (we favor a 45-degree angled telescope; we also favor having a 5-mm angled telescope for use through 5-mm ports if needed), access device, laparoscopic ports, special laparoscopic instruments (including, for example, preferred dissectors, right-angle dissectors), laparoscopic retractors, specimen retrieval bags, endoscopic staplers, endoclips, and other devices anticipated for the procedure.

The anterior approach was the first laparoscopic splenectomy technique to be described. However, with greater than 15 years of experience with laparoscopic splenectomy worldwide, the procedure has evolved. The most frequent approach to contemporary laparoscopic splenectomy is via a lateral approach.

HALS has been increasingly described for use in complex cases, particularly in patients with splenomegaly.[18]

All patients enter the operative suite and are placed on an electric operative table in the supine position on a beanbag. Pneumatic sequential compression devices are placed before induction of anesthesia. Evidence-based data on prophylaxis for deep venous thrombosis favor the use of perioperative heparin therapy. Perioperative antibiotics are administered. Once anesthesia monitoring devices are placed, general endotracheal anesthesia is established, and the airway is secured, the operative team repositions the patient in the lateral decubitus position with the right side down. Care is taken to ensure that adequate padding is in place. The beanbag is inflated, and additional tape with padding is placed to secure the patient. The security and safety of patient positioning are tested by moving the electric operating table to different planned positions before scrubbing to ensure adequacy of positioning and taping.

A "time-out" is conducted to ensure that the correct patient is in the correct operating room at the correct time for the correct procedure as reflected on the signed informed consent. The "time-out" also affords the operative team the opportunity to familiarize themselves with members of the team, with the objectives of the procedure and key steps, and with special equipment needs. We do not start the procedure unless all equipment requirements have been resolved. The patient is then prepared and draped in the usual sterile manner.

Regardless of approach, performance of laparoscopic splenectomy can be divided into systematic steps, which we review and often write on a white board in the operating room:

1. Positioning and safe access for pneumoperitoneum
2. Diagnostic laparoscopy, including a search for accessory spleens
3. Mobilization of the spleen with dissection of the splenic ligaments
4. Division of the splenic vessels, including the splenic hilum and short gastric vessels
5. Division of the remaining attachments and placement of the spleen in a specimen bag
6. Extraction of the spleen within the specimen bag from the peritoneal cavity
7. Inspection of the operative field
8. Removal of trocars, desufflation of pneumoperitoneum, and closure of the port site

Step 1: Positioning and Safe Access for Pneumoperitoneum

The Anterior Approach Once the standard laparoscopic approach, the anterior approach is now used less frequently because the lateral approach is thought to provide better exposure and more tactical options. The anterior approach may be better suited for dealing with a large spleen, particularly one that has previously undergone splenic artery embolization. It may be preferable for clearance of accessory spleens when suspected. For this group of patients, preoperative imaging with a technetium scan may be helpful, even supplemented by intraoperative localization with a laparoscopic gamma probe. The anterior approach may also be preferable if

other procedures such as diagnostic laparoscopy or cholecystectomy are planned.

For the anterior approach to laparoscopic splenectomy, the patient is placed in either a supine or a modified lithotomy position, with the left side elevated by means of a roll or a sandbag. If the lithotomy position is used, we favor placement of a beanbag to "cocoon" the patient with padding to avoid the patient slipping during intraoperative repositioning. The patient's right arm should be tucked to create more room for the operative team to work opposite the target organ. Equipment is positioned with the understanding that most of the laparoscopic procedure will be conducted from the patient's right, facing toward the patient's left upper quadrant.

Controversy remains regarding the optimal access technique to achieve pneumoperitoneum. Access for pneumoperitoneum is achieved with a "closed" Veress needle, "open" Hasson technique, "direct visualization" device, or a combination of these techniques, depending on the preference of the surgeon and patient characteristics. Despite strong individual surgeon opinion, evidence from tens of thousands of procedures has not provided compelling data favoring one technique over the others with regard to "open," "closed," and "direct visualization" access techniques. We favor the use of a combined Veress "closed" technique, followed by the use of a "direct visualization" device, while taking advantage of the initial pneumoperitoneum as a possible buffer for added safety. We avoid previous scars in the hope of avoiding adherent bowel and minimizing the risk for bowel injury. When we use an anterior approach, initial insufflation is performed at the umbilicus site with a Veress needle, and then the "direct visualization" device is placed in the left side of the abdomen, approximately a third of the distance between the umbilicus and the xiphoid process in the midclavicular line.

We preset the laparoscopic insufflator for an abdominal pressure of 12 mm Hg or less. The objective of laparoscopic insufflation is to establish and maintain a laparoscopic working space. Once this space is established, to minimize the effects of intra-abdominal hypertension, we favor utilization of the lowest insufflation pressure settings that maintain a safe working space and good visualization.

Four or five total laparoscopic ports are placed under direct visualization. Laparoscopic port size is up to the surgeon's choice. We place at least one 10- to 12-mm port to have immediate access for use of either a stapler or a large endoclip device. Current retractor devices often require a 10- to 12-mm port. The configuration of port placement for the anterior approach is typically in a V, with the initial port for the camera located at the base of the V, approximately a third of the distance between the umbilicus and the left costal margin in a line directly toward the splenic hilum. One line of the V extends from the initial port to the xiphoid process; the other line of the V extends from the initial port to the most lateral left subcostal region. After the initial port placement for the camera, all ports are placed under direct visualization. Two dissection ports are placed, one near the midline approximately half the distance between the umbilicus and the xiphoid process and one along the lateral V line in the left midportion of the abdomen at about the midclavicular line. We use a 10- to 12-mm port at this location because it is the probable port for introduction of a stapler or endoclip device. An additional port for retraction is placed further lateral along the lateral V line in the anterior axillary line. If a fifth port is needed for retraction, it is typically placed in the subxiphoid position. The patient is then placed in the reverse Trendelenburg position and tilted slightly to the right. The surgeon stands between the legs if the patient is in the low lithotomy position and adjacent to the patient's right hip if the patient is supine, with the surgeon's video monitor located at the head of the bed to the patient's right. Surgical assistants and the scrub nurse are positioned at the patient's sides.[19]

The Lateral Approach The lateral approach is the most popular for laparoscopic splenectomy, with most surgeons believing that this approach provides better exposure and more intraoperative management options. It is useful for normal and moderately enlarged spleens. Advantages of the lateral laparoscopic approach to splenectomy include the fact that it is technically easier, allows access to the splenic vasculature through the relatively avascular retroperitoneum, and decreases inadvertent trauma to the spleen because gravity is used for retraction more than instruments are. In addition, dissection planes open more easily, thereby enhancing identification of key ligaments, the tail of the pancreas is more accessible and less susceptible to injury, operative times are shorter, and dissection strategy options are increased.

Positioning for the lateral approach to laparoscopic splenectomy is similar to that used for posterolateral thoracotomy or laparoscopic left adrenalectomy, or both. The patient is placed on a beanbag in the right lateral decubitus position. An axillary roll is placed under the shoulders, the kidney rest is raised, and the operating table is flexed. The goal of positioning is to maximize the working space between the left costal margin and the left anterior superior iliac spine. All pressure points must be padded and protected. The patient should be well secured on the operating table; we typically use wide tape and padding. We assess the stability of the patient's position on the electric table by testing the various intraoperative positions that we may use before preparing and draping the patient.

The technique for access to the peritoneal cavity to achieve pneumoperitoneum is the surgeon's choice. As mentioned, we typically use a combination of Veress "closed" and "direct visualization" device techniques. In the lateral decubitus position, however, we avoid the umbilicus and favor placement of first the Veress and then the "direct visualization" device in a position approximately a third the distance from the umbilicus to the splenic hilum in a line between the umbilicus and spleen. After securing access to the peritoneal cavity, typically three additional ports are placed along the costal margin. Depending on spleen size and body habitus, it may be necessary to position the trocars inferiorly or medially to accommodate the size of the spleen. We typically place a

10- to 12-mm port capable of accepting a stapler or large endoclip device for dissection in the left subcostal anterior axillary line, a 5-mm port for dissection in the left subcostal region in the midaxillary line, and a third port, usually 5 mm, in the far left lateral subcostal position. All ports are placed under direct visualization. Occasionally, an additional port is required toward the midline near the xiphoid process for retraction.

Step 2: Diagnostic Laparoscopy, Including a Search for Accessory Spleens After gaining access to the peritoneal cavity, placing all laparoscopic ports under direct visualization, and optimally positioning the patient, diagnostic laparoscopy is performed to survey the abdominal cavity, confirm the location of the spleen, assess anatomic relationships of adjacent organs, search for accessory spleens, and enable the operative team to plan the operative strategy.

The type of splenic vascular anatomy usually can be determined by looking at the inner surface of the spleen. If the vessels appear to cover more than three quarters of the surface, a distributed pattern is present. In this case, the vessels can be dissected and isolated individually and then ligated with clips. If the vessels appear to enter the spleen more uniformly and cover only a third of the splenic surface, a magistral pattern is present. The magistral pattern may be amenable to management with a linear stapler.

Up to 20% of the population may harbor an accessory spleen. The majority of patients with accessory spleens have only one. However, as many as 20% of patients with accessory spleens may have two, and up to 17% may have three or more accessory spleens. Accessory spleens can range in size from 0.2 to 10 cm, but they are typically small, less than 1.5 cm in length, often the size of lymph nodes, and appear as miniature spleens in gross appearance. Approximately two thirds of accessory spleens are located at or near the splenic hilum. Twenty percent are within the substance of the tail of the pancreas. The remainder of accessory spleens are found in the omentum, along the splenic artery, in the mesentery, or along the left gonadal vessels.[20,21]

Operative Strategy of "Opportunity" Within a Systematic Framework Although most surgeons describe a systematic, methodical stepwise approach to laparoscopic splenectomy, the variable splenic anatomy forces a "strategy of opportunity" to guide our systematic framework.

Step 3: Mobilization of the Spleen with Dissection of the Splenic Ligaments Laparoscopic dissection typically begins by partially mobilizing the splenic flexure. This is accomplished by taking down the splenocolic ligament, the distal phrenocolic ligament, and the sustentaculum lienis. Such dissection can be performed with endoshears and the judicious use of electrocautery, one of the harmonic scalpel devices, or the LigaSure device. This dissection creates access to the gastrosplenic ligament, which is then easily separated from the splenorenal ligament. The lower pole of the spleen is carefully elevated. Dissection continues medially and cephalad to open the space like a book, with the spleen gradually rolling laterally as access to the splenic hilum increases. Gentle traction on the spleen is required to avoid a capsular tear and procedure-limiting bleeding. As the spleen is gently elevated and rolled laterally, pertinent dissection targets come into view. Some authors describe a "splenic tent," with the gastrosplenic ligament making up the left side, the lienorenal ligament the right side, and the stomach the floor of the tent. A cautious, stepwise approach is taken to divide the phrenocolic ligament so that the spleen can be rolled laterally away from the tail of the pancreas for visualization of the splenic hilum.

Step 4: Division of the Splenic Vessels, Including the Splenic Hilum and Short Gastric Vessels It is important at this stage to recognize that no two spleens are alike. Spleen size, shape, and vasculature can all vary. Vascular anatomy can be distributed or magistral. In the more commonly encountered distributed variant, defined by a short splenic truck and many long branches entering along the medial surface of the spleen, division of the distributed array of splenic vessels can be performed by sequential applications of an energy source device or endoclips. We typically use the harmonic scalpel device but caution that it must be used to completely traverse each vessel and only a single vessel at a time.

The less common magistral pattern is characterized by a long main splenic artery that divides into short branches close to the hilum.[22,23] The optimal approach for this pattern is to isolate the hilum as much as possible by preparing a window for the application of an endoscopic endovascular linear stapler across the splenic hilum. Before firing the endoscopic linear stapler, careful inspection is necessary to ensure that the tail of the pancreas has been dissected free and is not included within the stapler to avoid possible pancreatic injury or fistula formation.

The short gastric vessels are divided sequentially, individually, to the most cephalad portion of the spleen; one should note that the length of the short gastric vessels often becomes shorter as this dissection proceeds, with progressively less distance between the stomach and the spleen. Care must be exercised when placing energy devices adjacent to the stomach while dividing the short gastric vessels to avoid later gastric necrosis.

Step 5: Division of the Remaining Attachments and Placement of the Spleen in a Specimen Bag Final mobilization of the spleen is completed by dividing the proximal phrenocolic ligament along its entire length to the diaphragm and left crus. Careful inspection ensures complete mobilization and freedom of the now completely detached spleen for safe placement in the specimen bag. Some surgeons prefer leaving the superior-most portion of the phrenosplenic ligament intact until placement of the spleen in the specimen bag. This tactic leaves the spleen tethered to the diaphragm, which can facilitate placement of the spleen in the endoscopic specimen bag.

A large endoscopic specimen bag is introduced through the larger left midabdominal port. Several vendors have designed large endoscopic specimen bags that are especially strong for removal of the spleen. Some surgeons have used sterilized medium-duty or large

heavy-duty plastic freezer bags as an acceptable alternative.[23] The key is to ensure easy retrieval of the spleen and prevent the specimen bag from rupturing during extraction to avoid later splenosis. The spleen is placed in the endoscopic specimen bag under direct visualization.

Step 6: Extraction of the Spleen Within the Specimen Bag from the Peritoneal Cavity Preoperative discussion with the patient care team, including the hematologist and pathologist, should take place to determine whether morcellation of the spleen specimen is appropriate. When laparoscopic splenectomy is performed for malignancy, morcellation of the specimen may make histologic evaluation of the specimen difficult. The result of this discussion will guide the conduct of laparoscopic extraction of the splenectomy specimen.

After the spleen is placed in the endoscopic specimen bag, if the spleen was left tethered to the diaphragm, these final attachments are divided.

The endoscopic specimen bag is grasped and extracted through an appropriate port site. When the anterior approach is used, the extraction site is the umbilicus. When the lateral approach is used, the specimen bag is often extracted through one of the lateral left subcostal ports. Typically, the specimen bag is continuously observed as it is elevated to the abdominal wall. The surgeon can then morcellate the spleen within the bag to allow extraction of the fragmented specimen within the specimen bag through a small incision. Care is taken to not rupture the bag because peritoneal spillage of the fragmented spleen can lead to later splenosis (disseminated splenic implantation). To enable delivery of the spleen and specimen bag, it is rarely necessary to enlarge the extraction port incision more than a few centimeters. For larger spleens, extraction through a Pfannenstiel incision may be preferred or, if HALS has been used, through a hand port incision.

If the decision was made preoperatively to remove the spleen intact within the laparoscopic specimen bag, the surgeon must carefully select the best site for extraction. For larger specimens, most surgeons favor a Pfannenstiel site.

Step 7: Inspection of the Operative Field After the spleen has been successfully delivered or, possibly, before final laparoscopic specimen bag extraction and loss of pneumoperitoneum, the operative field is carefully inspected for hemostasis, previously undetected accessory spleens, or any other unexpected mischief.

No surgical drains are placed, in keeping with the experience established in open surgery.

Step 8: Removal of Trocars, Desufflation of Pneumoperitoneum, and Closure of the Port Site Once the operative team is satisfied with inspection of the operative field, all ports are removed under direct visualization. The pneumoperitoneum is desufflated. Fascia at all port sites greater than 5 mm in diameter is closed. The port sites are irrigated and injected with local anesthetic, the skin edges are approximated with subcuticular closure, and Steri-Strips or tissue sealant is placed, followed by simple dressings.

Minimally Invasive Surgical Approaches to Massive Spleens

Hand-Assisted Laparoscopic Splenectomy

Minimal access splenectomy using hybrid technologies such as HALS is increasingly reported for the management of massive spleens, those significantly larger than 25 cm in length.

HALS is performed via a combination of laparoscopic and "open" splenectomy techniques. It involves the use of a device to enable intra-abdominal placement of a hand and forearm through a small incision, while maintaining pneumoperitoneum, to facilitate the performance of laparoscopic surgery. HALS advocates argue that that use of a hand-assisted device enables tactile feedback (haptics); helps the surgeon judge the extent of disease, identify underlying structures, and palpate anatomic landmarks; augments manipulation of instruments intra-abdominally; assists in restoring depth perception and three-dimensional orientation; and can serve as a bridge to enhance laparoscopic skills. For large spleens, it can help the surgeon manipulate the spleen more safely than laparoscopic instrumentation may allow. Vendors have developed a variety of commercially available hand port devices with a wide range in cost. The length of the hand port incision required correlates mainly with the breadth of the surgeon's palm, with incision length usually approximating the size of the surgeon's glove (6.5 to 8.0 cm). Two centimeters should be subtracted if marking takes place before pneumoperitoneum is established. Surgeon hand and forearm size are key and can be limiting for surgeons with large hands.

Placement of the HALS device is important. A "stand off" distance is needed between the hand port and the target organ so that the surgeon's hand has working room within the abdomen and does not interfere with laparoscopic instruments. Options for hand port placement for left upper quadrant surgery include the midline just above the umbilicus, the lower midline or left lower quadrant via a muscle-splitting incision, or even a Pfannenstiel incision for surgeons with particularly small hands. Patient positioning for either a lateral or an anterior approach can be used for HALS, based on surgeon preference and experience. The most common location for the hand port is in the midline, between the xiphoid and the umbilicus. For massive spleens, use of a Pfannenstiel incision has also been described.[22]

Pneumoperitoneum is established after the hand port is placed. Additional laparoscopic port placement must be planned carefully to enable visualization and working access while maintaining hand port access.

Once the hand port and additional laparoscopic ports are placed and pneumoperitoneum is established, the principles of splenectomy remain the same. The biggest technical challenge is avoidance of hemorrhage. Small series have reported successful performance of HALS for severe splenomegaly (mean spleen length, 27.9 cm; range, 23 to 32 cm), with acceptable operative times, morbidity, and outcomes.[24] This approach combines the advantages of hand assistance with the benefits of mini-

mally invasive surgery and has resulted in shorter operative times, increased safety, and acceptable outcomes.

Robotic-Assisted Laparoscopic Splenectomy

Minimally invasive splenectomy for splenic disorders such as ITP results in the same patient benefits as demonstrated for laparoscopic cholecystectomy. Robotic-assisted laparoscopic splenectomy has been reported and may play a role in future minimally invasive surgical approaches to the spleen.[25]

The benefit of robotic systems for general surgery remains a matter of debate. In a retrospective review, six laparoscopic splenectomies were compared with six robot-assisted laparoscopic splenectomies, all for ITP, with patients matched for age, American Society of Anesthesiologists score, body mass index, and preoperative platelet levels. There were no conversions to open surgery, and no complications were reported. The median postoperative stay was 1 day longer in the robotic group, with mean average costs being almost a third higher. Operative times were about 20% longer in the robotic group. In this analysis, robot-assisted laparoscopic splenectomy resulted in prolonged operative time, length of stay, and procedural costs, and though feasible, no relevant benefit was demonstrated.[26]

With advancement in surgical robotic technology, robotic systems may play a more integral role in future minimally invasive surgery.

Postoperative Care

Postoperative care after laparoscopic splenectomy is straightforward, provided that the procedure was uneventful. The nasogastric/orogastric tube and Foley catheter can be removed immediately after the procedure. We do not leave a nasogastric tube in place overnight. A postoperative chest radiograph is not required in the postanesthesia care unit (PACU) to confirm the absence of pneumothorax. Pneumothorax after laparoscopic splenectomy is rare, and if it was not of consequence intraoperatively, it is unlikely to have clinical impact postoperatively. After meeting PACU discharge milestones, patients recover on the ward. Patients should be encouraged to perform deep breathing with incentive spirometry and begin assisted early ambulation within 8 to 10 hours after surgery. Pain should be well controlled to avoid splinting. Deep venous thrombosis prophylaxis is continued postoperatively with both pneumatic sequential compression devices and heparin, unless contraindicated. A diet is resumed when tolerated. We usually begin with a clear liquid diet the morning after surgery and advance the diet as tolerated.

The typical length of stay after laparoscopic splenectomy is 1 to 3 days. Most laparoscopic splenectomy series report that the length of stay is on average 2 to 3 days.

Counseling, Antibiotics, and Immunizations for Overwhelming Post-Splenectomy Sepsis

All patients undergoing splenectomy should be counseled regarding their increased lifetime risk for OPSI. Lifetime risk data, typically reported at 3% to 5%, were outlined earlier. Patients should be advised to seek medical care immediately if any sort of febrile illness develops.

The use of long-term prophylactic antibiotics after splenectomy remains controversial. Long-term antibiotic therapy risks selection of resistant microbial strains. The lowest-risk groups for OPSI are those whose spleen was removed for trauma. The highest-risk groups include those whose spleen was removed for a hematologic disorder, immunocompromised patients, and patients at the extremes of age. Pediatric hematologists often recommend treatment with a penicillin-based regimen for 2 years after splenectomy. Studies have demonstrated benefit from OPSI antibiotic prophylaxis in children with sickle cell disease, but there have been no studies in adults.

We discharge patients with a supply of oral antibiotics and clear instructions to initiate therapy at the onset of symptoms of infection as they simultaneously arrange to seek urgent medical attention. Though uncommon, when it does develop, OPSI can follow a fulminant, often lethal course and should be treated as a life-threatening emergency requiring immediate parenteral antibiotics and intensive care. Intravenous immune globulin may play a beneficial role. OPSI mortality rates are reported to be 38% to 70%.[15]

Surgical Complications

Surgical complications of laparoscopic splenectomy are similar to those for the "open" procedure.

Early complications include bleeding, pneumonia, left pleural effusions, atelectasis, and injury to other organs (colon, small bowel, stomach, liver, and pancreas).

Late complications include subphrenic abscess, splenic or portal vein thrombosis (or both), failure of the procedure to control the primary disease, recurrent disease as a result of accessory spleens, and OPSI.

Concerns regarding accessory spleens and whether there is a higher likelihood of accessory spleens being missed at laparoscopy versus "open" surgery appear to be unfounded. Data from laparoscopic splenectomy have not found an increased incidence of recurrence of the underlying hematologic disorder when compared with "open" historical controls. Moreover, surgeons experienced in laparoscopic splenectomy report an 18% to 27% incidence of discovering accessory spleens in the anterior and lateral approaches, respectively, as opposed to 15% to 30% with "open" surgery. The key is for laparoscopic surgeons to diligently assess for accessory spleens in the expected locations at the time of laparoscopic splenectomy.

Critical to success in laparoscopic splenectomy is being well organized and prepared, with an emphasis on avoidance of complications and technical misadventures. Laparoscopic splenectomy is unforgiving. Managing intraoperative complications, once they occur, can be challenging, particularly bleeding-related complications. Recognition that the splenic vascular anatomy is variable and complex and that the spleen is a fragile solid organ

with a delicate capsule underscores preemptive efforts to avoid bleeding. Dissection should be methodical, with sequential identification, isolation, and control of vessels individually. The lateral approach decreases traction requirements on the spleen, thereby decreasing traction-related splenic capsular tears. Constant intraoperative monitoring for hemostasis is critical. Energy sources have limitations, as do clip and linear stapler devices. Improper application of cautery can result in iatrogenic injury to organs adjacent to the spleen. Improper harmonic scalpel application can lead to hemorrhage from a partially sectioned vessel. Improper clip application can result in injury to an adjacent vessel. Blind linear stapler application can cause damage to the tail of the pancreas. Never bury the stapler and always visualize the tissue within the stapler and the tip of the linear stapler before firing. Hemorrhage can occur from partial division of a major splenic vessel after release of the stapler. Instruments should be introduced into the operative field under direct visualization to avoid inadvertent injury to the delicate splenic parenchyma.

Patients with persistent postoperative fever, an increased white blood cell count, and abdominal pain should undergo CT of the abdomen. Subphrenic abscesses are treated by drainage and intravenous antibiotics.

Splenic or portal vein thrombosis develops in approximately 6% to 10% of "open" splenectomy patients.[27] The incidence of portal vein thrombosis after laparoscopic splenectomy may be higher. In one series that specifically examined laparoscopic splenectomy patients, 14% were found to have portal vein thrombosis.[28] Another series prospectively investigated "open" splenectomy patients and laparoscopic splenectomy patients with helical CT imaging preoperatively and postoperatively and found portal venous thrombosis in 19% of the "open" splenectomy group and 55% of the laparoscopic splenectomy group. Anticoagulation therapy was initiated once the diagnosis was established, and complete recanalization, except for the distal splenic vein, was observed without adverse events.[29]

Symptoms are vague and include fatigue, nausea, vomiting, and nonspecific abdominal pain. If clinical suspicion is high, anticoagulation therapy should be initiated once the diagnosis is confirmed by imaging studies.

Overview

Laparoscopic splenectomy is an excellent option for an expanding group of indications, but it is best accomplished by an experienced laparoscopic team. Conditions that were once considered either relative or absolute contraindications to laparoscopic splenectomy have become fewer. Advances in surgical technique, evolving instrumentation and energy sources, and improved operative strategies are continuing to expand the indications and making laparoscopic splenectomy feasible with good outcomes and minimal morbidity for an increasing group of patients with a variety of pathologic splenic conditions.

IMAGE-GUIDED INTERVENTIONAL THERAPY FOR THE SPLEEN

By possessing a single, accessible feeding artery with a relatively simple branching pattern, the spleen is well suited to routine, safe catheter access. Its brisk blood flow and richly vascular parenchyma provide high-quality arteriograms, parenchymal opacification, and portal venous imaging with digital subtraction angiography. Minimally invasive vascular interventional techniques for the spleen were rapidly popularized in the 1970s and 1980s and played an increasing role in the algorithm of surgical practice, which saw a shift toward preservation of functioning splenic tissue through nonoperative management.

This section reviews the techniques and clinical applications of image-guided splenic interventions for splenic trauma, splenic artery pseudoaneurysm, hypersplenism, and drainage of splenic collections.

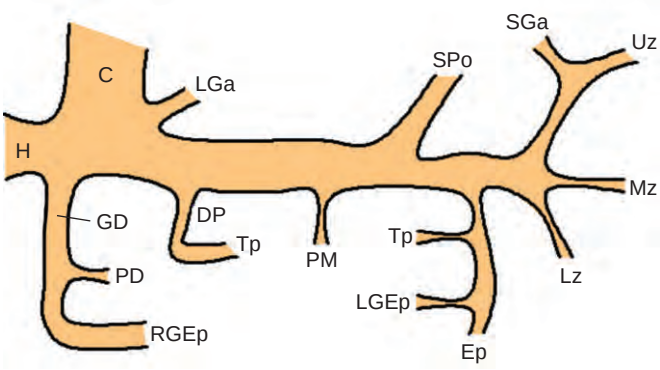
Technique of Transarterial Splenic Embolization

Anatomy

Although surgical splenectomy may be performed efficiently and safely, it is now clear that removal of this reticuloendothelial organ carries with it significant risks for overwhelming postoperative sepsis. The objective of catheter-directed therapy is to achieve the surgical therapeutic goals while preserving adequate functioning splenic tissue for host immunity. The splenic artery is usually a large single vessel arising anterolaterally from the celiac axis trunk. Anatomic variants of the splenic artery are uncommon but include a separate origin from the aorta.[30] The artery corkscrews clockwise or anticlockwise while undulating across the posterosuperior aspect of the pancreas body. It gives off sequentially the dorsal pancreatic and pancreatica magna arteries before dividing into extrasplenic polar branches in the region of the pancreatic tail (Fig. 127–1). The pancreas also receives blood supply from the pancreaticoduodenal and transverse pancreatic arcades, and the spleen has a rich vascular network from the short gastric and gastroepiploic arteries. This anatomy may be depicted on current three-dimensional multidetector row CT angiography and magnetic resonance angiography with a diagnostic quality comparable to that of invasive splenic angiography (Fig. 127–2).

Technique

Most splenic interventions may be performed with conscious sedation, although pediatric patients require general anesthesia. When functional partial or complete splenectomy is anticipated, pneumococcal vaccine and intravenous penicillin, metronidazole, and gentamicin antibiotics are administered. An initial aortogram is performed with a 5-French flush catheter through a 5-French sheath in the femoral artery to globally assess for sites of bleeding and depict normal and variant anatomy



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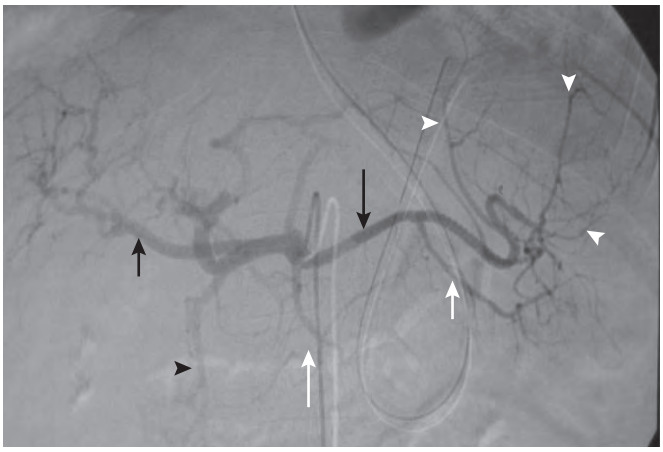

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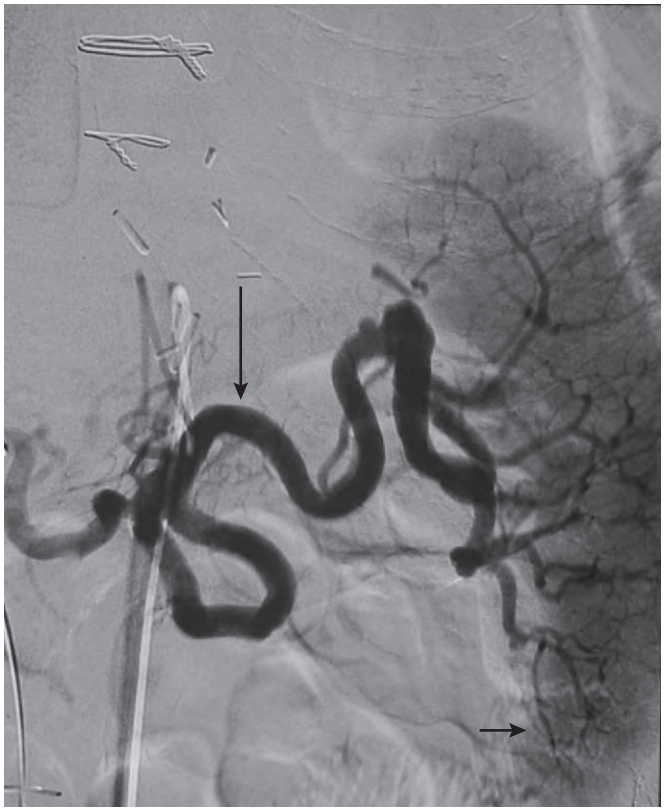


C

Figure 127–1. **A,** Schematic illustration of the splenic artery and branches seen at splenic arteriography. C, celiac artery; Ep, epiploic artery; GD, gastroduodenal artery; H, hepatic artery; LGa, left gastric artery; LGEp, left gastroepiploic artery; Lz, inferior pole splenic artery; Mz, midzone splenic artery; PD, pancreaticoduodenal artery; PM, pancreatica magna; RGEp, right gastroepiploic artery; SGa, short gastric arteries; SPo, superior polar artery; Tp, transverse pancreatic artery; Uz, upper pole splenic artery. **B,** Forty-one-year-old woman with gastrointestinal bleeding. A normal anteroposterior celiac arteriogram demonstrates the splenic artery *(long black arrow),* dorsal pancreatic artery *(long white arrow),* pancreatica magna *(short white arrow),* hilar branches of the splenic artery *(white arrowheads),* hepatic artery *(short black arrow),* and gastroduodenal artery *(black arrowhead).* **C,** Fifty-year-old man with pancreatic carcinoma. A normal anteroposterior celiac arteriogram demonstrates the splenic artery *(long arrow)* and parenchymal-phase enhancement of the spleen *(short arrow).*

for selective angiography. The celiac axis and splenic artery are selected with a combination of a 5-French Simmons 1 or Cobra glide catheter and an 0.035 glide wire. With proximal placement of the catheter, a selective splenic angiogram is performed with arterial, parenchymal, and portal venous phase timing of the contrast bolus. Smaller, more distal hilar and branch vessels may be selected with the 5-French catheter combined with a 3-French microcatheter over a 0.014 to 0.018 microwire. Standard digital subtraction angiography suffices, although newer three-dimensional fluoroscopy units may be of benefit in patients with difficult anatomy (Fig. 127–3).

Embolization is performed in a distal-to-proximal direction within the artery. Available embolic materials include Gelfoam, particles, and coils. Smaller, more distal arteries and parenchyma may be temporarily embolized with gelatin sponge pledgets or slurry or with autologous blood clot. Permanent distal parenchymal vascular occlusion is achieved with 3- to 900-µm particulate polyvinyl alcohol, silicone, or acrylic embolic spheres. The embolic agents may be soaked in antibiotic to decrease the risk for abscess formation. The splenic artery may be permanently embolized with metallic coils from the second-order branches into the main splenic artery. Coils are deployed distal to the dorsal pancreatic

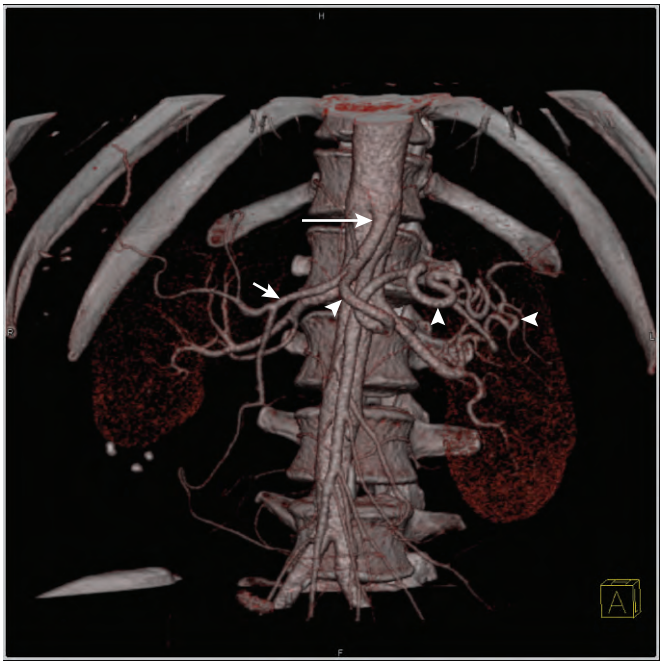


Figure 127–2. Thirty-year-old woman being evaluated for renal organ donation by three-dimensional, volume-rendered, anteroposterior projection, multidetector row computed tomography of the splenic artery *(arrowheads),* celiac axis *(long arrow),* and hepatic artery *(short arrow).*

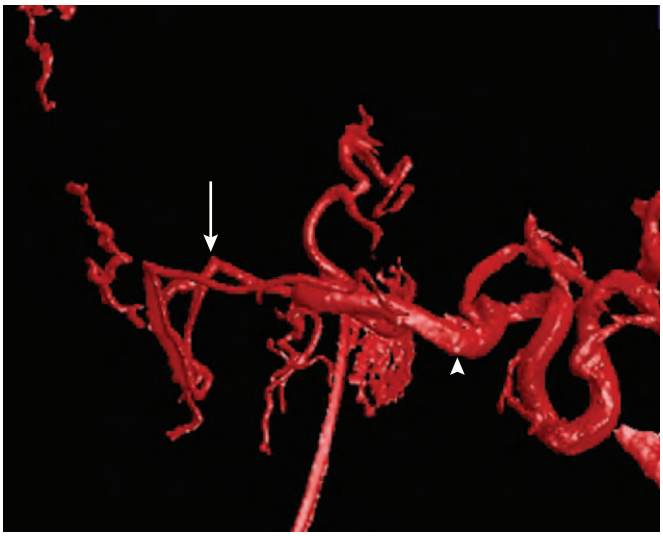


Figure 127–3. Forty-year-old woman undergoing hepatic chemoembolization. Three-dimensional fluoroscopic digital subtraction angiography offers infinite planes and projections for interpretation and can unravel complex anatomy. *Arrow,* hepatic artery; *arrowhead*, splenic artery.

and pancreatica magna arteries in an effort to avoid splenic infarction by preserving collateral blood supply to functioning splenic pulp.[31] Coils must be sized to the target vessel to avoid inadvertent distal embolization to nontarget vessels or proximal migration into the celiac axis or aorta. Depending on the indication, a combined approach of coil and embolic agents may be used. One must remain cognizant that proximally placed coils may limit future interventions if required.

Splenic Bleeding and Transarterial Splenic Embolization

Most cases of splenic bleeding seen in practice result from blunt or penetrating trauma to a normal-sized spleen. The spleen is the most commonly injured organ for which transarterial embolization is necessary and was first described by Sclafani et al. in 1995.[32] The algorithm for managing a patient with splenic injury is an evolving practice reflected by decreased splenectomies in adults and children and expansion of the number of patients managed nonoperatively by observation and transarterial splenic embolization (TASE). Assignment of patients to operative or nonoperative groups and to interventional and noninterventional groups is best achieved through reconciliation of the clinical picture, imaging findings, and injury scores (American Association for the Surgery of Trauma [AAST], Organ Injury Scale [OIS])[33] by the surgeon and interventionalist.[34] CT has largely eliminated the application of admission diagnostic angiography as routine practice for all splenic injuries. One should bear in mind that grading of the injury is now largely based on CT, which has some interobserver variation, is limited in depicting active bleeding on a single study, and cannot reliably distinguish arterial and venous extravasation. CT findings cannot be viewed in isolation for the management algorithm. A temporal change that is clinically occult may be an indication for intervention, but the presence of less remarkable features should not be used to deny intervention when they are discordant with the clinical picture.

Clinical features of patient age, the grade of splenic injury,[35,36] the amount of retroperitoneal bleeding,[37] the need for resuscitation, and associated injuries[38,39] are no longer absolute indications for surgery, nor do they absolutely preclude an interventional approach.[34,37] Broadly speaking, most would agree that a hypotensive, unstable patient refractory to resuscitation (usually grade 3 to 4 injury) mandates surgical exploration.[33] The majority of injuries occur in hemodynamically stable patients with a grade 1 or 2 injury and no signs of continued bleeding and may be managed conservatively with observation.[40,41] The role of endovascular therapy lies between these broadly defined groups and is still actively debated, and management today largely depends on local expertise and trauma team organization, which evaluates each case on its individual merits. Most splenic injuries treated by embolization are grade 2.8 to 3.[35,37,40] TASE has little role in a shattered or devascularized spleen. In centers with rapid access to interventional services as part of trauma triage, there is some evidence to support TASE in patients who respond transiently to minimal resuscitation[42] and for endovascular treatment of higher-grade injuries. Up to 10% of hemodynamically stable patients may have imaging signs of continued bleeding from grade III injuries and are potential candidates for TASE.

Endovascular therapy for splenic trauma begins with review of contrast-enhanced CT or magnetic resonance imaging (MRI). Aortography may demonstrate generalized vasoconstriction and renal retention of contrast in a patient in shock. Splenic angiographic findings include abrupt termination of vessels, vasospasm, pseudoaneurysm, and arteriovenous fistula formation. Intrasplenic vessels may be displaced and the extrasplenic artery may be accordioned as a result of hematoma. The parenchymal phase may demonstrate contrast extravasation, avascular segments, abnormal accumulation of contrast within the pulp, and loss of the smooth splenic contour. In the setting of large subcapsular hematoma, the spleen will be displaced anteromedially and the left kidney may be displaced inferiorly.

Bleeding may initially be treated with a temporary distal particulate agent to slow bleeding from the cut surface, but definitive therapy is permanent coil embolization of the splenic artery. If there are only two or three identifiable bleeding sites, they may be selectively coiled distally. However, if multiple bleeding sites are present, more proximal embolization will be required. Embolization slows arterial inflow and permits distal clot to form,[31] and Haan et al. noted no difference in outcomes between proximal and distal embolization.[37] After therapy one may see complete stasis or markedly slowed flow. Absence of extravasation at angiography is a reliable sign of successful therapy,[32] and such patients will probably not need laparotomy later.

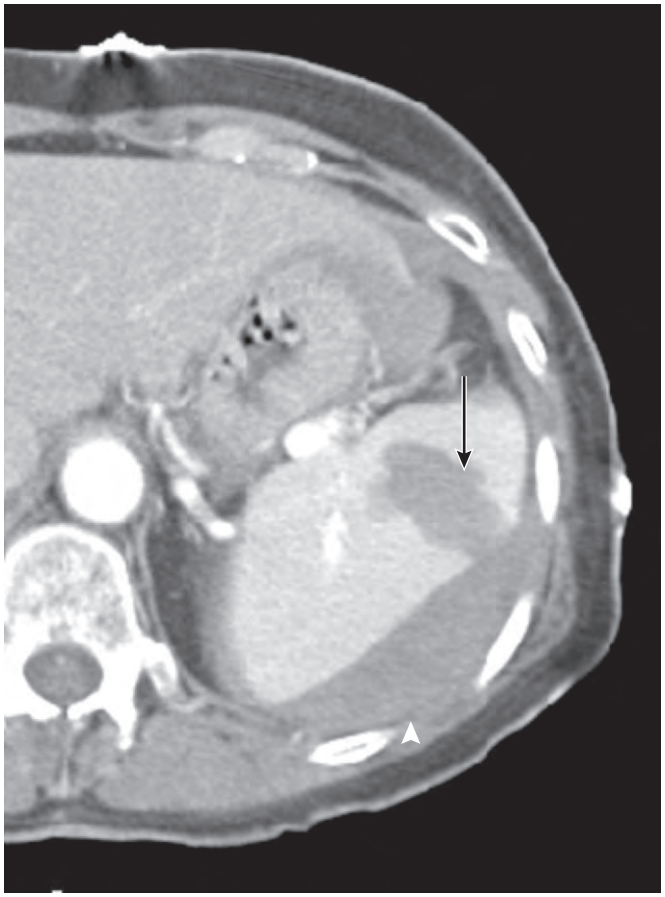
The success of TASE and its contribution to nonoperative management have largely been determined from retrospective data. Patients failing nonoperative management (3% to 17%) and requiring splenectomy are decreasing.[34,37] The overall success rate of TASE in controlling splenic bleeding and salvaging splenic tissue is quoted at over 80% in adults and children.[33,36,42,43] Haan et al. reviewed 648 patients with blunt splenic injury, 132 of whom underwent embolization, and noted a salvage rate of 90%.[37] The presence of an arteriovenous fistula may predict operative failure,[37] but this will depend on how aggressively the fistula is treated. Those who fail an initial TASE procedure may yet be considered for a second application if they remain stable; such patients account for 2% to 5% of those treated[37] (Fig. 127–4). One would expect failure rates to increase as the technique is increasingly applied to higher injury grades.

Complications of TASE include failure to treat sites where delayed recurrent bleeding occurs because of either continued bleeding through the embolization, lysis of the clot at the injured site, rupture of a pseudoaneurysm, or relaxation of acutely vasospastic vessels.[44-47] Delayed bleeds occur days to weeks after therapy. Postembolization syndrome consists of abdominal pain and fever and may be associated with CT findings of necrotic, air-containing parenchyma and left-sided pleural effusion. This syndrome is usually self-limited unless superimposed on infection. Bacterial peritonitis, septicemia, splenic abscess, and rupture are recognized complications. Hematomas may evolve into calcified splenic hematomas or cysts. Postembolization infarction rates are quoted to be as high as 20% but depend on the site of injury and the extent of embolization required.[44,47,48]

Pseudoaneurysm of the Splenic Artery

The splenic artery is the most common visceral artery affected by aneurysms and pseudoaneurysms and is second only to aortoiliac aneurysm formation. They share some causes with aneurysms elsewhere but are specifically associated with pancreatitis, hypersplenism, and pregnancy. Traumatic pseudoaneurysms presumably occur as a result of deceleration of the spleen on its vascular pedicle during blunt abdominal trauma.[44] It has been suggested that the increased nonoperative management of splenic injuries may lead to a greater prevalence of traumatic pseudoaneurysms that would otherwise have been resected,[49] but there is also increased detection of incidental splenic aneurysms because of the widespread application of cross-sectional imaging. Women have an increased prevalence and are more prone to rupture in pregnancy. Splenic aneurysms are typically saccular and situated in the distal third of the splenic artery. Rarely, intrasplenic aneurysms have been reported.[50] They contain a variable amount of mural thrombus, are frequently calcified, but do not affect splenic perfusion. CT angiography is highly accurate in the detection and characterization of splenic aneurysms, although three-dimensional reconstructions are required to differentiate the false-positive findings of normal vessel tortuosity and atherosclerotic change. There is some debate on which pseudoaneurysms should be treated. Most agree that aneurysms larger than 2 to 2.5 cm and enlarging or symptomatic aneurysms should be treated because up to 60% of those who bleed will be unstable and the mortality rate associated with bleeding is quoted to be as high as 15%.[49] Many also advocate therapy for smaller aneurysms in women considering childbearing. Some argue that lesions less than 2.5 cm and small pediatric splenic aneurysms may be managed conservatively with close follow-up imaging and surveillance, although some authors suggest that all pseudoaneurysms be actively treated given the low morbidity of the procedure.[49,51]

The majority of splenic aneurysms may be treated by embolization of the aneurysmal sac directly or its feeding artery. For broad-necked, saccular, or fusiform aneurysms, coils are deployed in a distal-to-proximal direction within the splenic artery. In saccular lesions with a narrow neck, one may deploy detachable coils or balloons within the aneurysm sac itself (Fig. 127–5). More recently, covered stents placed across the aneurysm neck have been suggested as a form of therapy that will exclude the aneurysm and preserve blood flow and future access.[52] This procedure, however, may be associates with higher risk in very tortuous and diseased arteries and requires careful patient selection. Percutaneous injection of thrombin has been reported but is an uncommon approach and perhaps less controlled because one cannot compress the neck as is done in peripheral arteries.[53] Localized treatment of a pseudoaneurysm and its neck preserves splenic function through more proximal branches. The results of endovascular management have been good, and it is a now a recommended consideration for all splenic aneurysms.[54] It is not clear to what extent splenic artery integrity is undermined by its proximity to the pancreas



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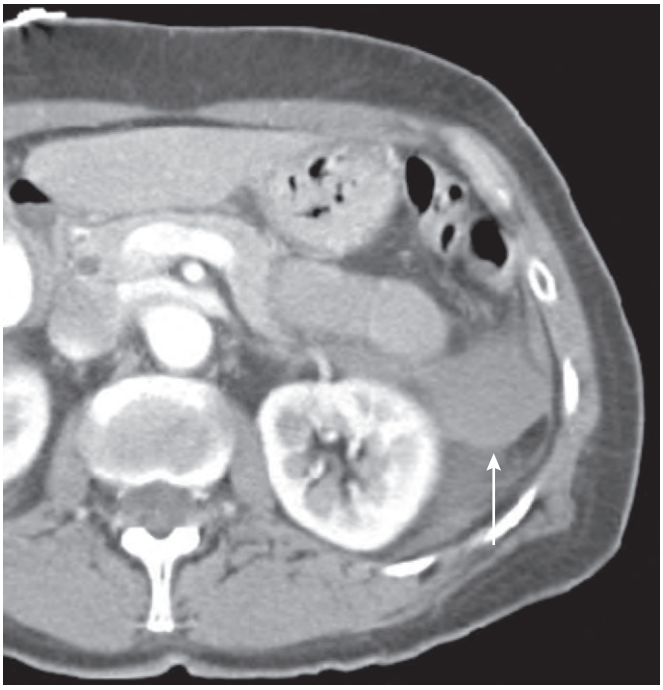

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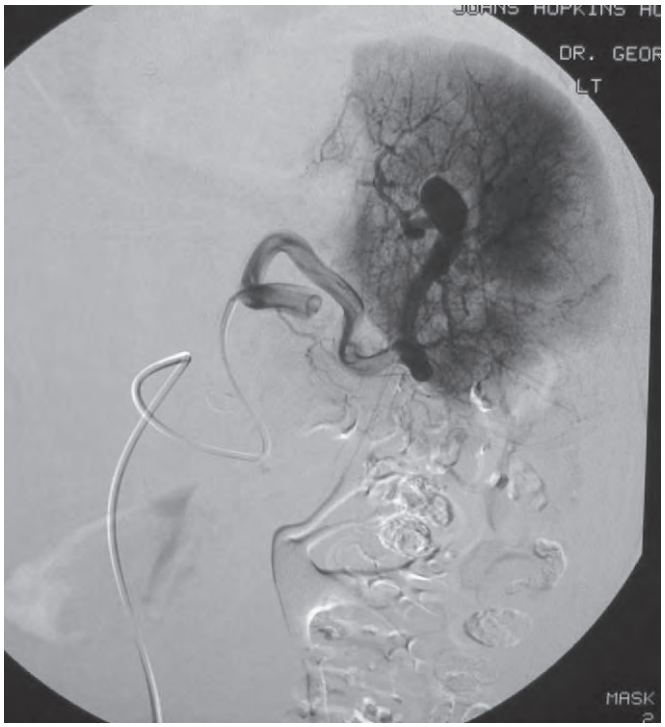

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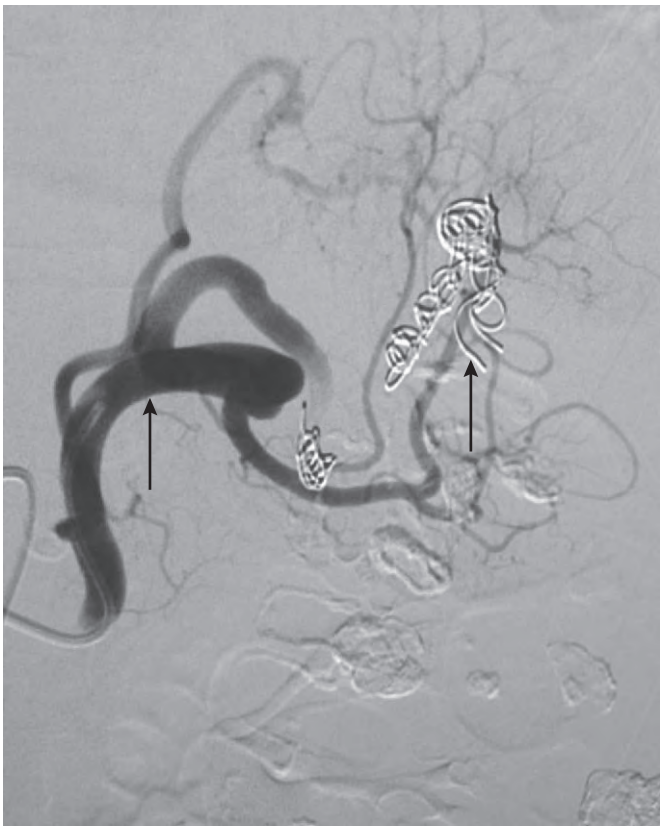

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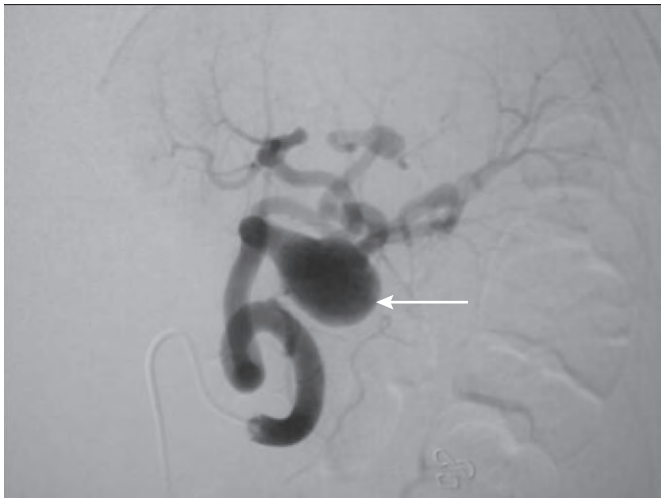
Figure 127–4. **A,** Axial contrast-enhanced computed tomography scan in a 32-year-old woman who fell from a horse and had active splenic bleeding. A grade IV laceration *(arrow)* and subcapsular hematoma *(arrowhead)* of the spleen are apparent. **B,** Moderate retroperitoneal hematoma in the left anterior pararenal space *(arrow).* **C,** Anteroposterior digital subtraction angiography (DSA) of a splenic arteriogram demonstrates the splenic artery supplying the remaining upper pole splenic pulp, although there is a sharp cutoff from the avascular lower pole segment because of expanding hematoma. **D,** Treatment with transarterial splenic embolization. Hemostasis was achieved with coil embolization of the splenic artery. Splenic artery DSA demonstrates decreased splenic perfusion and coils in the distal lobar branch of the splenic artery.



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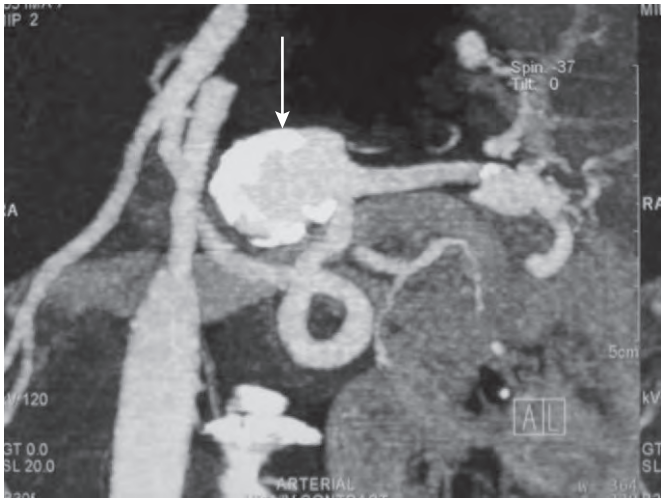

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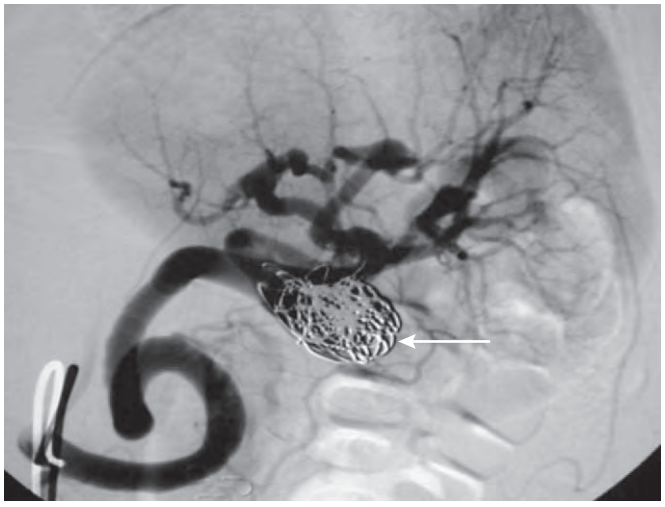

C

Figure 127–5. **A,** Pseudoaneurysm of the distal splenic artery. Anteroposterior digital subtraction angiography (DSA) demonstrates a large saccular pseudoaneurysm *(arrow).* **B,** An anteroposterior maximum-intensity multidetector row computed tomographic arteriogram demonstrates the saccular pseudoaneurysm *(arrow).* **C,** Anteroposterior DSA demonstrates successful coil embolization with detachable coils *(arrow).* (Courtesy of Dr. A. Arapally, Johns Hopkins Hospital.)

in pancreatitis, but it has been suggested that pseudoaneurysms related to pancreatitis may be better treated surgically. If surgery is anticipated, balloon occlusion catheters may control bleeding intraoperatively.[49]

Hypersplenism and Partial Splenic Embolization

Splenic embolization was introduced in the early 1970s and is for the treatment of hypersplenism and pancytopenia with or without massive splenomegaly (e.g., thalassemia, myelofibrosis).[26] As well as improving hematologic parameters and decreasing splenic size, it may improve liver function and decrease gastric or splenic variceal bleeding, but this will depend on the baseline splenic disease and hepatic reserve.[48,55-58] Although complete embolization was performed initially, the combination of antibiotic prophylaxis and partial splenic embolization[59] has been an effective, safer alternative to surgical splenectomy.

Treatment is usually performed with small (3- to 900-µm) permanent particulate embolic agents (e.g., polyvinyl alchohol or silicone or acrylic embolic spheres), which seek to deprive peripheral, intraparenchymal segmental regions of the spleen of their blood flow. Coils are not used because it is harder to gauge and stage the percentage of parenchyma treated and they limit access for future treatments, which are frequently required. The risk for pancreatitis is reduced by placement of the catheter as distal as possible to avoid particulate agents going to nontarget sites, and one may select individual hilar branches to better distribute the embolic agents throughout the spleen. Percent embolization is judged from parenchymal-phase angiography after injection of the particulate agent. It has been suggested that less than 50% embolization predisposes to relapse[48,60] but with over 70% embolization of the splenic pulp, greater long-term efficacy may be achieved.[56] Most achieve this 70% goal in staged applications to limit postembolization syndrome and complications. The response in organ size is best appreciated with CT or MRI and will be noticed within 2 to 4 months of therapy. A hematologic response may be seen within weeks,[61] but a prolonged long-term response has also been demonstrated[62] (Fig. 127–6). Although Nio et al. noted relapse

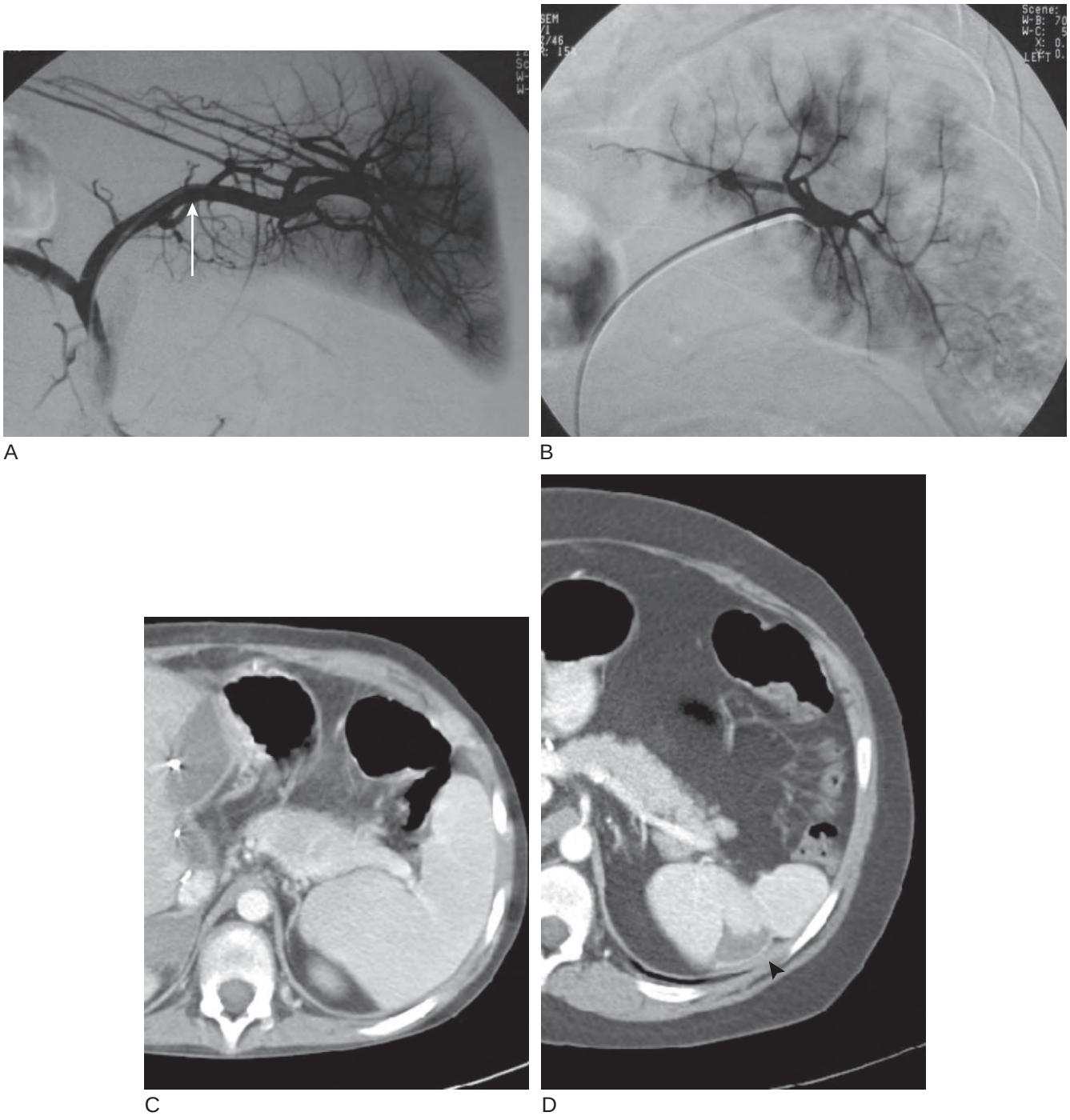

Figure 127–6. **A,** Normal splenic arteriogram *(arrow)* with parenchymal-phase enhancement in a 14-year-old with hypersplenism and thrombocytopenia after hepatic transplantation. (Courtesy of Dr. A. Arapally, Johns Hopkins Hospital.) **B,** Digital subtraction angiography of a splenic arteriogram after 70% embolization demonstrates a mottled enhancement pattern. **C,** Contrast-enhanced computed tomography (CT) scan before embolization. Note the size of the spleen. **D,** Contrast-enhanced CT scan 3 months after embolization. Note the decreased size of the spleen and small peripheral infarct *(arrowhead).*

of thrombocytopenia after a single partial splenic embolization treatment, long-term efficacy was achieved in 70% of patients.[56] Success rates are higher in patients with decreased variceal bleeding and improved liver function. Relapse may be related to the rate of splenic regeneration. Reported complications of the procedure include splenoportal venous thrombosis, splenic necrosis, abscess, and septicemia, which are potentially lethal in this patient population.[48,61]

A similar technique is used for pre-splenectomy splenic embolization. In general, the surgical approach to splenectomy permits good control of bleeding and

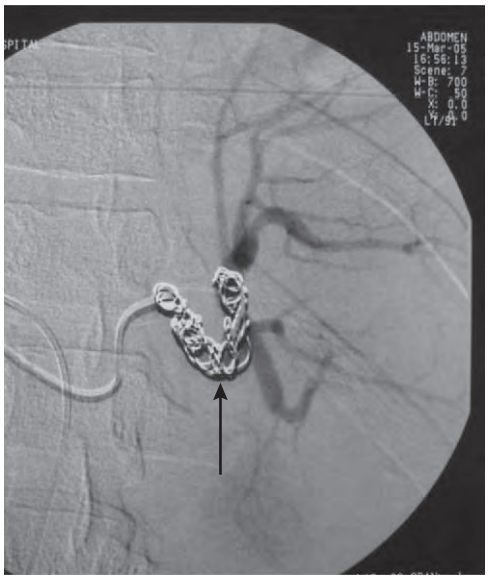

Figure 127–7. Sixty-two-year-old man who underwent preoperative embolization before splenectomy for lymphoma and splenomegaly. Note coils in the splenic artery *(arrow)* and decreased blood flow distally.

limited blood loss. However, it may be more challenging in a patient with massive splenomegaly (lymphoma or leukemia), in whom access to the hilum is more difficult. Coil embolization proximally may limit blood flow into the hilar vessels. Although the coils may affect placement of surgical clamps and ligatures, they can be removed easily if placed near the time of surgery. Intraparenchymal particulate Gelfoam slurry embolization may limit bleeding of an intrasplenic mass (hemangiosarcoma or fibrosarcoma) (Fig. 127–7). Typically, embolization is performed close to the time of surgery.

Splenic Abscess and Pseudocyst

The most common splenic collections include old hematoma, pseudocysts and cysts, (Fig. 127–8) and splenic abscesses (Fig. 127–9). Cysts are commonly seen on cross-sectional imaging and require therapy when they are large enough to cause early satiety or left shoulder pain. Noninfected splenic cysts may be treated by percutaneous puncture and aspiration with sclerosis. The volume of aspirate is replaced with 100% dehydrated ethanol or doxycycline, and the patient is placed in alternate postures for an hour before the fluid is aspirated.[63,64] Repeat therapy may be required. Splenic abscesses may be iatrogenic and may be complicated by a mycotic pseudoaneurysm. They are usually accessed with ultrasound guidance and a single-walled 18-gauge needle. A 10-French drain may then be placed over a 0.035 wire. When the drainage tapers off, repeat imaging will indicate whether the drain may be removed.[65,66] Sterile collections that continue to reaccumulate may be sclerosed with tetracycline.[66]

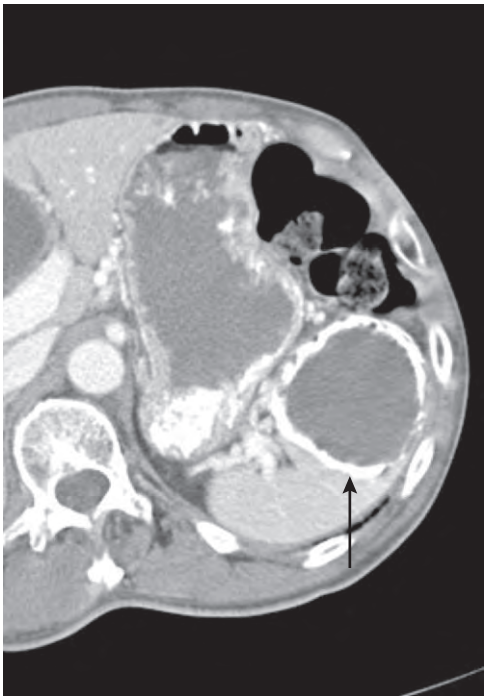

Figure 127–8. Axial contrast-enhanced computed tomography scan demonstrating a calcified splenic hematoma *(arrow).*

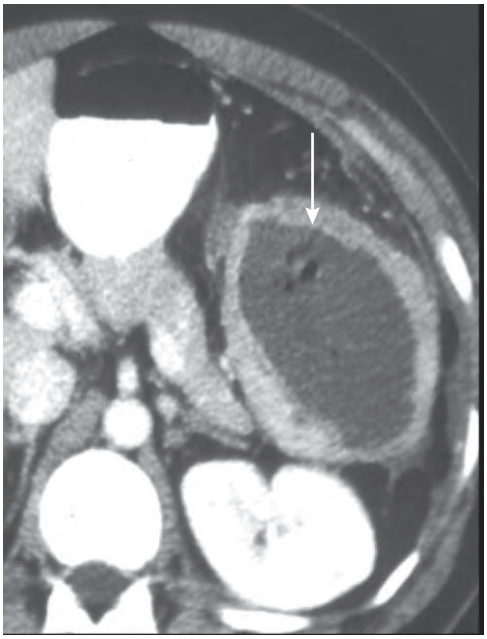

Figure 127–9. Axial contrast-enhanced computed tomography scan demonstrating an air-containing splenic abscess *(arrow).*

CONCLUSION

Splenic diagnostic angiography is shifting from interventional techniques to noninvasive three-dimensional CT and MRI, which produce studies of similar quality. There has been growth in splenic artery therapeutic embolization, which is safe and efficacious. It has expanded the proportion of patients treated by nonoperative management and complements the move in surgery to organ preservation whenever possible. It already has a clear role in trauma, hypersplenism, and splenic artery aneurysm, but with refinement of the algorithms, we will probably see a broadening of patient selection.

Future interventions for splenic disorders will be approached by a multidisciplinary team that includes the surgeon and interventional radiologist.

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Chapter

128

Management of Splenic Trauma in Adults

Anne Lidor

The spleen, an important component of the reticuloendothelial system in normal adults, is a highly vascular solid organ situated in the left upper quadrant of the abdomen that arises as a mass of differentiated mesenchymal tissue during early embryonic development. The normal adult human spleen weighs between 75 and 100 g; receives an average blood flow of 300 ml/min; and functions as the primary filter of the reticuloendothelial system, sequestering and removing antigens, bacteria, senescent or damaged cellular elements, and other particulate matter from the circulation. In addition, the spleen also plays an important role in humoral immunity, producing immunoglobulin M and the opsonins tuftsin and properdin[1]; is an important component of the complement activation system; and can serve as a source of extramedullary hematopoiesis.

Although the spleen is protected anteriorly, posteriorly, and laterally by the lower rib cage, it is nevertheless frequently subject to both blunt and penetrating trauma. In fact, although the spleen and liver are the two most commonly injured solid organs in the abdomen, splenic injuries are more clinically significant and more frequently require surgical intervention,[2] a reflection of the potential for sudden and catastrophic hemorrhage in splenic trauma. Isolated splenic injury after blunt trauma is common in children, whereas in adults associated injuries are more frequent, including injuries of the thorax, lungs, liver, kidneys, diaphragm, extremities, and head. Blunt splenic trauma is only infrequently accompanied by associated pancreatic or bowel injury, contrasting sharply with the experience seen with blunt liver injury, in which these two organs are frequently also involved.[3] In addition, the spleen is not infrequently the victim of iatrogenic injury: Although splenic injury complicates only 0.01% of all laparotomies, splenic injury may accompany as many as 10% of complex or revisional operations performed in the left upper quadrant.[4]

Clinical indicators of splenic injury depend largely on the mechanism of injury. In blunt trauma, a history of abrupt deceleration may result in vascular torsion of the splenic hilum, shearing of the short gastric vessels within the gastrosplenic ligament, or capsular tearing at sites of ligamentous fixation. Associated fractures of the lower left rib cage, when present, not only serve to indicate the severity of the initial blunt force injury but can also inflict severe laceration on an otherwise uninjured spleen. In instances of penetrating trauma, a wound track traversing the left upper quadrant necessarily raises suspicion for splenic injury. Additional clinical findings pointing toward possible splenic damage include extensive ecchymosis or abrasions of the left upper quadrant or left flank and left shoulder or subscapular pain caused by irritation of the left hemidiaphragm by subphrenic blood (Kehr's sign). Initial laboratory evaluation is that of the standard trauma survey, and it is important to recognize that the initial hemoglobin and hematocrit may be entirely normal and, as such, have little utility in ruling out the possibility of significant splenic injury. Any suspicion for splenic injury should immediately lead to more definitive diagnostic testing (discussed later).

DIAGNOSTIC MODALITIES

Diagnostic peritoneal lavage (DPL) has historically been the cornerstone diagnostic study used to detect significant intraperitoneal injury requiring surgical intervention. This quick, simple procedure can be easily performed in the resuscitation area of the emergency department. DPL is considered to be positive for the presence of significant intraperitoneal injury when more than 10 ml of gross blood is aspirated directly from the peritoneal cavity or when the returned effluent contains more than 100,000/mm^3 of red blood cells, more than 500/mm^3 of white blood cells, or demonstrable bacteria or bile. In cases of significant splenic trauma, the most common findings on DPL are either the return of gross blood or the presence of more than 100,000/mm^3 of red

blood cells. The sensitivity of DPL for detecting significant intra-abdominal injury has been reported to range from 82% to 96%, whereas its specificity ranges from 87% to 99%.[5] Despite this, it has been reported that between 25% and 36% of celiotomies performed solely on the basis of a positive DPL are negative. Moreover, DPL itself carries an incidence of complications approaching 2.5%.[6,7] Because of the inherent inaccuracies of DPL, as well as its invasiveness, this diagnostic modality has now largely been supplanted by the use of noninvasive imaging studies such as ultrasound and computed tomography (CT).

Ultrasonography is readily available, can be performed quickly, and offers a completely noninvasive method for rapidly surveying for intraperitoneal blood or solid organ injury in patients with blunt or penetrating abdominal trauma. The focused abdominal sonography in trauma (FAST) examination, though somewhat lacking in specificity, is nevertheless highly sensitive for detecting intraperitoneal blood—a frequent accompaniment to significant splenic trauma—and has emerged as a useful diagnostic tool in the evaluation of patients with suspected splenic injury. FAST is completely without risk of complications and, moreover, its performance does not preclude the subsequent performance of CT scanning. The sensitivity of FAST has been reported as anywhere between 42% and 93%, whereas its specificity ranges in various reports between 90% and 98%.[8] The primary limitations of FAST (and, no doubt, the reasons for the extraordinary variability of the reported sensitivity of this technique) are (1) the heavy operator dependence of ultrasonographic examinations and (2) the obscuring effect of intestinal gas, which can severely compromise the ability to obtain distinct and useful images. Although FAST has not emerged as the dominant diagnostic imaging modality in the evaluation and management of patients with abdominal trauma, it has proved useful as a preliminary study, helpful in guiding the performance of additional imaging studies (e.g., CT) to determine the need for surgical management.

CT scanning is the diagnostic imaging modality of choice in all hemodynamically stable patients in whom splenic injury is suspected. The sensitivity and specificity of CT scanning (approaching 100% and 98%, respectively)[9] are superior to both FAST and DPL in detecting significant intra-abdominal injury and determining the need for surgery. Moreover, the exceptional resolution afforded by current-generation multislice scanners provides extraordinary detail regarding specific intra-abdominal organs and retroperitoneal structures. CT allows detailed examination of the splenic architecture, enabling the differentiation of simple subcapsular hematomas from more significant intraparenchymal hematomas, splenic fractures, and massive crush injury involving the entire spleen. To maximize the diagnostic accuracy of CT, patients should be given both intravenous and oral contrast to enhance tissue definition. Another advantage of CT scanning is that studies are performed according to predetermined computer-guided protocols, eliminating dependence on individual operator ability. Disadvantages of CT include the administration of ionizing radiation, the potential for nephrotoxic or anaphylactic reactions to the contrast agent, and the time required to transport patients to the scanner and to perform the examination. This latter consideration accounts for the inapplicability of CT scanning in hemodynamically unstable patients. However, the ubiquity of CT scanners, their proximity to the trauma area in well-designed modern emergency departments, and the astonishingly rapid image acquisition times with the newest generation scanning units all are factors continually extending the applicability of CT for evaluation of all but the most unstable patients.

Several grading systems have been employed for classifying the severity of splenic injuries, and these have important implications in guiding both operative and nonoperative management decisions. We have found the system designed by the Organ Injury Scaling Committee (OISC) of the American Association for the Surgery of Trauma[10] to be quite helpful not only in stratifying the severity of splenic injuries and determining proper therapy but also in providing a standardized and reproducible nomenclature for reporting purposes. This grading system incorporates both CT findings and intraoperative assessment of the injured spleen and consists of five levels of splenic injury, as follows:

- Grade I injuries consist of small subcapsular hematomas and capsular tears less than 1 cm in length.
- Grade II injuries comprise subcapsular hematomas involving less than 50% of the surface area of the spleen and parenchymal lacerations 1 to 3 cm in length that do not involve a trabecular vessel.
- Grade III injuries consist of any subcapsular hematoma involving more than 50% of the splenic surface, all expanding (or ruptured) subcapsular hematomas, and parenchymal lacerations longer than 3 cm (with or without involvement of trabecular vessels).
- Grade IV injuries apply to patients with splenic lacerations involving the segmental vessels or with devascularization of more than 25% of the spleen.
- Grade V injuries consist of major hilar disruption, devascularization of more than 50% of the spleen, or complete splenic shatter (Table 128–1).

Such severity grading systems notwithstanding, decisions regarding management of individual patients with specific splenic injuries are not cut-and-dried and involve more than simply assigning a severity score and determining therapy. Other factors, such as the mechanism of injury (blunt versus penetrating), the presence of other associated injuries (both intra-abdominal as well as extra-abdominal), the age and overall condition of the patient, and the presence and duration of hypovolemic shock and/or hypothermia all must be taken into consideration and will influence the choice of management in cases of splenic trauma. Nevertheless, the severity of the splenic injury plays a dominant part in determining whether nonoperative management is appropriate or—if not—whether splenorrhaphy or splenectomy will be the more appropriate surgical option. As a general rule, younger, healthier patients with less severe splenic

Table 128–1 Splenic Injury Scale—1994 Revision

Grade* and Type of Injury	Injury Description
I	
Hematoma	Subcapsular, <10% surface area
Laceration	Capsular tear, <1 cm parenchymal depth
II	
Hematoma	Subcapsular, 10-50% surface area; intraparenchymal, <5 cm diameter
Laceration	1-3 cm parenchymal depth, does not involve trabecular vessel
III	
Hematoma	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma
Laceration	>3 cm parenchymal depth or involving trabecular vessels
IV	
Laceration	Laceration involving hilar vessels producing >25% devascularization of spleen
V	
Laceration	Completely shattered spleen
Vascular	Hilar vascular injury, spleen devascularized

*Advance one grade for multiple injuries, up to grade III.
Data from Moore EE, Cogbill TH, Jurkovich GJ, et al: Organ injury scaling: Spleen and liver (1994 revision). J Trauma 38:3, 1995.

injuries and fewer associated injuries and comorbidities are more likely to be able to be managed nonoperatively or with splenic repair, whereas unstable, actively hemorrhaging patients with more severe splenic trauma and/or multiple associated injuries are overwhelmingly likely to require splenectomy.

OPERATIVE TREATMENT

The earliest reports on the management of splenic trauma focused almost exclusively on splenectomy, and this constituted the mainstay of treatment of splenic injuries for the first half of the 20th century. Although suture repair of splenic injuries (as well as rudimentary attempts at formal splenorrhaphy) had been described as early as the latter half of the 19th century, these techniques failed to enter the mainstream of surgical management of splenic trauma until a resurgence of interest in them developed in the mid-20th century. By the 1950s, the potentially devastating complications of what would eventually come to be recognized as overwhelming postsplenectomy sepsis (OPSS) were being well documented in infants who had undergone splenectomy,[11] and this led to enthusiasm for nonoperative management of splenic trauma in the pediatric population.[12,13] It was not until the 1980s, however, that a similar emphasis on splenic salvage began to be extended to the management of splenic trauma in adults.[14]

General Principles

If operative management (either splenectomy or splenorrhaphy) has been deemed appropriate, certain standard principles of trauma care are followed. These include the establishment of reliable large-bore intravenous access, aggressive volume resuscitation, preparation of type and cross-matched packed red blood cells for anticipated intraoperative transfusion, nasogastric decompression, and preoperative intravenous antibiotic administration. It is our standard practice to utilize a vertical midline incision for all trauma celiotomies because this affords the quickest access to the peritoneal cavity and allows for thorough examination of the entire abdomen to evaluate for the possibility of concomitant injuries. For improved visualization of the left upper quadrant, the midline incision can be extended cephalad, to the left of the xyphoid process, and the left triangular ligament of the liver may be incised to allow reflection of the liver away from the area of interest. We have found it uniformly helpful to resist the temptation to perform an oblique left upper quadrant incision when an isolated splenic injury is suspected; this approach is invariably more time consuming than a midline approach, and one is spared the occasional embarrassment of attempting to evaluate or repair an unsuspected concomitant injury elsewhere in the abdomen through an awkward point of access.

On entering the peritoneal cavity, a standard initial trauma survey should be performed in all patients, no matter how high the index of suspicion may be that one is dealing with an isolated splenic injury. All four quadrants should be packed and systematically inspected for hematoma, active bleeding, or biliary or intestinal contents. Preoperative imaging studies may have indicated the presence of isolated splenic trauma, warranting a focusing of attention on the left upper quadrant; however, in the event that multiple intra-abdominal injuries are identified, common sense dictates that the most serious and immediately life-threatening injuries be treated first. If other injuries take precedence over the splenic injury, in almost all cases the left upper quadrant

and splenic bed can be packed with laparotomy tapes so that hemorrhage can be sufficiently controlled until such time that definitive treatment of the splenic injury is undertaken.

In all but the most inconsequential instances of splenic trauma, mobilization of the spleen from its deep and protected location in the left upper quadrant is mandatory to be able to assess fully the location and severity of the splenic injuries. The most helpful initial step in this is the liberal placement of laparotomy tapes posterior to the spleen, greatly facilitating its elevation into the operative field where it can then be carefully inspected and palpated to characterize the nature of the lesion(s). Following this preliminary maneuver, the spleen's ligamentous attachments to the diaphragm, kidney, and colon should be sharply incised. These connections are avascular and can be divided with impunity, except in patients with portal hypertension, in whom enlarged collateral veins may become prominent. Doing so will allow the spleen to be rotated to the midline and further elevated, thus enabling complete access to its anterior and posterior surfaces as well as to the hilum. Once accomplished, the operator can easily achieve virtually complete hemostasis of any splenic injury: either by direct manual compression of the splenic parenchyma at the site of bleeding or by direct control of the splenic artery and vein at the hilum. At this point, with the spleen fully mobilized, a judgment is then formulated as to whether splenectomy is required or splenorrhaphy should be attempted. In grade I or II splenic injuries, small surface lacerations can often be successfully treated with some combination of manual compression, the topical application of hemostatic agents (e.g., Surgicel, Gelfoam, Avitene, or fibrin glue), or argon beam coagulation.

Splenectomy

Once the spleen has been fully mobilized as described, if splenectomy is to be performed the short gastric vessels are next individually ligated and divided well away from the surface of the greater curvature of the stomach. This reduces the risk of gastric necrosis, which can occur if insufficient care is taken and a portion of the gastric wall is inadvertently incorporated into the ligatures. It is also at this point—as the short gastrics are divided and the splenic hilum is skeletonized—that particular attention must be directed to avoiding injury to the tail of the pancreas, which is closely applied to the splenic hilum. Inattentiveness here can result in the development of a pancreatic fistula with its attendant morbidity. With the short gastrics completely divided, the splenic artery is then doubly ligated and divided within the splenic hilum, followed by ligation and division of the splenic vein, which completes the splenectomy. Following removal of the spleen, the splenic bed is carefully inspected for hemostasis. If systemic coagulopathy has developed as the result of hemorrhagic shock, consumption of coagulation factors, or hypothermia, the left upper quadrant can be tightly packed with laparotomy tapes while fresh frozen plasma and platelets are administered and efforts are directed at rewarming the patient. Packs are then carefully removed, individual bleeding sites are electrocauterized, and the left upper quadrant is irrigated copiously. These steps are essential to minimize the chances of postoperative splenic bed hematoma, which in turn predisposes to the risk of subphrenic abscess. Although the data are inconclusive regarding the use of drains, we do not routinely drain the splenic bed following splenectomy or splenorrhaphy, preferring instead to emphasize meticulous hemostasis as the best path to avoiding splenic bed complications.

Splenorrhaphy

The term *splenorrhaphy* actually represents a variety of "spleen-sparing" techniques aimed at controlling the hemorrhage from a splenic injury while sparing the patient the long-term immunologic consequences of splenectomy. More often than not, some combination of these techniques is used to achieve this goal. The intraoperative decision to attempt splenorrhaphy should be made only after the spleen has been fully mobilized in the process of assessing the injuries.[15,16] As a general rule, splenorrhaphy is most appropriately considered in cases of less severe splenic injury (e.g., grades I and II, and occasionally grade III). Splenorrhaphy should not be attempted to repair extensive or complex shatter or crush-type injuries of the spleen, nor is it well-advised to undertake splenorrhaphy in the face of multiple concomitant traumatic injuries or associated hypotension. With the spleen fully mobilized and controlled with the surgeon's hand, splenorrhaphy may consist of nothing more than manual compression of the splenic parenchyma between thumb and finger to achieve hemostasis of simple lacerations. If this is insufficient to control bleeding, a variety of topical hemostatic agents may be applied directly to the bleeding surface, as already mentioned. The placement of a simple monofilament suture through the splenic parenchyma (often in a mattress technique and incorporating a piece of Gelfoam or an omental patch placed at the site of bleeding) will often bring about satisfactory hemostasis. Alternatively, wrapping the entire spleen with either absorbable or nonabsorbable mesh has been described as a means of effecting external tamponade and controlling bleeding and has not been associated with significantly increased risk of infectious complications.[15] In their review of a 9-year experience with splenorrhaphy at one trauma center, Feliciano et al.[17] found that, in 92% of cases, splenorrhaphy was accomplished without the need for mesh wrapping or partial splenectomy. The incidence of rebleeding in this series was 1.3% and was due to bleeding from other, initially overlooked, splenic injuries in two patients and rebleeding at the site of prior splenorrhaphy in only one patient.

Finally, and perhaps most important, as nonoperative management of splenic injuries has assumed a greater role in the management of splenic trauma (in large part owing to the increased availability of high-resolution CT scanning), the role of splenorrhaphy has correspondingly waned. As one would expect, as the less severe

splenic injuries (i.e., those most likely, if operated on, to be suitable for splenorrhaphy) are increasingly managed nonoperatively, it is only the most complex and severe injuries (i.e., likeliest to require splenectomy) that are managed surgically.

Laparoscopic Splenectomy

With the introduction and refinement of new technologies such as the harmonic scalpel and endoscopic staplers, laparoscopic splenectomy has become the preferred technique for the elective treatment of splenic disorders in many centers. In addition, laparoscopic performance of all of the aforementioned methods of splenic salvage (e.g., splenorrhaphy, partial splenectomy, hemostatic agent application) has been described in the trauma setting, although this consists mostly of scattered case reports,[18,19] and no one center has reported extensive experience with laparoscopy for splenic trauma. As with all types of laparoscopic surgery, there is a considerable learning curve with laparoscopic splenectomy, and in other than experienced hands, the increased time taken can have deleterious consequences in actively hemorrhaging or hemodynamically unstable patients. This, combined with the increasing role of nonoperative management and angiographic embolization techniques, makes it unlikely that laparoscopic splenic surgery will become the standard of care in the trauma setting.

Autotransplantation

Autotransplantation of splenic tissue has been described as a means of preserving some remnant of the spleen's reticuloendothelial function in cases of severe splenic trauma when splenorrhaphy is not possible and formal splenectomy would be the only surgical option. The efficacy of autotransplantation in maintaining immunologic competence has never been validated, and multiple cases of OPSS have been reported after autotransplanation.[20] Consequently, this technique remains controversial and is not to be endorsed for routine use.

OPSS, first described by Diamond in 1969,[21] is an infrequent but potentially catastrophic complication of splenectomy, resulting from an increased susceptibility to infection by encapsulated microorganisms. Although the precise incidence of OPSS remains ill defined, one retrospective review of 5902 postsplenectomy patients studied between 1952 and 1987 documented an incidence of OPSS of 4.4% in children younger than 16 years of age and 0.9% in adults.[22] Schwartz and coworkers,[23] using actuarial methods, estimated the risk of developing fulminant sepsis following splenectomy to be just 1 case per 500 person-years of observation; however, the cumulative incidence of infections severe enough to require hospitalization was 33% by the end of a 10-year follow-up period. Early reports of established cases of OPSS indicated mortality rates ranging from 50% to 70%, despite the use of intravenous antibiotics and intensive therapeutic intervention. With advances in antibiotic therapy and critical care, more recent evidence suggests that when informed patients seek medical attention promptly, the mortality rate of OPSS can be expected to be approximately 10%, with more than half of all fatalities occurring within 48 hours of presentation.[1,24]

Although no vaccination protocol has ever been proven effective in reducing the incidence of OPSS, it is nevertheless a widely accepted practice to immunize patients with pneumococcal vaccine shortly after undergoing splenectomy prior to discharge from the hospital.[25] The efficacy and clinical importance of meningococcal and *Haemophilus influenzae* type b vaccination in splenectomized individuals is unknown and can be considered in patients who may be more prone to infection with these organisms.[24] Irrespective of the vaccination schedule used, lifelong vigilance against serious infection is mandatory in all patients following splenectomy. Finally, the routine use of prophylactic antibiotics is not necessary after splenectomy in adults.[26]

NONOPERATIVE MANAGEMENT

Over the past several years an increasing number of patients with blunt splenic trauma have been successfully managed nonoperatively. The success of nonoperative management strategies has largely correlated with the increased availability of high-resolution CT scanning and advances in selective arterial catheterization and embolization techniques. In properly selected, hemodynamically stable patients with blunt splenic trauma, nonoperative management consists of bed rest, serial abdominal examinations, and hemoglobin and hematocrit determinations—all best carried out in a monitored setting. Clinical indices associated with failure of nonoperative management include higher grade of splenic injury, increased transfusion requirement, and hypotension at presentation. Patient age (>55 years) has been shown by some to augur poorly for nonoperative management[27,28]; however, the experience of others has failed to validate this.[29-32] The presence of associated intra-abdominal injuries or altered level of consciousness are significant obstacles to successful nonoperative management and should be considered relative contraindications. When proper selection criteria were used, the multi-institutional study of the Eastern Association for the Surgery of Trauma[33] demonstrated that a nonoperative management strategy could be employed in 61.5% of patients with blunt splenic trauma, with a success rate of 89%. Of the 11% of patients who failed nonoperative management in this study, 61% of these failed within the first 24 hours of observation. Similar findings have been reported by others.[34,35]

As vascular interventional techniques have evolved and become more prevalent in recent years, the selective use of splenic embolization as an adjunct to nonoperative management has resulted in improved success rates, with reduced need for delayed operative intervention.[36-38] In a multicenter review of four level I trauma centers,[39] a splenic salvage rate of 87% was achieved in patients undergoing adjunctive splenic embolization

during nonoperative management of splenic trauma, including an 80% success rate among patients with grades IV and V splenic injuries. With these techniques now more readily available and more widely used, even patients with CT findings of active extravasation—previously considered an absolute indication for immediate operative intervention—can often be managed nonoperatively if embolization can be successfully performed.[40,41] Unfortunately, CT or angiographic demonstration of traumatic splenic arteriovenous fistulization continues to be predictive of a high failure rate (40%) of nonoperative management.[35]

Most patients who fail nonoperative management require intervention (splenectomy, splenorrhaphy, or embolization) within 48 to 72 hours, whereas a minority (5% to 6%) develop complications more than 4 days following injury.[31,42] Such complications include delayed hemorrhage requiring operation or embolization, splenic artery pseudoaneurysm formation, and the development of splenic pseudocyst or abscess.

Delayed Splenic Rupture

Delayed splenic rupture, the sudden unheralded rupture more than 48 hours after initial trauma of a demonstrably normal spleen in a hitherto asymptomatic, hemodynamically stable patient, is an infrequent but potentially catastrophic complication of splenic injury. This phenomenon, separate and distinct from late splenic rupture after failed nonoperative management of documented splenic injury or unsuccessful splenorrhaphy, probably represents the late, sudden expansion of an occult subcapsular hematoma not detectable on the initial CT scan.[43] Minor, self-limited subcapsular bleeding that attains initial hemostasis and goes undetected on initial radiographic evaluation is thought to increase suddenly when endogenous thrombolysis is reactivated several days after injury. Increased subcapsular tension may be further aggravated by oncotic forces in the subcapsular space, leading to rupture and massive hemorrhage. Because of difficulties distinguishing this entity from either the missed or delayed diagnosis of a discernable splenic injury, the true incidence of delayed splenic rupture is not known.[44]

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Chapter

129

Management of Splenic Injury in Children

Paul M. Colombani · F. Dylan Stewart

An injured spleen in a child is a well-known entity to those involved in pediatric trauma care. The majority of children with a splenic injury now receive nonoperative intervention and therapy. This shift from operative to nonoperative treatment over the past several decades is a tremendous success story in which clinical judgment and reason triumphed over standard surgical dogma. Furthermore, this success has prompted surgeons to adopt similar management strategies for other pediatric solid organ injuries, as well as changes in the management of adult trauma patients. Recent work with clinical outcomes data in pediatric splenic trauma has given rise to model clinical practice guidelines. These guidelines serve to standardize and justify management decisions based on the best possible data and accepted clinical parameters. This chapter briefly discusses the history of this remarkable management shift, the immunologic imperative for splenic preservation, and the algorithm for evaluation and treatment of a child with suspected splenic injury.

THE SPLEEN IN HISTORY

Throughout much of the history of medicine, the value of the spleen has been trivialized, thereby contributing to the doctrine that the organ was expendable. That dictum was questioned near the turn of the 20th century by Nicholas Senn, who suggested that the spleen might have an as yet unrecognized function.[1] The first suggestion that the spleen might have important immune function came from Morris and Bullock in 1919.[2] They demonstrated, in well-designed animal experiments, that splenectomized rats were immunocompromised and went as far as to suggest that routine splenectomy might be unwarranted. Surgical opinion, however, did not significantly change until the first report of overwhelming post-splenectomy sepsis by King and Shumaker in 1952.[3] They reported two deaths in five infants in whom a septic syndrome developed after splenectomy for spherocytosis and gave the first description of overwhelming post-splenectomy sepsis. This syndrome was characterized by the subtle manifestation of fever, with rapid decompensation into septic shock, consumptive coagulopathy, and possibly death. First pneumococcus and then later other encapsulated organisms such as meningococcus, *Haemophilus influenzae*, and *Pseudomonas* species were implicated as the pathologic agents. Further experimental studies validated the increased susceptibility of splenectomized animals to pneumococcus.[4] Singer published a large series in 1973 in which it was found that the risk for sepsis in post-splenectomy patients was between 50 and 500 times greater than in the general pediatric population. Furthermore, these patients had a mortality rate of greater than 50% when these infections occurred.[5]

Even before the recognition and awareness of overwhelming post-splenectomy sepsis, sporadic reports of nonoperative management of an injured spleen could be found in the surgical literature.[1] However, none commanded attention until the 1968 publication by Upadhyaya and Simpson of successful nonoperative treatment of selected patients with splenic injury.[6] Remarkably, this very influential report involved only 12 children treated nonoperatively. The authors reviewed case records of 52 children with suspected splenic injury between 1954 and 1965 at Toronto Children's Hospital. Thirty patients had isolated splenic injuries and were treated by splenectomy. Ten children with splenic rupture were operated on and died, but as a result of associated injuries and not necessarily splenic hemorrhage. Twelve children with suspected splenic injuries were never taken to laparotomy and recovered without incident. The authors concluded that isolated splenic injury in children was well tolerated and made the first convincing plea for conservative management. In the

subsequent 10 years, numerous authors reported on successful nonoperative management of pediatric splenic injury, thus validating the early successes reported by Upadhyaya and Simpson. By the early 1980s, conservative management had become the universally accepted practice.[7]

IMMUNE FUNCTION AND CONSEQUENCES OF SPLENECTOMY

The spleen is an effective immune filter against a number of circulating antigens and blood-borne particles. Absence of the spleen results in profound immunologic changes. Defects in both cell-mediated and humoral immune function are present, as well as nonspecific immune defects.[8]

Cellular-mediated immune defects relate mainly to changes in peripheral T-lymphocyte populations and the ability of the host to effectively respond to circulating antigens. Antigens enter a normal spleen and are processed by macrophages of the red pulp.[9] Macrophages and dendritic cells then act as antigen-presenting cells in the periarteriolar lymphoid sheaths, where T cells are activated. These T cells then migrate to the marginal zones, where they may interact with B cells and influence specific antibody responses. Asplenia reduces these T-cell populations, with a resultant decrease in cell-mediated antigen response.

The humoral changes in asplenia involve altered levels of immunoglobulins, particularly significantly decreased IgM levels. The spleen provides the main anatomic site for lymphocyte sequestration during an immune response, and germinal centers in the spleen are the source of memory B cells. Asplenia is thought to attenuate this response.[8]

Nonspecific immune changes relate primarily to the important role that splenic macrophages play in the clearance of blood-borne bacteria and the prominent role that the spleen plays in overall phagocytic capability. Several groups have shown a significant reduction in monocyte-mediated phagocytosis and bacterial killing after splenectomy.[9] Decreases in cytokine production, specifically interleukin-12 (IL-12), may also contribute to susceptibility to pneumococcal infections because of lack of IL-12–mediated helper T-cell activation.[9]

Other studies have shown decreased phagocytic ability of alveolar macrophages in splenectomized animals, thus suggesting a role of the spleen in either alveolar macrophage maturation or activation.[8]

The timing of splenectomy may also be an important determinant in the risk for compromised immune function and overwhelming post-splenectomy sepsis. It has been observed that a younger patient may have a shorter interval before life-threatening infection, as well as a higher incidence of infectious complications in general.[10]

Much work remains before the exact relationship between asplenia and overwhelming sepsis is completely understood. However, the value of an aggressive approach to splenic preservation and salvage can no longer be understated.

EVALUATION OF A CHILD WITH ABDOMINAL TRAUMA

Trauma continues to be the leading cause of morbidity and mortality in the 1- to 18-year-old population in the United States.[11] Blunt trauma accounts for 90% of the injuries in children, with motor vehicle accidents and falls being the most common mechanisms. Head and extremity trauma is by far the most common pattern of injury; however, approximately 8% of children suffering blunt trauma will sustain an abdominal injury.[7] Several factors regarding body habitus make an injured child more likely to sustain intra-abdominal injury, including proportionally larger abdominal organs with respect to adult patients, an incompletely ossified rib cage that sits relatively higher and offers less protection to the intra-abdominal organs, and relatively less musculature and fat to absorb impact forces. The spleen is the most commonly injured solid organ in blunt abdominal trauma in children, followed closely in frequency by the liver and kidney.

The initial evaluation of a child with suspected blunt abdominal trauma follows the well-established advanced trauma life support protocols promulgated by the American College of Surgeons. Airway security plus confirmation of adequate ventilation is always a top priority. After a secure airway is established, the quality of circulation can be assessed. All children with suspected blunt abdominal trauma should have large-bore intravenous access established, preferably in one or both upper extremities. Femoral venous catheters are acceptable when peripheral access cannot be obtained, and intraosseous lines are also acceptable for both fluid resuscitation and administration of medications. Initial boluses of warmed lactated Ringer's solution should be used, typically given at 20 ml/kg. This bolus may be repeated if the child remains hemodynamically unstable, and the child should be prepared for possible blood transfusion, which should be strongly considered if a second 20 ml/kg bolus is not effective.

The secondary survey is begun after the ABCs (airway, breathing, circulation) and the primary survey are complete. Children in whom a strong suspicion of intra-abdominal injury exists should have both bladder and gastric catheters placed early in the resuscitation. The importance of decompressing the stomach, especially in a child who may have received positive-pressure breaths, cannot be overstated because the hemodynamic changes may simply be a result of massive gastric distention and not intra-abdominal hemorrhage. A careful secondary survey is performed to look for outward abdominal signs of internal injury, including contusions and seat belt signs, abdominal distention, and tenderness.

A child with abdominal distention, no response to fluid resuscitation efforts, and continued hemodynamic instability at the completion of the secondary survey should undergo prompt exploration in the operating room. Unfortunately, little further diagnostic work-up can be tolerated, and exploration to stop presumed intra-abdominal hemorrhage may be lifesaving. Of critical importance in this group of patients is early neurosurgical consultation, especially if a depressed Glasgow Coma

Scale score is present or if other signs of neurotrauma are found on the initial evaluation, because computed tomography (CT) scanning of the head is not indicated in an unstable patient.

Fortunately, most children with blunt abdominal trauma will stabilize after fluid resuscitation, and the diagnostic work-up can proceed safely. A lateral cervical spine film, chest radiograph, and pelvic radiograph should be obtained in all trauma patients. These films are unlikely to identify intra-abdominal injury, although left-sided rib fractures may be associated with significant transfer of force to the spleen.

Since the mid-1980s, CT scanning has been the standard of care in evaluating abdominal trauma.[12] Modern CT scanners can detect splenic injury with high specificity and sensitivity. The use of oral contrast agents is controversial, especially in the setting of trauma, where adequate time for small bowel opacification with contrast is not available. Several studies have suggested that detection of small bowel injuries, which may be associated with splenic trauma, is unaffected by the use of oral contrast agents.[13] There are also legitimate concerns regarding aspiration of orally administered contrast. It is our practice to perform the initial abdominal CT scan without oral contrast. If concern for small bowel or other missed injury persists during the patient's evaluation period, further scans with carefully administered contrast are performed.

Intravenous contrast, however, is an important element of quality CT scanning and should be used unless specifically contraindicated (Fig. 129–1). The significance of the "blush sign," or evidence of extravasation of contrast, is controversial in splenic trauma (Fig. 129–2). Cox et al. reviewed a series of patients and suggested that the blush sign might signify the need for early laparotomy.[14] Lutz and colleagues agreed that vascular blush did correlate with a higher degree of injury, but not the need for operative intervention.[15] It seems reasonable that management decisions should be dictated primarily by physiologic parameters, with CT findings serving only as a diagnostic adjunct.

A grading system has been established to further delineate the severity of splenic injury.[16] Grading is from I through V and summarized in Table 129–1. Figure 129–3 depicts five CT scans demonstrating the grades of splenic injury.

Focused abdominal sonography for trauma (FAST) is a relatively new imaging modality that has gained widespread use in adult trauma patients. FAST is sensitive for the detection of free intraperitoneal fluid; however, pediatric trauma patients may sustain significant splenic injury and have no free intra-abdominal fluid.[17] In addition, the presence of intraperitoneal fluid does not mandate operative exploration in the blunt abdominal pediatric population, thus further limiting the usefulness of FAST. It is likely that FAST will become a useful adjunct in blunt abdominal pediatric trauma but will not supplant the usefulness of CT scanning.

Diagnostic peritoneal lavage (DPL) is a time-honored technique that involves invasive evaluation of the peritoneal cavity for blood, bacteria, or particulate matter. It is a relatively simple and fast technique, although its applications are dwindling and surgical trainees are unlikely to be facile with the procedure. A simple positive DPL for hemoperitoneum is unlikely to change clinical management because many children with solid organ injury and hemoperitoneum are managed nonoperatively. DPL's usefulness lies mainly in patients with severe neurotrauma who require immediate neurosurgical intervention before radiographic evaluation of the abdomen can be performed. Given the speed of modern CT scanning, even that population of patients is decreasing because the additional time added by performing abdominal CT scanning in a child already undergoing head CT is minimal. DPL may be indicated for multiply injured patients undergoing surgery on an emergency

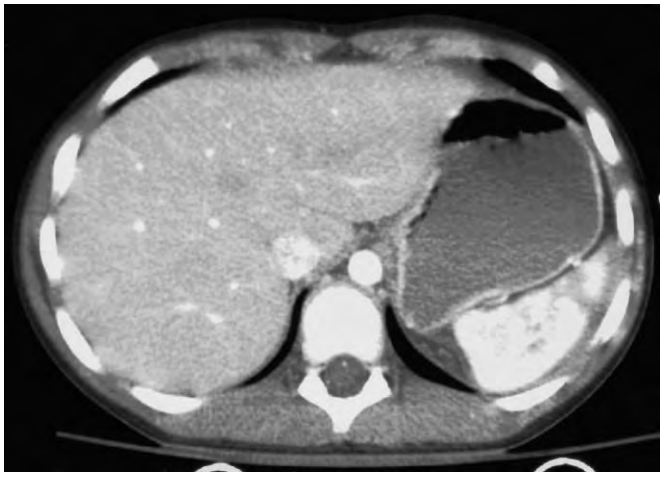


Figure 129–1. Abdominal computed tomography scan with intravenous contrast demonstrating a fracture in the upper pole of the spleen.

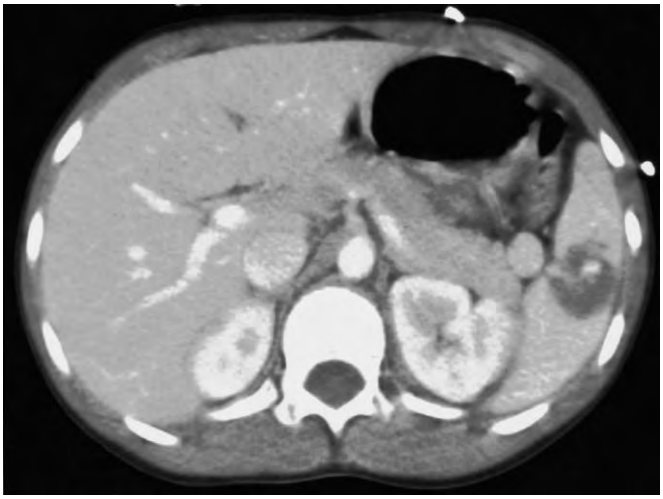


Figure 129–2. Abdominal computed tomography scan with intravenous contrast demonstrating a midsplenic laceration with extravasation of contrast (blush) into a hematoma.

Table 129–1 A Grading System Established to Further Delineate the Severity of Splenic Injury

Grade		Injury Characteristic
I	Hematoma	Subcapsular, nonexpanding, <10% of surface area
	Laceration	Capsular tear, nonbleeding, <1 cm of parenchymal depth
II	Hematoma	Subcapsular, nonexpanding, 10%-50% of surface area; intraparenchymal, nonexpanding, <2 cm in diameter
	Laceration	Capsular tear, active bleeding, 1-3 cm of parenchymal depth, no involvement of trabecular vessels
III	Hematoma	Subcapsular, >50% of surface area or expanding, ruptured subcapsular hematoma with active bleeding; intraparenchymal hematoma, >2 cm or expanding
	Laceration	>3 cm of parenchymal depth or involving trabecular vessels
IV	Hematoma	Ruptured intraparenchymal hematoma with active bleeding
	Laceration	Involves a segmental or hilar vessel and produces major devascularization (>25% of spleen)
V	Hematoma	Completely shattered spleen
	Laceration	Hilar vascular injury that devascularizes the spleen

Adapted from Moore EE, Cogbill TH, Jurkovich GJ, et al: Organ injury scaling: Spleen and liver (1994 revision). J Trauma 38:323-324, 1995.

basis for head or extremity trauma who become unstable in the operating room. DPL could then be used to assess the need for formal laparotomy in a minimally invasive manner.

Radiographic embolization of injured spleens has become commonplace in adult trauma populations. It should be noted, however, that many series report nearly a 10% greater failure rate of nonoperative management of splenic injuries in adults, thus providing a much larger patient population that might benefit from radiographic hemorrhage control. This outcome difference may be related to anatomic differences in the pediatric spleen, such as more efficiently contractile splenic arterioles and a thicker splenic capsule.[18] It seems likely that the already high success rate of nonoperative management of injured spleens in children will not be greatly influenced by the addition of arterial embolization and all its attendant risks. Figure 129–4 depicts the angiographic management of splenic injury in a pediatric patient.

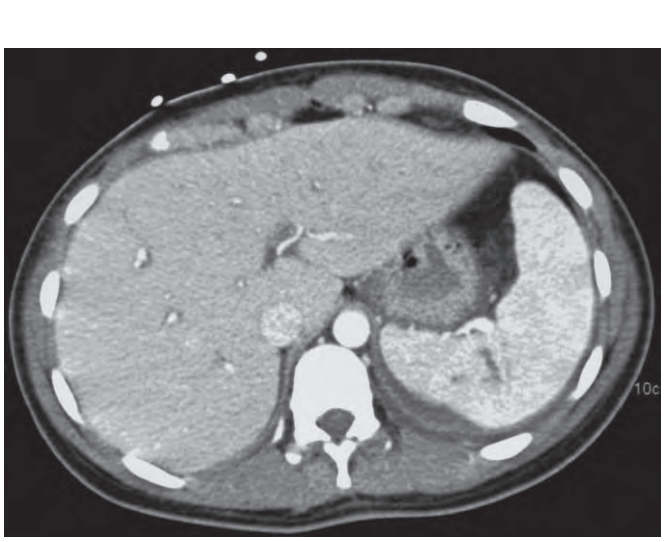
Splenic injuries seen on CT are graded as described earlier. Although the clinical usefulness of splenic injury grade is often not evident, the system is helpful for collecting meaningful data and comparing similar patient injuries, as well as comparing practice guidelines. This usefulness was clearly demonstrated in a report by Stylianos and the American Pediatric Surgery Association (APSA) Trauma Committee in 2000.[19] Case records of 856 children with splenic and liver injury at 32 pediatric trauma centers were reviewed, with the severity of injury classified by standard CT scan. The purpose of the study was to evaluate current clinical practice and develop evidence-based guidelines to best use resources without compromising patient safety or outcomes. The resultant guidelines are presented in Table 129–2. The author concluded that these evidence-based guidelines would need to stand up to prospective validation, and such evaluation was performed in 312 children at 16 pediatric trauma centers between 1998 and 2000.[19] The study concluded that compliance with the proposed guidelines had been high; improved utilization of resources was achieved by decreasing intensive care unit stay, hospital stay, and follow-up imaging; and patient safety had not been compromised.[20-22]

In accordance with the guidelines presented in Table 129–2, most children with splenic trauma have a relatively benign hospital course. Our routine is to maintain NPO status for three consecutive hematocrit determinations over a period of 24 hours. If the blood count remains stable, diet is resumed, bed rest restrictions are implemented for the prescribed period, daily hematocrit determinations are obtained, and discharge is planned at the selected interval based on the grade of injury. We do not obtain follow-up imaging. Resumption of physical activity also follows the APSA guidelines; however, resumption of full-contact sports is usually allowed on a case-by-case basis at the discretion of the attending surgeon.

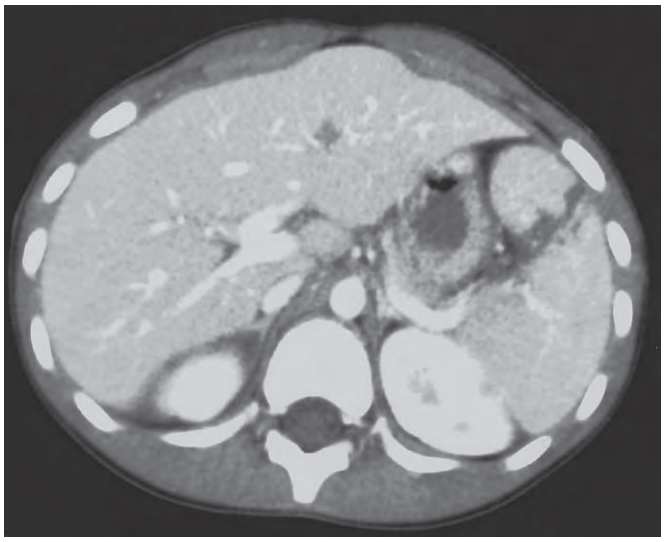
OPERATIVE MANAGEMENT

It is rare that a pediatric patient with an isolated splenic injury will fail nonoperative management—80% to 90% of children with splenic trauma are stable or respond to the initial fluid bolus.[17] Patients with splenic trauma, however, may also have other serious injuries that require laparotomy, so strategies for control of splenic bleeding and splenic preservation are crucial.

A patient with hemodynamic instability and a distended abdomen (after gastric decompression) should be taken immediately to the operating room. DPL may be useful in an unstable patient without obvious signs of abdominal trauma who has other causes for the hemodynamic changes that do not warrant laparotomy, such as pelvic fracture and bleeding. Large-bore intravenous access and type- and cross-matched blood should be available. Typically, a midline incision is used, with immediate four-quadrant packing after entry into the peritoneum. If the patient is in shock or has other severe injuries and the spleen is found to be the primary source



A



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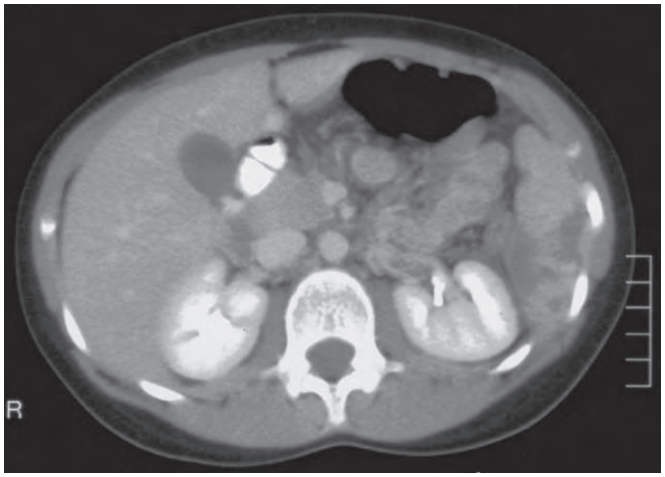

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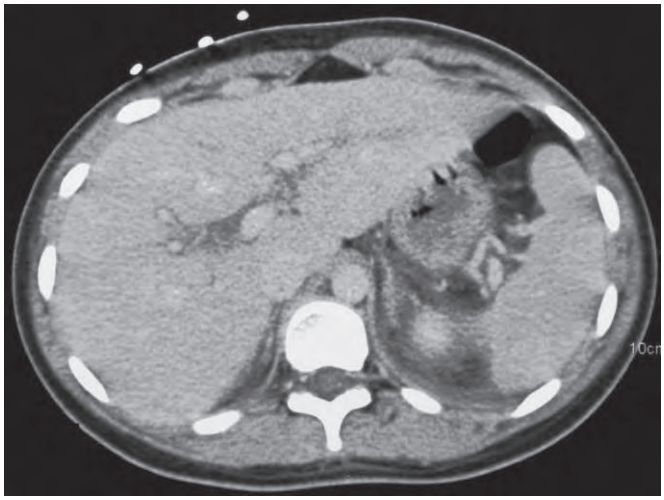

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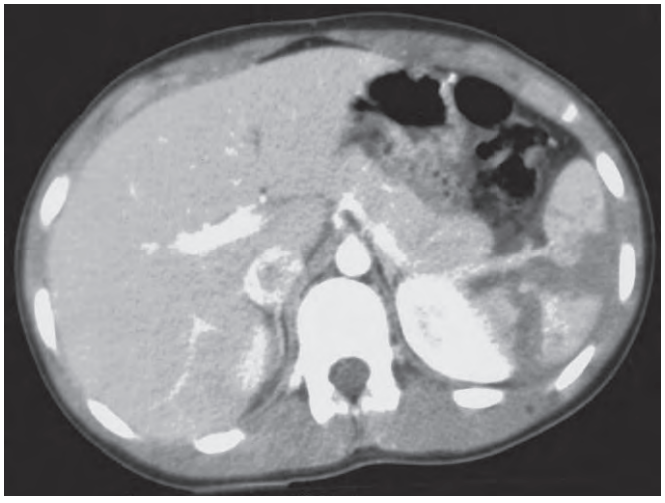

E

Figure 129–3. Abdominal computed tomography scans with intravenous contrast demonstrating typical splenic lesions. **A,** Grade I injury with a midsplenic subcapsular hematoma less than 10% of the surface area. **B,** Grade II injury demonstrating a laceration of the upper pole 3 cm in depth with no vascular injury. **C,** Grade III injury with a large intraparenchymal hematoma. **D,** Grade IV injury demonstrating a large ruptured hematoma in the lower pole with extravasation. **E,** Grade V injury demonstrating a shattered spleen.

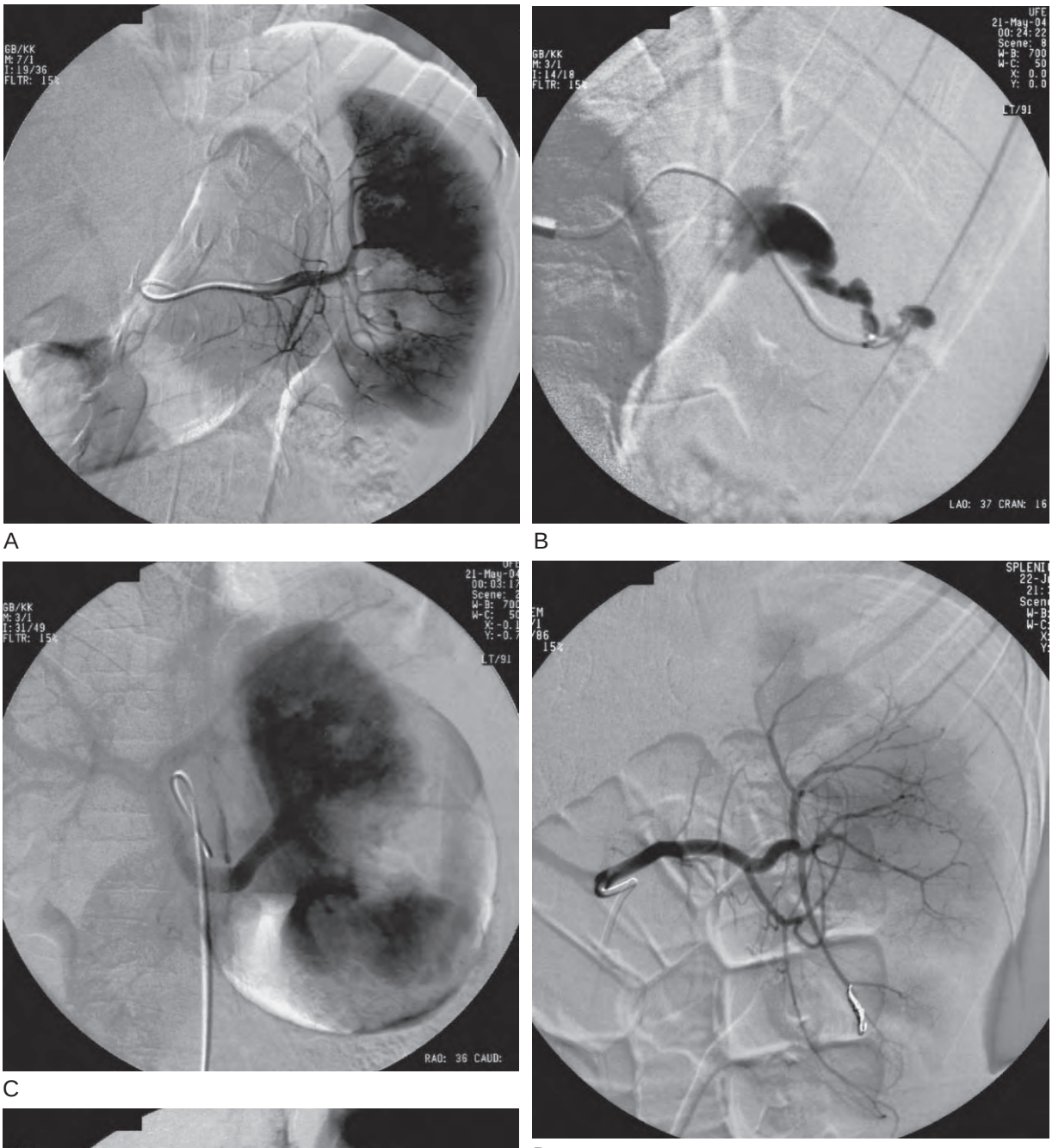

Figure 129–4. Sequential radiographs depicting successful embolization of a splenic injury with active arterial bleeding. **A,** Selective splenic artery catheterization demonstrating extravasation from the inferior pole of the spleen with decreased perfusion to the area. **B,** "Pseudovenule" of frank extravasation of contrast into the peritoneum. **C,** Extravasation of contrast delineating the hematoma. **D,** Coil embolization of a bleeding vessel. **E,** A postembolization contrast injection shows no further extravasation.

Table 129–2 Evidence-Based Guidelines for Resource Utilization in Children with Isolated Spleen or Liver Injury

	Grade I	Grade II	Grade III	Grade IV
Intensive care unit stay (days)	None	None	None	1
Hospital stay (days)	2	3	4	5
Predischarge imaging	None	None	None	None
Postdischarge imaging	None	None	None	None
Activity restriction (wk)	3	4	5	6

Adapted from Stylianos S: Evidence-based guidelines for resource utilization in children with isolated spleen or liver injury. J Pediatr Surg 35:164-169, 2000.

of the blood loss, it should be removed. The spleen should initially be assessed in situ, with splenic mobilization performed only if visible or palpable parenchymal tears are noted. Splenic mobilization begins with incision of the lateral-most attachments, the lienorenal ligaments. This allows rotation of the spleen medially into the wound, where it can be thoroughly inspected.

Hemorrhage from grade II and III splenic injuries can usually be controlled by direct suture splenorrhaphy with moderately sized absorbable suture. Omentum may also serve as a buttress when securing these sutures, as well as any number of topical hemostatic agents.[23]

Multiple or deeper injuries may be amenable to wrapping the spleen in absorbable mesh, as described by Delaney et al.[24] This mesh creates pressure to tamponade parenchymal bleeding while preserving function. Deeper parenchymal disruption can be treated by anatomic resection and closure of the cut splenic edges with mattress sutures or omental buttressing.

Splenic autotransplantation has been suggested as an alternative for preservation of functional splenic tissue, but no consensus exists with regard to the amount of immunocompetence retained by ectopic splenic fragments. Some surgeons continue to advocate routine reimplantation after splenectomy in adults, and a recent report from Dessouky suggests that some aspects of splenic function are preserved in pediatric patients undergoing splenectomy for thalassemia.[25] No class I evidence exists at this time to guide this practice.

ASPLENIA PROPHYLAXIS

Children with post-traumatic or functional asplenia need antibiotic prophylaxis. All these patients are at increased risk for infection, primarily with the encapsulated organisms *Streptococcus pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*. Life-threatening infections occur with a frequency of approximately 0.3% per year, with a 5% lifetime risk. Fifty percent of all life-threatening infections occur within the first 2 years after splenectomy. Exacting guidelines for immunization and antibiotic prophylaxis do not exist, but an excellent review by Castagnola and Fioredda in 2003 summarized the most current recommendations.[10] Prevention of life-threatening infection in post-splenectomy patients involves vaccination, antibiotics, and education.

Vaccination Vaccination against *S. pneumoniae* is highly recommended in all post-splenectomy patients. Two versions of vaccine exist—the polysaccharide vaccine, which includes 23 serotypes (PPV23), and the tetanus-conjugate heptavalent vaccine (PCV7). The heptavalent vaccine should be given to all children between the ages of 2 and 23 months, with asplenic and other high-risk groups receiving two additional doses after the age of 2 years. Additionally, the polysaccharide vaccine should be given 2 to 3 months after the final dose of PCV7, with consideration of boosters every 6 years. Some authors have advocated determination of antipneumococcal titers to document vaccine response and to identify poor responders, but this practice has not gained widespread acceptance.[10]

Vaccination against *H. influenzae* is thought to be safe and is recommended for all post-splenectomy patients. A course of three separate vaccines is given to infants, but a single dose should be effective for children older than 1 year.[10]

There are relatively few data regarding the response of splenectomized patients to the meningococcal vaccine. However, it has been shown to have an effective safety and immunogenic profile in adults, and many centers, including our own, routinely offer the meningococcal vaccine to asplenic patients.

Antibiotics All asplenic patients should be given daily oral antibiotic prophylaxis. Penicillin V, 125 mg twice daily for children younger than 3 years and 250 mg twice daily for those 3 to 14 years old, is the recommended dosage. The age at which prophylaxis is discontinued is controversial; however, most authors agree that all asplenic children younger than 5 years should receive prophylaxis and all children, regardless of age, should receive antibiotics for at least 2 years after splenectomy, when the risk for invasive infection is the highest.[10]

Education Patient and parental education is probably the most important aspect in preventing serious infection. Without creating paranoia, the surgeon needs to emphasize to parents that any fever in their asplenic

child constitutes a potential life-threatening emergency and medical care should be sought as soon as possible. Dosages of oral antibiotics should be readily available in the home and given to the child en route to seeking formal medical attention. Parents need to be counseled that their child's asplenic state is of utmost importance when presenting the medical history to the primary physician. Early and aggressive parenteral therapy targeted against encapsulated organisms should be standard when concerns of infection exist in this group of patients.

CONCLUSION

Splenic injury is relatively common in pediatric trauma. Isolated splenic trauma is extremely well tolerated; however, the presence of a splenic injury should alert surgeons to the possibility of other associated injuries. The expectation for these patients should be for successful nonoperative management under the watchful eye of the surgical team.

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Chapter

130

Cysts and Tumors of the Spleen

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Cysts and tumors of the spleen are rare lesions. Cysts are classified as either "true" cysts containing an epithelial lining or "false" cysts without an epithelial lining (pseudocysts).[1] True cysts are either parasitic or nonparasitic, whereas false cysts mainly arise as a result of blunt abdominal trauma.[2,3] Tumors of the spleen are divided into two categories: nonlymphoid and lymphoid. The most common nonlymphoid tumors are the vascular tumors consisting of benign and malignant hemangiomas, lymphangiomas, and hemangioendotheliomas. Lymphoid tumors are mainly of the Hodgkin and non-Hodgkin variety. Metastasis from melanoma, breast, and lung tumors make up the majority of secondary tumors found in the spleen.[4] Treatment options of cysts and tumors of the spleen have evolved greatly over the past few decades. Recognition of the immunologic function of the spleen and the occurrence of overwhelming postsplenectomy infection (OPSI) has changed the preferred procedure from splenectomy to splenic preservation whenever feasible. Cysts and tumors of the spleen in children pose different challenges for the surgeon, and management is discussed in this chapter.

Splenic surgery has a long and storied tradition. Galen believed that the spleen was an "organ of mystery." Aristotle viewed it as unnecessary, and Pliny the Elder (23-79 AD) among others thought it was where laughter was based. From William Shakespeare's *Twelfth Night,* Act 3, 2, 62-63 is the quote, "If you desire the spleen will laugh yourself into stitches, follow me." Adrian Zacarelli performed the first splenectomy in 1549 for splenomegaly on a 24-year-old Neapolitan woman. Franciscus Rosetti reported the first successful partial splenectomy for trauma in 1590. A total splenectomy for trauma was recorded by Nicolaus Matthias in 1678 in Capetown, South Africa, in a patient whose spleen protruded through a flank wound. In the United States, it was not until 1816 that Royal Navy surgeon O'Brien reported his first successful splenectomy for trauma. His patient was in the act of committing a rape when the female stabbed him on the left side. The protruding portion of the spleen was ligated and the man was discharged 20 days later, having been cured.[5] In England, 1866 marked the first successful splenectomy by Sir Thomas Spencer Wells. After discovering the condition at autopsy in 1829, Andral is credited with the first record of any nonparasitic splenic cyst.[7] Pean described the first splenectomy for a splenic cyst in 1867[2] and Grede, in 1881, performed the first splenectomy for a splenic pseudocyst that occurred after abdominal trauma.[7] In 1952, King and Shumacker described an increased rate of infection in children who had undergone splenectomy and efforts began to treat splenic cysts and tumors without resorting to total splenectomy.[8] Morgenstern and Shapiro are credited with the first successful open partial splenectomy for an epidermoid cyst in 1980.[9] With the advent of laparoscopic surgery in the 1990s, options for splenic preservation surgery increased. Seshadri et al. reported the successful performance of laparoscopic partial splenectomy.[10] Today, reported laparoscopic methods include both traditional and hand-assisted methods for marsupialization of splenic cysts and removal of splenic tumors.

CYSTS

Before one determines the most appropriate treatment, the type of splenic lesion must be determined. Fowler is credited with the first classification system for splenic cysts.[11] Martin revised this to a simpler more practical classification, which is used more commonly today.

Primary (true) splenic cysts are also known as congenital, epidermoid, or epithelial cysts. These true cysts can be divided into parasitic and nonparasitic. Parasitic cysts are more common worldwide, especially in areas endemic for *Echinococcus* such as south central Europe, South America, and Australia, but are extremely rare in

the United States. Two thirds or more of the splenic cysts are caused by echinococci, with *Echinococcus granulosus* as the most common species.[6] The echinococcal cyst is composed of an inner germinal layer and an outer laminated layer surrounded by a fibrous capsule, characteristically multilocular in appearance, and filled with fluid under pressure. It contains daughter cysts and infective scolices. Echinococcal cysts may be asymptomatic or may cause pressure symptoms when they reach a large enough size, become secondarily infected, or rupture. Diagnosis may be established by indirect hemagglutination or enzyme-linked immunosorbent assay tests, which are positive in about 90% of patients with echinococcal cysts. Ultrasound and computed tomography (CT) characteristically demonstrate a cystic mass that is septated and contains daughter cysts. Splenectomy is the treatment of choice. Care must be taken to avoid puncture of the cyst and spillage of the infective scolices, which can cause an anaphylactic reaction and hypotension. Sterilization of the cyst contents by instillation of 3% sodium chloride or alcohol has been attempted, but the potential for systemic absorption limits usefulness of this approach. If intraperitoneal spillage occurs, intravenous epinephrine may be needed to treat the anaphylactic hypotension.

Congenital nonparasitic cysts account for about 10% of all splenic cysts[12] and approximately 25% of nonparasitic cysts. Ough and associates in 1981 examined fetal and adult spleens and proposed that congenital splenic cysts form where there is an invagination of the mesothelium-lined splenic capsule during development.[13] This lining is pluripotential and may undergo metaplastic changes and fluid accumulation with resultant cystic expansion. The neoplastic nonparasitic cysts are less common and include epidermoid cysts, dermoid cysts, lymphangiomas, and cavernous angiomas. Of these, epidermoid cysts are the most common.[12-14]

Overall, the most common type of splenic cyst is the secondary (false) cyst. These cysts do not have a cellular lining and are, therefore, pseudocysts. Excluding parasitic cysts, pseudocysts constitute 75% of all splenic cysts. They are most commonly post-traumatic and most likely arise from encapsulation of a splenic hematoma with subsequent absorption of blood and persistence of a false cyst wall.[12] Eighty percent of splenic pseudocysts are large, solitary, and unilocular, two thirds being of the hemorrhagic variety with one third of the serous type.[7,11] Pachter and colleagues hypothesized that an increase in nonsurgical management of blunt splenic trauma could contribute to the formation of splenic pseudocysts.[3] In fact, 80% of patients with hemorrhagic splenic pseudocysts report a history of abdominal trauma.[3,7,11]

Splenic cysts are most common in the 2nd and 3rd decade of life, although they have been noted in all age groups, including infants. An asymptomatic painless abdominal mass is the presenting feature in approximately 30% to 45% of cases. Splenic cysts may present with localized or referred pain relating to splenomegaly, abdominal distention, and mass effect. The symptoms are primarily gastrointestinal and include vague abdominal pain, early satiety, nausea, vomiting, and dysphagia. The nonspecific symptoms, such as epigastric fullness or pain, may best be related to compression of adjacent organs such as stomach, kidneys, or diaphragm. A recurrent, intermittent, dull pain that is unabated with food or antacids haunts some patients. Other symptoms include left shoulder pain, shortness of breath and pleuritic chest pain, left lower lobe pneumonia, and/or atelectasis. Reversible hypertension due to renal artery compression may be seen. Vague urinary complaints may arise due to compression and/or pressure on the left kidney and ureteropelvic junction.[14] Acute abdominal pain with or without peritoneal signs may be secondary to rupture or infection.[9] Tsakayannis et al., in their study of 19 children with congenital cysts, reported that only those with cysts larger than 8 cm had clinical symptoms, mainly an abdominal mass and/or abdominal pain.[15] Walz et al. reported a 25% risk of rupture when the cyst is greater than 5 cm.[16]

Aside from the occasional abdominal mass, the physical examination is usually normal. Routine laboratory studies are also normal. Tumor markers carcinoembryonic antigen (CEA) and CA 19-9 may be elevated and should be checked if splenic cyst is in the differential diagnosis.[16] Although these are tumor markers associated with pancreatic, ovarian, uterine, and alimentary carcinomas, they may be elevated in patients with benign cystic diseases, such as bronchogenic, pancreatic, retroperitoneal, hepatic, thymic cysts, and true epithelial cysts of the spleen. According to Madia and Trompetas and their coworkers, there is a direct relationship between these tumor marker elevations and the presence of splenic cysts. Studies have demonstrated intense immunoreactivity of the cyst's inner lining to anti–CA 19-9 antibodies.[17,18] Serum levels of these tumors markers may lag behind actual elevations within the cystic cavity. Because increased CEA and CA 19-9 levels may be from benign or malignant processes, preoperative and postoperative levels documenting change are indicated.

Diagnosis of a splenic lesion is easily obtained with noninvasive radiographic imaging. Ultrasound and CT scanning are the diagnostic tools of choice. Ultrasound can distinguish between solid and cystic lesions and accurately measure size. Sonography also may be useful in demonstrating the internal echoes of abscesses and hematomas and differentiate them from cysts. When ultrasound is unsuccessful because of obesity, distortion of the signal from overlying bowel gas or the lower ribs, and/or the presence of small and multiple lesions, CT scan may be a better option. CT scanning can better delineate the trabeculated or septated nature of the cyst wall and wall calcification and has greater specificity in defining whether a lesion is cystic or solid. CT has the advantage of being able to examine the rest of the peritoneal cavity for mass effect, compression, extrasplenic involvement, or other abnormalities.[1,19-21]

Splenic cysts have historically been treated by splenectomy. However, since 1952, with the demonstration of the increased mortality of splenectomized patients due to OPSI, the trend has shifted to more conservative surgery. The incidence of OPSI is reported to be 0.2% to 4.3%, with a lifetime risk of OPSI of 5%.[2,22,23] Although the incidence is low, it still represents a 20- to 50-fold increase in the risk of dying from sepsis compared to the general population with intact spleens. OPSI may be preventable

by several interventions. The surgeon must keep in mind that preservation of at least 25% of the spleen is necessary to maintain protection against pneumococcal bacteria, the most common organism associated with OPSI.[13,15] Immunization against *Streptococcus pneumoniae* is recommended in all patients 10 days to 2 weeks prior to undergoing a splenectomy, with a booster dose in 5 to 10 years. *Hemophilus influenzae* type b and meningococcal immunizations are also available.[23]

Partial splenectomy with a TA-stapler or harmonic scalpel makes organ conservation possible.[24,25] Percutaneous aspiration or percutaneous drainage with an indwelling catheter has also been suggested as a treatment alternative to splenectomy. Pachter et al. believes that this might play a role in management of posttraumatic pseudocysts before surgical treatment is offered.[3] There are no studies to qualify this belief. In fact, one study is of three pediatric patients who were treated in this manner and all resorted to surgical intervention.[26] Laparoscopic puncture and creation of a cyst-peritoneal window has been reported as an alternative to percutaneous drainage.[27] However, one must be cognizant of the possibility of recurrence and, more important, of the presence of an echinococcal cyst with a false-negative serology. Aspiration or percutaneous drainage may also result in a dense inflammatory reaction around the spleen making subsequent surgical treatment that much more difficult, making the possibility of splenic preservation highly unlikely. We believe that attempts at percutaneous aspiration or drainage of splenic cysts should be avoided.

Another technique to avoid splenectomy is partial splenic decapsulation (marsupialization). This approach involves the trocar decompression of the cyst with removal of the outer splenic capsule. A running locking suture in the splenic wall is used to ensure hemostasis. External drainage is also performed. This method is performed with greater ease than a partial splenectomy and may be attractive in cases where previous percutaneous aspiration has been attempted and a dense inflammatory reaction resulted. However, the possibility of a malignancy developing in the splenic remnant raises doubts with this technique.[2,14]

SOLID TUMORS

Tumors of the spleen are uncommon lesions and are categorized as either nonlymphoid or lymphoid. The most common nonlymphoid tumors are the vascular tumors consisting of benign and malignant hemangiomas, lymphangiomas, and hemangioendotheliomas. Other tumors of the spleen such as hamartomas, fibrosarcomas, inflammatory pseudotumors, and lipomas are extremely rare and have been reported only briefly.[4,6,28-30]

Hemangiomas are the most common benign tumor of the spleen. These lesions are primarily asymptomatic and incidentally found at autopsy or in spleens removed for other purposes. Hemangiomas may be singular, multiple, or even involve the entire spleen. Symptoms result when the tumor enlarges to encroach on adjacent organs. Spontaneous rupture can occur in up to 25% of cases. A consumptive coagulopathy may be present due to the platelet trapping in the cavernous spaces of the lesion. Mass effect on the stomach, kidney, and splenic flexure of the colon may be seen with radiographic examination. CT scan demonstrates splenomegaly. Duplex ultrasound or magnetic resonance imaging can be used to establish the diagnosis. Angiography demonstrates a "laking" effect similar to that seen with hepatic hemangiomas. Nonsurgical treatment is employed for small, asymptomatic, incidentally detected hemangiomas, whereas splenectomy is the treatment of choice for larger and symptomatic hemangiomas.[4,6]

Lymphangiomas of the spleen are less common than hemangiomas. They are formed from congenital malformations of the lymphatic system and are composed of cystic lymphatic spaces lined with endothelium. These spaces are filled with eosinophilic proteinaceous material and may account for a significant part of the splenic weight. They may be part of a generalized lymphangiomatosis. Lymphangiomas are found incidentally and only become symptomatic due to their size. This is mainly a benign condition, although there exists one case of malignant degeneration reported from Tel Aviv, Israel, in 1983.[31] CT and angiography are helpful in the diagnosis, the latter revealing the absence of "lakes" characteristic of hemangiomas. Splenectomy is indicated for symptomatic lesions.[4,6,31]

Primary hemangiosarcoma of the spleen, although rare, is considered the most frequent primary malignancy of the spleen. This lesion is synonymous with hemangiosarcoma, angiosarcoma, and hemangioendothelial sarcoma. *Hemangiosarcoma* is the preferred term to distinguish it from lymphangiosarcoma, but *angiosarcoma* seems to be the term most widely used historically. This tumor arises from endothelial or mesenchymal cells, grows rapidly, and metastasizes to regional lymph nodes, liver, bone marrow, and lungs. Clinically, symptoms relating to splenomegaly predominate. Abdominal pain, tenderness over the spleen, general weight loss, and cachexia may be seen. Aranha et al. reported a 20% occurrence of ascites and 16% occurrence of pleural effusion associated with splenic neoplasms.[32] Angiopathic hemolytic anemia may be noted. Spontaneous rupture may be the presenting feature of this tumor. Although it has been the case for hemangiosarcomas of the liver, documentation of exposure to thorium dioxide, vinyl chloride, or arsenic is not associated with splenic cases. Angiographic findings are similar to those seen with hemangiomas. Splenectomy is indicated for hemangiosarcomas. However, prognosis remains poor in almost all cases.[4,6,31-34]

Lymphoid tumors of the spleen are mainly Hodgkin's disease and non-Hodgkin's lymphoma. As primary lesions of the spleen, these tumors are rare; however, the spleen is often the site of secondary involvement. Involvement of the spleen, either primarily or secondarily, is seen first in the white pulp. This process may be diffuse, as seen with nodular lymphoma, or localized with large irregular tumors, as seen with large cell lymphomas. In addition to the palliative attempts of splenectomy for symptomatic splenomegaly or hypersplenism, splenectomy may be performed as part of a staging laparotomy

for Hodgkin's lymphoma. There is considerable controversy regarding the usefulness of a staging laparotomy and splenectomy for Hodgkin's disease; it is beyond the scope of this chapter to explore that topic.

Metastasis from melanoma, breast, and lung tumors make up the majority of secondary tumors found in the spleen.[4] These metastases are relatively uncommon even though the spleen is the most vascular organ in the body. Lam gave the following explanations for this phenomenon: the sharp path of the splenic artery may inhibit tumor emboli from entering the spleen; the rhythmic contractions of the spleen prevent lodging of tumor emboli in the spleen; the lack of afferent lymphatics prevent transport of metastases to the spleen; and the high amount of lymphoid tissue in the spleen allows for high antitumor activity.[35] Lam reports the incidence of splenic metastasis from 0.3% to 7.3%, which seems to be dependent on the location of the primary tumor. This is also dependent on the part of the world in which the patient lives and which cancers are prevalent in that geographic location. It is extremely rare to find metastasis to the spleen in the absence of metastases to other organs. Splenic metastasis often occurs later in the disease process and is found at autopsy in a patient with disseminated disease. The latent period of metastatic lesions is variable and may occur up to 7 years after primary tumor detection. Therefore, a splenic mass seen in a patient with a history of carcinoma, even if a surgical cure had been obtained, should be treated as potentially metastatic disease until proven otherwise. Metastases to the spleen are typically asymptomatic, until they become large enough to cause mass effect symptoms. Spontaneous rupture of the spleen from metastatic tumor is exceedingly rare but may be the solitary presentation.[35]

To establish the diagnosis and to alleviate symptoms, tumors of the spleen should be removed. Surgical removal of a splenic tumor must adhere to the sound surgical principles for removal of any tumor. Good exposure, removal of the entire tumor without rupture, adequate margins, and perfect hemostasis must be achieved for a successful tumor operation. For most splenic tumors, these principles are best achieved with a splenectomy.

A left subcostal incision or midline incision can be used to expose the spleen. Although Morgenstern et al. believe the subcostal incision is the best approach, the midline incision may offer better exposure in the patient with gross splenomegaly.[4] The midline view allows for better isolation of the lower pole if it extends down into the pelvis. The first step is transection of the ligamentous attachments, including the splenophrenic ligament at the superior pole and the spenocolic and splenorenal ligaments at the inferior pole. Either blunt dissection or sharp dissection in the case of thickened ligaments accomplishes this task easily. Early double ligation of the splenic artery allows for possible reduction of the spleen size, decrease in venous outflow, and easier delivery of the spleen into the wound. Ligation of easily accessible veins including the short gastric veins, vessels to the anterior hilum, and lower pole should be accomplished before mobilization is attempted. To ensure gentle mobilization of an intact spleen and capsule, the surgeon should stand on the right side of the table while the assistant retracts the costal margin to the left. This allows for incision of the retroperitoneum parallel to the long axis of the spleen. Rarely, it may be necessary to remove a portion of the parietal peritoneum or diaphragm if the spleen is not easily separable from these areas. Once the spleen has been sufficiently mobilized to the midline and posterior hilar surface exposed, it is advisable to control the large posterior splenic veins. Attempts at control of the fragile veins from the anterior approach may result in venous disruption and massive bleeding. On removal of the spleen, attempts at sampling the hilar lymph nodes should be made. These are usually located near the major hilar vessels and may be useful in the grading of splenic tumors.[4,36]

Laparoscopic splenectomy for splenic tumors has been reported. The principles for open tumor surgery apply for laparoscopy. In the past, opponents of the laparoscopic splenectomy criticized the necessity of splenic morcellation for removal of the spleen from the peritoneal cavity. However, with a small 3-cm extension of one of the trocar sites, most spleens can be removed intact. Carroll et al. proved that the staging surgery for Hodgkin's disease could be performed entirely laparoscopically.[37] It is essential that the spleen be removed intact to avoid peritoneal dissemination of potentially malignant cells. Proponents believe that the spleen can be dissected more precisely and due to better visualization, vessels can be ligated safely and earlier in the course of the operation to prevent hematologic spread with dissection. However, Flowers et al. reported a learning curve of 20 laparoscopic splenectomies before surgeons were comfortable with the technique.[22] Therefore, laparoscopic splenectomy is feasible only if the laparoscopist is expert in advanced laparoscopic surgery.[22,37-39]

Hand-assisted laparoscopic splenectomy might be a practical alternative to pure laparoscopic removal. This offers both the benefits of close inspection with laparoscopy and palpation of the tumor as in open surgery. The hand offers easy exposure, more complete exploration of regional lymph nodes, stomach and pancreas by palpation, and immediate hemostasis with manual compression. Intact removal is easily accomplished through the hand port, and the patient receives much of the same advantages of laparoscopic surgery.[39]

Partial splenectomy has been successfully reported only for cysts of the spleen. However, for staging of Hodgkin's disease, the risk of a negative staging error with partial splenectomy has been reported and is advised against. In patients with splenic metastasis, if the metastasis is clearly part of disseminated metastatic disease, splenic biopsy is sufficient. Splenectomy should not be performed in these cases because there is no survival advantage to justify the risk.

CONCLUSIONS

When faced with a tumor or cyst of the spleen, the surgeon must first narrow the differential diagnosis, paying special attention to the possibility of infections or malignant etiology. Once the cause has been established,

the appropriate operative approach may be chosen. As described, laparoscopic and open techniques are equally effective and safe as long as the surgeon has the requisite experience.

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Chapter

131

Management of Splenic Abscess

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Splenic abscesses are rare, with less than 500 cases cited in the literature.[1] Splenic abscesses were lethal prior to the era of antibiotics and were usually diagnosed at autopsy[2] with incidences of 0.14% to 0.7%.[3,4] In recent times the incidence of splenic abscess has increased due to the growing number of immunocompromised patients.[5] However, with the development of new imaging techniques and improved antibiotics comes an advance in the management and resolution of splenic abscesses.

PRESENTING SYMPTOMS AND SIGNS

The clinical triad of fever, left upper quadrant pain, and leukocytosis is seen only in one third to two thirds of patients with splenic abscess.[6,7] At the time of diagnosis, patients may present with a variety of signs and symptoms or none at all. Reported symptoms and signs include nausea, vomiting, weight loss, decreased left-sided breath sounds, splenomegaly, and a new systolic murmur.[5,8-10] Immunocompromised patients usually present further in the disease process with generalized symptoms and signs such as fever, abdominal pain, and weight loss.[5]

DIAGNOSIS

The diagnosis of splenic abscess can be supported by microbiology and laboratory data. Leukocytosis (white blood cell count >12,000/μl) is reported in 60% of cases.[7] Idiopathic thrombocytosis in septic patients may suggest a splenic abscess.[11] Cultures of abscess fluid identify the offending organism 80% of the time.[7] However, blood cultures isolate the infecting organism in less than half of all cases.[7,8] Moreover, in 66% of cases, different organisms are identified from the abscess and blood cultures.[7,8] These factors need to be considered when choosing a patient's antibiotic regimen. Imaging studies can be invaluable when diagnosing splenic abscess. Plain chest radiographs cannot give a definitive diagnosis, however, because there are nonspecific findings in 33% to 80% of cases.[3,4,8,12,13] These findings include left pleural effusion, pleural thickening, left basilar pulmonary infiltrate, and an elevated left hemidiaphragm.[5,8,13,14] Nonspecific findings are also seen in about 25% to 69% of abdominal radiographs.[3,4,8,12,13] These studies may demonstrate a soft tissue mass, extraluminal gas shadow, or a nongastric air-fluid level in the left upper quadrant.[13,14] There is one reported case of a gas-forming splenic abscess causing pneumoperitoneum and generalized peritonitis in an immunocompromised patient, in which the plain abdominal film showed free air and extraluminal air bubbles in the left upper quadrant.[15] Ultrasound has a sensitivity of 75% to 90% for detecting splenic abscess.[4,13,16] Sonographic findings include an anechoic (13%) or hypoechoic (87%) mass, with an irregular wall, with or without internal echogenic foci that may represent septations, debris, or layering.[7,17-20] Computed tomography (CT) is more accurate than ultrasound, with a sensitivity of up to 96%[4] and specificity of 90% to 95%.[4,7] In addition, CT has a greater specificity over ultrasound in detecting gas, a diagnostic finding for splenic abscess.[7] CT also offers the advantage of being able to localize abscesses as small as several millimeters and enables the examiner to determine whether the abscesses are unilocular (Figs. 131–1 and 131–2) or multilocular (Fig. 131–3). Another advantage is being able to identify the anatomic location of the abscess in relation to the spleen and other organs, thus aiding in determining the appropriate management option. Findings on CT scan include low-density parenchymal areas with peripheral enhancement after intravenous contrast administration.[13,14] These scans can help differentiate splenic abscess from other diseases such as splenic cysts and infarctions and can be used serially to follow abscess response to therapy.[5] Furthermore, CT- or ultrasound-guided intervention can be used for both diagnosis and therapy.

In situations where the diagnosis remains unclear after the imaging and laboratory studies, fine-needle aspiration is recommended.[7]

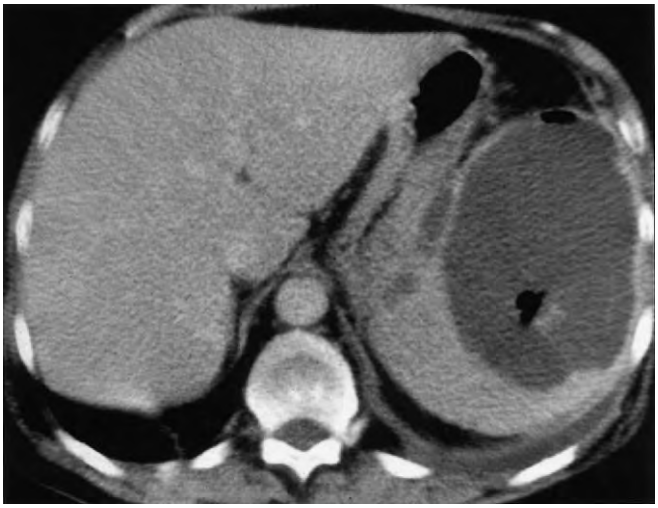

Figure 131–1. CT of the upper abdomen following intravenous contrast medium administration of the large fluid-filled cavity with enhancing borders and containing gas. (Courtesy of GE Healthcare BioSciences—Medical Diagnostics [http://www.medcyclopaedia.com]).

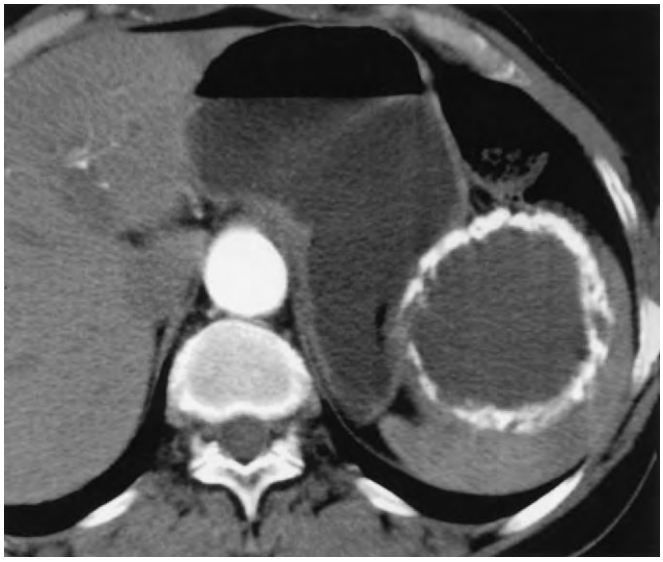

Figure 131–2. CT of the upper abdomen following intravenous contrast administration. There is a chronic abscess cavity with irregular and thick calcifications of wall. (Courtesy of GE Healthcare BioSciences—Medical Diagnostics [http://www.medcyclopaedia.com]).

ABSCESS CHARACTERISTICS

The pathogenesis of splenic abscess include hematogenous spread of a remote infection, hemoglobinopathy resulting in embolization/infarction, chemotherapy and other immunodeficiency states, trauma, and contiguous infection from adjacent organs.[1,3,21,22] Traditionally, the pathogenesis is related to the spread of microorganisms

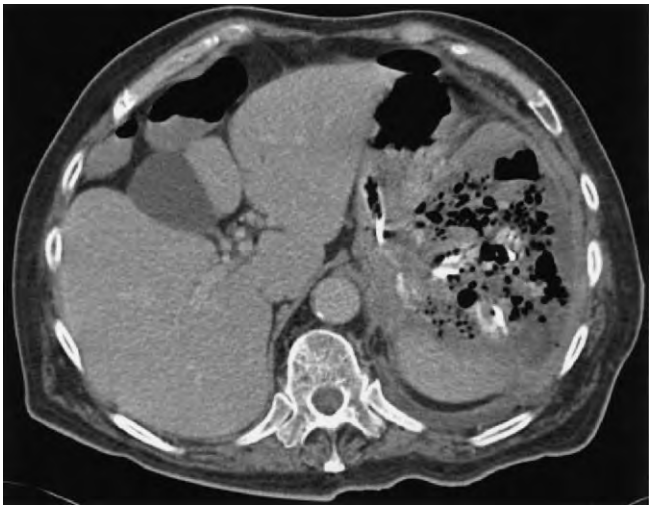

Figure 131–3. CT of the upper abdomen demonstrating a multilocular splenic abscess after splenic flexure lymphoma resection. There is a Penrose drain centrally.

from an infectious source via a hematogenous route. This route of infection has been reported in 49% to 68% of cases.[1,13,21] Metastatic hematogenous infections from endocarditis account for greater than 66% of splenic abscesses.[9] However, in recent times, 18% to 28% of splenic abscess cases are found in immunocompromised patients.[1,13] In this patient population, splenic abscesses are usually multilocular. Secondary to the increased population of immunocompromised patients, opportunistic pathogens such as fungi and gram-positive aerobes are more often identified than in the past.[1] Splenic abscess due to a contiguous septic process from adjacent organs such as the stomach, colon, pancreas, or kidney is seen less frequently, with an incidence of only 6% to 15% of reported cases.[1,4,13] Hemoglobinopathies such as sickle cell, thalassemia, and leukemia are known to predispose patients to splenic abscess.[13] These disorders are recently reported in 6% or less of cases.[1,4,13,21] Unilocular splenic abscess has an improved prognosis and is usually present with subacute bacterial endocarditis, drug abuse, trauma, or other septic episodes.[7]

There is a large variety of both aerobic and anaerobic bacteria responsible for splenic abscess. The most common being *Staphylococcus aureus, Streptococcus, Salmonella, Escherichia coli,* and anaerobes.[3,4,23] Polymicrobial abscesses have been found in 11% to 36% of cases,[23] with anaerobic bacteria being present most often.[4,23] With the increased number of immunodeficient patients, there has been an increase in fungal abscesses to 25.8% of cases.[1,4,13] *Candida* accounts for more than 70% of fungal abscesses with other isolates including *Aspergillus, Cryptococcus neoformans, Aureobasidium pullulans,* and *Blastomyces dermatitis.*[4,13] Fungal abscesses tend to be multilocular in 90% of patients,[13,24] whereas bacterial abscesses are multilocular in 26% of patients.[4,13,21] Splenic involvement with *Mycobacterium* species was once rare but recently has been reported in 4% to 7.8% of cases, mostly in immunocompromised patients.[4,13]

MANAGEMENT

If left untreated, splenic abscesses are universally fatal. Combined medical therapy and drainage is used to treat many splenic abscesses. Drainage can be accomplished by either splenectomy or percutaneously using radiographic guidance. Medical management alone is ineffective and is associated with a mortality rate as high as 80%.[5] However, splenic abscess caused by *Mycobacterium* species, *Pneumocystis carinii,* or fungal infection can be treated successfully with antibiotics alone.[1]

The traditional treatment for splenic abscess is splenectomy, but this is associated with morbidity and mortality rates of 11% to 28% and 6% to 14%, respectively, secondary to underlying disease and intra-abdominal rupture during operation.[1,4,7,8] Mortality is even greater in critically ill and immunocompromised patients.[1,5,7] Furthermore, splenectomy may be difficult in some patients because of extensive parasplenic inflammation and adhesions. In these situations, ligation of the splenic vessels through an opening in the gastrosplenic ligament may be more desirable prior to splenectomy. After splenectomy, the left subphrenic space should be drained. At the time of exploration, if dense adhesions prevent a safe splenectomy, the abscess can be aspirated and interval splenectomy performed at a later date. Infrequently, it may be necessary to remove the 10th and 11th ribs to gain access to a high-lying abscess, taking caution not to enter the pleural cavity.

Laparoscopic drainage of splenic abscess may be indicated when percutaneous drainage is not an option due to location or access or when prior percutaneous drainage attempts have failed. In such cases, laparoscopic drainage of splenic abscess can offer a minimally invasive alternative to open surgery. Additionally, with laparoscopic drainage, abscesses can be aspirated, larger drains placed, and if warranted, a total splenectomy completed. When using laparoscopic therapy for splenic abscess, the abscess may be aspirated at the onset of the procedure to facilitate splenectomy. Laparoscopic splenectomy[25] or drainage may also be successfully and safely implemented for cases of splenic abscess, with outcomes comparing favorably to open series.

An alternative to open splenectomy is CT- or ultrasound-guided percutaneous drainage. This carries a lower morbidity and mortality rate of 5% and 1%, respectively.[1,4,7] Reported complications associated with this modality include pneumothorax and hemothorax.[1] The advantage of the low mortality rate must be weighed against the disadvantage of the 30% recurrence rate from percutaneous drainage.[4] Multiple catheterizations have been required in some patients for complete resolution of an abscess. Furthermore, percutaneous drainage with serial attempts may be implemented as initial therapy for many cases of unilocular abscesses. Response to therapy is monitored with CT or ultrasound, and failure of response can be followed by splenectomy. Techniques of percutaneous drainage offer more advantages over splenectomy in that the therapy is tolerated even in severely debilitated, elderly, or critically ill patients.[5] Additionally, preservation of the spleen is vital in children and immunocompromised patients.[5] Adequate percutaneous drainage of a splenic abscess can be achieved by using 12- to 14-French catheters.[5,22]

Abscesses appropriate for percutaneous drainage are usually unilocular, solitary, and possess a well-defined wall with homogenous-appearing contents. Proper localization of the abscess is also essential for CT- or ultrasound-guided percutaneous drainage. For abscesses that are multiple, septated, or anatomically inaccessible, percutaneous drainage is relatively contraindicated.[5] Percutaneous drainage is not recommended in patients with coagulopathies, ascites, or associated diseases requiring surgical management.[5,6]

Selection of antibiotics in patients with splenic abscess should be guided by the sensitivity of isolates or by the most likely pathogens in culture-negative isolates.[13] The most common length of antibiotic therapy is 10 to 14 days.[13]

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Chapter

132

Splenectomy for Conditions Other Than Trauma

Y. Nancy You · John H. Donohue · David M. Nagorney

Splenectomy for nontraumatic disorders demands careful risk-benefit analysis and surgical planning. Crucial factors considered include the nature of the underlying disease, the severity of symptoms, alternative therapeutic options, the operative risk, and the success rate of splenectomy. During the last decade, the underlying diseases have become better understood; more and effective medical therapies have become available; laparoscopic techniques have decreased operative risks; and prophylaxis has minimized the risk of postsplenectomy infections. These advances have challenged some of the traditional concepts regarding splenectomy. This chapter aims to summarize the current indications and contemporary outcomes of splenectomy for nontraumatic conditions encountered by surgeons in consultation. These conditions mainly include hematologic disorders but also splenic mass lesions, splenic vascular disease, iatrogenic injuries, and other rare diseases.

SPLENECTOMY FOR HEMATOLOGIC DISORDERS

The spleen performs important hematologic and immunologic functions. It maintains the circulating blood components by filtering and removing damaged or senescent cells. As the largest aggregate of lymphoid tissue in the reticuloendothelial system, the spleen functions in both antibody production and phagocytosis. Accordingly, cytopenia and splenomegaly are two common manifestations of hematologic disorders involving the spleen. Cytopenia is associated with hypersplenism, the excessive destruction of one or more blood components. Splenomegaly, defined as splenic weight of more than 175 g (normal, 90–150 g), can become massive (>1000–15,000 g). Mechanical symptoms of splenomegaly include pain and early satiety. When the spleen is the sole site of the disease or a major contributor to the underlying pathophysiology, splenectomy is performed with curative intent. In most conditions, it is performed for effective palliation of symptoms and complications.

Disorders Causing Thrombocytopenia

Thrombocytopenia is defined as platelet count less than 150×10^9/L. Patients with platelet counts of 50×10^9/L or greater are usually asymptomatic and are discovered incidentally. Excessive oozing after surgery or bruising after minor trauma usually does not occur until the platelet count is below 30 to 50×10^9/L. Spontaneous internal bleeding may occur with counts of 10 to 20×10^9/L. Response of thrombocytopenia to therapy has been variably defined in previous studies. Complete response (CR) is most commonly defined as achieving platelet counts of 150×10^9/L for at least 30 days after splenectomy without additional therapy. Partial response (PR) results when platelet counts of at least 50×10^9/L are achieved, whereas no response (NR) is defined when counts remain below 50×10^9/L for 30 days. Relapse occurs when thrombocytopenia recurs after achieving a normal platelet count.[1]

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is the most common hematologic disease for which splenectomy is indicated. Affected patients may be asymptomatic or may present with petechiae, ecchymosis, epistaxis, gastrointestinal bleeding, or menorrhagia. Subarachnoid or intracranial hemorrhage suggests severe thrombocytopenia. ITP is mediated by autoantibodies, typically against multiple platelet membrane glycoproteins such as IIb/IIIa, Ib/Ix, Ia/IIa, IV, and V. Splenic macrophages clear platelets coated with IgG autoantibodies in an accelerated fashion.[2] When compensatory platelet production is impaired or outstripped, thrombocytopenia ensues. The test for antiplatelet antibodies has a sensitivity of

only 49% to 66% and a specificity of 78% to 92%.[2,3] A positive test does not definitively diagnose ITP, whereas a negative result cannot exclude it. ITP remains a clinical diagnosis of exclusion. A search for a secondary cause for thrombocytopenia should be prompted by a history of drug or toxin exposure, recent viral infections, splenomegaly on physical examination, an abnormal peripheral smear, or a hypoplastic bone marrow. Although peripheral smear has been required as a diagnostic test, bone marrow aspiration is considered for patients older than 60 years of age with atypical presentations and in whom other disorders are suspected and splenectomy is contemplated.[4]

The time of disease onset in childhood or adulthood determines the clinical presentation, natural history, and treatment approaches. Childhood ITP most commonly affects children between 2 and 5 years of age without a gender bias. In approximately 90% of the patients, the disease manifests as acute thrombocytopenia, associated with a sudden onset of petechiae occurring 4 to 8 weeks after the prodrome of viral illness, allergies, or immunizations.[5] Antibodies formed during the preceding illnesses cross-react against platelets. The natural history of childhood ITP is favorable; a vast majority (83%) spontaneously recover within 8 weeks without therapy, with approximately 10% to 15% persisting as chronic ITP.[6] Therefore, aggressive therapy is avoided. Typical management includes observation and avoidance of platelet-inhibiting medications and of activities predisposing to trauma. The decision to initiate any form of therapy is typically driven by a concern for the risk of intracranial hemorrhage, the development of refractory clinical symptoms, and activity restrictions that compromise a child's quality-of-life. First-line therapy is medical and includes intravenous immunoglobulin (IVIG), corticosteroids and, anti-IgD, and platelet transfusion. Splenectomy is delayed for as long as possible.[5] However, when it is performed, response rates of 63% to 76% may be expected. The response is sustained in the long-term in 45% of the patients.[7] Benefit from splenectomy may be predicted by preoperative response to IVIG, with positive predictive values of 74% to 91% and negative predictive values of 75% to 100%.[8-11] In the pediatric population, laparoscopic splenectomy does not compromise the response rates, can be safely performed, and allows faster recovery without increasing costs.[12]

Adult ITP has an insidious onset and affects women between 18 and 40 years of age most commonly. The natural history contrasts with that of childhood ITP in that spontaneous remission occurs only in 2% to 9% of all patients.[13] The majority develops chronic ITP. Although the disease course is usually benign, those with severe or refractory thrombocytopenia face four times the risk of mortality than the general population.[14] The decision to initiate therapy depends on the bleeding risk, estimated from patient's age, life-style, platelet count, and concomitant diseases.[4] Standard first-line options include corticosteroids, anti-IgD, and IVIG. Each therapy suffers from limitations: (1) corticosteroids may induce remission in 66% of the patients initially, but less than 20% maintain remission in the long-term; (2) IVIG is costly and is reserved for when steroids are ineffective or contraindicated (e.g. pregnancy); and (3) anti-IgD is only effective in Rh-D–positive nonsplenectomized patients.[4,14] Splenectomy is the most likely curative therapy for ITP. Currently, it is indicated when disease is refractory to 6 weeks of corticosteroid therapy, when maintenance of platelets is dependent on 10 mg or more of prednisone daily, or when options for alternative therapy are limited.[4]

Outcomes of splenectomy for ITP have been summarized in a systematic review by Kojouri et al. reporting on 130 articles.[1] The overall rate of platelet response to splenectomy is 67% (range, 37%–100%), with a sustained response rate of 64% after 7 years (range, 5–12.75 years) of follow-up. The average relapse rate after splenectomy is 15% (range, 0–51%), most occurring within the first postoperative year. One single-center experience of 140 adults revealed an overall complete platelet response rate of 78% initially and 74% after 1 year.[4] Corticosteroids, danazol, and/or IVIG salvaged 81% of those who relapsed.[15] Factors predictive of successful outcome after splenectomy have also been investigated.[1,13] Younger age (<30 years old) at splenectomy and previous response to glucocorticoids most consistently correlated with good response. Additionally, when platelets are mainly sequestered in the spleen rather than the liver and other lymphoid organs, as identified by indium-labeled platelet scans,[4] a superior response rate has been observed.

Laparoscopic splenectomy has become the gold standard for ITP patients. Operative mortality has decreased from 1% for open splenectomy to 0.2% for laparoscopic splenectomy. Similarly, operative morbidity has decreased from 12.9% to 9.6%.[1] Postoperative recovery is superior with less pain and earlier hospital discharge. These benefits are realized without increased cost and without compromising hematologic response rates.[16] In debilitated patients who are unsuitable for an operation, splenic irradiation or partial splenic embolization may be considered, but the experience with this treatment is limited.

Accessory splenic tissue may be present in 16% to 29% of patients with ITP.[1] The most common locations for accessory splenic tissue include the splenic hilum, the gastrosplenic ligament, gastrocolic ligament, greater omentum, mesentery, and presacral space (Fig. 132–1).[17]

A thorough search should be conducted intraoperatively whether the operative approach is open or laparoscopic, because a missed accessory spleen may be the cause for relapse of ITP. The presence of residual functioning splenic tissue after splenectomy is indicated by the absence of Howell-Jolly bodies on a peripheral smear.

ITP occurs in every 1 or 2 per 1000 pregnancies, with or without a preexisting diagnosis. Differential diagnosis should exclude hereditary thrombocytopenia, gestational thrombocytopenia, and syndrome of hemolysis with elevated liver enzymes and low platelets. In pregnant ITP patients, bleeding risks for both the mother and the fetus must be considered, because maternal IgG antibodies cross the placenta and can cause fetal thrombocytopenia. Treatment consists of careful monitoring of maternal platelet counts that typically reach a nadir in

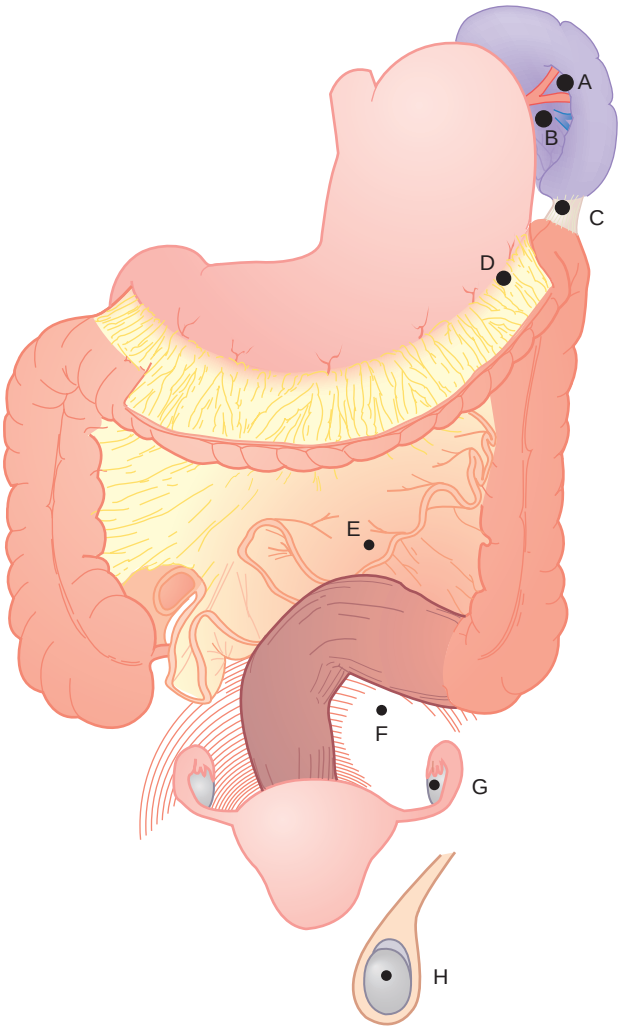

Figure 132–1. Common locations for accessory spleens: hilus of the spleen (A); along the splenic vessels (B); splenocolic ligament (C); omentum (D); mesentery (E); presacral region (F); adrenal region (G); and gonads (H). The weight of the dot corresponds to the frequency an accessory spleen may be found at that location. (From Martin JK: Staging laparotomy. In Donohue J, van Heerden J, Monson J [eds]: Atlas of Surgical Oncology. Cambridge, MA, Blackwell Science, 1995, p 150.)

the third trimester. Intervention is generally not needed in patients with platelet counts greater than 20×10^9/L until prior to delivery. A maternal count greater than 50×10^9/L is considered safe for any mode of delivery and is the goal of therapy. Treatment options of low teratogenic risk include corticosteroids or IVIG, but their side effects may be exacerbated in pregnancy and should be carefully monitored. Splenectomy is usually avoided, but if necessary, splenectomy should be performed during the second trimester. With maternal platelet count greater than 50×10^9/L, the incidence of fetal thrombocytopenia is 10% to 15% and that of fetal hemorrhage is less than 1%.[4,18]

Emergent intervention for ITP is indicated for patients with neurologic symptoms suggestive of intracranial bleeding, with evidence of internal or widespread mucocutaneous bleeding, and for those requiring an emergency operation for other reasons. First-line therapy consists of IVIG (1 g/kg/day for 2 days), intravenous methylprednisolone (1 g/day for 3 days), and platelet transfusions. Emergency splenectomy for refractory patients is rarely needed.[4]

Thrombotic Thrombocytopenia Purpura

Unlike ITP, thrombotic thrombocytopenia purpura (TTP) can be a highly lethal disorder. TTP is characterized by the pentad of thrombocytopenia, hemolytic anemia, fever, renal dysfunction, and, more rarely, neurologic impairment. Characteristic findings include peripheral schistocytes (fragmented erythrocytes) and evidence of microvascular thrombosis. The pathophysiology of TTP involves an undefined trigger of vascular endothelial injury, leading to the release of unusually large forms of the von Willebrand factor. Abnormal platelet agglutination and marked intrasplenic phagocytosis follow. Currently, the first-line therapy consists of total plasma exchange in conjunction with corticosteroids and antiplatelet drugs such as aspirin or dipyridamole. Total plasma exchange has revolutionized the care of TTP by increasing the previously dismal survival rate to approximately 70% to 85%.[19,20] Relapse rates remain as high as 36% over 10 years.[21] Splenectomy has also been advocated for patients who are refractory to or suffer a relapse after plasma exchange. In several small series of patients, splenectomy induced remission of TTP in 50% of refractory patients[22] and reduced the risk of relapse by 70% to 95%.[22-24] However, the operative morbidity in this patient population may be substantial at 17% to 39%. Only recent reports have suggested that laparoscopic splenectomy has lowered these operative risks.[23,25]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause. Antiplatelet antibodies are demonstrable in 78% of SLE patients. These pathogenic autoantibodies and immune complexes affect virtually every body system. Destruction of antibody-coated platelets leads to severe thrombocytopenia in 8% to 20% of these patients.[26] The first-line therapy involves agents aimed at reducing the pathogenic immune response: corticosteroids, danazol, IVIG, and immunosuppressive (e.g., CellCept) and antineoplastic (e.g., cyclophosphamide, vincristine) drugs. Response rates to medical therapy have been variable and transient. Splenectomy is considered for patients who are refractory, dependent, or intolerant of medical therapy. Despite previous concerns, the operative risks of splenectomy are acceptable. The most recent single-center experience of 25 patients undergoing splenectomy reported a 30-day mortality of 0% and morbidity of 24%, with bleeding and infection being the most common complications.[26] The hematologic response was comparable to that for ITP alone, with an initial response rate of 88% and a relapse-free long-term response rate of 64%. These are consistent with

previously reported initial response rates of 21% to 93% and exceeded previously reported sustained response rates of 10% to 32%.[26] Although 36% of the patients relapsed after initial response (consistent with previously reported rates of 6%–79%), additional medical therapy successfully salvaged 55% of these patients.[26] Because splenomegaly is typically not present, laparoscopic splenectomy is now the procedure of choice in this patient population.

Human Immunodeficiency Virus

Chronic thrombocytopenia affects approximately 10% of patients infected with the human immunodeficiency virus (HIV) and 33% of those with acquired immunodeficiency syndrome (AIDS). Bleeding complications are infrequent and rarely severe even in the 1% to 5% of the patients with severe thrombocytopenia.[27] Most patients have platelet counts higher than 50×10^9/L; some may even spontaneously correct their thrombocytopenia. The pathogenesis of HIV-thrombocytopenia involves (1) immune-mediated platelet destruction, similar to that in ITP, and (2) impaired platelet production due to infected megakaryocytes in the bone marrow.[27] Accordingly, first-line therapy consists of (1) corticosteroids, IVIG and anti-D, similar to those in ITP, and (2) antiviral agents such as azidothymidine (AZT) or combination highly active antiretroviral therapy to treat the primary disease.[28,29] However, the immunosuppressive effects of corticosteroids make them unsuitable for long-term administration. Splenectomy is indicated in patients unresponsive, refractory, or intolerant of medical therapy. Operative mortality is minimal,[30,31] though the complication rate approaches 24%.[32] Favorable response is achieved in 83% of HIV patients[30,33,34] and slightly fewer AIDS patients.[32] Splenectomy has not been shown to adversely impact the progression to AIDS, overall survival, and AIDS-free survival.[32,34] Despite encouraging results, the timing and patient selection for splenectomy during the course of HIV infection remain controversial.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency disorder characterized by thrombocytopenia, eczema, vasculitis, progressive immunodeficiency, and increased risk for malignancy. Its pathogenesis involves defective cytoplasmic scaffolding proteins.[35] Despite varied phenotypic expressions, thrombocytopenia is the most common manifestation of WAS. For patients with severe symptoms and available HLA-matched donors, bone marrow transplant is performed with curative intent. For symptomatic patients without appropriate donors, splenectomy is indicated in combination with prophylactic antibiotics and immunization. Median survival of up to 25 years has been reported,[36,37] representing substantial improvement over the previously dismal median survival of less than 5 years. IVIG may be used alone or in combination with splenectomy.

Disorders Causing Anemia

Hereditary Anemia

Hereditary anemias can be categorized by (1) defects of the erythrocyte membrane (e.g., hereditary spherocytosis, hereditary elliptocytosis); (2) defects of an erythrocyte enzyme (e.g., pyruvate kinase deficiency, glucose-6-phsophase dehydrogenase deficiency); and (3) defects of hemoglobin synthesis (e.g., thalassemias, sickle cell anemia). All of these mutations result in abnormal erythrocyte morphology and stability and lead to increased hemolysis and phagocytosis by the spleen. The benefit and use of splenectomy vary depending on the diagnosis.

Red Blood Cell Membrane Defects Hereditary spherocytosis (HS) is the most common inherited hemolytic disorder in North America and Europe. It is transmitted mainly as an autosomal dominant trait. The pathogenesis of HS involves deficiencies in membrane structural proteins. The affected family of spectrin proteins, including β spectrin, ankyrin, band 3, and protein 4-2, normally forms the supportive cytoskeleton of the red blood cell (RBC). Dysfunction of these proteins result in abnormal RBC morphology, increased cell membrane fragility, and shortened life span. Clinical findings are variable and include anemia, jaundice, and splenomegaly. Pigmented gallstones form in up to 41% of patients screened with ultrasonography, and their prevalence is higher in patients who coinherit Gilbert's disease.[38] HS is distinguished from other anemias by the findings of elevated reticulocyte counts, hyperbilirubinemia, negative direct antiglobulin test (DAT), spherocytes on peripheral smear, and increased erythrocyte osmotic fragility.[39,40]

The indication for splenectomy is not based on the diagnosis of HS, per se, but on its symptoms and complications (Table 132–1).[41] For patients with mild HS and no gallstones, splenectomy has no benefit.[42] For patients with moderate or severe disease, splenectomy is indicated but usually delayed until after the 6th year of life but before puberty to minimize the risk of postsplenectomy sepsis.[40] Children with accelerating anemia, frequent hemolytic crises, transfusion dependency, or intractable leg ulcers may require earlier intervention.[39] For patients with symptomatic cholelithiasis, splenectomy and cholecystectomy are indicated and can be performed safely together.[43] When gallstones are asymptomatic or found incidentally, the best approach has not been established. Options include observation, cholecystotomy with stone removal, or cholecystectomy.[44,45]

The optimal approach for splenectomy remains controversial. Laparoscopic splenectomy offers a faster postoperative recovery in the pediatric population. It should be the approach of choice when splenomegaly is not present to increase the operative risks.[12,46] Partial (80%–90%) open splenectomy has been advocated for very young patients with severe disease,[46] but preservation of splenic function must be balanced against the risks of disease recurrence. Recently, near-total splenectomy (98%) has been proposed as a means to optimize this balance.[47]

Table 132–1 Classification of Hereditary Spherocytosis

Variable	Trait/Carrier	Mild	Moderate	Severe
Hemoglobin, g/dl	Normal	11-15	8-12	6-8
Reticulocyte, %	<3	3-6	>6	>10
Bilirubin, µmol/L	<17	17-34	>34	>51
Spectrin per RBC, % normal	100	80-100	50-80	40-60
Splenectomy	Not indicated	Usually not indicated	Consider prior to puberty	Usually necessary, delay until age 6 yr if possible

RBC, red blood cell.

Hereditary elliptocytosis is a variant of HS also involving defective spectrin proteins. These patients typically have mild anemia requiring no intervention. Splenectomy does not correct the abnormal RBC morphology but is effective for the rare patient with severe transfusion-dependent anemia. HS must also be differentiated from other rare disorders of RBC membrane permeability, such as hereditary stomatocytosis or cryohydrocytosis. Splenectomy is ineffective and unwarranted and carries a high risk of postsplenectomy venous thrombosis in these patients.[39]

Red Blood Cell Enzymatic Defects Glucose-6-phosphate dehydrogenase deficiency is the most common RBC enzymatic defect. It manifests as a mild anemia and rarely splenomegaly. Experience with splenectomy in this disease is limited. Pyruvate kinase deficiency results in reduced energy generation in RBCs. The homozygous form of this disease results in a severe anemia with splenomegaly. Splenectomy is effective in reducing transfusion requirements.[48]

Hemoglobinopathies Sickle cell disease includes sickle cell anemia (SS), hemoglobin C disease (SC), and the sickle β thalassemia. The inherited point mutation on the sickle gene leads to an abnormal β-chain forming a hemoglobin with decreased solubility in its deoxygenated form. Pathogenesis of sickle disease results from abnormal polymerization of hemoglobin S with low cellular oxygen content. Exponential propagation of this process stiffens and distorts erythrocytes. Further compounding factors include abnormal endothelial adhesion, formation of heterocellular aggregates, dysregulation of nitric oxide–mediated vasodilation, and local inflammation. All of these factors lead to slowed RBC transit and their entrapment in the vasculature and in the spleen.[49] Microvascular occlusion results, and sickle patients suffer from end-organ damage of the eyes, kidneys, subcutaneous tissue, and bone. Splenic sequestration occurs when the RBC is trapped in the enlarged spleen, which then undergoes autoinfarction; it is observed in 7% to 30% of SS patients between 2 and 5 years of life. Acute manifestation, known as *acute splenic sequestration crisis* (ASSC), is potentially fatal. Patients present with profound acute anemia (decrease in hemoglobin by >2 g/dl), reticulocytosis, and thrombocytopenia. Acute therapy requires resuscitation by RBC transfusions. However, recurrence carries a 20% mortality rate and can occur in 50% of those who survive ASSC.[49] As a means to prevent future ASSC, elective splenectomy has been indicated in children older than 2 or 3 years of age after the first episode of ASSC. The operative mortality is 7%, and 5-year mortality is 3.4%.[50,51] The risk of postsplenectomy sepsis is approximately 2% in this patient population but increases substantially if splenectomy is performed prior to 4 years of age.[52-54] Although splenectomy has not been proven to increase survival, its benefits include reducing transfusion dependency, relief from pain from splenomegaly, and treatment of splenic abscesses resulting from splenic infarctions.[50,55]

Patients with thalassemia major (or homozygous β thalassemia) synthesize structurally abnormal hemoglobin that deforms erythrocytes. They typically depend on multiple transfusions to maintain a hemoglobin level above 10 g/dl. When complications of hypersplenism develop, as measured by transfusion requirement of greater than 250 ml/kg/year and iron overload, splenectomy is indicated.[56] Splenectomy reduces the requirements for both transfusions and deferoxamine (an iron chelator) in 32% of patients.[57] More than 80% of children with thalassemia regain normal weight and growth rates after splenectomy.[58] The risk for overwhelming postsplenectomy sepsis (OPSS) is high in this patient population, approximately 10% in the long term.[59] Therefore, splenectomy is usually delayed until after 6 to 8 years of age. Partial splenectomy has been advocated in younger children,[60] and laparoscopic splenectomy is definitely feasible in these patients.[61]

Acquired Hemolytic Anemia

Hemolytic anemia may result from numerous etiologies. Autoimmune hemolytic anemia (AIHA) is an IgG-mediated (so-called warm agglutinin) hemolytic anemia with a positive Coombs' antiglobulin test. Erythrocyte destruction is mediated by splenic macrophages. AIHA may be idiopathic or a manifestation of a systemic disease, such as viral infection, SLE, rheumatoid arthritis, ulcerative colitis, or chronic lymphocytic leukemia (CLL). Splenectomy is indicated when disease is refractory to corticosteroids. It succeeds in up to 64% of patients and reduces the steroid requirement in an

additional 21%.[48] The success rate is higher when AIHA is associated with systemic disease.[62] In contrast, so-called cold agglutinin hemolytic anemia is mediated by IgM. Erythrocytes are sequestered and destroyed in the liver, and splenectomy therefore plays no role in this condition.

Miscellaneous Hematologic Disorders

Evans's Syndrome

Patients with Evans's syndrome present with a combination of autoimmune thrombocytopenia (ITP) and hemolytic anemia (AIHA). Medical therapy typically involves multiple agents, with corticosteroids and IVIG being used most commonly.[63,64] Experience with splenectomy for this rare disease is limited.[65] Although long-term remission has been reported,[65] one study observed the median duration of response following splenectomy to be only 1 month.[64]

Felty's Syndrome

Felty's syndrome, defined as a combination of rheumatoid arthritis, splenomegaly, and neutropenia, affects a small subset of patients, particularly those with destructive rheumatoid arthritis, severe extra-articular symptoms, and an HLA DR4 haplotype.[66] Neutropenic sepsis is the main cause of patient demise. First-line therapy consists of hematopoietic growth factors and often leads to rapid, favorable responses.[67] Splenectomy is indicated when the neutropenia fails to improve adequately or rapidly enough. Neutropenia is corrected by splenectomy in 80% of patients, and active preoperative infections resolve in nearly half of patients.[67]

Autoimmune Neutropenia

Patients affected by autoimmune neutropenia, a rare disorder, usually have neutrophil counts of 500 to 1000/μl but manifest granulocyte-specific antibodies. It commonly presents in infancy as recurrent infections. When present in adults, it may be associated with underlying diseases such as viral infection, collagen vascular diseases, ITP, or AIHA. Autoimmune neutropenia is typically characterized by spontaneous disappearance of autoantibodies and does not require specific intervention. However, for acute infections or operative procedures, granulocyte-colony stimulating factors effectively improve the neutrophil counts. Fifty percent to 60% of the patients also respond to corticosteroids and IVIG.[68] Therefore, the role for splenectomy is limited only to the rare patient who is refractory to medical interventions.

Lymphoproliferative Disorders

Lymphoma

Lymphomas are categorized into two distinct types: Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). The surgeon's role in HD is to provide disease staging, a rare indication for splenectomy today, since most HD patients now receive chemotherapy. Splenectomy provides palliative and therapeutic benefits in several subtypes of NHL.

Hodgkin's Disease The diagnosis of HD is made when a tissue biopsy demonstrates Reed-Sternberg cells surrounded by reactive lymphocytes. Molecular alterations in the BCL2 or the NFκB pathways enable the malignant Reed-Steinberg cells to evade apoptosis and account for the pathogenesis of HD.[69,70] The clinical manifestations and course of HD are largely dependent on its histopathology. Classic HD includes the following histologic subtypes:

1. The most common nodular-sclerosing form affects the mediastinum predominately and carries a favorable prognosis.
2. The mixed-cellularity subtype is the second most common and has a high frequency of abdominal involvement.
3. The diffuse lymphocyte-predominant subtype is distinguished from the nodular lymphocyte-predominant form in its involvement of multiple anatomic regions.
4. The least common, lymphocyte-deplete subtype, is usually a subdiaphragmatic disease characterized by pancytopenia, abnormal liver function, minimal peripheral adenopathy, and poor prognosis.

Apart from classic HD, the nodular lymphocyte-predominant form of HD affects a minority (5%) of patients with limited cervical or inguinal disease and carries a favorable prognosis. Regardless of the histologic type, 30% to 60% of all patients with HD experience systemic symptoms consisting of fever, night sweats, and weight loss.

The therapy of HD depends on its clinical and pathologic stage, according to the Ann Arbor staging system with Cotswold modification (Table 132–2). Patients with advanced disease (stage III or IV) receive combination chemotherapy and radiation. The current gold standard therapeutic regimen is ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), with more intense drug regimens used for refractory disease. Patients with localized disease (stage I or II) may receive only radiation therapy to the involved fields. Short-cycle chemotherapy (ABVD) is added for high-risk disease.

Clinical staging of HD can be ascertained by physical examination, laboratory tests, bone marrow biopsy, chest radiograph, computed tomographic (CT) or magnetic resonance (MR) imaging scan of the chest, abdomen and pelvis, lymphangiogram, and possibly positron emission tomography. Pathologic confirmation of the disease extent is undertaken only when the information gained might change therapy. Surgical staging is indicated when patients are potential candidates for radiation as their sole therapy based on their clinical stage.[71] The goal of laparotomy is to rule out occult subdiaphragmatic disease that would upstage the disease and require systemic chemotherapy. It has been reported to detect occult splenic or upper abdominal disease in 20% to 35% of the patients with clinical stage I or II disease.

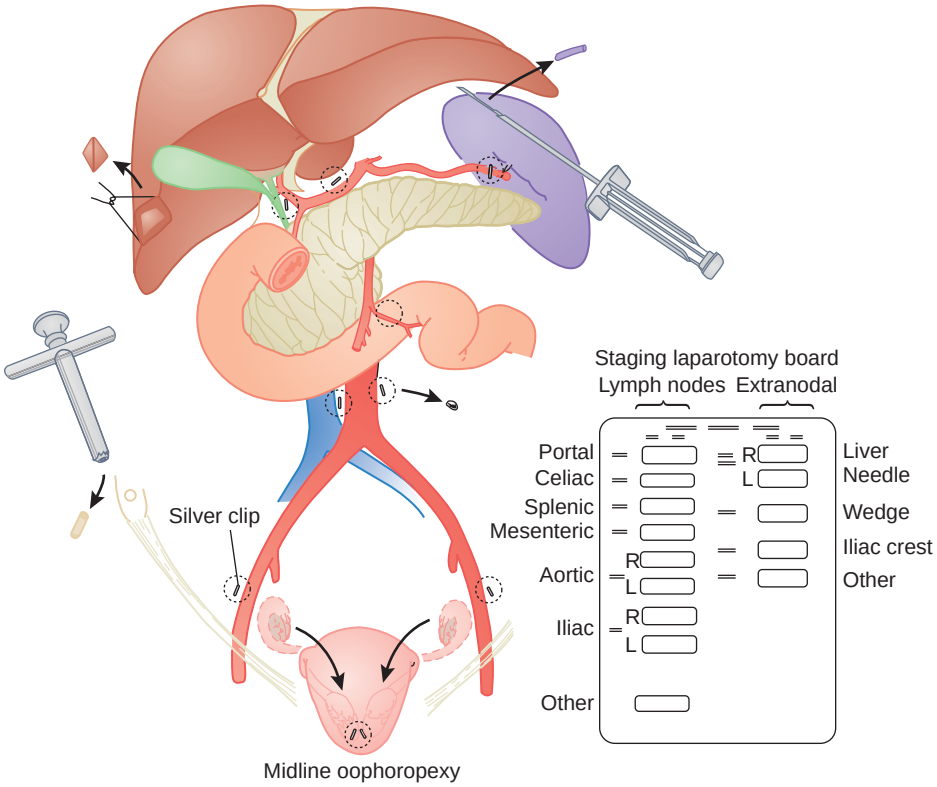

Figure 132–2. Components of a staging laparotomy for Hodgkin's lymphoma. These include splenectomy, bilobar liver biopsies (needle and wedge), and nodal sampling (including celiac, porta hepatitis, mesenteric, para-aortic, and iliac nodes). Oophoropexy to the midline is performed in women to exclude ovaries from the radiation field. Bone marrow biopsy may be performed as a part of the procedure. (From Martin JK: Staging laparotomy. In Donohue J, van Heerden J, Monson J [eds]: Atlas of Surgical Oncology. Cambridge, MA, Blackwell Science, 1995, p 150.)

Table 132–2 Hodgkin's Disease: Ann Arbor Classification with Cotswold Modification

		Modifying Features	
Classification Stage	**Description of Involvement**	*Classification Letter*	*Description*
I	1 lymph node/tissue (e.g., spleen, thymus, Waldeyer's ring)	A	No symptoms
II	≥2 lymph nodes/tissue, on same side of the diaphragm	B	Fever, night sweats, weight loss >10% in 6 mo
III	Lymph node/tissue, on opposite side of the diaphragm	X	Bulky disease
1	Splenic, celiac, portal nodes		
2	Para-aortic, iliac, mesenteric nodes		
IV	Extranodal sites	E	Involves single, contiguous, or proximal extranodal site

Currently, however, surgical staging plays only a limited role in HD because the use of radiation-only treatment regimens has decreased and accurate imaging and percutaneous biopsies are well developed. Current indication for surgical staging is limited to patients in whom acquisition of tissue is inadequate.

The components of staging laparotomy are summarized in Figure 132–2.[17,18,71] Exploration is performed through an upper midline incision and includes palpation of the liver, spleen, bowel, mesentery, and major nodal groups. Splenectomy is performed, with nodal clearance from the splenic hilum. The tied ends of the splenic vessels are marked with metal clips to guide postoperative radiation therapy. Both a wedge and core-needle biopsies are obtained from each lobe of the liver, plus a wedge biopsy of any abnormality. Finally, all abnormal nodes identified by preoperative lymphangiogram are removed. Systemic nodal biopsies then follow with celiac axis, hepatic artery, hepatoduodenal, bilateral para-aortic, and iliac nodes being sampled. All areas are marked with metal clips for future localization. Oophoropexy behind the uterus in the midline has been

Table 132–3 Experience with Splenectomy in NHL, Published Since 1990

Authors, Year	No. of Patients	Technique	Operative Mortality, %	Operative Morbidity, %	Initial Response (1 mo), %	Durable Response (Follow-up), %
Delpero et al., 1990[75]	62	Open	1.6	29	89	63 (26 mo)
Lehne et al., 1994[77]	35	Open	2.9	37	72	14
Brodsky et al., 1996[76]	12	Open	0	17	80 (3 mo)	N/A
Walsh & Heniford, 1999[79]	9	Laparoscopic	0	11	N/A	N/A
Xiros et al., 2000[78]	29	Open	3.5	14	88	N/A

NHL, non-Hodgkin's lymphoma; N/A, not available.

recommended for women of child-bearing age to exclude the ovaries from the radiation field. Operative complications (~10%) include small bowel obstruction, venous thrombosis, and subphrenic abscess.[18] Currently, staging laparoscopy is preferred over laparotomy. Adequate tissue biopsies, similar to those of traditional laparotomy, can be successfully obtained.[72] Laparoscopic ultrasonography may supplant digital palpation in doubtful areas. In experienced hands, staging laparoscopy can achieve an accuracy rate of 96% to 100% for primary or relapsed HD, without false-negative results[73,74] and lower complication rates. The reported rates of conversion to laparotomy range from 0 to 20%, mainly due to hemorrhage during splenectomy.[73]

Non-Hodgkin's Lymphoma NHL is a diverse group of more than 20 malignancies originating from B lymphocytes (~80%), T lymphocytes (~15%–20%), or natural killer cells (<5%). A specific NHL diagnosis requires histologic examination of lymphoid tissue plus flow cytometry and molecular marker studies. Patients with NHL frequently present with nonspecific symptoms of fever, night sweats, malaise, and weight loss. Peripheral lymphadenopathy is variably present and lymphatic spread is often noncontiguous. The spleen is involved in 30% to 40% of NHL patients.[74] Although NHL shares the same Ann Arbor staging system as HD, clinical staging is less crucial in NHL treatment because most patients present with advanced disease. There is no role for staging laparotomy in NHL because therapy is seldom redirected by staging information.[71]

There are three indications for splenectomy in NHL patients: (1) to correct hypersplenism and the resultant cytopenia(s), thereby allowing chemotherapy and/or independence from transfusions; (2) to relieve symptoms of splenomegaly from lymphocytic infiltration; and (3) debulking when the spleen is the main site of disease involvement, either as primary treatment or for residual disease. Operative mortality ranges between 0 and 3.5%, and reported operative morbidity is higher at 11% to 37% in studies published since 1990 (Table 132–3).[75-79] The most common severe complications are venous thrombosis and subphrenic abscess. A laparoscopic splenectomy is associated with reduced morbidity but requires technical expertise, particularly when splenomegaly is present.[79] Blood counts normalize in 72% to 89% of patient with NHL within the first postoperative month. A durable response is observed in a substantial proportion of patients (see Table 132–3). Finally, these potential benefits and risks of splenectomy must be balanced against the prognosis of the primary disease. The proposed World Health Organization classification system (Box 132–1)[80] categorizes subtypes of NHL by clinical behavior: Indolent subtypes have mean expected survivals measured in years, but aggressive subtypes generally have survivals measured only in months.

The spleen is the primary site of disease in several subtypes of NHL. Mantle cell lymphoma (MCL), an uncommon type, constitutes only 5% to 8% of NHL. Patients with MCL may have minimal adenopathy but prominent extranodal disease.[81] Up to 60% develop massive splenomegaly.[82] For patients with splenic-predominant MCL, splenectomy should be considered to palliate either or both hypersplenism and splenomegaly. Splenectomy may further benefit patients by stabilizing their disease, delaying the start of chemotherapy, and prolonging survival. A retrospective study of 26 patients[81] found that splenectomy is safe (no operative mortality and morbidity of 24%). Hypersplenism was corrected in 69% of patients with anemia, 90% with thrombocytopenia, and 50% for patients with both. In addition, 90% did not require chemotherapy until at least a year after splenectomy. The median survival is 5.5 years (typically 3 to 4 years), and splenectomy was the sole therapy in 15% of the patients.

The therapeutic role of splenectomy is more prominent in splenic marginal zone B-cell lymphoma (MZL). This primary lymphoma of the spleen comprises only 1% of NHL and is characterized by massive splenomegaly, lymphocytes with villous projections, anemia, thrombocytopenia, and mild monoclonal gammopathy.[83] Reversal of cytopenia occurs in 82% to 95% of patients following splenectomy,[83-87] with a median survival of 8.5 years[84,86] and 3-year survival of 82%[83] in patients with spleen-only MZL. These results suggest that they behave like those with localized stage I NHL. Longer overall survival correlated with prompt correction of cytopenia during the immediate postoperative period.[84] Splenectomy is a treatment of choice in patients with localized MZL.

Box 132–1 Proposed World Health Organization Classification of Lymphoid Neoplasms

Indolent Lymphomas

B-Cell Neoplasms

- Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia
- Lymphoplasmacytic lymphoma (± Waldenström's macroglobulinemia)
- Plasma cell myeloma/plasmacytoma
- Hairy cell leukemia
- Follicular lymphoma (grades I and II)
- Marginal zone B-cell lymphoma
- Mantle cell lymphoma

T-Cell Neoplasms

- T-cell large granular lymphocyte leukemia
- Mycosis fungoides
- T-cell prolymphocytic leukemia

Natural Killer Cell Neoplasms

- Natural killer cell large granular lymphocyte leukemia

Aggressive Lymphomas

B-Cell Neoplasms

- Follicular lymphoma (grade III)
- Diffuse large B-cell lymphoma

T-Cell Neoplasms

- Peripheral T-cell lymphoma
- Anaplastic large cell lymphoma, T/null cell

Highly Aggressive Lymphomas

B-Cell Neoplasms

- Burkitt's lymphoma
- Precursor B lymphoblastic leukemia/lymphoma

T-Cell Neoplasms

- Adult T-cell lymphoma/leukemia
- Precursor T-lymphoblastic leukemia/lymphoma

Table 132–4 Rai Classification of Chronic Lymphocytic Leukemia

Stage	Description
0	Lymphocytosis (WBC >150,000/ml, >40% lymphocytes in bone marrow)
I	Lymphocytosis and lymphadenopathy
II	Lymphocytosis and splenomegaly/hepatomegaly
III	Lymphocytosis and anemia (hemoglobin <11 g/dl)
IV	Lymphocytosis, lymphadenopathy, anemia, and thrombocytopenia (platelet <100,000/ml)

WBC, white blood cell count.

Leukemias Leukemia is hallmarked by a malignant clonal proliferation of hematopoietic stem cells. For patients with acute lymphocytic or acute myelogenous leukemia, there is consensus that splenectomy plays no role except for splenic rupture with hemorrhage.[18] For patients with chronic forms of leukemia, splenectomy may be indicated to palliate symptoms of splenomegaly or cytopenias. The survival benefit of splenectomy in patients with leukemia remains controversial.

CLL is the most common chronic leukemia. CLL is characterized by the accumulation of morphologically normal but functionally incompetent B lymphocytes. Patients follow either an indolent course requiring no therapy or an accelerated course with severe symptoms that require intervention.[88] CLL patients present with painless lymphadenopathy alone or with additional features including splenomegaly, cytopenia, and constitutional symptoms, as defined by the Rai classification (Table 132–4). Patients with stage 0 disease require no therapy, but selected patients with stages I and II disease and all patients with stage III and IV disease should receive chemotherapy, typically fludarabine.[71] Although cytopenia in CLL may result from bone marrow failure, hypersplenism, autoimmune destruction, chemotherapy, or any combination,[89] splenectomy is an efficacious method of reversing cytopenia (Table 132–5). A durable response of cytopenia in CLL is observed in at least 80% of patients, with higher response rates when splenectomy is performed for thrombocytopenia rather than for anemia.[82,89-94] However, no predicative factor of a hematologic response to splenectomy has been consistently identified.[90] The overall survival is longer in patients with a hematologic response than those who fail to respond,[90,94,95] but the survival benefit of splenectomy in patients with advanced CLL remains controversial. No significant difference in survival was observed in a case-matched study,[94] though in subgroup analysis of patients with severe anemia (hemoglobin <10 g/dl) or thrombocytopenia (platelet count $<50 \times 10^9$/L), splenectomy did significantly prolong median survival (19 versus 10 months and 17 versus 4 months, respectively). These results suggest that splenectomy should be considered

Table 132–5 Experiences with Splenectomy for Chronic Lymphocytic Leukemia, Published Since 1990

Authors, Year	No. of Patients	Operative Mortality, %	Operative Morbidity, %	Response for Cytopenia, Response %	Long-Term Cytopenia Response, %	Median Survival, mo
Thiruvengadam et al., 1990[89]	30	N/A	N/A	N/A	71-87 (18-62 mo)	36
Neal et al., 1992[90]	50	4	26	64-77 (3 mo)	84-86	36 (41, responders; 14, nonresponders)
Majumdar et al., 1992[91]	14	0	28.5	84.6 (2-3 mo)	N/A	44
Pegourie-Bandelier et al., 1995[92]	29	0	34	N/A	85-100	N/A
Seymour et al., 1997[93]	55*	9	25	38-81	N/A	27 (vs. 23, $P = 0.96$)
Cusack et al., 1997[94]	77*	7.8	54	61-69	N/A	34 (vs. 24, $P = 0.27$)
Ruchlemer et al., 2002[82]	47	6.4	35	47 (3 mo)	N/A	56.4

*Case matched with patients treated with fludarabine.
N/A, not available.

for all CLL patients with cytopenia, particularly those with severe anemia or thrombocytopenia.

Chronic myelogenous leukemia (CML) consists of a chronic benign phase followed by an acute blast transformation phase. Patients usually present during the chronic phase with systemic symptoms, splenomegaly, leukocytosis, and cytopenias. Chromosomal translocation t(9;22) (i.e., Philadelphia chromosome) is present in 90% of the CML patients; and treatment efficacy is monitored by decreased expression of the abnormal chromosome.[71] Therapeutic options in CML include chemotherapy (e.g., hydroxyurea or busulfan), interferon-α, and bone marrow transplant.[18] Splenectomy is used only for palliation of refractory cytopenia or painful splenomegaly. Splenectomy does not seem to increase survival or delay the onset of the acute blastic transformation. Acute blastic crisis, hallmarked by prolonged fever of unknown origin, leukocytosis, thrombocytopenia, and greater than 30% blasts in peripheral circulation, carries a grim prognosis, with mean survival measured in months. Splenectomy is contraindicated during the acute phase. However, when necessary for emergency indications, a low 30-day mortality rate of 3.5% can be achieved.[96] Additionally, splenectomy does not have an adverse impact on the incidence of infections, graft versus host disease, or overall survival if a bone marrow transplant is performed after splenectomy.[97]

Hairy cell leukemia (HCL) comprises 2% to 5% of leukemias and is a chronic B-lymphocyte disorder characterized by peripheral cytopenia and massive splenomegaly. The malignant cells have hairlike projections and accumulate mainly in the red pulp of the spleen but can be identified elsewhere by their positive tartrate-resistant acid phosphatase staining.[95] Cytopenia in HCL may result from hypersplenism, bone marrow failure, or other reasons. Prior to 1990, splenectomy was the only known effective therapy for HCL. Cytopenia improved after splenectomy in 60% to 100%,[95] and a survival benefit may even occur.[98] In the early 1990s, interferon-α was shown to be superior to splenectomy for cytopenia in a randomized trial.[98] Currently, medical therapies of interferon-α and purine analogues are efficacious. The indications for splenectomy in HCL are, therefore, limited to those patients with an uncertain diagnosis, emergency splenic rupture, severe splenomegaly with symptomatic cytopenia, or disease refractory to chemotherapy. Resection of residual splenic disease after interferon therapy may prolong progression-free survival.[98] However, the contemporary experience with splenectomy for HCL is limited.

Myeloproliferative Disorders

Chronic myeloproliferative disorders are marked by abnormal clonal proliferation of hematopoietic stem cells. Myelofibrosis with myeloid metaplasia (MMM) occurs when bone marrow develops a fibrotic reaction to the stem cell disease and can be divided into agnogenic (AMM), post-thrombocythemic (PTMM), and postpolycythemic (PPMM) types. PTMM and PPMM are preceded by essential thrombocythemia and polycythemic rubra vera, respectively, and splenectomy generally does not benefit these patients.[18,99,100] AMM is characterized by peripheral cytopenia and progressive extramedullary hematopoiesis in the spleen and the liver. Associated features include painful splenomegaly, increased portal blood flow, portal hypertension from venous thrombosis (~7%),[101] and cytopenia from splenic sequestration. The prognosis of AMM is poor, with a median survival ranging from 3 to 5 years. Nonoperative therapy has been limited.

Bone marrow transplant is frequently not an option for elderly AMM patients. Transfusions, androgens, corticosteroids, and interferon-α are largely palliative, and splenic irradiation is only transiently effective. Therefore, splenectomy should be considered in symptomatic patients. Symptomatic splenomegaly, constitutional symptoms, and portal hypertension improve in 100%, 67%, and 50% of the respective patients at 1 year postsplenectomy. Among those patients with transfusion-dependent anemia, 30% remain independent of transfusions for 6 months. No benefit for splenectomy is seen with thrombocytopenic patients.[102] Despite potential benefits, splenectomy in this patient population is a high-risk procedure.[99] Prior to 1940, operative mortality was prohibitively high at 40%. Currently, it ranges from 8% to 11%, with postoperative morbidity ranging from 31% to 40%.[102-105] Hemorrhage, infection, and thrombosis are the most common nonfatal complications. Several complications characteristic of this patient population have also been described.[102] Progressive hepatomegaly develops in 12% to 29% of the patients after splenectomy; as extramedullary hematopoiesis increases in the liver, 7% develops fatal hepatic liver failure. Severe thrombocytosis affects 18% to 50% of AMM patients after splenectomy, particularly if the preoperative platelet count is greater than 50×10^9/L. Postsplenectomy leukemic transformation occurs in 11.2% to 20% of patients and manifests as an accumulation of blasts in the bone marrow and periphery.[99] Whether postsplenectomy blast transformation affects overall patient survival remains controversial[99,100,102,106] and should not deter the surgeon from performing an otherwise appropriate splenectomy. The median overall postsplenectomy survival is 2.3 years.[102] The main causes of death include infection, thrombosis, bleeding, and acute leukemia. Current indications for splenectomy in patients with AMM remain palliative and include severe constitutional symptoms, mechanical symptoms of splenomegaly, portal hypertension complicated by ascites and variceal hemorrhage, and transfusion-dependent anemia.[99]

SPLENECTOMY FOR TUMORS, CYSTS, AND ABSCESSES

Tumors

Splenic masses are usually discovered incidentally. They present for surgical intervention with an unknown diagnosis, when the spleen ruptures, or when symptoms develop from their large size or associated hypersplenism.

The most common cause of a malignant splenic mass is metastasis from a primary carcinoma. Splenic metastases are present in 7% of patients dying from cancers of the breast, lung, ovary, stomach, and prostate.[18] Melanoma and other skin cancers also spread to the spleen. When the spleen is the only site of metastasis, splenectomy may prolong patient survival.

Primary, nonlymphatic, malignant tumors of the spleen include angiosarcoma, hemangioendothelioma, and malignant fibrous histiocytoma. Angiosarcoma is the most common of these rare tumors. Patients present at a median age of 60 years, with abdominal pain, splenomegaly, and microangiopathic hemolytic anemia. The tumors appear as well-circumscribed nodules with central necrosis or hemorrhage. The prognosis for angiosarcoma patients is dismal. Eighty-nine percent of patients die of metastatic disease, with a median survival of 5 months.[107] Splenectomy is indicated for palliation and for splenic rupture, which may occur in 25% of patients. The rarity of the disease has hindered identification of risk factors, but exposure to thorium dioxide (Thorotrast), vinyl chloride, and anabolic steroids has been implicated in isolated reports.[107]

Benign tumors of the spleen are uncommon and include hamartoma, inflammatory pseudotumor, and vascular lesions (hemangioma, lymphangioma, peliosis). Hemangiomas are the most common benign splenic lesions and arise from the red pulp of the spleen. They can become very large, with prominent cystic components. Nonexpanding and asymptomatic hemangiomas less than 4 cm are safely observed.[108] Splenectomy may be considered to prevent or treat complications such as hypersplenism and splenomegaly. Peliosis of the spleen occurs alone or in association with peliosis of the liver. It occurs more frequently in men and is the result of the ingestion of androgens or oral contraceptives or accompanies chronic debilitation from tuberculosis, diabetes, or a neoplasm.[18] Complications of peliosis include thrombosis and fatal hemorrhage from splenic rupture. Splenectomy is indicated when peliosis is incidentally discovered. Splenic hamartomas as large as 2 kg have been reported and require surgical intervention for diagnosis. Inflammatory pseudotumors are a poorly understood entity. Patients present with fever, night sweats, and weight loss. These tumors must be distinguished from malignant lymphoma by immunohistologic studies, making splenectomy necessary for diagnosis in many patients. Additional rare benign splenic lesions include Littoral cell angioma, hemangioendothelioma, and angiomyolipoma.

Cysts

Parasitic Cysts

Echinococcus cysts are common in endemic areas but rare in the United States. Humans serve as intermediate hosts after ingestion of food contaminated with feces laden with tapeworm eggs. Hydatid cysts most commonly develop in the liver and the lungs; their daughter cysts contain multiplying larvae called *scolices*. Cysts of *Echinococcus granulosus* are unilocular, but those of *Echinococcus multilocularis* and *Echinococcus volegi* are multilocular.[13] Intervention should be considered when disease is refractory to the antiparasitic drug albendazole or when cysts become large enough to risk rupture. Cystectomy or splenectomy should be performed with care to avoid cyst rupture or leakage. Anaphylaxis and disseminated scolices infection are serious operative complications. Administration of albendazole and instillation of hypertonic saline or ethanol prior to cyst manipulation have been advocated to decrease these risks.[13]

Nonparasitic Cysts

Nonparasitic splenic cysts were previously classified as true cysts (~20%) or pseudocysts (~80%) based on the presence or absence of an epithelial lining. True cysts may be epidermoid or, less commonly, dermoid in origin, resulting from splenic inclusion of embryonic tissue. They may also be associated with benign splenic hemangiomas or lymphangiomas. Pseudocysts are typically associated with antecedent splenic trauma or splenic infarction.[18] Splenic infarction occurs with hematologic disorders (most commonly sickle cell disease) in younger patients or with arterial emboli (the most common cause is atrial fibrillation) in patients older than 40 years.[109] Recently, however, the reliability of identifying the cyst lining has been questioned. A newly proposed system classifies cysts based on causes into congenital, neoplastic, true traumatic, and degenerative cysts.[110]

Intervention is not necessary for asymptomatic, small (<5 cm) splenic cysts that have imaging characteristics of a benign cyst, namely a smooth, regular cyst wall, with no solid component within the cyst interior or wall, either with or without calcification.[110] Total splenectomy is typically considered for patients with low operative risk who develop pain or early satiety due to their splenic cysts. Recently developed minimally invasive treatment options include cyst aspiration with sclerosis using alcohol or tetracycline, cyst marsupialization, and local cyst resection with or without a portion of the cyst wall contiguous with splenic parenchyma. However, their use is limited by the risks of cyst recurrence. Laparoscopic or partial splenectomy is now the preferred treatment because of their low complication and cyst recurrence rates.[111]

Abscesses

Although splenic abscess remains a rare entity, it is uniformly fatal if unrecognized or untreated. With an increasing incidence of immunosuppressive diseases and medications, splenic abscesses have become more common.[112] A high index of suspicion is required for timely diagnosis and favorable outcome.[113] Patients able to mount an immune response present with the triad of fever, leukocytosis, and left upper quadrant pain.[114] Chest or abdominal radiographs often show a left-sided pleural effusion, elevated hemidiaphragm, left upper quadrant mass, and extraluminal air. A CT scan has a sensitivity of 96% and is the imaging modality of choice. A splenic abscess typically has a thick, irregular rim with a hypodense center, but multiple or miliary abscesses may be difficult to identify.

Splenic abscesses are classified by their cause.[13,112] The must common cause is primary hematogenous seeding from a distant septic source (common sources include bacterial endocarditis associated with valvular disease, intravenous drug use, bacteremia, and intra-abdominal sepsis postoperatively or primary infection). The most commonly responsible organisms are *Streptococcus* and *Staphylococcus* species, but *Salmonella* species, gram-negative *E. coli,* and *Enterococcus* species, as well as fungal infections also cause splenic abscesses.[115] Although most splenic abscesses are solitary, multiple abscesses more frequently develop from hematogenous spread.[114] Secondary infection of splenic infarction is another cause of splenic abscess. Patients with an architecturally or functionally abnormal spleen are most susceptible to this type of infection. Common associated conditions include sickle cell anemia, lymphoproliferative and myeloproliferative diseases, trauma, and systemic arterial embolic events. Patients with sickle cell anemia characteristically develop splenic abscesses with *Salmonella* species. The direct extension of a local septic focus may also result in a splenic abscess. The infections may originate from a gastric, colonic, pancreatic, or perinephric source. Post-traumatic splenic abscesses occur after conservative management of splenic trauma or an iatrogenic intraoperative injury. Immunocompromised host accounts for up to 35% of patients with splenic abscesses. Associated conditions include malignancy, organ transplantation, chronic steroid use, and HIV/AIDS.

The treatment of choice for splenic abscess consists of broad-spectrum antibiotics, splenectomy, and drainage of the left upper quadrant.[113] Excellent outcome is usually expected. In critically ill patients who are unable to tolerate a surgical procedure, image-guided drainage should be attempted. When the abscess is discrete, unilocular, and filled with thin fluid, the success rate is as high as 51%.[112] Occasionally, dense inflammatory adhesions preclude splenectomy, leaving splenotomy or surgical drainage as the only surgical options. In this setting, delayed splenectomy is necessary since intravenous antibiotics alone are almost never sufficient treatment for a splenic abscess.[114] Mortality from splenic abscess remains substantial and ranges from 0 to 24%. Poor outcome occurs with immunocompromised patients, delayed diagnosis, and postponed operative intervention.[112,113]

SPLENECTOMY FOR VASCULAR DISORDERS

Splenic Artery Aneurysm

Splenic artery aneurysm (SAA) constitutes 60% of all visceral arterial aneurysms and is the third most common abdominal aneurysm after aortic and iliac artery aneurysms. The typical patient with SAA is a multiparous woman (in a series of 87 women, the average number of pregnancies per patient was 4.5).[116] Other associated conditions include portal hypertension, congenital vascular or connective tissue diseases, and trauma. SAA presents (1) after rupture with hemodynamic instability; (2) as a symptomatic mass; or (3) as an incidental finding. Rupture occurs most commonly in the third trimester of pregnancy and may be forewarned by a sentinel hemorrhage in 20% to 30% of patients.[117] In pregnant patients, the mortality rate after rupture is 70% and 100% for the mother and the fetus, respectively[118]; in nonpregnant patients, the mortality rate is 25%.[18] As soon as rupture is suspected, prompt resuscitation, emergent splenectomy, and resection of the aneurysm are indicated. For all symptomatic aneurysms, surgical intervention is indicated. For incidental and asymptomatic aneurysms, an

operation is indicated only if the SAA is longer than 2.5 cm in diameter or if the patient is pregnant or of child-bearing potential.[18,119] Operative treatment differs by location of the SAA. Proximal aneurysms are excised after proximal and distal ligations. Mid-splenic aneurysms are excluded by proximal and distal ligations of the splenic artery and all collateral vessels. The spleen can be preserved by blood flow via the short gastric arteries. Distal or hilar aneurysms are the most common and are treated with aneurysmectomy and splenectomy.[116,118,120] For patients unable to tolerate an operation, transcatheter embolization can be successful. However, it causes splenic infarction and has the risks of distant embolization, arterial disruption, and arterial recanalization with potential for future rupture.[117,119] Laparoscopic ligation and splenectomy have also been reported. The optimal approach to elective treatment of SAA depends on patient variables and physician expertise.

Splenic Venous Thrombosis

Splenic venous thrombosis (SVT) complicates acute pancreatitis and pancreatic neoplasms in 7 to 20% of patients. Nonpancreatic diseases, including primary retroperitoneal fibrosis, peptic ulcer disease, and a hypercoagulable state, may also be associated with SVT.[121] It results in a localized form of portal hypertension termed *sinistral portal hypertension*.[122] Collateral flow through the short gastric vessels leads to engorgement of submucosal veins of the gastric fundus or gastric varices. Esophageal varices may arise when the left gastric vein is also occluded by the thrombus and fails to decompress localized portal hypertension. The diagnosis of SVT should be suspected in patients with upper gastrointestinal hemorrhage following pancreatitis, in patients with splenomegaly but no hepatic or hematological disease, and when isolated gastric varices are noted on upper endoscopy. Ultrasonography, CT scan, and visceral angiography all can confirm the diagnosis. In patients presenting with hemorrhage, urgent splenectomy is indicated. The operative bleeding risk is substantial given the perigastric varices and inflammation. To reduce this risk, some surgeons advocate preoperative embolization of the splenic artery.[122] In unstable patients or those not fit for an operation, endoscopic variceal sclerotherapy or banding may be performed but are usually ineffective.[123]

Splenic artery embolization does not provide a definitive cure but should be attempted. In asymptomatic patients with SVT, the indication for splenectomy is controversial. Prophylactic splenectomy used to be uniformly recommended, because up to 51% of asymptomatic patients with SVT were thought to develop acute variceal bleeding.[124] Recent studies found that the natural history of gastric varices is more benign, with a 4% to 18% prevalence of clinical hemorrhage.[122,124] Expectant management, initially advocated by Loftus et al.,[125] has been more widely adopted. Prophylactic splenectomy should be considered for patients who are noncompliant, those undergoing an abdominal operation for another cause, or for patients who possess endoscopic features such as "red wale markings" indicating high risk for bleeding.[122,123]

Portal Hypertension

Patients with portal hypertension often develop thrombocytopenia from platelet sequestration in the splenic sinusoids.[18] Splenectomy may be considered in conjunction with other devascularization or stenting procedures when the bleeding risk from thrombocytopenia is excessive, when medical therapy cannot be administered, or when the varices are resistant to nonoperative management.[126] Portal hypertension is not an absolute contraindication to laparoscopic splenectomy, but a 9.6% conversion rate and 11% morbidity rate have been reported in this setting.[126]

"Wandering Spleen" and Splenic Torsion

A "wandering spleen" occurs when the spleen is attached only by a long, loose vascular pedicle without the usual peritoneal attachments. The spleen may be ectopic on imaging studies. Two main patient populations are affected. Wandering spleens in children arise from congenital atresia of the dorsal mesogastrium. When found in women between 20 and 40 years of age, wandering spleens result from an acquired tissue laxity associated with pregnancy.[127] The condition is complicated by acute torsion around the vascular pedicle, which manifests with acute abdominal pain, fever, vomiting, acute pancreatitis, and gastric compression. Without detorsion, splenic infarction and gangrene ensue. Chronic torsion typically causes venous congestion and splenomegaly. In children without splenic infarction, the procedure of choice is splenopexy, suturing the spleen to the diaphragm, abdominal wall, or omentum.[128] Traditionally performed as an open procedure, laparoscopic splenopexy has been recently reported.[129] Splenopexy allows for splenic preservation, but the long-term results are unknown. For adults, splenectomy is the preferred therapy.

SPLENECTOMY FOR IATROGENIC INJURY

An iatrogenic splenic injury is an unintentional injury caused by the operator during either an interventional radiologic or surgical procedure. The surgical operation most commonly associated with iatrogenic splenic injury include distal esophageal or gastric procedures, colon surgery, left nephrectomy, and upper abdominal vascular procedures.[18] Risk factors for iatrogenic injury include a prior left upper quadrant operation, malignant or inflammatory diseases, and obese body habitus.[130] The spleen, when tethered by its normal peritoneal ligaments plus additional dense adhesions, becomes prone to injury through inappropriate traction, retractor placement, or instrumentation.

When an iatrogenic splenic injury occurs, exposure to the left upper quadrant should be optimized, blood and clots are gently removed, and severe bleeding is temporized by pressure on the splenic artery at the superior pancreatic margin. Limited splenic capsular tears may not require any treatment or can usually be salvaged by electrocautery, argon beam coagulation, or hemostatic

agents such as fibrin adhesive, thrombin-soaked Gelfoam, and microfibrillar collagen. Deeper lacerations may be salvaged with argon beam coagulation, mattress sutures in the fibrous capsule with or without pledgets, wrapping the spleen in an absorbent mesh, or segmental splenectomy. In patients with severe (>grade 4) splenic injury or hemodynamic instability or in those requiring postoperative anticoagulation, total splenectomy is indicated. Splenectomy for iatrogenic injury prolongs hospital stay and increases morbidity from 0 to 32% to 16% to 84% in various series.[130] Whether incidental splenectomy compromises immune function and decreases survival in cancer patients is uncertain. The incidence of sepsis is low after unplanned splenectomy in adults: 1 per 545 adult years.[130] Measures to prevent iatrogenic injury include placement of the incision to maximize exposure, gentle retraction, careful medial or downward traction of the peritoneal ligaments, and manipulation of stomach and colon only after dividing splenic ligaments and other perisplenic adhesions.[130]

SPLENECTOMY FOR MISCELLANEOUS DISORDERS

Gaucher's disease is an inherited metabolic disorder manifesting with anemia, thrombocytopenia, hepatosplenomegaly, and bone dysplasia. The genetic deficiency in lysosomal glucocerebrosidase leads to accumulation of glucosyl ceramide-laden macrophages in the reticuloendothelial cells of the liver, bone, and spleen. Enzyme replacement therapy (alglucerase or imiglucerase) effectively ameliorates symptoms of Gaucher's disease.[131] Splenectomy is reserved for patients with compressive symptoms from massive splenomegaly or refractory cytopenia. The largest series to date reports operative mortality of 2.1% and morbidity of 27%.[132] In children with Gaucher's disease, partial splenectomy or another spleen-preserving technique is advocated.

Splenomegaly complicates 6% of patients with sarcoidosis and is associated with anemia, neutropenia, or pancytopenia. Most patients have mild and asymptomatic splenomegaly and do not require treatment. Splenectomy is considered for massive or painful splenomegaly, refractory hypersplenism, need to exclude lymphoma or other malignancy, and prophylaxis against splenic rupture. Outcome of splenectomy for sarcoidosis is favorable in isolated case reports.[133]

Amyloidosis is a systemic infiltrative disease. Splenic rupture occurs as amyloid deposits distend the capsule and increase vascular fragility.[134] Emergent splenectomy may be necessary for splenic rupture.

OPERATIVE CONSIDERATIONS FOR SPLENECTOMY

Preoperative Preparation

The indication for splenectomy, the underlying disease, and the patient's comorbidities, hematologic status and previous therapy, must be clearly reviewed.

Vaccinations are indicated whenever splenectomy or impaired splenic function is anticipated. They should be administered at least 2 weeks prior to splenectomy because the vaccine immunogenicity may be reduced if given after the splenectomy.[135] Pneumococcal vaccine is indicated for all patients; meningococcal and *Hemophilus influenzae* vaccinations are added for younger patients and those not previously immunized. The normal host defense against these encapsulated species involves antipolysaccharide antibodies and opsonization. Splenectomy renders both processes deficient and the patient more susceptible without vaccination. If the splenectomy is emergent and preoperative vaccination is precluded, postoperative administration is necessary.

Patients' hematologic reserve and the operative risks must be considered. The need for blood component transfusion is anticipated. Laboratory tests (e.g., crossmatch) are performed and appropriate blood components reserved. One unit of platelets usually elevates the platelet count by 5×10^9/L, whereas 1 unit of erythrocytes elevates hemoglobin by 1 g/dl. In selected high-risk patients with severe thrombocytopenia (platelet count $<20 \times 10^9$/L), transfusion of 6 units of platelets may be considered prior to anesthetic induction to reduce the risk of laryngeal hematoma during endotracheal intubation. Preoperative platelet transfusion should be avoided in patients with ITP because transfused platelets will not survive splenic circulation until the splenic vessels are ligated.[18] In patients with portal hypertension and massive splenomegaly, preoperative splenic artery embolization can be performed to reduce the bleeding risk. However, its potential benefit must be balanced against the risk for pancreatitis, splenic abscess from infarction, hematoma formation, and pain.

Immediately prior to splenectomy, several medications are administered in the operating room. Patients on chronic steroid therapy should receive a bolus of exogenous steroid for operative stress. Prophylactic antibiotics are indicated in immunocompromised patients or when the gastrointestinal tract may be opened. In patients prone to thrombosis (e.g., myeloproliferative disorders), administration of low-dose heparin (5000 IU subcutaneously three times daily) or antiplatelet agent (e.g., aspirin) may be beneficial.[136]

Operative Considerations

Splenectomy can be performed via the open, hand-assisted, or totally laparoscopic approach. This chapter focuses on techniques of open splenectomy, whereas the latter two approaches are discussed in Chapter 127.

The most commonly used surgical incisions for open splenectomy are the left subcostal and the midline incisions. The latter is preferred for patients with narrow costal arches or with marked splenomegaly. A left thoracoabdominal incision with a midline vertical extension has been described but is rarely needed.[136] Most surgeons prefer gastric decompression via an orogastric or nasogastric tube.

The initial steps of splenectomy generally involve mobilizing the spleen. The stomach and the spleen are

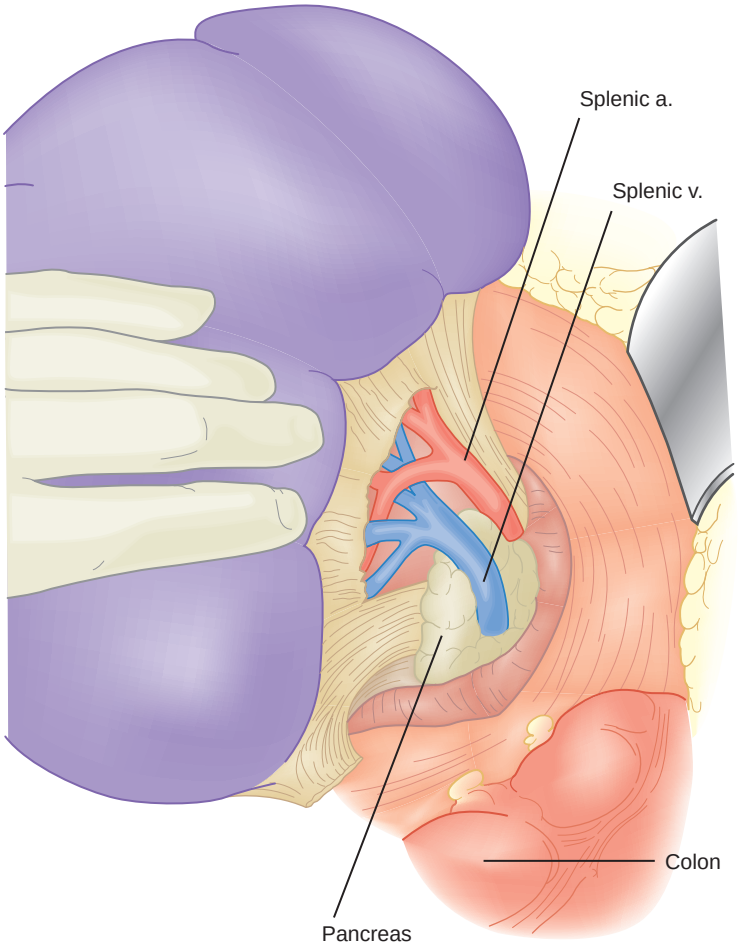

Figure 132–3. Mobilization of the spleen from its peritoneal ligamentous attachments. (From Scott-Conner CEH: Chassin's Operative Strategy in General Surgery: An Expositive Atlas. Stamford, NY, Springer, 2002, p 736.)

retracted medially to expose the splenophrenic and splenorenal ligaments. Unless venous varices are present, the ligaments are avascular and can be divided by blunt or sharp dissection. After the spleen is freed from its posterior attachments to the diaphragm and Gerota's fascia, the splenocolic ligament is divided, releasing the splenic flexure and the omentum from the inferior splenic pole. The spleen can then be lifted into the abdominal incision (Fig. 132–3). This maneuver should not be performed with excessive force, to avoid a capsular tear or avulsion of the splenic vessels. The splenogastric ligament is incised with identification, division, and ligation of the short gastric vessels. Suture ligation of these vessels on the gastric wall has been advocated by some surgeons to prevent postoperative loosening of the ligatures if the stomach becomes distended. At this point, the spleen is attached only by the hilar vessels.

An alternative approach to splenectomy involves control of the splenic vessels at the hilum as the initial step. The gastrocolic omentum is opened outside the gastroepiploic arcade (Fig. 132–4A). The splenic artery is palpated along the superior border of the pancreas. Dissection of the vessels should be carried out close to the splenic hilum to avoid injury to the tail of the pancreas (see Fig. 132–4B to D). The splenic artery and vein may be divided together; however, separate division is preferable to prevent the formation of an arteriovenous fistula. The splenic artery should be controlled by double ligation and suture ligature. The splenic vein is divided after double ligation; a continuous vascular suture or a vascular stapler is used when the vein is substantially enlarged. This approach of initial vascular control may be particularly suitable in the presence of massive splenomegaly, marked hilar lymphadenopathy, or dense perisplenic adhesions. It has also been advocated for ITP, where early ligation of the vessels allows earlier administration of platelet transfusion. Similarly, it may be preferred for splenic malignancies, because it can prevent inadvertent tearing of the vessels during splenic mobilization and spillage of malignant cells.

When a partial splenectomy is considered, branches of the vasculature are identified before they enter the spleen and ligated separately. Once the plane of vascular demarcation is recognized and marked, transection of the splenic parenchyma should be performed with total hilar occlusion to reduce hemorrhage at the surface. Moreover, placement of pledgets under through-and-through sutures during inflow occlusion reduces hemorrhage related to partial splenectomy.

After removal of the spleen for hematologic diseases, the abdomen should be explored for accessory splenic tissues at their common locations (see Fig. 132–1).

Prior to closure, hemostasis of the left upper quadrant should be ascertained by inspection of the inferior

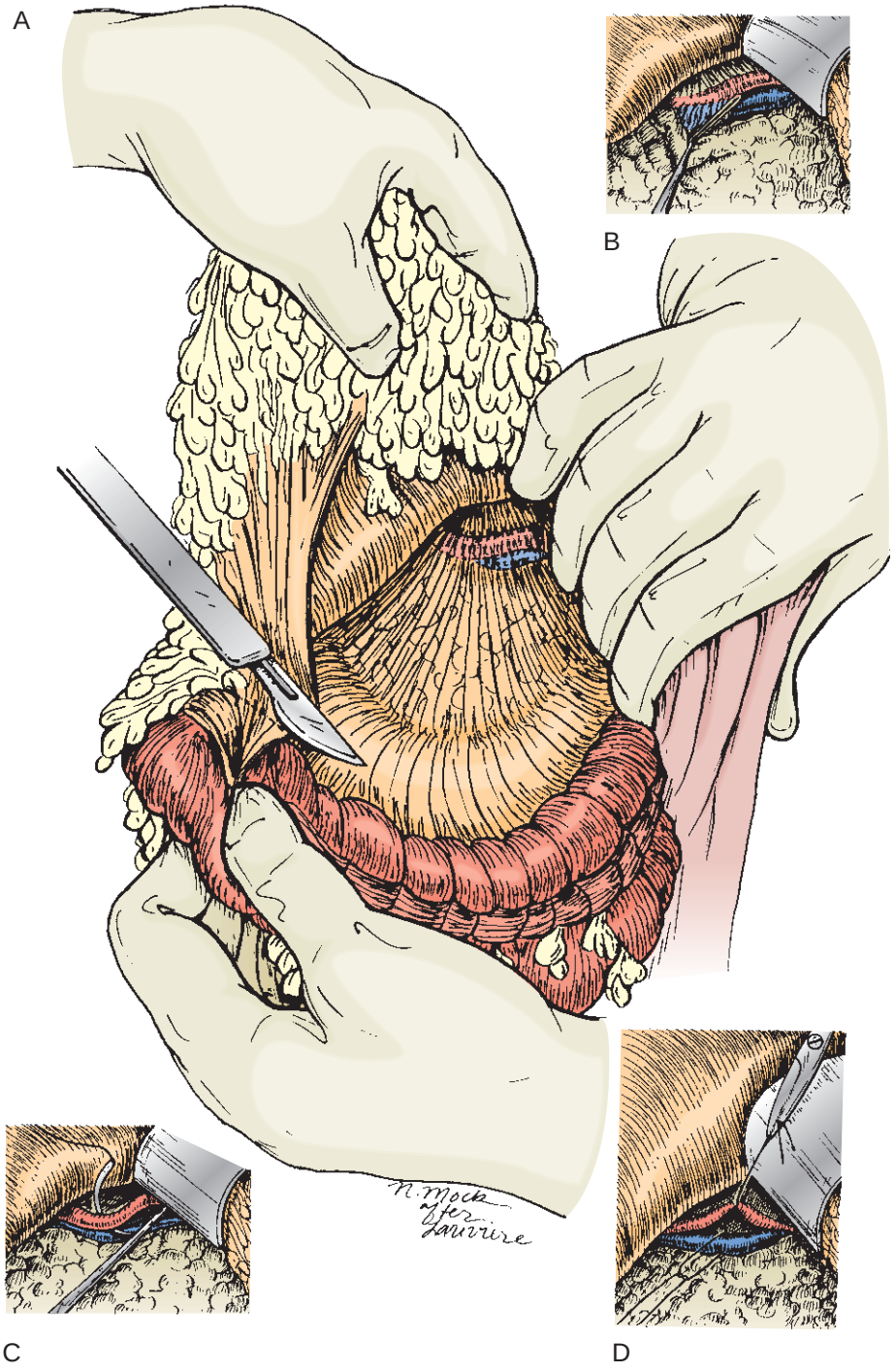

Figure 132–4. Approach to the splenic hilum through the lesser sac **(A)**. Splenic vessels are identified **(B)** and controlled **(C** and **D)** along the superior border of the pancreas. (From Schwartz S: The spleen. In Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations. Stanford, CT: Appleton & Lange, 1997, p 2058.)

surface of the diaphragm, the left cephalad retroperitoneum, the greater curvature of the stomach, and the splenic hilum. The left upper quadrant may be packed to promote hemostasis. The greater curvature of the stomach should be imbricated with interrupted Lembert sutures if any serosal damage is present to prevent a gastric fistula. Closed-suction drainage of the left upper quadrant is not indicated unless injury to the tail of the pancreas is suspected or encountered.

Postoperative Course and Complications

The highest rate of postoperative complications is anticipated in patients with massive splenomegaly (splenic weight >1500 mg) or myeloproliferative diseases, where a morbidity of up to 52% has been reported. [137,138]

All patients are closely monitored during the early postoperative period for hemorrhage. Immediate postoperative bleeding most commonly arises from an

unligated short gastric vessel high on the greater curvature or from small veins around the tail of the pancreas. When indicated by a fall in hemoglobin and signs of hypovolemia, exploration should be performed promptly. Another common complication, pulmonary atelectasis, can be prevented with adequate pain control and incentive spirometry. A subphrenic abscess occurs rarely but may develop with poor hemostasis and clot formation in the splenic bed or when the gastrointestinal tract is opened. Percutaneous or operative drainage plus parenteral antibiotics are required. A gastric or pancreatic fistula occurs in less than 1% of the patients and is associated with iatrogenic injury to these organs.

Leukocytosis occurs as a physiologic response to splenectomy. It may be difficult to distinguish from a septic state. Traumatic splenectomy patients with white blood counts greater than 20×10^9/L after postoperative day 10 are more likely to be septic,[139] but leukocytosis after splenectomy for nontraumatic indications has not been investigated. Similarly, reactive thrombocytosis may occur immediately postsplenectomy, with the platelets peaking at 2 to 3 weeks postoperatively. In the absence of hemostatic or vascular complications, no therapy is indicated for secondary thrombocytosis.

Venous thrombosis involving the mesenteric and portal veins is a serious complication after splenectomy. The incidence of clot formation may be as high as 50% if all patients are screened, but only 8% of these are symptomatic. Predisposing factors include myeloproliferative disease or hemolytic anemia, postoperative thrombocytosis, previously undiagnosed systemic hypercoagulable state, and a long splenic vein stump.[140] Laparoscopic splenectomy may be associated with a higher incidence of portal and splenic vein thrombosis than the open technique (55% vs. 12% in one retrospective series[141]). Patients usually present within 10 days of splenectomy with vague symptoms including generalized abdominal pain and distention, fever, nausea, and anorexia. The diagnosis is best obtained by contrast-enhanced abdominal CT, MR imaging, or ultrasonography, systemic anticoagulation is initiated promptly and maintained for 6 months. Recannulation occurs in 90% of those on appropriate anticoagulation.[142]

All asplenic patients are at risk for OPSS. The incidence of OPSS ranges between 1% and 2.4% and is fatal in 45% to 75% of patients. The elevated risk of mortality is life-long.[47] Any febrile asplenic patient must be promptly evaluated and initiated on a broad-spectrum antibiotic regimen such as a third-generation cephalosporin.[135] Measures to prevent OPSS include vaccination and prophylactic antibiotics.[143] Preoperative vaccination is preferred. When the vaccines are administered postoperatively, they are conventionally given on the day of dismissal to avoid confusing febrile reactions to the vaccine with a postoperative complication. In the absence of established guidelines, repeat vaccination should be considered every 5 years. Prophylactic antibiotics, particularly advocated for children, include two commonly used strategies. First, a daily prophylactic antibiotic is given to asplenic children (<5 years old) for the first 2 years after splenectomy. The traditional regimen has been a single daily dose of penicillin, amoxicillin, or erythromycin. Recently, antibiotics with broader spectrum, including amoxicillin/clavulanic acid, cefuroxime, and trimethoprim/sulfamethoxazole, have been used. Prophylactic antibiotics can reduce the infection rate by 47% and mortality rate by 88%.[144] Concerns of increasing pneumococcal resistance and patient noncompliance have recently brought this practice into question. Alternatively, asplenic adults are given a supply of "standby" antibiotics to be started if symptoms of infection develop. It should be emphasized that such patients should still seek medical attention. All patients and caretakers should be educated regarding OPSS. Documentation of patient's asplenic state and vaccination status should be issued, along with a medical alert bracelet.

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Part

1

Anatomy, Physiology, and Diagnosis of Colorectal and Anal Disease

Chapter

133

Anatomy of the Colon

James M. D. Wheeler · Neal James McCready Mortensen

The colon extends from the end of the ileum to the peritoneal reflection at the junction of the sigmoid colon with the rectum and includes the ileocecal valve and appendix. It may be considered from its proximal end to be made up of *cecum,* which leads into the ascending, transverse, descending, and sigmoid colon. Together with the rectum and anus, they make up the large intestine (Fig. 133–1), which differs considerably from the small intestine. The *large intestine* originates from both the midgut (cecum to distal transverse colon) and the hindgut (distal transverse colon to rectum and anus) embryologic structures. The colon is approximately 150 cm long, and its greatest caliber is 7.5 cm at the cecum, from where it gradually diminishes to 2.5 cm at the rectosigmoid. Although older studies have shown the length of colon to be as much as 180 cm in men and 157 cm in women,[1] other studies that involved the use of laparotomy have shown the colon to be shorter—about 114 cm in men and about 115 cm in women.[2] The longitudinal muscle layer is concentrated to form three linear bands that are equidistant from each other and make up the taeniae coli. These shorter taeniae cause the circular muscle coat to be puckered and thrown into haustral sacculations because the length of the taeniae is less than that of the bowel wall. The taeniae extend from the tip of the cecum to the rectosigmoid and are approximately 6 mm wide. Most of the colon, other than the appendix and cecum, is peppered with peritoneum-covered adipose pieces known as *appendices epiploicae.* They are most numerous along the taeniae and are relatively flat in the right-sided colon, but they are elongated and pedunculated in the sigmoid.

SURFACE ANATOMY

The surface projection of the cecum (Fig. 133–2) is bounded by the right lateral plane, the transtubercular plane, and the inguinal ligament. From here, the ascending colon moves up to the right of the lateral plane until a point midway between the subcostal and transpyloric planes at the hepatic flexure. Here, the ascending colon meets the transverse colon, which drops to the umbilicus before passing upward and to the left to a point (splenic flexure) above and lateral to where the left lateral and transpyloric planes meet. The transverse colon may show both intraindividual and interindividual differences in position, varying by as much as 17 cm in the same person between standing upright and lying flat.[3] The descending colon then passes down just lateral to the left lateral plane to the inguinal ligament, where it becomes the sigmoid colon. Surface projections of the sigmoid colon vary considerably due to its length, movement on its mesocolon, its distention, and the condition of other pelvic viscera (rectum, bladder, and uterus in females).

CECUM

The cecum is the commencement of the large intestine and is the portion located below a transverse line passing just above the ileocecal valve. The ileum, the vermiform appendix, and the ascending colon all are continuous with the cecum. Its average axial diameter is approximately 6 cm, with a breadth of about 7.5 cm. It is related posteriorly to the iliacus and psoas major muscles and to

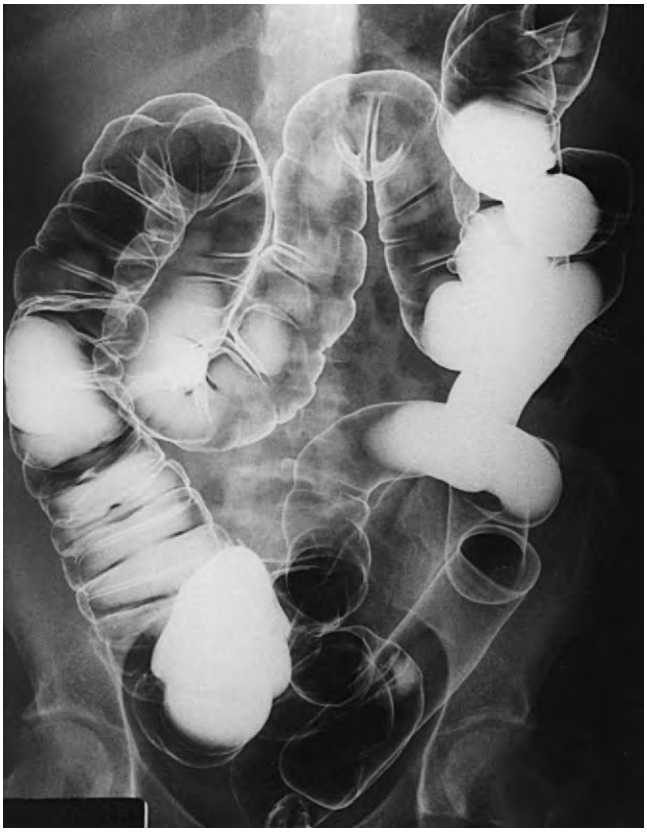

Figure 133–1. Double-contrast barium enema demonstrating the tortuous route that is commonly followed by the colon.

the lateral cutaneous nerve of the thigh, which lies on the iliacus. Anteriorly, the cecum is in contact with the anterior abdominal wall but may have greater omentum or coils of small intestine overlying it. The cecum is mobile and has a complete covering of peritoneum, although this may be absent at the superior part of the posterior surface, which is then connected to iliac fascia by areolar tissue. Although the mesocecum is usually short, the mobility of the cecum may cause it to twist on its mesenteric axis to form a cecal volvulus or to herniate through the right inguinal canal. The area of tenderness in acute appendicitis may be unusually located if the cecum has a long mesocecum. Several mammals have sphincteric anatomy and function at the cecocolonic junction. Faussone-Pelligrini and associates[4] performed functional anatomy studies on 100 patients (including an endoscopic examination in vivo and both macroscopic and microscopic examinations of the ileocecocolonic region from surgical specimens) and concluded that the cecocolonic junction contained both sphincter morphology and function.

ILEOCECAL VALVE

The ileum opens into the large intestine through the ileocecal valve medially and posteriorly where the cecum joins the ascending colon. This "valve" forms a sphincter as a result of the continuation of the circular and longitudinal muscle layers of the terminal ileum. The valve not only prevents reflux from the cecum into the ileum but probably also acts as a terminal ileum sphincter that prevents small intestinal contents from passing too quickly into the cecum. An absolutely competent ileocecal valve together with a colonic obstruction results in a closed-loop obstruction, and in the absence of surgical intervention this will result in perforation of the colon. Barium enema studies have shown that the ileocecal valve is frequently incompetent in persons without any disease.

VERMIFORM APPENDIX

The vermiform appendix is a blind-ending tube that varies from 2 to 20 cm in length (it is longer in the child), with an average length of about 9 cm. It arises from the posteromedial wall of the cecum about 2 cm below the end of the ileum. Its serous coat is complete except for the attachment of its mesentery. Although the position of the appendix base is constant, the appendix itself may occupy one of the following positions:

1. Posterior to the cecum and lower part of the ascending colon (retrocecal and retrocolic)
2. Descending over the pelvic brim (pelvic/descending)
3. Below the cecum (subcecal)
4. Anterior to the terminal ileum and in relation to the anterior abdominal wall (preileal)
5. Posterior to the terminal ileum (postileal)

Despite much anatomic and surgical literature, there remains debate as to the incidence of each appendix position. In a large study of 10,000 subjects in 1933,[5] the appendix was retrocecal or retrocolic in 65%. *McBurney's point,* the junction of the lateral and middle thirds of the line that joins the right anterior superior iliac spine to the umbilicus, is used as a surface marking for the base of the appendix. The three teniae coli converge at the tip of the cecum to form the continuous longitudinal muscle layer of the appendix. The base of the appendix can be located by tracing the anterior taenia coli to the tip of the cecum. The ileocecal fold of peritoneum, which connects the terminal 2.5 cm of ileum to the cecum, can also be used to locate the base of the appendix. A short, triangular mesoappendix extends along the length of the appendix and connects it to the lower portion of the mesentery of the ileum. The mesoappendix contains the main artery to the appendix, which is a branch of the lower division of the ileocolic artery. The lumen of the vermiform appendix communicates, via an opening, with the cecum below and behind the opening of the ileocecal valve.

ASCENDING COLON

The ascending colon is narrower than the cecum at its origin and is about 15 cm long, ascending to the inferior surface of the right lobe of the liver. It then turns down,

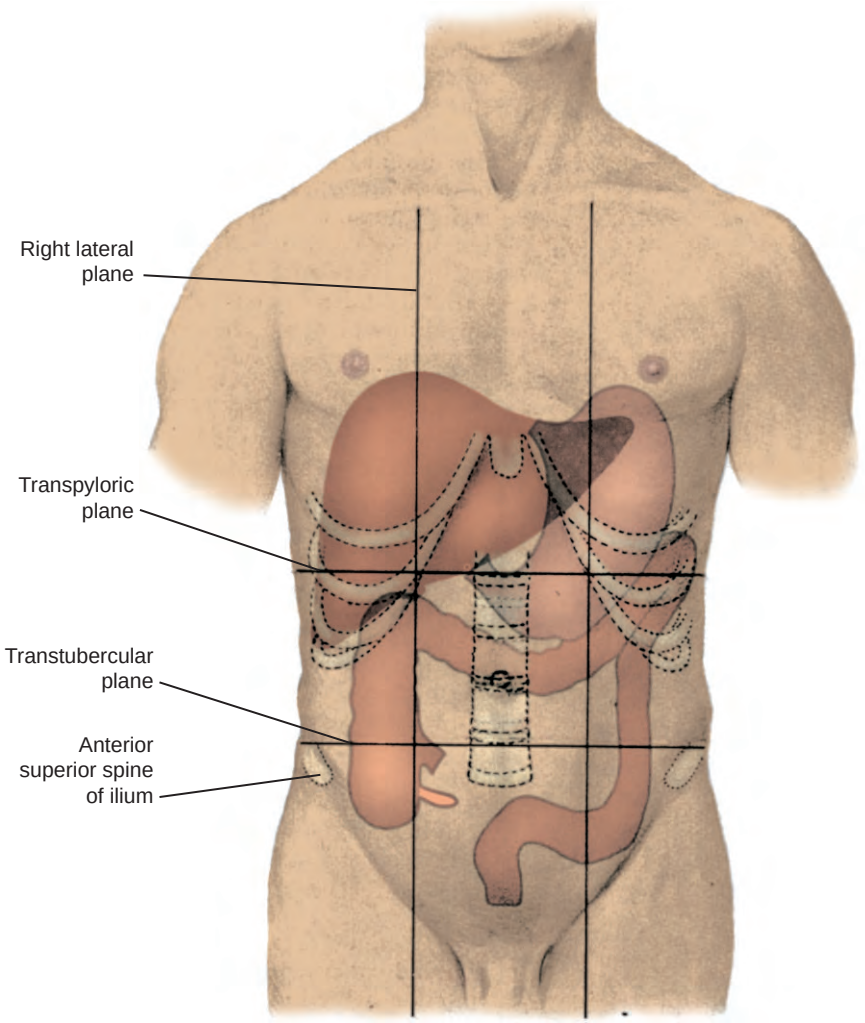

Figure 133–2. Surface projection of the stomach, liver, and colon. The outlines of the lumbar vertebral bodies, lower ribs, xiphoid process, and parts of the iliac crests are indicated. (From Williams PL, Warwick R: Gray's Anatomy, 36th ed. London, WB Saunders, 1980.)

forward, and to the left, forming the *hepatic flexure*. It is related posteriorly to the iliacus, iliolumbar ligament, quadratus lumborum, the origin of the transversus abdominus, the perirenal fascia anterior to the inferolateral part of the right kidney, the lateral cutaneous nerve of the thigh, the fourth lumbar artery, and the ilioinguinal and iliohypogastric nerves. Anteriorly, it is related to the small intestine, the right edge of the greater omentum, and the anterior abdominal wall. The ascending colon is covered on all sides except its posterior surface and is bound by areolar tissue to the posterior abdominal wall (Fig. 133–3). It is not uncommon for it to be completely covered with peritoneum and to contain a narrow mesocolon. Treves[6] found an ascending mesocolon in 12% of cadavers, a descending mesocolon in 22%, and both mesocolons in 14%. The posterior aspect of the hepatic flexure is in direct contact with the inferolateral part of the right kidney, whereas above and anterolaterally, it is related to the right lobe of the liver. The descending portions of the duodenum and fundus of the gallbladder lie anteromedially. The hepatic flexure has a vertical mobility of 2.5 to 7.5 cm with respiration.[7]

TRANSVERSE COLON

The transverse colon begins at the hepatic flexure and passes across the abdomen into the left upper quadrant, where it curves acutely onto itself (more so than at the hepatic flexure), down and backward, to form the *splenic flexure*. It is about 50 cm long, and in its course across the abdomen, it forms an arch with its concavity facing backward and up. The transverse colon is almost completely covered with peritoneum between the head of the pancreas and the splenic flexure. It is attached to the anterior surface of the body of the pancreas and lower pole of the left kidney by the transverse mesocolon, which divides the abdominal cavity into supracolic and infracolic compartments. This division of the abdominal cavity acts as a natural barrier to reciprocal infections between these two areas. The right extremity of the transverse colon is related posteriorly to the front of the descending part of the duodenum and head of the pancreas, being separated by areolar tissue. On its superior aspect, it is related to the liver and gallbladder, the greater curvature of the stomach (to which it is attached by the gastrocolic omentum), and the lateral end of the

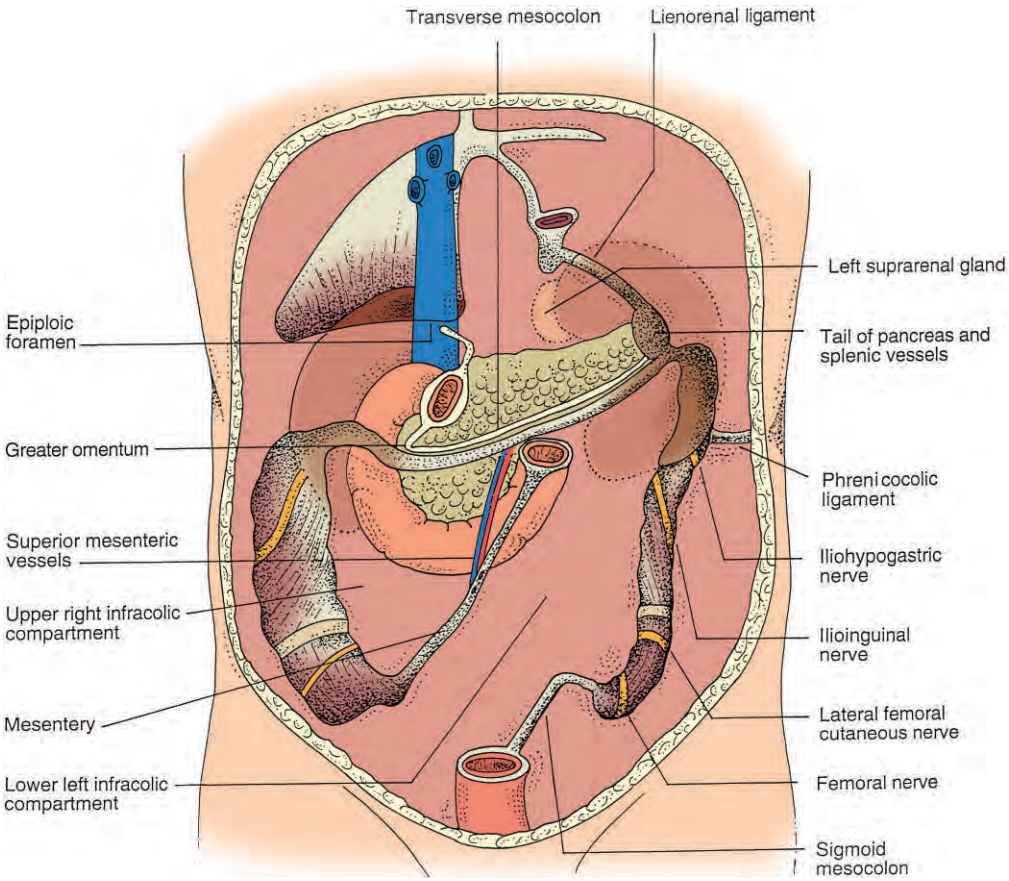

Figure 133–3. Posterior abdominal wall. The colon is removed, demonstrating the attachments of the parietal peritoneum.

spleen. Inferiorly, it is related to the small intestine. It is covered on its anterior surface with the posterior layers of the greater omentum to which it is attached. Posterior to the transverse colon are the descending part of the duodenum, the head of the pancreas, the mesentery, the duodenojejunal flexure, and the small intestine. The transverse colon joins the descending colon at the splenic flexure. This may be so acute that the distal transverse colon lies anterior to the descending colon. Superior to the splenic flexure is the lower part of the spleen and the tail of the pancreas, whereas the anterior aspect of the left kidney lies medially. The splenic flexure is connected to the diaphragm by the phrenicocolic ligament, at the level of the 10th and 11th ribs, and lies at a higher level than the hepatic flexure (Figs. 133–4 and 133–5).

DESCENDING COLON

The descending colon is 25 cm long and extends from the splenic flexure down to the pelvic brim. From the lateral border of the left kidney, it descends between the psoas major and quadratus lumborum to the iliac crest. It then turns medially in front of the iliacus and psoas major to end in the sigmoid colon. Its posterior surface is related to the lower pole of the left kidney, the origin of the transversus abdominis, the quadratus lumborum, the iliacus and psoas major, the subcostal vessels and nerve, the iliohypogastric and ilioinguinal nerves, the fourth lumbar artery, the lateral femoral cutaneous, the

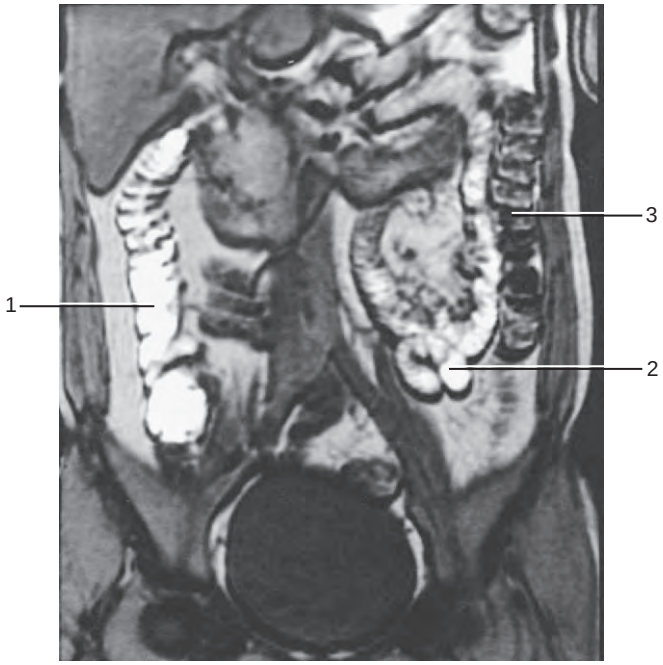

Figure 133–4. Coronal section of MRI: ascending colon (1), small bowel (2), and descending colon (3).

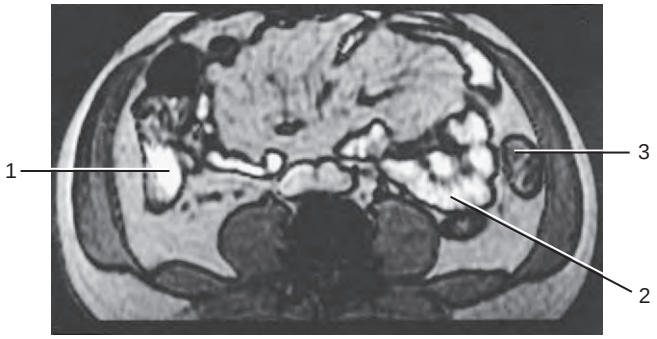

Figure 133–5. Axial section of MRI: ascending colon (1), small bowel (2), and descending colon (3).

femoral and genitofemoral nerves, the gonadal vessels, and the external iliac artery. It is covered by peritoneum over its anterior surface and sides, although like the ascending colon, it may have a narrow mesocolon. On its anterior aspect, it is related to the coils of the small intestine, and in its lower portion, it is related to the anterior abdominal wall. The descending colon is both more narrow and more deeply placed than the ascending colon.

SIGMOID COLON

The sigmoid colon begins at the pelvic brim and forms a loop of about 40 cm (although this may vary greatly) that lies within the pelvis. It becomes continuous with the rectum at the level of the third sacral vertebra and is marked by the lower end of the sigmoid mesocolon. The sigmoid loop is made up of the following parts:

1. *Descending* in contact with the left pelvic wall
2. *Crossing* the pelvic cavity between rectum and bladder (or uterus in the female), where it may reach the right pelvic wall
3. *Arching backward* to reach the median plane

The sigmoid colon is completely surrounded by peritoneum, which forms the sigmoid mesocolon. The sigmoid mesocolon has a V-shaped attachment that is greatest in length at its center and decreases in length toward the end of the loop, so that the sigmoid colon is relatively fixed at its junctions with the descending colon and rectum. The apex of the V is at the bifurcation of the common iliac vessels that overlies the left sacroiliac joint. The left ureter lies between the peritoneum and common iliac artery at this point and is an important landmark for the identification of this structure. The lateral limb of the mesocolon passes forward along the pelvic brim midway to the inguinal ligament. The medial limb slopes down into the hollow of the sacrum, where it reaches the median plane at the level of the third sacral vertebra. As a consequence of the mobility of the loops, the sigmoid colon has variable anatomic relations. On its posterior aspect are the left internal iliac vessels, the ureter, the piriformis, and the sacral plexus. Laterally, it is related to the left external iliac vessels, the obturator nerve, the ovary or ductus deferens, and the lateral pelvic wall. The bladder (and uterus in the female) lies inferior. Above and medially, the sigmoid colon is related to the coils of the small intestine. The rectosigmoid junction has the following six distinguishing features:

1. The diameter of the large intestine narrows.
2. There is an absence of complete peritoneal investment.
3. There is no true mesentery.
4. The three taeniae coli diverge to form a continuous longitudinal muscle coat on the rectum.
5. There are no appendices epiploicae.
6. Endoscopically, an acute angle is encountered at the narrowing of the rectosigmoid and the rectal mucosa is smooth and flat, whereas the mucosa of the sigmoid forms prominent rugal folds.

ARTERIAL SUPPLY

The colon receives its arterial supply from two main branches of the aorta (Figs. 133–6 to 133–8). The *superior mesenteric artery* is the artery of the midgut, and it supplies the colon (and the small intestine from the level of the entrance of the bile duct into the duodenum) to a level just short of the splenic flexure. The *inferior mesenteric artery* is the artery of the hindgut, and it supplies the large intestine as far as the mucous membrane of the upper third of the anal canal.

The superior mesenteric artery arises at the level of the L1 vertebra, approximately 1 cm below the celiac trunk. It descends behind the splenic vein and neck of the pancreas and accompanies the superior mesenteric vein (which lies on its right side) into the upper end of the small intestine mesentery, with the left renal vein, uncinate process of the pancreas, and third part of the duodenum lying behind them. They continue to a point approximately 60 cm from the cecum, passing to the right along the root of the mesentery. The following branches are responsible for supplying the colon:

1. The *ileocolic artery* branches early from the superior mesenteric trunk in the base of the mesentery. Having reached the ileocecal junction, it gives off ileal and colic branches (Fig. 133–9). The colic branch follows the left side of the ascending colon behind the peritoneal floor to anastomose with the right colic artery. The artery then divides into anterior and posterior cecal arteries to supply the cecum. The larger posterior cecal artery supplies the medial, lateral, and posterior walls of the cecum and gives off the appendicular artery, which passes toward the tip of the appendix in the mesoappendix. The appendicular artery is an end artery and does not anastomose with other arteries.
2. The *right colic artery* has its origin at the right side of the root of the superior mesenteric artery in the mesentery. Anatomic studies have shown that this artery originates from the superior mesenteric artery in only 40% of subjects.[8] In 30% of subjects, it arises from the middle colic artery, and in 12% of subjects, it arises from the ileocolic artery. In the

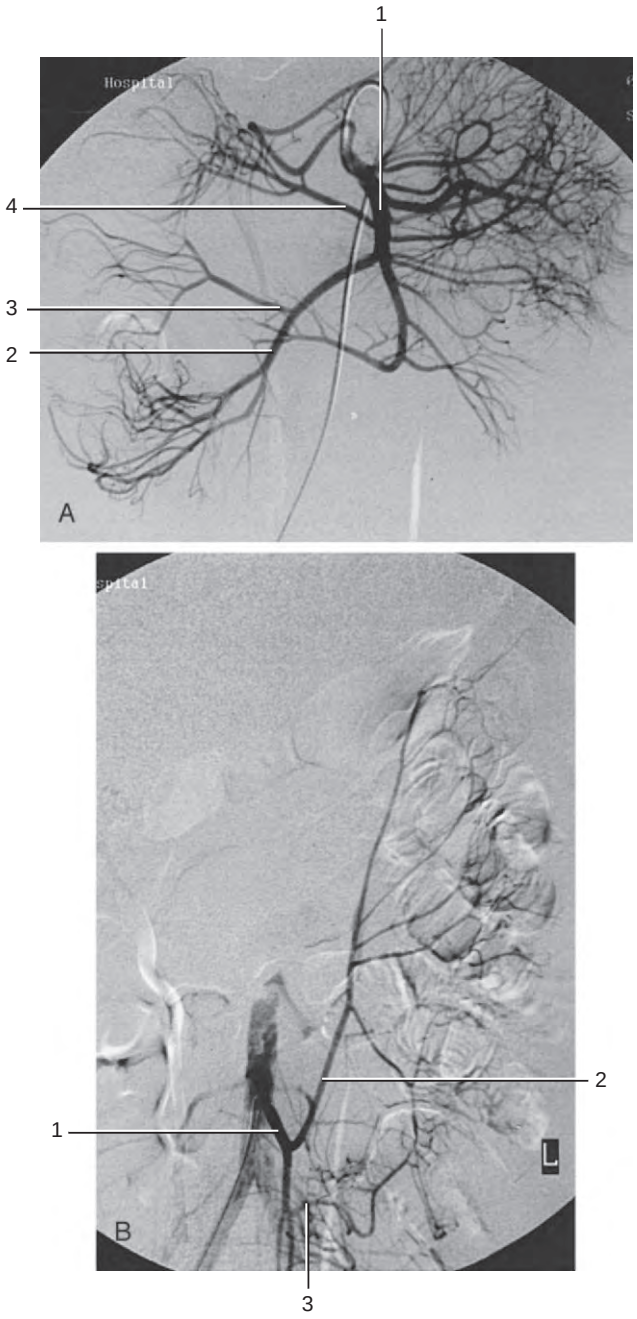

Figure 133–6. **A,** Superior mesenteric angiogram: superior mesenteric artery (1), ileocolic artery (2), right colic artery (3), and middle colic artery (4). **B,** Inferior mesenteric angiogram: inferior mesenteric artery (1), left colic artery (2), and sigmoid artery (3).

remaining 18% of subjects, there was no identifiable right colic artery. It runs behind the peritoneal floor to the ascending colon lying anterior to the right psoas muscle, gonadal vessels, ureter, genitofemoral nerve, and quadratus lumborum. At the left side of the colon, it divides into a descending branch, which anastomoses with the colic branch of the ileocolic artery, and an ascending branch, which runs anterior to the lower pole of the right kidney to the hepatic flexure, where it anastomoses with a branch of the middle colic artery.

3. The *middle colic artery* is the most proximal branch of the superior mesenteric artery, and it arises from the artery at the lower border of the neck of the pancreas, passing into the transverse mesocolon. It travels to the right of the midline in the transverse mesocolon and divides into right and left branches at the transverse colon that run along its length. The right branch anastomoses with the ascending branch of the right colic artery, whereas the left branch anastomoses with a branch of the left colic artery (branch of inferior mesenteric artery) just proximal to the splenic flexure. A large avascular window is left in the transverse mesocolon to the left of the middle colic artery and is often used for surgical access to the lesser sac and posterior wall of the stomach. Unrecognized injury to the middle colic artery will usually result in gangrene of a significant portion of the transverse colon.

The inferior mesenteric artery arises opposite the L3 vertebra from the front of the aorta at the lower border of the third part of the duodenum. It is smaller than the superior mesenteric artery and runs beneath the peritoneal floor of the left infracolic compartment to the pelvic brim. Here, it crosses the bifurcation of the left common iliac vessels and converges on the left ureter. In its descent, it lies anterior to the aorta, left psoas muscle, left sympathetic trunk, left common iliac artery, and hypogastric nerve. On crossing the pelvic brim, the inferior mesenteric artery becomes the superior rectal artery (supplying the rectum) and continues along the pelvic wall in the root of the sigmoid mesocolon. Branches of the inferior mesenteric artery pass to the left in front of the ureter in the floor of the left infracolic compartment. The following branches supply the left side of the colon:

1. The first branch is the *left colic artery,* which, lying beneath the peritoneal floor, passes up and laterally to the splenic flexure. It branches after a short course into the ascending branch, which continues laterally and up, and a descending branch. The ascending branch lies anterior to the left psoas muscle, gonadal vessels, ureter, genitofemoral nerve, and quadratus lumborum and is crossed by the inferior mesenteric vein. It then divides into the upper branch, which crosses the lower pole of the left kidney on its way to the splenic flexure, and the lower branch, which passes across to the descending colon. Both branches further divide into branches that anastomose with the left branch of the middle colic artery. The descending branch passes laterally and down (anterior to the same structures as the ascending branch), and at the pelvic brim, it divides into two or three branches that pass laterally behind the peritoneal floor of the left iliac fossa and form anastomoses with each other to supply the lower portion of the descending colon.
2. The *sigmoid arteries* are three or four branches that arise from a common origin at the inferior

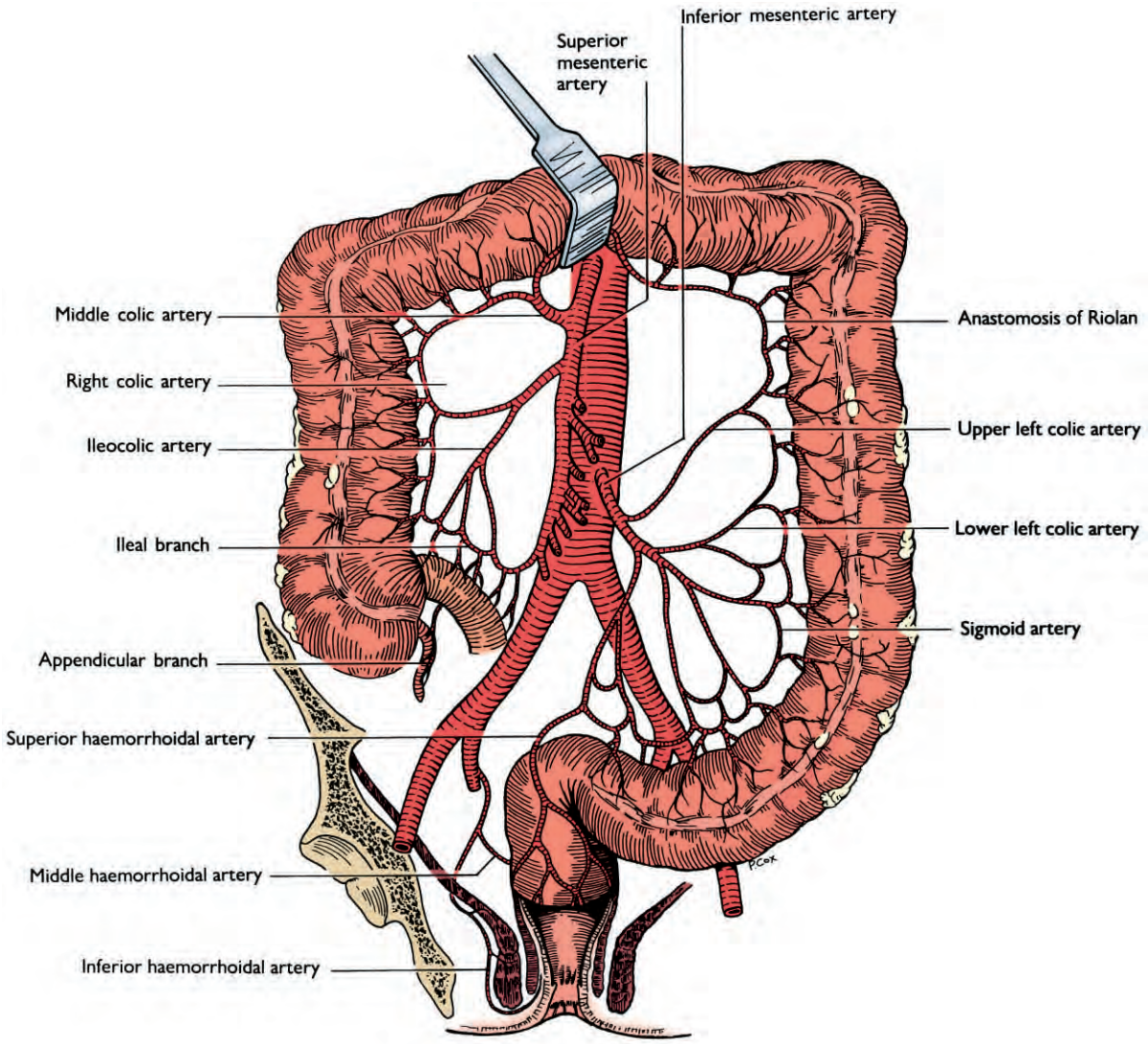

Figure 133–7. The arterial supply to the colon and rectum. The normal distribution of supply to the ileum, right colon, and right side of transverse colon from the middle colic artery and ileocolic arteries is shown. The distribution of the arterial supply from the inferior mesenteric artery to the left side of the transverse colon, the descending colon, the sigmoid, and the upper rectum is also demonstrated. (From Keighley MRB, Williams NS: Surgery of the Anus, Rectum, and Colon. Philadelphia, WB Saunders, 1995.)

mesenteric artery below the left colic artery. They pass forward in the sigmoid mesocolon and supply the sigmoid colon.

The *marginal artery* is the name given to a single arterial trunk made up of anastomoses around the concave border of the large intestine from the ileocecal junction to the rectosigmoid junction. The marginal artery is therefore made up of branches of both the superior and inferior mesenteric arteries. Moynihan[9] remarked that the importance of the marginal artery "cannot be overemphasized." Vessels arise from this artery that run perpendicular to and sink into the walls of the colon to supply the large intestine. Short vessels supply the mesocolic two thirds of the large bowel circumference, whereas the long vessels penetrate the serosa, encircling the bowel to supply the antimesenteric third of the large bowel circumference (Fig. 133–10). The weakest link in this anastomosis is between the middle and left colic arteries in the region of the splenic flexure. Hall and colleagues[10] measured tissue oxygen tension and showed that after "high tie" of the inferior mesenteric artery (flush with the aorta), the marginal artery remains able to adequately supply the transverse and descending colon but not the sigmoid colon. Furthermore, Dworkin and Allen-Mersh[11] demonstrated with the use of laser Doppler flowmetry that there is a *50% reduction* in blood perfusion of the sigmoid colon after ligation of the inferior mesenteric artery.

VENOUS DRAINAGE

Venous blood returns from the colon in veins with names that correspond to those of the artery, having drained an area similar to that supplied with arterial blood (Fig. 133–11).

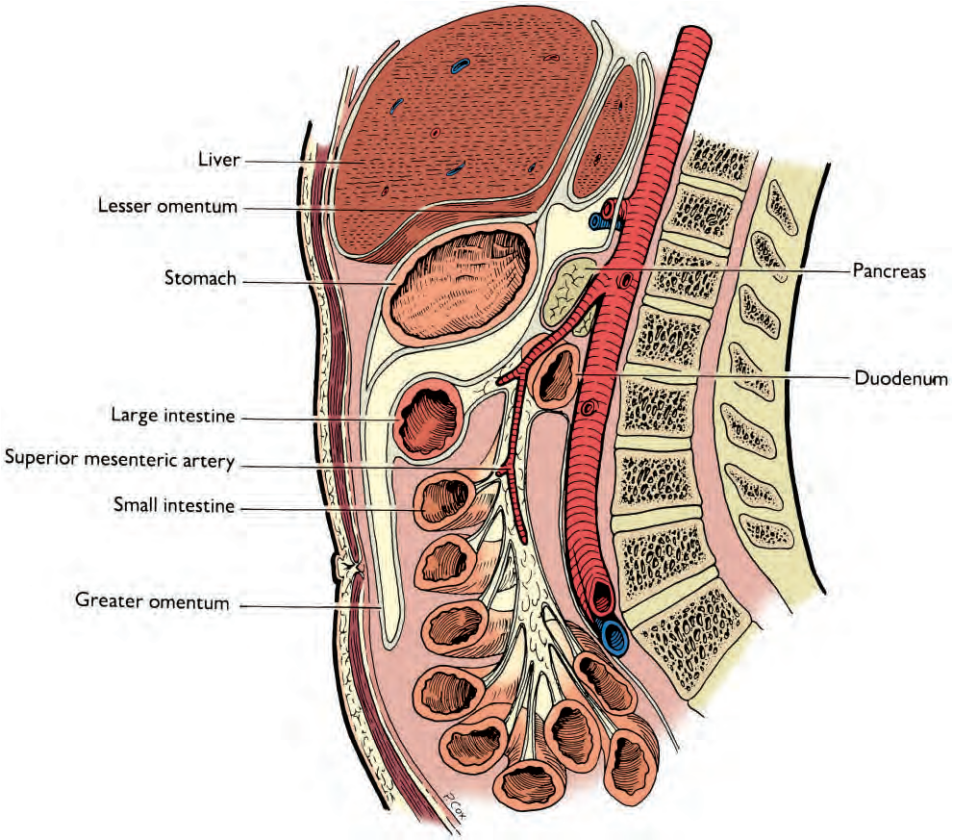

Figure 133–8. Sagittal section of the abdomen to demonstrate the blood supply to the transverse colon and small bowel, the greater omentum, the greater sac, and the lesser sac. (From Keighley MRB, Williams NS: Surgery of the Anus, Rectum, and Colon. Philadelphia, WB Saunders, 1995.)

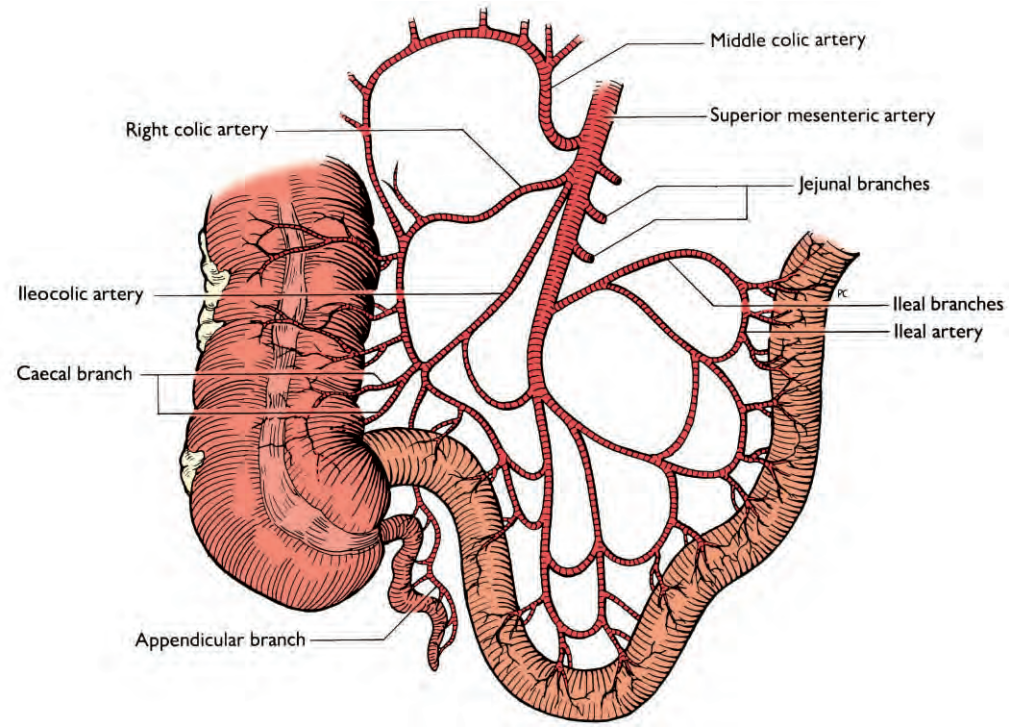

Figure 133–9. Detailed anatomy of the arterial supply to the terminal ileum and right colon is shown. In particular, the normal divisions of the ileocolic artery and arcade with the middle colic artery are demonstrated. (From Keighley MRB, Williams NS: Surgery of the Anus, Rectum, and Colon. Philadelphia, WB Saunders, 1995.)

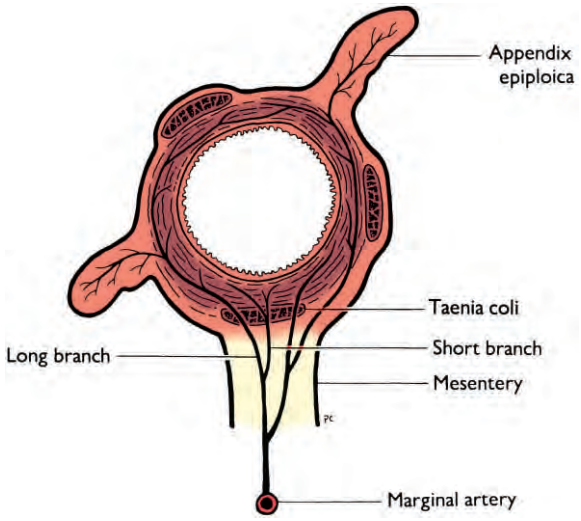

Figure 133–10. The terminal arterial supply to the colon and its relation to the taeniae coli and appendices epiploicae are demonstrated. (From Keighley MRB, Williams NS: Surgery of the Anus, Rectum, and Colon. Philadelphia, WB Saunders, 1995.)

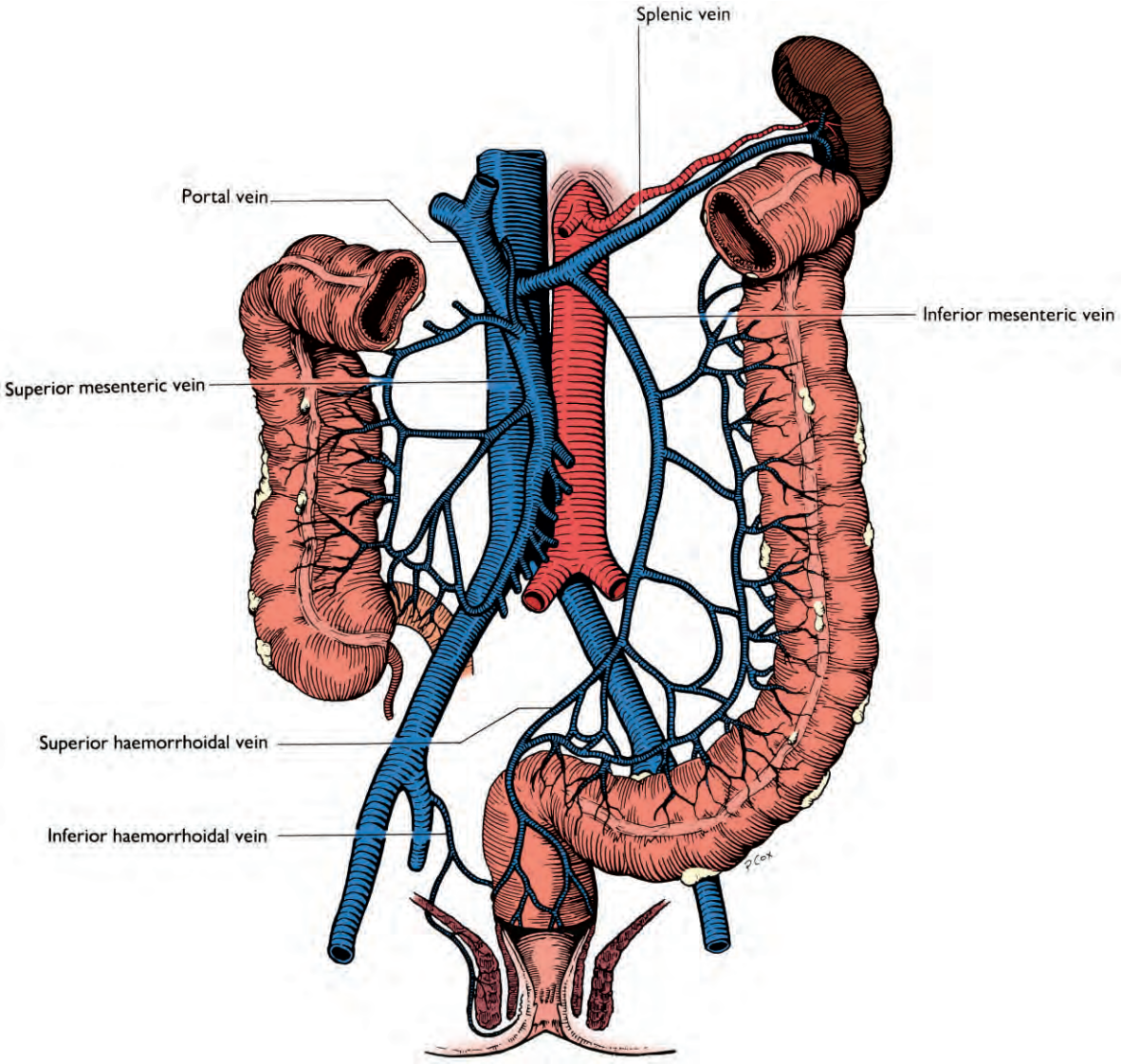

Figure 133–11. The venous drainage of the large bowel and rectum is illustrated; in particular, the drainage of the left colon via the inferior mesenteric vein to the splenic vein is shown. (From Keighley MRB, Williams NS: Surgery of the Anus, Rectum, and Colon. Philadelphia, WB Saunders, 1995.)

Veins from the right side of the colon flow into the superior mesenteric vein, which drains the midgut. This large vein lies to the right side of the artery, crossing the third part of the duodenum and ascending between the uncinate process and the neck of the pancreas to join with the splenic vein and to form the portal vein. The portal vein continues up behind the first part of the duodenum.

Veins from the left side of the colon flow into the inferior mesenteric vein, which drains the hindgut. The inferior mesenteric vein is the continuation of the superior rectal vein, which lies to the left of its artery. The inferior mesenteric vein runs vertically up beneath the peritoneal floor of the left infracolic compartment and is well to the left side of the artery. It lies anterior to the left psoas muscle, gonadal vessels, ureter, and genitofemoral nerve. The vein continues to the left side of the duodenojejunal flexure and passes behind the lower border of the body of the pancreas (anterior to the left renal vein) and joins the splenic vein. The inferior mesenteric vein may open directly into the superior mesenteric vein, having taken a course farther to the right and passing behind the pancreas, below and parallel with the splenic vein.

LYMPHATIC DRAINAGE

Lymph vessels of the gastrointestinal tract run along arteries, in the reverse direction, to their draining lymph nodes, which lie along the aorta at the origin of the relevant artery (Fig. 133–12). The lymphatic vessels of the left colon drain into lymph nodes at the inferior mesenteric trunk, which drain into the superior mesenteric trunk, which drained the right colon (and most of the small intestine). They then pass via efferent lymph vessels to the celiac group of nodes and ultimately into the cisterna chyli.

The appendix drains into lymph nodes in the mesoappendix and from there into paracolic nodes that lie along the ileocolic artery. The cecum and ascending colon drain into epicolic nodes that lie along the left side of the bowel, into the paracolic nodes along the ileocolic and right colic arteries behind the peritoneal floor, and then into the superior mesenteric group of preaortic lymph nodes. The transverse colon drains via epicolic nodes into the paracolic nodes along the middle colic artery in the transverse mesocolon and then into the superior mesenteric nodes.

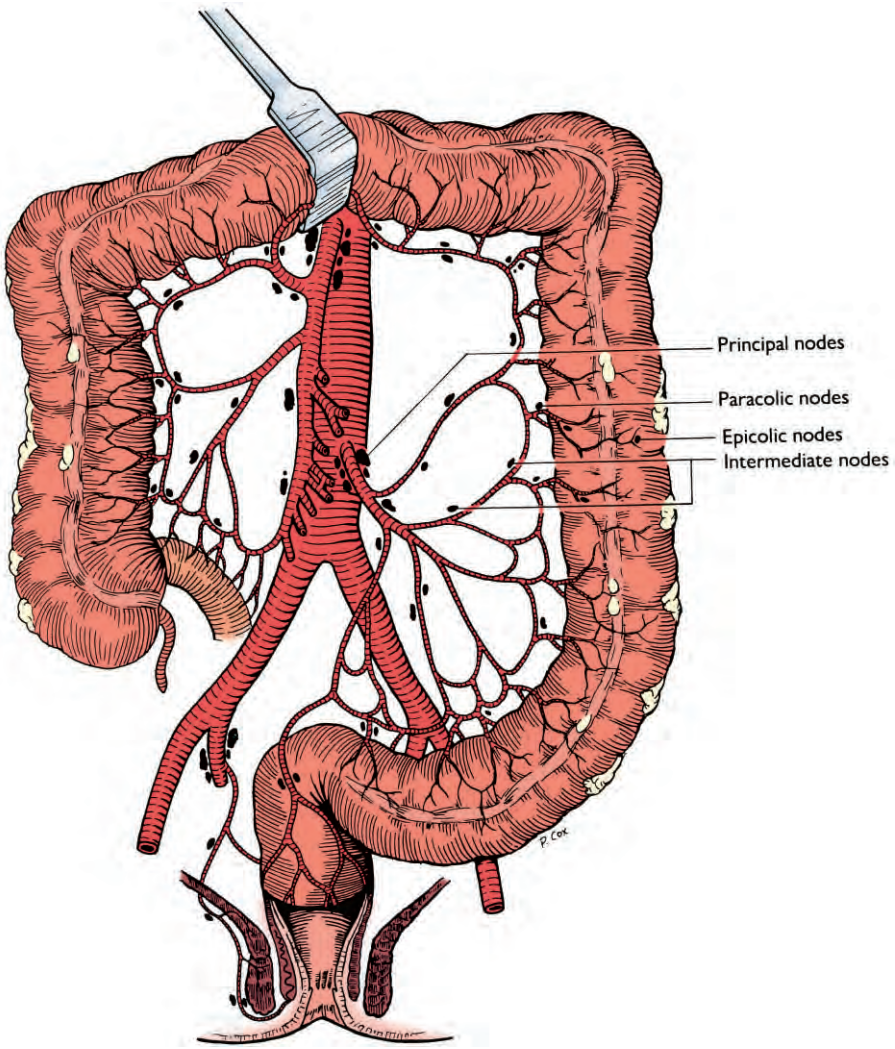

Figure 133–12. The lymphatic drainage of the colon and rectum is illustrated, showing that the lymph nodes are distributed around the arterial supply to the large intestine. Four tiers of nodes are recognized: paracolic, epicolic, intermediate, and principal lymph nodes. (From Keighley MRB, Williams NS: Surgery of the Anus, Rectum, and Colon. Philadelphia, WB Saunders, 1995.)

The lymphatic vessels of the left side of the colon from the splenic flexure to the start of the rectum drain into epicolic nodes along the right side of the bowel. From here, they drain into paracolic nodes that lie along branches of the inferior mesenteric artery behind the peritoneal floor (although the paracolic nodes draining the sigmoid colon lie in the root of the sigmoid mesocolon) and then into the inferior mesenteric nodes.

INNERVATION

The colon is innervated by both the sympathetic (from the 11th and 12th thoracic and 1st and 2nd lumbar nerves) and parasympathetic (from the vagus and 2nd, 3rd, and 4th sacral nerves) divisions of the autonomic nervous system (Fig. 133–13). The sympathetic nerves are thought to have an inhibitory effect on colonic

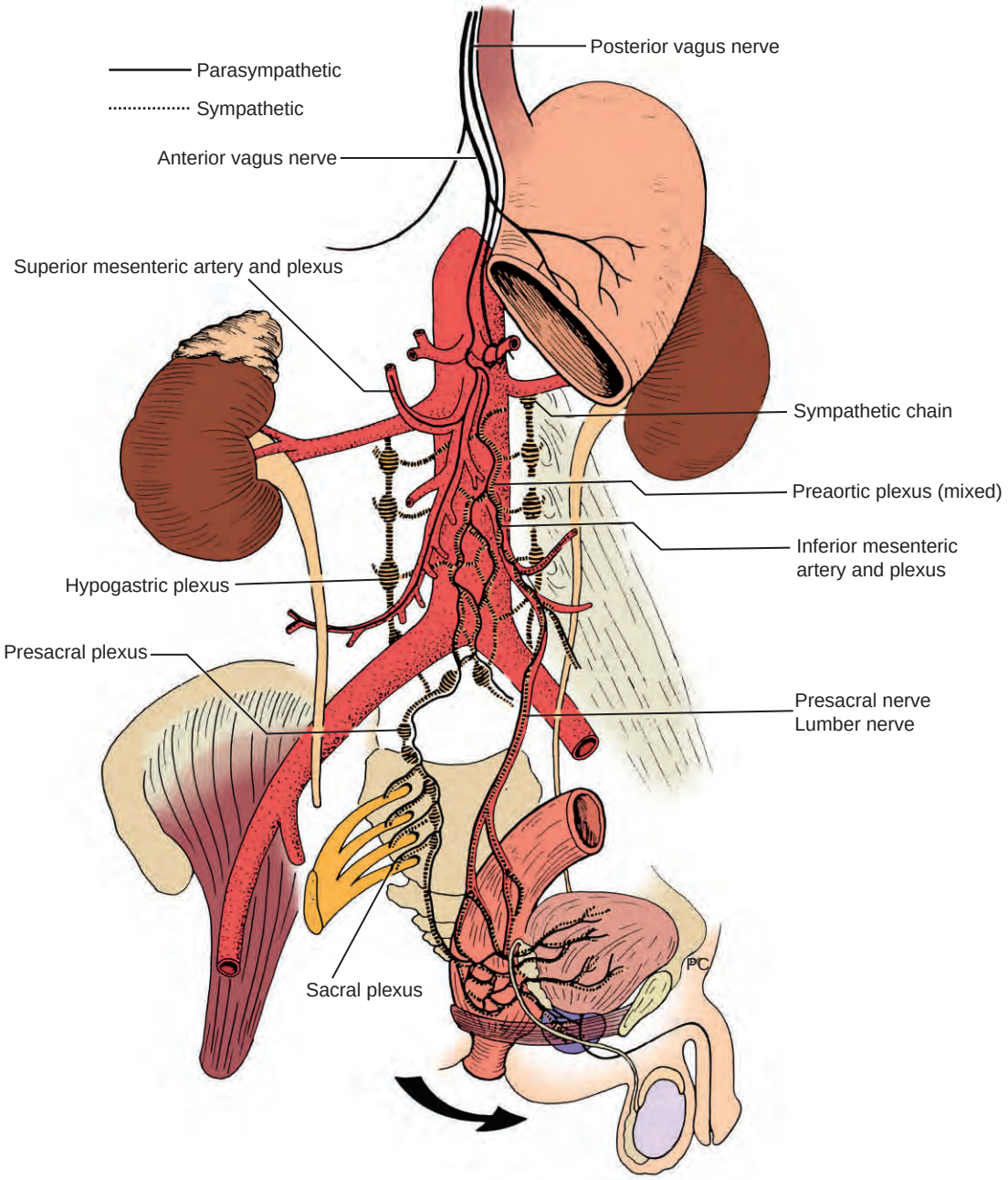

Figure 133–13. The autonomic supply to the colon and rectum is diagrammatically illustrated in an oblique plane. The contribution of the vagus nerve and the nervi erigentes to the parasympathetic supply to the pelvis is demonstrated. The sympathetic chain is shown together with the perivascular plexus to provide the autonomic innervation to the large bowel and rectum. (From Keighley MRB, Williams NS: Surgery of the Anus, Rectum, and Colon. Philadelphia, WB Saunders, 1995.)

peristalsis and secretions, whereas the parasympathetic nerves increase colonic peristalsis and secretions.

The right half of the colon obtains its sympathetic supply via the celiac and superior mesenteric ganglia of the sympathetic trunk, whereas the left side of the colon is supplied with sympathetic fibers from the lumbar part of the sympathetic trunk, via the superior hypogastric plexus, which sends nerves along branches of the inferior mesenteric artery. The parasympathetic supply of the right side of the colon comes from the vagus, and together with the sympathetic supply, the nerves are distributed along branches of the superior mesenteric artery. The parasympathetic supply to the left colon occurs via the pelvic splanchnic nerves (nervi erigentes). Nerves travel up through the superior hypogastric plexus, often referred to as the *presacral nerve* (nerves to the rectum and anus pass to the inferior hypogastric plexus), without interruption and follow branches of the inferior mesenteric artery. The splenic flexure and descending colon also receive branches of the pelvic splanchnic nerves, which have traveled up behind the peritoneal floor and independent of the inferior mesenteric artery.[12]

Colonic pain may be referred to a site distant to the organic insult. Nash[13] described a study of intestinal pain reference in which a balloon was inflated at various points of the gastrointestinal tract. Pain from the cecum is referred to McBurney's point with spread to the epigastrium, whereas pain from the hepatic flexure is referred to the right upper quadrant. Pain from the ascending, transverse, and descending colons is referred to the lower abdomen in the midline and to the left. Rectosigmoid pain is referred to the suprapubic and coccygeal areas.

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Chapter

134

Embryology and Anatomy of the Colon

Luca Stocchi · John H. Pemberton

EMBRYOLOGY

The colon develops from the primitive midgut, which opens ventrally into the yolk sac. Starting at the 5th gestational week, the midgut rapidly grows and reorganizes to delineate the permanent gastrointestinal tract structures, including the colon. This progression is traditionally divided into three separate stages (Fig. 134–1). In the first stage, the elongated midgut loop enters the extraembryonic celom into the umbilical cord, a process referred to as *physiologic umbilical herniation*. The superior mesenteric artery (SMA) also exits the abdominal cavity along with this bowel loop and within its corresponding mesentery. The SMA thus separates the midgut in a proximal and anterior portion, referred to as *prearterial,* which carries the omphalomesenteric duct at its apex, and a posterior and distal portion. The herniated intestine then rotates counterclockwise by 180 degrees around the SMA axis. In particular, the prearterial segment moves posteriorly and to the left of the SMA and delineates what will become the third and fourth portions of the duodenum.

In the second stage, the primitive intestine returns into the abdominal cavity and undergoes an additional 90 degrees of rotation, thus completing a total of 270 degrees. At this point, the duodenum has rotated counterclockwise around and below the SMA, and the small bowel is located mostly on the right side of the midline. At variance with that, the primitive colon rotates over the SMA, starting from the left. In particular, the cecum is the last segment to reenter the abdominal cavity, where it is initially located right below the liver and then migrates toward its permanent position in the right iliac fossa. Meanwhile, the small bowel elongates while its mesentery shortens, before becoming fixed to the posterior peritoneum.

A number of anomalies of rotation can occur at this stage, including nonrotation, incomplete rotation, reversed rotation, and the range of intermediate conditions collectively considered under the definition of malrotation (Fig. 134–2).[1] In general, individuals with anomalies of rotation are at an increased risk for mesenteric volvulus and extrinsic duodenal compression from abnormal peritoneal attachments, also referred to as *Ladd's bands*. In the nonrotation, the midgut is unable to complete the physiologic 270 degrees of rotation and lies at 0 or 90 degrees with the colon in the left abdomen, the cecum near the midline, and the small bowel to the right. This anomaly can be encountered in approximately 0.2% of radiologic studies and predisposes to midgut volvulus and extrinsic compression of the duodenum. In incomplete rotation, the rotation progresses to approximately 180 degrees. Therefore, the prearterial segment does not reach the posterior location, and the cecum does not rotate anteriorly to the SMA but typically remains in the left upper abdomen. The colon becomes fixed to the posterior wall by abnormal peritoneal bands, which can cause duodenal obstruction. The reversed rotation is the result of a clockwise rotation around the SMA, with the prearterial segment ending up anteriorly to the posterior segment, which can become entrapped in a mesocolic hernia. The transverse colon lies posteriorly to the duodenum and the SMA, in a tunnel beneath the mesentery, which predisposes to the onset intestinal obstruction (Fig. 134–3).

The third and final developmental stage occurs at approximately the 12th week and consists of cecal descent and colon fixation to the posterior peritoneum. In particular, the cecum reaches the right iliac fossa, whereas the ligament of Treitz becomes an identifiable anatomic structure located to the left of the aorta, and the small bowel mesentery retracts in its permanent oblique and broad-based position. When the migration of the colon is complete, the posterior mesentery of the ascending and descending colon fuses with the posterior abdominal wall and forms the fascia of Toldt, also referred to as *white line of Toldt,* which is an essential landmark for a bloodless dissection (Fig. 134–4).

Anomalies of the third phase include undescended, mobile, or hyperdescended cecum; persistent colon

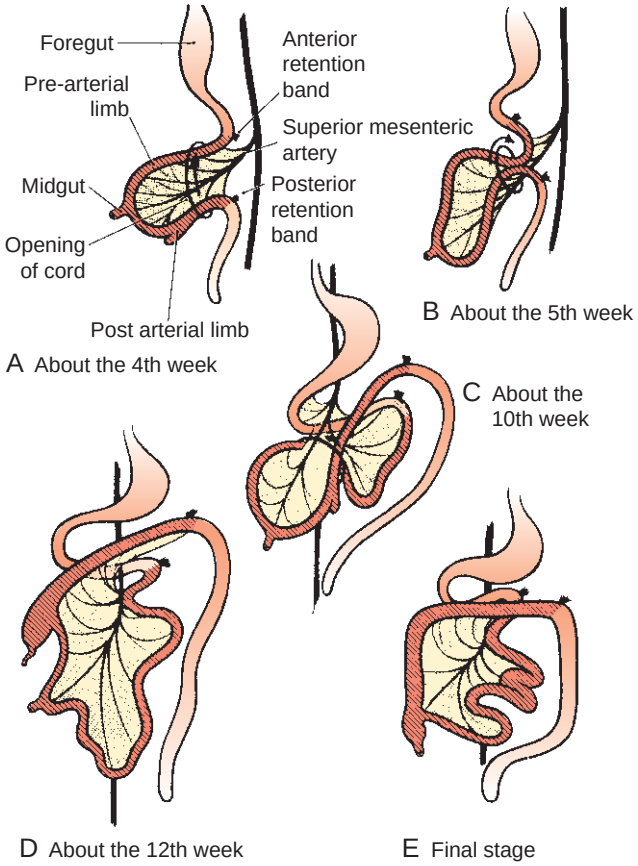


Figure 134–1. Normal rotation. **A,** Human embryo at 4th or 5th week. Note that the midgut supplied by the superior mesenteric artery has "herniated" into the cord. The foregut and hindgut derivatives do not enter this "hernia"; the retention bands are points of fixation. **B,** The prearterial segment of the midgut loop has returned into the abdomen first, as the gut has rotated counterclockwise. The duodenum thus comes to lie behind the superior mesenteric artery. Note the splenic flexure is fixed on the left. **C,** Embryo at the 10th week. The postarterial segment has also reduced and comes to lie in front of the superior mesenteric artery. The cecum is in the upper abdomen and must migrate to the right lower quadrant as counterclockwise rotation continues to 270 degrees. **D,** Embryo at the 12th week. Rotation has been completed; the viscera have attained their normal relationships. **E,** Gradually, fusion of parts of the primitive mesentery occurs fixing the duodenum and ascending and descending portions of the colon to the posterior abdominal wall. (**A**-**E,** From Haller JD, Morgenstern L: Anomalous rotation and fixation of the left colon: Embryogenesis and surgical management. Am J Surg 108:331, 1964.)

mesentery; and ileocecal mesentery. In these anomalies, the laxity of the posterior attachments increases the risk of volvulus.

Anomalies of Fixation

When the posterior fixation of the colon is incomplete, abnormal spaces result that may favor the onset of internal hernias. The most common types of internal hernias are referred to as *mesocolic* or *paraduodenal hernias,* which can occur either on the right or to the left (Fig. 134–5).[2-5] A right mesocolic hernia results from a failure of the prearterial limb to rotate around the SMA so that the intestinal loops become entrapped into the right colon mesentery. Surgical repair is accomplished by mobilization of the right colon and rotation to the left, which is essential to free the small bowel.

The more frequent left mesocolic hernia results from migration and protrusion of the small intestine through the space between the superior mesenteric vein (SMV) and the descending colon mesentery. In this case, the surgical repair consists of mobilization of the inferior mesenteric vein (IMV) and reduction of the hernia through the sac, which is then closed to prevent the creation of an empty space.

Rarely, anomalies of rotation and fixation coexist, and these can occur in the left colon. The primary disorder is fixation of the left colon on the right side, followed by a physiologic counterclockwise rotation of the transverse colon, which concludes its trajectory behind the SMA and the duodenum.

Atresia of the Colon

Atresia of the colon is a rare disorder that resembles the analogous condition of the small bowel and constitutes 5% to 12% of all the intestinal atresias. Three different types have been described. In type I, there is simple mucosal diaphragm, whereas in type II, two blind ends are connected by a fibrous cord derived from the mesentery. In type III, the two blind ends are associated with a corresponding mesenteric gap. The most accepted pathogenetic theory postulates that this disorder originates from an intrauterine derangement in the development of the vascular supply to the involved segment of bowel. A more recent theory supported by experimental evidence correlates colonic atresia to the absence of embryonic expression of fibroblast growth factor or its corresponding receptor.[6] The three types occur with approximately similar frequency without any gender predilection.

In approximately 20% of cases, a number of associated congenital abnormalities have been described, including Hirschsprung's disease, duodenal atresia, bladder exstrophy, and ophthalmic defects. Symptoms are not distinctively different from other types of intestinal obstruction and include bilious vomiting, abdominal distention without bowel movements, and absent or minimal passage of meconium. Barium enema is diagnostic and should be promptly followed by surgery to avoid the risk of necrosis and perforation. A delayed diagnosis predisposes to profound dehydration and electrolyte imbalance.

Duplication of the Colon

A number of different disorders are included in this category; they are basically divided into mesenteric cysts, colonic diverticula, and true colon duplications.

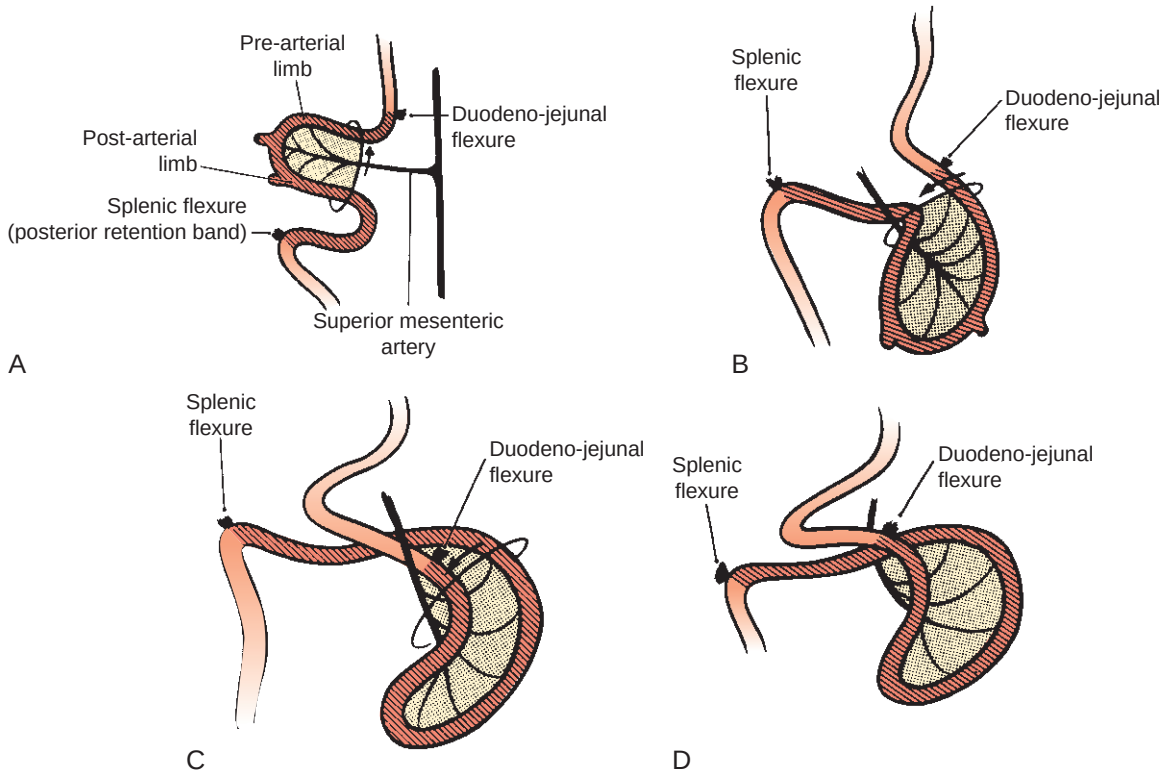


Figure 134–2. Mechanism for producing anomalies of rotation and fixation of the entire left colon. **A,** The splenic flexure fixes on the right side rather than on the left. This is the first and basic anomaly. **B,** Rotation begins in the normal counterclockwise direction. Because the splenic flexure is already fixed on the right, the adjacent segment of bowel, the transverse colon, reduces first and comes to lie behind the superior mesenteric artery. Thus, the first anomaly of fixation has produced the second anomaly of rotation. **C,** The next loop to reduce is the duodenum, as is normal. By projecting from this diagram, one can see that the reduction of the cecum last, as also is normal, will throw the proximal transverse colon in front of all of the other structures. **D,** If duodenal reduction is delayed or its rotation is incomplete, it may reenter the abdomen later and come to lie anterior to the superior mesenteric artery. (**A-D,** From Haller JD, Morgenstern L: Anomalous rotation and fixation of the left colon: Embryogenesis and surgical management. Am J Surg 108:331, 1964.)

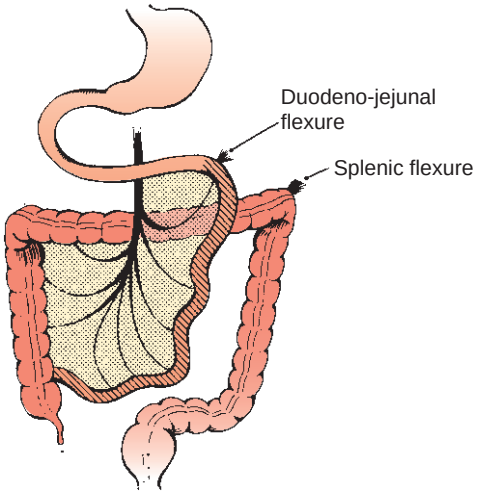


Figure 134–3. Reversed rotation. Note that (1) the locations of all parts of the large and small bowel are normal and (2) the only anomaly is the reversed relationship of the transverse colon and duodenum with the superior mesenteric artery; the colon is posterior and the duodenum is anterior. (From Haller JD, Morgenstern L: Anomalous rotation and fixation of the left colon: Embryogenesis and surgical management. Am J Surg 108:331, 1964.)

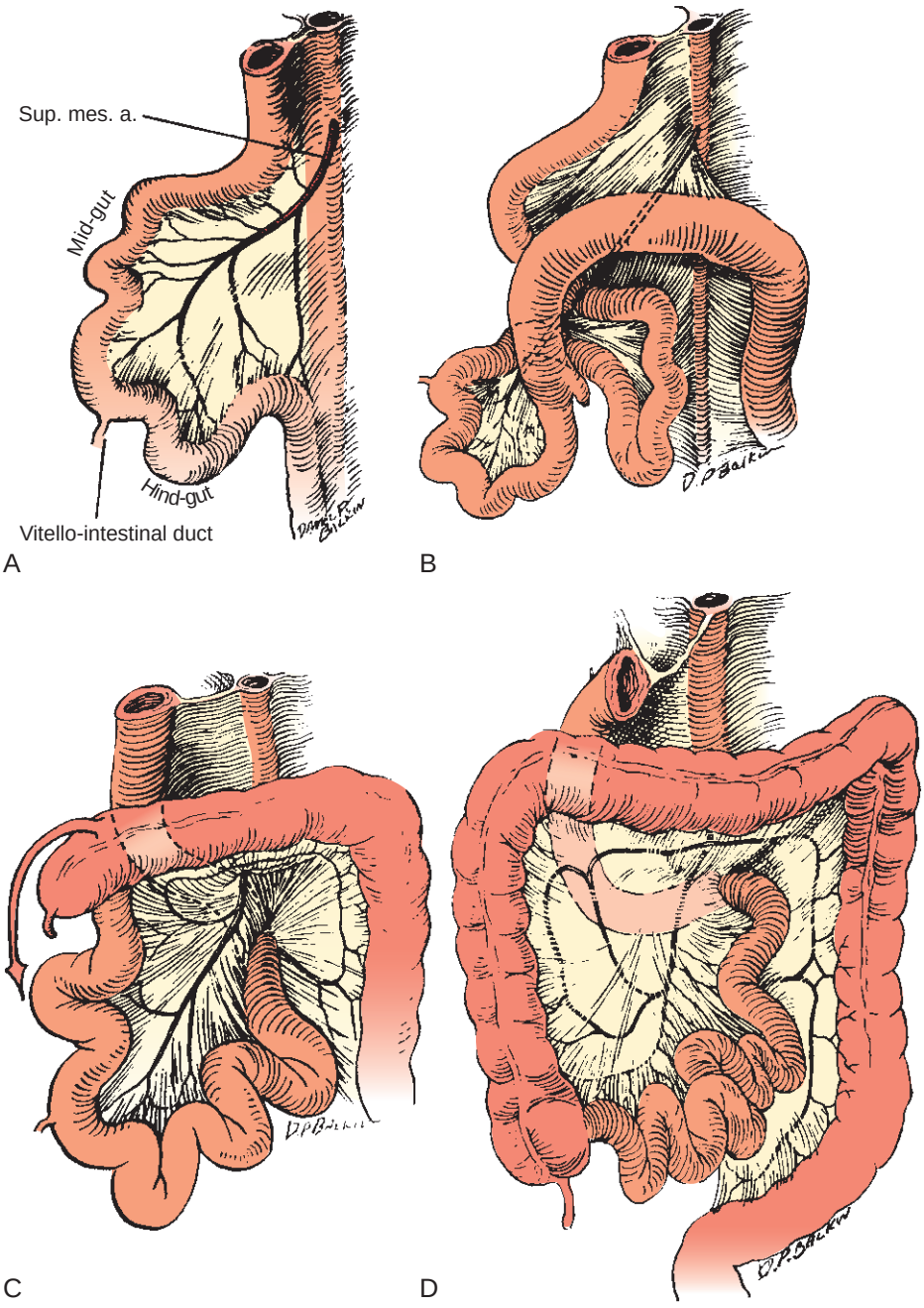


Figure 134–4. Normal intestinal rotation. **A,** Loop formed by midgut. **B,** Rotation of midgut and extracoelomic position. **C,** Orderly return of intestinal loops into peritoneal cavity below the transverse mesocolon and further rotation of 180 degrees in counterclockwise direction. **D,** Descent of cecum and fixation of ascending colon to posterior parietal peritoneum. Sup mes a, superior mesenteric artery. (**A-D,** From Zimmerman LM, Laufman H: Intra-abdominal hernias due to developmental and rotational anomalies. Ann Surg 138:82, 1953.)

Mesenteric cysts are generally located in the mesocolon. They can communicate or not with the intestinal lumen and can have an independent blood supply. They are lined with intestinal epithelium and present as palpable masses or with symptoms of intestinal obstruction.[7]

A different variant of colonic duplication is the presence of colonic diverticula. Congenital disorders are often difficult to differentiate from acquired diverticula, a quite common condition in elderly individuals living in Western countries. Acquired diverticula are common and generally located in the sigmoid colon and tend to increase in frequency with age. In contrast, right colon diverticula are much rarer and are equally frequent in elderly and younger patients. Therefore, it has been speculated that right colon diverticula are most likely congenital. In general, congenital diverticula can be located on the mesenteric or antimesenteric border of the colon and can undergo mucosal metaplasia, most frequently gastric or pancreatic. Accumulation of fecal material can increase the dimensions of the diverticulum, which becomes manifest as an abdominal mass. Alternatively, the diverticulum can present with bleeding from gastric ectopic mucosa, or it can prompt colonic intussusception with intestinal obstruction.

A truly bilateral colon duplication is a rare disorder often accompanied by duplication of other structures, most frequently the spine, bladder, and vagina (Fig. 134–6). In its complete form, two distinct gastrointesti-

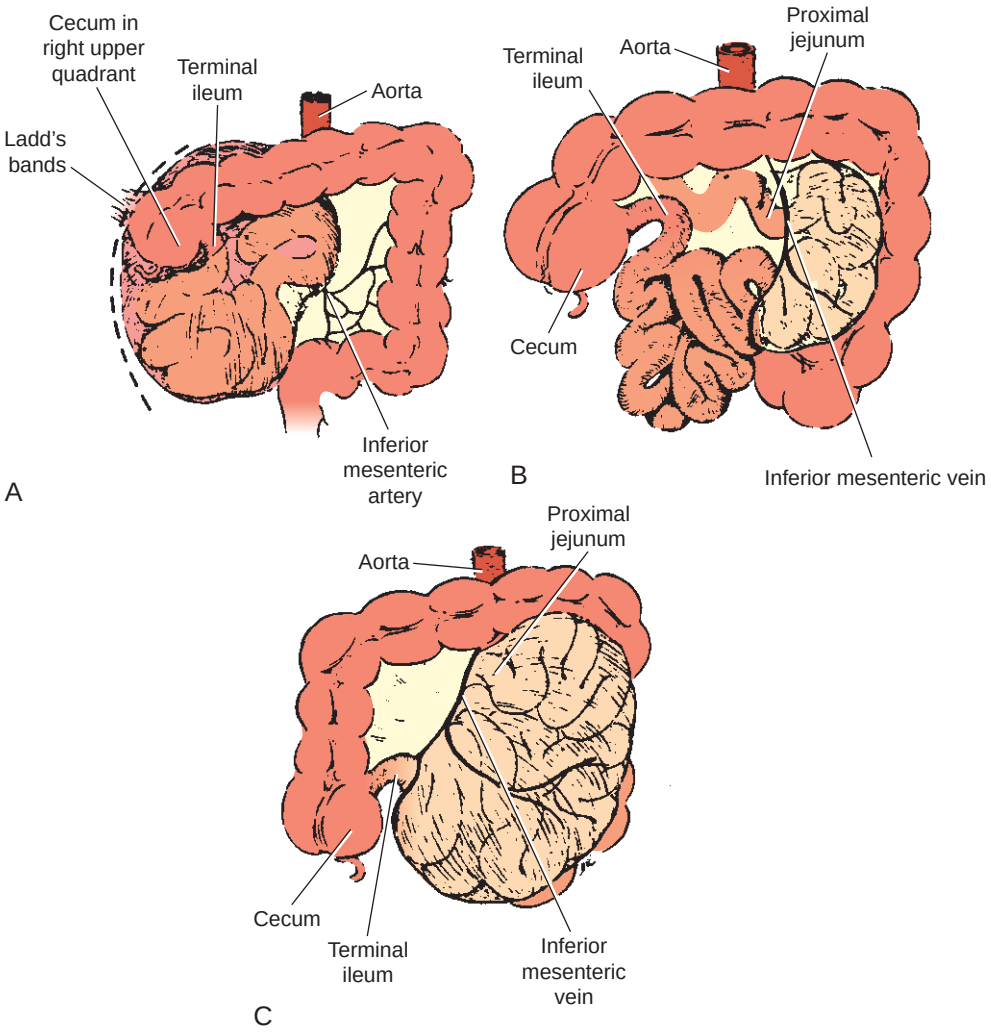


Figure 134–5. Mesocolic hernias. **A,** Right mesocolic hernia. Prearterial segment of the midgut has failed to rotate. Postarterial segment does not rotate and traps most of the small bowel behind the right mesocolon. The *hatched line* indicates the surgical incision used to reduce the hernia. **B,** Left mesocolic hernia. Initial rotation of the small intestine is normal. During migration to the left superior portion of the abdomen, the bowel invaginates an avascular portion of the left mesocolon posterior to the interior mesenteric vein. **C,** Left mesocolic hernia. Small intestine, except for portions of the distal ileum, is trapped beneath the left mesocolon. Note that the inferior mesenteric vein delineates the right margin of the sac and is an integral part of the neck of the sac. (**A,** From Willwerth BM, Zollinger RM, Izant RJ: Congenital mesocolic (paraduodenal) hernias: Embryologic basis of repair. Am J Surg 128:358, 1974; **B** and **C,** Adapted from Callander CL, Rusk R, Nemir A: Mechanism, symptoms, and treatment of hernia into the descending mesocolon. Surg Gynecol Obstet 60:1052, 1935.)

nal tubules are encountered from the terminal ileum to the rectum. The two proceed distally while sharing a common wall and terminate in two separate anal openings.[8] However, in most cases, the duplication is incomplete and involves only a segment of the large bowel, which can terminate in one anus or an anus and a fistula.[9] Other anomalies may coexist, such as horseshoe or absent kidney and clubfoot.

ANATOMY

The colon has been traditionally described as the gastrointestinal segment that extends from the ileocecal valve to the rectum (Fig. 134–7). Whereas these landmarks have been widely accepted, their definition is more controversial. At the proximal end, the term *ileocecal valve* is considered a misnomer by several authors,[10] who postulate that the valve mechanism is located entirely in the terminal ileum. On the other hand, the delimitation between the colon and the rectum is not uniformly accepted. Some surgeons consider the sacral promontory or the changes in the characteristics of the longitudinal muscular layer at the end of the sigmoid to be landmarks. Others simply measure the rectum as the last 10, 12, or 15 cm of the large bowel from the anal verge and consider as colon the entire remaining large bowel. The location of the colon in the peritoneal cavity

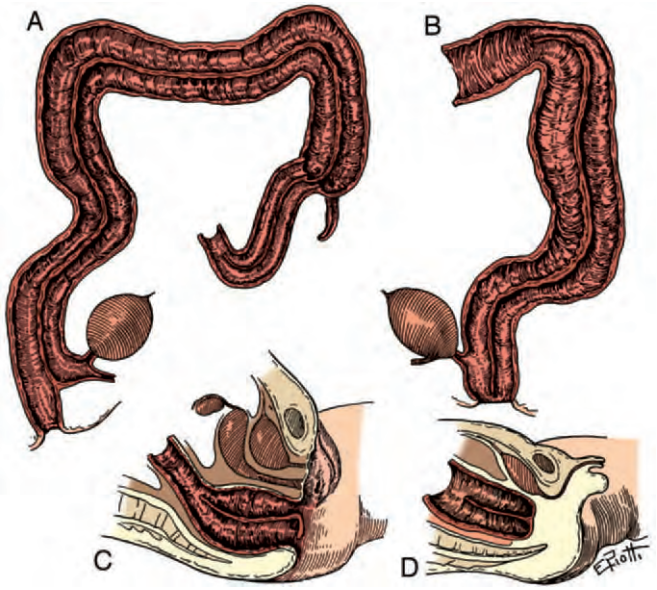


Figure 134–6. Examples of tubular duplications of the intestine. **A,** Duplication from ileum to rectum. One canal ends at a normal anus, and the other ends in a fistula to the urethra. **B,** Duplication of the descending colon with double anus and a fistula to the urethra. **C,** Short duplication of the rectum, with two anal openings. **D,** Duplication of the rectum, with both canals ending blindly (more frequently, the cranial end of the duplication is blind). (**A-D,** From Skandalakis JE, Gray SW [eds]: Embryology for Surgeons, 2nd ed. Baltimore, Williams & Wilkins, 1994, p 249.)

varies greatly based on individual shape and extent of mesenteric attachments. In most cases, the hepatic flexure lies lower than the splenic flexure, as can be seen on barium enema. In general, the ascending and descending colons are retroperitoneally located, whereas the transverse and sigmoid colons have mesenteries. The colonic length ranges between 120 and 200 cm and depends on gender as well as individual variations. In a study that compared colonic length as measured on barium enema, despite a significantly smaller stature, women had a longer colon than men, with a median of 155 versus 145 cm. In addition, women have a longer transverse colon, which also carries an increased likelihood of location within the pelvis.[11] These anatomic data might explain why colonoscopies are generally more difficult to perform in women than in men. Similarly, there is evidence that Western patients have an increased incidence of sigmoid colonic adhesions and colonic mobility compared with Asian counterparts, which again would confirm the increased technical difficulty in performing colonoscopy that is observed in Western patients.[12] It has been reported that the transverse colon lies below the umbilicus in as many as 10% of women, a detail that might carry importance for laparoscopic surgery.[13]

Three distinctive basic macroscopic features in the colon help differentiate it from the small bowel: the presence of taeniae coli, the presence of haustra coli, and appendices epiploicae, or fatty appendices (Fig. 134–8). The taeniae coli are condensations into three bundles of the longitudinal muscular layer of the large bowel that are macroscopically visible, although a thinner longitudinal layer remains to completely encircle the lumen. The taeniae extend from the cecum to the end of the sigmoid. The taeniae are traditionally named after their location in the transverse colon. The taenia mesocolica is connected to the mesocolon; the taenia omentalis is attached to the greater omentum; and the taenia libera has no attachments and is more clearly identifiable on the surface of the bowel wall. The taeniae contribute to the configuration of the haustra as convex folds of colonic wall, which confer to the colon its saccular appearance. Last, the appendices epiploicae are similar to droplets of yellow adipose tissue that surround the colonic wall. They are especially noticeable in the sigmoid, and they become absent in the rectum.

Cecum

The cecum is the proximal portion of the colon after the ileocecal valve. At this level, it continues into the ascending colon and measures approximately 6 cm in length and 7.5 to 8 cm in width. The cecum is generally covered by peritoneum, although in most cases, there is no distinct mesentery and the mobility is limited. Occasionally, the cecum can be particularly mobile, which facilitates the dissection but predisposes to cecal volvulus and may contribute to unusual clinical presentations of acute appendicitis. Such a varying degree of attachments corresponds to a variable position of the cecum that lies on the iliac muscle but can cover part of the psoas or abut the pelvis. The lowest haustrum corresponds to what can be endoscopically viewed as the cecal fundus, where the appendiceal orifice is generally visible and is a useful indicator of a complete colonoscopic exploration. A mucosal fold referred to as *Gerlach's valve* inconsistently covers the appendiceal orifice. An additional landmark visible endoscopically is the ileocecal valve, with the ileal orifice delimited by two distinct lips: the ileocolic, or superior, lip and the ileocecal, or inferior, lip. Although the term *ileocecal valve* is still largely used, some authors have objected to its accuracy in consideration that the valve mechanism might actually lie in the terminal ileum. Externally, the junction between the ileum and the cecum is associated with a number of peritoneal folds and recesses. The superior ileocecal fold extends anteriorly as a mesenteric appendage where the anterior cecal artery runs. The fold covers the corresponding superior ileocecal recess. Inferiorly, the inferior ileocecal fold connects the antimesenteric aspect of the terminal ileum with the mesenteriolum of the appendix. Because this fold does not contain any vessel, it is also referred to as the *bloodless fold of Treves*. A small inferior ileocecal recess lies inferior and posterior to the corresponding fold.[14]

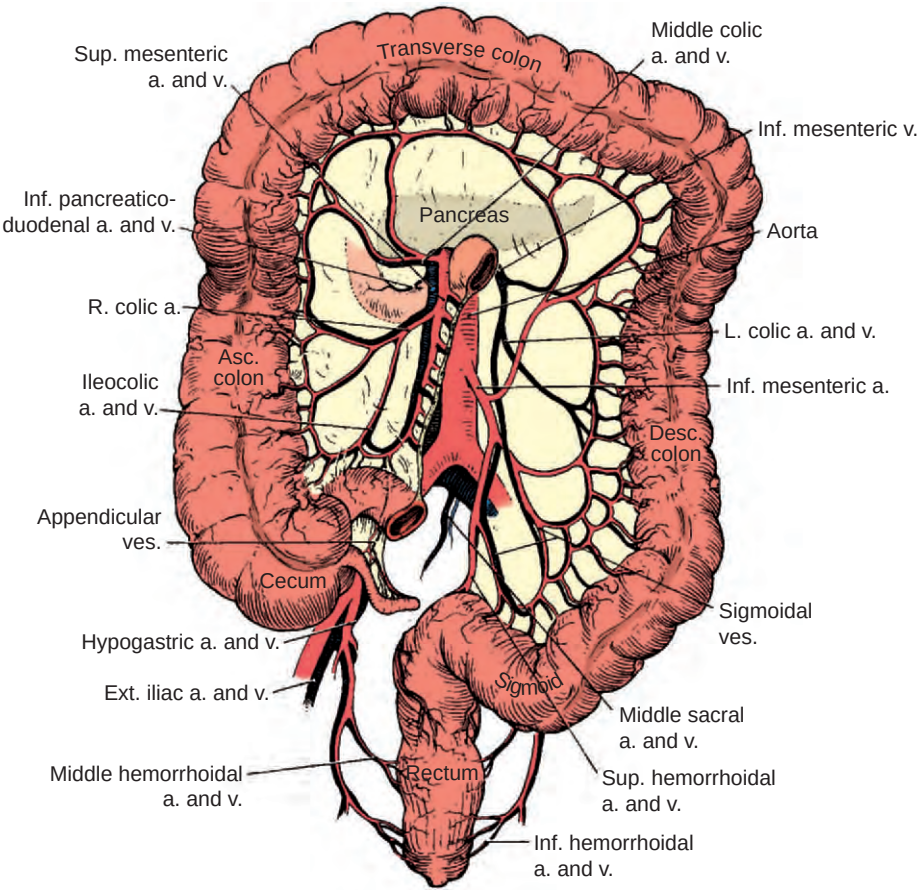


Figure 134–7. The colon, showing its anatomic divisions and its blood supply (the veins are shown in black lines). (Modified from Jones T, Shepard WC: A Manual of Surgical Anatomy. Philadelphia, WB Saunders, 1945.)

Appendix

The vermiform appendix is in continuation with the cecum through the appendiceal orifice and is surrounded by a continuous longitudinal muscular layer, which results from the union of the three taeniae. It is approximately 8 to 9 cm long, although it can range from 5 to 35 cm. It generally originates at the posteromedial border of the cecum, although it can be connected to the cecal fundus or even located in close proximity to the ileocecal valve. In approximately 65% of patients, the appendix courses vertically in the retrocecal recess, whereas in 31%, it descends into the iliac fossa. More rarely, it can course laterally in the retrocecal recess, immediately below the posterior cecal serosa, or it can be encountered in a paracecal, preileal, or postileal location (Fig. 134–9). The appendix is accompanied by its corresponding mesenteriolum, which contains the appendicular artery, a terminal artery without any arterial arcades. It is postulated that this anatomic condition predisposes to inflammatory damages due to the inability to meet the demand for an increased blood supply. Conversely, branches derived from the anterior and posterior cecal arteries provide additional blood supply to the base of the appendix. The venous circulation drains into the ileocolic and the right colic veins, whereas the lymphatics drain into the ileocecal nodes and then along the SMA nodes into the celiac nodes.

Ascending Colon

The ascending colon lies on the right side of the abdominal cavity, in front of the quadratus lumborum and transversus abdominis muscle. It extends from the cecum to the hepatic flexure and averages 12 to 20 in length. The existence of a physiologic sphincter zone at the cecocolonic junction has been suggested based on manometric studies performed during right hemicolectomy.[15] In most cases, the ascending colon is covered by peritoneum on its anterior and lateral aspects and is fixed posteriorly, whereas in about 25% of individuals, mesentery can be identified. Rarely, a tenuous adhesion from the right abdominal wall to the anterior taeniae of the ascending colon has been observed, which is referred to as *Jackson's membrane*. The ascending colon lies anterior to the lower pole of the right kidney, from which it is separated by perirenal fat and Gerota's fascia. It also relates posteriorly to the right ureter and gonadal vessels, which lie on the surface of the psoas muscle (Fig. 134–10). At the lower margin of the liver and lateral or adherent to the gallbladder, the ascending colon turns to the left at the point traditionally described as *hepatic flexure*. The hepatic flexure lies immediately above the second portion of the duodenum, to which it is sometimes attached by a peritoneal fold referred to as *duodenocolic ligament*. In addition, a hepatocolic ligament can be occasionally found, in continuity with the lesser omentum (Fig. 134–11).

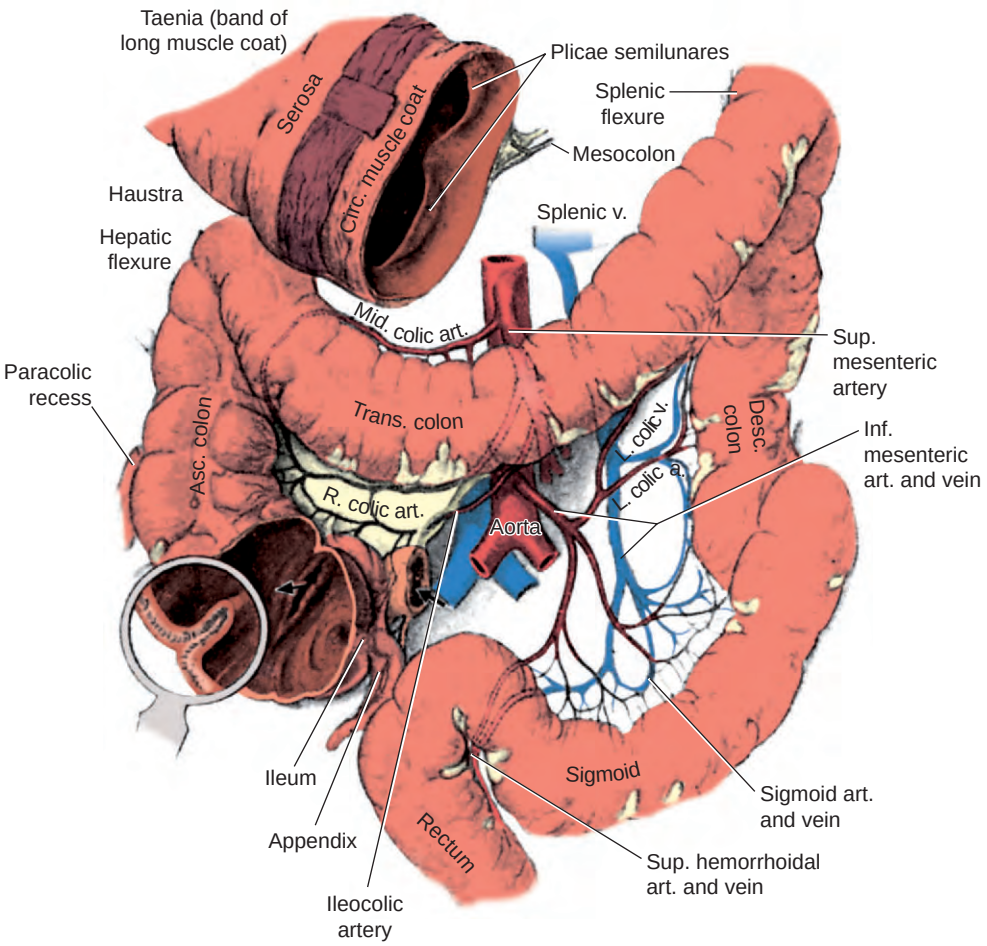


Figure 134–8. The large intestine. The position of the colon as shown is based on radiographic study in living humans. The anterior wall of the cecum is removed to show the ileocolic valve, characteristic folds, and opening of the appendix. Note that the blood supply is from two sources: (1) the superior (sup) mesenteric artery through the middle, right, and ileocolic branches; and (2) the inferior (inf) mesenteric artery through the left colic, sigmoid, and superior hemorrhoidal branches. An enlarged segment of transverse colon is shown above with details of the wall and plicae. A magnified portion of cecum wall is seen at the lower left. (From Bockus HL: Gastroenterology, Vol 2, 3rd ed. Philadelphia, WB Saunders, 1976.)

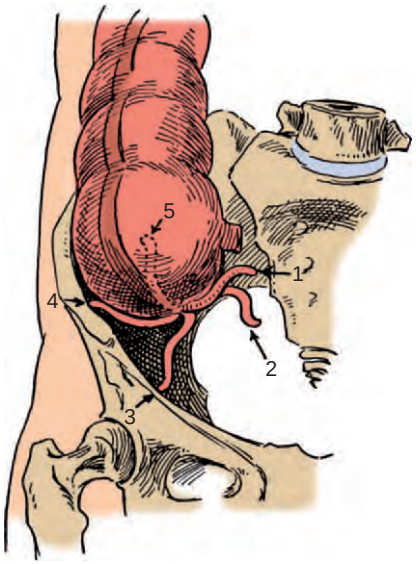


Figure 134–9. Various positions (1 to 5) occupied by the appendix.

Transverse Colon

The transverse colon connects the ascending and descending colon and courses horizontally across the abdominal cavity. It is attached to the posterior abdominal wall by a long mesentery, which renders it extremely flexible. The transverse colon can therefore be quite long, even 40 or 50 cm, and reach the iliac crests or even lie deep into the pelvis. The root of the transverse mesocolon lies anteriorly to the lower pole of the right kidney and extends over the second portion of the duodenum; the head, body, and tail of the pancreas; and, finally, on the hilum of the left kidney. It is generally accepted as the anatomic landmark that separates the supramesocolic from the inframesocolic compartments. The duodenojejunal junction, also referred to as the *ligament of Treitz,* lies just inferior to the root of the transverse mesocolon. The greater omentum covers the transverse colon along almost its entire length and is connected to it by the gastrocolic ligament. This structure is usually dissected in case of transverse colectomy or to obtain access to the lesser sac. The distal transverse colon generally lies in front and above the descending colon and is connected to the diaphragm by the phrenocolic ligament. The splenic flexure generally forms an acute angle in the

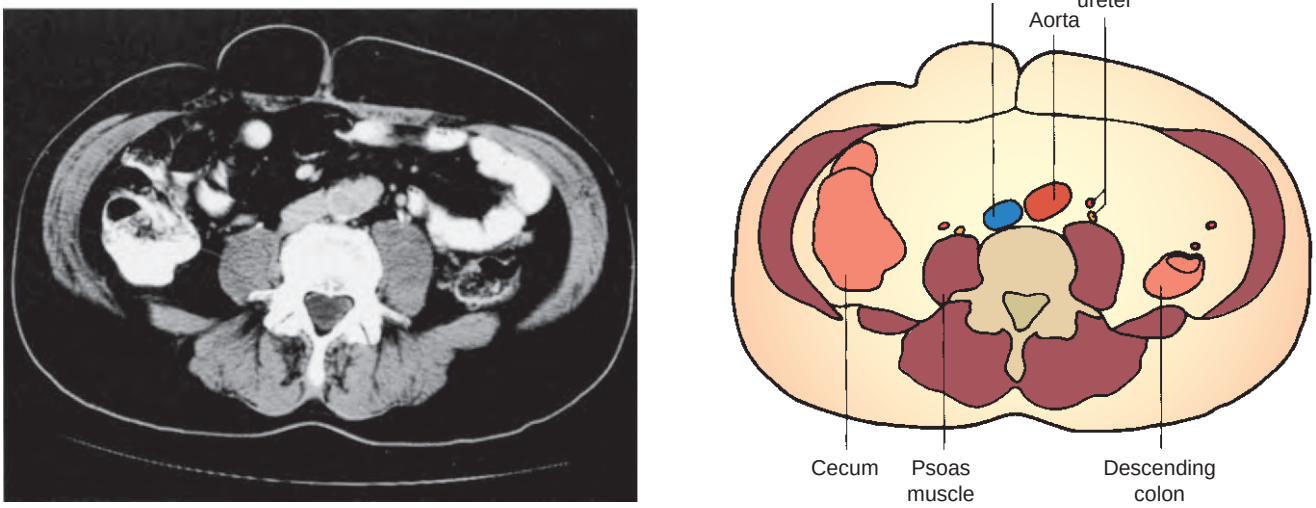


Figure 134–10. **A** and **B,** The right colon is related posteriorly to the right ureter, gonadal vessels, duodenum, and kidney. (**A** and **B,** From Fozard JBJ, Pemberton JH: Applied surgical anatomy: Intra-abdominal contents. In Fielding LP, Goldberg SM [eds]: Rob and Smith's Operative Surgery of the Colon, Rectum, and Anus, 5th ed. Philadelphia, Chapman & Hall, 1994.)

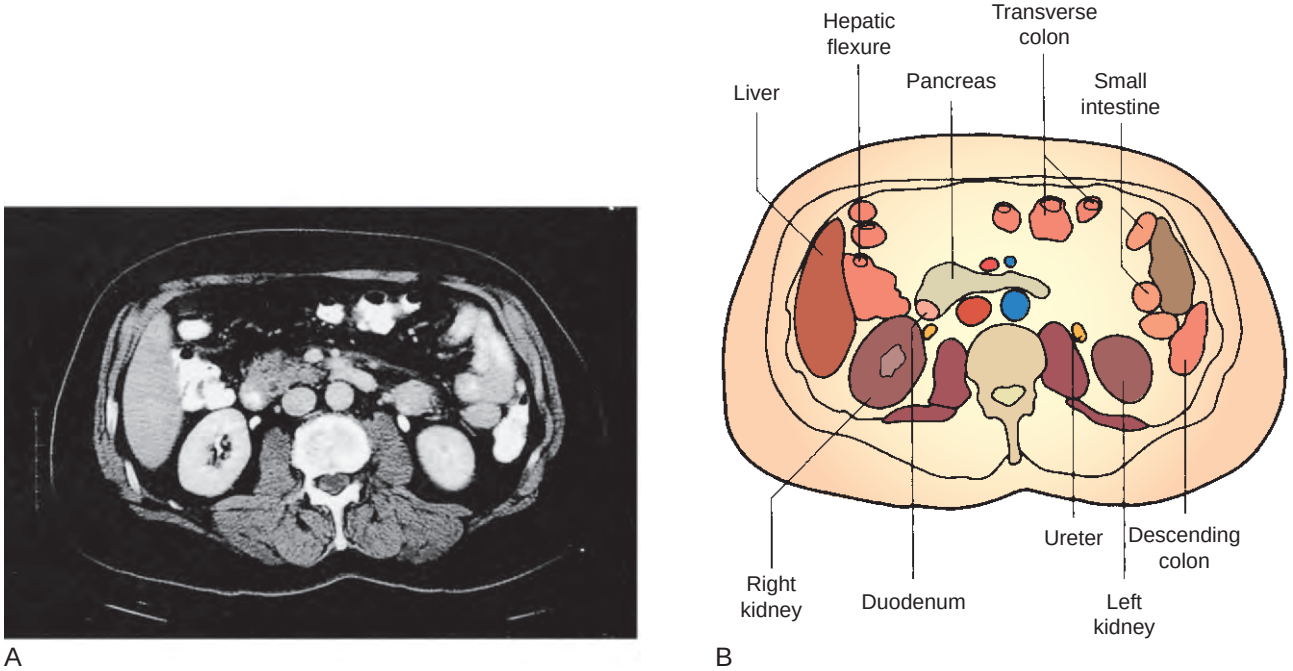
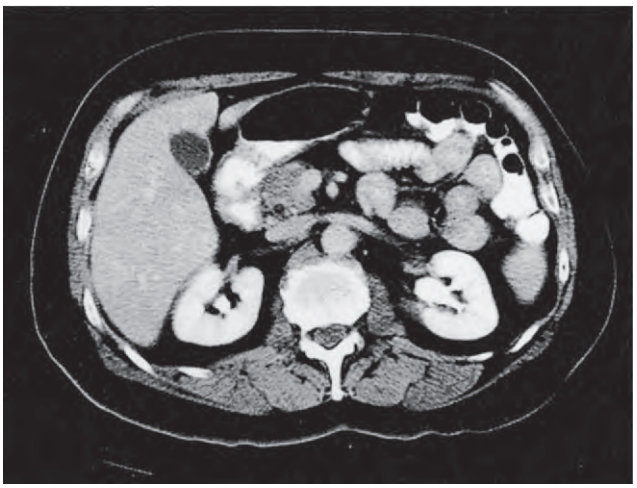


Figure 134–11. **A** and **B,** If the peritoneum is divided along the line of Toldt and the right colon is mobilized medially, the root of the small intestinal mesentery is exposed. The right ureter and gonadal vessels run on the surface of the psoas muscle. The hepatic flexure may be free or adherent to the gallbladder. The hepatic flexure mesentery crosses over the second and third portions of the duodenum. (**A** and **B,** From Fozard JBJ, Pemberton JH: Applied surgical anatomy: Intra-abdominal contents. In Fielding LP, Goldberg SM [eds]: Rob and Smith's Operative Surgery of the Colon, Rectum, and Anus, 5th ed. Philadelphia, Chapman & Hall, 1994.)



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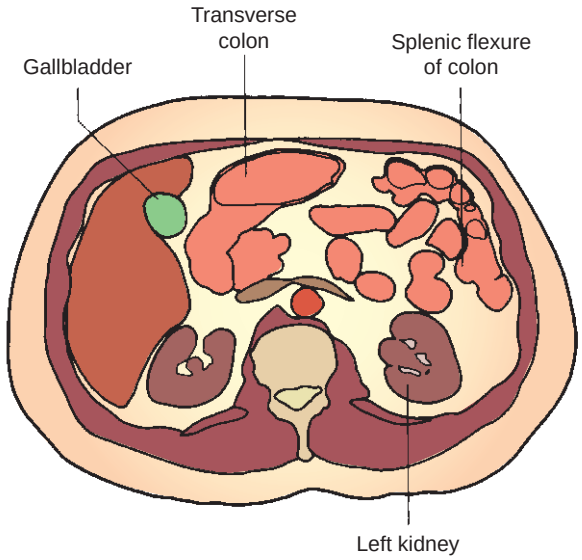

B

Figure 134–12. **A** and **B,** The splenic flexure is related to the left kidney, adrenal gland, and tail of the pancreas. (**A** and **B,** From Fozard JBJ, Pemberton JH: Applied surgical anatomy: Intra-abdominal contents. In Fielding LP, Goldberg SM [eds]: Rob and Smith's Operative Surgery of the Colon, Rectum, and Anus, 5th ed. Philadelphia, Chapman & Hall, 1994.)

left upper quadrant of the abdominal cavity in front of the left kidney, also in close relationship to left adrenal gland, and the tail of the pancreas. It lies higher than the contralateral hepatic flexure and is connected by flimsy adhesions to the lower pole of the spleen, which contributes to render it a fixed bowel segment (Fig. 134–12). Such anatomic location is often difficult to access, which poses the spleen at increased risk of inadvertent tears during surgical dissection of the splenic flexure. A retrosplenic colon variation has been described in 3 of 1000 patients examined by thoracoabdominal CT scan.[16]

Descending Colon

The descending colon extends from the left upper quadrant to the pelvic brim and connects the splenic flexure to the sigmoid colon. It measures approximately 30 cm and descends vertically and slightly toward the midline in the groove between the psoas and the quadratus lumborum. It is surrounded by the peritoneum anteriorly and bilaterally, whereas in most cases, it is fixed on the posterior peritoneum through the Toldt fascia. This is an important surgical plane to allow for a bloodless dissection. The descending colon tends to be in a more posterolateral position in young women.[17]

Sigmoid Colon

The sigmoid starts at the pelvic brim at the point where the descending colon turns medially and acquires a mesentery (Fig. 134–13). It terminates approximately at the level of the sacral promontory where the three taeniae commonly coalesce into a diffuse longitudinal muscular layer devoid of any epiploicae. The presence of a distinct sigmoidorectal sphincter is generally not recognized, although Shafik and colleagues have identified distinct, thickened smooth muscle bundles at the junction of sigmoid and rectum.[18] The diameter of the sigmoid colon decreases along its course, and its length, position, and fixation are extremely variable. It is commonly accepted that a long mesocolon with a short base predisposes to the onset of sigmoid volvulus, whereas a long convoluted sigmoid has been implicated in the origin of constipation. The base of the mesosigmoid generally extends from the left iliac fossa to the pelvic brim and then across the sacroiliac joint at the 2nd or 3rd sacral space, thus having a course described as an inverted V. In a study on the anatomic dimensions of the sigmoid colon of 70 North Indian subjects, the sigmoid colon of females tended to be wider rather than long, whereas the opposite was true for male subjects.[19] The lateral wall of the sigmoid often presents with adhesion to the lateral wall of the iliac fossa (Fig. 134–14), which must be freed to allow mobilization of the left colon. Once lateral adhesions are taken down and the lateral peritoneal reflection is incised, the fascia of Toldt can generally be appreciated. The mesosigmoid contains a recess, referred to as the *intersigmoid fossa,* which can be used as a landmark for identification of the ureter. In fact, the ureter can usually be identified deep to the intersigmoid fossa, where it courses along the surface of the psoas muscle and grossly parallel to the gonadal vessels, as it descends and crosses medially into the pelvis above the common iliac artery bifurcation. However, the intersigmoid fossa can also be the location of internal hernias, when a small bowel loop remains entrapped into this blind pouch.

Endoscopic View of the Colon

The cecum is identified on colonoscopy by the following three distinct features:

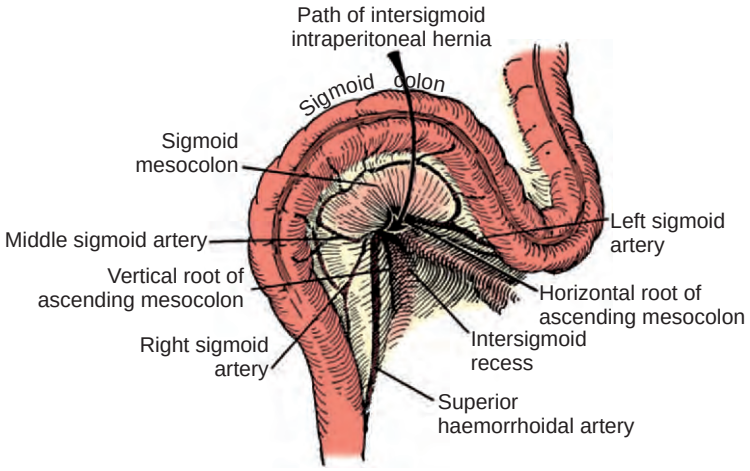

Figure 134–13. Sigmoid colon, its mesentery and arterial supply, and the intersigmoid recess. The sigmoid colon and mesocolon are raised forward and upward to show the vertical and horizontal attachments of its two roots. The *arrow* indicates the apex of the intersigmoid recess into which a loop of small bowel may insinuate and travel up behind a partially unfused descending mesocolon to form an intraperitoneal hernia. The superior hemorrhoidal artery, which is the main arterial supply to the rectum, lies between the leaves of the vertical root of the sigmoid mesocolon.

1. Ileocecal valve—This appears as "pouting lips," which lie transversely. These in part are responsible for the valvular continence in that reflux back to the small bowel is prevented. It is viewed "side on" from the colonoscope. It may have a lobular appearance that resembles a lipoma, and the mucosa appears more velvety, typical of small bowel. It moves rhythmically, and this movement can often be accentuated by inflating and deflating the cecum with the colonoscope. Finally, bile-stained ileal effluent may be seen discharging intermittently.
2. "Mercedes-Benz" sign—The convergence of the three taeniae at the cecum results in a three-pointed star, which has been associated with the German Marque. The three taeniae are located anteriorly, posteromedially, and posterolaterally.
3. Appendiceal orifice—At the site of the convergence of the taeniae should be the orifice of the appendix.

Two of these three signs are usually sufficient for a diagnosis of the cecum endoscopically, because occasionally one of the signs may be obscured by a less-than-perfect bowel preparation.

On withdrawal up the ascending colon, the hepatic flexure may be recognized by the bluish indentation of the liver. In addition, once past the flexure, the easiest way to advance the colonoscope is usually to shorten the endoscope while applying suction. This causes a "paradoxical advance," allowing the ascending colon to concertina over the colonoscope.

The transverse colon has a highly characteristic endoscopic triangular shape. This is the result of the attachment of the peritoneum at three points to the colon (e.g., gastrocolic omentum, greater omentum, and transverse mesocolon). Occasionally, the length of the transverse colon may cause difficulty in advancement of the colonoscope through because of the resulting "looping." External pressure on the colonoscope in the epigastrium often fixes the transverse colon, facilitating intubation. However, the best way to avoid this situation completely is to insufflate the colon minimally, thus avoiding lengthening it. Suction applied here often allows advancement of the colonoscope without pushing. This, in addition to avoiding looping, also makes the procedure less uncomfortable.

Further distally, the splenic flexure may be difficult to negotiate and is marked by a turn at the end of the descending colon as well as the bluish tinge of the spleen.

The sigmoid/descending colon junction is probably the most difficult curve to negotiate endoscopically. It marks the end of the free sigmoid and ends in a tunnel-like appearance of the descending colon.

Finally, the sigmoid is easily identified, because of the multiple turns and bends that occur as soon as the rectosigmoid junction is negotiated. Moreover, the haustra of the sigmoid colon are quite thickened (muscular).

Arterial Blood Supply

The vascular supply of the colon is variable (see Figs. 134–7 and 134–8). It receives its blood supply from both the SMA and the inferior mesenteric artery (IMA) systems. The branches of each system and the connections between the two systems are variable.

As mentioned, the colon receives its blood supply from two arterial systems: the SMA and the IMA. The SMA system supplies the right and the proximal transverse colon, whereas the IMA system send tributaries to the distal transverse, descending, and sigmoid colon.

The SMA arises anteriorly from the aorta at the level of L1. After supplying the small intestine, it terminates into the ileocolic artery, which is constantly present. The ileocolic artery divides into an ascending colonic branch, which anastomoses with a descending branch from the right or middle colic artery (MCA), and a descending branch, which anastomoses with the distal ileal branches. Three additional branches of the ileocolic artery form the anterior and posterior cecal arteries and the appendiceal artery. The right colic artery (RCA) originates 1 to 3 cm below the takeoff of the MCA and supplies the ascending colon with ascending and descending branches. The MCA arises from the SMA posterior to the pancreas and courses superiorly within the mesocolon

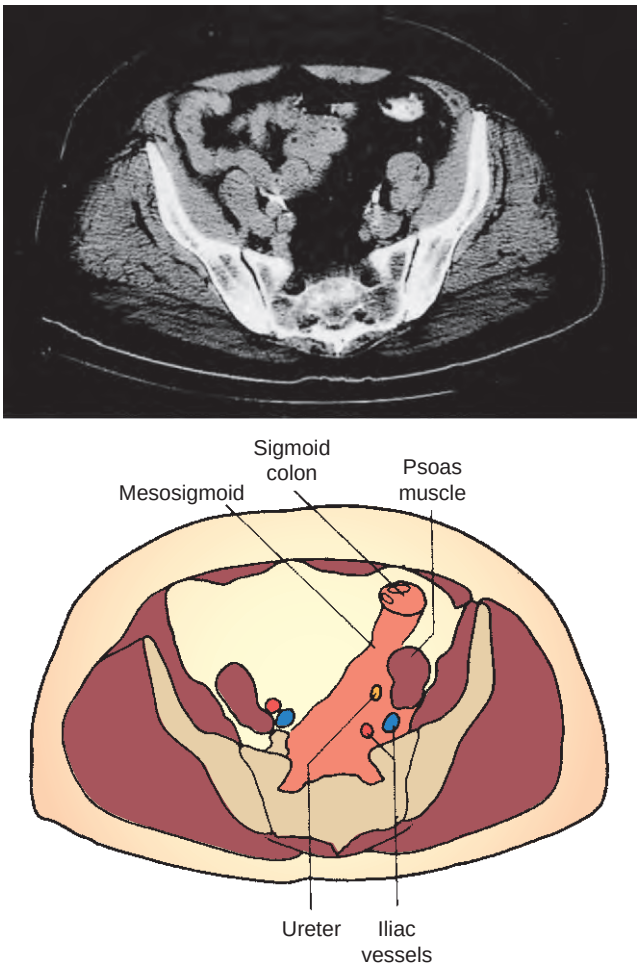

Figure 134–14. Near the pelvic brim, the colon acquires a mesentery. This marks the junction of the descending with the sigmoid colon, which in turn becomes the rectum at the sacral promontory. The sigmoid colon is variable in length and position. A long mesosigmoid colon with a short base predisposes to volvulus. Commonly, the sigmoid colon loops down into the pelvis to lie anterior to the rectum. (From Fozard JBJ, Pemberton JH: Applied surgical anatomy: Intra-abdominal contents. In Fielding LP, Goldberg SM [eds]: Rob and Smith's Operative Surgery of the Colon, Rectum, and Anus, 5th ed. Philadelphia, Chapman & Hall, 1994.)

and toward the hepatic flexure. It divides into right and left branches, which anastomose with the ascending branch of the RCA and the ascending branch of the left colic artery (LCA), respectively.

The IMA originates from the aorta at the level of L3. The LCA originates from the IMA approximately 2 to 7 cm distally and supplies the distal transverse and proximal descending colon. After a brief course directed caudad, the LCA turns cranially toward the splenic flexure and divides into an ascending and a descending branch. The ascending branch anastomoses with the left branch from the MCA, whereas the descending branch contributes to the marginal artery (see later). The sigmoid branches of the IMA supply the sigmoid colon and there are classically three, although their number varies. The descending branch of the IMA continues into the superior hemorrhoidal artery to supply the proximal rectum.

The earlier-mentioned vascular systems are connected by arterial collateral vessels that carry important clinical implications. The marginal artery of Drummond courses in close proximity and parallel to the bowel wall. It is variably anastomosed to the terminal portions of the named colic trunks as well as peripheral branches and gives origin to the terminal vasa recta that directly supply the bowel wall. It has been observed that the marginal artery is less consistently encountered at the level of the splenic flexure, where the vascular arcades connecting the MCA and LCA are often absent, in a critical colonic segment that has been described as the *Griffith's point*. It has been speculated that an inconsistent marginal artery might also enhance a more tenuous vascular supply at the junction of the lowest sigmoid branch and the superior hemorrhoidal artery, referred to as *Sudek's point*.

The meandering artery or Arc of Riolan is an additional collateral branch that can occasionally be observed intraoperatively. This branch connects the proximal MCA to the LCA and runs in the transverse mesocolon parallel to the left branch of the MCA.

Variations in the Arterial Supply Based on Anatomic Studies

Angiographic and autopsy studies have often challenged the vascular anatomy as traditionally accepted. Yada and colleagues[20] reported on 344 patients with colon cancer who were preoperatively studied with angiography. Four possible branching patterns of the RCA were detected. In 41% of cases, the RCA arose from the SMA; in 19%, it originated from the MCA; and in 14%, it arose from the ileocolic artery. It is of note that the RCA was absent in 26% of cases. In two different smaller series, although the ileocolic artery was ubiquitously found, an RCA emanating from the SMA was encountered in only 11% and 30% of cases, respectively.[21,22] Based on a superior mesenteric angiogram conducted in 273 patients, the MCA forked into the right and left branches in 160 cases (59%). Of these, 3 patients had a completely replaced MCA originating from the IMA. The remaining 113 patients had an independent origin for the left branch of the MCA, mainly from the SMA (90%) and less commonly from the IMA, dorsal pancreatic artery, or splenic artery.[20] Rare cases of an MCA originating from the celiac trunk[23] or a common trunk from which celiac, SMA, and IMA originate[24] have been reported. For every possible anatomic configuration, it is important to ensure that before resection of the right colon, the proximal vascular ligation is properly carried out at the level of the ileocolic artery. An excessively proximal ligation would actually occur at the level of the SMA and imperil the blood supply of all or part of the small bowel. Similar anatomic variations have been observed in the distal colon, where three distinct patterns of branching have been observed for the LCA. In the most common, encountered in 58% of cases, the LCA and the first sig-

moidal artery were distinct branches that arose from the IMA. However, in 27% of cases, the LCA and the main sigmoid artery shared a common trunk, and in 15% of patients, the LCA and the first sigmoidal artery arose simultaneously from the IMA.

Venous Return

The venous supply to the colon has been less extensively investigated than the arterial system. It is generally accepted that the venous return corresponds to the arterial supply. In general, although the right side of the colon drains into the SMV and from there into the portal vein, the left colon drains into the IMV, which drains into the splenic vein and only then into the portal system. In particular, the cecum and the appendix drain into the ileocolic vein, which is a tributary of the SMV. The ascending colon and hepatic flexure venous return follows the corresponding arteries and also drain into the SMV. Similarly, the middle colic vein drains into the SMV from the transverse colon and part of the splenic flexure. In a study examining the venous anatomy of the right colon on 58 cadavers, there was a single ileocolic vein in all cases. The right colic vein was absent in 57% of cadavers and single in the remainder. When present, the right colic vein joined the SMV in 56% of cases and the gastrocolic trunk in the remaining 44%. The middle colic vein was double in 50% of cases, but it could also be single or triple. It generally drained in the SMV (85%) but could also drain into the gastrocolic trunk and more rarely into the splenic or IMV.[25] The left colic veins provide additional return from the same area, although their drainage is into the IMV, which is a tributary of the splenic vein and secondarily of the portal system. A similar pathway applies to the venous return from the descending and the sigmoid colon, following the respective arterial distribution.

Lymphatic Drainage

Colonic lymphatics are traditionally divided into four drainage levels (Fig. 134–15). The lymphatic plexuses located on the bowel wall drain first into the epicolic nodes, located in the epiploic appendages and subserosally. The epiploic nodes then drain into the paracolic nodes, which are located behind the peritoneum on the upper border of the transverse and on the mesenteric side of the remaining colon. The intermediate nodes are the third lymphatic station and are encountered along the course of the main colonic vessels, namely, the ICA, RCA, MCA, LCA, and sigmoid branches. The intermediate nodes ultimately drain into the lymph nodes that accompany the two main colonic tributaries, that is, the SMA and IMA. From these two main trunks, the lymphatic drainage continues into the iliolumbar chain and terminates into the thoracic duct. The significance of metastatic involvement of each of these specific stations is controversial. The current TNM classification considers only the number, not the location, of positive nodes as the preferred criterion with which to establish

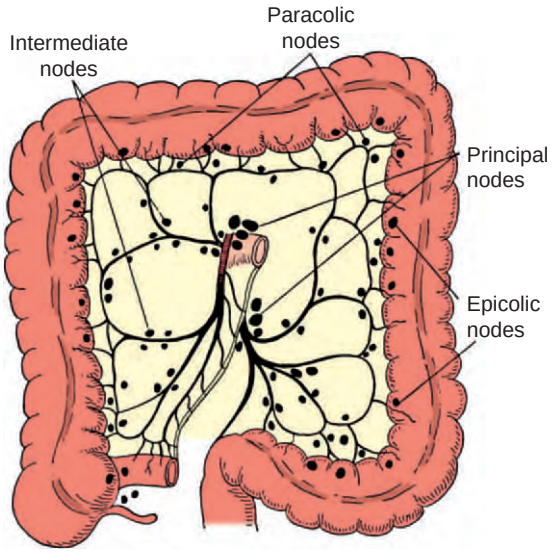

Figure 134–15. Diagram showing the epicolic, paracolic, intermediate, and principal lymph node groups that accompany the vessels of the colon. (From Grinnell RS: Lymphatic metastases of carcinoid of the colon and rectum. Ann Surg 131:494, 1950.)

the N stage. Novel information regarding the lymphatic drainage of the colon might derive from ongoing studies on sentinel lymph node–mapping techniques in relation to colorectal cancer,[26] similar to what has been shown for melanoma and breast cancer.

Innervation

The colon is widely innervated by the autonomic system, which follows the arterial distribution (Fig. 134–16). In particular, the parasympathetic system increases colonic peristalsis and secretion, with simultaneous inhibition of the sphincteric musculature. The sympathetic system acts in an opposite fashion. The sympathetic nerves originate from the intermediolateral neurons of the lower five thoracic segments and the first three lumbar segments. Preganglionic fibers proceed to the respective paravertebral chains of ganglia and then organize themselves into bundles, which give origin to the splanchnic nerves. The splanchnic nerves form distinct network-like structures referred to as *prevertebral ganglia,* such as the celiac, the superior, and the inferior mesenteric ones, which basically follow the course of the respective arteries. In these structures, synapses occur, and the emerging postganglionic fibers travel as mesenteric nerves into the mesocolon to reach the bowel wall. Similar to the arterial distribution, the proximal half of the colon is supplied by the celiac plexus through the superior mesenteric plexus, whereas the distal colon receives its sympathetic fibers from the inferior mesenteric plexus. The parasympathetic innervation of the proximal colon is derived from the celiac branch of the right vagus nerve, which reaches the celiac plexus. Fibers that exit this plexus move to the preaortic and superior mesenteric plexuses

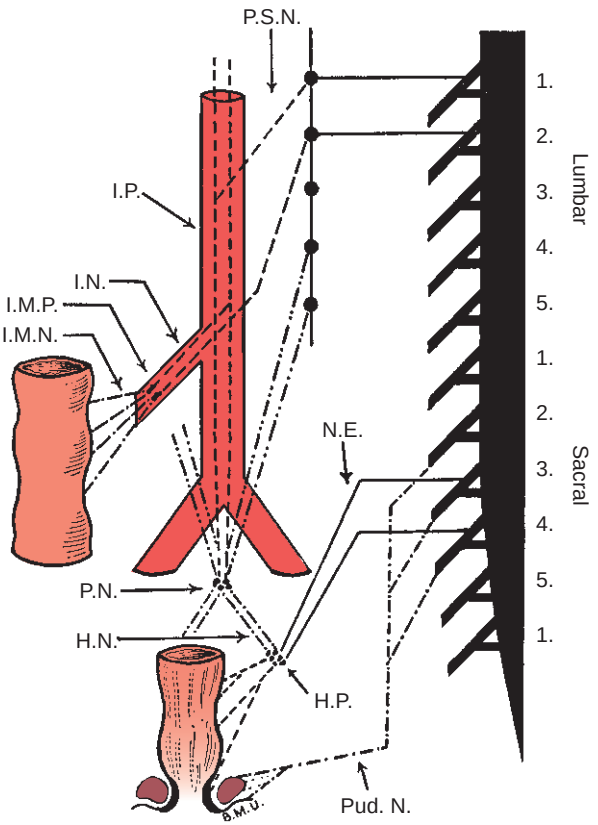

Figure 134–16. Nerve outflow to the distal part of the colon in humans. HN, hypogastric nerve; HP, hypogastric plexus; IMN, inferior mesenteric nerve; IMP, inferior mesenteric plexus; IN, intermesenteric nerve; IP, intermesenteric plexus; NE, nervi erigentes; PN, presacral nerve; PSN, pelvic splanchnic nerve; Pud N, pudendal nerve. (From Quigley JP: The physiology of the small and the large intestine. In Portis SA [ed]: Diseases of the Digestive System, 3rd ed. Philadelphia, Lea & Febiger, 1953.)

and then follow the course of the SMA and its branches and ultimately reach the bowel wall. The distal colon receives its parasympathetic innervation through the nervi erigentes, also referred to as *pelvic splanchnic nerves,* which originate from S2 to S4. Fibers that exit from the nervi erigentes then move cranially into the presacral plexus and supply the distal transverse, descending, and sigmoid colon, traveling in close proximity to the IMA. Preganglionic fibers enter the bowel wall and synapse in the myenteric and submucosal plexuses.

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Chapter

135

Physiology of the Colon and Its Measurement

Adil E. Bharucha ▪ Michael Camilleri

The human colon serves to absorb water and electrolytes, store intraluminal contents until elimination is socially convenient, and salvage nutrients after bacterial metabolism of carbohydrates that have not been absorbed in the small intestine. These functions are dependent on the colon's ability to control the distal progression of contents; in healthy adults, colonic transit normally requires several hours to almost 3 days for completion. There are differences in colonic structure and function even among mammals[1]; unless otherwise stated, this chapter focuses on the physiology of colonic function in humans. Although the colon is regarded as a single organ, there are regional differences between the right and left colon, indicated in Table 135–1. The right and left colon are derived from the embryologic midgut and hindgut, and the junction is located just proximal to the splenic flexure.

ANATOMY

In adult cadavers, the colon is approximately 1.5 m long. The musculature in the colonic wall comprises outer longitudinal and inner circular layers. From the cecum to the rectosigmoid junction, the longitudinal layer is organized in three thick bands, the taeniae, with a thin layer of longitudinal muscle in between these bands.[2] At the rectosigmoid junction, the three taeniae broaden to form a uniformly thick layer throughout the rectum. In the anal canal, the longitudinal muscle layer merges with the external anal sphincter while the circular muscle layer extends into the internal anal sphincter. Other than humans, only primates, horses, guinea pigs, and rabbits have taenia coli[3]; the taenia coli are thought to function as suspension cables on which the circular muscle arcs are suspended, facilitating efficient contraction of the circular muscle. Thus, a 17% contraction of circular muscle reduces the luminal diameter of the colon by two thirds.[4] If the longitudinal muscles were arranged concentrically, an identical contraction of circular muscle would only reduce luminal diameter by one third. Whether or not longitudinal and circular muscles contract synchronously during peristalsis is controversial.

The colon is suspended from the posterior abdominal wall by a mesentery. The mesentery is relatively narrow, restricting mobility of the cecum, ascending colon, and descending colon. Around the transverse and sigmoid colon, the mesentery is broader, permitting considerable movement and contributing to the tendency in some individuals to have a pendulous transverse colon. This also partly contributes to the fluctuations associated with looping of the colonoscope during examination.

The colon is innervated by extrinsic and intrinsic nerves.[1] The extrinsic input includes sympathetic and parasympathetic components. In several species, including primates, the vagus innervates the proximal colon. The parasympathetic input to the distal colon is derived from the sacral (S2 to S4) segments of the spinal cord via the pelvic plexus. After entering the colon, these fibers form the ascending colonic nerves, traveling orad in the plane of the myenteric plexus to supply a variable portion of the left colon. The sympathetic fibers originate in the paravertebral "chain" ganglia, segments from the T12 to L4 levels of the spinal cord, and are conveyed to the colon via arterial arcades of the superior and inferior mesenteric vessels. The sympathetic nervous system provides excitatory input to the sphincters and a tonic inhibitory input to nonsphincteric muscle. Norepinephrine is the major neurotransmitter released by sympathetic nerves throughout the small and large intestine. The intrinsic or intramural nerves are organized into myenteric and submucous plexuses and the interstitial cells of Cajal (ICCs). The myenteric plexuses and interstitial cells are primarily responsible for controlling motility; the submucous plexus regulates mucosal absorption. The extrinsic nerves modulate the intrinsic neural activity. For example, the sympathetic nervous system exerts a tonic inhibitory input on colonic motor function, primarily via stimulation of α_2-adrenergic receptors, which hyperpolarize cholinergic neurons in

Table 135–1 Comparison of Right and Left Colon

Feature	Right Colon	Left Colon
Embryologic origin	Midgut	Hindgut
Blood supply	Superior mesenteric vessels	Inferior mesenteric vessels
Extrinsic nerve supply		
Parasympathetic	Vagus	Pelvic nerves from sacral S2-4 segments
Sympathetic	Superior mesenteric ganglion	Inferior mesenteric ganglion
Function	Mixing and storage	Conduit

the myenteric plexus. Thus, the α_2 agonist clonidine decreases colonic tone whereas the α_2 antagonist yohimbine increases colonic tone in humans[5]; clonidine also enhances mucosal absorption of fluid and salt.

FUNCTIONS

Regional Heterogeneity in Colonic Function

Although the colon is regarded as a single organ, there are regional differences in normal motor function and mucosal absorption: the right colon functions primarily as a reservoir for mixing and storage processes, the left colon as a conduit, and the rectum and anal canal enable defecation and continence. The ileocolonic sphincter regulates the intermittent aborad transfer of ileal contents into the colon, mainly after meals. The rate of delivery of liquids into the proximal colon can influence colonic transit. Thus a liquid marker injected directly into the proximal colon is emptied more rapidly than after oral ingestion of the same marker.[6] There is evidence for adaptation in these regional functions. Within 6 months after a right hemicolectomy, isotope movement from the small to the large bowel normalizes in response to the augmented storage capacity in the residual transverse and descending colon.[7] In humans, the ileocolonic sphincter plays only a minor role in regulating ileocolonic transit.

Colonic Fluid and Electrolyte Transport

Under basal conditions, the healthy colon receives approximately 1500 ml of chyme over 24 hours, absorbing all but 100 ml of fluid and 1 mEq of sodium and chloride, which are lost in the feces.[8] Colonic absorptive capacity can increase to 5 to 6 L and 800 to 1000 mEq of sodium and chloride daily when challenged by larger fluid loads entering the cecum, as long as there is a slow infusion rate (i.e., 1 to 2 ml/min). In addition to the ascending and transverse colon, the rectosigmoid may also participate in this compensatory absorptive response.[9] For 25 years, secretory and absorptive processes were believed to be segregated to crypt and surface epithelial cells, respectively. It is now recognized that absorptive mechanisms are constitutively expressed in crypt epithelial cells; secretion is regulated by one or more neurohumoral agonists released from lamina propria cells, including myofibroblasts.[10]

When the colon is perfused with a plasma-like solution, water, sodium and chloride are absorbed, whereas potassium and bicarbonate are secreted into the colon.[11] Absorption of sodium and secretion of bicarbonate in the colon are active processes occurring against an electrochemical gradient. There are several different active (transcellular) processes for absorbing sodium, and these show considerable segmental heterogeneity in the human colon. The regional differentiation of colonic mucosal absorption is also demonstrated by regional effects of glucocorticoids and mineralocorticoids on sodium and water fluxes. For example, in the *distal* colon, epithelial Na^+,K^+,ATPase is activated by mineralocorticoids.[12] On the other hand, the Na^+/H^+ exchange is activated in *proximal* colonic epithelium by the mineralocorticoid aldosterone.[13] Specific channels are involved in water transport across surfaces and epithelia. These water channels, or aquaporins, are a diverse family of proteins, of which aquaporin-8 is expressed preferentially in colonic epithelium and small intestinal villus tip cells.

Potassium is absorbed and secreted by active processes; it is unclear if chloride is absorbed by an active process. In contrast with the small intestine, glucose and amino acids are not absorbed in the colon.

Colonic conservation of sodium is vital to fluid and electrolyte balance, particularly during dehydration, when it is enhanced by aldosterone.[14] Patients with ileostomies are susceptible to dehydration, particularly when placed on a low-sodium diet or during an intercurrent illness. In addition to glucocorticoids and mineralocorticoids (aldosterone), other factors enhancing active sodium transport include somatostatin, α_2-adrenergic agents and short-chain fatty acids (SCFAs). Clonidine mimics the effects of adrenergic innervation by stimulating α_2 receptors on colonocytes. In contrast, stimulation of mucosal muscarinic cholinergic receptors inhibits active NaCl absorption and stimulates active chloride secretion. Somatostatin, a peptide released by submucosal and myenteric nerves, also has potent antisecretory effects.

Colonic Metabolism

In the proximal colon, bacteria ferment organic carbohydrates to SCFAs, predominantly acetate, propionate, and butyrate.[15] There is a low, normal rate of SCFA production from "malabsorbed" (≤10% of ingested) carbohydrates; diets high in fiber, beans, resistant starches, and complex carbohydrates increase the production of SCFA. SCFA are rapidly absorbed from the colon, augment sodium, chloride, and water absorption and constitute the preferred metabolic fuel for colonocytes. SCFA may also serve to regulate proliferation, differentiation, gene expression, immune function, and wound healing in the colon.

Colonic Motility

Assessment of Colonic Motor Function

Radiopaque Marker Methods of Colonic Transit Since the original description by Hinton and colleagues, there have been several refinements to the radiopaque marker technique for measuring colonic transit.[16] In the modification described by Metcalf, a capsule containing 20 radioactive markers is ingested at the same time on each of 3 consecutive days; a plain abdominal radiograph is taken on the 4th day. The number and distribution of markers in the abdomen provide a measure of overall and regional colonic transit (Fig. 135–1). The maximum whole-gut transit time with a single plain radiograph on day 4 is 72 hours, which is barely 2 SDs above the mean for healthy controls. This upper limit can be extended to 120 hours by administering a capsule containing 24 radiopaque markers once daily for 5 days and taking a plain abdominal radiograph on the 6th day, 24 hours after the last capsule.[17]

Scintigraphic Techniques of Colonic Transit Colonic transit can also be assessed by scintigraphy (Fig. 135–2).[16] To avoid dispersion of the radiolabel during passage through the gastrointestinal tract, the isotope is delivered into the colon by orocecal intubation or a delayed-release capsule. The delayed-release capsule contains activated charcoal or polystrene pellets radiolabeled with ^{99m}Tc or ^{111}In and covered with a single coating of a pH-sensitive polymer, methacrylate. The capsule dissolves at a pH between 7.2 and 7.4, generally within the distal ileum, releasing the radioisotope within the ascending colon. The colonic distribution of radioisotope on scans taken 4, 24, and 48 hours after administration of the capsule is highly sensitive and specific for identifying rapid or slow colonic transit. The proportion of counts in each of four colonic regions of interest (i.e., ascending, transverse, descending, and rectosigmoid colon)

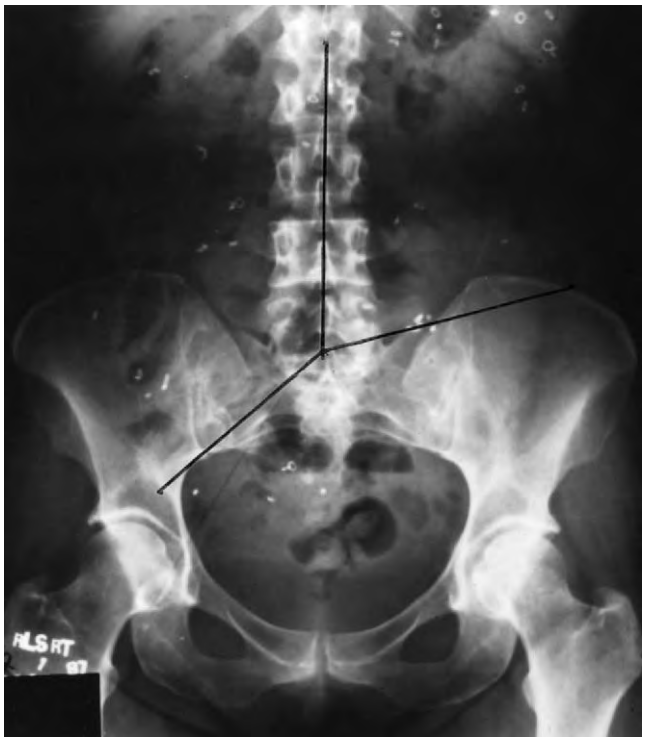

Figure 135–1. Abdominal radiograph demonstrating radiopaque markers and lines used to demarcate markers in the left, right, and sigmoid colon/rectum.

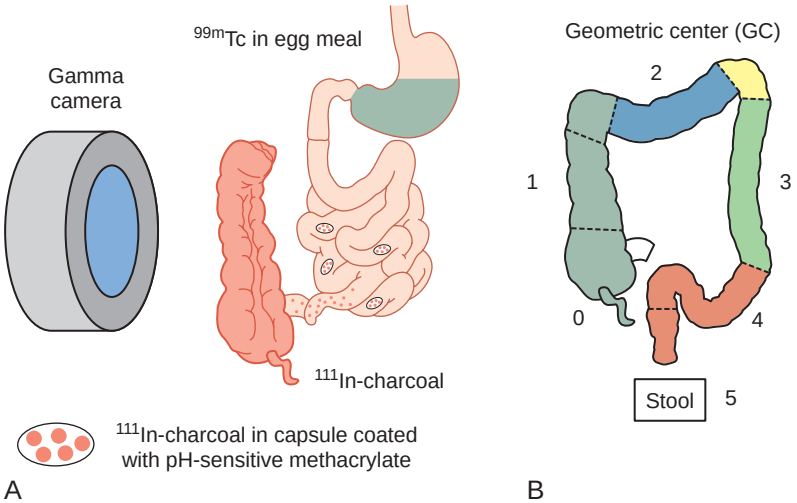

Figure 135–2. Scintigraphic assessment of gastrointestinal transit. **A,** Gastric emptying and small intestinal transit are assessed with ^{99m}Tc-labeled polystyrene pellets while ^{111}In-labeled charcoal in delayed-release capsules measures colonic transit. **B,** Proportion of ^{111}In counts in each of four colonic regions of interest and stool is multiplied by the appropriate weighting factor, ranging from 1 to 5.

and stool is multiplied by a specific weighting factor that ranges from 1 (for the ascending colon) to 5 (for stool), respectively. The aggregate of these products (proportion of counts × weighting factor), provides the geometric center of overall colonic transit. A low geometric center implies that most radiolabel is close to the cecum, whereas a high geometric center implies that most radiolabel is close to stool.

Both radiopaque markers and scintigraphy are sensitive for identifying colonic transit delays in patients with slow-transit constipation. Colonic transit measurements by radiopaque markers and scintigraphic techniques are correlated with each other and involve similar total-body radiation exposure (i.e., 0.08 rad for the radioactive capsule and for each abdominal radiograph). Scintigraphy is a useful research tool that allows more thorough assessment of regional colonic functions.

Recording Techniques of Colonic Motility Colonic motor activity can be assessed by recording electrical signals or variations in luminal pressure by pressure transducers, either water perfused or solid-state, or, a balloon controlled by a barostat.[18,19] There are several limitations to recording colonic motor activity in humans. Intraluminal colonic recording devices can only be positioned using flexible colonoscopy, per oral intubation, or per nasal intubation techniques. Cleansing of the rectosigmoid and occasionally the entire colon is necessary to facilitate placement and accurate recording. Cleansing can accelerate colonic transit but does not, with the exception of more frequent high-amplitude propagated contractions (HAPCs), fundamentally alter motor activity.[20]

Recording myoelectrical activity with serosal, mucosal, or intraluminal electrodes is fraught with technical difficulties and has fallen out of favor. Currently, few centers utilize manometry to record colonic motor activity in clinical practice. Although manometry is reasonably reliable for identifying the colonic motor response to a meal (see later) or to a stimulatory agent such as neostigmine or bisacodyl, intraluminal pressure changes may not necessarily reflect colonic contractions. Indeed, simultaneous endoscopic and manometric recordings in the human colon suggest that most manometric deflections coincide with relaxation rather than colonic contraction or real-time observation.[21] The barostat system appears to have the potential to overcome this limitation, since the balloon is continuously apposed to the colonic mucosa and haustrations, permitting identification of colonic contractions and relaxation (Fig. 135–3).

The barostat system comprises an infinitely compliant polyethylene balloon connected by tubing to the barostat. The barostat is a rigid piston within a cylinder that can adjust either the pressure or volume within the bag using a servomechanism. When the balloon is inflated to a low constant pressure, colonic contraction is accompanied by expulsion of air from the balloon into the barostat. Conversely, when the colon relaxes, the balloon volume increases to maintain a constant pressure. The advantages of the barostatic balloon over manometry are greater sensitivity for recording contractions that do not occlude the lumen, particularly when the colonic diameter is larger than 5.6 cm.[22] Moreover, a barostat can record changes in baseline balloon volume and phasic fluctuations, colonic relaxation, and colonic pressure-volume relationships. Thus, the barostat is primarily a research tool that has been introduced into clinical practice in selected centers.

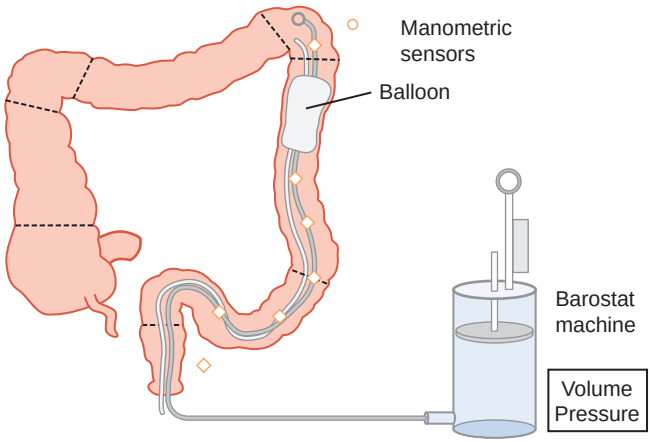

Figure 135–3. Barostat-manometric assembly positioned in the descending colon with polyethylene balloon in apposition with colonic mucosa.

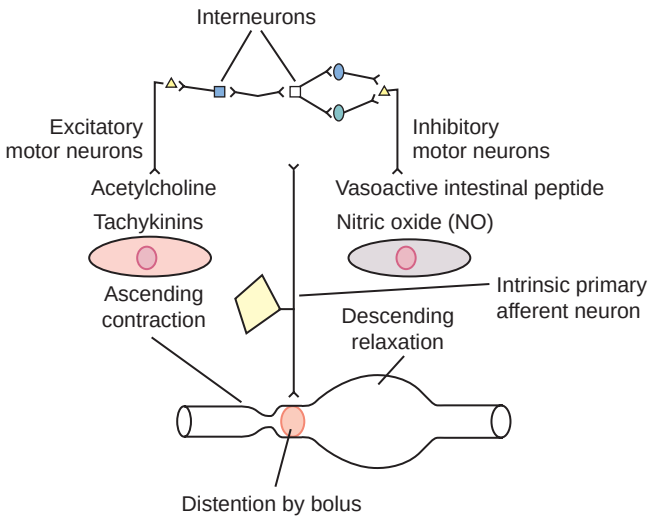

Figure 135–4. Schematic representation of major neurotransmitters mediating peristaltic reflex. Mechanical distention activates sensory neurons, whereas interneurons transmit messages between sensory and motor neurons.

Peristalsis

Distention of a viscus evokes the peristaltic reflex, characterized by coordinated contraction of the orad segment and relaxation of the distal gut, facilitating propulsion. The neural pathways and neurotransmitters mediating this reflex are depicted in Figure 135–4. In the human colon, the principal excitatory neurotransmitter

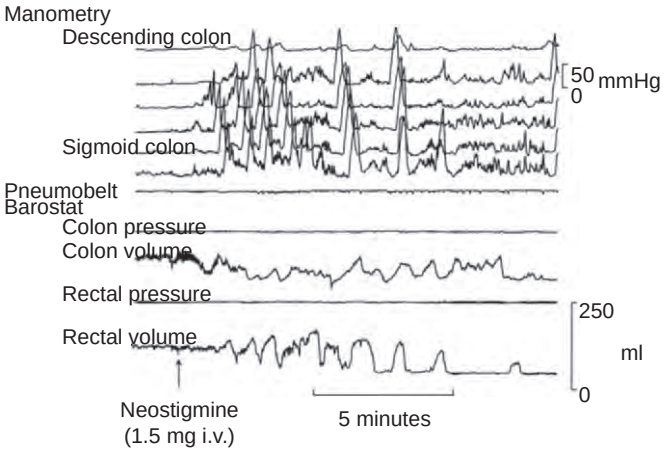

Figure 135–5. High-amplitude propagated contractions induced by neostigmine. (From Law NM, Bharucha AE, Undale AS, et al: Cholinergic stimulation enhances colonic motor activity, transit, and sensitivity in humans. Am J Physiol Gastrointest Liver Physiol 281:G1228-G1237, 2001.)

is acetylcholine, whereas in vitro studies suggest that NO and ATP are inhibitory neurotransmitters in the human colon.

Cellular Basis for Motility

Contraction of smooth muscle results from interactions between smooth muscle, the ICCs, the intrinsic or enteric nervous system, and the extrinsic nervous system. ICCs are the pacemaker cells, responsible for generating slow-wave activity which drives smooth muscle contraction. ICCs also amplify neuronal input, act as mechanotransducers, and regulate smooth muscle membrane potential. ICCs are located in two networks: one in the myenteric plexus region and the other in the submucosa. They are also found interspersed in longitudinal and circular muscle layers (Fig. 135–5). The three basic electrical events recorded from human colonic circular smooth muscle in vitro are (1) slow-wave activity with a frequency of two to four contractions per minute, originating along the submucous plexus border of the circular muscle layer; (2) membrane potential oscillations (MPOs), with a frequency of about 18 contractions per minute, originating in the myenteric plexus border of circular muscle; and (3) action potentials superimposed on slow waves and MPOs.[23]

Slow waves and MPOs summate in the central region of circular muscle, producing a complex pattern of activity that regulates contractile amplitude and frequency. The predominant contractile rhythm recorded from the human colon in vitro and in vivo corresponds to the slow-wave frequency of two to four per minute. Repolarization of membrane potential during slow waves result in opening of L-type Ca^{2+} channels and, when a firing threshold is reached, action potentials. The result is Ca^{2+} influx through L-type Ca^{2+} channels initiating smooth muscle contraction. L-type Ca^{2+} channels are blocked by nifedipine. In the presence of nifedipine, smooth muscle contraction is inhibited and action potentials are absent. Tonic contractions are generated by continuous action potentials. In contrast to regular cyclical contractile activity in the stomach and small intestine, colonic motility is markedly irregular. This irregularity is partly attributable to the variable frequency and duration of action potentials but is not well understood.

Colonic Motor Function in Health

In contrast with the canine colon, contractile activity in the human colon is not cyclical. Colonic motor activity may vary from no activity or quiescence, isolated contractions, bursts of contractions, or propagated contractions. Irregular phasic activity constitutes a major proportion of colonic motor activity and probably serves to segment and mix intraluminal contents. Combined assessments of motor activity and transit in the cleansed colon of healthy subjects reveal that transit is associated with nonpropagated and propagated contractions; propagated contractions propel contents over longer distances than nonpropagated contractions.[24] However, only one third of propagated contractions are accompanied by propulsion of colonic contents. Propagated contractions are subclassified as low (5 to 40 mm Hg) or high amplitude (>75 mm Hg). In ambulatory, prolonged colonic manometry studies, HAPCs occur on an average of six times per day, originate predominantly in the cecum/ascending colon, and migrate over a variable distance. These HAPCs are probably responsible for mass movement of colonic contents. HAPCs occur more frequently after awakening and after meals and may account for the urge to defecate in healthy subjects and in patients with irritable bowel syndrome (IBS) (see Fig. 135–5). The mechanisms that underlie HAPCs are poorly understood. In addition to occurring spontaneously, HAPCs can be induced by luminal distention, by the parenteral administration of cholinesterase inhibitor neostigmine, or by intraluminal stimuli (i.e., glycerol, bisacodyl and oleic acid).

Eating is accompanied by a brisk increase in tone and phasic activity throughout the colon (Fig. 135–6).[25] Because this response is preserved even after a gastrectomy, the term *colonic motor response to eating* is preferred to *gastrocolonic reflex*. The response may begin within a few seconds after eating and last, to a varying degree, for up to $2^1/_2$ hours. A biphasic response with early (first 60 minutes) and late (120 and 150 minutes) components has also been described.[26] Meal composition and caloric content both influence the response. A mixed meal containing more than 500 kcal predictably elicits a response. Gastric distention and chemical stimulation by nutrients elicit comparable responses; lipids are the most potent stimuli, whereas amino acids appear to inhibit the response.[27]

The precise mechanisms mediating the response are uncertain, but neural and hormonal mechanisms have been implicated. It is conceivable that different mechanisms regulate the early and late components.[28] The early, particularly the immediate, component is likely to be neurally mediated. The later component temporally

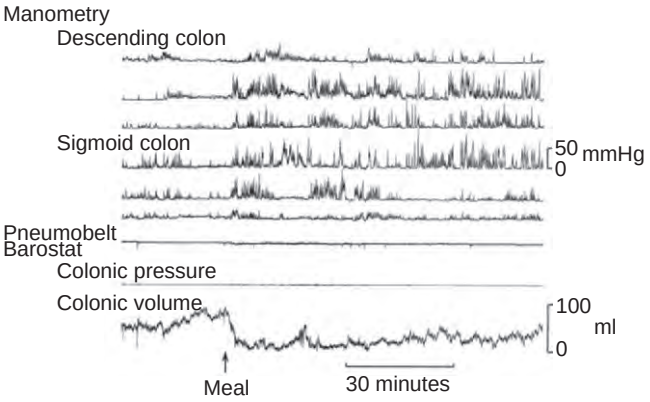

Figure 135–6. Colonic motor response to a 1000-kcal meal. Note the increased phasic pressure activity recorded by manometric sensors and reduction in barostat balloon volume maintained at constant pressure, indicating increased tone.

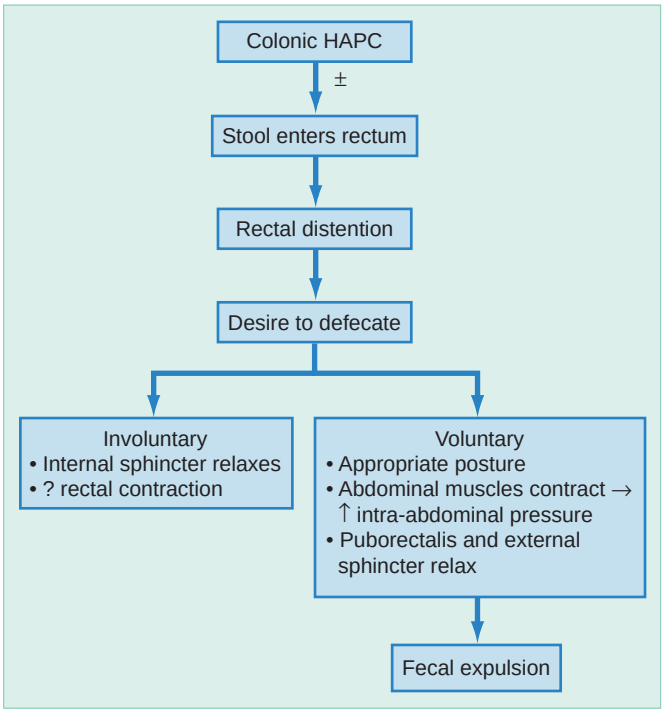

Figure 135–7. Schematic representation of events preceding defecation. HAPC, high-amplitude propagated contraction.

coincides with arrival of chyme into the ileum and may be mediated by humoral factors such as peptide YY, neuropeptide Y, and neurotensin released from the ileal mucosa. Although serum levels of gastrin and cholecystokinin rise after a meal, intravenous cholecystokinin actually induces colonic relaxation.[29] Atropine, naloxone, and the 5-hydroxytryptamine-3 (5-HT_3) antagonist ondansetron inhibit the response indicating that cholinergic, opiate, and serotoninergic 5-HT_3 receptors may be involved in mediating the response.[30] There is also evidence to suggest that efferent vagal fibers contribute to the colonic motor response in primates.[31]

The colon relaxes during sleep, after intraluminal administration of SCFAs or glycerol, during balloon distention of the rectum, and in response to parenterally administered pharmacologic agents. In addition to the α_2-adrenergic agonist clonidine, morphine, atropine, the 5-HT_{1A} agonist buspirone,[28] and the 5-HT_{1D} agonist sumatriptan all reduce colonic tone in humans.[32-34] Rectal distention by a balloon to subnoxious levels induces colonic relaxation in humans.[35] Colocolonic reflexes mediated via local nervous pathways through the prevertebral ganglia and independent of central nervous system activity have been well characterized in animal preparations.[36] This propensity for colonic relaxation, particularly that induced by sympathetic stimulation and opiates, may be relevant to the pathophysiology of acute colonic dilation or pseudo-obstruction.[37] Colonic relaxation induced by rectal distention may explain left-sided colonic transit delays in patients with obstructed defecation since restoration of normal defecation tends to restore colonic motility to normal.[38]

There are regional and age-related differences in biomechanical properties of the colon.[4] These biomechanical properties can be assessed by stress-strain relationships in vitro and by the pressure-volume relationships during balloon distention by a barostat in vivo. In ex vivo and in vivo studies, stiffness declines from the rectum to the transverse colon. These observations are probably relevant to the segmental heterogeneity in function depicted in Table 135–1 and to the pathophysiology of diverticulosis, as discussed later. Thus, the compliant ascending and transverse colon are ideally suited to function as a reservoir. Conversely, the descending and sigmoid colonic segments are suited to function as conduits, tend to have lower compliances, and are the primary sites of diverticula since intraluminal pressures are transmitted to weak points in the colonic wall.

Defecation

In health, rectal distention evokes the desire to defecate and reflex relaxation of the internal anal sphincter (Fig. 135–7). If social circumstances are conducive, defecation is accomplished by adoption of a suitable posture and contraction of the diaphragm and abdominal muscles to raise intra-abdominal pressure. Concomitant relaxation of the puborectalis and external anal sphincter, both striated muscles, enables widening of the anorectal angle by 15 degrees or more, reduction of pressure within the anal canal, and perineal descent. Appropriate coordination between abdominal contraction and pelvic floor relaxation is crucial to normal fecal expulsion. In addition, there is evidence to suggest that these somatic processes are integrated with visceral components such as colonic HAPCs during defecation.

Colonic Sensation

Healthy individuals, for the most part, do not perceive physiologic processes within the gut except for the

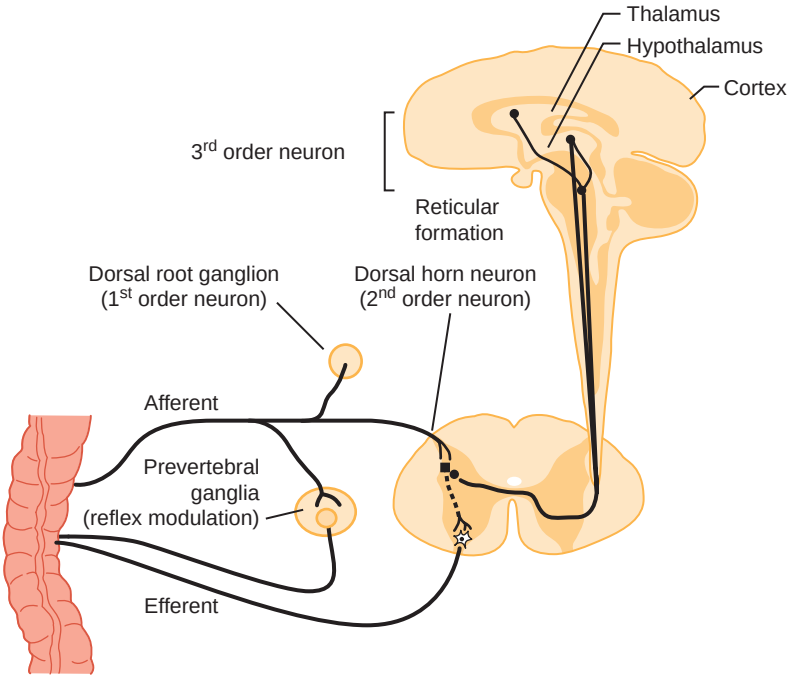

Figure 135–8. Visceral sensory pathways include reflexes mediated through prevertebral and other autonomic ganglia and a third-order neuron chain that ultimately projects to supraspinal centers. Convergence of visceral and somatic afferents at the dorsal horn explains referral of visceral discomfort to the body surface. Third-order neurons originating in thalamus project to the cerebral cortex; those from the reticular formation project to the thalamus and hypothalamus. (From Camilleri M, Saslow SB, Bharucha AE: Gastrointestinal sensation: Mechanisms and relation to functional gastrointestinal disorders. Gastroenterol Clin North Am 25:247-258, 1996.)

Table 135–2 Visceral Afferent Pathways

Functions	Discriminative	Affective-Motivational
Afferent fibers	Rapidly conducting Aδ fibers	Unmyelinated C fibers
Thalamic nuclei	Lateral	Medial
Cortical area	Somatosensory cortex	Frontal, parietal, and limbic regions

sensation of fullness and the desire to defecate. Over the past few years, it has been proposed that symptoms associated with functional gastrointestinal disorders are partly related to enhanced sensory perception.[39] Visceral sensation is perceived in peripheral receptors and conveyed centrally by a three-neuron chain (Fig. 135–8).[40] Although visceral afferents can respond to one or more stimulus modality (e.g., tension, temperature, osmolarity), mechanoreceptors are particularly important in the context of functional gastrointestinal diseases. Mucosal mechanoreceptors respond to mucosal pinching or stroking, whereas serosal mechanoreceptors respond to movement or strong distention of a viscus. Visceral perception is characterized by discriminative (localizing, precise) and affective-motivational (diffuse, emotional) aspects, which are conveyed by discrete mechanisms, demonstrated in Table 135–2.

The predominant afferent fibers are rapidly conducting myelinated Aδ fibers and slowly conducting unmyelinated C fibers. The Aδ fibers convey the sensation of first pain, which is well localized and lasts as long as the stimulus. The C fibers convey the "second" pain, which is diffuse, lasts longer than the duration of the stimulus, and is associated with the affective-motivational aspects of pain. In the spinal cord, visceral afferents project centrally via spinothalamic and spinoreticular tracts and a nociceptive dorsal column. The spinothalamic tracts project to the medial and lateral thalamic nuclei, which are associated with affective-motivational and discriminative aspects of pain, respectively. These thalamic nuclei project to the cortical areas indicated in Table 135–2. Descending (chiefly serotoninergic and adrenergic) pathways originating in the frontal cortex, hypothalamus, and brain stem reticular formation inhibit spinal cord dorsal horn neurons, thereby reducing pain perception.

In humans, colonic (and rectal) perception is assessed during balloon distention. The rate and pattern of balloon distention are important parameters. Perception is assessed by asking subjects to indicate when they perceive a given sensation, such as first threshold, desire to defecate, or discomfort. To avoid bias resulting from gradually increasing stimuli, the distending stimuli can be randomized. The contractile response is more pronounced during fast than during slow distention. It is conceivable that this partly explains why rapid rectal distention is more likely than slow distention to be perceived in healthy subjects and to evoke visceral hypersensitivity in IBS.[41,42]

An alternative method involves asking patients to rate the intensity of perception during balloon distentions of standardized intensity delivered in random order.[43] Perceptual intensity is recorded on separate visual analog scales for gas, desire to defecate, and discomfort. With this technique, subjective perceptual ratings are

proportional to the intensity of the stimulus. Moreover, this technique is responsive to alterations in visceral perception induced by psychological stress and relaxation, by the α_2 agonist and antagonist clonidine and yohimbine, respectively, and by the cholinesterase inhibitor neostigmine.

In humans, balloon distention of the left colon evokes abdominal discomfort in the midline or left iliac fossa. The rectum is more sensitive than the colon and can distinguish between flatus and feces. Rectal distention induces rectal or sacral discomfort, akin to the desire to defecate, or urgency. The anal canal is exquisitely sensitive, with sensitivity to touch, pain, and temperature comparable to the dorsum of the hand.

Perturbations of Colonic Physiology in Disease States

Examples of illnesses that derange colonic physiology, as discussed in the following sections, include constipation, obstructed defecation, acute colonic pseudo-obstruction, chronic megacolon, functional diarrhea or diarrhea-predominant IBS, other diarrheal illnesses, and diverticulosis.

Constipation

Constipation may result from alterations of colonic transit and pelvic floor function; an algorithmic approach for the management of constipation includes tests of both physiologic processes (Fig. 135–9).[44] Colonic transit is frequently delayed in patients with obstructed defecation, which should be considered in all patients with delayed colonic transit. Patients with normal-transit constipation usually respond to dietary fiber supplementation[45]; those with slow-transit constipation frequently require judiciously administered laxatives, and pelvic floor retraining is necessary to reverse pelvic floor dysfunction in patients with obstructed defecation. In patients with chronic constipation, intraluminal measurements may demonstrate fewer HAPCs over a 24-hour period and/or a reduced colonic motor response to eating.[46] Thus, intraluminal measurements are useful for confirming the presence of severe colonic motor dysfunction prior to surgery in patients with slow-transit constipation. Patients with colonic inertia represent one end of the spectrum of slow-transit constipation that is characterized by absence of a colonic motor response to a meal or a stimulatory agent such as bisacodyl or neostigmine. Detailed histopathologic studies with special stains reveal a marked loss of nerves and ICCs throughout the colon in slow-transit constipation and megacolon (Fig. 135–10).[47] Rarely, constipation may be the presenting manifestation of a generalized gastrointestinal motility disorder resulting from a paraneoplastic syndrome, (e.g., due to small cell carcinoma of the lung).[48]

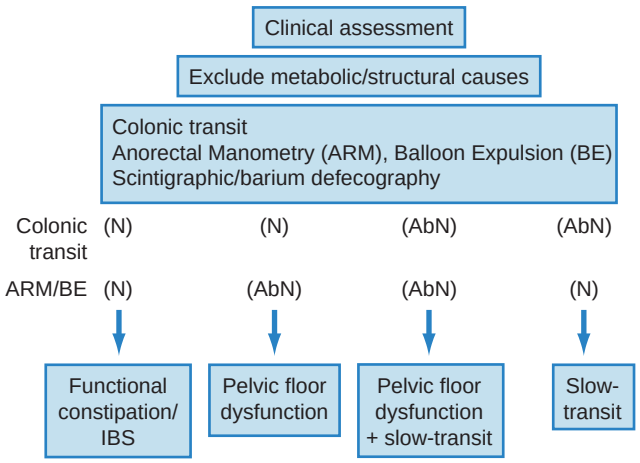

Figure 135–9. Diagnostic tests in the management of constipated patients in clinical practice. Note that these simple tests permit categorization of patients and choice of therapy. AbN, abnormal; IBS, irritable bowel syndrome; N, normal.

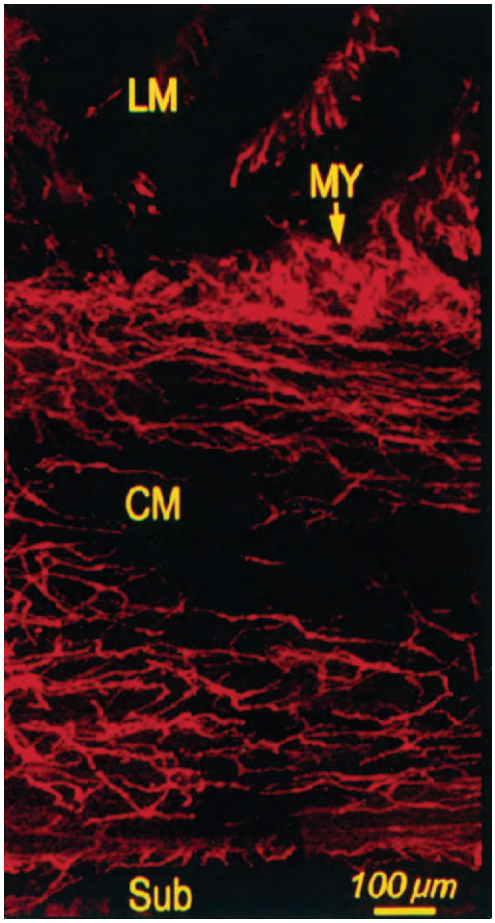

Figure 135–10. Distribution of interstitial cells of Cajal (ICC) as demonstrated by c-*Kit*–positive immunoreactivity, in the normal human sigmoid colon. Sections were cut parallel to the longitudinal muscle layer. CM, circular muscle; LM, longitudinal muscle; MY, myenteric plexus region; Sub, submucosal border. (From He CL, Burgart L, Wang L, et al: Decreased interstitial cell of Cajal volume in patients with slow-transit comstipation. Gastroenterology 118:14, 2000.)

Obstructed Defecation

Patients with obstructive defecation strain excessively to overcome the functional obstruction caused by inadequate relaxation of the external anal sphincter and/or puborectalis muscle sling.[49] The distinction between these two components (i.e., puborectalis and external anal sphincter) is often blurred by the term *anismus* to describe pelvic floor dyssynergia. Symptoms that are suggestive, but not necessarily specific, of obstructed defecation include frequent straining, a sensation of incomplete evacuation, dyschezia, and digital evacuation of feces. The physical examination may reveal high resting anal sphincter tone, failure of puborectalis relaxation and/or perineal descent during simulated defecation, or anatomic abnormalities such as anal fissure or rectocele. The latter may occur alone or may be accompanied by pelvic floor laxity and organ prolapse (descending perineum syndrome). The clinical impression can be corroborated by objective assessments of pelvic floor function, beginning with anal manometry and a rectal balloon expulsion test (Box 135–1). With anal manometry or sphincter electromyography, paradoxical sphincter contraction or anismus can be observed in up to 20% of healthy subjects with no symptoms of obstructed defecation. This underscores the importance of considering clinical features in diagnosing obstructed defecation. The rectal balloon expulsion test, performed by measuring the time required to expel, or external traction required to facilitate expulsion of a rectal balloon filled with water or air, is a useful, highly sensitive (89%) and specific (84%) test for evacuation disorders.[50] The balloon expulsion test is a useful screening test but does not define the mechanism of disordered defecation nor does a normal balloon expulsion study always exclude a functional defecation disorder.[51] Anal manometry and an abnormal balloon expulsion test suffice to confirm the diagnosis of an evacuation disorder in most patients with typical symptoms and reduced perineal descent (i.e., <1 cm) at clinical examination. However, if the results of anal manometry and the rectal balloon expulsion test are discrepant, or conflict with the clinical impression, then anorectal imaging may be necessary to clarify the diagnosis. Defecography is a dynamic technique to evaluate rectal and pelvic floor motion during attempted defecation. This test can detect structural abnormalities (rectocele, enterocele, rectal prolapse) and assess functional parameters (anorectal angle at rest and during straining, perineal descent, anal diameter, indentation of the puborectalis in the posterior aspect of the recto-anal junction, degree of rectal emptying).[52,53] The diagnostic value of defecography has been questioned primarily because normal ranges for quantified measures are inadequately defined and because some parameters such as the anorectal angle cannot be measured reliably because of anatomic variations in rectal contour and location (e.g., in the presence of perianal discomfort). Magnetic resonance imaging (MRI) is the only imaging modality that can visualize both anal sphincter anatomy and global pelvic floor motion (anterior, middle, and posterior compartments) in real time without radiation exposure. Dynamic MRI depicts the heterogeneity in functional defecation disorders and may be useful for clarifying the diagnosis in selected patients.[54,55] Patients with obstructed defecation may also have delayed left colonic transit, attributable to obstruction of luminal contents by retained stool, colonic motor dysfunction unrelated to obstructed defecation, rectocolonic inhibition, or decreased colonic motor response to a meal. The latter is reversible after biofeedback therapy.[38]

Box 135–1 Diagnostic Tests for Obstructed Defecation*

- Anorectal manometry/anal sphincter EMG—would show failure of anal canal pressure/EMG activity to decline
- Balloon expulsion—would show an inability to expel the rectal balloon within established norms for weight to facilitate expulsion
- Barium/scintigraphic defecography—would show (1) an increase in rectoanal angle of <15 degrees; and (2) perineal descent by <1 or >4 cm

*During simulated defecation.
EMG, electromyography.

Acute Colonic Pseudo-obstruction (Ogilvie's Syndrome)

In *acute megacolon* (Ogilvie's syndrome), colonic dilation is attributed to a sympathetically mediated reflex response to a number of serious medical or surgical conditions in elderly patients.[37] Cholinesterase inhibitors such as neostigmine enhance colonic contractility, reducing colonic distention in patients with acute colonic pseudo-obstruction by increasing the availability of acetylcholine in the myenteric plexus and neuromuscular junction.[56]

Chronic Megacolon

Chronic megacolon may be congenital (due to Hirschsprung's disease) or may represent the end stage of any form of refractory constipation. The initial treatment for Hirschsprung's disease is surgery. In chronic idiopathic megacolon, medical measures such as colonic evacuation with enemas, fiber supplementation, and laxatives may suffice; if severe motor dysfunction is confined to the colon, a subtotal colectomy with an ileorectal anastomosis or an ileostomy may be necessary.

Functional Diarrhea or Diarrhea-Predominant Irritable Bowel Syndrome

A subset of patients with functional diarrhea or diarrhea-predominant IBS have accelerated proximal colonic transit,[57] more frequent HAPCs,[58] and an exaggerated colonic motor response to eating. These result in

postprandial abdominal discomfort and urgency to defecate in some patients with diarrhea-predominant IBS. Other studies have shown that approximately 50% of patients with diarrhea-predominant IBS have rectal hypersensitivity or project sensation to a wider cutaneous area during balloon distention. However, the significance of visceral hypersensitivity during balloon distention to symptoms in patients with IBS is unclear and several methodologic issues need clarification.[59] Moreover, the association between rectal hypersensitivity and intensity of symptoms in patients with IBS is weak, and rectal hypersensitivity does not accurately predict the response to therapy.

The etiopathogenesis of IBS is still incompletely understood. In some patients, symptoms may be preceded by acute gastroenteritis, psychological stress, or pelvic surgery. In a prospective study, hypochondriasis or a recent stressful life event predicted which patients would have abnormal colonic physiology and IBS symptoms after an attack of acute gastroenteritis.[60]

Other Diarrheal Illnesses

In carcinoid syndrome there is accelerated small intestinal transit and increased jejunal secretion. However, there is also evidence for altered *colonic* physiology. Increased delivery of contents to the colon is compounded by reduced capacitance in the ascending colon and an exaggerated colonic motor response to eating, causing rapid proximal colonic emptying.[61] 5-HT_3 antagonists, such as ondansetron and alosetron, reduce the colonic tonic response to eating and the rate of emptying, respectively, suggesting that 5-HT_3 receptors may partly mediate the motor dysfunction in these patients.[30]

Disturbances in motility and NaCl absorption have been described in patients with *ulcerative colitis*. Patients with active proctitis have a stiff, noncompliant rectum, which may explain the enhanced sensation of urgency prior to defecation.[62]

Diarrhea after *ileal resection* of less than 100 cm is induced by the secretory effects of bile acids, associated with mild steatorrhea (<20 g/day), and responsive to cholestyramine (4 to 6 g/day).[63] After more extensive ileal resection (>100 cm) steatorrhea is severe (>20 g of fat/day) and attributable to fat maldigestion and malabsorption secondary to low jejunal concentrations of bile acids. Cholestyramine will not ameliorate and may aggravate diarrhea in these patients.

Clonidine ameliorates the diarrhea related to *diabetic neuropathy* by restoring the α_2-mediated sympathetic "brake," such as promoting intestinal and colonic absorption of NaCl and inhibiting motility.[64]

Diverticulosis

Considerations relevant to the pathophysiology of diverticulosis include the orientation of taeniae coli, the course taken by perforating arteries supplying the colonic wall, and changes in the biomechanical properties of the colon that accompany diverticulosis. Colonic diverticula are mucosal pouches that are pushed out between arcs of circular muscle at weak points, such as where arteries pierce the muscularis propria in the spaces between the mesenteric taenia and the two antimesenteric taeniae. Thus, diverticula do not occur where the taeniae fuse to form a longitudinal muscle layer surrounding the rectum.[65]

Thickening of the colonic circular and longitudinal muscle layers, partly due to elastin deposition with shortening of taeniae coli, may narrow the colonic lumen in diverticulosis. Recent studies also reveal colonic motor disturbances (i.e., more propulsive activity, more 2- or 3-cycle/min regular, phasic, nonpropagated activity) and heightened perception of colonic distention in patients with uncomplicated, symptomatic diverticulosis.[66] Thus, it is conceivable that increased motor activity, particularly rhythmic contractions, may lead to mucosal outpouching and formation of diverticula, particularly when the colon is less compliant and/or narrower, such as in the sigmoid colon or in the presence of long-standing disorders of defecation. These motor disturbances may be partly attributable to cholinergic hypersensitivity.[67] It has been speculated that a low-residue diet with diminished fecal bulk predisposes to colonic luminal narrowing and ultimately diverticulosis. However, there is no direct evidence to corroborate a cause-effect relationship between lack of dietary fiber and luminal narrowing or elastin deposition in the taeniae coli.

Implications of Colonic Physiology for Surgical Practice

The physiological concepts discussed earlier have considerable implications for colorectal surgical practice. For example, it is crucial to treat pelvic floor dysfunction in patients with severe constipation prior to considering colectomy in those with delayed colonic transit. A colectomy with ileorectostomy is the preferred procedure for patients with intractable constipation and adequate anal sphincter function.[68] Assessment of gastric and small intestinal transit or motor activity may permit recognition of patients with generalized gut dysmotility disorders in whom long-term success rates after a colectomy for constipation are lower than in patients with selective colonic dysmotility. Left-sided colectomy may result in postoperative colonic transit delays in the unresected segment; this likely represents parasympathetic denervation, since ascending intramural fibers travel in retrograde manner from the pelvis to the ascending colon. The sigmoid colon and rectum are also supplied by descending fibers that run along the inferior mesenteric artery. These nerves may be disrupted during a low anterior resection, leaving a denervated segment that may be short or long depending on whether the dissection line includes the origin of the inferior mesenteric artery.[69] A long denervated segment is more likely to be associated with nonpropagated colonic pressure waves and delayed colonic transit than a short denervated segment. In addition to colonic denervation, a low anterior resection may also damage the anal sphincter and reduce rectal compliance[70]; in contrast to anal sphincter injury, rectal compliance may recover with time.[71] Physiologic assessments confirm clinical observations suggesting that colonic

motor function recovers more rapidly after laparoscopic-assisted compared with open sigmoid colectomy.[72]

Surgeons should also be aware of the fluid-absorptive capacity of the colon and its importance in fluid and electrolyte homeostasis. The retention of a segment of colon can make an enormous difference to the postoperative management of short bowel syndrome after massive resection for mesenteric vascular thrombosis or Crohn's disease.

Motor disorders of the colon may manifest with colonic dilation. Not all dilation is secondary to obstruction and, in the presence of comorbidity or electrolyte imbalance, megacolon should be considered early, particularly since it can be treated medically or endoscopically without resorting to resection.

Finally, colorectal surgeons, like gastroenterologists, encounter many patients in their practice in whom the diagnosis is functional diarrhea, constipation, or fecal retention. These patients deserve a compassionate, careful appraisal and advice on how to restore normal colonic physiology. Avoidance of unnecessary colonic or other surgery is the best course of management—*primum non nocere*.

ACKNOWLEDGMENTS

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Chapter

136

Diagnosis of Colon, Rectal, and Anal Disease

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It is self-evident that the appropriate treatment of diseases of the colon, rectum, and anus relies on a correct diagnosis. A correct diagnosis is built on three pillars: history, examination, and investigation. Taking a good, accurate, and targeted history; performing a careful and revealing physical examination; and choosing the right investigations require skill and acumen. The wisdom that comes with experience is of great value in perfecting these diagnostic techniques. Clinical diagnostic skills have, in general, been less valued as part of a diagnostic work-up since the 1980s, as easy access to a plethora of imaging techniques has tended to encourage taking "the easy way out." As clinicians are asked to account for the costs of every investigation, we are reminded to begin with as thorough a clinical assessment as possible, saving expensive investigative tests for well-defined indications. We need to ask the right questions of our patients, know what to look for on examination and how to look for it, and choose only tests that will make a difference. In this chapter, we hope to provide some directions toward attaining these goals. We consider diagnosis under the broad headings of history, examination, and investigation, and because other chapters follow a disease-oriented approach, we focus on symptoms.

HISTORY

General Principles

The history of a patient with colon, rectal, or anal disease can be the key to the diagnosis. When the patient describes symptoms, the likely site and nature of the problem direct the remainder of the history. Keeping an open mind is important, though, as a patient may use diagnostic terminology in a lay application and misguide the investigation. For example, "hemorrhoids" could mean rectal prolapse, an abscess, or a fissure. Basic history-taking skills are important and are refined by a mental differential diagnosis that impels specific questions. The astute clinician should inquire about the patient's bowel habits, typical diet, and use of medications. Apart from the history of the presenting complaint, it is important to document comorbid diseases, medication use that includes over-the-counter drugs, drug allergies and intolerances, past operations, and family history of related diseases or colorectal cancer (CRC). Anal disorders in particular may be sexually transmitted and a history of sexual practices might be necessary. After a thorough history, the differential diagnosis should be fairly well established. Examination and investigation can therefore be planned to confirm or exclude some of the possible diagnoses and to exclude other common complicating conditions.

Symptoms

Bleeding

Rectal bleeding can be categorized as typical outlet bleeding, suspicious bleeding, or hemorrhage. *Outlet bleeding* is bright red, seen only on the toilet paper or in the water, and not associated with any risk factors for colorectal neoplasia (e.g., past history or family history for colorectal neoplasia). *Suspicious bleeding* includes dark blood, blood associated with mucus, blood on or in the stool, and blood associated with either a personal or familial risk or a change in bowel habits. *Hemorrhage* is an acute, large-volume blood loss; this is discussed in detail in Chapter 145.

Outlet bleeding is usually associated with an obvious anal cause. The history provides important clues. If the bleeding is associated with pain, suspect fissure, or excoriation. If it is painless, consider internal hemorrhoids or brim irritation. Suspicious rectal bleeding has a wider differential diagnosis than outlet bleeding. Internal hemorrhoids are still a likely cause, but rectal mucosal prolapse, occult full-thickness rectal procidentia, and even solitary rectal ulcer may present in this way.

Constipation, difficult defecation, and rectal pain can be highly suggestive of one or all of these conditions.

Anorectal Pain, Itching, and/or Swelling

Anal pain is a common symptom in Western societies, because the modern Western diets' effect on bowel function places a strain on the anal canal. The pattern of the pain is usually highly suggestive of the cause, and this is confirmed on examination. Burning pain after a bowel movement that lasts for 30 minutes to 2 hours and is often accompanied by traces of blood suggests an anal fissure. The pain can be quite severe and is sometimes traced to an episode of diarrhea or constipation. Alternatively, burning pain may be due to perianal excoriation, which can also bleed if the perianal skin becomes ulcerated. A history of itching, mild incontinence, seepage, or an anastomosis that involves the anus suggests that excoriation may be present. A pressure-type pain associated with a tender lump could be either a thrombosed external hemorrhoid or a perianal abscess. Hemorrhoid pain is of sudden onset, usually occurring after an episode of difficult defecation. Acutely thrombosed hemorrhoids can be suspected when there is a history of a reduction in pain accompanied by bleeding independent of bowel motions. Abscess pain is more insidious, with slowly but relentlessly increasing severity.

Itching, or pruritus ani, has a wide differential diagnosis list. Clues in the history include the timing of the pruritus, its relationship to food and clothing, the use of specific soaps, and its response to topical medications. Patients who are obsessed with cleanliness are prone to damaging the perianal skin, as are those who are unable to keep their perianal skin clean. Frequent stooling, especially when the stool is liquid, is also a risk factor for pruritus. In the absence of specific causes, nonspecific pruritus can be diagnosed.

Nonpainful lumps include skin tags, fibrous anal polyps, or a large rectocele. Anal swellings that are reducible may be prolapsing internal hemorrhoids or full-thickness rectal prolapse.

A patient with rectal pain carries a complex differential diagnosis of poorly defined conditions. History taking establishes the pattern and nature of the pain. A constant, gradually worsening pain may indicate a tumor or an abscess; both should be palpable or visible on imaging or proctoscopy. A pressure-like pain that worsens on sitting is likely to be levator syndrome. Sharp, fleeting pains like electrical shocks are suggestive of proctalgia fugax. Constant anterior pain in a man may suggest prostatitis, whereas painful defecation in the absence of anal problems may imply a solitary rectal ulcer. Tenesmus is a type of rectal pain best described as a feeling of intense rectal contraction that is associated with rectal mucosal inflammation; it is typically associated with acute proctitis or a low-lying rectal tumor.

Abdominal Pain and/or Distention

Abdominal pain is a common symptom that has a vast differential diagnosis. This differential diagnosis can be considerably focused by analyzing the pain according to its timing, nature, pattern, site, and context. Sharp, steady pain is likely to be due to some infectious process or a tumor, whereas colicky pain or intermittently crampy (pain that builds to a crescendo, then eases, and then builds again) is due to either obstruction or spasm. When a constant pain is made worse by breathing or moving, infection is likely. Pain associated with diarrhea may be due to colitis, irritable bowel, diverticulitis, or a stenosing tumor. When painful diarrhea is bloody, colitis is more likely. Pain associated with abdominal distention and reduction in bowel movements may be caused by a large bowel obstruction. Sudden-onset pain indicates an acute event (e.g., perforation, volvulus); gradually increasing pain is more likely due to contained sepsis or tumor. Colonic pain may be felt anywhere in the abdomen, chest, back, or pelvis. Pain from an infectious process is generally felt near the site of the sepsis. Pain from spasm of the sigmoid colon is commonly felt in the lower abdomen. Patient age, gender, and past history are important in setting the differential diagnosis for a patient who presents with abdominal pain. For example, colon cancers are more common in elderly patients, and colitis is more typical in the young.

Abdominal distention may be a sign of colonic distention. If it is associated with pain, the distention is likely to be due to a mechanical obstruction. If there is no pain, there may be a colonic ileus (i.e., pseudo-obstruction). Distal small bowel obstruction may also produce considerable distension but is more often associated with nausea and vomiting.

Constipation

The word *constipation* has many definitions, and patients may imply different things by its use. Constipation may be used to describe small stools, hard stools, large stools, stools that are difficult to pass, stools that come infrequently, or stools that are incompletely passed. Patients need to realize that the range of normal stool frequency is three times per day to three times per week. Persons do not need to have a stool every day to be normal.

Small, hard stools are usually a result of lack of fiber. "Pebbles" may come from inside diverticula. Hard stools have been in the colon too long and have become inspissated. Infrequent stools may be caused by a lack of bulk in the diet or decreased colonic peristalsis due to one of a number of causes (see Chapter 135). A full history of medications and coexisting diseases may reveal the cause.

Serious constipation, with stools passed once a week or less often, is usually due to either colonic inertia or rectal outlet obstruction. Patients with colonic inertia usually do not feel the urge to defecate. As time passes, they become more uncomfortable and distended. They may try to strain and pass stool, but this is usually unsuccessful. These patients typically ingest high doses of laxatives to initiate their bowel motions. Contrarily, with rectal outlet obstruction, stool reaches the rectum and is often sensed but cannot be passed. Affected persons classically report difficult defecation as their main symptom, but they may experience abdominal cramps due to colonic contractions. They commonly spend prolonged

periods on the toilet straining to pass stool and often need to use their finger or some other instrument to push on the perineum or into the anus to help evacuate the stool. The most common causes of rectal outlet obstruction are a nonrelaxing puborectalis and rectal mucosal prolapse. Some patients may develop secondary colonic inertia after years of rectal outlet obstruction, in which case the clinical presentation may be confusing.

A feeling of incomplete defecation may be due to truly inefficient evacuation of stool. It may, however, be due to a rectal tumor or redundant rectal mucosa as occurs in occult rectal prolapse. Incomplete defecation differs slightly from frequently repeated calls to stool. If a patient appears to completely evacuate but then is called to stool again soon, this suggests either stool stacking (fragmentation) or a rectocele. Stool stacking is common after a proctosigmoidectomy, which interrupts the normal defecation mechanism. The collection of stool in a rectocele can be sensed and is often associated with a feeling of perineal fullness or bulge. The use of a finger to splint the vagina or perineum to aid defecation is characteristic of persons with a symptomatic rectocele.

Diarrhea

Many causes of diarrhea exist; some are disorders of the small bowel, and others involve the large intestine. An analysis similar to that presented for abdominal pain may be helpful. Constant diarrhea is usually due to an infectious or inflammatory process in either the small or large bowel. Endoscopy of the colon usually excludes a colonic cause or establishes the diagnosis. Postprandial diarrhea usually suggests some form of malabsorptive illness (e.g., celiac disease, lactose intolerance) but may also reflect short bowel syndrome. Intermittent diarrhea associated with abdominal cramps is a common variant of irritable bowel syndrome. Diarrhea with blood implies some variant of colitis such as infectious, ischemic, ulcerative, or Crohn's disease. Sometimes blood associated with diarrhea is secondary to internal hemorrhoids or anal fissure/irritation. Diarrhea associated with abdominal pain may indicate ischemic colitis if it is of abrupt onset or an inflammatory colitis if it is chronic. The extent of disease in colitis can somewhat be predicted by the presence of diarrhea; generally patients with distal colitis or proctitis have formed stool, whereas pancolitis leads to diarrhea. A history of a trip abroad or the ingestion of questionable food raises the possibility of infectious diarrhea. The sensation of impending loss of control or the urgent need to use the lavatory is usually associated with rectal inflammation or strong muscular contractions characteristic of irritable bowel syndrome. Sometimes the well-meaning patient reports diarrhea when he or she actually has urgency.

Urgency and Incontinence

Urgency of stool is a sensation of impending defecation (see Chapters 135 and 138). It is associated with increased sensitivity of the rectal mucosa due to inflammation (e.g., proctitis) or an increased pressure of stool (e.g., irritable bowel syndrome). Intermittent urgency is more likely due to irritable bowel syndrome, whereas constant urgency, especially in association with rectal bleeding, signifies proctitis.

Fecal incontinence can be defined as an inability to defer passage of stool to a socially acceptable time and place. The history is crucial to making an initial diagnosis as to the cause of incontinence. A history of trauma or irradiation to the anal sphincter mechanism suggests sphincter damage. Classically, this is caused by obstetric trauma but may be secondary to surgical injury or other physical damage. Neurologic diseases may also contribute to or cause incontinence, whereas concomitant chronic bowel disease (e.g., inflammatory bowel disease, irritable bowel syndrome) is also important to document. *Urge incontinence,* defined as an inability to control the urge to defecate, implies external sphincter dysfunction, whereas the loss of control of stool unrelated to an urge (i.e., seepage) implicates the internal sphincter. Involuntary loss of stool suggests a loss of rectal sensation or fecal impaction with overflow of liquid waste.

EXAMINATION

General Principles

Examination is primarily directed to the region of the body responsible for the presenting problem, but persons seen for the first time or in the remote past should undergo a more generalized physical examination. Along with a general survey and recording of vital signs, this procedure typically includes an examination of the eyes, mouth and pharynx, thorax and lungs, heart, peripheral vascular system, gross neurologic function, and mental status. Patients examined for colorectal symptoms should have a digital rectal examination. An abdominal examination is required for older patients (>50 years) or for younger persons whose symptoms are not obviously caused by an anorectal disorder. The abdomen examination is conducted with the patient supine and should include inspection from the xyphoid to pubis with particular attention to scars, deformities, distention, and masses. Auscultation characterizes the quality of the bowel sounds and identifies any bruits. Percussion helps differentiate among distended bowel, ascites, and solid masses and identifies hepatomegaly or splenomegaly. Palpation of all four abdominal quadrants should identify abnormal masses that are evaluated for size, mobility, and pulsation. Last, the groins should be palpated for hernias and significant adenopathy.

Patients with a disease of the colon, rectum, or anus bear the burden of embarrassment in addition to concerns about their symptoms, likely diagnosis, and prognosis. They appreciate a professional attitude, consideration to covering sensitive areas where possible, and a minimal number of observers in the room. A nurse should be present during the examination and ideally should be of the same gender as the patient. Gentleness in examination is paramount to minimizing discomfort, especially when performing anal examinations. Maximum information can be gleaned only if the patient is able to tolerate the examination and relax. Anoscopy

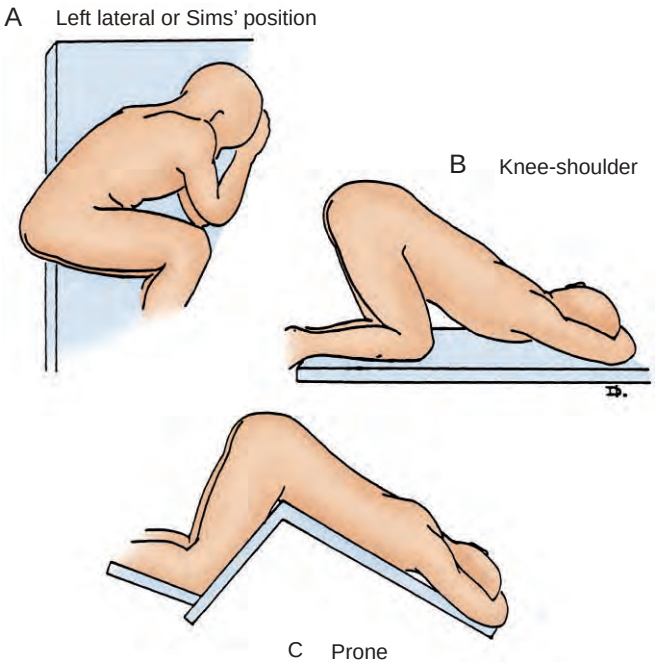


Figure 136–1. Positions of patient for anorectal examination. **A,** Left lateral (Sims') position. **B,** Knee-shoulder position. **C,** Prone (jackknife) position using proctoscopy table. (**A** to **C,** From Hill GJ II: Outpatient Surgery, 2nd ed. Philadelphia, WB Saunders, 1980.)

allows visual evaluation of anal complaints, and proctosigmoidoscopy is similarly important if rectal symptoms predominate.

Position

Most patients undergo anorectal examination in the prone jackknife or left lateral decubitus position (Fig. 136–1). The former position provides the examiner with the greatest comfort, whereas the latter is easiest for the patient.

The prone jackknife position requires a special examination table that can be flexed to 90 degrees and tilted head-down. The patient kneels on a shallow ledge that is height adjusted to allow comfortable hip flexion and lowers his or her clothing and undergarments while shielded from direct view by a sheet held between the patient and examiner. The patient then lays his or her chest flat on the table, and the table is tilted to bring the anoperineum into clear vision after adjustment of the sheet. This position allows the rectum to fill with air while the liquid and solid luminal contents will dependently settle into the rectosigmoid region.

If a specialized table is unavailable, colonoscopy is planned, or the patient is more easily positioned from prior abdominal examination, a left lateral decubitus position is recommended. With the patient covered with a sheet and lying in the left lateral decubitus (Sims') position, the hips and knees are flexed, and the patient's hips are positioned on the edge of the table. The head, knees, and feet are situated opposite the examiner, angling the patient's body across the table. The anoperineum is then undraped to allow isolated exposure of the examination area.

Inspection and Palpation

Examination of the perineum and anus must be systematic, incorporating both inspection and palpation, and the patient should be informed of all maneuvers before they occur to minimize anxiety, discomfort, and the potential for harm. The physician and assistant should position themselves on opposite sides of the patient and then gently separate the buttocks, with the examiner leaving his or her dominant hand free. The sacrococcygeal region is first surveyed to exclude pilonidal disease. The skin overlying the ischioanal fossae is then inspected for abnormalities that include excoriation, maceration, ulceration, drainage sites, lesions, and masses. The perianum is observed for external hemorrhoids, skin tags, scarring, and deformity. Last, retraction allows inspection of the anal verge and distal canal for a fissure, ulcer, and prolapsing anal papillae or internal hemorrhoids. If rectal procidentia is suspected, the patient is asked to perform the Valsalva maneuver while the examiner watches for prolapsing mucosa or rectal wall. The position of the anus and quality of the perineal body, including descent of these structures, should be consciously noted when a woman is inspected, especially when the presenting complaint is seepage, urgency, or incontinence.

Palpation of the perineum is performed next. This tactic may elicit tenderness and detect fluctuance or induration suggestive of an abscess. Fistula tracts can be felt as they course from an external os toward the anal canal. After palpation of the skin overlying the external sphincter, an anal wink is elicited by drawing a finger quickly across the sphincter while applying light pressure. A well-lubricated finger is then gently and slowly inserted into the anal canal to assess sphincter tone. As the pad of the finger passes along the anoderm above the intersphincteric groove, the canal should feel smooth and nonulcerated. The examiner might encounter scarring or stricturing at this level; pain may preclude further examination except under anesthesia. The dentate line can be appreciated as the mucosa transitions into more irregular tissue. Hypertrophied anal papillae and masses can be best appreciated by slowly rotating the digit around the circumference of the canal. Internal hemorrhoids are rarely palpable unless they are hypertrophied due to chronic prolapse. Before the examination continues above the anorectal ring, the patient is asked to squeeze around the examining finger to assess external sphincter and puborectalis function. The thumb of the examining hand should be placed into the posterior vaginal fourchette to permit bidigital appreciation of an anterior anal sphincter defect. For patients who complain of nonspecific pelvic pain, the puborectalis and levators should be firmly palpated bilaterally and the coccyx bimanually manipulated, while the patient is

asked whether the various maneuvers reproduce his or her presenting pain.

The distal rectum is examined last, beginning with palpation of the prostate or cervix through the anterior rectal wall; laxity of the rectal wall with significant anterior bulging is suggestive of a symptomatic rectocele. Bidigital examination of the rectovaginal septum often allows the identification of an enterocele that is palpable with straining. Like the anal canal, the rectum is circumferentially palpated to exclude tenderness, induration, polyps, and masses. The velvety soft texture of a large, sessile villous adenoma can be easily missed if the examiner is unaware of the subtle mucosal changes associated with these lesions. Any neoplasms that are encountered should be characterized according to size, position, and location relative to the anorectal ring to assist in planning the appropriate operative approach. In addition, palpation of the tumor for firmness, mobility, and ulceration that predict wall invasion and palpation of the posterior rectal wall for retrorectal lymph nodes that suggest local nodal metastases are pivotal for accurate clinical staging.

Examination of Specific Complaints

Anorectal Pain and/or Swelling

Examination of the painful anus must be done gently, duly warning the patient of what can be expected. Typically, a patient with a fissure has a "shy" anus that resists distraction. However, the fissure, or its external component, usually can be seen with the use of gentle pressure to pull the anus slightly open. An acute fissure has no tags or rolled edges; these are signs of chronicity. If the principal complaint is that of mild pain or itching, specific causes of pruritus should be sought, such as infections, infestations, dermatitis, allergies, and mucus leakage due to prolapsing hemorrhoids or rectal mucosa. Examination of the perianal skin may show minor excoriations that can be quite tender or the whitish appearance of lichenified skin that has been subjected to chronic wetness and irritation. Bowen's disease may appear as asymmetrical patches of discolored skin, whereas a reddish hue is more suggestive of Paget's disease and must be excluded by biopsy in any patient with unremitting pruritus and discolored perianal skin. Last, painful perianal ulcerations in the appropriate setting may be due to herpes simplex infection, and a swab sample should be taken for culture.

A thrombosed external hemorrhoid appears as a swelling at the anal verge and may be small or involve nearly half of the anal circumference. A bluish tinge is usually visible as the clot shines through the skin. The skin over acutely thrombosed hemorrhoids is tight with edema and appears smooth. As days pass, the edema tends to disappear and the skin starts to wrinkle, whereas the clot occasionally erodes through the skin. An abscess is typically visible as a localized swelling in the perianal or ischioanal area. Fluctuance, erythema, tenderness, and sporadic skin discoloration may or may not be present because the deeper the sepsis, the less obvious are the signs. For instance, a deep postanal space abscess classically presents with pain and toxicity but a normal-appearing anal area. Examination under anesthesia and needle aspiration of the postanal or perianal space is the best method of diagnosis.

Although a painful perianal lump is usually a thrombosed external hemorrhoid or an abscess, nonpainful lumps may include skin tags, fibrous anal polyps, or a large rectocele. Anal swellings that are reducible may be prolapsing internal hemorrhoids or full-thickness rectal prolapse. Perianal condylomata are usually obvious, but anoscopy is necessary to exclude intra-anal condylomata or prominent hemorrhoids.

Rectal pain can be poorly defined and difficult to treat. Again, taking a detailed history leads the direction of the necessary examination. Tumors and abscesses causing constant or gradually worsening pain should be palpable or visible on proctoscopy or imaging. Digital rectal examination may reveal an asymmetrically tender levator muscle in levator syndrome. The prostate is usually tender on digital rectal examination when prostatitis is causing constant anterior rectal pain. Although a digital examination is limited to the length of the examining finger, it is usually adequate to diagnose or exclude a mass lesion or sepsis in or around the lower rectum. Regardless, when a patient who complains of anal or rectal pain cannot be adequately examined or when the examination reveals no abnormalities, examination under anesthesia is warranted.

Bleeding

Perineal excoriation, anal fissure, internal hemorrhoids, or a low-lying neoplasm can cause outlet rectal bleeding. Excoriation and fissures can be identified through simple inspection of the perineal skin and anal verge. Inspection of the perianum may reveal grade III or IV internal hemorrhoids, especially if the hemorrhoids remain prolapsed after an enema. Although they are occasionally associated with external skin tags, internal hemorrhoids are rarely palpable unless they are hypertrophied due to chronic prolapse. Instead, symptomatic internal hemorrhoids are best diagnosed with anoscopy and appear as bulging mucosal cushions, often with prominent veins or arteries that tend to lie anteriorly and posterolaterally on both sides of the anal canal. Chronically prolapsing internal hemorrhoids develop a whitish-gray lining, *pseudoepitheliomatous hyperplasia.*

Suspicious rectal bleeding has a wider differential diagnosis than outlet bleeding. Internal hemorrhoids are still a likely cause, so anoscopy is important. Rectal mucosal prolapse, occult full-thickness rectal procidentia, and even solitary rectal ulcer may present in this way. Proctoscopy may show erythematous, redundant rectal folds that descend into the anus with a Valsalva maneuver. Suspicious bleeding may also herald neoplasia, and evaluation of the proximal colon is required. It is always important to recall that rectal bleeding is never normal and invariably requires further investigation because it should never be assumed that the cause is "merely" hemorrhoids.

Urgency and Incontinence

Examination of the anus and rectum confirms the diagnosis suggested by the history. The sensation of the perianal skin and the wink reflex of the corrugator cutis ani muscle can be tested with a light touch. This simple maneuver provides useful information about the innervation of the external sphincter. Perianal scarring suggests previous trauma, and a sphincter defect is usually visible or palpable. The thickness of the perineum in women provides a clue to sphincter bulk.

Constipation

Once the diagnosis of an outlet obstruction is suspected on the basis of the history, examination can often suggest which of the common causes contributes. The ability of the puborectalis to relax while bearing down can be assessed during a digital examination. At the same time, laxity of the rectal mucosa or tendency of the rectal wall to prolapse can be noted. Similarly, a digital examination can exclude an anal stricture or a rectocele. If a rectocele is present, it will be noted as an anterior defect in the rectal wall, bulging into the perineum. Rectoceles are usually asymptomatic, and the mere presence of a rectocele does not mandate treatment.

Examination of the anus may reveal a rectocele in women, or a megarectum may be identified. Careful inspection can expose prolapse of the rectal mucosa during a Valsalva maneuver, or, occasionally, the pelvic floor fails to relax when the patient bears down.

INVESTIGATION

Blood and Stool Testing

Routine blood and stool tests are helpful in the evaluation of some disorders of the large bowel and anus. Occasional abnormalities in blood levels directly cause a malady; some are signs that are associated with the disease that causes symptoms and others are the result of the disorder itself. For instance, serum electrolyte abnormalities can affect bowel frequency with few other systemic manifestations. Alternately, altered thyroid-stimulating hormone levels may identify the cause of intestinal symptoms related to thyroid dysfunction. Contrarily, a bleeding colorectal neoplasm may be the cause of a microcytic, hypochromic anemia. Infectious and neoplastic abnormalities of the colon and rectum are also investigated by stool and blood studies.

Stool tests for ova, parasites, and other pathogens can lead to the diagnosis of infectious colitides. Examples of common pathogens include *Giardia* and *Clostridium.* Giardiasis, acquired from contaminated water, is more likely found in the younger outpatient population. *Clostridium difficile* colitis has a particularly high prevalence in the older, institutionalized, or hospitalized population, though; the stool of any patient with colitis after antibiotic use should be tested for the *C. difficile* antigen.

Serum and stool tests are used in the evaluation of CRC. Screening tools for new and recurrent cancers include serum carcinoembryonic antigen (CEA), a glycoprotein found in the cell membrane of CRCs that is the tumor marker most often used clinically. The marker enters the circulation and can be detected by radioimmunoassay in 70% of patients with CRC but in fewer than half of patients with localized disease.[1] Unfortunately, CEA is not specific for the gut epithelium or malignant neoplasms and is not useful as a screening tool. Preoperative CEA levels herald postoperative disease recrudescence and recurrence. If an elevated preoperative level does not return to normal, undetected disease is suspected; if the level normalizes but begins to return to abnormal range, recurrence will likely be discovered with further investigation.[2]

Although colonoscopy, discussed in a later section, is considered the gold standard as screening for CRC, several less invasive screening modalities exist. A common test is guaiac-based fecal occult blood testing, (FOBT). Despite onerous dietary restrictions and collection processes, FOBT has been used widely for more than 30 years. The low cost of FOBT does not compensate for the spot test low sensitivity, low specificity, and inconvenience, but FOBT is the only noninvasive screening test shown, as of yet, to decrease mortality from CRC. Sensitivity of FOBT is slightly higher with serial examinations; however, newer stool studies, applying innovative DNA testing, promise to greatly improve noninvasive CRC screening.

Selected DNA alterations, (i.e., K-*ras, p53, APC,* BAT-26, and "long" DNA) are seen in sloughed colonocytes collected in stool sampled of CRC patients. Multitargeted DNA-based stool testing for these alterations has been shown to be four times more sensitive (52% compared to 13%) and just as specific at screening for invasive CRC than guaiac tests.[3] As with all DNA-based tests, however, costs are currently prohibitive outside of the experimental setting.

Blood testing for gene abnormalities can be used for persons with particular forms of inherited CRC, such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Although a specific adenomatous polyposis coli *(APC)* gene mutation is identified in approximately 80% of FAP families, the mismatch repair germline mutation is demonstrated only in approximately 50% of families meeting HNPCC criteria.[4,5] Because of heterogeneity of the mutations of mismatch genes, tests for the disease-causing mutation is first sought in a family member clinically known to have the disease. Once a mutation is found in the index case, other family members can be tested with about 100% accuracy, as all affected family members would have the same mutation. A negative result on genetic testing only rules out FAP or HNPCC if an affected family member has an identified mutation.

Stool tests for ova, parasites, and other pathogens can lead to the diagnosis of infectious colitides. *C. difficile* antigen can be detected in the stool of patients with this bacterial colitis, which causes diarrhea after antibiotic use. Stool assays are also used to help diagnose large bowel neoplasms. The FOBT, however, is a relatively insensitive and nonspecific marker for large (>1 cm) polyps (sensitivity of 12%) and CRC (sensitivity of 22% to 28%).[6] In fact, FOBTs fail to detect most asymptomatic

cancers and the vast majority of large adenomas; most positive FOBT results are due to non-neoplastic causes. A new stool assay panel of selected DNA alterations (i.e., K-*ras, p53, APC,* BAT-26, "long" DNA) does hold promise as a potential screening tool. In a study, the sensitivity of this panel was 91% for cancers and 82% for large (>1 cm) adenomas, whereas the specificity was 93%.[7]

Endoscopy

Anoscopy Inspection of the anal canal is best performed with an anoscope. Various types of anoscopes are manufactured but are described on the basis of size and whether they are disposable, lighted, and bivalved, slotted, or beveled (Fig. 136–2). Regardless of the type of instrument that is used, digital examination should always precede insertion of the anoscope. The patient is informed of the ensuing procedure, the well-lubricated anoscope is gently applied against the anus, and gradual pressure is applied to pass the scope into the canal. If resistance is encountered because of increased sphincter tone, the patient is asked to strain because this will involuntarily relax the sphincter and allow passage of the anoscope. Continued difficulties are suggestive of anal stenosis, mandating the use of a smaller-caliber anoscope, or of anal pathology that necessitates examination under anesthesia. Once the anoscope is appropriately inserted, it is used to circumferentially inspect the anal canal and, occasionally, the lower rectum. The scope is partially withdrawn in each quadrant to allow visualization of all mucosa.

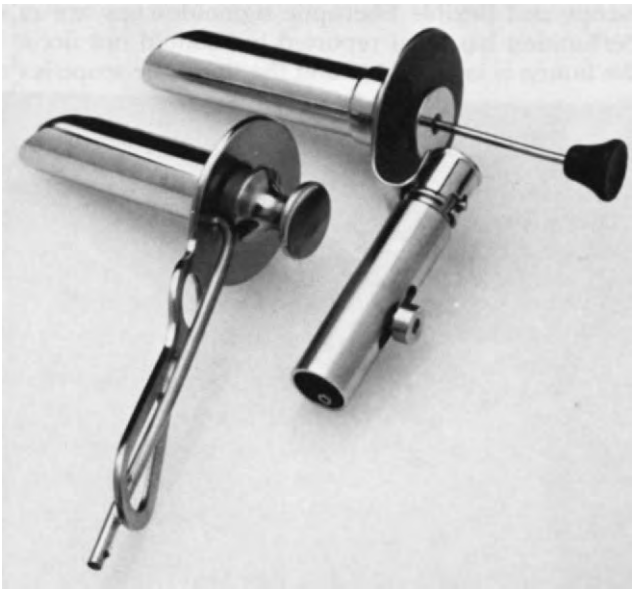


Figure 136–2. Large modified Hirschman anoscopes.

Rigid Proctosigmoidoscopy Historically, rigid proctosigmoidoscopy was used for routine visualization of the rectum and distal sigmoid colon. Rigid endoscopy remains the procedure of choice for evaluation and treatment of distal rectal lesions. In addition, a rigid scope more accurately measures the location of a tumor relative to the anal verge than a flexible endoscope, which adds at least 3 cm of length to the distance in 80% of patients.[8] The rigid instruments are 25 cm long and have a diameter of 11, 15, or 19 mm (Fig. 136–3). The smaller instruments are used in patients with strictures, whereas the larger proctosigmoidoscopes enable the evacuation of stool or blood and the treatment of larger polyps. The scope is inserted after anoscopy has been completed and is passed similarly to the anoscope. After the rigid proctosigmoidoscope has passed through the sphincters while typically directed toward the umbilicus, the obturator is removed, and the scope is advanced under direct visualization. Luminal contents that obscure adequate inspection are aspirated or swabbed as the examination progresses, but close mucosal examination is best performed during scope withdrawal. If stool obscures significant segments of mucosa, the procedure is halted until an enema is delivered to clear the lower bowel.

Although the direction of rigid proctosigmoidoscope passage must be individualized, the general route is directed posteriorly along the sacral hollow, around the inferior (left posterior), middle (right anterior), and upper (left posterior) valves of Houston. The rectosigmoid junction will come into view after the proctosigmoidoscope has been inserted 17 to 19 cm. At this point, further insertion will cause many patients to experience

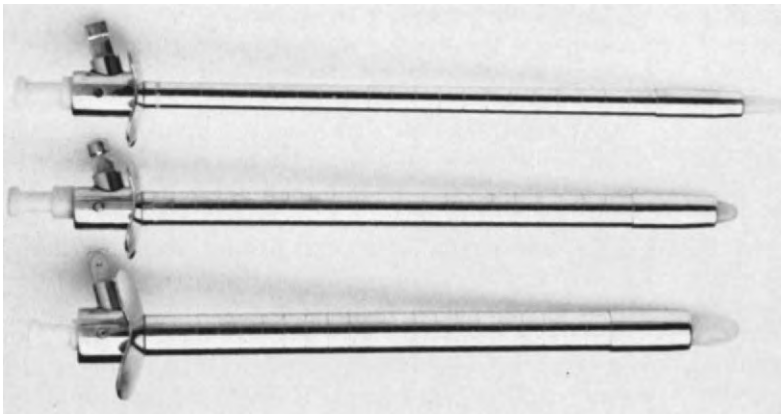


Figure 136–3. Large-, medium-, and small-diameter Welch-Allyn rigid sigmoidoscopes.

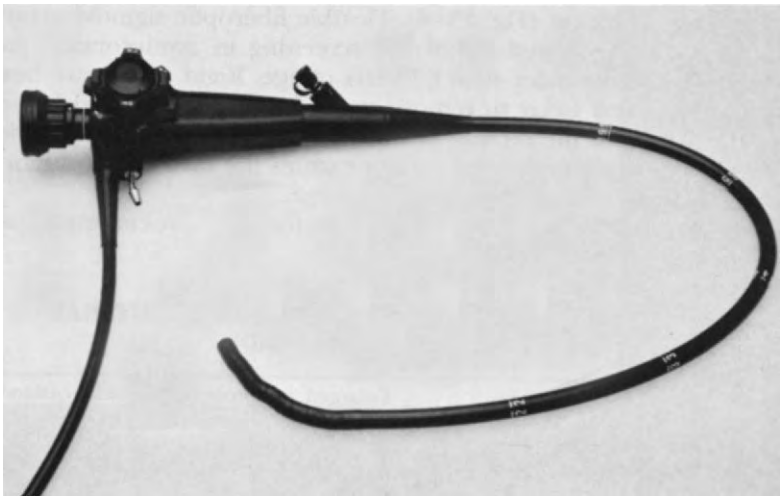


Figure 136–4. Pentax 65-cm flexible fiberoptic sigmoidoscope.

crampy visceral pain that resolves with instrument withdrawal. The angulated rectosigmoid may appear as a blinded end to the rectum with no visible rectum. Gentle manipulation to the left and then to the right will often open the sigmoid lumen to inspection. Moderate air insufflation facilitates the procedure, but excessive use is painful and interferes with the examination. Examination is performed during withdrawal while sweeping the scope around to allow careful inspection of all mucosal surfaces, flattening the rectal valves to survey their cephalad components.

Biopsy samples are obtained posteriorly along the folds of the valves if possible to minimize the risk of perforation. Small lesions can be fulgurated, and larger polyps can be excised with a Frankfeldt snare. Anterior biopsies above the middle rectal valve are especially prone to intraperitoneal perforation because this area is situated above the peritoneal reflection; perforation complicates 0.005% to 0.01% of rigid procedures.[9] Perforation by the tip of the scope occurs at areas of angulation, bowel wall weakness, and intestinal fixation. Bleeding after biopsy with the larger forceps or snare rarely occurs and usually spontaneously ceases. In the event that hemorrhage persists, a small artery is usually implicated, but it can be controlled by a combination of pressure and coagulation. Explosion has occurred during electrocoagulation in the presence of methane and hydrogen gases.[10] Fortunately, the lumen of the rigid scope is vented to room air, which prevents explosion.

Flexible Proctosigmoidoscopy In many units, flexible proctosigmoidoscopy has replaced rigid examination for most clinical indications, with the exception of those mentioned earlier. This shift in practice is because the length, flexibility, magnification, and optics of the newer instruments make flexible proctosigmoidoscopy better tolerated and more sensitive in detecting distal large bowel lesions while allowing greater length of intestine to be inspected (Fig. 136–4). After at least one hypertonic sodium phosphate enema, the scope is inserted into the rectum, and air insufflation is used to open the ampulla. The scope is advanced to the rectosigmoid, where the lumen can be difficult to visualize. Passage through this area requires a combination of torque and in-out motion to avoid loop formation that causes discomfort, precluding further examination. Through a straightened sigmoid colon, the flexible instrument is advanced with care taken to avoid intubation of wide-mouthed diverticula. Patience is required to allow segmental spasms to resolve. The descending colon can usually be negotiated with ease but occasionally requires the assistant to splint the abdominal wall to avoid looping. In most patients, the flexible proctosigmoidoscope can be inserted to at least 50 cm but should be halted earlier if the patient becomes too uncomfortable.

Biopsy samples are obtained from haustral folds, but electrocoagulation should be avoided because of the risk of explosion. Alternatively, polyps can be "cold biopsied" or snared when the risk of hemorrhage is small. If a polyp is better treated with electrocautery, exceeds 1 cm in size, or appears adenomatous on biopsy, complete colonoscopy is recommended to safely remove the lesion and to exclude synchronous neoplasms. Perforation occurs in 0.01% of patients, whereas other complications such as infection transmission and bleeding are quite rare.[9,11,12]

Colonoscopy Colonoscopy is essential in the diagnosis of several benign and any malignant diseases of the colon and rectum. Routinely used in the asymptomatic patient as screening for early neoplasms, colonoscopy is an important diagnostic tool in adenomatous, bleeding, and inflammatory conditions.

In the acutely bleeding patient, emergent colonoscopy can identify the bleeding source in 70% to 92% of patients with moderate or severe lower gastrointestinal hemorrhage (LGIH). Endoscopic management of LGIH can be achieved in many cases with coagulation, injection, and occlusion devices.[13]

For screening or nonemergent diagnostic colonoscopy, the patient is usually prepared with clear liquids and aboral gut lavage with polyethylene glycol or sodium

phosphate during the 12 to 24 hours before examination. Prophylactic antibiotic therapy is warranted if the individual has a history of prosthetic heart valve, endocarditis, surgically constructed systemic-pulmonary shunt, complex cyanotic congenital heart disease, or vascular graft within the past 6 months.[15] Although colonoscopy can be safely and comfortably performed without medication in many persons, most individuals prefer to receive a sedative, analgesic, or both. Regardless, monitoring of blood pressure, pulse, and oxygen saturation is necessary in all instances because cardiopulmonary adverse effects complicate 2% of all colonoscopies.[14]

The technique of colonoscopy is beyond the scope of this chapter, but the procedure is performed in a manner similar to flexible proctosigmoidoscopy. Cold biopsy, brushing, and cytologic washing are used for diagnostic colonoscopy in appropriate individuals. Moreover, the therapeutic endoscopist's armamentarium must include competency with hot biopsy and snare polypectomy. Expert endoscopists possess further experience with hydrostatic balloon dilation for short benign strictures and endoscopically dispatched stents used to palliate selected malignant obstructions.

The risks of colonoscopy include diagnostic and therapeutic perforation, as well as hemorrhage related to polypectomy or splenic injury. A review of more than 10,000 scopes performed over 10 years was completed at the Mayo Clinic. Twenty perforations (0.19%) occurred during colonoscopy; 65% of these occurred in the sigmoid colon. This larger review confirms previously reported iatrogenic perforation rates of 0.09% to 0.3%.[15,16] Increased risks include female gender, diagnostic or therapeutic electrocoagulation, and colitis or obstruction symptoms of any etiology.[17,18] Patients with perforation but no peritoneal signs can be safely managed with careful monitoring. Operative intervention is warranted if peritonitis develops.

Intestinal hemorrhage complicates 0.7% to 3.3% of colonoscopies.[19] Immediate bleeding usually follows inadequate control of an artery during polypectomy, whereas delayed bleeding results from subsequent clot retraction and dislodgment 1 to 2 weeks after polypectomy. Delayed hemorrhage occurs more commonly with hot biopsy than with snare polypectomy and on the right side of the colon than on the left side. Immediate hemorrhage or moderate delayed bleeding usually can be controlled by endoscopic techniques, whereas severe delayed bleeding may require assistance from the interventional radiologist. Surgical intervention is necessary only when these other modalities fail or the hemorrhage is life-threatening.

Radiologic Tests

Plain Films Plain film radiography of the abdomen and pelvis requires interpretation of varying radiolucency that is characteristic of the different structures (Fig. 136–5). This differentiation depends on the gas (intestine), water (fat, muscle, hollow organs, solid organs), and calcium (bones, calculi, nodes, thrombi, plaques)

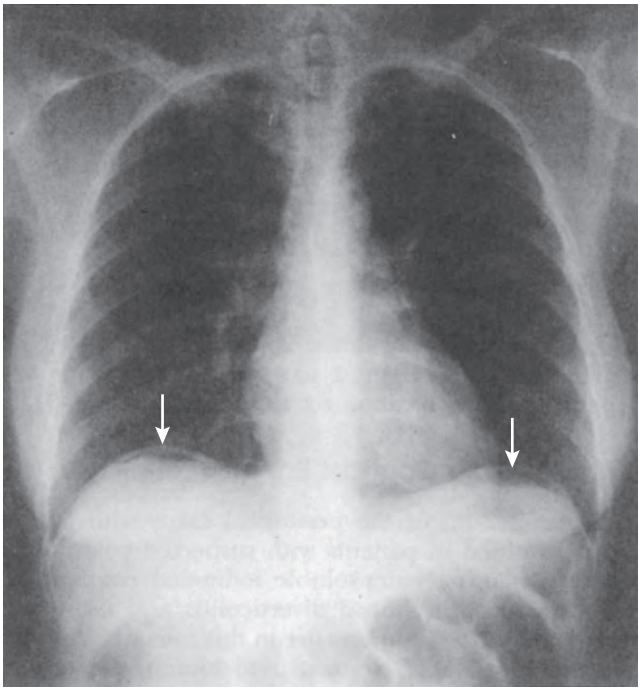


Figure 136–5. Erect chest film showing free air in the abdomen under the diaphragm *(arrows).* (Courtesy of Ruedi F. Thoeni, MD.)

content of the structures. Normally, the stomach contains at least some gas, whereas a fair amount is distributed throughout the large bowel, especially the hindgut portion. In the healthy ambulatory adult, the small intestine occupies the center of the peritoneal cavity and contains little or no gas, but bedridden adults often demonstrate considerable amounts of small bowel gas without any causative abdominal pathology. The large bowel usually frames the abdomen, and parts of colon sometimes contain semisolid feces mixed with bubbles of gas that create a distinctive speckled shadow; these speckled fecal shadows are not seen in the small intestine. Abnormalities in the usual character and pattern of radiolucencies should alert the physician to potential intra-abdominal disease processes.

Colonic Transit Study The indications for and interpretation of a colonic transit study are thoroughly discussed in Chapter 135. Briefly, the test was initially designed as a method to measure whole and segmental gut transit with radiopaque markers and serial plain radiographs. Alternatively, radioisotopes that emit gamma radiation can be used, but this method is more time-consuming.

Single-Contrast Barium Enema As alluded to earlier, soft tissue differentiation is limited on plain radiography by subtle differences in radiolucency. A radiopaque agent can enhance the interpretation of these studies by outlining the large bowel and its mucosa (Fig. 136–6). A liquid that contains low concentrations of barium sulfate has been used for nearly a century to visualize the colon and rectum and to demonstrate its configuration. The

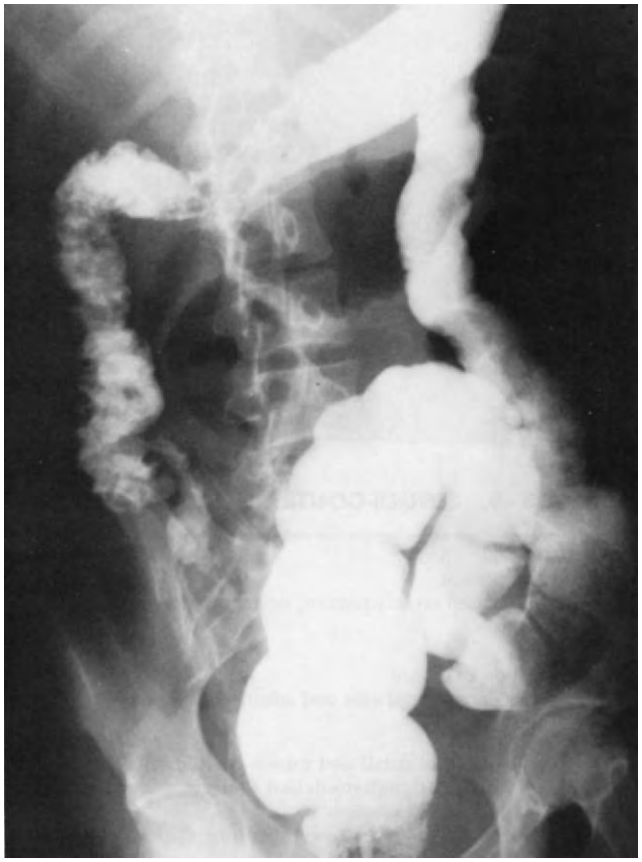


Figure 136–6. Single-contrast barium enema demonstrating Crohn's disease involving right colon and distal ileum (oblique view). (Courtesy of Henry I. Goldberg, MD.)

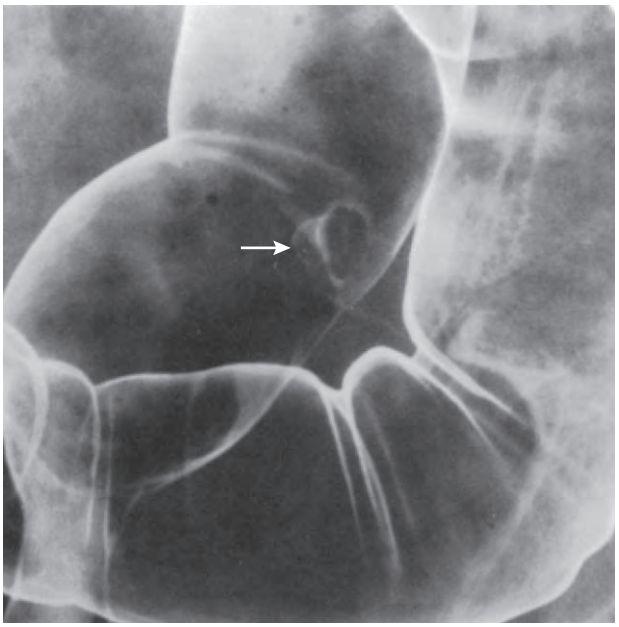


Figure 136–7. Double-contrast barium enema showing a colonic polyp *(arrow).* (Courtesy of Ruedi F. Thoeni, MD.)

bowel must be viewed in different projections, and subtle abnormalities are discernible only when the beam is passing tangential to the bowel edge. Otherwise, lesions are visible only if they are large enough to displace enough barium that the beam absorption is significantly reduced. Compression of the bowel and postevacuation films can somewhat compensate for this limitation, but the results are still less than desirable. Nearly one third of filling defects seen on single-contrast barium enema are found to represent mere artifacts when colonoscopy is subsequently performed. Similarly, a large number of lesions are missed by the technique, especially smaller (<1 cm) polyps.[20] Good bowel preparation is pivotal to an accurate examination because retained residue and stool reduce the specificity of the study. The procedure is still used routinely for patients who would have difficulty with colonoscopy or double-contrast barium enema, such as the aged, seriously ill, and disabled persons. Moreover, a single-contrast barium enema is the procedure of choice for the evaluation of fistulas and the exclusion of obstruction, assuming that concomitant perforation is unlikely. Perforation is the most common (0.01%) complication associated with barium enema, and it usually occurs when there is weakness of the bowel wall secondary to the underlying disease, traumatic insertion of the enema tip, overinflation of the rectal balloon, or excessive hydrostatic pressure associated with the study. Unfortunately, perforation and barium peritonitis confer a high mortality rate because barium concretions that contain small foci of viable bacteria are dispersed through the peritoneal cavity and cannot be adequately cleared.

Double-Contrast Barium Enema The double-contrast barium enema was designed to overcome some of the shortcomings associated with the single-contrast study, such as identification of small polyps and diagnosis of colitis (Fig. 136–7). Even more than the earlier-generation single-contrast study, the double-contrast barium enema relies on good bowel preparation to clear all stool and residue. A combination of dietary manipulation, oral hydration, cathartics, and optional enemas is recommended. The procedure is performed in a relatively standard manner in which barium is run into the transverse colon and the bowel is then distended with air. The patient is rolled into various positions so gravity and palpation can manipulate the barium column around the entirety of the large bowel that is continuously distended with air. Multiple spot and overhead films are generated and collected to create a composite evaluation of the adherence of the contrast agent to the large bowel.

Few clinicians will argue that double-contrast barium enema is simpler, safer, and less expensive than colonoscopy. However, even under ideal conditions with interpretation by experienced radiologists, the double-contrast barium enema is inferior to colonoscopy for the detection of CRC and polyps. Historically, the sensitivity of the procedure for detecting polyps smaller than 5 mm was poor, improving with polyps of 5 to 9 mm and best for polyps larger than 1 cm. According to a literature

review, the sensitivity for these larger polyps is approximately 80% and the specificity is approximately 95%.[21] Although the overall sensitivity of a double-contrast study for the detection of CRCs ranges from 80% to 100%, nearly one fourth of the rectosigmoid carcinomas will be missed. The combination of sigmoidoscopy with double-contrast barium enema overcomes some of the deficiencies but adds costs and risks to screening.[22]

As part of the National Polyp Study, a prospective, blinded trial studied the relative accuracy of double-contrast barium enema compared with colonoscopy in 580 patients.[23] The sensitivity for the detection of advanced (>1 cm) adenomas of the contrast study and colonoscopy was 46% and 100%, respectively. The investigators concluded that colonoscopy detects many more adenomas than double-contrast barium enema and that the combination of the two studies adds little to the use of colonoscopy alone. The benefits and limitations associated with imaging and endoscopy will continue to fuel the debate that ensues when the indications for double-contrast barium enema and colonoscopy are discussed.

Water-Soluble Contrast Enema A water-soluble contrast enema with Gastrografin or Urografin is favored over a barium study when the risk of perforation is at all likely because the water-soluble compounds will not cause the peritonitis mentioned earlier. Instead, the water-soluble agents are absorbed so that no peritoneal reaction ensues. The low viscosity of the agents makes them more likely than barium to identify fistulas and anastomotic leaks, but the clarity of the images is compromised, because these hypertonic, water-soluble compounds quickly become diluted. This hypertonicity feature can also be therapeutic, because diarrhea usually occurs after the study, which may be helpful in patients with pseudo-obstruction. However, for the same reason, the agent can be detrimental in persons with obstruction because rare perforation might result from the massive amounts of fluid that can be drawn into the closed segment of bowel proximal to the obstructing lesion. In addition, dehydration might result in some individuals but is unlikely when small (<500 ml) volumes of contrast material are used.

Contrast Fistulography Contrast fistulograms may provide valuable information and alter the treatment of select patients. Anal fistulas are rarely assessed with fistulography, but the modality can be useful for persons with chronic complex fistulas and suspected extrasphincteric fistulas. More often magnetic resonance (MR) imaging or endorectal ultrasound (ERUS) is used to best discern anal fistula anatomy.[23] Conversely, reliable information can be gleaned from fistulography performed for an enterocutaneous fistula. The test is usually part of a group of investigations and should be performed before any other imaging examinations because retained barium can obscure the fistulography results. A small Foley catheter is inserted as deep as possible into the tract, and the balloon is inflated to secure the position of the catheter, seal the tract against reflux of contrast medium, and allow opacification of the entire proximal tract. Water-soluble contrast material should be used, and spot films are obtained perpendicular to the fistula tract.

Vaginography is indicated when a rectovaginal or colovaginal fistula is suspected and a water-soluble enema failed to identify the communication. The test is performed in a manner similar to fistulography with a large Foley catheter used to occlude the vaginal introitus. Cystograms uncommonly identify enterovesical or colovesical fistulas. Instead, a bladder deformity is often seen, which suggests an extrinsic mass or inflammatory process that often accompanies the fistula. Again, MR and ERUS are more sensitive imaging modalities.

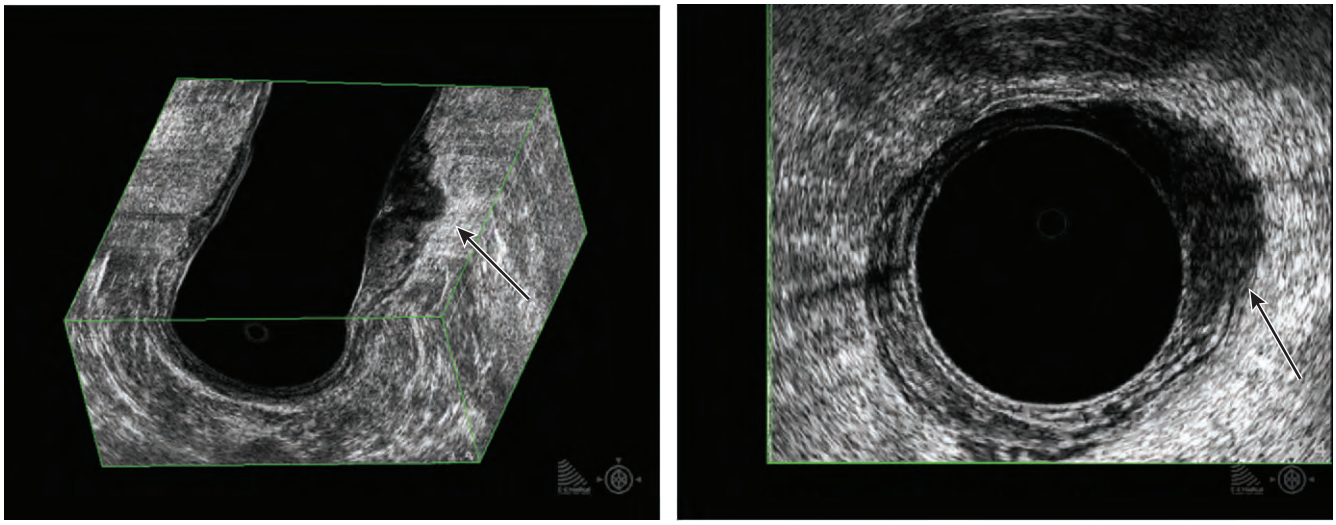
Defecography Evacuation proctography is used to study the dynamics of voluntary rectal evacuation, and techniques vary considerably. The indications for and interpretation of defecography are thoroughly discussed in Chapter 139.

Endoluminal Ultrasound Without radiation exposure, ERUS provides excellent evaluation of the distal colon, rectum, and anal canal. Rivaled only by MR with endorectal coil, ERUS shows details of anorectal anatomy, benign disorders, and malignant tumors (Fig. 136–8).

Typically performed after an enema preparation, rigid, 10-MHz endoscopy using endoluminal contact for structure definition is used to evaluate fecal incontinence, rectal cancers, and perianal inflammatory conditions. Evaluation of ill-defined anal pain and anal cancers are also indications. Obstetric injuries to the sphincters, occult and complex fistula tracts, and perianal Crohn's disease additionally are clarified by ultrasound examination.

In regard to cancer, ERUS is used for tumor staging. The examination is performed with either a rigid or flexible probe and stages all cancers with more than 70% accuracy compared to surgical specimen. Ultrasound is the least accurate for bulky T4 tumors, and nearly 20% of all tumors may be over-staged. But as an available modality used to guide preoperative neoadjuvant therapies, ultrasound is the gold standard.[24] The flexible endoluminal ultrasound allows for evaluation of low colon cancers and higher rectal tumors than the rigid transducer probe. By this flexible probe technique, the iliac nodal basin is also evaluated. Biopsy of tumors and suspicious nodes is possible through a side port on either the rigid or flexible probe. The flexible probe technology is less widely available and performed than the rigid method. Radiologists, gastroenterologists, and colorectal surgeons perform the rigid examination, whereas the flexible method is predominantly performed by gastroenterologists at larger centers.

CT Scanning Computed tomographic (CT) scanning is useful in the diagnosis of benign and malignant diseases of the colon, rectum, and anus (Fig. 136–9). Its role in the diagnosis and management of diverticulitis is unparalleled because it identifies extraluminal disease and features of severe inflammation (e.g., extraluminal gas and contrast, abscess) that predict or define a complicated disease course. Inflammatory bowel diseases are associated with nonspecific findings such as bowel wall



A B

Figure 136–8. **A** and **B,** Endorectal ultrasound showing stage T3 rectal cancer *(arrows).* (Courtesy of B-K Medical, Herlev, Denmark.)

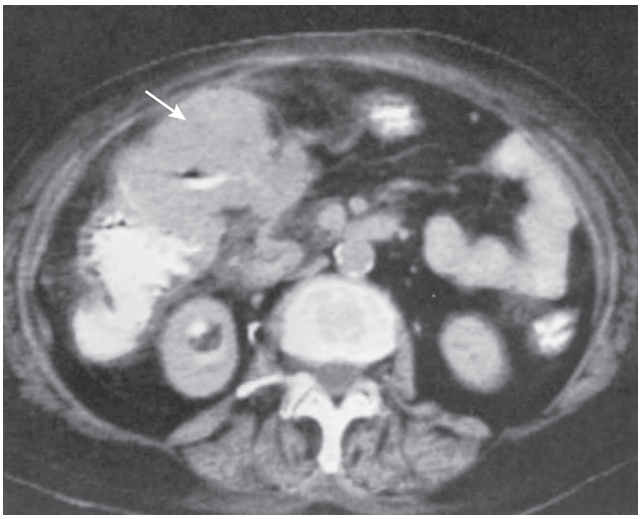


Figure 136–9. Abdominal CT scan showing carcinoma of hepatic flexure of the colon *(arrow).* (Courtesy of Ruedi F. Thoeni, MD.)

thickening on CT scanning, but again, extraluminal disease can be visualized. Right lower quadrant masses in Crohn's disease, for instance, caused by terminal ileal inflammation can be readily distinguished from abscesses related to perforative disease. Last, the role of CT in the diagnosis and treatment of complex anoperineal sepsis is evolving as experience grows but is typically disappointing because the levators are not well defined and sphincter resolution is poor.

Although conventional CT scanning is insensitive for the diagnosis of intraluminal CRCs, it is still useful in evaluation of the patient with a known malignancy because it can demonstrate extracolonic spread to adjacent and remote organs. This knowledge might significantly alter the planned clinical and operative management of the primary lesion. CT scanning also might play a role in the postoperative surveillance and identification of suspected disease recurrence (see later).

CT Enterography CT enterography and CT colonography (so-called virtual colonoscopy) provides an effective means of imaging the bowel. The procedure requires adequate bowel preparation and low-dose, high-resolution helical CT imaging. The patient is initially placed in the supine position, and a barium enema tip is placed transanally to allow inflation of the large bowel with air or carbon dioxide to maximum patient tolerance. After adequate distention is ensured with a localizing CT scout, a helical CT scan of the abdomen and pelvis is performed. The procedure is then repeated in the prone position.

This minimally invasive approach to bowel evaluation provides information about the entire bowel, particularly sensitive for inflammatory abnormalities and larger cancers. Crohn's disease and rare tumors of the small bowel may be found with this modality (Fig. 136–10). Used for CRC screening, CT colonography has the advantages of no sedation or recovery time. Only low-dose radiation exposure is required for this test, which can also provide three-dimensional reconstructions of the bowel and any observed abnormalities.

Reports of sensitivity for lesions greater than 1 cm have ranged from 55% to 90% when compared with colonoscopy. Flat lesions, easier to miss on colonoscopy, are reportedly detected with nearly 70% sensitivity, 100% greater than 4 mm being detected.[25] A review from St. Mark's Hospital reports the American Cancer Society Colorectal Cancer Advisory Group recommendations of CT colonography as a promising technique, which is not yet endorsed as a screening tool.[26]

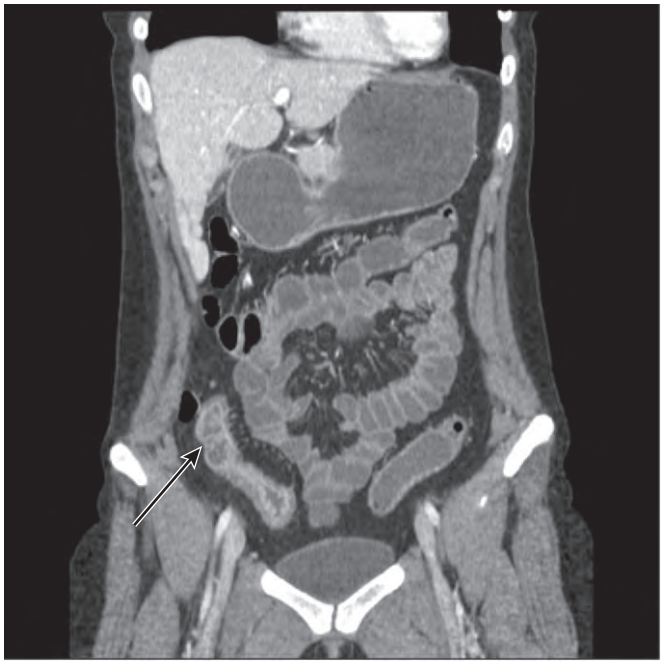


Figure 136–10. Crohn's disease of the terminal ileum *(arrow)* as seen on CT enterography.

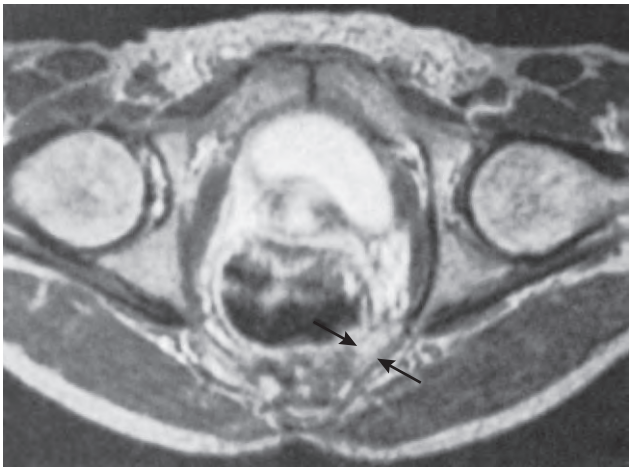


Figure 136–11. MR imaging of pelvis demonstrating recurrent carcinoma *(arrows)* after anterior resection of rectal adenocarcinoma. (Courtesy of Ruedi F. Thoeni, MD.)

MR Imaging MR imaging is one of the more recent modalities used to study structural and functional disorders of the anus, rectum, colon, and surrounding structures (Fig. 136–11). The examination is typically used to focus on an area of abnormality rather than to survey the entire abdomen and pelvis, like CT scanning. Usually, T1- and T2-weighted images are obtained in the axial plane with coronal, oblique, and sagittal planes selected when necessary to view a particular area of interest. Gradient-echo images depict flowing blood and make lesions more distinct, whereas chemical shift images determine the fat content of a lesion. Similar to contrast-enhanced CT scans, gadolinium-based contrast agents are used intravenously to demonstrate vascularity and enhance lesion patterns. In addition, various radiofrequency coils can be used depending on the anatomic structure that is to be imaged. External and internal coils that are relevant to imaging in this area include the body, surface (abdomen- or pelvis-phased multicoils), and endorectal coils. In general, higher resolution is seen with the smaller viewing fields because the dedicated coils are placed closer to the region of interest and this increases the signal-to-noise ratio.

MR imaging is used in the diagnosis of benign colorectal conditions. MR imaging more accurately delineates structural defects of pelvic floor disorders and of anal fistulous disease than does plain film or CT.[23] In addition, MR imaging is more useful than digital examination in the diagnosis and differentiation of ischioanal and perirectal abscesses.[27] MR imaging is also commonly used in the diagnosis of malignant colorectal disease. Staging of rectal cancer by MR is used to guide neoadjuvant therapy and allows for accurate restaging preoperatively.[28] This modality is also efficacious in the evaluation of metastatic liver disease and recurrent rectal cancer, especially when adjacent organ or bony invasion is suspected.

Positron Emission Tomography Just as MR can provide a three-dimensional image through reconstruction, emission imaging allows for a three-dimensional representation of distribution to be created. If a single photon emission is studied, such as technetium or thallium, a single-photon emission CT (SPECT) test is possible. The details of tests such as a SPECT are discussed with nuclear medicine tests.

PET using ^{18}F-fluorodeoxyglucose (FDG-PET) is indicated in the evaluation of patients with known or suspected recurrent CRC. Because positron emission tomography (PET) images can help differentiate postoperative changes from recurrent or residual tumor, this modality is particularly useful in the early postoperative period. FDG-PET can be used as a screening tool, though prohibitive costs and restricted availability have led to limited indications including evaluation of increased CEA levels without an obvious tumor recurrence or preoperatively for the exclusion of widespread disease in a patient with one known area of recurrence. Where available, CT-PET fusion tests provide the most powerful integrated images (Fig. 136–12).[29]

Nuclear Medicine Imaging Nuclear medicine imaging uses various radioisotopes (e.g., ^{131}I, ^{111}In, ^{99m}Tc) that are bound to a variety of materials and cells, including monoclonal antibodies, leukocytes, and erythrocytes (Fig. 136–13). After intravenous injection or ingestion of the radiolabeled compounds, the patient is imaged with a gamma camera designed for the 140-MeV energy at one or several time points. This modality can be used to evaluate a variety of disease processes, including the detection of metastatic cancer, the identification of bowel infection or inflammation, the localization of intestinal hemorrhage, and the measurement of colonic transit.

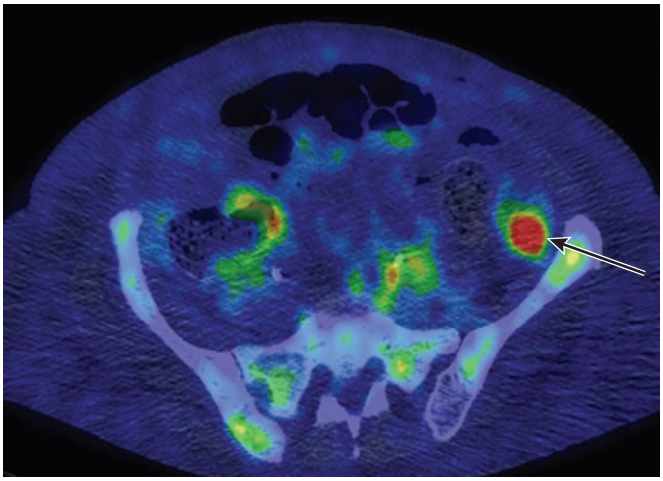


Figure 136–12. Left pelvic tumor *(arrow)* seen by positron emission tomography–CT adjacent to the descending colon at the level of the iliac spine, which was found after normal colonoscopy and examination in a patient with a history of colorectal cancer and a rising carcinoembryonic antigen level.

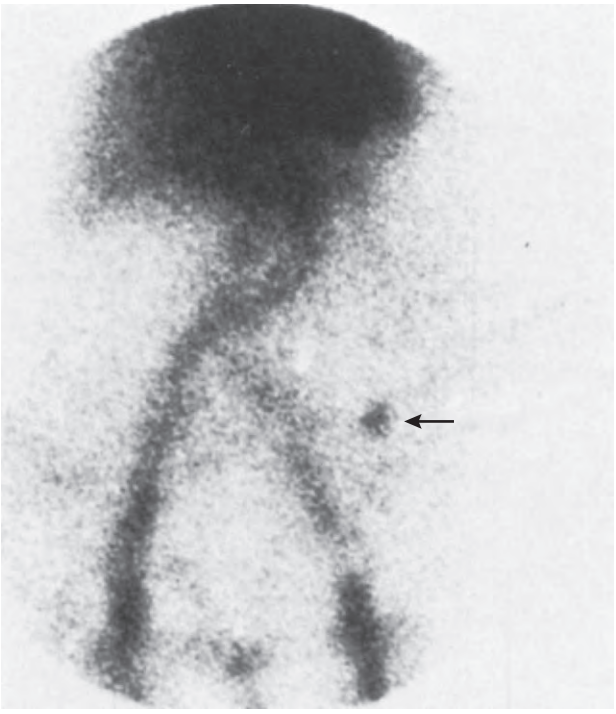


Figure 136–13. ^{99m}Tc red blood cell scan showing abnormal activity in area of sigmoid colon *(arrow)* 10 minutes after injection. Lesion subsequently proved to be a bleeding diverticulum. (Courtesy of Barry L. Engelstad, MD.)

These uses are discussed elsewhere in detail, but their use in the diagnosis of disease deserves brief comment.

Radionuclide imaging of colon malignancies must be interpreted in conjunction with review of findings from physical examination and other investigative studies. The reported sensitivities of monoclonal antibody staging of CRC varies from 65% to 86%, with specificities for the detection of primary, metastatic, and recurrent disease ranging from 77% to 92%.[30] Thus, this principal contribution of the modality in the management of CRC lies in its ability to target potential sites of occult tumor and confirm the absence of distant metastases in persons with disease amenable to resection. At this time, most clinicians would not base treatment solely on the outcome of a nuclear medicine scan.

Radiolabeled white blood cell scans can reliably contribute to the evaluation of a postoperative patient who develops fever and in the assessment of inflammatory bowel disease,[31] but the use of other radiolabeled agents in these scenarios is still under investigation. Similarly, radionuclide-based colonic transit assessment may contribute to an improved understanding of normal and abnormal colonic motility and might assist in the management of disorders such as idiopathic constipation, fecal incontinence, and megarectum.

For many surgeons, the most common indication for radionuclide imaging involves the management of intestinal hemorrhage. Most early series reported sensitivities of more than 90% for the detection of bleeding with radionuclide scans.[32] Because this sensitivity was higher than that reported with angiography, it was recommended that a radionuclide study be performed before arteriography to identify a source of bleeding. The implication was a negative scan would dismiss the usefulness of emergent angiogram. However, several reports have produced compelling data (radionuclide scan sensitivity of 20% to 46%) that contradict this practice.[33] These series suggest that the value of the ^{99m}Tc-labeled red blood cell scan as a screening tool before arteriography is questionable and that the scan is a poor diagnostic test for the localization of LGIH. This apparent discrepancy arises from the manner in which the sensitivity rate was calculated in the early compared with the late studies. In the early reports, patients who presented with bleeding but whose scans were negative and did not rebleed were assumed not to be bleeding and were excluded from the sensitivity denominator. Conversely, the late series included all patients with documented significant hemorrhage, regardless of the scan result. This latter practice clearly lowers the sensitivity rate but probably is a more reliable measurement. A yield of less than 50% accuracy for a study with possible complications (most important, delayed diagnosis) has led to the abandonment of scintigraphy in the management of lower intestinal hemorrhage in favor of mesenteric angiography or colonoscopy, which can be both diagnostic and therapeutic.[34]

Intestinal transit can be measured using a radiolabeled nonabsorbable marker in solid food. The particulars of this method are thoroughly discussed in Chapter 135.

Mesenteric Angiography Mesenteric angiography may be performed by specially trained vascular surgeons or interventional radiologists and is commonly used to identify the source of intestinal hemorrhage and to determine acute arterial occlusion of the main visceral trunks (Fig. 136–14). Discussed in Chapter 145 on gastroin-

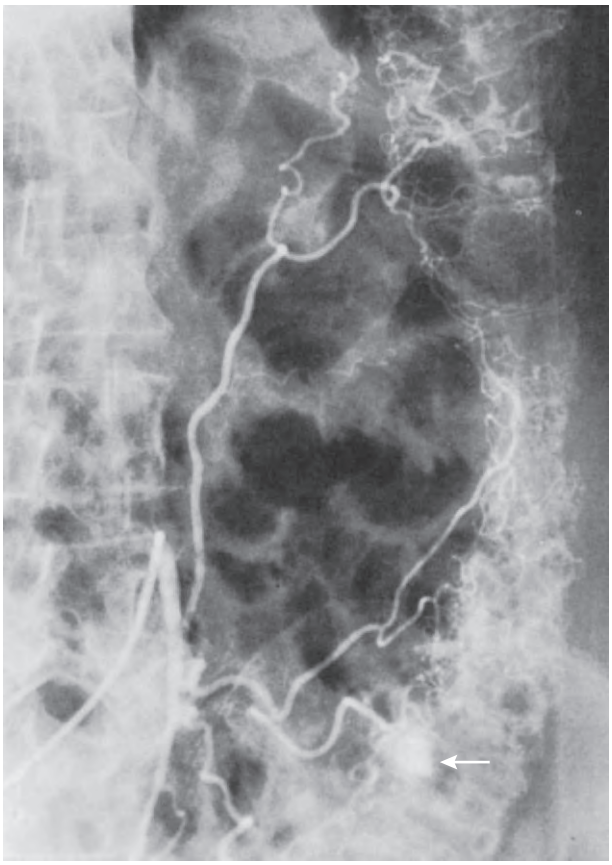


Figure 136–14. Selective inferior mesenteric arteriogram demonstrating bleeding site in sigmoid colon *(arrow).* (Courtesy of Ernest J. Ring, MD.)

testinal bleeding, the application of mesenteric angiography specific to colorectal bleeding is briefly covered here. The important role of mesenteric angiography in the management of lower intestinal hemorrhage is as a diagnostic and possibly interventional tool. The key to successful localization of bleeding is early, prompt arteriography in the face of active, massive bleeding. The timing is crucial because angiography best identifies the site of bleeding when the bleeding occurs at a rate exceeding 0.5 ml/min. Aggressive pharmacologic techniques with systemic heparinization, selective intra-arterial vasodilators, and/or thrombolytic agents have been used to prolong or reactivate bleeding in an attempt to improve the diagnostic yield.

Although the yield of bleeding site localization by angiography in acute lower gastrointestinal bleeding is low relative to the reported complications, if selective embolization is possible, clear benefits exist. Local injection of vasopressin at the mesenteric site of hemorrhage can be attempted. This technique can successfully arrest bleeding in more than 80% of cases, although rebleeding occurs in nearly half.[35,36] Selective transcatheter coil embolization is successful in at least 70% of cases, but there is a 6% to 22% risk of clinically significant ischemia and infarction. Stabilization in the acutely bleeding patient by interventions in the angiography suite may allow for medical optimization and bowel preparation before an urgent, rather than emergent, surgery.[37,38]

Arteriography also is the procedure of choice for the diagnosis of acute mesenteric ischemia. MR arteriography and CT arteriography are sensitive for diagnosis and carry less risk than arteriography, but the ability to perform simultaneous diagnosis and therapy initiation in the emergent setting make arteriography superior. Flush abdominal aortography with anteroposterior and lateral projections may visualize the main vascular trunks, but selective angiography, especially with digital subtraction, defines the artery and its branches. Moreover, this latter modality can differentiate among the three principal causes of acute ischemia and allows medical or mechanical revascularization without laparotomy in some instances. Chronic mesenteric ischemia, however, is better evaluated with noninvasive procedures such as abdominal duplex ultrasonography, laser Doppler flow analysis, and MR imaging.

Tests of Pelvic Floor Function The diagnosis and treatment of pelvic floor dysfunction are discussed more thoroughly in Chapter 139. Anorectal manometry quantifies the luminal pressures in the anus and rectum to provide a direct measure of internal and external sphincter function. Microballoon systems, water-perfused catheters, or solid-state transducers can be used to measure these pressures, but each laboratory should establish its own standards. Balloon distention or mucosal electrosensitivity testing can evaluate rectal sensitivity. Defecography is used to diagnose anatomic abnormalities such as symptomatic internal intussusception and rectocele. Pudendal nerve damage can accompany chronic defecation disorders and is best elucidated with tests of motor and sensory conduction. Colonic inertia must also be excluded in these patients, and normal colonic transit should be documented.

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Chapter

137

Ultrasonographic Diagnosis of Anorectal Disease

Dimitra G. Barabouti · W. Douglas Wong

Endorectal ultrasound (ERUS) is the diagnostic procedure of choice in the evaluation of many anorectal disorders. It is the best imaging modality for local staging of rectal and anal cancer and has an important role in surveillance for local recurrence. ERUS is used in the diagnosis of benign mucosal lesions, extrarectal masses, anal incontinence, fistula-in-ano, and anorectal abscesses. It is a valuable tool in the office setting, where it is performed by the surgeon, providing information essential for treatment decisions. In this chapter, we focus on the role of ERUS in the evaluation of benign and malignant conditions of the rectum and anus.

Technique

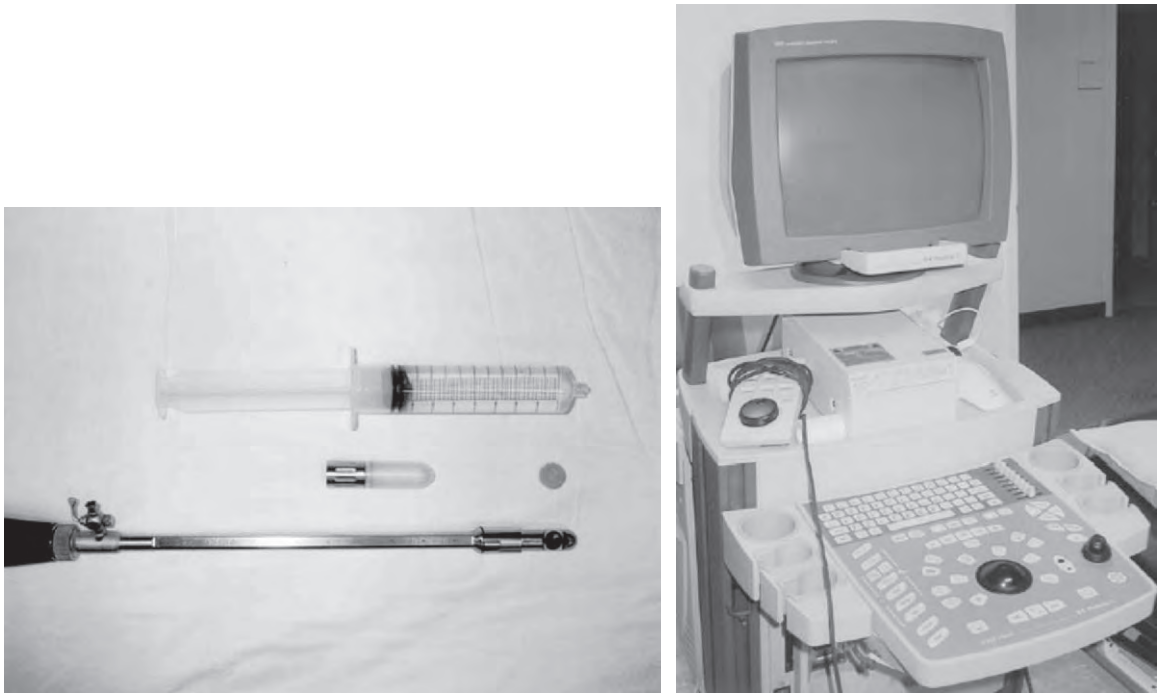
ERUS requires minimal patient preparation with two enemas the morning of the examination. The test is well tolerated, without need for sedation. Patients are preferably examined in the left lateral decubitus position. For rectal cancer staging, we perform a digital rectal examination (DRE) to determine the location of the tumor and its relation to the anorectal ring. We then evaluate the rectum using a 20-mm wide rigid proctoscope (ElectroSurgical Instrument Company, Rochester, NY) to document the morphologic characteristics of the lesion (size, distance from the anal verge, location on the rectal wall, and appearance) and to ensure that a complete sonographic evaluation can be performed. At this time residual stool, mucus, and enema effluent are removed to avoid image artifacts.

It is important to advance the proctoscope proximal to the lesion, to facilitate complete imaging of the lesion from its most proximal to its most distal extent. The examination is complete only when the entire length of the tumor is imaged, because the findings at the lower end of the tumor may differ markedly proximally. Moreover, positive lymph nodes, when present, are most commonly found in the mesorectum proximal to the lesion. Blind insertion of the ultrasound probe into the rectum may distort the lesion, miss proximal areas of the tumor and surrounding mesorectum, and cause discomfort to the patient.

At Memorial Sloan-Kettering Cancer Center (MSKCC) we use a Brüel & Kjaer (B & K) 2101 Hawk (Naerum, Denmark) scanner with an 1850 rotating endosonic probe and a 10-MHz 6004 transducer (Fig. 137–1). We also use a 2050 probe with capability for 10-, 12- or 16-MHz (multifrequency transducer). The 10-MHz transducer with a focal length of 1 to 4 cm is the one most commonly used, providing superior near-image clarity and excellent visualization of the perirectal tissues. A 7.0-MHz transducer, which provides a focal length of 2 to 5 cm, may be used if there is a need to evaluate deeper structures. A 90-degree scanning plane is rotated at four to six cycles per second to provide a 360-degree radial scan of the rectum and surrounding structures. We use the rigid ultrasound probe, because we find it provides better maneuverability and optimizes the image. However, a rigid probe cannot evaluate areas more than 12 to 15 cm from the anal verge. Flexible endosonoscopes are also available. Steele et al. compared the two probes, with results suggesting a more reliable learning curve for the rigid devices and less accuracy of the flexible devices for visualizing depth of invasion.[1]

Once the proctoscope is advanced above the tumor, the ultrasound probe is lubricated and inserted gently through the proctoscope, allowing the transducer to be advanced above the cancer. The proctoscope is then pulled back and the balloon over the ultrasound crystal is instilled with fluid. The amount of fluid is estimated based on the luminal diameter from proctoscopy, patient discomfort, and ability to pass the balloon beyond the lesion. For the 1850 probe, 30 to 60 ml is used on average, whereas the 2050 probe usually requires between 90 and 120 ml. It is important to make sure no air bubbles are present, to minimize acoustic impedance.

The key to the procedure is to keep the probe centered in the lumen of the rectum. Scanning is best conducted from proximal to distal. The probe and attached



A B

Figure 137–1. **A,** Brüel & Kjaer rotating endosonic probe with a 10-MHz 6004 transducer, with balloon and hard cap shown. **B,** Brüel & Kjaer Hawk 2102 unit. (**A** and **B,** Courtesy of Brüel & Kjaer, Inc., Naerum, Denmark.)

proctoscope are slowly withdrawn together, assessing the mesorectum for evidence of nodal metastases and the tumor for depth of penetration. Optimal evaluation often requires several passes back and forth across a lesion or a suspected lymph node. Measurements of lymph nodes' size and tumor dimensions are made, including any radial extension of tumor into the perirectal fat.

Endoanal ultrasound (EAUS) is used to evaluate disease in the anal canal. In the case of malignancy, EAUS follows the assessment of the mesorectum with the balloon for nodal metastases. A fluid-filled, hard translucent plastic cap is used rather than the balloon. The ultrasound transducer is then inserted into the anal canal without a proctoscope.

Ultrasonographic evaluation of the anorectum is based on real-time imaging. We routinely videotape all examinations and have found this to be helpful in the review of difficult cases. Spot images may be copied and printed. These are useful for documentation and for following suspicious areas.

Normal Endorectal Ultrasound Anatomy

The five-layer model for ERUS anatomy was proposed by Beynon et al. in 1986 and is the one used today. Beynon and colleagues demonstrated that the proposed five ultrasonic layers correspond to the anatomy of the rectal wall by correlating in vitro ultrasound scanning and sequential microdissection of the normal layers of the rectum from operative specimens.[2]

In this model, the first and innermost line encountered is hyperechoic (white), representing the interface between the fluid-filled balloon and the mucosa. Next is the first hypoechoic (black) line, which represents the mucosa and the muscularis mucosa. The middle hyperechoic (white) line represents the submucosa. The next hypoechoic line correlates to the muscularis propria. The third and outermost hyperechoic line represents the interface between the muscularis propria and the perirectal fat (Fig. 137–2). Occasionally, a seven-layer model may be visualized in which the muscularis propria is observed as two black rings separated by a white ring. In this case, the inner circular and outer longitudinal layers of the muscularis propria appear as two distinct hypoechoic (black) layers, separated by a hyperechoic interface. In addition to the rectal wall, the mesorectum, urinary bladder, cul-de-sac and its contents, seminal vesicles, prostate, uterus, vagina, and cervix are visualized with ERUS. The ultrasonographic appearance of the normal rectal wall is depicted in Figure 137–3.

RECTAL CANCER

Accuracy of ERUS in the Local Staging of Rectal Cancer

Accurate preoperative staging is necessary to determine prognosis and select optimal treatment for patients, in terms of cure and quality of life, for patients with rectal cancer. Knowledge of the depth of rectal wall invasion and perirectal lymph node involvement is essential to

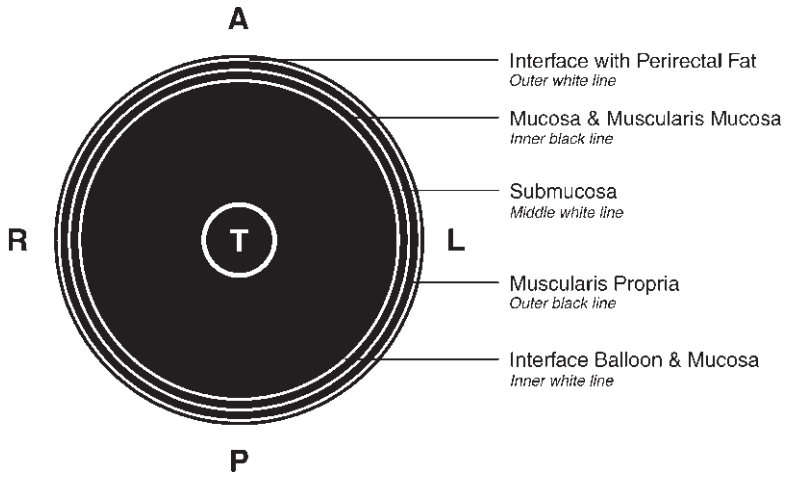


Figure 137–2. Five-layer anatomic model for interpretation of endorectal ultrasonographic scans. Three hyperechoic (*white*) layers and two hypoechoic (*black*) layers can be visualized. A, anterior; L, left; P, posterior; R, right; T, transducer.

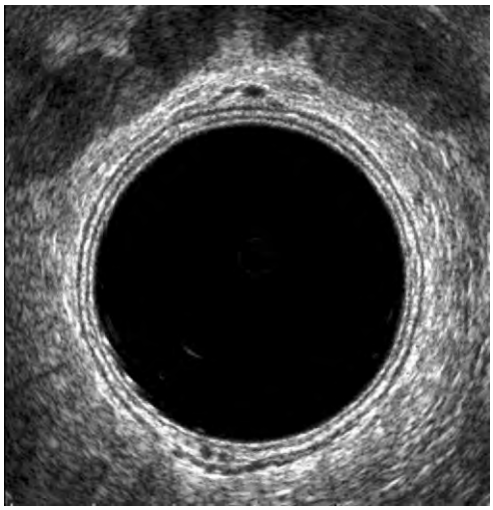


Figure 137–3. Normal rectal wall. Three hyperechoic (*white*) and two hypoechoic (*black*) layers are clearly visualized in the ultrasonographic image of the normal rectal wall. The seminal vesicles are seen anteriorly as bilateral hypoechoic structures.

select early cancers amenable to local excision and identify locally advanced cancers that are treated with neoadjuvant chemoradiotherapy. DRE, ERUS, computed tomography (CT), and magnetic resonance imaging (MRI) have been applied in the local staging of rectal cancer, and their diagnostic accuracy has been evaluated by comparing results to the final pathologic staging from surgical specimens.

DRE by an experienced surgeon is an important part of the evaluation of the patient and may predict pathologic stage, particularly for advanced tumors. However, DRE is subjective; it cannot assess tumors in the proximal third of the rectum, and it is unreliable in staging early lesions. The accuracy of DRE versus ERUS for the staging of rectal cancer was compared in a prospective study by Rafaelsen et al.[3] They found that ERUS demonstrated significantly more accuracy in staging rectal cancer, particularly in the setting of less advanced tumors. Moreover, ERUS successfully detected 11 out of 19 regional lymph node metastases as opposed to DRE, which detected none. Beynon studied 100 patients with ERUS; 76 had palpable tumors, but only 46 of these were also assessed by DRE for depth of invasion. The accuracy of DRE was 58% compared to the 93% accuracy shown by ERUS.[4] The accuracy of ERUS in predicting nodal involvement was 83%. Other studies have also demonstrated an accuracy with DRE in the range of 68% to 88% for reachable lesions.[5-8] Overall, it is well established that DRE is less accurate compared to other methods and should rarely be used alone in the local staging of rectal cancer.

CT is routinely used in the preoperative staging of rectal cancer and is particularly useful in detecting contiguous organ involvement and distant metastases. Its accuracy in local staging, however, appears to be relatively low. Beynon reported an accuracy for CT of between 74%[4] and 82%[5] for depth of invasion and 57% for nodal involvement.[4] Goldman et al. compared CT and ERUS in 32 patients and found accuracy rates of 52% and 81%, respectively, for perirectal fat invasion, and 64% and 68%, respectively, for lymph node involvement.[9] Similar results were reported by Herzog et al.[10] In 87 patients, ERUS was accurate 91% of the time in assessing depth of invasion, whereas CT was accurate 74% of the time. ERUS was 81% accurate in predicting nodal disease. It is possible that advances in technology will increase the accuracy of CT in detecting local invasion and nodal disease. Recently, Kulinna et al. evaluated the accuracy of multislice CT (MSCT) with double-contrast (rectal and intravenous) and three-plane reconstruction in 92 patients.[11] A subgroup of 63 patients was also evaluated with ERUS. The accuracy of MSCT for depth of invasion was 86%, compared with the 60% accuracy of ERUS. The accuracy rate of MSCT for nodal disease was 81%, compared with 65% for ERUS.

MRI is another modality used in the staging of rectal cancer. Starck et al. compared plain MRI with ERUS in 35 patients in 1995.[8] MRI had lower accuracy than ERUS in the detection of tumor penetration (66% vs. 88%, respectively), and similar accuracy in nodal evaluation

(72% and 71%, respectively). The addition of new technology to conventional MRI has improved its anatomic definition and diagnostic accuracy. Schnall et al. examined 36 patients using MRI with endorectal coil (ERC-MRI).[12] The MRI stage agreed with pathologic findings in 81% of the cases. Although sensitive for demonstrating perirectal lymph nodes (nodes as small as 2 mm were visualized), ERC-MRI had a specificity of only 72% for nodal disease.

In 1999, Kim et al. reported on 89 patients; ERUS and ERC-MRI were equivalent, and superior to CT, with an accuracy of 81% versus 65% in staging depth of invasion.[13] In staging lymph node metastasis, the rates were 63% (ERUS and ERC-MRI) versus 56% (CT). In 2000 the same group published their experience with contrast-enhanced MRI for the preoperative staging of 217 patients with rectal cancer and reported similar accuracy rates (81% for T stage, 63% for N stage).[14] Hunerbein et al. compared ERUS, three-dimensional ERUS (3D-ERUS) and ERC-MRI in 25 patients and found comparable accuracy between the three modalities for evaluating depth of invasion (84%, 88%, and 91%, respectively).[15] ERUS and ERC-MRI assessed the lymph node status correctly in 80% and 89% of the patients, respectively. The duration of the MRI examination, including placement of the coil and application of the contrast agent, was between 60 and 75 minutes. The time required for ERUS and the acquisition of 3D scans was shorter, ranging from 10 to 15 minutes.

The endorectal coil device has larger diameter than the ultrasonic probe. This sometimes limits its use in the setting of locally advanced rectal cancers. New MRI techniques aiming to avoid the disadvantages of the endorectal coil have been developed and evaluated in small studies. Pelvic phased-array coil (PA) MRI uses external coils without an endorectal probe to assess rectal tumors. Matsuoka et al. in 2003 compared the ERC-MRI with PA-MRI in 19 patients.[16] Only 10 patients were evaluated with the ERC-MRI, because of difficulties in the placement of the endorectal coil. The PA-MRI could be obtained in all patients. In the 10 patients examined with both modalities, the diagnostic accuracy of depth of invasion was the same (80%). In lymph node staging, ERC-MRI yielded an accuracy of 70%, and PA-MRI yielded an accuracy of 90%. In 2004 the same group evaluated 54 patients with rectal cancer (4 with gadolinium-enhanced endorectal coil and 50 with an air-enema technique).[17] Gadolinium-enhanced ERC-MRI accurately diagnosed depth of tumor invasion in all 4 patients and accurately diagnosed nodal disease in 75% of cases. The air-enema MRI had promising results, with an accuracy of 82% in staging depth of invasion and 72% in detecting lymph node metastasis.

There are two meta-analyses in the literature comparing ERUS, MRI, and CT in rectal cancer staging. In 2000, Kwok et al. published a systematic review of 83 studies conducted between 1980 and 1998, with data on 4897 patients.[18] The authors used descriptive analysis of pooled data, with no statistical analysis, due to the diversity of the studies. The overall pooled results indicated that ERUS had the highest sensitivity, specificity, and accuracy (93%, 78%, and 87%, respectively) in assessing depth of invasion, compared with MRI (86%, 77%, and 82%, respectively) and CT (78%, 63%, and 73%, respectively). For assessment of nodal status, the sensitivity, specificity, and accuracy were similar between ERUS (71%, 76%, and 74%, respectively) and MRI (65%, 80%, and 74%, respectively). CT had the lowest sensitivity, specificity, and accuracy for assessing nodal involvement (52%, 78%, and 66%, respectively). Subgroup analysis showed that ERC-MRI had sensitivity, specificity, and accuracy similar to ERUS for assessing T stage (89%, 79%, and 84%, respectively) and a higher sensitivity, specificity, and accuracy for assessing N stage (82%, 83%, and 82%, respectively). For T1 lesions the accuracy of ERUS was 96%, versus 91% for MRI and 94% for ERC-MRI.

Recently, Bipat et al. published a meta-analysis of 90 articles written between 1985 and 2002, to compare ERUS, CT, and MRI in rectal cancer staging.[19] Statistical analysis of their data revealed that ERUS had sensitivity similar to that of MRI for detecting T2 stage but significantly higher specificity (86% vs. 69%). For evaluating perirectal tissue invasion (T3 stage), the sensitivity of ERUS (90%) was significantly higher than that of CT (79%) and MRI (82%); specificities were comparable. Sensitivity and specificity for adjacent organ invasion (T4 stage) were similar between the three modalities. For lymph node involvement, the analysis did not show any difference in sensitivity, specificity, or accuracy between ERUS, CT, or MRI. Compared to MRI and CT, ERUS is more readily available, portable, and less expensive. It requires the least amount of time and causes minimal patient discomfort. In addition, ERUS is performed by the surgeon, who can direct the examination with specific operative considerations in mind, in the preoperative setting as well as during postoperative surveillance. Over the past 15 years, ERUS has become the standard of care in local staging of rectal cancer. Table 137–1 cites many of the studies that have evaluated the diagnostic accuracy of ERUS, alone or in comparison with other modalities. In the hands of experienced clinicians, ERUS has a reported accuracy of up to 80% to 90% in preoperative assessment of T stage and up to 70% to 80% in assessment of N stage for rectal cancers.[3-6, 8, 10, 11, 14, 16, 19-27]

The technique involved in ERUS is highly operator dependent, with a significant learning curve. This was demonstrated by Orrom et al., who evaluated 77 patients with rectal cancer staged by ERUS and assessed the accuracy of the examination over three time periods.[23] In the first time period, examinations were performed by several clinicians, including nonsurgical staff. The accuracy of ERUS for determining the T stage during this period was only 58%, with 37% of lesions overstaged and 4% understaged. In the second and third time periods, all examinations were performed by one surgeon, and the use of a rigid proctoscope for the introduction of the ERUS probe was instituted. Accuracy of assessment during the second time period increased to 77%, with 20% overstaging and 3% understaging. In the third time period, all scans were interpreted according to the five-layer model of ERUS anatomy. Accuracy increased to 95%, with only 5% overstaging and no understaging. The accuracy for determining N stage also improved from

Table 137–1 Accuracy of Endorectal Ultrasound in the Staging of Rectal Cancer

Study Authors, Year	No. of Patients*	Accuracy, %	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %	Overstaging, %	Understaging, %
Beynon et al., 1986[5]	44 (T)	91 (T)	94 (T)	87 (T)	97 (T)	78 (T)	5 (T)	5 (T)
Holdsworth et al., 1988[20]	36	86 (T)	96 (T)	50 (T)	87 (T)	80 (T)	11 (T)	3 (T)
		61 (N)	57 (N)	64 (N)	50 (N)	70 (N)	22 (N)	17 (N)
Beynon, 1989[4]	100 (T)	93 (T)	99 (T)	91 (T)	97 (T)	95 (T)	5 (T)	2 (T)
	95 (N)	83 (N)	88 (N)	79 (N)	78 (N)	89 (N)	11 (N)	2 (N)
Rifkin et al., 1989[21]	101 (T)	72 (T)	67 (T)	77 (T)	73 (T)	72 (T)	12 (T)	16 (T)
	102 (N)	81 (N)	50 (N)	92 (N)	68 (N)	84 (N)	6 (N)	13 (N)
Hildebrandt et al., 1990[22]	113	79 (N)	72 (N)	83 (N)	72 (N)	83 (N)	11% (N)	11 (N)
Orrom et al., 1990[23]	77 (T)	75 (T)	ND (T)	ND (T)	ND	ND	22 (T)	3 (T)
	61 (N)	82 (N)	62 (N)	88 (N)			ND (N)	ND (N)
Glaser et al., 1990[6]	86 (T)	88 (T)	97 (T)	90 (T)	90 (T)	98 (T)	8 (T)	3 (T)
	73 (N)	79 (N)	78 (N)	80 (N)	76 (N)	82 (N)	11 (N)	10 (N)
Goldman et al., 1991[9]	32	81 (T)	90 (T)	67 (T)	82 (T)	80 (T)	12 (T)	6 (T)
		68 (N)	50 (N)	88 (N)	63 (N)	71 (N)	ND (N)	ND (N)
Herzog et al., 1993[10]	87 (T)	91 (T)	98 (T)	75 (T)	89 (T)	95 (T)	10 (T)	1 (T)
	111 (N)	80 (N)	89 (N)	73 (N)	71 (N)	90 (N)	15 (N)	5 (N)
Rafaelsen et al., 1994[3]	107 (T)	89 (T)	96 (T)	77 (T)	88 (T)	91 (T)	8 (T)	3 (T)
	53 (N)	70 (N)	58 (N)	76 (N)	58 (N)	76 (N)	15 (N)	15 (N)
Starck et al., 1995[8]	34 (T)	88 (T)	91 (T)	91 (T)	95 (T)	83 (T)	6 (T)	6 (T)
	31 (N)	71 (N)	64 (N)	76 (N)	69 (N)	72 (N)	13 (N)	16 (N)
Sailer et al., 1997[24]	162	78 (T)	97 (T)	80 (T)	83 (T)	97 (T)	19 (T)	3 (T)
Akasu et al., 1997[25]	152	82 (T)	ND (T)	ND (T)	ND (T)	ND (T)	11 (T)	7 (T)
		77 (N)	79 (N)	75 (N)	78 (N)	76 (N)	12 (N)	11 (N)
Kim et al., 1999[13]	89 (T)	81 (T)	ND (T)	ND (T)	ND (T)	ND (T)	10 (T)	9 (T)
	85 (N)	64 (N)	53 (N)	75 (N)	71 (N)	59 (N)	12 (N)	25 (N)
Hunerbein et al., 2000[15]	30	83 (T)	ND	ND	ND	ND	4 (T)	12 (T)
		80 (N)					0 (N)	5 (N)
Kwok et al., 2000[18]	2915 (T)	87 (T)	93 (T)	78 (T)	87 (T)	87 (T)	11 (T)	5 (T)
	2032 (N)	74 (N)	71 (N)	76 (N)	69 (N)	78 (N)	ND (N)	ND (N)
Garcia-Aguilar et al., 2002[26]	545 (T)	69 (T)	ND (T)	ND (T)	72 (T)	93 (T)	18 (T)	13 (T)
	238 (N)	64 (N)	33 (N)	82 (N)	52 (N)	68 (N)	11 (N)	25 (N)
Marusch et al., 2002[27]	422	63 (T)	83 (T)	70 (T)	ND	ND	24 (T)	13 (T)

*T, tumor; N, node; ND, not done.

71% for the first period to 88% for the second and third periods.

In 2002, Garcia-Aguilar et al. published the largest single-institution study to date, based on 10 years of ERUS experience at the University of Minnesota.[26] From a population of 1184 rectal cancer patients who had ERUS staging, they focused on 545 patients who underwent surgery without neoadjuvant chemoradiotherapy (307 were treated with local excision and 238 with radical surgery). Of the remaining 639 patients who were excluded for various reasons, 270 had preoperative chemoradiotherapy. Three surgeons performed 97% of the examinations. The overall accuracy of ERUS in assessing T stage was 69%, with 18% overstaging and 13% understaging. The accuracy of ERUS in diagnosing nodal disease was 64%, based on assessment of the 238 patients who underwent radical surgery. These rates are lower than those of previous reports. However, it is possible that this study underestimated the overall accuracy of ERUS, due to the exclusion of patients with locally advanced cancers who underwent neoadjuvant treatment. ERUS was most accurate in detecting benign villous adenomas.* Contrary to the suggestion of earlier, smaller studies,[24,28] the distance of the tumor from the anal verge did not influence the accuracy of the examination. Only the T stage of the tumor, and the surgeon performing the ERUS, were independent factors affecting T stage accuracy.

*Stage-specific accuracy: T0, 87%; T1, 47%; T2, 68%; T3, 70%; T4, 50%.

Table 137–2 Ultrasound Staging Classification (uTNM) for Rectal Cancer

Classification	Criteria
uT0	Noninvasive lesion confined to the mucosa
uT1	Tumor confined to the mucosa and/or submucosa
uT2	Tumor confined to the muscularis propria
uT3	Tumor extending into the perirectal fat
uT4	Tumor involving adjacent structures
uN0	No evidence of lymph node metastasis (no definable lymph nodes by ultrasound)
uN1	Evidence of lymph node metastasis (ultrasonographically apparent lymph nodes)

uTNM, ultrasonographic staging of tumor, node, metastasis.

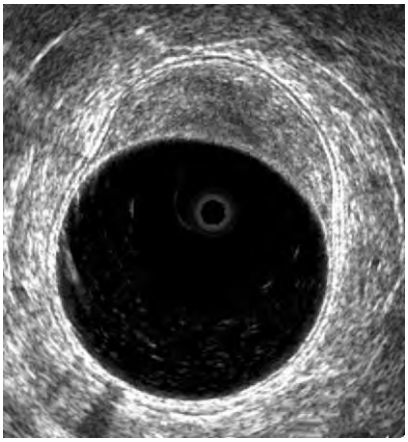


Figure 137–4. Benign villous tumor of the rectum (uT0). The middle white line is intact around the entire breadth of the tumor, indicating that the submucosa is not involved. (From Wong WD, Orrom WJ, Jensen LL: Preoperative staging of rectal cancer with endorectal ultrasonography. Perspect Colon Rectal Surg 3:315, 1990.)

Depth of Invasion

In 1985 Hildebrandt and Feifel introduced the ultrasonographic staging of rectal cancer as a modification of the TNM staging system.[7] This is depicted in Table 137–2. The prefix "u" denotes ultrasound staging, as opposed to the prefix "p," which denotes pathologic staging. Sonographically, a rectal cancer appears as a hypoechoic mass that causes disruption of the layers of the rectal wall. The depth of tumor invasion is classified as follows:

- uT0 lesions are benign, noninvasive lesions, confined to the mucosa
- uT1 cancers invade the submucosa
- uT2 lesions invade into but not through the muscularis propria and remain confined to the rectal wall
- uT3 lesions penetrate through the entire thickness of the bowel wall and invade the perirectal fat
- uT4 lesions invade an adjacent organ (i.e., uterus, vagina, cervix, bladder, prostate, seminal vesicles), the pelvic sidewall, or the sacrum

uT0 Lesions

Lesions staged as uT0 are noninvasive and confined to the rectal mucosa. Benign villous adenomas are uT0 lesions. On ERUS imaging, the mucosal layer is expanded but the middle white line (submucosa) remains intact. The middle white line is the key to determining whether a lesion is benign (Fig. 137–4). Benign lesions accurately identified by ERUS may be treated with local excision in the submucosal plane. ERUS is reliable in distinguishing benign lesions, with accuracy ranging from 87%[26] to 96%.[29] On biopsy of villous tumors, foci of malignancy may not be detected due to biopsy sampling error. However, ERUS can detect a malignant focus within a villous adenoma.[30] Worrell et al. performed a meta-analysis on the data for 258 biopsy-negative rectal adenomas from five studies. Focal carcinoma was detected in 24% of these tumors on histopathology. ERUS correctly established a diagnosis of cancer in 81% of these cases, thus decreasing the misdiagnosis rate from 24% to 5%. ERUS should be routinely used in the preoperative work-up of rectal villous adenomas.[31]

uT1 Lesions

A uT1 lesion is an early cancer that invades the mucosa and submucosa but not the muscularis propria. The ERUS finding is an irregular middle white line (submucosa) without alteration of the outer black line (muscularis propria) (Fig. 137–5). Irregularities of the middle white line are seen as a thickening or stippling but must not constitute a distinct break. If a break is seen in the submucosa, the muscularis propria has been invaded and the tumor is a T2 lesion. Garcia-Aguilar et al. reported 47% accuracy in the subgroup of 105 patients with T1 stage disease.[26] In their meta-analysis, Kwok et al. reported a 96% accuracy rate for T1 lesions.[18]

Accurate staging of uT1 lesions is important, because select uT1 lesions are amenable to local therapy. However, lymph node involvement occurs in 6% to 15% of T1 rectal cancers.[32,33] ERUS may identify this subgroup of patients with uT1 tumors and metastatic lymph nodes, for whom local therapy is contraindicated. Accurate staging of uT1 lesions with ERUS is particularly important if endocavitary radiation therapy is elected, because pathologic staging cannot be obtained with this technique. In the setting of favorable tumor characteristics and proper patient selection, local resection with negative margins can lead to low recurrence, survival rates comparable to radical surgery, and excellent quality of life.[34-36] We approach these patients with curative intent. Use of adjuvant chemoradiotherapy is based on the pathology of the excised tumor.

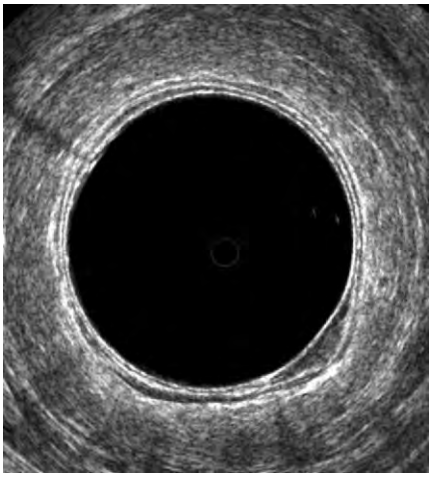


Figure 137–5. A uT1 lesion. There is invasion into the submucosa, and although the middle white line is not disrupted, it is thickened and irregular. The muscularis propria (outer black line) is not expanded, and the outer white line is intact.

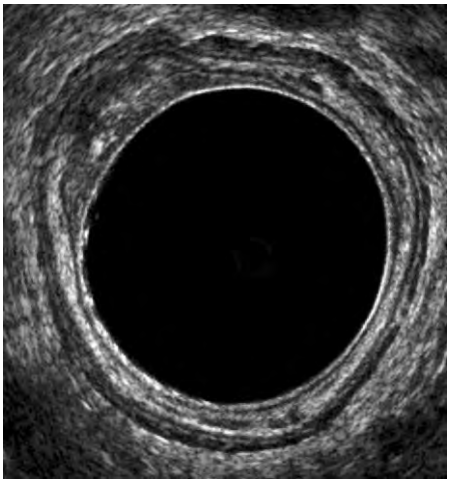


Figure 137–6. A uT2 lesion. The submucosa (middle white line) is disrupted, and there is expansion/invasion of the muscularis propria (outer black line). The outer white line (perirectal fat) is intact, demonstrating that the tumor is confined to the bowel wall.

uT2 Lesions

A uT2 cancer disrupts the middle white line and invades the second hypoechoic layer (muscularis propria) but remains confined to the rectal wall. Characteristically there is expansion of the muscularis propria, but the interface between the muscularis propria and perirectal fat (outermost white line) remains intact. The expansion of the muscularis propria may be variable, depending on the degree of invasion. "Early" uT2 lesions may just penetrate the muscularis propria with minimal expansion of this layer. A distinct break in the middle white line must be identified. "Deep" uT2 lesions have a significant degree of expansion of the muscularis propria that may also appear as "scalloping," but they do not invade the perirectal fat. There is a significant tendency to overcall deep T2 lesions as T3 cancers because of their "scalloped" appearance. An example of a uT2 lesion is shown in Figure 137–6.

Accuracy of ERUS in detecting T2 stage is in the range of 68%.[26] Lymph node metastases occur in up to 17%[32] to 28%[37] of patients with T2 tumors. Local recurrence rates of T2 tumors treated with local surgery alone have reportedly been as high as 47%, with survival rates as low as 65%.[35,36,38] We recommend radical surgery (either a sphincter-sparing resection or abdominoperineal resection) for patients who are acceptable surgical candidates and for whom there is a curative intent. Local therapy is reserved for patients with uT2 tumors who are poor-risk surgical candidates, those approached with palliative intent, or those who require an abdominoperineal resection but refuse a permanent colostomy despite appropriate counseling. When local therapy is used for the treatment of uT2 lesions, postoperative chemoradiation treatment is recommended to lower the risk of local recurrence.[34]

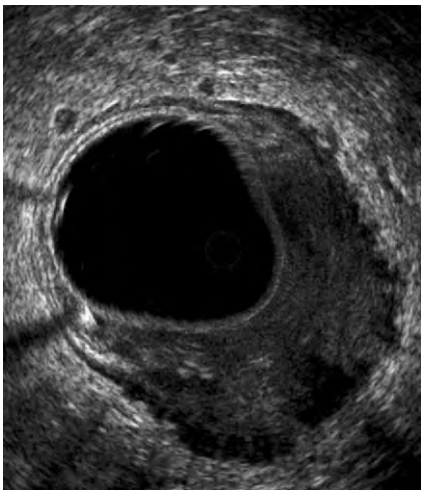


Figure 137–7. A uT3 lesion. The interface between the muscularis propria and perirectal fat (the outer white line) is irregular and interrupted, indicating extension of tumor into the perirectal fat.

uT3 Lesions

A uT3 lesion is a locally advanced cancer that penetrates through the full thickness of the rectal wall and invades into the perirectal fat. Contiguous structures are not involved. The ERUS findings are a disruption of the outer white line, with extension (like a thumbprint) of the tumor into the perirectal fat. An example of a uT3 lesion is shown in Figure 137–7.

The accuracy of ERUS in detecting T3 stage is reportedly between 70%[26] and 81%.[10] Early superficial uT3 lesions can be difficult to distinguish from deep uT2 lesions. Deep uT3 lesions with extensive invasion into the perirectal fat are readily recognized and reliably staged.

Patients with uT3 lesions are candidates for neoadjuvant chemoradiotherapy, followed by surgery. Local therapy is not appropriate treatment for uT3 lesions because lymph node metastases may occur in up to 66%[33] of cases, and local surgery carries a high rate of local recurrence, even with the addition of adjuvant therapy.[39,40]

uT4 Lesions

uT4 cancers are locally advanced tumors that invade into adjacent structures such as the bladder, uterus, cervix, vagina, prostate, or seminal vesicles. These tumors are clinically fixed. Sonographically, there is loss of the normal hyperechoic plane between the tumor and the adjacent organ. Specifically, Denonvilliers's fascia, which normally appears as a hyperechoic interface between the rectal wall and prostate gland in men, becomes obscured by a uT4 tumor with prostatic invasion. Similarly, obliteration of the distinct hyperechoic plane between the rectum and vagina in women is characteristically seen with a uT4 rectal tumor invading the posterior vaginal wall. An example of a uT4 rectal cancer invading the posterior vaginal wall is shown in Figure 137–8.

The treatment of uT4 tumors requires neoadjuvant chemoradiotherapy and in-continuity organ resection for potential cure. However, uT4 rectal cancers are resectable for cure in fewer than half of the cases. The use of preoperative chemoradiotherapy can shrink the tumor, allowing for increased resectability and decreased local recurrence rates. Intraoperative radiation therapy is used in some specialized centers; when used in combination with preoperative radiation, this appears to improve local control in T4 rectal cancers.[41]

Nodal Involvement

ERUS is used to detect potentially malignant mesorectal lymph nodes in patients with rectal cancer. However, the accuracy of ERUS in identifying metastatic lymph node involvement has been lower than its accuracy in determining depth of tumor invasion and is in the range of 64%[26] to 83%.[4] Undetectable or benign-appearing lymph nodes are classified as uN0. Malignant-appearing lymph nodes are classified as uN1. Normal, nonenlarged lymph nodes are generally not seen with ultrasound. Inflamed, enlarged lymph nodes appear hyperechoic, with ill-defined borders. Metastatic lymph nodes that have been replaced by tumor appear hypoechoic, with an echogenicity resembling that of the primary tumor. Malignant lymph nodes tend to be round rather than oval, have discrete borders, and are most commonly found in the mesorectum adjacent or proximal to the primary tumor.[42] Distal lymphatic spread in rectal cancer is unusual without the involvement of proximal lymphatics. An example of a metastatic lymph node detected on ERUS is depicted in Figure 137–9.

Both size and echogenic pattern of the lymph nodes have been evaluated as indicators of metastatic nodal involvement. Tio and Tytgat first recognized the hypoechoic pattern of malignant lymph nodes on ERUS imaging.[43] Hildebrandt et al. demonstrated that two main groups of lymph nodes are visualized on ultrasound: hyperechoic nodes and hypoechoic nodes.[22] In vitro, it has been shown that the ultrasound properties of involved and uninvolved lymph nodes differ significantly. Lymph nodes involved by tumor appear hypoechoic because less sound energy is reflected from the homogeneous tumor tissue. Uninvolved lymph nodes appear hyperechoic because most of the sound energy is reflected if the lymphatic structure remains unchanged. ERUS cannot detect lymph nodes with micrometastases, however, because these do not significantly alter the sound-reflecting characteristics of lymph node tissue. This limitation of ERUS explains, in part, its lower rates of accuracy detection of nodal disease.

We consider lymph nodes seen on ERUS as potentially positive if they are larger than 3 mm in diameter, round, hypoechoic, and in an appropriate location. Sunouchi

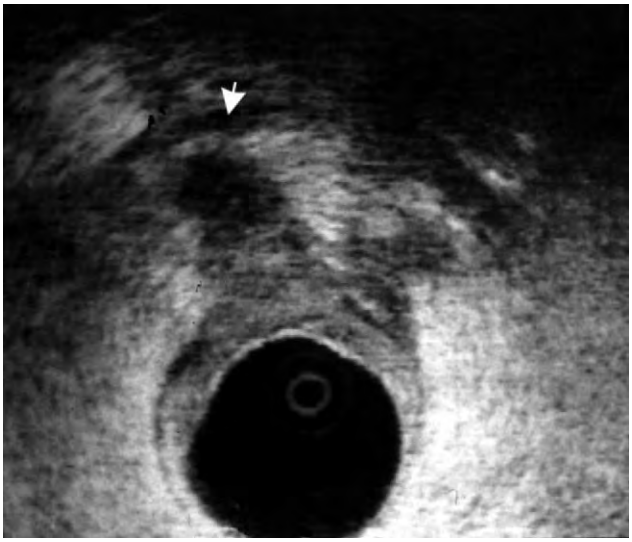


Figure 137–8. A uT4 lesion. There is invasion of the posterior vaginal wall *(arrow).*

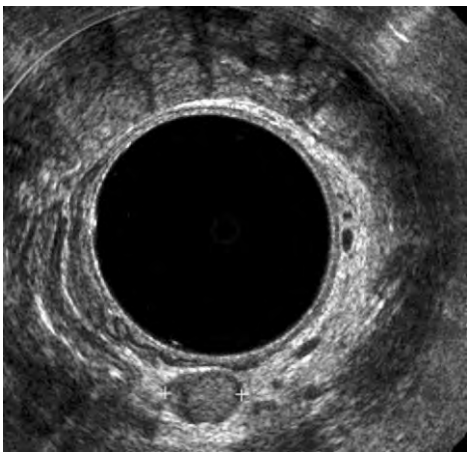


Figure 137–9. Metastatic lymph node (1.2 cm) detected with endorectal ultrasound.

et al. studied hypoechoic lesions larger than 5 mm, reporting that 20% were tumor deposits and 68% were metastatic lymph nodes.[44] It is possible that nodal size alone may not be an accurate predictor of metastatic disease. Akasu et al. found that approximately 50% of lymph nodes with diameters of 3 to 5 mm harbored metastases, making prediction based on size difficult.[25] In a pathologic study by Herrera-Ornelas et al., two thirds of metastatic lymph nodes from colorectal cancer were smaller than 5 mm in diameter.[45] Sunouchi et al. also described a "small-spot sign" for lesions identified in the mesorectum measuring 1 to 3 mm in diameter and suggested that small hypoechoic spots may correlate with tumor deposits or massive lymphovascular invasion histologically. The finding of small spots may indicate a high risk of hematogenous metastasis and local recurrence.[46]

The major error in the diagnosis of lymph node metastases has been with false-positive results (overstaging). False-positive results may occur due to inflammatory lymph nodes. The cross-sectional appearance of blood vessels in the perirectal fat may also be confused with positive lymph nodes. Careful, repeated scanning of the area in question can demonstrate the sonographic continuity of hypoechoic vessels over a distance greater than the cross-sectional diameter, thus distinguishing them from hypoechoic lymph nodes. Another criterion is that blood vessels branch or extend longitudinally. Additionally, it may be difficult to differentiate the appearance of islands of tumor outside the bowel wall from that of involved nodes. Demonstrating continuity with the main tumor is helpful in making this distinction.

False-negative results (understaging) are also a problem. This is partially due to the presence of lymph node micrometastases, which current ERUS technology cannot detect. Moreover, involved lymph nodes may be missed when they lie beyond the imaging range of the ultrasound transducer. This is particularly true for nodes in the proximal mesorectum, above the reach of the rigid probe. Advances in technology and increased operator experience will likely improve the sonographic accuracy and sensitivity of metastatic lymph node detection.

Proposed Modification of the ERUS Staging System

We have modified the uTNM classification into a treatment-oriented staging system to address clinical considerations for each stage (Table 137–3). In this system, uTw lesions include uT0 and uT1 tumors which are amenable to local excision. The second group, uTy, consists of uT2 and select superficial uT3 lesions; the recommended treatment for this group is radical surgery without neoadjuvant therapy. The third group, uTz, includes deep uT3 and uT4 lesions, which are best treated with neoadjuvant therapy followed by radical resection. The stratification of rectal tumors into groups amenable to specific treatment plans constitutes the major advantage of this modified system. We are currently using this system at MSKCC, along with the uTNM classification, to stage our rectal cancer patients.

Table 137–3 Proposed Modified Endorectal Ultrasound Staging System (uTNM) for Rectal Cancer

Classification	Criteria
uTw: uT0/uT1	Amenable to local excision
uTy: uT2/superficial uT3	Recommend radical surgery
uTz: Deep uT3/any uT4	Recommend neoadjuvant treatment followed by radical surgery
uN1: probable or definite	Recommend neoadjuvant treatment
uNx: equivocal	Base treatment on T stage and pathologic features

uTNM, ultrasonographic staging of tumor, node, metastasis.

Limitations of ERUS

The ERUS technique is highly operator dependent and requires experience in accurate interpretation of the results, with a significant learning curve.[23] Overall staging accuracy improves with adequate training and experience, optimal technique, and high-quality equipment. Overstaging has been reported in the range of 11%[18] to 18%[26] for depth of wall invasion. Understaging occurs less frequently, with rates between 5%[18] and 13% (see Table 137–2).[26] Understaging is significantly more serious than overstaging because it may result in inadequate management; with overstaging potentially more aggressive management is advised than might be required. Overstaging depth of invasion may result from inflammation at the deep edge of the tumor, preoperative radiation, hemorrhage in the rectal wall following biopsy, or a tendency of the observer to fear understaging depth of invasion. ERUS tends to understage disease in the setting of stenotic, near-obstructing tumors; examination may not be possible or complete in the setting of lesions that cannot accommodate passage of the endosonic probe.

Overstaging of lymph node involvement occurs between 5%[4] and 22%[20] of the time. This is due to the presence of inflammatory lymph nodes, blood vessels, or tumor deposits in the mesorectum. Understaging occurs between 2%[4] and 25%[13] of the time and is partially due to the inability of ERUS to detect lymph node micrometastases.

It is particularly important to recognize factors that affect the accuracy of ERUS and may lead to misinterpretation of ultrasound images.[47] For example, if the ultrasound probe is not at a 90-degree angle with the region of interest, balloon-wall separation may occur, mimicking a (nonexistent) rectal lesion. Poor bowel preparation or retained air can produce shadowing artifacts. Finally, cautery burns from endoscopic biopsies or excisions may alter the image and significantly affect the accuracy of sonographic assessment.

Accuracy of ERUS After Neoadjuvant Therapy

Neoadjuvant chemoradiotherapy is used to treat locally advanced rectal cancers, producing a complete pathologic response in up to 30% of cases.[48] Radiation causes inflammation, edema, and fibrosis and obscures differentiation of the layers of the rectal wall, making sonographic distinction between residual tumor and radiation-induced changes difficult. Re-evaluation of rectal tumors with ERUS after neoadjuvant chemoradiotherapy is inaccurate, with high rates of overstaging.[49]

ERUS after chemoradiotherapy appears to be least accurate in patients with visual and sonographic evidence of response. Rau et al. used ERUS to evaluate 84 patients with locally advanced rectal cancers following completion of neoadjuvant chemoradiotherapy and found that the misinterpretation of T stage, including overstaging and understaging, correlated with downstaging.[50] Accuracy of ERUS for assessing T stage in the 51 downstaged patients was only 29%, whereas 82% of the 33 nonresponders were correctly staged ($P < 0.001$). Gavioli et al. suggested that, after radiation therapy, ERUS no longer stages the tumor but rather the fibrosis that takes its place.[51] They concluded that the extent of fibrosis in the rectal wall is a direct indication of the depth of residual cancer and that residual tumor, when present, is always present within the fibrosis. However, they were unable to correlate the echo-pattern changes they recorded on ERUS with response of the tumor to treatment.

Unfortunately, all the conventional imaging modalities (ERUS, CT, MRI) are unreliable in the detection of complete response following neoadjuvant treatment and cannot identify a subgroup of patients who might safely avoid radical surgery.[52] Imaging modalities such as positron emission tomographic scan[53] and 3D-ERUS are currently being evaluated in the setting of post-chemoradiotherapy staging of rectal cancer.

ERUS for Postoperative Follow-up

Local recurrence rates of rectal cancer have decreased significantly over the last decade, with use of improved surgical technique and combined-modality therapy. Nevertheless, the detection and treatment of local recurrence continues to represent a challenge. Mellgren et al. reported local recurrence rates of 4% for T1 and T2 rectal cancers after radical surgery, and 28% after local excision.[36] Steele et al. reported a local recurrence rate of 9% for T1 and T2 cancers treated with local excision and adjuvant therapy.[34] Local recurrence rates for locally advanced rectal cancer treated with combined-modality therapy and total mesorectal excision are in the range of 6%.[54] Early detection of recurrence is clearly important, and follow-up programs should address this issue if they are to be successful. Such programs should focus on detection of resectable anastomotic and locoregional failures, in addition to treatable systemic metastases and metachronous colonic tumors.

A number of methods have been used to detect local recurrence at an early stage. Clinical evaluation, including history, physical examination, sigmoidoscopy, and serial carcinoembryonic antigen (CEA) determinations will detect local recurrences, but often at a late, unresectable stage.[55] CT is useful in the assessment of local recurrence, especially in the case of bulky lesions, but it is not sufficiently accurate in distinguishing recurrent tumor from inflammation or fibrosis. For accurate diagnosis of tumor recurrence with CT, lesions generally must be a minimum of 1 to 1.5 cm in diameter.[56] MRI is not used routinely for postoperative surveillance. However, if local recurrence is suspected, MRI may be superior to CT because there is more accurate tissue characterization.[57] The main problem with most follow-up modalities (including CT and MRI) is that they rarely detect local recurrence in the asymptomatic patient at an early and treatable stage.

ERUS has been used to follow patients after local excision or low anterior resection for rectal cancer. Transvaginal ultrasound may be performed in female patients after abdominoperineal resection. ERUS is also used to follow patients treated with chemoradiation therapy for anal canal carcinomas. Both hand-sewn and stapled anastomoses may be identified with ERUS, and staples do not interfere with the sonographic image. ERUS cannot establish that a recurrent lesion is malignant with absolute certainty, so biopsy of suspicious lesions is recommended for definitive diagnosis. It is recommended that a "baseline" ultrasound be performed approximately 3 months after surgery, with future comparisons at 3- to 4-month intervals. A good baseline examination is useful in documenting postoperative scarring and evaluating possible changes over time. Serial ultrasound evaluations may identify and confirm suspicious areas, which may then be biopsied via a transrectal, ultrasound-guided approach.[58]

Locally recurrent cancer that is advanced and detected by digital and endoscopic examination has hypoechoic ultrasound characteristics similar to those of primary rectal cancers. Tumor recurrence is often first identified outside of the rectal wall, in an area adjacent to the anastomosis. Extrarectal recurrent tumor often appears on ERUS as a circumscribed, hypoechoic lesion in the para-anastomotic extrarectal tissues, with all or a portion of the rectal wall intact on the luminal aspect. Furthermore, ERUS may identify metastatic lymph nodes that develop in the mesorectum after local excision of a rectal cancer. An example of a locally recurrent tumor detected by ERUS is illustrated in Figure 137–10.

ERUS has been shown to be particularly useful in the evaluation of asymptomatic patients for evidence of early local recurrence. Lohnert et al. followed 338 patients, after curative resections for rectal and left colon cancers, with DRE, endoscopy, CEA levels, and ERUS.[59] All cases of local recurrence (116 patients [34%]) were identified by ERUS; additionally, local recurrence was proven by ultrasound-guided needle biopsy in all cases showing unclear pararectal structures that could not be verified by endoscopic biopsy. In 28% of local recurrence cases, both DRE and endoscopy results were normal. These results indicate that ERUS is able to detect local recurrence at an earlier and asymptomatic stage, compared with other surveillance methods. Similar results were obtained by De Anda et al., in a study of 275 patients

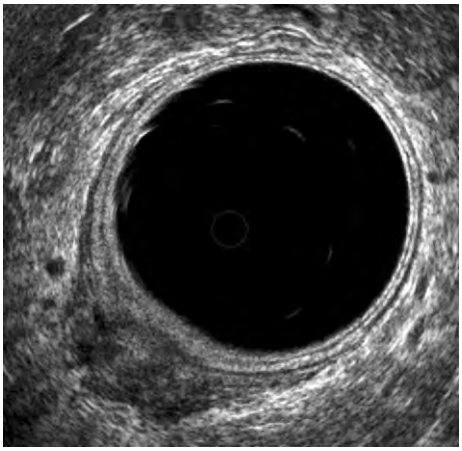


Figure 137–10. Locally recurrent rectal cancer. There is a hypoechoic mass in the extrarectal tissues, and the inner rectal wall appears normal. Sigmoidoscopy revealed normal rectal mucosa.

placed on ERUS surveillance after curative surgery for rectal cancer.[60] ERUS identified one third of asymptomatic local recurrences missed by DRE or proctoscopic examination. The impact of earlier diagnosis of local recurrences in patient survival has not been documented due to the lack of large, prospective, randomized trials; however, aggressive surveillance seems reasonable for patients who may be candidates for salvage treatment.[61] ERUS follow-up is particularly useful for patients treated with local therapies for early rectal cancers, because early diagnosis of tumor recurrence is critical if curative salvage surgery is to be considered.

Although the optimal interval for repeat follow-up examinations has not been determined, and the cost-effectiveness of follow-up ERUS has not been assessed, ERUS is recognized as an important and accurate test for postoperative follow-up. Certainly, ERUS should not be considered the sole constituent of any follow-up program; rather, ERUS should complement clinical examination, proctoscopy, and serum CEA levels as part of a comprehensive rectal cancer surveillance strategy. At MSKCC, we perform ultrasound examinations every 4 months for the first 3 years after local excision for rectal cancer and every 6 months for the next 2 to 3 years.

Three-Dimensional Endorectal Ultrasound

Three-dimensional ERUS is a novel technique that provides high-resolution multiplanar images. The examination displays volume data in three orthogonal planes as a three-dimensional view, closely resembling the original anatomy. This is particularly valuable for assessment of small structures (e.g., lymph nodes). This study has the potential to improve the examiner's understanding of spatial relations between the tumor and anatomic structures and to increase the diagnostic accuracy of ERUS.

Initial small reports on 3D-ERUS have suggested an accuracy for T and N stage similar to that of conventional ERUS.[62,63] Hunerbein has compared 3D-ERUS to endorectal coil-MRI in the staging of 25 rectal cancer patients; both methods showed equivalent accuracy in the assessment of rectal wall invasion.[15] Three-dimensional ERUS has also been evaluated in the staging of obstructive, stenotic rectal cancers[64] and in diagnosis of locally recurrent rectal cancer,[65] with promising results. At MSKCC, we have ongoing studies assessing the value of 3D-ERUS in the staging of rectal cancer following neoadjuvant chemoradiotherapy.

ENDOANAL ULTRASOUND: ENDOSONOGRAPHY OF THE ANAL CANAL

EAUS is the diagnostic test of choice for evaluation of anal sphincter anatomy and the identification of sphincter defects associated with fecal incontinence. It has particular value in the diagnosis of complex perianal fistulas. Furthermore, EAUS is used in staging and follow-up of both benign and malignant anal neoplasms.

The equipment used is the same as the equipment used for ERUS, with a minor modification. A translucent plastic cap (Brüel & Kjaer WA0453) is placed over the transducer and is filled with water, which provides the acoustic medium. A pinhole in the apex of the plastic cap allows for removal of the air bubbles through displacement with water. The technique for EAUS is similar to that for ERUS. Patients should be reassured that this examination will be no more uncomfortable than a DRE. The patient is examined in the left lateral decubitus position. Inspection of the perineum and digital examination precede EAUS assessment. The probe is lubricated with water-soluble jelly and gently inserted into the anus to the level of the upper anal canal. The entire length of the anal canal is evaluated while the probe is withdrawn slowly.

Normal Endoanal Ultrasound Anatomy

The anatomy of the anal canal is generally imaged sonographically at three levels (upper, mid, and distal anal canal).[66] The upper anal canal is illustrated in Figure 137–11. The puborectalis muscle is an important landmark for the upper anal canal and is seen as a horseshoe-shaped white structure (hyperechoic striated muscle) that forms the lateral and posterior portions of the upper anal canal.

In the mid-anal canal, the internal anal sphincter appears as a complete dark band around the probe (hypoechoic smooth muscle), surrounded by the hyperechoic external anal sphincter. A hyperechoic ring is seen between the transducer and the internal sphincter, representing subepithelial, hemorrhoidal, and submucosal tissues. The mid-anal canal is illustrated in Figure 137–12. The internal anal sphincter is most prominent at the level of the mid-anal canal. The perineal body is usually measured at this level. With the ultrasound probe in place, the index finger of the examiner's right hand is simultaneously inserted into the vagina. The distance between the ultrasound reflection of the finger and the

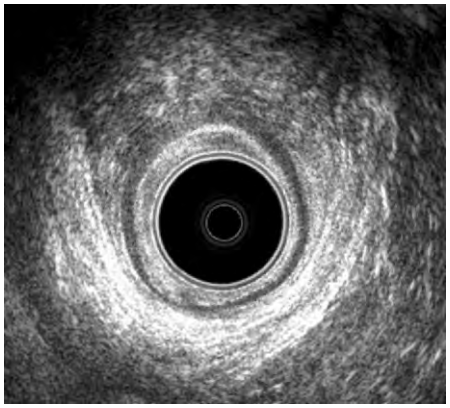


Figure 137–11. Upper anal canal. The puborectalis muscle is seen as a horseshoe-shaped hyperechoic structure and is an important landmark for the upper anal canal.

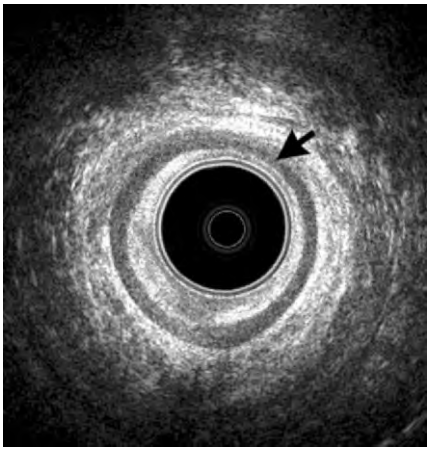


Figure 137–12. Mid-anal canal. The internal anal sphincter appears hypoechoic *(arrow)* and is surrounded by the hyperechoic external anal sphincter.

inner aspect of the internal sphincter may be measured and corresponds to the perineal body, as illustrated in Figure 137–13. Normal values for perineal body thickness (PBT) are approximately 10 to 15 mm.[67] Measurement of the perineal body is useful in evaluation of women with incontinence from anterior sphincter defects and pelvic floor disorders.

In the distal anal canal (Fig. 137–14), the internal anal sphincter is not seen. Only the hyperechoic external anal sphincter and surrounding soft tissues are visualized.

Anal Sphincter Defects and Fecal Incontinence

EAUS is a valuable tool in the work-up of fecal incontinence, detecting anatomic anal sphincter defects and identifying patients who would benefit from surgery. Causes of sphincter defects include obstetric injury, perianal trauma, anorectal surgery, and congenital abnormalities.

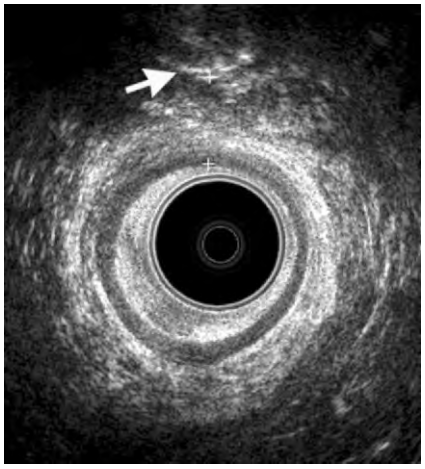


Figure 137–13. Perineal body measurement. The distance between the hyperechoic reflection of the examiner's finger *(arrow)* and the inner aspect of the internal sphincter is measured.

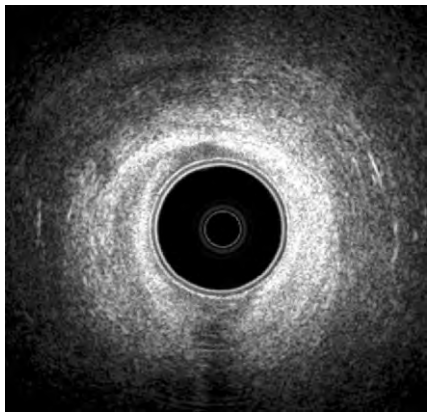


Figure 137–14. Distal anal canal. The internal anal sphincter is not seen, and only the hyperechoic external anal sphincter and surrounding soft tissues are visualized.

Obstetric injury to the anal sphincter is the most common cause of incontinence in young women. Most patients will have had primary repair of a fourth-degree tear at the time of vaginal delivery, with subsequent fecal incontinence. However, in some patients, a tear injury may remain asymptomatic and initially unrecognized, due to sufficient residual sphincter function. Sultan et al. prospectively studied 202 women before and after delivery, using EAUS and anorectal neurophysiologic tests.[68] They found that occult sphincter defects were common after vaginal delivery (especially forceps delivery), with an incidence of 35% in the primiparous women evaluated. Similarly, Zetterstrom et al. demonstrated a significant frequency of sphincter injuries (20%) after vaginal delivery.[69] Oberwalder et al. performed a meta-analysis of 717 vaginal deliveries that revealed a 27% incidence of anal sphincter defects in primiparous women and an

8.5% incidence of new sphincter defects in multiparous women.[70] Overall, 30% of anal sphincter defects were symptomatic. Three percent of women without an anal sphincter defect experienced postpartum fecal incontinence.

Patients often develop delayed symptoms of incontinence several years following an unrecognized sphincter injury.[71] Since the peak incidence of fecal incontinence among women occurs in the 5th and 6th decades, the effects of aging, menopause, and progression of a neuropathy all may contribute to sphincter weakness in the long term. It appears that nerve damage is cumulative, whereas direct sphincter damage most likely occurs on first delivery.

Defects in the external anal sphincter muscle usually appear sonographically as hypoechoic defects, although some may be hyperechoic or may demonstrate mixed echogenicity. In the case of complete sphincter disruption, the ends of both internal and external sphincter muscles are widely separated and bridged by scar tissue. In many patients, complete sphincter disruption is not seen; rather, significant attenuation of the sphincter muscle is present anteriorly, suggestive of a significant deficit. Zetterstrom et al. have shown that perineal body measurement as part of the EAUS can help to identify anterior sphincter defects in most patients.[67] Normal values for PBT are approximately 10 to 15 mm. However, Oberwalder et al. recently evaluated 89 patients with fecal incontinence and found that PBT of 10 to 12 mm was associated with a sphincter defect in one third of the patients, whereas patients with a PBT of 12 mm or more were unlikely to harbor a defect.[72]

The importance of EAUS in the diagnostic evaluation of fecal incontinence has been demonstrated in several studies.[73,74] Other anorectal physiologic tests, such as anorectal manometry and electromyography, are complementary. Women with symptoms of fecal incontinence and history of vaginal deliveries should be evaluated with EAUS for an anatomic sphincter defect that might account for the incontinence. This is important, since some defects are amenable to surgical repair.[75] EAUS is well tolerated, produces minimal discomfort, and provides high-resolution images of both the external and the internal sphincter. EAUS identifies sphincter injuries with a very high degree of accuracy when these injuries are present; however, it may falsely identify anterior sphincter injuries in normal, intact sphincters. By recognizing a potential high false-positive sphincter injury rate, and limiting evaluation of the anal canal to the most distal 1.5 cm, Sentovich et al. were able to decrease the rate of false-positive findings to a range between 5% and 25%.[76] An anterior internal and external anal sphincter defect is depicted in Figure 137–15.

Other causes of anal sphincter defects are perianal trauma and anorectal surgery. Major blunt and penetrating perineal trauma often involves the anal sphincter. Fecal diversion is often required, in addition to débridement, in the case of major soft tissue perineal injuries. After the injuries have healed, EAUS may be used to assess the remaining anatomy and to determine whether reconstructive surgery is necessary before stomal closure. Fecal incontinence may also occur after anorectal surgery. Most of the time this is transient, but occasionally it persists, warranting evaluation. EAUS has been used to evaluate potential sphincter defects associated with postoperative fecal incontinence following hemorrhoidectomy, lateral internal sphincterotomy,[77] or sphincteroplasty.[78]

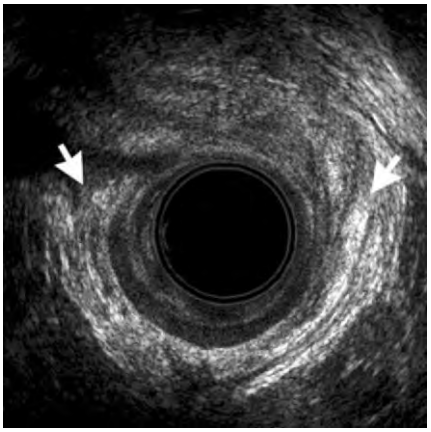


Figure 137–15. Anterior anal sphincter defect in a woman with incontinence. The distance between the two *arrows* represents an anterior defect in both the internal and external anal sphincters.

Perianal Sepsis and Fistula-in-Ano

The diagnosis of a perianal abscess is usually made by clinical examination and requires only proper recognition and prompt drainage. However, sometimes an abscess is strongly suspected by history but is not readily evident on physical examination. EAUS may be used intraoperatively or in the office to localize an obscure abscess and aid in planning the appropriate incision for drainage.[79] Such an example is an intersphincteric abscess, which is often difficult to diagnose clinically but may be suspected due to a history of severe anal pain. Abscesses appear on EAUS as hypoechoic areas, often surrounded by a hyperechoic border.

EAUS may be applied in the evaluation of complex and recurrent fistula-in-ano. It can anatomically delineate the fistula tract in relation to the anal sphincters. Sonographically, fistula tracts are generally hypoechoic defects and can be followed for direction and extent. Examination should include ultrasound scanning of the anal canal, as well as the distal rectum, to search for high blind tracts. An example of a fistula-in-ano demonstrated with EAUS is illustrated in Figure 137–16.

Deen et al. reported a 94% correlation between EAUS and operative findings in 18 patients with complex anal fistulas. EAUS was highly accurate in identifying fistula tracts, horseshoe tracts, and fluid collections but was less accurate in identifying internal fistula openings.[80] Seow-Choen et al. proposed criteria for identification of the internal opening that included a hypoechoic gap in the subepithelial layer, a defect in the internal anal sphincter, and a hypoechoic area in the intersphincteric space.[81]

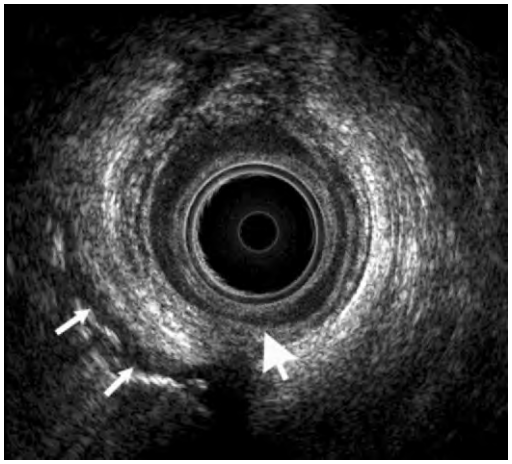


Figure 137–16. Fistula-in-ano. The fistula tract appears hypoechoic *(small arrows)*. The internal opening was identified in the midline posteriorly *(large arrow)*.

Cho et al. defined the following three criteria for localization of the internal opening[82]: I, a rootlike budding, formed by the intersphincteric tract, that contacts the internal sphincter; II, a rootlike budding with an internal sphincter defect; and III, a subepithelial breech connecting to the intersphincteric tract through an internal sphincter defect. The combination of these criteria produced a sensitivity of 94%, a specificity of 87%, and positive predictive value of 81%. In a more recent study of 151 patients with fistula-in-ano, Lengyel et al. reported an 82% concordance of EAUS with the operative findings and a 93% accuracy of the test in predicting the internal opening of the fistula.[83]

EAUS is useful in patients with Crohn's disease, where it can delineate complex fistula tracts and abscesses. Schratter-Sehn et al. compared EAUS and CT in the evaluation of 25 patients with perianal Crohn's disease and suggested that EAUS was superior to CT in diagnosing fistulas and inflammatory infiltration of the lower pelvic muscles.[84] The two methods were equivalent in diagnosing perianal abscesses. Solomon et al. performed EAUS, pouchography, and CT in patients with dysfunctional ileoanal pouches and inconclusive clinical and endoscopic examinations.[85] Their results suggested higher sensitivity of EAUS in the detection of anastomotic leaks and peripouch sepsis.

A variety of techniques are used alone or in conjunction with EAUS in the identification of complex fistulous tracts. These include careful probing; fistulography; and injection with methylene blue dye, milk, hydrogen peroxide, or contrast agents such as Levovist.[86] Hydrogen peroxide injection is used along with EAUS to enhance the imaging of complex and recurrent anal fistulas.[87] The release of oxygen accentuates the fistula tract, which shows as a brightly hyperechoic image on the sonogram. An example of a fistula-in-ano visualized on EAUS with hydrogen peroxide enhancement is depicted in Figure 137–17.

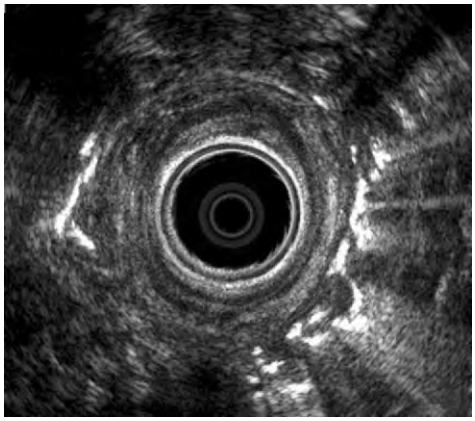


Figure 137–17. Fistula-in-ano. Hydrogen peroxide injected into the external orifice of the fistula appears brightly hyperechoic and outlines the fistulous tract.

Rectovaginal Fistula

EAUS can be used in the diagnosis of a suspected rectovaginal fistula (RVF) when clinical examination fails to identify a communication.[88] Furthermore, EAUS is valuable in the preoperative work-up of patients with RVF. Tsang et al. reviewed the experience of the Minnesota Group with RVF repair.[89] EAUS or anal manometry was used preoperatively to detect sphincter defects. If a defect was found, then endorectal advancement flap was more likely to fail and overlapping sphincteroplasty was more likely to be successful, although this difference did not reach statistical significance. The authors proposed that all patients with RVF undergo preoperative evaluation for occult sphincter defects. This becomes especially important if the patient has symptoms of fecal incontinence or if the cause of the RVF is obstetric trauma.

Anal Canal Neoplasms

EAUS shows the anal canal anatomy well and has an important role in the evaluation of benign and malignant anal neoplasms. Lesions of the anal canal appear as hypoechoic areas on EAUS, and the size and extent of lesions can be detailed. Tissue confirmation may be obtained with ultrasound-directed needle biopsies, if needed. Benign neoplasms such as lipomas and leiomyomas can be visualized with EAUS, and their relationship to other structures of the anal canal can be defined.

Malignant neoplasms of the anal canal include squamous cell carcinomas, adenocarcinomas, leiomyosarcomas, and melanomas. Squamous cell or epidermoid carcinoma is the most common anal canal malignancy. EAUS is effective in the initial evaluation and follow-up of patients with squamous cell carcinoma of the anal canal.[90] Because this cancer is primarily treated with combined chemoradiotherapy, an accurate method of staging the tumor and assessing response to treatment is essential.

EAUS complements the DRE in determining actual size and circumferential involvement of anal canal

Table 137–4 Ultrasound Staging Classification (uTNM) for Anal Canal Cancer

Classification	Criteria
uT1	Maximal diameter <2 cm
uT2	Maximal diameter 2-5 cm
uT3	Maximal diameter >5 cm
uT4	Adjacent organ invasion
uN0	No evidence of lymph node metastasis
uN1	Evidence of lymph node metastasis

uTNM, ultrasonographic staging of tumor, node, metastasis.

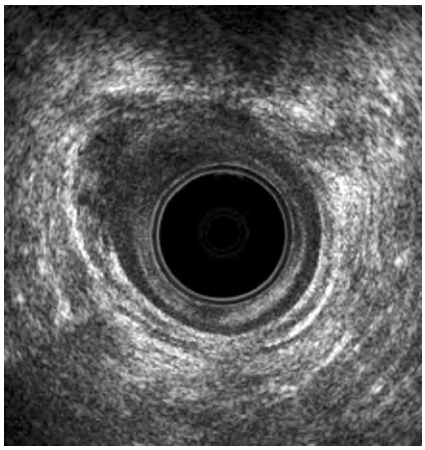


Figure 137–18. Squamous cell carcinoma of the anus. The lesion measured 2.4 cm in maximal diameter, indicating a uT2 anal canal tumor involving both internal and external anal sphincters.

tumors. EAUS staging (uTNM) of anal canal cancers corresponds to TNM (International Union Against Cancer [UICC]) staging (Table 137–4). EAUS accurately measures the greatest diameter of the tumor, which is the basis of T staging for anal canal cancer. Furthermore, EAUS can demonstrate the extent of sphincter muscle involvement. ERUS should always be performed to assess the mesorectum for metastatic lymph nodes. An EAUS image of a squamous cell carcinoma of the anal canal is depicted in Figure 137–18.

Some authors have proposed that ultrasound-based staging systems for cancers of the anal canal include depth of tumor invasion. Tarantino and Bernstein proposed a modified endoscopic staging system that emphasized depth of penetration over size of the tumor and used it to distinguish early lesions that might be amenable to less aggressive treatment.[91] In this system, a uT1 tumor was confined to the submucosa; a uT2a lesion invaded only the internal anal sphincter; a uT2b lesion penetrated into the external anal sphincter; a uT3 lesion invaded through the sphincter complex into the perianal tissues; and a uT4 lesion invaded adjacent structures. They demonstrated that EAUS was highly accurate in determining depth of penetration into the sphincter complex and assessing response of the tumor to chemoradiotherapy. Giovannini et al. proposed a different ultrasound staging system (with a uT2 lesion defined as involving the internal sphincter and a uT3 lesion defined as invading the external sphincter).[92] In a multicenter study of 146 patients, they compared this system with the UICC staging (done by clinical examination only). Their results suggest that ultrasound staging is superior to clinical staging in predicting local recurrence and patient survival.

The value of EAUS in detecting residual tumor as well as early local recurrence after treatment has been supported by small prospective[93] and retrospective[94] studies. Conversely, Lund et al. performed a retrospective study to evaluate the necessity of EAUS in detecting local recurrence.[95] They focused on 52 patients followed by EAUS out of 82 patients treated in their institution for anal canal cancer; 9.6% developed local recurrence, all of which were detected by clinical examination prior to EAUS. The authors concluded that EAUS was unnecessary in the follow-up of anal cancer.

Currently, EAUS is part of most surveillance programs for anal cancer. The small percentage of these patients who fail chemoradiotherapy may undergo abdominoperineal resection for salvage, with a reasonable chance for cure.[96]

Miscellaneous Anorectal Conditions

Retrorectal Tumors

Retrorectal tumors are rare and include developmental cysts, teratomas, chordomas, meningoceles, and miscellaneous neurologic and osseous tumors. CT and MRI are the best imaging modalities for identifying these tumors and their relationships to adjacent anatomic structures, such as the sacral nerves. However, ERUS is useful in assessing possible involvement of the rectal wall and may help in planning the appropriate surgical approach. An ultrasound image of a retrorectal tumor is depicted in Figure 137–19.

Solitary Rectal Ulcer Syndrome and Colitis Cystica Profunda

ERUS can be used in the evaluation of patients with solitary rectal ulcer syndrome or colitis cystica profunda. These conditions are uncommon, but it is important for them to be accurately recognized and not mistaken for malignancy. The endoscopic appearance of a solitary rectal ulcer ranges from that of a typical ulcer with a fibrinous central depression to that of a polypoid lesion. It is always located on the anterior aspect of the rectum, 4 to 12 cm from the anal verge. The fold with the ulcer is thought to represent the lead point of an intussusception into the anal canal. Chronic, repeated straining or prolapse of this lead point result in ischemia and ulceration. Pathologic evaluation reveals obliteration of the lamina propria by fibrosis. In the case of colitis cystica profunda, pathologic examination reveals mucin-containing glands

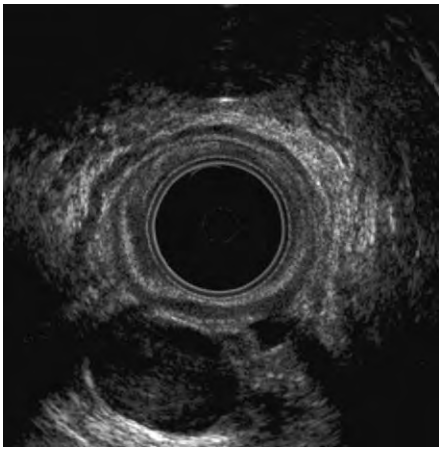


Figure 137–19. Retrorectal/presacral tumor. Note that the rectal wall is not involved on the basis of ultrasound assessment.

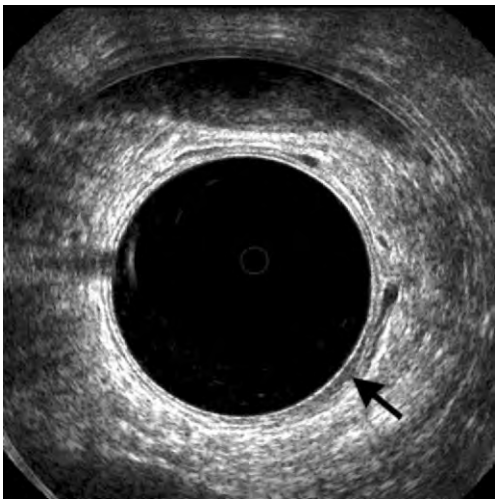


Figure 137–20. Solitary rectal ulcer syndrome. There is thickening of the mucosa and irregularity of the submucosa *(arrow).*

misplaced in the submucosa and lined with normal colonic epithelium.

Sonographically, a solitary rectal ulcer appears as an area of thickened submucosa. The submucosa appears hyperechoic in patients with solitary rectal ulcer due to fibrosis. In contrast, in patients with colitis cystica profunda, the submucosa appears hypoechoic due to mucus-filled cysts.[97] An example of a solitary rectal ulcer identified on ERUS is depicted in Figure 137–20.

SUMMARY

ERUS has proved to be a valuable tool in the diagnosis and management of many anorectal disorders. The accuracy of examination is operator dependent and improves with experience. ERUS is the best available imaging modality for preoperative local staging of rectal and anal canal cancers. Moreover, it has an important role in surveillance after treatment of rectal and anal cancers. ERUS is the diagnostic test of choice for evaluation of fecal incontinence and can be used in the diagnosis of several other benign anorectal conditions. The use of endorectal ultrasonography by surgeons has contributed greatly to the understanding and management of anorectal disease.

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De Anda EH, Suk-Hawn L, Finne CO, et al: Endorectal ultrasound in the follow-up of rectal cancer patients treated by local excision or radical surgery. Dis Colon Rectum 47:818-824, 2004.

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Part

2

Benign Colon, Rectal, and Anal Conditions

Chapter

138

Diagnosis and Management of Fecal Incontinence

Susan C. Parker ▪ Robert D. Madoff

Fecal incontinence is the inability to defer the passage of feces until a desired time and place. Although incontinence of gas, liquid, or solid stool is not a life-threatening disorder, it can dramatically affect an individual's lifestyle and lead to social isolation. Fortunately, most incontinence is amenable to medical or surgical therapy.

The prevalence of fecal incontinence depends on the definition used and the population under study. Community prevalence has been estimated to range from 0.5% to 11%.[1] A Wisconsin telephone survey reported that 2.2% of the general population experienced fecal incontinence of varying degrees.[2] The prevalence increases to 13.4% in outpatients seeing their primary care physicians and 26% in outpatients seeing their gastroenterologist.[3] The highest rates of incontinence are seen in institutionalized individuals; a survey of 18,000 Wisconsin nursing home residents found that 47% of them had fecal incontinence.[4]

EVALUATION

The causes of fecal incontinence are divided into factors that alter anorectal anatomy (trauma, surgery), overwhelm physiologic control mechanisms (diarrhea, secretory tumors, fecal impaction), or interfere with neurologic function (diabetes, spinal cord injury, pudendal nerve injury). In many cases, a combination of factors leads to incontinence (Box 138–1). For example, incontinence associated with rectal prolapse is due to excessive physical stretching of both the anal sphincter and pudendal nerves. Similarly, diminished sphincter strength associated with aging can unmask a previously well-compensated obstetric sphincter injury.

Initial evaluation of the incontinent patient is performed in the physician's office and requires only careful elicitation of pertinent history and performance of a directed physical examination. However, while the initial evaluation can indicate the probable cause of incontinence in many patients, further testing is used to confirm the initial clinical impression. Pudendal nerve injury is not in and of itself visible, and sphincter injury due to surgery or childbirth can be undetectable on later examination after healing has occurred. Laboratory evaluation is also used to quantify the severity of the physiologic deficit, identify specific anatomic abnormalities, and elucidate the causes of incontinence when the diagnosis is obscure or there are multiple abnormalities.

History

Fecal incontinence is embarrassing, and many patients are reluctant to discuss their condition or even identify it by name. Accordingly, one of the first steps in evaluating the incontinent patient may be getting the patient to admit to the problem. Many patients present with complaints of "diarrhea," which on close questioning turns out to be involuntary loss of normal stool. It is also common for a patient to complain of the sudden onset

Box 138–1 Causes of Fecal Incontinence

Normal Pelvic Floor

- Diarrheal states
  - Infectious diarrhea
  - Inflammatory bowel disease
  - Short-gut syndrome
  - Laxative abuse
  - Radiation enteritis
- Overflow
  - Impaction
  - Encopresis
  - Rectal neoplasms
- Neurologic conditions
  - Congenital anomalies (e.g., myelomeningocele)
  - Multiple sclerosis
  - Dementia, strokes, tabes dorsalis
  - Neuropathy (e.g., diabetes)
  - Neoplasms of brain, spinal cord, cauda equina

Abnormal Pelvic Floor

- Congenital anorectal malformation
- Trauma
  - Accidental injury (e.g., impalement, pelvic fracture)
  - Anorectal surgery
  - Obstetric injury
- Aging
- Pelvic floor denervation (idiopathic neurogenic incontinence)
  - Vaginal delivery
  - Chronic straining at stool
  - Rectal prolapse
  - Descending perineum syndrome

From Madoff RD, Williams JG, Caushaj PF: Fecal incontinence. N Engl J Med 326:1002, 1992.

of fecal incontinence and, on careful questioning, reveal that a change in stool consistency preceded the onset of incontinence. Certain risk factors or associated conditions should alert the physician to the presence of fecal incontinence: anal trauma or surgery[5]; vaginal deliveries,[6] especially multiple, difficult, or traumatic ones; pelvic radiation[7,8]; diabetes mellitus, especially with neuropathy; chronic diarrheal states; congenital conditions,[9] such as imperforate anus and spina bifida; urinary incontinence; or complaints of rectal prolapse or anal protrusion.[10,11]

The extent of incontinence should also be quantified. The key components of severity assessment include the nature of the material being lost (flatus, liquid stool, or solid stool), the frequency of loss, and the need to wear a pad. Although it is agreed that solid stool incontinence reflects a greater degree of physiologic impairment than incontinence for liquid stool only, it is noteworthy that patients perceive liquid stool incontinence to be more of a problem because it is more difficult to manage. Numerous scoring systems have been proposed for the evaluation of incontinence, but none has achieved universal acceptance to date.[12] However, the Fecal Incontinence Severity Index (FISI) is being used increasingly because its scores were derived from both patient and colorectal surgeon-based weighting of severity.[13]

Quality-of-life assessment is a critical component to the evaluation of fecal incontinence and the success of its management. The concept itself is obvious, but quantification has proved to be difficult. General scales such as the SF-36 have not proved to be sufficiently sensitive to reflect real changes in patient status. Several incontinence scales combine a subjective quality-of-life assessment with a quantitative severity score to produce a single global incontinence score, an approach that, despite providing a single score per patient, combines two distinctly separate variables.[14] A validated fecal incontinence-specific quality of life score (FIQL) has been developed and is now enjoying widespread use.[15]

Physical Examination

Physical examination of the patient with fecal incontinence begins with external examination of the perianal area. Profuse incontinence, particularly of liquid stool, can lead to excoriation of the surrounding perianal skin. The perianal area should be inspected for scars from previous trauma, episiotomies, or anal surgery. The "keyhole deformity" is a groove in the anal canal, most commonly seen in the posterior midline, caused by a sphincterotomy, fissurectomy, or fistulotomy, that permits seepage of stool or mucus. The female patient with an obstetric injury may have a thin perineal body, an associated rectovaginal fistula, or a cloacae due to loss of the distal portion of the rectovaginal septum and perineal body.

The patient with rectal prolapse may have a visibly patulous anus or one that gapes with traction. The prolapse itself, with its characteristic concentric folds, can be demonstrated by asking the patient to bear down, optimally while seated on a commode. Rectal mucosal prolapse, characterized by radial folds, can cause mucus seepage and staining but is not a cause of more severe incontinence.

The anocutaneous reflex is a test of perianal sensation that is elicited by stroking the perineal skin and observing an anal "wink" due to sphincter contraction. This spinal reflex has its afferent and efferent pathways in the pudendal nerve and is abolished if S4 is transected.

The findings to note on digital examination are the tone of the anal canal, the strength of the squeeze, and whether it seems symmetrical. A strong contraction of the gluteal muscles should not be confused with contraction of the external anal sphincter muscle. Voluntary contraction of the external anal sphincter normally fatigues to a basal level over 3 minutes. A more rapid fatigue may be elicited in the incontinent patient.[16] Puborectalis function is evaluated separately from the external anal sphincter. This muscle forms a sling at the top

of the anal canal that the examining finger can hook around posteriorly. Contraction of the muscle lifts the examining finger or is felt as a generalized tightening at the top of the anal canal. Fecal impaction leading to overflow incontinence should be evident on the initial digital examination. If there is a history of obstetric trauma, the examiner should palpate for a rectal vaginal fistula along with assessment of the perineal body width. Obstetric tears usually occur in the anterior midline, leaving a thin perineal body due to retraction of the sphincter muscle posterolaterally. A rectocele is present if there is a weakness in the rectovaginal septum that allows a digit placed in the rectum to push into the vagina. If a large rectocele is present, the posterior wall of the vagina can be pushed out the introitus.

The anoscope is used to look for prolapsing hemorrhoids, scarring in the anal canal from previous surgery, internal fistula openings, and mucosal inflammation. Any patient under evaluation for fecal incontinence should undergo a flexible sigmoidoscopy to exclude proctitis, cancer, or a benign secretory tumor such as a large rectal villous adenoma. A full colonic or small bowel evaluation is not usually necessary unless there is a history of diarrhea in addition to incontinence.

Laboratory Assessment

In most patients, the history and physical examination determine the cause of fecal incontinence. For the patient with a minor degree of fecal incontinence, medical management is instituted and further testing can be deferred. For most patients, testing at an anorectal physiology laboratory documents the degree of dysfunction, fully determines anatomic defects, and better directs the treatment plan.[17-19] Relevant tests include anal manometry, pudendal nerve latency testing or more advanced electrodiagnostics, endoanal ultrasound, and defecography or peritoneography.

Manometry

Anal manometry determines anal canal pressure to provide an assessment of internal and external anal sphincter function. The entire length of the anal canal is evaluated, using either a "station" or continuous pull-through technique, and any one of a number of available catheters (e.g., water perfused, microballoon, and solid state). Despite the lack of methodologic standardization, the essential measurements are resting pressure, squeeze pressure, and rectoanal inhibitory reflex. The internal anal sphincter tone supplies 55% to 85% of the resting pressure,[20] and accordingly, manometric resting pressure, whether expressed as a maximum or mean, is an indication of internal anal sphincter function. Squeeze pressure reflects external anal sphincter function but, because it is under voluntary control, requires a cooperative patient to be accurate. Both resting and squeeze pressures are higher and sphincter length is longer in males than in females and pressures decrease with age.[21,22]

Rectal sensation is determined by inflating a rectal balloon with air and recording the volume of first sensation, sensation of fullness (urge to defecate), and maximum tolerated volume. Abnormal rectal sensation can lead to incontinence in two ways. Hyperacute sensation is seen when proctitis is present, typically due to inflammation or radiation therapy. Under these circumstances, the rectum is unable to tolerate an adequate volume of stool, and reservoir function is lost. Conversely, dulled sensation, as is seen in megarectum and some neurogenic disorders, leads to overflow incontinence.

The rectoanal inhibitory reflex is a decrease in resting pressure that occurs in response to rectal distention (accomplished in the laboratory by inflation of a rectal balloon). It is absent in Hirschsprung's disease and immediately after rectal resection with coloanal anastomosis, and it can be difficult to detect in the presence of a megarectum or when resting pressures are very low. The rectoanal inhibitory reflex has been postulated to permit anal "sampling" of rectal contents to determine the appropriate sphincter response, such as expelling gas or withholding feces.[20] The exact nature of this sampling, however, has yet to be determined.

Pudendal Nerve Terminal Motor Latency

The pudendal nerve provides motor innervation to the external anal sphincter and sensory innervation to the perineum. Pudendal nerve injury is caused by traction on the nerve during straining (as seen during childbirth or prolonged efforts at defecation), and it results in denervation and subsequent reinnervation of the external anal sphincter and pelvic floor musculature. This reinnervation can be documented with needle electromyography (EMG), which demonstrates polyphasic motor unit action potentials and an increase in fiber density.[23] However, because the examination is uncomfortable, needle EMG is not widely used. Additional useful tests include the pudendoanal and anal reflex (or anal "wink"). The levels of the sacral cord involved in sacral reflexes are S2 to S4. The pudendoanal reflex is elicited by stimulating the dorsal nerve of the penis or clitoris. The pudendoanal reflex is absent or delayed in many patients with fecal incontinence. The absence of an anal wink can also indicate injury, but it is more unreliable.[24]

Pudendal nerve integrity is now most commonly assessed by determination of pudendal nerve terminal motor latency (PNTML). PNTML is measured using the finger-mounted St. Mark's electrode, which stimulates the pudendal nerve at the level of the ischial spine and records the conduction time to the sphincter.[25] Prolonged conduction times are indicative of pudendal neuropathy, which is caused by traction injury to the nerve from vaginal childbirth, prolonged straining, rectal prolapse, or excessive perineal descent.[25] The test is affected by the skill of the examiner and body habitus of the patient; therefore, the significance of an undetectable PNTML is uncertain. Furthermore, because the test evaluates the function of the fastest remaining nerve fiber, incomplete nerve injuries can be missed with this technique. Indeed, fiber density but not pudendal nerve latency correlates with clinical and manometric variables in patients with fecal incontinence.[26] Some investigators

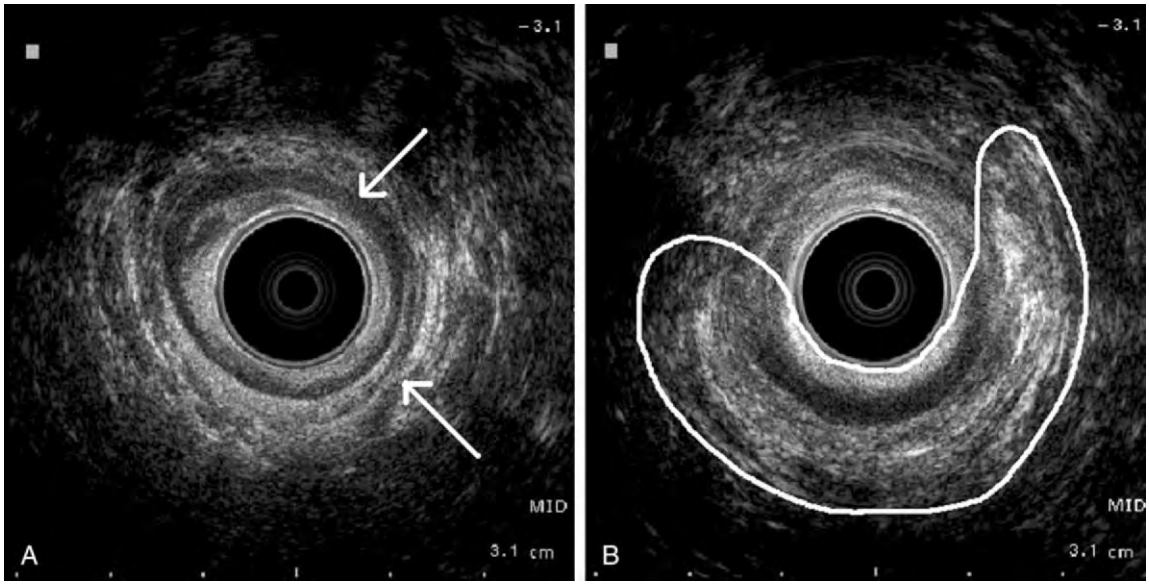

Figure 138–1. Endoanal ultrasound. **A,** Normal sphincter, mid-anal canal: the *arrow* at 1 o'clock indicates the internal anal sphincter, and the *arrow* at 4 o'clock points to the external anal sphincter. **B,** Disruption of anterior internal and external anal sphincter muscles with posterior retraction of muscles. The *line* indicates retracted muscle.

have found an abnormal PNTML to be highly predictive of failure after sphincteroplasty,[27,28] but many others have observed no such correlation.[29,30]

Endoanal Ultrasound

Sphincter mapping helps the surgeon by confirming the presence of a sphincter defect and localizing the site and severity of the defect (Fig. 138–1). The preferred method for sphincter mapping is endoanal ultrasound, optimally using a 360-degree rotating transducer probe that images through a plastic cap. The usual finding after an obstetric injury is an anterior (between rectum and vagina) disruption of the anal sphincters. Other common findings are disruptions of the internal anal sphincter after hemorrhoidectomy or sphincterotomy and disruptions of both sphincter muscles after fistulotomy or trauma. Endoanal ultrasound, in conjunction with manometry, can be particularly useful when evaluating trauma patients for continence before reversing a diverting stoma, because the degree of anal sphincter injury can be difficult to determine at the time of the initial trauma. Sphincter mapping is also described using magnetic resonance imaging (MRI), but its use is limited and MRI may be less accurate at detection of internal anal sphincter defects.[31]

Defecography

Defecography, also termed *evacuation proctography,* is a dynamic study of rectal emptying. The rectum is filled with thick barium paste, which the patient is asked to evacuate under videofluoroscopy. Defecography is useful for evaluation of suspected rectal prolapse, including both internal intussusception and true procidentia. Patients with severe incontinence may be unable to hold the contrast agent without involuntary leakage, a finding that confirms the presence of a severe functional deficit. Defecography is also useful in demonstrating associated pelvic floor disorder that may be seen in the incontinent patient. The failure of appropriate pelvic floor relaxation is well visualized on defecography along with the degree to which flow of contrast is impeded. Although this is more often of significance in the evaluation of constipation, defecography can be helpful to identify a patient with overflow incontinence or incontinence due to a poorly emptying rectocele, especially if the patient also has sphincter dysfunction. Visualization of other associated disorders, such as enteroceles and pelvic floor hernias, can be optimized by the addition of a vaginal, small bowel, or peritoneal contrast agent.[32]

Benefits and Limitations of Physiology Testing for Incontinence

Over the years, many surgeons have argued that anorectal physiology tests add little to the "educated finger" in the evaluation of the incontinent patient. It is true that much can be learned by a careful physical examination and equally true that physiologic findings do not necessarily correlate with clinical status, but we believe that the appropriate use of anorectal physiology testing does improve the care of the incontinent patient. An early branch point in the algorithm for incontinence therapy is the presence or absence of a sphincter defect. Sphincter defects may be clinically obvious, or they may be subtle and difficult to detect. Anal ultrasonography

provides a rapid and definitive answer. Anal manometry provides an objective assessment of internal and external sphincter function, even if there is an underlying broad range of normal. Mild unilateral pudendal neuropathy may not accurately predict functional failure after sphincteroplasty, but the presence of severe bilateral neuropathy may help surgeons pick the best therapy for a given patient or at least counsel the patient regarding a diminished likelihood of success. In short, we believe that careful and complete patient evaluation leads to accurate categorization, appropriate treatment, and optimized outcome.

TREATMENT

Medical Therapy

Because fecal incontinence can be exacerbated by abnormal bowel function, initial treatment efforts should be directed at correction of any associated underlying disorders. Severe diarrhea can overcome even a normal sphincter mechanism, and even mild chronic diarrheal states can be sufficient to tip a marginally compensated individual with abnormal sphincter function into frank clinical incontinence. Incontinent patients with loose stool should be evaluated for a cause of their diarrhea, including infection, malabsorption syndromes, and, in particular, occult inflammatory bowel disease. Irritable bowel syndrome is an important related entity. Although this disorder alone is not a cause of incontinence, it is widely prevalent and often complicates the management of patients with incontinence due to other disorders.

Management of the incontinent patient depends on the severity of his or her symptoms. Mild incontinence is usually best treated by conservative medical management. Food intolerance causing malabsorption can contribute significantly to symptoms, and patients should be alerted to this possibility. The classic example of this phenomenon is occult lactose intolerance, which can lead to liquid stool and excessive flatulence with consequent urgency and diminished bowel control.

Because solid stool is easier to control than liquid and because liquid stool incontinence is more distressing to patients than solid, all efforts should be made to optimize stool consistency. This goal is often best achieved by the consumption of adequate quantities of dietary fiber. Although 30 g/day of dietary fiber is most commonly quoted as the therapeutic goal, many patients find this level unachievable, and for most, 20 to 25 g/day is a reasonable target. Patients are able to best reach this goal with appropriate dietary counseling and the use of a stool-bulking supplement such as psyllium or methylcellulose. Increased dietary fiber and supplemental psyllium should be gradually instituted to diminish the side effects of bloating and increased flatulence.

Patients with mild to moderate incontinence frequently improve with antidiarrheal medicines such as loperamide or diphenoxylate with atropine. Loperamide is related to haloperidol and decreases intestinal motility and secretion. Diphenoxylate with atropine has a mode of action similar to that of other related narcotics, such as morphine. Of these, only loperamide is a sphincter agonist that can increase sphincter pressure.[33] These drugs are often best used prophylactically when patients can predictably expect difficulty, such as at bedtime for patients with nocturnal incontinence and before leaving the home for patients with limited ability to defer evacuation. Patients with mild seepage may also benefit from several simple ancillary measures, including tap water irrigation of the rectum after bowel movements using a bulb syringe, use of a small absorbent cotton wick placed adjacent to the anal orifice, and regular application of a barrier cream to the perianal skin.

Biofeedback

Although Kegel exercises have been a popular approach to the incontinent patient, especially in the postpartum period, results for patients with significant incontinence are unimpressive. One reason for this may be that patients attempting to strengthen their pelvic floors may or may not be exercising the muscles they intend to exercise. In addition, because fecal incontinence is often related to several physiologic abnormalities, it is reasonable to suspect that addressing voluntary sphincter contraction alone may not improve a problem that is multifactorial in origin.

Biofeedback describes a class of techniques that use monitoring devices to provide information regarding a physiologic function so an individual may voluntarily alter or control that function. In the case of the anorectum, patients attempting to activate their sphincter mechanisms receive feedback confirming the extent to which muscle contraction is actually occurring.

Although initially popularized using the Schuster three-balloon system,[34] most centers now use either EMG or standard anal manometric approaches. Sensory training is variably provided, either to improve rectal sensation or to increase maximally tolerated rectal volume. Some stress the importance of coordinating appropriate sphincter contraction to rectal sensation.[34,35] However, the physiologic mechanism by which biofeedback exerts its effect is uncertain. Although much biofeedback training is directed at improving voluntary sphincter contraction, successful results appear to correlate more with improved sensation[35,36] than improved motor function.[37,38]

Incontinent patients are candidates for biofeedback if they are adequately motivated and intellectually capable of following instructions. It is commonly held that they should have some ability to contract their anal sphincter and at least some rectal sensation, but these latter qualifications are vague and poorly substantiated in the literature. The cause of incontinence does not appear to affect the outcome of therapy, although patients with keyhole deformities do poorly because of continued stool leakage through the anatomic defect.[37]

A systematic review of biofeedback and pelvic floor exercises for treating fecal incontinence in adults identified 46 studies involving 1364 patients[39]; 49% of patients were reported cured, and 72% improved or cured. However, only 8 of the 46 studies reviewed included a

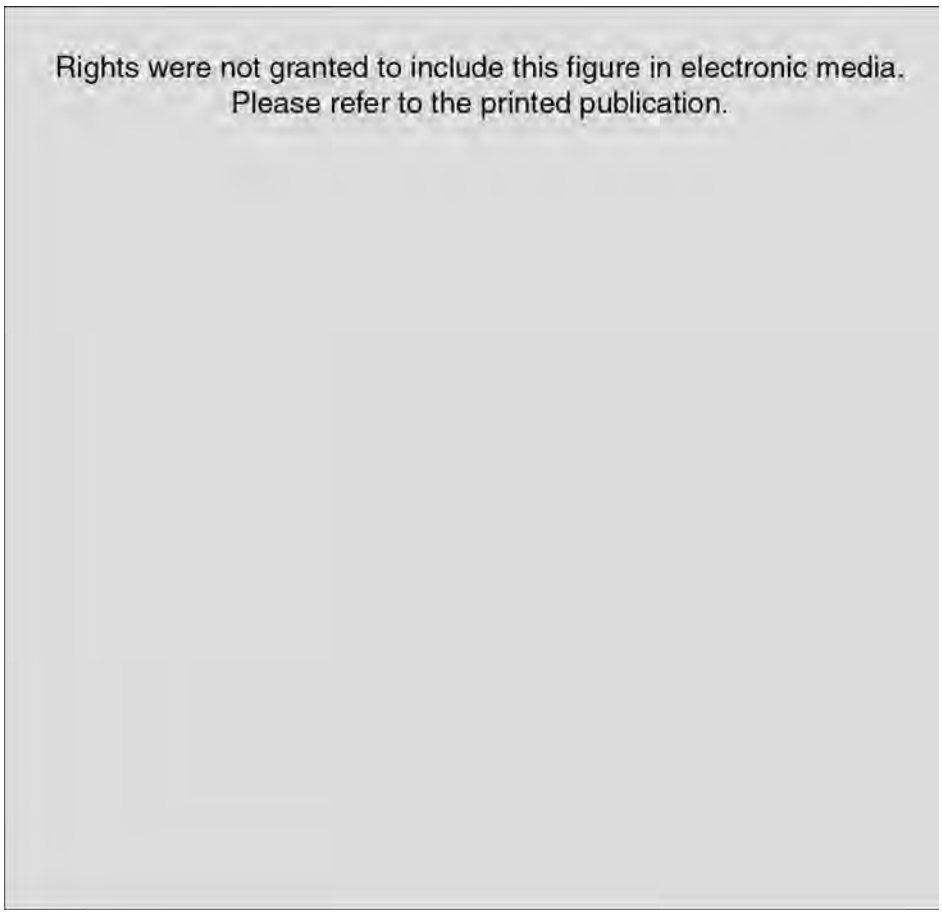

Figure 138–2. Sphincteroplasty. **A,** With the patient in the prone jack-knife position, a curvilinear incision is made. Inferior rectal nerves cross the ischiorectal fossa posterolaterally. **B,** Anterior levatoroplasty is performed, and overlapping sphincter repair is then initiated. **C,** Sphincter repair is completed. **D,** The incision is closed, with drains in place (optional), and V-Y plasty is done to restore the perineal body. (**A-D,** From Baxter NN, Madoff RD: Motility disorders. In Souba WW, Fink MJ, Jurkovich GJ, et al [eds]: ACS Surgery: Principles and Practice, section "Alimentary Tract and Abdomen." New York, WebMD, 2005.)

control group, and most individual reports are subject to criticism due to small patient numbers, short follow-up periods, heterogeneous patient groups, poor quantification of incontinence severity, and the addition of concurrent therapy (e.g., dietary counseling) and physician encouragement, each of which may alone lead to clinical improvement. Indeed, a recent randomized, controlled trial called the efficacy of biofeedback into question because it showed no benefit when biofeedback was added to standard medical care (advice from a nurse specialist) or standard care plus sphincter exercises.[40] Despite these caveats, many clinicians continue to believe that biofeedback is an effective treatment option for patients with fecal incontinence. Indeed, there are few contraindications to a trial of biofeedback, and the technique is painless and risk free. It plays a particularly important role in the treatment of patients with minor degrees of incontinence in whom no anatomic sphincter defect is present and for whom surgery is therefore not indicated. Biofeedback has also been shown to be useful to improve the function of patients with suboptimal results after sphincteroplasty.[41]

Surgery

Surgery for fecal incontinence varies considerably depending on the clinical situation. Traumatic sphincter disruptions are repaired. Should sphincter repair not be indicated or fail, salvage procedures including insertion of an artificial anal sphincter, placement of a sacral nerve stimulator, or injection of sphincter-bulking agents are new options. For patients with persisting refractory incontinence, fecal diversion remains an excellent choice.

Sphincter Reconstruction

Direct sphincter repair (Fig. 138–2) can be performed in the acute setting in the presence of an isolated and easily definable sphincter disruption; this scenario most often occurs in the delivery room after obstetric injury. These injuries are typically repaired with simple sphincter apposition, but up to 70% of women have persisting sphincter defects and 50% persisting incontinence after repair in this setting.[42] Nonoperative traumatic injuries can

often be treated in a similar fashion; however, when severe associated pelvic injuries are present, when the patient is unstable, or when long-standing local contamination is present, débridement with the placement of a diverting stoma plus planned delayed sphincter repair is a better option. Delayed sphincter repair is also required to treat unrecognized sphincter injuries, failed primary repairs, and incontinence after fistulotomy. In each of these cases, definitive surgery should be delayed 3 to 6 months until all local inflammation has resolved.

Patients undergoing elective sphincter repair should have a complete mechanical bowel preparation preoperatively. The operation is best performed with the patient in the prone jack-knife position with the buttocks taped apart. General or regional anesthesia may be used. For anterior defects, a curved circumanal incision is performed along the perineal body and extended laterally over the ischiorectal fossae. A flap of anoderm and, proximally, rectal mucosa is raised along the length of the anal canal anteriorly. Next, the external anal sphincter is mobilized from the vagina anteriorly and laterally until the retracted scarred ends can be easily overlapped to form the repair. Posterior dissection of the sphincter muscle should not extend beyond the mid-lateral line to avoid potential injury to the pudendal nerves, which enter the sphincter posterolaterally. Proximal dissection continues until a proximal nonscarred plane is reached or the inferior fibers of the puborectalis are encountered as they run anteriorly to the pubis.

The midline scar is divided but not excised to minimize the risk of suture pull-through. The buttock tapes are released. Many surgeons perform an anterior levatoroplasty in an effort to lengthen the functional high-pressure zone. Some also advocate reefing of the rectovaginal septum to provide additional anterior support. The divided sphincter is then overlapped to create a "snug" wrap, and this is secured with a series of interrupted 2-0 polydioxane or polyglycolic acid horizontal mattress sutures. Most surgeons perform a "mass" overlap of the combined internal and external sphincter muscles. Others advocate individual dissection and repair of the internal and external sphincter muscles, but the hypothetical superiority of this approach remains to be clinically demonstrated.[27] The skin is loosely closed in a T-shaped configuration, vertically in the anterior aspect to provide adequate length for the perineal body and transversely in the posterior aspect adjacent to the anal verge. No covering stoma is raised.

Results of incontinence surgery vary with definitions of success and closeness of patient follow-up. For many years the reported results after overlapping sphincteroplasty were remarkably consistent: approximately 60% to 75% of patients achieved a "good to excellent" surgical outcome, which in practice entailed perfect or near-perfect control of solid stool, occasional difficulties with control of liquid stool, and episodic "minor" accidents such as seepage or uncontrolled passage of flatus. An additional 15% to 20% of patients achieved lesser degrees of improvement, whereas the remaining 15% to 20% were unchanged or, rarely, worse.[27,29,43,44] Recent series, however, have raised questions about the quality and durability of results following sphincteroplasty.[45-48] Karoui et al. found that 49% of patients were completely continent 3 months after sphincteroplasty, but only 28% were completely continent 40 months after surgery.[47] Halverson and Hull reported that 54% of patients were incontinent to liquid or solid stool 69 months after sphincteroplasty, and only 14% were completely continent.[46] Malouf et al. found that no patients were fully continent 77 months after sphincteroplasty; 84% had fecal urgency and 79% had passive soiling.[45] At the University of Minnesota, we assessed long-term results in 191 consecutive patients after sphincteroplasty. At 10 years' follow-up, just 6% were completely continent, 57% were incontinent of solid stool, and 16% were incontinent of gas only. Results worsened significantly between 3 and 10 years after the procedure.[48]

Salvage Therapy: Postanal Repair and Anal Encirclement

There are a number of options available as salvage therapy for incontinent patients who have failed or are not candidates for standard therapy. The Parks postanal repair was initially devised as an operation for patients with intact but poorly functioning sphincters.[49] The procedure, a posterior plication of the levatores ani and external sphincter, is performed via an intersphincteric dissection. Although once popular in the United Kingdom, the operation never gained widespread acceptance in North America and is performed relatively infrequently. Long-term results from St. Mark's Hospital showed that 26% of patients were continent to stool at a median follow-up of 6 years.[50] However, despite imperfect continence, most patients were improved from baseline.

Anal encirclement in a variety of forms has been used to treat fecal incontinence. The simplest form of this operation, using silver wire, was described by Thiersch in the 19th century.[51] Despite a trend toward the use of softer and more pliable encircling materials, the operation has been plagued by a high local complication rate due to erosion and infection. In 1952, Pickrell et al. devised an operation in which the anal canal was encircled by a transposed gracilis muscle whose neurovascular bundle was maintained intact in the proximal thigh.[52] Pickrell's operation was attractive both because it avoided foreign material and because it created a sphincter that the patient could voluntarily contract (by abducting the thighs). Unfortunately, functional results were generally poor with this procedure, and it never gained widespread acceptance. Several modifications of gluteus maximus transposition have also been described, with highly variable functional results being reported.[53-55]

Dynamic Myoplasty

Interest in gracilis transposition was renewed with the introduction of electrical stimulation by means of an implantable pulse generator.[56] Electrical stimulation is used first to convert the gracilis from predominantly type 2 ("fast-twitch," fatigable) to predominantly type 1 ("slow-twitch," fatigue-resistant) muscle fibers. The stimulator is

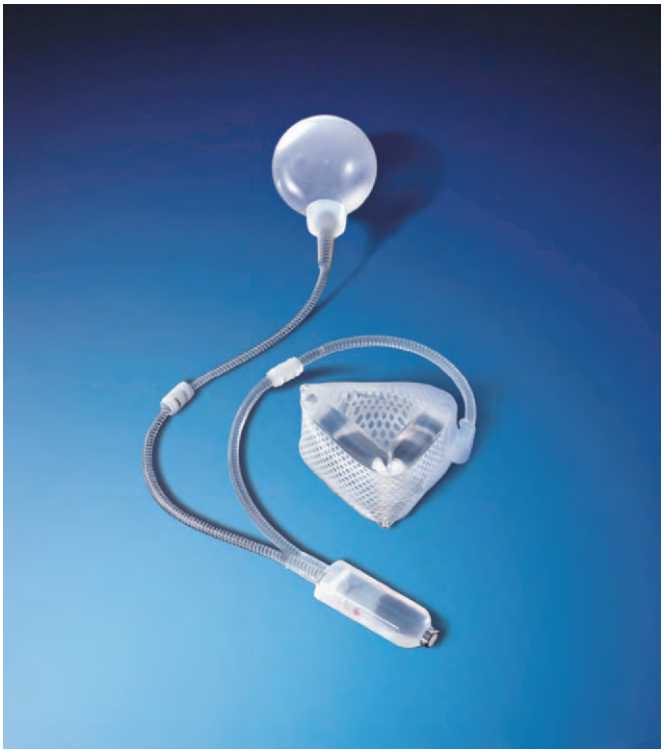

Figure 138–3. Acticon neosphincter. (Courtesy of American Medical Systems, Inc., Minnetonka, MN. *www.AmericanMedicalSystems.com*)

Figure 138–4. Artificial anal sphincter. The recommended placement of the artificial anal sphincter device in the patient is shown. (From Baxter NN, Madoff RD: Motility disorders. In Souba WW, Fink MJ, Jurkovich GJ, et al [eds]: ACS Surgery: Principles and Practice, section "Alimentary Tract and Abdomen." New York, WebMD, 2005.)

then used to maintain tonic contraction of the transposed muscle, thereby providing continuous sphincter function. Defecation is effected by switching off the stimulator with a hand-held programmer.

Baeten et al. reported a continence rate of 73% in 52 patients who underwent dynamic graciloplasty for refractory fecal incontinence. The success rate was highest (92%) in patients with sphincter trauma (including obstetric, operative, and accidental) and lowest in patients with anal atresia (50%).[57] Similar success rates were documented in two multicenter trials of dynamic graciloplasty, but both also documented a prohibitively high rate of operative morbidity.[58,59] Because of this high morbidity rate, dynamic graciloplasty has not been approved for use in the United States, and its use worldwide is limited to a small number of specialty centers.

Artificial Anal Sphincter

The artificial anal sphincter (Figs. 138–3 and 138–4) provides an alternative option for patients with severe refractory fecal incontinence. Compared with dynamic graciloplasty, it offers the advantages of simplicity, placement in a single operation, and use of the device 6 weeks after placement without the need for muscle conditioning.

The artificial anal sphincter in use is a modification of an artificial urinary sphincter. It is an implantable device composed of a silicone elastomer that maintains continence via a fluid-filled cuff that surrounds and compresses the anal canal. The patient controls the device via a pump placed in the scrotum or labia. Squeezing the pump 9 to 12 times forces the fluid from the cuff into a reservoir balloon, which is implanted in the space of Retzius. This deflates the cuff and opens the anal canal, allowing the passage of stool. The cuff then automatically slowly reinflates and occludes the anal canal, providing continence until defecation is again desired.

The implantation of an artificial anal sphincter for fecal incontinence was first reported by Christiansen and Lorentzen in 1987.[60] Reported results reflect the early use of the modified urinary sphincter (AMS 800) and the later use of a similar device (Acticon neosphincter) with additional modifications for use around the anal canal.[61-63] Wong et al. performed a multicenter prospective trial of the Acticon neosphincter in 115 patients[64] and found that 46% of implanted patients required revisional surgery, frequently because of infectious complications; 41% of patients required device explantation (17% of these were able to be reimplanted); and 85% of patients who retained their device had a successful outcome, but intention-to-treat success was only 53%. There is some evidence that results improve with surgical experience,[65] but the long-term explantation rate is 40% or greater.[61,66,67] A multicenter study using a specific antibiotic regimen decreased the infection rate of 25%, experienced in the initial multicenter trial, to 9%.[68] Despite several single-center series that have reported successful results in the majority of patients,[65,69,70] a recent systematic review concluded that implantation of the artificial anal sphincter was "of uncertain benefit."[71]

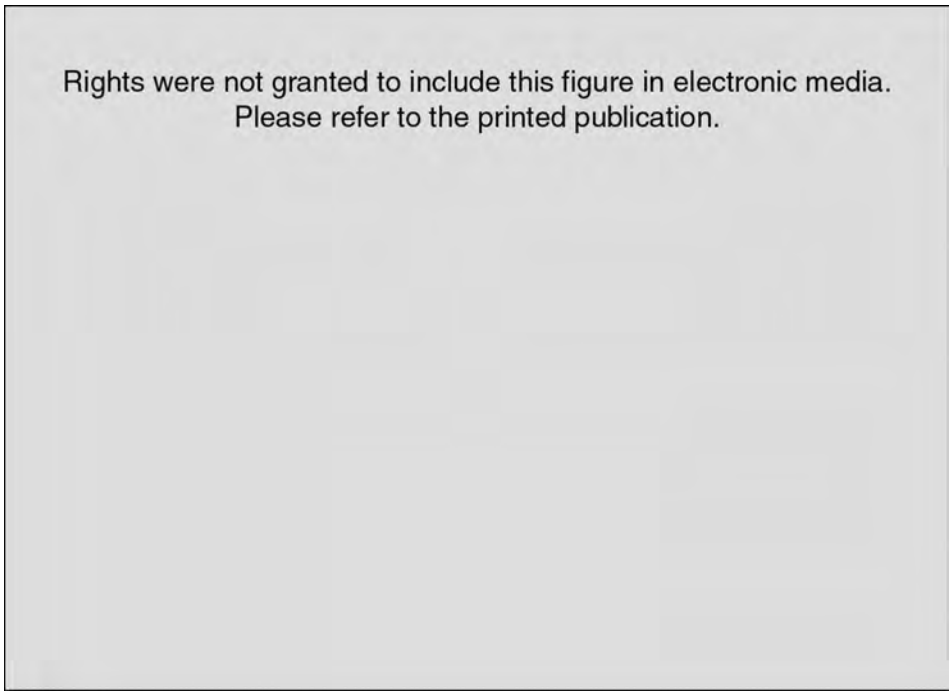

Figure 138–5. Sacral nerve stimulation (SNS). **A,** A lead containing four electrodes is used for SNS. **B,** The sacral foramina are identified; in most cases, S3 is the optimal choice for stimulation. **C,** The quadripolar lead is shown in position. (**A-C,** From Baxter NN, Madoff RD: Motility disorders. In Souba WW, Fink MJ, Jurkovich GJ, et al [eds]: ACS Surgery: Principles and Practice, section "Alimentary Tract and Abdomen." New York, WebMD, 2005.)

Sacral Nerve Stimulation

Sacral nerve stimulation (Fig. 138–5) represents a novel alternative approach to the management of fecal incontinence in highly selected patients. The technique, like the artificial anal sphincter, was initially devised for urinary incontinence. The pudendal nerve is composed of fibers emanating from S2, S3, and S4, and each of these sacral nerves is evaluated using a percutaneous electrode via the sacral foramen. Because these sacral nerves also contribute fibers to the nerves of the lower extremity, it is not surprising that their stimulation leads to the contraction of both the pelvic floor and various leg and foot muscles. It is important that the sacral foramen selected provides maximal pelvic floor and minimal lower extremity stimulation. In clinical practice, this site is most often S3. Once the optimal site has been selected, patients undergo a test period of stimulation with an external pulse generator. If function has improved adequately at the end of the test period, implantation of the permanent leads and pulse generator is performed.

The clinical use of sacral nerve stimulation was pioneered by Matzel et al. in Erlangen.[72] Vaizey and associates reported the results of short-term stimulation for patients with fecal incontinence, a structurally intact external anal sphincter, and manometrically weak internal or external anal sphincters.[73] Successful results, with a marked decrease in incontinent episodes, occurred in 11 of 12 patients. Physiologic studies demonstrated an increase in resting and squeeze anal pressures and a decrease in rectal sensitivity. Ambulatory manometry showed a qualitative decrease in rectal motor complexes and episodes of spontaneous anal relaxation, effects suggesting autonomic nerve effects. However, the mechanism of improvement after sacral nerve stimulation remains unknown. Possible alternatives include a decrease in gastrointestinal transit, decrease in rectal contractility, altered rectal sensation, improved coordination of sensorimotor function, and alterations in anal tone and pressures. The exact nerves that effect changes in incontinence in response to sacral nerve stimulation are unknown. Which nerves are stimulated depends both on the placement of electrode and on the diameter of the nerve in the vicinity of the electrode. Because the largest nerves have the lowest stimulation thresholds, it is most likely that somatic motor efferents and sensory afferents are involved. However, the physiologic findings also suggest that smaller autonomic nerve fibers are also being stimulated.

Sacral nerve stimulation is widely used for urinary incontinence, with more than 15,000 operations worldwide. As the operation is identical for the patient with fecal incontinence, safety and complications are well documented, whereas efficacy is still unknown. To date, most single-center reports of sacral nerve stimulation have reported small cohorts of patients with limited follow-up periods.[74-76] However, a recent prospective, multicenter trial demonstrated a dramatic decrease in incontinent events at 12 and 24 months' follow-up in a cohort of 34 patients who underwent implantation.[77] Quality of life as measured by the FIQL score significantly improved. A multicenter trial is underway in the United States, and results are expected in 2006.

Injectable Biomaterials

Several recent studies have investigated the role of injectable biomaterials in the management of fecal incontinence.[78,79] To date, only relatively small series with limited follow-up have been reported, but success rates have generally been good. Injected materials have

included autologous fat, cross-linked collagen, silicone Bioplastique, and carbon-coated beads. Potential advantages of this technique include simplicity and the ability to offer treatment in an outpatient setting. A successful result can require repeated injections and migration of the injected material is reported. Manometric pressures are not significantly altered. Controlled trials with long-term follow-up are needed.

Fecal Diversion

Despite the broad range of therapies available to the incontinent patient, there inevitably remains a subgroup of patients who fail therapy or simply are not candidates for major reconstructive surgery. In most cases, unmanageable anal incontinence can be converted to a manageable situation by the creation of a stoma, most often a sigmoid colostomy. Although many patients shy from this approach, the loss of body image is generally more than compensated for by the gain in control, self-esteem, and freedom of action. Although available data are quite limited, one questionnaire study of patients who underwent colostomy for fecal incontinence documented marked improvement in subjective quality-of-life assessment after surgery.[80] Counseling by an enterostomal therapist and discussion with other ostomates are invaluable resources in assisting the patient to make an appropriate and informed choice regarding stoma creation. Furthermore, because patient satisfaction is critically dependent on the quality of the stoma provided, preoperative stoma site selection and careful attention to the technical details of stoma creation are mandatory.

CONCLUSIONS

Fecal incontinence is a clinically important disorder whose impact on the individual can range from distressing to devastating. An orderly approach to patient history and physical examination will lead to the diagnosis and its cause in most patients. Patients with mild incontinence often improve with medical therapy. Those with more severe symptoms or an uncertain cause or who are medically refractory should undergo formal physiologic evaluation to optimize their treatment. Most of these patients are successfully treated using biofeedback or standard surgical approaches. For those for whom these strategies fail, salvage therapy with what are now investigational techniques will increasingly become an option in the future.

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Chapter

139

Surgical Treatment of Constipation

David J. Maron · Steven D. Wexner

Constipation is one of the most frequently experienced gastrointestinal complaints and one of the most common indications for medical consultation.[1] It is estimated that more than 4 million patients in North America suffer from constipation, and laxatives are prescribed for 2 million individuals annually at a cost of more than $800 million.[2] In the United States, more than 90,000 patients are hospitalized each year for constipation-related problems.[3] Constipation has been shown to be more prevalent in persons of lower socioeconomic background,[3,4] females,[5] and the elderly.[3]

The definition of constipation includes both subjective and objective aspects. In addition to decreased frequency of defecation, patients may present complaining of incomplete or difficult evacuation, abdominal or rectal pain, hard stools, decreased stool bulk or caliber, straining for evacuation, nausea, bloating, and tenesmus. Whitehead et al.[6] proposed that at least two of the following need to be present in a patient who has not used laxatives for at least 12 months: (1) straining during more than 25% of bowel movements; (2) feeling of incomplete evacuation after more than 25% of bowel movements; (3) hard stool on more than 25% of bowel movements; and (4) bowel movement frequency of less than two per week with or without symptoms of constipation. Agachan et al.[7] proposed a scoring system that includes frequency of bowel movements, painful evacuation, incomplete evacuation, abdominal pain, length of time per attempts, assistance for defecation, unsuccessful attempts for evacuation per 24 hours, and duration of constipation. After evaluating more than 230 patients, the authors concluded that a score of 15 or greater represents constipation.[7] However, the Rome II criteria are probably the most widely used set of definitions for constipation.[6]

ETIOLOGY

Numerous diseases can cause constipation. Therefore, before attributing constipation to functional or idiopathic reasons, other diagnoses (Box 139–1) must be excluded.

EVALUATION

History and Physical Examination

The significant and critical information obtained from a highly detailed clinical history is mandatory. Thorough abdominal and perineal examinations must be undertaken, with the performance of an inspection of the anal region, including a digital examination, anoscopy, and a rigid or flexible sigmoidoscopy. The abdominal examination should identify any masses, distention, scars, or tenderness. A digital examination can exclude distal obstructive causes of constipation and unveil the presence of any hard stool in the rectum. This latter finding may be common in patients who present with irritable bowel syndrome, inadequate fiber intake, or adequate fiber intake with suboptimal fluid ingestion.

Diagnostic Studies

Barium Enema/Colonoscopy

No patient who complains of constipation should be considered to have a functional cause until mechanical and extracolonic causes are excluded. Therefore, sigmoidoscopy or proctoscopy should be supplemented by a double-contrast barium enema. Although colonoscopy

Box 139–1 **Classification of Constipation**

Congenital

- Hirschsprung's disease

Acquired

- Chagas' disease

Mechanical (obstructive)

- Neoplasia
- Adhesions
- Hernia
- Volvulus
- Endometriosis
- Severe sigmoid diverticulitis
- Anal stenosis

Functional

- Inadequate fiber intake
- Irritable bowel syndrome

Idiopathic

Colonic
- Inertia
- Dolichocolon

Pelvic
- Intussusception/rectal prolapse
- Rectocele
- Sigmoidocele
- Descending perineum
- Paradoxical puborectalis contraction
- Perineal hernia

Extraintestinal

Pharmacologic
- Analgesics
- Anesthetics
- Anticholinergics
- Anticonvulsants
- Antidepressants
- Antiparkinsonian agents
- Antacids
- Barium sulfate
- Diuretics
- Ganglionic blockers
- Iron
- Hypotensives
- Laxative abuse
- Metallic intoxication (arsenic, lead, phosphorus)
- Monoamine oxidase inhibitors
- Opiates
- Paralytic agents
- Parasympatholytics
- Phenothiazines
- Psychotherapeutic

Metabolic and endocrine
- Amyloidosis
- Diabetes
- Hypercalcemia
- Hyperparathyroidism
- Hypokalemia
- Hypopituitarism
- Hypothyroidism
- Pheochromocytoma
- Porphyria
- Pregnancy
- Scleroderma
- Uremia

Neurogenic

Peripheral
- Autonomic neuropathy
- Von Recklinghausen's disease
- Multiple endocrine neoplasia 2b

Spinal
- Cauda equina tumor
- Iatrogenic
- Meningocele
- Multiple sclerosis
- Paraplegia
- Resection of nervi erigentes
- Shy-Drager syndrome
- Tabes dorsalis
- Trauma

Central
- Parkinson's disease
- Stroke
- Tumors

is a better means of excluding neoplasia, it may be technically challenging due to the redundancy associated with constipation. Alternatively, a barium enema gives the physician a view of the anatomic configuration of the colon, including its size and length.[8] Both constipated and nonconstipated persons can present with large, dilated colons (megacolon) and dolichocolon (Fig. 139–1).

Clinical Approach

Before referral for expensive and invasive physiologic testing, all anatomic and extracolonic causes of constipation must be excluded. Therefore, after the initial office evaluation and air-contrast barium enema, the aim of the general evaluation should be to exclude all of the extracolonic entities listed in Box 139–1. After such

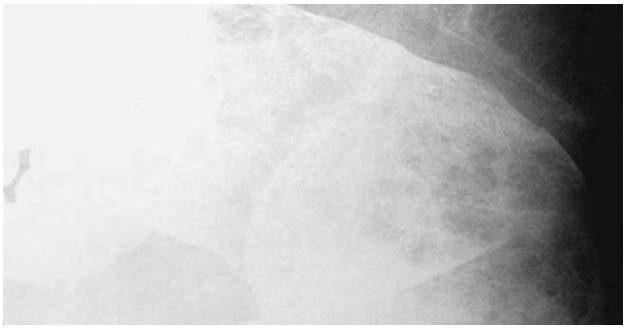

Figure 139–1. Barium enema of a patient with chronic constipation. Typical findings of megarectum include a very elongated and redundant colon.

exclusion, a 6-month course of fiber supplementation, dietary measures, and exercise should eliminate patients who have inadequate fiber or water intake as the source for their constipation.[9] The patient should strive to develop regular bowel habits and try to have a bowel movement in the morning or after meals to take advantage of the gastrocolic reflex. The prompt discontinuation of any stimulant laxative is generally advised, because the earlier mentioned measures should suffice. If laxatives must be prescribed, stool softeners and lubricants are the preferred choices (Box 139–2).

The failure of such measures should prompt physiologic investigation. Rantis et al.[10] reviewed 51 patients with chronic constipation regarding the cost of the diagnostic evaluation and treatment outcome. Fiber, cathartics, and biofeedback therapy were successful in 33 (65%) of 51 patients, and 12 of the 18 remaining patients underwent surgery, with 10 achieving good results. Although an average of $2752 was charged during extensive diagnostic testing, ultimately only the 12 patients who underwent surgery truly benefited from the workup. This study was small and included an analysis of charges rather than of costs; therefore, it does not allow elucidation of the problem or even support the authors' claims. In our department, constipated patients undergo a colonic transit time study, manometry, defecography, and anal electromyography (EMG). The distinction between colonic inertia and a pelvic outlet obstruction syndrome is crucial, because it will have a direct influence on therapy.

Box 139–2 General Classification of Laxatives

Bulk-Forming Agents
- Dietary
- Synthetic or processed
- Methylcellulose
- Polycarbophil
- Psyllium

Lubricants
- Mineral oil

Emollients
- Docusate (calcium, sodium, or potassium)

Saline Laxatives (osmotic agents)
- Magnesium-containing compounds (citrate, hydroxide, sulfate)
- Sodium phosphate
- Lactulose
- Lactilol
- Sorbitol

Stimulant (irritant)
- Bisacodyl
- Senna
- Phenolphthalein
- Danthron
- Casanthranol
- Castor oil
- Cascara

From Wexner SD, Bartolo DCC: Constipation: Etiology, Evaluation, and Management. Oxford, Butterworth-Heinemann, 1995.

Physiology Laboratory

Colonic Transit

Colonic motility studies have demonstrated that electric activity occurs in the colon as rhythmic or sporadic nonpropagating bursts and sporadic propagating bursts (mass movements) that occur approximately six times per day.[11] Colonic motility is modulated by gastrointestinal hormones such as gastrin, serotonin, vasoactive intestinal peptide, and substance P, as well as by a number of local colon reflexes.

The measurement of colonic transit through the ingestion of radiopaque markers has been used and often modified since 1981.[12-15] In its most "user-friendly" form, the test includes the ingestion of a single capsule containing 24 radiopaque markers (Sitzmarks) followed by radiographs taken on the 5th day after the capsule ingestion. All laxatives, enemas, and suppositories must be discontinued prior to the examination. The diagnosis of colonic inertia is made if 20% or more of the markers are found to be diffusely scattered throughout the colon by the 5th day (Fig. 139–2).[16] Pelvic retention of the markers is consistent with the diagnosis of outlet obstruction.

Advantages of this method determining colonic transit are simplicity, reproducibility, and low cost. Nam and associates[17] studied a group of 51 patients with

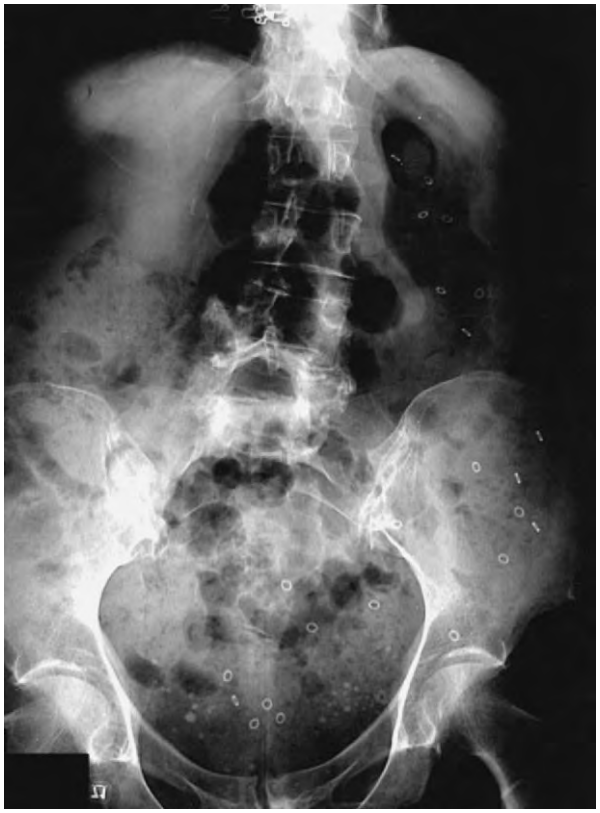

Figure 139–2. The radiograph shows the markers distributed diffusely throughout the colon on the 5th postingestion day. The diagnostic finding is consistent with colonic inertia.

chronic idiopathic constipation, each of whom underwent two colonic transit studies. Patients were divided into three groups: colonic inertia, anismus, and chronic idiopathic constipation. In 35 patients (69%), the results were equal between the two studies, and in 16 patients (31%), the results were disparate (gamma correlation coefficient [CC] = 0.53, $P < 0.01$). When the tests were repeated within 1 year, the CC was 0.38 ($P < 0.05$), whereas for periods of more than 1 year, the CC was 0.79 ($P < 0.01$). The authors concluded that colonic transit studies are reproducible, despite the duration between tests. In an attempt to study segmental colonic transit, some authors have used different types of markers administered on successive days with plain abdominal films taken either serially[12,13] or on a single day.[14] Because there is no evidence that segmental colonic resection is an appropriate option in the treatment of colonic inertia, however, the determination of segmental transit does not justify the increased complexity of this approach.

Scintigraphy can also be applied to the measurement of colonic transit. A method of delivery by orocecal intubation was devised to avoid dispersion of the radiolabeled material (In-DTPA) during its passage through the stomach and small intestine.[18] The need for orocecal intubation, however, is eliminated when labeled pellets are incorporated into a gelatin capsule coated with a methacrylate polymer[19] or activated charcoal.[20] Images can be obtained at three time points: 28, 52, and 60 hours after ingestion.[21] Disadvantages of this method include less-than-ideal image resolution and the difficult interpretation of the anatomy of the colon.

Small Bowel Transit

Studies have indicated that there may be a subset of constipated patients in whom orocecal transit time is delayed.[22] When a subtotal colectomy is being planned, measurement of small bowel transit is important to distinguish between isolated colonic inertia and panenteric inertia. The first group of patients are known to benefit from colectomy; the second group may remain constipated even after colectomy.

The breath hydrogen test was first described in 1975 by Bond et al.[23] to measure orocecal transit time. This test is based on the principle that the bacterial metabolism in the colon produces hydrogen. Hydrogen is insoluble in water and highly diffusible; therefore, it is promptly absorbed by the intestinal mucosa, transported to the lungs, and then exhaled. An expiratory breath specimen is measured by means of a gas chromatograph analyzer after the patient ingests a dose of 10 g of lactulose diluted in 100 ml of water; breath samples are taken every 10 minutes for a minimum of 2 hours. The time between the ingestion of the lactulose and the first breath hydrogen peak should represent the time of arrival of the substrate to the colon. This test can be altered by smoking or exercise,[24] as well as by small bowel bacterial overgrowth.

A standard meal labeled with mTc-DTPA can also be used to measure gastric emptying and small bowel transit; other radioisotopes may also be used (iodine, indium). The patient must ingest the meal after an overnight fast, and a gamma camera is used to obtain the images until the meal arrives in the cecum. The actual small bowel transit is determined as the time between 10% gastric emptying and the appearance of scintigraphic activity in the cecum. Apart from the exposure to radiation generated by this examination, the major disadvantage of this method is the difficulty in identifying cecal filling due to the overlap of small bowel loops. Bonapace et al.[25] evaluated 73 patients with chronic constipation using whole-gut transit scintigraphy. Nineteen percent of patients were found to have delayed gastric emptying, and 7% had delayed small bowel transit time.

The detection of plasma sulfapyridine after the ingestion of sulfasalazine has also been described and corresponds to orocecal transit.[26] This technique has not been widely accepted due to its complexity and cost and the requirement for a nuclear camera. The use of a barium-labeled test meal to assess small bowel transit is not recommended, because alterations in small bowel physiology can be caused by barium. Moreover, radiation exposure is significant.

Manometry

Anorectal manometry measures intra-anal and intrarectal pressures by means of a transanally inserted catheter. Measurements can be taken in either a stationary pull-through or a motorized continuous withdrawal technique. We use a water-perfused catheter and measure

pressures at 1-cm increments, in a proximal-to-distal orientation. With this method, we are able to establish the anal canal length (high pressure zone), resting and squeeze pressures, and rectal capacity volume to first sensation. Most important in constipated patients, we are also able to elicit the rectoanal inhibitory reflex (RAIR). Because of the diversity of methods used in performing anorectal manometry, normal values do not always coincide among institutions; however these parameters should remain identical within the same laboratory.[27]

Despite these pressure variations, the absence of the RAIR is abnormal. The lack of this reflex in patients with chronic constipation may suggest Hirschsprung's disease. In addition, the same absence is noted in patients with Chagas' disease and should be suspected in patients from endemic countries. An abnormal reflex may also be encountered in patients with dermatomyositis or scleroderma and after any coloanal or ileoanal anastomosis[28]; elicitation of the RAIR is qualitative and not quantitative.

Defecography

Defecography is a method to assess simulated evacuation under direct real-time fluoroscopic visualization.[29-32] The rectum is filled with a radiopaque material similar in consistency to stool, and the patient is seated on a water-filled commode. The evacuation process is then observed under fluoroscopic guidance. Radiographs and videos are taken during four distinct activities: at rest, during squeeze, while pushing, and after evacuation. The radiographs allow the measurement of the anorectal angle, perineal descent, and puborectalis length. Because the study is dynamic, one of the criticisms has been the reproducibility of the test. However, Pfeifer et al.[33] from the Cleveland Clinic Florida confirmed an 83% accuracy rate for the examination when four independent observers used the same definition for each of the pathologic findings.

Under normal circumstances, the rectum is emptied during straining within 8 to 12 seconds, depending on the viscosity of the contrast medium.[33] Even though the examination may disclose multiple abnormalities such as rectoceles and sigmoidoceles, intussusception, or perineal descent, one should be cautious to not attribute clinical significance to normal anatomic variants.[34] Jorge et al.[35] found that because defecography had the ability to detect associated abnormalities, it was superior to anal EMG in the diagnosis of nonrelaxing puborectalis syndrome.

The failure to eliminate rectal contents during defecography may not be due to obstructed defecation but rather to the patient's inhibition to evacuate in the presence of an audience. To overcome potentially false-positive results, other methods have been devised, such as attempting the evacuation of a balloon from the rectum.[36-38] Radioactive isotopes can also be used to quantitatively assess evacuation.[39] The introduction of a radiolabeled artificial stool into the rectum is followed by the capture of images with a standard gamma camera, and the percentage of emptying is calculated using an equation. Even though this test provides good qualitative information about the percentage of rectal content evacuated, the low resolution of scintigraphic defecography does not permit the detection of abnormalities such as intussusception, mucosal prolapse, or many rectoceles.

Recently, dynamic pelvic magnetic resonance (MR) imaging has been used to diagnose pelvic floor disorders.[40,41] Matsuoka et al.[40] compared MR defecography with conventional videoproctography. Although all 22 patients preferred MR defecography to videoproctography due to greater comfort, MR defecography was inferior in detecting rectoceles, rectoanal intussusception, and perineal descent. The authors concluded that the routine use of MR defecography in the work-up of constipated patients could not be justified by the high cost of the test.

Electromyography and Pudendal Nerve Terminal Motor Latency

EMG and pudendal nerve terminal motor latency (PNTML) are the only methods available to analyze the neurologic status of the striated component of the anal sphincter muscles and its neural supply, respectively. This examination is based on the concept of the motor unit,[42] which consists of an anterior horn cell, its axon and axonal branches, motor end plates, and muscle fibers innervated by that cell. The examination is undertaken with the patient in the left lateral decubitus position, using concentric needle EMG to study the four quadrants of the external anal sphincter, during rest, squeeze, cough, and simulated defecation. A disposable anal plug electrode may also be used for anal EMG. This technique has the advantage of being less invasive; however it is not as accurate as the needle examination. The electrical activity of the muscular action potentials is recorded and analyzed by means of a computer-assisted system (Nicolet Viking II EMG System).

The number of muscle fibers in the anal sphincter innervated by each axon is small due to its fine, continuously contracted activity. In a normal anal EMG, continuous electrical activity may be seen even at rest,[43] with an increase in its activity during squeezing and coughing; it should return to its resting pattern during evacuation. Its role in the evaluation of constipation is that it can help diagnose paradoxical puborectalis contraction (PPC), and it can be used as a tool in its treatment.[44,45]

The PNTML technique was described by Kiff and Swash in 1984.[46] It can be measured with an electrode mounted on the examiner's finger and introduced into the rectum. The examiner's index finger is positioned so that the electrode is brought into contact with one of the ischial spines. The time between the application of the electric stimulus and the external sphincter contraction is called the *terminal motor latency of the pudendal nerve.* Initially, in small series some authors argued for a correlation between the chronic straining encountered in constipated patients and abnormally prolonged PNTML.[47-49] Significantly larger series, however, have not substantiated this theoretical correlation between increased perineal descent and pudendal neuropathy.[50]

Regarding the sensory components of the anal canal, two techniques have been described: temperature sensation[51] and mucosal electrosensitivity.[52] The first consists of a water-perfused thermode to assess the thermal sensitivity of the anorectum. Even though the ability to discriminate temperature has been implicated in fecal continence, no studies have shown any aberration in constipation. For the assessment of mucosal electrosensitivity, a specially constructed probe that generates constant current is applied to the upper anal canal. The stimulus is increased until the patient feels a tingling sensation, which is recorded as the threshold of sensation. The use of rectal electrosensitivity in constipation[53] is based on the fact that rectal sensation may be decreased in these patients, although this observation may be due to damage to sensory innervation of the surrounding muscles or to feces that prevent optimal mucosal contact.[54]

Minnesota Multiphasic Personality Inventory Assessment

The Minnesota Multiphasic Personality Inventory (MMPI) assessment was created in 1943 by Hathaway and McKinley.[55] It has been used to compare the psychological function of patient populations with different medical diagnoses. It describes how effectively the individual is functioning on an interpersonal and intrapersonal level. The test consists of 550 questions, which must be answered on a "true or false" basis. All scale scores are based on a mean of 50 and a standard deviation of 10, whereas 2 standard deviations from the mean is indicative of psychopathology.[56] When Devroede and associates[57] compared constipated women and women with arthritis, they found a "conversion V" pattern on the MMPI of the constipated patients, a pattern indicating the presence of a somatization defense structure for dealing with psychological distress.

Heymen et al.[58] used MMPI to analyze three groups of patients who complained of constipation, fecal incontinence, and rectal pain. They found that constipated patients showed an elevation in the hypochondriasis, depression, and hysteria scales, which are referred to as the *neurotic triad*.[57] This indicates that these subgroups of patients use somatization as a defense mechanism, which is a good prognostic factor for psychotherapy. For these reasons, we believe that constipated patients who are candidates for colectomy should undergo the MMPI assessment before surgery, since they may benefit from preoperative psychotherapy or psychotropic medications.

Interpretation of Results

The aim of the diagnostic evaluation is to determine whether the patient who presents with constipation has any objective abnormalities. As mentioned previously, the initial strategy should therefore be to exclude extracolonic and structural disorders with a barium enema or colonoscopy. If no cause for constipation is identified, a colonic transit study should be performed. If transit is normal, an assessment of the pelvic floor should be undertaken with defecography and EMG. Recurrent volvulus, Hirschsprung's or Chagas' disease, and systemic sclerosis must be excluded in patients who present with megabowel.

After completing the diagnostic evaluation, functional constipation can be categorized as follows:

1. Colonic causes—colonic inertia, idiopathic megabowel, adult Hirschsprung's disease
2. Pelvic outlet obstruction—pelvic floor dysfunction, PPC, combined pelvic floor dysfunction and PPC
3. Combined colonic inertia with pelvic outlet obstruction
4. Normal transit constipation (usually as a result of irritable bowel syndrome)

TREATMENT

Surgical Approach

Colonic Inertia

Patients with abnormal transit and normal pelvic floor physiology who do not respond to conservative therapy are candidates for surgery. Surgical management for clinically intractable constipation was first attempted more than 90 years ago.[59,60] Three surgical techniques have been described to treat colonic inertia: subtotal colectomy with ileorectal anastomosis (IRA), ileosigmoid anastomosis, and cecorectal anastomosis (CRA). Many series have been reported, with variable results (Table 139–1). Despite early suboptimal results, the development and availability of anorectal physiologic testing have made better results possible during the past decade. Subtotal colectomy with IRA has been established as the current procedure of choice for the treatment of colonic inertia. Pikarsky and associates[61] assessed by telephone interview a group of 30 patients who underwent IRA at a minimum of a 5-year follow-up. All 30 patients rated their outcome as excellent, although during this period, 6 patients (20%) required hospitalization for small bowel obstruction, of whom 3 (10%) required laparotomy. In this series, 2 patients (6%) still required assisted bowel movements, 1 patient used laxatives, and 2 patients needed antidiarrheals to control frequency. FitzHarris et al.[62] recently reported on 75 patients who underwent IRA. Eighty-one percent were at least somewhat pleased with their bowel movement frequency; however, 41% had persistent abdominal pain and 21% reported incontinence.

Subtotal colectomy with CRA has the theoretical advantage of retaining the ileocecal valve to improve the absorption of water. Patients who undergo this procedure, however, may suffer from persistent cecal dilation.[73] Most series reporting results of CRA have been small. Yoshioka and Keighley[82] compared results of 5 patients who underwent CRA with 34 patients who underwent IRA and found no difference in the success rate. Sarli et al.[102] recently reported the results of 26 patients. At 1-year follow-up, the mean number of bowel movements per day was 1.7. and all 26 patients were satisfied with the results of their surgery.

Table 139–1 Results of Subtotal Colectomy for Constipation

Authors, Year	No. of Patients (% Female)	Mean Age, yr	Follow-up, yr	Barium Enema	Biopsy	No Megacolon		Megacolon	
						n	Success Rate, %	*n*	Success Rate, %
Watkins, 1966[60]	3‡ (100)	43	0.7	Yes	Yes	—	—	3	100
Lane and Todd, 1977[63]	3‡ (33)	46	2.2	Yes	Yes*	—	—	3	33
Smith et al., 1977[64]	1‡ (100)	18	3	Yes	Yes	—	—	1	100
McCready and Beart, 1979[65]	6‡ (65)	32	2.4	Yes*	Yes*	—	—	6	100
Hughes et al., 1981[66]	17‡ (94)	35	—	Yes	Yes	10	80	7	100
Belliveau et al., 1982[67]	9‡	—	5.4	Yes*	—	—	—	7	78
Klatt, 1983[68]	9§ (100)	39	2.1	Yes	—	3	100	6	100
Gilbert et al., 1984[69]	6‡ (86)	36	0.7	Yes	—	—	—	6	100
Keighley and Shouler, 1984[70]	10‡ (100)	27	—	Yes	—	10	90	—	—
Preston et al., 1984[71]	8‡ (100)	26	5.7	Yes	Yes	8	63	—	—
Krishnamurthy et al., 1985[72]	12‡ (100)	33	—	—	—	12	100	—	—
Todd, 1985[73]	16‡	—	—	—	—	16	88	—	—
Barnes et al., 1986[74]	6‡ (43)	38	5	Yes	Yes	—	—	6	67
Roe et al., 1986[52]	7‡	—	0.7	Yes	Yes	7	71	—	—
Beck et al., 1989[75]	14‡ (100)	41	1.2	Yes	Yes*	14	100	—	—
Gasslander et al., 1987[76]	6‡ (86)	37	2	Yes	Yes*	6	100	—	—
Leon et al., 1987[77]	13‡ (100)	31	2.6	Yes*	Yes	13	77	—	—
Walsh et al., 1987[78]	19‡ (86)	—	3.2	Yes*	Yes*	17	65	2	50
Akervall et al., 1988[79]	12‡ (100)	39	3.4	Yes	—	12	66	—	—
Kamm et al., 1988[80]	33‡ (100)	34	2	Yes	Yes	33	50	—	—
Vasilevsky et al., 1988[81]	51‡ (94)	45	4	Yes	—	24	71	14	93
Yoshioka and Keighley, 1989[82]	40† (98)	35	3	Yes	Yes	32	58¶	8	58¶
Zenilman et al., 1989[83]	12‡ (100)	35	2	Yes*	Yes*	12	100	—	—
Coremans, 1990[84]	11‡ (100)	46	3.8	Yes	Yes	10	60	1	100
Kuijpers, 1990[85]	12‡	42	—	—	—	12	50	—	—
Stabile et al., 1991[86]	11‡ (64)	43	7	Yes	—	—	—	11	100
Tajana et al., 1990[87]	7‡	—	—	Yes	—	5	100	2	100
Pemberton et al., 1991[88]	38‡ (84)	40	—	Yes	—	38	100	—	—
Wexner et al., 1991[89]	16‡ (92)	45	1.2	Yes	Yes	16	94	—	—
Mahendrarajah et al., 1994[90]	9‡ (100)	38	1.3	—	—	9	88	—	—
Stewart et al., 1994[91]	1‡	11	2	—	—	—	—	1	100
Takahashi et al., 1994[92]	38‡	—	3	Yes	Yes	37	97	—	—
Piccirillo et al., 1995[93]	54‡ (78)	49	2.2	Yes	Yes	54	94	—	—
Redmond et al., 1995[94]	34‡ (92)	43	7.5	Yes	—	34	90**,††	13	—
Lubowski et al., 1996[95]	59‡ (55)	42.3	3.6	—	Yes*	—	35	—	96
Nyam et al., 1997[96]	74‡ (68)	43	5	Yes*	—	—	72	—	96
Bernini et al., 1998[97]	106‡ (98)	41	6.5	Yes	—	106	74	—	—
Pikarsky et al., 1999[61]	30‡ (21)	—	9.8	—	—	30	100	—	—
Fan and Wang, 2000[98]	24 (79)	37	1.9	Yes	—	24	87.5	—	—
Sarli et al., 2001[99]	26¶	40	1	—	—	10	100	—	—
Verne et al., 2002[100]	13‡	22.9	—	Yes	Yes	13	92	—	—
FitzHarris et al., 2003[62]	75	—	3.9	—	—	75	92	—	—
Glia et al., 2004[101]	14	46	5	Yes	Yes*	14	100	—	—

*Not all patients.
†Thirty-four ileosigmoid anastomoses, five cecorectal anastomoses, and one ileorectal anastomosis.
‡Ileorectal or ileosigmoid anastomosis.
§Ileosigmoid anastomosis.
¶Cecorectal anastomosis.
¶Overall success.
**For colonic inertia.
††For gastrointestinal disease.
Adapted from Pfeifer J, Agachon F, Wexner SD: Surgery for constipation: A review. Dis Colon Rectum 39:444, 1996.

Because some patients may experience diarrhea or frequent bowel movements after subtotal colectomy with IRA, some authors have proposed segmental colectomy to avoid these unwanted side effects. The results of these procedures, however, have been less impressive, with an overall success rate of less than 70%. In addition, up to half of patients will develop megabowel of the remaining colon.

The use of laparoscopic surgery for diseases of the colon and rectum began in the early 1990s and has now become standard of care in some disease states. Several authors have reported on the use of laparoscopy in the treatment of colonic inertia.[103-105] Ho et al.[104] compared 7 patients who underwent laparoscopic-assisted colectomy with 17 patients who underwent open colectomy. Operative time was significantly longer in the laparoscopic group, but functional outcome was equal in both groups. Complications and length of stay were also equal in both groups; however, patients who underwent open surgery were less satisfied with the cosmetic outcome.

Regardless of the type of surgery selected to treat constipation, patients must understand the risks. In addition to the standard risks such as anastomotic leak and postoperative bowel obstruction, problems specific to colectomy for constipation also exist. Specifically, although frequency of bowel movements will probably improve, bloating, pain, nausea, and other constitutional symptoms may persist or even worsen. Furthermore, patients without these symptoms preoperatively may develop them following surgery. No patient should undergo colectomy for constipation without understanding that the operation will not help ameliorate these associated symptoms. In addition, patients must also be aware of the possible need for a stoma at any time following surgery. Patients with unrealistic psychological expectations, no matter how well suited by physiologic testing for surgery, are not surgical candidates.

Pelvic Outlet Obstruction

Sigmoidocele may account for symptoms of obstructed defecation, particularly in patients who have previously undergone hysterectomy. The mechanism of pelvic outlet obstruction is believed to be caused by collapse of the rectal wall as a result of extrinsic compression of the hernia contents and stasis of the sigmoid loop. Jorge et al.[106] elaborated a classification system for sigmoidoceles based on the degree of descent of the lowest portion of the sigmoid: first degree, above the pubococcygeal line; second degree, below the pubococcygeal line and above the ischiococcygeal line; and third degree, below the ischiococcygeal line (Fig. 139–3). First- and second-degree sigmoidoceles may represent normal anatomic variants, although a nonemptying sigmoidocele can be the cause of sensation of incomplete evacuation. Patients with first- and second-degree sigmoidocele can be treated conservatively with biofeedback therapy, whereas third-degree sigmoidoceles may benefit from operative therapy.

Jorge et al.[106] reported their experiences with 9 patients who had first-degree sigmoidocele, 7 patients with second-degree, and 8 patients who had third-degree sigmoidocele. Impaired rectal emptying was present in 16 patients (67%). Five of 8 patients with third-degree sigmoidocele underwent colonic resection with or without rectopexy, whereas the other 3 patients were managed conservatively. One of 7 patients with second-degree sigmoidocele underwent colectomy, and the other 6 were managed conservatively, as were all 9 patients with first-degree sigmoidocele. Post-treatment improvement was noted in all patients who underwent resection, but in only 6 (33%) of 18 patients treated conservatively. Furthermore, the clinical significance of third-degree sigmoidocele is supported by the fact that all 5 of the patients with third-degree sigmoidocele who underwent colonic resection reported symptomatic improvement at a mean follow-up period of 23 months.

Rectocele is a protrusion of the rectal wall into the vagina during defecation. It may be commonly seen in healthy women,[107] but is also associated with multiparity,[108] obstetric damage, and the presence of PPC.[109] Rectoceles can be classified as high level (usually due to stretching or disruption of the upper third of the vaginal wall and the cardinal and uterosacral ligaments), mid level (usually caused by loss of pelvic floor support secondary to parturition), or low level (usually the consequence of perineal body defects).

The clinical significance of rectoceles is uncertain. Rectoceles may cause mild to severe anorectal symptoms, such as perineal pressure, the sensation of a pouch in the vagina, or incomplete evacuation requiring rectal or vaginal digitation.[34] In our institution, patients are chosen for surgery according to the size of the rectocele (>2 cm), the inability to empty the rectocele at defecography, and the use of digitation or perineal support to empty the rectum (Fig. 139–4). Rectoceles can be repaired via a transvaginal[110,111] or transrectal[112-114] approach. Overall success rates range from 65% to 100%.

Rectal intussusception is an infolding of the rectum into but not beyond the anal verge. Although rectal intussusception is a common finding in defecography (Fig. 139–5), it is not usually the cause of constipation. Treatment should consist of adequate fiber intake and the use of enemas or laxatives to assist in evacuation, as well as biofeedback. Surgical repair including rectopexy has had poor long-term results.[115,116] Choi et al.[117] compared patients with large rectal intussusception treated with conservative dietary therapy, biofeedback, or surgery. Although 60% reported subjective improvement following surgery, half of these patients developed new symptoms such as rectal bleeding or pain, incomplete evacuation, or liquid stools. In addition, biofeedback showed a significant improvement in number of bowel movements per week when compared to a high-fiber dietary regimen alone.

Paradoxical Puborectalis Contraction

The normal evacuatory mechanism includes the voluntary relaxation of the external anal sphincter and the pelvic floor muscles, thus increasing the anorectal angle. However, failure of relaxation or paradoxical contraction of the puborectalis muscle during evacuation is

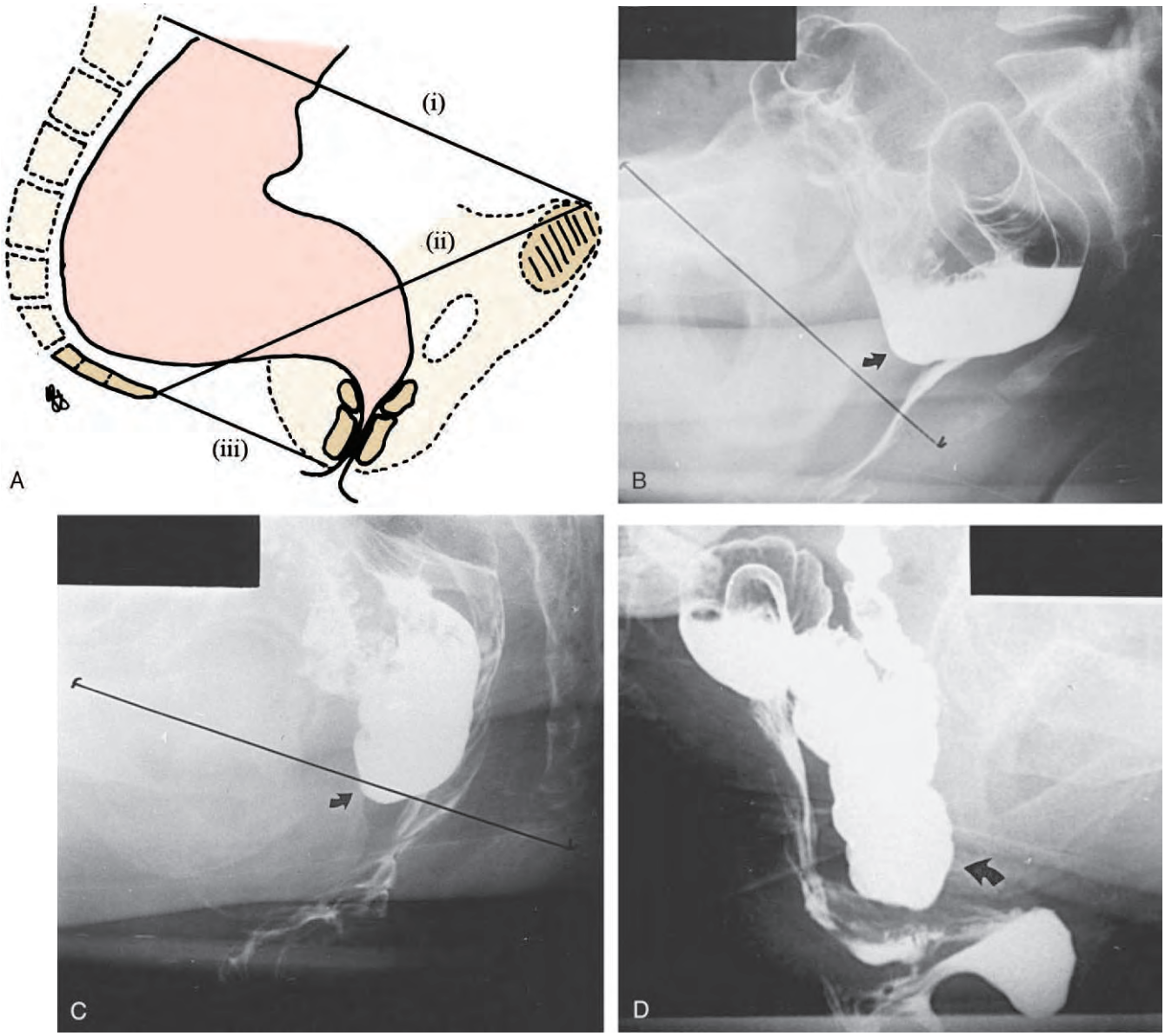

Figure 139–3. **A,** Schematic of the three degrees of sigmoidocele: (i) pubosacral line, (ii) pubococcygeal line, and (iii) ischiococcygeal line. **B,** First-degree sigmoidocele is the descent of the lowest portion of the sigmoid to above the pubococcygeal line. **C,** The second degree is to below the pubococcygeal line but above the ischiococcygeal line. **D,** The third degree is below the ischiococcygeal line.

responsible for obstructed defecation,[118] a condition that is termed *PPC*. This syndrome has also been termed *anismus*, *nonrelaxing puborectalis syndrome*, *spastic pelvic floor syndrome*, and *rectal dyschezia*. The cause of this entity is unclear and may involve a generalized pelvic floor disorder with a strong psychological component.[119] Patients typically complain of straining, tenesmus, and the sensation of incomplete evacuation, as well as the frequent need for suppositories, enemas, or digitation.

Diagnosis is achieved with a combination of defecography (Fig. 139–6) and EMG (Fig. 139–7) to assess the function of the puborectalis muscle. The use of one test does not always ensure a diagnosis (the patients' inhibition may lead to nonrelaxation of the pelvic floor during defecography),[118] and pain may have the same effect during EMG,[70] both of which will lead to false-positive results. Jorge and associates[35] prospectively assessed the role of defecography and EMG in the diagnosis of PPC in 112 constipated patients. In this series, EMG had a sensitivity of 67%, a positive predictive value of 70%, and a specificity of 83%, whereas the values for defecography were 70%, 66%, and 80%, respectively. The authors concluded that although these parameters are suboptimal for both examinations, defecography may be a superior test due to its ability to detect associated abnormalities. Moreover, the inability to relax the puborectalis muscle has been demonstrated in normal control subjects[120]; the diagnosis of PPC, therefore, must be consistent with the

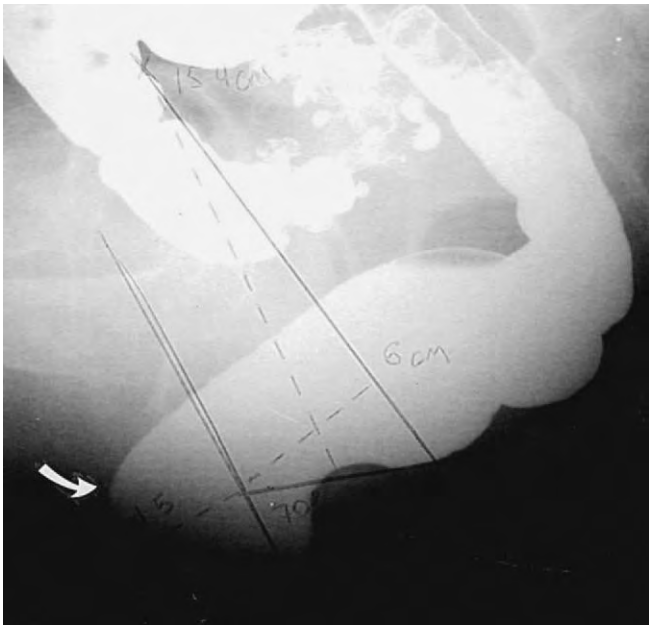

Figure 139–4. A nonemptying anterior rectocele is shown *(arrow)*.

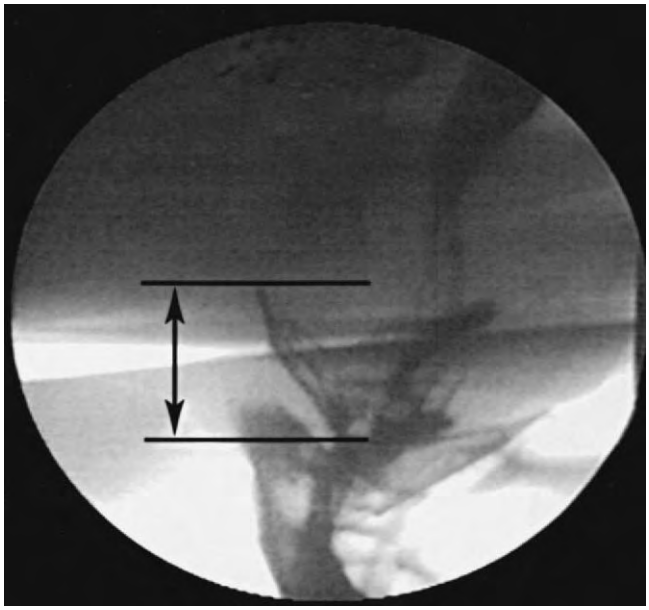

Figure 139–5. Rectoanal intussusception is shown.

clinical findings and the results of more than one physiologic test.

Because of the intense psychologic component in PPC, the treatment of choice for these patients is pelvic floor retraining with biofeedback. The success rate for this modality of treatment applied to PPC ranges from 29% to 100% depending on the series and the techniques that are used (Table 139–2). Attempts have been made to treat PPC through surgical division of the puborectalis muscle. Independent of the site of division on the muscle, either posteriorly or laterally, symptoms of obstructed defecation did not improve and adverse results including fecal incontinence occurred in a high number of patients.[80,121]

Pelvic Floor Retraining and Biofeedback

Biofeedback is based on the concept that patients can be taught to recognize bodily functions of which they were not previously aware. Achieving control of such functions can be translated into visual or aural stimuli by means of different electronic devices. Electrical and hydrostatic information is displayed in such a way that patients can better understand the contraction and relaxation process. Both pressure-based (manometry) and electrical signal-based (EMG) systems have been used.[122,124,130,142] Heymen et al.[143] recently performed a meta-analysis and found that the mean success rate of pressure-based biofeedback was 78%, whereas the success rate for EMG feedback was only 70%. In addition, there was no significant difference between the success rates using either intra-anal sensors or perianal EMG sensors. These modalities have also been combined with rectal sensation training,[122,142] in which patients with a poor recognition of the rectal urge were taught to perceive progressively decreasing volumes of distention. In addition to these methods, portable units are available for use at home, which allows training in a friendly, familiar environment.[127,128,130,131]

Biofeedback training consists of 3 to 10 1-hour-long sessions under the supervision of a biofeedback therapist. The patients are also instructed to keep a daily record of bowel movements, medications, and the use of enemas, laxatives, or digitation. The training is done on an outpatient basis, with the patient dressed and seated on a chair after insertion of the anal plug. Patients are taught to recognize three events: rest, push, and squeeze. The push exercises are done only under supervision during the biofeedback session, whereas the squeeze and rest exercises (Kegel maneuvers) should be practiced at home as well. Discharge conditions include the demonstration of control of pelvic floor musculature as shown with EMG, a reduction in the use of cathartics, and objective resolution of constipation as indicated in a bowel habit diary. Gilliland et al.[136] reviewed the outcome of 194 patients who underwent biofeedback therapy; patients who self-discharged from therapy had a success rate of only 29% compared with patients who were discharged by the therapist, who had a 63% success rate ($P < 0.0001$). In this multivariate analysis, which included duration of symptoms, age, gender, and multiple other variables, the self-discharge rate was the only predictor of successful outcome. The results of biofeedback are dependent both on the expectations of the patient and the expertise of the therapist. Currently, a multicenter prospective, randomized trial is underway to assess the placebo effect of biofeedback.

For the subset of patients who do not benefit from biofeedback, the use of *Clostridium botulinum* type A (BTX-A) in the treatment of PPC has been reported.[144-147] This potent neurotoxin causes paralysis of

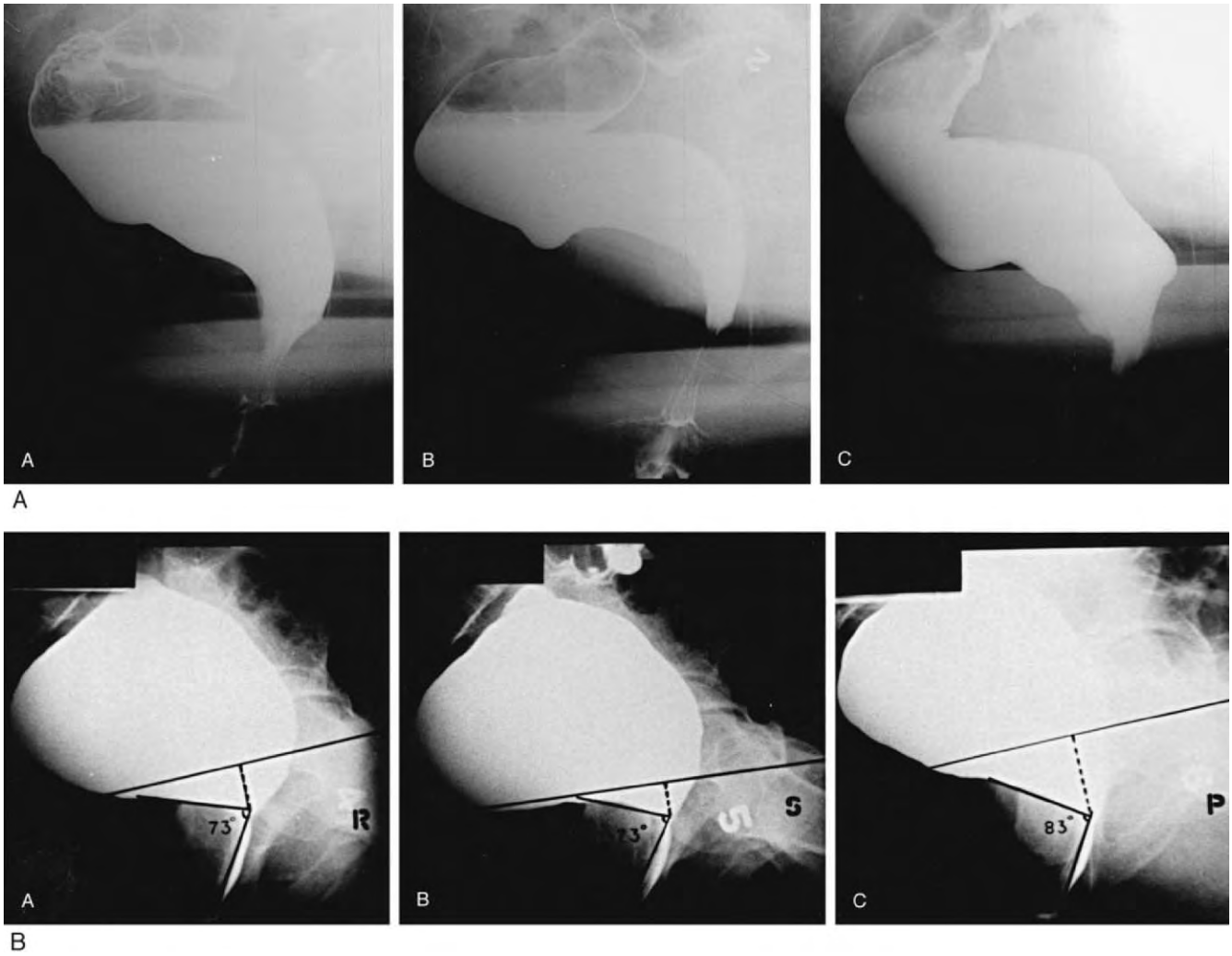

Figure 139–6. **Top Row (A),** Normal cinedefecogram sequence at rest (A), squeeze (B), and attempted evacuation (C). **Bottom Row (B),** Cinedefecogram shows paradoxical puborectalis contraction at rest (A), squeeze (B), and attempted evacuation (C). Contrasting these cinedefecograms, it can be seen that a normal sequence includes shortening of the anal canal and flattening of the anorectal angle with evacuation of barium contents. In comparison, paradoxical puborectalis contraction includes maintenance of the length of the closed anal canal and the anorectal angle or, in some instances, accentuation of these features by an even longer, more closed anal canal and an even more acute anorectal angle.

muscles through presynaptic inhibition of acetylcholine release. Joo and associates[145] treated a group of 4 patients diagnosed with intractable constipation due to PPC with BTX-A injections for a maximum of three sessions during a 3-month period. Under EMG guidance, the BTX-A was injected into the left and right sides of the puborectalis muscle. All patients were relieved of constipation between 2 and 4 days after BTX-A injection without any local or systemic side effects. However, 3 months after BTX-A injection, 2 of the 4 patients experienced symptomatic recurrence. Maria et al.[147] recently reported improvement in 13 of 15 patients treated with injection of 25 units of BTX-A. Improvement, however, was maintained for a mean of only 5 months, requiring reinjection of the toxin.

CONCLUSIONS

Although only a small group of patients may benefit from surgical intervention, the evaluation of these patients must be extensive to ensure both the inclusion of appropriate candidates as well as the exclusion of inappropriate candidates.[148] In addition, the psychological status of these patients requires thorough assessment and often requires treatment. Through careful testing and selection, satisfactory results can be obtained in more than 90% of patients. Patients must understand, however, that although bowel frequency will improve and dependence on laxatives will be eliminated or significantly reduced, other symptoms such as abdominal bloating and pain may persist, develop anew, or become exacerbated.

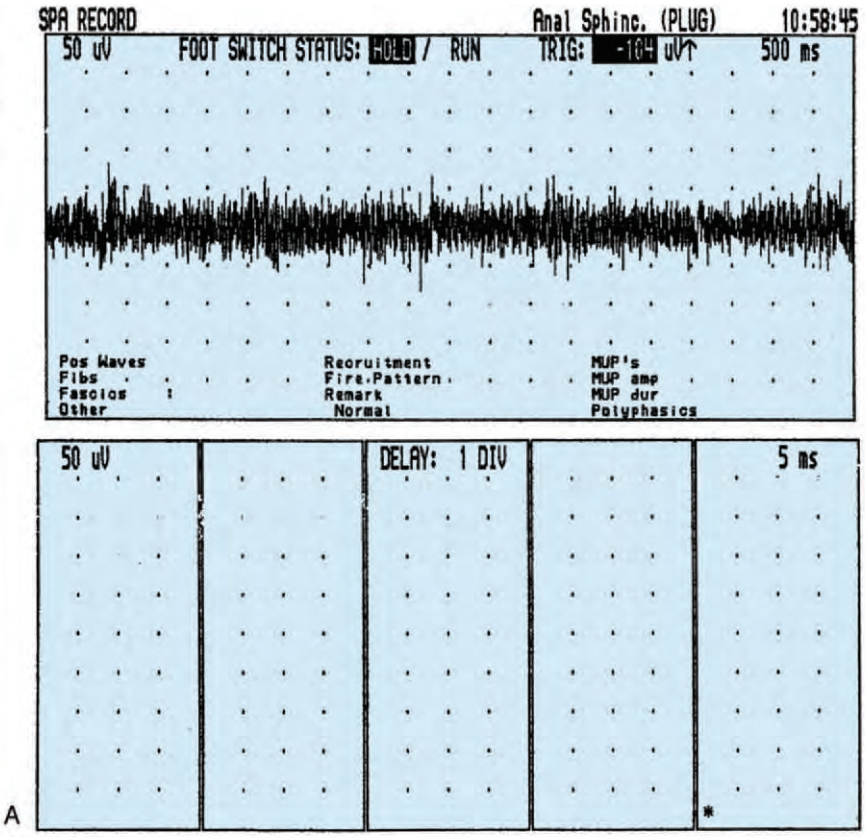

Figure 139–7. **A,** Normal electromyography during attempted evacuation is compared with paradoxical puborectalis contraction **(B). B,** Paradoxical increase in the recruitment of the external anal sphincter muscle and puborectalis is noted during attempted evacuation. The normal study shows appropriate external anal sphincter and puborectalis relaxation.

Table 139–2 Success of Biofeedback for Pelvic Floor Dysfunction

Authors, Year	No. of Patients	Mean Age or Range, yr	Diagnosis	Method of Treatment	Success Rate, %
Wald et al., 1987[122]	9	6-15	PPC	Manometry	67
Bleijenberg and Kuijpers, 1987[123a]	10	19-48	PPC	EMG	70
Keren et al., 1988[124]	12	8.3	PPC	Manometry	100
Loening-Baucke, 1990[125]	22	5-16	Encopresis	EMG	77
Loening-Baucke, 1991[126]	38	6-15	Encopresis	EMG	37
Lestar et al., 1991[127]	16	42	PPC	Manometry/balloon	44
Kawimbe et al., 1991[128]	15	45	PPC	EMG	87
Dahl et al., 1991[129]	14	6-60	PPC	EMG/balloon	93
Turnbull and Ritvo, 1992[130]	7	29-42	PPC	Manometry	71
Wexner et al., 1992[131]	18	67	PPC	EMG	89
Bennings et al., 1993[132]	29	5-16	Encopresis	Manometry	55
Bleijenberg and Kuijpers, 1994[123]	11	35	PPC	EMG	73
Papachrysostomou and Smith, 1994[133]	22	42	PPC	EMG/balloon	86
Cox et al., 1994[134]	13	7	Encopresis	EMG	90
Siproudhis et al., 1995[135]	27	46	PPC	Manometry/balloon	52
Gilliland et al., 1997[136]	194	71	PPC	EMG	29
Karlbom et al., 1997[137]	29	46	PPC	EMG/balloon	43
Glia et al., 1997[138]	26	55	PPC	EMG/balloon	58
Weisel et al., 2000[139]	13	38	PPC	EMG/balloon	38
Lau et al., 2000[140]	108	66	PPC	EMG	55
Battaglia et al., 2004[141]	24	27-54	PPC	EMG	50

PPC, paradoxical puborectalis contraction; EMG, electromyography.

Patients must also realize that they may eventually require a stoma as well.

SUGGESTED READINGS

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Chapter

140

Rectovaginal and Rectourethral Fistulas

Patricia L. Roberts

RECTOVAGINAL FISTULAS

Rectovaginal fistulas are epithelial-lined communications between the rectum and vagina. Although they are relatively uncommon, accounting for approximately 5% of all anorectal fistulas, they may cause significant physical symptoms in addition to adversely affecting intimate relationships and sexual function. The operative approach to such fistulas depends on a variety of factors, including the size, location, condition of the surrounding tissues, and association with concomitant disease, such as inflammatory bowel disease.

ETIOLOGY

Rectovaginal fistulas may occur from both congenital and acquired disorders.

The most common cause of a rectovaginal fistula is obstetric trauma. A prolonged second stage of labor with ischemic necrosis of the rectovaginal septum may contribute to development of a fistula. Other risk factors include a high forceps delivery, shoulder dystocia, midline episiotomy, and third- or fourth-degree perineal laceration.[1] Although fistulas after prolonged labor are rare in developed countries, they are still a relatively frequent occurrence in undeveloped countries.[2] There are few reliable data on the prevalence of obstetric fistula from underdeveloped countries; however in 1989, the World Health Organization estimated that 2 million women and girls had the condition and 50,000 to 100,000 cases were added each year.[3,4] The backlog of unrepaired cases is believed to approach 1 million in such areas as northern Nigeria alone.[2,5] For every 100 obstetric fistulas encountered, 74% are vesicovaginal, 21% are vesicovaginal and rectovaginal, and 5% are rectovaginal alone.[6] In one series in the United States, rectovaginal fistula after vaginal delivery occurred in 25 women out of 22,050 vaginal deliveries (0.1%).[2] A single rectovaginal fistula was reported after 2635 deliveries in another series.[7] Crohn's disease, a transmural inflammatory disease of the bowel, is associated with rectovaginal fistula in more than 10% of women with the disease.[8] Anorectal suppurative disease, including abscesses in the rectovaginal septum and anterior horseshoe abscesses, may be associated with rectovaginal fistulas.

Rectovaginal fistulas can occur as a postoperative complication after a variety of rectal, vaginal, and pelvic operations, including hysterectomy, low anterior resection with stapled anastomosis, ileal pouch–anal anastomosis, and stapled hemorrhoidectomy.[9] The complication occurs more commonly after stapled than hand-sewn anastomoses and may result if the stapler incorporates a portion of the vaginal wall or surrounding perivaginal tissues or as a consequence of an anastomotic leak. Rectovaginal fistulas have been reported in 2.9% to 9.9% of women undergoing resection for rectal cancer and are more common if concomitant vaginectomy has been performed.[10,11] Pouch-vaginal fistulas occur in 2.6% to 16% of women undergoing the ileoanal pouch procedure and may be caused by unsuspected Crohn's disease or other technical problems such as sepsis, ischemia, or tension on the anastomosis.[12-17]

Rectovaginal fistulas are also associated with malignant disease of the cervix, rectum, uterus, or vagina and may be a manifestation of recurrent disease but may also occur after radiation therapy; although radiation delivery techniques have improved, the incidence of rectovaginal fistulas ranges between 0.3% and 6%.[18-20]

Less common causes of rectovaginal fistulas include fecal impaction, long-standing pessary usage, sexual assault, bacterial and viral infections associated with human immunodeficiency viral disease, and ergotamine suppository usage.[21,22]

DIAGNOSIS, CLASSIFICATION, AND CLINICAL EVALUATION

Presentation

The chief presenting complaint of women with a rectovaginal fistula is the passage of stool or air per vagina. On occasion, foul-smelling vaginal discharge with recurrent vaginitis or urinary tract infections may be the presenting complaint. In women with rectovaginal fistulas from an obstetric injury, the incidence of incontinence is close to 50%.[23] The true incidence of incontinence is difficult to determine because passage of air and stool through the vagina may be interpreted as fecal incontinence. Associated symptoms, such as diarrhea, abdominal pain, or mucous discharge, are suggestive of inflammatory bowel disease and should be investigated accordingly. Although many women will seek medical attention immediately, it is not uncommon for some patients to delay evaluation because of social embarrassment, the desire to have more children, or the belief that such symptoms "are to be expected" after childbirth.

Although rectovaginal fistulas occur anywhere along the rectovaginal septum, they most commonly arise from the region of the dentate line and communicate with the posterior vaginal fornix.[24] Fistulas distal to the dentate line are more appropriately termed *anovaginal fistulas* but common usage terms all such fistulas as *rectovaginal fistulas.*

Fistulas are classified in addition as low, mid, or high. In *low fistulas,* the opening is near the posterior vaginal fourchette; in *high fistulas,* the opening is behind or near the cervix; and *mid rectovaginal fistulas* are midway between the two. From a practical standpoint, fistulas may be classified as those palpable on digital examination and within view of an anoscope or those that are not. Simple fistulas arise from obstetric trauma or infection and are relatively small, whereas complex fistulas are caused by inflammatory bowel disease, irradiation, cancer, or failed prior repairs. Complex fistulas may also result from complications of surgery such as after low anterior anastomosis (as a consequence of anastomotic leak) or after hysterectomy (as a result of unrecognized injury to the rectum).

Some authors have suggested a classification scheme based not on the location of the fistula but on the underlying cause since this may provide the best tool for the treating physician as it assesses the integrity of the surrounding tissues and the overall medical condition of the patient.[25]

Examination and Diagnosis

The initial approach to rectovaginal fistula is not only identify the fistula but also to assess the surrounding tissues particularly with respect to any inflammatory change. In addition, the entire rectovaginal septum should be assessed; patients with an obvious sphincter repair require both repair of the sphincter for improvement of continence and also to bring healthy tissue into the repair. Patients with significant scarring, stenosis and tissue defects may require tissue transfer techniques to maximize the change of success with repair.

Low rectovaginal fistulas are easily visualized and palpated on examination. A dimple is felt on digital rectal examination and confirmed on anoscopic or speculum examination. This method results in confirmation of the fistula in most low fistulas, and other diagnostic modalities are rarely needed. A probe can generally be passed quite easily through a short tract into the vagina. Examination with one finger in the rectum and one in the vagina assists in assessing the surrounding tissues and the bulk (usually quite attenuated) of the rectovaginal septum. The size and location of the fistula are noted. An attenuated or absent perineal body and anterior sphincter defect are often noted in patients with previous obstetric injury.

If a fistula is not seen on initial examination but is suspected on clinical grounds, a variety of other maneuvers may be performed to diagnose the fistula. Limited barium enema examination with a lateral view may be performed. It is important to visualize the distal rectum and anal canal because the balloon of the catheter may obscure a fistula. Alternatively, a tampon may be placed in the vagina and a dilute methylene blue enema instilled in the rectum, with care not to contaminate the string of the tampon. The presence of methylene blue on the tampon confirms the fistula is present and open. Another method is to examine the patient in the lithotomy position. Water is placed in the vagina, and air is insufflated into the rectum with a sigmoidoscope. The presence of air bubbles in the vagina indicates a fistula. Imaging studies, such as transrectal ultrasound with use of hydrogen peroxide, vaginography, and magnetic resonance imaging (MRI), may also demonstrate a rectovaginal fistula; however, information from such studies must then be used transformed into in vivo identification of the fistula in the affected patient.

It is essential to assess the anatomy and function of the sphincter muscles, especially in patients who have a rectovaginal fistula resulting from obstetric injury. In one study of primiparous women who had undergone a vaginal delivery alone,[26] 28% had a sphincter defect on ultrasound examination 6 weeks after delivery. One study suggested a 100% incidence of sphincter injuries on endoanal ultrasound in patients who sustained a rectovaginal fistulas after vaginal delivery.[27] Furthermore, in one series of 52 women who had a rectovaginal fistula from obstetric injury,[23] 50% had preoperative incontinence. If available, preoperative studies, including ultrasound and anal manometry with pudendal nerve terminal motor latency studies, are helpful in evaluating patients with associated incontinence. A poorer outcome of repair has been associated with prolonged pudendal nerve terminal motor latency, although this has been questioned recently.[28]

TREATMENT OPTIONS

Although most rectovaginal fistulas require surgical management, there are a few exceptions. A small number of fistulas may close spontaneously after obstetric trauma. Case reports have used of hyperbaric oxygen to heal fistulas in very small series of patients with rectovaginal fistulas from obstetric trauma.[29]

Patients with Crohn's disease and rectovaginal fistulas may be treated with antitumor necrosis factor, or infliximab; such fistulas may either spontaneously or with the use of infliximab become relatively asymptomatic. The natural history of rectovaginal fistulas in Crohn's disease has not been well documented in terms of how many patients ultimately require surgery and how many can be treated medically. In one recent series, 60% of women with rectovaginal fistulas required fecal diversion.[30] The ACCENT II trial treated 25 patients with rectovaginal fistulas with infliximab infusion.[31] Use of infliximab for rectovaginal fistulas in the ACCENT II trial was associated with healing in 60.7% of patients at 10 weeks and 44.8% of patients at 14 weeks. Use of MRI has shown that although fistulas have apparent healing, they may actually simply become less symptomatic with less drainage as tracks persist on radiographic studies. Furthermore, closure of the fistulas was associated with the development of an abscess in 10% of patients presumably since the external opening heals over before the tract has healed.[32] Poritz and colleagues have suggested that use of infliximab does not avoid the need for surgery in more than 70% of patients; however, such patients may be rendered relatively asymptomatic and have reasonable quality of life before requiring surgical intervention.[33] Infliximab has been used as an adjunct to surgery, with some evidence that injection into the tracts may improve healing.[34]

A number of surgical options are available for patients with rectovaginal fistulas (Box 140–1). Local repairs are performed through a rectal, vaginal, or perineal approach and may be augmented with tissue transfer, such as gracilis and bulbocavernosus muscle, if the surrounding tissues are deficient or unsatisfactory. High rectovaginal fistulas or those associated with previous surgery or radiation therapy generally require an abdominal approach. Local repairs and abdominal repairs can be performed with fecal diversion, and fecal diversion may also be used, in selected patients, as the sole treatment for rectovaginal fistula. The choice of repair depends on a variety of factors, including the presence of associated incontinence, the size and location of the fistula, the degree of complexity of the fistula, and the status of the surrounding tissues.

All procedures for rectovaginal fistula repair have a not insignificant failure rate; many reported series measure ultimate success rates and not initial success rates. Preoperative discussion should focus on the anticipated results and at times abnormally high patient expectations need to be adjusted.

Box 140–1 Treatment Options for Rectovaginal Fistulas

Local Repair

- Transanal approach
  - Advancement flap
  - Advancement sleeve flap
- Vaginal approach
  - Advancement flap
- Perineal approach
  - Sphincteroplasty
  - Perineoproctotomy and layered closure
  - Fistulotomy
- Other
  - Injection of fibrin sealant
  - Repair with interposition of polyglycolic acid mesh

Abdominal Procedures

- Low anterior resection
- Coloanal anastomosis
- Onlay patch anastomosis
- Abdominoperineal resection
- Fecal diversion

Tissue Transposition

- Bulbocavernosus
- Gluteus maximus
- Gracilis
- Pudendal thigh
- Sartorius

Other

- Hyperbaric oxygen
- Infliximab (for Crohn's rectovaginal fistulas)

Timing of Surgery

The timing for when to perform a repair for a rectovaginal fistula remains controversial and there is no level I evidence comparing immediate repair with secondary repair particularly with respect to immediate outcome and long-term outcome and continence. For obstetric fistulas, primary repair is generally under the purview of the obstetrician at the time of the delivery.

In general, surgery may be performed for rectovaginal fistulas as long as the surrounding tissues are soft and pliable. The convention, particularly for fistulas of obstetric origin, has been to wait approximately 3 months, to maximize the condition of the surrounding tissues and also since a small percentage of fistulas close spontaneously. Data from series of patients with rectovaginal fistulas who have undergone MRI have challenged this dogma, since obstetric fistulas have short tracts and little associated inflammatory change on MRI compared with perianal fistulas.[35]

For patients whose previous repair has failed, a waiting period of 3 to 6 months has been advocated that permits some healing of the surrounding tissues and often decreases the size of the recurrent fistula.[36] Waiting for 3 to 6 months may also give both surgeon and patient a much needed reprieve from further surgical intervention.

Local Repair

Sliding Flap Repair

The sliding flap repair for the treatment of patients with rectovaginal fistulas was first reported by Noble[37] in 1902. He advocated splitting the rectovaginal septum, dissecting the lower end of the rectum from the vagina, and drawing the anterior wall down through and external to the anus. Since that time, many modifications of the sliding flap technique have been proposed. In 1948, Laird[38] described the use of a flap of mucosa, submucosa, and some fibers of the internal sphincter. Kodner et al.[39] advocated the use of a flap similar to the Laird technique. Other authors[40] have advocated the use of a flap of mucosa, submucosa, and the full thickness of the internal sphincter. Regardless of the thickness of the flap used, the procedure is generally used for patients with simple low fistulas who have not had previous repairs.

Patients undergo a full mechanical and antibiotic bowel preparation the day before surgery. This practice may be re-examined in view of accumulating evidence that mechanical bowel preparation is maybe unnecessary and does not reduce infectious complications after elective bowel resection.[41] The patient is placed in the prone jack-knife position, with the buttocks taped apart and the anal canal and fistula tract exposed (Fig. 140–1). A urinary catheter is placed. The intersphincteric groove is infiltrated with a combination of saline solution and epinephrine.

A trapezoidal flap composed of mucosa, submucosa, and a portion of the internal sphincter is raised. The base of the flap should be at least twice the width of the apex, and mobilization should be continued for at least 4 cm. Before the flap is advanced, the internal sphincter is mobilized and approximated over the fistula. The flap is then advanced down the anal canal and secured with absorbable sutures. If the patient is incontinent or has a sphincter defect, a concomitant sphincteroplasty is performed. Patients are observed overnight if a sliding flap has been performed. A longer hospitalization period is generally required if concomitant sphincteroplasty is performed. Vaginal intercourse is avoided for 6 to 8 weeks.

Other modifications in flap construction have been reported. Ozuner and colleagues[42] have recommended a curvilinear flap incorporating mucosa, submucosa, and internal sphincter to avoid ischemia at the angled corners. Advancement of the entire rectal wall has been advocated by Fazio and colleagues for treatment of rectovaginal fistulas associated with Crohn's disease with extensive scarring of the anal canal and multiple fistula tracts.[43,44] The influence of the technical nuances of flap construction including the thickness of the flap on the outcome of repair has not been determined.

Potential advantages of a sliding flap include the fact that no perineal wound is created and therefore pain is minimized, no sphincter (other than the internal sphincter if this is used for the flap) is cut, other procedures such as a concomitant sphincter repair can be per-

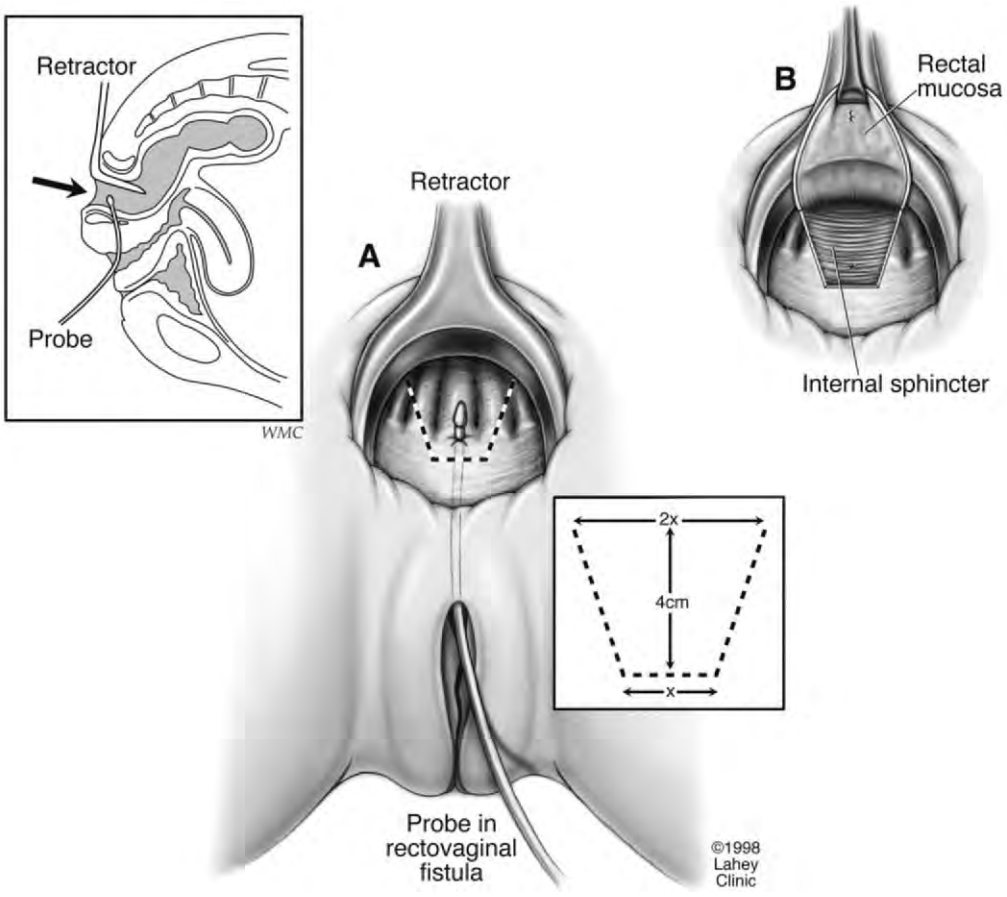

Figure 140–1. Endorectal sliding flap. The patient is placed in the prone jack-knife position, and the fistula is demonstrated *(inset, arrow)*. **A,** The flap should extend for at least 4 cm, and the base should be at least two times the width of the apex. **B,** The flap should include mucosa and submucosa in addition to a portion of the internal sphincter muscle.

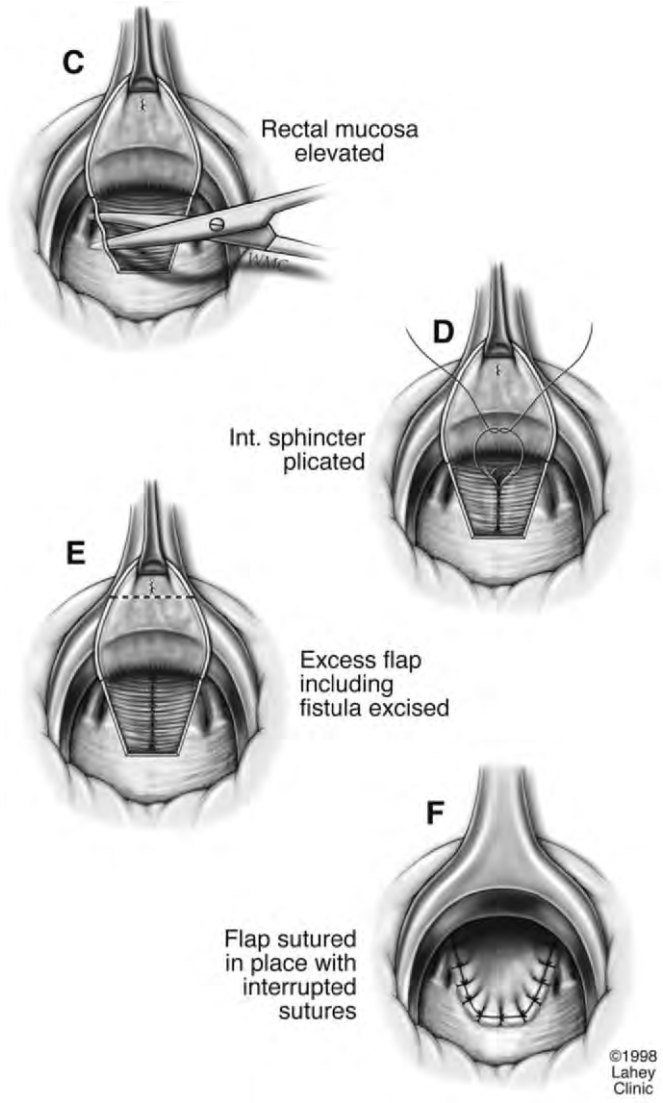

Figure 140–1, cont'd. **C,** The flap is raised, and dissection is performed laterally to permit a tension-free closure. **D,** The internal sphincter muscle is plicated over the area of the fistula. **E,** Excess flap, including the site of the internal opening of the fistula, is trimmed. **F,** The flap is secured with absorbable sutures. (**A-F** and **Inset,** ©1998, Lahey Clinic, Burlington, MA.)

formed, a diverting stoma is not necessary, and deformities such as a keyhole deformity, which may occur from fistulotomy, are avoided.

The success rate varies considerably, from 29% to 100% (Table 140–1).[23,39,40,45-56] Common causes of flap failure include ischemia of the flap and hematoma and/or the development of infection under the flap. Considerable variation has even been reported in the same group of surgeons, with a success rate of 41% to 78%.[23,40] A variety of factors most likely account for the differing success rates after sliding flap repair, including the number of previous repairs, whether the initial or ultimate success rate was reported, the presence of a concomitant sphincter defect, and the cause of the rectovaginal fistula. If a patient has had one[48] or two[40] previous rectovaginal fistula repairs, the success rate with a sliding

Table 140–1 Results of Endorectal Advancement Flap for Rectovaginal Fistulas

Authors, Year	No. of Patients	Success, %
Lowry et al., 1988[40]	56	78
Wise et al., 1991[45]	40	95
Kodner et al., 1993l[39]	71	93
Khanduja et al., 1994[46]	16	100
Athanasiadis et al., 1995[47]	37	78
MacRae et al., 1995[48]	17	29
Mazier et al., 1995[49]	19	95
Watson and Phillips, 1995[50]	12	58
Ozuner et al., 1996[42]	101	71*
Tsang et al., 1998[23]	27	41
Joo et al., 1998[51]	20	75
Hyman, 1999[52]	12	91
Yee et al., 1999[27]	25	92
Baig et al., 2000[53]	19	74
Mizrahi, 2002[54]	32	56
Sonoda et al., 2002[55]	37	43
Zimmerman et al., 2002[56]	21	48

*Included patients with cryptoglandular and rectourethral fistulas.

Adapted from Sullivan B, Lowry AC: Surgical options for rectovaginal fistulas secondary to obstetrical injury. Semin Colon Rectal Surg 10:17, 1999.

flap repair decreases significantly; therefore, a sliding flap repair should generally not be considered in a patient whose previous repairs have failed. Assessment of sphincter function and repair of sphincter defects appear to improve the outcome of sliding flap repair. The success rate for patients undergoing flap repair and sphincteroplasty with or without levatoroplasty was significantly higher than the success rate for patients who underwent flap repair only (80 vs. 41%; $P = 0.02$).[23] As a result, some surgeons have advocated that anal ultrasonography and manometry be performed to detect occult sphincter defects in patients undergoing repair of rectovaginal fistulas; sphincter defects, however, in the majority of cases, can be determined by a thorough history and physical examination and then confirmed on manometry and ultrasound.[27] The underlying cause of the fistula may also determine the success of a flap repair. Patients with obstetric injuries as the cause of the rectovaginal fistula have a better outcome than patients with inflammatory bowel disease.

A transvaginal approach for sliding flap may also be used to repair rectovaginal fistulas. Although a transvaginal approach addresses the fistula from the lower pressure vaginal side, not the higher pressure rectal side, this technique allows for good exposure and, as with transrectal advancement flap, the ability to perform a concomitant sphincteroplasty if needed. An incision is made in the posterior vaginal wall by the introitus, and the flap is raised in a similar manner on the vaginal side

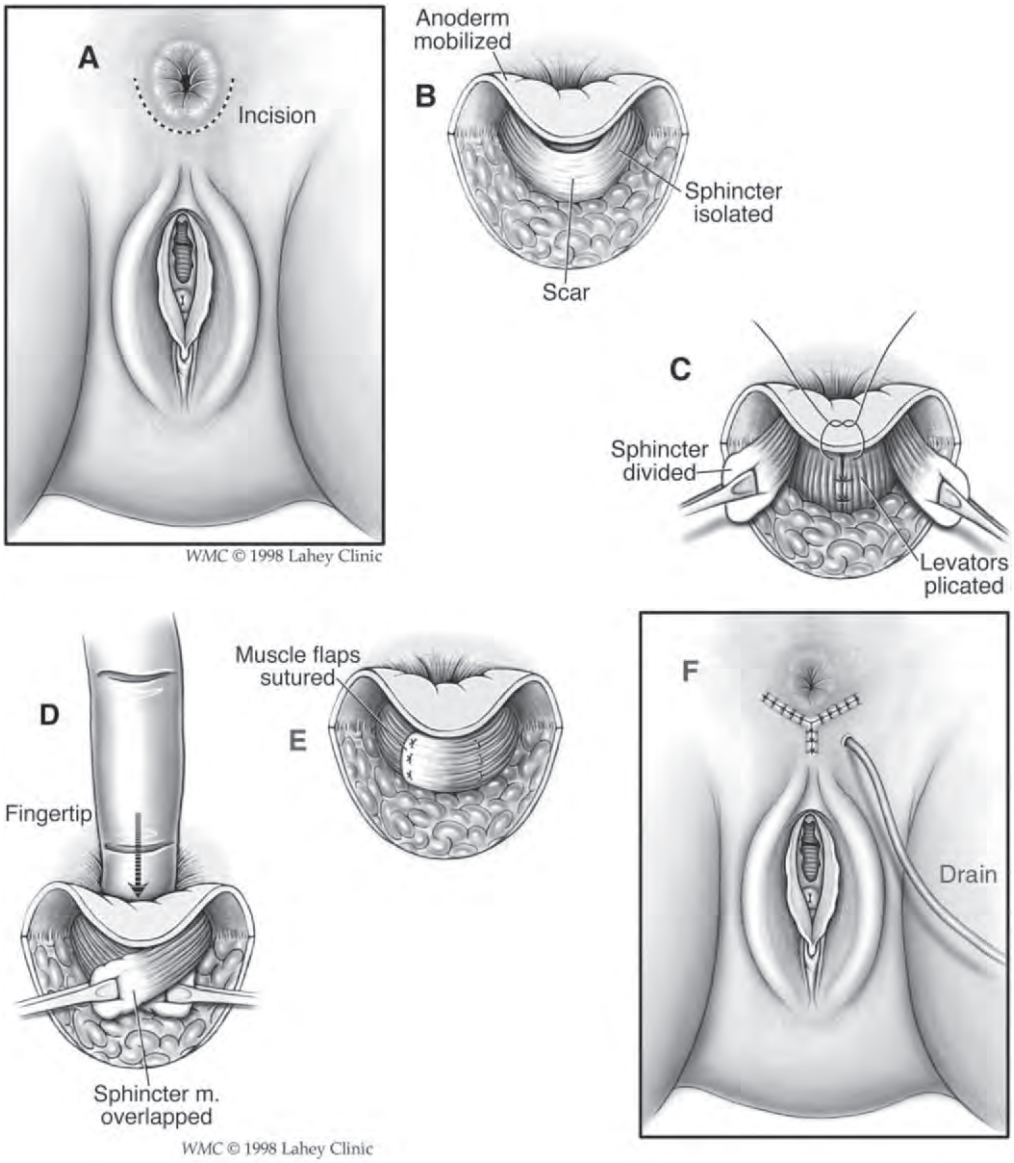

Figure 140–2. Overlapping sphincteroplasty. **A,** The patient is placed in the prone jack-knife position, and a curvilinear incision is made approximately 180 degrees around the anus. **B,** Dissection is carried out medial to the ischiorectal fat, and the external sphincter is identified. **C,** Dissection is carried up to the level of the levatores, which are plicated. **D,** If sufficient muscle is present, an overlapping sphincter repair is performed. If not, simple apposition of the sphincter muscle is performed. **E,** The completed repair. **F,** The perineal body is reconstructed, and the wound is secured in a Y configuration. A drain may be placed. (**A-F,** ©1998, Lahey Clinic, Burlington, MA.)

and advanced. As with a rectal flap, the flap should be wide enough to ensure good blood supply and mobility. This approach may have an advantage in selected patients, especially patients with Crohn's disease, because nondiseased, pliable vaginal tissue is used to form the flap, and there is little manipulation or dissection in the diseased rectum. Using this technique, Bauer et al.[58] reported cure of the rectovaginal fistulas in 12 of 13 women with Crohn's disease, with mean follow-up time of 50 months. Plication of the levator muscles was believed to be crucial to the repair. A transvaginal flap may also be useful in patients with pouch-vaginal fistulas after ileoanal pouch construction, obviating the need for a potentially difficult transanal approach.

There is a limited experience with use of anocutaneous flaps, raising anoderm and perianal skin and advancing this into the anal canal.[59] This technique may be used for very distal fistulas but has limited application because of the lack of adequate perineal skin between the rectum and vagina in most patients with rectovaginal fistulas.

Sphincteroplasty

An overlapping sphincteroplasty is one of the most common operations performed for rectovaginal fistula and may be performed as the sole procedure or combined with sliding flap repair. It corrects any underlying sphincter defect in addition to providing good muscle bulk to interpose in the rectovaginal septum (Fig. 140–2). It is indicated for simple rectovaginal fistulas with an associated sphincter defect. A curvilinear incision is made in the perineum around the anus, and the edges of the external and internal sphincter muscles are identified and mobilized. Scar tissue is usually left in place on the muscle and not débrided. Care is taken to preserve the pudendal nerves that enter posterolaterally; however, a significant sphincter injury usually causes retraction of

Table 140–2 Results of Sphincteroplasty for Rectovaginal Fistula

Authors, Year	No. of Patients	Success, %
Lowry et al., 1988[40]	25	88
Wise et al., 1991[45]	15	100
Khanduja et al., 1994[46]	11	100
MacRae et al., 1995[48]	7	86
Tsang et al., 1998[23]	35	80
Yee et al., 1999[27]	22	91
Halverson et al., 2001[36]	14	65

Adapted from Sullivan B, Lowry AC: Surgical options for rectovaginal fistulas secondary to obstetrical injury. Semin Colon Rectal Surg 10:17, 1999.

the nerves to a more posterior location and, therefore, injury is usually easily avoided. In the course of the dissection, the fistula is identified, and the dissection is carried cephalad, separating the rectum and vagina for several centimeters until soft pliable tissue is reached. The levator muscles are identified and plicated, which adds to the muscle bulk and appears to provide better results from a continence standpoint.[23,60] The perineal skin may be either closed loosely or left open. The vaginal mucosa is left open for drainage. Combining sphincteroplasty with an anoplasty for further separation of the distance between the rectum and vagina has also been advocated.[61]

Sphincteroplasty for rectovaginal fistula is associated with success rates of 65% to 100% (Table 140–2).[23,36,40,45,46,48]

Advancement Sleeve Flap

It is estimated that a rectovaginal fistula will develop in up to 10% of women with Crohn's disease. These fistulas can be difficult to treat. For patients with associated severe anorectal and colonic disease, proctocolectomy with ileostomy is the best option. In selected patients with Crohn's disease and a normal rectum, a local procedure can be considered. Although a sliding flap may be performed in selected patients, for patients with anal canal ulceration, a normal rectum, and rectovaginal fistula, an advancement sleeve flap may be performed (Fig. 140–3). Hull and Fazio[43] initially reported the use of the advancement sleeve flap in 5 women with anorectal ulceration, Crohn's disease, and rectovaginal fistulas. The fistula eventually healed in four patients with this technique, and one patient subsequently required proctocolectomy and ileostomy. In a subsequent report,[44] which included patients with Crohn's disease and a rectovaginal fistula in addition to other complex fistulas, a successful outcome was achieved in 8 of 13 patients. The advancement sleeve flap is a good option for patients in whom the only other option is fecal diversion.

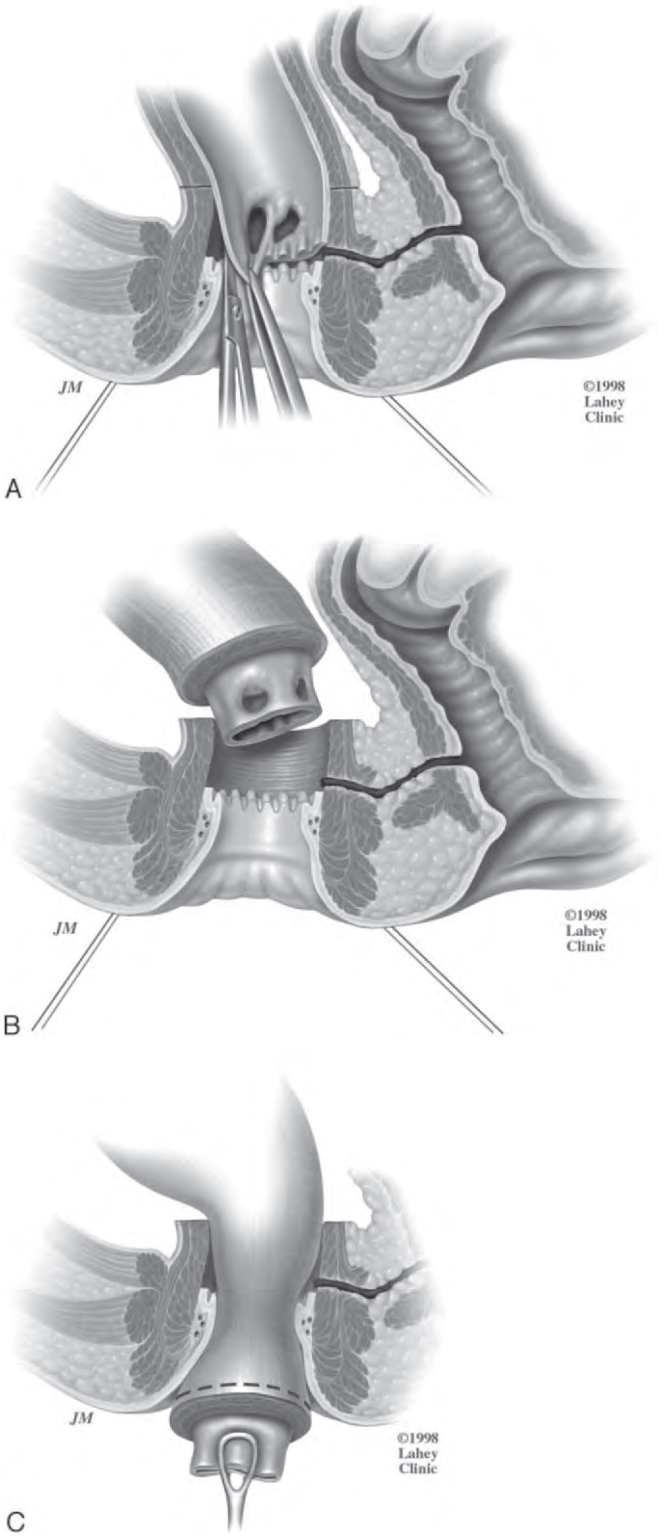

Figure 140–3. Advancement sleeve flap. **A,** Commencing at the level of the dentate line, a circumferential dissection of mucosa and submucosa is performed, thus excising the ulcerated areas of the anal canal. **B,** The dissection is continued cephalad and into the supralevator space, completing rectal mobilization. **C,** The fistula can then be cored out and closed, and the distal cuff *(dotted line)* of the rectum is trimmed and secured to the anoderm. (**A-C,** ©1998, Lahey Clinic, Burlington, MA.)

Perineoproctectomy with Layered Closure

In this procedure, the fistula is converted to a fourth-degree perineal laceration. The tract is then excised, and the vagina, sphincter muscles, and rectal mucosa are identified, mobilized, and repaired in layers. Excellent results have been reported in several series.[7,49,62] Mazier and colleagues[49] reported a success rate of 100% in 38 patients who underwent perineoproctectomy.

Fistulotomy

Simple fistulotomy for the treatment of patients with rectovaginal fistula is mentioned only to be condemned because it is associated with significant incontinence. In a small series[28] of eight patients who underwent this procedure, all patients had postoperative incontinence and required a second procedure.

Autologous Fibrin Glue

Autologous fibrin tissue adhesive initially appeared to have some success in the treatment of patients with rectovaginal fistulas and is used for selective anal fistulas, particularly those with a long tract. The advantage of fibrin glue or treatment of fistulas is that it can be done as a minimally invasive technique without significant complications. However, the technique has, with the exception of one series, has a high failure rate because the tract is characteristically too short to hold the glue for any length of time.[64-66] Modifications in the technique including closure of the internal opening and use of use of intra-adhesive antibiotics have not improved the outcome.[67]

Fibrin glue has also been used as an adjunct with other procedures such as endorectal advancement flap; in one series[54] fibrin glue was combined with endorectal advancement flap in 12 patients; the failure rate was 50% which was not significantly different than patients who had endorectal advancement flap alone.

Miscellaneous

Some authors have reported use of a folded polyglycolic (Vicryl) mesh interposed between the vaginal and rectal suture line.[68] Four patients had successful repair by this technique. The concern with such a technique is possible infection of the mesh.

Tissue Transfer Procedures

Tissue interposition for the treatment of patients with rectovaginal fistula is intended to interpose normal well-vascularized healthy tissue between suture lines. Although several types of tissues have been used, such as the gracilis, sartorius, and gluteus maximus muscles, the most commonly used is the bulbocavernosus muscle. This technique was first described by Martius[69] in 1928 and was originally used for the repair of vesicovaginal fistulas; however, it is also useful for radiation-induced rectovaginal fistulas, large obstetric fistulas, those for which previous repairs have failed, and pouch-vaginal fistulas after restorative proctocolectomy. Details of the procedure are outlined in Figure 140–4. Since the description by Martius,[69] Elkins et al.[70] have shown that the bulbocavernosus muscle itself does not need to be included in the graft since the labial adipose tissue has excellent blood supply, thus decreasing the morbidity of using the bulbocavernosus muscle and reducing the operative time. Using this technique for complex fistulas, Pinedo and Phillips reported healing in 6 of 8 patients.[71] Modifications in surgical technique have been outlined by Hoskins et al.,[72] who used a full-thickness island graft from the labia majora, and Symmonds and Hill,[73] who used a full-thickness graft from labia minor and majora. Boronow[74] reported a success rate of 84% in 25 women with rectovaginal fistulas. Dyspareunia, infrequently reported as an outcome variable, but noted in 25% of women in one series of bulbocavernosus flaps, is a potential concern with the procedure.[56]

Abdominal Procedures

Complex fistulas, particularly those secondary to radiation or previous pelvic surgery, are generally not suitable for a local repair. Fistulas may occur after operations that involve anterior rectal mobilization and mobilization of the rectovaginal septum, such as low anterior resection, coloanal anastomosis, and ileal pouch–anal anastomosis. After colorectal procedures, such fistulas arise from dehiscence of the anastomosis, with subsequent tracking into the vagina. Previous hysterectomy appears to predispose the patient to this complication, presumably because of the difficulty with adhesions between the anterior rectal wall and vaginal cuff.[75] Although rectovaginal fistula is reported after both hand-sewn and double-stapled anastomosis, the double-staple technique seems to be implicated in most cases. The most likely reason is that the staple line includes an edge of vagina. Gynecologic surgery, such as hysterectomy, rectocele repair, and vaginal vault prolapse suspension, may also be complicated by rectovaginal fistula. In one series,[76] rectovaginal fistulas occurred in 1.2% of women undergoing repair of vaginal vault prolapse. These fistulas tend to be higher than obstetric fistulas and have surrounding tissues that are abnormal and poorly vascularized. Abdominal procedures permit excision of abnormal tissue, with interposition of well-vascularized normal tissue to correct the fistula. Preservation of the sphincter is possible with such procedures as coloanal anastomosis and onlay patch anastomosis.

Coloanal Anastomosis

Patients with radiation proctitis and rectovaginal fistula may be treated by resection and coloanal sleeve anastomosis as first reported by Parks and colleagues.[77] The technique involves proximal loop diversion, rectal resection below the level of the fistula, and mobilization of the left colon. Although Parks and colleagues described a distal mucosectomy followed by a coloanal anastomosis, a double-staple technique (as is used for the ileoanal

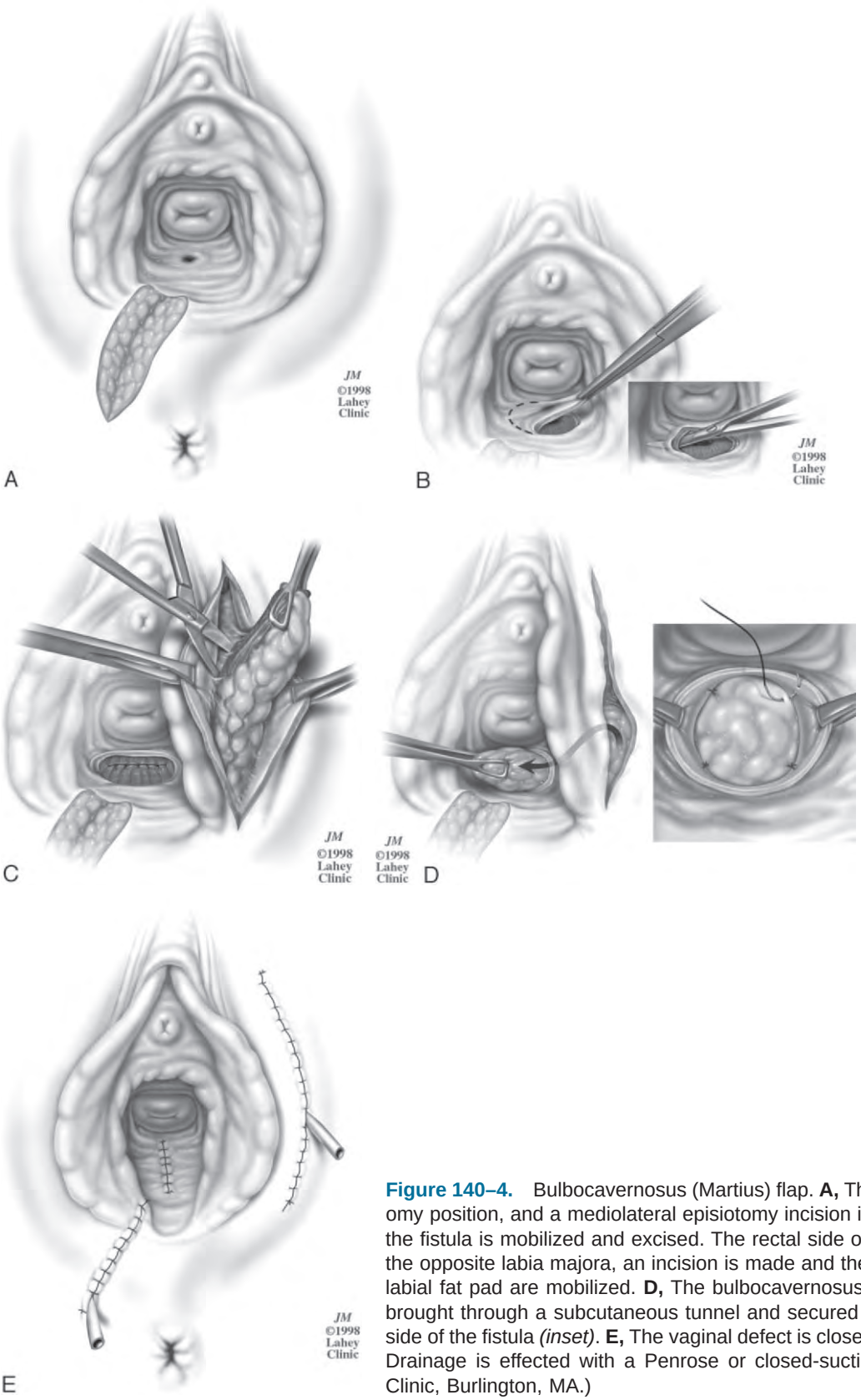

Figure 140–4. Bulbocavernosus (Martius) flap. **A,** The patient is placed in the lithotomy position, and a mediolateral episiotomy incision is made. **B,** The vaginal side of the fistula is mobilized and excised. The rectal side of the fistula is closed. **C,** Along the opposite labia majora, an incision is made and the bulbocavernosus muscle and labial fat pad are mobilized. **D,** The bulbocavernosus muscle and labial fat pad are brought through a subcutaneous tunnel and secured to the previously closed rectal side of the fistula *(inset)*. **E,** The vaginal defect is closed, and the incisions are closed. Drainage is effected with a Penrose or closed-suction drain. (**A-E,** ©1998, Lahey Clinic, Burlington, MA.)

pouch procedure) may also be used, and a colonic J-pouch may be added to improve neorectal function. If available, omentum is interposed between the anastomosis and the vagina. Using the coloanal anastomosis, Cooke and Wellsted[78] reported a 93% success rate in 55 patients. A modification of the coloanal technique has been reported by Simonsen and colleagues,[79] who used the anterior rectal wall to construct a neovagina. The authors reported no operative deaths and no recurrent fistulas in 19 patients.

Onlay Patch Anastomosis

Bricker and Johnston[80] described an alternative approach for radiation-induced rectovaginal fistulas and particularly fistulas that involve large portions of the vagina. Although several modifications of the procedure have been described, the procedure involves mobilization of the rectosigmoid and exposure of the fistula. After transection of the rectosigmoid, an end stoma is formed. Subsequently, the distal rectosigmoid is rotated down, and the open end is anastomosed to the débrided edges of the fistula opening in the rectum. After healing has been confirmed with radiographic studies, the proximal sigmoid is sutured in end-to-side fashion to the loop in the rectosigmoid. The advantage of this procedure is that posterior rectal mobilization and entry into the presacral space are not necessary; however, it is still a technically difficult procedure and a disadvantage is that a portion of the diseased rectum is left in place for the anastomosis. Using this technique, Bricker and Johnston[80] reported excellent or satisfactory results in 19 of 20 patients.

Role of Diversion

For a patient with a rectovaginal fistula who is a poor medical risk and cannot tolerate major surgery, simple fecal diversion with either a loop ileostomy or colostomy may provide good symptomatic relief and return to a reasonable quality of life.

Fecal diversion also has a role in patients who have undergone repair of complex fistulas by coloanal anastomosis or Bricker onlay patch anastomosis. Patients who have Crohn's disease and patients whose multiple previous local repairs have failed may also benefit from fecal diversion as an adjunct to primary repair or as a primary procedure.

SUMMARY

The optimal treatment for patients with rectovaginal fistulas depends on a number of factors, including the site of the fistula, the cause of the fistula, surgical expertise, and the presence of an associated sphincter defect and incontinence. With thorough preoperative evaluation, consideration of optimal treatment options, and meticulous surgical technique, a successful outcome is achieved in the majority of patients.

RECTOURETHRAL FISTULAS

Rectourethral fistulas are rare and may occur from either congenital or acquired causes. Congenital fistulas are often associated with other anorectal abnormalities, whereas acquired fistulas may result from trauma, previous surgery, Crohn's disease, infection, and malignancy, especially prostate cancer. Fistulas arising from prior surgery have previously been noted after such procedures as surgery for benign prostatic hypertrophy, perineal prostatectomy, and perineal biopsy of the prostate; however, the last 2 decades have seen a shift in cause due to increasing numbers of patients undergoing high-dose or salvage brachytherapy, cryotherapy, and radical prostatectomy by either an open or laparoscopic approach for prostate cancer. Thus, there has been a shift from relatively simple small fistulas to larger, more complex fistulas often associated with necrosis, substantial tissue defects, urethral strictures, and radiation effects. This shift in cause has mandated a shift in the surgical treatment of such fistulas. The diagnosis and approach to such fistulas are discussed, and further details are outlined in the Suggested Readings list.

Rectal injury is a well-recognized complication of prostate surgery occurring in 1% to 11%,[81,82] with the subsequent development of a rectourethral fistulas reported in 0.4% to 8.8% of patients undergoing brachytherapy.[83,84] A higher incidence of fistulas has been noted in patients undergoing salvage therapy and patients who have rectal biopsy after brachytherapy.

The clinical presentation of such fistulas is generally straightforward, with most patients complaining of passage of urine per rectum and a number complaining of fecaluria and pneumaturia. Patients who develop fistulas after brachytherapy or cryotherapy may initially complain of severe pain. Retrograde urethrography, voiding cystourethrography, and urethroscopic cannulation and injection of the fistula may help define the fistulas. Digital examination, anoscopy, and either flexible sigmoidoscopy or colonoscopy help identify the rectal opening, assess the anal sphincter and assess the rectum for evidence of intrinsic rectal disease such as inflammatory bowel disease and radiation proctitis.

There are a number of surgical procedures for repair of rectourethral fistulas, and determining the optimal repair must take into account the complexity of the fistulas, the status of the surrounding tissues, the size of the defect, and prior radiation treatments. Although small simple fistulas in patients who have not had previous radiation may be repaired without fecal diversion, this procedure is performed in most complex fistulas and particular those associated with previous failed repairs, complex causes (including radiation), cryotherapy, or large fistulas and those that cannot be repaired without use of patch graft and/or interposition muscle flap. Our preference is the performance of a loop ileostomy, ideally performed by a laparoscopic approach.

One of the most widely used techniques for repair in the last decade has been the York-Mason posterior transanosphincteric approach. The approach, performed in the prone jack-knife position with posterior midline division of the sphincter muscles, allows for good

exposure through unscarred planes and allows for adequate closure. A one-stage procedure without fecal diversion can generally be performed. Excellent results were reported by Renschler and Middleton, who repaired 22 of 24 fistulas with such an approach.[85] Low, simple fistulas may also be repaired by an endorectal sliding flap. The main advantage of such a repair is minimal morbidity and a fairly quick recovery, whereas the main disadvantage of this procedure is that the high-pressure urethral side is not addressed and a period of prolonged catheter drainage is needed. Using such an approach, an initial closure was achieved in 8 (67%) of 12 patients with an ultimate success rate of 83%.[86]

The York-Mason approach and sliding flap do not allow for repair of large complex fistulas, which may require an interposition flap, concurrent urethral reconstruction, or buccal patch graft for large defects or associated urethral strictures. Large fistulas and large defects require interposition of additional tissue, and the gracilis muscle is ideally suited for this technique. The gracilis has been used extensively in colorectal surgery for construction of a neosphincter around the anus, for treatment of unhealed wounds after proctectomy for cancer and Crohn's disease, for treatment of rectourethral fistulas. Gracilis muscle transposition has been reported with good success for rectourethral fistula.[87,88]

These large, complex fistulas are increasingly the type of fistulas seen, and those fistulas associated with urethral defects or strictures require repair of the urethral defect also. These fistulas pose difficult surgical challenges, and few surgeons have significant expertise with repair. At the Lahey Clinic, a variety of surgical techniques, perfected by Dr. Leonard Zinman, have been used. The procedures have previously been reported.[89] The approaches used have included an anterior perineal approach with division and subsequent reapproximation of the sphincter, an anterior sphincter–preserving perineal approach through a classic inverted U-shaped incision, and an anterior perineal approach with preservation of the sphincter with use of a gracilis buttress and of a buccal mucosa graft if required for a urethral defect. From 1980 to 2003, a total of 68 rectourethral fistulas have been treated with these techniques, including anterior perineal repair with interposition of gracilis ($n = 28$), anterior transanosphincteric repair with interposition of gracilis ($n = 9$), anterior perineal repair with buccal graft patch and muscle flap ($n = 27$), and rectal excision and urethral repair with either gluteus maximus or rectus abdominis ($n = 4$).

Patients with rectourethral fistulas are a heterogeneous group, and consideration for treatment needs to address both rectal and urinary function. Large tissue defects associated with radiation require interposition of muscle, ideally gracilis, for treatment and significant urethral defects or stricture require repair and are addressed with buccal grafts.

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Chapter

141

Complete Rectal Prolapse

Amir L. Bastawrous · Herand Abcarian

Complete rectal prolapse or procidentia is a circumferential, full-thickness descent of the rectum (and maybe the sigmoid colon). Classically, eversion of the rectum is externally visible. The spectrum of associated disorders linked with the putative pathophysiology of rectal prolapse includes lesser degrees of "hidden" prolapse and solitary rectal ulcer syndrome. True rectal prolapse should be distinguished from rectal mucosal prolapse and hemorrhoidal disease. On examination the former has thick, concentric, circumferential folds while the latter has radial folds often shaped like a three-pointed star (Figs. 141–1 and 141–2).

HISTORICAL PERSPECTIVE

Rectal prolapse has been described for centuries. In the Ebers Papyrus the ancient Egyptians described honey-containing suppositories, laxatives, and enemas in the treatment of rectal prolapse. The ancient Greeks used the method of hanging a patient by the heels and shaking to reduce a prolapse. Rectal prolapse was recognized as an intussusception of the colon in the 18th century. Moschocowitz identified rectal prolapse as a sliding perineal hernia on identifying a deep cul-de-sac in affected patients.

PATHOPHYSIOLOGY

The anatomic defect of complete rectal prolapse is relatively easy to describe. The pathophysiology, however, has been more difficult to define. The development of rectal prolapse occurs over a period of years making it difficult to identify a specific cause. It is unclear whether the intussusception of the rectum is the main responsible factor or the result of some other anatomic or physiologic defect. Several findings have been associated with rectal prolapse. These include weak levator ani and anal sphincter muscles, a redundant rectosigmoid colon, a deep cul-de-sac, and loss of fixation of the rectum to the sacrum.

Regardless, the prevailing theory is one of distal intussusception of the rectum. Numerous diseases have been linked to rectal prolapse including connective tissue disorders, pelvic outlet obstruction, pelvic floor laxity, spina bifida, multiple sclerosis, cystic fibrosis, anorexia and bulimia nervosa, and excess straining or Valsalva maneuver. A history of mental illness has been linked to rectal prolapse with a four-fold higher rate in that population.

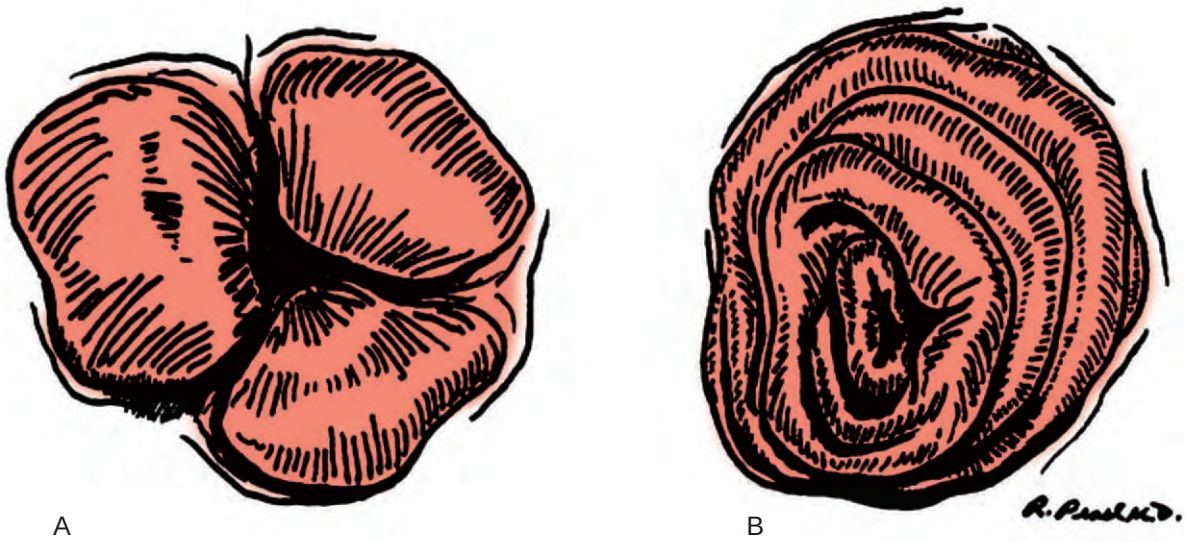
Straining at stool is often associated with rectal prolapse. A history of constipation is seen in up to 67% of patients and diarrhea in 15%. Paradoxically, incontinence is reported to be present in up to 70% of patients with rectal prolapse. Women are six times more likely than men to develop rectal prolapse. There is also a different age distribution in women and men, with men presenting in their twenties and thirties while women present more commonly after the sixth decade. Most patients who require surgery for rectal prolapse are elderly.

PHYSICAL EXAMINATION

The typical patient with complete rectal prolapse will present with a history of bleeding and a "bulge" in the anal region after bowel movements. The rectum is often obvious on inspection. Occasionally, the prolapse may become evident only when asking the patient to squat or sit on a toilet and strain. An evaluation of resting anal tone and squeeze pressures is important in the workup. Identification of other concomitant pelvic floor defects including rectocele, cystocele, vaginal prolapse, and enterocele is necessary and may influence the operative approach.

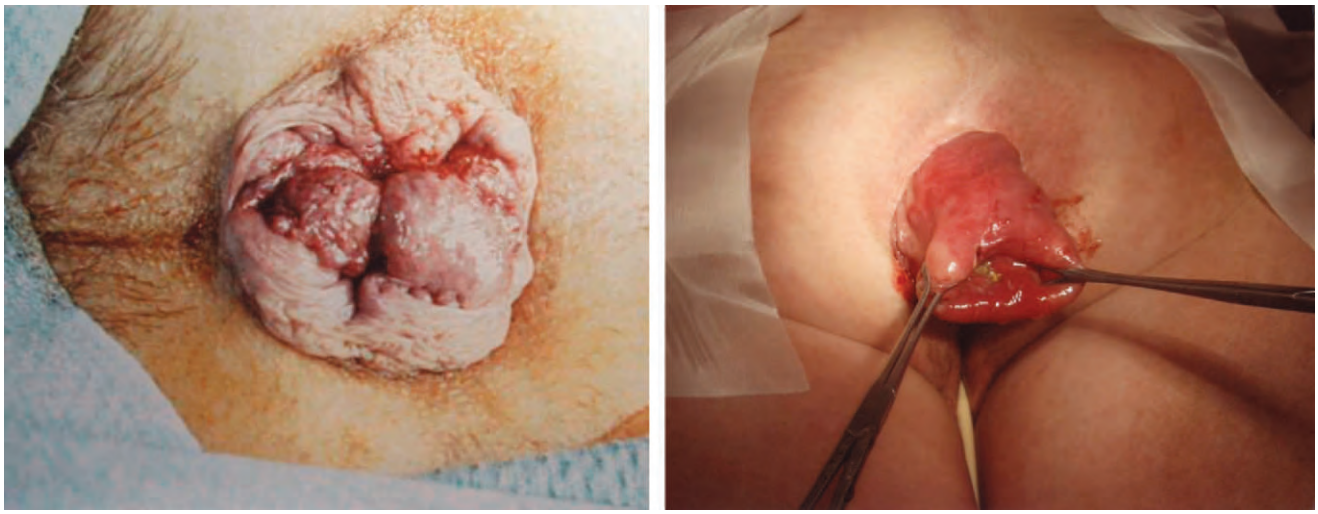
DIAGNOSIS AND TESTING

Patients with a history of incontinence associated with rectal prolapse should be evaluated with anal manometry, ultrasonography, and pudendal nerve terminal motor latency to document baseline anorectal anatomy



A B

Figure 141–1. Prolapsing hemorrhoids **(A)** and complete rectal prolapse **(B).**



A B

Figure 141–2. Prolapsing hemorrhoids **(A)** and rectal prolapse **(B).**

and function prior to repair.[1] Plain radiographs of the sacrum are useful to identify patients with occult spina bifida. Cinedefecography can be useful to diagnose "hidden" rectal prolapse or internal intussusception for patients in whom the rectum is not visible externally. Colonoscopy is essential to rule out synchronous or causative neoplasm prior to a planned surgical repair.

Colonic transit time should be evaluated with marker studies for patients with a history of constipation and rectal prolapse. This subgroup of patients may benefit from an abdominal approach with resection as rectopexy alone typically worsens the constipation.[2]

If a perineal approach is planned and associated urinary or uterine prolapse is seen, intravenous pylogram will help identify course of the ureters, which may travel quite low in the pelvis. Combined repair of enterocele, cystocele, and rectal prolapse has been described.

TREATMENT

Acute Management of Rectal Prolapse

The acute treatment of complete rectal prolapse involves early reduction. Often, especially in the mentally ill in whom persistent straining or valsalva has contributed to the prolapse, the rectum will immediately re-prolapse. Gentle constant pressure is often successful in reducing the prolapse and if the rectum continues to prolapse after reduction, taping the buttocks together may help temporarily.

If the prolapse has been neglected or unrecognized for a prolonged period, it may not easily reduce. Unless the rectum is frankly non-viable or necrotic, a few techniques may help return the bowel to its anatomic position. Sedation, placing the patient in the Trendelenburg

position, and placement of salt or sugar topically can decrease the bowel edema and assist reduction.[3] Injection of hyaluronidase has also been described in the acute situation. These maneuvers can often be done at the bedside, but may need to be done in an operating room setting in certain cases.

If the incarcerated rectum cannot be reduced, or if there is evidence of ischemic compromise, then operative resection, typically a perineal proctosigmoidectomy is indicated.

Surgical Treatment of Rectal Prolapse

A surgical intervention is nearly always necessary to correct rectal prolapse. The "perfect" treatment should offer safe, complete and durable resolution of the anatomic and physiologic problems.[4] The current treatment modalities all have a recurrence rate, albeit low and decreasing. The search for the best surgical treatment of rectal prolapse spawned a multitude of approaches beginning in the 19th century. Over 100 different procedures or modifications have been described in the medical literature. In fact newer innovations continue to appear in the literature.[5-9] The spectrum of current operative techniques includes both abdominal and perineal procedures. Laparoscopic approaches have gained popularity as surgeons have become comfortable operating on the colon laparoscopically.[10-14] Generally, patients who can tolerate laparotomy should be offered an abdominal approach to correct their prolapse, while elderly or debilitated patients are better managed with a perineal procedure. The exception may be young men who may prefer to accept the higher risk of recurrence of their prolapse with a perineal procedure over the increased risk of impotence or infertility with an abdominal procedure.

As is generally accepted at this time, all patients receive a mechanical bowel preparation the day prior to surgery, perioperative antibiotics, and prophylaxis against deep venous thrombosis.

Abdominal Approaches

General anesthesia is usually employed, but regional anesthesia has been successfully used. Patients are placed in low dorsal lithotomy position for all laparoscopic or open laparotomy procedures. For laparoscopic approaches, the patients' arms are tucked at the side. Furthermore, it is important to place the patient on a torso-sized beanbag with which to cradle the body, as it will be tilted into a steep Trendelenburg position. This will help prevent the patient from sliding on the operative table.

Rectopexy The various modifications of the technique described by Ripstein[15-20] all have in common a posterior mobilization of the rectum to the level of the coccyx. Ripstein's approach was to wrap a 5-cm wide non-absorbable polytetrafluoroethylene (Teflon) mesh around the anterior rectum, then suture it to the presacral fascia on the sides of the rectum 5 cm below the sacral promontory. The Well's modification (Fig. 141–3) places the Ivalon sponge posteriorly, leaving a 2 cm gap anteriorly to allow for rectal compliance. Successful rectopexy has been

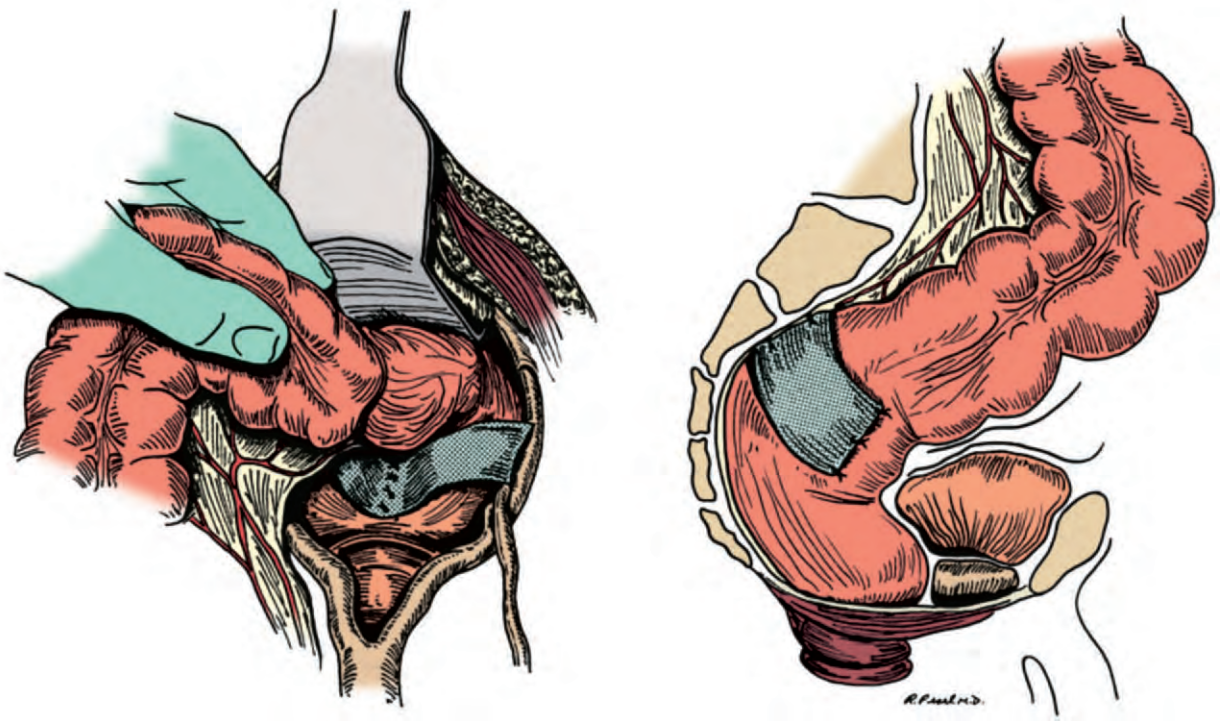


Figure 141–3. Rectopexy (Ripstein procedure).

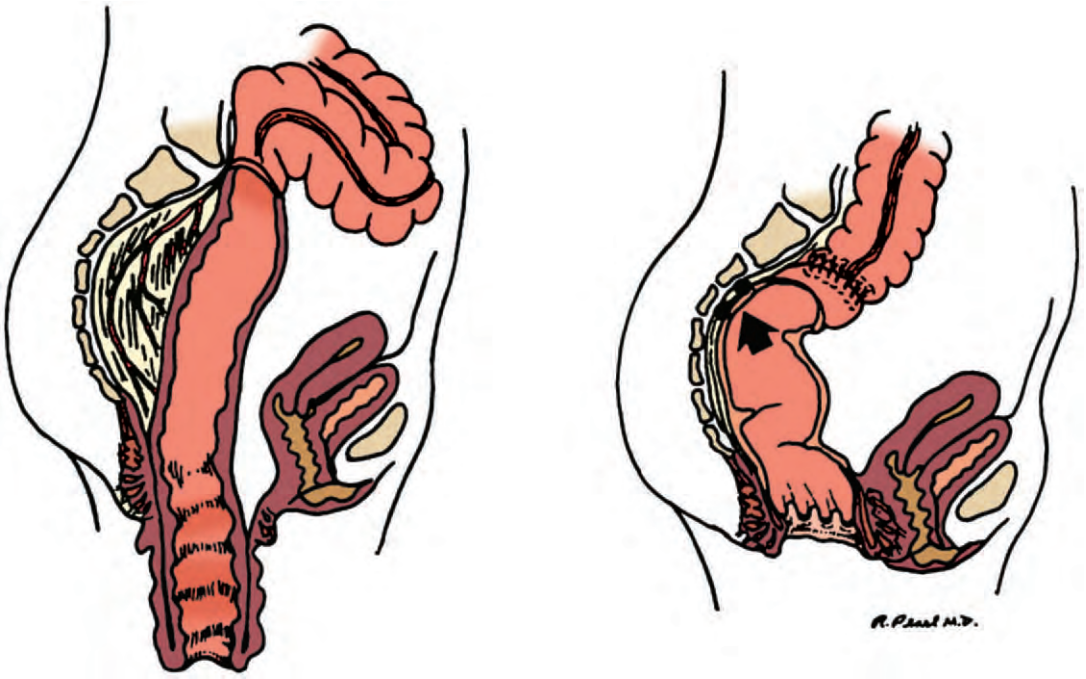


Figure 141–4. Sigmoid resection plus rectopexy (Fuykwan procedure).

described with simply using non-absorbable suture or metal staples to fix the rectum to the sacrum and thus re-create the normal rectal angulation. Recently it was suggested that mobilization of the rectum itself is sufficient to produce enough fibrotic scar to fix the bowel to the sacral curvature.[19] Patients with constipation preoperatively will have worsening of their symptoms with rectopexy alone, because it results in acute angulation of the rectosigmoid position by allowing the sigmoid colon to fall anteriorly into the pelvis. Speakman et al. have reported that division of lateral stalls will allow for better rectal mobilization and fixation and prevents recurrence but at a cost of worsening constipation.[20]

Resection Anterior resection of the colon and rectum is familiar to most general, laparoscopic, and colorectal surgeons. This may partially explain the popularity of this approach. Through a low midline or transverse incision or laparoscopically, the rectum is mobilized to the level of the coccyx to produce fibrotic fixation to the sacrum. Next, the redundant sigmoid colon and rectum are resected and re-anastomosed. The anastomosis should be at the level of the sacral promontory. The splenic flexure should not be mobilized as lack of left upper quadrant fixation may theoretically contribute to recurrence of the prolapse. Resection procedures tend to alleviate preoperative constipation symptoms.

Resection-Rectopexy The technique of resection plus rectopexy combines the benefits and risks of both procedures. Resection rectopexy has the advantage of removing excess bowel and restoring the normal rectal angulation (Fig. 141–4). There are reports that this approach improves symptoms of both incontinence and constipation.[22]

Laparoscopy Laparoscopic approaches to rectal prolapse have gained popularity as surgeons have obtained expertise at laparoscopic colon surgery in general and as safety concerns have abated.[10-14] Proponents describe a lower perioperative morbidity than open procedures.[14] The key steps of the operation should be the comparable to the open technique.

Randomized, controlled trials by Solomon et al.[13,14] comparing laparoscopic and open rectopexy showed both a lower cost and improved clinical outcome with the laparoscopic technique. Laparoscopic resection and resection-rectopexy can be performed with or without hand assistance. The resected colon can be removed from the abdomen either through a hand port or through an extension of a port incision.

Perineal Approaches

Many general surgeons shy away from perineal approaches to complete rectal prolapse because of a lack of training in and understanding of the anorectal anatomy and physiology. Nevertheless, many patients won't tolerate laparotomy or laparoscopy. These patients are better served with the minimally invasive approach of perineal proctosigmoidectomy (Altemeier), anorectal mucosectomy with muscular plication (Delorme procedure) or anal encirclement (Thiersch). Furthermore, recurrence rates in some series approach those described in abdominal treatments of rectal prolapse. Given that most patients with rectal prolapse are elderly women (many with multiple co-morbidities) and young men (who may fear the risk of sexual dysfunction with injury of the hypogastric nerves during an abdominal approach) some argue that perineal procedures are the preferred operations for most patients with procidentia.

The various perineal procedures can be performed either in the lithotomy position, or preferably in the prone jack-knife position. Regional anesthesia is typically used, but some patients may require general anesthesia. A self-retaining–type retractor (e.g. Lone Star) helps with exposure (Fig. 141–5).

Perineal Proctosigmoidectomy Altemeier popularized the technique of resecting the prolapsed bowel directly.[23,24] The Prasad modification is the only surgical approach to correct each of the anatomic defects associated with rectal prolapse.[23] The first step is to completely prolapse the redundant rectum by gently pulling on the rectal wall. The dentate line will be easily visible on the everted rectum (see Fig. 141–5). A dilute epinephrine solution is injected 1 to 2 centimeters proximal to the dentate line in the prolapsed rectal wall. Next, the rectal wall is incised full thickness, circumferentially with electrocautery at the level of the injection. The vascular supply to the prolapsed rectum and sigmoid is then carefully ligated. Nonabsorbable suture is used to fix the non-prolapsing bowel to the pre-sacrococcygeal fascia reproducing the normal posterior fixation of the rectum. The widely open pelvic floor is closed with a posterior levatorplasty. This recreates the normal anorectal angulation. The excess bowel is resected and a coloanal anastomosis is performed. The anastomosis can be hand sewn with absorbable suture or stapled by any of several stapling techniques.

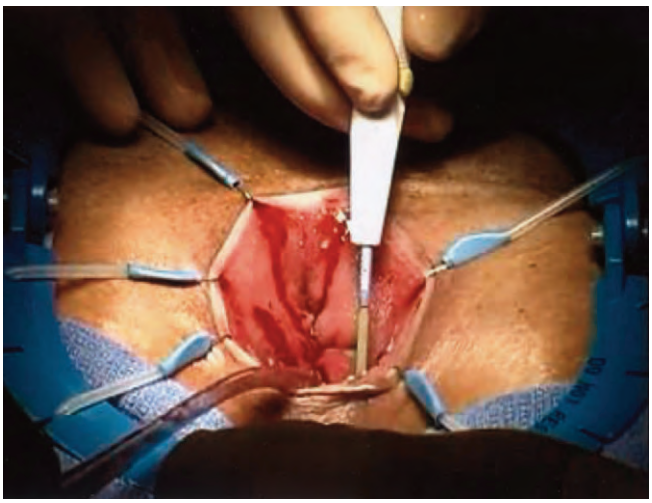


Figure 141–5. Lone Star retractor and incision for Delorme or perineal proctectomy.

Anorectal Mucosectomy with Muscular Plication (Delorme) The Delorme procedure first described in 1900 continues to be employed in select situations. The advantage of the procedure is that no bowel resection and anastomosis is needed.[9,25,26]

Once the bowel is completely prolapsed, a dilute epinephrine solution is injected judiciously in the submucosal plane (Fig. 141–6). The mucosa is circumferentially incised 1 cm proximal to the dentate line with electrocautery. The incision is deepened only to the level of the submucosa. The muscular layers are left intact. The mucosa is then stripped off the rectal wall musculature, continuing proximally to the extent of the redundant bowel (Fig. 141–7). The mucosal sleeve is then excised. Longitudinal plicating sutures are placed along the length of the rectal wall musculature approximately 1 cm apart. The sutures are tied once all 6 to 8 rows have been placed. Next, the proximal mucosal edge is re-sutured to the initial mucosal incision with absorbable sutures.

A modification utilizing a double purse-string suture and a circular stapler has been described.[6] The Delorme

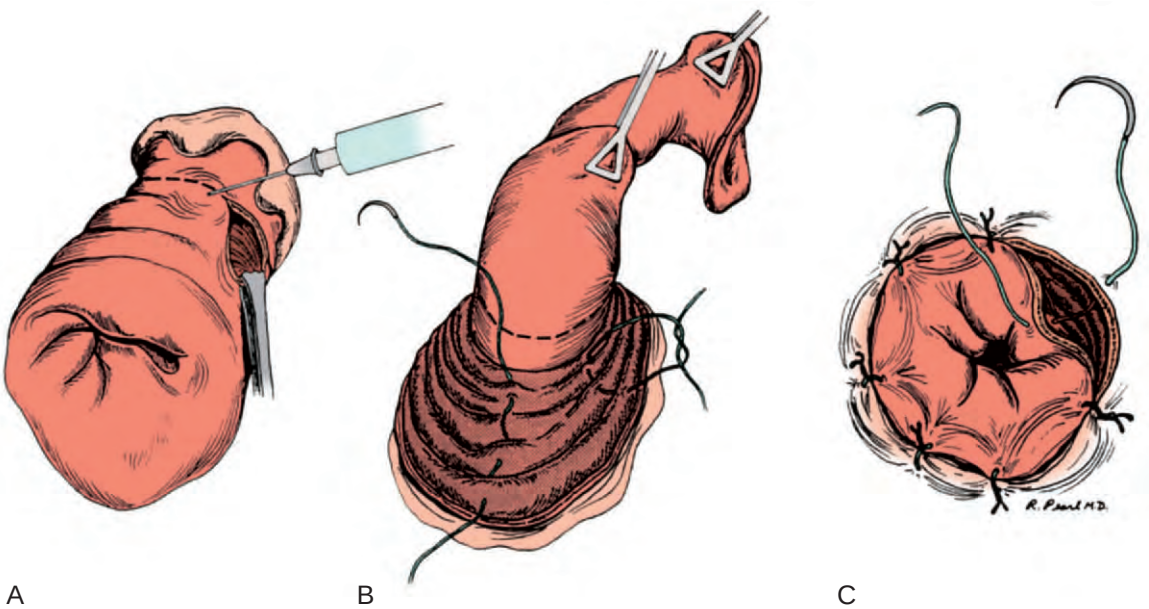
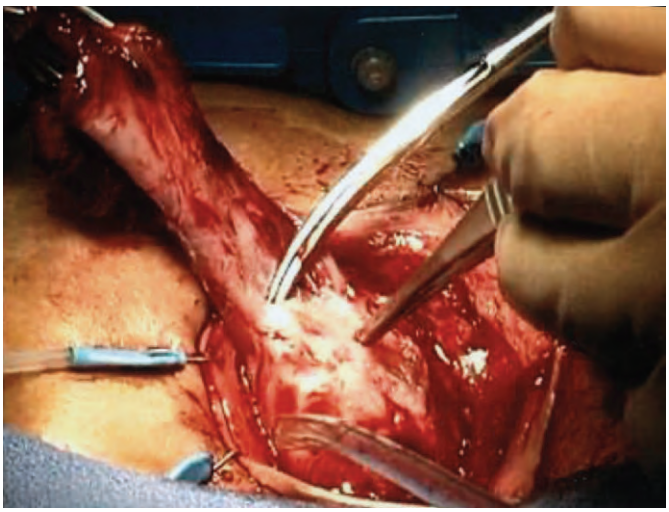


Figure 141–6. **A** to **C,** Anorectal mucosectomy and plication (Delorme procedure).



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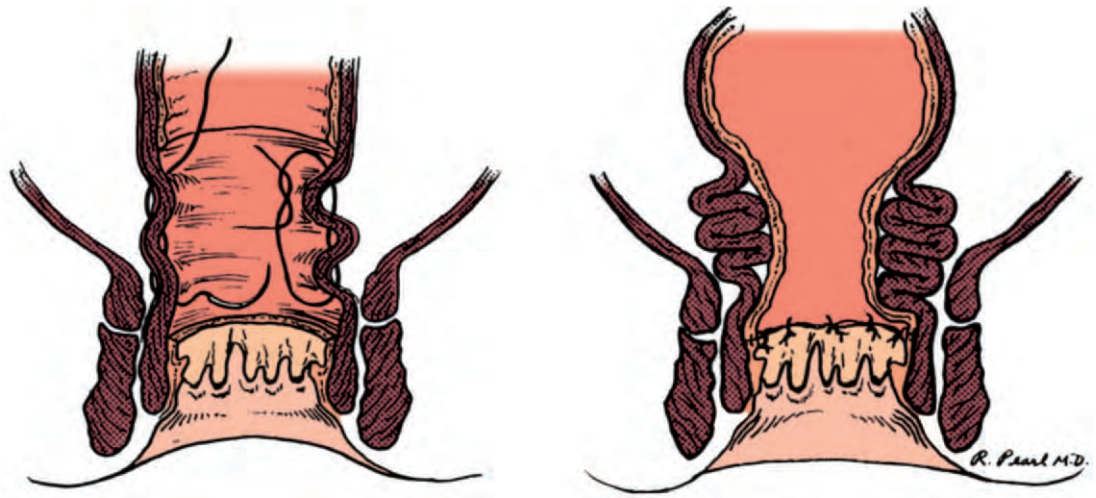

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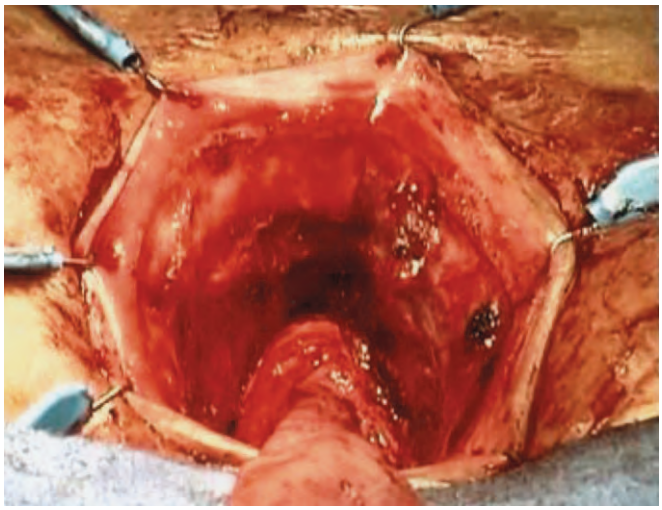

C

Figure 141–7. The Delorme procedure. Mucosal stripping **(A),** illustration of muscular plication and mucosal anastomosis **(B),** and after mucosal stripping and prior to plication **(C).**

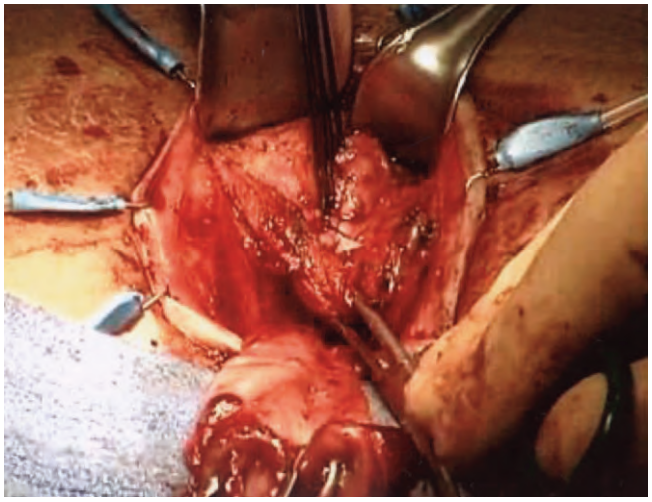

Figure 141–8. Delorme procedure combined with posterior levatorplasty.

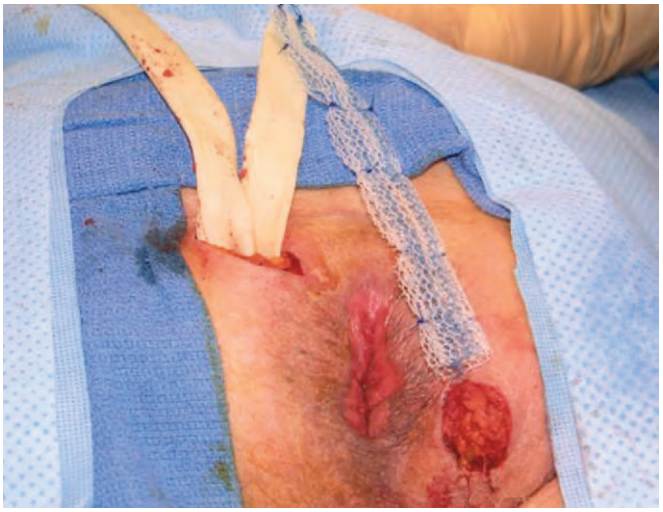

Figure 141–9. Thiersch encirclement. Note the two incisions 180 degrees apart and the already placed Penrose drain encircling the anus that will be used to pull the mesh around.

Table 141–1 Procedures for Rectal Prolapse

Procedure	Major Risks	Major Benefits	Best for
Rectopexy	Higher operative risk, presacral bleeding, pelvic abscess	Lower recurrence rate	Young, healthy patient without redundant sigmoid or constipation
Resection	Higher operative risk, anastomotic leak	Lower recurrence rate, correction of constipation	Young, healthy patient with redundant sigmoid and constipation
Resection-rectopexy	Higher operative risk, anastomotic leak, presacral bleeding, pelvic abscess	Lower recurrence rate, correction of constipation	Young, healthy patient with redundant sigmoid and constipation
Perineal proctosigmoidectomy (Altemeier)	Higher recurrence rate, technique unfamiliar to many surgeons	Lower operative risk, correction of incontinence, may be combined with other pelvic floor reconstructive procedures	Older patient with comorbidities, and long-segment rectal prolapse
Anorectal mucosectomy with muscular plication (Delorme)	Higher recurrence rate, technique unfamiliar to many surgeons	Lower operative risk, correction of incontinence, may be combined with other pelvic floor reconstructive procedures	Older patient with comorbidities, and short-segment rectal prolapse
Anal encirclement (Thiersch)	High recurrence rate, mesh infection, erosion into bowel	Lower operative risk	Elderly poor risk patient, short life expectancy

procedure can be combined with posterior levatorplasty[9] in an attempt to improve continence (Fig. 141–8).

Anal Encirclement (Thiersch) Some surgeons have stated that anal encirclement[27,28] is a procedure which should be relegated to historical interest only. However, for the bed-ridden patient with short life expectancy, multiple co-morbidities and possible dementia or Alzheimer's disease and who may not tolerate even a perineal resection of rectal prolapse, the Thiersch technique can still be useful. It may also have a place after failure of the perineal procedures. This simple

procedure can be performed quickly, with very low morbidity.

Two perianal skin incision 180-degrees apart and lateral to the midline are made. The incisions are connected with a tunnel through the ischiorectal fossa. A strip of polypropylene mesh 1.5 cm wide is placed around the deep external sphincter. The mesh is passed around the anus from one incision to the second and then back to the first to completely encircle the anus (Fig. 141–9). The mesh is tightened and sutured to itself allowing an anal diameter only large enough to admit one finger in the anus. The risks of the procedure include erosion of the mesh into the rectum, infection of the mesh, recurrence of the prolapse, and impaction secondary to tight encirclement.

RESULTS AND PATIENT SELECTION

Proponents of abdominal rectopexy in its various forms claim lower recurrence rates (0-5%) than perineal procedures (10-15%). Surgeons with a preference for perineal proctosigmoidectomy and Delorme's procedure point to their relative safety and ease of reoperation in the event of recurrence. Most likely, each clinical situation will favor one approach from the other (Table 141–1). As such, proficiency in each approach is necessary.

Caution must be employed if a perineal approach is contemplated for recurrent rectal prolapse previously treated with an abdominal resection or, alternatively, if an abdominal resection is planned after a perineal resection. Unless the prior anastomotic line is resected, there is a risk of ischemia and necrosis of the intervening bowel between the two anastomoses can occur.[29]

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Chapter

142

Pilonidal Disease

Debra Holly Ford · H. Randolph Bailey

Pilonidal disease is a common recurring chronic disease. Since its first description in the early 1800s,[1,2] pilonidal disease and its treatment have been the subject of debate and controversy. It is believed to be an acquired infectious process leading to high rates of morbidity. This condition often results in discomfort and inconvenience. Patients are often prevented from working or attending school for extended periods. Although pilonidal disease has been described in other parts of the body, such as the hands, umbilicus, axillae, and external genitalia,[3] our discussion focuses on the disease as it affects the gluteal cleft region.

Sacrococcygeal pilonidal disease occurs predominately in young males at a ratio of 3:1. The peak incidence is between 15 and 24 years of age. Symptoms rarely present before 15 years of age or after the age of 40.[3,4] The disease is most common in whites; however, all ethnic groups can develop the condition.[5] Other factors affecting its incidence are obesity, poor personal hygiene, increased sweating activity, and local trauma.

ETIOLOGY

The pathogenesis of pilonidal disease remains the subject of debate. Approaches to the treatment of pilonidal disease have closely paralleled the theories of its development. For many years, the cause of pilonidal disease was thought to be congenital in origin. The *congenital theory*, which describes the pilonidal tract as a caudal remnant of the medullary canal or as a faulty coalescence of caudal dorsal ectodermal segments, still has its proponents.[6-8] Although true pilonidal cysts have been reported, such cysts are quite rare. Most well-informed surgeons treat the disease as an acquired condition. Patey and Scarff,[9] with additional evidence from Bascom,[10] have provided a plausible explanation in support for the acquired theory.

The *acquired theory* emphasizes the role that hair plays in the development of pilonidal disease. Bascom's histologic studies demonstrate a sequence of stages in the development of this condition (Fig. 142–1).[10] He describes a folliculitis that leads to the development of small subdermal abscesses that increase in size to form a large abscess cavity. He also explains that hair is drawn into the pilonidal cavity through the suction effect of gluteal movement. Other factors believed to contribute to the creation of pilonidal disease are related to the condition of the gluteal cleft, including a catch basin effect, the depth of the gluteal cleft, and gluteal cleft friction.[10]

The uncertain etiology of pilonidal disease has led surgeons to approach this condition in various ways, from the most conservative approaches to extensive plastic procedures.[6]

PATHOLOGY

Pilonidal disease is essentially a foreign body reaction. Midline pits are lined with squamous epithelium. Although 1% of the tracts associated with these pits may be completely lined with squamous epithelium, most are lined with only granulation tissue.[3] Hair, in the form of broken hair shafts, is found in the cavities at least 50% of the time. Typical pilonidal cavities do not contain epidermis, sweat glands, or hair follicles. The tracts usually extend cephalad and lateral from the midline pits. Pilonidal tracts have, however, been described as extending toward the anus and being misdiagnosed as fistula-in-ano in 7% of cases.[3]

CLINICAL PRESENTATION

The prevalence of pilonidal disease is not accurately known. Patients may present to the surgeon with findings of asymptomatic small midline pits in the gluteal cleft (which may contain hair) or as an obvious, painful abscess. After surgical or spontaneous drainage, chronic pilonidal disease may result. The presentation that is most distressing and challenging for the surgeon is recurrent pilonidal disease or an unhealed wound after prior surgical treatment.

The patient with a pilonidal abscess typically presents with a history of increasing pain and the eventual

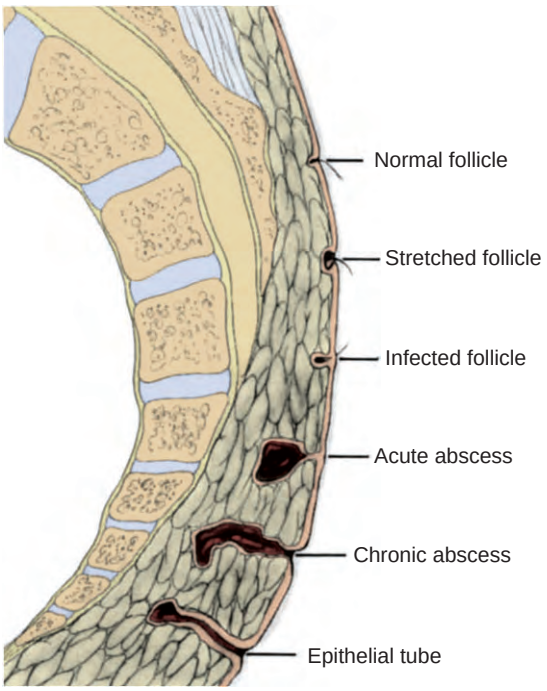

Figure 142–1. Pathogenesis of pilonidal abscess and sinus. (From Bascom J: Pilonidal disease: Origin from follicles of hairs and results of follicle removal as treatment. Surgery 87:567, 1980; redrawn in Nivatvongs S: Pilonidal disease. In Gordon PH, Nivatvongs S [eds]: Principles and Practice of Surgery for the Colon, Rectum, and Anus, 2nd ed. St. Louis, Quality Medical, 1999, p 288.)

development of a tender fluctuant mass in the sacrococcygeal area, often situated slightly off the midline. Cellulitis of the surrounding skin, as well as fever and leukocytosis, is occasionally present. An acute abscess is the presenting finding in approximately 50% of patients with pilonidal disease.[3,11] Most patients with chronic pilonidal disease have pain, intermittent discharge, or both. They may present with recurrent bouts of infection. Rarely, they present with fever and chills. On physical examination, there may be evidence of past drainage with or without cellulitis and induration. The midline pit or pits are usually present, and hair may be protruding from the orifice. The differential diagnosis of sacrococcygeal pilonidal disease includes furuncle, hidradenitis suppurativa, fistula-in-ano, perianal abscess, sacral osteomyelitis with draining sinus, tuberculosis, and actinomycosis.

TREATMENT

Many operations have been proposed for the definitive management of pilonidal disease. These treatment options have paralleled the theories of pilonidal development. During the period when widespread acceptance of the congenital theory prevailed, procedures were described that completely removed all tissue down to the sacral fascia.[7,8,12] These operations were done under general anesthesia and resulted in lengthy inpatient hospitalization. These aggressive operations produced wounds graphically described as "shark bites" that in many instances failed to heal properly and were the source of prolonged disability and discomfort.

Acceptance of the acquired theory has led to a "less is best" approach.[11,13,14] Current emphasis is placed on the elimination of factors that favor pilonidal development. In caring for patients with pilonidal disease, the surgeon should strive for complete wound healing with minimal patient disability, a low recurrence rate, and early return to activities of daily living. Contemporary management of pilonidal disease is frequently performed in an ambulatory setting.

Acute Pilonidal Abscess

An acute pilonidal abscess usually presents as a painful fluctuant mass located in the sacral midline or lateral to the midline. Immediate incision and drainage provide prompt relief of symptoms. Although anaerobic and aerobic bacteria have been cultured from these abscess cavities, antibiotics are not required in the management of most cases of pilonidal abscess.[15] Drainage may be performed in the emergency department or the office using only local anesthesia. A large abscess may require drainage in the operating room using intravenous sedation or general anesthesia. Because the abscess and the surrounding edema often obscure the midline sinus (the source of the abscess), performing a definitive procedure must usually be delayed until the edema subsides.

Technique of Drainage

Essentially all operations for pilonidal disease are best performed in the prone jack-knife position with the buttocks taped apart for better exposure. After preparation of the skin and infiltration with local anesthesia containing epinephrine, the gluteal area is shaved and a cruciate lateral incision is made over the abscess cavity with excision of the four corners of skin to allow for adequate drainage. Bascom favors a linear incision off the midline.[16] All debris and hair should be removed from the cavity if possible. Electrocautery usually suffices for hemostasis. On occasion, temporary light packing may be required. The patient is instructed to take warm tub baths at least twice daily and to return weekly for wound care and shaving. After simple incision and drainage, healing may take as long as 4 to 10 weeks.[3,17]

Several reports have favored immediate unroofing of tracts during the initial drainage of the pilonidal abscess.[3,14,18] If the midline pits can be identified, a probe is inserted through the orifice into the cavity. The abscess cavity and associated tracts are unroofed with cautery. The cavity is débrided, and wound edges are loosely packed apart to facilitate drainage and healing of the wound. Hair remaining in an inadequately drained abscess cavity is the major factor for persistence or recurrence of the abscess. The hair must be shaved surrounding the edges of the wound.[13,19] We have achieved an unreported 80% "cure" rate with this simple technique.

Chronic Pilonidal Disease

The progression to chronic pilonidal disease is expected in 40% to 60% of patients after incision and drainage.[3,5,11,17,19,20] Because of this high rate of continued or recurrent disease, Bascom[10,16] has suggested that incision and drainage be followed by a definitive surgical procedure.

As mentioned earlier, the midline pits, which are the origin of pilonidal disease, lead into a cavity lined with granulation tissue. The removal of all involved tissue is unnecessary. There is no clear consensus as to the preferred definitive treatment; however, acceptance of the acquired theory of origin has led to more operations with a minimalist approach and a strong emphasis on meticulous postoperative wound care. The treatment options usually fit into one of the following categories: conservative, nonresectional approach[12]; midline follicle excision and lateral drainage[2,16,21]; incision and curettage with minimal excision followed by marsupialization or saucerization of the wound[5,13,22]; and excision with or without primary closure.[23,24]

It is desirable to select an approach that can be carried out in an ambulatory setting with minimal patient inconvenience and disability. The role of antibiotics is not clear; there have been reports that have suggested antibiotics directed at anaerobic bacteria may improve healing rates.[15]

Conservative, Nonresectional Approach

Armstrong and Barcia[12] advocated conservative, nonexcisional therapy consisting of meticulous hair control by shaving, good perineal hygiene, and limited lateral incision and drainage for abscesses. There have been reports describing the instillation of liquid or crystalline phenol into the pits.[5,25] Healing rates have been reported from 59% to 95% in an average of 40 days.[25] Laser depilation of the natal cleft is now commonly available. Odet et al.[26] have reported 14 patients with recurrent pilonidal disease, all of whom were successfully healed by laser hair removal. We have no experience with this technique.

Technique of Midline Follicle Excision and Lateral Drainage

Although popularized by Bascom,[10] a similar technique was originally described by Lord and Millar.[2,21,27] The patient is re-examined in an outpatient setting approximately 5 days after drainage of the abscess when the edema and induration from the abscess have subsided. After the patient's gluteal cleft region is infiltrated with local anesthesia and shaved, a long, laterally placed incision is made over the previously drained cavity. The cavity is wiped clean with gauze or curetted and left open. The midline epithelium-lined pits are excised, leaving small wounds. These midline wounds are primarily closed with fine suture material (Fig. 142–2). The patient is instructed to keep the wound clean and to return for weekly visits for shaving and débridement, if necessary, until the wound has healed. Bascom[16] reported a 15% recurrence rate with minimal disability and healing within 3 weeks. However, other surgeons have not been as successful with this approach.[11]

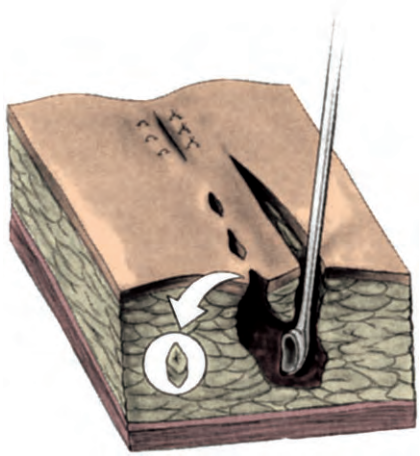

Figure 142–2. Treatment of pilonidal abscess by lateral incision into the abscess with curetting of granulation tissues and excision of midline pits. (From Bascom J: Pilonidal disease: Origin from follicles of hairs and results of follicle removal as treatment. Surgery 87:567, 1980; redrawn in Nivatvongs S: Pilonidal disease. In Gordon PH, Nivatvongs S [eds]: Principles and Practice of Surgery for the Colon, Rectum, and Anus, 2nd ed. St. Louis, Quality Medical, 1999, p 293.)

Technique of Incision and Curettage with Marsupialization or Saucerization

The option of laying open of tracts, minimal excision with marsupialization, or saucerization of the wound edges is commonly selected by surgeons.[6,13,14,18,28] The patient is prepared in the ambulatory setting. Local anesthesia with or without intravenous sedation is appropriate; rarely is general anesthesia needed. A probe is introduced into the midline pit or pits, and all primary and secondary tracts are opened. The resulting small open cavity is cleared of debris and hair, usually with a curette. The wound edges are beveled or saucerized to create a skin-level opening that is larger than the base of the cavity. The edges and base of the cavity are not disturbed except for the curettage. This allows for adequate drainage and prevents premature healing of the edges of the wound.

Marsupialization involves a similar technique, except that the skin edge is not saucerized but rather sutured to the lateral wall of the cavity. Recurrence rates with this procedure have ranged from 1% to 19%, with healing time averaging 34 days.[5,6] It has been our experience that suturing the skin edges to the wound does not consistently result in primary healing. Patients also seem to complain of more pain after marsupialization than after saucerization. For these reasons, we prefer to manage the skin edges with saucerization.

Technique of Excision With or Without Closure

Surgical procedures that involve the radical bloc excision of the pilonidal cavity with secondary healing of the

wound or primary closure are, unfortunately, still performed frequently.[29,30] Because pilonidal disease does not involve a true cyst, there is little justification for removal of the entire cavity. Wide excision of all affected pilonidal tissue down to the sacral fascia is unnecessary for treatment of this disease and has resulted in a high rate of unhealed wounds and prolonged morbidity. Rarely, the chronic cavity may be lined with epithelium, and in this instance the entire cavity may have to be excised.

It is difficult to interpret the literature with regard to recurrence rates after such excision. The extent of excision is usually unclear. In those situations where wide excision down to the sacral fascia with primary closure is performed, recurrence rates have been reported as high as 38%.[23,24,29] Reports have suggested that limited excision encompassing only the involved cavity followed by primary closure is a reasonable option for definitive treatment.[23,24] Primary healing is reported to occur within 2 weeks in 90% of cases.[3] Recurrence rates of 2% to 20% have been reported.[23,24,29,31] Failure of healing after primary closure is about 12%, and the incidence of wound infections varies among reports.[24] As mentioned, excision is usually not required to control chronic pilonidal disease. Although the concept of excision and primary closure is appealing and parallels the approaches that surgeons take to most other problems, the high rate of recurrence and the significant pain experienced due to the sutures make this approach low on our list of treatment choices. Anecdotally, almost all patients who we see with recurrent pilonidal disease have wounds with the telltale cross-hatches typically produced by primary closure.

Postoperative wound care requires diligent attention to gluteal hygiene to reduce the incidence of secondary hair (i.e., scalp hair) from invading the healing wound. Local hair is shaved at weekly office visits. The patient is instructed to take warm tub baths twice a day. Dry gauze or wet-to-dry dressings are used to prevent premature healing and to minimize granulation tissue in the open wound. The use of a Water-Pik[32] or hand-held showerhead will aid in cleaning the cavity. It is well documented that without careful follow-up even the best operation will have a poor result.

Recurrent or Unhealed Pilonidal Disease

Recurrence rates following primary surgical treatment of pilonidal sinuses range from 3% to 40%.[5] Most recurrences respond to reoperation using one of the earlier mentioned techniques. The patient with the unhealed chronic wound after multiple attempts at eradication of disease usually presents with significant tissue loss. These situations are probably best treated by excision, débridement, and closure with myocutaneous or cutaneous flaps. Many procedures have been described, including Z-plasty,[33] V-Y fasciocutaneous flap,[33] Limberg flaps,[33-35] gluteal myocutaneous flaps,[33] advancement flap[4,8] (Karydakis' operation), and the cleft lift (closure) procedure (Fig. 142–3).[36,37] These procedures have a recurrence rate in the range of 2% to 11%. However, these flap procedures carry significant morbidity and require hospitalization. They should be reserved for highly complex pilonidal disease. The cleft lift or closure operation as described by Bascom takes into account the problems of a healing wound in the midline with its associated negative factors, such as a deep cleft in an anaerobic environment. Therefore, the goal of the cleft closure technique is to place the final incision lateral to the midline and to flatten the gluteal cleft.

Technique of Cleft Lift

With the patient in an ambulatory setting and in the prone jack-knife position, the buttocks are held together and the area of contact is marked (see Fig. 142–3A). The buttocks are then taped apart. (see Fig. 142–3B). The gluteal cleft region and buttocks are shaved, prepped, and generously infiltrated with 1% lidocaine containing 1:100,000 epinephrine. To raise a skin flap, an incision is made above the top of the cleft and then crosses the midline at the top of the unhealed wound at an acute angle. Below the wound, the incision again crosses the midline at a right angle and then circles around cephalad to the anus. The lower end of the incision points to the anus. The unhealed wound is excised in a triangular shape (see Fig. 142–3C). A skin flap is then created out to the marked line (see Fig. 142–3D). The tapes are then released. The skin flap is positioned to overlie the edges of the wound on the opposite side. Excess skin is excised. A closed-suction drain is placed in the subcutaneous tissue and brought out through a separate stab wound. The subcutaneous tissue is approximated with 3-0 absorbable sutures (see Fig. 142–3E). The skin is closed in a subcuticular fashion, and adhesive strips are applied. A light dressing is applied. Complete healing is expected, and recurrence rate is reported at 3.3%.[36,37]

The concept of reverse taping to promote wound healing in the obese patient has met with some success.[38] This technique involves taping the buttocks apart by passing tape from one buttock anteriorly around to the other buttock. The tape keeps the buttocks apart promoting drainage of the wound and reducing the anaerobic environment. Meticulous shaving and reapplication of the tape on a weekly basis are important for successful healing. A few patients may benefit from this technique.

PILONIDAL DISEASE AND CARCINOMA

Malignant degeneration of chronic pilonidal wounds is a rare complication.[27,39,40] Such patients have had long-standing disease, averaging 23 years' duration. Most tumors are squamous cell carcinoma. Approximately 80% of these malignancies have been described in men in their 50s. The tumors are aggressive and locally invasive. Inguinal lymph node metastasis is present in 14% of patients. The presence of carcinoma in a pilonidal wound *is* an indication for wide en bloc excision of the mass including the sacral fascia. Flap techniques are usually required to close the defect. Recurrence rates have been reported at 38%. With a mean follow-up time of 28 months, 20% of all patients died as a result of the

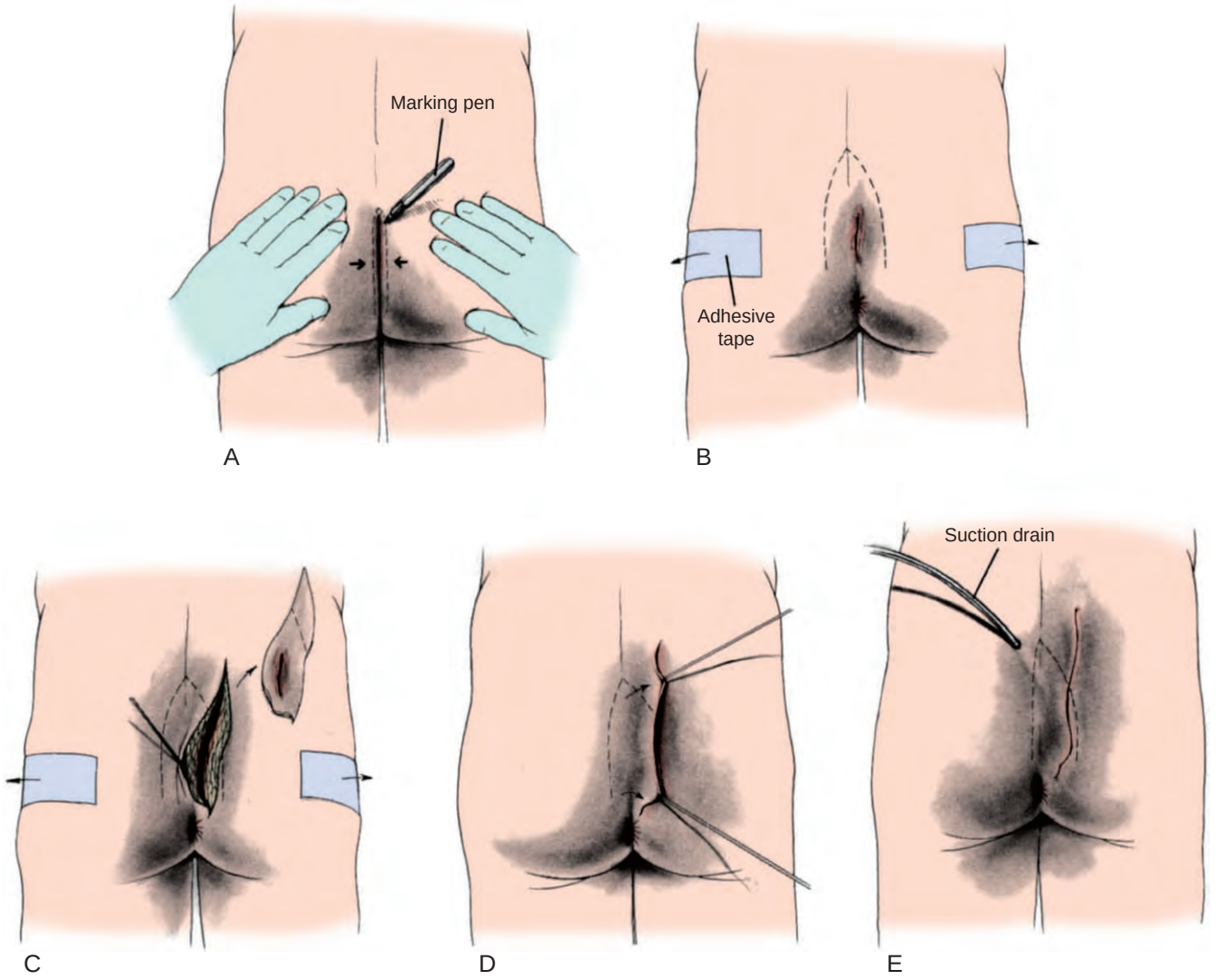

Figure 142–3. **A** to **E,** Cleft closure technique. (**A-E,** From Bascom J: Repeat pilonidal operations. Am J Surg 154:118, 1987; redrawn in Nivatvongs S: Pilonidal disease. In Gordon PH, Nivatvongs S [eds]: Principles and Practice of Surgery for the Colon, Rectum, and Anus, 2nd ed. St. Louis, Quality Medical, 1999, p 299.)

neoplasm.[5,39] Local recurrence rates seem to be lower when radiation therapy is added to surgical resection. There also appears to be some advantage to adding chemotherapy to the treatment regimen.[5,39]

SUMMARY

Sacrococcygeal pilonidal disease is a potentially disabling disease that is often made worse by overly aggressive treatment. Understanding the pathophysiology helps the surgeon manage the problem with less destructive techniques than were used previously. Treating pilonidal disease as an abscess with a feeding sinus tract instead of as a "cyst" allows treatment approaches that can be performed with satisfactory results, often on an ambulatory basis.

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Chapter

143

Traumatic Colorectal Injuries, Foreign Bodies, and Anal Wounds

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COLORECTAL TRAUMA

The management of injuries to the colon and in particular to the rectum may create problems for general and trauma surgeons who are not completely familiar with the advanced concepts and techniques that are associated with anorectal physiology and reconstruction. Similarly, even the most skillful colorectal surgeon may be presented with major problems in the overall management of diseases associated with that organ in the multiple trauma scenario. The purpose of this chapter is to describe the treatment of injuries to the colon, rectum, and anus, in which the best skills of both the trauma surgeon and the colorectal surgeon will be brought to bear in managing an individual patient.

The history of colon trauma is old, with at least one reference to it in the Old Testament (2 Samuel 20:9-10). Colorectal trauma was nearly uniformly fatal during the American Civil War, but the mortality rate began to decline during World War I. In World War II, the mortality rate declined again to about 25% to 30% as a result of the availability of blood transfusion and the standard practice of fecal diversion. Patient transportation during the Korean and Vietnam wars, as well as the continued refinement of resuscitation and the judicious individualization of colorectal wounds, also increased survival rates. Currently, the mortality rate is about 3% in the civilian scenario. In the United States, trauma is the major cause of death in people younger than 40 years and accounts for nearly 150,000 deaths a year, with a lower life expectancy rate than for cardiovascular disease and cancer combined.

Trauma-related deaths have a tripartite distribution. There are *immediate deaths* that occur soon after injury and before hospital transport and, typically, in association with major neurologic and cardiovascular injury. There are *early deaths* that occur at and about the time of transfer to the hospital and within a few hours after injury due to major hemorrhage, such as hemorrhage in the chest and abdomen, and due to severe blood loss from multiple, less-specific injuries. The third time of trauma death occurs *secondary to infection,* beginning toward the end of the first week of hospitalization and continuing well into the 2nd and 3rd months after injury. Infection, overt sepsis, and multiorgan failure are special problems in colonic injury because of the bacterial contamination that frequently coexists with hemorrhagic shock. In civilian practice in the United States, a gunshot wound to the colon is the most common cause of penetrating injury, with stab wounds being second, and shotgun wounds being third. Blunt trauma occasionally causes colorectal trauma and presents special diagnostic problems (discussed later).

Table 143–1 provides a summary of selected studies from the past 30 years that lists the collective causes of penetrating colonic injury.[1-9] With the increasing use of therapeutic endoscopy that is often performed by nonsurgeons, iatrogenic or unintentional perforation of the colon has become a special problem that deserves separate comment in terms of overall management (see "Iatrogenic Injury"). The frequency of iatrogenic injury, especially in tertiary centers, is vastly underestimated.

Colonic injury, when combined with other injuries such as to parenchymal organs (i.e., liver, pancreas, spleen), is especially important in contributing the second part of the "two-hit" hypothesis (i.e., bacterial contamination combined with hemorrhagic shock). It therefore has a substantial influence on survival rate and an even greater effect on infectious morbidity rates. Table 143–2 provides a summary of associated injuries for gunshot wounds to the colon, which again emphasizes

Table 143–1 Collected Causes of Penetrating Colonic Injuries

Types of Injury	Flint et al., 1981[1]	Samhouri et al., 1979[2]	Bartizal et al., 1974[3]	Wiener et al., 1981[4]	Kirkpatrick and Rajpal, 1975[5]	Steele and Blaisdell, 1977[6]	Thomson et al., 1996[7]	Stone and Fabian, 1979[8]	Jacobsen et al., 1997[9]	Totals
Gunshot	101	124	279	99	124	76	35	220	42	1100
Stab	12	18	111	27	31	37	30	37	9	312
Blunt trauma	21	6	16	20	2	10	3	4	—	82
Shotgun	7	—	9	17	8	4	3	7	7	62
Iatrogenic	—	2	—	10	—	—	—	—	—	12
Foreign bodies	—	—	—	8	—	7	—	—	—	15

From Galandiuk S: Injuries to the colon and rectum. In Keighly MRB, Williams NS (eds): Surgery of the Anus, Rectum, and Colon, 3rd ed. London, Elsevier, 2006.

Table 143–2 Distribution of Associated Injuries in Gunshot Wounds to the Colon

Location of Injury	Wiener et al., 1981[4]	Thompson et al., 1981[10]	Matolo and Wolfman, 1977[11]	Jacobsen et al., 1997[9]
Stomach	11	16	4	10
Duodenum	5	8	—	5
Small bowel	39	39	26	26
Gallbladder	5	7	1	3
Pancreas	3	9	—	6
Liver	8	32	7	11
Spleen	3	15	6	4
Kidneys	7	—	5	9
Bladder	4	—	2	1
Vascular	6	6	11	34
Diaphragm	3	—	5	9
Bone	—	—	9	10

From Galandiuk S: Injuries to the colon and rectum. In Keighly MRB, Williams NS (eds): Surgery of the Anus, Rectum, and Colon, 3rd ed. London, Elsevier, 2006.

the influence of the small bowel, liver, stomach, major vessels, and pancreas.[4,9-11]

The major factor in the assessment of patients with colorectal injuries, which is discussed in detail in "Intraoperative Management," depends on the severity of injury. Table 143–3 provides a grading system for both intra-abdominal colon and rectal injuries that is helpful in recognizing the severity of the injury and in determining preferred therapy.

All of these factors contribute significantly to the possibility of infectious complications and in turn are closely related to the likelihood of late death.[12] For example, there is a steady increase in infectious complications that parallel the number of units of blood transfused during a laparotomy for colon injury, rising to as much as 60% when more than 10 units of blood have been transfused. Similarly and not surprisingly, the risk of infection approaches 100% when more than five organs have been injured, but the risk is only half that when four or fewer organs have been injured. Patient age also has a substantial effect on the infectious complications rate. Patients younger than 30 years have only a 12% to 15% infection rate, whereas those older than 30 years have an infection rate that exceeds 40%.

INITIAL RESUSCITATION AND ASSESSMENT

It is appropriate to review the important issues of the basic principles of care of the trauma patient.[13]

Care of the trauma patient begins at the scene. Before transport, the patient must receive basic emergency medical services such as the use of a cervical collar, stabilization with a spinal board, and endotracheal intubation with in-line cervical traction if the patient is not breathing spontaneously. Attention to the cervical spine is critical. Intravenous access should be obtained and

Table 143–3 Gradation of Injuries to Colon and Rectum

Injured Structure	Grade	Characteristics of Injury	AIS-90 Score
Colon	1	Contusion or hematoma; partial-thickness laceration	2
	2	Small (<50% of circumference) laceration	3
	3	Large (>50% of circumference) laceration	3
	4	Transection	4
	5	Transection with tissue loss; devascularized segment	4
Rectosigmoid and rectum	1	Contusion or hematoma; partial-thickness laceration	2
	2	Small (<50% of circumference) laceration	3
	3	Large (>50% of circumference) laceration	4
	4	Full-thickness laceration with perineal extension	5
	5	Devascularized segment	5

AIS-90, Abbreviated Injury Score, 1990 version.
From Lucas CE, Ledgerwood AM: Injuries to the stomach, duodenum, pancreas, small bowel, colon, and rectum. In Souba WW, Fink MP, Jurkovich GJ (eds): ACS Surgery, 2005. Copyright WebMD.

crystalloid solutions should be infused during transport. Extremity fractures are splinted with pneumatic devices or other kinds of rigid support system.

On arrival at the treatment facility, the old adage of *ABC* (airway, breathing, and circulation) remains the fundamental catechism of the advanced trauma life support system of the American College of Surgeons.[14]

The presence of a patent airway must be redefined at every step in the process. If intubation is not technically feasible, cricothyrotomy may be required, especially if there has been associated trauma to the head, such as a mid-face fracture. Correct positioning of the endotracheal tube must be determined with chest films, and intubation of the right main stem bronchus should always be considered if no left-sided breath sounds are heard. Hemothorax must be excluded on the basis of chest films and physical examination. The adequacy of circulation is determined through a variety of measures, including blood pressure and assessment of capillary refill. If the patient is hypovolemic, two large-gauge peripheral intravenous lines must be established, and lactated Ringer's solution must be infused rapidly, pending the availability of type-specific blood.

Further assessment of individual injuries should be undertaken once the airway is secured, breathing is accomplished, and circulatory resuscitation is under way. Penetrating injuries to the abdomen, including ecchymoses, must be noted. If an intra-abdominal injury is likely, a broad-spectrum, safe cephalosporin should be administered with one of the first liters of intravenous fluid. We continue to believe that the scenario of trauma with shock and resuscitation is ideal for the use of very large doses of safe antibiotics[15] and their continuous infusion.[16] As part of the care of the trauma patient, an evaluation of pelvic fractures is especially important with respect to bladder injuries or laceration to the anus or rectum. It is important to examine the perineal area and to determine the presence or absence of blood at the urethral meatus or on rectal examination. If there is blood at the urinary meatus or if the prostate is not palpable on rectal examination, one must especially consider transection of the urethra, and a urethrogram should be done *before* Foley catheter insertion.

Depending on the patient's stability, if a pelvic fracture is present, it must be stabilized with an appropriate external fixator or with a military antishock trouser (MAST) device after the Foley catheter has been inserted. This will stabilize the fracture and provide some control of the hemorrhage, which may complicate pelvic fractures.[17]

While resuscitation and the initial assessment are ongoing, the insertion of a nasogastric tube, by nose or mouth, will permit the detection of blood within the stomach, as well as decompress the patient in preparation for an anesthetic. Any penetrating wound below the level of the nipples must be considered a possible intra-abdominal injury.

The evaluation of the abdomen in the unconscious patient continues to represent a serious problem. Diagnostic peritoneal lavage (DPL) has been a reliable procedure for nearly 3 decades; it is performed under direct vision, with care. If no gross blood is encountered, lavage of the peritoneal cavity with saline is performed. DPL is considered positive and indicative of intra-abdominal injury if the effluent contains more than 100,000 red blood cells/mm^3 or more than 500 white blood cells/mm^3, with a hematocrit value of more than 2, or in the presence of bile, bacteria, and vegetable or fecal matter. If DPL is negative but there still is suspicion of intra-abdominal injury, further evaluation by ultrasound examination or computed tomography (CT) scanning may be helpful. Ultrasound examination, when carried out by the examining surgeon, is a most efficient, inexpensive, and reliable aid to patient care.[18,19] Ultrasound has replaced DPL and CT studies,[20] and the focused abdominal ultrasound for trauma (FAST) has replaced DPL in most trauma centers.[21,22] Focused abdominal ultrasound includes evaluation of the pericardium, right

and left upper quadrants, and pelvis. Skills in ultrasound evaluation of the acute abdomen have become as important as laparoscopy to the contemporarily trained general surgeon. Needless to say, FAST should always be performed by the operating surgeon.

The overall priorities of trauma care are important and are dealt with elsewhere.

SPECIAL DIAGNOSTIC PROBLEMS

Colorectal injury associated with *blunt trauma* is especially treacherous and is uncommon enough to worry even the most experienced trauma surgeons. It represents only about 1 in 30 such injuries, and the diagnosis is often made only at the time of laparotomy for other injuries. The diagnosis will often not have been made, and the surgeon will have to be alert intraoperatively to take appropriate measures. Reported data regarding these injuries are suspect in the sense that diagnosis is often delayed and then involves the treatment of a late-recognized colon perforation as opposed to the more frequently and promptly diagnosed penetrating trauma.[23]

There is a 1% incidence of hollow viscus injury with blunt trauma and approximately a 0.3% incidence of colon or rectal injury.[24] No diagnostic test or combination of findings reliably excludes blunt colon injury. This diagnosis is often made at the time of laparotomy for other injuries. The presence of colonic injury at laparotomy is associated with an increased risk of complications but not necessarily mortality.[24]

The proposed mechanisms of colon injury during blunt abdominal trauma are several. This injury is most commonly thought to occur secondary to direct compression between the blunt object and the vertebral column or bony pelvis. This compression produces a tearing or lacerating effect. A second mechanism of injury is thought to involve sudden deceleration, producing bowel-mesenteric disruption and subsequent devascularization. This makes the transverse and sigmoid colon most vulnerable during sudden deceleration injuries because these segments are on a mesenteric stalk.[25]

A further opportunity for diagnostic error regarding injury to the large bowel is the failure to carry out a careful, well-illuminated, and detailed perineal examination in the often unstable multitrauma victim. Lacerations of the perineum or rectum must be presumed to be associated with open pelvic fractures. Shards of bone associated with some pelvic fractures can readily lacerate all pelvic structures, including major blood vessels. The careful examination of the perineum and the rectum, including an examination for occult blood, is important in this scenario and can be difficult. There is no substitute for a careful examination by a person who is knowledgeable of and especially suspicious of the bizarre ramifications of perineal lacerations and pelvic fractures. The standard of care often includes the use of sigmoidoscopy, but this can be technically difficult in the trauma patient. Triple-contrast CT scanning with intravenous, peroral, and rectal contrast medium can identify many rectal extraperitoneal injuries.

Diagnostic dilemmas occur in several typical scenarios, most commonly when a retroperitoneal portion of the colon has been injured and the patient presents with few anterior peritoneal signs, no pneumoperitoneum, and symptoms that may be masked by other overt manifestations of trauma or by treatment. Opening of the peritoneal reflection usually discloses the true nature of the problem.

GENERAL PRINCIPLES OF PREOPERATIVE MANAGEMENT

The fundamental principles of preoperative management are, of course, securing and maintaining an airway and restoring vital organ perfusion. This is ordinarily possible, but there may be circumstances of major vascular injury or liver trauma in which a patient may need to undergo emergency surgery while incompletely resuscitated. Under these circumstances, the injury to the large bowel is seldom the major contributor to hemorrhage. Control of the site of primary blood loss and stabilization of the patient take first priority. Resectional débridement of the colon, or its simple stapling, as an early part of a procedure to control contamination while ongoing hemorrhage is being addressed may be a wise and proper choice. The most significant advance in this field in the past decade has been the recognition that the secure packing of some parenchymal organ injuries often can be the best possible temporizing measure. It will allow the patient to return to the operating room in 24 to 48 hours for more definite management of a variety of injuries when he or she is hemodynamically stable, no longer coagulopathic, and warm. The concept of the damage control laparotomy as a staged approach to severe trauma and associated shock has been a major advance for trauma care in the past decade.[26]

Notwithstanding these circumstances of near exsanguination, one of the most important points in the early care of the trauma patient is the intravenous administration of a broad-spectrum antibiotic. The agent of choice should be a safe drug such as a second- or third-generation cephalosporin. Antibiotic regimens should *seldom* include nephrotoxic aminoglycosides or unnecessary and occasionally harmful agents aimed at anaerobic bacteria. We believe the continuous infusion of a relatively large dose of antibiotics is warranted, given the hemodynamic instability, shock, and transfusion.[15,16] As soon as the condition of the patient has stabilized and contamination is controlled, antibiotics often can be discontinued. If contamination is minimal, antibiotics can be discontinued postoperatively. If contamination is moderate, an antibiotic probably should be continued for 72 hours. Regardless of the degree of contamination, antibiotic administration should not continue beyond 7 days. There is little evidence that continuing use of such drugs for 7, 10, or 14 days accomplishes anything but predisposition to the development of resistant bacterial forms for later infection. Table 143–4 provides a

Table 143–4 Antibiotic Priorities

Factor	Authors, Year	Recommendation
Timing	Richardson et al., 1987[27]	First intravenous infusion solution
Duration	Polk and Christmas, 2000[43]	Single dose to 24 hours when favorable; never longer than 5 days
Doses	Livingston and Wang, 1993[16]	Very large if a cephalosporin is chosen and/or hemorrhage and transfusion are significant
Route	Livingston and Wang, 1993[16]	Parenteral; continuous infusion may be better
	Galandiuk et al., 1997[28]	Special role for prolonged antibiotic beads in wound if closed and high risk
Drug preferences	Price and Polk, 1994[44]	Cefotetan or ceftriaxone; aztreonam for gram-negative coverage
		Metronidazole if overt evidence of established anaerobic infection
		Seldom: clindamycin/amikacin/tobramycin-gentamicin only for rare allergy and/or positive culture scenarios
Cost-control issues	Author's choice, 2005	Safest antibiotic is always the best choice; drugs that require monitoring of levels are prohibitively expensive

summary of our views and practices with respect to the use of antibiotics in colorectal trauma.[16,27,28]

INTRAOPERATIVE MANAGEMENT

If the abdomen is the site of injury, our preferred approach for virtually all patients with such trauma is through a midline abdominal incision that can be extended in either direction depending on the nature of the intraoperative findings. The laparoscopic approach to major abdominal injury is still evolving as are the requisite skills for minimal access surgery among younger surgeons; selected applications in experienced laparoscopic hands may become more acceptable. The burden of proof of overlooked injury is obviously substantial. We emphasize the need to stabilize the patient intraoperatively and to control or ameliorate ongoing blood loss. When that is accomplished, one is ready to turn attention to the possibly injured colon. A system of grading colon injuries is especially helpful to the surgeon (who is not often in this situation) in making a wise choice regarding options, ranging from primary repair to occasional resection and anastomosis, with or without protective proximal stoma. Just as the surgeon must begin to make that determination, he or she must constantly be alert to the stability of the patient and the patient's capacity to tolerate a preferred method of repair. The choices may include rapid stapling and discarding of a section of colon in a patient with a massive liver injury and multiple transfusions who is being packed to control a major hepatic parenchymal hemorrhage. The other end of the spectrum is represented by a stable patient who has an isolated injury of the lower sigmoid and is an excellent candidate for excision of the injured segment and primary repair in the best of circumstances.

In general, options for the treatment of colon injury include (1) proximal diversion and repair, (2) exteriorization of the wound itself as a colostomy, (3) simple suture of even lengthy colon lacerations, and (4) resection and anastomosis. The latter should be applied only with special thought. The patient with injuries requiring resection often has associated injuries and therefore is seldom a candidate for an extensive and complex operation and may be better suited for resection and temporary diversion. On the other hand, if contamination is not extensive, the patient is hemodynamically stable and well-vascularized colon is available, then resection and anastomosis may be suitable. The algorithm (Fig. 143–1) is especially helpful to a surgeon who is unfamiliar with the treatment of colonic injury. It is clear that many tangential, and even penetrating, wounds of the colon can be dealt with safely by primary suture in a stable patient. Even longitudinal tears can be repaired safely. A recent meta-analysis of currently published randomized trials favors primary repair over fecal diversion for penetrating injuries of the colon.[29] The method of anastomosis following colon resection for penetrating trauma does not seem to affect the incidence of abdominal complications.[30] There are special technical considerations, depending on the site of injury. We and others have debated the relative merits of different standards for the management of right and left colon injuries. Resection and anastomosis in the injured right colon have almost identical mortality and morbidity rates as the more conservative procedure of resection and ileostomy. Anastomotic failure is an uncommon phenomenon in the judicious management of right colon injury. Table 143–5 lists the main issues of some studies.[31-35] In 1994, Stewart et al.[35] examined penetrating injuries of the colon in patients with significant risk factors (preoperative or intraoperative transfusion of more than 6 units of packed red blood cells, significant comorbid diseases) and identified a leak rate of 42% in this high-risk group. Based on this and other data, one should avoid an anastomosis in such a severely injured patient.[36]

IATROGENIC INJURY

Colonoscopic perforation is remarkably infrequent, and, even then, it is clear that many patients tolerate delayed

performed if there is blood within the rectum on digital examination or if there is evidence of a bladder or urethral injury, blood within the vagina, severe pelvic fracture, or bullet trajectory above the mid thigh and below the pelvic rim.[40] If a rectal injury is suspected, the patient should be positioned in stirrups so there is free access to the perineum. In general, if such an injury has been complicated by delayed diagnosis, then diversion is preferred, complemented by the removal of palpable rectal fecal material, rectal "washout," and drainage of the presacral space. The efficacy of rectal washout has not been demonstrated prospectively. Rectal washout can be performed via sterilized ventilator tubing inserted transanally after anal canal dilation. A large Foley catheter (e.g., 24 French) can be inserted into the distal rectum, and irrigation is performed until the effluent is clear.[41] Saline is most frequently used, often with a final irrigation of povidone-iodine.

Contrary to common attitudes among trauma surgeons, the promptly diagnosed anorectal injury is often best treated by a definitive early repair, assuming the patient is otherwise stable. This in particular applies to lacerations of the anal sphincter and anal valve region. Obviously, if the patient is badly hurt or in shock or the diagnosis is delayed, diversion becomes part of the care plan for the patient. The operating surgeon must be particularly careful that drainage of the area does not produce further sphincter injury. It requires the best of the trauma surgeon's overall assessment and the colorectal surgeon's anatomic expertise to optimize results in these challenging wounds.

POSTOPERATIVE COMPLICATIONS

Complications that may follow colorectal injury encompass the surgeon's entire repertoire. Bacterial contamination, if accentuated by diagnostic delay, hemorrhage, transfusion, or other major organ damage, is the overriding concern once the ABCs of trauma care have been established. Infection is both the most frequent and the most dangerous problem. The specter of multisystem organ failure and its supportive and definitive care are always the first priority. If the patient does not thrive after treatment, the surgeon must reassess the patient and must be certain that an error in diagnosis or treatment has not occurred. In general, mechanical treatment (drainage and diversion) is far better than reliance on medications and organ system support.

Colostomy is a special complication of several of the therapeutic options in colorectal trauma.[13] In a comparison of outcomes—morbidity and mortality—as well as cost, the closing of a complementary stoma must always be considered. We examined our practices and provide some highlights of that experience in Table 143–6. Colostomy closure requires as much mental preparation for the surgeon as it does technical expertise. The practice in many respected residency programs of assigning "simple" colostomy closure to junior staff is a case in point. Furthermore, choosing a time to perform the closure has become especially contentious in this cost-obsessed era. Surely, if the stoma is complementary (i.e., to a primary repair or for exteriorization of an injury), then early closure is feasible. Although that might safely and wisely be performed within 8 weeks, the stoma constructed as part of the care of a rectal laceration produced by a major pelvic fracture or for a complicated sphincter repair secondary to a straddle injury is another matter, and structural and functional healing for 90 days or more may well be in order before the closure of a stoma. It should not be forgotten that one of the most common complications after blunt or penetrating colonic trauma is development of pneumonia, which may significantly affect mortality. The incidence of intra-abdominal abscess formation ranges from approximately 8% to 12%[24,42] but may be even higher with multiple other injuries.

Psychologically, the surgeon who plans a colostomy closure of a Hartmann-style stoma must also be ready to perform a major laparotomy, and the patient should be prepared as well. Our practice has been to either perform this within 2 weeks or delay it for 90 days, with a hope of minimizing technical issues and errors.

Table 143–6 Lessons Regarding Colostomy Closure in the Trauma Patient

Issues	Comment
Timing	Despite preferences, little differences in morbidity rate can be attributed to early vs. later closure
Preoperative contrast study of distal bowel	Assuming the patient is well physically and no lesions were detected at first operation
Management of the stoma site	Delayed primary or secondary closure often never occurred Closure with prolonged local antibiotic instillation is safe
Home health care follow-up	Home care leads to uniform prolongation of wound closure and increases in cost

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Chapter

144

Colonic Intussusception and Volvulus

Robin P. Boushey · David J. Schoetz, Jr.

INTUSSUSCEPTION

The invagination of one segment of the intestine into another is defined as *intussusception*. This disease entity is the most common cause of bowel obstruction in children. On the other hand, only 5% to 10% of intussusceptions occur in adults, and it is a rare cause (<1%) of adult bowel obstructions.

Types of intussusception include *enteric* (small bowel into small bowel), *ileocolic* (small bowel into colon), and *colonic* (colon into colon). Although colonic intussusception is rare in children, it accounts for approximately 50% of adult cases.[1] The clinical presentation is that of mechanical bowel obstruction: crampy abdominal pain, nausea, vomiting, and subsequent obstipation or diarrhea. Subacute or recurrent acute attacks are not uncommon in adults compared with children. Radiographic investigation of an individual with recurrent episodes of bowel obstruction should include barium contrast radiography or computed tomography (CT) scanning during an acute episode (Fig. 144–1). The demonstration of an invaginated portion of the bowel secures the diagnosis.

Unlike in children, in whom more than 80% of episodes are idiopathic, in adult patients with intussusception there is a demonstrable pathologic process acting as a lead point, causing the condition in 80% to 90% of patients.[1-4] Potential causes include benign and malignant tumors of the small and large bowel, inflammatory lesions, appendiceal disease, and Meckel's diverticulum. Consequently, all adults who have been demonstrated to have intussusception should be offered operative resection of the involved bowel. This may be necessary in the acute setting because of bowel ischemia or nonresolution of the obstructive episode. In patients in whom the condition spontaneously resolves, elective resection should be performed after appropriate investigation of the gastrointestinal tract to exclude synchronous disease.

If intussusception is present at the time of exploration, an assessment is made regarding the length of bowel that would be required to be resected without reducing the invaginated segment. Nonviability mandates resection with primary anastomosis in most instances. Attempts to reduce the nonviable bowel risks intraoperative rupture and contamination of the peritoneal cavity with both succus entericus and tumor cells. Debate continues as to whether reduction should be attempted in patients without ischemia, with concerns regarding rupture being weighed against the resection of excessive bowel length. Patients with colonic intussusception can most often be treated successfully with subtotal colectomy because involvement of the descending colon and sigmoid is rare. If the lead point is in the left colon and preoperative mechanical bowel preparation cannot be achieved, resection with end colostomy and Hartmann's closure of the rectum or on-table lavage with primary anastomosis should be considered.[5]

VOLVULUS

Volvulus is derived from the Latin word *volvere,* which means "to twist upon." In the colon, it refers to a condition in which the colon is twisted on its mesentery causing acute, subacute, or chronic colonic obstruction. For a volvulus to occur, the colon must be mobile and have sufficient length to rotate around a relatively narrow and fixed mesenteric base. As a result, the most commonly involved sites are the sigmoid colon and the cecum. Volvulus of the colon accounts for approximately 5% of intestinal obstructions and 10% to 15% of colonic obstructions in patients in the United States.[6,7] Ballantyne in a series of 546 cases of colonic volvulus in the United States found the incidence of colonic volvulus to be cecum, 34.5%; transverse colon, 3.6%; splenic flexure, 1%; and sigmoid colon, 60.9%.[8]

The clinical presentation of volvulus of the colon is similar regardless of the site of the twist. Crampy abdominal pain, distention, diminished stool output, and nausea and vomiting consistent with obstruction are the

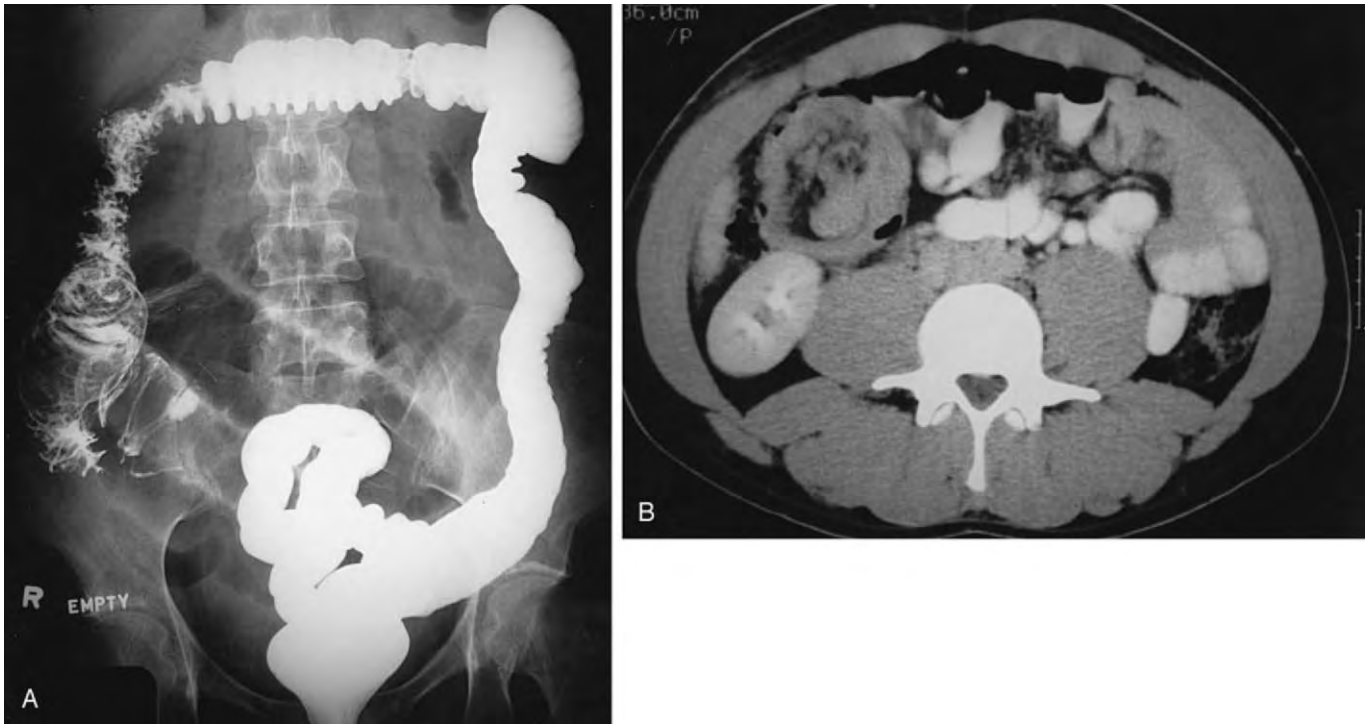

Figure 144–1. **A,** Barium enema of ileocolic intussusception demonstrating an invaginating mass into the right colon with the "coiled-spring" appearance of proximal small bowel obstruction. **B,** CT scan showing ileocolic intussusception, with the typical "bull's eye" appearance of bowel within bowel in the right abdomen.

hallmark complaints. Progression to constant abdominal pain implies the development of serositis of the involved segment, which may act as a closed-loop obstruction with increasing intraluminal pressure that leads to ischemia. Furthermore, the mesenteric vasculature may be compromised by mechanical torsion of the volvulus around the mesenteric pedicle. Acute presentations such as this represent more than half of the total episodes of volvulus. A subgroup of patients with colonic volvulus describes similar episodes in the past that resolved spontaneously, often with an associated explosive bowel movement or passage of gas. Patients with recurrent volvulus need a careful assessment to rule out the diagnosis of colonic inertia and megacolon, which may mandate a more extensive colonic resection.

Predisposing factors common to all sites of volvulus include previous abdominal surgery and a history of chronic constipation. A detailed history should include potential comorbidities that must be incorporated into the overall treatment plan as many of these patients are elderly, debilitated, and have multiple coexisting medical conditions. Examination of the abdomen reveals abdominal distention, varying degrees of tenderness over the obstructed segment, a tympanic mass, and, in instances of vascular compromise or perforation, fever and hypotension.

After physical examination, plain radiographs of the chest and abdomen are obtained. An upright radiograph of the chest excludes the presence of free intraperitoneal air, and abdominal films generally demonstrate a massively distended segment of colon with obstruction proximal to the twist (Fig. 144–2). Lower gastrointestinal contrast radiography should be obtained to confirm the diagnosis. A barium enema should be used only if there is no evidence of peritonitis and in the patient fit enough to undergo the procedure. The classic finding is a "bird's beak" deformity or mucosal spiral pattern at the site of the volvulus (Fig. 144–3). When performing a contrast enema, minimal contrast should be used. Excessive use of rectal contrast may temporarily reduce the volvulus, which may quickly reform, trapping contrast and further dilating the proximal colon. As well, the presence of barium can make subsequent endoscopic reduction of the volvulus difficult. CT scan can also be used to diagnose a volvulus and usually demonstrates a "whorl sign," that is, mesenteric fat with engorged vessels that converge toward the center.

The management of volvulus of the colon, regardless of site, is by either nonoperative or operative means (Fig. 144–4). Evidence of gangrene or perforation is a surgical emergency that necessitates prompt preoperative preparation and laparotomy. The types of available nonoperative therapy depend on the site of the volvulus and are discussed individually.

Sigmoid Volvulus

Etiology and Pathophysiology

In the United States, the sigmoid colon is the most common site of volvulus and sigmoid volvulus is the

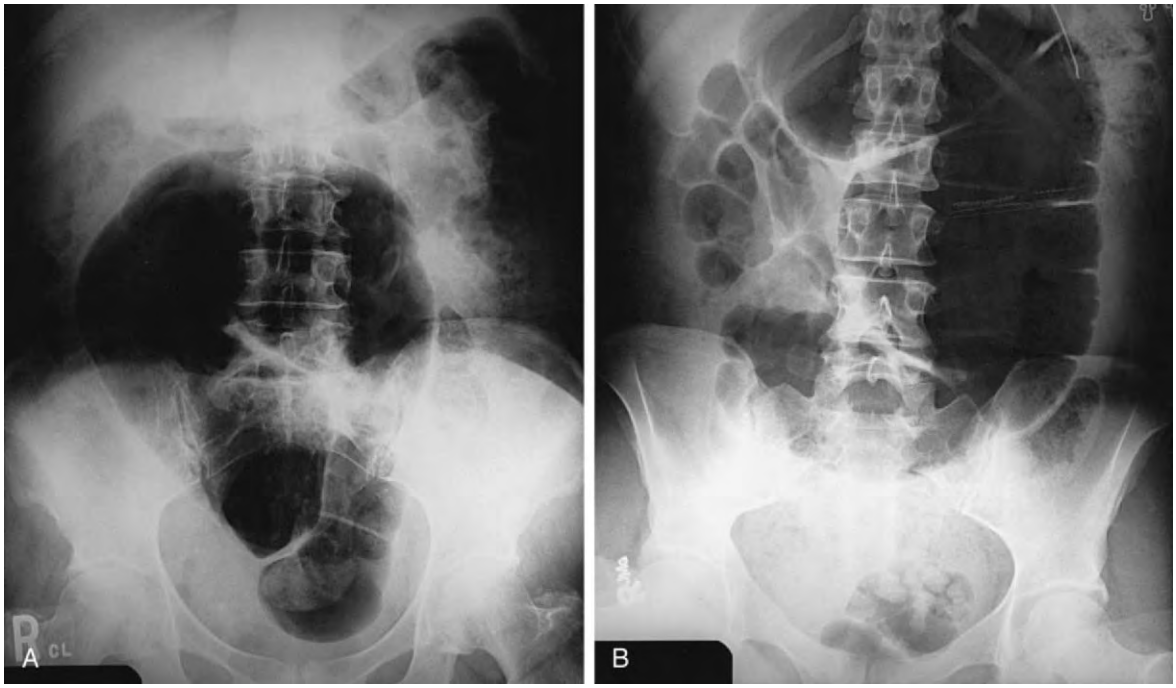

Figure 144–2. **A,** Plain abdominal radiograph of a sigmoid volvulus with the "bent inner tube" sign. The colon is the shape of a coffee bean, with proximal fecal impaction. **B,** Plain radiograph of a cecal volvulus with the kidney bean–shaped rotated ileocecal region and proximal small bowel obstruction.

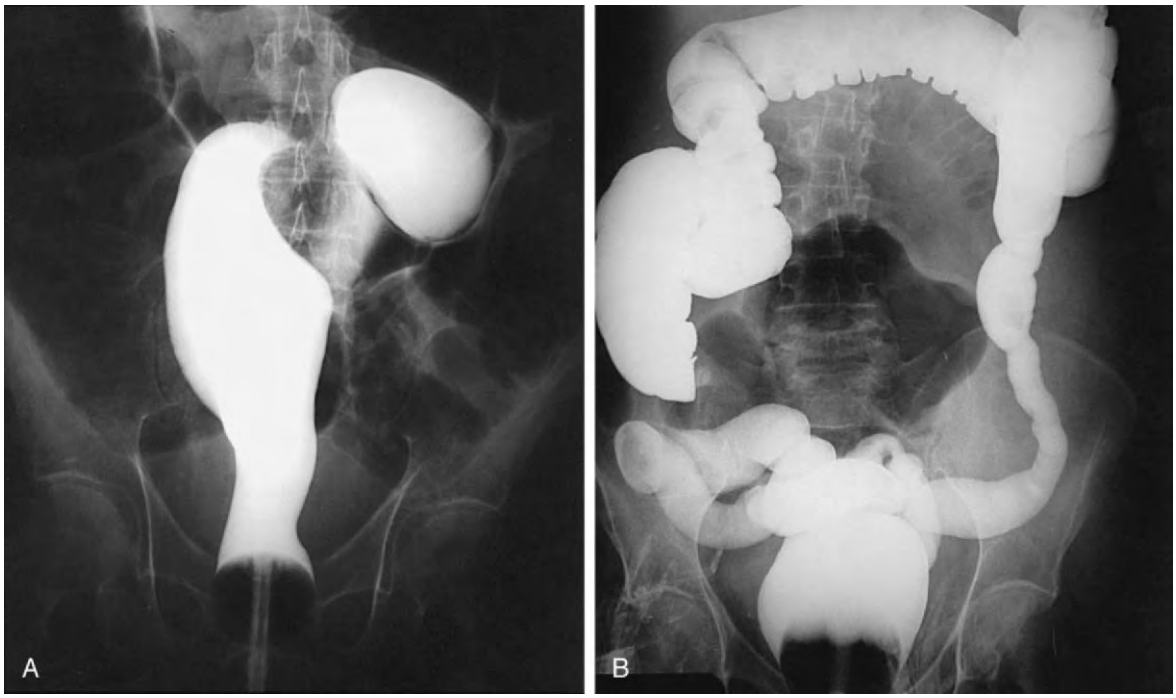

Figure 144–3. **A,** Barium enema of sigmoid volvulus demonstrating the classic "bird's beak" at the point of the twist. **B,** Barium enema of cecal volvulus, with the bird's beak in the ascending colon and proximal colonic distention.

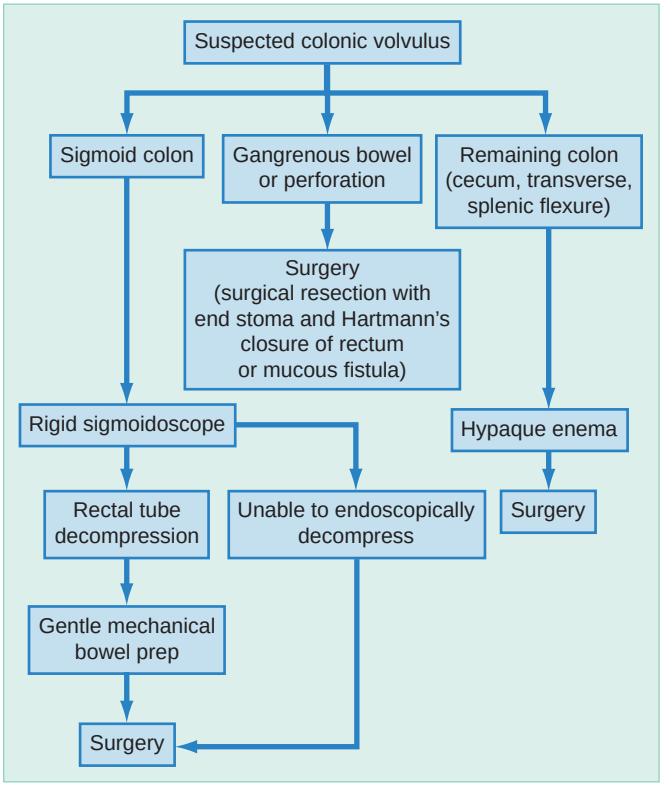

Figure 144–4. Treatment algorithm for patients with suspected volvulus.

second commonest cause of large bowel obstruction following colon cancer. Geographic variations in incidence are well established, with a much higher frequency in countries whose inhabitants consume a high-fiber diet, such as Africa, India, Pakistan, Middle East, and eastern Europe.[8-10] High-fiber diet is thought to lengthen the colon, with resulting elongation of the sigmoid mesentery. A genetic predisposition has also been identified within certain families and tribes.[11,12]

The average age of patients with sigmoid volvulus in the United States is in the 60s and 70s, whereas patients in endemic areas tend to be younger. The two sexes are equally affected in English-speaking countries, but males predominate in other parts of the world. It has been suggested that there is a higher prevalence of neuropsychiatric disorders in patients from Western countries with sigmoid volvulus. In a collected series of 244 patients, Ballantyne[8] found that 32.4% of patients were admitted from mental institutions and 12.7% were admitted from nursing homes. In addition, sigmoid volvulus is more common in patients with conditions associated with a redundant sigmoid colon such as Chagas' disease, Parkinson's disease, chronic neurologic disorders, diabetes, chronic constipation, laxative abuse, and previous surgery involving mobilization of the sigmoid colon. It is the second commonest cause of intestinal obstruction following adhesions in pregnant women, presumably because a redundant sigmoid colon is prone to torsion as the uterus grows out of the pelvis during the second and third trimester. A high index of suspicion is needed in this patient population as symptoms of nausea, vomiting, and abdominal pain can often be incorrectly attributed to pregnancy. Urgent surgical intervention is often required because of the risk to both the mother and fetus.

Torsion of the sigmoid colon involves at least 180 degrees of rotation usually in a clockwise direction around its vascular pedicle, resulting in a closed-loop obstruction of the sigmoid colon and possibly a second closed-loop obstruction of the proximal colon if the ileocecal valve is competent. As a result, intestinal ischemia and necrosis may result in both closed-loop segments either indirectly as a result of significant luminal distention and venous compromise or as a result of arterial vascular compromise resulting from torsion and occlusion of vessels within the sigmoid mesocolon. Plain abdominal radiographs reveal a dilated sigmoid colon that takes the appearance of an "ace of spades" or "bent inner tube" or "omega loop" which arises from the left lower quadrant (see Fig. 144–2A).

Treatment

Nonoperative The initial treatment in the patient with no evidence of bowel necrosis based on history and physical examination should involve an urgent nonoperative endoscopic attempt at reduction of the volvulus.[13] Rigid sigmoidoscopy is the preferred diagnostic and therapeutic modality that can be easily performed with minimal air insufflation in the emergency department. This modality allows for direct visualization of the rectal mucosa to exclude the presence of tissue necrosis and a distal neoplastic lesion. The sigmoidoscope can usually be gently passed through the narrowed edematous twisted point of obstruction to reduce the volvulus. A well-lubricated large-diameter rectal tube (No. 30 to 36 French) is then inserted through the sigmoidoscope across the twisted segment and secured to the skin for several days to maintain colonic decompression. An abdominal radiograph should be obtained following endoscopic detorsion to confirm resolution of the volvulus. Ballantyne[9] reported a success rate of 59% in a series of 352 consecutive patients with sigmoid volvulus living in the United States. Alternatively, flexible endoscopy using minimal air insufflation and manipulation has been used to permit inspection of the mucosa at and proximal to the point of obstruction; again, a rectal tube is left in place in patients with viable bowel.[14,15] At the time of flexible endoscopy, a blunt-ended guidewire can be inserted under direct visualization proximal to the volvulus and a rectal tube passed over the guidewire following removal of the endoscope. To a much lesser extent, reduction with enemas and the blind insertion of a rectal tube are techniques that can avoid urgent surgery.

Operative Following initial reduction of the sigmoid volvulus by sigmoidoscopy, the volvulus will recur in at least 40% of patients.[14-17] Such a high recurrence rate justifies an elective prophylactic sigmoid resection *during the same hospitalization* after the first episode of volvulus in all patients except in high-risk surgical candidates. Under

these circumstances, a mechanical bowel preparation can be administered and a primary anastomosis performed. Laparoscopic resection can be attempted in patients managed conservatively with adequate colonic decompression and in those able to tolerate both pneumoperitoneum and steep Trendelenburg positioning. In patients with significant comorbidities, our bias has been to use a transverse muscle-splitting incision to perform a sigmoid resection combined with postoperative epidural analgesia.

Failure to successfully reduce the volvulus endoscopically or clinical evidence of vascularly compromised bowel mandates emergent celiotomy. Resection of gangrenous bowel is required, with the creation of an end colostomy and Hartmann's or mucous fistula being the safest option in the absence of formal mechanical bowel preparation. If the bowel is of questionable viability, derotation usually in a counterclockwise manner with observation for the return of adequate perfusion may avoid resection. Often the use of a Doppler probe or Wood's lamp following intravenous administration of fluorescein can help in further evaluating for bowel viability. Under these circumstances, a colopexy involving fixation of the sigmoid to the anterior abdominal wall to prevent recurrent volvulus can be performed but is associated with a high incidence of recurrence.[16] Alternatively, single-stage resection with on-table lavage and primary anastomosis may be considered. In our experience, this is performed in only a small subgroup of patients that are hemodynamically stable and otherwise healthy individuals that are able to tolerate the added operative time and the potential risk of anastomotic dehiscence. In the presence of associated megacolon, total colectomy with ileorectal anastomosis may be considered, again with a goal of avoiding a multistage operative approach that requires a temporary stoma.

Outcomes Following Treatment

Operative mortality rates for emergent surgery for sigmoid volvulus are considerably higher in the presence of intestinal gangrene or failed nonoperative reduction, approximating 40%.[9] In comparison, the mortality rate for an elective resection following successful endoscopic reduction is less than 10%.[9]

Ileosigmoid Knot

Ileosigmoid knotting is an unusual entity that is most often confused with sigmoid volvulus.[18,19] In this condition, a loop of ileum wraps around the base of a redundant sigmoid loop, causing a double obstruction of both the colon and the small bowel. Attempts at endoscopic reduction of the volvulus are always unsuccessful, and this diagnosis should be considered in the subgroup of patients in whom endoscopic decompression is not possible. Rapid progression to gangrene of the colon and small bowel is the rule, necessitating urgent operative intervention. Resection of the involved small bowel is added to whatever procedure is dictated by the condition of the sigmoid.

Cecal Volvulus

Etiology and Pathophysiology

In the United States, the cecum and right colon represent the second most common site of volvulus but only account for 1% of all intestinal obstructions. The lack of retroperitoneal fixation of the right colon during fetal development predisposes to axial rotation of the ileocolic junction most commonly in a clockwise direction resulting in a cecal volvulus. The term *cecal volvulus* is misleading as this process is often not limited to the cecum alone but usually involves terminal ileum, ileocecal valve, cecum, and ascending colon. Clinical presentation and evaluation are as outlined earlier and mimic small bowel obstruction. Typically, plain abdominal radiographs reveal a dilated kidney bean–shaped ileocecal region with associated proximal small bowel dilation (see Fig. 144–2B).

A variant of cecal volvulus termed *cecal bascule*, is a condition in which a mobile cecum folds anteriorly and superiorly over a fixed ascending colon without rotation on the vascular pedicle. Consequently, this is not a true volvulus since axial rotation of the intestine is not associated with twisting of the associated mesentery and blood vessels. Although local ischemia and infarction have been reported, vascular embarrassment occurs less frequently. Radiographic investigation with barium enema is useful in diagnosing a cecal bascule, which accounts for 10% of instances of cecal volvulus.[7,10]

Although cadaveric dissections estimate that between 11% and 22% of adults have a sufficiently mobile right colon to allow for development of a cecal volvulus, it remains a rare condition. Predisposing epidemiologic factors are similar to those discussed for sigmoid volvulus and include a history of chronic constipation, obstructing colon lesions, malrotation, use of cathartics, pregnancy, and previous abdominal surgery. Cecal volvulus occurs more commonly in females and has been reported in all age groups, with an average age of presentation in the 40s.[10]

Treatment

Nonoperative Nonoperative treatment of cecal volvulus with endoscopy is much less successful than in patients with sigmoid volvulus. Colonoscopy is usually reported to be successful in fewer than 30% of patients.[15,20] Debate continues as to whether it should even be attempted because the procedure insufflates air into the obstructed segment and may precipitate ischemic changes by increasing the intraluminal pressure. Colonoscopic decompression with minimal air insufflation and manipulation can be effective in high-risk surgical patients with no clinical or biochemical evidence of bowel ischemia to avoid or temporarily defer surgery. A contrast enema is often useful in establishing a diagnosis of cecal volvulus as well as ruling out a distal partially obstructing colon lesion that may have predisposed to cecal distention; however, attempts at reduction using barium insufflation pressure enemas are contraindicated and potentially dangerous.

Operative Cecal volvulus is usually treated by urgent celiotomy. Controversy exists regarding the most appropriate procedure for viable bowel: detorsion alone (usually in a counterclockwise manner), detorsion with fixation, detorsion with cecostomy, and segmental resection all have been advocated.[21-23] This controversy relates in part to the lack of prospective data comparing the various surgical approaches. Resection of the involved bowel is required for ischemic or perforated colon, usually with a primary ileocolonic anastomosis. An ileostomy rather than an anastomosis may be required in selected circumstances. Cecal bascule can often be managed with a well-performed cecopexy as long as there is no evidence of bowel necrosis or gangrene.

Outcomes Following Treatment

When surgical resection has been performed, the recurrence rate for volvulus is nearly 0% compared with approximately 15% for cecopexy or detorsion alone. Cecopexy involves suturing the right colon to the lateral peritoneal surface and risks the sutures pulling though the thin-walled, distended cecum. Although the recurrence rate is low after cecostomy, postoperative management of a cecostomy tube is associated with a high incidence of abdominal wall and wound complications, as well as a persistent fecal fistula in up to 50% of patients.[24] Furthermore, this is not an option in the presence of nonviable bowel. As a result, our preference has been to perform a resection and primary anastomosis in most patients with cecal volvulus. Operative mortality rates are substantially higher in the presence of intestinal gangrene or perforation.[25]

Transverse Colon and Splenic Flexure Volvulus

Etiology and Pathophysiology

Volvulus of the transverse colon or splenic flexure is rare, accounting for fewer than 5% of all cases.[7,10] Presumably, the broad mesenteric attachment of the transverse colon combined with fixation at the hepatic and splenic flexures precludes rotation of the transverse colon in most patients. Epidemiologic studies suggest that the incidence increases in patients with chronic constipation, distal obstructing lesions, previous abdominal surgery, pregnancy, and hypermobile colonic flexures. Hypermobile colonic flexures can occur as a result of congenitally absent or surgically divided important support structures that include the gastrocolic, lienocolic, and phrenocolic ligaments.

Clinical presentation is, again, as outlined earlier and cannot be distinguished from other causes of large bowel obstruction. However, vomiting is thought to be an earlier symptom due to twisting of the transverse mesocolon and compression of the duodenojejunal junction.

Treatment

Nonoperative Plain abdominal radiographs show nonspecific colonic dilation and are frequently misread as a sigmoid volvulus due to the variable position of the transverse colon. As a result, patients are frequently colonoscoped with no clear transition point evident in the sigmoid colon. Under these circumstances, further attempts to identify a transition point should be terminated and a contrast enema study obtained. Although successful colonoscopic decompression has been previously described, there is a risk of excessive insufflation resulting in increased cecal distention and vascular compromise.

Operative Confirmation of transverse or splenic colon volvulus by contrast enema study is generally followed by surgical intervention. Resection of the involved segment is usually required, with primary anastomosis when possible. This can be accomplished with either an extended right hemicolectomy, partial left colectomy, or segmental transverse colectomy. Subtotal colectomy with ileocolonic anastomosis is an attractive single-stage option in the unprepared bowel if the sigmoid colon is not long and tortuous. A technique of fixation without resection has been described in which the redundant transverse colon is sutured to the ascending and descending colon.[26] Derotation followed later by elective resection offers the disadvantage of a second laparotomy. Perforation may require an end colostomy and mucous fistula because of concerns regarding anastomotic security.

Outcomes Following Treatment

Given the rarity of both transverse and splenic flexure volvulus, limited data are available regarding long-term results following the various surgical interventions. Anderson et al. reported a 75% recurrence rate in patients treated with colopexy alone.[27] As a result, our bias has been to perform either an extended right hemicolectomy or subtotal colectomy with ileocolonic anastomosis.

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Chapter

145

Colonic Bleeding and Ischemia

Ronald Kaleya · Scott J. Boley

During the past 4 decades, vascular lesions of the colon have been recognized as a major cause of rectal bleeding, especially in the geriatric patient population. However, despite the plethora of articles published on these vascular abnormalities, confusion and controversy remain concerning the pathogenesis, natural history, appropriate therapy, and proper naming of these lesions. Although many reports have grouped them together, several distinct entities can be identified (Box 145–1), each having as its common feature the passage of blood via the rectum.

VASCULAR ECTASIAS

Vascular ectasias of the colon are by far the most common vascular lesions found in the colon and are probably the most frequent cause of recurrent lower intestinal bleeding after 60 years of age.[1] They are distinct pathologic[2] and clinical[3] entities, and in our concept of their pathogenesis, they arise from age-related degeneration of previously normal colonic blood vessels. Vascular ectasias almost always occur in the cecum or the proximal ascending colon, are usually multiple, are less than 5 mm in diameter, are rarely identified with gross inspection or routine pathologic examination, are diagnosed with colonoscopy or angiography, and unlike many congenital or neoplastic vascular abnormalities, are not associated with synchronous angiomatous lesions of the skin, mucous membranes, or other viscera.

Incidence and Pathophysiology

There is no sex predilection for the development of vascular ectasias. Most patients are older than 50 years and two thirds are older than 70. Mucosal vascular ectasias of the right colon can be found in more than 25% of asymptomatic patients older than 60 years who undergo routine colonoscopy.[4]

Any hypothesis concerning the formation of colonic vascular ectasias must account for their prevalence in elderly persons, their small size and multiplicity, and their preponderance in the cecum and right colon. Although the cause of these lesions has not been definitively established, injection and clearing studies have led us to postulate that vascular ectasias are degenerative lesions associated with aging and represent a unique entity distinct from previously described intestinal vascular abnormalities. We believe that over time, normal contraction and distention of the colon cause repeated, partial, intermittent, low-grade obstruction of submucosal veins, especially at the point where they pierce the muscular layers of the colon. These repeated episodes of transiently elevated venous pressure initially cause dilation and tortuosity of the submucosal veins and then, in a retrograde manner, of the venules and the arteriolar/capillary/venular units draining into them. Ultimately, the capillary rings surrounding the crypts dilate and the competency of the precapillary sphincters is lost, thereby creating a small arteriovenous communication (Fig. 145–1). The latter produces an early-filling vein, which was the original angiographic criterion for diagnosis of this lesion. These abnormal submucosal veins, found in the absence of a mucosal lesion or underlying a minute mucosal ectasia supplied by a normal artery, suggested that submucosal vein dilation was the primary pathologic change rather than arterialization from an arteriovenous communication. The theory that intramural veins are partially obstructed by functional colonic activity is supported by several earlier studies. Venous flow in the bowel is diminished by colonic motility, increased wall tension, and increased intraluminal pressure.[5-7] Rhythmic alterations in venous blood flow and venous pressure related to colonic contractions have also been demonstrated.[8] The presence of these degenerative lesions in the cecum and right colon may be explained by Laplace's law; specifically, during periods of colonic distention, wall tension will be greatest in the portion of bowel with the widest diameter (cecum and right colon).

Box 145–1 Vascular Lesions of the Colon

- Vascular ectasia
- Hemangioma
- Congenital arteriovenous malformation
- Colonic varices
- Telangiectasia
- Syndrome-related lesions (e.g., Klippel-Trénaunay-Weber syndrome, Maffucci's syndrome)
- Others
  - Vascular spiders and venous stars of liver disease
  - Degenerative phlebectasia of the elderly
  - Vasculitic lesions
  - Focal hypervascularity of ulcerative, Crohn's, and ischemic colitis
  - Neovascularity of radiation colitis
  - Angiosarcoma (e.g., Kaposi's sarcoma)

Approximately 25% of patients with bleeding ectasias have a diagnosis of aortic stenosis. Some investigators ascribe a causative role for ectasias to aortic valvular disease. We do not believe that there is an etiologic relationship between aortic stenosis and the development of colonic ectasias. Rather, there may be some feature of aortic stenosis, perhaps the low pulse pressure or decreased systemic perfusion characteristic of this disorder, that can increase the chance of bleeding in individuals who have vascular ectasias. For instance, a low-flow state may lead to ischemic necrosis of the single endothelial layer that separates the ectatic vessels from the colonic lumen. Alternatively, a roughened or stenotic aortic valve could produce a mild consumptive coagulopathy or a subtle alteration in platelet function, and these defects, combined with a thin-walled, dilated, mucosal vascular lesion, may cause an ectasia to bleed.[9]

In view of these factors and contradictory evidence concerning the beneficial effect of aortic valve replacement in the treatment of bleeding ectasias, it seems prudent to consider cardiac disease and colonic lesions as separate and only potentially related entities. A rational approach appears to be that initial therapy should be directed to the colonic lesion if the patient's cardiac status does not require surgical correction. If valvular replacement is indicated, however, it should be done first and treatment of the colonic ectasia deferred unless or until there is continuing or recurrent postoperative bleeding.

Histologic identification of vascular ectasia is difficult without special techniques, as demonstrated by our early experience. Of seven patients with angiographically demonstrated colonic ectasia who were studied only by routine gross examination and microscopic study of random or selected colonic sections, a mucosal ectasia could be identified in only two patients. Our technique for localization and identification of vascular ectasia consists of injection of a silicone rubber compound (Microfil) through catheters placed in one or more of the arteries supplying the colon. Specimens are then dehydrated in increasing concentrations of ethyl alcohol and are cleared with methyl salicylate. This process produces a transparent specimen with a filled vascular bed that is studied by dissection microscopy under direct light, as well as transillumination. In the first 25 colons in which we used this technique, one or more mucosal ectasias, measuring 1 mm to 1 cm in diameter, were identified in all of the specimens (Fig. 145–2). Seven colons contained two lesions, and 11 colons contained three or more lesions. The ectasias were all located within the cecum and the proximal part of the ascending colon; the most distal one was 23 cm from the ileocecal valve. All the cleared specimens had prominent dilated and tortuous submucosal veins, both beneath the ectasias and in areas in which the mucosal vessels appeared normal (Fig. 145–3). The colon from the oldest patient, an 88-year-old man, contained approximately 50 mucosal ectasias of various size.

Microscopically, vascular ectasias consist of dilated, distorted, thin-walled vessels, mostly lined only by endothelium and, less frequently, by a small amount of smooth muscle. Structurally, they appear to be ectatic veins, venules, and capillaries. The degree of distortion of the normal vascular architecture varies in different lesions, but the most consistent and apparently the earliest abnormality noted in all of the lesions we have studied is the presence of dilated, often huge, submucosal veins (Fig. 145–4A). Progressively more extensive lesions show increasing numbers of dilated and deformed vessels traversing the muscularis mucosa and involving the mucosa until, in the most severe lesions, the mucosa is replaced by a maze of distorted, dilated vascular channels (see Fig. 145–4B).

Clinical Aspects

Except for lower intestinal bleeding, vascular ectasia of the colon is asymptomatic. Bleeding from ectasias is usually recurrent and low grade. Approximately 15% of patients, however, have massive hemorrhage and, less frequently, are in hemorrhagic shock. During repeated episodes, bleeding in an individual patient may range from gross hematochezia to maroon-colored stools, melena, and occult blood in the stool. Tarry stools are passed in 20% to 25% of episodes, and blood loss is manifested as iron deficiency anemia and stools that intermittently contain occult blood in 10% to 15% of patients. This spectrum reflects the varied rate of bleeding from the ectatic capillaries, venules, and in advanced lesions, arteriovenous communications. In more than 90% of patients, the bleeding stops spontaneously.

In the early series, as many as 30% of patients with colonic vascular ectasia had previously undergone surgery for other suspected sources of intestinal bleeding, including partial gastrectomy, vagotomy with antrectomy or pyloroplasty, and left colon resection for purported diverticular bleeding. None of the patients in our series who underwent left colectomy had angiographic or histologic documentation of a bleeding site at

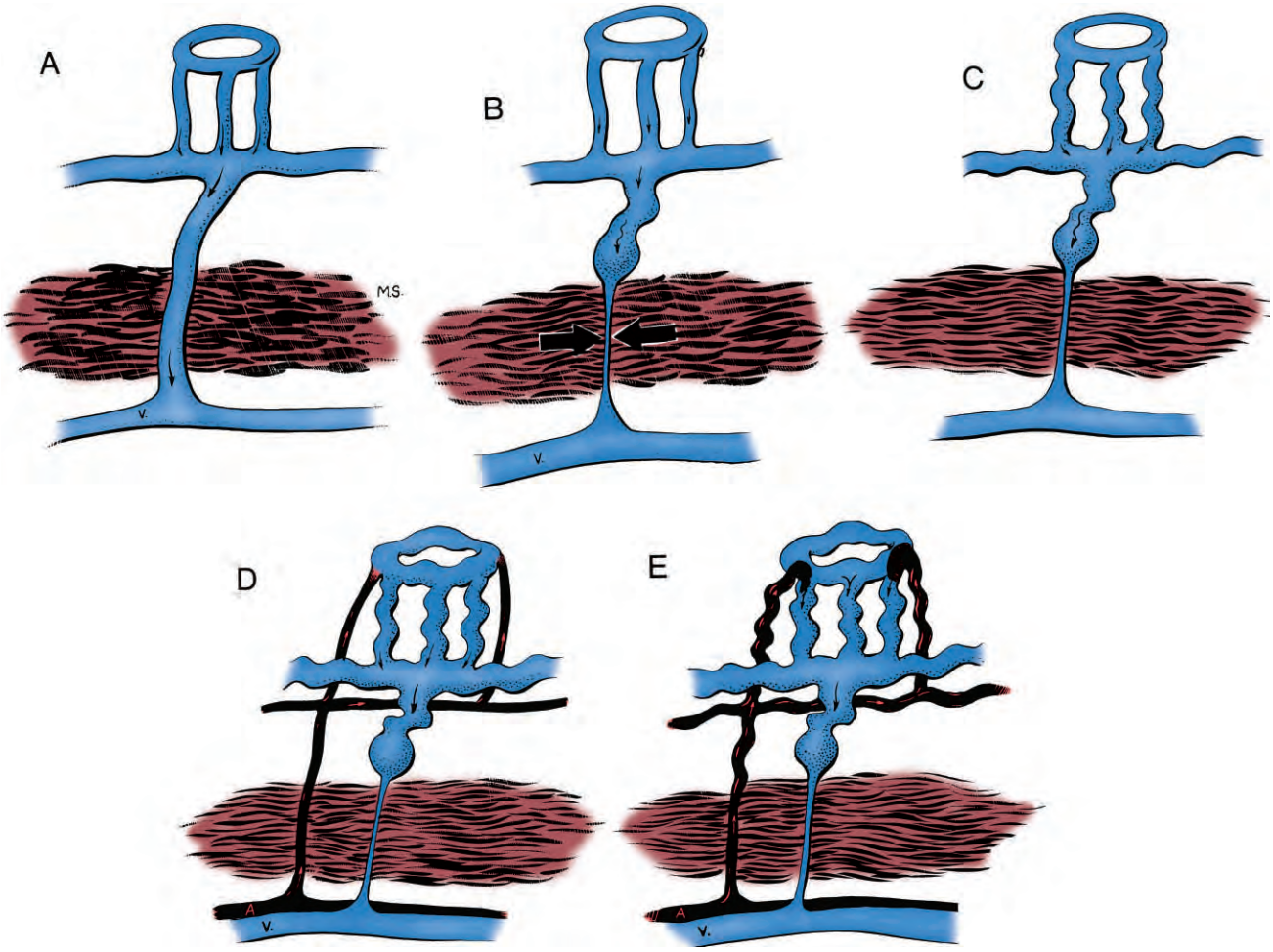

Figure 145–1. Diagrammatic illustration of a proposed concept of the development of cecal vascular ectasia. **A,** Normal state of a vein perforating the muscular layers. **B,** With muscular contraction or increased intraluminal pressure, the vein is partially obstructed. **C,** After repeated episodes over a period of many years, the submucosal vein becomes dilated and tortuous. **D,** Later, the veins and venules draining into the abnormal submucosal vein become similarly involved. **E,** Ultimately, the capillary ring becomes dilated, the precapillary sphincter becomes incompetent, and a small arteriovenous communication is present through the ectasia. (From Boley SJ, Sammartano RJ, Adams A, et al: On the nature and etiology of vascular ectasias of the colon: Degenerative lesions of aging. Gastroenterology 72:650, 1977, with permission.)

the time of the previous operations. However, the proportion of patients who have undergone previous operations has decreased because the diagnosis is established earlier and physicians are more willing to refer patients for endoscopic ablation or surgery before repeated episodes of bleeding occur.

The problem of differentiating blood loss from vascular ectasias or diverticulosis when bleeding is not demonstrated endoscopically or angiographically is compounded by the frequent occurrence of these lesions without bleeding in persons older than 60 years. Diverticulosis occurs in up to 50% of persons older than 60 years, and nonbleeding mucosal vascular ectasias of the right colon have been found in more than a fourth of persons of the same age. Therefore, in the absence of a demonstrated site of hemorrhage, bleeding can be attributed to an ectasia or diverticulosis only indirectly by observing the course of the patient after resection of the suspected lesion. Furthermore, in some patients with angiographically confirmed vascular ectasias, another unrelated and undetected nondiverticular lesion may be responsible for the blood loss.[10,11] The prevalence of a second type of lesion in patients with vascular ectasias is not known. However, recurrent lower intestinal bleeding is noted in 15% to 20% of patients who have undergone right hemicolectomy for angiographically proven vascular ectasias,[12,13] thus suggesting that a second source may have been present in as many as a fifth of affected patients.

Diagnosis

The diagnostic approach that we use in patients with lower gastrointestinal (LGI) bleeding (Fig. 145–5) varies with their age, the presence or absence of active

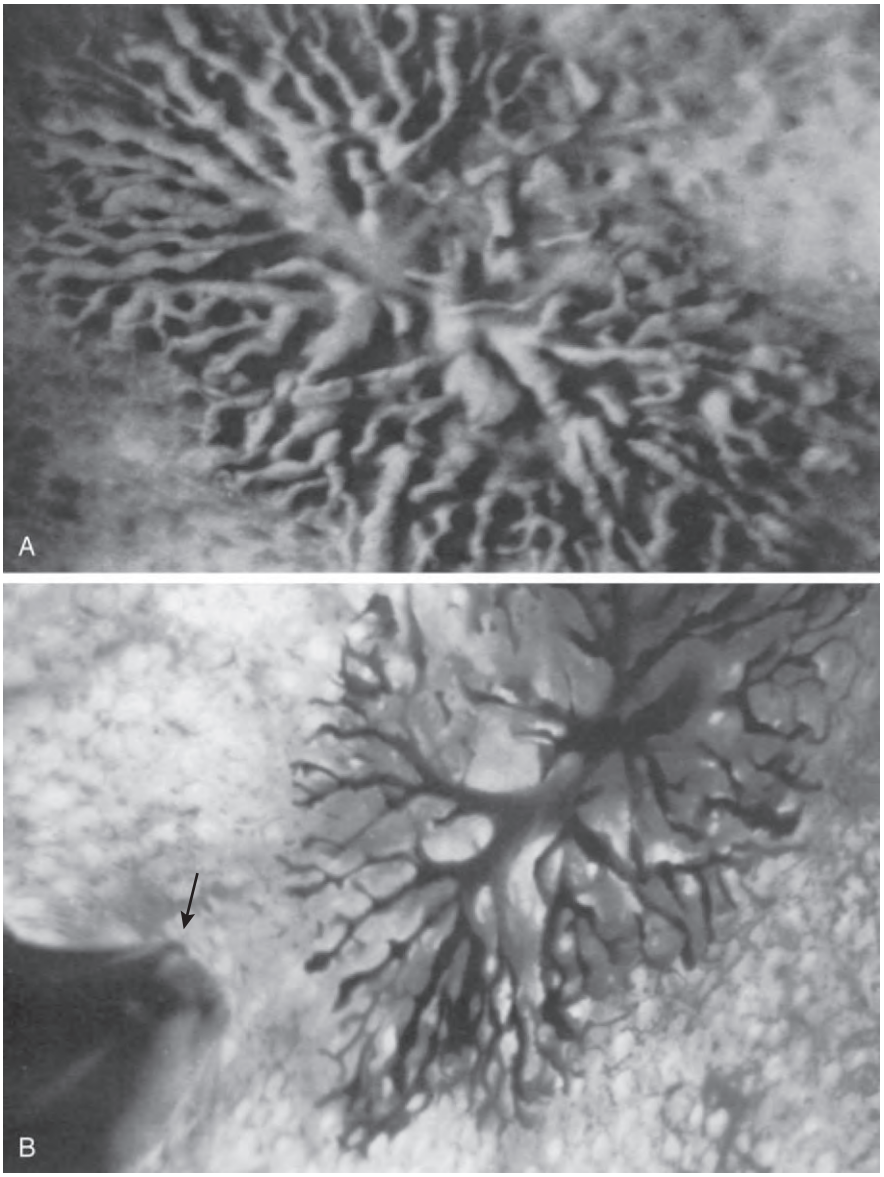

Figure 145–2. **A,** "Coral reef" appearance of an ectasia in an injected, but not cleared colon. Normal crypts are seen surrounding the ectasia. **B,** Transilluminated, cleared colon showing ectasia involving the mucosal capillaries and venules. A pinhead is shown for size comparison (*arrow*). (**A,** From Mitsudo S, Boley SJ, Brandt LJ, et al: Vascular ectasias of the colon. Hum Pathol 10:585, 1979, with permission; **B,** from Sprayregen S, Boley SJ: Vascular ectasias of the colon. JAMA 129:962, 1978. Copyright © 1978, American Medical Association.)

Figure 145–3. Transilluminated, cleared colon showing a mucosal ectasia surrounded by normal crypts with ectatic venules leading to a large, distended, tortuous, underlying submucosal vein. A sharp constriction (*arrow*) can be seen where the vein traverses the muscle layers. (From Boley SJ, Brandt LJ, Mitsudo S: Vascular lesions of the colon. Adv Intern Med 29:301, 1984.)

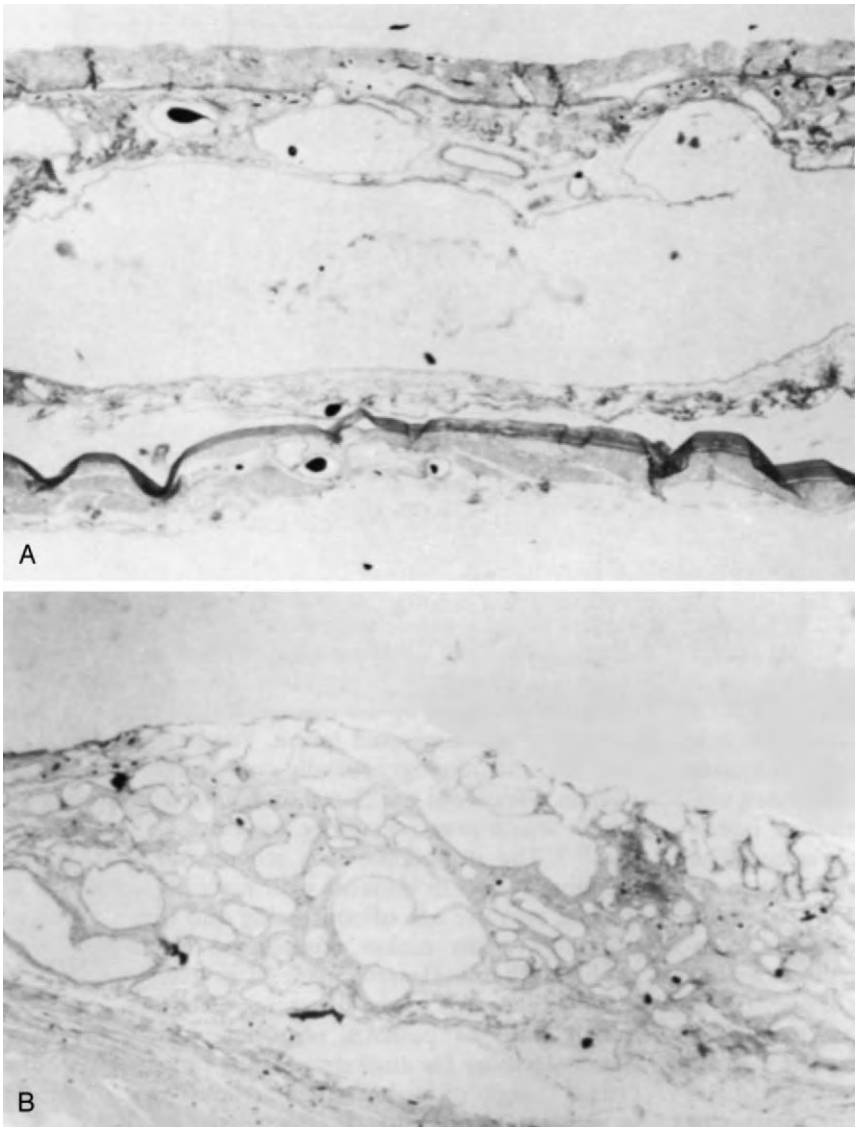

Figure 145–4. **A,** Large distended vein completely filling the submucosa with a few dilated venules in the overlying mucosa. This is the hallmark of early ectasia (hematoxylin-eosin stain, ×50). **B,** Advanced lesion showing total disruption of the mucosa with replacement by ectatic vessels. Only one layer of endothelium separates the lumen of the cecum from the lumens of the dilated vessels (hematoxylin-eosin stain, ×50). (**A,** From Boley SJ, Sammartano RJ, Adams A, et al: On the nature and etiology of vascular ectasias of the colon: Degenerative lesions of aging. Gastroenterology 72:650, 1977, with permission; **B,** from Boley SJ, Brandt LJ, Mitsudo S: Vascular lesions of the colon. Adv Intern Med 29:301, 1984.)

bleeding, and the severity of hemodynamic compromise caused by the blood loss. All patients with LGI bleeding should have a coagulation profile performed, including a platelet count, prothrombin time, and partial thromboplastin time, to identify clotting abnormalities. Further evaluation of patients with LGI bleeding depends on the rate of blood loss.

Major Bleeding Major bleeding is defined as (1) acute blood loss causing hemodynamic signs of hypovolemia or (2) the sudden passage of large amounts of bloody, maroon, burgundy, or melenic stools in the absence of hemodynamic compromise.

Because 10% to 15% of major LGI bleeding begins in the upper gastrointestinal (UGI) tract,[14] nasogastric lavage follows assessment of the coagulation status and digital rectal examination. A bloody aspirate indicates UGI bleeding in most cases, whereas the absence of blood and the presence of bile in the aspirate virtually exclude bleeding proximal to the ligament of Treitz. A clear, nonbilious aspirate is, however, an indication for UGI endoscopy in actively bleeding patients because there may be a lesion distal to a closed pylorus. A blood urea nitrogen level of less than 30 mg/dl occurs in approximately two thirds of patients with major bleeding proximal to the colon and may help guide the clinician toward a putative bleeding site. A standard proctosigmoidoscopic examination is conducted to exclude anorectal and distal sigmoid pathology.

Rigid sigmoidoscopy is followed by abdominal scintigraphy in actively bleeding patients because the latter may localize the bleeding site or, alternatively, confirm the cessation of bleeding, thereby enabling the clinician to choose colonoscopy or angiography as the next diagnostic modality. Scintigraphy is noninvasive, safer than angiography and colonoscopy, more sensitive in detecting active bleeding than angiography is, and capable of identifying bleeding over a 24-hour period, not just during the brief period of a colonoscopic examination or injection of an angiographic contrast agent.[15,16] Two

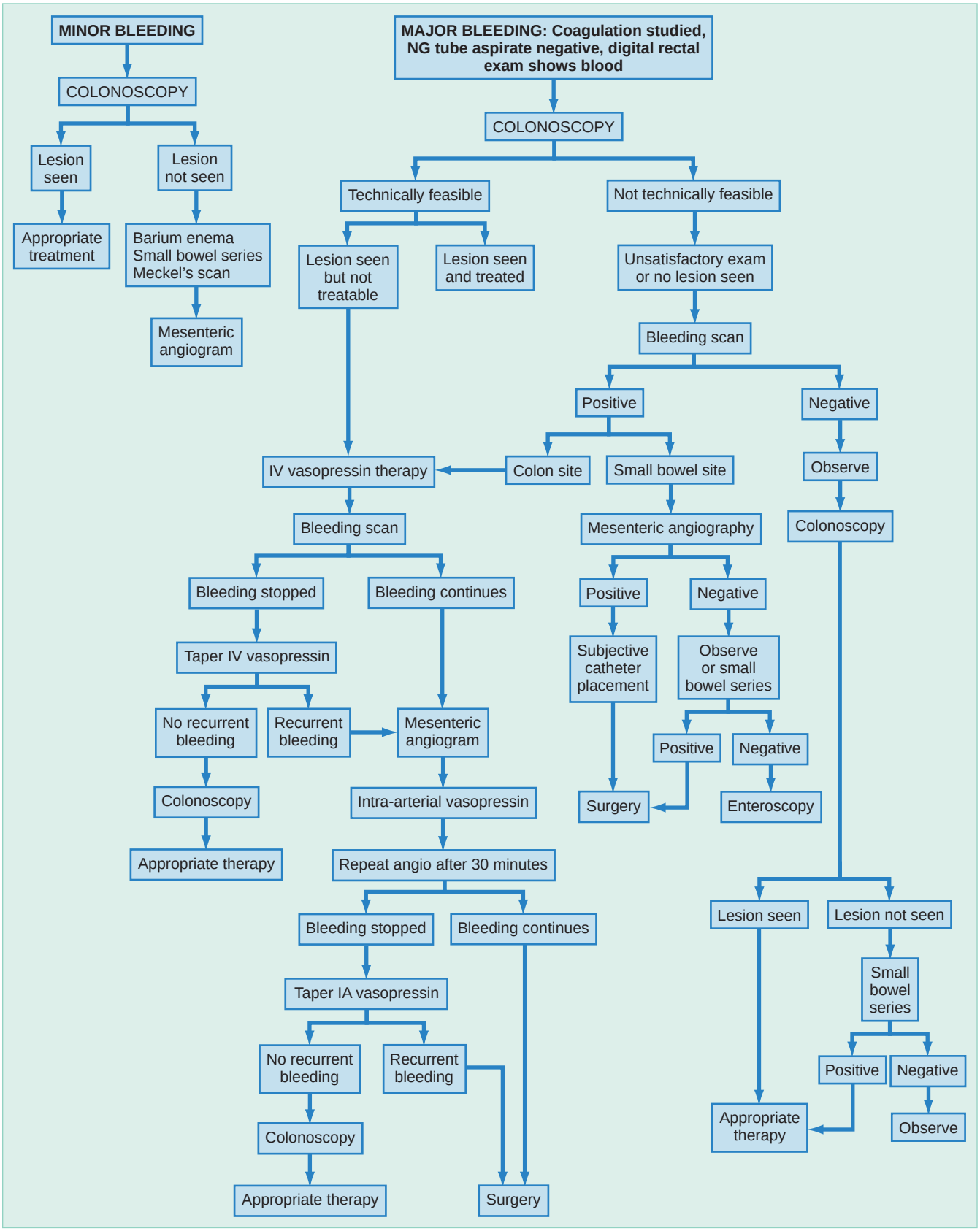

Figure 145–5. Diagnostic algorithm for lower intestinal bleeding. IA, intra-arterial; IV, intravenous; NG, nasogastric.

radionuclides commonly used to detect intestinal bleeding are ^{99m}Tc-labeled sulfur colloid and ^{99m}Tc-labeled red blood cells (RBCs). Previously, ^{99m}Tc–sulfur colloid scanning was considered the more sensitive of these two techniques and, because it is rapidly cleared from the circulation (plasma half-life of only 2 to 3 minutes), the best agent for detecting active bleeding. Although it was thought to be less sensitive than sulfur colloid scanning, ^{99m}Tc-RBC scanning was considered very useful for detecting intermittent bleeding, primarily because of the 24-hour half-life of Tc-labeled RBCs. It now appears that only ^{99m}Tc-RBC labeling is necessary because both clinical[17] and experimental[18] studies have found that it is as sensitive as sulfur colloid and can reliably detect active bleeding even at rates below 0.1 ml/min. Unlike sulfur colloid scanning, with RBC scintigraphy, serial studies can be obtained for up to 36 hours after a single injection of the radionuclide, thus detecting lesions that bleed intermittently. Furthermore, unlike sulfur colloid, ^{99m}Tc-labeled RBCs are not cleared by the liver and spleen, so bleeding in the area of these organs, which is often obscured with sulfur colloid, can be visualized.

Active Major Bleeding If scintigraphy demonstrates a bleeding site in the colon and the patient is hemodynamically stable, colonoscopy is performed. In this circumstance, clotted blood within the colon often obscures visibility and increases the risks associated with the procedure. Because of this increased risk, if the bleeding site is shown by the scan to be proximal to the midportion of the transverse colon, colonoscopy should be abandoned if technical difficulties are encountered. If a site of hemorrhage is identified distal to the midportion of the transverse colon, extra effort to cleanse the bowel and proceed cautiously is usually rewarding.

Although colonoscopy is playing an increasing role in the diagnosis of colonic vascular lesions, the endoscopist's ability to diagnose the specific lesion is limited by the similar appearance of many vascular, inflammatory, neoplastic, and iatrogenic abnormalities. Indeed, vascular ectasias can be mimicked by any of the lesions listed in Box 145–1. Thus, vascular lesions should preferably be evaluated on entering the colon rather than on withdrawal to avoid traumatic and suction artifacts that limit the endoscopist's ability to identify and differentiate these lesions.[19]

Angiography is performed if neither scintigraphy nor colonoscopy reveals the bleeding site, if colonoscopy is not technically feasible, if scintigraphy demonstrates bleeding within the small bowel, or if the patient continues to bleed actively. A selective superior mesenteric arteriogram is the initial study performed because 50% to 80% of all LGI bleeding occurs in the vascular bed fed by the superior mesenteric artery (SMA). Selective inferior mesenteric artery (IMA) and celiac axis (CA) studies are performed in that order if the initial superior mesenteric arteriogram does not identify the lesion. Flush aortography is of no use in identifying bleeding lesions and is not performed.

Mesenteric arteriography may be productive both in patients with active bleeding and in those who have stopped bleeding. Extravasation of contrast material is the angiographic hallmark of active hemorrhage and can be seen with bleeding rates as low as 0.5 ml/min.[20] Angiographic signs of tumor neovascularization or vascular ectasias may identify a presumed cause and location of the hemorrhage.

Angiography can be diagnostic and provide access for treatment. In 80% of cases, active bleeding can be at least temporarily stopped by the transcatheter infusion of vasopressin. Transcatheter embolization of ectasias has been reported but should be used only in desperate situations because it may result in bowel infarction.

Angiography successfully identifies the source of lower intestinal bleeding in approximately two thirds of patients. Pooling of extravasated contrast material in a diverticulum is the angiographic sign of diverticular bleeding and was present in 75% of patients with diverticular bleeding in the series reported by Welch and colleagues.[21] In contradistinction, extravasation has been shown in only 10% to 20% of patients bleeding from vascular ectasias of the colon because the bleeding is usually episodic. However, the presence of other angiographic signs enables the diagnosis of colonic ectasia or other vascular lesions of the small and large bowel to be made even in the absence of active bleeding. There are three major angiographic signs of ectasia (Fig. 145–6). The earliest sign to develop in the evolution of an ectasia, and hence the one most frequently seen, is a densely opacified, dilated, *tortuous, slowly emptying intramural vein* that reflects ectatic changes in the submucosal veins. This sign is present in more than 90% of patients with ectasias. A *vascular tuft*, present in 70% to 80% of patients, represents a more advanced lesion and corresponds to extension of the degenerative process to mucosal venules. An *early-filling vein* is a sign of even more advanced changes and reflects an arteriovenous communication through a dilated arteriolar/capillary/venular unit. It is a late sign, present in only 60% to 70% of patients. All three angiographic signs are present in more than half of patients with bleeding ectasias. Intraluminal extravasation of contrast material alone is inadequate to diagnose an ectasia, but when seen in conjunction with at least one of the three signs of ectasia, it is indicative of a ruptured mucosal lesion.

On rare occasion, vigorous resuscitation with intravenous fluids and blood products may fail to stabilize a patient with major bleeding. Colonoscopy is best avoided in hemodynamically unstable patients, and therefore emergency angiography is the procedure of choice. Transcatheter or intravenous vasopressin will usually control such bleeding and convert an emergency situation into an elective one, thus saving the patient unnecessary and potentially debilitating surgery.

Major Bleeding That Has Ceased In patients with major LGI bleeding in whom proctosigmoidoscopy and nasogastric aspiration are negative and bleeding has ceased, scintigraphy is not performed and colonoscopy is the initial diagnostic procedure. Again, the presence of blood clots may severely limit visualization, obscure lesions, and make passage of the colonoscope technically difficult and hazardous. In these instances, enemas delivered through the colonoscope can be used to clean the

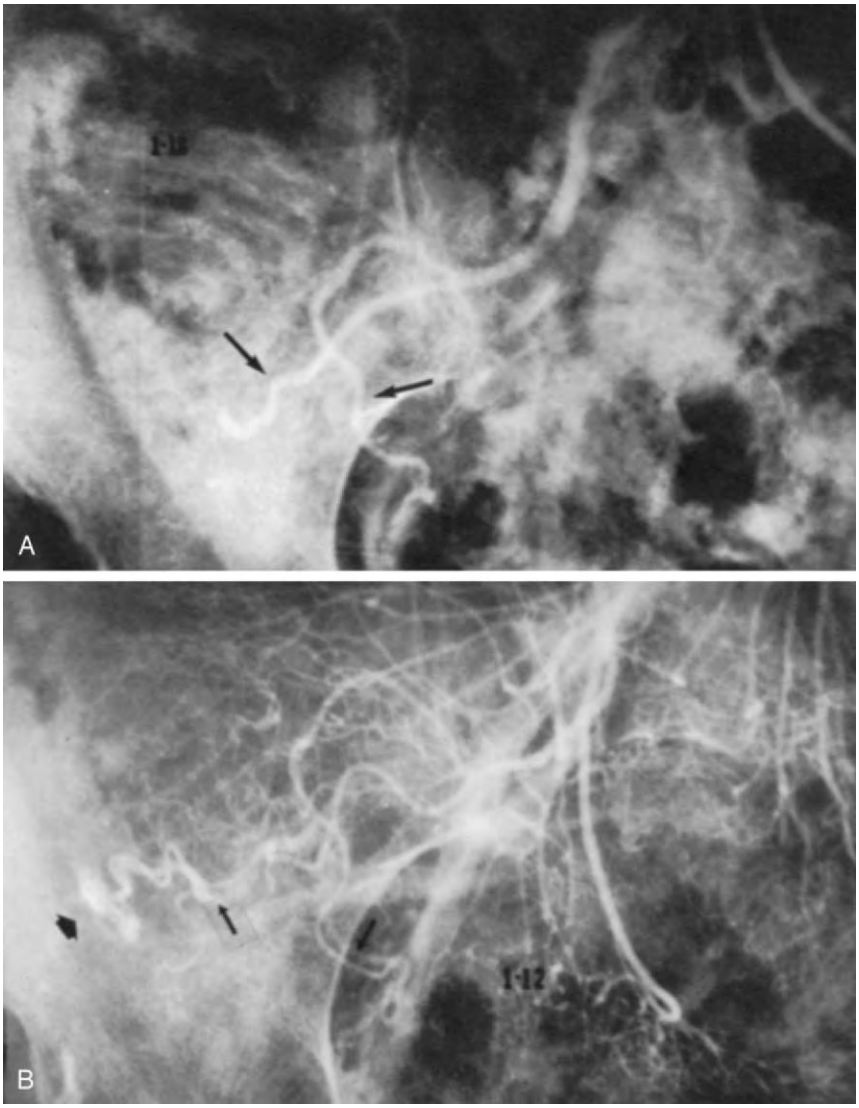

Figure 145–6. **A,** Superior mesenteric arteriogram from a patient with vascular ectasias showing only two densely opacified, slowly emptying, dilated, tortuous cecal veins (*arrows*) at 14 seconds. Note the late visualization of the ileocolic vein after other veins have cleared. **B,** Arterial phase from the same arteriogram showing an avascular tuft (*large wide arrow*) and two early-filling veins (*small arrows*) at 6 seconds. (From Boley SJ, Sprayregen S, Sammartano RJ, et al: The pathophysiologic basis for the angiographic signs of vascular ectasias of the colon. Radiology 125:615, 1977, with permission.)

lumen and bowel wall. If these efforts fail, the examination is postponed to prepare the patient with a polyethylene glycol–based agent (GoLYTELY, Colyte).

If complete and satisfactory colonoscopic examination reveals no explanation for the bleeding other than diverticulosis, double-contrast barium studies of the colon, the UGI tract, and the small bowel are indicated. If both colonoscopy and barium opacification studies are normal or show only the presence of diverticula, selective mesenteric angiography has been the most informative study in our experience. During angiography, the SMA, IMA, and CA are injected, in that order. Arteriography, when performed in patients whose bleeding has stopped, is used primarily to diagnose tumor neovascularity or vascular lesions, many of which have characteristic angiographic findings, thereby permitting them to be identified in the absence of extravasation. Other techniques, such as sequential long-tube aspiration of the intestine and small bowel enteroscopy, may also be of value.

Occasionally, an initially negative ^{99m}Tc-RBC study, performed because it was not clinically apparent whether the bleeding had stopped, may reveal extravasation during serial scanning and localize a lesion that bleeds intermittently. Patients with recurrent or persistent major bleeding for which no site of hemorrhage is found may require exploratory laparotomy with attempts at intraoperative localization (e.g., intraoperative enterocolonoscopy) to avoid blind resection of part or all of the colon.

Nonmajor Bleeding Nonmajor bleeding is defined by (1) a chemical test for blood in stool (occult LGI bleeding) or (2) the passage of hemodynamically insignificant amounts of either gross blood per rectum or melena. Although bleeding of this type has been identified in 25% to 30% of patients with ectasias, it is probably less common. Evaluation of patients with minor bleeding had consisted of rigid proctosigmoidoscopy, followed by single-contrast barium enema. However, this approach is

inadequate because (1) even flexible fiberoptic sigmoidoscopy cannot visualize the right colon and will therefore miss 40% of mass lesions and all vascular ectasias and (2) double- or air-contrast barium enema will be equivocal in 20% of cases and will regularly miss 40% of polyps, a third of cancers, 60% of discrete ulcerations and colitides, and all mucosal or submucosal vascular lesions.[22-24] Conversely, colonoscopy can reliably visualize the entire mucosal surface of the colon and should be the initial diagnostic study in patients with nonmajor bleeding. Retroflexion of the colonoscope in the rectal vault combined with meticulous examination of the anus during withdrawal of the instrument will provide sufficient examination of the anorectum to eliminate the need for rigid proctosigmoidoscopy. Barium enema is necessary only when the entire colon cannot be visualized endoscopically.

If colonoscopy is negative, esophagogastroduodenoscopy is performed, preferably on the same day, to examine the UGI tract. Negative esophagogastroduodenoscopy is followed by double-contrast radiography of the UGI tract and small bowel. On rare occasion, repeat endoscopic studies or barium enema may be contributory. If these studies are repeatedly normal but occult or slow bleeding continues, small bowel enteroscopy,[25] ^{111}In-labeled platelet scintigraphy,[26] or mesenteric angiography may at times be helpful. Less commonly, exploratory laparotomy with attempts at intraoperative localization may be the only alternative.[27]

Treatment

Once a colonic vascular ectasia has been identified, management consists of control of the acute hemorrhage and then definitive treatment of the lesion itself. Major changes in management have occurred since the original descriptions of vascular ectasia and include the increasing roles of radionuclide scanning and colonoscopy in identifying the cause and site of bleeding and transcolonoscopic ablation of focal lesions.

Control of Acute Hemorrhage

In most patients, acute hemorrhage can be controlled by nonoperative means, and an emergency operation, with its increased morbidity and mortality rates, can be avoided. In patients in whom colonoscopy has been successful and an actively bleeding ectasia or fresh mucosal thrombus (i.e., a sentinel clot) has been identified, transendoscopic ablation of the lesion is an effective mode of therapy. In patients who undergo angiography because colonoscopy was unsuccessful or not technically feasible, vasopressin infusions, either intravenously or intra-arterially through the angiographic catheter, successfully arrest hemorrhage in more than 80% of patients in whom extravasation is demonstrated. The intravenous route appears to be as effective as the intra-arterial route when the bleeding is in the left colon, but intra-arterial administration has been more successful when the bleeding is from the right colon or small bowel.

Definitive Treatment

During the first 15 years after vascular ectasias were described, definitive treatment consisted of some type of colon resection. Endoscopic electrocoagulation was a therapeutic option reserved mainly for elderly persons with complicated medical illnesses. Today, use of the argon laser, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, endoscopic sclerosis, monopolar electrocoagulation, bipolar electrocoagulation, and the heater probe for miscellaneous vascular lesions throughout the gastrointestinal (GI) tract is well described. In institutions where physicians experienced in endoscopic surgery are available, a greater number of patients can be managed endoscopically, and resection is often reserved for patients whose bleeding cannot be stopped or in whom endoscopic treatment is unsuccessful.

Asymptomatic vascular ectasias are frequently noted incidentally during colonoscopy in many elderly patients. Most surgeons do not recommend treating asymptomatic cecal vascular lesions, but if increasing experience demonstrates some of the newer modes of therapy (e.g., bipolar electrocoagulation and the heater probe) to be safe, a more aggressive approach to these lesions may be warranted.

In patients who have bled and in whom an ectasia of the right colon has been identified by either colonoscopy or angiography, right hemicolectomy remains the treatment of choice if (1) the bleeding cannot be stopped, (2) an endoscopist experienced in transcolonoscopic ablation is not available, and (3) endoscopic ablation has been unsuccessful or is not feasible for technical reasons, such as large or multiple lesions. In the latter two situations, right hemicolectomy is performed as an elective procedure once active bleeding is controlled. The extent of colonic resection is not altered by the presence or absence of diverticulosis in the left colon; only the right half of the colon is removed. It is important that the entire right half of the colon be removed to ensure that no ectasias are left behind. Because up to 80% of bleeding diverticula are located in the right side of the colon, the risk of leaving the left colon is far outweighed by the increased morbidity and mortality rates for subtotal colectomy. Recurrent bleeding can be expected in up to 20% of patients so treated and was observed in 4 of our first 27 patients with angiographically proven ectasias. Subtotal colectomy should be performen only in patients with persistent colonic bleeding and normal colonoscopy and selective angiograms.

OTHER VASCULAR LESIONS

As shown in Box 145–1, many vascular lesions other than ectasias can affect the LGI tract—some as part of a syndrome or systemic disease and others as single or multiple lesions unrelated to disease elsewhere in the body.

Hemangiomas

The second most common vascular lesion of the colon is hemangioma. Although these lesions are considered by

some to be true neoplasms, they are generally thought to be hamartomas because of their presence at birth in most cases. Colonic hemangiomas may occur as solitary lesions, as multiple growths limited to the colon, or as part of diffuse GI or multisystem angiomatoses. Individual hemangiomas may be broadly classified as cavernous, capillary, or mixed. Most hemangiomas are small and range from a few millimeters to 2 cm. Larger lesions do occur, however, especially in the rectum.

Clinically, bleeding from colonic hemangiomas is usually slow and produces occult blood loss with anemia or melena. Hematochezia is less common, except in the case of large cavernous hemangiomas of the rectum, which can cause massive hemorrhage. The diagnosis is best established by colonoscopy; roentgenologic studies, including angiography, may be normal. In the presence of GI bleeding, hemangiomas of the skin or mucous membranes should suggest the possibility of associated bowel lesions.

Pathologically, hemangiomas are well circumscribed but not encapsulated. Grossly, cavernous hemangiomas appear as polypoid or mound-like reddish purple lesions of the mucosa. Sectioning of the lesion reveals numerous dilated, irregular blood-filled spaces within the mucosa and submucosa, sometimes extending through the muscular wall to the serosal surface. The vascular channels are lined by flat endothelial cells with flat or plump nuclei. Their walls do not contain smooth muscle fibers but are composed of fibrous tissue of various thickness (Fig. 145–7). Capillary hemangiomas are plaque- or mound-like reddish purple lesions composed of a proliferation of fine, closely packed, newly formed capillaries separated by very little edematous stroma. The endothelial lining cells are large, usually hypertrophic, and in some areas may form solid cords or nodules with ill-defined capillary spaces. There is little or no pleomorphism or hyperchromasia.

Small hemangiomas that are either solitary or few in number can be treated by colonoscopic laser coagulation. Large or multiple lesions usually require resection of either the hemangioma alone or the involved segment of colon. The hemangioma can either be palpated directly or be revealed by transilluminating the bowel wall with an operative endoscope. The affected area can be resected, which can frequently be accomplished without opening the bowel.

Cavernous Hemangiomas of the Rectum

A distinct form of colonic hemangioma is a cavernous hemangioma of the rectum. These lesions are not usually associated with other GI hemangiomas and are extensive, with involvement of the entire rectum, portions of the rectosigmoid, and the perirectal tissues. They cause massive, sometimes uncontrollable hemorrhage, often beginning in infancy. The diagnosis can generally be suggested on plain films of the abdomen by the presence of phleboliths and by displacement or distortion of the rectal air column.[28] A barium enema study showing narrowing and rigidity of the rectal lumen, scalloping of the rectal wall, and an increase in size of the presacral space further supports the diagnosis. Endoscopically, elevated nodules or vascular congestion causing a plum-red coloration is seen. Ulcers and signs of proctitis may be evident. Angiography can be used to demonstrate these lesions but is rarely necessary to establish the diagnosis.

The massive bleeding resulting from these rectal hemangiomas often necessitates excision of the rectum by either abdominal perineal or low anterior resection, but because lesions occasionally involve the perirectal tissues, attempts at maintaining continence via pull-through procedures may fail. Ligation plus embolization of major feeding vessels has been used with varying degrees of success, and although local measures (e.g., electrocoagulation, sclerotherapy) are usually only temporarily effective, they have been of value in some instances.

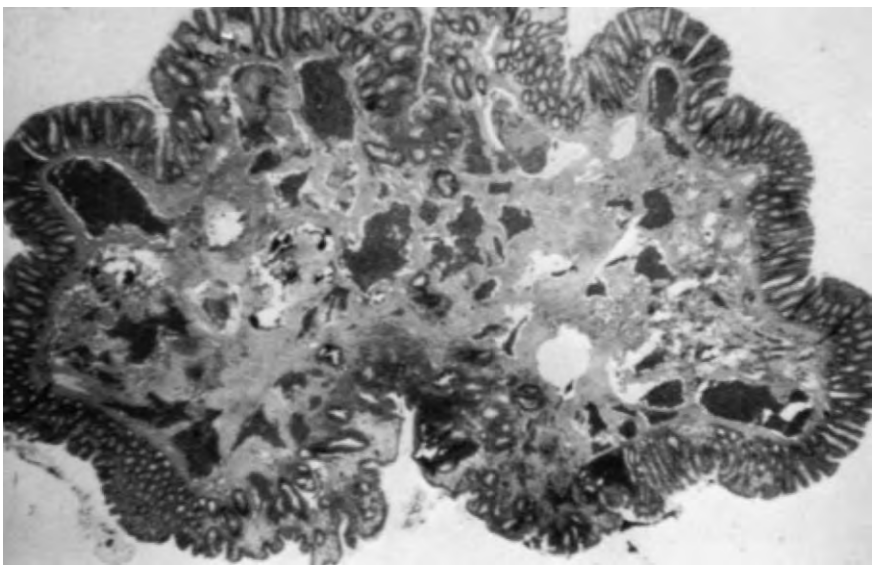

Figure 145–7. Polypoid cavernous hemangioma located in the submucosa with focal extension into the mucosa. Note the large, irregular vascular channels with fibrous walls of various thickness (hematoxylin-eosin stain, ×20). (From Boley SJ, Brandt LJ, Mitsudo S: Vascular lesions of the colon. Adv Intern Med 29:301, 1984.)

Colonic and Extracolonic Involvement

Diffuse Intestinal Hemangiomatosis

This condition is characterized by numerous, as many as 50 to 100, lesions involving the stomach, small bowel, and colon.[29] Bleeding or anemia generally leads to the diagnosis in childhood. Hemangiomas of the skin or soft tissues of the head and neck are frequently present. Continuous slow, but pernicious, bleeding requiring transfusions or intussusception led by one of the lesions may necessitate surgical intervention. The diagnosis may be made by endoscopy and barium studies; angiographic findings can be normal despite numerous lesions. The hemangiomas are similar in appearance to solitary lesions and are generally cavernous, although some have the histologic appearance of hemangioendotheliomas (benign lesions in children). At surgery, all identifiable lesions should be excised either through enterotomies or by limited bowel resections. Transillumination and compression of the bowel wall are helpful in finding small lesions. When they are multiple, the colon can be opened along a taenia and then intussuscepted on itself. Each hemangioma can be ligated with a surgical clip or polyglycolic acid sutures. Unfortunately, repeated operations may be necessary to control blood loss.

Universal (miliary) hemangiomatosis is usually fatal in infancy. It is, fortunately, a rare condition in which there are hundreds of hemangiomas involving the skin, brain, lungs, and abdominal viscera. Death results from congestive heart failure secondary to large arteriovenous shunts, or it may be due to local effects of the lesions. Colonic lesions are rarely of significance.

Blue Rubber Bleb Nevus Syndrome (Cutaneous and Intestinal Cavernous Hemangiomas)

In 1860, Gascoyen reported an association between cutaneous vascular nevi, intestinal lesions, and GI bleeding. Bean[30] later coined the name blue rubber bleb syndrome and distinguished it from other cutaneous vascular lesions. A familial history is infrequent, although a few cases of transmission in an autosomal dominant pattern have been reported.

The lesions in this syndrome are distinctive. They vary in size from 0.1 to 5.0 cm, are blue and raised, and have a wrinkled surface. Characteristically, the blood contained in the lesion can be emptied by direct pressure such that a wrinkled sac remains. The hemangiomas may be single or innumerable and are usually found on the trunk, extremities, and face, but not on mucous membranes. They increase in size and number with advancing age and do not undergo malignant transformation.[31] They may be present in any portion of the GI tract but are most common in the small bowel. In the colon, they occur more commonly on the left side and in the rectum. They are infrequently seen by barium opacification or angiographic studies and are detected best by endoscopy if they are proximal to the ligament of Treitz or in the colon. Microscopically, they are cavernous hemangiomas composed of clusters of dilated capillary spaces lined by cuboidal or flattened endothelium with connective tissue stroma. In the bowel, they are located in the submucosa. Resection of the involved segment of bowel is recommended for recurrent hemorrhage, although endoscopic laser coagulation is an attractive therapeutic option.

Less Common Vascular Lesions

Congenital Arteriovenous Malformations

Congenital arteriovenous malformations are embryonic growth defects and are considered to be developmental anomalies. Although they are found mainly in the extremities, they occur anywhere in the vascular tree. In the colon, they may be small, similar to ectasias, or they may involve a long segment of bowel. The more extensive lesions are most often seen in the rectum and sigmoid.

Histologically, arteriovenous malformations are persistent communications between arteries and veins located primarily in the submucosa. Characteristically, there is arterialization of the veins: tortuosity, dilation, and thick walls with smooth muscle hypertrophy and intimal thickening and sclerosis (Fig. 145–8). In longstanding arteriovenous malformations, the arteries are dilated with atrophic and sclerotic degeneration.

Angiography is the primary means of diagnosis. Early-filling veins in small lesions and extensive dilation of arteries and veins in large lesions (Fig. 145–9) are pathognomonic of arteriovenous malformations. Patients with significant bleeding should undergo resection of the involved segment of colon.

Colonic Varices

Varices of the colon are very rare but may be a cause of hematochezia or melena. In most cases, the varices are located in the rectosigmoid; they are found progressively less often in the more proximal portion of the colon. The most common cause of colonic varices is portal hypertension, with congenital anomalies, mesenteric venous obstruction, congestive heart failure, and pancreatitis accounting for the other causes.[32] Why varices form so rarely in the colon and why they bleed are unclear. Varices are easily diagnosed by proctosigmoidoscopy, colonoscopy, or angiography and may even be seen on conventional barium studies of the colon. Therapy consists of segmental colonic resection, portocaval shunting, or local ligation or sclerosis.

Telangiectasia

Telangiectases are small vascular lesions found on cutaneous, mucocutaneous, and mucosal surfaces throughout the body. Grossly and at endoscopy, they are millet seed sized and appear as cherry-red spots, vascular spiders, smooth hillocks, or lesions resembling ectasias. They may be hereditary or acquired and have been

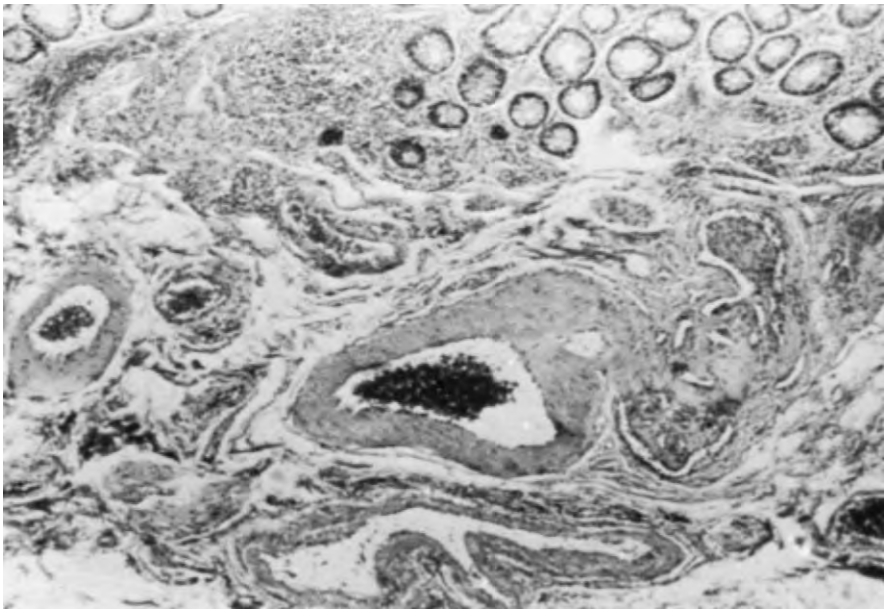

Figure 145–8. Arteriovenous malformation characterized by tortuous veins with sclerotic intima, hypertrophied smooth muscle, and thick-walled sclerotic arteries (hematoxylin-eosin stain, ×100). (From Boley SJ, Brandt LJ, Mitsudo S: Vascular lesions of the colon. Adv Intern Med 29:301, 1984.)

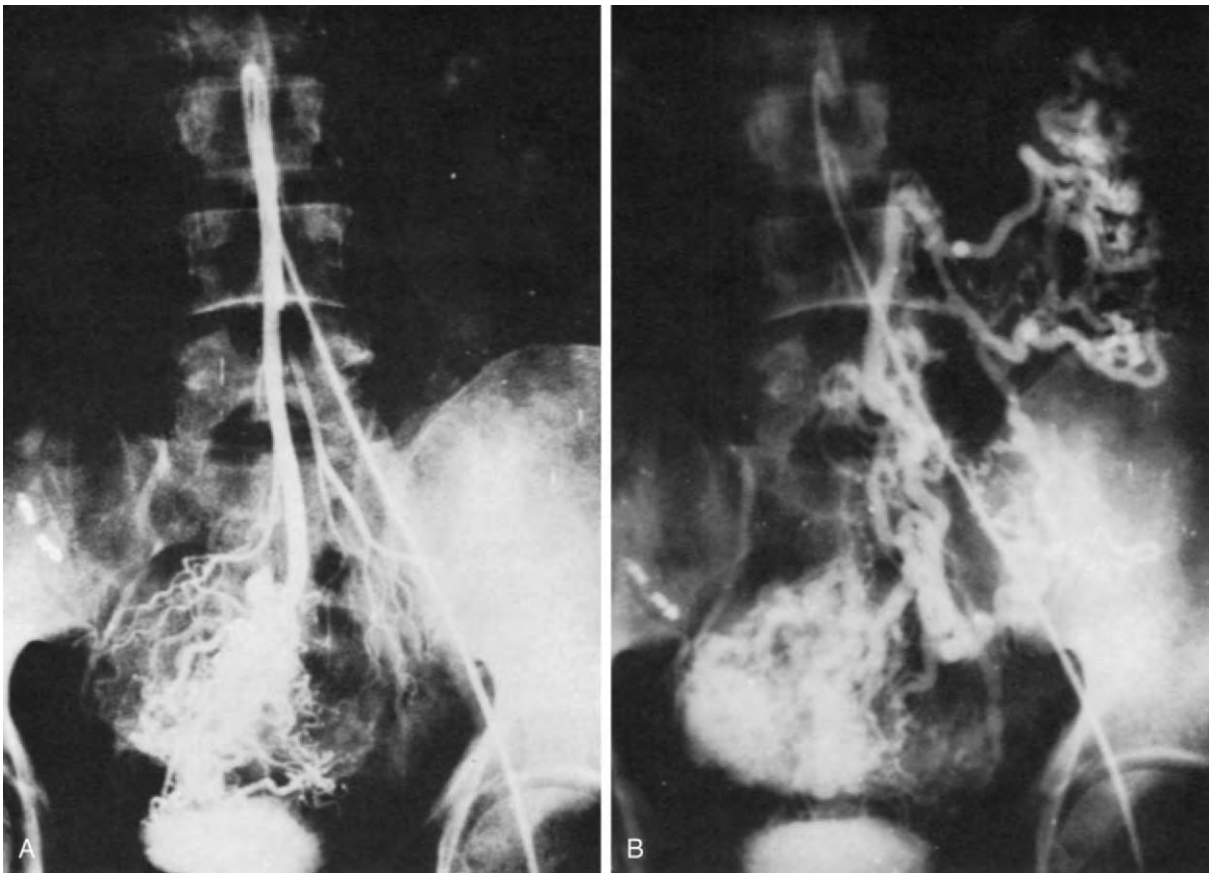

Figure 145–9. **A,** Arterial phase of an inferior mesenteric arteriogram from a patient with a congenital arteriovenous malformation showing multiple dilated arteries going to a large segment of the rectosigmoid. **B,** Venous phase of the same arteriogram showing dilated tortuous vessels to the same segment, as well as to other more proximal areas. (From Boley SJ, Brandt LJ, Mitsudo S: Vascular lesions of the colon. Adv Intern Med 29:301, 1984.)

described in association with many disorders (e.g., chronic renal failure, progressive systemic sclerosis, von Willebrand's disease, CREST syndrome [calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia])[33-35] but are best known as part of Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia.

Hereditary hemorrhagic telangiectasia is a familial disorder characterized by telangiectases of the skin and mucous membranes and recurrent GI bleeding. Lesions are frequently noticed in the first few years of life, and recurrent epistaxis in childhood is characteristic of the disease. By the age of 10 years, about half of patients will have had some bleeding, but severe hemorrhage is unusual before 30 years of age and has a peak incidence from 50 to 60 years. In almost all patients, bleeding is manifested as melena, whereas epistaxis and hematemesis are less frequent. Bleeding may be quite severe, and patients commonly receive more than 50 transfusions in a lifetime. A family history of disease has been reported in 80% of patients with the disorder, but less commonly in those with bleeding, especially when the bleeding occurs later in life.

Telangiectases are almost always present on the lips, oral and nasopharyngeal membranes, tongue, or hand, and lack of involvement of these sites casts suspicion on the diagnosis. Lesions on the lips are more common in patients with GI bleeding than in those without. Telangiectases occur in the colon but are far more common in the stomach and small bowel. UGI lesions are more apt to cause significant bleeding.

Telangiectases are not demonstrable on barium enema examination but are easily seen on endoscopy. Occasionally, in the presence of severe anemia and blood loss, they transiently become less visible, but with blood replacement they again increase in prominence. Findings on angiography are usually normal, but it may demonstrate arteriovenous communications or small clusters of abnormal vessels.

Pathologically, the major changes involve the capillaries and venules, but arterioles may also be affected. The lesions consist of irregular, ectatic, tortuous, blood-filled spaces lined by a delicate single layer of endothelial cells and supported by a fine layer of fibrous connective tissue. No elastic lamina or muscular tissue is present in these vessels. The arterioles show some intimal proliferation and often have thrombi in them, suggestive of vascular stasis, but the most conspicuous findings are in the venules. In contrast to those in vascular ectasia, these venules are abnormally thick and have very prominent, well-developed longitudinal muscles. Apparently, these abnormal venules play a major role in regulating blood flow to the telangiectases.

Many treatments have been recommended, including oral and parenteral estrogen therapy and multiple resections of involved bowel. Endoscopic electrosurgery or laser coagulation appears to be most promising and may be performed during active bleeding or before any bleeding episodes. Although endoscopic therapy has diminished the need for resecting bowel in some cases, long-term follow-up studies are needed to evaluate the ultimate course of patients so treated.

Klippel-Trénaunay-Weber Syndrome

Originally described by Klippel and Trénaunay in 1900, this syndrome is characterized by unilateral congenital lesions of the lower extremities, including (1) cutaneous hemangiomas, usually of the flat, diffuse capillary type; (2) varicose veins dating from childhood; and (3) soft tissue hypertrophy and bony elongation. Involvement of the colon is uncommon and poorly defined, but when LGI involvement does occur, the rectum or rectosigmoid is generally affected.[36]

The cause of the syndrome has been variably ascribed to congenital arteriovenous fistulas or to aplasia, hypoplasia, dysplasia, atresia, or obstruction of the deep venous system. Rectal lesions usually cause bleeding during childhood and have been described by some as being cavernous hemangiomas or varicosities of the rectal veins.[37] Computed tomography scanning and ultrasonography were found helpful in determining the extent of colonic and other visceral disease.[38]

Major rectal or bladder bleeding has occurred in a few children, with one reported death. Ligation of bleeding hemorrhoids or sclerosis of rectal veins is often temporarily effective, but proctectomy may be necessary in some patients.

COLONIC ISCHEMIA

Before 1950, colonic ischemia (CI) was considered synonymous with colonic infarction or gangrene. Since that time, CI has become recognized as one of the more common disorders of the colon in elderly persons and the most common form of ischemic injury of the GI tract. CI is used to describe a general pathophysiologic process that leads to varied clinical outcomes. The spectrum includes (1) reversible ischemic colopathy (submucosal or intramucosal hemorrhage), (2) reversible or transient ischemic colitis, (3) chronic ischemic ulcerative colitis, (4) ischemic colonic stricture, (5) colonic gangrene, and (6) fulminant universal colitis (Fig. 145–10).

Colonic Circulation

The colon is normally protected from ischemia by its abundant collateral circulation. Communications between the CA, SMA, IMA, and iliac artery beds are numerous. Collateral flow around small arterial branches is made possible by the multiple arcades within the colonic mesentery, and SMA or IMA occlusions are bypassed via the arch of Riolan, the central anastomotic artery, and the marginal artery of Drummond. In addition, within the bowel wall there is a network of communicating submucosal vessels that can maintain the viability of short segments of the colon when the extramural arterial supply has been compromised.

The colon has inherently lower blood flow than the small intestine does and is therefore more sensitive to injury during acute reductions in blood flow. Moreover, experimental studies have shown that functional motor activity of the colon is accompanied by decreased blood flow. In contrast, blood flow to the small intestine

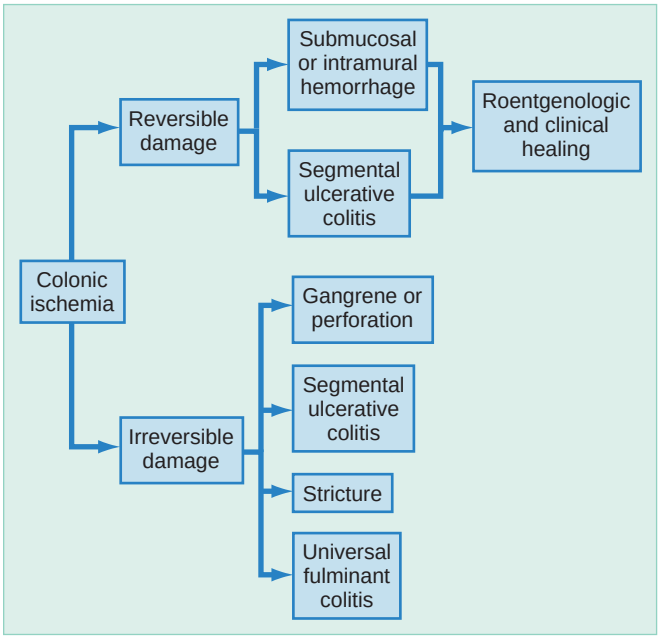

Figure 145–10. End results of colonic ischemia.

increases markedly during periods of increased peristalsis and digestion. In addition, the pronounced effect of straining on systemic arterial and venous pressure in constipated versus normal patients provides indirect evidence that constipation may accentuate the adverse circulatory effects of defecation. Geber[39] postulated that "the combination of normally low blood flow and decreased blood flow during functional activity would seem to make the colon (1) rather unique among all areas of the body where increased motor activity is usually accompanied by an increased blood flow and (2) more susceptible to pathology." Other factors that decrease colonic blood flow include changes in the environment, digestion, and emotionally stressful situations. Experiments evaluating the hypothalamic influence on GI blood flow in the awake cat model suggest that "of the entire GI tract, the colon blood flow is most affected by autonomic stimulation."[40]

Pathophysiology of Colonic Ischemia

What ultimately triggers the episode of CI remains conjectural in most instances. Whether it is increased demand by colonic tissue superimposed on already marginal blood flow or whether the flow itself is acutely diminished has not been determined. However, because CI is a disease of the elderly, an association with degenerative changes of the mesenteric vasculature has been postulated. Histologically, narrowing of small arteries, arterioles, and veins is evident in colons resected for nonocclusive CI. Autopsy studies have also shown abnormal musculature in the wall of the superior rectal artery in the elderly population, which confirms an age-related alteration in the mesenteric vasculature.[41] In addition, postmortem angiographic studies have revealed an age-related tortuosity of the longer colonic arteries that may cause increased resistance to colonic blood flow, thus predisposing the patient to ischemia.[42]

Despite this suggestive evidence for a vascular or autonomic cause of CI, most cases have no identifiable cause. These spontaneous episodes are thought to be the result of local nonocclusive ischemia in association with small vessel disease. Colonic blood flow can be further compromised by alterations in systemic perfusion. The inadequate systemic perfusion accompanying congestive heart failure, digitalis toxicity, or arrhythmias is a rare cause of CI. Many other conditions, spontaneous or iatrogenic, have been associated with CI, although a direct cause-and-effect relationship has not been established (Box 145–2). Two specific and well-recognized exceptions include the development of CI proximal to a potentially obstructing stricture—carcinoma or diverticulitis—and after aortic reconstruction.

Box 145–2 Causes of Colonic Ischemia

- Inferior mesenteric artery thrombosis
- Arterial embolus
- Cholesterol emboli
- Cardiac failure or arrhythmias
- Shock
- Digitalis toxicity
- Volvulus
- Periarteritis nodosa
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Necrotizing arteritis
- Thromboangiitis obliterans
- Strangulated hernia
- Drug induced (e.g., oral contraceptives, cocaine)
- Polycythemia vera
- Parasitic infestation
- Allergy
- Trauma—blunt and penetrating
- Ruptured ectopic pregnancy
- Iatrogenic causes
  - Aneurysmectomy
  - Aortoiliac reconstruction
  - Gynecologic operations
  - Exchange transfusions
  - Colon bypass
  - Lumbar aortography
  - Colectomy with inferior mesenteric artery ligation

Demographics

The diagnosis of CI is usually made after the period of ischemia has passed and blood flow to the affected segment of colon has returned to normal. Many cases of transient or reversible ischemia are probably missed because the condition resolves before medical attention is sought or because a barium enema or colonoscopy is not performed early in the course of the disease. In addition, many cases of CI are misdiagnosed as infectious colitis or inflammatory bowel disease. Thus, to date, no study has provided an accurate determination of the incidence of CI.

Several retrospective reviews of older clinical material have revealed many cases of CI that were either undiagnosed or misdiagnosed because the various clinical manifestations of this disorder were not recognized. Using the modern clinical, roentgenologic, and pathologic criteria for the diagnosis of CI, two retrospective reviews of 154 patients in whom colitis was identified after the age of 50 revealed that approximately 75% of the patients had probable or definite CI.[43,44] In half of these patients, inflammatory bowel disease had been erroneously diagnosed.

At Montefiore Medical Center, approximately 50 cases of GI ischemia are seen each year, and of these cases, 50% to 60% are CI. Acute mesenteric ischemia accounts for an additional 30% to 40% of cases, and focal segmental ischemia or chronic mesenteric ischemia makes up the remainder.[45]

In our experience with more than 300 cases of CI, there was no significant sex predilection. Approximately 90% of patients are older than 60 years and have other evidence of systemic atherosclerotic disease. This prevalence has been confirmed in other reports.

CI affecting young individuals has been recognized more frequently in case reports or small series. Causes in the younger population include vasculitis (especially systemic lupus erythematosus),[46] medications (estrogens,[47,48] danazol,[49] vasopressin,[50] gold,[51] psychotropic drugs[52]), sickle cell anemia,[53] coagulopathies (thrombotic thrombocytopenic purpura,[54] protein C and protein S deficiency,[55] antithrombin III deficiency[56]), competitive long-distance running,[57] and cocaine abuse.[58]

Clinical Manifestations

Symptoms

CI is usually manifested as a sudden onset of mild, crampy abdominal pain, usually localized to the lower left quadrant. Less commonly the pain is severe, or conversely, in other patients the description of pain can be elicited only retrospectively, if at all. An urgent desire to defecate frequently accompanies the pain and is followed, within 24 hours, by the passage of either bright red or maroon blood in the stool. The bleeding is not vigorous, and blood loss requiring transfusion is so rare that it should suggest an alternative diagnosis. Physical examination may reveal mild to severe abdominal tenderness elicited in the location of the involved segment of bowel.

Distribution of Colonic Ischemia

Any part of the bowel may be affected, but the splenic flexure and descending and sigmoid colon are the most common sites (Fig. 145–11). Although specific causes, when identified, tend to affect defined areas of the colon, no prognostic implications can be derived from the distribution of the disease. Nonocclusive ischemic injuries generally involve watershed areas of the colon—the splenic flexure and the junction of the sigmoid and rectum—whereas ligation of the IMA produces changes in the sigmoid. Similarly, the length of bowel affected varies with the cause. For example, atheromatous emboli

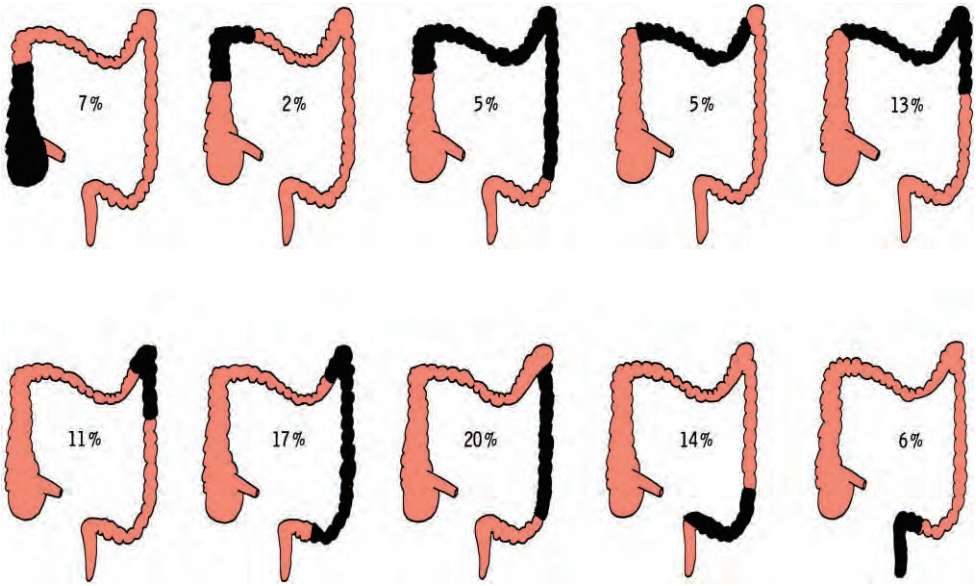

Figure 145–11. Distribution and length of involvement in 250 cases of colonic ischemia. More frequent involvement of the left half of the colon is apparent.

result in short segment changes, and nonocclusive injuries usually involve much longer portions of the colon. Depending on the severity and duration of the ischemic insult, fever or leukocytosis may develop. There is generally no acidemia, hypotension, or septic shock. In more severe ischemia, signs of peritonitis may develop.

Natural History of Colonic Ischemia

Despite similarities in the initial manifestation of most episodes of CI, the outcome cannot be predicted at its onset unless the initial physical findings indicate an unequivocal intra-abdominal catastrophe. The ultimate course of an ischemic insult depends on many factors, including (1) the cause (i.e., occlusive or nonocclusive), (2) the caliber of an occluded vessel, (3) the duration and degree of ischemia, (4) the rapidity of onset of the ischemia, (5) the condition of the collateral circulation, (6) the metabolic requirements of the affected bowel, (7) the presence and virulence of the bowel flora, and (8) the presence of associated conditions, such as colonic distention.

Most commonly, symptoms subside within 24 to 48 hours, and clinical, roentgenographic, and endoscopic evidence of healing is seen within 2 weeks (Fig. 145–12). More severe, but still reversible ischemic damage may take 1 to 6 months to resolve. The majority of patients with reversible disease exhibit only colonic hemorrhage or edema, whereas transient colitis develops in about a third. At times, with more severe yet reversible ischemia, the entire mucosa may slough as a tube. In half of patients with CI, the ischemic damage is too severe to heal, and irreversible disease ultimately develops. In approximately two thirds of these patients, CI follows a more protracted course and develops into either chronic segmental ulcerative colitis or ischemic stricture. In the remaining third, signs and symptoms of an intra-abdominal catastrophe develop, such as gangrene with or without perforation, and become obvious within hours of the initial manifestation.

Patients in whom CI develops as a complication of shock, congestive heart failure, myocardial infarction, or severe dehydration have a particularly poor prognosis. These are typically elderly patients taking digitalis preparations, which may act as potent splanchnic vasoconstrictors and exacerbate the already compromised colonic perfusion. In one series, these factors were present in a fourth of patients with CI, and 12 of 13 patients who were initially seen in shock died.[59]

Because the outcome of an episode of CI cannot usually be predicted, patients must be examined serially for evidence of peritonitis, rising temperature, elevation of the white blood cell count, or worsening symptoms. In patients with diarrhea or bleeding that persists beyond the first 10 to 14 days, perforation or, less frequently, a protein wasting enteropathy generally develops. Strictures may develop over a period of weeks to months and may be asymptomatic or produce progressive bowel obstruction. Some of the asymptomatic strictures resolve spontaneously over a span of many months.

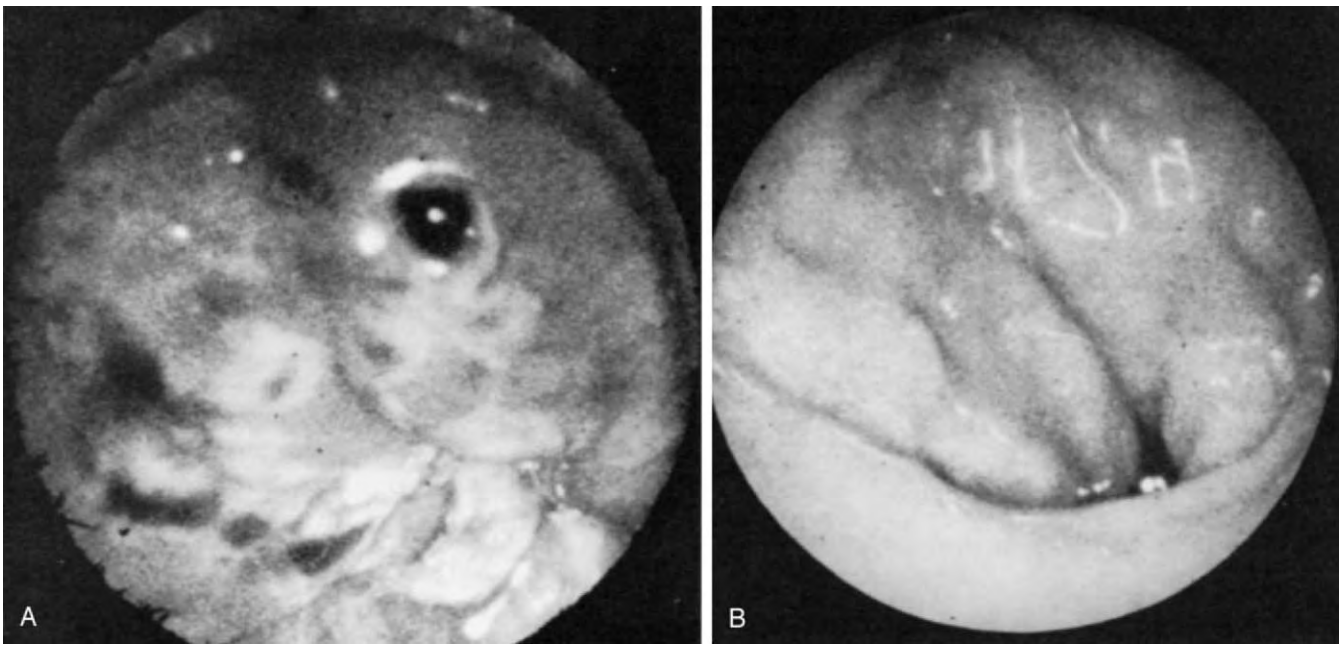

Figure 145–12. **A,** Endoscopic appearance of the colon during the initial evaluation of a patient with colonic ischemia. The dark nodular mass is a submucosal hemorrhage below which are ulcerations where other areas of hemorrhage have broken down. **B,** A follow-up study 3 weeks later demonstrates complete healing of the colonic mucosa. (From Littman L, Boley SJ, Schwartz S: Sigmoidoscopic diagnosis of reversible vascular occlusion of the colon. Dis Colon Rectum 6:142, 1963, with permission.)

Diagnosis

Early and appropriate diagnosis of CI depends on serial radiographic or colonoscopic evaluation, or both, of the colon, as well as repeated clinical evaluations of the patient. More severe cases of CI may be difficult to distinguish from acute mesenteric ischemia, whereas patients with less severe cases may have findings similar to those with acute or chronic idiopathic ulcerative colitis, Crohn's colitis, infectious colitis, or diverticulitis. A combination of radiographic, colonoscopic, and clinical findings may be necessary to establish the diagnosis of CI.

In a patient with suspected CI, if abdominal radiographs are nonspecific, sigmoidoscopy is unrevealing, and there are no signs of peritonitis, a gentle barium enema or colonoscopy should be performed in the unprepared bowel within 48 hours of the onset of symptoms. The most characteristic finding on barium enema is "thumbprinting" or "pseudotumors" (Fig. 145–13) and on colonoscopy is hemorrhagic nodules or bullae. Hemorrhagic nodules seen at colonoscopy represent bleeding into the submucosa and are equivalent to the "thumbprints" seen on barium enema. Segmental distribution of these findings, with or without ulceration, is very suggestive of CI, but the diagnosis of CI cannot be made conclusively on the basis of a single study. In fact, persistence of the thumbprints suggests a diagnosis other than CI, such as lymphoma or amyloidosis.

Repeated radiographic or endoscopic examination of the colon together with observation of the clinical course is necessary to confirm the diagnosis. Segmental colitis associated with a tumor or other potentially or partially obstructing lesions is also characteristic of ischemic disease. The radiographic findings of universal colonic involvement, loss of haustrations, or pseudopolyposis are more typical of chronic idiopathic ulcerative colitis, whereas the presence of skip lesions, linear ulcerations, or fistulas suggests Crohn's colitis.

It is imperative to perform the diagnostic study early in the course of the disease because the thumbprinting disappears within days as the submucosal hemorrhages are either resorbed or evacuated into the colon when the overlying mucosa ulcerates and sloughs. Barium enema or colonoscopy performed 1 week after the initial study should reflect the evolution of the disease, either by return to normal or by replacement of the thumbprints with a segmental ulcerative colitis pattern.

If colonoscopy is chosen as the initial study, caution is indicated. Distention of the bowel with air to a pressure greater than 30 mm Hg diminishes colonic blood flow, shunts blood from the mucosa to the serosa, and causes a progressive decrease in the arteriovenous oxygen difference.[60] If intraluminal pressure exceeds 30 mm Hg during routine endoscopic examination of the colon,[61] colonoscopy can potentially induce or exacerbate CI. This risk can be minimized by insufflation with carbon dioxide, which increases colonic blood flow at similar pressures. Furthermore, carbon dioxide is rapidly absorbed from the colon, thus decreasing the duration of distention and elevation of intraluminal pressure.[62]

Biopsies of nodules or bullae identified endoscopically early in the course of CI reveal submucosal hemorrhage, whereas biopsies of the surrounding mucosa usually show nonspecific inflammatory changes.[63] Histologic evidence of mucosal infarction, though rare, is pathognomonic for ischemia. Angiography seldom shows significant occlusions or other abnormalities and is not indicated in patients suspected of having CI. Computed tomography may show thickening of the bowel wall, but this finding is not specific for CI.

When the clinical findings do not allow a clear distinction to be made between CI and acute mesenteric ischemia and plain films of the abdomen do not show the characteristic thumbprinting pattern of CI, an "air enema" performed by gently insufflating air into the colon under fluoroscopic observation is obtained. The submucosal edema and hemorrhages that produce the thumbprinting pattern of CI can be accentuated and identified in this manner.

Once the provisional diagnosis of CI is made, a gentle barium enema is performed to determine the site and distribution of the disease, as well as to determine any associated lesion that predisposes to the episode of ischemia (i.e., carcinoma, stricture, or diverticulitis). If, however, thumbprinting is not observed and the air enema does not suggest the diagnosis of CI, a selective mesenteric angiogram is immediately performed to exclude the diagnosis of acute mesenteric ischemia. Because acute mesenteric ischemia progresses rapidly to an irreversible outcome and because optimal diagnosis and treatment of this condition require angiography, the diagnosis of acute mesenteric ischemia must be established or excluded before a barium study. Residual barium from a contrast study of the colon may obscure the mesenteric vessels and therefore preclude adequate angiographic examination and intervention.

Management of Colonic Ischemia

General Principles

Once the diagnosis of CI has been established and the physical examination does not suggest intestinal gangrene or perforation, the patient is treated expectantly. Parenteral fluids are administered, and the bowel is placed at rest. Broad-spectrum antibiotics that provide coverage of *Enterococcus* and anaerobic organisms are administered. Antibiotic therapy has been shown to reduce the length of bowel damaged by ischemia, although it will not prevent colonic infarction. Cardiac function is optimized to ensure adequate systemic perfusion. Medications that cause mesenteric vasoconstriction (e.g., digitalis and vasopressors) should be withdrawn if possible. Urine output is monitored and maintained with parenteral isotonic fluids. If the colon appears distended, either clinically or radiographically, it can be decompressed with a rectal tube, with or without gentle saline irrigation. Contrary to their efficacy in ulcerative colitis, parenteral corticosteroids are contraindicated because they increase the possibility of

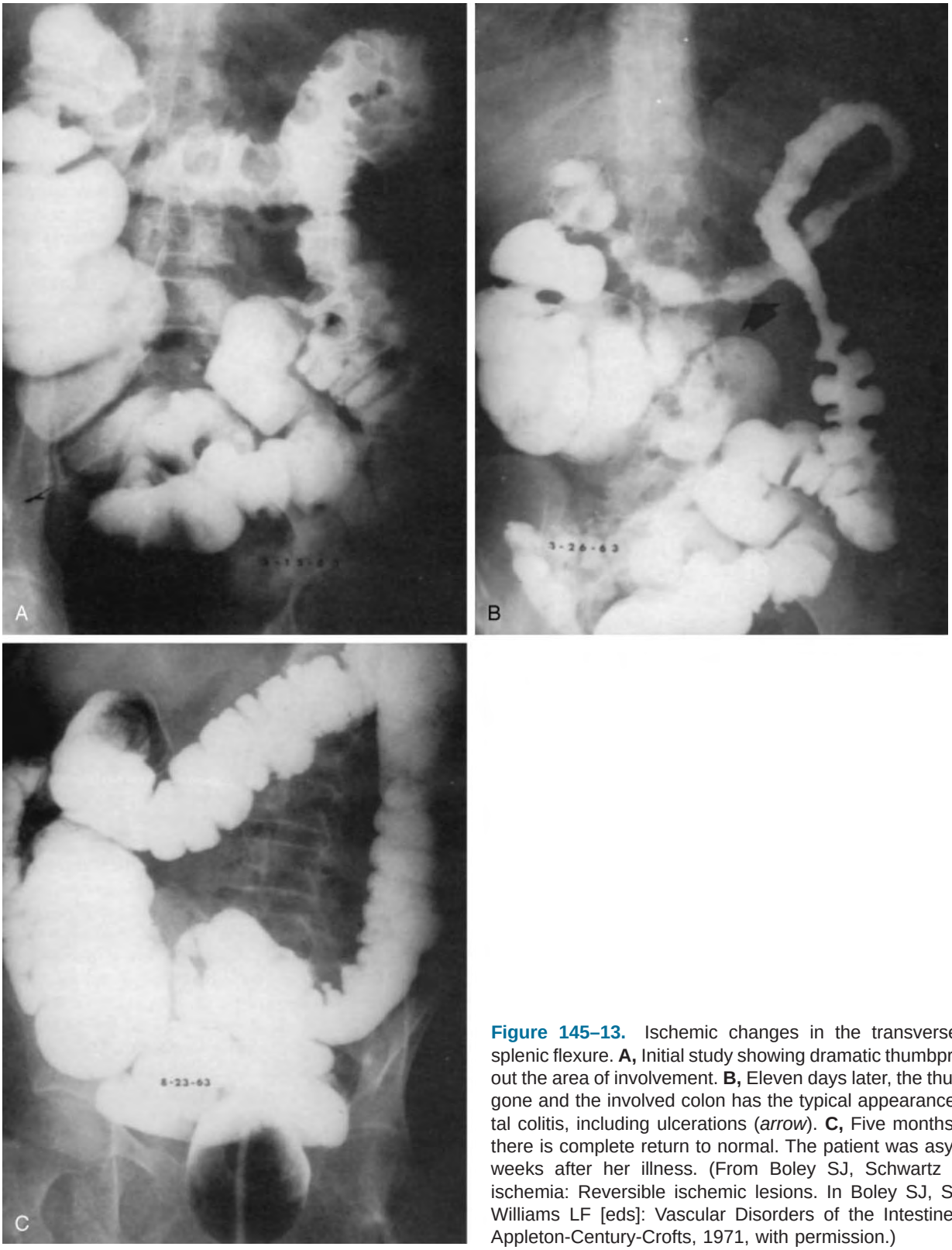

Figure 145–13. Ischemic changes in the transverse colon and splenic flexure. **A,** Initial study showing dramatic thumbprints throughout the area of involvement. **B,** Eleven days later, the thumbprints are gone and the involved colon has the typical appearance of segmental colitis, including ulcerations (*arrow*). **C,** Five months after onset, there is complete return to normal. The patient was asymptomatic 3 weeks after her illness. (From Boley SJ, Schwartz SS: Colonic ischemia: Reversible ischemic lesions. In Boley SJ, Schwartz SS, Williams LF [eds]: Vascular Disorders of the Intestine. New York, Appleton-Century-Crofts, 1971, with permission.)

perforation and secondary infection. Appropriate management of patients seen during or soon after the ischemic episode requires serial radiographic or endoscopic evaluation of the colon and continued monitoring of the patient.

Determination of the white blood cell count, hemoglobin, and hematocrit should be repeated frequently during the acute episode. Though rarely needed, blood products should be administered according to the patient's requirements. Serum potassium and magnesium levels must be monitored because the levels of these electrolytes may be disturbed by the associated diarrhea and tissue necrosis. Systemic levels of lactate dehydrogenase, creatine phosphokinase, aspartate aminotransferase, and alanine aminotransferase may reflect the degree of bowel necrosis, but these serum markers are neither sensitive nor specific for CI. Patients with significant diarrhea are started on parenteral nutrition early. Narcotics should be withheld until it is clear that an intra-abdominal catastrophe is not present and that the patient is clinically improving. Cathartics are contraindicated. No attempt should be made to prepare the bowel for surgery in the acute phase because such preparation may precipitate a perforation.

Increasing abdominal tenderness, guarding, rebound tenderness, rising temperature, and paralytic ileus during the period of observation suggest colonic infarction. These signs, though not distinct indicators of transmural CI or infarction, dictate the need for expedient laparotomy for resection of the affected segment of colon. At laparotomy, the serosal appearance of infarcted colon ranges from wet tissue paper to mottled, thickened, aperistaltic bowel. The resected specimen should be opened in the operating suite and examined for mucosal injury, and if the margins are involved, additional colon should be removed until the margins appear grossly normal.

Management of Reversible Lesions

In the mildest cases of CI, in which the signs and symptoms of illness disappear within 24 to 48 hours, submucosal and intramural hemorrhages are resorbed, and there is complete clinical and radiographic resolution within 1 to 2 weeks (see Fig. 145–13), no further therapy is indicated. More severe ischemic insults result in necrosis of the overlying mucosa with ulceration and inflammation and the subsequent development of segmental ulcerative colitis. Various amounts of mucosa may slough, which may ultimately heal over a period of several months. Patients with such protracted healing may be clinically asymptomatic, even in the presence of persistent radiographic or endoscopic evidence of disease. These asymptomatic patients are placed on a high-residue diet, and frequent follow-up evaluations are performed to confirm complete healing or the development of a stricture or persistent colitis. Recurrent episodes of sepsis in asymptomatic patients with unhealed areas of segmental colitis are generally caused by the diseased segment of bowel and are an indication for elective resection.

Management of Irreversible Lesions

Perforation usually develops in patients with persistent diarrhea, rectal bleeding, protein-losing enteropathy, or recurrent sepsis for more than 10 to 14 days. Hence, early resection is indicated to prevent this complication. A polyethylene glycol bowel preparation is administered along with oral and intravenous antibiotics before surgery. Again, enemas should not be used to prepare the bowel.

Despite a normal serosal appearance, there may be extensive mucosal injury, and the extent of resection should be guided by the distribution of disease as seen on preoperative studies rather than by the appearance of the serosal surface of the colon at the time of surgery. As in all resections for CI, the specimen must be opened at the time of surgery to ensure normal mucosa at the margins. If at the time of surgery the segmental ulcerative colitis is found to involve the rectum, a mucous fistula or Hartmann's procedure with an end colostomy should be performed. The mucous fistula can be fashioned through diseased bowel, and in some cases, this segment will heal sufficiently to allow subsequent restoration of bowel continuity. Local steroid enemas may be helpful in this setting; however, parenteral steroids are, again, contraindicated. Simultaneous proctocolectomy is rarely indicated except in the case of CI after abdominal aortic replacement.

In instances in which the patient has suffered a concurrent or recent myocardial infarction or if the patient has major medical contraindications to surgery, a trial of prolonged parenteral nutrition with concomitant intravenous antibiotic therapy may be considered as an alternative, albeit less optimal, method of management.

Management of Late Manifestations of Colonic Ischemia

CI may not be accompanied by clinical symptoms during the acute insult but may still produce chronic segmental ulcerative colitis. This form of CI may frequently be misdiagnosed if not seen during the acute episode. Barium enema studies may show a segmental colitis pattern, a stricture simulating a carcinoma, or even an area of pseudopolyposis (Fig. 145–14). The clinical course at this stage of disease is often indistinguishable from that of other causes of colitis or stenosis unless the patient has been observed from the time of the acute episode. Crypt abscesses and pseudopolyposis, generally considered histologically diagnostic of chronic idiopathic ulcerative colitis, can also be seen in ischemic colitis. Regardless, the de novo occurrence of a segmental area of colitis or stricture in an elderly patient should be considered to most likely be ischemic and be treated accordingly.

The natural history of noninfectious segmental colitis in the elderly is that of ischemic colitis; the involvement remains localized, resection is not followed by recurrence, and the response to steroid therapy is usually poor. Patients with chronic segmental ischemic colitis are initially managed symptomatically. Local steroid enemas may be helpful, but parenteral steroids should be avoided. In patients whose symptoms cannot be

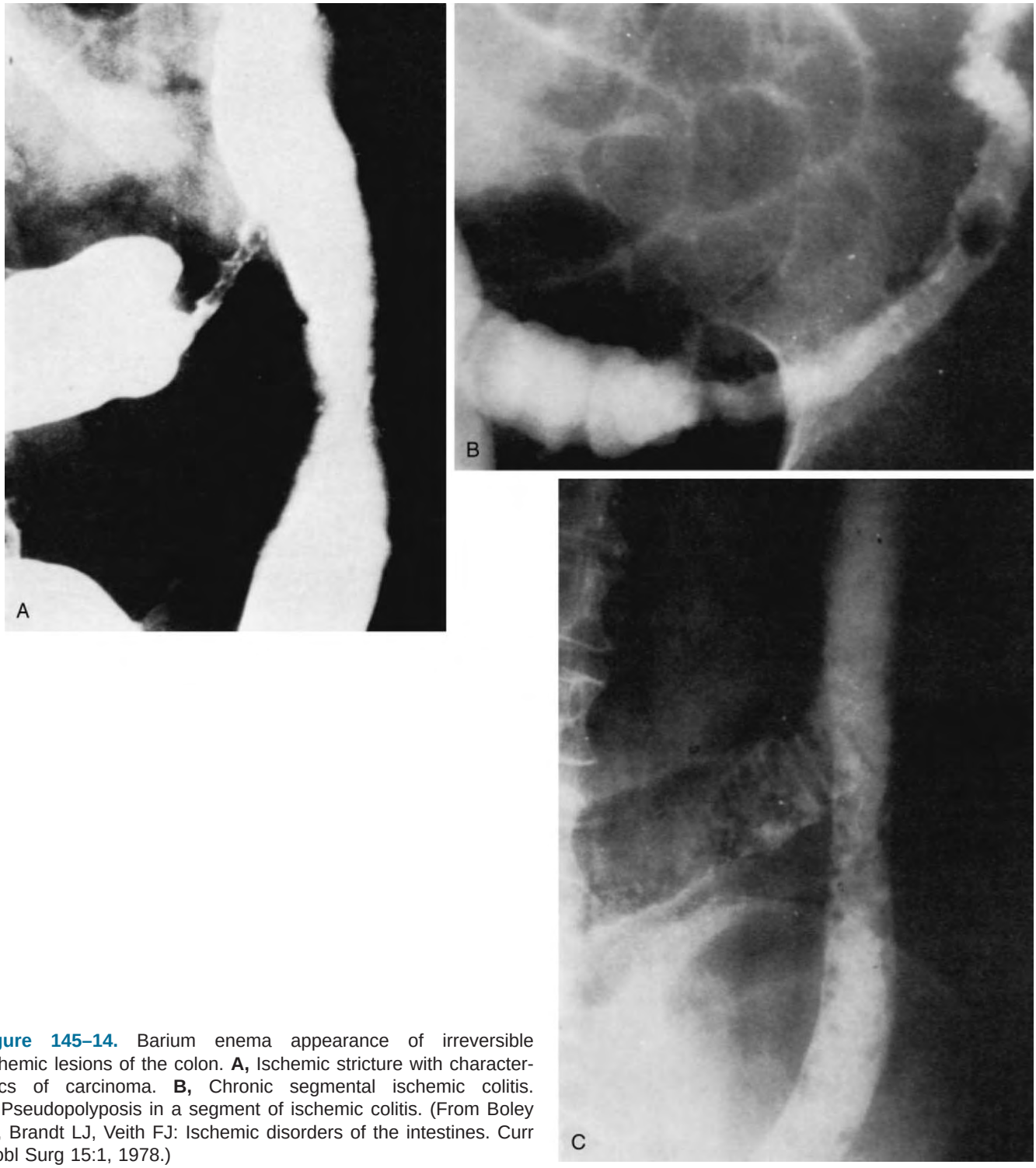

Figure 145–14. Barium enema appearance of irreversible ischemic lesions of the colon. **A,** Ischemic stricture with characteristics of carcinoma. **B,** Chronic segmental ischemic colitis. **C,** Pseudopolyposis in a segment of ischemic colitis. (From Boley SJ, Brandt LJ, Veith FJ: Ischemic disorders of the intestines. Curr Probl Surg 15:1, 1978.)

controlled by medication, segmental resection of the diseased bowel should be performed.

Management of Ischemic Strictures Stenosis or stricture of the colon may develop in patients with asymptomatic segmental ulcerative colitis (Fig. 145–15). Strictures that produce no symptoms should be observed, and some of them will return to normal over a 12- to 24-month period with no further therapy. If, however, symptoms of obstruction develop, segmental resection is required.

Management of Specific Clinical Problems

Colonic Ischemia Complicating Abdominal Aortic Surgery Mesenteric vascular reconstruction is not indicated in most cases of CI, but it may be required to

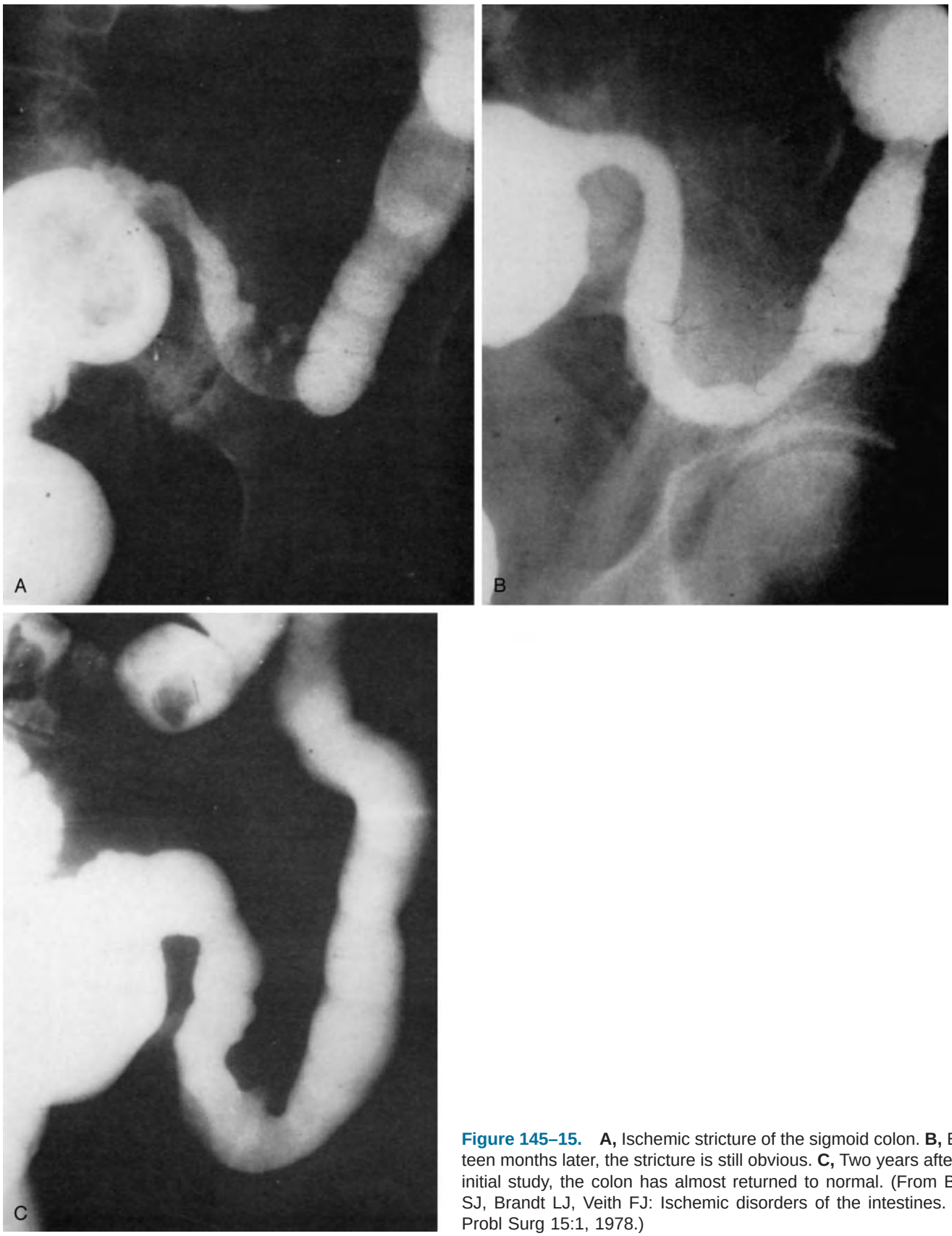

Figure 145–15. **A,** Ischemic stricture of the sigmoid colon. **B,** Eighteen months later, the stricture is still obvious. **C,** Two years after the initial study, the colon has almost returned to normal. (From Boley SJ, Brandt LJ, Veith FJ: Ischemic disorders of the intestines. Curr Probl Surg 15:1, 1978.)

prevent CI during and after aortic reconstruction. After elective aneurysmectomy, colonoscopic evidence of CI develops in 3% to 7% of patients.[64,65] The incidence of CI after repair of ruptured aortic aneurysms has been reported to be as high as 60%.[66] Although clinical evidence of this complication occurs in only 1% to 2% of patients, when it does occur, it is responsible for approximately 10% of the deaths that take place after aortic replacement.[67] Factors that contribute to the occurrence of postoperative CI include rupture of the aneurysm, hypotension, operative trauma to the colon, hypoxemia, arrhythmias, prolonged cross-clamp time, and improper management of the IMA during aneurysmectomy.

The most important aspect of management of CI after aortic surgery is its prevention. Collateral blood flow to the left colon after occlusion of the IMA comes from the SMA via the arch of Riolan ("the meandering artery") or the marginal artery of Drummond and from the internal iliac arteries via the middle and inferior hemorrhoidal arteries. If these collateral pathways are intact, postoperative CI can be minimized. Therefore, aortography and full mechanical and antibiotic bowel preparation are essential before aortic reconstruction. Aortography is advised to determine the patency of the CA, SMA, IMA, and internal iliac artery. The presence of a meandering artery does not, in and of itself, allow safe ligation of the IMA because blood flow in the meandering artery frequently originates from the IMA and reconstitutes an obstructed SMA. Ligation of the IMA in the latter circumstance can be catastrophic and result in infarction of the small and large bowel (Fig. 145–16). Ligation of the IMA is safe only when it has been confirmed angiographically that blood flows in the meandering artery from the SMA to the IMA. Reimplantation of the IMA and revascularization of the SMA are therefore required in instances in which the SMA is occluded or tightly stenosed and the IMA provides inflow to the meandering artery (Fig. 145–17).

Occlusion of both hypogastric arteries on the preoperative arteriogram indicates that rectal blood flow is dependent on collateral flow from the IMA or from the SMA via the meandering artery. In this circumstance, reconstitution of flow to one or both hypogastric arteries is desirable at the time of aneurysmectomy (Fig. 145–18).

At surgery, cross-clamp time should be minimized, and hypotension must be avoided. If a meandering artery is identified, it should be carefully preserved. Because the serosal appearance of the colon is not a reliable indicator of collateral blood flow, several methods have been suggested to determine the need for IMA reimplantation. Stump pressure greater than 40 mm Hg in the transected IMA or a mean IMA stump pressure–to–mean systemic blood pressure ratio of greater than 0.40 indicates adequate collateral circulation and can be reliably used to avoid IMA reimplantation.[68] The presence of Doppler ultrasound flow signals at the base of the mesentery and at the serosal surface of the colon with temporary occlusion of IMA inflow also suggests that the IMA can be ligated safely without reimplantation.

Tonometric determination of the intramural pH of the sigmoid colon has been used to identify inadequate colonic blood flow during aneurysmectomy.[69,70] A tonometric balloon is passed into the sigmoid colon through the anus before cross-clamping the aorta to enable one to evaluate the effect that occlusion and restoration of aortic flow have on colonic intramural pH. Intramural pH is a metabolic marker of tissue acidosis and will reflect any clinically significant ischemia, thus indicating the need for revascularization while the abdomen is open. An abnormal tonometric study of the sigmoid colon, loss of arterial pulsation, or decreased transcolonic oxygen saturation after aortic surgery is an indication for reimplantation of the IMA. When IMA reimplantation is deemed necessary, the IMA should be excised with a patch of aortic wall (Carrell patch), and this patch should be sutured into the side of the aortic prosthesis.

If it is occluded, the SMA can be revascularized by reimplantation into the graft wall or, alternatively, by creating a lateral extension of the prosthesis and performing an end-to-side anastomosis to the SMA. Liberal use of these adjunctive procedures has, in one prospective

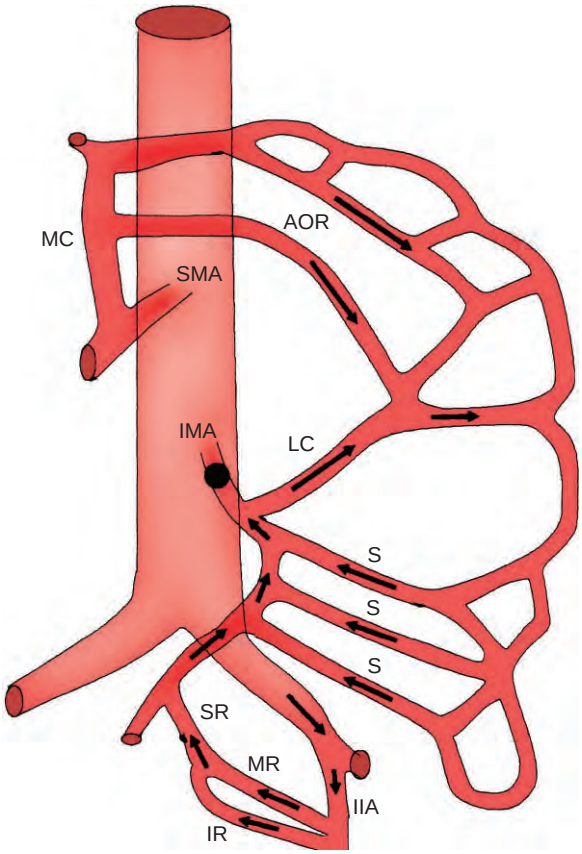

Figure 145–16. Collateral blood flow to the colon from the marginal artery, arch of Riolan, and internal iliac artery via the inferior and middle rectal arteries to an occluded IMA. AOR, arch of Riolan; IIA, internal iliac artery; IMA, inferior mesenteric artery; IR, inferior rectal artery; LC, left colic artery; MC, middle colic artery; MR, middle rectal artery; S, sigmoid arteries; SMA, superior mesenteric artery; SR, superior rectal artery.

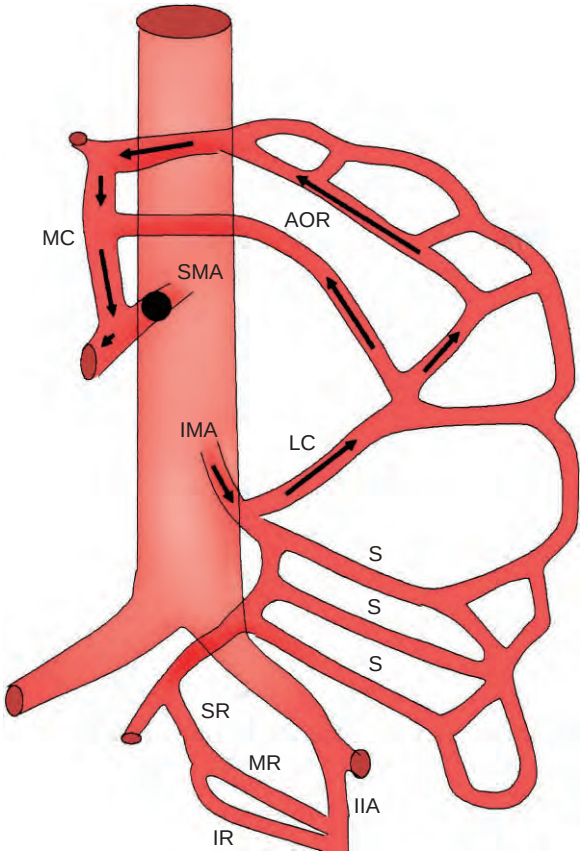

Figure 145–17. Collateral blood flow from the IMA via the marginal artery and arch of Riolan to an occluded SMA. AOR, arch of Riolan; IIA, internal iliac artery; IMA, inferior mesenteric artery; IR, inferior rectal artery; LC, left colic artery; MC, middle colic artery; MR, middle rectal artery; S, sigmoid arteries; SMA, superior mesenteric artery; SR, superior rectal artery.

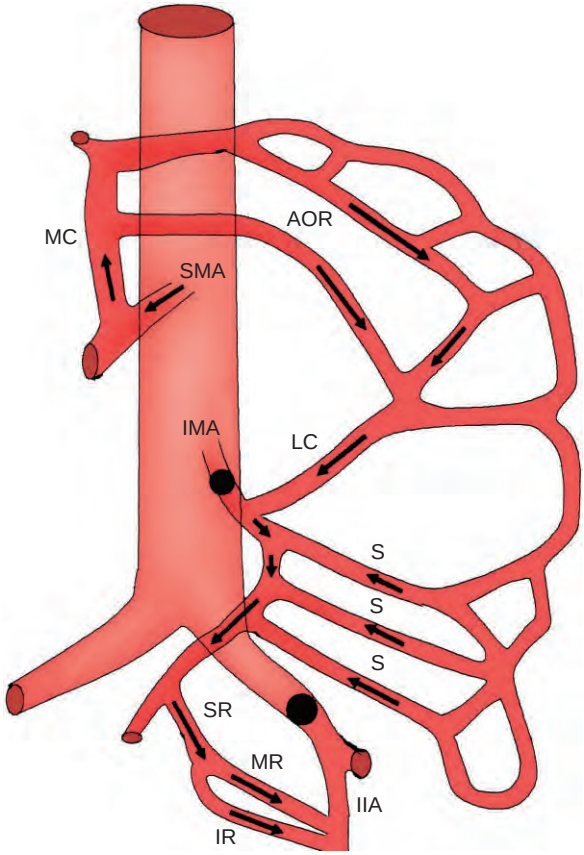

Figure 145–18. The entire rectal blood flow is dependent on collateral flow after occlusion of both internal iliac arteries. In this figure, the IMA is also occluded, so rectal blood flow is dependent on collateral flow from the SMA via the arch of Riolan and the marginal artery and then via the superior rectal vessel to the middle and inferior rectal arteries. AOR, arch of Riolan; IIA, internal iliac artery; IMA, inferior mesenteric artery; IR, inferior rectal artery; LC, left colic artery; MC, middle colic artery; MR, middle rectal artery; S, sigmoid arteries; SMA, superior mesenteric artery; SR, superior rectal artery.

study, both substantially reduced the incidence of CI and eliminated it as a cause of death after aortic surgery.

The difficulty in accurately assessing CI after surgery and the significant mortality rates associated with its occurrence mandate that postoperative colonoscopy be performed in high-risk patients. Patients at high risk for the development of postoperative CI after aortic reconstruction are those with ruptured abdominal aortic aneurysms, prolonged cross-clamping time, a patent IMA on preoperative aortography, nonpulsatile flow in the hypogastric arteries at surgery, and postoperative diarrhea. In these cases, colonoscopy is routinely performed within 2 to 3 days of the operation, and if CI is identified, therapy is begun before major complications develop. Clinical deterioration indicating progression of the ischemic insult to transmural necrosis necessitates reoperation. These patients should undergo resection and colostomy. Primary anastomosis is contraindicated because of potential contamination of the aortic prosthesis in the event of an anastomotic leak. If the rectum is involved, it must also be resected. Every effort should be made to protect the aortic graft from contamination; as such, the retroperitoneum overlying the graft should be reperitonealized with local tissues or omentum.

Fulminating Universal Colitis A rare fulminating form of CI involving all or most of the colon and rectum has been identified in a few patients. These patients experience the sudden onset of a toxic universal colitis. Bleeding, fever, severe diarrhea, and abdominal pain and tenderness, often with signs of peritonitis, have been noted. The clinical course is rapidly progressive. Management of this condition is similar to that for other forms of fulminating colitis. Total abdominal colectomy with an ileostomy is generally required. A second-stage proctectomy has been necessary in some patients within 1 month of the original surgery. The histologic appearance of the resected colon is a combination of ischemic changes, severe ulcerating colitis, and necrosis.

Lesions Mimicking Colon Carcinoma Ischemic colitis can be accompanied by lesions that appear, on barium

enema and colonoscopy, to be colon carcinoma. Colonoscopy may be able to distinguish malignant lesions from those resulting from ischemic cicatrization and is advisable when an annular lesion is identified on barium enema. Treatment is local resection with immediate restoration of bowel continuity.

Colitis Associated with Colon Carcinoma Acute colitis in patients with carcinoma of the colon has been recognized for many years.[71] The colitis is usually, but not always, proximal to the tumor and occurs with and without clinical obstruction. It is of ischemic origin and has the radiologic and endoscopic appearance of ischemic colitis. Clinically, patients may have symptoms of CI or symptoms related to the primary cancer (i.e., crampy pain of a chronic nature, bleeding, or acute colonic obstruction). In most cases, however, the predominant complaints are related to the ischemic episode—sudden onset of mild to moderate abdominal pain, fever, bloody diarrhea, and abdominal tenderness.

It is imperative for both the radiologist and surgeon to be aware of the frequent association of CI and colon cancer. The radiologist must be careful to exclude cancer in every case of CI, and for the surgeon, it is vital to examine any colon resected for cancer to exclude the presence of an ischemic process in the area of the anastomosis because involvement may lead to stricture or a leak.

Colonic Ischemia as a Manifestation of Acute Mesenteric Ischemia CI localized to the right side of the colon may be a manifestation of acute mesenteric ischemia. If a thumbprinting pattern or colonoscopy reveals evidence of CI isolated to the right colon, we consider this an indication for selective mesenteric angiography before discharge to evaluate the status of the SMA. Demonstration of a partially or completely obstructed SMA is an indication for revascularization of this artery.

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Chapter

146

Diverticular Disease

Jeffrey L. Cohen · John P. Welch

Diverticular disease refers to a spectrum of clinical scenarios that can vary from an asymptomatic state to life-threatening peritonitis. This chapter gives a clinical overview of the pathophysiology, diagnosis, and clinical management of a wide variety of complications of the disorder.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY

Colonic diverticulosis refers to the presence of 0.5- to 1-cm saccular outpouchings termed *diverticula*. Anatomically, diverticula are situated between the single mesenteric taenia and one of the antimesenteric taeniae (Fig. 146–1). Virtually all patients with diverticulosis have sigmoid involvement (95%), although other segments may be affected as well. About 5% have cecal diverticula.[1]

At least two factors account for formation of diverticula: weak areas in the colonic wall, and a pressure differential between the colonic lumen and the serosa. Diverticula may form in response to development of localized high-pressure zones or segments in the colon and hence the term *segmentation* has been coined (Fig. 146–2). Typically they are "pseudodiverticula," with a thin-wall component of a flattened mucosa and submucosa and an attenuated or absent muscularis propria. Diverticula are essentially herniations through the muscular wall of the colon. In addition, there may be gross thickening of the less compliant colonic wall and derangement of the collagen fibers. Increased elastin content in the taeniae may cause shortening of the taeniae, which in turn leads to corrugation of the circular muscle. A defect in cholinergic innervation of the colon has been identified in patients with diverticulosis.[2]

Ten percent to 20% of patients with diverticula develop symptoms from them. Inflammation of one or more diverticula (diverticulitis) sometimes develops, with spread of infection into adjacent or less commonly distant sites. The diverticular wall may be devitalized, due to mechanical trauma from fecaliths or from high intracolonic pressures in the presence of an overgrowth of bacteria. Perforation of a diverticulum may be facilitated by commonly ingested nonsteroidal anti-inflammatory drugs (NSAIDs) such as low-dose aspirin.[3] Smoking,[4] corticosteroids, opioid analgesics,[5] and alcoholism have also been associated with diverticular complications. "Diverticular colitis" has occurred in the presence of diverticular disease, even in the absence of inflammation of the diverticula themselves.[6] Diverticula can bleed as well, since they occur at sites where intramural vessels penetrate the colonic wall.

Diverticular disease is an affliction that reached prominence in the 20th century. The incidence of diverticulosis increases linearly with age after 20 years of age, and hospitalized patients tend to be elderly. The prevalence approaches 50% in Western adults older than 60 years of age. The direct cost of treating diverticular disease in the United States in 1998 has been estimated at $2.4 billion.[7] The sexes tend to be affected similarly; however, males are affected more frequently under the age of 40 years, whereas females predominate over 40.[8] Epidemiologic studies suggest that fiber-deficient diets in the Western world lead to the development of smaller, firmer bowel movements, as well as higher pressures within the sigmoid colon, with areas of segmentation. In areas where high-fiber diets are common (rural Africa), diverticulosis is unusual.

Myoelectric studies of patients with symptomatic diverticular disease show an abnormal slow-wave pattern that returns to normal when they ingest bran. Asymptomatic patients with diverticulosis have unchanged motility patterns after eating bran. Dietary supplementation with fiber increases stool weight, decreases intraluminal pressure, and alters transit time. However, firm evidence is lacking that ingestion of a high-fiber diet actually slows the progression of established diverticulosis or the risk of complications.[9]

DIAGNOSTIC MODALITIES

A number of modalities are available to make the diagnosis of diverticular disease. In the noninflamed colon, diverticula are easily recognized during colonoscopy,

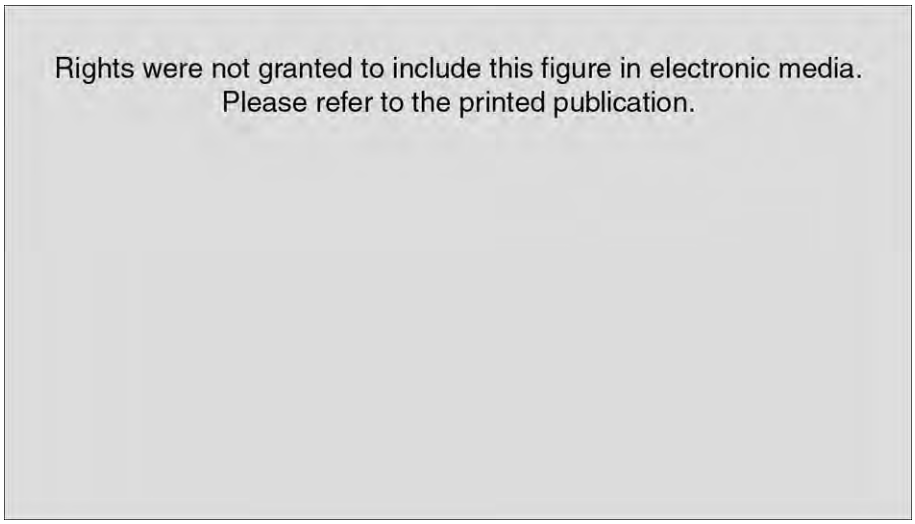

Figure 146–1. Anatomy of the colon that contains diverticula. (From Rodkey GV, Welch JP: An overview. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 8.)

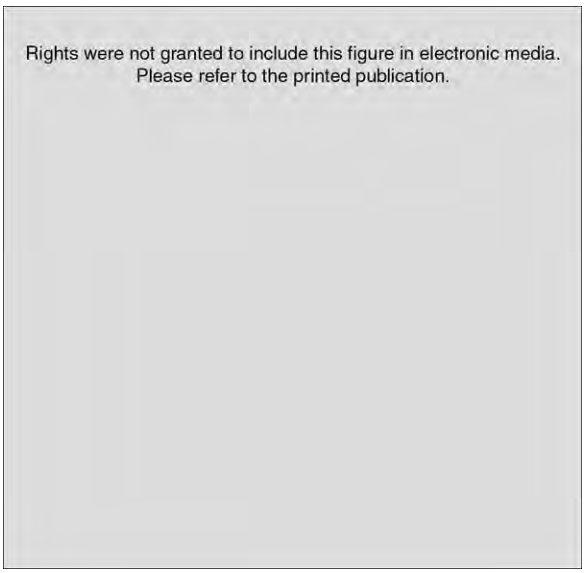

Figure 146–2. Schematic representation of the process of segmentation in the colon. (From Pemberton JH, Armstrong DN, Dietzen CD: Diverticulitis. In Yamada T [ed]: Textbook of Gastroenterology, 2nd ed. Philadelphia, Lippincott, 1995, p 1879.)

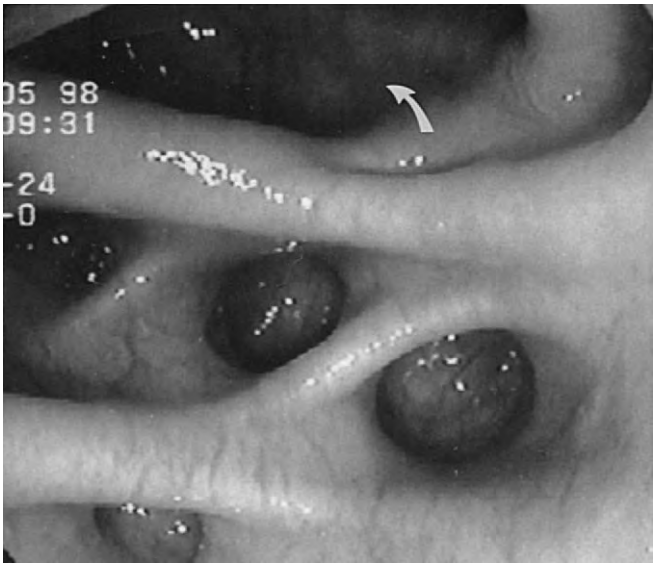

Figure 146–3. Multiple sigmoid diverticula seen with the colonoscope. The lumen is seen in the upper portion of the photograph *(arrow)*.

although numerous diverticula can make visualization of the colonic lumen more confusing (Fig. 146–3). Radiating folds enter the colonic lumen and by lessening colonic peristalsis, administration of glucagon facilitates identification of the lumen. In the case of active diverticulitis, colonoscopy is generally not indicated since there is risk of converting a minor site of intestinal perforation into a free perforation. (Table 146–1). The lumen may also be narrowed by edema and spasm, and the procedure is apt to be painful with fixation of the bowel wall. Little air should be insufflated. The value of the test is limited as well by the fact that diverticulitis is usually extraluminal. In the case of a chronic stricture, it may be quite difficult to enter the area of disease and even to differentiate it from cancer (see later).

Contrast studies provide a "road map" in the elective setting (after the acute process has subsided) in that they show mucosal details and the anatomic distribution of diverticula (Fig. 146–4). The examination is accurate and of relatively low cost, and it is widely available. Contrast studies should be used judiciously in the acute setting, however, since they can be complicated by perforation of the colon. The clinician should request that the enema be done under low pressure with visualization only of the involved sigmoid. If a localized perforation is suspected, a water-soluble agent such as Gastrografin should be used because of the deleterious effects of stool and barium in the peritoneal cavity. Water-soluble agents are less

Table 146–1 Diagnostic Tools for Acute Diverticulitis

Type of Study	Advantages	Disadvantages
Barium enema	Inexpensive, widely available	Potential for extravasation
CT scan	Extramural detail, abdominal evaluation, therapeutic potential	No mucosal detail
Endoscopy	Mucosal evaluation, ability to biopsy	Perforation, inability to completely evaluate

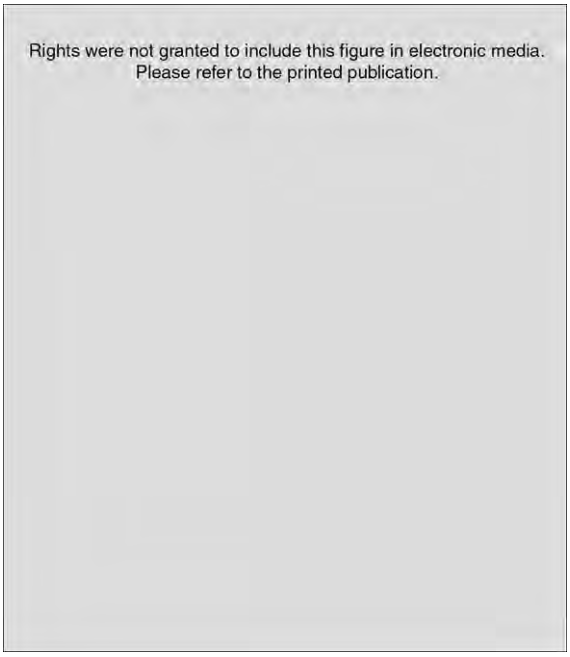

Figure 146–4. View from a barium enema showing sigmoid diverticulosis *(arrows)*. (From Oliveira L, Werner SO: Abdominal pain and diverticulosis. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 39.)

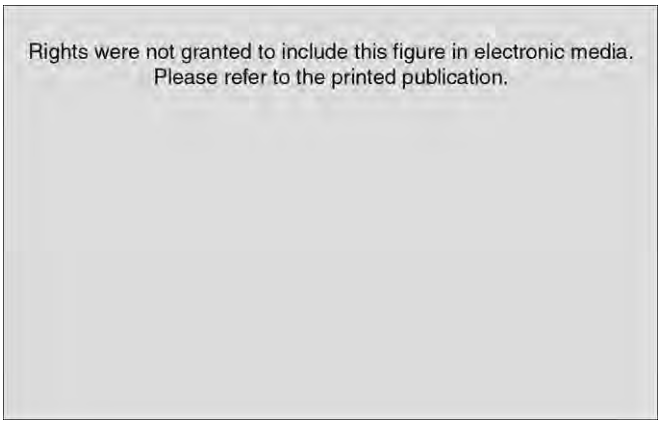

Figure 146–5. A pelvic CT view shows an inflamed sigmoid colon and adjacent tissues together with extraluminal gas confirming the diagnosis of diverticulitis. (From Markowitz SK, Kirejczyk W: Radiologic evaluation of the small and large intestines. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 103.)

reactive in the peritoneal cavity and will be absorbed over time; they cause few artifacts if a computed tomographic (CT) scan is done subsequently.

Although some favor a contrast enema as the initial study, CT scanning has become the most useful modality for the evaluation of acute diverticulitis in hospitalized patients.[10] It not only defines the nature of the process involving the colon (Fig. 146–5) but extracolonic changes as well, such as fluid collections, abscesses, extraluminal air, or fistulas. The sensitivity is as high as 97% (Box 146–1).[11] Diseases in other organs such as the ovaries or appendix can also be evaluated.

Good candidates for CT scans are patients with suspected abscess, with deteriorating clinical status despite appropriate medical treatment, or with suspected complicated diverticulitis. In the uncommon event that findings are unclear, a contrast enema is useful.[10] Helical CT

Box 146–1 **CT Criteria for Diagnosing Diverticulitis**

- Presence of sigmoid diverticula
- Inflammatory infiltration of pericolonic fat
- Thickened colonic wall (>4 mm)
- Fluid and/or contrast collection within thickened colonic wall
- Pelvic abscess associated with inflamed sigmoid colon
- Extrapelvic abscess and/or peritonitis associated with inflamed sigmoid
- Fistula formation (especially sigmoidovesical)

From Neff CC, van Sonnenberg E: CT of diverticulitis: Diagnosis and treatment. Radiol Clin North Am 27:744, 1989.

with colonic contrast alone has been suggested to avoid the risks, costs, and delays of oral and intravenous contrast administration. CT scanning may result in more appropriate patient care and allow cost savings. In some hands, ultrasound has also been useful, showing a thickened colon, diverticula, and sites of local tenderness. This modality is limited by patient obesity and underlying bowel gas, and the results are more subjective and operator dependent than those of CT. Transrectal sonography can increase the sensitivity of abdominal ultrasound for diverticulitis involving the lower sigmoid colon.[12]

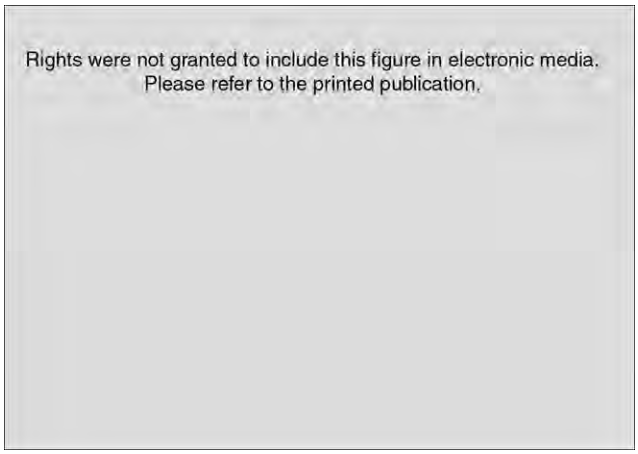

Figure 146–6. Barium enema view of a long stricture of the colon. (From Morgenstern L: "Malignant" diverticulitis. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 184.)

CLINICAL FEATURES

Diverticulitis

The classic signs and symptoms of uncomplicated acute diverticulitis are fever, left lower quadrant abdominal pain, irregular bowel habits, and variable urinary symptoms. Patients complain of diarrhea or of constipation with rectal urgency. The abdomen is maximally tender in the left lower quadrant with some rebound tenderness. Plain abdominal films are of limited value. The white blood cell count is frequently elevated with a left shift, and the urinalysis is normal. Usually the erythrocyte sedimentation rate is elevated. Patients with uncomplicated diverticulitis are managed either on an outpatient basis or in the hospital, depending on the severity of the attack, with antibiotics and a liquid diet or intravenous fluids. Such attacks may recur after variable time periods, and the frequency of such recurrences weighs in the decision whether to treat patients medically or surgically.

Diseases Confused with Diverticulitis

Diverticulitis and colon cancer are common disorders that may coexist. Differentiating a perforated cancer from diverticulitis or detecting a sigmoid carcinoma amidst numerous diverticula may be difficult. Since a perforated cancer will ordinarily require early operation, an effort should be made to establish the correct diagnosis.

CT scanning can be a valuable early test.[13] The patient should receive oral and rectal contrast if possible to increase sensitivity. Certain signs are suggestive of diverticulitis, including (1) localized thickening of the colonic wall; (2) the presence of diverticula; (3) inflammation of the adjacent pericolic fat; and (4) a possible associated collection. Despite these signs, making the correct diagnosis sometimes is difficult using CT alone.

If contrast studies are done, water-soluble contrast rather than barium is used because of the risk of extravasated barium. Only the left colon is examined. Several signs suggest diverticulitis rather than carcinoma, including (1) a gradual rather than abrupt transition from normal to diseased colon; (2) intact mucosa in the abnormal segment; (3) a long involved segment (≥6 cm) (Fig. 146–6); and (4) an intramural mass deforming the colon with intact mucosa. The greater the number of diverticula, the more difficult it is to detect a neoplasm lying within them; thus, most incorrect diagnoses are false negatives. Other radiologic tests such as ultrasound (endoluminal or transabdominal) or nuclear imaging are of limited value.

Does endoscopy play a role? If rectal bleeding has occurred, the risk of neoplasm is increased and the procedure should be done if possible. Unfortunately, endoscopy can be difficult because of narrowing or spasm of the colon. A risk of worsening a site of local perforation exists as well. If the diseased segment can not be completely traversed, a neoplasm cannot be ruled out and operative exploration may be necessary. Colonoscopy is facilitated if associated inflammation is allowed to subside (a useful approach if acute diverticulitis appears more likely than a neoplasm) over a period of 4 to 6 weeks.

Usually diverticulitis and Crohn's colitis can be differentiated, except in a few difficult cases. "Red flags" suggesting the possibility of Crohn's disease include rectal bleeding, perianal inflammation, unusual fistulas, extraintestinal signs, multiple operations, or postoperative complications. Patients with diverticulitis tend to be older and to have more localized pain. Ongoing diarrhea is suggestive of inflammatory bowel disease. Differential radiologic findings also exist (e.g., presence versus absence of transverse fissures, or short vs. long paracolic tracts). Histologic features suggesting a Crohn's disease type of reaction in a localized segment of diverticulitis should not be given undue weight if diverticulitis is suspected as the primary disease. However, the finding of noncaseating epithelioid granulomas along with deep-fissuring ulcers is virtually pathognomonic for Crohn's disease.

Individuals hospitalized in the intensive care unit following cardiovascular or aortic surgery occasionally develop abdominal catastrophes attributed to the colon; ischemic colitis is characteristic in this setting rather than complicated diverticulitis. Patients with ischemic colitis

and diverticulitis complain of abdominal pain, but rectal bleeding is more characteristic of ischemia. An abdominal mass suggests a diverticular phlegmon or abscess rather than ischemia. Endoscopy is the most accurate way to differentiate the two disorders.

Patients with diverticulosis may develop abdominal pain resembling that of diverticulitis. The term *painful diverticulosis* has been coined to describe episodes of abdominal pain and irregular bowel habits. This condition and another source of abdominal pain, the irritable bowel syndrome, are managed with a high-fiber diet and increased fluid intake, as well as antispasmodics. Other illnesses that can be confused with diverticulitis include appendicitis, pelvic inflammatory disease, and pyelonephritis.

Complicated Diverticular Disease

Included under this designation are a number of complications of diverticular disease that challenge the clinical acumen, judgment, and technical abilities of the surgeon. These include obstruction, abscess or fistula formation, free perforation, and bleeding.

Subacute (Persistent) Diverticulitis

Some patients develop a persistent form of inflammation following the onset of diverticulitis that fails to respond to treatment with antibiotics and bowel rest. Characteristically an abscess is not present but the patient does have persistent pain, a low-grade fever, possible urinary symptoms, and failure to thrive. An abdominal mass may be present. Some patients have few symptoms such as vague pelvic discomfort. Due to the varied clinical presentation, definitive surgical treatment is often delayed, and the irritable bowel syndrome must be ruled out.[14]

Since the inflammation is persistent rather than episodic or brief, the colon tends to thicken with development of fibrosis. Patients will often develop chronic symptoms of partial large bowel obstruction. Attempts should be made in these patients to prepare the bowel for a one-stage resection and anastomosis, as the obstruction is rarely complete.

Diverticular Hemorrhage

In a literature review, hemorrhage of colonic origin was caused by diverticular disease (40%), inflammatory bowel disease (21%), neoplasia (polyps and cancer) (14%), coagulopathy (12%), benign anorectal disease (11%), and arteriovenous malformations (2%). Disorders proximal to the ligament of Treitz caused 10% to 15% of rectal bleeds and small bowel disease accounted for 3% to 5%.

Patients with diverticular bleeding tend to be elderly males[8] with diseases such as hypertension and atherosclerosis, and hospitalizations for this complication will likely increase in the future. In half the cases bleeding originates in the right colon, despite the fact that diverticula are situated much more commonly in the sigmoid.

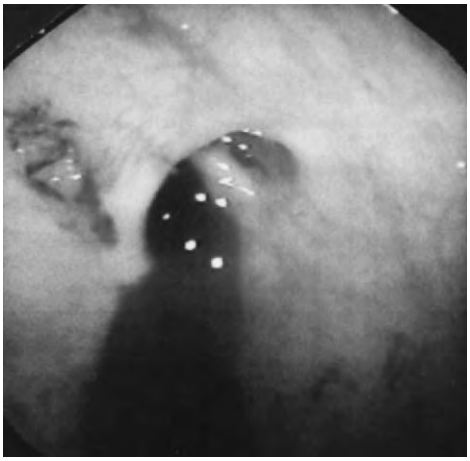

Figure 146–7. Colonoscopic view of an actively bleeding diverticulum.

Regular use of NSAIDs may potentiate bleeding from diverticula.

Most diverticular bleeds are self-limited. Monitoring is appropriate, with its intensity based on the severity of the bleeding and the patient risk. Transfusions may be needed, especially in patients with anemia or heart disease. Colonoscopy can then be performed (Fig. 146–7). There are a few reports of aggressive colonoscopy within hours of hospitalization (following an oral purge). Just as with an upper gastrointestinal bleed, endoscopists can employ epinephrine injections or coagulation at the site of the diverticular bleed, and the colon can be tattooed to facilitate surgical recognition of the bleeding site. There are also reports of endoscopic band ligation[15] and of endoclip usage[16] on the protruding vessels in bleeding diverticula.

Rarely the bleeding is massive, accompanied by hypotension. Such patients need aggressive resuscitation followed by arteriography or bleeding scan (Figs. 146–8 and 146–9). Operative exploration is the only alternative if the blood pressure cannot be controlled. The sensitivity of angiography can be improved with the use of drugs such as urokinase, heparin, and tolazoline. Contrast studies should not be done since retained contrast interferes with the ability to perform arteriography. Vasopressin and more recently embolization techniques have been used in the event of a positive arteriogram.

Pericolic Abscess

An inflammatory mass adjacent to the colon may develop into an abscess, the most common complication of acute diverticulitis, occurring in 10% to 68% of patients. It begins as a small abscess in the sigmoid mesentery and may remain localized by adherence of omentum and adjacent viscera. The collection may also enlarge and extend to more distant sites such as the pelvis. Retroperitoneal abscesses have extended into extra-abdominal areas such as the hip, flank, or leg.

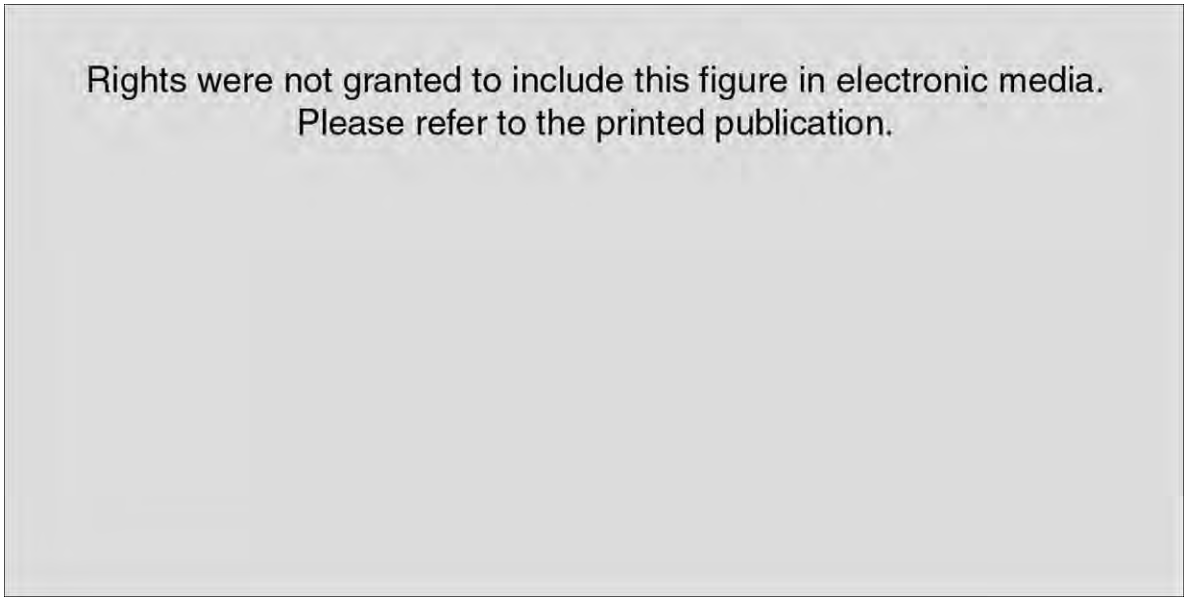

Figure 146–8. **A,** Arteriographic view shows extravasation of contrast *(arrow)* in patient with lower gastrointestinal bleed. **B,** Following embolization with coils *(arrows)*, the active bleeding has ceased. (**A** and **B,** From Pennoyer W, Cohen J: Diverticular hemorrhage. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 84.)

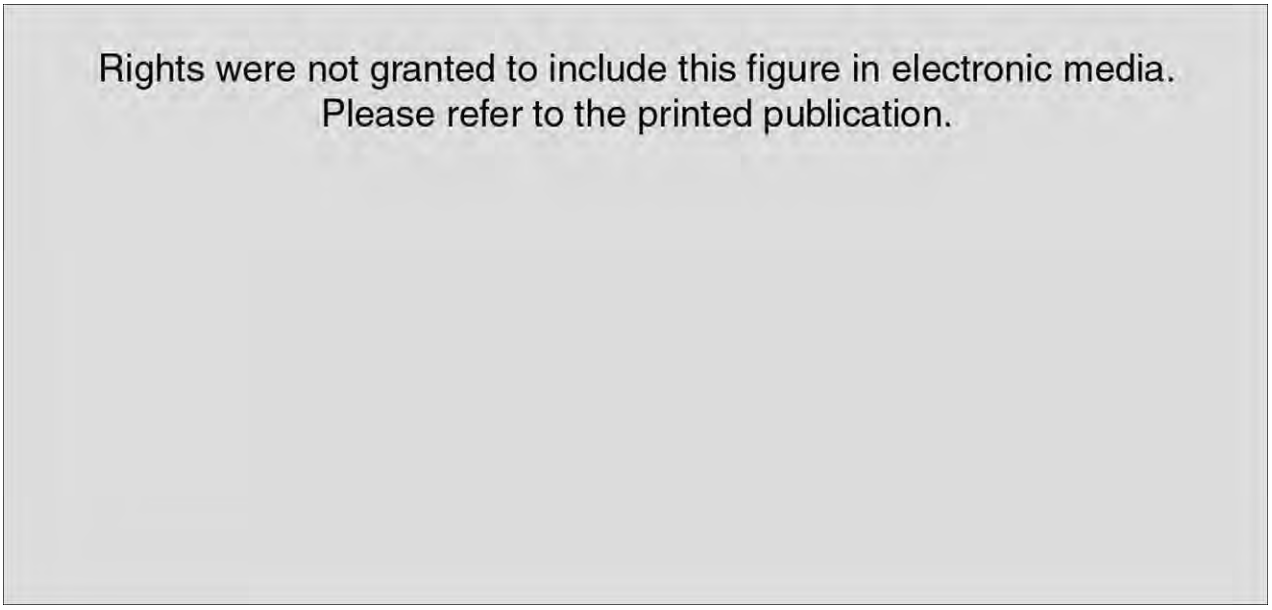

Figure 146–9. Site of bleeding *(arrow)* is detectable in this view from a nuclear scan. (From Pennoyer W, Cohen J: Diverticular hemorrhage. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 82.)

Abscesses cause fever and chills, and a tender mass may be felt on abdominal, rectal, or vaginal examination. Leukocytosis is characteristic.

When an abscess is suspected, a CT scan is the imaging test of choice, since the study delineates the size and the location of the collection.

Fistula

Some abscesses complicating diverticulitis lead to the formation of fistulas by rupturing into adjacent viscera. The most common (50% to 65%) are colovesical fistulas. These develop more frequently in males because of the

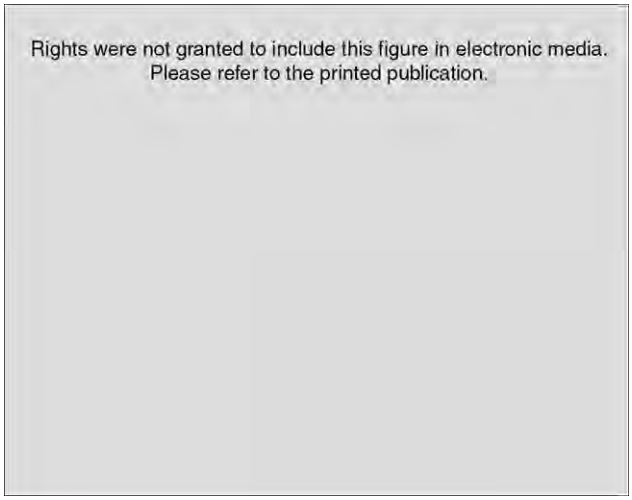

Figure 146–10. In this patient who had a sigmoidovesical fistula, rectal contrast was administered and contrast filling of the bladder is present *(arrow)*. (From Markowitz SK, Kirejczyk W: Radiologic evaluation of diverticular disease of the small and large intestines. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 119.)

Figure 146–11. Depiction of a colovaginal fistula caused by diverticulitis. The fistula is occurring at the site of the vaginal cuff. (From Chinn BT, Eisenstat TE: Colovaginal fistulas. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 168.)

protective effects of the uterus. Symptoms caused by the fistula are usually urologic, including recurrent urinary tract infections, pneumaturia, and fecaluria. The most sensitive diagnostic test is a CT scan with contrast agent that shows a thickened bladder wall, thickening of the bowel adjacent to the bladder, an abscess or extraluminal mass, an opacified fistula, and oral contrast in the bladder (Fig. 146–10). Cystoscopy may show bullous edema or erythema at the site of the fistula.

Most colovaginal fistulas occur in women with diverticular disease who have undergone a hysterectomy. The fistula occurs at the site of contact of the inflamed colon with the vaginal cuff (Fig. 146–11). Vaginal discharge is the most frequent complaint. CT scans with contrast are of significant diagnostic value. Vaginography using a Foley catheter is a highly sensitive test as well.

Colocutaneous fistulas rarely occur spontaneously and should raise the suspicion of Crohn's disease. They tend to complicate a previous operation for diverticulitis.

The diagnosis of Crohn's disease should be ruled out in all patients with fistulas.

Generalized Peritonitis

Generalized peritonitis complicates only 1% to 2% of cases of acute diverticulitis, when an abscess ruptures or when the surrounding tissues are unable to wall off an open rent in a diverticulum. Immunocompromised patients taking steroids are at particular risk to develop the latter complication. In the Hinchey classification of the pathologic stages of perforated diverticulitis, free perforation of a localized peridiverticular abscess site into the peritoneal cavity with purulent peritonitis is termed *stage III* and diffuse feculent peritonitis is *stage IV* (Fig. 146–12). Patients usually present with rather severe abdominal pain, but pain and tenderness may be limited to the left lower quadrant. Plain films may or may not show pneumoperitoneum. Early CT scanning allows visualization of small amounts of free air or fluid, suggesting free perforation. Use of a barium contrast enema for diagnosis is dangerous if free perforation is suspected.

These patients require urgent laparotomy (see later).

Intestinal Obstruction

Large bowel obstruction is caused by diverticular disease in approximately 10% of patients. The usual mechanisms include circumferential colonic thickening and fibrosis, as well as marked angulation of the pelvic colon, with adherence to the pelvic sidewall. Stricturing of the colon develops as a result of recurrent attacks of diverticulitis (symptomatic or subclinical) or of persistent inflammation.

Patients complain of chronic constipation and narrowed stools. The obstruction is typically partial in nature, although complete obstruction may occur. Since carcinoma is a much more frequent cause of obstruction,

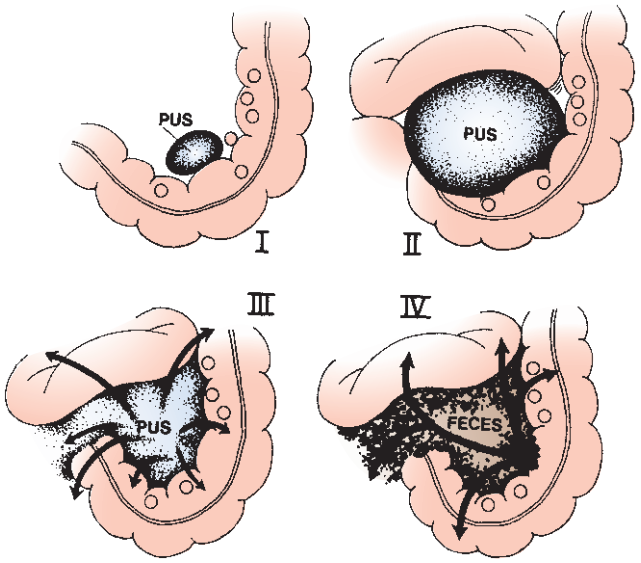

Figure 146–12. A grading system for perforated diverticulitis. I represents a localized pericolic abscess. In II, there is a larger mesenteric abscess spreading toward the pelvis. III depicts a free perforation causing purulent peritonitis. IV shows fecal peritonitis caused by free perforation. (From Hinchey EJ, Schaal PG, Richards GK: Treatment of perforated diverticulitis of the colon. Adv Surg 12:89, 1978.)

the two diseases must be differentiated. Making this distinction may be difficult and, therefore, may be an indication for surgery (see earlier). Limited barium studies (see Fig. 146–6) or flexible sigmoidoscopy are useful diagnostic adjuncts.

Although 10% of operations carried out for diverticular disease involve intestinal obstruction, the risk of acute high-grade obstruction is only in the range of 3% in patients with acute diverticulitis. In the latter group, edema of the colon contributes to the mechanical obstruction; some resolution may occur following administration of antibiotics along with bowel rest. If distention of the colon is marked, there is risk of cecal perforation, and the cecal diameter is monitored with periodic abdominal films and physical examinations.

The clinical picture may be confusing if acute small bowel obstruction complicates acute diverticulitis. Small bowel may adhere to the point of colonic inflammation or to the walls of a pericolic abscess. Fistula formation into the adherent small bowel should raise suspicion of possible Crohn's disease. The presence of one illness may be obscured by the other depending on the clinical presentation. Signs of small bowel obstruction can be obscured by symptomatic diverticulitis, or conversely, the patient may be suspected of having small bowel obstruction alone. Symptoms such as diarrhea or lower abdominal pain should alert the clinician to possible colonic disease accompanying small bowel obstruction. Small bowel obstruction is suggested by symptoms such as periumbilical crampy pain, vomiting, and abdominal distention as well as physical findings of dehydration, tachycardia, and abdominal tenderness.

Abdominal films or CT scans are particularly useful tests in making the differentiation. Contrast material can also be administered per rectum to determine if there is a stricture of the colon. Small bowel studies following oral barium are less desirable, since the colon may be obscured by contrast and any operation is complicated by considerable barium within the bowel.

Unusual Problems

Diverticulitis of the Cecum

The incidence of right-sided diverticulitis appears to be related to the number of diverticula. Thus the highest incidence comes from areas in Asia where the disorder is most common.[17] The natural history of this disease appears to be mild and self-limited in most cases,[18] as opposed to left-sided diverticulitis requiring emergent surgery.[19] Acute appendicitis is usually suspected because of similar symptoms of right lower quadrant pain and tenderness, emesis, fever, and leukocytosis. This disorder should be considered in patients who have undergone appendectomy or when cecal diverticulosis has been detected previously. The appropriate diagnosis can be made with CT scans,[20] although the differentiation from appendicitis or carcinoma may still be difficult.

A useful classification scheme has been proposed by Thorsen and Ternent[21] (Fig. 146–13), as follows:

- Grade I is a discrete, inflamed diverticulum.
- Grade II represents a simple cecal wall mass.
- Grade III refers to a localized abscess or fistula.
- Grade IV is associated with peritonitis (purulent or feculent).

Grades III or IV cecal diverticulitis are easily mistaken for a perforated adenocarcinoma.

Nonresection or diverticulectomy can be applied to grade I and possibly grade II lesions.[22] If the degree of inflammation is minimal, nonresectional treatment is favored with antibiotic therapy (and incidental appendectomy if the cecum at the base of the appendix is uninvolved). If perforated carcinoma is suspected (grades III to IV lesions), colectomy is recommended; anastomosis is reserved for the stable patient with limited contamination.

Giant Diverticula

Rarely a diverticulum can increase to a large size (as much as 40 cm), termed a *giant diverticulum,* or less commonly a giant air cyst, solitary gas cyst, or pneumocyst of the colon. Some have speculated that growth occurs because of a ball-valve mechanism that is a result of fecal material intermittently occluding the neck of the diverticulum and trapping air within it.[23]

Most patients are asymptomatic or present with chronic symptoms such as mild abdominal pain or bloating; rarely, acute complications such as perforation or torsion develop. Classically a soft, somewhat mobile mass is palpable; this is seen as a solitary gas-filled cyst in plain films of the abdomen. The cyst and its relation to the

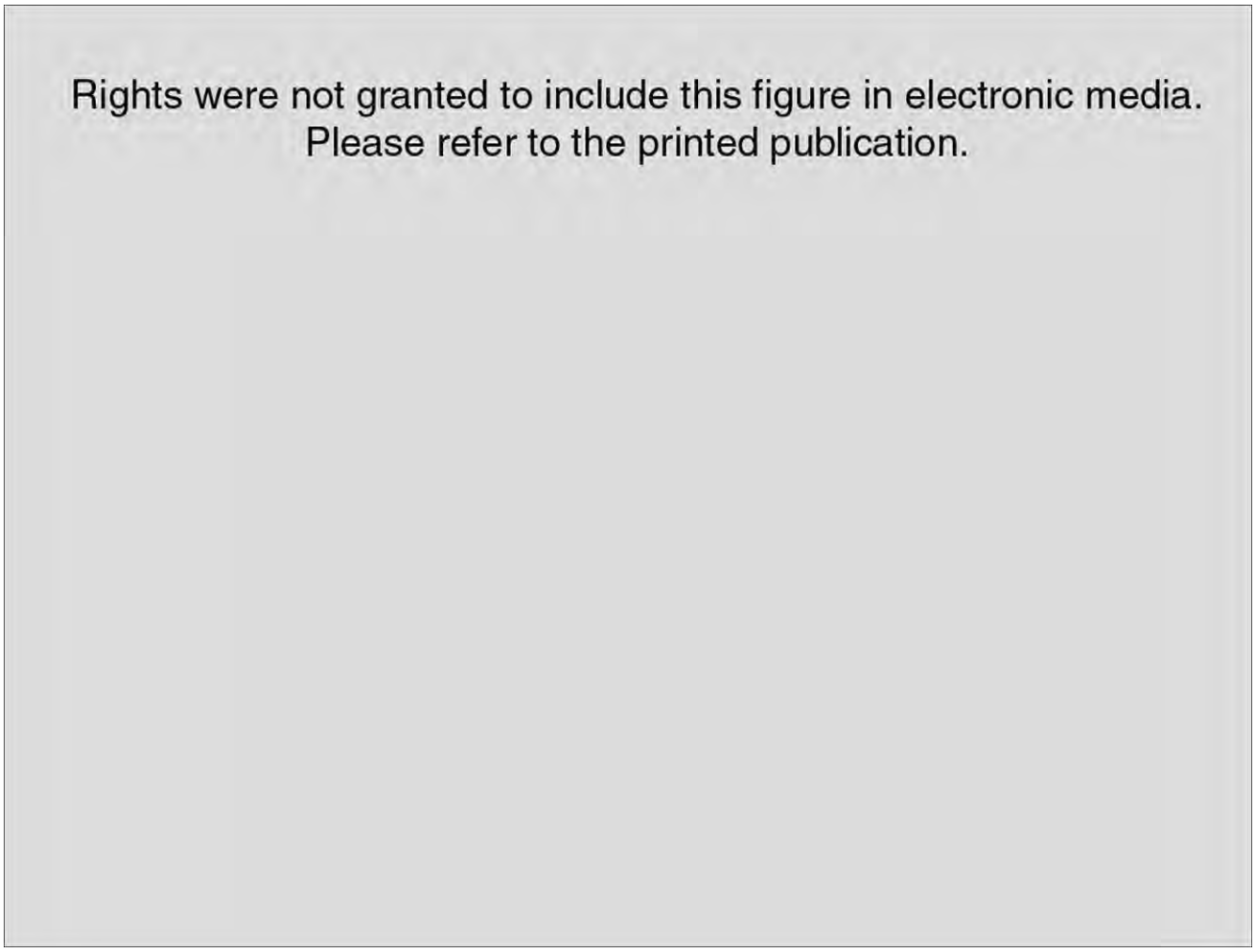

Figure 146–13. The spectrum of pathologic findings in cecal diverticulitis is depicted in these illustrations. **A,** Grade I is a well-identified projecting inflamed cecal diverticulum. **B,** Grade II is a cecal mass. **C,** In Grade III there is a localized abscess or fistula. **D,** Grade IV represents a free perforation or ruptured abscess with peritonitis. (**A-D,** From Thorsen AG, Ternent CA: Cecal diverticulitis. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 435.)

colon are apparent with a barium enema or CT scan (Fig. 146–14). The contrast studies are useful in differentiating other causes of gas-filled masses such as an intra-abdominal abscess or a duplication of the colon. The diverticulum tends to adhere to adjacent structures such as the bladder or small bowel. Once discovered, the diverticulum should be resected in most patients along with the adjacent sigmoid colon. Recurrence is not seen following this procedure. Diverticulectomy alone can lead to formation of a colocutaneous fistula.

The Immunocompromised Patient

Increasing numbers of immunocompromised patients (alcoholics, diabetics, transplant recipients, or patients receiving chemotherapy or steroids) are being hospitalized with diverticulitis. Patients with adult polycystic kidney disease may be at particular risk.

Of interest, immunocompromised patients do not have a higher risk of developing diverticulitis from asymptomatic diverticulosis.[24] However, once diverticulitis develops, it is more complex and severe in the immunosuppressed individual. Corticosteroids serve to mask symptoms and signs of peritonitis in these patients because of their known anti-inflammatory effects. As a consequence, definitive treatment may be delayed and the mortality increased. Surgical mortality has been in the range of 40%.

If diverticulitis is suspected, the clinician should be particularly observant. Toxic granulations are a "red flag" for a septic process. If the patient is receiving high doses of steroids, few physical findings should be expected. Contrast-enhanced CT scans provide important information about perisigmoidal inflammatory changes and possible free perforation in the presence of an "unimpressive" physical examination.

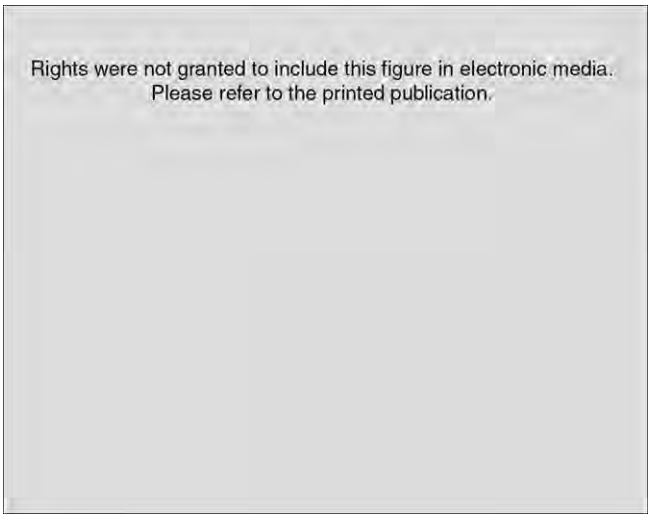

Figure 146–14. Barium enema view showing a giant diverticulum arising from the sigmoid colon. (From de Oliveira NC, Welch JP: Giant diverticula of the colon. In Welch JP, Cohen JL, Sardella WV, et al [eds]: Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 414.)

Table 146–2 Unusual Extra-abdominal Presentations of Diverticulitis

Type of Presentation	Specific Manifestation
Dermatologic	Pyoderma gangrenosum
Urinary	Ureteral obstruction, coloureteral fistula
Soft tissue	Thigh abscess, necrotizing fasciitis
Orthopedic	Osteomyelitis
Gynecologic	Colouterine fistula, ovarian tumor/abscess
Genital	Epididymitis, pneumoscrotum
Neurologic	Coloepidural fistula
Vascular	Femoral vein thrombosis, mesenteric vein thrombosis, pylephlebitis, colovenous fistula
Perineal	Fournier's gangrene, complex anal fistula

From Polk HC, Tuckson WB, Miller FB: The atypical presentations of diverticulitis. In Welch JP, Cohen JL, Sardella WV, et al (eds): Diverticular Disease: Management of the Difficult Surgical Case. Philadelphia, Lippincott Williams & Wilkins, 1998, p 385.

Diverticulitis in the Young

Autopsy studies suggest that only 6% to 9% of patients younger than 40 years of age have colonic diverticular disease. Young patients diagnosed with diverticulitis are usually obese men, perhaps due to underdiagnosis of the disease in women of reproductive age. Diverticulitis may be missed in men as well, since it may not be suspected by the treating clinician. The theory that younger patients may have more virulent forms of diverticulitis is countered by significant numbers of undiagnosed patients who are never hospitalized. Since young patients do not tend to have comorbid illnesses (unlike elderly patients), those hospitalized have advanced diverticulitis.

An aggressive surgical approach has been advocated for diverticulitis occurring in young patients. Support for this approach is predicated on the impression that young patients experience a more aggressive variant of the disease, as well as an increased rate and severity of recurrence. The higher operative rate following the first presentation of these patients is more likely due to the mistaken diagnosis of appendicitis than to an increased virulence of the initial presentation. Furthermore, although the patients who develop a recurrence may be more likely to require surgery than the general population, there does not appear to be an increased rate of recurrence. Furthermore, young patients who develop a recurrence generally undergo an elective procedure and do not require a staged resection. For these reasons, diverticulitis in young patients does not need to be distinguished from and treated separately from the disease in the general population.[25,26]

Atypical Presentations

Inflammatory diseases originating in bowel such as diverticulitis, Crohn's disease, or appendicitis can be accompanied by unusual systemic manifestations or complications. The atypical presentations of diverticulitis are summarized in Table 146–2 and can be classified as either intra-abdominal or extra-abdominal. Immunosuppressed patients are at increased risk of developing these complications.

Intra-abdominal fistulas usually are colovesical, colocutaneous, or colovaginal but may be coloureteral, colorenal, colouterine, colovenous (involving the mesenteric veins), or colobiliary. Pylephlebitis developing as a complication of diverticulitis can lead to a pyogenic liver abscess. Adnexal masses managed surgically by a gynecologist can prove to be a diverticular phlegmon or abscess.

Pyoderma gangrenosum may complicate diverticulitis. Arthritis may also be seen. Distant abscesses have been seen in the brain. Retroperitoneal perforations can manifest in a number of ways. Anatomic communication to the thigh, genitalia, or knee can lead to cellulitis or abscesses in these locations.[27] The usual portals include the psoas muscle, the femoral canal, the obturator foramen, or the sacrosciatic notch. Escape of air into the mediastinum can lead to subcutaneous emphysema in the neck.[28]

MEDICAL MANAGEMENT

The medical therapy of diverticular disease depends greatly on the severity of the clinical presentation. In its mildest form, symptomatic diverticulosis may be manifested solely by left lower quadrant discomfort. In the absence of signs of infection, empirical therapy can be initiated and directed toward the treatment of a colonic motility problem. The initiation of a high-fiber diet has been demonstrated to have a beneficial effect on patients with symptomatic diverticulosis. Increased fecal bulk may increase bowel wall diameter, thereby lessening wall tension according to Laplace's Law. Furthermore, increased fiber probably decreases intestinal transit time, lessening the deleterious effects of constipation, including the development of diverticular complications.

Patients who present with localized abdominal pain and tenderness but without systemic signs of toxicity are usually managed successfully on an outpatient basis. A liquid or low-residue diet is initiated along with oral antibiotic therapy directed at the bacterial flora of the gut. In a prospective Italian trial, cyclic intake of a broad-spectrum antibiotic together with fiber was more effective than fiber alone in decreasing subsequent episodes of diverticulitis.[29] For mild cases of diverticulitis, we tend to prescribe trimethoprim-sulfamethoxazole or ciprofloxacin in conjunction with metronidazole. Unfortunately, it may be difficult for patients to tolerate the combination of trimethoprim-sulfamethoxazole and metronidazole when they may already be experiencing some degree of gastrointestinal upset. Within several days, the patient's symptoms usually begin to resolve and antibiotic therapy is continued for a 7- to 10-day period. If a patient has not been previously diagnosed with diverticulitis, an elective evaluation of the colon is performed once the clinical symptoms have resolved.

Patients who present with a more advanced form of acute diverticulitis generally require admission to the hospital. The disease may be manifested by high fevers, lower abdominal peritonitis, and dehydration secondary to nausea or vomiting. Bowel rest is initiated with intravenous hydration and antibiotic therapy. Although cost-effective treatment for these more serious infections may still include triple-antibiotic therapy with ampicillin, gentamicin, and metronidazole, newer combinations of third-generation cephalosporins with metronidazole or even single-drug therapy such as ampicillin/sulbactam may be preferable in certain hospitals or regions. Furthermore, if the patient improves clinically and can tolerate oral intake, intravenous antibiotic therapy can be completed on an outpatient basis. Generally, antibiotic therapy is continued for 10 to 14 days in this setting, although occasionally a prolonged course for up to 1 month may be beneficial.

For most patients presenting with acute diverticulitis severe enough to require hospitalization, early evaluation with CT imaging is extremely beneficial. Not only does CT scanning confirm the diagnosis, but it also reliably assesses the degree of surrounding inflammation. Although this information can assist in predicting the treatment course for the patient, the ability to detect diverticular abscesses can also lead to further therapeutic benefit. Percutaneous drainage of diverticular abscesses is now routinely performed in the treatment of complicated diverticular disease. The ability to drain these abscesses percutaneously, either under CT or ultrasound guidance, has led to more elective, single-stage resections.

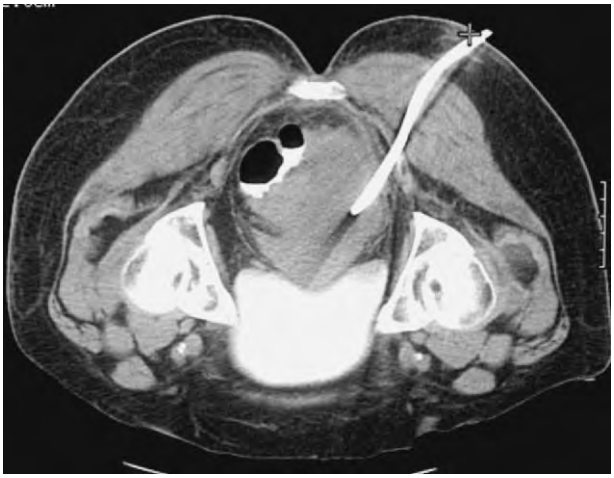

Figure 146–15. CT view of patient with a large pelvic abscess secondary to acute diverticulitis. A drainage catheter introduced via the transgluteal approach is seen within the cavity.

Small pericolic abscesses (<5 cm) generally resolve with bowel rest and intravenous antibiotics and are amenable to resection of the diseased segment en bloc with the abscess. Larger abscesses should be drained percutaneously, provided several caveats are followed. The abscess cavity should be well defined, localized, and have a safe access route, either via an abdominal route or transgluteally (Fig. 146–15). Deep pelvic abscesses can be difficult to drain.[30] Furthermore, pneumoperitoneum and gross feculent peritonitis are contraindications to this approach.

The timing of surgery following percutaneous drainage depends on factors such as the patient's response to drainage, the degree of surrounding inflammation on CT scan, and the nutritional status. If patient improvement is rapid following drainage of a single abscess and minimal surrounding inflammation is seen on CT scan, an operation may be performed during the same admission. Alternatively, if the CT demonstrates significant surrounding inflammation or the patient is otherwise debilitated, a more prudent course is to delay surgery for 4 to 6 weeks.

SURGICAL MANAGEMENT

Elective Resection

It has been estimated that 20% of patients with acute diverticulitis ultimately require surgery. Although many of these patients develop a complication necessitating emergency operative intervention, there remain several indications for elective surgical intervention.

Following an episode of acute diverticulitis, recurrent attacks requiring readmission to the hospital occur in 20% to 40% of patients. Complication rates related to diverticulitis increase with subsequent attacks, exceeding 50% after two episodes. Because of the natural history of the disease, the most common indication for elective surgery in diverticular disease is recurrent episodes of acute diverticulitis interfering with the quality of the patient's daily living. The actual number of attacks warranting elective resection is somewhat controversial.[31] Other indications for elective sigmoid resection are fistula formation and previous percutaneous drainage of a diverticular abscess. Although some evidence exists that percutaneous drainage of an abscess does not mandate follow-up surgery, most surgeons believe that this complication is serious enough to warrant definitive surgical treatment.

Given the difficulty in distinguishing the symptoms of recurrent diverticulitis from other sources of abdominal pain, especially irritable bowel syndrome, some objective evidence of diverticulitis should be present prior to recommending surgery. This is most commonly obtained with a CT scan, although signs of acute diverticulitis, such as sinus tracts or extraluminal barium, can be seen in contrast studies. Even when operated on for proven diverticulitis, the patient should be cautioned regarding the possibility that not all of the abdominal symptoms will resolve following surgery.

Patients undergoing elective diverticular resection receive a mechanical and antibiotic bowel prep. Placing the patient in the lithotomy position allows access to the anus for performing a stapled anastomosis. Furthermore, should difficulty arise in identifying the ureter, this position allows for intraoperative urologic manipulations. For elective resections, preoperative placement of ureteral stents is unnecessary and adds cost to the procedure. Should an unexpected inflammatory mass be found and ureteral identification and preservation be difficult, stents can then be placed intraoperatively. They clearly save time during the operation, although placement of the stents may not actually prevent ureteral injury.

At the time of operation, the abnormally thickened and diseased sigmoid colon should be resected. Although this may involve only a small portion of the sigmoid colon, the distal point of resection must extend to the rectosigmoid junction. This can be identified by the loss of the taeniae coli. Failure to resect the distal sigmoid colon increases the incidence of recurrent diverticulitis from 6% to 13% to 23% (see later). The extent of proximal resection is not as important but should always be performed through soft, healthy-appearing bowel. Mobilization of the splenic flexure is performed if there is concern regarding anastomotic tension. Often mobilization of the rectum from the presacral space will obviate the need for splenic flexure mobilization.

Recent advances in laparoscopic surgery have facilitated its use in the treatment of diverticular disease. In general, laparoscopic surgery results in decreased postoperative pain and hospital length of stay, leading to an earlier return of normal patient function.[32] Once the bowel has been mobilized laparoscopically, the increasing use of the technique of hand-assisted laparoscopic surgery (HALS), or "handoscopy," has allowed for the use of minimally invasive surgery even in complicated diverticular disease (Fig. 146–16).[33] The opportunity for the surgeon to preserve tactile sense facilitates dissection of the chronically inflamed sigmoid colon and shortens operative time and the learning curve. HALS has had its greatest impact in separating the colon from the left pelvic sidewall and in resecting the thickened sigmoid mesentery (Fig. 146–17). The use of the surgeon's hand (usually nondominant) simplifies maneuvers such as control of bleeding, manipulation of staplers into position, or occlusion of the bowel during testing of a

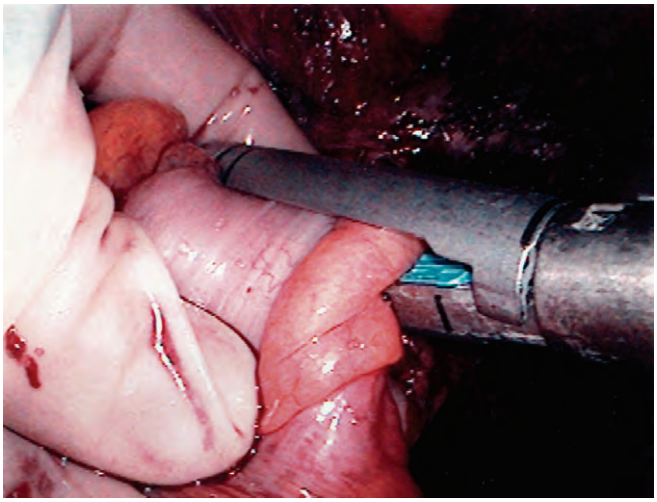

Figure 146–16. Hand-assisted laparoscopic surgery demonstrating transection of rectosigmoid colon with an endoscopic stapler.

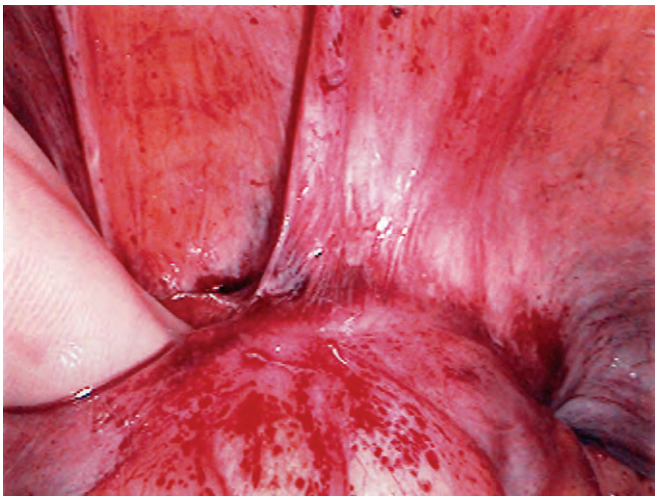

Figure 146–17. Inflamed sigmoid colon stuck to the left pelvic sidewall. Separation is facilitated using hand-assisted laparoscopic surgery.

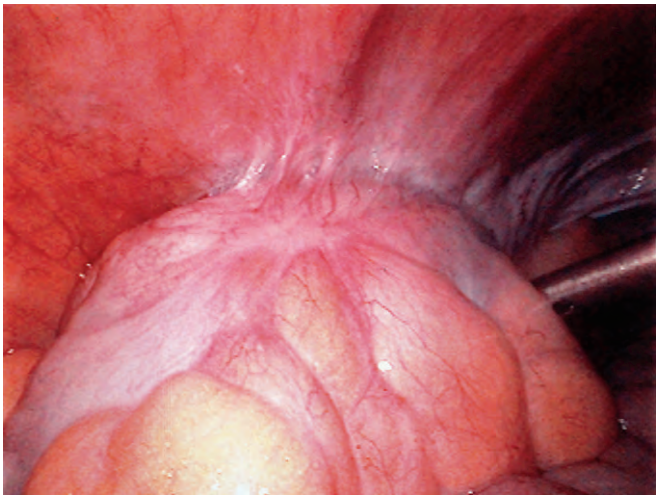

Figure 146–18. Appearance of a colovesical fistula. There is fusion of the chronically inflamed sigmoid colon to the urinary bladder.

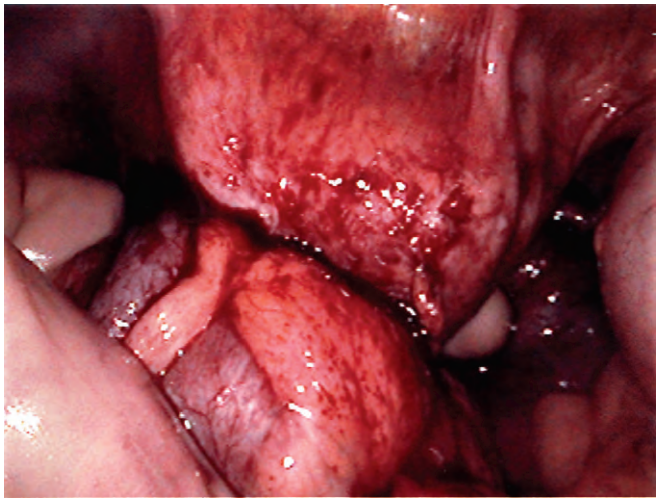

Figure 146–19. Hand-assisted laparoscopic surgical approach to a colovesical fistula. The surgeon's finger is encompassing the fistula prior to division.

low-stapled anastomosis. It is clear that HALS is becoming increasingly common when managing surgical disorders of the colon.[34,35]

Diverticular fistulas can usually be treated on an elective basis, since they tend to develop slowly and rarely lead to sepsis with patient instability. Most of these fistulas presumably develop from the sigmoid colon to the bladder or vagina after a diverticular abscess has developed (Fig. 146–18). Once other etiologies have been excluded, treatment essentially involves disconnection of the fistula with resection of the diseased sigmoid colon. It is not necessary to repair the defect in either the bladder or vagina, although a bladder repair is usually performed with an omental flap interposition between the colonic anastomosis and the bladder. A study of 37 patients from the Cleveland Clinic with colovesical fistulas did not demonstrate a benefit for any single type of repair.[36] Postoperatively the bladder is routinely drained for 5 to 7 days, although this time interval can be shortened if a voiding cystogram is obtained.

There are several technical aspects to division of the diverticular fistula that facilitate the dissection and increase the safety of the procedure. It is beneficial to divide the proximal bowel early in the operation and to identify the ureter at the pelvic brim. If a phlegmon is present, dissection distal to the fistula at the level of the proximal rectum can facilitate isolation of the fistulous segment.

Finally, the fistula can be "pinched" between the surgeon's fingers, allowing safe separation of the fused organs and minimizing injury to the bladder or ureter. If performed laparoscopically, this maneuver is made significantly easier by using handoscopy (Fig. 146–19). In a series of 36 HALS performed for colovesical fistulas, 75% were successfully completed without the need for conversion.[37] With increased experience over a 6-year period, the conversion rate decreased below 15%.

In most patients, primary anastomosis can be performed safely since the degree and extent of the surrounding acute inflammation are minimal. The surgeon's experience appears to be a variable in the success of this procedure, with the goal of avoiding the need for temporary diversion. In one study of surgery for diverticular fistulas, colorectal surgeons experienced a lower rate of diverting procedures and postoperative complications as compared with general surgeons.[38]

Emergency Surgery

Many patients with diverticular disease develop a surgical emergency as their first presentation.[39] Generalized peritonitis, free perforation, and high-grade obstruction all require urgent surgical intervention, and bleeding may also lead to an emergency operative procedure.

Historically, surgery for diverticular disease was performed in stages. By the 1980s, however, it had become clear that leaving the diseased colon in place while merely diverting the fecal stream (three-stage resection) was associated with unacceptably high morbidity and mortality rates. Removing the septic focus at the time of the initial operative intervention decreased mortality from 25% to 30% to less than 10%. Given these findings, as well as the decreased likelihood of ever completing all three operations and restoring intestinal continuity, a three-stage approach is rarely used today in the treatment of complicated diverticular disease.

When operating on unprepped bowel in the case of perforation, generalized peritonitis, or obstruction, the most difficult decision relates to restoration of intestinal continuity. Systemic issues such as hemodynamic instability, malnutrition, or coagulopathy are of paramount concern and may preclude any consideration of performing an intestinal anastomosis. Otherwise, the degree of peritoneal contamination at the time of surgery reliably predicts the safety of performing a primary anastomosis versus resection with diversion. The classification system devised by Hinchey et al. attempts to describe the

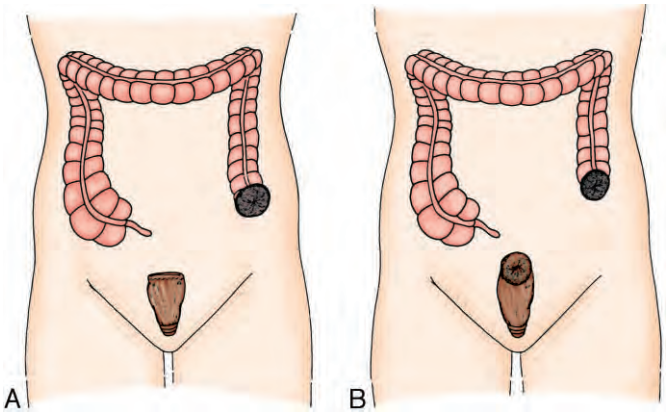

Figure 146–20. The Hartmann procedure is commonly done for patients who have perforated diverticulitis without a bowel prep **(A)**. If the distal bowel reaches the abdominal wall, a mucous fistula is constructed **(B)**. (**A** and **B,** From Gordon PH: Diverticular disease of the colon. In Gordon PN, Nivatvongs S [eds]: Principles and Practice of Surgery for the Colon, Rectum, and Anus. St. Louis, Quality Medical, 1992, p 766.)

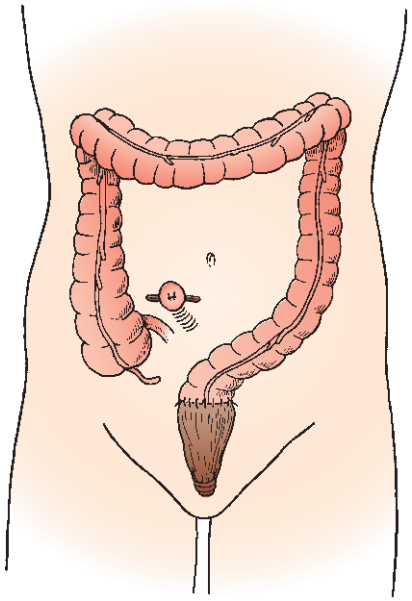

Figure 146–21. An alternative to the Hartmann procedure, including sigmoid resection, primary anastomosis, and proximal diverting loop ileostomy.

degree of inflammation associated with complicated diverticular disease (see Fig. 146–12), but it does not account for patient comorbidities. Resection with primary anastomosis (one stage) appears to be safe for Hinchey I and II stages, whereas we favor resection and diversion in cases of free purulent or feculent peritonitis (Hinchey stages III and IV).[40,41] Controversy exists, however, and there are reports of successful resection and primary anastomosis for stage III and IV cases employing extensive abdominal lavage and on-table colonic lavage.[42-46]

The Hartmann procedure is the most widely practiced two-stage operation for the treatment of diverticulitis. First described by the French surgeon, Henri Hartmann, in 1921 as an alternative for the treatment of carcinoma of the rectosigmoid, it involves resection of the sigmoid colon with proximal diversion and oversewing of the distal stump (Fig. 146–20A).[47] Alternatively, the distal segment may be exteriorized to facilitate subsequent restoration of intestinal continuity (see Fig. 146–20B). However, the latter procedure usually is not feasible for diverticulitis, since resection of the involved segment does not leave enough length to reach the anterior abdominal wall. The operative mortality of performing a Hartmann procedure for perforated diverticulitis ranges from 0 to 15%. A disadvantage of this approach is that a second major procedure with attendant risks is needed to restore intestinal continuity.

Silvis and Keeman attempted to distinguish between one- and two-stage resections when stratified for Hinchey classification. While mortality rates were similar between the two types of operations for Hinchey I and II classes, the mortality rate was more than double for one-stage operations when used for Hinchey III (17% vs. 8%) and Hinchey IV groups (64% vs. 28%).[48]

The timing of the second operation to reverse the colostomy after the Hartmann procedure is of some importance. Most surgeons recommend waiting at least 3 months to allow for postoperative inflammation to resolve. Furthermore, patients can return to complete health after having undergone emergency surgery. The second operation can be technically difficult, leading to a complication rate of 20% to 46%, including an anastomotic leakage rate of 16%. Furthermore, at least 30% of patients who undergo a Hartmann procedure will never have intestinal continuity restored.

An alternative procedure attempts to reduce the difficulties of reversing the Hartmann procedure. At the time of initial resection, a primary anastomosis is performed with creation of a proximal diverting loop ileostomy (Fig. 146–21).[49,50] This is a much easier stoma to reverse, and the procedure avoids reoperation in the pelvis.

Obstruction

Obstruction is the indication for surgery in approximately 10% of patients requiring operation for symptomatic diverticular disease. Only rarely, however, is emergency surgery required because of a high-grade obstruction placing the patient at risk for cecal perforation. Typically, patients experience repeated bouts of acute diverticulitis that heal with progressive scarring. This leads to mild obstructive symptoms including pain, bloating, and chronic constipation.

When a patient presents with complete obstruction and develops proximal colonic dilation, urgent surgery is required to prevent the life-threatening complication of perforation. In this setting it is difficult, if not impossible, to perform an adequate preoperative mechanical preparation. Since proximal fecal loading has been

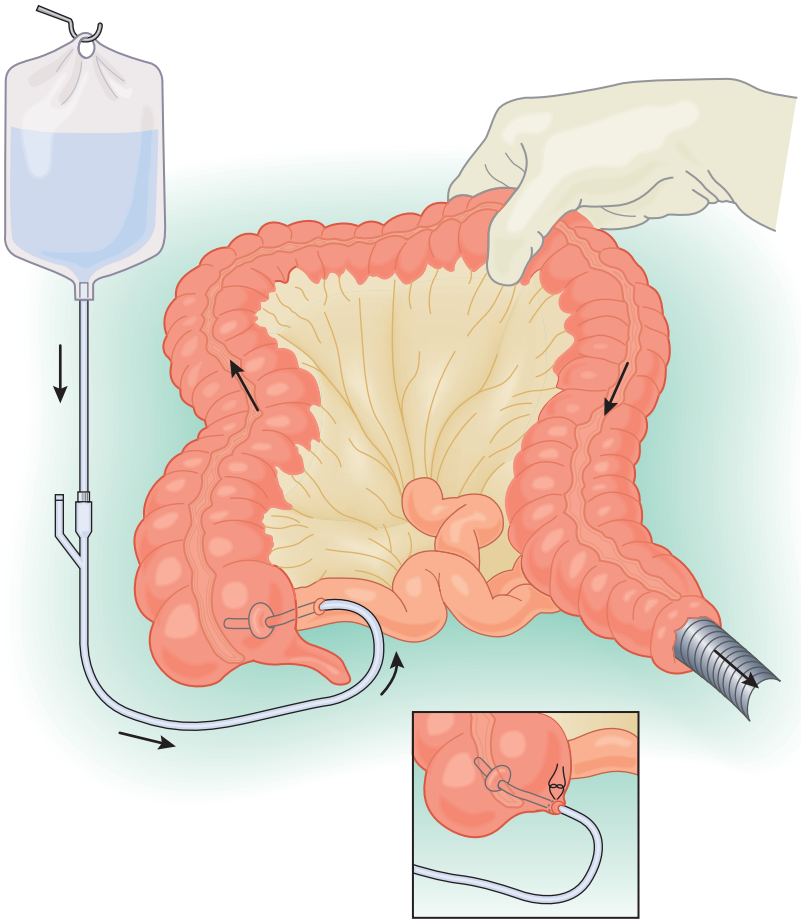

Figure 146–22. Technique of on-table lavage. The Foley catheter is introduced through the base of the appendix. If the appendix has been removed, the catheter can be placed through an enterotomy in the ileum or a cecotomy. Corrugated plastic tubing introduced into the colon is passed off the table into canisters. (From Ross HM, Roberts PL: Role of on-table lavage for complicated diverticular disease. Semin Colon Rectal Surg 11:219, 2000.)

demonstrated to impair anastomotic healing, this situation has generally mandated a staged resection such as a Hartmann procedure, with delayed restoration of bowel continuity. Alternatively, an anastomosis can be performed with proximal diversion by a loop ileostomy. If a diverticular stricture cannot be reliably diagnosed preoperatively, a wide mesenteric resection must be performed in case the obstruction is secondary to sigmoid carcinoma.

In the absence of hemodynamic instability or a perforation with feculent peritonitis, on-table colonic lavage can be used to prepare the bowel intraoperatively for a primary anastomosis. The technique was first described by Muir in 1968 and refined by Radcliffe. Following intestinal resection, both flexures are mobilized, an appendectomy is performed, and an appendicostomy tube is placed through the base of the appendix. Corrugated tubing is inserted into the end of the colon proximal to the resection and secured with a Dacron tape (Fig. 146–22). Three to six liters of saline are used to wash out any feculent material from the colon. Using this technique, Lee et al. reported a series of 33 patients undergoing on-table lavage for complicated diverticular disease.[51] One patient developed an anastomotic leak and was the only mortality reported. There was a 42% morbidity rate, but the technique appears safe for patients with obstruction who are hemodynamically stable during the operation.

Bleeding

Lower gastrointestinal bleeding occurs in approximately 20% of patients with diverticulosis, of whom 5% experience severe hemorrhage. Although bleeding spontaneously ceases in 80% to 90% of patients, the risk of rebleeding approaches 25%. For this reason, a rapid evaluation of the patient should take place even while the patient is being resuscitated in the emergency department.

Since 10% of all lower gastrointestinal bleeding ultimately arises from a gastroduodenal source, a nasogastric tube should be placed early in the evaluation. Furthermore, proctoscopy must be performed to confirm that the source of bleeding is not from the rectum or anal canal.

Every attempt should be made to localize the source of bleeding preoperatively, since the mortality rate of emergency subtotal colectomy ranges from 10% to 50%. Although nuclear imaging scans can detect bleeding at rates as low as 0.1 ml/min, surgery based solely on this evaluation misses the source of bleeding 25% of the time. Angiography has the benefit of localizing the bleeding site prior to surgery accurately, reducing the operative mortality from 50% to 10%. Furthermore, superselective embolization can be performed safely, obviating the need for surgery in more than 80% of patients in whom it is used (see Fig. 146–8).

An alternative approach for localizing a colonic source utilizes colonoscopy. Advocates of emergency colonoscopy during the initial period of presumed ongoing bleeding point to the high rate of localization (74% to 85%) while incurring low complication rates. The examination is facilitated by either rapid whole-gut lavage via a nasogastric tube or, alternatively, the use of cleansing enemas combined with frequent, aggressive pulsatile irrigations during the colonoscopy procedure. Additional arguments for this approach point to the potential therapeutic benefit of colonoscopy and its cost-effective advantage when compared with arteriography.

Admittedly, emergency colonoscopy in a patient with ongoing bleeding is a difficult technical exercise, even for the experienced endoscopist. Furthermore, hemodynamic instability limits the ability to sedate patients well for colonoscopy, thereby increasing the difficulty of the examination. Given these considerations, a more reasonable, safe approach is to stabilize the patient first and then perform early colonoscopy after a rapid gut lavage with polyethylene glycol. Only if the patient presenting with lower gastrointestinal bleeding cannot be easily stabilized should other diagnostic modalities be employed first. The diagnostic accuracy of early colonoscopy for lower gastrointestinal bleeding has been reported to be 40% to 90%. Although the varied results depend to a large degree on the timing of the procedure, the criteria for diagnosis also play a role. Findings at colonoscopy that help support a definitive source include an actively bleeding site, isolated fresh blood in one segment of the colon only, or adherent clot to a "lesion."

Should emergency surgery be necessary without the benefit of preoperative localization, intraoperative colonoscopy can be performed to assist in identifying the bleeding site. If a localized site of bleeding is not found within the colon, an emergency subtotal colectomy should be performed. The mortality rate in this setting is equal to that of a blind segmental resection but with a much lower rebleeding rate. If a localized site of bleeding is not found intraoperatively, maneuvers such as multiple colotomies or a transverse colostomy should be discouraged—they only increase the complication rate without controlling the source of bleeding.

Postresection Diverticulitis

Recurrent diverticulitis following resection is uncommon, occurring in 1% to 10% of patients. Given the unusual nature of this situation, a complete evaluation should be performed to eliminate other potential causes. Symptoms of irritable bowel syndrome frequently overlap those of diverticular disease, with the exception of fever and leukocytosis. Other conditions such as Crohn's disease, carcinoma, and ischemic colitis may be confused with acute diverticulitis. Previous pathology specimens should be reviewed with the differential diagnosis in mind.

The most likely explanation for the development of recurrent disease is an incomplete resection at the time of the initial operation. While the inflammatory process frequently involves only a small portion of the sigmoid colon, a complete sigmoidectomy needs to be performed. The distal point of resection should be through soft, pliable bowel at the rectosigmoid junction. This area is identified by the convergence of the taeniae coli into a confluent sheet of longitudinal muscle surrounding the rectum. In a series of 501 patients undergoing a resection for diverticular disease, recurrent diverticulitis developed in 12.5% in whom the sigmoid colon was used as the distal resection margin. This contrasts to a 6.7% recurrence rate when the anastomosis was performed to the rectum.[52]

Although the routine use of ureteral stents is unnecessary for diverticular resections, they can be beneficial when operating for recurrent disease. Typically the inflammatory process involves the left pelvic sidewall that has been dissected previously. The preoperative placement of a left ureteral stent may not prevent injury in this setting, but it can facilitate the dissection and allow for rapid identification of an injury should it occur.

As with the initial operation, reoperative surgery should commence by dissection through noninflamed tissue with early identification of the left ureter. Splenic flexure mobilization becomes mandatory, and often the anastomosis will be to the transverse colon. Most important, the previous anastomosis must be resected and the new anastomosis must incorporate the noninflamed rectum.[53]

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Chapter

147

Hemorrhoids

Anthony J. Senagore

There are few diseases more chronicled in human history than symptomatic hemorrhoidal disease.[1,2] References occur in ancient texts dating back to Babylonian, Egyptian, Greek, and Hebrew cultures.[1,2] Included in many of these writings are multiple recommended treatment regimens, including anal dilation, topical ointments, and the intimidating red hot poker.[3,4] Although few people have died of hemorrhoidal disease, many patients wish they had, particularly after therapy, and this fact led to the beatification of St. Fiachre, the patron saint of gardeners and hemorrhoidal sufferers.[5] Hopefully, this discussion will guide the practitioner in a more humane approach to hemorrhoidal disease, with the emphasis on cost-effectiveness with minimal morbidity and mortality.

ANATOMY AND ETIOLOGY

The hemorrhoidal cushions appear predictably in the right anterior, right posterior, and left lateral positions, although there may be intervening secondary hemorrhoidal complexes that blur this classic anatomy.[6] The blood supply is similarly constant, deriving from the superior rectal artery, a branch of the inferior mesenteric; the middle rectal arteries arising from the internal iliac arteries; and the inferior rectal arteries arising from the pudendal arteries. The venous drainage transitions from the portal venous system above the level of the dentate line to the systemic venous system below this level.[6]

It was originally reported that the vascular cushions from the termination of the vascular supply within the anal canal contributed to the maintenance of anal continence.[6] Hemorrhoidal disease occurs as the result of abnormalities within the connective tissue of these cushions, producing bleeding with or without prolapse of the hemorrhoidal tissue.[7] This can occur as the result of excessive straining, chronic constipation, or low-fiber dietary intatke.[8] A clear understanding of the pathophysiology is important when considering therapeutic interventions. At the earlier stages of disease progression, when the major manifestation is transudation of blood through thin-walled, damaged veins and/or arterioles, ablation of the vessels should be adequate. Conversely, in late stages of the disease, when there is significant disruption of the mucosal suspensory ligament, a technique requires fixation of the mucosa to the underlying muscular wall for effective therapy.[9] Internal anal sphincter dysfunction may play a role, since a number of investigators have demonstrated increased internal anal sphincter tone in patients with hemorrhoidal disease.[10-12] In reality, probably a combination of all of these factors is important for the ultimate development of large prolapsing hemorrhoidal disease.

The standard classification for hemorrhoidal diseases[13] is as follows:

- Grade I = bleeding
- Grade II = protrusion with spontaneous reduction
- Grade III = protrusion requiring manual reduction
- Grade IV = irreducible protrusion of hemorrhoidal tissue

Although this staging system tends to correlate with patient's symptoms, it is unclear that it can be completely relied on when making therapeutic decisions. As outlined later, it is important to consider the relative role of internal hemorrhoidal tissue as well as external hemorrhoidal skin tagging when choosing a modality for complete resolution of all of the patient's symptoms.[7]

CLINICAL EVALUATION

Bleeding, protrusion, and pain are among the most common symptoms associated with hemorrhoidal disease. However, Mazier reported on a series of 500 patients with anorectal complaints they associated with their hemorrhoids and ultimately only 35% of patients were found to have any significant hemorrhoidal disease.[14] Hemorrhoidal bleeding typically results in bright red blood either on the toilet paper or actually

into the commode after bowel movements, generally painless in nature. More vigorous bleeding can occur, however, as the hemorrhoids enlarge and particularly in advanced stages when a portion of the complex is fixed externally, allowing the blood to drip or spurt into the commode. Usually, prompt reduction of the protruding mass causes this symptom to abate. Acute thromboses of internal or external hemorrhoids are usually associated with severe pain in association with a palpable perianal mass. These patients are generally quite uncomfortable, and the diagnosis is immediately obvious on clinical examination.

Examination of the patient with hematochezia, although tailored by the age of the patient, should include sufficient investigations to rule out a proximal source of bleeding such as inflammatory bowel disease and neoplasia. Hemorrhoids should not be dismissed as the cause of iron deficiency anemia as this is an uncommon occurrence.

I prefer to examine the patient in the left lateral position with the knees drawn up toward the chest as high as possible. This approach allows relative patient comfort and the ability to clearly inspect the perianal skin and perform anoscopy and proctosigmoidoscopy. A careful digital examination of the anal canal and distal rectum should be performed to include the prostate in men. An anoscope is essential to clearly inspect the hemorrhoidal tissue and anal canal. The three common locations for hemorrhoids should be inspected, and the size, friability, and ease of prolapse of these areas should be recorded. Following this, the decision regarding the need for more proximal colorectal evaluation should be considered, although rigid proctoscopy would be the minimum in all patients. After the hemorrhoids are appropriately graded, a discussion can be enjoined with the patient regarding treatment options.

NONEXCISIONAL OPTIONS

Most patients evaluated for hematochezia that ultimately proves to be hemorrhoidal in origin can be managed with fiber supplementation and a variety of available anal ointments. Although it is not clearly proven that constipation is causal, it appears of practical utility to improve bowel function and thereby reduce hemorrhoidal complaints in most early-stage patients. Similarly, the ointments available, although homeopathic, may minimize ongoing trauma to the hemorrhoidal cushions and similarly reduce symptoms. The remaining nonoperative and operative interventions should be reserved for patients with advanced hemorrhoidal disease who are unresponsive to conservative medical management.

SCLEROTHERAPY

Sclerotherapy of symptomatic internal hemorrhoidal disease was first advocated by Mitchell in 1871 and has enjoyed significant experience.[15] The purpose of sclerotherapy is ultimately to scar the submucosa, resulting in atrophy of the tissue injected and scarification with fixation of the hemorrhoidal complex within its normal location in the anal canal. A variety of solutions have been advocated, although it appears that sodium morrhuate and sodium tetradecyl sulfate predominate currently. This modality is most effective in situations with minimal enlargement of hemorrhoidal complexes where the primary complaint is bright red rectal bleeding.

The procedure is performed with the patient in the left lateral decubitus position. An anoscope is inserted to clearly identify the symptomatic complex and a 25-gauge spinal needle is used to instill the sclerosant into the submucosal space (Fig. 147–1). The syringe should be

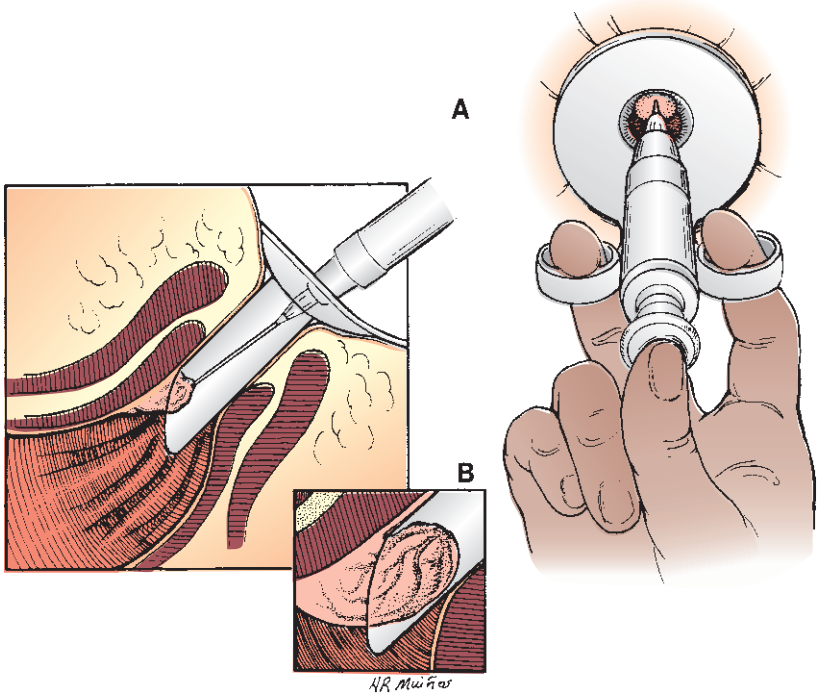

Figure 147–1. **A,** Injection of internal hemorrhoid. **B,** Postinjection striations.

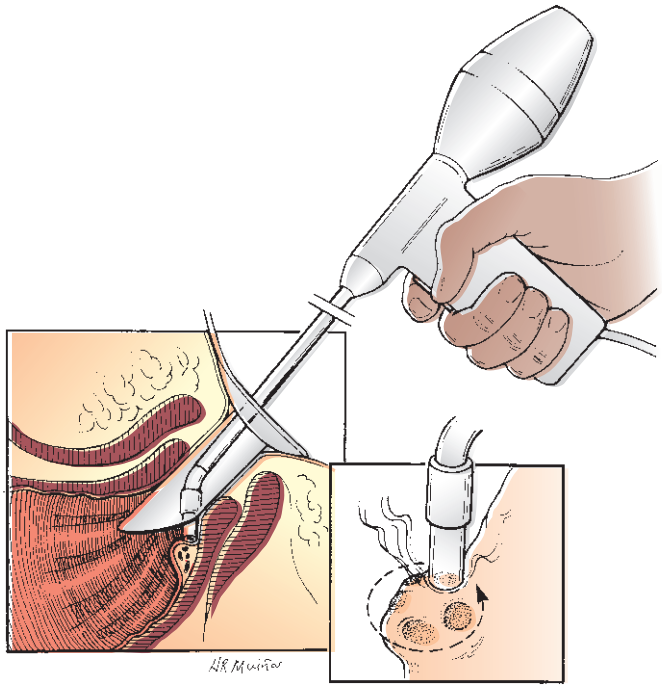

Figure 147–2. Infrared coagulation. *Left,* Coagulator inserted through a Hirschman anoscope. *Right,* Coagulation points.

aspirated prior to injection to avoid a direct intravascular injection. Typically 1 to 2 ml of sclerosant is adequate. The surgeon can inject as many locations as desired because the procedure is essentially painless. It is important, however, not to circumferentially inject the anal canal because this may induce stricture formation.

BIPOLAR DIATHERMY

Bipolar diathermy employs electrical current to coagulate the hemorrhoidal tissue, including the mucosa and submucosa.[16,17] The machine generates a 2-second pulse of energy to accomplish the treatment. Once again, this approach is applicable for small bleeding hemorrhoids and probably has no greater efficacy than does sclerosing.

Other variations on the use of energy to destroy internal hemorrhoids includes infrared coagulation and Ultroid (direct-current) therapy.[17,18] The infrared coagulation employs a tungsten halogen lamp that generates heat energy generally for a 1.5-second period resulting in destruction of the mucosa and submucosa at the application site (Fig. 147–2). The depth of penetration of this injury is usually 3 mm. Conversely the Ultroid uses electrical current that is applied for up to 10 minutes per complex treated. Ultimately, all of these new modalities are a variation on the theme of local tissue destruction and fixation of the hemorrhoidal tissue at the appropriate level. There is probably no advantage of one technique over the other; however, sclerotherapy offers an advantage to the physician since minimal instrumentation is required.

HEMORRHOIDAL LIGATION WITH RUBBER BANDS

Barron was the first to describe hemorrhoidal banding using rubber bands in 1963.[19] Since this original description there have been a number of reports that have documented the significant efficacy banding offers for the management of most patients with grades II and III internal hemorrhoids.[20-24] The procedure is generally well tolerated without the need for prescription analgesia if the band is placed above the level of the dentate line. The technique is demonstrated in Figure 147–3. It is important to ask patients if they experience any pain during placement of the bander, prior to deployment of the band. If they have pain prior to placement of the bander, it will worsen after deployment. Discomfort immediately after band placement may be reduced by the injection of a local anesthetic agent; however, this does not appear to be a long-lasting benefit.[25] Banding does carry the rare but frequently fatal complication of postbanding sepsis, which is heralded by the symptoms of increasing rectal pain, fever, and inability to void.[26-29] It is essential to treat these symptoms early and aggressively with early antibiotic treatment coupled with aggressive surgical drainage.[26]

Bayer et al. reported a series of 2934 patients with 79% of patients achieving complete relief of symptoms following a single session of banding at only one or two locations.[21] Using this approach, patients required multiple sessions for control of symptoms (2 sessions, 32%; 3 sessions, 17%; 4 sessions, 25%; and ≥5 sessions, 20%). Although the multiple sessions required are a negative aspect of this technique, only 2.1% of patients required excisional hemorrhoidectomy. It may be possible to achieve a similar outcome with a shorter duration of therapy, albeit at the expense of greater post-treatment pain, by banding all symptomatic hemorrhoidal sites at the initial visit.[30-32] Banding techniques appear to be durable after initial control of symptoms, with 69% of patients maintaining long-term relief and only 7.5% ultimately requiring excisional hemorrhoidectomy.[22]

EXCISIONAL HEMORRHOIDECTOMY

The decision to proceed to excisional hemorrhoidectomy requires a mutual decision by the physician and patient that medical and nonexcisional options have either failed or are not appropriate. The usual clinical symptoms that lead to surgical excision are frequent prolapsing of the internal hemorrhoids that results in discomfort and anal seepage. Alternatively, the thickened and prolapsing internal/external hemorrhoidal complexes may make anal hygiene difficult for the patient and may make excision preferable. The final indication for excisional hemorrhoidectomy, although debatable, is the development of acutely thrombosed and gangrenous internal hemorrhoids. Surgical excision of acutely thrombosed external hemorrhoids may also be warranted, primarily for more rapid pain relief and avoidance of a residual skin tag. These external thromboses are usually easily managed in the office setting with local

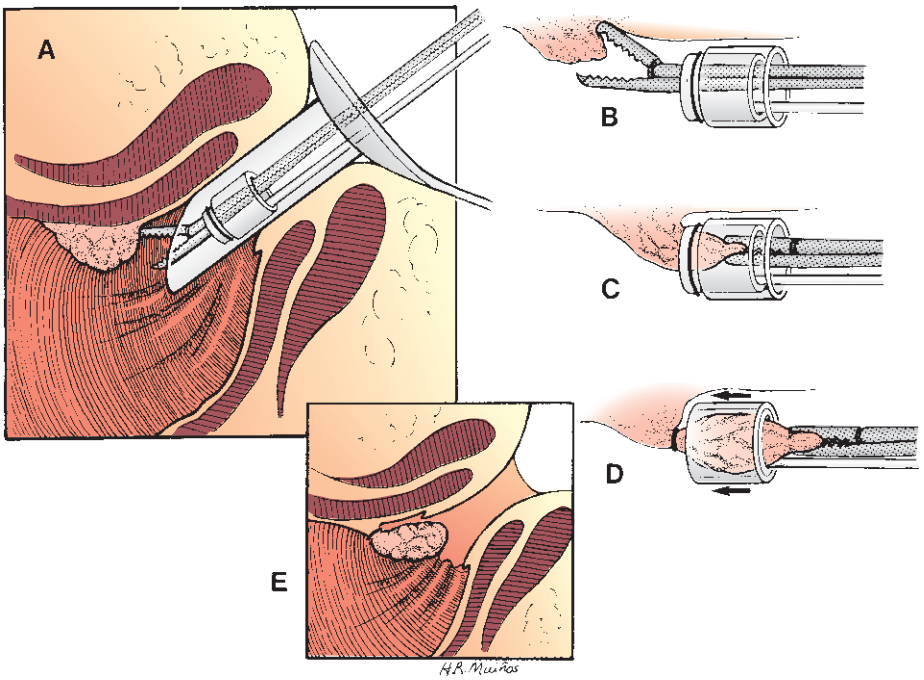

Figure 147–3. **A,** Ligator in a Hirschman anoscope. **B,** Internal hemorrhoid being grasped. **C,** Internal hemorrhoid pulled up into drum. **D,** O-ring applied to internal hemorrhoid. **E,** Appearance of hemorrhoid after ligation.

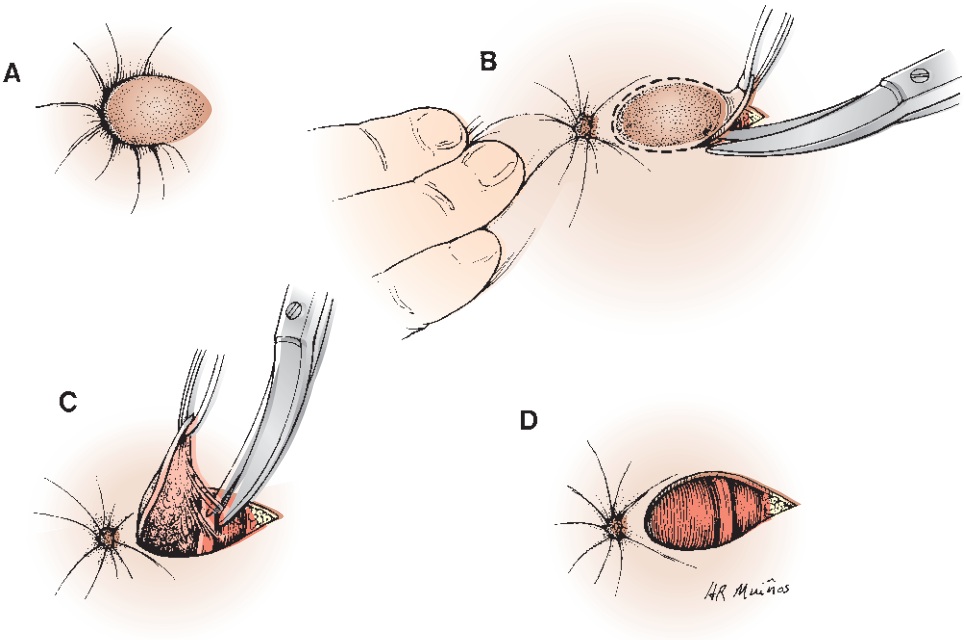

Figure 147–4. **A,** Thrombosed external hemorrhoid in the right lateral quadrant. **B,** Allis clamp applied to apex of thrombosis and elliptical incision made. **C,** Thrombosis dissected free of sphincter. **D,** Appearance of wound after thrombectomy.

anesthesia and complete excision with or without skin closure (Fig. 147–4).

Options for excisional hemorrhoidectomy include the following techniques: Milligan-Morgan hemorrhoidectomy; Ferguson closed hemorrhoidectomy; Whitehead hemorrhoidectomy; and the more recently described stapled hemorrhoidectomy. The procedures are usually performed in the operating theater after minimal preoperative preparation of the bowel. The use of lasers for excisional hemorrhoidectomy offers no advantage and in fact causes delayed healing, increased pain, and increased cost.[33] Anesthetic selection is usually left to the anesthesiologist and patient; however, local anesthesia supplemented by the administration of intravenous narcotics and propofol is highly effective and short acting. The use of spinal anesthesia, although effective, may increase the risk of postoperative urinary retention due to a higher intraoperative administration of intravenous fluids.

The Milligan-Morgan hemorrhoidectomy, which is widely practiced in Europe, was originally described in 1937, and its efficacy has been documented in many

series subsequently.[34-36] This technique includes resection of the entire enlarged internal hemorrhoid complex, ligation of the arterial pedicle, and preservation of the intervening anoderm.[33] The distal anoderm and external skin are left open to minimize the risk of infection in the wounds. Results from this technique have shown this to be a safe and effective means for managing advanced hemorrhoidal disease.[33] However, the fact that the external wounds are left open for delayed healing can be a cause of considerable discomfort and prolonged morbidity after this procedure. The closed Ferguson hemorrhoidectomy was proposed as an alternative to the Milligan-Morgan technique and enjoys a similar large body of evidence regarding its safety and efficacy.[37-40] This technique employs an hourglass-shaped (centered at the midportion of the anoderm) excision of the entire internal/external hemorrhoidal complex, preservation of the internal and external anal sphincters, and primary closure of the entire wound. Occasionally, it is necessary to undermine flaps of anoderm and perianal skin to allow removal of intermediate hemorrhoidal tissue while preserving the bridges of anoderm between pedicles. This technical adjustment avoids postoperative strictures.

The Whitehead hemorrhoidectomy, described in 1882, was devised to eradicate the enlarged internal hemorrhoidal tissue in a circumferential fashion and to relocate the prolapsed dentate line that is often a component of prolapsing hemorrhoids.[41] Although this technique enjoyed a long period of widespread application, it was subsequently largely abandoned because of the high rates of mucosal ectropion and anal stricture.[42-45] The technique has enjoyed renewed support, with several authors documenting minimal stricture rates and no occurrences of mucosal ectropion.[46,47] Despite these promising reports, the Whitehead procedure is technically demanding because of the need to accurately identify the dentate line and relocate it to its proper location.

INSTRUMENTATION FOR EXCISIONAL HEMORRHOIDECTOMY

The specific techniques for excisional hemorrhoidectomy were reviewed earlier, and this section discusses the relative benefits of scalpel and the available energy-delivering excisional tools. Cold scalpel or scissor excision has long been the mainstay of surgical hemorrhoidectomy, and the data on outcomes are well validated. Over the past 10 to 15 years, a variety of new devices have been advocated for hemorrhoidectomy. These energy-based cutting devices have been devised to allow simultaneous tissue division and coagulation. The main advantage proposed for these devices is provision of hemostasis without need for suture ligation and therefore reduction in postoperative pain. However, these benefits must be interpreted in the context of the significant cost of acquisition of the devices compared to a disposable scalpel blade.

The first energy cutting tool applied to hemorrhoidectomy is standard monopolar electrocautery. The tool has been reported widely for the two dominant types of hemorrhoidectomy. Surgeons using this tool have also employed various degrees of wound closure by suture, ranging from pedicle ligation only to complete wound closure.[48-50]

Laser technology has been evaluated both as a means of cutting hemorrhoidal tissue and as a technique for ablation. Zahir et al. evaluated the role of the Nd-YAG laser for excision and coagulation of residual tissue and reported a reduction in postoperative pain and a greater percentage of patients returning to work at 1 week.[51] Alternatively, we found delayed wound healing, increased cost, and increased pain scores with Nd-YAG hemorrhoidectomy compared with scalpel excision.[52] Hodgson and Morgan evaluated a series of patients with second- and third-degree hemorrhoids managed by CO_2 excision, with only one patient readmitted for postoperative hemorrhage.[53] The data suggest that either Nd-YAG or CO_2 laser excision may be performed; however, it is not clear that the added expense or benefits are superior to scalpel or scissor excision.[54]

A bipolar cautery device capable of simultaneous tissue division and blood vessel coagulation is the LigaSure. This device has been compared to monopolar diathermy hemorrhoidectomy with most of the data suggesting reductions in operative time and early postoperative pain.[55,56] Chung and Wu compared a sutureless LigaSure technique to the standard closed Ferguson hemorrhoidectomy and confirmed a reduction in operative time and pain reduction during the first 48 hours.[56] However, there were no significant differences in wound complications or time to full recovery. Similarly, a comparison of LigaSure to a standard Milligan-Morgan hemorrhoidectomy confirmed reduction in operating time and early postoperative pain.[55]

A competing technology is the Harmonic scalpel, which relies on a rapidly reciprocating blade to generate heat for coagulation and tissue transection. The largest reported experience was provided by Armstrong et al. with 500 consecutive excisional hemorrhoidectomies.[57] They reported a low postoperative hemorrhage rate (0.6%). The overall postoperative complication rates were low, with urinary retention in 2%, fissure in 1%, and abscess/fistula in 0.8%. Several subsequent prospective, randomized comparisons of diathermy to Harmonic scalpel failed to confirm any advantages between the two tools.[58-60]

Probably the best guidance on this topic is the study by Chung et al., who evaluated scissor/Milligan-Morgan, Harmonic scalpel, and bipolar scissors for hemorrhoidectomy: Harmonic Scalpel™ demonstrated superior early pain scores to scissor; however, the long-term recovery was similar between the groups.[61] Therefore, the cumulative data suggest that patient benefits are modest for any of the energy-delivering techniques and the cost differential is significant.

PROCEDURE FOR PROLAPSING HEMORRHOIDS

A new management option for advanced hemorrhoidal disease is a nonexcisional hemorrhoidectomy or pexy procedure referred to as the *procedure for prolapsing hem-*

orrhoids (PPH).[62] The technique (Fig. 147–5) uses a circular, transanally placed pursestring suture placed 4 cm from the dentate line and within the enlarged internal hemorrhoids. A 31-mm stapler is then placed transanally to perform a circumferential excision of rectal mucosa just rostral to the hemorrhoidal columns. The procedure provides for a repositioning of both the anoderm and hemorrhoidal columns to the appropriate locations within the anal canal and fixation of these structures via the rectal staple line.

Since the introduction of the PPH technique there have been a large number of prospective randomized trials comparing this approach to excisional hemorrhoidectomy.[63-66] Most of the data support the concept that PPH is associated with a lesser degree of early postoperative pain and a general reduction in the duration of this pain after surgery.[63-67] A recently published multicenter trial comparing PPH to Ferguson closed hemorrhoidectomy confirmed similar benefits and reported a reduction in the need for early reoperation for complications in the PPH group.[68] Although the bulk of the data supports the safety of this new technique, there have been several reports of complications. Molloy and Kingsmore reported a case of severe pelvic sepsis, probably resulting from an inadvertent rectal injury.[69] Cheetham et al. also raised a concern over persistent severe anorectal pain as a possible sequela of PPH.[70]

POSTOPERATIVE MANAGEMENT AFTER HEMORRHOID SURGERY

Regardless of the excisional technique used for treatment of advanced hemorrhoidal disease, the key to effective patient management is avoidance of postoperative complications. Pain is the most frequent complication and is the most feared sequelae of the procedure from the patient's perspective. A variety of analgesic regimens have been recommended, usually consisting of a combination of oral and parenteral narcotics.[71-75] The use of local infiltration of bupivacaine into the wounds and perianal skin has been variably successful in long-term pain reduction.[76,77] Conversely, ketorolac has demonstrated considerable efficacy in managing posthemorrhoidectomy pain.[78] The use of alternative administration routes for narcotics either by patch or subcutaneous pump have been successful in controlling pain; however, the management of these routes of administration can be risky in the outpatient setting because of the risk of narcotic-induced respiratory depression. The most appropriate regimen following outpatient hemorrhoidectomy appears to be intraoperative use of ketorolac, sufficient doses of oral narcotic analgesics for home administration, and supplementation of the narcotics by an oral nonsteroidal medication.

Urinary retention is a frequent postoperative problem following hemorrhoidectomy, ranging in incidence from 1% to 52%.[79-82] A variety of strategies have been used to treat the problem, including parasympathomimetics, α-adrenergic blocking agents, and sitz baths.[83,84] The best approach, however, seems to be a strategy of prevention that includes limiting perioperative fluid administration to 250 ml, an anesthetic approach that avoids use of spinal anesthesia, avoidance of anal packing, and an aggressive oral analgesic regimen.[85]

Early postoperative bleeding (<24 hours) occurs in approximately 1% of cases and represents a technical error requiring return to the operating theater for resuturing of the offending wound.[86] Delayed hemorrhage occurs in 0.5% to 4% of cases of excisional hemorrhoidectomy at 5 to 10 days postoperatively.[87-89] The etiology has been held to be early separation of the ligated pedicle before adequate thrombosis in the feeding artery can occur.[90] The bleeding in this scenario is usually significant and requires some method for control of ongoing hemorrhage. Options include return to the operating theater for suture ligation or tamponade at the bedside by Foley catheter or anal packing.[90-92] The subsequent outcome after control of secondary hemorrhage is generally good with virtually no risk of recurrent bleeding. It may be helpful to irrigate out the distal colorectum with posthemorrhage enemas or at the time of intraoperative control of bleeding to avoid confusion when the residual clots pass per anum.

CONCLUSION

The management of symptomatic hemorrhoidal disease should be directed at the symptom complex of the individual patient. Most of these patients can be successfully treated by improving bowel function, correcting constipation, and using any of a variety of anal ointments. For persistent symptoms, either injection or banding of the internal hemorrhoids is predictably successful. Only a few patients should require excisional hemorrhoidectomy by any of the described techniques. Circular stapled hemorrhoidectomy may prove to be an effective, less painful technique to manage grade III hemorrhoids.

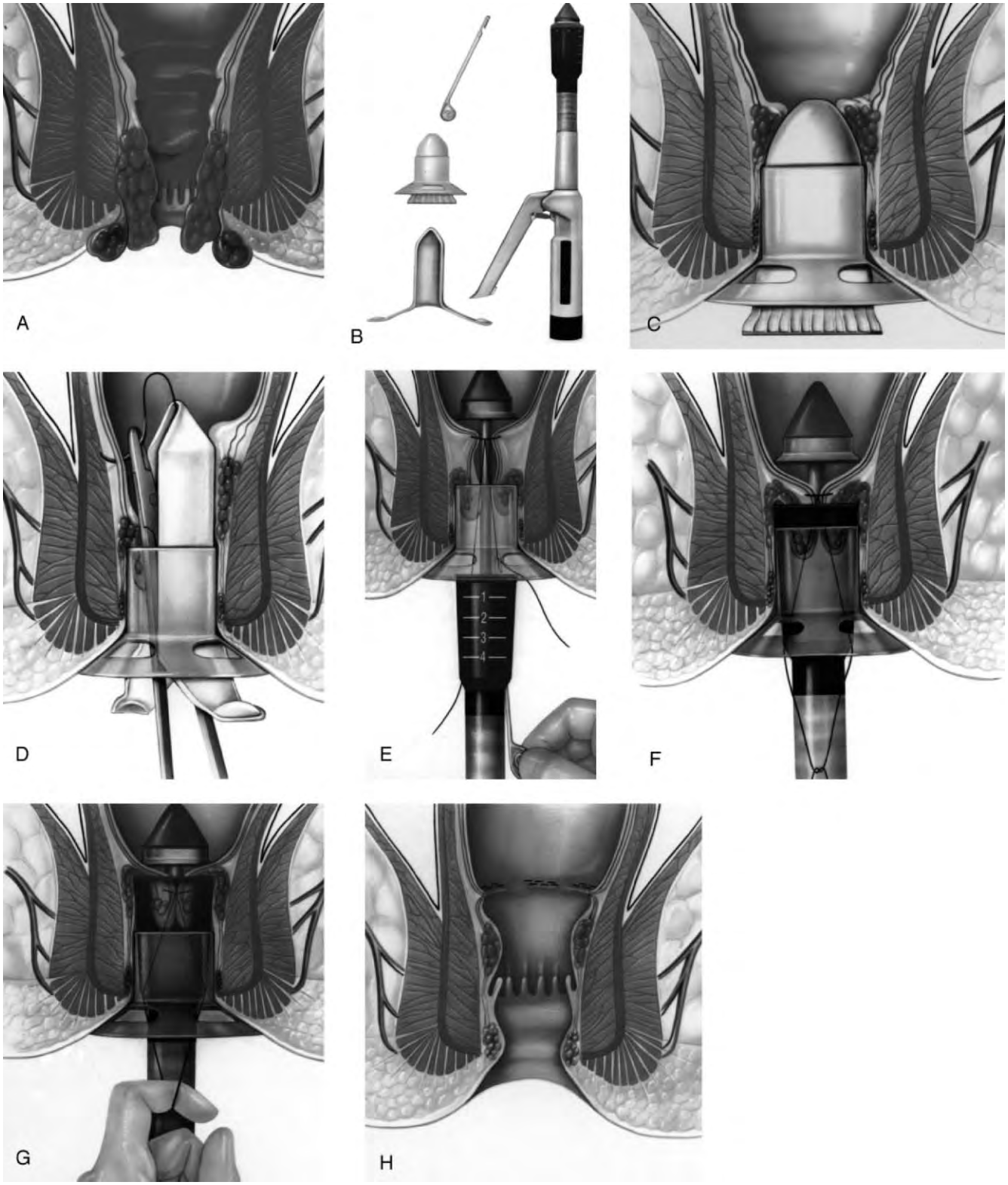

Figure 147–5. **A** and **B,** Identification of the internal hemorrhoidal complexes and the instrumentation utilized for a stapled hemorrhoidectomy are shown. **C** and **D,** A pursestring suture is accurately placed 4 cm above the dentate line by the use of an anoscope. **E** to **G,** The pursestring is tied securely around the rod of the stapling anvil, which allows the hemorrhoidal tissue to be pulled into the barrel of the stapler head. **H,** The stapler is closed, fired, and held in place for 20 to 30 seconds. The staple line should be inspected and any bleeding sites suture-ligated.

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Chapter

148

Fissure-in-Ano

Harry T. Papaconstantinou · Philip Huber, Jr. · Clifford L. Simmang

Anal fissure (fissure-in-ano) is a common condition that usually presents as anal pain on defecation. Bleeding occurs but is usually scant, bright red, and found on the tissue when cleansing after a bowel movement. Anal fissure is described as a linear defect, or laceration, in the anoderm, located between the dentate line and the anal verge. An acute fissure is a simple laceration, whereas a chronic anal fissure has exposed internal anal sphincter muscle fibers at the base and built-up edges. In addition, there may be a perianal skin tag at the external margin of the fissure and a hypertrophied papilla at the dentate line. Chronic fissure is defined by these three findings: (1) visible muscle, (2) a skin tag (sentinel tag), and (3) hypertrophied papilla (Fig. 148–1). Acute and chronic anal fissures are almost always located in the midline, with the posterior location predominating (women, 90%; men, 99%). Fissures located off the midline are usually associated with more serious systemic diseases such as Crohn's disease and immunodeficiency syndromes (Fig. 148–2).

ETIOLOGY

Trauma to the anal canal, due to passing hard stools, is probably the most frequent cause of fissure-in-ano. Loose, watery stools are also associated with the development of anal fissures. Preexisting anal canal irritation has been postulated to lead to fissure. Scarring, stricture, and stenosis from prior anal injury or surgery are recognized conditions that predispose to fissure formation.[1] Because fissures occur most often in the posterior midline, various structural theories have been proposed as causes,[2-4] the most compelling of which suggests that the vascular anatomy of the internal sphincter may be a factor.

In 1989, Klosterhalfen and associates[5] reported on anatomic dissections that detailed the blood supply of the inferior hemorrhoidal artery. In most cadaver specimens (85%), the posterior commissure of the anal canal was not directly perfused except by end arterioles. Moreover, branching from the sphincteric arterioles occurred at right angles to the parent vessels and coursed perpendicularly through the circular fibers of the internal sphincter. These anatomic findings established the possibility of decreased mucosal perfusion, particularly in the posterior midline. In addition, sphincter spasm or hypertonicity further decreases blood flow. Schouten and colleagues[6,7] have shown increased anal canal pressures correlated with decreased mucosal blood flow as measured by laser Doppler flowmetry. Reports of normal anal maximal resting pressure are highly variable, ranging from 60 to 100 cm H_2O in women and slightly higher in men; however, the measurement is defined as the maximal pressure recorded at rest.[8] The higher pressures seen in patients with anal fissures produce a sawtooth pattern on manometry tracings. This vascular-anal resting pressure hypothesis has prompted trials aimed at improving blood flow and lowering anal canal resting pressures. Whether sphincter hypertonia is a cause or effect is unknown.

The most common systemic conditions that are associated with atypical anal fissure/anal ulcer are Crohn's disease and acquired immunodeficiency syndrome. Both of these conditions lead to an immunocompromised patient. Atypical features include fissures off the true midline, shaggy large defects with undermined edges, and granulation tissue in the base. Actual cavitation of the internal sphincter is another ominous clue to the presence of systemic disease. In the immunocompromised patient, a fissure or an ulcer and a concomitant mass should raise the question of malignancy. Lymphoma, leukemic ulcer, and anal canal epithelial tumors are often associated with surface defects. There are subtle changes that distinguish these conditions from uncomplicated acute or chronic anal fissure.

Infections also cause fissure-in-ano. Although uncommon in the United States today, syphilis and tuberculosis were seen not infrequently in the last century. More commonly seen today are the viral conditions of

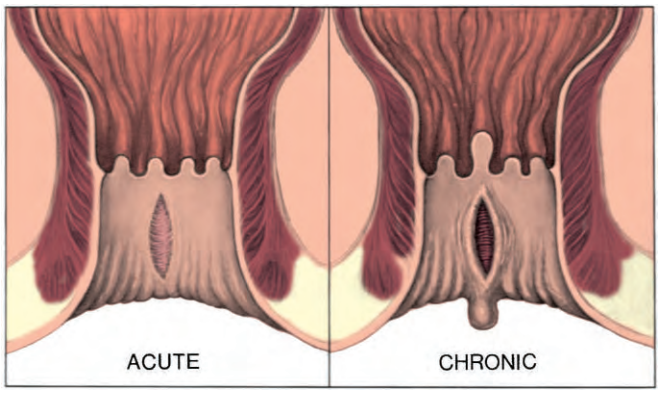

Figure 148–1. Acute and chronic fissure. (Modified from Hicks TC, Ray JE: Rectal and perianal complaints. In Polk HC Jr, Stone HH, Gardner B [eds]: Basic Surgery, 3rd ed. Norwalk, CT, Appleton-Century-Crofts, 1987, p 455.)

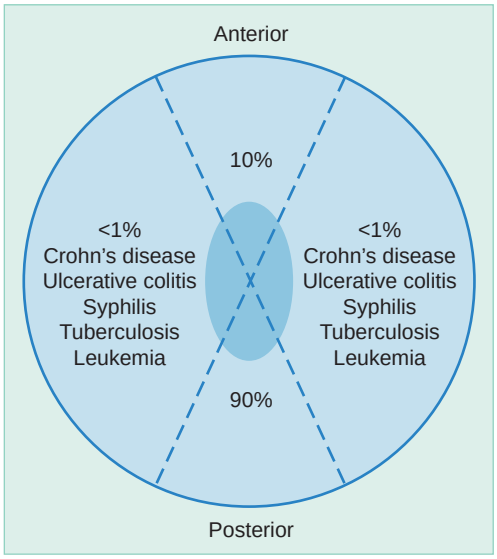

Figure 148–2. Diagram of the location of typical fissures and atypical fissures where a systemic illness should be suspected.

herpes simplex, cytomegalovirus, and chancroid associated with sexual transmitted diseases and immunocompromised conditions. Herpes simplex infection manifests multiple superficial ulcers and vesicles at presentation; syphilitic ulcers are purulent and have a granular base. It is important to understand the difference between anal canal fissures and atypical anal canal ulcers (see Fig. 148–2).

DIAGNOSIS

A tearing or burning discomfort during defecation is by far the most common symptom of anal fissure. Bleeding is usually only detected on the toilet paper. The pain associated with anal fissure lasts for minutes to hours, and in

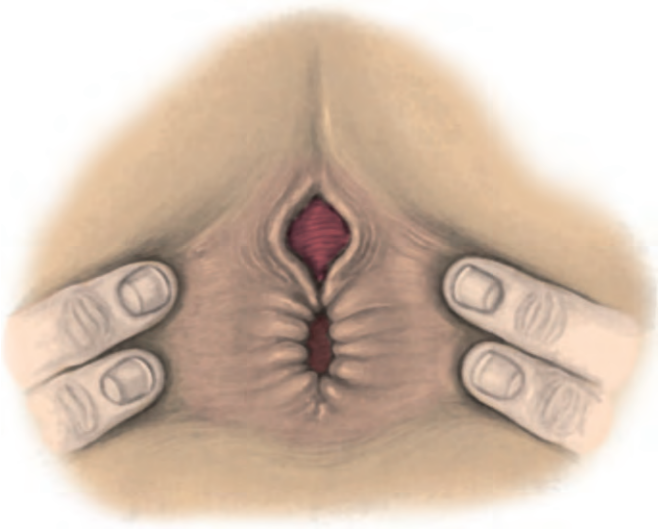

Figure 148–3. Inspection of fissure.

patients with a chronic fissure, it is most often described as profound anal "tightness" or "spasm." Examination must be carefully performed; the pain caused by an aggressive examination of an anal fissure is not easily forgotten. Simple spreading of the buttocks to gently roll open the anal verge usually demonstrates the fissure (Fig. 148–3). Endoscopy, which must be performed as part of the complete evaluation of patients with fissure, should be postponed; a more complete anorectal examination can be better accomplished when the fissure is healed. Topical anesthetics do not facilitate pain-free examinations.

Atypical-appearing fissures require more intensive inquiry. Symptoms of inflammatory bowel disease should be sought. Sexual activity and drug history should likewise be documented. High-risk behavior for human immunodeficiency viral infection necessitates screening and may explain the presence of the atypical fissure. Syphilitic ulcers can be diagnosed with dark-field, wet-prep microscopy. Tuberculous ulcer, although commonly superinfected, shows acid-fast bacilli on staining. The critical issue in patients with atypical-appearing fissures is a high index of suspicion. If an atypical fissure is treated the same way as a typical fissure, a large nonhealing wound could result.

Most diagnostic tests are not tolerated as office procedures. Examination under anesthesia permits a thorough evaluation of the anus and rectum. Cultures, biopsies, and possible therapeutic interventions can be safely and carefully performed with anesthesia. Indeed, patients embrace the opportunity to have a pain-free evaluation under anesthesia.

NONSURGICAL MANAGEMENT

General Approaches

The first-line therapy for patients with simple, acute fissure-in-ano includes warm water sitz baths and stool-

bulking agents. Warm water soaks likely relieve anal discomfort by lowering anal canal pressures, but results from prospective studies are contradictory.[9] Nevertheless, heat provides dramatic relief to most patients with acute and chronic fissure-in-ano and should be used in all patients. Stool-bulking agents, such as psyllium, bran, and fiber, draw water into the stool, changing its consistency, and therefore prevent the formation of hard, stool that causes sustained trauma to the anal canal. Furthermore, bran has been shown to be effective in preventing recurrence of acute anal fissure.[10] Topical creams and steroids are of limited utility and not routinely recommended as management options, since these modalities do not address the underlying problem. These conservative, nonsurgical measures successfully heal 90% of acute anal fissures but only 40% of chronic fissures. Chronic anal fissures are managed with medications that provide a "chemical sphincterotomy" (described later).

Topical Nitroglycerin

It has been suggested that poor posterior anal canal blood flow and generalized hypertonia of the internal anal sphincter are causes of anal fissures. Therefore, improvement in the blood supply and sphincter relaxation should facilitate healing. Nitric oxide is a potent smooth muscle relaxant and promotes vasodilation. Topical nitroglycerin is a nitric oxide donor that is absorbed transcutaneously and, when applied to the anus, has been shown to reduce anal canal pressure.[11] Indeed, nitroglycerin has become an important adjuvant treatment option in patients with fissures that do not heal with stool-bulking agents and local heat therapy.[12,13] A recent meta-analysis of randomized, controlled trials comparing nitroglycerin ointment to placebo for the treatment of anal fissures has shown that nitroglycerin is significantly more effective than placebo in primary healing of anal fissure (46% versus 33%; $P < .0001$).[14] In fact, several independent studies have demonstrated the therapeutic efficacy of nitroglycerin paste in 60% to 75% of patients with anal fissures.[15-20]

The dosage and strength of the nitroglycerin have varied from study to study, but there is some correlation between dose and degree of sphincter relaxation.[21] Application of 200 to 500 mg of 0.2% nitroglycerin paste (about the size of a pea) to the anus is performed at least twice daily. It is important to inform patients that either they should use a cotton-tipped applicator or a glove should be worn to protect against absorption of the nitroglycerin through the skin on the finger. The ointment should be protected from exposure to air and light because nitroglycerin paste is volatile and will deactivate. Pain relief is nearly immediate (5 minutes) and lasts for up to 12 hours.[12,15,16] Headache is a significant side effect and limits the amount of paste that can be applied. When nitroglycerin ointment is used specifically for the treatment of chronic anal fissures, 34% of patients can be expected to developed headaches.[14] With this therapy, healing of the fissure takes 4 to 6 weeks. Patients with fissures that fail to heal often have persistently elevated anal canal pressures despite the use of nitroglycerin. Recurrent disease after initial healing can be successfully retreated.[15,16] Other adverse effects such as orthostatic hypotension, syncopal attacks, and tachyphylaxis are well described and may limit the use of this treatment modality.[21-23]

Calcium Channel Blockers and Botulinum Toxin

Alternatives to nitroglycerin ointment that can produce a similar so-called chemical sphincterotomy effect include topical application of calcium channel blockers (nifedipine and diltiazem) and botulinum toxin A injection. Topical nifedipine has been shown to reduce resting anal sphincter pressures and heal significantly more chronic anal fissures than control (95% versus 16%; $P < .001$).[24] These positive effects were achieved with no significant side effects of this medication. Other calcium channel blockers, such as topical 2% diltiazem, have been shown to be as effective as nitroglycerin in the treatment of chronic anal fissures.[25,26] In fact, topical diltiazem heals between 48% and 75% of fissures that have failed to heal with nitroglycerin alone.[27,28] This class of drug may ultimately supersede nitroglycerin in the treatment of chronic anal fissure because it is equally effective in treating chronic anal fissures and has a superior side effect profile.

Botulinum toxin A is an exotoxin produced by the bacterium *Clostridium botulinum* that causes paralysis of skeletal muscle by preventing the presynaptic release of acetylcholine. Botulinum toxin A has been shown to be efficacious in the treatment of chronic anal fissure. In one study, 73% of anal fissures were healed at 8 weeks, with no recurrences at a mean of 16 months' follow-up.[29] Results of a randomized, double-blind, placebo-controlled trial comparing botulinum toxin A injection to topical nitroglycerin ointment showed that at 8 weeks anal fissures were healed in 96% of patients injected with neurotoxin and 60% of those treated with nitroglycerin.[30] There was no recurrence in either group at a mean follow-up of 15 months. The optimal dose and injection site of botulinum toxin A for the treatment of chronic anal fissures is unclear. Injection of up to 50 units of botulinum toxin A is well tolerated,[31] and healing of posterior anal fissures is accelerated in patients injected with neurotoxin in the anterior anus when compared to posterior injection.[32] Although initial studies reported injections into the external anal sphincter, recent studies have performed intersphincteric injections or injection into the internal sphincter with excellent results.[30,33] Complications of this form of treatment are infrequent and include transient incontinence to flatus and perianal hematoma. Although botulinum toxin A injection has been supported as a first-line therapy for the treatment of chronic anal fissures, cost and convenience issues argue for its second-line use after nitroglycerin failure. Nitroglycerin remains an ideal first-line treatment because it is cheap, convenient, and widely available; however, topical diltiazem may challenge its role in the future.

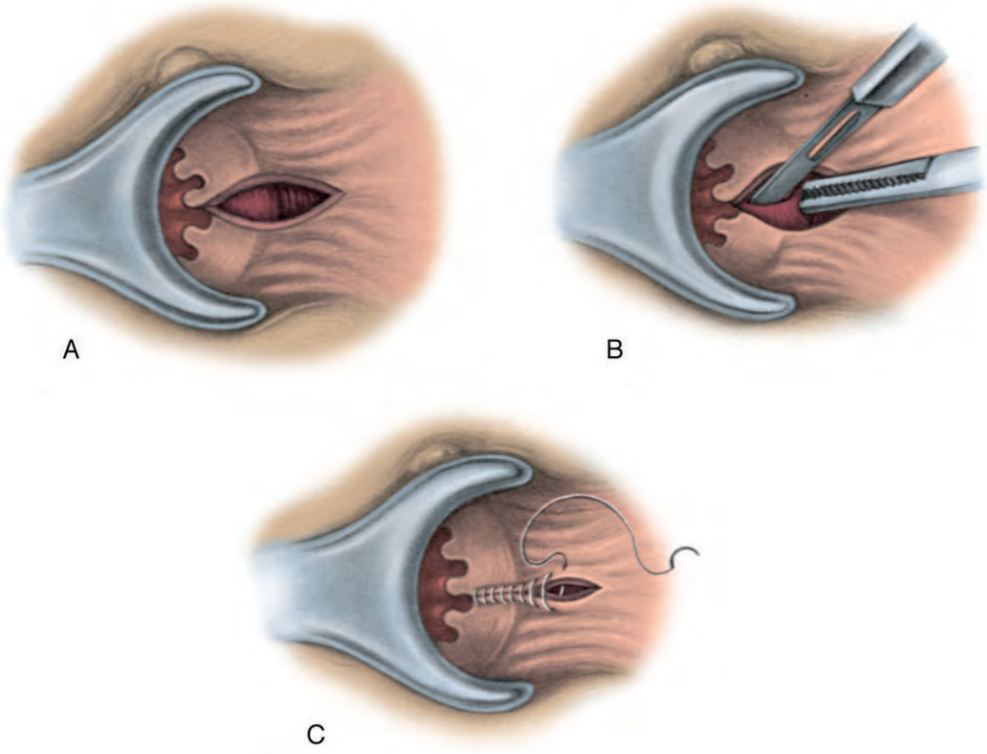

Figure 148–4. Lateral internal anal sphincterotomy. **A,** Internal anal sphincter visible through incision. **B,** Lateral division of internal anal sphincter. **C,** Wound closure. **(A-C,** Modified from Storer EH, Goldberg SM, Nivatvongs S: Colon, rectum and anus. In Schwartz SI [ed]: Principles of Surgery, 4th ed. New York, McGraw-Hill, 1984, p 1169.)

SURGICAL THERAPY

Internal anal partial sphincterotomy (Fig. 148–4) is reserved for chronic anal fissures that fail nonsurgical management, and this technique does require the surgeon to be familiar with anal canal anatomy. The strategy of operative sphincterotomy is to divide the hypertonic portion of the internal anal sphincter muscle to reduce anal canal pressure and facilitate healing of the anal fissure. This procedure was originally described by Eisenhammer in 1951 as a midline posterior incision through the fissure.[3] However, subsequent studies noted problems with wound healing and the formation of a "keyhole" deformity to the anus.[2] Keyhole deformities are a persistent groove in the midline following sphincter division that may result in a significant degree of anal seepage or incontinence. Subsequent modifications to this procedure included repositioning the incision to the right or left lateral position that has effectively eliminated the complication of this deformity.[4] Notaras is credited with introducing the "closed" sphincterotomy that is performed through a stab incision at the intersphincteric groove (Fig. 148–5) rather than an "open" exposure of the internal sphincter.[34] This closed technique can be done in the office setting with local anesthetic using either a small anoscope or a finger in the anal canal to guide division of a portion of the sphincter.

Lateral sphincterotomy has produced excellent results for the treatment of chronic anal fissure with an 85% to 100% healing rate and low incidence of persistent or early relapse (Table 148–1).[35-42] There has been a low, but persistent complication rate for soiling (1% to 22%) and incontinence to flatus (0 to 28%) and stool (0 to 11%). Comparing open versus closed techniques has not shown any differences of significance in postoperative pain, treatment success, complication of incontinence, or overall outcome. However, the length of internal sphincterotomy may influence outcome in terms of healing and incontinence, and division of the sphincter limited to the length of the fissure seems most appropriate.[40,43] Some degree of transient incontinence may be experienced by the patient in the early postoperative period, but this usually improves with time.[42] Therefore, given the low but persistent rate of incontinence with lateral internal sphincterotomy, this operation should be performed in select patients who have failed nonsurgical therapy. Absence of preoperative continence problems and meticulous surgical techniques are necessary to achieve good results.

Other surgical procedures for the management of chronic anal fissures exist but are performed less frequently and are mentioned only for completeness. Fissurectomy is the excision of the anal fissure and is still performed today. This procedure results in a defect in the anoderm that can be covered with a rotation or advancement flap to avoid a keyhole deformity and address a coincidental stricture or anal stenosis.[44] Finger dilation of the anal canal has fallen out of favor and should be discouraged because this procedure results in an uncontrolled stretching of the anal sphincters and results in unacceptable levels of postoperative incontinence. Furthermore, a recent meta-analysis showed that anal dilation resulted in significantly greater persistence of disease than sphincterotomy.[45] Retractors and balloon-tipped dilating catheters have been used for dilation in the treatment of chronic anal fissures.[46-49] These more

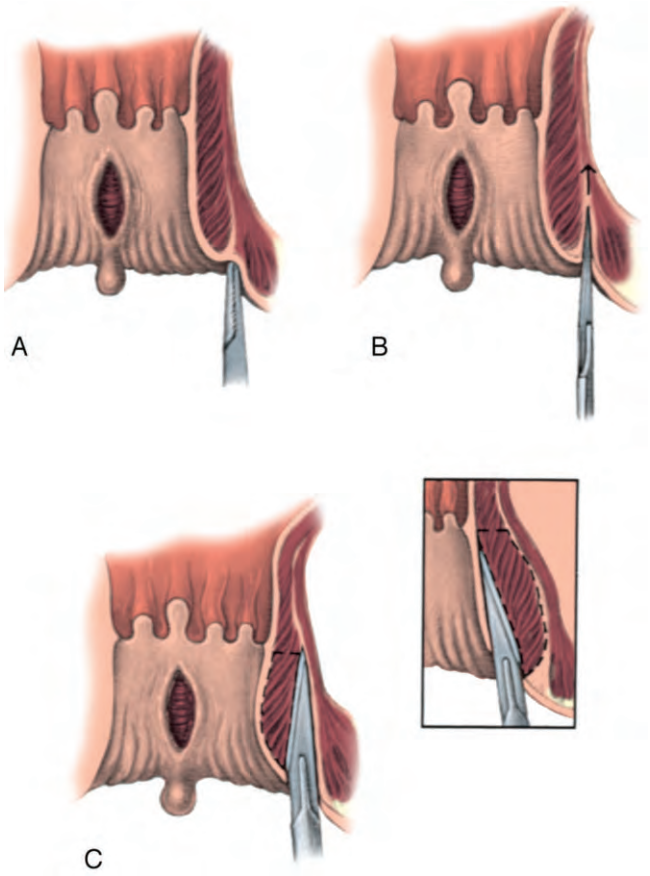

Figure 148–5. Blind lateral subcutaneous internal anal sphincterotomy. **A,** Hemostat demonstrating intersphincteric groove. **B,** Insertion of scalpel between internal and external sphincters. **C,** Sphincter division by inward motion of the scalpel. **Inset,** Original Notaras technique showing outward motion of scalpel. (**A-C,** Modified from Notaras MJ: The treatment of anal fissure by lateral subcutaneous internal sphincterotomy: A technique and results. Br J Surg 58:96, 1971.)

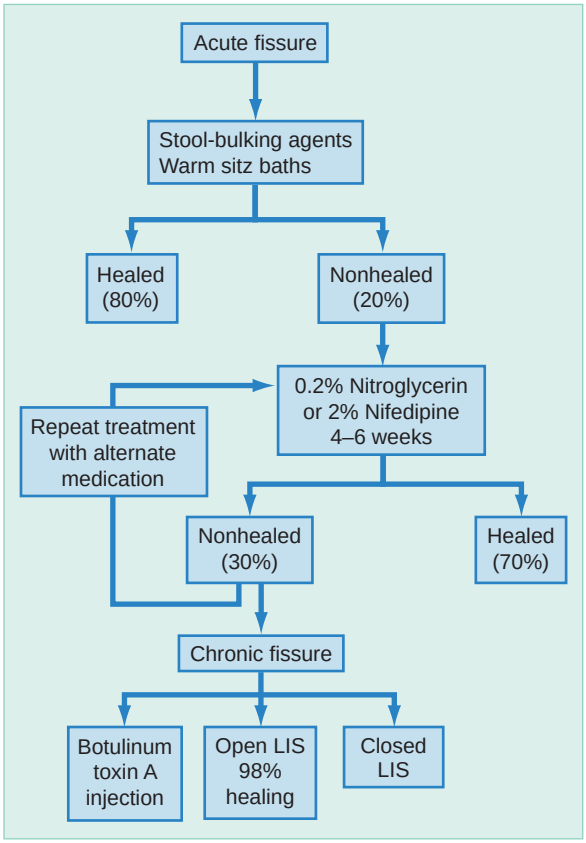

Figure 148–6. Algorithm for therapeutic options in decision making for managing anal fissures. LIS, lateral internal sphincterotomy.

Table 148–1 Impaired Anal Incontinence After Lateral Internal Sphincterotomy

Authors, Year	No. of Patients	Healed, %	Recurrence/Persistence, %	Impaired Anal Continence, %		
				Soiling	*Flatus*	*Stool*
Hoffman and Goligher, 1970[35]	99	97	3	1.0	6.1	7.1
Notaras, 1971[36]	82	100	0	1.4	2.7	5.5
Rudd, 1975[37]	200	99.5	0.5	0	0	0
Boulos and Araujo, 1984[38]	23	100	0	0	17.9	NA
Pernikoff et al., 1994[39]	500	97	3	4	3	1
Garcia-Aguilar et al., 1996[40]	549	89	11	22	28	8
Hananel and Gordon, 1997[41]	312	99	1	1	1	1
Nyam and Pemberton, 1999[42]	487	96	4	8	6	1

NA, not available.

controlled dilation procedures have been reported to be as efficacious as lateral internal sphincterotomy; however, its use should be discouraged since there is no way to reliably standardize the procedure, and both the internal and external sphincters can be disrupted or fragmented in an irregular manner,[50,51] with reported incontinence rates ranging from 12.5% to 24.3%.[49,51]

CONCLUSION

Most acute anal fissures heal with conservative measures. Those that become chronic may respond to medical therapies or injection of botulinum toxin. Persisting fissures should be considered for lateral partial internal sphincterotomy. A reasonable approach is outlined in the algorithm (Fig. 148–6).

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Chapter

149

Anal Sepsis and Fistula

Michael A. Jobst · Alan G. Thorson

DEFINITION

Anorectal suppurative disease may manifest itself in an acute or a chronic setting. Anal sepsis (abscess) represents the acute manifestation, and anal fistula represents the chronic form of the suppurative process. In its simplest form, an anal fistula represents a communication between an internal opening in the anal canal and an external opening through which an abscess drained. A fistula and abscess may coexist or be associated with atypical internal openings and multiple tracts that result in a complex suppurative process.

ETIOLOGY

Foreign bodies, malignancy, trauma, tuberculosis, actinomycosis, leukemia, postoperative infection, inflammatory bowel disease, and simple skin infections have *long* been associated with anal sepsis. Recently, an association between anal abscess-fistula and history of concurrent or recent cigarette smoking has been demonstrated.[1] This association diminishes as the history of cigarette smoking grows more remote. Most anal sepsis, however, is related to an infection of the anal glands and ducts. Fecal bacterial plugging of the ducts leads to obstruction and subsequent abscess formation. This process represents the cryptoglandular theory of anal sepsis. Robinson,[2] Seow,[3] and their associates have suggested that the description of the anal glands by Chiari in 1878 and the subsequent histologic studies of Parks in 1961 contributed to the acceptance of the cryptoglandular theory as the most common cause for anal sepsis.

CLASSIFICATION

Anorectal Abscess

Anorectal abscesses are classified according to the perirectal space involved in the suppurative process; these include the perianal, ischiorectal, intersphincteric, submucosal, deep postanal, and supralevator spaces (Fig. 149–1). A given suppurative process may involve multiple perirectal spaces. For example, the classic "horseshoe" abscess originates in an infected gland in the posterior midline extending through the intersphincteric and deep postanal spaces to one or both of the ischiorectal spaces. A condition known as "floating anus" may occur with circumanal spread of intersphincteric, supralevator, or ischiorectal collections.

It is difficult to accurately assess the incidence of various abscesses due to the varying classifications and referral patterns reflected in large series.[4-8] However, perianal abscesses account for the largest number in most series (Table 149–1).

Anal Fistula

Historically, anal fistulas have been classified in many different ways.[9-12] However, the Parks classification introduced in 1976 is the most comprehensive and widely used. It is derived from the cryptoglandular hypothesis and has therapeutic implications.[13] Parks classified fistulas into four main subgroups according to the course taken by the main tract: intersphincteric, trans-sphincteric, suprasphincteric, or extrasphincteric.[13] Each category can be further subclassified based on associated secondary tracts and other anatomic details (Fig. 149–2).

As with abscesses, the incidence of various fistulas is difficult to quantify. Overall, however, intersphincteric fistulas seem to predominate (Table 149–2).

DIAGNOSIS

Anorectal Abscess

History

Symptoms common to all abscesses include the slow, gradual onset of pain, increasing in intensity to the sensation of pressure and fullness. This is a constant, not intermittent, sensation. These symptoms should always lead to the consideration of an abscess even in the

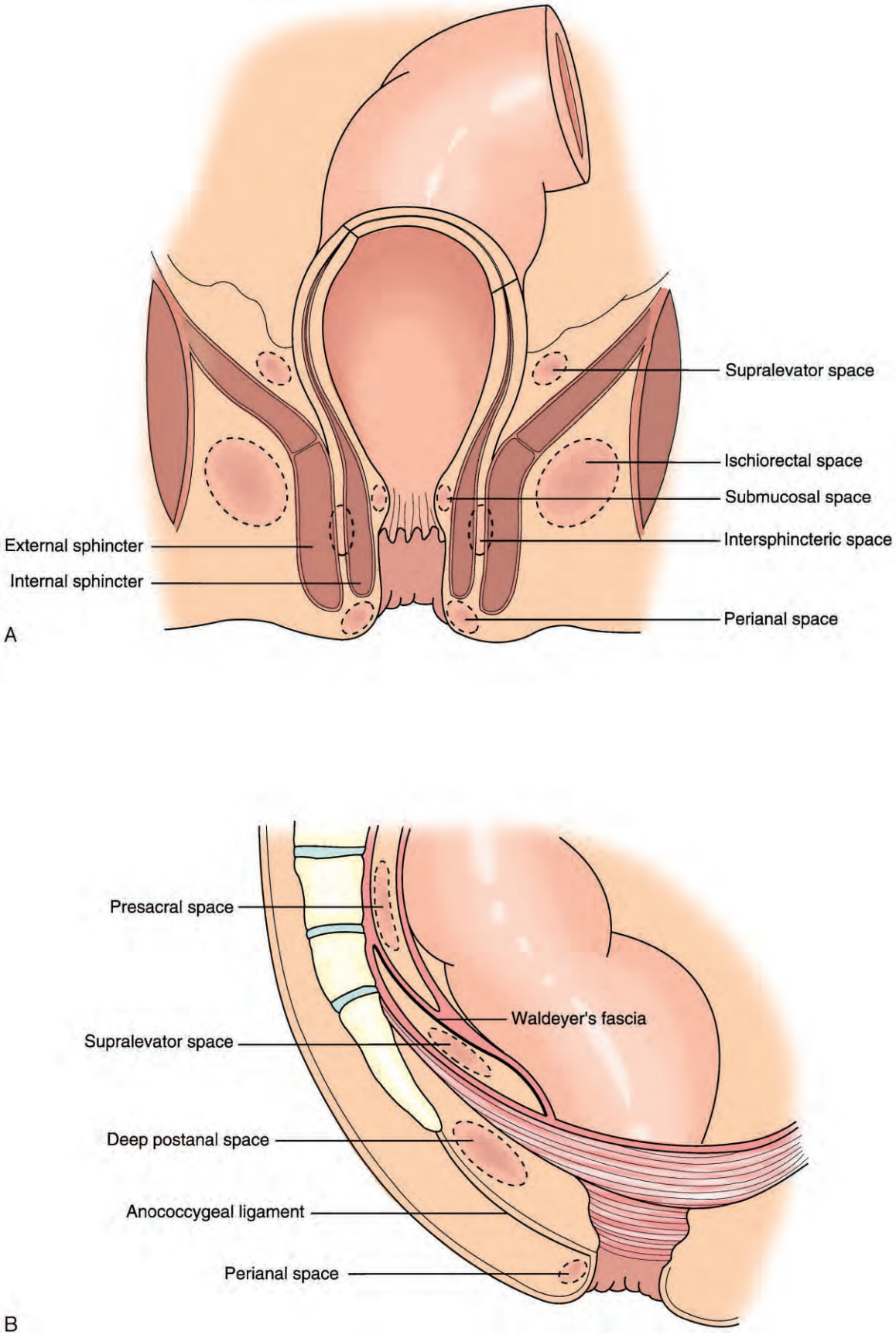

Figure 149–1. Classification of anorectal abscesses by location. **A,** Coronal view. **B,** Sagittal view.

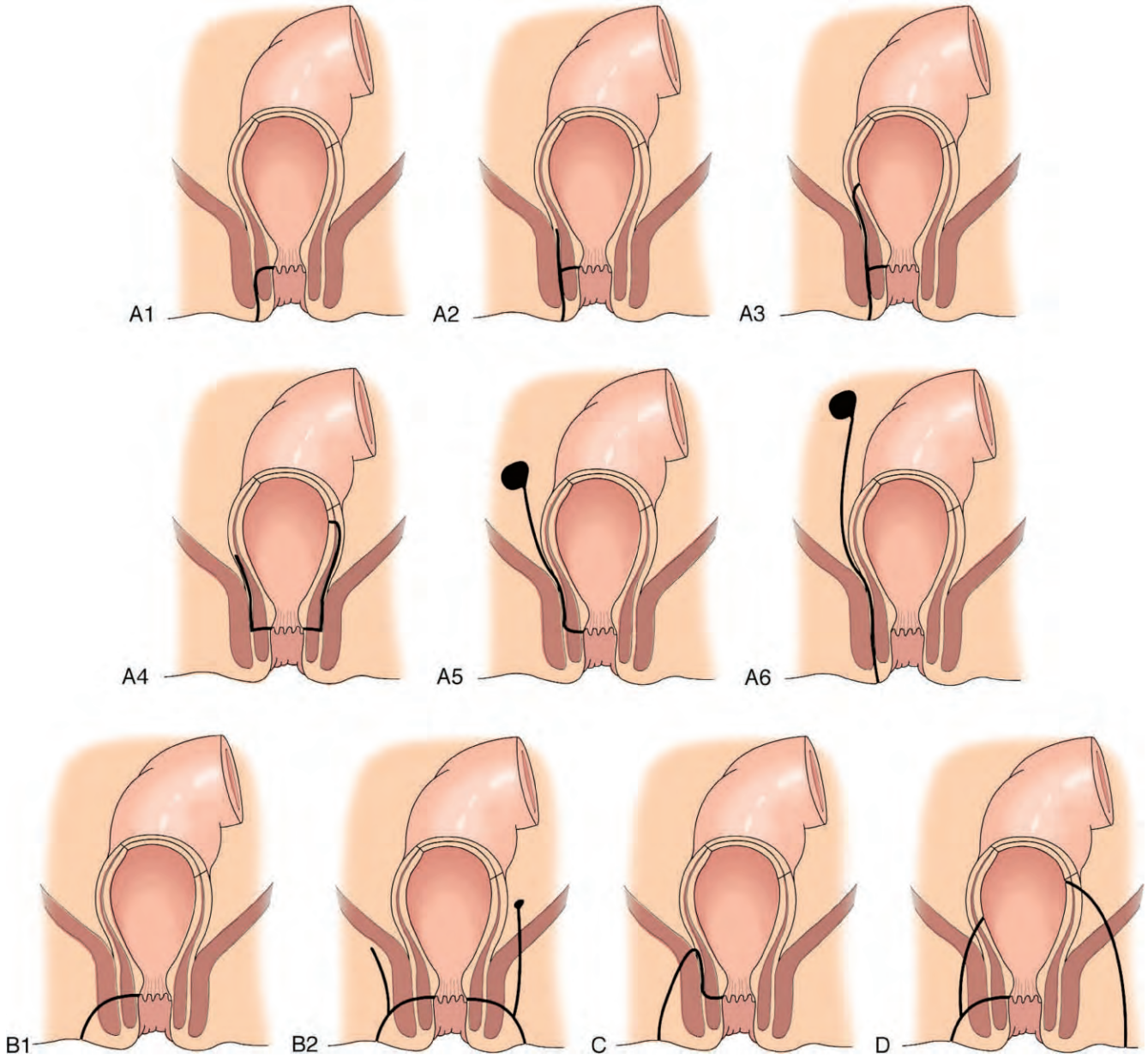

Figure 149–2. Classification of anal fistulas. **A,** Intersphincteric: The tract remains in the intersphincteric plane. *1,* Simple. *2,* High blind tract. There is a high extension of the fistula between the internal sphincter and the longitudinal muscle of the upper anal canal. *3,* High tract with rectal opening. *4,* High intersphincteric fistula without a perineal opening. There may or may not be a rectal opening. *5,* High intersphincteric fistula with a pelvic extension. The infection spreads up to reach the true pelvic cavity lying above the levator musculature. *6,* Intersphincteric fistula secondary to pelvic disease. This fistula results from the spread of pelvic collections via the intersphincteric plane. This does not represent a true anal fistula because its origin is outside the anal area. There is no opening at the dentate line. **B,** Trans-sphincteric: The fistula tract passes from the intersphincteric plane through the external sphincter muscle. *1,* Uncomplicated. *2,* High blind tract. The upper tract extension may go to the apex of the ischiorectal fossa or extend higher through the levator musculature into the pelvic cavity. **C,** Suprasphincteric: There is an upward extension of the fistula tract in the intersphincteric plane. The tract then passes above the level of the puborectalis muscle and continues downward through the ischiorectal fossa to the perianal area. **D,** Extrasphincteric: There is a tract that passes from the skin of the perineum through the ischiorectal fossa and the levator muscles before entering the rectal wall. This fistula may be a consequence of an extension of a trans-sphincteric fistula or secondary to trauma, anorectal disease, or pelvic inflammation.

Table 149–1 Incidence of Anorectal Abscess by Location

Abscess Locations	No. of Patients					Total	
	McElwain et al.[4]	*Scoma et al.*[7]	*Vasilevsky and Gordon*[8]	*Schouten and van Vroonhoven*[6]	*Ramanujam et al.*[5]	*No. of Patients*	*%*
Perianal	456	174	20	—	437	1087	44.8
Submucosal	3	—	—	—	—	3	0.1
Intermuscular	541	30	—	—	59	630	26
Intersphincteric	—	—	18	28	219	265	11
Trans-sphincteric	—	—	—	30	—	30	1.2
Ischiorectal	—	14	63	—	233	310	12.8
Supralevator	—	9	2	—	75	86	3.6
Retrorectal	—	5	—	—	—	5	0.2
Unclassified	—	—	—	8	—	8	0.3
Total	*1000*	*232*	*103*	*66*	*1023*	*2424*	*100*

Table 149–2 Incidence of Anal Fistulas

Fistula Type	No. of Patients				Total	
	Parks et al.[13]	*Marks and Ritchie*[14]	*Vasilevsky and Gordon*[15]	*Garcia-Aguilar et al.*[16]	*No. of Patients*	*%*
Intersphincteric	180	428	67	180	855	49.5
Trans-sphincteric	120	167	83	108	478	27.7
Suprasphincteric	80	24	3	6	113	6.5
Extrasphincteric	20	24	0	6	50	2.9
Miscellaneous or nonclassified	—	150	7	75	232	13.4
Total	*400*	*793*	*160*	*375*	*1728*	*100*

absence of obvious physical findings (hidden abscesses). Approximately 20% to 33% of all patients give a history of a previous episode of anorectal sepsis.[8,17]

Physical Examination

The physical findings associated with anorectal abscesses vary depending on the anatomic location of the abscess. The presence of pus in any of the perianal and perirectal spaces may be confirmed with needle aspiration. An examination under general anesthesia may be necessary to confirm a diagnosis.

Perianal Abscess Localized swelling, hyperemia, induration or fluctuance, and tenderness are present adjacent to the anus. A purulent discharge may be present if spontaneous drainage has occurred. Although there usually are no systemic symptoms, the patient may have fever or malaise or be acutely ill.

Ischiorectal Abscess Although small collections may present with discrete localized swelling, more commonly there is a large, erythematous, and indurated mass in the buttock. Large volumes of purulent material may accumulate in the ischiorectal space. Fever and leukocytosis are common. A large ischiorectal abscess frequently represents a horseshoe extension (see later). A source in the posterior midline should be sought.

Intersphincteric and Submucous Abscess In intersphincteric and submucous abscess, there usually is no visible evidence of sepsis because these "hidden abscesses" are confined to the anal canal. Owing to the patient's discomfort, a digital rectal examination is not always possible. In this situation, an examination under general anesthesia is warranted to identify the abscess.

Supralevator Abscess Supralevator abscess may occur as an upward extension of a collection in the distal anal canal, usually an intersphincteric abscess, or as a true pelvic abscess secondary to intra-abdominal or pelvic pathology. Possibilities include appendicitis, diverticulitis, pelvic inflammatory disease, or ruptured viscus. The

patient may be systemically ill. A pelvic mass may be identified by rectal or vaginal examination.

Postanal Abscess and Horseshoe Extension Transsphincteric extension of an intersphincteric abscess in the posterior midline leads to the accumulation of purulent material in the deep postanal space. This space is difficult to evaluate clinically, making these the second type of hidden abscess. Inspection does not reveal any inflammatory skin changes because the abscess is deep. There may be tenderness posterior to the anus but anterior to the coccyx. The collection may be apparent only by needle aspiration or with an examination under general anesthesia. A horseshoe abscess is the result of a direct extension of a postanal abscess into the ischiorectal space (see Ischiorectal Abscess). It may be unilateral or bilateral.

Anorectal Fistulas

History

Most patients with a fistula-in-ano have a previous history of anorectal suppuration. The patient usually presents with complaints of intermittent or persistent purulent or serosanguineous drainage from an external opening in the perianal area. Symptoms classically consist of a build-up of pain, slight fever, and pain on defecation followed by mucopurulent drainage and abatement of the pain.[18] Pruritic symptoms may be present due to skin irritation associated with the chronic discharge.

Physical Examination

Fistula tracts are fibrous inflammatory tubes with a diameter of 3 to 7 mm. They are lined with infected granulation tissue. Many fistulas may be palpated during a careful digital rectal examination. Essential points that should be obtained from a clinical examination were described nearly 100 years ago by Goodsall and Miles[9]; they include the identification of the external and internal openings, the course of the primary and any secondary tracts, and an assessment for the presence of an underlying complicating disease.

Using an anoscope, systematic inspection and palpation can define most of these characteristics. The gentle use of a number of malleable anorectal probes and crypt hooks can help delineate the fistula by attempting to pass these instruments via the internal or external opening. It is important not to force the passage of the probe because the development of false tracts can complicate evaluation and management. Secondary tracts may be present when induration is palpated or asymmetry is noted between the right and left sides of the anorectum.[3] In only a few cases will the use of sophisticated diagnostic imaging techniques be required.

The external opening is identified as a small pit surrounded by scar or granulation tissue. Active seropurulent drainage may be present. Intersphincteric tracts usually open externally close to the anal verge; transsphincteric and other complicated tracts open farther away. Occasionally, the external opening may be localized inside the anal canal or at the distal end of a fissure. Several external openings may be present due to multiple complex fistula tracts; this condition is known as "watering-pot perineum."

The internal opening may be felt as an indurated nodule, most often at the dentate line. This is consistent with the cryptoglandular theory of anorectal sepsis. The use of saline,[19] milk,[20] dye,[21] or dilute hydrogen peroxide[22] as an injection into the external fistula opening has been made in an attempt to localize the internal opening. An enlarged papilla may be noted at this site. Because most of the anal glands are located in the posterior midline,[23] it is not surprising that 61% to 69% of internal openings can be traced to this location.[3]

Goodsall's rule may be helpful in locating the internal opening. This rule states that an external opening anterior to an imaginary transverse anal line in the coronal plane most likely communicates with an internal opening lying at the end of a radial line drawn to the nearest crypt at the dentate line. If the external opening is posterior to this line, the internal opening will most likely be located in the posterior midline with the tract following a curved route to reach its source. Exceptions to this rule include anterior openings more than 3 cm from the anal verge and the presence of multiple external openings. In these cases, the internal opening will most likely be in the posterior midline (Fig. 149–3). However, the predictive accuracy of Goodsall's rule has been challenged, especially with anterior external openings[24] or when Crohn's disease or carcinoma is present.[18]

Special Studies

Sigmoidoscopy and Colonoscopy

Sigmoidoscopy should be performed in all patients with anorectal fistulas. The presence of associated pathology such as neoplasms, inflammatory bowel disease, or associated secondary tracts in the rectum must be sought. Such findings may dictate the need for full colonoscopic evaluation.

Fistulography

Fistulography may be warranted in patients with recurrent fistulas or when a prior procedure has failed to identify the internal opening.[25] With this technique, the external opening is cannulated with a small-caliber tube and contrast material is injected under minimal pressure while films are taken in several projections. Fistulography may be useful in identifying unsuspected pathology, planning surgical management, and demonstrating anatomic relationships.[26-28] However, a study by Kuijpers and Schulpen[29] found fistulography to be unreliable compared with operative findings. They observed a prohibitively high incidence of false-positive results that could lead to unnecessary and harmful surgical exploration.

Anorectal Ultrasonography

Transanal ultrasound can delineate the muscular anatomy of the anal sphincters in relation to an abscess or a fistula. *Most commonly,* ultrasonographic examination

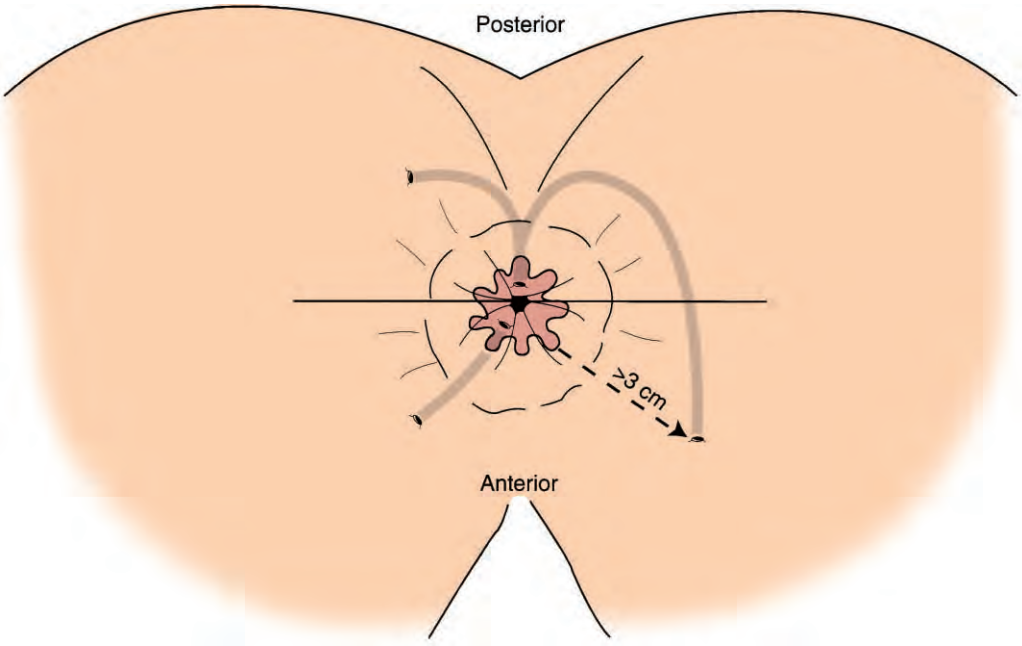

Figure 149–3. Goodsall's rule.

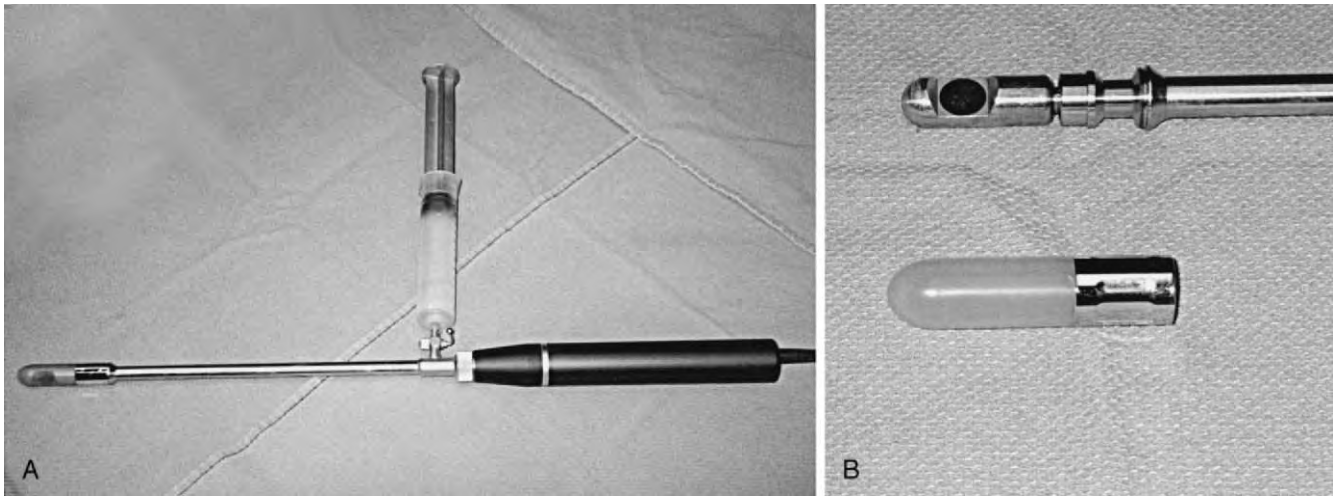

Figure 149–4. **A,** Transanal ultrasound probe (type 1850; Brüel and Kjaer, Naerum, Denmark). **B,** The rotating transducer is covered by a hard plastic sonolucent cone, which is then filled with water to provide an acoustic interphase.

of the anal canal is performed with the use of a 360-degree rotating probe using a 7- or 10-MHz transducer with a hard plastic water-filled sonolucent cone over the transducer (Fig. 149–4).[25] Fistula tracts and abscesses appear as hypoechoic defects within the muscular elements of the anal canal (Fig. 149–5). The internal opening is not distinctly identified. Although generally accurate in the localization of abscesses and fistula tracts,[30,31] primary superficial, extrasphincteric, and suprasphincteric tracts or secondary supralevator or infralevator tracts may be missed.[32] The use of hydrogen peroxide injected into fistulas as an image enhancer has been shown to be safe, effective, and more accurate than conventional transanal ultrasound in the evaluation of anal sepsis (Fig. 149–6).[33,34] However, the complication of oxygen embolization arising from hydrogen peroxide irrigation of wounds, particularly when irrigated under pressure, has been described.[35-37] This has led some to investigate alternative echo-enhancing media such as galactose particles and palmitic acid (Levovist), which has been proven safe in echocardiography.[38]

The use of a linear 7-MHz ultrasound device instead of a radial probe has been described and may carry the advantages of greater focal depth, improved ischiorectal

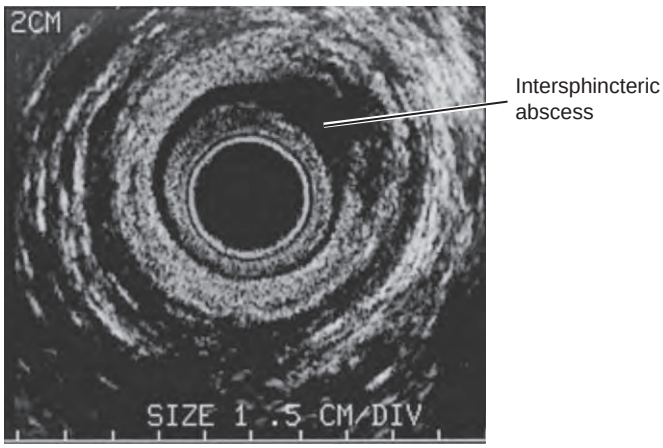

Figure 149–5. Intersphincteric abscess as seen with the use of transanal ultrasound.

and supralevator visualization, multiplanar views of complex fistulas, and less need for echo-enhancing injection.[39] Finally, it has been shown that vaginal endosonography may increase the diagnostic yield of perianal sepsis in 25% of patients and may obviate the need for uncomfortable digital or endoanal ultrasound examinations in those patients with hidden abscesses or anal stenosis.[40]

Magnetic Resonance Imaging

Using surface and body coils, Myhr et al.[41] studied the use of magnetic resonance imaging (MRI) with saline solution as a contrast agent in the evaluation of anorectal sepsis. Multiplanar MRI defined soft tissue anatomic abnormalities in 15 of 16 patients. The administration of a gadolinium enema greatly enhanced T2-weighted images and improved lesion identification, especially in cases of chronic or recurrent fistula.[42] Others have found high concordance rates between MRI and operative findings.[43,44] Lunniss et al.[45] compared MRI with anal endosonography and operative findings in the evaluation of 20 patients with anal fistula. The overall concordance for the primary tract between MRI and surgery was 85% compared with 65% for endosonography. MRI also proved to be superior for the assessment of secondary tracts (100% concordance for MRI vs. ≤50% with endosonography). The use of an MRI endoanal magnetic coil has been found to be superior to surface coil MRI and endoanal ultrasonography in fistula evaluation.[46,47] In all of these studies, however, the use of endosonic-enhancing media was not used when comparing endoanal ultrasound with MRI.

Computed Tomography

The use of computed tomography (CT) in the evaluation of anal fistulas is limited due to poor visualization of the levators and sphincter complex. The role of CT in anal sepsis and fistula is thus limited to the assessment of associated pelvic pathology in patients with supralevator abscesses and in patients with some complex anal fistulas.

Anorectal Manometry

Anorectal manometry is an objective method for studying the contribution of the anorectal sphincter to the physiologic process of defecation.[48] Normal anorectal manometric parameters in adults have been established.[49] Manometry can thus assist in identifying patients at the greatest risk for postoperative incontinence. Surgical management can be tailored accordingly, improving clinical and functional outcome.[50,51] The selective use of anorectal manometry is warranted in patients with suspected sphincter impairment; patients suspected of needing substantial portions of the external sphincter divided for fistula cure; and women with a history of multiparity, forceps delivery, third-degree perineal tear, high birthweight, or prolonged second stage of labor.[18] Patients with lower preoperative resting pressures have significantly poorer continence control following surgery for intersphincteric fistula when compared prospectively to patients with normal preoperative resting pressures.[52]

Fistuloscopy

Anorectal fistuloscopy using flexible ureteroscopes has been recently described.[53] This is a potentially useful intraoperative technique to identify primary fistula openings, multiple or complex tracts, and iatrogenic tracts. Modified flexible ureteroscopes are in the early developmental stages. We look forward to their evolution because they represent a novel diagnostic and therapeutic tool that may significantly improve the outcomes of complex fistula diagnosis and treatment.

TREATMENT

Anorectal Abscess

The treatment of anorectal abscesses should be considered a surgical emergency, with early drainage the mainstay of treatment. There is no place for conservative management. Treatment delay may result in chronic infection and tissue destruction with fibrosis and long-term impairment of function. The condition of the patient and the type of abscess usually determine whether drainage can be performed in the office or emergency department or in the operating room. Antibiotics should be used as adjunctive therapy in special circumstances only; these include patients with valvular heart disease, immunosuppression, extensive associated cellulitis, and diabetes.[25]

Anorectal abscesses associated with gut-derived organisms are more likely to be associated with an underlying fistula and have a higher incidence of recurrence than are abscesses associated with skin-derived organisms.[54-56] However, the positive predictive value for this association has been found to be quite low[57]; therefore, cultures are rarely indicated.

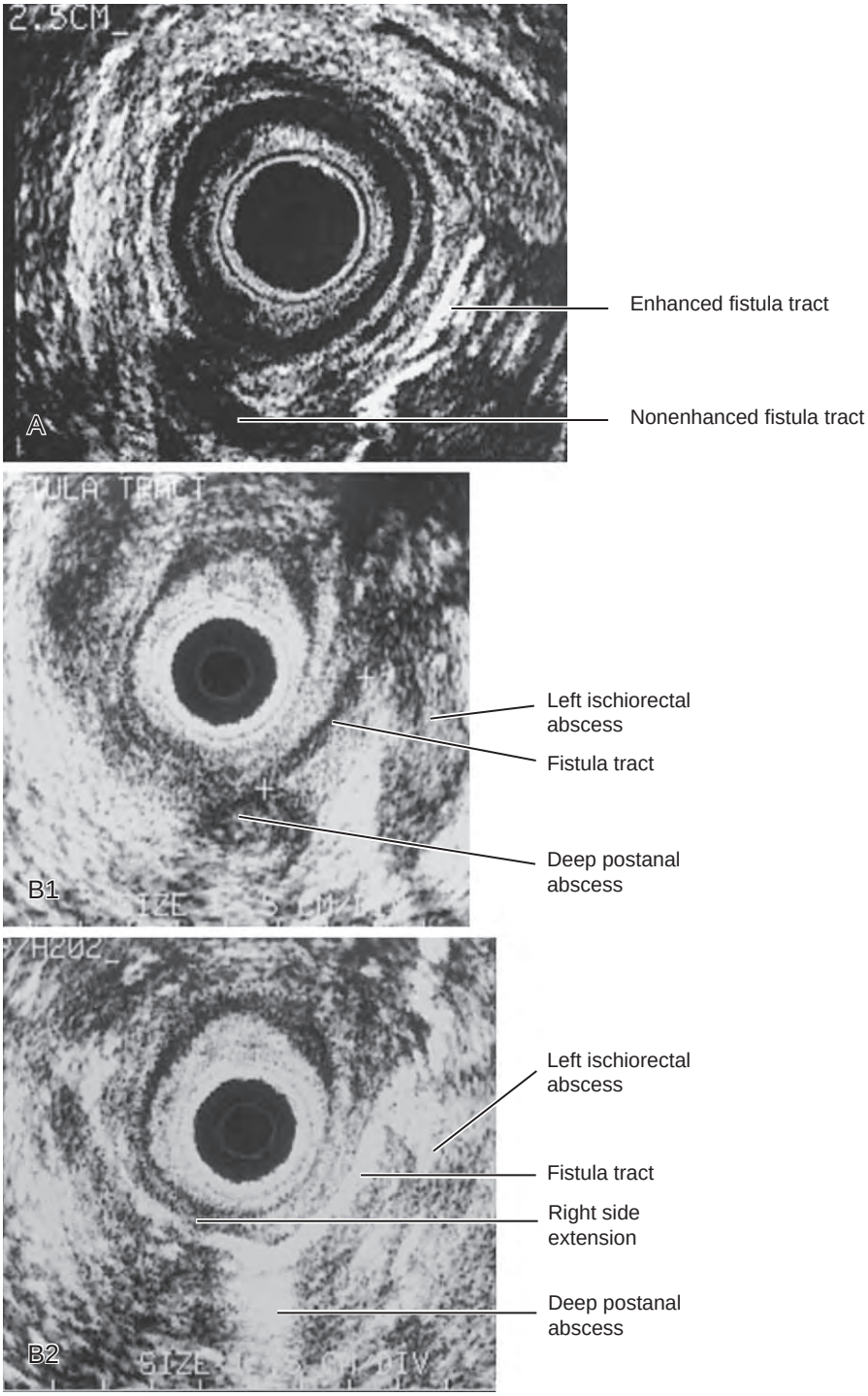

Figure 149–6. A, Trans-sphincteric hypoechogenic tract extending toward the posterior midline. The tract is enhanced as hydrogen peroxide is injected into the external opening. **B,** Complex fistula tract and collections as seen without *(1)* and with *(2)* hydrogen peroxide enhancement. Hydrogen peroxide enhancement allowed for a more precise delineation of the tracts in addition to a right-sided extension of the tract.

Perianal Abscess

Simple perianal abscesses can almost always be drained as an office or outpatient procedure, usually under local anesthesia. A cruciate incision is made over the most tender or fluctuant point as close to the anal verge as possible. If a fistula develops, the external opening will be close to the verge, so a fistulotomy would require division of the least amount of muscle. The skin edges are usually excised to avoid early coaptation, which could seal the cavity prematurely and lead to recurrence (Fig. 149–7).

After all loculations are broken, packing is not required; packing contributes to significant discomfort and does not allow for free drainage of the abscess cavity. Continued drainage of large cavities may be achieved with the use of a 3- to 5-mm de Pezzer or similar catheter left in situ until drainage subsides.[58] This technique may

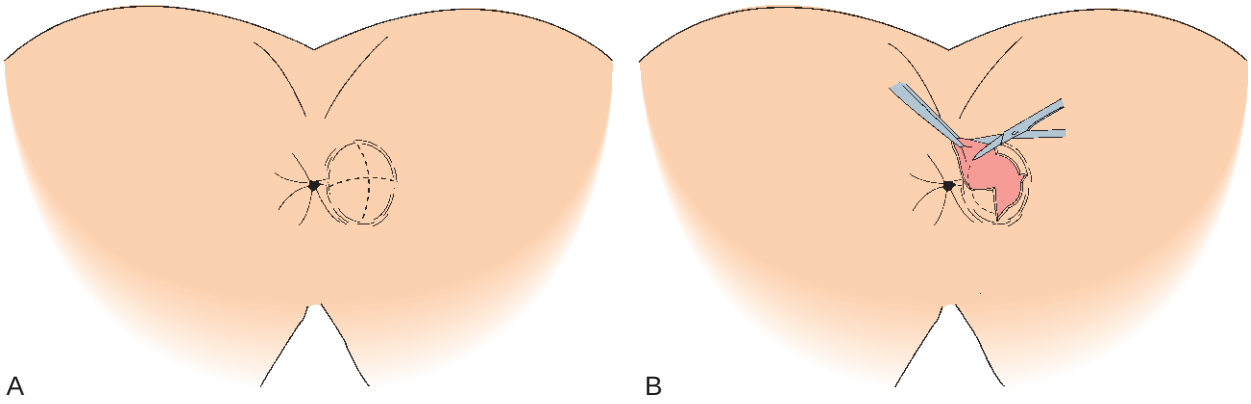

Figure 149–7. **A,** Cruciate incision made over the most tender or fluctuant area. **B,** The skin edges are excised.

be used in a number of different abscesses but is not suitable for use in cases of submucous or intersphincteric abscess.

Ischiorectal Abscess

After horseshoe extension is excluded by ensuring that the deep postanal space is not involved, unilateral ischiorectal abscesses may be drained through a single incision or several counterincisions over the area of maximal swelling, pain, and fluctuance but as close to the anal verge as possible. Here, too, a de Pezzer catheter may be used to enhance the drainage of large cavities.

Intersphincteric Abscess

An intersphincteric abscess is drained by laying open the internal sphincter (sphincterotomy) overlying the cavity. By definition, a fistulotomy is performed by destruction of the inciting anal gland. For hemostasis, adequate drainage, and faster healing, the edges of the wound may be marsupialized.

Submucosal Abscess

Submucosal abscesses are drained internally by incising the mucosa over the abscess. The edges of the wound may be marsupialized. No packing or drainage catheter is indicated.

Supralevator Abscess

Anatomic localization of the septic origin is of paramount importance in the management of supralevator collections. Collections that result from abdominopelvic disease may be drained transrectally or transabdominally. Overall management depends on the underlying pathology. Supralevator collections that result from an upward extension of an intersphincteric abscess should be drained transrectally. Transperineal drainage through the ischiorectal fossae could result in a suprasphincteric fistula. Supralevator collections that result from the cephalad extension of a trans-sphincteric fistula or an ischiorectal collection should be drained transperineally through the ischioanal fossae. If erroneously drained transrectally, the result will be an extrasphincteric fistula. Transperineal drainage of this type of collection will likely result in a trans-sphincteric fistula that is relatively easy to manage (Fig. 149–8).

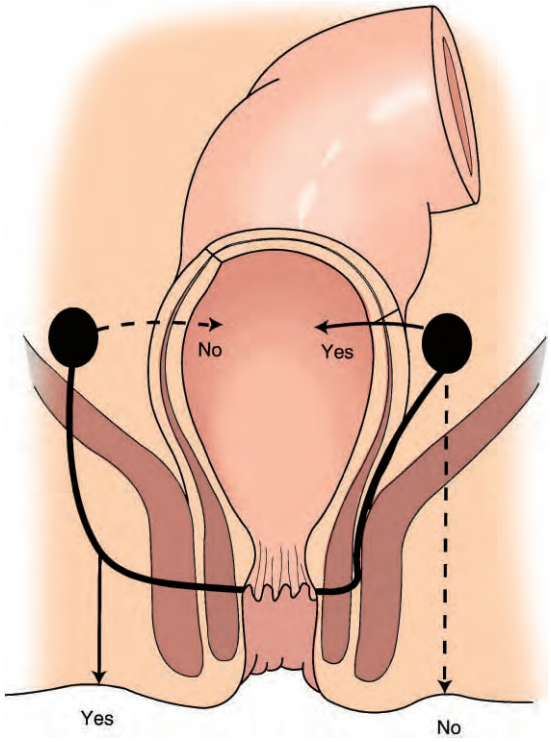

Figure 149–8. Appropriate type of drainage of supralevator abscesses depending on the course taken by the fistula tract.

Postanal Abscess and Horseshoe Extension

Patrick H. Hanley first described the conservative surgical approach to a horseshoe abscess that preserved function and anatomy.[59] The abscess in the postanal space is drained by a deep posterior midline incision. All of the muscles attached to the coccyx, the superficial external

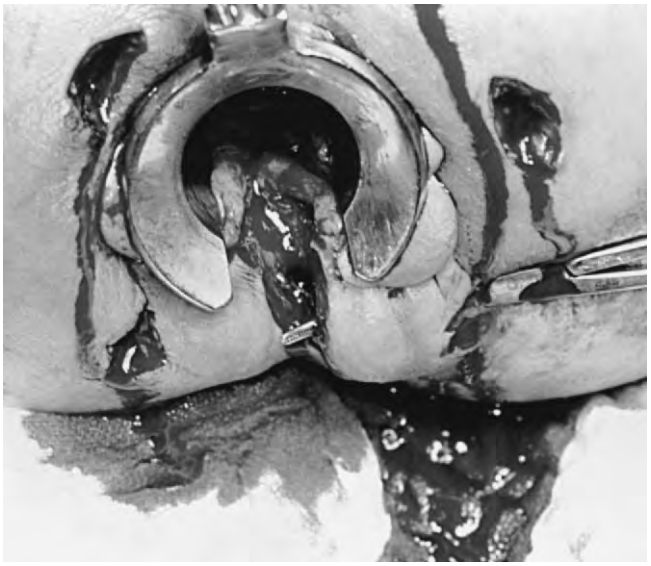

Figure 149–9. Drainage of a postanal abscess with horseshoe extension. The postanal space has been laid open as described by Hanley. Secondary incisions are placed in the skin overlying the ischiorectal space.

sphincter, and the lower edge of the internal sphincter are divided. When the suppurative process extends to the ischiorectal spaces as a horseshoe, one or multiple secondary incisions are placed in the skin overlying the ischiorectal space. These may be connected to each other with soft drains to allow for continuous drainage. We favor a modification of Hanley's technique in which the posterior midline incision consists of only a partial distal internal sphincterotomy to include a fistulotomy with destruction of the anal gland at the dentate line. The external sphincter and the muscular attachments to the coccyx are not divided. This allows for faster healing while maintaining adequate drainage (Fig. 149–9). Counterincisions and drains are used for horseshoe extensions as previously described.

Primary Versus Delayed Fistulotomy

The use of primary fistulotomy when draining an abscess remains controversial. Issues that surround this controversy include the ability to localize an internal opening at the time of an acute septic event and the effect of primary fistulotomy on recurrence and continence. Does the type of abscess affect the risk of recurrent fistula? Is it cost-effective to take a patient for whom an outpatient procedure is performed under local anesthesia to the operating room for a thorough examination under general anesthesia and a primary fistulotomy in the hope of avoiding a second procedure for a fistula that might develop if only simple drainage were performed?

A one-stage procedure theoretically destroys the cryptoglandular source of sepsis, decreasing the incidence of fistula formation. However, internal openings may not always be found. Attempts to define a primary opening in the setting of an acute infection may be a hazardous undertaking. Because not all abscesses lead to fistulas, some patients would undergo an unnecessary procedure that puts them at risk for incontinence.

The reported incidence of recurrent abscess and subsequent development of anorectal fistula varies considerably. Scoma et al.[7] found that 66% of 232 patients developed a fistula or recurrent abscess after incision and drainage alone. Vasilevsky and Gordon[8] found that 11% of 83 patients developed recurrent abscess and 37% developed a fistula after incision and drainage. They noted that the greatest risk of recurrence was in patients who had ischiorectal abscesses, an observation we have also made. The subset of patients with no previous episode of anorectal suppuration had a lower incidence of recurrence. Both authors advocated incision and drainage alone for acute abscesses, reserving fistulotomy as a secondary procedure in patients with recurrence.

In contrast, several authors favor a policy of immediate fistulotomy in the treatment of anorectal abscesses. In a series of almost 800 cases, Eisenhammer[60] described a nearly 100% cure rate obtained with a single operation. McElwain and colleagues[4] reported on the outcome of 1000 cases of primary fistulotomy for anorectal abscesses, including intersphincteric and postanal abscesses. The recurrence rate was 3.6%, and the disturbance of continence rate was 3.2%. However, this approach requires the consistent finding of an internal opening to perform fistulotomy. In two studies, the internal opening could be identified in only approximately 34% of acute abscesses.[5,61] In other series, 69% to 88% of the internal openings were identified.[62,63]

Ramanujam et al.[5] found long-term recurrence to be less in a group of 323 patients (1.8%) who had primary fistulotomy compared with a group of 668 patients with incision and drainage alone (3.7%). A small prospective, randomized study of 45 patients by Tang and colleagues[64] did not show such a difference. However, a larger prospective, randomized study by Schouten and van Vroonhoven[6] did show a difference: Of 32 patients, 10 developed a recurrent abscess and 3 developed a persistent fistula in the drainage-only group; in the primary fistulotomy group, 1 patient of 34 developed a persistent fistula. The incidence of anal functional disturbances did not differ among the groups. In a randomized, prospective trial of 200 patients, Oliver and colleagues demonstrated that drainage with fistulotomy was safe (incontinence 6% at 1 year) and effective (recurrence 5% at 1 year) when compared with drainage alone (0% incontinence and 29% recurrence).[65]

In summary, a percentage of patients who have drainage alone for the treatment of anal abscess develop a recurrent abscess or subsequent fistula. A primary fistulotomy in this setting may decrease this risk but at the expense of a small increase in the risk for disturbances of continence. Primary fistulotomy should be considered in patients who have a history of previous anorectal sepsis or who present with an ischiorectal abscess with an internal opening that is readily apparent. This controversy has no impact in dealing with postanal abscesses with horseshoe extensions or intersphincteric abscesses. In these

cases, a fistulotomy is performed when the sphincterotomy is the primary drainage technique.

Anorectal Fistulas

Once diagnosed, patients with anorectal fistulas should undergo surgical treatment. Anorectal fistulas rarely heal spontaneously. Untreated patients frequently develop chronic abscess formation and complex fistula tracts. Surgical treatment for most anorectal fistulas is best accomplished in the operating room, with good lighting and appropriate instrumentation. The patient is positioned in prone jackknife position with the buttocks taped apart. General, regional, or local anesthesia with intravenous sedation should be selected based on individual patient characteristics. The three basic surgical techniques for the treatment of anorectal fistulas are fistulotomy, use of a seton, and endorectal advancement flaps. The use of fistulectomy is not recommended except when it is necessary to provide histologic material.[25]

Fistulotomy

Most anorectal fistulas may be adequately treated by the classic laying-open technique or fistulotomy. Recurrence rates are low, and risks for continence disturbances are minimal.[3] A fistulotomy is accomplished by passing a fistula probe via the external opening, along the tract, and through the internal opening. With the probe in place, the relationship of the fistulous tract to the external sphincter muscle can be determined. If the tract lies distal to the majority of the external muscle, then cautery is used to lay it open. Secondary tracts should be drained through the fistulotomy incision after all tracts have been curetted. Marsupialization with a running continuous absorbable suture is associated with faster healing.[66]

In patients with otherwise normal continence, the perianal skin, anal epithelium, a portion of the internal anal sphincter, and a few fibers of subcutaneous external sphincter may be divided without risk to continence. However, in women with anterior fistulas, such a fistulotomy is associated with an unacceptably high risk of incontinence due to the intrinsic thin nature of the sphincter mechanism in this area. Therefore, other techniques should be used in the treatment of anterior fistulas in women.

Traditional fistulotomy has been performed with scalpel or electrocautery in the lay-open technique. Very recently, Gupta has described a lay-open fistulotomy technique using radiofreqency.[67] Also known as *radiofrequency fistulotomy,* this technique employs very high-frequency radio waves that vaporize intracellular water without utilization or generation of heat. The hand-held terminal has different attachments that can be selected by the surgeon to cut, cauterize, or shave tissue without collateral heat damage to healthy surrounding tissues. How this technology compares to traditional electrocautery in terms of fistula recurrence, incontinence, and cost remains to be studied.

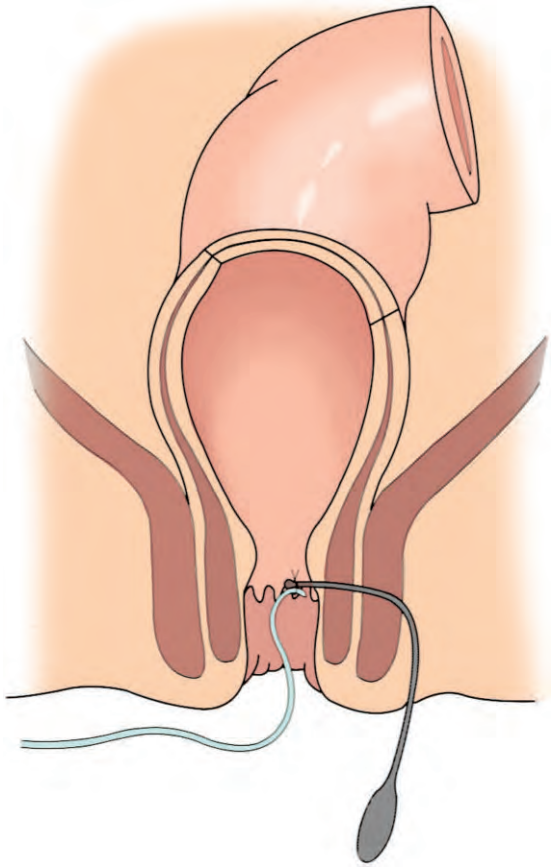

Figure 149–10. Insertion of a seton with the aid of a fistula probe.

Seton Management

The word *seton* is derived from the Latin word *seta,* meaning "bristle." It refers to any foreign material that can be inserted into the fistula tract to encircle the sphincter muscles. These materials include silk,[68,69] Penrose drains,[70,71] Silastic vessel loops, rubber bands,[72] nylon or polypropylene,[73] and braided steel wire.[74] Setons are placed by securing the selected material to the end of a fistula probe after the probe has been passed through the internal opening (Fig. 149–10).

Setons are useful in the management of complex anorectal fistulas where there is an appreciable risk of incontinence or poor healing; such cases include patients with Crohn's disease, immunocompromised and incontinent patients, patients with chronic diarrheal states, and anterior fistulas in women. Complete healing of selected anorectal fistulas has been reported solely with the use of long-term setons.[75]

Setons may be used for marking, draining, cutting, or staging.[76] A marking seton is useful when it is difficult to determine the amount of muscle the fistula tract crosses. Encircling the tract with a seton allows the surgeon to assess the amount of muscle, particularly the puborectalis, once the patient is awake. If adequate muscle is present above the fistula tract, a fistulotomy may be performed without significant risk for incontinence.

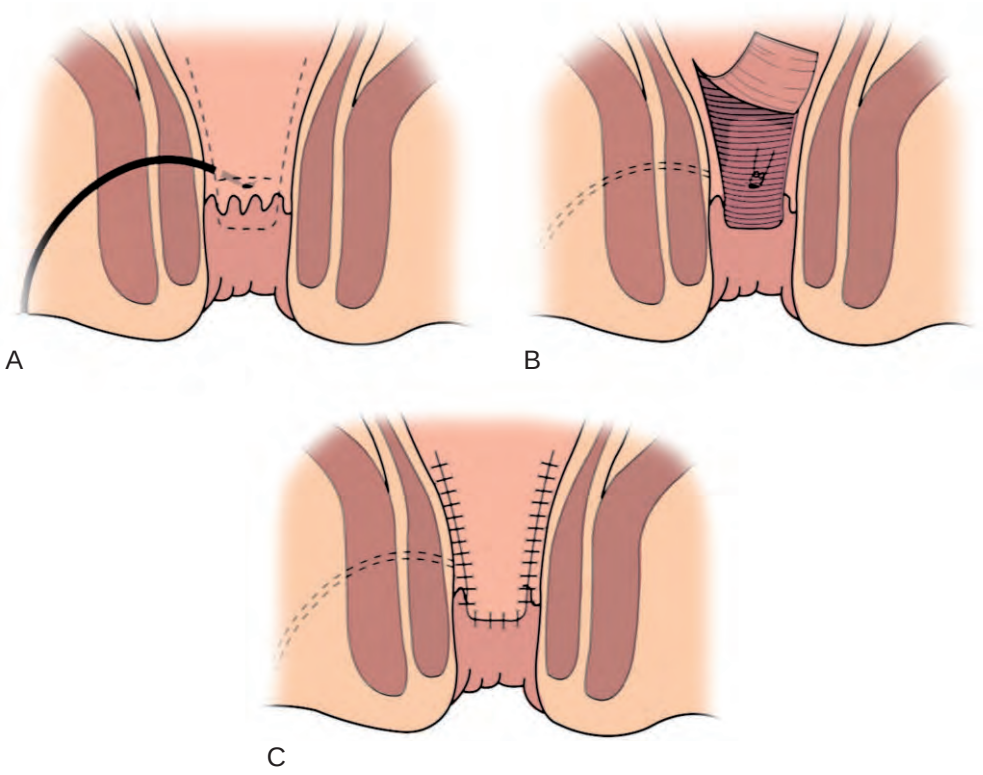

Figure 149–11. **A,** Anorectal advancement flap for closure of the internal opening in the treatment of perianal fistulas. The base of the flap should be wider than the apex. **B,** With the flap elevated, the internal opening is débrided and closed with a suture. **C,** The apex of the flap is advanced and sutured over the defect.

A draining seton traverses a fistula tract to provide long-term drainage of a septic process. It may be used as a bridge to definitive surgical therapy or be left in place for long periods. Epithelialization of the tract prevents recurring abscesses. Long-term draining setons are tied loosely. They are particularly useful in the management of complex fistulas associated with Crohn's disease.[77] The combination of draining seton and immunomodulation therapy with infliximab appears to improve outcomes while maintaining sphincter function in Crohn's patients with complex anal fistulas.[78]

A cutting seton is used to gradually transect the striated sphincter muscle. This technique promotes fibrosis in the tissue surrounding the muscle encircled by the seton. At regular intervals (2 weeks), the seton is progressively tightened, dividing the muscle by a process of ischemic necrosis. The cut edge of the divided muscle does not separate because of the fibrosis that forms during the time it takes to divide the muscle. The seton can be progressively tightened with silk ligatures. Alternatively, a hemorrhoid ligator may be used to progressively tighten the seton with rubber bands.[79]

When a staging seton is used, the fistula tract is identified and only the most superficial portion is divided. The seton is placed through that portion of the fistula tract that traverses the sphincter, thus encircling the muscle. This portion of the tract is divided as a second procedure once adequate fibrosis occurs (usually 8 weeks). A "high" fistula may be converted to a "low" fistula by dividing only the proximal portion of the tract, leaving the distal tract encircled with a seton for division at a later date.

Whether to use a cutting seton or a staging seton with second-stage fistulotomy appears to be up to surgeon preference. In a study of 59 patients with high anal fistula, Garcia-Aguilar et al.[68] showed no difference in fistula eradication, incontinence, and patient satisfaction between 12 patients treated with cutting setons and 47 treated with two-stage seton fistulotomy.

Closure of the Internal Opening: Anorectal Advancement Flaps

Advancement flaps consist of mucosa, submucosa, and part of the internal sphincter. The underlying fistula tract is débrided, and the internal opening is sutured at the level of the muscle. The edge of the elevated flap containing the internal opening is excised, and the flap is advanced and sutured over the internal defect (Fig. 149–11).

Advancement flaps offer the advantage of a one-stage procedure, quicker healing, limited damage to the underlying sphincter, and minimal risk of anal canal deformity.[3] Several studies have reported good success with few complications using anorectal advancement flaps in the treatment of both simple and complex fistulas.[80-82]

Fibrin Glue

The use of fibrin glue in the management of anorectal fistulas has been popularized.[83,84] A prepared mixture of fibrinogen and thrombin is injected into the fistula tract after it has been curetted. The resulting coagulum plugs the fistula tract. This technique represents an alternative mode of treatment in complex cases for which standard treatment has failed. The complete healing rate in one

series was 60% and included patients with Crohn's disease and human immunodeficiency virus (HIV)-associated anal disease.[83] Sentovich performed a two-stage fistulotomy with injection of fibrin glue into the external opening after seton removal at the second operation with 69% success in 48 patients.[85] Buchanan et al.[86] found only a 14% complex fistula closure rate in 22 patients. Though results have been mixed, fibrin glue remains a viable treatment option due to its safety, ease of application, and low risk of sphincter injury. A biodegradable "collagen plug" derived from porcine submucosa has been trialed against fibrin glue in a small sample of patients with promising results: 13 (87%) of 15 patients enrolled in the collagen plug arm of the study had complete fistula healing compared with 4 (40%) of 10 who were treated with fibrin glue ($P < .05$).[87]

POSTOPERATIVE CARE

In general, if surgery is performed as an outpatient procedure, patients are instructed in consuming a high-fiber diet. No bowel confinement regimen is required for the treatment of simple conditions. For complex procedures, bowel confinement has been recommended,[82] but it is of questionable value.[88] Sitz baths are recommended for perianal hygiene and comfort. More complex procedures may require inpatient status for pain management and wound care. Wound healing after fistulotomy usually takes 4 to 8 weeks. Patients with anorectal abscess should be followed closely after drainage for possible fistula development.

COMPLICATIONS

Complications after surgical intervention for anorectal suppurative disease are numerous and related to surgical technique. Urinary retention is the most common complication, occurring in up to 25% of patients.[89] Other complications include hemorrhage, acute external thrombosed hemorrhoids, cellulitis, fecal impaction, stricture, rectovaginal fistula, incontinence, and recurrence.[89] Local wound problems and complications associated with anesthesia, such as hypotension, hypertension, and seizures, have also been reported.[61] The issue of fistula recurrence after drainage of anorectal abscess has been discussed previously.

The rate of recurrent fistula after fistulotomy ranges from 0% to 18%,[90] although the true incidence is probably around 3% to 7%.[5,16] The primary causes of fistula recurrence relate to unrecognized internal openings and inadequate drainage of abscess cavities.[2] In a study of 375 patients, Garcia-Aguilar[16] found that recurrence was also associated with lateral location of internal openings and fistulas with horseshoe extension.

The rate of disorders of continence after fistulotomy ranges from 18% to 52%.[90] Factors associated with incontinence risk include the complexity of the fistula, female sex, division of a significant portion of the external sphincter, the use of two-stage seton or cutting seton fistulotomy (probably due to complexity of the fistula), and a history of prior fistula surgery.[16]

SPECIAL CONSIDERATIONS

Crohn's Disease

The incidence of perianal complications in patients with Crohn's disease (see Chapters 151 and 153) varies from 22% to 54%, with many due to anorectal sepsis and fistula.[91-93] Anorectal abscess in patients with Crohn's disease should be treated with prompt drainage. Long-term catheter drainage has been found to be safe and effective and may be of benefit in preventing or delaying recurrence and the subsequent need for proctectomy.[94,95]

The treatment of anorectal fistulas in patients with Crohn's disease should be tailored to the specific situation encountered. Consideration should be given to the complexity of the fistula and the presence of active Crohn's disease in the rectum. In general, treatment modalities should be conservative. Extensive procedures may increase the risk of incontinence and nonhealing wounds. A simple fistula in a patient with a normal rectum can be treated by primary fistulotomy with good outcome and satisfactory healing rates.[96-98] Complex fistulas in patients with active rectal Crohn's disease remain a therapeutic challenge. These cases are better served with prolonged drainage to achieve long-term palliation.[99] In selected cases, rectal advancement flaps may be used with good functional results.[82,100] Some patients with complex anorectal fistulas in the presence of anal Crohn's may require diversion of the fecal stream for symptomatic relief.[101] Ultimately, between 5% and 18% of patients require a proctectomy.[25] Shinozaki et al., in a series of 39 patients, found that simultaneously performing a bowel resection for active Crohn's disease at the time of drainage of perianal sepsis or draining seton placement led to better healing of the anal fistula.[102] It is theorized that control of the intra-abdominal Crohn's disease improves healing of perianal Crohn's fistulas.

The long-term administration of metronidazole may be beneficial in the management of patients with perianal manifestations of Crohn's disease. Symptomatic improvement has been reported in the range of 71% to 100%, although complete healing is less frequent.[103-107] Side effects associated with the chronic use of metronidazole include paresthesias, metallic taste, and pancreatitis. These complications have been reported to occur in 50% to 100% of patients.[103-105,108]

A monoclonal antibody to tumor necrosis factor (TNF)-α was approved in August 1998 by the U.S. Food and Drug Administration for the treatment of patients with fistulizing Crohn's disease. Infliximab (Remicade) is a genetically constructed murine-human chimeric immunoglobulin. It neutralizes the biologic activity of TNF-α and inhibits binding to its receptors.[109] A randomized trial in which infliximab was used in the management of patients with Crohn's fistulas (perianal and abdominal) demonstrated a 62% clinical response (defined as >50% reduction from baseline in the number of draining fistulas) and a 46% complete closure of all fistulas compared with 26% and 13%, respectively, of patients in the placebo group.[110] However, the duration of response is short lived. Repeat treatment or

chronic use may be required for a long-term beneficial effect.

The safety and efficacy of infliximab for long-term use have not been established. Severe infusion reactions have been reported.[111] The development of human antichimeric antibodies that may result in delayed hypersensitivity reactions and the possibility of attenuation of therapeutic effect with the subsequent exposure to the drug are issues under investigation. The development of a purely human TNF-α monoclonal antibody, adalimumab (Humira), may obviate these concerns. Associations between biologic disease-modifying antirheumatic drugs, such as infliximab and adalimumab, and lymphoid malignancies are anecdotal and similar to the associations seen between other immunomodulatory drugs and malignancy.

Fistula in Infancy

Anal fistula in infancy occurs almost exclusively in otherwise healthy boys younger than 2 years of age. The cause of this condition appears to be a congenital abnormality of the anal glands with abnormally deep and thick crypts of Morgagni. These factors predispose the patients to cryptitis with abscess and fistula formation.[112] Simple fistulotomy is recommended in this patient population with expected good results.[113] A concomitant cryptotomy has been recommended by some to decrease the likelihood of recurrence.[114] Nonoperative management is favored by those who believe that abscess and fistula are self-limited in this population.[115] Opponents argue that such fistula disease is seldom time limited. They argue that the process is truly characterized by frequent intermittent relapse or a prolonged silent state with late recurrence requiring subsequent intervention.[116]

Malignant Transformation in Chronic Anal Fistula

Carcinoma arising in an anorectal fistula is a rare condition. Rosser[117] established the first association between adenocarcinoma and anal fistula. There is controversy regarding the possibility of malignancy arising from a benign anorectal fistula. A slow-growing cancer may not become evident for years, and in some cases the fistula could result from the breakdown of a neoplasm. To rule out the preexistence of even the slowest growing cancer, it has been arbitrarily determined that a fistula should have been present for at least 10 years before the diagnosis of carcinoma if malignant transformation is to be considered.[118]

Carcinoma arising in anorectal fistulas in patients with Crohn's disease has been reported; the estimated incidence is 0.7%.[119] Deep biopsy samples, careful histologic examination of atypical cells obtained from ductal structures, and a high index of suspicion in cases of long-standing anorectal fistulas may provide a clue to the diagnosis of underlying carcinoma.[120] Resection with either wide local excision or abdominoperineal resection has the potential to result in cure.[121]

Anorectal Sepsis and Fistula in Human Immunodeficiency Virus Disease

Anorectal disease is a prevalent problem in the HIV-positive population, with an estimated frequency of 6% to 34%.[122] Although there is concern in performing elective anorectal surgery in this population because of the fear of poor healing, symptomatic anorectal sepsis and fistula often require surgical management. Treatment should be tailored to the patient's severity of illness. The risk for disturbed wound healing increases as the preoperative $CD4^+$ count decreases.[122] The presence of an acquired immunodeficiency syndrome–indicator condition (Kaposi's sarcoma, immunoblastic lymphoma, and so on) and a white blood cell count of less than $3000/mm^3$ are also associated with poor wound healing.[123,124] In the absence of these risk factors, fistulotomy for simple fistulas may be performed with expected good results. For complex fistulas and patients with risk factors for poor healing, the liberal use of draining setons is recommended for symptomatic relief.[25,124]

Anorectal Complications in Patients with Leukemia

Anorectal complications in patients with leukemia represent a rare but potentially life-threatening problem. The incidence of concomitant symptomatic anorectal disease has been reported to be as high as 5.8%. Acute anorectal sepsis accounts for almost half of all cases.[125] The mortality rate for patients with acute perianal sepsis in this population has been reported to be from 16% to as high as 54%.[125-127] In general, surgical treatment of anorectal sepsis in uncontrolled acute leukemia has been avoided because of the fear that the septic process would spread and wound healing would be impaired. Historically, this led to a policy of combined radiation therapy and symptomatic care as primary treatment, with surgical management reserved for the drainage of an obviously fluctuant abscess.[128] Symptomatic care consisted of sitz baths or warm compresses, stool softeners, analgesic agents, and broad-spectrum antibiotics. Additional precautionary measures included no rectal examinations, no instrumentation, and no enemas. However, reports indicate that surgical intervention in the form of incision and drainage appears to be safe in this patient population. Two studies found no difference in morbidity and mortality rates between patients who had surgical drainage versus those who did not.[125,129] Barnes et al.[130] found that when spontaneous drainage did not occur, mandatory surgical drainage of anorectal abscess contributed to a better outcome in terms of mortality rates and wound healing.

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Chapter

150

Miscellaneous Disorders of the Rectum and Anus

David E. Beck

Stricture, Pruritus Ani, Pain Syndromes, Solitary Rectal Ulcer, Colitis Cystica Profunda, and Hidradenitis Suppurativa

Other chapters in this text have covered the more common anorectal conditions. A group of less common but still important conditions are discussed here. This summary of the disease process, evaluation, and management will prepare the provider to manage patients with these conditions.

STRICTURE

Nonmalignant stricture or stenosis of the anal canal is an uncommon but potentially debilitating condition. Patients with this condition have anal pain, obstipation, and frequent bleeding. The scarred anal canal may also be sufficiently noncompliant to cause incontinence. Anal stenosis is most commonly (87%) caused by excessive excision of the anoderm during hemorrhoidectomy.[1] An improperly performed hemorrhoidectomy may also produce an ectropion (rectal mucosa in the distal anal canal), also referred to as a *Whitehead deformity*. Other causes of anal stenosis include recurrent anal fissure; chronic diarrhea; recurrent abscess and fistula requiring surgical treatment; anal Crohn's disease; radiation; and excision of perianal skin lesions as in Paget's or Bowen's disease.[1,2]

The treatment of anal stenosis depends on its severity and position in the anal canal. High anal strictures that are covered entirely by mucosa are more difficult to treat than the low anal strictures at the level of the anoderm. Mild anal stenosis responds to more conservative therapy, whereas severe anal stenosis may require more extensive surgical procedures.

Medical Therapy

Medical therapy for anal stenosis combines bulking of the stool with dilation in the office or at home using the finger or calibrated rubber dilators and topical anesthetics. Dilation is an ideal treatment for patients with Crohn's disease or high-risk patients with otherwise weakened external sphincters.[3]

The combination of repeated dilation and steroid suppositories may prevent early recurrence of the stenosis, but no well-controlled trials have been reported. Anal stenosis in elderly patients has been shown to cause megarectum. These patients are usually nursing home residents who require daily enemas for constipation.

Surgical Therapy

The surgical treatment of anal stenosis includes lateral internal sphincterotomy, any one of a number of flaps, and occasionally a colostomy. Anal strictures may be associated with an *ectropion* (a distal protrusion of mucosa onto the anoderm as the scarring tissue retracts toward the perineum). A lateral internal sphincterotomy has been suggested as a means of treating anal stenosis that is mild and low in the anal canal. Although the results have been adequate, sphincterotomy does not treat the ectropion or add additional tissue to enlarge the anal canal.

Several varieties of flaps have been used to manage anal stenosis. Some, as described later, also address the problem of the ectropion. The flaps are formed with

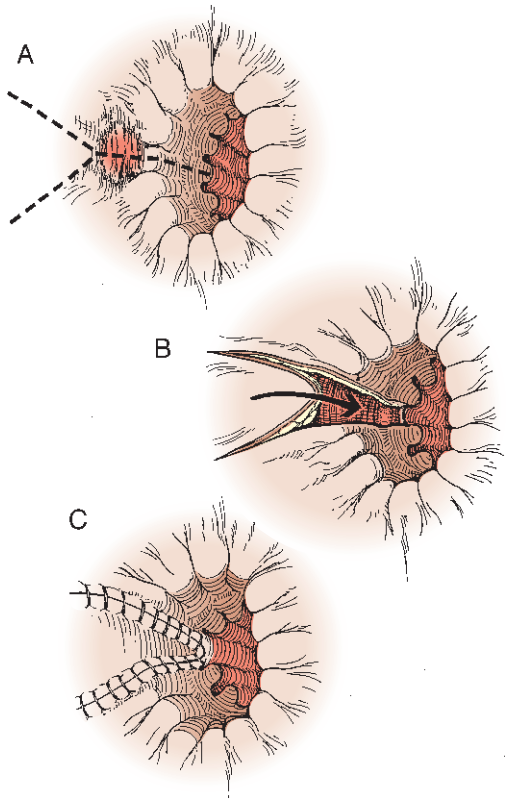

Figure 150–1. Y-V advancement flap. **A,**Y-flap inscribed outside ectropion and stenosis. **B,** Ectropion excised, Y-flap incised. **C,** Flap sutured with V closure. (**A-C,** From Fleshman JW: Fissure-in-ano and anal stenosis. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, pp 209-224.)

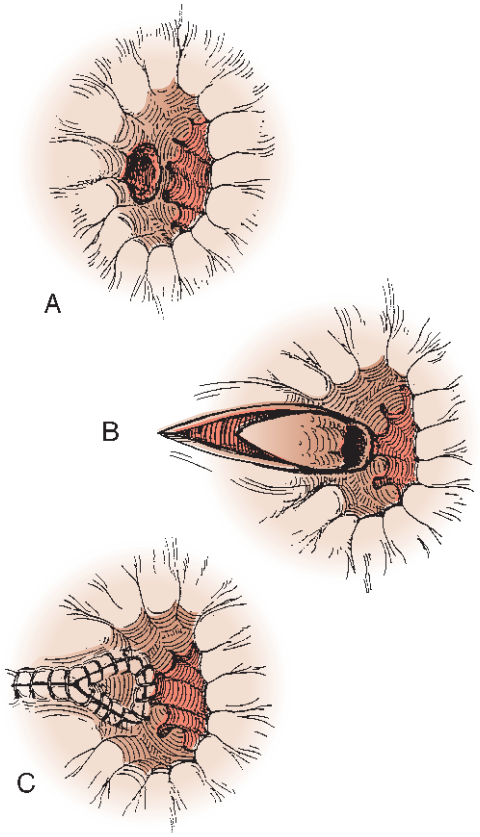

Figure 150–2. V-Y advancement flap. **A,** Lateral inverted-V inscribed over ectropion or mucosal defect. **B,** Flap mobilized to preserve vasculature after stenosis is divided or ectropion is excised. **C,** Flap sutured in place with Y closure. (**A-C,** From Fleshman JW: Fissure-in-ano and anal stenosis. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, pp 209-224.)

either mucosa or skin and include advancement, island, or rotational flaps.

Advancement Flaps

Advancement flaps advance mucosa or skin supported by muscle or subcutaneous fat.

The blood supply for this tissue comes from the adjacent intact lateral or inferior tissue. The *mucosal advancement flap* (Martin anoplasty) advances a pedicle of mucosa into the anal canal by way of an incision made through the stenotic area.[4] This posterior or lateral flap results in a mucosal ectropion that prevents repeat stricturing. This technique is simple and safe but creates an ectropion with associated mucous discharge. This type of flap is best used for proximal anal canal stenosis.

A *Y-V advancement flap* moves perianal skin into the distal anal canal.[1] The vertical limb of the Y is inscribed on the anal canal at the level of the stenosis, and the V of the Y is drawn on the lateral perianal skin (Fig. 150–1). The skin is incised, and the V-shaped flap of skin is freed laterally. The blood supply of the flap comes from the adjacent or underlying subcutaneous tissue. The V is then introduced into the stenotic anal canal to close the wound as a V-shaped incision. This can be used unilaterally or bilaterally with good results. Because the V is still attached to the buttock skin, the flap will not remain within the anal canal if the tension is too great and stenosis will recur.

Island Flaps

An island flap differs from advancement flaps in a division of all adjacent mucocutaneous edges. The blood supply is derived solely from the inferior supporting tissue. The increased mobility of these flaps makes them especially useful to treat anal stenosis.[4] Following incision of the stenotic scar at the dentate line a flap is created. The *V-Y flap* advances a triangular or V-shaped portion of skin into the anal canal. The V is drawn with the wide base at the dentate line and incised through the skin (Fig. 150–2). The subcutaneous attachments in the lateral edges of the V are released to allow mobilization of the skin into the anal canal. The blood supply to the flap relies on perforating vessels in the subcutaneous fat. The skin is then closed behind the V at the external

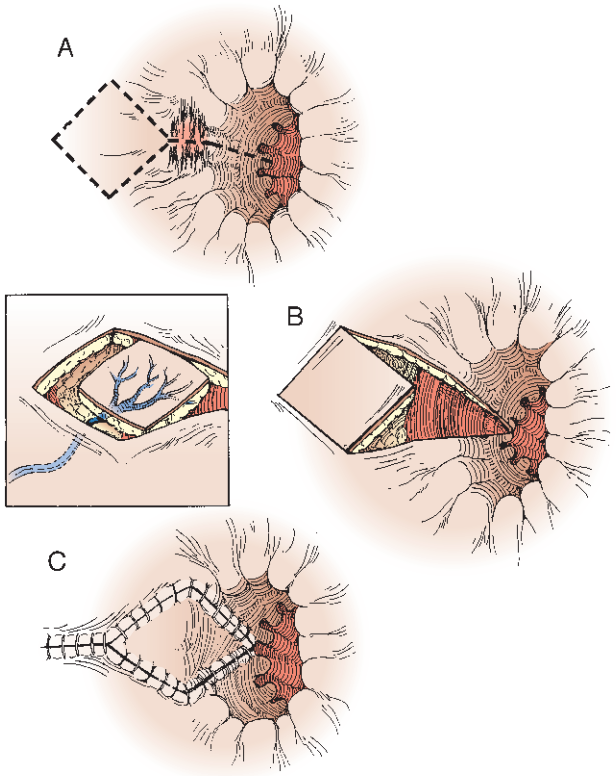

Figure 150–3. Diamond island flap. **A,** Stenosis incised in lateral midline and diamond inscribed laterally to match defect. **B,** Diamond flap incised and advanced into anal canal. **C,** Flap secured with wide point at stenosis line. (**A-C,** From Fleshman JW: Fissure-in-ano and anal stenosis. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, pp 209-224.)

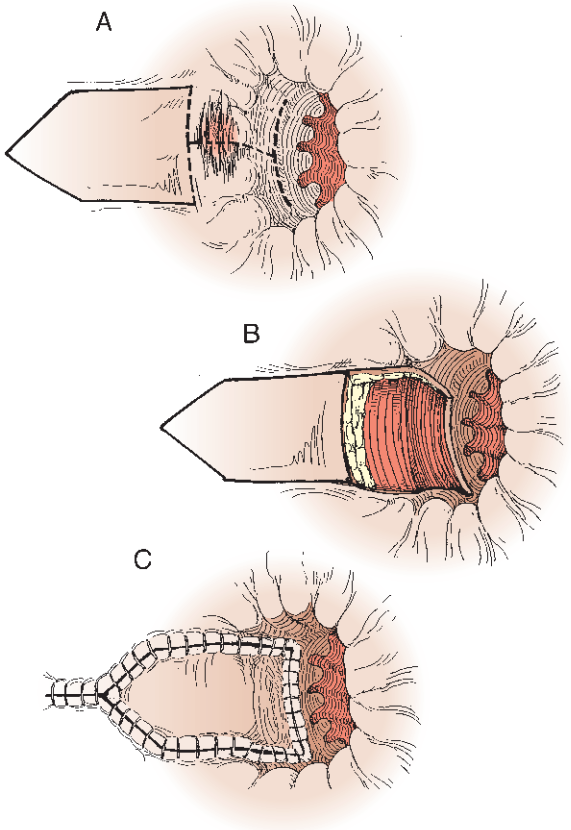

Figure 150–4. House advancement flap. **A,** House-shaped flap is created. **B,** The flap is advanced into the anal canal. **C,** The flap is sutured in place. (**A-C,** From Fleshman JW: Fissure-in-ano and anal stenosis. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, pp 209-224.)

portion of the perineum to push the V into the anal canal and widen the stenotic area. This method may be used for the treatment of ectropion or low stenosis. However, the flap does not advance a wide portion of skin into the scar. The benefit obtained with this flap is derived from soft pliable tissue inserted into the nonpliable scar. If more tissue is needed to allow the canal to dilate, this technique may be repeated on the opposite side of the anal canal.

A *diamond-shaped island* of skin from the lateral perineum is inscribed to match the defect in the anal canal made by this incision (Fig. 150–3). The flap is then mobilized from its lateral subcutaneous attachments and advanced into the incision made in the stenotic anal canal. This flap of skin opens the stenosis widely when the lateral corners of the diamond are sutured at the level of the stenosis. This flap allows advancement of maximal skin to the point of stenosis with minimal tension. A *U-shaped flap* as described by Pearl and associates[5] is especially useful for patients with Whitehead deformity and ectropion. The U is a broader-based version of the V-Y flap but allows the ectropion to be excised across a wide base and the inverted U to be advanced into the anal canal to fill the defect.

Christensen et al.[6] proposed the "house" advancement pedicle flap. This flap is easy to construct, can cover as much as 25% of the anal circumference, and permits primary closure of the donor site (Fig. 150–4). This type of flap is the most frequent type used by the author. If additional coverage is needed, two, three, or even four flaps may be used.

Rotational Flaps

The S-plasty is a rotational flap that is used to provide a wide area of skin to cover a perineum that is entirely excised for disease such as Bowen's or Paget's disease. It does not open a stricture as well as the previously described advancement flaps. The base of the S is drawn on the lateral buttock, and the necessary tissue is excised (Fig. 150–5). The skin and subcutaneous tissue in the S are rotated down to the mucosal incision and sutured in place. The opposite curve of the S is treated similarly on the other side of the anal canal. This shape provides for adequate blood supply and avoids tension; unilateral or bilateral S-flaps can be performed.

Advancement, rotational, or island flaps can be fashioned using local or regional anesthesia. Each type of

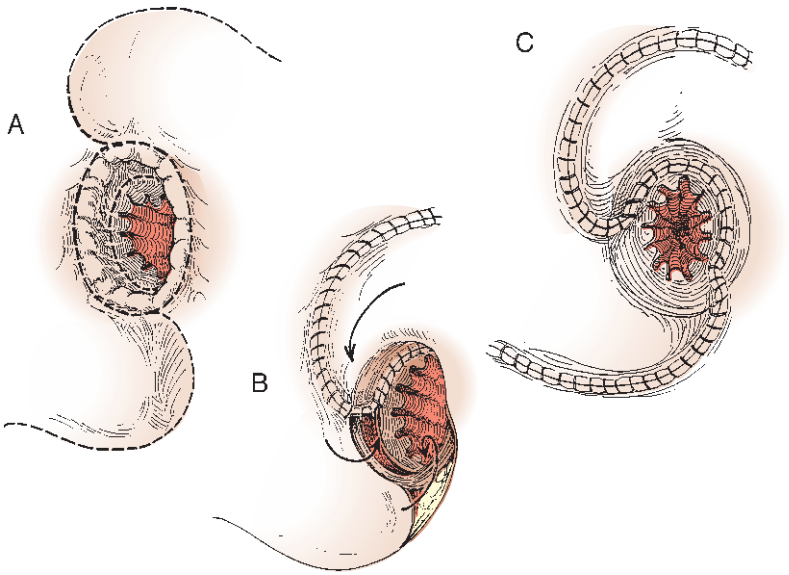

Figure 150–5. S-plasty. **A,** Perianal skin lesion requiring removal of large skin area. **B,** Area of perianal skin excised, with lateral curves incised onto buttocks. **C,** Curves of skin advanced into perianal defect and secured laterally to produce S-shaped closure of rotated flaps. (**A-C,** From Fleshman JW: Fissure-in-ano and anal stenosis. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, pp 209-224.)

flap has advantages, and proper selection produces good results. Surgeons should therefore be experienced in all types, allowing individualized treatment. Rotation and advancement flap techniques require more mobilization of tissue, more suture lines, and a complete bowel preparation. Flap anoplasty techniques are reserved for the most severe problems after conservative measures have failed. Complications of anoplasty include infection, failure of the anoplasty to correct the stenosis, and slough of the flap. These can usually be avoided with adequate preparation and adherence to good technique. In certain settings, a diverting stoma may be considered.

Patients with strictures secondary to Crohn's disease, lymphogranuloma venereum, or syphilis usually respond best to repeated dilation.[3] Only rarely has anal stenosis secondary to inflammatory bowel disease been treated with anoplasty. The patients may require anoderm release incisions with repeated dilation. It is difficult to use anoplasty because the underlying disease process is continuous and may affect the healing.

PRURITUS ANI

Pruritus ani is a symptom complex that consists of an intense itch and burning discomfort of the perianal skin. It has a multiplicity of causes, several of which may coexist. It is frequently associated with varying degrees of skin breakdown, weeping, maceration, lichenification, and superinfection. Pruritus may be refractory until the specific cause is identified, but many symptoms can be successfully treated without determining a specific cause.[7]

History

A carefully taken history can often aid in identification of the cause of pruritus.[8] This history should include the onset of symptoms and their relationship to diet, medication, bowel evacuation, and anal hygiene practices. Pruritus may begin insidiously, with the patient complaining of the sensation of uneasiness or itching in the perianal region. As the area of involvement spreads and the intensity of itching increases, the patient reflexively begins scratching and clawing at the skin. This leads to further skin damage, excoriation, and potentially a secondary skin infection.

All medications should be identified because many can contribute to pruritus; special attention should be given to antibiotics, colchicine, quinidine, and topical medicines that contain corticosteroids, estrogens, or "-caine" drugs. Systemic illnesses, such as diabetes mellitus, chronic renal failure, or lymphoreticular diseases such as polycythemia vera or Hodgkin's disease, should be identified. The history should also elicit any symptoms of inflammatory bowel disease or acholic stools. Prior anorectal surgery may suggest deformed anorectal anatomy, which in turn can lead to poor continence. The physician should also document allergies or any generalized dermatoses such as psoriasis or seborrhea. A sexual history should include sexual orientation and specific practices, especially the practice of anal receptive intercourse. The immune status is also important, not only because of primary immunodeficient states or contracted states such as acquired immunodeficiency syndrome but also in transplant recipients who are receiving immunosuppressive medications. A careful gynecologic and obstetric history should be obtained from female patients and should include contraceptive practices and any history of inflammatory or ulcerative lesions. A history of difficult vaginal deliveries or perineal trauma should increase the suspicion for anatomic or functional sphincter compromise; manometry and rectal ultrasonography can be helpful in selected cases. A brief psychological profile may be beneficial to identify any association between symptoms and social or financial stresses with which the patient may be confronted.

Physical Examination

After completing a detailed medical history, the clinician should perform a meticulous physical examination. Initially, the general dermatologic evaluation may isolate conditions such as psoriasis, seborrheic dermatitis, or fungal or other infections. The patient should come to the examining suite without bowel preparation and with instructions not to have applied any creams or ointments to the perianal area. The examining room should be well stocked, with a bright light source and magnifying glass along with disposable enemas for bowel preparation and all clinical equipment necessary to obtain appropriate cultures, scrapings, or biopsy samples. After the patient is assisted into the prone jackknife position, the perianal region should be carefully inspected for signs of excessive moisture, soiling, excoriation, skin maceration (Fig. 150–6), or any perianal dermatoses. After giving instructions to the patient to strain (Valsalva maneuver), the clinician can evaluate the perianal region for possible prolapsing hemorrhoidal tissue. An initial digital examination should be performed without bowel preparation to evaluate the consistency of the stool. All abnormalities should be carefully documented, as should an assessment of the resting and squeeze sphincter strengths.

Next, the clinician can take any culture materials, biopsy samples, or scrapings that are thought necessary to make an appropriate clinical diagnosis. Suspicious skin lesions can be biopsied using a punch biopsy technique.[8] This technique involves the subdermal infiltration of a few milliliters of 1% lidocaine with epinephrine (1:200,000) under the biopsy site. A punch biopsy tool is driven into the area with a circular motion by swirling the punch between the thumb and index fingers. After the punch is 4 to 5 mm beneath the skin, it is gently raised and the resulting circular wedge of skin and subcutaneous tissue is excised with a fine scissors. Bleeding should be minimal, and simple pressure or treatment with a silver nitrate stick should adequately effect hemostasis. A simple gauze dressing or Band-Aid is all that is required. The punches are available in a number of sizes ranging in diameter from 1.0 mm to 1.0 cm. For convenience, I use disposable punches. Two disposable enemas should then be administered to the patient, after which a careful sigmoidoscopy and anoscopy are performed. Evaluation for hemorrhoids, polyps, cancer, fistula, mucosal prolapse, stenosis, or evidence of previous surgery is documented. Sigmoidoscopy may be helpful to identify proctitis, inflammatory bowel disease, rectal lesions, or active infections. Pruritus ani may be associated with colorectal neoplasms at a disproportionately high rate,[8] particularly when the symptom is chronic. The examiner should adhere to universal precautions when evaluating any patient and should decide on a case-by-case basis whether to perform pelvic examinations in women or to recommend pelvic examination performed by a gynecologist.

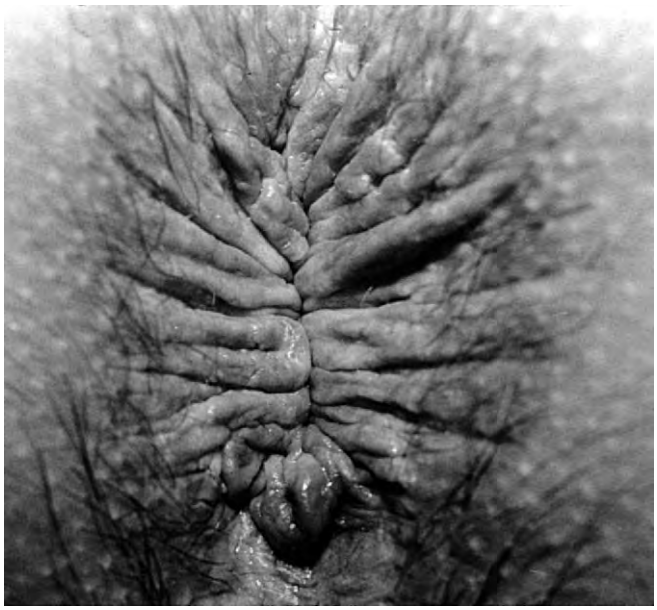

Figure 150–6. Pruritus ani. (From Hicks TC, Stamous MJ: Pruritus ani: Diagnosis and treatment. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, p 199.)

Pathophysiology

The perianal skin is richly supplied with sensory nerve endings that mediate a variety of sensations.[9] These sensations may be elicited by local irritation from excoriation, alkaline secretions, and various chemical irritants. The receptor apparatus for both itch and pain is located at the dermo-epidermal junction of the skin and consists of a plexus of free nerve endings. Damage to cells in close proximity to these nerve endings causes a release of diffusible mediators that may stimulate the receptors. Slow-conducting neurons transmit the itch sensation to the lateral spinothalamic tracts through synapses that connect with secondary fibers and send the sensation to the thalamus. It is questionable whether tertiary neurons relay the itch sensation to the cortex. Greaves[9] pointed out that pain and itch are served by the same receptors and neural pathways, which explains the effectiveness of pain (scratching) in relieving itch.

Causes

The cause of pruritus ani is appropriately categorized under the headings of idiopathic and secondary types. The specific etiologic factors responsible for the diagnosis of secondary pruritus ani are nearly encyclopedic, yet despite comprehensive evaluations, in more than one half of patients with pruritus ani the cause is categorized as idiopathic. The major contributors to secondary pruritus ani are listed in Table 150–1.

Personal Hygiene

Clinicians have long been aware of the irritant effect of feces on the perianal area, especially in cases of prolonged contact. In patients with continued fecal contamination, the use of bulking agents and an appropriate

Table 150–1 Major Causes of Pruritus Ani

Cause	Examples
Personal hygiene	Poor cleansing habits resulting in chronic exposure to residual irritating feces; conversely, overmeticulous cleansing with excessive rubbing and soap use
Diet	Consumption of large volumes of liquids; coffee (caffeinated and decaffeinated, coffee-containing products), chocolate, citrus, spicy foods, tea, beer, and foods high in milk content; vitamin A and D deficiencies, fat substitutes
Anatomic compromise	Obesity, deep anal clefts, excessive hair, tight-fitting clothing (tight clothing or clothing that impairs adequate ventilation), fistula, fissure, skin tags, prolapsing papilla, or mucosal prolapse
Systemic disease	Jaundice, diabetes mellitus, chronic renal failure, iron deficiency, thyrotoxicosis, myxedema, Hodgkin's lymphoma, polycythemia vera
Gynecologic conditions	Pruritus vulvae, vaginal discharge (endocervicitis, vaginitis)
Neoplasms	Bowen's disease, extramammary Paget's disease, squamous cell carcinoma, cloacogenic carcinoma, anorectal polypoid lesions
Diarrheal states	Irritable bowel syndrome, Crohn's disease, chronic ulcerative colitis
Radiation	Postradiation changes
Psychogenic	Anxiety, neuroses, psychoses
Drugs	Quinidine, colchicine, antibiotics (tetracycline), intravenous hydrocortisone phosphate, ointments or creams that contain "-caine" drugs, and nonprescription medications for personal hygiene (e.g., perfumed soaps and ointments that may contain alcohol, witch hazel, or other astringents)
Dermatologic conditions	Psoriasis, seborrheic dermatitis, atropic dermatitis, lichen simplex and lichen sclerosis
Infections	Viruses: herpes simplex, cytomegalovirus, papillomavirus Bacteria: *Staphylococcus aureus,* erythrasma, mixed infections, syphilis Fungi: dermatophytosis, candidiasis Parasites: pinworms, scabies, pediculosis
Idiopathic	—

cleansing regimen often alleviates symptoms. Another group of patients, known as the "overachiever group," have pruritus secondary to their personal hygiene practice of compulsively cleaning the perianal area. Their meticulous cleansing is usually associated with abrasive rubbing and the use of irritating alkaline soaps, which can result in chronic pruritus. Physicians have categorized this maneuver as the "polishing the anus syndrome." Symptoms often resolve immediately once patients adopt a less traumatic perianal hygiene program.

Anatomic Compromise

An estimated 25% of patients with pruritus ani have causative or contributory anorectal disorders.[10] Lesions such as anal fistula, fissure, skin tags, prolapsing anal papillae, or mucosal prolapse may lead to the seepage of fluid from the anal canal onto the perianal skin, which in turn leads to inflammation, ulcerations, and, if infected, suppuration. Surgical intervention to relieve pruritus has been reported to be successful in fewer than 15% to more than 80% of patients.[8] Thus, it becomes important for the clinician to be highly selective in choosing surgical candidates, preferably only after appropriate medical therapy has failed.

Obese patients are predisposed to pruritus because their anatomy produces a persistently moist environment that may lead to difficulties in achieving appropriate personal hygiene. Patients with weak sphincter tone may have mucosal prolapse or fecal contamination of the perianal area, leading to pruritus. Wearing tight clothing (tight jeans, underwear, and girdles) or clothing that does not allow proper ventilation also predisposes to this trapped moisture syndrome.

Systemic Diseases

On occasion, systemic diseases may lead to generalized itching; perhaps the best recognized of these disorders is jaundice. Cholestatic jaundice has been associated with oral contraceptives, testosterone, and chlorpromazine. The itching associated with jaundice has long been attributed to elevated bile salt levels in the skin and blood, but this theory has not been substantiated. However, the administration of cholestyramine or colestipol hydrochloride is often helpful in reducing itching in this group of patients.[9]

Chronic renal failure is the most common systemic illness that elicits pruritus. Clinical manifestations are thought to be present in more than 90% of patients receiving hemodialysis. The cause of the itching is unclear; ultraviolet B radiation is the most successful treatment.[9] Diabetes mellitus is often associated with vulvar and anogenital pruritus because of the frequent association of the disease with candidiasis. Pruritus can

also be associated with iron deficiency, anemia, thyrotoxicosis, myxedema, Hodgkin's disease, and polycythemia vera.[9]

Diet

Dietary factors may represent the most significant cause of secondary pruritus ani. Diet may incite symptoms through three major pathways. First, it affects the consistency of the stool, which in turn can lead to fecal soiling. Second, the components of the diet may lead to direct irritation secondary to their chemical composition. Third, if an excessive volume of liquid is consumed, it could directly lead to more watery stools and pruritus as a result of frequent contact irritation. Many food groups, such as coffee (caffeinated and decaffeinated), chocolate, citrus, spicy foods, tea, beer, and foods with a high milk content, have been implicated in initiating or promoting symptoms. Patients with vitamins A and D deficiencies are also believed to be predisposed to pruritus ani.[8]

Most patients with diet-induced pruritus ani can relate the onset of their symptoms to the ingestion of coffee or dairy products. Coffee is an irritant that can elicit pruritus when it is ingested in any form (fresh, instant, decaffeinated, or when used as a flavor additive to other foods, such as ice cream). An apparent threshold for coffee drinkers usually varies between 2 and 4 cups per day. A similar threshold, noted in milk-drinking patients, arises at the ingestion of 6 to 10 oz daily.[11] Pruritus caused by chocolate, tea, and cola is believed to be related to the xanthine content of these substances. Olestra, a fat substitute, may result in pruritus ani secondary to fecal seepage induced by the nonabsorbed, oily food additive. The appearance of diet-induced pruritus is often symmetrical.[11]

Gynecologic Conditions

Pruritus ani often can be attributed specifically to diseases of gynecologic origin. Pruritus vulvae may extend posteriorly to involve the anal skin and can often be attributed to vaginal discharge or urinary incontinence. Irritation secondary to vaginal discharge may also lead to pruritus as the result of endocervicitis, trichomonal vaginitis, or candidal vaginitis, which cause a leukorrhea that irritates the perianal skin. Physicians should be prepared to perform pelvic examinations and to obtain appropriate cultures and stains in this subset of patients. Pruritus ani can be reported in women during menopause independent of any identifiable local causes, probably secondary to estrogen deficiency.

Neoplasms

Neoplasms of the perianal region can be responsible for pruritus ani. The clinician must be cognizant of these potential causes and should exclude them by performing a careful physical examination and biopsy if necessary. Polypoid tumors of the anorectum may lead to soiling, which may be secondary to changes in the normal anatomy or mucous secretions, as seen in the case of villous lesions. Bowen's disease is a unique form of squamous cell carcinoma in situ. The disease can present as pruritus or may be found incidentally in an anorectal surgical specimen. The lesion is characteristically an erythematous, hyperkeratotic plaque sharply demarcated from the surrounding skin. The size of the lesions ranges from a few millimeters to several centimeters. Because these lesions remain stable in size for long periods, they are often clinically overlooked or may be mistaken for psoriasis. If these lesions become pigmented, they can be confused with superficially spreading melanoma. Small lesions may be treated successfully with topical 5-fluorouracil, but generous local excision with an adequate margin remains the preferred therapy.[8]

Extramammary Paget's disease is an intraepidermal adenocarcinoma. Although the cell type of this lesion is still undefined, it is believed to be a pluripotential epithelial cell that borders on differentiation into sweat gland tissue. The lesions are usually red, indurated, scaling plaques often confused with eczema.[8] The treatment for the noninvasive lesion is wide local excision.

Squamous cell carcinoma of the perianal region may also present as pruritus. The lesion is usually a nodular plaque with a warty appearance often confused with condyloma acuminatum. The clinician must be cognizant of the lesion's metastatic potential and should know its pattern of nodal spread, although wide local excision is usually sufficient curative therapy. Basal cell carcinomas are rare tumors of the anorectal area. The characteristic appearance is similar to that found elsewhere on the body. This nodular growth, with its classic central depression, is usually treated by wide local excision. More radical surgery may be necessary for invasive or neglected tumors. In situ squamous carcinomas and cloacogenic carcinomas of the perianal region are being seen in increasing numbers in immunodeficient patients and male homosexuals.[12] It is imperative that the clinician take a biopsy sample of any suspicious or nonresponding lesions of the perianal region.

Anorectal melanoma, a rare tumor of ectodermal origin, is the most devastating perianal tumor. Regardless of the lesion's size, most anorectal melanomas have metastasized by the time of diagnosis. Unfortunately, these tumors usually do not respond to radiation or chemotherapy, and heroic efforts such as abdominoperineal resection yield only a 5% to 10% 5-year survival rate. Because of these dismal survival statistics, palliative therapy is often the treatment plan.

Diarrheal States

Clinical and experimental data have shown that skin trauma secondary to moisture is one of the primary contributors to pruritus ani. Such moisture is seen not only in patients with colitis (Crohn's, ulcerative, or nonspecific) but also in patients who abuse laxatives or who ingest an excessively high-fiber diet. Patients with dumping or malabsorption syndromes, such as lactose intolerance, are also predisposed to pruritus. In the diarrheal patient, not only is the stool a direct skin irritant but also the frequent hygiene it necessitates leads to abrasive trauma.

Radiation

Patients with rectal or anal canal cancers are often treated with a combination of chemotherapy and radiation. Radiation to the skin causes alterations in the normal cell cycle that induce erythema and edema, which may progress to sclerosis and fibrosis. If the injury progresses, a full-thickness radiation burn will lead to ulcerations. Patients complain of pain, burning, and itching due to perianal skin injury. In addition, radiation proctitis leads to diarrhea, which further exacerbates local perianal skin irritation. Radiation proctitis can be managed with dietary measures and bulking agents or a trial of hydrocortisone retention enemas. Radiation dermatitis is difficult to treat; initially, the physician should closely inspect the anoderm and take a biopsy sample of all suspicious areas. Controlling pruritus is often difficult; treatment should include cleansing the anoderm with a mild emollient soap substitute such as Balneol and water. If these simple maneuvers fail to control symptoms, a short trial of topical hydrocortisone (1% to 2.5%) may be helpful.

Psychological Factors

The clinician should not underestimate the significance that psychological factors play in the cause of pruritus ani. Often, the patient with pruritus can relate its onset to anxiety. The "stress years" of midlife produce the largest patient population that complains of pruritus ani, perhaps suggesting more than a casual relationship with other etiologic factors.

Drugs

Several oral medications have been implicated in eliciting pruritus ani through both contact irritation and increased leakage of fecal material from the anal opening. Quinidine and colchicine can initiate the acute onset of pruritus, although these medications may have been taken in consistent dosages for years. Pruritus is usually controlled when the medication is temporarily stopped, which may be related to a threshold phenomenon. Mineral oil (taken orally) has also been detected as an offending agent; in this instance, pruritus is believed to be secondary to the pasty stool that develops and the associated perianal seepage. The ingestion of tetracycline also may cause pruritus by irritating the gut, which leads to a loose stool. In addition, tetracycline facilitates the occurrence of secondary perianal candidal infections. The intravenous administration of hydrocortisone phosphate has also been shown to produce pruritus ani. The application of certain topical ointments, creams, or cleansing agents may also elicit pruritus. Preparations containing the "-caines" are notorious for producing intense inflammation in some susceptible patients. Many over-the-counter hygiene products, such as scented soaps, deodorants, colored toilet tissues, and laundry detergents, contain chemicals that may cause increased skin sensitivity and irritation. These chemicals include formaldehyde, alcohol, perfumes, and astringents that elicit symptomatology by depriving the skin of its natural acidity. The increased use of anal wipes that are alcohol based or that contain witch hazel may lead to excoriation if used frequently or if left in contact with the skin for a prolonged period. Because of this, many of the new personal cleansing tissues are free of alcohol and witch hazel. Patients must be assisted in their selection of appropriate nonirritating, atraumatic perianal cleansing products.

Dermatologic Conditions

A large proportion of cases of pruritus ani may be attributable to nonmalignant dermatologic lesions. *Perianal psoriasis* may be a cause of refractory pruritus ani. The clinician should carefully inspect the patient for the presence of characteristic psoriatic patches elsewhere on the body, such as the scalp, knees, elbows, or other bony prominences. A perianal lesion may be the first or the only psoriatic lesion and is usually found in the gluteal cleft spreading toward the sacrum. Although a perianal psoriatic lesion has a definitive border, it does not have the scaling of systemic psoriatic plaques. A multitude of treatment modalities exist for psoriasis, including local lubrication to prevent fissuring and to maintain flexibility of the skin, topical corticosteroids, coal tar applications, phototherapy (ultraviolet A light used in conjunction with the photosensitizing properties of psoralen compounds [PUVA]), methotrexate, and low-dose cyclosporine.[8]

Seborrheic dermatitis may also be a factor in perianal pruritus, and *contact dermatitis* may be allergic or irritant in nature. *Allergic dermatitis* is the result of a cell-mediated immune response to a specific exogenous allergen, which may be the chemical component of a plant or an animal, a fabric, or a medicinal product. The most frequent offenders are poison ivy, poison oak, nickel, rubber (latex) compounds, procaine, neomycin, and the topical anesthetics of the "-caine" family. The lesions from contact dermatitis may vary from vesicles to eczematoid plaques with ill-defined borders. Dermatologic skin testing can often identify the offending agent. Treatment is aimed at prevention of allergen exposure supplemented by topical or systemic steroids if a reaction occurs. Nonallergenic contact dermatitis, or irritant dermatitis, is caused by exposure to such substances as acids, alkalis, the salts of metals, and hydrocarbons. The treatment is avoidance of exposure to these irritants and symptomatic measures on occasions when such exposure leads to dermatitis. All soaps, laundry detergents, and fabrics should be inventoried to detect any temporal relation between the onset of pruritus and the acquisition of new clothing, soap, toilet tissue, or laundry detergent.

Lichen sclerosis et atrophicus is a rare condition most commonly referred to as *lichen sclerosis*. Its cause is unknown, and it affects women in a ratio of 5:1 over men. In women, the disease often presents around the time of menopause and in many cases is associated with a previous episode of vaginitis. The lesions are elevated, ivory white, and macular. When several lesions coalesce, they form a "cigarette-paper crinkling" of the skin surface. There is no cure for the disease, and treatment is

symptomatic, involving the use of topical steroidal creams in conjunction with estrogen-containing creams.[8]

Atopic eczema is a chronic, relapsing pruritic dermatitis that usually occurs in adults and is localized to the flexural surfaces of the face, neck, cubital or popliteal fossa, and hands. The dermatitis usually occurs in patients with a personal or family history of atopy or hay fever/asthma/urticaria; lesions may present as papular, scaly, or chronic lichenified plaques. The cause is unknown but is believed to be IgE mediated.[8] Some researchers support food allergies and proteinaceous aeroallergens as possible causes. Patients with atopic dermatitis are likely to acquire both bacterial and viral infections. Treatment is directed at skin hydration, corticosteroid administration, and antibiotics if secondary infections are present. Unfortunately, eczema is a chronic disease and relapses are common.

Infections

Infectious agents must be considered in the differential diagnosis of secondary pruritus ani. The etiologic agents may be bacterial, viral, mycotic, or parasitic. Primary bacterial infections are an unusual occurrence, and when infectious agents can be documented, they are usually superimposed on preexisting perianal skin trauma. Pruritus secondary to infectious agents often has an asymmetrical appearance around the anus.[11]

Bacteria *Hidradenitis suppurativa* (HS), as described later, may cause pruritus. *Staphylococcus aureus* can frequently be cultured from the perianal area of patients with pruritus. *Erythrasma* is an uncommon bacterial infection caused by *Corynebacterium minutissimum,*[8] producing lesions that initially present as a reddish scaly area that is well demarcated but eventually change to a tannish color during the course of the disease. The diagnosis can be confirmed by using a Wood's ultraviolet lamp, which allows the examiner to observe the characteristic red fluorescence of these lesions. A 10-day course of erythromycin usually relieves the symptoms, but the condition sometimes recurs. *Syphilitic lesions* in their primary or secondary stages may have an associated exudate. Continued local irritation secondary to moisture may lead to maceration and pruritic complaints.

Viruses Pruritus ani may be associated with three major sexually transmitted viruses: herpes simplex virus (anogenital herpes), papillomavirus (condyloma acuminatum), and cytomegalovirus (CMV). Patients with *herpes simplex virus* present with painful small vesicles surrounded by an erythematous areola. The vesicles usually rupture at approximately 48 hours and then progress over weeks to scaly eschars; the diagnosis can be confirmed by viral culture. Oral acyclovir is the current treatment of choice; studies have indicated that the prophylactic use of this medication is successful for frequent recurrences.[8] *Condylomata acuminata* are wart-like lesions found in the perianal region and the anal canal. The clinician should remember that the main reason for recurrence of these lesions is failure to eradicate anal canal lesions. Patients with *immunodeficiency states* are likely to develop CMV anal ulcerations or CMV colitis. Biopsy of these lesions can confirm the diagnosis. Unfortunately, these organisms are notoriously resistant to antiviral therapy.

Mycotics Mycotic organisms such as *Epidermophyton, Trichophyton,* and *Candida* can produce pruritus. Candidiasis of the perianal region as a primary source of pruritus is rare, identified in fewer than 1% of random skin scrapings.[8] These lesions are usually erythematous with classic well-defined borders and are usually either secondary to the overgrowth of mycotic organisms after the use of antibiotics or topical corticosteroids or associated with vaginal infections. Mycotic etiology can be confirmed by microscopic inspection or select cultures.

Parasites Parasitic infection should always be included in the differential diagnosis of patients with perianal pruritus. *Pinworms (Enterobius vermicularis)* are the most common cause of perianal itching in children. The diagnosis can be made by microscopically evaluating perianal skin samples collected on cellulose tape. It is imperative that other family members be evaluated so they can be treated and recontamination does not occur. The symptoms usually occur in the evening, when these 6-mm-long parasites migrate to the perianal skin. *Scabies,* a contagious skin infestation due to the mite *Sarcoptes scabiei,* can elicit severe pruritus. Although usually found on the finger webs or sides of the fingers, these lesions can often be identified in the perianal region. The diagnosis of scabies can be confirmed by demonstrating the mite or its products, such as ova or feces, from scrapings prepared on a slide with one drop of 10% potassium hydroxide. Lesions appear initially as vesicles as the mite burrows its way into the stratum corneum. Treatment consists of the application of an appropriate scabicide such as Kwell lotion. The parasite *Pediculosis pubis* (crab or louse) can often be found grasping the base of a hair shaft and is noted to produce macular steel-gray spots, especially on the thighs and chest. With careful examination under magnification, this parasite strikingly resembles a crab. Management requires the treatment of all infected family members; appropriate delousing of all fomites such as clothes, bedding, and upholstery; and showering with an appropriate pediculicide such as permethrin.[8]

Treatment

Once the clinician has acquired a comprehensive history, performed a thorough examination, and obtained appropriate culture samples, scrapings, and biopsy samples, the primary cause for pruritus ani may be identified and appropriate therapy instituted. Treatment may include the following:

- Conservative dietary changes to identify offending agents or their symptomatic thresholds
- Appropriate medical therapy for infections, dermatoses, or systemic disorders
- Surgical intervention for the few anatomic deformities that contribute to pruritus

- Nonspecific therapy for most cases of pruritus with no identifiable etiology

Treating idiopathic pruritus requires a focused therapeutic approach, which includes clear instructions tempered with realistic expectations for a response and a consistent follow-up pattern. Instruction should begin with appropriate perianal hygiene. These initial efforts are directed toward keeping the perianal skin dry, clean, and slightly acidic. Any nonessential antibiotics should be discontinued, as should other irritants to the perianal area such as harsh toilet paper, soaps, and any personal hygiene products being applied to the area. The use of any topical steroid agents also should be discontinued initially because of harmful thinning of the perianal skin. Trauma incurred by scratching must be stopped, and for patients with severe symptoms, wearing white cotton gloves at bedtime may be necessary. An alternative to harsh toilet paper is small nonalcoholic towelettes, with appropriate drying of the perianal region with either a soft towel or a hair dryer. Substitute soap preparations such as Balneol are useful and can be applied with the fingertips or moist cotton balls. During the day and at bedtime, it may be helpful to apply a thin cotton pledget directly into the anal crease. The pledget should be small enough that the patient is not conscious of its presence. Dusting the pledget with baby powder (nonperfumed) or cornstarch may improve moisture control.

The patient should also be counseled on dietary changes. As mentioned earlier, food products such as coffee, teas, cola, chocolate, beer, and tomatoes have been identified as offending agents, but there appears to be a threshold at which these products elicit pruritus. For this reason, the patient should discontinue ingestion of these items and then slowly reinstate them into the diet in an attempt to isolate the offending agent. Once the offending agent, such as coffee, is identified, it may be possible to find the patient's threshold so that total abstinence from the product is unnecessary. Any habit-forming cathartics should be discontinued, and a bulking agent should be taken instead to keep the stool soft, large, and nonirritating. The psyllium decreases trauma to the anal canal and helps maintain better perianal hygiene.

For continued uncontrolled leakage, rectal irrigation performed with a 4-oz bulb syringe and warm water is an acceptable adjunct.[8] Daily sitz baths in warm water may also be helpful, but no chemicals should be added. In the unfortunate patient who has intractable pruritus ani, many therapies have been tried, including injection of alcohol- or oil-soluble anesthetics, injection of methylene blue, tattooing of the perianal skin with mercuric sulfide, surgical undercutting, and radiation therapy, most of which have had unacceptable results.[8] These procedures have been associated with complications such as skin necrosis, local sepsis, and sloughing of the perianal skin. The use of sedation, tranquilizers, and biofeedback by well-trained practitioners may demonstrate some clinical benefit. Regardless of the treatment or initial success, intermittent recurrences of the disease are common. The patient should be instructed not to become despondent but to reconsult the physician so that the appropriate therapeutic corrections can be made. If symptoms continue despite aggressive therapy and if appropriate changes in therapy fail to give relief, a second opinion from a dermatologist, gynecologist, or internist should be considered.

PAIN SYNDROMES

Pain syndromes of the pelvic, rectal, and perianal region are referred to by a variety of names: *levator syndrome, levator spasm, proctalgia fugax, coccygodynia,* and *chronic idiopathic rectal pain*. These terms describe a "wastebasket" of pain syndromes that are localized to the rectal area. Each of these syndromes may describe a distinct entity or these pain syndromes may overlap.[13] Once organic causes have been excluded, the patient can present a therapeutic challenge.

Levator spasm is characterized by episodic pelvic or rectal pain caused by spasm in the levator ani muscles. Symptoms of this syndrome are variable and include complaints of pressure or discomfort and the feeling "like sitting on a ball." Left-sided involvement is more common, and the pain occasionally radiates into the gluteal region. The syndrome is more common in women and sometimes occurs after pelvic infections or surgery. The clinical finding in this group of patients is levator sling tenderness on transanal palpation.

Proctalgia fugax is described as brief and sometimes severe episodes of rectal pain similar to "having a knife inserted up the rectum." Patients are often awakened from sleep and have associated irritable bowel syndrome and constipation. The syndrome is more common in men, and there are no physical signs. It is theorized that the pain results from spasm of the rectal muscle wall. For the purpose of this discussion, proctalgia fugax is considered a variant of levator spasm.

Coccygodynia refers to a syndrome of rectal and perineal discomfort associated with coccygeal injury.[14] This is a rare cause of rectal pain. Tenderness is elicited by coccygeal motion in excess of that elicited by the levator muscle. True coccygodynia is a secondary condition of the coccyx and so is not a variant of this functional syndrome.

Multiple factors associated with these syndromes include irritable bowel syndrome, previous pelvic surgery, and disordered defecation syndromes. Occasionally, the rectal or pelvic pain does not match the classic descriptions, in which case it is labeled as *chronic idiopathic rectal pain*.

Evaluation of the patient with levator spasm, proctalgia fugax, and pelvic pain must include a methodical history and careful examination of the pelvic viscera to rule out an organic cause for the discomfort. Inspection, digital rectal examination, and sigmoidoscopy reveal most common anorectal pathology. Diagnostic imaging may be helpful and includes computed tomography (CT) scanning, magnetic resonance imaging (MRI), and endorectal ultrasonography to seek less obvious sources of rectal pain. The role for anorectal physiologic testing in these conditions is uncertain.[15] Finally, many patients with pelvic pain syndrome have a psychiatric illness.[16]

The following overview of the organic and functional perineal pain syndromes provides a framework for the evaluation and the results of treatments for this commonly encountered condition.

Anatomic Considerations

As previously stated, proctalgia fugax, levator spasm, and pelvic pain can involve overlapping presentations. Pain syndromes may involve any or all of the structures of the pelvis. Disorders of the following organs or organ systems can lead to the complaint of pelvic pain. A complete assessment should exclude each of these as potential causes. An integrated approach may be required and may necessitate orthopedic, neurosurgical, gynecologic, and urologic consultation.

Spine and Bony Pelvis

Primary and secondary diseases of the pelvic girdle and the lower axial skeleton may present as pelvic pain. Trauma, inflammatory conditions, or malignancy can affect these supporting structures. *Coccygodynia* refers to primary coccygeal injury that causes pain localized to the coccyx. Used in this specific fashion, the term denotes a coccyx that is tender to touch and movement.

Pelvic Musculature

The pelvic floor or pelvic diaphragm is composed of the levator ani muscles. The levator ani are striated muscles: the puborectalis, pubococcygeus, and iliococcygeus. Inferiorly, the external sphincter encircles both the anal canal and the internal sphincter. As is the case in all striated muscles, the levator ani are subject to sustained contractions that can produce local ischemia and pain. Most authors attribute the pain of levator spasm to spasm in this muscle group. The internal sphincter is smooth muscle and is located medial to the striated muscle of the external sphincter. Physiologic testing suggests hypertrophy of the internal anal sphincter as a possible cause of this pain syndrome.

Other Causes

Previous pelvic surgery can also produce pain in this region. Dissection of the pelvic floor during a low anterior resection of the rectum can produce mechanical trauma, which might result in pain in some patients, although the pain most likely is caused by an infection. Inflammatory conditions or malignancy of the prostate and seminal vesicles can be diagnosed in men by eliciting tenderness of these structures on digital rectal examination. In women, diseases of the vagina, uterus, fallopian tubes, or ovaries may present as pelvic pain. Careful inspection and bimanual examination of the female patient are critical to an accurate assessment of pelvic pain. Malignancy and inflammatory conditions of the lower alimentary tract may produce complaints of pain.

Nervous System

Any condition that affects the cauda equina, roots S2 through S4, and the pudendal nerve can cause pelvic pain. Degenerative disease of the spine, primary or metastatic disease of the spine, primary or metastatic tumors, cysts, and local trauma all must be considered. Other neurologic disease, such as multiple sclerosis or spastic neuropathy, can produce pain. Laxity of the pelvic floor may cause traction on the pelvic nerves, creating this type of pain syndrome. Specific physiologic testing, such as electromyography (EMG), anorectal manometry, and dynamic proctography, may be useful in the assessment of these conditions. Finally, psychiatric illness is frequently associated with the complaint of pelvic pain. When indicated, competent psychiatric evaluation may be illuminating.

Causes of Pelvic and Rectal Pain

Considering the number of anatomic structures, there are many disease processes that cause pelvic and rectal pain. In some patients, no actual disease process can be identified. Box 150–1 describes a classification system that provides the clinician with a systematic approach to the diagnosis and management of pelvic pain syndromes.

Organic: Inflammatory Diseases That Affect the Pelvis and Anorectum

Common anorectal disorders that present as perineal or pelvic pain readily lend themselves to diagnosis; these include abscesses (cryptoglandular, intramuscular), fistulas, Crohn's disease, and ulcerative proctitis. These conditions must be excluded as the source of pelvic pain.

In men, chronic or acute prostatitis may present as rectal or pelvic pain. Urinary symptoms are often present and should be elicited in questioning. Digital rectal examination in men should always include careful prostatic palpation to exclude these conditions. Transrectal ultrasound may be helpful to diagnose pelvic pain, revealing pathology of the male reproductive organs. In women, tubo-ovarian infections, ectopic pregnancy, endometritis, and endometriosis are potential sources of pelvic pain. Bimanual pelvic examination with speculum visualization of the cervix usually suffices to eliminate these concerns. Occasionally, ultrasonography or CT of the pelvic viscera is necessary to complete the evaluation.

Occasionally, complicated diverticular disease of the sigmoid colon or a pelvic appendicitis may present as pelvic pain. The history generally directs the clinician to a more specific gastrointestinal work-up. Contrast radiography, CT, and ultrasonography may assist in this determination.

Mechanical

Pelvirectal pain may be multifactorial. Causes include constipation or dyschezia, pudendal neuropathy, descending perineum syndrome, incomplete or internal rectal prolapse, rectal ulcer, and pelvic floor hernias.

Box 150–1 Classification of the Causes of Pelvic Pain

Organic

- Inflammatory diseases of the pelvis and anorectum
  - Cryptoglandular abscess
  - Fistula-in-ano
  - Crohn's disease
  - Ulcerative colitis
  - Radiation proctitis
  - Endometriosis
  - Infectious proctitis
  - Prostatitis
  - Tubo-ovarian abscess
  - Endometritis
  - Pelvic appendicitis
- Ectopic pregnancy

Mechanical

- Incomplete rectal prolapse
- Descending perineum syndrome
- Torsed ovary
- Fissure
- Pelvic surgery

Neoplastic

- Nonmalignant tumors
  - Nerve
  - Muscle
  - Bone
  - Endometrioma
- Malignant tumors: primary and recurrent
  - Rectum
  - Prostate
  - Ovary
  - Uterus
  - Bladder
  - Nerve
  - Muscle
  - Bone
  - Metastatic gastric

Neurologic

- Multiple sclerosis
- Peripheral neuritic/degenerative disease

Orthopedic

- Coccygeal trauma—coccygodynia
- Degenerative disease of the lumbosacral spine
- Osteogenic tumors

Functional/Idiopathic Causes

- Levator spasm/proctalgia fugax
- Depression
- Chronic idiopathic rectal pain

Other mechanical causes of pelvic and rectal pain are muscle spasm or inflammation of surrounding tissue. Anal fissures commonly cause perineal pain. Simple mechanical trauma due to straining can produce this condition. Pain of fissure can be exacerbated by an inflammatory response in internal sphincter spasm and secondary hypertrophy. Anorectal or pelvic surgery is a frequently associated factor in patients with this type of pelvic pain. The pain of pelvic surgery may be due to a perioperative inflammatory process, traumatic neuropathy, or fibrosis of the pelvic floor. After anorectal surgery, levator spasm and sphincter spasm frequently result in anorectal pain complaints. Fortunately, these complaints are often self-limited and resolve spontaneously in time.

Neoplastic

In a report by Oliver et al.,[17] 12 of 102 patients with the diagnosis of levator spasm were subsequently found to have organic causes of their rectal pain. Two patients had pelvic recurrence of visceral cancer, and 1 patient had prostate cancer. This highlights the importance of considering malignant recurrence in patients presenting with complaints of pelvic pain and a known history of previous malignancy.

Nonmalignant tumors rarely cause levator spasm. Symptoms are related to their mass effect on adjacent structures. Neurogenic benign tumors (rhabdomyomas and leiomyomas), cysts, and endometriosis should be sought when preliminary tests are suggestive or when an obvious cause is lacking. Endometriosis produces pain via its ectopic growth pattern and subsequent sclerotic tissue reaction. The cyclic nature of the pain and bleeding should alert the clinician to consider this diagnosis. Although endometriosis is common, it is uncommon as a cause of isolated pelvic pain.

Both primary and recurrent pelvic malignant tumors can cause pain by direct extension and by involvement of the sensory pathways in this region. Most commonly, advanced rectal, prostate, ovarian, uterine, or bladder cancer is the cause of malignant pelvic pain syndromes. Occasionally, pelvic metastases from gastric carcinoma produce this syndrome. Less commonly, malignant bone, muscle, or nerve tumors are the cause. The chronic, progressive, and persistent nature of pain due to malignant disease suggests its consideration in the evaluation of this complaint. A history of pelvic organ malignancy should

provoke a thorough search for recurrent disease in any patient who complains of pelvic or perineal pain.

Neurologic

Multiple sclerosis, peripheral neuritis, and degenerative conditions that affect the cauda equina may produce rectal pain. Degenerative disease of the lumbosacral spine not infrequently causes complaints of pain, although pain related to such disorders is more commonly noted in the buttock or thigh region. Radicular symptoms should prompt a search for a reversible neurologic process. Evaluation might necessitate CT, MRI, or EMG testing.

Orthopedic

The classic orthopedic condition associated with rectal pain is coccygodynia. Injury to the coccyx may result in degenerative joint disease, arachnoiditis, and/or secondary spasm of the muscles with insertion or origin on the coccyx. This diagnosis should be made only when direct manipulation of the coccyx results in painful complaints. Radiologic confirmation of coccygeal damage reinforces the diagnosis. Postacchini and Massobrio[18] argued that anatomic variations in coccygeal shape and configuration are responsible for a condition they term *idiopathic coccygodynia.* They advocate surgical coccygectomy, partial or complete, based on the radiologic configuration noted. Overall, the treatment of any form of coccygodynia by coccygectomy is a questionable practice. For all cases of coccygodynia not due to direct trauma, a thorough search for the precipitating cause will provide a rational approach to therapy.

Functional

Functional or idiopathic cases of rectal pain occur with disturbing frequency. A recent U.S. survey confirmed that between 8% and 19% of the population experience functional rectal pain.[19] This study also demonstrated a great deal of overlap in patients who experience functional gastrointestinal symptoms. Only 22.6% of patients with functional anorectal pain sought medical care. Although the syndrome of paroxysmal rectal pain is quite common, few patients will ever see a physician because of this complaint.

Evaluation

The evaluation of the patient with pelvic pain begins with a thorough history. This is followed by inspection, palpation, and local endoscopy, which are the first steps in excluding organic causes. On palpation of the levator ani muscle group, palpation of the right levator ani reproduces the patient's discomfort exactly. Diagnostic tests such as transrectal ultrasound, anorectal manometry, cinedefecography, and EMG all have been used in the assessment of the patient with levator spasm and its variants with varying results.[16] The problem seems to be in correlation of the findings with the symptoms.

CT scanning and MRI are useful to rule out mass lesions that may cause rectal pain. Transrectal ultrasonography further reveals tumors or abscesses of the anorectum. For patients in whom the specific pathology is elusive, however, specific anorectal physiologic testing has been performed to elucidate the cause of pain, but anorectal manometry, for example, has been found to have a low diagnostic yield for patients with levator spasm. There are studies, however, that report abnormalities in anal resting pressures in patients with rectal pain.[16]

Unlike manometry, EMG and nerve conduction study of the patient with rectal pain frequently show abnormalities. These abnormalities include paradoxical puborectalis contraction and prolonged pudendal nerve terminal motor latency on electrophysiologic testing. Unfortunately, these can also be found in patients with no symptoms.[16] Thus, it appears that this occurrence can be a cause of rectal pain in a subgroup of patients.

Cinedefecography can demonstrate dysfunction of pelvic floor musculature, although EMG is more sensitive for the diagnosis of paradoxical puborectalis contraction.[16] Cinedefecography can also show rectocele, increased perineal descent, and early rectovaginal intussusception. Because these radiologic findings can be detected in patients who are completely asymptomatic, some authors have questioned the clinical significance of these findings as far as providing clues for therapeutic intervention.

Despite the diagnostic tools available, the cause of levator spasm remains unknown or at least multifactorial. Most evidence points to actual spasm of the pelvic floor. The precise cause of the spasm is unknown, and most therapies are directed at relieving the spasm.

Treatment

When an organic cause of rectal pain is diagnosed, treatment is directed at that cause. For most patients, the cause of their discomfort remains unknown. First, these patients must be reassured that they do not have a malignancy. The next level of therapy is local massage. This entails massaging the levator sling with the examiner's index finger until the muscle feels relaxed. For patients with refractory symptoms, consideration may be given to adding a muscle relaxant or an oral analgesic. This treatment is combined with local heat provided by warm soaks in a tub, heating pads, or heat lamps.

In 1982, Sohn et al.[20] introduced electrogalvanic muscle stimulation (EGS) for the treatment of levator spasm. Low-frequency oscillating electrical current applied to a muscle induces fasciculation and fatigue. The success of EGS is quite variable in the literature.[16,21]

Biofeedback may also benefit patients with levator spasm. When conservative management fails to relieve severe pain, biofeedback, EGS, and other therapeutic alternatives are available but are investigational. Pharmacologic agents that relax smooth muscle such as β-adrenergic agonists and calcium channel blockers have been demonstrated to decrease the frequency and intensity of pain in some patients with proctalgia fugax.[16] The

results are preliminary, and more research is required to evaluate the effectiveness of these forms of therapy. Local anesthetic steroid mixtures block the nerves that may have contributed to the spasm of the muscle. Botulinum toxin type A injected into the levator muscle to cause local paralysis has also been used with some success; however, further research is needed before more patients can be offered this form of therapy for the treatment of levator spasm. Finally, short-wave diathermy (available through physicians who are interested in physical medicine and rehabilitation) is an excellent approach for patients with levator spasm.

Anxiety and depression are common in patients with levator spasm. Regardless of whether this psychiatric state is a coexisting, separate illness or secondary to the chronic painful state engendered by the most extreme forms of levator spasm, expert psychiatric help may be mandatory. The clinician who treats a patient with levator spasm must be alert to the more serious signs of psychiatric illness. With this in mind, it is ill advised to prescribe antianxiety agents or narcotic analgesics for long periods. Although most patients do well with a conservative regimen, the few with serious psychological problems will be helped only with an appropriate referral to receive competent psychiatric care. The management of patients with levator spasm is summarized in Box 150–2.

Box 150–2 Management of Levator Spasm and Its Variants

Evaluation of Underlying Cause

- History and physical examination
- Radiologic investigation where appropriate
- Physiologic testing when indicated by associated symptoms

Conservative Measures

- Local heat (tub soaks, diathermy)
- Stool softeners
- Short-term muscle relaxants, analgesics, antidepressants

Refractory Cases

- Levator massage
- Electrogalvanic stimulation
- Nerve blocks, steroid injection, local anesthetic, botulinum toxin type A injection (investigational)

SOLITARY RECTAL ULCER SYNDROME AND COLITIS CYSTICA PROFUNDA

Solitary rectal ulcer syndrome (SRUS) is an uncommon benign condition characterized by rectal bleeding, copious mucous discharge, anorectal pain, tenesmus, and feelings of obstructed defecation or incomplete evacuation that results in intense, prolonged straining to defecate. This straining to defecate results in trauma and possibly ischemic ulceration of the anterior rectal wall. Occasionally, the straining results in anterior mucosal prolapse, rectal intussusception, or rectal procidentia. SRUS has its peak incidence in the 20s and 30s, with the female predominance emerging after the age of 30.[22] These symptoms lead to numerous daily trips to the toilet, many of which produce nothing more than frustration. Self-digitation to facilitate evacuation is a not uncommon practice.

SRUS is actually a misnomer because in many patients, no ulceration is present and occasionally multiple ulcerations are evident. When present, the typical solitary rectal ulcer ranges from 1 to 5 cm in size and is located on the anterior rectal wall 5 to 8 cm from the anal verge. These traumatic ulcers can be distinguished from malignant ulceration because they are punched out and shallow with a gray-white base and have a surrounding zone of edema or hyperemia without a thickened margin. A biopsy is performed to rule out rectal cancer because an SRUS can mimic rectal cancer in appearance. Often, there is granularity, friability, and localized proctitis. In general, up to 70% of solitary rectal ulcer lesions are located in the anterior rectum.[23,24] Some patients exhibit circumferential ulceration, particularly those with associated rectal prolapse or internal intussusception. The ulceration can also present as a fungating polypoid mass or nodules or as an area of serpiginous ulceration with intervening pseudopolyps. These lesions are far more difficult to differentiate from carcinoma or inflammatory bowel disease, and a biopsy is almost always necessary.

Diagnosis

The diagnosis is almost invariably established by endoscopy and biopsy. This procedure also excludes benign and malignant neoplasms, localized areas of inflammatory bowel disease, radiation proctitis, and pseudomembranous colitis. Contrast enemas are occasionally useful in confirming other abnormalities, but the actual ulcer is identified in fewer than half.[25] A cinedefecogram is best used to document the presence of associated rectal intussusception and anterior rectal mucosal prolapse. It is occasionally necessary to document complete rectal prolapse in cases where the patient is unable to reproduce the prolapse in the office. The cinedefecogram can suggest the presence of nonrelaxing puborectalis syndrome if the anorectal angle remains acute during straining, but as was stated earlier, this finding can occur in asymptomatic subjects. Defecography can also demonstrate the extent of rectal emptying and perineal descent. The goal of physiologic studies of patients with SRUS has been to explain its cause and prominent symptoms of disordered evacuation. Paradoxical puborectalis and overt or internal rectal intussusception have been described. Internal intussusception is neither a necessary

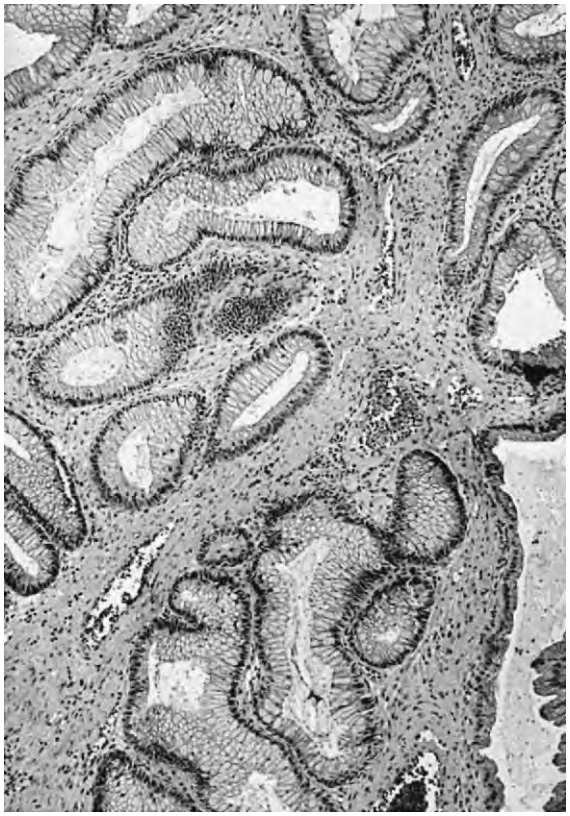

Figure 150–7. Photomicrograph of colitis cystica profunda (Hematoxylin-eosin, ×100). (From Timmcke AE: Functional anorectal disorders. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, pp 90-98.)

nor a sufficient condition for the development of SRUS, because patients can develop the syndrome without intussusception and not all patients with rectal intussusception develop SRUS. Despite these criticisms, it appears likely that in many cases, a causal relationship does exist between internal rectal intussusception and SRUS. Supporting this notion is the fact that surgical approaches designed to correct rectal intussusception are often beneficial in the treatment of the rectal ulceration.

The histologic features of solitary rectal ulcer and colitis cystica profunda are essentially the same and pathognomonic. Muscle fibers are seen streaming out into the lamina propria below and between glands (Fig. 150–7). There is thickening of the muscularis mucosae with intense fibrosis of the lamina propria. The epithelium is hyperplastic with a preponderance of sialomucins, as opposed to the usual sulfomucins. And most important, mucous glands are displaced deep within the submucosa and muscularis mucosae—hence, the name *colitis cystica profunda.* Rutter and Riddell[26] believed that the displaced glands represented the healing phase of a rectal ulcer. These displaced mucinous glands associated with ulceration make it imperative to differentiate this lesion from well-differentiated mucinous adenocarcinoma lest an unwarrantably radical operation be performed. Cellular atypia, multilayering of the cystic glandular mucosa, intraglandular budding, and papillation, as well as a desmoplastic host stromal response, are features characteristic of carcinoma.

Treatment

Medical management should be attempted in all cases except for those patients with complete full-thickness rectal prolapse. Such treatment consists primarily of avoidance of straining and the use of bulk agents, stimulating suppositories, and enemas or laxatives to retrain the patient to achieve a regular bowel habit. With this approach, as many as 70% of patients were improved and showed healing of the ulcer.[27] Those patients with concomitant nonrelaxing puborectalis syndrome may benefit from biofeedback, as discussed earlier.

Local excision of the rectal ulcer is not recommended because this procedure does not address the responsible pathophysiology and because the lesions tend to recur. Surgery should be considered only in those patients refractory to persistent attempts at medical management. Surgery that is attempted to correct the results of a behavioral disorder is seldom successful, as evidenced by the large number of surgical procedures that have been used to treat SRUS (e.g., local excision, DeLorme procedure, Gant-Miwa procedure, and excision of anterior rectal mucosal prolapse).[28] A DeLorme procedure can be difficult to perform secondary to fibrosis. Furthermore, any surgery performed for rectoanal intussusception is fraught with the potential for resolution of the anatomic problem without any symptomatic improvement. Abdominal rectopexy and anterior resection have been successful in the treatment of patients with concomitant complete rectal prolapse, and these procedures have also had some success in treating patients with rectal intussusception and anterior mucosal prolapse.[23,29]

HIDRADENITIS SUPPURATIVA

HS is a chronic and often debilitating inflammatory disorder of the skin that involves apocrine gland–bearing tissue, notably in the axilla, groin, perineum, and perianal regions. The disease usually exhibits a chronic course marked by recurrent suppurative events that result in chronic draining wounds. Recurrence after surgical treatment is common and reflects the aggressive nature of the disease.[30]

Pathophysiology

Fundamentally, HS occurs secondary to a mechanical plugging or obstruction of the apocrine gland unit with keratotic debris, which leads to infection in the gland. Glandular obstruction leads to apocrine sweat retention, followed by suppuration secondary to bacterial proliferation. As the gland ruptures into the surrounding subcutaneous tissues, multiple small epithelial tracks develop. Ultimately, these tracks emerge on the epidermis as tiny pits. Left untreated, apocrine infections and

the associated inflammatory responses result in thickening and fibrosis of the involved skin. In support of this proposed pathogenesis, HS has been experimentally induced by the application of occlusive tape to apocrine gland–bearing areas.[31]

HS presents clinically in a distribution strictly related to the distribution of apocrine glands in the inguinal, axillary, and perianal regions. Because apocrine glands typically become activated with the onset of puberty, HS usually presents after puberty, with the highest incidence in the teens, 20s, and 30s.[32] Although HS most commonly occurs in the axillary region, the second most frequently affected area is the perianal region. Approximately 16% of all patients with HS have perianal involvement.[24] Overall, HS is more common in women and blacks; however, perianal HS has been reported to be twice as common in men than in women.[33]

The exact cause of HS remains unknown.[34] Histologic studies have not convincingly demonstrated significant differences in apocrine gland size or density between normal control subjects and patients with HS.[35] Because anatomic glandular differences do not account for susceptibility to HS, presumably HS occurs in patients with an increased propensity to apocrine duct occlusion. Factors predisposing to duct occlusion that have been implicated in HS include close shaving, poor personal hygiene, tight-fitting clothes, and the use of antiperspirants and depilatories.[36] Many different bacteria identified in association with HS include *Staphylococcus aureus, Streptococcus milleri,* and *Chlamydia trachomatis.*[37,38]

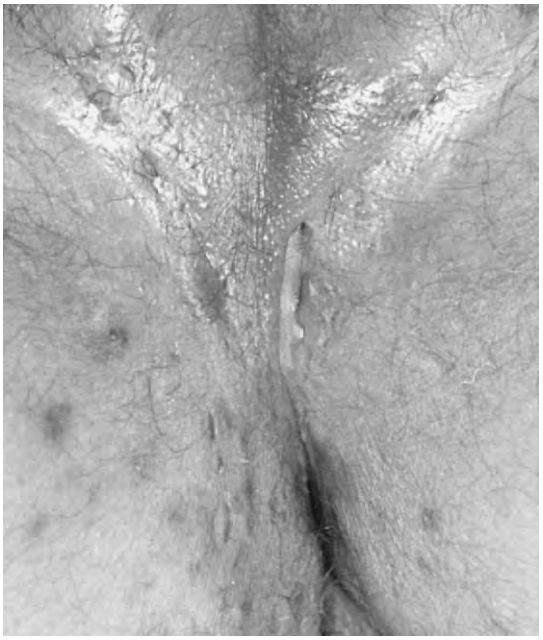

Figure 150–8. Hidradenitis suppurativa. (From Timmcke AE: Functional anorectal disorders. In Beck DE, Wexner SD [eds]: Fundamentals of Anorectal Surgery, 2nd ed. London, WB Saunders, 1998, pp 90-98.)

Clinical Presentation

Patients with perianal HS typically present with complaints of pain and swelling. Early in the course of the disease, they will be found to have localized disease with tender, subcutaneous nodules in the perianal region or buttocks. Patients with a previous history of HS demonstrate chronic inflammatory changes in the skin with findings of diffuse induration and multiple pits (Fig. 150–8). Evidence of the disease should be sought in other body regions, including the axilla, groin, and perineum, to confirm the diagnosis and to ensure complete treatment of all disease.

Although frequently simple, the clinical presentation and management of perianal HS may be complicated by two factors. First, the presenting signs and symptoms are often nonspecific. Second, perianal HS may coexist with other diseases, specifically Crohn's disease and squamous cell carcinoma.

The clinical presentation of perianal HS can be readily confused other perianal disorders, including lymphogranuloma venereum (diagnosed by positive titers for *C. trachomatis*), granuloma inguinale (diagnosed by staining of biopsy for Donovan bodies), tuberculosis of perianal skin (diagnosed by demonstration of acid-fast bacillus in biopsy specimens), and actinomycosis (diagnosed by culture of tissues or exudates or by the demonstration of sulfur granules). Finally, the suppurative disease and resulting fistula tracks from HS may be difficult to distinguish from those of complex cryptoglandular disease or isolated perianal Crohn's disease.[36,38,39] In the absence of a clear history or physical evidence in support of cryptoglandular abscesses leading to fistula formation or other gastrointestinal manifestations of Crohn's disease, HS can be differentiated from these diseases by examination for the origin of the fistula tracks. Although cryptoglandular fistulas arise at the level of the dentate line, Crohn's disease typically originates cephalad and HS originates caudad to the dentate line.[40]

As well as confounding the diagnosis of perianal HS, Crohn's disease can coexist with perianal HS. A series of 61 patients with perianal HS revealed that 38% also had Crohn's disease.[41] Although this series comprised selected patients and probably overestimated the true coexistence of HS and Crohn's disease, the two diseases should be considered when perianal HS is coupled with gastrointestinal symptoms or when tracks originate proximal to the dentate line.[40]

Squamous cell carcinoma has also been identified in association with perianal and perineal HS. Of 27 cases reported in the literature since 1958, all have involved perineal, perianal, or buttocks skin.[39,42-44] The incidence of squamous cell carcinoma in patients with perianal HS is not known, but these reported cases underscore the importance of early intervention to prevent chronic wounds and close observation to ensure early detection.

Treatment

Perianal HS presents a spectrum of disease, with regard to both severity and chronicity, ranging from single acute episodes of mild disease that require simple surgical

drainage to recurrent aggressive disease that requires extensive excision and tissue coverage.

In its simplest form, perianal HS may present as a single painful inflamed nodule with or without a draining sinus track. The treatment of uncomplicated disease should be directed toward symptomatic relief with heat, improved hygiene, and drainage of any collections of purulence. Many systemic remedies have been prescribed, including antibiotics, isotretinoin,[45] and steroids; however, none of these have proved to be beneficial over drainage. Although antibiotics do not play a major role in the management of HS, associated cellulitis may at times indicate the use of antibiotics, with target organisms being those of skin flora, as discussed earlier. Oral erythromycin (500 mg four times daily) is recommended to treat the most commonly encountered organisms. In addition to drainage, emphasis should be placed on the prevention of recurrence. Specifically, patients should be counseled on factors that may predispose to apocrine gland occlusion, such as poor hygiene and the wearing of tight-fitting garments such as synthetic support stockings.

Chronic perianal HS often requires more aggressive treatment. Approaches include unroofing of tracks, incision and drainage, or limited excision and/or wide local excision. Unroofing of all sinus tracks with secondary healing has been reported as a successful treatment option for perianal HS.[40,46] This approach involves the opening and exposure of all involved tracks with preservation of the floor of the track to aid in closure by secondary intent. Because the floor of the track is an epithelialized surface, preservation of this surface allows quick and complete healing through rapid re-epithelialization. With this approach, healing rates without recurrence have been reported as high as 100%.[40]

For extensive perianal disease, wide excision appears to be the most frequently used surgical approach.[47] Anderson and Dockerty reported on 117 cases of perianal HS, of which 64 were treated with wide local excision.[32] Two thirds of the patients were successfully treated with a one-stage excision; the remaining third required multiple-staged excisions. Of all patients available for follow-up, 21% had no further symptoms, 32% had mild symptoms but did not require further surgery, and 45% required further treatment, usually surgery. Another report included 43 patients with perianal HS treated in large part (72%) by wide local excision.[48] This aggressive treatment was considered more effective than unroofing or incision and drainage; however, 9 (21%) of 43 patients had a recurrence at the surgical site and 12 (28%) of 43 had a flare of disease at another perianal site, for a combined perianal recurrence rate of 49%. These studies have established that even with wide surgical excision, recurrence can be expected.

Due to the pathophysiology of HS, the most appropriate therapy for severe disease should achieve ablation of involved and surrounding apocrine glands, removal of infected tissue, and establishment of a clean wound bed for optimal healing. Because aggressive wide local excision achieves all of these objectives, it should be considered the procedure of choice for severe chronic cases of perianal HS.

Just as the extent of resection remains controversial, so does the best strategy for wound management. For small and moderate wounds, primary closure (sometimes with flaps) can often be performed. For large wounds, options include split-thickness skin grafting and closure by delayed healing or secondary intent. Skin grafting offers the advantages of early wound coverage, rapid healing, and reduction in the pain and inconvenience of chronic open wounds.[39,49] This technique requires that the patient be motivated and able to comply with early postoperative wound care and avoid behavior detrimental to graft healing, including smoking, poor perianal hygiene, and direct pressure or trauma to the new graft. Healing by secondary intent eliminates the early risks of the grafting procedure and has been reported as satisfactory to patients. Wound healing can take 2 to 3 months, and the care of these large wounds is cumbersome.[19] For patients who cannot comply with early postoperative wound care, secondary healing may be the best option. However, because of more rapid wound healing and avoidance of chronic dressing changes, split-thickness skin grafting is the preferred method of coverage of these large wounds in most patients.

The possibility of coexisting cancer must be considered, especially in cases where there is a mass lesion or chronic, nonhealing component. Biopsies are indicated for all suspicious lesions. In cases complicated by squamous cell carcinoma, excision must provide margins wide enough for oncologic clearance. Because these are principally skin cancers, as such they will rarely if ever require abdominoperineal resection. In cases associated with severe perianal Crohn's disease or in association with severe rectal Crohn's involvement, wide excision may be combined with proctocolectomy. In general, standard guidelines for treatment of associated disorders should principally be followed, with complementary management of HS as indicated.

In summary, perianal HS is a chronic inflammatory condition of the skin that involves the infection of apocrine glands in the perianal region.[46] The disease causes chronic scarring with persistent sinus tracks. It can be confused with other inflammatory and infectious disorders and in rare cases can occur in association with other benign and malignant conditions such as Crohn's disease and squamous cell carcinoma. Treatment should be tailored to the severity and chronicity of the presenting disease. Acute localized infections can be drained, and preventive measures are stressed. For intermediate lesions that are chronic but not severe, unroofing is preferred, yet for severe chronic disease, wide excision with grafting or delayed healing may be required. Despite aggressive surgical therapy, high recurrence rates can be anticipated.

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Part

3

Inflammatory Diseases

Chapter

151

Inflammatory Bowel Disease

Edward V. Loftus, Jr. ▪ Robert R. Cima

ULCERATIVE COLITIS

Epidemiology and Etiopathogenesis

Ulcerative colitis (UC) is an idiopathic inflammatory condition involving the mucosa of the colon and rectum. The adjusted incidence of UC in Olmsted County, Minnesota, in the 1990s was 8.8 cases per 100,000 person-years, and the adjusted prevalence in the same location on January 1, 2001, was 246 cases per 100,000 persons.[1] If these figures are extrapolated to the estimated national population of 297 million persons in 2005, then approximately 26,000 new cases of UC are diagnosed annually in the United States, and overall there are approximately 730,000 people with UC.[2]

UC is most likely caused by a complex interplay of genetic factors, immune dysregulation, and environmental factors. Genetic susceptibility is likely, given the 5% to 15% prevalence of the disease occurring in families,[3-5] compared with a 0.25% occurrence in the general population.[1] Twin studies also suggest a genetic basis for UC (albeit weaker than what has been observed in Crohn's disease)—the concordance for UC in monozygotic twins is 15% to 20% compared with a concordance of 0% to 5% in dizygotic twins.[6-8] The incidence of UC may be higher among Jews in a given geographic region compared to non-Jews[9]; furthermore, the familial risk of UC in Jews appears to be higher than in non-Jews.[10]

Well-established environmental influences on the risk of UC include cigarette smoking and a history of appendectomy.[2] Current cigarette smokers are significantly less likely than never smokers to develop UC, while former smokers are at increased risk.[11] The "protective effect" of smoking may be explained by nicotine, which exerts important changes in rectal blood flow, colonic mucus, and cytokine and eicosanoid production.[12] Appendectomy in childhood for appendicitis also appears to diminish the risk of UC, suggesting that removing the appendix might influence the mucosal immune system.[13] The role of dietary factors in UC remains controversial, but increased carbohydrate and animal fat intake may be deleterious.[14,15] An infectious cause of UC has been suggested, but no specific bacterial or viral agent has been isolated. However, specific pathogens such as cytomegalovirus or *Clostridium difficile* that result in acute colitis may trigger UC in susceptible hosts.[16] Historically, psychosomatic factors were thought to play a major role in the etiology of UC, but this hypothesis has been discarded for the most part. In certain patients with established UC, increased stress may result in disease exacerbation, but studies are conflicting in this regard.[17,18]

Since immune dysregulation is suspected to play a major role in inflammatory bowel disease (IBD) etiopathogenesis, much effort is being made to understand the role of cytokines in IBD. Cytokines modulate the intestinal immune system. It is hypothesized that regulation of the immune response is a result of the balance between proinflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, IL-6, IL-8, and IL-12, and anti-inflammatory cytokines such as IL-1 receptor antagonist (IL-1RA), IL-4, IL-10, IL-11, and transforming growth factor (TGF)-β. Perturbations in this balance may result in a loss of gut homeostasis and uncontrolled bowel inflammation.[19]

Table 151–1 Characteristics of Crohn's Colitis and Ulcerative Colitis

Features	Crohn's Colitis*	Ulcerative Colitis*
Macroscopic		
Thickened bowel wall	+++	+
Narrowing of bowel lumen	+++	+
Discontinuous disease	++	⊕
Rectal involvement	⊕	+++
Deep fissures and fistulas	++	⊕
Confluent linear ulcers	++	⊕
Perianal disease	++	⊕
Microscopic		
Transmural inflammation	+++	+
Submucosal infiltration	+++	+
Submucosal thickening, fibrosis	+++	⊕
Ulceration through mucosa	+++	++
Fissures	+++	+
Granulomas	++	⊕

*Features are characterized as being present consistently (+++), frequently (++), infrequently (+), or rarely (⊕).

Figure 151–1. Nonspecific ulcerative colitis. The colonic lumen is greatly narrowed throughout, particularly in the upper left (proximal transverse colon). Even more striking is the degree of thickening of the wall and total lack of any semblance of normal mucosa. (From Roth JA: Ulcerative colitis. In Bockus HL [ed]: Gastroenterology, 3rd ed. Philadelphia, WB Saunders, 1974.)

Pathologic Features

In general, UC is present in the rectum and extends proximally to involve the remainder of the colon in a diffuse, continuous manner (Table 151–1). The disease process may end gradually or abruptly at any level within the colon. Approximately 10% to 20% of patients with extensive UC have mild mucosal inflammation of the terminal ileum, or "backwash ileitis." The extent of the disease may vary from proctitis (i.e., involvement of the rectum alone, 25% of patients in most population-based cohorts) to left-sided colonic involvement (distal to splenic flexure, 25%) to extensive colonic involvement (proximal to splenic flexure, 50%).[20]

On gross examination, the lesions of UC begin with erythema, granularity, mucosal edema, and loss of the normal vascular pattern (see Table 151–1).[21] Mucosal friability increases with activity, and this produces the bleeding that is seen with the disease. Ulcerations occur with moderate and severe UC. These may be superficial and smooth or ragged and undermined. Eventually, ulcers may replace the entire colonic mucosa. With ongoing chronic inflammation, marked narrowing, thickening, and rigidity of the bowel occur as the muscular coats are replaced by scar tissue (Fig. 151–1). Polypoid masses or pseudopolyps, caused by hyperplasia of remaining small islands of mucosa and by the margins of ulcerations, may be present and may persist or recede as the inflammatory process becomes quiescent.

Microscopic examination of the inflamed colon shows distortion of crypt architecture and infiltration of the lamina propria not only with polymorphonuclear leukocytes but also basal plasma cells (see Table 151–1).[21] Distortion of the crypt architecture is a hallmark feature of chronic colitis. Microscopic crypt abscesses are common and penetrate just into the submucosa with the production of wide areas of ulceration of the overlying mucosa. Depletion of goblet cell mucin and superficial erosions are also commonly seen. There usually is an increase in the number of Paneth cells in the colonic crypts distal to the hepatic flexure. Granulomas, which are often seen in Crohn's disease, are extremely uncommon in UC.

Clinical Course

Like many chronic inflammatory conditions, UC is highly variable in severity, clinical course, and ultimate prognosis. In general, the severity of the disease correlates with the extent and severity of the changes in the bowel wall. UC has a peak incidence in the 3rd and 4th decades of life—the median age at diagnosis in most series is in the early 30s.[2] The condition may be slightly more common among males, but data are conflicting.[2] After its onset, the disease may take one of several courses. In a few patients (<10%), UC may be fulminant, typically becoming its most severe in the first few months

after diagnosis, often requiring surgery.[22] In most cases, UC becomes a chronic condition characterized by remissions and exacerbations.[23] Approximately 75% of patients have intermittent attacks of symptoms with complete symptomatic remissions between attacks. Disease activity in the preceding year and the presence of systemic symptoms such as fever and weight loss appear to be the strongest predictors of UC relapse.[23] A few patients (<5%) are troubled by continuous symptoms without any remission. Up to 20% of patients have only one attack with no subsequent symptoms.[23]

The most common symptoms of active UC are diarrhea and the passage of blood and mucus.[24] Unlike Crohn's colitis, in which hematochezia may be absent, bloody diarrhea is the hallmark of UC. The amount of blood may vary from a small amount of bright red blood, which is mistaken for hemorrhoidal bleeding, to massive bleeding. The diarrhea may be minimal, or patients may have 10 to 20 bowel movements per day. Patients who complain of constipation usually have proctitis or left-sided inflammation. These patients often have tenesmus and urgency but pass only a bloody mucous discharge, so it is important to inquire not only about the number of stools per day but also the number of trips to the bathroom.

In patients with acute severe colitis, abdominal pain is a frequent manifestation. It tends to be colicky. On examination of the abdomen, there may be tenderness over the colon, especially in the left lower quadrant. Large doses of corticosteroids may mask clinical signs in acute disease.

With milder forms of distal colitis, there may be only slight impairment of general health. In severe UC, systemic symptoms can be profound, and the patient may become rapidly debilitated and emaciated. Associated with these effects is fever; however, a temperature of more than 38° C is unusual, except in the rare fulminating type of colitis or in cases in which there is an intra-abdominal perforation. Weight loss and anemia tend to occur in proportion to the severity of symptoms.

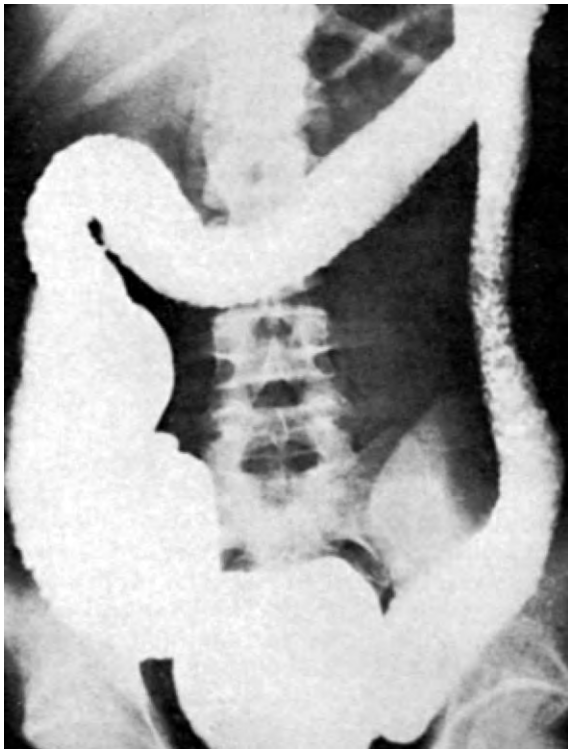

Figure 151–2. Barium enema film taken during the course of a recurrent chronic type of ulcerative colitis of 6 years' duration. The entire colon is involved with an extensive polypoid change, giving a honeycombed effect, which is more marked in the descending colon. (From Bockus HL [ed]: Gastroenterology, Vol. 2. Philadelphia, WB Saunders, 1946.)

Diagnosis

The diagnosis of UC should be suspected in patients with a history of bloody diarrhea in whom an infectious cause has been eliminated.[24] Flexible sigmoidoscopy and colonoscopy are the cornerstones of diagnosis. Colonoscopy with biopsies is more accurate than barium radiography, particularly for detecting mild colitis and determining extent. Colonoscopy with intubation of the ileocecal valve and examination of the terminal ileum allows an assessment for backwash ileitis or Crohn's ileitis. Sigmoidoscopy or colonoscopy reveals the typical gross features already described. Frequently, there also is a purulent exudate with bloody mucus, an adherent membrane, or both. With chronic inflammation, one can expect to find loss of haustral markings associated with narrowing of the lumen and shortening of the colon (Fig. 151–2). Colonoscopy is generally the preferred endoscopic test, but sigmoidoscopy is useful as an office procedure requiring little preparation or in the case of a severely ill UC patient. To complete the gastrointestinal investigation, a small bowel imaging study (i.e., small bowel follow-through, enteroclysis, or computed tomographic enterography) should be performed to exclude the possibility of Crohn's disease of the small bowel.

Colorectal Cancer and Dysplasia

Patients with UC are at increased risk of colorectal cancer (CRC).[25,26] In well-designed studies of population-based cohorts, the relative risk of CRC in UC is two to eight times higher than that in the general population.[27] The two most important risk factors for cancer are the duration of the colitis and the extent of colonic involvement.

The incidence of CRC increases with the duration of the disease.[28] The incidence rate varies widely, and, in general, population-based studies yield lower cancer incidence rates than referral center–based or hospital-based studies. A recent meta-analysis pooled the results of 116 observational studies of CRC risk in UC, involving more than 54,000 patients, and concluded that annual cancer incidence was 0.2% in the 1st decade of disease, 0.7% in the 2nd decade, and 1.2% in the 3rd decade.[29] Altogether, the cumulative risk of CRC was estimated to be 18% after 30 years of disease. Since the pooled analysis included referral center–based studies, the "real"

absolute risk of CRC in UC may actually be lower than 18%.[29] Indeed, in some population-based cohorts, the risk of CRC is no higher than expected in the general population.[30,31] Whether variations in cancer incidence among population-based cohorts can be explained by differences in treatment policies (e.g., higher rates of 5-aminosalicylate use or higher colectomy rates) remains unclear.

The extent of the colitis is an important determinant of CRC risk in UC.[28] Patients with proctitis alone do not have a significantly increased risk of developing carcinoma relative to the background population.[27] Patients with pancolitis have the highest relative risk, and patients with left-sided colitis carry an intermediate risk.[27] Significant differences in CRC risk according to UC extent have been demonstrated both in referral center–based[25,26] and population-based studies.[27,32-34]

Whether age at onset of UC is a risk factor for CRC independent of duration of disease remains controversial.[25,27,35,36] Although some studies have suggested that childhood-onset UC has a higher risk of CRC, independent of duration,[25,27,35] at least one study has suggested that patients diagnosed in the 6th and 7th decades of life have a higher relative risk of CRC.[36]

Another controversial point is whether disease activity is a risk factor for colorectal neoplasia in UC.[37] Studies focusing on clinical activity (i.e., symptoms) could not demonstrate a relationship between disease activity and CRC.[38] Indeed, a common clinical scenario is the UC patient with clinically quiescent disease who is lost to follow-up and returns years later with a symptomatic malignancy. A recent study from St. Mark's Hospital, focusing on endoscopic and histologic activity (rather than symptoms), suggested that increased endoscopic activity was associated with a twofold increase in the risk of colorectal neoplasia, while increased histologic activity increased the risk by a factor of five.[37] Confirmatory studies on this point are needed.

Two additional risk factors warrant comment. The presence of concomitant primary sclerosing cholangitis (PSC) appears to be another important cancer risk factor.[39-41] It can be debated whether PSC is an independent risk factor or whether it is a marker for long-standing pancolitis. One study of newly diagnosed PSC patients with no history or symptoms of UC showed that the vast majority had subclinical pancolitis, and one patient already had low-grade dysplasia present.[42] Regardless of the mechanism for increased cancer risk, PSC-IBD patients are at high risk for CRC.[43] Family history of CRC (regardless of the family history of IBD) is another independent indicator of cancer risk in several studies, increasing the risk by a factor of at least two.[44,45]

Unlike sporadic CRC, which tends to occur more frequently within the left colon, cancers in UC patients are more evenly distributed throughout the colon.[46] There is a higher likelihood of synchronous tumors in UC-related CRC. These lesions are more likely to be mucinous and poorly differentiated. For these reasons, they may escape detection via colonoscopy or even at surgery. As a result, they tend to be discovered at a later stage. Another reason for the late detection of UC-related CRC is that the common symptoms of abdominal pain, change of bowel habit, bleeding, and mucous discharge are often attributed by both patient and physician to the underlying UC rather than to CRC.

Despite these differences in tumor characteristics, most recent studies show no significant differences between sporadic and UC-related CRC with respect to prognosis. The most recent study compared the prognosis of 241 UC patients with CRC diagnosed at Mayo Clinic between 1976 and 1996 with the prognosis of a group of sporadic CRC patients matched on age at cancer diagnosis, gender, and cancer stage.[46] The 5-year survival in the UC-CRC group was 55%, compared to 53% in the sporadic CRC group.

In the past, prophylactic proctocolectomy was recommended for patients with long-standing disease, regardless of their disease activity, because of the risk of the development of cancer. However, with the availability of colonoscopy for surveillance of the entire colon and the recognition that premalignant changes on rectal biopsy were associated with CRC, the standard practice in the gastroenterology community is to recommend periodic colonoscopic surveillance in a search for premalignant lesions ("dysplasia") in the colonic epithelium. The objective of this course of action is to recognize dysplastic changes before the onset of carcinoma.

More than 20 years ago, the Inflammatory Bowel Disease-Dysplasia Morphology Study Group published a consensus report on the classification of colorectal dysplasia.[47] Histologic changes were classified as positive, negative, or indefinite for dysplasia. Definite dysplasia was further classified into low grade and high grade. There is reasonably good evidence that dysplastic change precedes frank carcinoma in most cases. Unfortunately, however, carcinoma may already be present when dysplastic changes are detected. It is also recognized that the pathologist may have difficulty deciding whether microscopic changes are due to the normal regenerative changes seen in UC or represent true dysplastic changes. Despite the availability of a standardized classification system for colorectal dysplasia for more than 2 decades, there remains considerable interobserver variability among pathologists for the finding of dysplasia.

Numerous professional societies have issued practice guidelines or consensus statements regarding the practice of surveillance colonoscopy in UC. The most recent recommendations, issued by a task force of the Crohn's and Colitis Foundation of America (CCFA), recommend surveillance colonoscopy every 1 to 2 years in patients with left-sided or extensive colitis with approximately 8 to 10 years of disease duration.[48] Patients with proctitis alone do not require surveillance, whereas patients with concomitant PSC should enter a surveillance program immediately regardless of UC duration.

The patient must be properly prepared for colonoscopy so that all of the mucosa can be visualized. The colonoscopy must be complete to the cecum, and the endoscopist must search for any suspicious plaque-like or nodular lesions. The CCFA consensus statement recommends that at least 33 random biopsies of the colon be obtained, typically in a four-quadrant fashion every 10 cm in the proximal colon and every 5 cm in the rectosigmoid.[48] At our institution we obtain a total of 32

biopsies divided into four bottles (eight pieces from the cecum and ascending colon, eight pieces from the transverse colon, eight pieces from the descending colon and proximal sigmoid colon, and eight pieces from the rectosigmoid). Visible lesions should be biopsied separately. Dysplasia may be present in grossly flat mucosa or may have a villous or nodular appearance. With accurate endoscopic and pathologic assessment of the mucosa, a reasonable course of management can be recommended to the patient.

Although there is broad consensus that patients with high-grade dysplasia should undergo immediate colectomy, there is no consensus on how to manage a finding of low-grade dysplasia.[48] Some recommend attempting to manage the disease medically and repeating colonoscopy and biopsy in 3 months. If there is no further dysplasia, the patient will undergo colonoscopy in 1 year. If low-grade dysplasia is again present, the patient will undergo repeat colonoscopy in 3 months, and if dysplasia is still present, serious consideration will be given to surgical intervention. However, others (including us) recommend colectomy for a finding of low-grade dysplasia, since several studies of patients with low-grade dysplasia have suggested that the actuarial rate of progression to high-grade dysplasia or cancer may be higher than 50% after 5 years.[49,50]

As the optical capabilities of endoscopes improve and our diagnostic awareness of dysplasia increases, we are beginning to understand that not all colorectal dysplasia in IBD is flat. Indeed, recent studies suggest that polypoid dysplasia is more common than flat dysplasia.[51] Patients with "dysplasia-associated lesion or mass (DALM)" were once thought to be at a particularly high risk for synchronous or metachronous CRC. Blackstone and colleagues reported that invasive carcinomas were present in 7 (28%) of 25 patients in whom mild dysplastic changes were found in so-called villous lesions.[52] However, more recent studies suggest that certain polypoid dysplastic lesions can be managed via endoscopic polypectomy.[53-55] If the lesion is well defined and amenable to endoscopic polypectomy, and if biopsies of the flat mucosa immediately surrounding the polypectomy site do not demonstrate dysplastic change, then these patients can be managed with close colonoscopic follow-up. For lesions that are not amenable to endoscopic polypectomy or have surrounding dysplasia, colectomy is recommended.

Acute, Severe Colitis

Although acute severe colitis is an uncommon form of UC, affecting approximately 15% of all patients with the disease, it can be life-threatening.[56] Fortunately, the mortality of acute severe colitis has dropped at referral centers over the past half-century from 30% to much less than 5% with increased recognition of the more toxic forms of the condition and with more intensive therapy.[57] Nevertheless, among those requiring hospitalization for acute severe colitis, approximately 30% to 40% require colectomy.[57] *Toxic megacolon,* the most fulminant form of acute colitis, is defined as a severe attack of colitis with total or segmental dilation of the colon (usually defined as a colonic diameter >5.5 cm on plain films). In a case series of 55 UC patients with toxic dilation, Jalan and colleagues defined toxicity as the presence of any three of the following conditions: fever higher than 38.5° C, tachycardia (>120 beats/min), leukocytosis (>10,500 cells), and anemia (hemoglobin <60% of normal).[58] In addition, one of the following conditions must have been present: dehydration, mental changes, electrolyte disturbances, or hypotension. This degree of toxicity, coupled with clinical or radiographic evidence of colonic distention, completes the presentation of toxic megacolon.

Toxic megacolon can complicate long-standing UC or can occur in patients presenting with their first attack. Various precipitating factors for toxic megacolon have been identified, including antidiarrheal agents, opioid analgesics, barium enema, and electrolyte abnormalities (including hypokalemia). The cause is unknown but is thought to be due to a paralysis of the myenteric plexus, perhaps resulting from transmural inflammation occurring acutely.

Toxic dilation of the colon is generally considered the most serious complication of UC. The colon loses its ability to contract and becomes widely distended, resulting in a thinned wall in danger of perforation. The most common sites of perforation are around the peritoneal attachments of the splenic flexure and at the cecum.

The clinical presentation of toxic megacolon is dramatic. Patients may suddenly become acutely ill with rapid progression of symptoms that include fever, mental aberrations, tachycardia, tachypnea, and bloody diarrhea. Abdominal pain may be diffuse and severe but may be lacking, particularly in patients who are taking high-dose corticosteroids. Sigmoidoscopy may reveal changes typical of UC. Biopsies should be obtained, and the pathologist should be instructed to exclude the possibility of cytomegalovirus superinfection as a cause of the exacerbation.[59] A stool sample for *C. difficile* toxin should be obtained, as *C. difficile* toxin can be recovered from approximately 20% of patients with UC exacerbations, and treatment with metronidazole or vancomycin frequently results in improvement.[60] The diagnosis of toxic megacolon can usually be made on a plain radiograph of the abdomen, which shows dilation of the large bowel (Fig. 151–3). Although colonoscopy appears to be surprisingly safe in "garden variety" acute severe colitis, it remains contraindicated in the patient with toxic megacolon.[61]

Patients who present with signs of localized or generalized peritonitis, radiographic evidence of perforation, or systemic instability should undergo immediate surgery. Otherwise, intensive medical management, consisting of high-dose parenteral steroids and intravenous (IV) fluids, should be initiated immediately. Patients tend to be dehydrated and may have electrolyte imbalances because of losses from vomiting and diarrhea. These imbalances must be corrected, and the patients who are anemic should undergo transfusion. Restriction of oral intake is initiated along with nasogastric suction to avoid further intestinal distention. Although randomized trials have not shown convincing benefit, broad-spectrum antibiotics are frequently administered in this

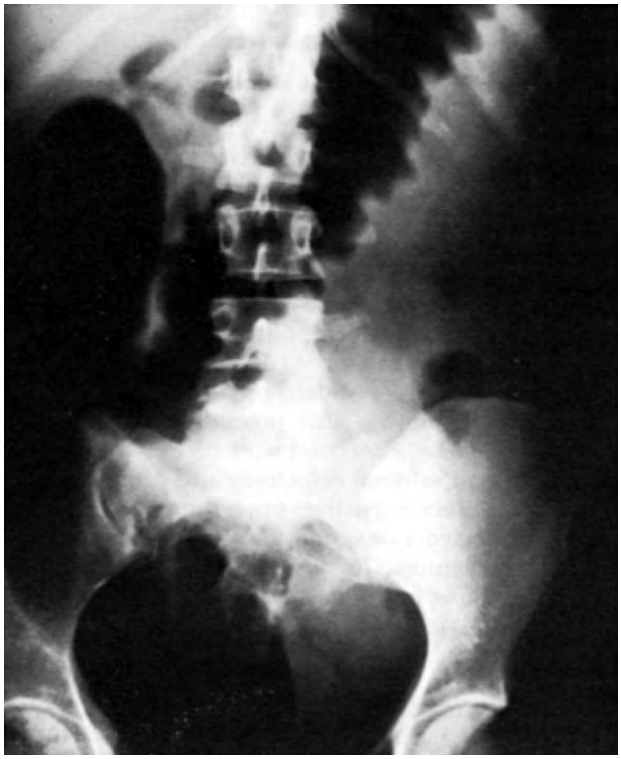

Figure 151–3. Toxic dilation of the colon. Note the gross enlargement, particularly of the transverse colon and cecum.

setting because of the potential for bacteremia or microperforation.

The patient with toxic megacolon must be observed very closely with serial physical examinations every 2 to 4 hours and serial plain films of the abdomen daily. The timing of surgery in toxic megacolon remains controversial, with some authors advocating early colectomy (i.e., shortly after recognition of toxic megacolon) and others noting little or no mortality by treating with IV corticosteroids and antibiotics for up to 7 days in patients who appear to be improving. Most authors agree that patients who are not improving or are deteriorating need surgery urgently. Several studies indicate that the presence of more than eight stools daily, or a combination of elevated C-reactive protein (>4.5 mg/dl) and more than three stools daily, on the 3rd hospital day predict colectomy in about 85%.[57,62] Close follow-up by both the medical and surgical teams, with open lines of communication between the two, is required.

Massive Hemorrhage

Although rectal bleeding is a common symptom of UC, massive hemorrhage that necessitates rapid blood transfusion and emergency treatment is unusual, occurring in fewer than 5% of patients. Most frequently, it occurs in patients with acute severe colitis. The treatment of these patients is usually twofold. First, treatment of the UC necessitates the use of high-dose steroids and other supportive measures. Second, the bleeding must be treated expeditiously and any coagulation abnormality corrected. In most patients, hemorrhage subsides spontaneously. It is unusual that the bleeding originates from a discrete site. The indication for surgery is not arbitrary but must be individualized for each patient. Once the decision is made to operate, the standard procedure has been proctocolectomy. However, this procedure, as previously mentioned, can be associated with higher mortality and morbidity rates than subtotal colectomy and it obviates the possibility of a reconstructive procedure in the future. Thus, in selected cases, one might consider a total abdominal colectomy, leaving a short rectal stump, sufficient to allow future reconstructive surgery. In most instances, this type of surgery controls the bleeding, although continuing massive hemorrhage can still occur in approximately 10% to 12% of patients.

CROHN'S (GRANULOMATOUS) COLITIS

Epidemiology and Etiopathogenesis

Crohn's disease is the other major subtype of idiopathic IBD. Crohn's disease results in transmural, often granulomatous, inflammation that can occur anywhere in the gastrointestinal tract, and it has a propensity to cause intestinal fistulas and/or strictures. It is now well accepted that Crohn's disease of the large and small intestine is one disease, but it is separate and distinct from UC. The incidence and prevalence of Crohn's disease are similar to that of UC. In the 1990s, the adjusted incidence of Crohn's disease was approximately 6 cases per 100,000 person-years, and the adjusted prevalence on January 1, 2001, was 162 cases per 100,000 persons.[1] Extrapolating these figures to a U.S. population suggests that about 19,000 patients are diagnosed annually and that there are approximately 480,000 people with Crohn's disease.[2] As is the case with UC, Crohn's disease appears to be more common in whites, especially Jews, less common in African Americans, and more frequent in populations of westernized cultures than those of Africans and Asians.[63] However, a number of studies suggest that these differences are narrowing over time. For example, one pediatric study from Atlanta suggested that Crohn's disease was as common among African American children as among whites. Studies from Japan, South Korea, Singapore, and now India suggest that IBD is becoming more common in these areas, too.[63]

In contrast to UC, cigarette smoking is a risk factor for Crohn's disease, and patients with Crohn's disease who smoke have a more severe clinical course (i.e., requiring more corticosteroids, immunosuppressive agents, and surgery) than those who do not.[12] Similar to UC, a family history of IBD is one of the strongest risk factors for Crohn's disease identified. Studies of twin registries suggest a strong genetic component in the pathogenesis of Crohn's disease—approximately 50% of monozygotic twin pairs are concordant for the disease versus only 20% concordance among dizygotic twins.[6-8] The identification in 2001 of the *CARD15/NOD2* mutations provided the first definitive genetic link to the condition.[64-66] Up to

40% of Crohn's disease patients carry at least one of three mutations in this gene, which appears to encode a protein important in the innate immune system.

Crohn's disease primarily affects young individuals, with the median age at diagnosis being in the late 20s. There may be a slight female predominance in Crohn's disease, in contrast to the slight male predominance seen in UC. Approximately 40% to 50% of Crohn's disease patients have both small bowel and colonic involvement, 20% have isolated small bowel (usually ileal) involvement, and one third have colonic disease alone. Disease in which the colon is primarily involved may occur more frequently in patients diagnosed at a somewhat older age.

The colon may be involved with Crohn's disease in one of several ways. First, the colon alone may be the site of Crohn's disease. The large bowel may be involved in its entirety, but more often there is segmental disease with sparing of the rectum and part of the sigmoid. In addition to Crohn's colitis, there may be involvement of the small bowel. This form of ileocolitis is the most common type of Crohn's disease. The colon may become involved with Crohn's disease only after surgery for ileitis, but this is not particularly common, because most recurrences appear proximal to the ileocolonic anastomosis. Finally, the colon may be involved indirectly via fistula formation from a loop of small bowel that is the site of the primary disease. In this case, most commonly there is no primary disease in the colon but only secondary inflammation from the disease in the small intestine.

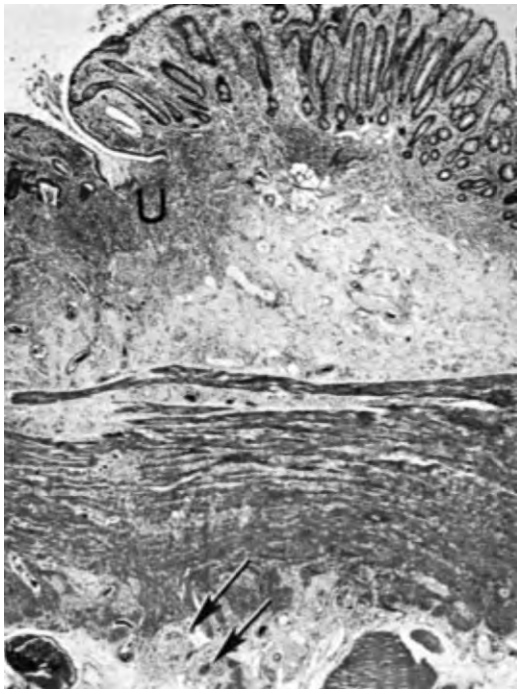

Figure 151–4. Crohn's disease of the colon. Transmural involvement is present with mucosal ulceration (U), edema of the entire bowel wall, and serosal noncaseating granulomas *(arrows)* (hematoxylin-eosin, ×25). (Courtesy of Stanley Hamilton, MD, Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, Maryland.)

Pathologic Features

Crohn's colitis typically involves all layers of the bowel wall as a transmural reaction (Fig. 151–4). This transmural reaction may be noted grossly but is present in the early phases of the disease when only microscopic changes are noted.[21] Although the gross and microscopic features of Crohn's disease are well established, there is no pathognomonic feature. The features of UC and Crohn's disease are listed in Table 151–1. In approximately 10% to 15% of patients, it may be difficult to unequivocally differentiate Crohn's disease from UC. The term *indeterminate colitis* has been used in these cases in which a definitive pathologic diagnosis cannot be made.[67]

On macroscopic examination, the bowel wall appears to be thickened, particularly in the submucosal layer (see Table 151–1).[21] There is a corresponding narrowing of the lumen. Edema, thickening, and overgrowth of the mesenteric fat encroaching on the serosal aspect of the bowel wall are extremely common in Crohn's disease of both the small and large intestine (Fig. 151–5). The serosa tends to be hyperemic, and there are chronic subserosal inflammatory changes with exudate production. Mesenteric lymphadenopathy may be present. The gross appearance of the mucosal surface varies depending on the extent and severity of the disease. The mucosa may appear to be normal except for hyperemia and edema, or there may be longitudinal ulcers that cause the mucosal surface to have a cobblestone appearance. The ulcers vary in depth but usually extend at least to the

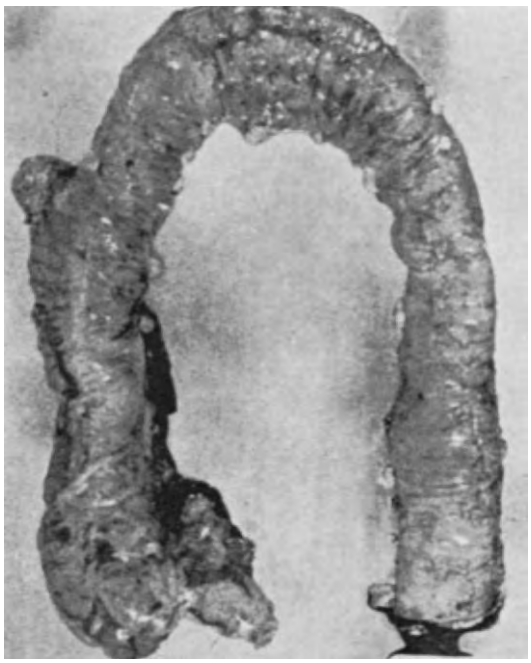

Figure 151–5. Serosal surface of colon resected for granulomatous colitis. (From Barnett WO, Mora LO, Varner JE: Granulomatous colitis. South Med J 62:373, 1969.)

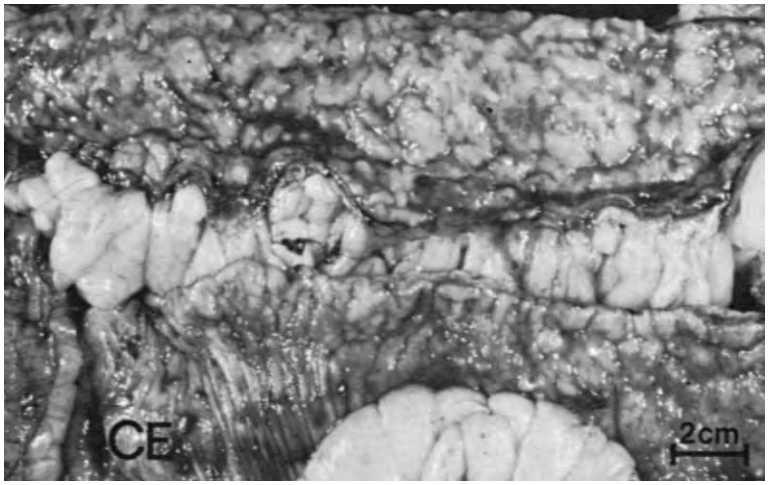

Figure 151–6. Crohn's disease of the colon. The mucosal surface shows serpiginous ulceration and has a cobblestone appearance. The cecum (CE) is less severely involved than is the remainder of the colon. (Courtesy of Stanley Hamilton, MD, Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, Maryland.)

submucosa and often to the serosa (Fig. 151–6). Because of this, frequently other loops of intestine adhere to the involved segment, and fistulas may occur. In addition, skip areas may be seen.

Microscopic changes include infiltration of inflammatory cells in all layers and marked submucosal and subserosal thickening and intramural fissures that can extend through to the mesenteric fat (see Table 151–1). Giant cells or epithelioid granulomas may occur either intramurally or within regional lymph nodes (Fig. 151–7). Other histologic findings include transmural fibrosis, submucosal lymphangiectasia, chronic serositis when there has been no prior surgery, muscle wall thickening (more than twice that of normal), and segmental involvement.

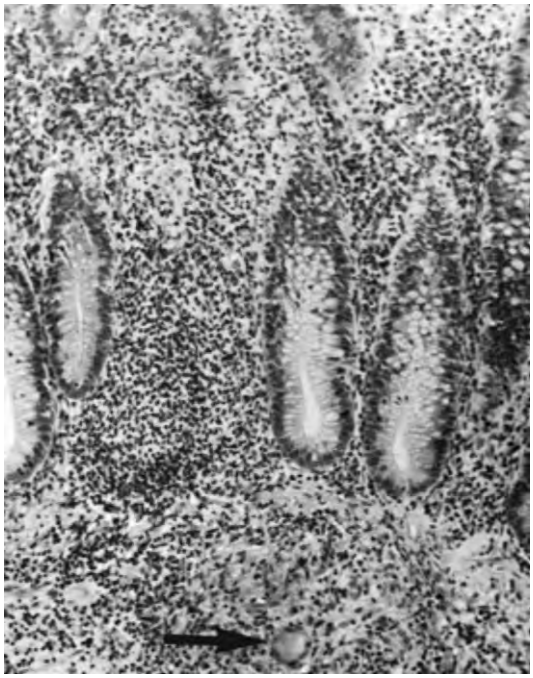

Figure 151–7. Crohn's disease of the colon. A noncaseating granuloma with epithelioid macrophages and a multinucleated giant cell *(arrow)* is present in the submucosa (hematoxylin-eosin, ×160). (Courtesy of Stanley Hamilton, MD, Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, Maryland.)

Clinical Features

Symptoms of Crohn's colitis include diarrhea, midabdominal and lower abdominal crampy pain, malaise, and weight loss.[24] Other symptoms and clinical findings include fever, rectal bleeding, anemia, nausea, and vomiting. Occasionally, patients may present with symptoms suggestive of an acute abdomen. It is now recognized that toxic megacolon can complicate Crohn's colitis as well as other forms of colitis. Extraintestinal manifestations are common, with musculoskeletal manifestations being the most frequent.

Clinically, Crohn's colitis often has an extremely variable onset and course. Although diarrhea is a dominant feature of both UC and Crohn's colitis, colonic bleeding is less common with Crohn's disease.[24] However, massive bleeding from acute Crohn's colitis can occur on occasion. Colonic sinuses, fistulas, and strictures are characteristic of Crohn's colitis. However, these internal complications do not occur as frequently in colon disease as they do in terminal ileum disease.

Perianal Crohn's disease is a frequent complication. It is an extremely troublesome problem and difficult to treat successfully. Population-based studies suggest that up to 40% of Crohn's disease patients develop perianal involvement at some point during their clinical course.[68] The perianal lesions can precede the clinical appearance of the colitis by a variable number of years. Perianal Crohn's disease has been classified into the following categories: skin lesions, anal canal lesions, fistulas, and hemorrhoids.[69] *Skin lesions* include maceration, erosion, ulceration, abscess formation, and skin tags. Because of the frequency of diarrhea in this disease, the skin around the anus may become macerated, leading to ulceration

and subcutaneous abscess formation. Skin tags are frequent manifestations. They tend to be edematous and larger, thicker, and harder than those seen in patients without Crohn's disease. *Anal canal lesions* include fissures, ulcers, and stenosis of the anal canal. The fissures tend to be deep and wide, with undermined edges. The fissures may be eccentrically placed in any position around the anus, in contrast to uncomplicated midline fissures in patients who do not have Crohn's disease. *Fistulas* and *abscesses* are perhaps the most difficult of the perianal lesions to treat. They may arise from an infected anal gland, as in patients without Crohn's disease. More commonly, however, they result from penetration by anal canal or rectal fissures or ulcers. The most superficial fistulas can be treated in a conventional manner, but more complex fistulas may have a high internal opening with multiple indirect tracts opening on the buttocks or scrotum. Fistulas tend to be chronic, indurated, and cyanotic, but despite their appearance, they are often painless. If the patient does complain of pain, one should suspect an abscess.

Rectovaginal fistulas can also complicate Crohn's disease and tend to result from direct penetration of rectal wall fistulas into the vagina. They are a relatively frequent complication of severe perianal disease, with rates varying from 3.5% to 20%.[70-72] Quite frequently, these fistulas are asymptomatic, and no surgical intervention should be attempted. However, if the patient is symptomatic, surgery is indicated. Various local procedures have been described, but none are extremely successful. Some patients require proctectomy (see Chapter 153).

Diagnosis of Crohn's Colitis

Endoscopic evaluation of the colon and rectum is essential. Colonoscopy is particularly important to determine the extent of the disease and is more sensitive than radiographic examination. The often discontinuous nature of Crohn's colitis can be seen better with the colonoscope than on barium enema. All patients who undergo surgery for Crohn's disease, including those with presumed ileitis, should undergo a preoperative colonoscopy to fully determine the extent of the disease. The endoscopic appearance of Crohn's colitis is usually quite different from that of UC. The rectum is spared in approximately 50% of patients with large bowel involvement. Depending on the extent and severity of the disease, there may be isolated aphthous ulcers with normal intervening mucosa, or there may be irregular mucosal thickening, congestion, edema, and a cobblestone appearance with deep linear ulcerations and fistulas. Pathognomonic histologic features of Crohn's disease (i.e., granulomas) are present only infrequently.

Radiographic features characteristic of Crohn's colitis are similar to those seen in terminal ileum disease. The radiographic features that substantiate the diagnosis of Crohn's colitis include skip areas, longitudinal ulcerations, transverse fissures, eccentric involvement, pseudodiverticula, narrowing, strictures, pseudopolypoid changes, a cobblestone pattern, internal fistulas, sinus tracts, and intramural fistulas that extend parallel to the lumen of the thickened bowel (Fig. 151–8). Any portion of the colon may be involved with Crohn's colitis. The segment least frequently involved is the rectum. Skip

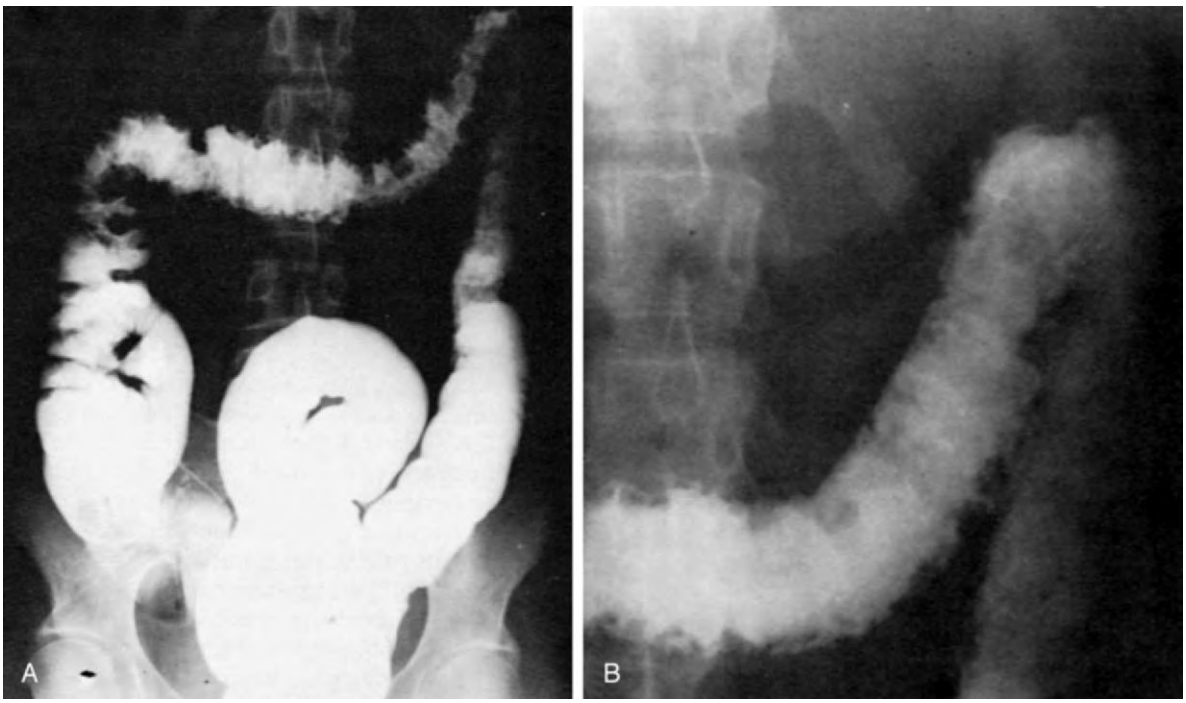

Figure 151–8. Granulomatous colitis. **A,** Barium enema showing segmented colonic narrowing and mucosal ulceration, especially of the proximal descending colon. **B,** Barium enema showing intramural fistulous tract of medial aspect of distal transverse colon.

areas must be sought carefully, because discontinuous involvement may be limited to one wall, may appear as a nodular filling defect, or may involve straightening and rigidity of a short segment of the colon. The combination of longitudinal ulcers, edematous mucosa, and transverse linear ulcers produces the cobblestone pattern previously described. Transverse linear ulcers may penetrate so deeply into the wall of the colon that they appear in contour as numerous long, thin spicules perpendicular to the long axis of the bowel or as a sinus tract. They may ultimately lead to small intramural abscesses or fistulas. A small bowel enema or enteroclysis should be included as part of the work-up in patients with Crohn's colitis to document the total extent of the disease.

Crohn's Colitis and Colorectal Cancer

Crohn's colitis has been recognized as a condition predisposing to the development of CRC. The risk of developing carcinoma in Crohn's disease is not as well defined as in UC, with relative risks in well-designed population-based studies ranging from no increased risk[73-76] to a sixfold elevation.[77] Carcinoma may also occur in chronic perianal fistulas. Although the incidence of cancer in Crohn's colitis is increased, it is still unclear how frequently these patients should be followed with surveillance colonoscopy and biopsies. Our recommendations for patients with Crohn's colitis are similar to those for patients with chronic UC of similar extent (see earlier).

THERAPY OF ULCERATIVE COLITIS AND CROHN'S DISEASE

Although traditional drugs such as corticosteroids, sulfasalazine (Azulfidine), and 5-aminosalicylic acid (5-ASA) compounds are the mainstays of the medical management of IBD (especially UC), many other modalities and drugs are used, including antibiotics, the purine analogues azathioprine and 6-mercaptopurine, methotrexate, cyclosporine, and infliximab.

Sulfasalazine and 5-Aminosalicylic Acid Compounds

Sulfasalazine is composed of sulfapyridine linked to 5-ASA by an azo bond. It is poorly absorbed in the upper gastrointestinal tract and is degraded into its two components by colonic bacteria containing azoreductase. The 5-ASA moiety is the active anti-inflammatory compound of sulfasalazine, whereas sulfapyridine acts only as the carrier for 5-ASA.[78] It is the sulfapyridine moiety to which many patients have side effects and allergic reactions. Various 5-ASA compounds have been developed and have been shown to be as effective as sulfasalazine but with reduced side effects. Olsalazine (Dipentum) is a 5-ASA dimer joined by an azo bond. Mesalamine, or 5-ASA alone, is commercially available in two delivery systems in the United States. Asacol is mesalamine coated with an acrylic-based resin, Eudragit S, which does not dissolve until the luminal pH rises to 7.0 or higher. In general, this agent is released in the terminal ileum and colon. Pentasa is an ethylcellulose-coated, controlled-release formulation of mesalamine. Approximately 20% to 30% of this agent is released and absorbed in the small bowel, with the remainder delivered to the colon. Finally, balsalazide (Colazal) is a nonsulfa 5-ASA prodrug, containing 5-ASA and 4-aminobenzoyl-β-alanine joined by an azo bond. Free active 5-ASA is released in the colon similar to sulfasalazine and olsalazine. Mesalamine in enema formulation (Rowasa) is efficacious in mildly to moderately active left-sided UC and proctitis. Mesalamine suppositories (Canasa) are efficacious for active ulcerative proctitis.

Sulfasalazine and the 5-ASA compounds inhibit various products of the metabolism of arachidonic acid (e.g., prostaglandin G_2, leukotriene B_4, and thromboxane A_2)—all known to play a major role in the inflammatory process in the intestinal mucosa.[79] They also decrease the synthesis of other inflammatory cytokines (IL-1 and TNF-β) and inhibit the action of IFN.

Sulfasalazine

Sulfasalazine is the oldest and the least expensive 5-ASA compound in use. In a low dosage (1 to 2 g/day), it is used to maintain remission in patients with UC, whereas in a higher dosage (4 to 6 g/day), it can be used to treat active UC.[80,81] In Crohn's disease, the efficacy of sulfasalazine is less clear and depends on the site of the disease. Because sulfasalazine is cleaved into its active compounds in the colon, its use is limited to Crohn's disease with ileocolonic or colonic involvement.[82,83] It is of little known benefit in isolated small bowel disease.

Adverse events following sulfasalazine therapy are common and include nausea, headaches, malaise, and vomiting.[84] These side effects can be minimized or prevented by initiation of therapy with a low starting dose (500 mg every 6 to 12 hours) and gradual increase in the dosage. Hypersensitivity reaction to sulfasalazine can cause rash, fever, hemolytic anemia, and hepatotoxicity. We typically coadminister folic acid 1 mg daily to prevent folate deficiency. The drug may cause a reversible but clinically significant azoospermia in men, so discontinuation of the drug should be considered in the family planning stage. This particular effect is not seen with the nonsulfa 5-ASA compounds.

Olsalazine

Olsalazine delivers intact 5-ASA to the terminal ileum, which is then cleaved by the colonic bacteria to free 5-ASA. Olsalazine has been shown to be of benefit in the maintenance of remission of patients with UC.[80] At higher doses it may result in a watery secretory diarrhea.[84] No therapeutic benefit has been shown in patients with mild to moderate attacks of Crohn's disease.[85]

Mesalamine

At a dosage of 2.4 to 4.8 g/day (usually given in three to four divided doses), mesalamine has been shown to be efficacious in patients for both induction and maintenance of remission of mildly to moderately active UC.[80,81] It was found in a recent meta-analysis to be nearly as effective as sulfasalazine in maintaining remission in patients with UC.[80] Mesalamine enemas at dosages of 1 to 4 g/day are effective in treating patients with distal UC, whereas patients with limited ulcerative proctitis can benefit from mesalamine suppositories at a dosage of 500 mg twice a day.[86]

The role of mesalamine for treatment of mildly to moderately active Crohn's disease remains controversial. Although mesalamine at dosages between 3.2 and 4 g/day has been associated with clinical improvement or remission in mildly to moderately active Crohn's disease,[87,88] other studies have failed to demonstrate a benefit.[89,90] A pooled analysis of three trials using the Pentasa formulation of mesalamine (including two unpublished trials that were negative) suggested that Pentasa resulted in a net decrease of 18 points on the Crohn's Disease Activity Index (CDAI), which, although statistically significant, may not represent a clinically meaningful response.[90] The role of mesalamine and other 5-ASA therapies to maintain remission and prevent relapse in Crohn's disease remains controversial, too. A 1997 meta-analysis of all available trials suggested that the net incremental benefit of mesalamine compared to placebo in maintaining medically induced remission was only 4.7%.[91] The number needed to treat (NNT) to prevent one additional relapse would therefore be more than 20 patients. In contrast, the net incremental benefit of mesalamine in maintaining surgically induced remission was slightly better at 13.1% (NNT, 7). A more recent meta-analysis, incorporating additional studies, suggested that mesalamine provided no benefit whatsoever in maintaining medically induced remission in Crohn's disease.[85] Mesalamine does not carry an indication approved by the U.S. Food and Drug Administration (FDA) for the treatment of Crohn's disease.

Potential adverse events from mesalamine therapy include headache, abdominal pain, nausea, and diarrhea.[84] Mesalamine can less commonly cause hypersensitivity colitis, pancreatitis, pleuritis, interstitial pneumonitis, interstitial nephritis, and hepatotoxicity.

Balsalazide

Balsalazide at a dosage of 6.75 g/day (in three divided doses) has been shown to be effective for the treatment of mildly to moderately active UC.[92] It is equivalent to mesalamine in efficacy.[92] Adverse events include headache, abdominal pain, nausea, and diarrhea.[84] Rare reports of aggravation of colitis, pancreatitis, and hepatotoxicity have been described.

Corticosteroids

The benefit of corticosteroid therapy for UC was first reported by Truelove and Witts.[93] Corticosteroids still remain the cornerstone of medical treatment of moderately to severely active IBD. Their broad mechanism of action occurs through modification of gene expression, ultimately resulting in inhibition of proinflammatory cytokines; repression of phospholipase A, cyclooxygenase-2, and nitric oxide synthase; and inhibition of adhesion molecules.[79] The end result is reduction in leukocyte migration and inhibition of multiple inflammatory mediators.[79]

The initial treatment in patients with moderate to severe UC is prednisone at 40 to 60 mg daily. In severely ill, hospitalized patients, initial therapy consists of 100 mg IV hydrocortisone three times daily or its equivalent. Corticosteroids are also effective in the treatment of moderate to severe Crohn's disease. In the National Cooperative Crohn's Disease Study, prednisone administered at dosages of 0.25 to 0.75 mg/kg/day to 85 patients with active Crohn's disease resulted in remission in 60% of patients compared with a rate of only 30% in a placebo group.[82] Although corticosteroids are highly effective in the short term for inducing remission, only a few patients remain in remission off corticosteroids over the longer term.[94,95] Studies of population-based cohorts in the preimmunosuppressive era suggest that approximately one third of patients receiving corticosteroids will be steroid dependent and about one third will have required surgical resection at the end of 1 year.[94,95] These studies highlight the need for early and aggressive use of steroid-sparing medications in IBD patients whose disease is active enough to require corticosteroids.

The systemic side effects of conventional corticosteroids have led to the development of modified formulations that are more potent and more rapidly metabolized. Modified corticosteroids offer the promise of being as effective as traditional corticosteroids with fewer systemic side effects. Similar to 5-ASA preparations, different packaging of these agents is available, which offers the possibility of drug delivery to the small bowel and the colon with minimum side effects. Oral delayed-release budesonide (Entocort EC) is the most notable of these new corticosteroids.[96] This controlled ileal release formulation is indicated for induction of remission in mildly to moderately active Crohn's disease involving the ileum or right colon. In one head-to-head study, budesonide at 9 mg/day was more efficacious than mesalamine 4 g/day for this indication.[97] In a pooled analysis of four maintenance trials (each individually negative), budesonide was associated with a significantly longer median time to relapse (268 days) than placebo (154 days).[98]

Topical corticosteroids may be of benefit in patients with either limited distal disease or with rectal involvement along with more proximal disease.[86] Corticosteroid enemas or foams can be used for the treatment of active disease, but no role in maintenance therapy has been proved.

Antibiotics

Multiple lines of evidence suggest that bacteria may play a role in the pathogenesis of IBD, perhaps due to an unusual response of the mucosal immune system to

normal intestinal flora, or a breakdown in the intestinal defenses allowing microorganisms to invade the intestinal mucosa. Some have even hypothesized that a specific bacteria such as *Mycobacterium avium* subspecies *paratuberculosis* may be responsible for Crohn's disease, but this remains extremely controversial.[2]

In patients with UC, both IV and oral antibiotics have been studied in placebo-controlled trials. No statistically significant results have been reported in IV studies involving patients with severe UC.[99] Two studies of oral antibiotics in patients with mild to severe UC have reported statistically significant results: one with tobramycin 120 mg orally three times a day (78% improvement at 4 weeks versus 43% with placebo; $P = .008$)[100] and one with ciprofloxacin 500 to 750 mg orally twice a day (79% response at 6 months versus 56% with placebo; $P = .02$).[101] However, the difference in the latter study was of borderline significance after 12 months of follow-up (55% response in the ciprofloxacin group versus 40% in the placebo group; $P = .07$). Furthermore, another randomized, placebo-controlled trial of oral ciprofloxacin in mildly to moderately active UC was negative.[102] A small placebo-controlled trial of rifaximin showed numerical but not statistical superiority against placebo in active UC (response rates 64% versus 42%; P = NS).[103] At the present time, oral antibiotics are not routinely prescribed for UC; however, the conflicting trial results suggest that additional studies need to be performed to definitively prove or disprove the role of oral antibiotics in mildly to moderately active UC.

Evidence for antibiotic use in Crohn's disease from randomized, controlled trials is limited. Sutherland et al. performed a study comparing metronidazole to placebo in patients with active Crohn's disease.[104] According to the CDAI scores, the metronidazole group showed significantly greater improvement in disease ($P = .001$). This improvement was greatest in patients with colonic involvement ($P = .05$) but less remarkable in those with ileitis (P = NS). This finding appears to be common in Crohn's disease; patients with colonic involvement seem to benefit the most from antibiotic treatment. The adverse effects of metronidazole, however, are substantial. They include nausea, anorexia, metallic taste in the mouth, furry tongue, candidiasis, and dose-dependent peripheral neuropathy.

Ciprofloxacin has also been evaluated in Crohn's disease. Although somewhat safer than metronidazole, ciprofloxacin is associated with notable adverse events, including nausea, the potential for drug interactions (and possibly prolongation of the QT interval), and the risk of tendonitis or tendon rupture, particularly when combined with corticosteroids. In one study, investigators compared ciprofloxacin and high-dose mesalamine.[105] In this study, comparable proportions of patients had improvement (17% ciprofloxacin, 5% mesalamine) and achieved remission (56% ciprofloxacin, 55% mesalamine) with either ciprofloxacin (1000 mg/day) or mesalamine (4 g/day). Although fewer patients failed treatment with ciprofloxacin (17% versus 36%), there were no significant differences between groups.[105] Another study compared the combination of ciprofloxacin and metronidazole with methylprednisolone.[106] After 12 weeks of treatment, 46% of the antibiotic group and 63% of the steroid group obtained clinical remission. This difference was not significant. The results of this study suggest that combinations of antibiotics may be worthwhile in patients prior to initiating steroid therapy.[106] A small open-label study evaluated rifaximin 200 mg three times a day for 16 weeks in patients with mildly to moderately active Crohn's disease.[107] The average decline in CDAI score after 1 month of treatment was 100 points. Most patients also achieved and maintained remission through the 4-month study.[107]

Immunosuppressive Agents

Immunosuppressive agents such as azathioprine/6-mercaptopurine and methotrexate are being increasingly used to treat IBD patients who do not respond to first-line therapies or who are steroid dependent or steroid refractory. In general, the threshold to use these agents is lower in Crohn's disease than in UC, likely a reflection of the relatively poor efficacy of first-line agents in maintaining remission in Crohn's disease. These drugs are thought to act by blocking the proliferation and activation of the T-helper lymphocytes, which play a major role in the inflammatory cascade through the production of various cytokines such as IL-1, IL-2, IL-6, IL-8, TNF-β, and IFN-γ.[79]

Azathioprine and 6-Mercaptopurine

Azathioprine (Imuran, Azasan) and 6-mercaptopurine (Purinethol) are thiopurine compounds used in the management of steroid-dependent IBD, steroid-refractory IBD, and fistulizing Crohn's disease. They act either via inhibition of purine RNA synthesis and cell proliferation or via inhibition of natural killer cells and suppression of cytotoxic T-cell functions.[79] Azathioprine is a prodrug of 6-mercaptopurine, and both drugs are converted via several enzymatic steps to the 6-thioguanine nucleotides, which are thought to be the active metabolites. These mechanisms of action likely explain the 3- to 4-month delay in the onset of their clinical effectiveness. One of the inactivating enzymes in the metabolism of these agents, thiopurine methyltransferase (TPMT), has a trimodal distribution of activity in the population.[108] About 89% of patients have normal TPMT activity, 11% have intermediate activity, and 1 in 300 persons have minimal or no enzyme activity, such that normal doses of purine analogues can result in prolonged bone marrow suppression and fatal infectious complications. Many physicians routinely obtain a TPMT genotype or enzyme activity level prior to initiation of these agents to better predict a dosage that will not result in early leukopenia.

Azathioprine and 6-mercaptopurine are both used in the management of patients with active Crohn's disease and UC who have not responded to systemic steroids.[109,110] In addition, both drugs have been successfully used as steroid-sparing agents in patients with IBD who are unable to be weaned from steroid therapy.[109,110] Furthermore, both drugs have been shown to be

effective for maintenance of remission in both conditions. For IBD patients with normal TPMT levels, the typical dose of azathioprine is 2 to 2.5 mg/kg body weight daily and the dose of 6-mercaptopurine is 1 to 1.5 mg/kg body weight daily. The typical dose of these agents in those with intermediate TPMT levels is half that of patients with normal enzyme activity.

Unfortunately, observational studies suggest that 20% to 25% of IBD patients taking these agents need to discontinue them due to adverse events.[111] Among the side effects of azathioprine and 6-mercaptopurine are pancreatitis, which occurs in approximately 3% of patients, usually presents within the first 6 weeks of therapy, and resolves promptly when the drug is withdrawn.[112] Other adverse events include nausea, fatigue, and hepatotoxicity, all of which seem to be dose related. Other idiosyncratic reactions that can occur include fever, influenza-like symptoms, and abdominal pain. Patients on these agents should undergo monthly complete blood counts to monitor for leukopenia, and quarterly hepatic biochemistries to monitor for hepatotoxicity. Like all immunosuppressive agents, these drugs seem to be associated with an increased risk of non-Hodgkin's lymphoma. A recently published meta-analysis of observational studies suggested a threefold to fourfold increased relative risk[113]; however, the absolute risk of lymphoma remains low (probably <1 case per 1000 person-years), and decision analysis models suggest that the benefit far outweighs the risk in properly selected patients.[114]

Methotrexate

Methotrexate acts via inhibition of dihydrofolate reductase to impair DNA synthesis and reduce production of IL-1, IL-6, and TNF-α.[79] A multicenter, placebo-controlled trial with 141 patients with active Crohn's disease confirmed that methotrexate at a dosage of 25 mg administered intramuscularly or subcutaneously once a week, over 16 weeks, allowed steroid tapering and maintenance of remission in 39% of patients treated compared with 19% in those receiving placebo.[115] A subsequent trial randomized Crohn's disease patients with methotrexate-induced remission to continued methotrexate at 15 mg weekly or placebo.[116] Patients receiving methotrexate were significantly less likely to experience relapse (35%) compared to those receiving placebo (61%). Although several open-label uncontrolled studies have suggested efficacy for methotrexate in UC,[117-120] a randomized trial of this agent failed to demonstrate efficacy[121]; therefore, its routine use in steroid-dependent or steroid-refractory UC is not recommended.

Potential side effects of methotrexate include leukopenia, requiring monthly monitoring of the blood count, and hepatic fibrosis, necessitating monthly hepatic biochemistries. Patients with risk factors for fatty liver disease (e.g., obesity, diabetes mellitus, ethanol use) and those with persistent elevations in hepatic biochemistries should undergo percutaneous liver biopsy. Methotrexate-induced pneumonitis is occasionally encountered, so patients who develop cough or fever while on this agent should be investigated thoroughly.

Cyclosporine and Tacrolimus

Cyclosporine is a potent immunosuppressive drug that is used in organ transplantation as well as "rescue therapy" in patients with acute severe UC.[122] It blocks transcription of cytokines that activate T-helper lymphocytes, thus inhibiting the production and liberation of proinflammatory cytokines.[79] IV cyclosporine has been shown to be effective in the short term in patients with acute severe colitis.[123] The major problem with the drug is that although short-term improvement may be achieved, long-term maintenance with the oral form of the drug produces excessive side effects.[123] Side effects and toxicity of treatment with cyclosporine include electrolyte abnormalities, seizures, paresthesias, hypertrichosis, nephrotoxicity, hypertension, tremors, and headaches, which can occur in up to 60% of patients treated.[79] Fatal opportunistic infections have been reported with the use of this agent; therefore, the risks of cyclosporine therapy must be weighed against the benefits on a case-by-case basis.

Infliximab and Other Biological Therapies

It would not be an exaggeration to state that the availability of infliximab (Remicade), a chimeric monoclonal antibody to TNF-α, has significantly altered the way gastroenterologists treat steroid-dependent, steroid-refractory, and fistulizing Crohn's disease. Randomized trials have established that infliximab is effective for inducing and maintaining remission of Crohn's disease in patients who failed to respond to conventional therapy[124,125] and that the antibody significantly reduces the number of open, draining perianal and enterocutaneous fistulas and maintains this response.[126,127] Endoscopic studies suggest that infliximab is associated with a significant reduction in endoscopic activity of Crohn's disease and in some cases is associated with complete mucosal healing.[128] Patients receiving infliximab on a regularly scheduled basis appear significantly less likely to require hospitalization and surgery.[129,130] Recent trials in patients with moderate to severe UC also demonstrated efficacy,[131,132] and infliximab was recently approved by the FDA for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in those with moderately to severely active UC who have not responded to conventional therapy.

The typical starting dose of infliximab is an infusion of 5 mg/kg body weight over a 2- to 4-hour period. A three-dose induction is administered at 0, 2, and 6 weeks, and maintenance doses are administered every 8 weeks thereafter. The chimeric nature of the molecule results in significant immunogenicity, and improper administration of the drug may result in the formation of antibodies to infliximab, which are associated with infusion reactions and, more important, a loss of response to the drug over time.[133] For this reason, maintenance use (and

not episodic use) of the drug is strongly recommended. Many physicians routinely coadminister a concomitant immunosuppressive such as azathioprine, 6-mercaptopurine, or methotrexate because there is considerable evidence that this will further reduce the risk of antibody formation.[133] Some physicians also administer corticosteroids as IV premedication to reduce antibody formation on the basis of a randomized trial.[134]

Adverse events following infliximab therapy have included serious (and sometimes fatal) infections including tuberculosis, histoplasmosis, coccidiomycosis, listeriosis, and *Pneumocystis carinii* pneumonia.[79] Hepatotoxicity, worsening of congestive heart failure, serious hematologic events, demyelinating disorders (e.g., multiple sclerosis and optic neuritis), and malignancies (lymphoma, lung malignancies) have been reported following the use of the drug. As with all immunosuppressive agents, the potential benefits of infliximab need to be weighed against the possible risks, but with proper selection of patients the risks appear manageable.[135]

Other anti-TNF agents have been studied in IBD. Etanercept (Enbrel) did not demonstrate efficacy in Crohn's disease.[136] Adalimumab (Humira) is a fully human antibody to TNF that has demonstrated efficacy in Crohn's disease in several randomized and open-label trials.[137-141] This drug is administered subcutaneously every 1 to 2 weeks and is already commercially available in the United States for treatment of rheumatoid arthritis. Certolizumab pegol (formerly known as CDP870) is a humanized Fab TNF antibody fragment that has been "PEG-ylated" (i.e., attached to a polyethylene glycol [PEG] molecule) to improve the half-life of the drug. Randomized trials have also demonstrated efficacy for this agent in Crohn's disease with once-monthly subcutaneous dosing.[142]

Other biological therapies that are being actively investigated for IBD include natalizumab (Tysabri), a monoclonal antibody to the adhesion molecule α_4 integrin[143]; MLN-02, an antibody to α_4/β_7 integrin, which may have more gut specificity[144]; antibodies to IL-12[145]; visilizumab, a non–Fc receptor-binding anti-CD3 antibody[146]; and fontolizumab, an antibody to INF-γ.[147]

SURGICAL CONSIDERATIONS IN INFLAMMATORY BOWEL DISEASE

Surgical intervention in IBD patients is primarily reserved for patients with disease complications or for those who have failed to respond to medical therapy to control symptoms of the disease. Depending on the underlying disease process, surgery may be curative for the intestinal manifestations of the disease, as is seen with UC, or as an adjunct to medical therapy in controlling symptoms or as treatment of disease complications, as is often the case in Crohn's disease. No matter the surgical indication, good communication between the treating gastroenterologist and surgeon is extremely important. The surgeon must be aware of the history of the patient's medical therapy, the current specific treatment objective, and possible future therapies that might influence the surgical decision making. In the following section, we briefly discuss the indications, surgical approaches, and reported outcomes of surgical intervention in UC and Crohn's disease. We also discuss the role of laparoscopy in the surgical management of both diseases.

Surgical Management of Ulcerative Colitis

The surgical approach to patients with UC can be divided into two broad categories: emergent and elective surgical intervention. Indications for emergent intervention in UC include fulminant colitis, toxic megacolon, colonic perforation, and massive hemorrhage. Fortunately, with better understanding of the disease and improved medical treatments, these situations arise less frequently, but even today approximately 10% of newly diagnosed UC patients present with fulminant colitis. In these emergent situations, the goal of the surgical procedure is to address a life-threatening clinical situation without precluding a future restorative procedure. In nearly all emergent situations, there is no role for proceeding with a rectal dissection because this is time-consuming, increases the complexity of the surgery, and makes possible future ileal pouch reconstruction extremely difficult. In a patient with known UC or indeterminate colitis who requires emergent operation for a complication related to their colonic disease, the procedure of choice is the subtotal colectomy with end ileostomy. This procedure removes most of the diseased organ but leaves the rectum in situ and avoids any disturbance to the important dissection planes in the pelvis. This approach addresses the complication that prompted surgical intervention and also allows the patient to improve their overall health and nutritional status and to transition off medications such as corticosteroids. The patient can then proceed at a later date to a restorative or definitive operation without any deleterious impact on the functional outcomes. If the rectal disease does become troublesome, it can usually be managed with topical corticosteroids or mesalamine. Until recently, emergent subtotal colectomies were considered a contraindication to a laparoscopic approach. However, it has recently been shown to be equally effective and safe in an experienced surgeon's hands and to provide some patient benefits related to recovery.[148] The more common situation in the UC patient is to address electively the failure of medical therapy to control disease symptoms, long-term deleterious side effects of medications, or the development of intestinal dysplasia or cancer.

As discussed more fully in Chapter 152, the currently accepted surgical approaches to treating UC are total proctocolectomy with end ileostomy or total proctocolectomy with ileal pouch–anal anastomosis (IPAA). Both operations cure the patient of the intestinal manifestations of the disease. However, the IPAA avoids the requirement for a permanent ileostomy. Parks and Nicholls first described the IPAA procedure in 1978.[149] IPAA is an ideal operation for the treatment of UC because it removes the entire diseased organ while simultaneously preserving the normal anatomic route for

defecation.[150] Construction of the ileal pouch is the key to the success of this operation, since it provides an adequate fecal reservoir to allow voluntary defecation, albeit at a higher but manageable daily frequency than patients with a normal rectum. The decision to proceed with an operation other than IPAA for UC is based on individual patient circumstances or preexisting medical or physiologic conditions that are considered contraindications for this type of restorative procedure. Previously, "advanced age" (i.e., age >50 years) was considered a contraindication; however, a recent publication suggested that chronologic age itself should not be considered a contraindication because many older patients seem to have quite comparable surgical and functional outcomes relative to younger patients.[151]

Details of the IPAA procedure are beyond the scope of this chapter and are discussed more fully in Chapter 152. Although each surgeon might have slightly different ways of performing the operation, the operation basically involves the following four steps:

1. Removal of the intra-abdominal colon
2. Dissection and removal of the rectum, sparing the pelvic nerves and the anal sphincter mechanism
3. Construction of an ileal reservoir
4. Anastomosis of the ileal reservoir to the anal canal

Even though a large number of surgeons and institutions have reported their experience with IPAA procedure, the functional results are quite similar.[152-157] Most patients report good to excellent function with their ileal pouch. In a Mayo Clinic series of more than 1300 IPAAs, the average number of daytime bowel movements at the time of discharge after closure of the ileostomy was six per day, and the average number of nocturnal bowel movements was one per night.[152,153] During the day, 79% of patients reported complete continence, 19% had occasional incontinence and 2% had frequent episodes of incontinence. During the night, 59% of patients had no incontinence whatsoever, whereas 49% reported occasional nocturnal incontinence. A recent report of patients from this cohort who were followed for more than 15 years showed that pouch function is relatively stable over time, with no real significant decline in functional parameters, except for an increase in episodes for both day and nocturnal incontinence.[158] Although it would appear at first glance that these functional changes might result in a decline in satisfaction with the outcome of the surgery, the patients reported no such decline.

Although the functional results of the surgery are fairly well described and are consistent among the many reported series, it is unclear if patient quality of life (QoL) is consistently improved by the IPAA.[159] Most patients report a high degree of satisfaction with the functional result from their IPAA. Fazio and colleagues have shown that the QoL after IPAA is comparable to the norms for the general healthy U.S. population.[160] Most QoL assessments of these patients are confounded by the differential impact on QoL of the removal of the diseased bowel with respect to overall health, the ability to discontinue medications, and the ability to voluntarily control stools. The literature contains conflicting reports on this point. Some authors report improved QoL after IPAA compared to end or continent ileostomy,[161-163] whereas others have shown that QoL improves no matter what procedure is performed and is probably due to eradication of the disease.[164-166] In a recent report using specific and generic QoL questionnaires and a survey instrument that estimated the monetary value for continuing disability related to the surgical procedure, they found that the patients with an IPAA had much better body image compared to patients with a Brooke or Kock ileostomy.[167] However, all patients assigned an equal monetary value to the disability associated with each operation. The IPAA patients actually reported altered bowel emptying function as more disabling than patients with stomas. The findings in the literature would suggest that the currently available instruments to measure QoL might not be sensitive or specific enough to detect the many facets of a patient's QoL after a period of prolonged illness and possibly multiple surgeries.

Although there are a few technical issues related to the IPAA procedure that are still debated, such as hand-sewn versus double-stapled anastomosis, or the role of a temporary ileostomy, the most recent advance related to the procedure is the role of laparoscopic surgery. As surgeons have become more familiar with laparoscopic colorectal surgery, and newer instrumentation has been developed specifically for complex laparoscopic colorectal surgery, an increasing number of institutions have reported their results with laparoscopic IPAA.[168,169] A number of different laparoscopic techniques have been described, including purely laparoscopic, a combined laparoscopic mini-laparotomy, or a hand-assisted laparoscopic technique. These reports have presented small series of patients and have demonstrated fairly similar perioperative complication rates and short-term functional outcomes as compared to traditional open techniques. Although laparoscopic IPAA surgeries usually have longer operative times compared to open procedures, they usually result in shorter postoperative lengths of stay, decreased postoperative narcotic use, and improved cosmesis. In the only reported long-term matched case-control study of laparoscopic versus open IPAA, there were no long-term functional or QoL differences between the two surgical modalities.[170] Aside from the technical challenge associated with performing this complex procedure laparoscopically, there is no reason to believe that it is not equivalent to the traditional open surgery and that it might provide some substantial benefits to the patient.

Surgical Management of Crohn's Disease

Unlike UC, where surgery can be considered curative for the intestinal manifestations of the disease, surgery in Crohn's disease is directed at relieving symptoms or complications of the disease. Surgery should only be considered once maximal medical therapy has failed in controlling symptoms of Crohn's disease, to treat complications of the disease that prevent the initiation of medical therapy, or to treat emergent conditions. Because Crohn's disease can manifest itself anywhere along the intestinal tract, the location of disease and the

indications requiring surgery are numerous. However, in the most general terms, surgical intervention for abdominal Crohn's disease is directed at three areas: relief of obstruction, treatment of intestinal fistulas, or treatment of medically refractory disease. Less frequent indications for surgery include addressing free perforations and cancer. An essential component of treating Crohn's disease patients is a close collaboration between the treating gastroenterologist and the surgeon. A thorough review of the patient's medical options and planned postoperative medical follow-up and treatment schedule needs to be considered during the surgical planning. Finally, surgical planning should always be directed at performing the minimal amount of surgery to resolve the problem. Given the recurring nature of Crohn's disease, surgical resection of the intestine, especially the small intestine, needs to be minimized to avoid the possible complications related to short bowel syndrome.

As previously noted, the main indications for surgical intervention in the treatment of abdominal Crohn's disease are relief of obstruction, treatment of intestinal fistulas, or treatment of medically refractory disease. These different indications seem to be influenced by the site of primary disease activity. In a review of patients who underwent surgery at Cleveland Clinic, bowel obstruction and internal fistula or an abscess tended to be the most common reasons for surgery in patients with small bowel disease. The indications for surgery in 127 patients with colonic disease were poor response to medical care (25%), internal fistula and abscess (23%), toxic megacolon (20%), perianal disease (19%), and intestinal obstruction (12%).[171] A detailed discussion of the specific indications and surgical treatment options for Crohn's disease patients is presented in Chapter 153. Important to the discussion of the surgical treatment of abdominal Crohn's disease is a consideration of the natural history after surgery. Surgery is rarely curative, with nearly 60% to 80% of patients with Crohn's disease developing endoscopic recurrence by 1 year after surgery, 10% to 20% experiencing clinical relapse, and 5% developing recurrence that requires repeat surgical intervention.[172,173] The impact of the standard use of immunosuppressives (azathioprine and 6-mercaptopurine) to reduce the need for surgery or recurrence after surgery in Crohn's disease patients is not clearly understood. A recent French report could not demonstrate a significant decline in the risk of intestinal complications or the need for surgery in patients who had been treated with immunosuppressive agents.[174] The role of the new biological agents, such as infliximab, in slowing the progression of disease to the point that it would not require surgery, or reducing the incidence of recurrence after surgery, is not clear at this time. Large well-designed and well-powered clinical trials need to be performed to test the efficacy of these novel but expensive agents before they become routinely recommended as agents that can change the need for or prevent a clinical recurrence of the disease that requires surgery.[175]

Although abdominal complications of Crohn's disease can be challenging to treat, the surgical decision making is often fairly straightforward; however, treatment of perianal Crohn's disease can be quite difficult for both the patient and treating physician. The dreaded end result of unsuccessful treatment can lead to removal of the entire rectum and anus and the need for a permanent ostomy. As in treatment strategies for proximal intestinal Crohn's disease, judicious surgery combined with maximal medical therapy with an eye toward symptomatic disease control as opposed to disease eradication needs to be the therapeutic goal. The incidence of perianal involvement has been reported to range from 13% to 43% of patients with Crohn's disease.[68,176,177] Although the manifestations of perianal Crohn's disease are numerous, encompassing enlarged anal tags to complex abscesses and fistulas, the most difficult problem to manage is fistulas. Before embarking on treatment of perianal Crohn's disease fistulas, it is important to ensure that any abscess that might be perpetuating the fistula is adequately drained. It is not uncommon to have both abscess and fistula occurring either simultaneously or close in time. As the complexity of the fistula tract increases, the higher the likelihood of a persistent abscess.[178]

The most important component of treatment is evaluating the perineum and determining the anatomy of the fistula. Traditionally, an examination under anesthesia has been the mainstay of determining the perianal anatomy. However, advanced radiographic imaging modalities have demonstrated good success in determining the path of anal fistulas. In a study in which each patient had anal endoscopic ultrasound, pelvic magnetic resonance imaging (MRI), and surgical examination under anesthesia, the anal ultrasound was found to be more sensitive in determining the extent and course of anal fistulas than MRI and equivalent to surgical evaluation.[179]

Once the fistula tract is identified, primary surgical management should be directed at controlling any septic process associated with the fistula. Once any local sepsis is drained, a minimalist approach to further surgery should be considered. As discussed in greater detail in Chapter 153, liberal use of draining setons to maintain adequate drainage of the tract should be encouraged for all but the most superficial fistulas. Surgical drainage combined with maximal medical therapy including infliximab has dramatically improved treatment outcomes for this difficult problem. In a recent report by Talbot and colleagues, combined infliximab and surgery for complex perianal Crohn's fistula disease resulted in complete resolution of the disease in 47% of patients and marked improvement in all of the remaining patients.[180] Essential to the successful treatment of perianal Crohn's disease is bringing under control rectal and more proximal disease. Failure to control the rectal disease leads to a much higher rate of proctectomy and permanent ileostomy than in patients whose proximal and rectal disease is improved. If perianal disease continues and is symptomatic, proctectomy may be necessary. Before a proctectomy is performed, it is important that the patient be in optimal medical condition, because this operation is associated with relatively high morbidity rates. Preoperative measures to decrease local sepsis and improve healing should be undertaken, including improved control of local sepsis, maximal nutritional supplemen-

tation, and decreasing corticosteroid use if possible. To decrease local sepsis and improve the patient's overall medical condition, a staged procedure may be planned by performing an initial subtotal colectomy and ileostomy or ileostomy alone. Overall, the successful management of perianal Crohn's disease, just as treatment of Crohn's disease elsewhere in the intestine, requires close collaboration with the treating gastroenterologist to ensure that appropriate maximal medical therapy is being administered. Furthermore, a conservative surgical approach, to improve the patient's symptoms and not with the goal of eradicating the disease, should be employed.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE

IBD is a chronic disease that profoundly impacts the patient's daily QoL. Many of patients are diagnosed in their early adulthood, which means that they will require chronic medical attention, medication use, frequent surgeries, or live with the after-effects of surgical treatment for the remainder of their lives. A patient's health-related QoL (HR-QoL) comprises three general domains: physical, social, and psychological.[181] Although many generic HR-QoL instruments exist that are useful for measurements across all diseases and medical intervention, they evaluate the three health domains in general terms. The most commonly used validated disease-specific QoL instrument for IBD patients is the Inflammatory Bowel Disease Questionnaire (IBDQ) developed by Guyatt,[182] Irvine,[183] and their associates.

Chronic medical conditions have been linked to increased psychological distress in numerous community and clinical studies.[184,185] Overall, patients with IBD demonstrate a higher degree of psychological distress compared to healthy controls.[186] Not surprisingly, the level of distress correlates with the level of disease activity.[186,187] Also, nearly all studies have shown that patients with Crohn's disease have more psychological distress and, in general, worse QoL than patients with UC.[187] In a large population-based study in Sweden using both a generic HR-QoL instrument (the SF-36) and the IBDQ, the authors found that UC patients reported superior QoL in all dimensions of health-related and disease-specific QoL than did patients with Crohn's disease.[188] The latter reported more anxiety and depression, which was directly related to the severity of their symptoms. Having an ileostomy in either the Crohn's disease or UC patient groups was not associated with a negative impact on QoL. However, among UC patients with either an ileostomy or an IPAA, there was overall better QoL in those patients with an ileostomy, due to better physical function, emotional function, and fewer bowel-related symptoms. This finding differs from many other studies that have shown that patients with a properly functioning IPAA reported a HR-QoL comparable to the general public.[189]

An important issue to consider when discussing QoL measurement in patients with IBD is the difficulty in comparing how the interaction of medical and surgical therapy affects QoL. For example, in Crohn's disease surgical therapy often is reserved for patients who have progressive symptoms or complications in spite of medical therapy. In this setting a comparison of patients with medically controlled disease to those who undergo surgery might demonstrate a negative impact on QoL due to surgery. However, the confounder is that those patients that underwent surgery were in general sicker or had a more chronic course of their disease. Similarly, it is difficult to compare UC patients on chronic medical management for UC to those that underwent surgery. Patients who are on chronic medical therapy even with good symptom control perceive themselves as having a chronic disease, whereas patients who have undergone surgery are cured of the intestinal manifestations of the disease but now have altered bowel function. In general, QoL assessments in both Crohn's disease and UC patients have shown that the most important predictor of good or improved QoL is directly related to the severity of symptoms and the success of interventions that control patient symptoms.

SUMMARY

IBDs, which are broadly divided into Crohn's disease and chronic UC, are notable for relapsing disease activity. In most cases, initial management is directed at symptom control using medical management. Current medical therapy includes a broad array of options including agents directed at local control of the inflammatory process, immunosuppressive agents, and monoclonal antibodies directed at specific inflammatory mediators. Surgical interventions in Crohn's disease should be directed at controlling complications from the disease that are unresponsive to maximal medical therapy. Although surgery for UC can cure the intestinal manifestations of the disease, it often requires a staged approach associated with significant morbidity and change in lifestyle. For IBD patients, the most important contributor to a patient's QoL is controlling the disease symptoms. To achieve this goal, there needs to be a coordinated treatment approach between gastroenterologists and surgeons to ensure that complementary medical and surgical interventions are instituted directed at achieving long-term control of disease symptoms.

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Chapter

152

Surgery for Inflammatory Bowel Disease: Chronic Ulcerative Colitis

Peter M. Sagar ▪ John H. Pemberton

The optimal surgical procedure for most patients with chronic ulcerative colitis (CUC) is ileal pouch–anal anastomosis (IPAA).[1] Patients with CUC need no longer live with the fear that their ultimate surgical fate is to be a permanent ileostomy with its attendant psychological, social, physical, and sexual problems. Indeed, IPAA confers a good quality of life. The principal aim of this chapter is to review the technical details of IPAA and the available choices of ileal pouch and ileoanal anastomosis, as well as the complications and their sequelae. Alternative procedures will also be discussed.

INDICATIONS FOR SURGERY

Indications for surgery can be divided into two major types: elective and emergency.

Indications for Elective Surgery

Failure of Medical Therapy

Patients with CUC may require surgery either because they have failed to respond to medical therapy or because the complications of the medical therapy outweigh its benefits. CUC can cause debilitating symptoms and lead to a poor quality of life despite appropriate medical treatment. Persistent anemia, undernutrition, and protein-losing enteropathy should prompt consideration of surgical intervention. Close consultation between the patient, gastroenterologist, and surgeon is important. Careful explanations of the long-term side effects and implications of medical therapy and the risks, benefits, goals, and alternatives of the surgical options need to be given.

Presence of Cancer and Dysplasia

Cancer complicating long-standing colitis is an obvious indication for surgery. Patients with ulcerative colitis for more than 10 to 15 years have a well-recognized increased risk for cancer. Those with sclerosing cholangitis as a complication of ulcerative colitis seem to have a particularly high incidence.[2] Colonoscopic surveillance is recommended in patients with long-standing ulcerative colitis. The development of an obstructing lesion, dysplasia, or a dysplasia-associated lesion of the mucosa is an indication for surgery.

Indications for Emergency Surgery

Fulminant Colitis

Patients with a severe attack of ulcerative colitis should be resuscitated and treated medically. Deterioration of the patient's condition or failure to improve within 5 days is an indication for surgical intervention. In an ill patient, intervention should take the form of emergency total colectomy with preservation of the rectum and an end ileostomy. The rectal stump may be oversewn or brought up to the abdominal wall as a mucus fistula.

Toxic Megacolon

Toxic megacolon is a life-threatening condition. Although it may occur as an acute exacerbation of the disease, it is an initial manifestation in most patients. There is segmental or total dilatation of the colon. Patients are very ill with high fever, abdominal pain and tenderness, tachycardia, and leukocytosis. Prompt resuscitation and medical therapy are essential, along with early recourse to resection.

Hemorrhage, Perforation, and Obstruction

Massive hemorrhage is uncommon and accounts for up to 10% of emergency colectomies in patients with CUC.[3] Perforation of the colon is a clear indication for surgery. If it occurs in the absence of megacolon, the possibility of Crohn's disease should be raised. High doses of steroids mask the symptoms and signs. Strictures in patients with CUC are rare unless a carcinoma has developed.

ILEAL POUCH–ANAL ANASTOMOSIS

Overview of the Operation

The operation is usually performed in two stages.[4] First, the cecum, colon, and rectum are mobilized and removed. Care is taken to preserve the pelvic nerves. The ileum is preserved in its entirety. A reservoir (ileal pouch) is constructed from 30 to 44 cm of distal ileum and anastomosed to the anal canal at or just above the dentate line. IPAA can be performed with sutures or stapling instruments and with or without transanal rectal mucosectomy. A temporary ileostomy is used to protect the pouch and anastomosis. The ileostomy is closed 8 to 12 weeks later. IPAA removes all diseased tissue and yet maintains normal bowel function and fecal continence. As experience has been acquired with the procedure, the technique has been simplified, which has led to improved outcomes. Quality of life in patients with a pelvic ileal reservoir is better than that of patients with Brooke ileostomies, continent Kock ileostomies, and medically treated colitis.[5,6]

Laparoscopic Ileal Pouch–Anal Anastomosis

Techniques for laparoscopic colectomy have been developed and now provide an adjunct to traditional operative modalities for colonic surgery. The use of these techniques has expanded, and they have been applied to the performance of IPAA. Laparoscopic surgery appeals to patients undergoing IPAA because they are generally young and hope to gain the potential benefit of reduced disability, more rapid recovery, and a better body image as a result of more cosmetic incisions. Most reports have consisted of relatively small series and have tended to avoid patients with a body mass index greater than 30, toxic megacolon, or treatment with high-dose steroids. The best laparoscopic technique to use, be it laparoscopically assisted[7-10] or hand assisted,[11,12] is presently the subject of intense debate.

Operative Technique

The patient is placed in the dorsolithotomy position with Allen stirrups and minimal hip flexion (Fig. 152–1). A 12-mm port is placed at the umbilicus, and pneumoperitoneum is initiated at 15 mm Hg. A 10-mm, 30-degree laparoscope is used throughout. Additional ports are placed at the lateral edge of the rectus sheath: a 12-mm port at the site of the temporary ileostomy, a 5-mm port at the lateral edge of the future Pfannenstiel incision, a 5-mm suprapubic port, and a 5-mm left upper quadrant port. With the patient in a steep reverse Trendelenburg position and rotated to the right, the dissection begins at the left lower quadrant. The colon is retracted with atraumatic graspers and mobilized with a harmonic scalpel up to the splenic flexure. The patient is then rotated to the left and the ascending colon is mobilized similarly. The omentum is retracted in a cephalad direction and mobilized from the colon, again with the harmonic scalpel. The transverse mesocolon is approached from either side and divided with the harmonic scalpel, and the major mesenteric vessels are ligated with clips. With the patient then in a steep Trendelenburg position, the presacral space is entered and the dissection continued to the pelvic floor while avoiding damage to the autonomic nerves and ureters. A 6-cm Pfannenstiel incision is used to complete the mobilization of the lower portion of the rectum, and the rectum is transected at the anorectal junction with a linear stapler. The ileal pouch is then constructed through the Pfannenstiel incision after securing the anvil of a circular stapler within the pouch with interrupted sutures. The IPAA is then constructed with a double-staple technique. A suitable loop of ileum is identified for the diverting loop ileostomy at the right midquadrant trocar site.[13]

Alternatively, laparoscopic proctocolectomy can be accomplished with a hand-assisted technique. Here, a 7- to 8-cm Pfannenstiel or low midline incision is made at

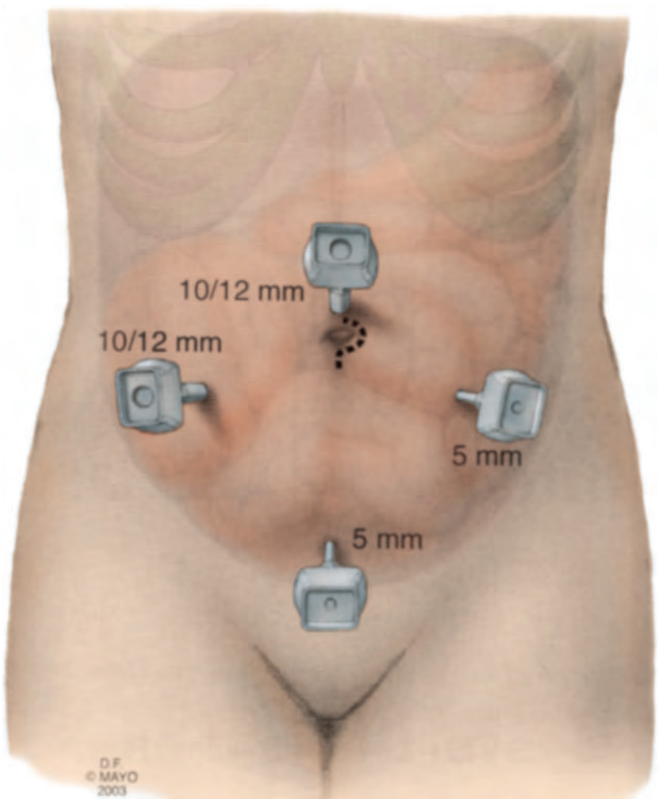


Figure 152–1. Laparoscopic ileal pouch–anal anastomosis.

the start of the operation through which the hand port is placed. Two or three additional trocars are used, one 5 or 10 mm above the umbilicus (laparoscope), a 5-mm port in the epigastrium (for dissection), and a 12-mm trocar in the lower left quadrant (for dissection, stapling, and clipping). A randomized trial that compared 30 patients after hand-assisted laparoscopic IPAA with 30 patients after open IPAA by measuring postoperative recovery and quality of life in the 3 months after surgery found no difference between the two procedures in quality of life at 3 months after surgery. Operative times were longer in the laparoscopic group than in the open group (210 versus 133 minutes, $P < .001$). No significant differences were found in morphine requirements, morbidity, or postoperative hospital stay between the two groups. However, postoperative stays were quite long in both groups, and 10% of patients required a reoperation. The median overall cost was 16,728 Euros for the hand-assisted laparoscopic procedure and 13,406 Euros for the open procedure.[14]

Laparoscopic IPAA is technically feasible and can be carried out within a reasonable time frame. It is safe. The operative technique will undoubtedly undergo modification, and operating times will decrease as laparoscopic surgeons become more experienced with the technique. Concern about operative cost needs to be balanced with earlier return to work and economic benefit to the community. Furthermore, maintenance of the integrity of the abdominal wall may also benefit patients by reducing long-term disability, including the development of incisional hernias and late interventions for adhesions. Operative cost analysis alone should not condemn laparoscopic surgery.

The functional outcome after laparoscopically assisted IPAA is no different from that after conventional IPAA. In a case-control study of 16 patients after laparoscopic IPAA, questionnaires were completed to assess functional outcome, quality of life, body image, and cosmesis. No differences were found in functional outcome and quality of life. Satisfaction with the cosmetic result was significantly higher in the laparoscopic group than in the conventional group.[15] Similarly, a case-control study of 20 patients who had undergone laparoscopic IPAA versus 20 open cases found significantly longer operative times, quicker return of bowel function, and shorter length of stay in laparoscopic versus open cases.[10] A case-matched series of 33 laparoscopically assisted and 33 open IPAA procedures reported a postoperative morbidity rate of 6% in the laparoscopic group versus 12% in the open group.[8] No differences were observed in functional outcome between the two groups, and quality of life was similar.

DESIGN OF THE ILEAL POUCH

The pelvic ileal reservoir may be constructed from two, three, or four limbs of distal ileum anastomosed in side-to-side fashion (Fig. 152–2).[16] There is no agreement regarding the ideal configuration, and there is little difference in functional outcome among the available designs of pouch. However, some pouches are easier to

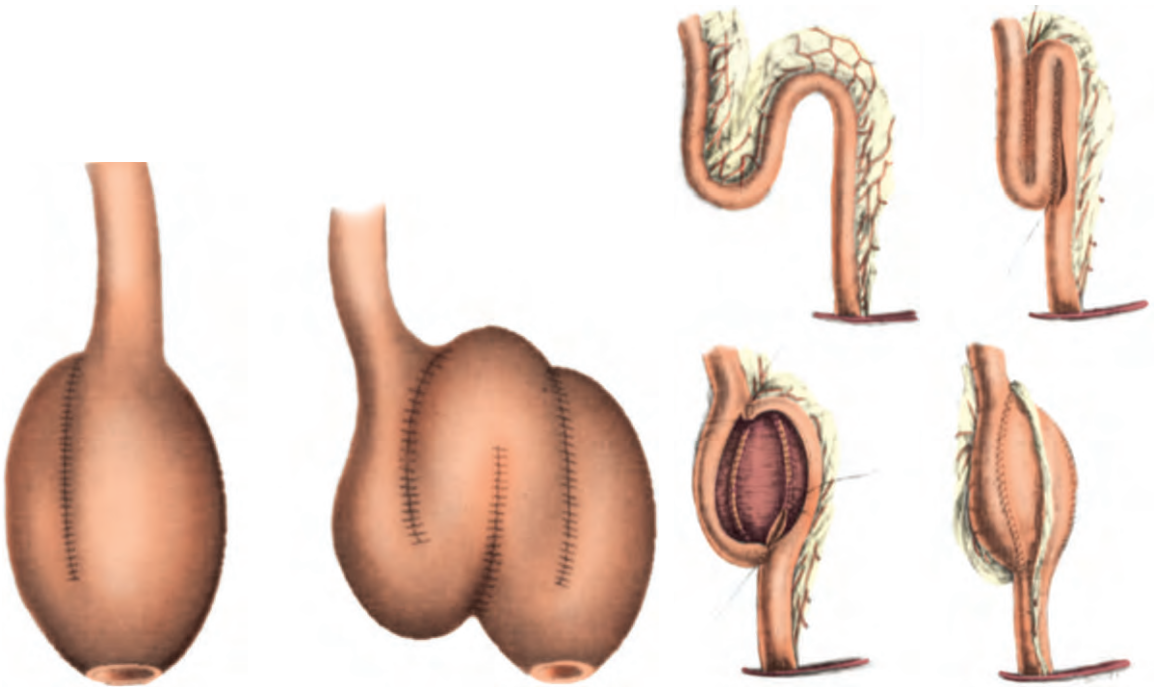


Figure 152–2. **A** and **B,** The pelvic ileal reservoir.

construct than others, and the patient's body habitus may influence the choice of pouch.

Three-Limbed Pelvic Ileal Reservoir—S Pouch

The S pouch was the first pelvic ileal reservoir to be described (see Fig. 152–2).[17] It was a modification of the reservoir originally described by Kock for use as a continent ileostomy[18] and was constructed from 30 cm of distal ileum. A 25-cm segment was opened along the antimesenteric border and folded three times, and the adjacent edges were sutured together. The most distal 5 cm was not incorporated into the reservoir but rather acted as an efferent conduit or spout. Unlike the Kock reservoir, there was no inverted nipple valve. Self-catheterization was needed to empty the pouch in four of the original five patients,[19] but this problem was largely overcome by reducing the length of the efferent spout and avoiding a long rectal muscular cuff. A long efferent limb (4 to 6 cm) would tend to impede evacuation because of acute angulation between the pouch and the efferent spout. The longer the limb, the more likely it was to angulate and hence obstruct.[20]

Although it is not widely used, the S pouch is of value in a patient in whom it is difficult to mobilize the ileum sufficiently to allow the apex of a conventional two-limbed pelvic ileal reservoir to reach the anal canal without tension. In this situation, the most distal part of the ileum can usually be made to reach low enough in the pelvis to allow construction of a tension-free anastomosis.

There is no firm rule with regard to the length of ileum used to construct the S pouch or, indeed, any pouch. After the initial descriptions, most S pouches have been constructed from three limbs of 15 cm of ileum. If too large a pouch is made, however, there is a tendency for it to become distended and atonic. Although such pouches may be both capacious and compliant, the tone of the muscular wall may be low, which can lead to stasis and incomplete evacuation. Furthermore, the efferent spout possesses peristaltic activity that is independent of the body of the ileal reservoir, and this may further impede emptying.[21] The S pouch can be constructed with no efferent spout. The distal end of the ileum is oversewn and an enterotomy made at the apex of the first and second loops at the most dependent part. The IPAA is constructed in side-to-end fashion between the most dependent part of the reservoir and the anal canal. Such construction permits spontaneous evacuation. Although the S pouch is usually hand-sutured, linear stapling instruments can be used with no increase in morbidity.[22]

The efficiency of evacuation of S pouches is less than that of J- and W-pouches, and a small minority of patients still need to self-catheterize.[23] Self-catheterization is not popular with patients because it is messy, time-consuming, and unpleasant.[24] Such pouches can be revised, particularly if the efferent limb is too long either because of the original construction or because the spout has lengthened with time after surgery. A small group of patients who have an efferent spout of only 1 cm at the time of surgery return with a 4- or 5-cm spout. Revision of the segment, without changing the configuration of the pouch, can restore satisfactory function.[25] Long efferent limbs may be shortened or excised, or the S pouch may be converted to a J pouch.[25] Resection of a long efferent limb and reanastomosis may be performed by means of a transanal approach, but the success rate is low.[26] Revision usually requires complete mobilization of the reservoir and its efferent conduit by a transabdominal approach, which can be a challenge. The ileoanal anastomosis is taken down and the entire efferent spout excised. The IPAA is then re-established. Most of the small number of patients who have undergone such revision surgery have been able to evacuate their reservoir spontaneously.[27] Alternatively, the septum between the pouch and the efferent limb may be divided transanally with the linear stapler,[28] or the efferent spout may be shortened by inserting a circular staple gun into the pouch and positioning it such that when the gun is closed, part of the efferent spout is trapped. When the gun is subsequently fired, the spout is shortened and the IPAA simultaneously re-created. Nevertheless, the difficulties of revision surgery on the IPAA must not be underestimated, and only about 50% of these patients will eventually have good function.[25]

Two-Limbed Pelvic Ileal Reservoir—J Pouch

The two-limbed J-shaped reservoir was introduced by Utsunomiya and colleagues[4] in 1980 (see Fig. 152–2) and is now by far the most popular pouch. The J pouch is constructed from a long side-to-side anastomosis along the antimesenteric border of the ileum with the limbs arranged in an iso-antiperistaltic fashion. The apex of the ileal loop that reaches to the level of the anal canal without tension is chosen to form the most dependent part of the reservoir. Transillumination of the mesentery helps identify the vessel arcades. The ileocecal artery may be divided to increase the mobility of the ileal mesentery. Reach may be increased by making windows in the ileal mesentery and scoring the peritoneum over the mesentery, although this may predispose to the development of hematomas. The length of the two limbs is variable and depends partly on the amount of fat in the ileal mesentery and the distribution of the ileal arcades. There is no difference in functional outcome between J pouches constructed from two 10-cm limbs or two 20-cm limbs.[29] The J-shaped reservoir is simple and quick to construct, particularly if linear stapling devices are used.

Despite the aforementioned maneuvers, difficulty may be experienced in allowing the apex of the ileal loop to reach down to the anal canal without tension. In this event, two further tactics are useful. First, an efferent limb may be constructed by division of the apex of the ileal loop. The two ileal limbs are then anastomosed in the usual iso-antiperistaltic fashion, with a 2-cm efferent spout emerging from the isoperistaltic limb (see Fig. 152–2). This design facilitates greater length of the reservoir and reduces the possibility of tension on the IPAA. Alternatively, the ileal loop may be divided at a point

proximal to the apex. An efferent spout is fashioned such that the ileal spout is positioned in an antiperistaltic manner, which may result in improved continence and reduced fecal leakage, although this might be outweighed by a tendency for the antiperistaltic efferent limb to impede evacuation. In practice, careful division of the ileocolic vessels will usually permit a tension-free anastomosis. Division of the visceral peritoneum on either side of the ileal mesentery allows the mesentery to stretch, but this can be risky because tension on the pouch as it is brought down to the anal canal may tear the terminal branches of the superior mesenteric arcades at the apex of the J, which are now unsupported by their protective mesentery. Generally, if the most dependent part of the pouch will reach to a level 5 to 6 cm below the upper border of the symphysis pubis, there is sufficient length to allow a tension-free anastomosis.

Quadruplicated Pelvic Ileal Reservoir—W Pouch

The quadruplicated or W pouch was introduced in 1985 in an attempt to answer the problems of incomplete evacuation of the S pouch and to improve the functional results obtained with the J pouch.[30,31] It was constructed from four 12-cm lengths of ileum that were sutured in a W arrangement.[32] The IPAA was created in side-to-end fashion between the most dependent part of the reservoir and the top of the anal canal.

The spheroidal design gives the greatest volume for a given length of ileum,[33] the pouch sits well within the confines of the pelvis, and the horizontal diameter of the W pouch is similar to that of the normal rectal ampulla.[34] One drawback, however, is that the bulky nature of this pouch can cause difficulty, especially in an obese male patient with a narrow pelvis. The design of the reservoir may be modified such that the distal two limbs are each 11 to 12 cm in length whereas the more proximal two limbs are 9 to 10 cm long (see Fig. 152–2). The reservoir is then effectively two J-shaped reservoirs anastomosed together but slightly offset. This arrangement allows the reservoir to sit more comfortably within the bony confines of the pelvis while maintaining its large capacity.

Comparative Studies of Pouch Design

There is an inverse relationship between the frequency of bowel movements and the volume of the reservoir. The volume of expansion, however, may be less in J pouches and W pouches than in S-shaped pouches, where outflow obstruction may lead to dilation of the reservoir.

A 2 × 2 prospective randomized trial that compared J and W pouches, as well as large and small pouches (2 × 20 versus 2 × 10 cm and 4 × 10 versus 4 × 15 cm), showed no statistically significant difference between the pouch designs; indeed, the smaller reservoirs in the study paradoxically seemed to offer slightly better functional outcome.[35] Improved results for the W pouch may be related to both the volume and the shape of the configuration. Studies of the influence of pouch design on function during the so-called maturation period after closure of the ileostomy have been conducted in a randomized setting in which 24 patients randomly assigned to J-pouch or W-pouch construction were studied at regular intervals in the 12 months after closure of the ileostomy. During the maturation period, the frequency of defecation decreased in both groups, but patients with a W reservoir had significantly lower values than did patients with a J reservoir. Similarly, both nighttime defecation and the use of antidiarrheal medication were significantly lower for patients with a W reservoir.[36]

Comparative studies have suggested that W pouches have some benefits over other designs of pouch in terms of capacity, compliance, and evacuation characteristics,[23,32] but prospective randomized studies have not shown a significant benefit in functional outcome.[37] Essentially, the few published prospective randomized studies that have compared the design of the ileal reservoir have failed to provide a convincing argument for surgeons to abandon the relatively quick and easy J pouch in favor of the W pouch, which tends to be hand-sutured and take much longer to construct than the stapled J pouch.

The J pouch has therefore become established as the most popular design of ileal reservoir.

FUNCTION OF THE ILEAL POUCH

Pouch Compliance and Capacity

The maximum tolerated capacity of the rectum is 300 to 400 ml.[38] At these volumes, intrarectal pressure rarely exceeds 15 to 20 cm H_2O, and compliance (rate of increase in pressure per unit increase in volume) is about 18 ml/cm H_2O. Compliance of the distal ileum is considerably lower, however, at 2 ml/cm H_2O.[39]

In contrast to the ileum, the capacity and compliance of ileal pouches differ little from those of a normal rectum. One study of 23 patients found the maximum capacity to be 320 ± 36 ml with a compliance of 14.7 ± 1.4 ml/cm H_2O.[38]

Ileal Motility

In terms of motor function, the principal difference between normal rectum and ileum is the response to distention. The rectum relaxes, whereas the ileum responds by contraction and forceful peristalsis. The rectum acts as a reservoir, whereas the ileum acts as a conduit.

Two types of motor waves are generated by the ileum—a low-amplitude (<10 mm Hg) phasic contraction of short duration (3 to 6 seconds) and a tonic contraction of longer duration (40 to 60 seconds) and large amplitude (>25 mm Hg). The frequency and amplitude of high-pressure waves increase after feeding[40] and are abolished by evacuation.[41] Tonic waves occur in response to ileal distention, and patients feel the need to evacuate. Both phasic and tonic waves are also seen in patients with Kock continent reservoirs, straight ileoanal anastomoses,[39] and pelvic ileal reservoirs.[42] Tonic waves are

generated in response to distention, and the volume required to provoke these high-pressure contractions is significantly less in a single-lumen ileum (30 ml) than in three-limbed pouches (322 ml). The ileal reservoir therefore acts more like a capacitance organ with the ability to distend without contraction before a significant volume has amassed, whereas a single-lumen ileum constantly attempts to clear its contents.

Propulsive peristaltic waves are seen in a single-lumen ileum even when not distended.[43] Although ileal reservoirs develop similar propulsive peristaltic waves, they occur only during distention of the reservoir when the filling pressure exceeds 20 cm H_2O. The frequency and amplitude of the peristaltic waves are proportional to the degree of distention. Measurement of myoelectrical activity confirms the motor findings, with uncoordinated activity being present in the ileal reservoir at rest. Myoelectrical spike activity becomes coordinated in the reservoir only in response to distention and produces coordinated propulsion.

As the pouch fills with effluent, high-pressure waves are produced. They are recognized by the patient as a desire to evacuate the pouch or as lower abdominal discomfort. They occur more frequently after meals and are largely abolished by evacuation of the pouch. The interval between onset of the high-pressure waves is directly related to the frequency of bowel action.[41] Therefore, the volume of distention at which high-pressure waves occur is a major determinant of stool frequency. The *threshold volume* at which high-pressure waves occur is related to stool frequency: the larger the threshold volume, the lower the frequency of bowel movements.[38] An increase in pressure within the lumen of the pouch is associated with increased resting anal canal pressure and rate of contraction.[44] The pressure gradient between the anal canal and pouch is less in incontinent patients, who have lower resting anal pressure, higher nocturnal pouch pressure, and larger-amplitude high-pressure waves in the pouch than continent pouch patients do.[45] The pressure gradient in the neorectal canal is frequently reversed in incontinent patients. These patients have lower resting anal pressure during sleep, and this lower pressure, together with marked variations in mean anal canal pressure, leads to incontinence. In a small minority of patients, high-pressure waves may be generated within the ileal wall at low volumes of distention. The amplitude of these waves may exceed that of resting anal pressure and thus may lead to seepage or soilage of the perineum.

Continuous manometric recordings at spaced intervals throughout the jejunoileum have demonstrated the presence of large-amplitude waves that propagate rapidly throughout the jejunum of patients who have undergone IPAA. Such waves are normally confined to the distal ileum of healthy individuals.[46] They have been shown to propel intestinal contents through canine ileum.[47] These waves may be a manifestation of increased storage and distention of the distal ileum.

The presence of a pouch influences proximal gut transit. Although gastric emptying is similar in patients with pouches, patients with Brooke ileostomies, and controls, small bowel transit of radiolabeled material was significantly longer in patients with pouches than in controls or those with Brooke ileostomies.[48]

The use of radiolabeled artificial stool has shown that as the ileal reservoir fills to its threshold volume and defecation is postponed, the pouch does not continue to distend, but rather there is retrograde reflux of up to 40% of the stool into the ileum immediately proximal to the reservoir. As this more proximal part of the ileum distends, high-pressure waves are generated that tend to propel the ileal contents back into the pouch. As the volume of distal ileal and pouch contents increases, the frequency and intensity of the high-pressure waves increase and will eventually produce abdominal discomfort and urgency of defecation.[38] Reflux of stool into the proximal ileum at the time of defecation does not appear to occur.[49]

Efficiency of Evacuation

The desire to evacuate the pouch occurs as it distends to the threshold volume. The time between one evacuation and the desire to evacuate again is influenced by a number of factors, such as capacity and compliance, the rate at which fecal contents reach the reservoir, and the completeness of evacuation. Most ileal reservoirs fail to empty as completely as normal rectum.[50,51] Nevertheless, studies with radiolabeled gel have shown that two-limbed pouches generally evacuated 60% to 70% of their contents.[41] The rate of evacuation of ileal pouches is about 11 ml of stool per second. In the absence of pouch dysfunction, the intrinsic motility of the pouch is not directly responsible for evacuation. The frequency of bowel action is directly correlated with the efficiency of evacuation. Thus, pouches that evacuate most efficiently result in the lowest frequency of bowel action.[38] Similarly, the slower the reservoir fills to its threshold volume, the lower the frequency of bowel movements and the volume of stool produced each day. This is one of the most important determinants of the frequency of bowel action.[38] Therefore, factors that either hasten filling of the reservoir or impede emptying promote earlier onset of reservoir contractions and lead to a greater frequency of defecation.

Postprandial Pouch Tone

Small intestinal motility is propagated into the ileal pouch, and this may influence pouch function. Both the tone of the pouch and motility have been shown to increase after a meal.[52] The extent to which pouch function is influenced by changes in pouch tone and motility induced by a meal has been studied with the electronic barostat. The electronic barostat is an ideal instrument to characterize not only the compliance and sensory characteristics of the pouch but also postprandial changes in pouch tone and motility. The electronic barostat used to distend the ileoanal pouch involves the use of a polyethylene bag tied to the end of a 19-French multilumen tube, and this catheter in turn is connected to the barostat. The barostat is able to induce distention at constant pressure (isobaric distention), and the

pressure is kept constant by electronic feedback regulation of the air volume within the bag.[53] A functional study of 19 patients with ileal pouches and either high stool frequency ($n = 8$) or adequate stool frequency ($n = 11$) were studied in this way. This comparative study found similar pouch compliance and sensitivity between the two groups of patients but demonstrated that postprandial pouch tone was increased significantly in patients with high stool frequency.[54] Many patients report the urge to defecate directly after a meal. Not only is pouch tone increased after a meal, but the increase in pouch tone also appears to be related to pouch function—the postprandial increase in pouch tone is greater in patients with poor pouch function than in patients with adequate pouch function. Therefore, in the absence of differences in pouch compliance, sensitivity, and 24-hour stool volume, the postprandial meal response may have an important influence on pouch function. The increase in pouch tone depends on the state of filling of the pouch. When the pouch is full, an increase in tone will increase pouch pressure. This results in urgency. If the pouch is empty, an increase in tone will reduce pouch volume. Therefore, it will be full earlier and the frequency of stool evacuation will increase.[54] Although there is a significant correlation between postprandial pouch tone and pouch function, the correlation between pouch compliance and pouch function is less strong, thus implying that the clinical significance of postprandial pouch tone may be greater than that of pouch compliance in patients with ileal reservoirs. Reports of rupture of J reservoirs after the rapid consumption of high-calorie, high-fiber meals support this hypothesis and suggest that the meal response can lead to serious complications.[55]

Ecology of the Pouch

The bacterial flora of pouches, together with their products of metabolism, especially volatile fatty acids, may have an important influence on the function of pouches. Major differences have been observed between the ecology of three- and four-limbed pouches.[23] Significantly greater numbers of bacteroides and concentrations of acetic, propionic, butyric, and valeric acid are seen in the effluent from three-limbed pouches than in the effluent from four-limbed pouches. The absolute numbers of bacteroides and bifidobacteria, the ratio of anaerobes to aerobes, and the concentrations of volatile fatty acids are also greater in the effluent from patients with pouches than in the effluent from patients who have undergone conventional panproctocolectomy with ileostomy. The flora of ileal reservoirs therefore more closely resembles that of the colon than normal ileum. There appears to be no correlation between the proportion of stool retained after defecation and the number of anaerobic bacteria.[56]

Volatile fatty acids may be beneficial to pouches. Within the colon they are the major substrate, and butyrate promotes sodium and hence water absorption.[57,58] Indeed, increased production of volatile fatty acids in experimental animals is associated with suppression of enteropathic bacteria.[59]

Functional Outcome

The choice of reservoir design is largely a question of personal preference and occasionally operative restraints. The decision is usually a compromise between the smaller-capacity, but easily constructed duplicated (J) pouch and the larger-capacity, but more time-consuming three-limbed or four-limbed pouches.[37]

Frequency of bowel action correlates inversely with the capacity of the reservoir.[38] The best results should therefore be obtained in patients with the largest reservoirs. However, huge reservoirs are associated with impaired contractility and poor evacuation, and several authors have noticed an improvement in bowel frequency with a decrease in size of the reservoir.[24,60]

Patients with a pouch pass about 600 to 700 ml of semiformed stool each day, which is about four times that of healthy controls with intact anorectums. Loperamide reduces intestinal motility and thus may improve intestinal absorption and reduce the volume of stool and the frequency of bowel action. Although dietary discretion and stool-bulking agents may decrease the urgency of defecation and perianal irritation by increasing stool consistency, these measures seem to have minimal effect on stool volume. Studies have shown little difference in the efficiency of evacuation of pouches according to the consistency of stool, which implies that measures to alter the consistency of stool will have no influence on pouch function.[61]

The frequency of bowel action has been shown to be significantly less in patients with three-limbed pouches than in those with two-limbed pouches[62,63] and significantly less in patients with four-limbed pouches than in those with either two- or three-limbed pouches.[30] However, the only prospective randomized trial that compared the functional results of duplicated (J) with quadruplicated (W) pouches failed to show any significant difference in the frequency of bowel action.[37] Compliance of the pouch is closely related to capacity: the larger the pouch, the greater the compliance. The correlation between frequency of bowel action and compliance of the reservoir is not, however, as strong as the correlation with capacity of the pouch. Larger reservoirs have lower contractility, which may lead to stasis and progressive dilation, particularly in the presence of a long efferent limb with its potential to impede evacuation.[21,50]

The perfect pouch has not been described. The choice of pouch design depends on the characteristics of the patient and the surgeon's preference. The functional outcome varies little between the basic options, and most patients will find that they will have bowel action between four and seven times per 24 hours with perhaps one nocturnal evacuation. They will experience a normal urge to defecate and will be able to defer defecation and to discriminate between flatus and feces.

THE ILEOANAL ANASTOMOSIS

The method used to construct the IPAA is debatable, and there are two options:

1. Transanal mucosal resection with a hand-sutured anastomosis between the pouch and the internal anal sphincter fashioned at the level of the dentate line[64]
2. Single- or double-stapled technique with construction of the IPAA at a slightly higher level[65]

An advantage of transanal mucosectomy is that all diseased mucosa is removed with no possibility of symptoms from residual diseased mucosa. The risk of cancer developing in the persistent rectal mucosa is eliminated. Resting anal pressure falls after IPAA, irrespective of the surgical technique used.[66] However, significant recovery of anal sphincter function, with a rise in resting anal pressure, return of the recto-anal inhibitory reflex, and improvement in clinical outcome, is seen to occur for at least 12 months after stapled IPAA.[67] Similar recovery may or may not occur after transanal mucosectomy.[64,68] Surgeons in favor of the double-stapled technique suggest that it is an easier operation with improved functional outcome. This latter point is debatable, however, because most reports of studies in which comparisons have been made between the two operative techniques have not been randomized and have included historical controls, which have invariably been taken from the learning curve of the surgeon's experience. The few randomized trials[69] and case-control studies[70] published to date, though small in numbers, show no functional differences.

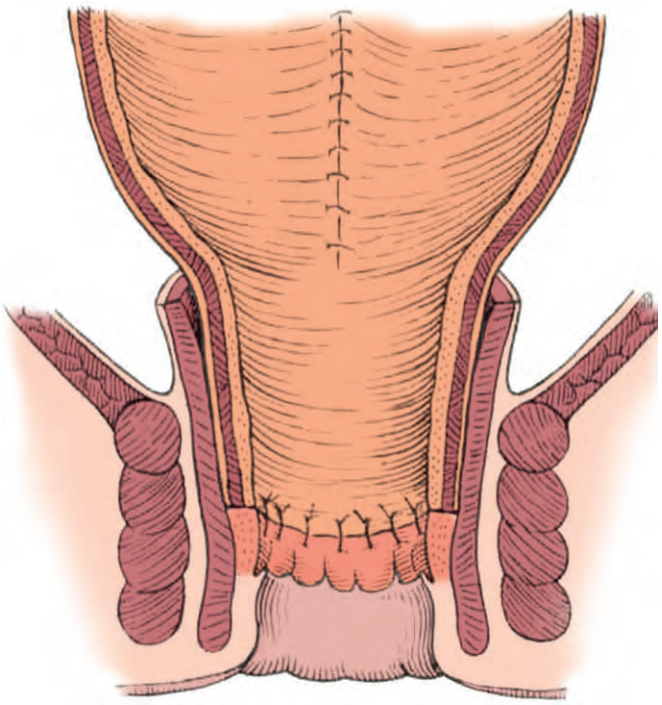


Figure 152–3. Ileal pouch–anal anastomosis with mucosal resection.

Transanal Mucosectomy

To preserve normal rectal sensation, it was long thought necessary to preserve a long muscular cuff of rectum. Preservation of a 10- to 12-cm rectal cuff denuded of its mucosa was very tedious and difficult, especially in the presence of severe disease, and it often required a combination of both abdominal and transanal dissection. Transanal mucosal resection required a long period of anal retraction, which was associated with significant functional impairment of the anal sphincter,[66] although this problem was minimized if the amount of anal retraction was reduced.[71] Extensive rectal mucosectomy was also associated with a high incidence of postoperative pelvic sepsis in the form of cuff abscesses despite meticulous hemostasis and drainage of the cuff space.[27] The realization that the sensation of rectal fullness and the need to evacuate were preserved in the absence of a rectum allowed the length of mucosal resection to be shortened significantly. Transanal mucosal resection is now carried out for a distance of only 3 to 4 cm and can be completed with minimal retraction on the anal sphincter, especially if a specifically designed ring retractor is used.

After the rectum has been fully mobilized to the pelvic floor, the surgeon moves to the perineum. With the patient in the modified Lloyd-Davies position, retraction hooks are placed circumferentially into the dentate line to splay the mucosa of the anal canal (Lone Star retractor, Lone Star Company, Texas). The submucosal plane is infiltrated with a solution of 1:100,000 epinephrine, and the mucosa is dissected off the underlying rectal wall with either scissors or diathermy. Dissection is continued to the level of the pelvic floor, at which point the muscularis is incised and the presacral space is entered. The rectum is fully divided at this level and the mucosectomy specimen retrieved through the anus. The pouch is then delivered into the pelvis and its apex brought down to the pelvic floor. An abdominal operator may insert four-quadrant sutures into the incised apex of the pouch, which are then passed in turn to the perineal operator to complete the IPAA (Fig. 152–3).

Single- or Double-Stapled Technique

This technique, in which either a purse-string suture is inserted into the anal stump or the anal stump is cross-stapled about 2 cm above the dentate line and a circular stapling device is inserted into the anal stump to perform the IPAA, has acquired wide popularity. The technical difficulties of transanal mucosal resection and hand-sutured IPAA are eliminated.

An early stimulus to the development of this procedure was the high incidence of nocturnal incontinence after mucosectomy and hand-sutured anastomosis. The anal transitional zone (ATZ) is richly innervated and seems to be important in the discrimination between flatus and feces.[72,73] Preservation of the ATZ improves anal sensation,[74] and several authors have demonstrated recovery of motor function of the anal sphincter.

The cecum, colon, and rectum are mobilized in the usual manner, with care taken to preserve the pelvic nerves. The rectum is mobilized fully to the pelvic floor

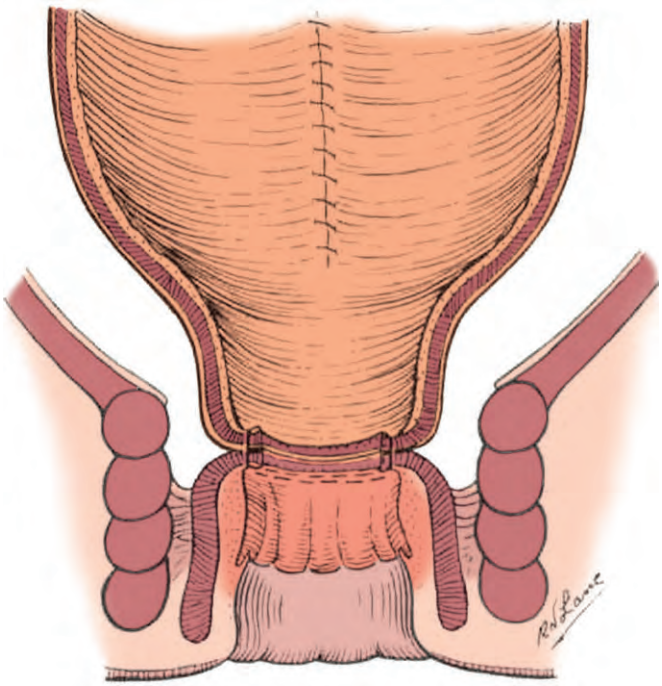


Figure 152–4. Double-stapled ileal pouch–anal anastomosis.

and a small (35-mm) linear cross-stapler is maneuvered into the lower portion of the pelvis. When the surgeon is confident that the stapler is in the correct position, which is confirmed by measuring the distance above the dentate line by insertion of a digit, the linear stapler is closed and fired. This leaves a stapled anal stump with the ATZ intact. A circular stapling device is then inserted into the anal stump and the central trocar advanced through the cross-staple line. The detached head of the gun, positioned within the ileal pouch, is manipulated into line with the shaft of the circular gun. The gun is closed and fired, and the double-stapled IPAA is complete (Fig. 152–4). Concern about the possibility of an anastomotic leak after stapling across a staple line (double-stapled technique) has led some surgeons to use a purse-string suture to close the anal stump around the shaft of the circular stapler (single-stapled technique).

The exact distance between the level of the ileoanal anastomosis and the dentate line may be critical in terms of functional outcome. A comparison of ileoanal anastomoses made at the dentate line, at the top of the anal columns of Morgagni, and at a level 1 cm above the columns showed the importance of this region in terms of fecal continence and fine control of defecation.[75] Construction of the ileoanal anastomosis at the dentate line was associated with a higher incidence of seepage and soilage than when the anastomosis was made at the top of the anal columns. If the anastomosis was made too far proximal, however, recurrence of disease was noted. It can be very difficult to accurately place the linear stapler, particularly if the patient is a thick-set male with a narrow pelvis. However, it remains surprising just how low the stapler can be placed, even in such large patients. Conversely, in a thin female with an accessible pelvis, the linear stapler may be positioned too low on the rectum such that the doughnuts of the stapling device may include part of the internal sphincter. To permit direct inspection of the upper border of the ATZ, the anorectum can be everted by fully mobilizing the rectum to the level of the upper anal canal. The rectum is then transected at midbody. Stay sutures are inserted into the lateral walls of the rectal stump and passed transanally to the perineal operator. Strong distal traction on the anorectum everts it through the anal canal and allows direct visualization of the ATZ and accurate placement of the cross-stapler. The residual rectal sleeve is then removed and the blind anal stump allowed back into the pelvis. The IPAA is then stapled into position in the usual manner.[76] This technique is more likely to result in a true IPAA than in an ileal pouch–rectostomy.

Despite full rectal mobilization, quite firm traction is required by the perineal operator to achieve complete eversion. Early reports of this technique suggested that the functional results of everted and noneverted ileoanal anastomoses were similar.[77] However, measurements of anal sphincter function have shown increased pudendal nerve latency times and blunted electrosensation after double-stapled IPAA with anorectal eversion.[78] This appears to result in some impairment in anal sensation and a greater tendency of patients to experience seepage than after conventional IPAA.

The Critical Level of the Ileal Pouch–Anal Anastomosis

The precise relationship between the level of the ileoanal anastomosis and the dentate line may be critical in terms of recurrence of disease and objective measurements of pouch and anal function. Preservation of the ATZ may be associated with a potential for the development of proctitis, dysplasia, and cancer. The upper border of the ATZ is irregular, with fingers of ATZ interdigitating with true rectal columnar mucosa. The rectal tongues may extend all the way down to the dentate line. Ulcerative colitis has been shown to be present within the transitional area in 90% of specimens resected by conventional proctocolectomy.[79] Mucosal columnar epithelial cells may remain within the ATZ in up to 20% of patients after mucosectomy.[80] However, mucosectomy does not guarantee elimination of the disease.[81] Indeed, the only reports to date of rectal cancer after restorative proctocolectomy have been in patients who had undergone mucosectomy with hand-sutured anastomoses and preservation of a rectal cuff.[82] Most patients with a stapled IPAA will have inflammation at the margin of the staple line.[83] The incidence of dysplasia in mucosal strippings from the anal stump was 2.5% in a series of 118 patients with ulcerative colitis.[84] A retrospective study of 254 patients who underwent restorative proctocolectomy for ulcerative colitis with a stapled IPAA revealed low-grade dysplasia in 8 patients (3.1%).[85] Neither high-grade dysplasia nor cancer was identified in the ATZ. However, biopsies of the ATZ taken 6 months later revealed dysplasia in two patients, in one of whom the

initial diagnosis was chronic ulcerative colitis with concurrent colon cancer (T3, N0, M0), whereas the other patient had CUC with concurrent high-grade dysplasia. Both subsequently underwent completion mucosal resection. Although the incidence of low-grade dysplasia in the ATZ is low after restorative proctocolectomy with stapled IPAA[85] and it remains to be determined whether low-grade dysplasia always progresses to high-grade dysplasia and cancer, it is probably wiser to perform total mucosectomy with a hand-sutured IPAA in patients with a preoperative diagnosis of concurrent colon carcinoma or dysplasia.

Resting anal pressure falls after restorative proctocolectomy irrespective of surgical technique. Factors other than simple traction on the sphincter have been implicated. Submucosal dissection may result in inadvertent dissection of the inner circular muscle fibers with consequent fibrosis.[86] Similarly, the submucosal neurologic plexus may be partially disrupted and the autonomic nervous supply to the anal sphincter may be injured. Extrinsic sympathetic nerves reach the anorectum from two sources: the presacral nerves, which form two nerve trunks and run along the lateral pelvic walls, and the inferior mesenteric nerves, which form a periarterial plexus around the inferior mesenteric and later the superior rectal arteries.[87] Although the presacral nerves can be easily identified at the pelvic brim and swept out of the operative field, their direct connections to the internal sphincter are at risk in the later stages of mobilization and division of the rectum. Division of the superior rectal artery and therefore the periarterial mesenteric nerves results in an immediate drop in resting anal pressure of about 20%.[88] Complete mobilization of the rectum and division at the anorectal junction also contribute to the fall in resting anal pressure. However, significant recovery in anal sphincter function, with a rise in resting anal pressure and improvement in clinical outcome, is seen to occur for at least 12 months after stapled restorative proctocolectomy.[67] Similar recovery has not been reported in patients after mucosectomy. Therefore, avoiding significant anal manipulation with the stapled technique provides better manometric results than transanal mucosectomy does.[89]

Any potential benefit in terms of functional outcome achieved by preservation of the ATZ must be balanced against the potential need for intervention if symptomatic inflammation or malignancy develops. The majority of patients who undergo restorative proctocolectomy are young adults. They are likely to require good anal sphincter function for many years, but conversely, any residual rectal mucosa will potentially have that long to undergo malignant degeneration. This may be dealt with by reoperation consisting of transanal dissection of the residual mucosa, disconnection of the IPAA, resection of any rectal cuff, and reanastomosis.[90]

Two Stage or One Stage: Use of a Diverting Ileostomy

Pelvic sepsis is the bête noire of IPAA. Postoperative leakage from either the pouch or the pouch-anal anastomosis leads to a high rate of eventual failure and excision of the pouch.[25,91] Concern about sepsis has meant that most surgeons use a temporary diverting ileostomy as a matter of routine to divert the intestinal contents away from the pouch and anastomosis until they have healed.

The temporary ileostomy is itself a potential source of morbidity.[92] Intestinal obstruction, before and after closure of the stoma, is more common in patients with a temporary ileostomy than in patients whose IPAA is completed as a one-stage procedure. Inevitably, the stoma is located more proximal than with a conventional ileostomy and is therefore more commonly associated with dehydration secondary to high stomal losses. The stoma may also be associated with peristomal skin breakdown, retraction, stenosis, and prolapse.

Several centers have presented the outcome of one-stage IPAA.[83,93-96] These studies suggest that a one-stage procedure is safe. Selection of patients is critical, however. An acutely unwell malnourished colitic patient taking high-dose steroids is not a candidate for a one-stage procedure. If a surgeon opts for a one-stage operation, even when all factors are favorable, a heavy burden is assumed. The surgeon must have a low threshold to reoperate if signs suggestive of pelvic peritonitis develop. Patients who undergo this one-stage procedure should (1) not be taking high-dose steroids, (2) undergo an uneventful operation, and (3) be in good general health. The postoperative course is more difficult for patients because they must adapt to the ileal reservoir at the same time as recovering from their operation.

A number of precautions can be taken to minimize the risk for complications after one-stage IPAA. The distal ileum should be irrigated with a solution of antibiotics before construction of the pouch. Likewise, the anorectum should be irrigated before division of the rectum, and a 24-French urinary catheter should be placed in the pouch and brought out through the anal canal to allow drainage of accumulated blood, mucus, and other secretions in the postoperative period.

There have been no randomized trials of sufficient power to adequately address the question of the advantages and disadvantages of one-stage versus two-stage IPAA.

Most centers perform the ileal pouch–anal anastomosis procedure with the use of a protective ileostomy, although reports continue to emerge of large series of patients operated on by one surgeon with relatively low complication rates.[97] It is, however, important to remember that reports of a single surgeon's experience may not always be extrapolated beyond that surgeon's practice. Most surgeons in institutions where randomized controlled trials are being carried out to compare the ileal pouch procedure with and without a diverting stoma continue to believe that they would rather deal with the complications associated with the ileostomy and its subsequent closure rather than deal with the potentially catastrophic complications of pelvic sepsis and failure of the pouch that may occur in patients without a diverting stoma.

MANAGEMENT OF POUCH-SPECIFIC POSTOPERATIVE COMPLICATIONS

Postoperative Hemorrhage

The linear stapling devices used to construct J pouches are not hemostatic. If marked bleeding is noted at the time of construction of the pouch, the pouch should be inverted and the bleeding points under-run. A large Foley catheter can be passed into the pouch for irrigation. Most bleeding will promptly stop. Sometimes the anal sphincter will retain blood in the pouch and obscure hemorrhage. Persistent bleeding warrants examination under anesthesia. Frequently, a single point of bleeding may be identified and controlled with diathermy coagulation or under-running with a suture, but more often bleeding of this extent is secondary to a disrupted suture line either in the pouch or at the ileoanal anastomosis. If the bleeding is uncontrollable by the transanal approach, laparotomy is indicated. Intra-abdominal bleeding that is not pouch related may be from one of three sites: the colonic bed, the lateral pelvic walls, particularly in the region of the lateral ligaments, and slipped ligatures from the mesenteric vessels.

If a defect in the ileoanal anastomosis is seen and no sepsis has occurred, the problem may be corrected by interrupted sutures. A significant hematoma developing within the walls of the pouch does not augur well and may be a prelude to a leak from the pouch. The patient should be treated with broad-spectrum antibiotics, careful observation, and laparotomy if indicated.

Small Bowel Obstruction

Small bowel obstruction is the most common complication seen after IPAA. Most large studies report a combined incidence of between 15% and 40% after IPAA and closure of ileostomy.[64] This rate is higher than that reported after construction of a Brooke ileostomy. A previous colectomy with avoidance of the use of a temporary ileostomy reduces but does not eliminate the problem.[25,95] Most episodes respond to conservative management such as intestinal rest, nasogastric suction, and intravenous fluids. Failure to respond necessitates laparotomy. Most cases are due to adhesions. If adhesiolysis is indicated, care must be taken to prevent damage to the pouch that may otherwise go unrecognized and lead to pelvic sepsis. If laparotomy is undertaken in the interval before closure of the ileostomy, reversal of the stoma is appropriate as long as contrast studies have demonstrated satisfactory healing of the pouch and ileoanal anastomosis. Occasionally, the afferent limb to the pouch may be identified as the site of obstruction either by becoming stuck in the pelvis and creating a flap valve or by herniating behind the pouch. Once mobilized, it is wise to tack the limb to the abdominal wall to prevent recurrence.

Intra-abdominal Abscess

An intra-abdominal abscess is usually the result of a defect in the pouch or a leak from the site of closure of the ileostomy. Patients have abdominal pain, diarrhea, localized or generalized peritonitis, and fever. A computed tomography (CT) scan will confirm the presence of an abscess. Pelvic sepsis develops in up to 25% of patients[98] and is likely to be secondary to pouch dehiscence or a defect in the ileoanal anastomosis. The risk for sepsis decreases as surgical experience increases.[25]

Intra-abdominal abscesses require drainage either percutaneously or surgically, together with broad-spectrum antibiotics. Immediate management of a pelvic abscess includes examination under anesthesia, catheterization of the pouch, and drainage of any collection of pus. Drainage of pus from above or even removal of the pouch may be required.

A pouchogram and examination under anesthesia will reveal whether a pelvic abscess is due to dehiscence of the ileoanal anastomosis or disruption of the pouch itself. A collection associated with dehiscence of the ileoanal anastomosis is best drained through the suture line because the incidence of pouch-vaginal fistula and fistula-in-ano is high if the collection is drained through the perineum or vaginal vault. A pelvic collection may discharge spontaneously through the IPAA with subsequent formation of a fistula or stricture. Fifty percent of patients with pelvic sepsis require laparotomy, and a secondary ileostomy may need to be created. Prompt treatment is essential if the pouch is to be saved. Pelvic sepsis results in a stiff, noncompliant reservoir. The ultimate functional result is likely to be poor, and these patients have a high rate (40%) of excision of the pouch.[91] In contrast, more than 90% of patients in whom no reoperation is required may expect a satisfactory outcome.[91]

Anastomotic Cuff Abscess

Sepsis in the space between the residual rectal muscle and the pouch, often accompanied by partial separation of the anastomosis, is associated with persistent anal pain, diarrhea, and fecal leakage.[99] The clinical findings can be subtle, so a high index of suspicion is essential. Predisposing factors are a difficult mucosectomy with troublesome hemostasis and a long rectal cuff. The incidence of cuff abscess has decreased with the use of shorter rectal cuffs.[99] A cuff abscess may be the result of an ascending infection from anastomotic disruption or a descending infection as a result of intraoperative contamination or a pelvic hematoma. A cuff abscess may drain through the IPAA and create a sinus or a fistula. A pouchogram with water-soluble contrast medium and examination under anesthesia should establish the diagnosis, and a CT scan will identify any associated collections in the pelvis. A sinus should be treated by curettage, whereas a fistula should be managed by fistulotomy, curettage of the fistula, insertion of a seton, or mucosal flap advancement.[25] The fecal stream should be diverted or reversal of the stoma delayed. Late manifestation of anastomotic sinuses or fistulas months or years after the original operation are often subsequently found to be associated with Crohn's disease.

Stricture at the Ileal Pouch–Anal Anastomosis

Stricture at the site of the IPAA has been reported in up to 38% of patients. It is persistent and severe in 16%.[100] Tension and ischemia are predisposing factors. Stricture is more likely to develop if there was dehiscence of the IPAA, with or without pelvic sepsis, or if a small-diameter (25 mm) stapling gun was used. If the pouch is placed under tension or if the sutures between the pouch and anus are placed haphazardly or break such that the anastomosis separates, the denuded anal sphincter is left exposed. Heavy scarring and a dense stricture result. A pouch that has been brought down under some tension is more likely to be associated with anastomotic stricture, probably because of ischemia or partial disruption of the anastomosis with healing by secondary intention and stenosis. Patients with an IPAA stricture usually have frequent watery stools and urgency of defecation associated with straining and a sensation of incomplete evacuation. The stricture generally responds to dilatation with a digit in the clinic or Hegar's dilators under a brief general anesthetic. A lumen that allows insertion of an index finger to the level of the distal interphalangeal joint is adequate.[28] Self-dilatation with a St. Marks' dilator is useful. In the absence of pelvic sepsis, the anastomotic stricture is usually web-like after a stapled IPAA but long and narrow after mucosectomy and a hand-sewn anastomosis.[100] Pelvic sepsis leads to longer strictures that are less likely to yield to simple dilatation. Refractory strictures are best treated by pouch advancement and a new ileoanal anastomosis.[101] The functional outcome of patients who have undergone successful treatment of their strictures is no different from that of other patients with pouches.[25]

A study of 1884 pouch-anal anastomoses constructed at the Mayo Clinic between 1981 and 1996 was carried out to identify and define different types of strictures and the factors that influence their occurrence.[102] Strictures developed in 213 patients, 86% of which were nonfibrotic and 14% were fibrotic. A greater number of strictures were seen in patients who had undergone a hand-sewn anastomosis than in those with a stapled anastomosis. Intraoperative technical difficulties were noted in 13% of patients, with anastomotic tension being the most commonly described problem. Postoperative complications such as abscess, fistula, and pouch retraction occurred in 13% of cases and were primary associated with fibrotic strictures. The time between construction of the IPAA and the appearance of nonfibrotic and fibrotic strictures was 9 and 6.2 months, respectively. Anal canal anastomotic dilatation was successful in 95% of the nonfibrotic strictures but in only 45% of the fibrotic strictures, and the average number of dilatations was 1.5 (range, 1 to 7). In the Mayo series, surgical procedures were necessary in 12% of all strictures (mainly fibrotic). The surgical procedures included (1) excision of the strictured segment with advance of a flap of ileal mucosa over the excised area; this technique was used for segmental and short strictures that appeared as a fibrous ring with the rest of the pouch remaining supple; (2) excision of the pouch and permanent ileostomy; almost all of these patients had other perianastomotic complications—abscess, fistula, pouch retraction; (3) disconnection with segmental excision of the fibrotic segment and reanastomosis of the pouch to the anus; and (4) repeated anal dilatation with drainage of abscess, division of an obstructing bridge, or débridement and curettage of a fistula.[102]

Symptomatic Proctitis or Dysplasia in Residual Rectal Mucosa

Symptomatic proctitis may develop after double-stapled IPAA, especially if an excessively long anorectal stump has been left in situ. Foci of high-grade dysplasia may also be seen in surveillance biopsies of retained ATZ.[90] Although proctitis may respond to topical or oral steroids, some patients prove resistant.

The troublesome mucosa is mobilized via a perineal approach with submucosal infiltration of a solution of 1:100,000 epinephrine. Mucosal resection is performed from the level of the dentate line to the level of the stapled IPAA. The anastomosis is then dissected radially and circumferentially mobilized to allow delivery of the pouch to the level of the anal verge. A new IPAA is made with interrupted sutures.[90] Although this technique may seem to be an attractive option, the mucosal resection and mobilization of the IPAA are actually quite difficult because of extensive fibrosis and adhesions between the pouch and the sphincter. The lack of mobility of the pouch may prevent the construction of a tension-free anastomosis. In practice, it may be necessary to perform transabdominal mobilization of the pouch or sacrifice the anal canal altogether and create a permanent ileostomy.

Enterocutaneous Fistulas

Enterocutaneous fistulas typically occur after unrecognized injury to the small bowel, often at the time of closure of the abdominal wound or after closure of the ileostomy. Usually, they can be managed conservatively with total parenteral nutrition as long as there is no distal obstruction. If the fistula arises from the pouch itself, a prolonged period of diversion of the intestinal stream, excision of the fistula, or closure of the defect in the pouch will generally be successful. Persistence of a fistula suggests unresolved sepsis or Crohn's disease.

Pouch-Vaginal Fistulas

Fistulas from the pouch to the vagina may be the result of sepsis and anastomotic dehiscence or may represent technical error. The use of stapling instruments places the posterior vaginal wall at risk. Fistulas may develop in patients with transmural inflammation, and deep ulceration of the pouch may occur in those with unsuspected Crohn's disease. Fistulas related to technical error occur early, whereas disease-related fistulas tend to occur late.

Investigation involves pouchoscopy and a vaginal speculum examination with the instillation of either methylene blue or 1% hydrogen peroxide solution.

Water-soluble contrast studies via the pouch or vagina may delineate the fistulous tract. Pouch biopsy and small bowel contrast studies are needed when Crohn's disease is suspected. Fecal diversion should be established. A small low fistula may be managed by means of mucosal flap advancement via a transanal or transvaginal approach if no significant sepsis is present. Large high tracts, especially if stapled, require reconstruction or abandonment of the IPAA.

A retrospective review of 60 females with pouch-vaginal fistulas managed at the Cleveland Clinic found that the average time to pouch-vaginal fistula formation after IPAA was 21 months (range, 1 to 132 months).[103] Postoperative pelvic sepsis had occurred in 17 patients (28%). The primary treatment modality was local repair (77%), the majority of which took the form of an ileal advancement flap, redo restorative proctocolectomy (10%), and excision of the pouch (8%). Initial healing was achieved in 20 of 52 evaluable patients, and an additional 11 patients had a successful outcome, albeit with repeat procedures. The overall healing rate was 52% at a mean 50 months' follow-up. A delayed diagnosis of Crohn's disease was eventually made in 24 patients, and the chance of success after an ileal advancement flap was significantly lower in patients with Crohn's disease than in those without Crohn's disease (25% versus 48%, respectively).

The reported experience in the Cleveland Clinic mirrors that of other major centers—about half the patients with a pouch-vaginal fistula will eventually achieve a successful outcome, with a quarter of the patients having persistence of a fistula but with the pouch in situ and a further quarter of patients undergoing long-term diversion or pouch excision. The majority of patients with pouch-vaginal fistulas can be managed by local methods, and several key technical points should be stressed. Adequate drainage of any septal sepsis must be achieved preoperatively—usually with draining setons with or without antibiotics. Careful and thorough hemostasis must be achieved. Any concurrent stricture should be débrided or excised, and the repair should be free of any tension.

A transvaginal approach to a pouch-vaginal fistula allows direct access to the internal opening and permits closure without damage to the anal sphincter[104] (Fig. 152–5). With the patient in the lithotomy position and the bladder catheterized, an inverted T-shaped incision is made along the midline longitudinal access of the posterior vaginal wall. With the horizontal limb located at the junction of the perineal skin and the posterior vaginal wall, the vagina is then dissected from the anal canal and ileal pouch, and two lateral flaps are created to expose the anterior wall of the pouch and the pouch-anal anastomosis. The internal opening of the fistula (pouch end) is then excised and the defect closed transversely with dissolvable sutures. The vaginal flaps are replaced and closed with dissolvable suture, and a vaginal pack is inserted to reduce the formation of hematoma by opposing the vaginal wall to the pouch and therefore reducing the dead space. Because the vagina has an excellent blood supply, creation of a full-thickness flap is technically straightforward. This technique avoids trauma to the anal sphincters and therefore reduces the risk for sphincter injury and subsequent fecal incontinence. Although there is no definite evidence that a diverting stoma reduces recurrence of a pouch-vaginal fistula, an argument can be made for its use in this situation first to give the patient some relief from symptoms and second to maximize the chance for success of the repair. This technique achieved success in 11 of 14 patients at St. Marks Hospital, London.[104]

Functional Results After Perineal Complications

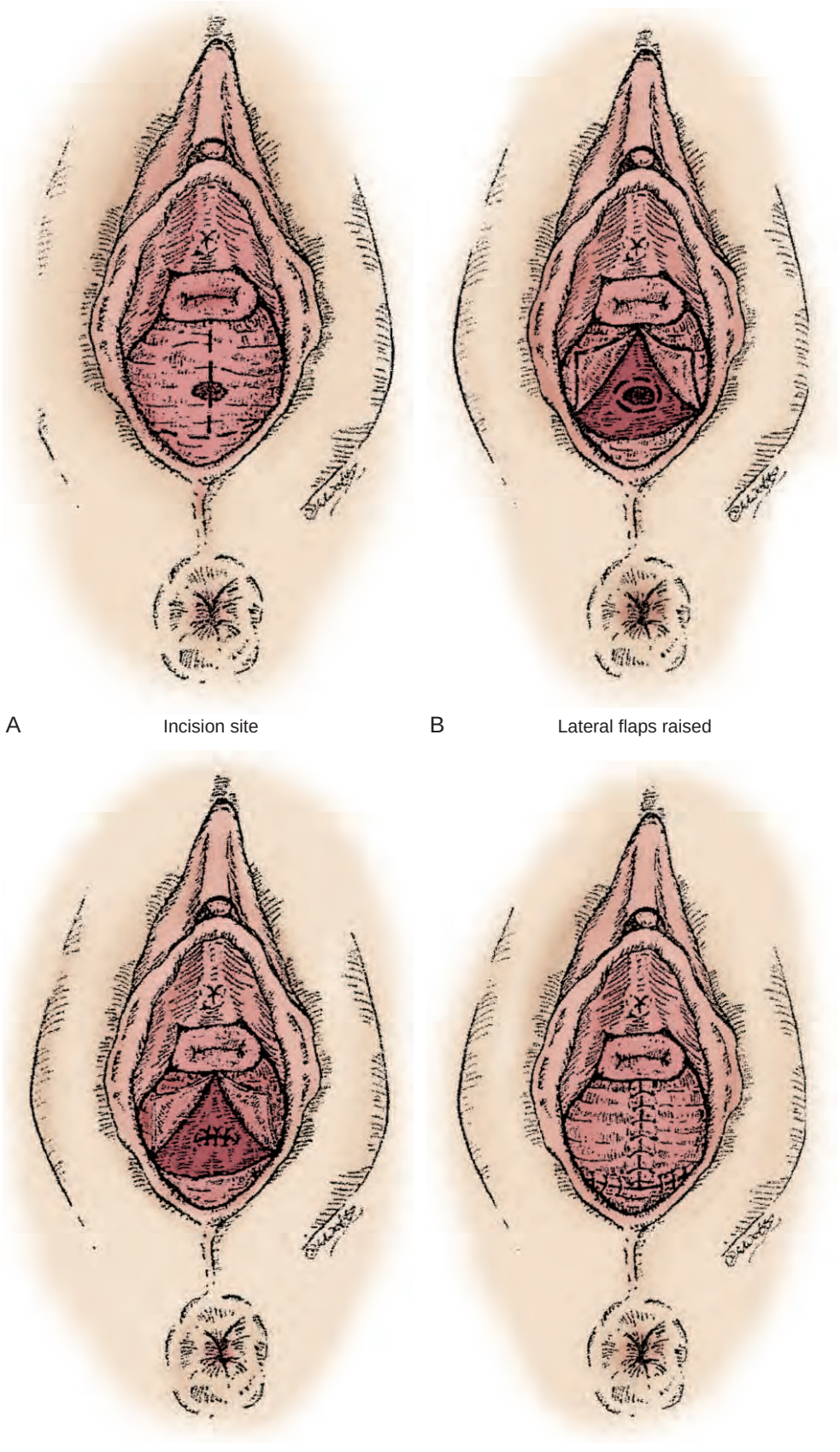
As noted earlier, there are a significant number of complications that involve the perineum after IPAA. Although the various complications can be minor, some lead to poor functional results or even loss of the pouch. A review of a registry of 628 patients from the Lahey Clinic identified 24.4% of patients in whom perineal complications had developed—anastomotic strictures, anastomotic separation, pouch fistulas, and pelvic sepsis. If the complications were addressed, the pouch failure rate was low (10%). Indeed, most of the pouch failures that occurred were the result of pouch fistulas, and in turn, most of these fistulas occurred in patients in whom the ultimate diagnosis was Crohn's disease. The functional result in patients in whom the perineal complications were successfully dealt with were no different from those of control patients in whom no such complications developed.[105]

Pouchitis

The pelvic ileal reservoir may become nonspecifically inflamed—pouchitis. The incidence of pouchitis varies from 11% to 34%, depending on the diagnostic criteria used,[106,107] and it increases with time after surgery. The cause is unknown.

Pouchitis is associated with episodes of increased frequency of bowel action along with the passage of loose, blood-stained stools usually accompanied by malaise, low-grade fever, and lower abdominal discomfort. Extraintestinal manifestations similar to those seen in colitis, such as erythema nodosum, uveitis, and arthritis, may occur at the same time as relapse of pouchitis.[108] The mucosa is inflamed and extensively ulcerated, produces a copious exudate, and bleeds on contact. Biopsies reveal a marked acute inflammatory infiltrate with villous atrophy and crypt abscesses. Neutrophils migrate from the circulation to an inflamed pouch. A positive indium-labeled granulocyte scan together with increased 4-day fecal indium granulocyte excretion may help identify patients with pouchitis and allow assessment of response to treatment.[109] A subgroup of patients are eventually found to have Crohn's disease or an indeterminate form of colitis.[100]

The use of these descriptive diagnostic criteria is open to misinterpretation. There has been a tendency to set the threshold for each of the three components too high such that only patients with severe pouchitis are included. Therefore, more objective quantification of pouchitis is neded. A Pouchitis Disease Activity Index (PDAI) has been developed that quantitates clinical



A Incision site

B Lateral flaps raised

C Lateral opening excised and closed

D Flaps replaced

Figure 152–5. **A** to **D,** Transvaginal repair of a pouch-vaginal fistula.

Table 152–1 Pouchitis Disease Activity Index

Criteria	Score
Clinical	
Stool frequency	
Usual postoperative BM	0
1-2 BM more than usual	1
3+ more than usual	2
Rectal bleeding	
None	0
Present daily	1
Fecal urgency or cramps	
None	0
Occasional	1
Usual	2
Fever	
Absent	0
Present	1
Endoscopic Inflammation	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucous exudate	1
Ulceration	1
Acute Histologic Inflammation	
Leukocyte infiltration	
Mild	1
Moderate with crypt abscess	2
Severe with crypt abscess	3
Ulceration per low-power field (mean)	
<25%	1
25%-50%	2
>50%	3

Pouchitis is defined as a total score greater than 7 points.
BM, bowel movement.
From Sandborn WJ, Tremaine WJ, Batts KP, et al: Pouchitis after ileal pouch–anal anastomosis: A Pouchitis Disease Activity Index. Mayo Clin Proc 69:409-415, 1994.

findings and the endoscopic and histologic features[110] (Table 152–1). It includes several clinical symptoms, not simply diarrhea, and expresses the endoscopic and histologic findings on a continuous scale rather than requiring minimum scores. Patients with pouchitis of mild or moderate severity can therefore be included in the diagnosis. The PDAI is significantly greater in patients with pouchitis than in patients without pouchitis, and it provides a simple, objective, and reproducible scoring system for pouchitis

Pathogenesis of Pouchitis

The causes of pouchitis are not well understood. Previous expectations that the knowledge of inflammatory bowel diseases in general would be expanded by means of studies of pouchitis have not been achieved. A number of etiologic factors involved in the development of pouchitis have been suggested, such as mucosal ischemia, immune deficiency, stasis of pouch contents, bacterial imbalance, or a recurrent form of ulcerative colitis or a variation of Crohn's disease. Certainly, the incidence of pouchitis is higher in patients with ulcerative colitis associated with primary sclerosing cholangitis and is very low in patients with familial adenomatous polyposis. Therefore, there may be a persistent predisposition to inflammation in patients with ulcerative colitis after IPAA, and this predisposition, with or without other factors, may result in pouchitis. Patients with extraintestinal manifestations of ulcerative colitis before IPAA had a 10-fold increased risk for the development of pouchitis (48% versus 4.6%, $P = .01$).[111] There is some evidence that dietary factors may play a role by modification of the ecology of the ileal pouch. A study that looked at interactions between nutritional factors, fecal and mucosal bacterial flora, and mucosal morphology in 21 patients with pouchitis versus 11 patients with healthy ileal pouches found no difference in mean nutrient intake, fecal bile acids, or microbial tissue biopsy cultures between the two groups, but there was a significantly higher concentration of anaerobes and aerobes in the feces of patients with pouchitis. Differences in the composition of the pouch microbial flora may be of key importance in the interaction with epithelial cells within the pouch mucosa and thus in the subsequent development of pouchitis.[112] Sulfate-reducing bacteria (a species of strict anaerobes) appear to exclusively colonize ileal pouches in patients with ulcerative colitis. There appears to be an increase in the ratio of strict to facultative anaerobes in ileal pouch patients with pouchitis as compared with those who have normal ileal pouches.[113]

Because pouchitis has been suggested to be a recurrence of ulcerative colitis in colonic-type mucosa, topical steroids have been used as a therapeutic alternative. A randomized trial of 26 patients randomized to receive either budesonide enema plus placebo tablets or oral metronidazole plus placebo enema found similar efficacy but improved tolerability of budesonide enemas in comparison to oral metronidazole.[114]

Anti–Tumor Necrosis Factor

Monoclonal antibodies have been successfully used in the treatment of fistulating perianal Crohn's disease. The efficacy of one such monoclonal antibody (infliximab) has been studied in the treatment of chronic refractory pouchitis complicated by perianal fistulas after IPAA. An open study of seven patients with pouchitis complicated by fistulas in whom Crohn's disease had been carefully excluded were treated with infliximab, 5 mg/kg at 0, 2, and 6 weeks. At 10-week follow-up, six of the seven patients had a complete clinical response.[115]

Severe Pouchitis

Severe refractory pouchitis is rare, and when it occurs, other causes such as infection with cytomegalovirus or *Clostridium difficile* needs to be considered. Pouchitis induced by cytomegalovirus requires treatment with

antiviral therapy such as ganciclovir. *C. difficile*–associated infection requires treatment with oral metronidazole or vancomycin.[116]

Morphologic Changes in Ileal Pouch Mucosa

A number of studies have demonstrated morphologic changes in the ileal pouch mucosa, including villous atrophy and crypt hyperplasia. The changes are classified as colonic metaplasia. It is not clear whether such changes represent long-term adaptation or response to inflammation. A study of 24 patients with no history of pouchitis, 31 patients with a history of pouchitis, and 8 patients in whom IPAA was carried out because of familial adenomatous polyposis found that the colonic metaplasia score was higher in patients with inflammation. The greater the colonic metaplasia score, the greater the inflammation score, and the authors concluded that colonic metaplasia is found primarily on a background of inflammation and therefore probably represents a reparative response.[117]

Treatment of Acute Pouchitis

Patients with pouchitis generally respond to metronidazole either orally or applied topically. The usual oral dose is 750 to 1500 mg/day for 7 to 14 days, and clinical improvement is generally prompt (within 3 days). A randomized, double-blind, placebo-controlled crossover trial in 13 patients has confirmed the long-held view of the efficacy of this form of treatment. The side effects of oral therapy are avoided by topical therapy, in which serum concentrations of metronidazole are very low. Patients who are unresponsive to metronidazole may respond to cyclic courses of three or four antibiotics given at weekly intervals, corticosteroids, ciprofloxacin, amoxicillin/clavulanic acid, erythromycin, tetracycline, allopurinol, Salazopyrin, or 5-aminosalicylic acid. Budesonide suppositories (1.5 mg/day) have also been shown to be efficacious. Frequent relapses of pouchitis require treatment with long-term, low-dose suppressive metronidazole therapy.

The fecal concentration of lactobacilli and bifidobacteria is significantly decreased in patients with pouchitis. A randomized, double-blind, placebo-controlled trial evaluated use of the probiotic VSL#3, which consists of eight bacterial strains, in the prevention of recurrence of pouchitis. In the treatment group, 17 of 20 patients were still in remission at 9 months, as compared with 0 of 20 patients treated with placebo. All patients who received VSL#3 relapsed within 4 months of concluding the treatment. The fecal concentrations of lactobacilli and bifidobacteria were significantly increased in the treatment group during the study but returned to baseline 1 month after completion of the study.[118] It remains unclear whether multiple bacterial strains are required to induce remission.

Other Complications

Polyps may develop within a pouch as in the rest of the small bowel. Inflammatory polyps may occur in up to 20% of patients with ulcerative colitis.[119] Inflammatory fibroid polyps, though rare, may cause bleeding or obstruction. Such polyps may occasionally grow sufficiently to fill the lumen of the pouch and require resection[120] with conversion to a permanent ileostomy.

There have been occasional reports of alopecia after IPAA. Indeed, one series reported a somewhat surprising incidence of 38% (in a series of 24 patients).[121] Fortunately, it is a temporary phenomenon, but female patients in particular should be warned. Treatment, if it occurs, is reassurance.

Lateral popliteal nerve palsy has been reported and is related to compression damage from pressure exerted by the leg supports after particularly long procedures. Anterior compartment syndrome of the lower limbs has similarly been reported after lengthy operations and may result in myonecrosis and footdrop unless fasciotomy is carried out. Careful positioning and adequate padding should eliminate these complications.

Risk for Neoplasia

There are suggestions that the mucosa of ileal pouches may be at risk for the development of neoplasia. If true, the likelihood is that the incidence of such events is very low. In a series of 160 patients undergoing routine pouch surveillance with multiple biopsies and a mean length of follow-up of 8.4 years, only one patient was found to have low-grade dysplasia, but even this was not confirmed on further routine follow-up. The incidence of cancer after IPAA is very low, with only 19 reported cases of adenocarcinoma of the pouch or anal canal after this operation in the literature.[122] The majority of these cases have occurred either in the rectal stump or around the anastomosis, and in all but two cases the original pathologic specimen demonstrated either dysplasia or cancer.

The widespread adoption of the use of stapled IPAA with preservation of the ATZ has raised questions about the need for long-term surveillance. The Cleveland Clinic group carried out a prospective evaluation with a minimum 10-year follow-up on 289 patients who were studied by serial ATZ biopsy. ATZ dysplasia developed in only eight patients between 4 and 123 (median, 9) months after surgery. The dysplasia was high grade in two patients and low grade in six patients. No cancers developed in the ATZ during the study period. This group recommended that in patients in whom there had been no dysplasia in the original proctocolectomy specimen and no other risk factors such as primary sclerosing cholangitis or a strong family history of colorectal cancer, a biopsy specimen should be taken from the ATZ at 1 year and then every 2 to 3 years thereafter. In patients in whom there was dysplasia in the original proctocolectomy specimen but no involvement of the lower two thirds of the rectum, biopsy of the ATZ should be performed every year. In patients in whom there was either a carcinoma complicating ulcerative colitis or dysplasia in the lower two thirds of the rectum at the time of proctocolectomy, a stapled IPAA was not performed but rather transanal mucosectomy and a hand-sewn anastomosis. Even within this group the option of a stapled IPAA would be offered to obese or elderly patients or

those with low sphincter pressure, in whom mucosectomy and a hand-sewn anastomosis might not be easily feasible because of reach or concerns about poor pouch function. In patients in whom low-grade dysplasia is found on biopsy, repeat biopsy should be performed every 6 months for up to 3 years. If no further dysplasia is detected, annual biopsies would be required thereafter, but if persistent low-grade or, indeed, high-grade dysplasia is found on three consecutive samples, the patient should undergo mucosectomy and pouch advancement.[123]

Male Sexual Function

Most patients who undergo the IPAA procedure are young, sexually active, and concerned about their sexual function after pelvic surgery. Pelvic surgery may cause male sexual problems such as erectile dysfunction, absence of ejaculation, or retrograde ejaculation. Only a small percentage (2% to 4%) of male patients have severe sexual problems after surgery.[124,125] Sexual function of males has been examined in a systematic manner by means of a validated scoring system, the International Index of Erectile Function (IIEF). The IIEF was used to study 122 males who underwent IPAA between 1995 and 2000, with comparison of results before and after IPAA. There was a statistically significant improvement in erectile function, sexual desire, intercourse satisfaction, and overall satisfaction, with patients having improved scores after surgery versus before surgery. The mean erectile function score was higher after surgery than before surgery. Overall psychometric sexual satisfaction and sexual quality of life were increased, most likely because of enhanced general health. This study would suggest that male patients undergoing IPAA may be counseled that their sexual function is likely to be retained after surgery.[126]

Female Reproductive Health

IPAA does not seem to affect menstrual function or gynecologic symptoms. Overall sexual satisfaction may be improved with surgery, although the ability to experience orgasm and the frequency of coitus are unchanged. There is an increase in dyspareunia after IPAA, and fertility is adversely affected, most likely because of pelvic adhesions. During pregnancy there is a transient increase in the frequency of stools both by day and by night. Nocturnal incontinence increases, but this resolves after delivery. The ideal route of delivery has yet to be determined, but vaginal delivery is safe and does not appear to directly influence pouch function.[127]

Ileal Pouch–Anal Anastomosis and the Menstrual Cycle The majority of women report no change in their menstrual cycle after IPAA. Any noted change in menses or related symptoms seem to be infrequent. A study of 46 women who had undergone IPAA with a follow-up of 28 months showed no change in menses in 68%, increased regularity in 26%, and dysmenorrhea in 15%.[128] A similar study of 21 women a mean of 38 months after IPAA noted dysmenorrhea in 10%; no patients identified changes in their cycle.[129]

Ileal Pouch–Anal Anastomosis and Female Sexual Function Although most women report no change in overall sexual satisfaction, 16% to 50% reported an increase in satisfaction after IPAA.[130] Nine percent to 26% of women reported decreased overall satisfaction. IPAA does not seem to affect the ability to experience orgasm, with a similar frequency of orgasm before and after surgery (range, 67% to 86%).[128-130] An increase in the ability to attain orgasm was noted in 9% to 18% of patients, whereas 0% to 15% of patients reported decreased ability. Although the frequency of coitus remains unchanged or is increased after IPAA, 3% to 18% of women fear leakage of stool at the time of sexual intercourse. This concern is alleviated by emptying the pouch before intercourse. Preexistent dyspareunia may be exacerbated by surgery. In studies that included preoperative baseline data, the incidence of dyspareunia rose from 5% to 10% to as high as 15% to 22% after surgery.[124,131] This may be due to alterations in pelvic anatomy or the formation of adhesions after IPAA.

Ileal Pouch–Anal Anastomosis and Fertility A number of studies (mostly characterized by small number of subjects attempting conception after surgery) suggest reduced fertility in women after IPAA. Two large studies that were methodologically sound have shown decreased postoperative fertility. A postal questionnaire of 300 women of reproductive age who underwent IPAA between 1983 and 2001 found that before IPAA, 48 (38%) of 127 patients were unsuccessful in their attempt to conceive after 1 year of unprotected intercourse whereas after IPAA, 76 (56%) of 135 patients were unsuccessful. The infertility rate was higher after surgery than before ($P < .001$). In a subgroup of 56 women who tried to get pregnant both before and after surgery, the infertility rate was higher after surgery than before (69% versus 46%, $P = .005$). The use of an intraoperative blood transfusion was associated with a higher rate of infertility than in patients who did not have an intraoperative blood transfusion (54% versus 21%, $P = .023$).[132] A Scandinavian study of 237 women compared the rate of preoperative fertility from the age of 15 until colectomy and the rate of postoperative fertility from 12 months after closure of ileostomy until data collection or menopause. There was a mild decrease in observed preoperative births (87% of expected, $P < .05$), whereas the incidence of postoperative births was only 35% of expected after IPAA ($P < .001$) Successful in vitro fertilization was excluded from the study.[133] This decrease in postoperative fertility has been attributed to probable tubal occlusion from adhesions, although the possibility that physicians and surgeons have recommended against conception after IPAA and the possibility of patient concerns about having children affected with ulcerative colitis may well play a role.

Mode of Delivery After Ileal Pouch–Anal Anastomosis In theory, a vaginal delivery may increase the risk for pudendal nerve damage, injury to the anal sphincter complex, and loss of fecal continence in patients after

IPAA as compared with cesarean section before the onset of labor. However, a postal questionnaire study that addressed this issue in 29 subjects who had undergone 49 deliveries found that there were 25 vaginal deliveries and 24 cesarean sections. A third of the subjects had disturbances in pouch function during pregnancy, almost exclusively during the third trimester, with an increase in stool frequency by day and by night and transient loss of nighttime control. There was no correlation between the mode of delivery and pouch complications or functional impairment. In particular, vaginal delivery was not shown to adversely affect pouch or anal function. Vaginal delivery after IPAA would appear to be safe, and the method of delivery should be dictated by obstetric or specific local perineal conditions.[134]

Age-Related Surgical Results and Functional Outcome

Although no age cutoff for patients undergoing IPAA has been defined, many surgeons would anecdotally suggest an upper age limit of 60 or 65 years. There is little evidence to support such a recommendation, and the relative infrequency of IPAA in older patients has made it difficult to assess outcomes of surgery according to age. The Cleveland Clinic carried out a prospective evaluation of the functional outcome and quality of life in 1895 patients who had undergone IPAA, with stratification of patients by age at the time of surgery into younger than 45 years, between 46 and 55 years, between 56 and 65 years, and older than 65 years. Functional outcome and quality of life were assessed at 1, 3, 5, and 10 years of follow up. The study reported incontinence and nighttime seepage to be more common in older patients, and there were minor differences in quality of life, health, energy, and happiness, with a slight benefit for those younger than 45 years. There were no differences in the level of happiness with surgery at 1, 3, 5, or 10 years of follow-up. At all times in the study, at least 95% of patients in each group would undergo their surgery again and would recommend IPAA to someone else with the same diagnosis.[135]

The effect of the aging process itself on functional outcome and the quality of life of patients with an ileal pouch was studied by the Mayo Clinic group, with the functional and quality-of-life outcomes of 409 patients being assessed at 5, 10, and 15 years. Over this time frame there was little change in daytime stool frequency, whereas nighttime frequency increased from one stool to two stools per night. Incontinence to gas and stool increased from 1% to 10% during the day and from 2% to 24% at night over the 15-year period. After 15 years, more than 90% of patients were in the same job, and social activities, recreational sports, long-distance travel, and sexual activity all improved after surgery and did not show deterioration over time.[136]

Revision Pouch Surgery

In a small subset of patients the long-term functional result is poor. Although in many of these cases the problem may be related to recurrent episodes of pouchitis or postoperative pelvic sepsis, some patients may benefit from surgical intervention.

Patients who are being evaluated for pouch dysfunction months or years after the original operation should undergo a series of investigations, including inspection and palpation of the anastomosis, stool culture, pouchoscopy and multiple biopsies, water-soluble contrast enema, manometry of the anal sphincter and pouch, and a small bowel contrast study if Crohn's disease is suspected. Mechanical causes of dysfunction may be identified, such as an excessively long efferent spout, a small pouch, a long mobile blind limb capable of obstructing outflow from the pouch, twisted pouches, or intussusception of bowel proximal to the pouch within the pouch. Problems specific to the IPAA included partial separation, residual disease after a double-stapled anastomosis, and a long stenosis.

Surgical Technique

With the patient in the synchronous (combined) position, the abdomen is opened through the previous laparotomy incision. Adhesiolysis is performed and the ileal pouch identified and dissected out with a combination of electrocautery and sharp dissection. In most cases, mobilization of the pouch can be achieved without major difficulty and without entering the lumen. Once the IPAA has been identified from above, attention is turned to the perineal dissection. Again, a combination of electrocautery and scissors dissection is used to dissect out the IPAA. Further transanal mucosectomy is performed if residual mucosa is identified. Great care is taken to identify and preserve the sphincter musculature. The IPAA is then disconnected and the pouch delivered out of the abdomen. The pouch is revised according to the nature of the problem, which may involve excision of a long efferent spout with or without sacrifice of the original pouch, excision of the original pouch with construction of a new pouch, excision of a long blind end, rotation of the pouch on its longitudinal axis, and excision of fistulous tracts with repair of the pouch. The new pouch is then anastomosed to the anal canal with four anchoring sutures placed into the walls of the pouch and the levator muscles and then a series of interrupted absorbable sutures placed between the pouch and the anal mucosa. The procedure should be covered with a diverting ileostomy in all cases. Intestinal continuity is restored 2 to 3 months later after a water-soluble contrast study has demonstrated satisfactory healing.

A series of 23 patients in whom disconnection, pouch revision, and reanastomosis were carried out has been reported.[137] Functional problems included impaired evacuation ($n = 15$), excessive frequency ($n = 4$), and fistulas ($n = 4$). At surgery, the functional problems were found to be due to a long efferent spout ($n = 9$), a redundant or perforated blind limb ($n = 6$), a twisted pouch ($n = 3$), or other causes ($n = 5$). The pouch was salvaged in 14 patients and a new pouch was constructed in 9. The pouch-anal anastomosis was resutured in 22 patients and stapled in 1. Postoperative complications (all minor) occurred in 5 of 23 patients. Two patients underwent

Table 152–2 Disconnection, Pouch Revision, and Redo Ileal Pouch–Anal Anastomosis

Author	*N*	Problem	Outcome
Liljeqvist[138]	7	Long spout	Good function in 5 patients, 2 failures
Pogglioli[139]	6	Twisted pouch (1) Afferent limb stricture (1) Pouch-urethral fistula (1) Pelvic sepsis (1) Ischemic pouch (1) Outflow obstruction (1)	Good function in 4 patients, pouch excised in 1, and stoma not closed in 1
Nicholls[30]	6	Long spout	Good function in 4 patients, 2 self-catheterize
Fazio[90]	2	Residual disease, dysplasia	Good function in both patients
Sagar[137]	23	Long spout (9) Sepsis (4) Blind limb (3) Twisted pouch (3) Revision of IPAA (3) No pouch (1)	Success in 17 patients
Herbst[140]	16	Pouch outlet obstruction	Improved function in 12 patients
Fonkalsrud[141]	58	Elongated IPAA spout	Improved function in 93%
Baixauli[142]	100	Chronic leak (27) PV fistula (47) Stricture (22) Long spout (36) Previous pouch excision (6)	5-year survival rate of pouch = 74%
MacLean[143]	57	PV fistula (21) Pelvic sepsis (14) Long spout (14) Stricture (5) Perineal fistula (2) Pouchitis (1)	Success in 89%

IPPA, ileal pouch–anal anastomosis; PV, pouch-vaginal.

revision IPAA twice. At a median follow-up of 5 years (range, 1 to 10), 11 patients reported good to excellent function, 5 patients reported fair function, and 1 patient reported recurrent pouchitis. Revision surgery was unsuccessful in 6 of 23 patients (gross incontinence in 3, excessive bowel movements in 2, Crohn's disease in 1), and they subsequently underwent pouch excision. Table 152–2 shows the results of studies of redo IPAA.[30,90,137-143]

A series of 63 reconstructive procedures were performed in 57 patients. The primary indication for reconstruction was a pouch-vaginal fistula in 21 patients, a long outlet in 14, pelvic sepsis in 14, IPAA stricture in 5, pouch-perineal fistula in 2, and chronic pouchitis in 1 patient.[143] All patients received a covering loop ileostomy. Forty-two patients (73.7%) have a functioning pouch, whereas 7 (12.3%) have had their pouch excised and an ileostomy has not been closed in the other 8 (14.0%) patients. The functional results in the patients with a pouch in use were categorized as good, and this group of patients rated their physical and psychological health as good to excellent.

Good results can be obtained by experienced surgeons after abdominoperineal reconstruction for a failed IPAA. Selection of patients is important. The original pathology and current pouch biopsies should be reviewed by an experienced gastrointestinal pathologist and every effort made to rule out Crohn's disease. Active sepsis must be controlled, and on occasion it may be necessary for the pouch to be made nonfunctional for a period before reconstructive surgery is attempted. A major commitment is required by both the patient and surgeon, but the effort is worthwhile when satisfactory function and quality of life are obtained.

Alternative Techniques for Pouch Salvage

A technique to treat and salvage an ileal pouch affected by chronic fistulating disease on a background of ulcerative colitis has been described and involves an abdominoperineal approach with transabdominal mobilization of the pouch to the level of the anastomosis and then perineal dissection to disconnect the anastomosis transanally (Fig. 152–6). The pouch is delivered out of the abdomen and the pouch fistulous connections are excised. This part of the pouch is then closed and the pouch inverted through the cone formed by the J pouch

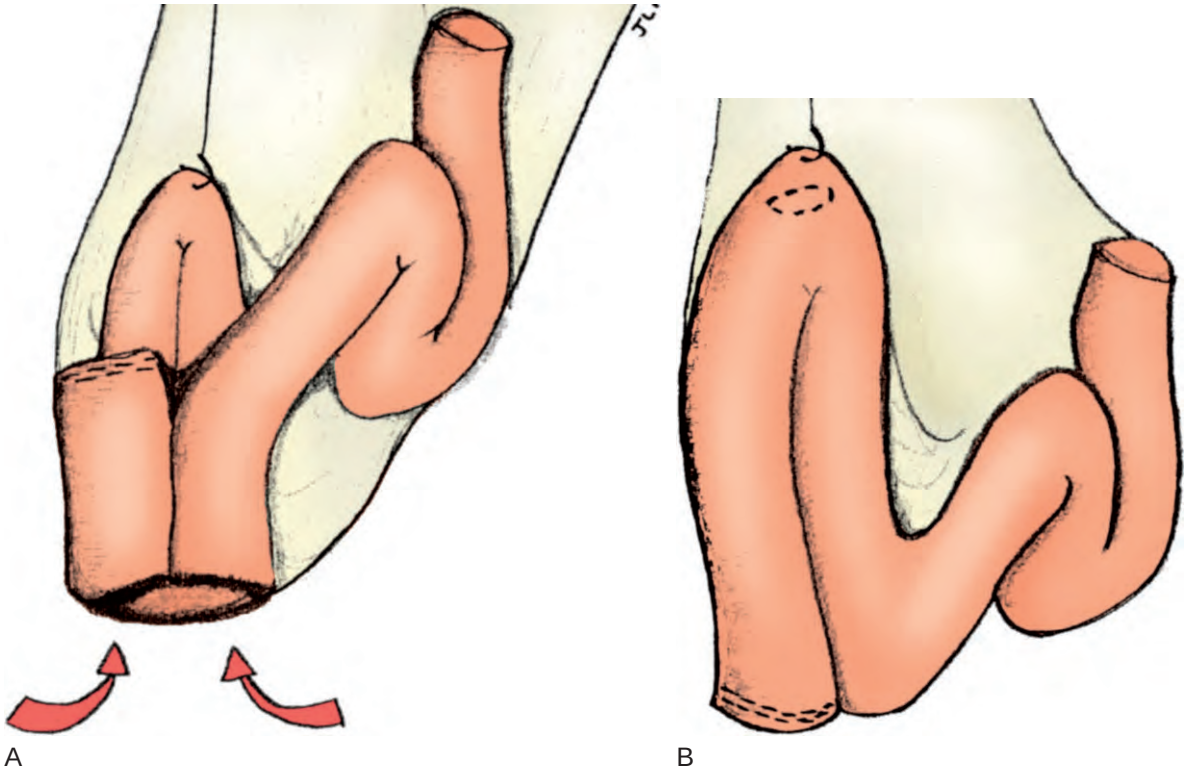


Figure 152–6. **A** and **B,** Inversion, 180-degree forward rotation, and then 180-degree axial rotation.

anteriorly and the mesentery posteriorly. The formerly hidden part of the pouch then becomes the apparent one and vice versa. A 180-degree forward rotation with 180-degree axial rotation permits enough length to bring a new healthy part of the same pouch to the anus. The pouch-anal anastomosis is constructed after any granulation and fibrotic tissue has been fully curetted and a mucosectomy has been performed to remove any residual mucosa distal to the previous anastomotic site. The anastomosis and pouch are protected with a temporary diverting ileostomy. This is a useful technique to perform before admitting defeat and excising the pouch so that the patient is left with a permanent ileostomy, although difficulties may result if there is insufficient mesenteric length remaining after pouch inversion and double rotation. Usually, however, the mesentery has elongated several months after the original IPAA has been formed, so length is not generally a problem. The technique permits excision of all inflamed tissue related to the fistulating disease, it permits diagnosis and closure of all fistula tracts, the anastomosis is constructed with a new healthy part of the pouch, and the inflamed bowel specimen excised from the pouch can be examined histologically and Crohn's disease excluded.[144]

A short small bowel mesentery can create difficulty with reach of the pouch to the pelvic floor at the time of the original IPAA. Indeed, this may account for a number of postoperative problems and pouch dysfunction. If such patients come to revision or redo surgery, it may prove technically impossible for the new pouch to reach down to the pelvic floor if the original pouch has had to be sacrificed because of sepsis or other problems. A technique to overcome this problem has been described in which a new 18-cm J pouch is formed with a jejunal segment (Fig. 152–7). Selective division of axial vessels allows adequate length to form a jejunal pouch anal anastomosis, and the small bowel distal to the pouch is then interposed between the proximal jejunum and the J pouch. This technique of jejunal J-pouch formation and small bowel interposition offers a useful alternative to definitive ileostomy or Kock pouch in patients undergoing salvage surgery after failed IPAA.[145]

Quantification of the Risk for Pouch Failure

Although IPAA is an effective and safe surgical option for patients with ulcerative colitis and is associated with low perioperative mortality and acceptable functional results, there are marked variations in the characteristics of patients in whom the pouch procedure is ultimately shown to fail. For instance, a study from Birmingham, England, reported a failure rate of 12.7% as a result of pouch ischemia (19.3%), pelvic sepsis or fistula (35.5%), Crohn's disease (12.9%), anastomotic stricture (16.1%), or pouchitis (16.1%),[146] whereas a series from Rochester, Minnesota, reported a failure rate of only 3.8% with the principal causes being anastomotic stricture (19%), pelvic sepsis or fistula (73%), and poor function (8%).[25] These and similar discrepancies together with the move

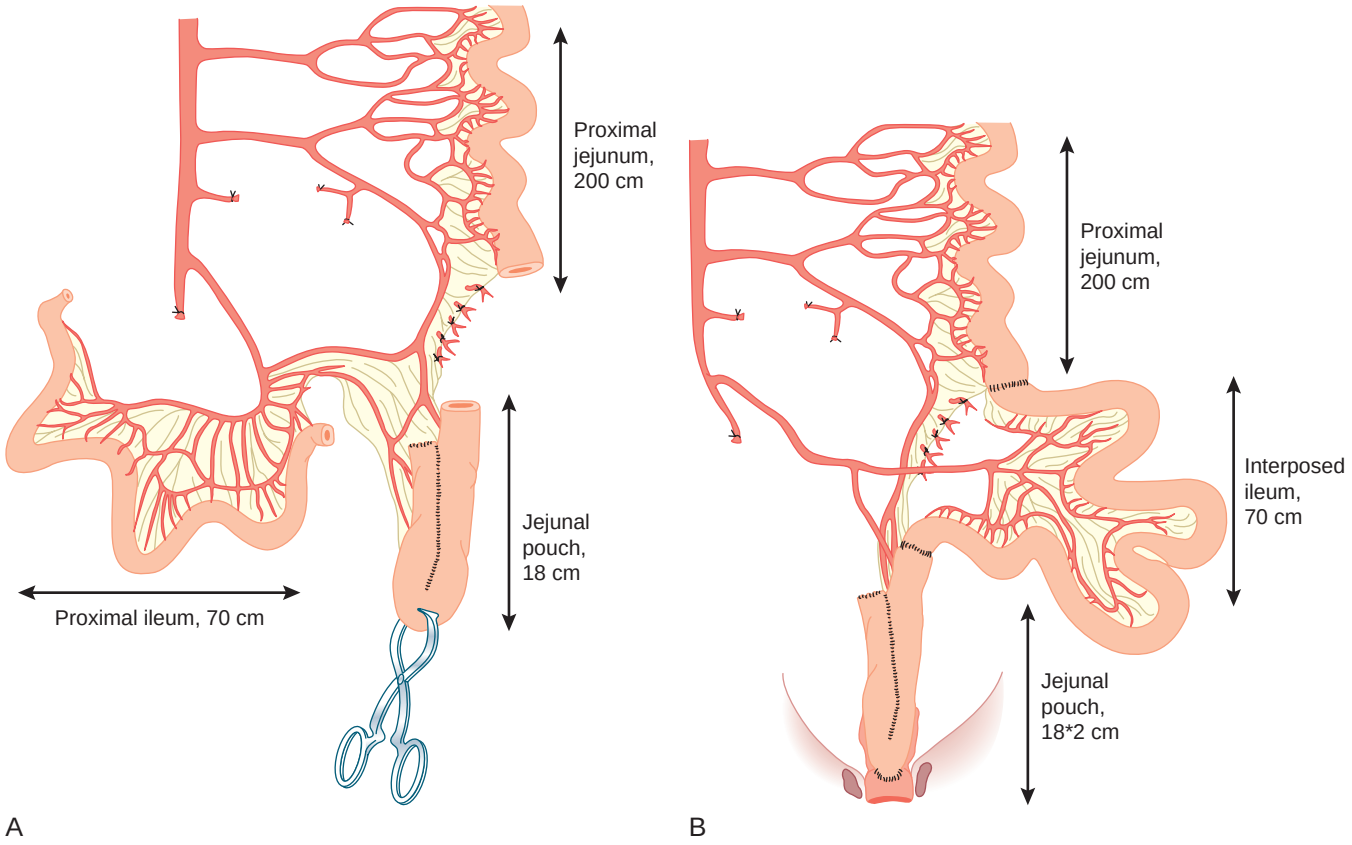


Figure 152–7. Salvage ileal pouch–anal anastomosis with a jejunal pouch and ileal interposition.

into an era of public and professional accountability for clinical outcomes have led to a need for predictive indices to allow quantification of operative risk after IPAA that is based on the comorbid condition of the patient and the complexity of the procedure. The Cleveland Clinic Foundation (CCF) ileal pouch failure model is one such index.[147] Data on 23 preoperative, 7 intraoperative, and 10 postoperative risk factors were recorded from 1965 patients between 1983 and 2001. With ileal pouch failure as the primary end point, the CCF ileal pouch failure model was developed by means of parametric survival analysis and a 70%-30% split-sample validation technique for model training and testing. This split-sample validation procedure was repeated 10,000 times to calculate standard errors and correct bias. Independent predictors of pouch survival were patient diagnosis, previous anal pathology, abnormal anal manometry, comorbidity, pouch-vaginal or pouch-perineal fistula, pelvic sepsis, anastomotic stricture, and anastomotic separation. The CCF ileal pouch failure model is to be commended because it was based on extensive preoperative, intraoperative, and postoperative data with good follow-up (median 4.1 years). It is a simple additive scoring system with eight risk factors used to calculate the risk for pouch failure at a particular time interval after IPAA. It can be readily applied to surgical practice.

Crohn's Disease

A recently completed meta-analysis of more than 8500 patients who have undergone IPAA over the last 20 years in 20 major centers around the United States suggested an overall failure rate of 6%. If only reports from the last 5 years are considered, however, the failure rate appears to have fallen to around 2%, probably as a result of selection of patients, more experience and better surgical techniques, and improved postoperative care. Today, the main contributor to failure appears to be Crohn's disease or suspected Crohn's disease–related complications. Crohn's disease is an independent predictor of pouch failure.

Patients with Crohn's disease have generally been excluded as candidates for IPAA. Clinical and histopathologic distinction between ulcerative colitis and Crohn's disease can be difficult. The pouch failure rate in patients in whom IPAA has been carried out inadvertently and Crohn's disease proved to be the ultimate diagnosis is about 50%.

Somewhat controversially, a number of authors have suggested that IPAA can indeed be used in selected patients with colorectal Crohn's disease in whom proctocolectomy with permanent end ileostomy would be the only alternative. Rather than compare the results of IPAA in patients with Crohn's disease against IPAA for other

conditions such as ulcerative colitis and familial adenomatous polyposis, perhaps we should consider IPAA in Crohn's disease just as a restorative operation in its own right. A French group reported the results of IPAA in 41 patients with Crohn's disease limited to the large bowel, that is, with no past or present history of small bowel involvement or anal manifestations. At a median follow-up of about 2 years, 27% of patients had experienced Crohn's disease–related complications—seven with pouch-perineal fistulas treated surgically, two with extrasphincteric abscesses, and two with persistent anal ulceration with pouchitis and granulomas on pouch biopsy.[148] In a subset of 20 patients with follow-up greater than 10 years, 35% had experienced Crohn's disease–related complications and in 2 patients the pouch was eventually excised. The authors concluded that such good long-term results justified the results of IPAA in selected patients.

The disparity in outcome between previous studies of patients undergoing inadvertent IPAA for Crohn's disease and the French group raised the question of whether the latter study population had suffered from indeterminate or even ulcerative colitis rather than Crohn's disease. There were questions over the exact pathologic criteria used. It is well recognized that patients with indeterminate colitis, although it has a lower success rate than ulcerative colitis does, do much better than those suffering from Crohn's disease. The situation may of course change with the advent of the era of monoclonal antibodies raised against tumor necrosis factor-α. The selection of future patients for IPAA may well change as we gain longer patient follow-up and are able to correlate clinical, endoscopic, and histologic features with outcome. Ultimately, it is for the patient to decide with appropriate and thorough counseling from the surgeon and physician.[148]

ALTERNATIVES TO ILEAL POUCH–ANAL ANASTOMOSIS

Panproctocolectomy with Ileostomy

This procedure removes all diseased tissue and thus "cures" the disease. Gastrointestinal output is effectively managed by an ileostomy appliance. All patients are suitable candidates for the operation irrespective of age, size, and body shape. However, the fatter the patient, the more difficult it is to construct a stoma and the more likely the patient is to run into problems with the stoma. Rectal mobilization is carried out close to the rectum, the sympathetic nerves are protected at the sacral promontory, and the hypogastric plexus is protected in the pelvis. The perineal phase completes the dissection, and the intersphincteric plane is used to afford protection to the external anal sphincter and the puborectalis and levator muscles. Bladder paralysis and sexual dysfunction occur rarely with this approach.[149] The perineal wound is small and can be closed relatively easily.

The downside of the operation is obvious. Patients are incontinent of gas and stool and must always wear an appliance. Some patients consider life with a stoma to be worse than the disease itself. The quality of life of patients with ileostomies seems to have improved little since the original description of Brooke ileostomy in 1952.[150]

Colectomy with Ileorectal Anastomosis

Ileorectostomy removes most of the diseased colon but leaves the diseased rectum in situ. The operation avoids the need for a stoma and reduces the risk of damage to the pelvic nerves. The functional results are variable and depend largely on the capacity and compliance of the residual rectum. Interval proctectomy may be required in up to 40%, and the risk for rectal cancer is about 15% after 30 years.[151-153] The operation is, however, a viable alternative in patients with good rectal compliance and minimal quiescent rectal disease if they are willing to undergo regular screening for rectal cancer. Although quality of life is generally good, patients do not feel as though they have been cured because they are still at risk for relapse from their rectal disease and must undergo regular surveillance.

Kock Continent Ileostomy

The Kock pouch consists of an ileal pouch with a valve, created by intussuscepting the terminal ileum into the pouch, and an exit spout (see Fig. 152–7). The pouch is emptied intermittently by intubation.[18] This option has the advantage that although a stoma is constructed, the effluent can be controlled. An external appliance is not needed. The main problem, however, is a *high* complication rate. Reoperation is common, particularly for prolapse and intussusception of the valve. The role of the Kock pouch is minor and it is probably restricted to patients who have undergone panproctocolectomy and wish to have control over their ileostomy effluent and those undergoing restorative proctocolectomy in whom the ileal reservoir cannot be safely brought down to the anal canal because of a short mesentery. Other patients should be discouraged.

CONCLUSION

The development of IPAA has led to significant advances in the surgical treatment of CUC. IPAA is safe and successful in about 95% to 98% of patients. The procedure may be performed laparoscopically. The vast majority of patients, if carefully selected, can expect a good outcome after IPAA. Two factors are critical: an anal sphincter capable of providing an adequate high-pressure zone to act as a barrier to pouch contents and the construction of a pouch with adequate capacity to act as a reservoir. The duplicated J pouch with a stapled IPAA is the most widely practiced variant of the procedure. The operation is undoubtedly complicated, as illustrated by the relatively high rates of associated morbidity. The specific choice of the type of IPAA performed continues to be the subject of debate, and the cause of pouchitis remains a challenge. Nevertheless, IPAA is now an established procedure that offers cure of disease and good quality of life.

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Chapter

153

Surgery for Inflammatory Bowel Disease: Crohn's Disease

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Crohn's disease presents multiple surgical challenges and has done so since the first description of the disease by Penner and Crohn.[1] Although new medications such as FK-506 (tacrolimus) and infliximab (Remicade) have changed the way Crohn's disease is managed medically, underlying surgical principles remained unchanged.

The philosophy of bowel and sphincter preservation, along with a combined approach to the treatment of Crohn's disease, is central to the management of this disease. The historical concern that surgery is futile and leads to further complications has largely disappeared. With changes in preoperative care, improved medical therapy, and new and more noninvasive surgical techniques, the gastroenterologist and surgeon, working in concert, now offer more options to Crohn's patients. From a technical perspective, one of the most important changes in the surgical management of Crohn's disease has been the widespread adoption of laparoscopic resection techniques.

INDICATIONS FOR SURGERY

Between 70% and 90% of patients with Crohn's disease undergo an operation for the disease at some time during their life.[2] It is an unpredictable and insidious disease that affects patients in the prime of their lives. There is a bimodal distribution of incidence, with patients developing Crohn's in their 20s and 30s and others in their 60s and 70s. By far the leading indication for operation is the failure of medical management. The most common complication leading to surgery is intestinal obstruction, which is rarely complete. Other surgical indications include fistula or abscess, gastrointestinal bleeding, and the rare cases of spontaneous perforation with peritonitis.[3] Unique indications for operative intervention include children who experience growth failure; these patients often benefit dramatically and rapidly from surgery, experiencing accelerated growth after resection. Toxic megacolon and fulminant colitis are fortunately unusual presentations. The ultimate choice to intervene surgically is one that is based on the informed discussion among the patient, surgeon, and gastroenterologist.

MEDICAL TREATMENT OF CROHN'S DISEASE

Crohn's disease may present as one of three different subtypes: fibrotic, fistulizing, or inflammatory. Many patients present to the surgeon with the diagnosis of Crohn's already made and on medical therapy. The current options for medical therapy of Crohn's are extensive and complex. Many patients have been treated with 5-aminosalicylate (ASA) products including sulfasalazine, oral mesalamine (Pentasa, Asacol), and rectal mesalamine (Rowasa). Controlled trials of sulfasalazine, 3 to 5 g/day, in patients with mildly to moderately active Crohn's disease have not demonstrated efficacy for inducing remission.[4,5] In a subset of patients with Crohn's colitis there were trends toward a benefit, but this was not statistically significant.[3,4] Likewise, doses of 2.5 to 3 g/day were not effective for maintaining remission in patients with Crohn's disease.[3,4] The data for oral mesalamine in the treatment of Crohn's disease are also unclear. Data from controlled trials[4,5] of oral mesalamine, 1 to 4 g/day, for maintenance of medically induced remission or postoperative remission in patients with Crohn's disease are conflicting.[6] Overall, sulfasalazine or mesalamine appears to provide minimal benefit for inducing remission, and both are less effective than oral corticosteroids for active Crohn's disease.

The data for use of antibiotics in Crohn's disease are conflicting. A placebo-controlled trial of metronidazole, 750 mg/day or 1500 mg/day, did not demonstrate efficacy in patients with active Crohn's disease.[4,5] A single controlled trial demonstrated that metronidazole, 1500 mg/day, was effective for maintaining postoperative remission.[4,5] Studies of patients with fistulizing disease include only uncontrolled series that have reported that metronidazole, 750 to 1500 mg/day, and ciprofloxacin, 1000 mg/day, may be effective in patients with fistulizing Crohn's disease, particularly with perianal fistulas. Based on these results, the role of antibiotic therapy in patients with Crohn's disease is controversial.

The uses of steroids, azathioprine, and methotrexate have evolved to become the mainstay of medical treatment of Crohn's disease. Controlled trials have demonstrated that oral prednisone administered at a dose of 60 mg/day is effective for inducing remission in mildly to moderately active Crohn's disease. In contrast, low-dose corticosteroids are not effective for maintaining remission. Controlled trials have also demonstrated that azathioprine (Imuran) at doses of 2 to 3 mg/kg/day and 6-mercaptopurine at a dose of 1.5 mg/kg/day is effective for inducing remission and closing fistulas in patients with active Crohn's disease.[4,5] Further study has demonstrated that azathioprine at 2 to 3 mg/kg/day and 6-mercaptopurine, 1.5 mg/kg/day, is effective for maintenance of remission and steroid sparing in Crohn's disease.[4,5] Controlled trials have demonstrated that higher dose methotrexate (25 mg/week intramuscularly and 15 mg/week orally) is effective for inducing remission in patients with steroid-dependent and steroid-refractory active Crohn's disease. Methotrexate at doses of 15 to 25 mg/week intramuscularly is effective for maintenance of remission and steroid sparing in patients with Crohn's disease.[4,5]

The newest agents in the treatment of Crohn's include infliximab, which is a chimeric monoclonal antibody directed at tumor necrosis factor-α. Controlled trials have demonstrated that infliximab, 5 mg/kg, administered one to three times over 6 weeks as an intravenous infusion is effective for inducing remission and closing fistulas.[7] A preliminary maintenance of remission study showed that infliximab, 10 mg/kg, administered intravenously every 8 weeks is effective in maintaining remission in patients with Crohn's disease.

In summary, initial treatment of mild to moderately active Crohn's disease should consist of budesonide or oral corticosteroids (alternatively, many clinicians would use 5-ASA and/or antibiotics prior to beginning corticosteroids). Patients with persistent symptoms may require oral corticosteroids, azathioprine or 6-mercaptopurine, methotrexate, infliximab, or surgical resection. Treatment of fistulizing Crohn's disease should initially consist of antibiotics and surgical incision and drainage of abscesses and/or fistulotomy if necessary. Patients with more refractory fistulizing disease may require treatment with azathioprine or 6-mercaptopurine and/or infliximab. Remission in patients with Crohn's disease should be maintained with oral mesalamine (minimal benefit), azathioprine or 6-mercaptopurine (these medications are also steroid sparing), methotrexate (also steroid sparing), and infliximab.

PREOPERATIVE PREPARATION

Once the decision to operate has been made, it is important to categorize the patient's preoperative comorbidities. Evaluating the nutritional status of patients is important because it is often compromised by severe disease and long-standing poor nutrition. If needed, total parenteral nutrition (TPN) is occasionally indicated in patients who are chronically ill. In a study of 395 malnourished patients, those who received 1 week of TPN had fewer noninfectious complications[8] than did those who did not receive TPN (43%).[9] Issues such as anemia can also be addressed prior to operative intervention.

Standard bowel preparation is provided to the patient and typically consists of laxatives and enemas, or 2 L of a lavage solution such as GoLYTELY. Metronidazole and neomycin are administered after completion of the mechanical preparation.[10] Alternatively, broad-spectrum intravenous antibiotics can be administered before and during the operation. We do not believe it is necessary to administer both preoperative and intraoperative broad-spectrum antibiotics unless an infectious complication is present at the time of surgery. Patients who have been treated with steroids are administered dexamethasone intravenously intraoperatively and postoperatively to avoid adrenal crisis induced by the stress of surgery. In addition to these measures, preoperative urethral stent placement can be an important adjunct to surgical therapy in situations such as a large abdominal abscess or phlegmon.

OPERATIVE CONCERNS

Intraoperative assessment of remaining bowel length is an important part of any surgical exploration in patients with Crohn's disease. Not only does this allow assessment of nutritional viability but it provides needed information for future discussions about additional surgical resections. The dreaded fear of short bowel syndrome, although real, has been significantly reduced with the addition of newer medications and a more conservative operative approach. In general, the mean length of small bowel in healthy people is approximately 640 cm.[11] Important anatomic markers of resection such as the terminal 80 cm of ileum are important because resection of this leads to disruption of the enterohepatic circulation and subsequent diarrhea, as well as hyperoxaluria and vitamin B_{12} malabsorption. In addition, surgeons must keep in mind that with greater resection length, a greater degree of malabsorption of fat-soluble vitamins and lactose may occur. It is well known that resection of more than 50% of the small bowel almost always produces malabsorption, and if 70% of the small bowel is resected, supplemental parenteral nutrition is nearly always required.

Recurrence

Possible predisposing factors for recurrence of disease are age and onset of disease; sex; site of disease (ileocolic having the highest risk); number of resections; symptomatic status at the time of surgery; length of small bowel resection; fistulizing versus obstructing forms of disease; proximal margin length; microscopic margin histology; strictureplasty; number of sites of disease; and the presence of colonic-only disease, granulomas, blood transfusions, family history, and prophylactic treatment.[12] Several authors have reported that there may indeed be cofactors or stimulants in the luminal contents that may induce early recurrence of Crohn's disease at a preanastomotic site.[13,14] Cameron et al.[13] have shown that patients who have a side-to-end ileocolonic anastomosis have recurrent involvement of the portion of ileum adjacent to the colon but not of the blind pouch distal to the anastomosis. Rutgeerts et al.[15] have shown that proximal diversion above an ileocolonic anastomosis prevents recurrence at that anastomotic site but that with closure of the proximal ileostomy, any possible recurrence will present promptly.

Anastomotic Technique

As with all bowel anastomosis, the principles of a successful anastomosis (no tension, good blood flow, and no contaminants) are followed in surgery for Crohn's disease. Options include the hand-sewn and the stapled anastomosis. It is helpful for surgeons to remember that when choosing a stapling device, there are 3.6- and 4.8-mm staple sizes. The largest staple length may be more appropriate for very thickened bowel. However, hemostasis may not be as good as that obtained with the 3.6-mm-length staple. Although resectional procedures can be performed in either manner, we have found that stapling strictureplasties can be difficult in fibrotic bowel.

The technical question of whether a wide side-to-side anastomosis as opposed to an end-end would reduce recurrence rates, perhaps by reducing stasis, is one which is currently being evaluated. Clearly patients undergoing an ileocolonic anastomosis face high rates of recurrence—42% by 15 years.[16-18] Whether a wide (90- to 100-mm) stapled anastomosis would result in a lower recurrence rate is the subject of the prospective Canadian-American Surgical Trial (CAST). The technique of a large side-to-side anastomosis is illustrated in Figure 153–1.

However, controversy exists, in that Cameron et al.[13] found no differences in recurrence for either anastomotic technique. Several retrospective studies have found that a stapled anastomosis achieved longer intervals of time between recurrences. Trials by Hashemi,[19] Yamamoto,[20] and Munoz-Juarez[21] and their colleagues have documented that stapled anastomoses are superior to hand-sewn ones in this regard. Specifically, Hashemi et al.[19] reported a reoperative rate of 2% in the stapled anastomotic group compared with 43% in the sutured end-to-end anastomotic group. Munoz-Juarez et al.,[21] in a bi-institutional retrospective study of 138 patients, found that 46 developed symptoms of recurrent Crohn's disease, of whom 33 were in the sutured conventional end-to-end group (48%) and 13 (19%) were in the wide-lumen stapled anastomotic group. The current CAST group study has completed enrollment of 173 patients in a prospective, randomized, controlled trial on this issue and is in the follow-up period.

Resection Margin

The role that margins play in recurrence of Crohn's disease is controversial as well. A long-term retrospective study by Krause et al.[22] compared two groups of patients: one with a "radical" resection of more than 10 cm of disease-free margins incorporated into the resection versus one with less than 10 cm of uninvolved bowel. They found, after a 14-year follow-up, that patients with longer margins have a lower recurrence rate (31%) and a better quality of life than patients with a shorter margin (83%). A similar retrospective review[23] reported similar results: A margin of normal tissue of less than 4 cm was associated with a 10-fold higher recurrence. In contrast, a study by Raab et al.[24] showed that the length of disease-free resection margins did not influence the risk of recurrence in a univariate and multivariate analysis in 353 patients undergoing a "curative" resection between 1969 and 1986. The only prospective study to address this issue compared patients undergoing ileocolic resection who were randomly assigned to one of two groups: (1) proximal margin of 2 cm or (2) proximal margin of 12 cm from the macroscopically involved disease.[25] There was no significant difference in recurrence rate in the 56 patients undergoing extended resection in contrast with the 75 patients undergoing limited resection, although the recurrence rate in the extended group was lower (18% vs. 25%).[25] These studies, along with several retrospective ones, have small numbers of patients and may harbor type II errors. This includes our own study, which did not show a significant difference between a proximal margin length of less than 5 cm versus a margin of 5 cm or more.[6]

How to proceed if all gross disease is resected, but microscopic changes remain at the margin of the resection, is controversial. Retrospective studies have yielded opposite results, with several reports showing a benefit of microscopically disease-free margins.[26-28] Other studies[25,29-34] have shown no difference in recurrence rates based on microscopic changes at the resection margin. The proximal histology at the margin of resection was examined in our prospective, randomized trial in which we compared nonspecific changes versus normal features on light microscopy and found no difference in recurrence rate.[6] Again, as in many other studies, there is a possibility of not detecting a true difference due to the small numbers in each group. Most recently we looked at 140 primary Crohn's resections and found that microscopic disease at the margin did indeed increase the risk for recurrence even in the setting of prophylactic medical therapy.[35]

In hopes of preserving bowel length, most surgeons accept an observed grossly negative margin of 1 or 2 cm. Few surgeons rely on frozen section margins. Although

a study of such a phenomenon in a large number of patients might show some difference (i.e., a lower recurrence rate) with negative margins or increasing length of resection, the theoretical benefit of a lower recurrence rate is outweighed by the inherent disadvantage of losing small bowel length. In addition, the widespread use of prophylactic medical therapy may have rendered this issue moot.

SITE-SPECIFIC CROHN'S DISEASE

Colonic Crohn's Disease

Crohn's disease involving only the colon occurs in 10% of patients. Most present with ileocolonic (40%) or small bowel only (30%) disease. The issue of retaining intestinal continuity is one that has been debated for years. Goligher[36] reported on 207 patients who underwent resection for colonic Crohn's disease. He found that there was a significantly higher recurrence rate in those undergoing subtotal colectomy and ileorectal anastomosis than in those undergoing proctocolectomy and ileostomy. These observations have also occurred in other series.[3,37] In our series of patients[6] with colonic Crohn's disease there was a significantly lower risk of recurrence in the group of patients who underwent a total proctocolectomy versus any other procedure. Having said this, our own follow-up series on the use of segmental resection clearly showed that long-term intestinal continuity can be maintained with a conservative surgical approach.[38] Given these observations, segmental resection should be the primary surgical procedure when appropriate, with an ostomy reserved for patients when extensive disease prompts proctocolectomy.[38]

Ileal Pouch–Anal Anastomosis in Patients with Crohn's Disease

Can surgeons successfully perform ileal pouch–anal anastomosis (IPAA) in patients with Crohn's disease?

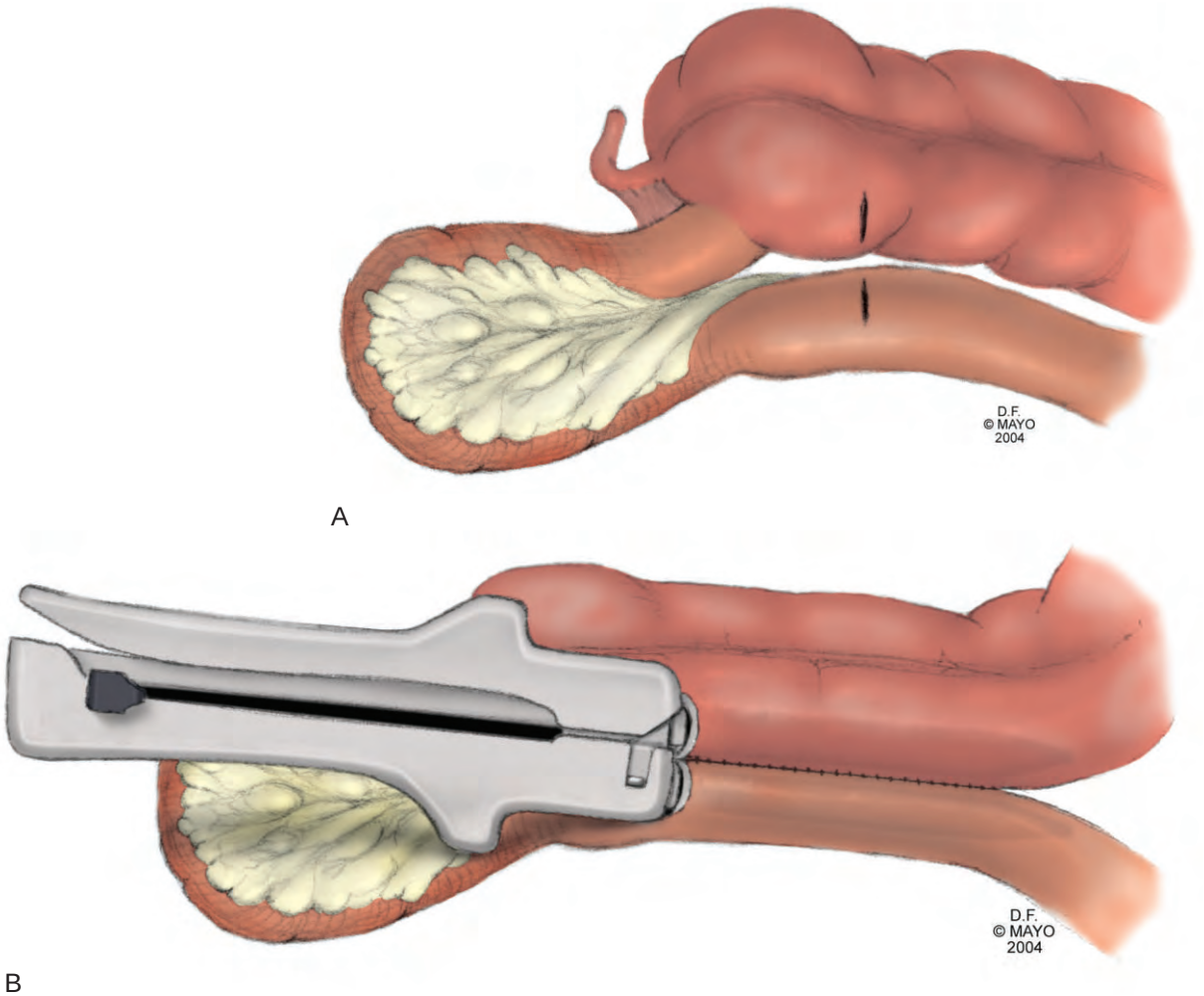
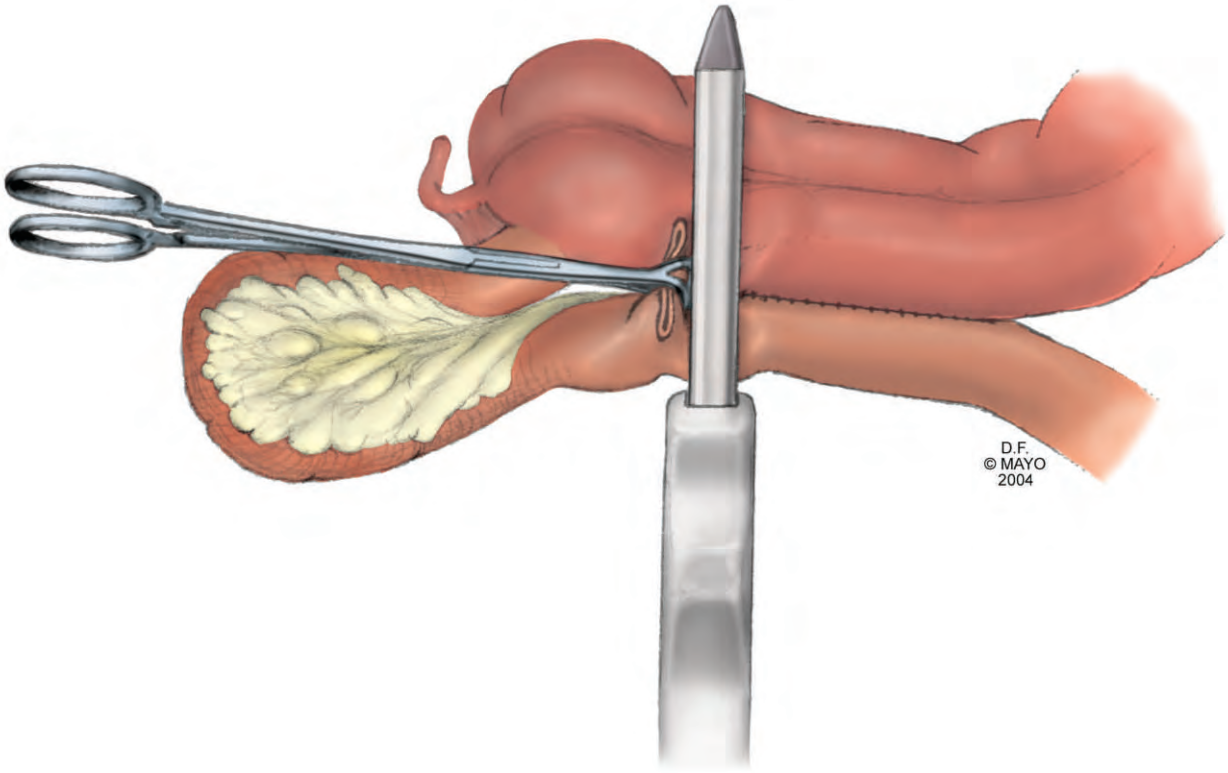


Figure 153–1. Line of resection for a right hemicolectomy done for cancer. **A,** One-centimeter transverse incisions are made on the antimesenteric borders of the ileum and colon to begin a stapled anastomosis. **B,** The first of two staple firings needed to create an anastomosis.



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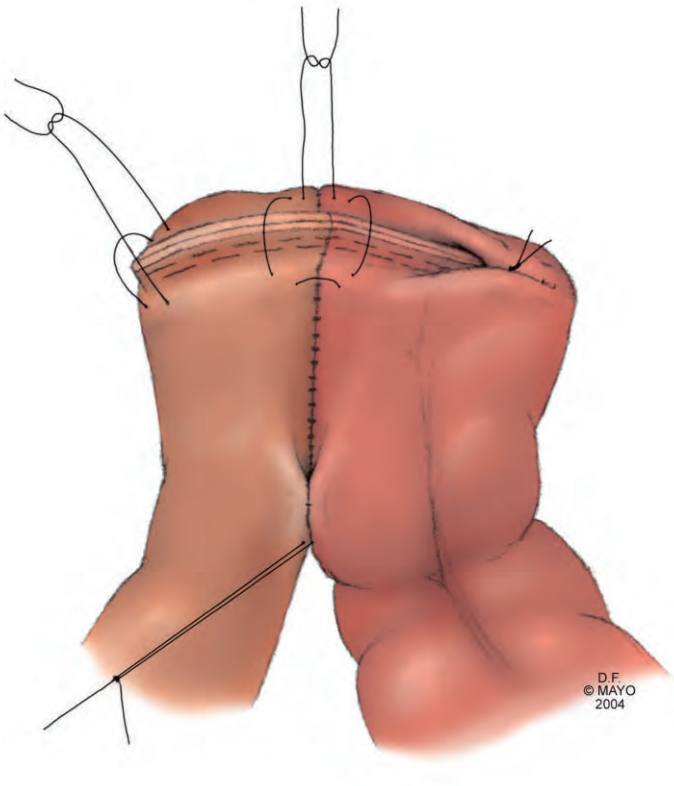


D

Figure 153–1, cont'd. **C,** The second of two staple firings needed for completion of a stapled anastomosis. **D,** Oversewing the staple line with interrupted suture. (**A-D,** ©Mayo, 2004.)

Although it is certainly technically possible, complication rates have been high.[39-41] In our series[42] of 37 patients who developed Crohn's disease subsequent to IPAA, 34 had manifestations of Crohn's in the pouch and/or anal canal; 45% of these patients required diversion or pouch excision. A series from Lahey Clinic[39] found that among their 32 patients with IPAA and Crohn's disease, 93% had complications and 29% experienced pouch failure within 5 years of surgery. Recently, our group reported pouch salvage rates with infliximab of 67% in patients with Crohn's disease.[43]

IPAA may be indicated for patients with Crohn's disease limited to the colon without evidence of anal canal involvement or small bowel disease. In a series by Regimbeau et al.,[44] only 35% of such highly selected patients experienced morbidity, with 10% experiencing failure. Although we believe that Crohn's disease remains a contraindication for IPAA, aggressive preoperative management with azathioprine and infliximab may facilitate IPAA in patients with Crohn's disease in the near future.

Laparoscope-Assisted Surgery for Crohn's Disease

Minimally invasive techniques are ideally suited for patients with Crohn's disease and have been shown in both randomized and nonrandomized studies to demonstrate similar or improved morbidity and mortality when compared with open resection.[45-60] Although the technique is less successful in patients with Crohn's disease who have large fixed masses, multiple complex fistulas, or recurrent disease, it may be still technically possible. Duepree et al.[51] reported that patients who underwent laparoscopic ileocolic resection for Crohn's disease had a shorter time to resumption of diet, time to bowel function, and length of stay. Others such as Milsom et al.[46] found that recovery of pulmonary function returned earlier in the laparoscopic group but time to first bowel movement and hospital stay were not significantly different. Bergamaschi et al.[49] found not only shorter hospital stay but a decreased rate of small bowel obstruction (35% in the open group, 11% in the laparoscopic group). In our own case-matched series of 70 laparoscopic versus 70 open resections for Crohn's disease, we found shorter operative times, decreased narcotic use, shorter length of stay, and a similar quality of life.[35]

SPECIFIC OPERATIONS

With improvements in medical therapy and acute care, emergency procedures for Crohn's disease are uncommon. If one is faced with acutely perforated Crohn's, depending on the degree of peritonitis,[61] one can either resect with a primary anastomosis or perform a diverting ileostomy or colostomy. Even though hemorrhagic episodes, especially life-threatening ones, are rare, this can occasionally occur, and all of the usual methods to localize bleeding points, including mesenteric arteriography, should be used. With localization of the disease and surgical resection, results should be excellent.[62]

Small Bowel

The three operative options that have been widely used for small bowel Crohn's disease are bypass, resection, and strictureplasty. Bypass was commonly used in the decades of the 1950s and 1960s but is rarely used now because a severely diseased segment of bowel left in place may cause continued symptoms, require treatment with steroids, and perhaps harbor a malignancy.[63] Small bowel bypass might be useful in patients with an already shortened small bowel or in patients with extensive strictures throughout the small bowel. Gastrojejunal bypass is useful in gastroduodenal Crohn's disease as an alternative to duodenal strictureplasty.

Resection

Resection and primary anastomosis are used in patients with fistulous disease of the small bowel, contained abscess, and isolated stenotic lesions in patients in whom there is adequate bowel remaining. During exploration—whether it be open or laparoscopic—bowel length is measured. Careful assessment of the extent of the disease is made. Typically, ileal Crohn's disease affects the distal 25 to 30 cm of terminal ileum and may continue into the cecum (Fig. 153–2). This type of resection for isolated Crohn's disease accounts for 80% to 90% of operations for Crohn's disease. An end-to-end ileoascending colostomy can be sutured, or a wide-stapled side-to-side, functional end-to-end anastomosis can be made with the linear stapler (see Fig. 153–1).

Strictureplasty

If the patient has the stenosing form of Crohn's disease, with skip areas present in the more proximal ileum and jejunum, strictureplasty is useful. Frequently, a combination of resection and strictureplasty is the optimal choice and has become widely accepted. Strictureplasty plays a prominent role in the surgical management of small bowel Crohn's disease. Isolated strictures under 10 cm in length are often considered best for strictureplasty (Fig. 153–3). Our original experience with 35 patients, in whom 71 strictureplasties were performed, and who were followed for more than 3 years, found no significant increase in postoperative morbidity and symptomatic recurrence rates of 20%.[64] Two more recent reports of more than 1400 strictureplasties, followed for more than 7 years, found reoperation rates of between 34% to 44% and symptomatic relief in more than 95% of patients.[65,66] The technique of strictureplasty is shown in Figure 153–3. It may be helpful to use a Baker tube, after making the initial transverse incision for strictureplasty, to define proximal and distal strictures that may be subtle or undetected. This also provides a method to further decompress the small bowel. Biopsy of the wall of each strictureplasty occasionally reveals an unsuspected adenocarcinoma.

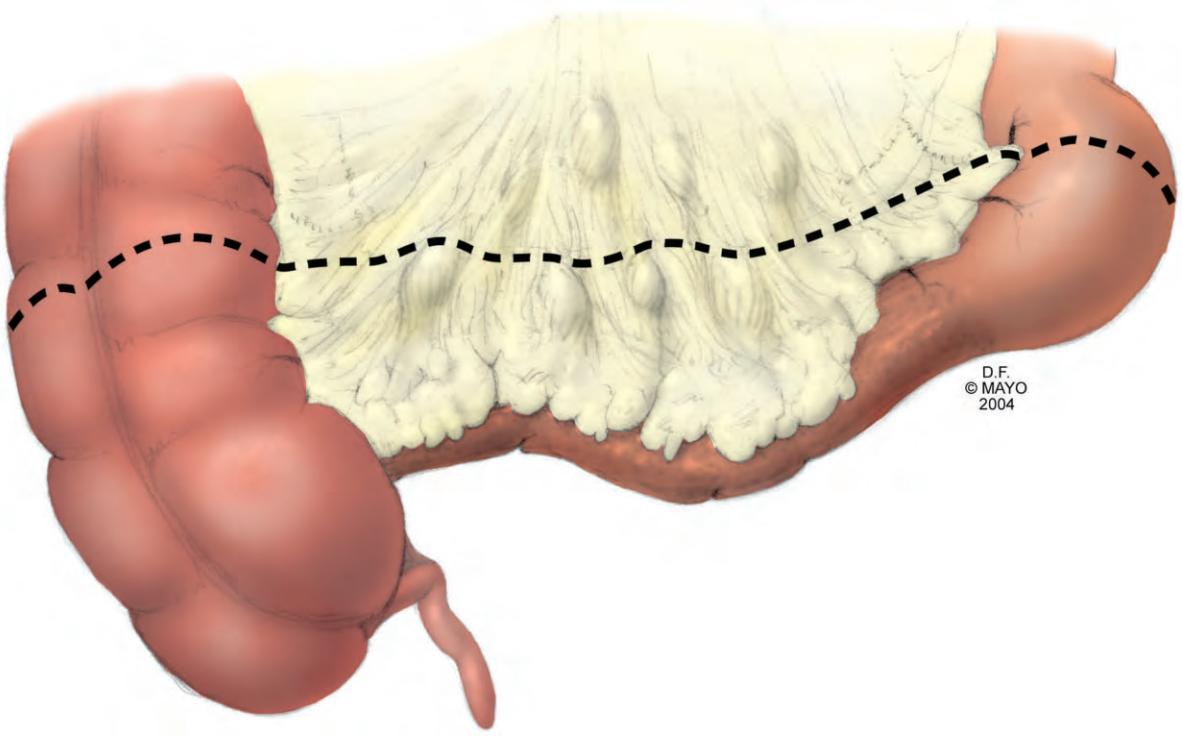


Figure 153–2. Ileocolonic Crohn's disease with line of transection. (©Mayo, 2004.)

Colonic Crohn's Disease

Preservation of bowel length and intestinal continuity remains the primary goal in patients with Crohn's disease of the colon. For those patients with severe disease scattered throughout the colon, subtotal colectomy and an ileorectostomy can be safely performed. Of the 42 patients who had this operation at the Mayo Clinic, 91% had improved health and quality of life after surgery, and 66% maintained an acceptable, functioning ileorectal anastomosis for at least 10 years.[67] Some patients may have more limited colonic involvement, and in this situation a segmental resection with anastomosis is indicated; 86% of these patients will remain stoma-free over a 14-year follow-up.[38]

Long colonic strictures may harbor an adenocarcinoma.[68] Strictureplasty has been occasionally used for colonic Crohn's disease, but one must question its use because strictures often represent carcinomas and recurrent Crohn's disease is common. Given the success of medical therapy, recently some would argue that if the patient has mild rectal disease and minimal perianal involvement, it would be reasonable to leave a short segment of rectum and anal canal in place but excluded from the fecal stream. In this way, the patient with anorectal Crohn's disease may respond to diversion and local treatment, with an opportunity for future reanastomosis.[19] In one study,[69] the long-term chances for closure of a temporary stoma were 75% when used for anastomotic protection or avoidance, 79% after postoperative complications, but only 40% for perianal or genital fistulas or for rectal inflammation or stenosis. Rectal disease and perianal fistula were independent predictors of a low possibility of stoma closure during follow-up. Unfortunately, many patients have not only severe colonic disease but mild to severe rectal disease with anorectal complications. These patients are best served with proctocolectomy and Brooke ileostomy.[70]

On those rare occasions that a patient presents with toxic megacolon from Crohn's disease, colectomy with closure of the proximal rectum and end-ileostomy is the procedure of choice. This operation can be done expeditiously and leaves no anastomosis in the abdomen. A common concern remains the treatment of the distal rectal stump.[71] It is our practice to oversew the stump or, in severe cases, to exteriorize it as a mucus fistula. In extreme cases, when both the colon and the rectum are severely involved, proctocolectomy with permanent end-ileostomy (Brooke ileostomy) may be required.[72] Occasional decompression of the stapled rectal remnant may decrease the incidence of stump "blowout."

It is well known that Crohn's patient are at high risk for perianal wound complications. Among 32 patients with Crohn's disease treated with complete proctectomy and primary closure at the Mayo Clinic, 50% had a healed perineum by 1 month after surgery, and 90% had healed by 1 year.[73] Persistent nonhealing of perineal wounds requires excision of the wound surface and secondary closure, skin grafts, a musculocutaneous flap, or some combination thereof.[74] To avoid the problem of a nonhealing wound, endorectal and sphincter-saving excisions rather than wide excision of the entire anorectum are useful. By using the well-vascularized muscles of the

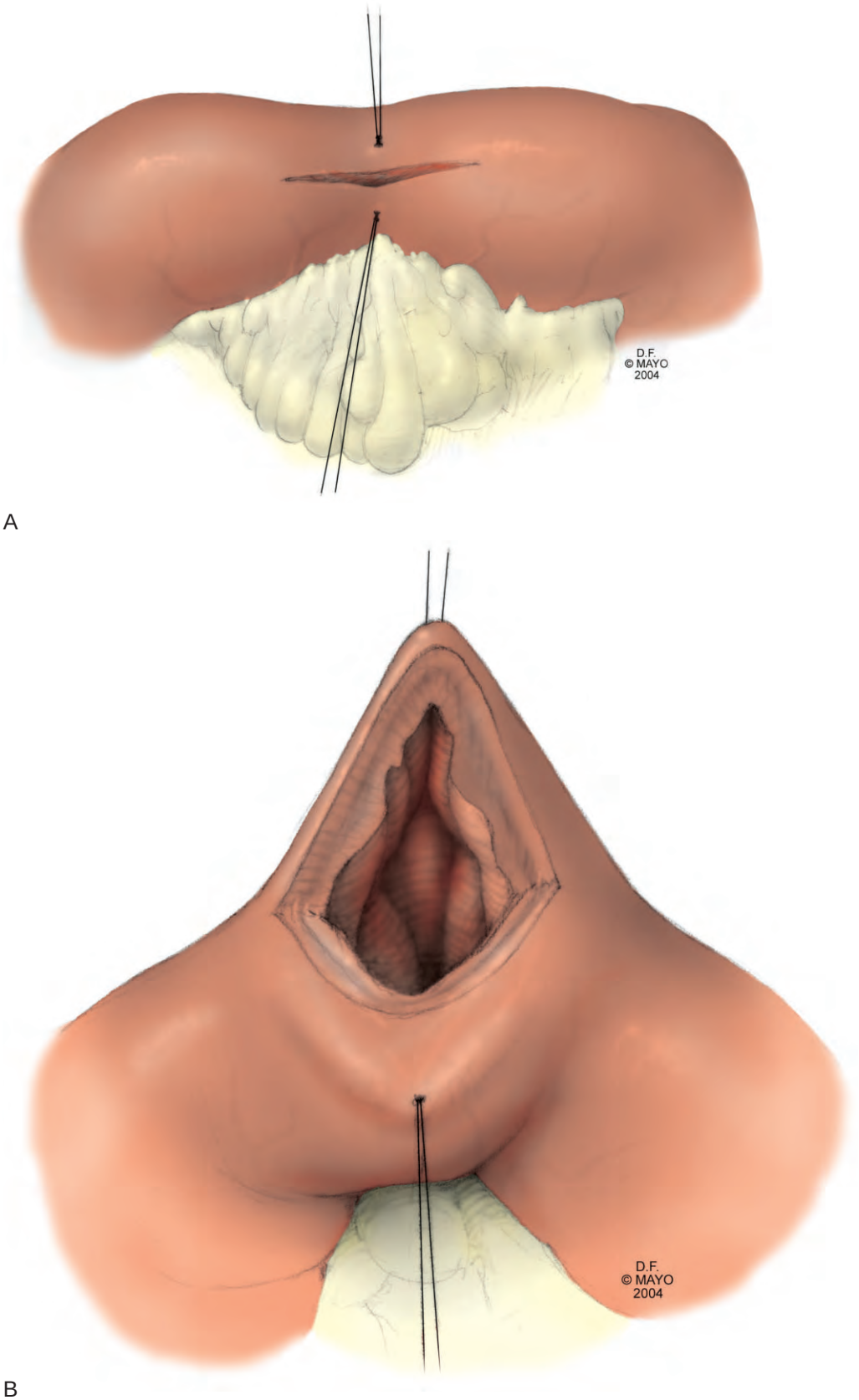
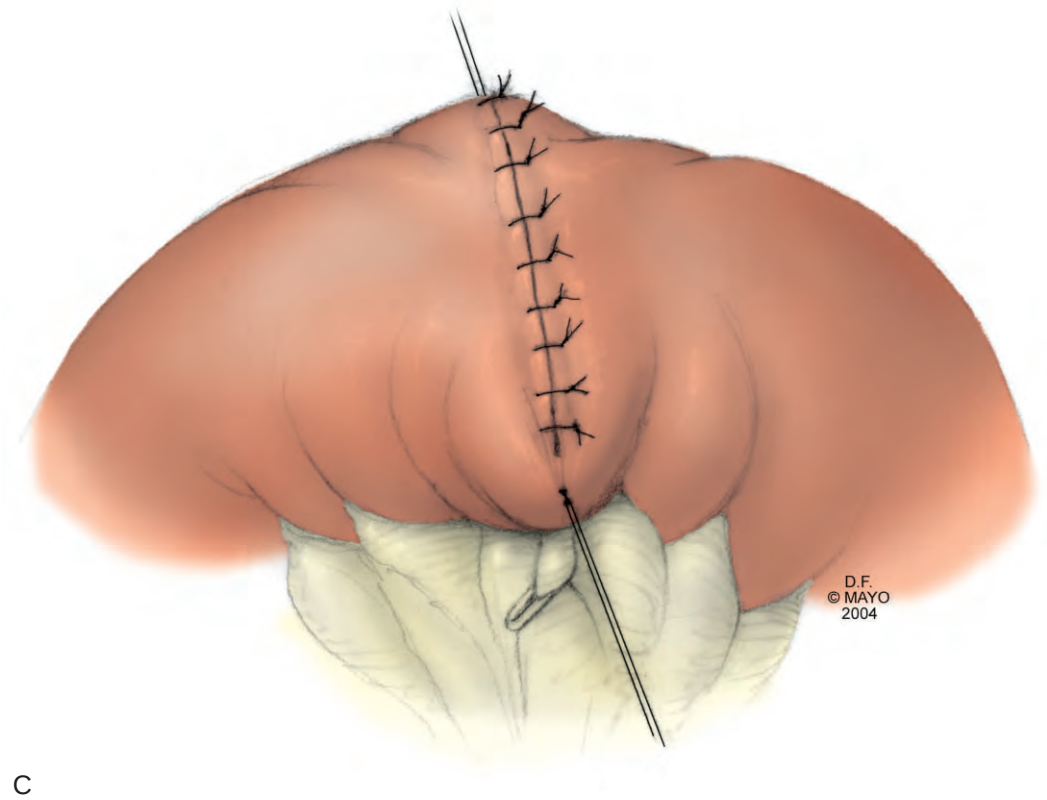


Figure 153–3. **A,** Longitudinal opening of a small bowel Crohn's stricture. **B,** Preparing for a strictureplasty.



C

Figure 153–3, cont'd. **C,** Completing the anterior interrupted row of sutures for a strictureplasty. (**A-C,** ©Mayo, 2004.)

anal canal, more rapid and complete healing can be expected.

The practice of proximal diversion is controversial. This operation may have its greatest role in patients who are extremely ill with Crohn's colitis. Proponents have reported improvement from fecal diversion.[75,76] In light of medical therapy such as the use of infliximab, the future treatment of diseased segments and the ability to close existing stomas may indeed be improved. Future studies in this area will be needed. In the past, it has been commonly noted that once the stoma is reversed, the disease flares again, requiring surgical treatment.[75]

Anorectal Crohn's Disease

The surgical treatment of perianal Crohn's disease is evolving. Today management is customarily a combined approach, encompassing both aggressive medical and conservative surgical management.[77] Anorectal Crohn's disease typically presents in three ways: ulceration, fistula, and stricture.[78-80] Michelassi et al.[81] observed that 23% of patients with Crohn's disease manifested perineal fistulas, 18% stenoses, 16% abscesses, 9% rectovaginal fistulas, 5% incontinence, and 29% a combination of problems. The cumulative incidence of perianal fistulas in Crohn's disease has been estimated by two population-based studies. Hellers et al.[82] reported a cumulative incidence of perianal fistulas of 23%. In a Mayo series, Schwartz et al.[83] showed that the cumulative incidence of fistulizing Crohn's disease in Olmsted County, Minnesota, between 1970 and 1993 was 38%. The lifetime risk for developing a fistula is 20% to 40%.[83-87] The key concept when operating on patients with anorectal Crohn's disease is to be conservative. Wide excisions of large amounts of tissue should not be performed. With conservative medical and surgical therapy, symptoms are often improved.

Perianal Abscess

The treatment of perianal abscess is prompt and adequate surgical drainage. Superficial abscesses require simple incision and drainage. Abscesses that are deep (supralevator or ischiorectal) should be drained using a mushroom catheter and/or a noncutting seton to provide adequate drainage with as little tissue trauma as possible (Fig. 153–4).[88]

Fistulas

Fistula disease is common among Crohn's patients. The surgical treatment of Crohn's fistula most commonly involves using a noncutting seton.[89-93] A seton is a nonabsorbable suture (or vessel loop) that is placed through the fistula tract (Fig. 153–5). The purpose of the seton is to promote drainage; thus, it decreases the risk of recurrent abscess while aggressive medical therapy is being

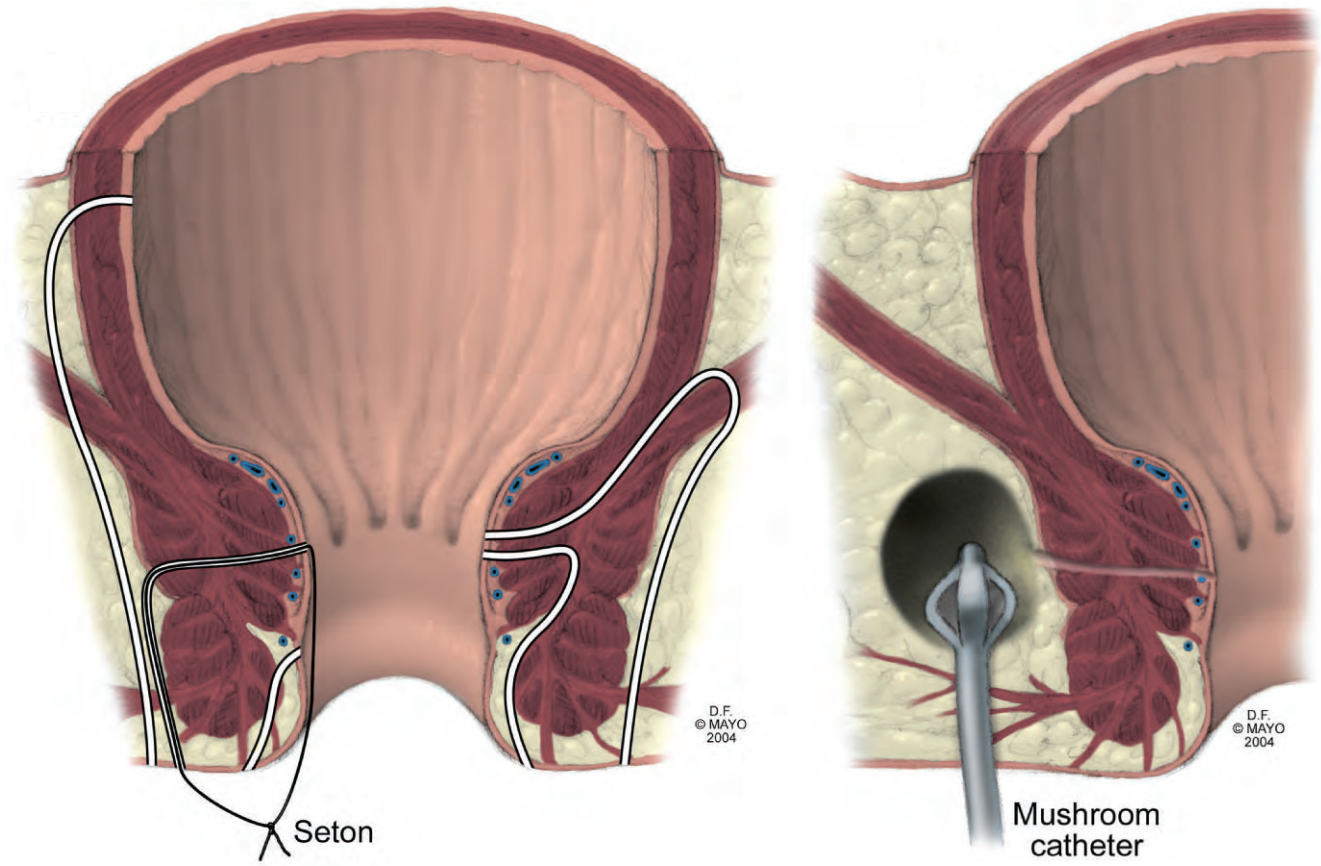


Figure 153–4. **A,** Draining seton in place, through a trans-sphincteric fistula. **B,** Perianal abscess treated with a Malecot catheter. (**A** and **B,** ©Mayo, 2004.)

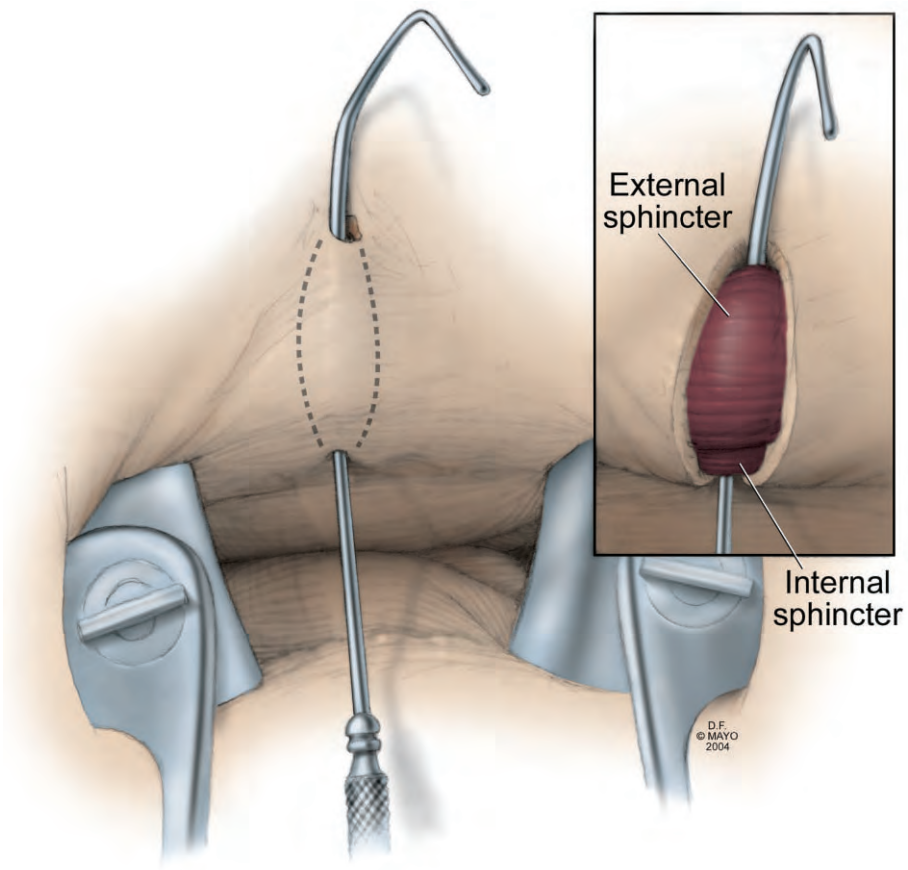
instituted. At the Mayo Clinic, 110 patients were surgically treated for perianal Crohn's fistula with either seton or superficial fistulotomy and aggressive medical therapy. After a median follow-up of 3 years, 86% of patients had complete healing or were asymptomatic.[94]

Others have studied similar patients. Among 27 patients with fistulizing Crohn's disease, Scott and Northover[92] reported that 85% of patients treated with noncutting setons experienced fistula closure. A high recurrence rate, which may be as much as 40% after removing the seton,[89,95] lends legitimacy to our use of concomitant antibiotics, azathioprine, or 6-mercaptopurine and infliximab.[77,95] With the use of medications such as infliximab, long-term and initial healing rates may be improved. The Mayo Clinic gastroenterology group recently reported that infliximab along with seton led to the complete resolution of perianal fistulas in 68% of patients.[96] We found that the addition of seton placement with infliximab reduced the rate of recurrent abscess. In a comparative study by Regueiro and Mardini,[97] perianal fistulas were treated with infliximab alone versus combination infliximab plus seton placement. They found that the initial response was improved with seton placement (100% versus 82.6%), lower recurrence rates (44% versus 79%), and longer time to recurrence (13.5 versus 3.6 months).

Although improvements in medical therapy and conservative surgical management of perianal Crohn's may lead to healing, some patients go on to proctectomy. In our own long-term series of patients with anorectal Crohn's,[98] two groups emerged. The first suffered severe rectal involvement and proceeded to proctectomy quite early in the disease process. The second group had more limited rectal disease and has been managed well with conservative treatment. Within this series, the cumulative probability of avoiding proctectomy was 92% at 10 years and 83% at 20 years.[99] In our more recent surgical study of 110 patients treated surgically for perianal disease, the severity of proctitis, the extent of fistulas and abscesses, and the presence of recurrent abscess all lead to a higher incidence of failure.[94]

Rectovaginal Fistula

Rectovaginal fistula is a particularly distressing complication of Crohn's disease. About 2% of women with Crohn's disease develop a rectovaginal fistula.



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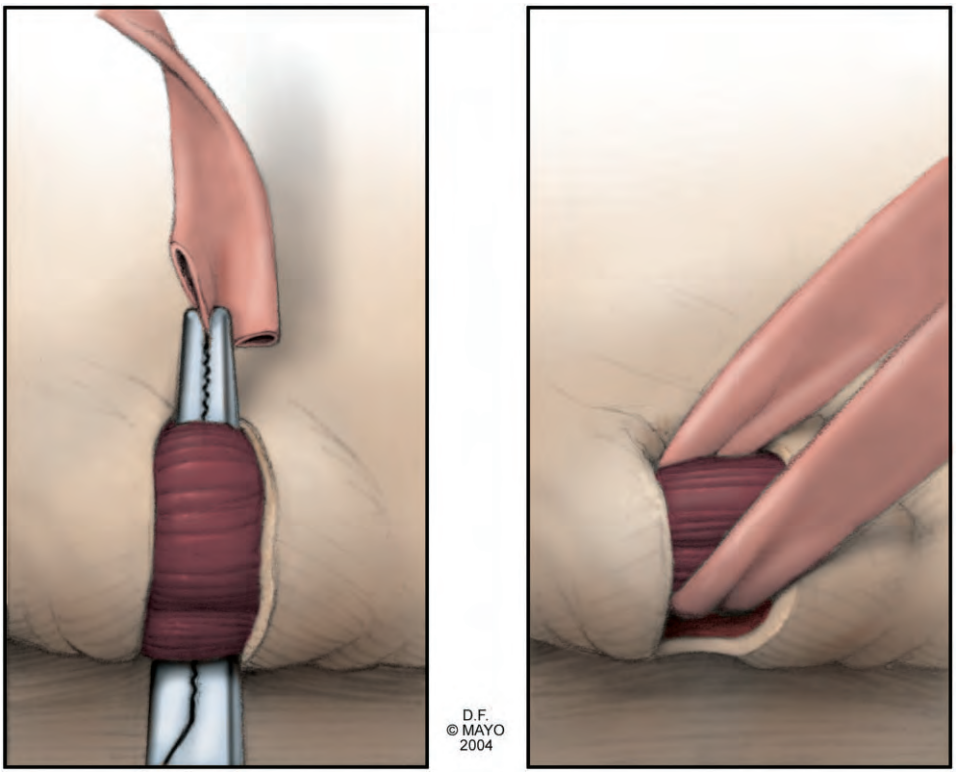

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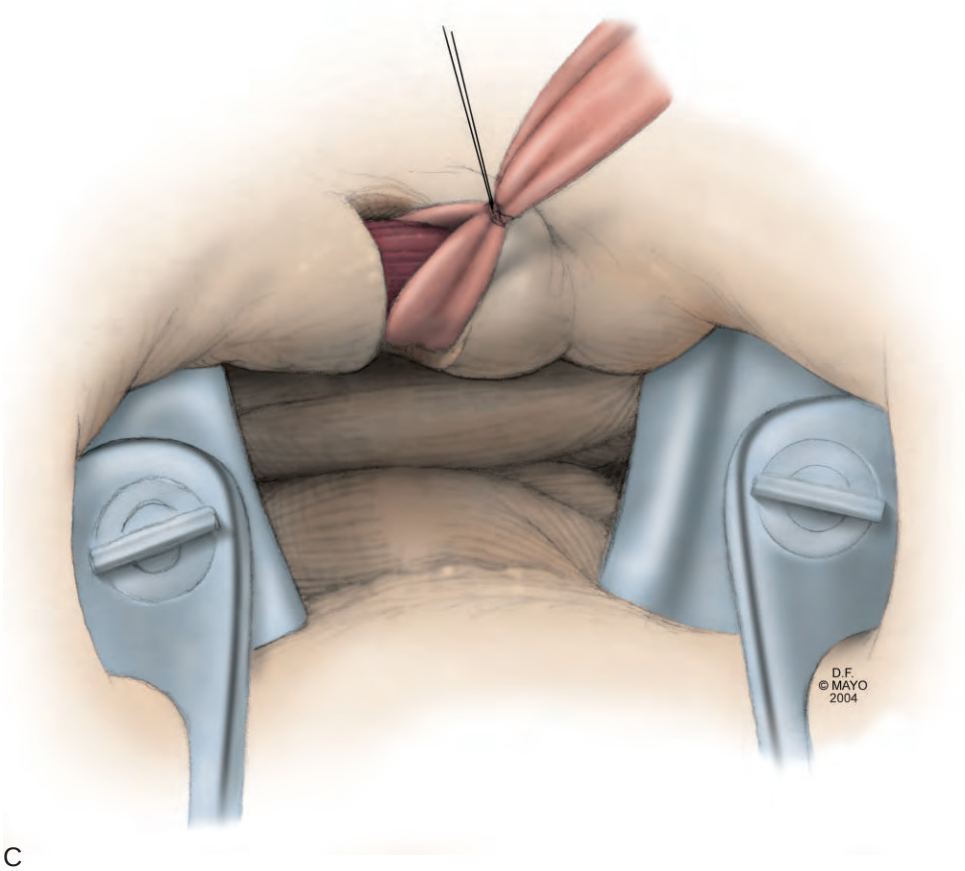
Figure 153–5. **A,** Probe through a perianal fistula with the internal sphincter exposed. **B,** Placement of a seton. *Continued*



C

Figure 153–5, cont'd. **C,** Securing a seton in place. (**A-C,** ©Mayo, 2004.)

Fortunately, most fistulas are very low and have no associated symptoms. Surgical treatment is reserved for those patients with an unacceptable quality of life in whom medical treatment has failed. The development of a rectovaginal fistula is a poor prognostic sign and may require proximal diversion to decrease local sepsis and/or eventual proctectomy. In patients undergoing rectovaginal fistula repair, the disease should be quiescent and the rectum distensible. In general, for very low rectovaginal fistula (<15% of the sphincter involved) and normal sphincter function, simple fistulotomy is a viable option. However, some surgeons advocate use of an endorectal advancement flap as an alternative to fistulotomy or noncutting setons in patients with a simple fistula who do not have active rectal inflammation.[99,100] An advancement flap involves creating a flap of tissue around the internal opening of a fistula and then moving healthy tissue over the excised area.[99,101] Joo et al.[99] reported sustained closure in 74% of 26 patients with fistulizing Crohn's disease treated with endorectal advancement flap. Hull and Fazio[102] reported that among 35 patients with an advancement flap for low anovaginal fistulas, the initial healing rate was 54% and an ultimate healing rate with repeat procedure was 68%, but few others have reported such good outcomes. Although these reported successes exist, in our experience this approach yields unpredictable results at best.

SUMMARY

In summary, surgery for Crohn's disease can be both extremely frustrating and highly rewarding. Surgeons must be familiar with a variety of techniques and options to adapt to the multitude of possible presentations in this disease. Innovation, research, and a combined medical-surgical approach will aid surgeons in conserving bowel length, preserving intestinal continuity, restoring patients to active lives, and improving their quality of life.

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Chapter

154

Appendix

Gordon L. Telford · James R. Wallace

ACUTE APPENDICITIS

Acute appendicitis is one of the most common causes of an abdominal emergency and accounts for approximately 1% of all surgical operations.[1] Although rare in infants, appendicitis becomes increasingly common throughout childhood and reaches its maximal incidence between the ages of 10 and 30 years. After 30 years of age, the incidence declines, but appendicitis can occur in individuals of any age. Among teenagers and young adults, the male-to-female ratio is about 3:2. After age 25 years, the ratio gradually declines until the sex ratio is equal by the mid-30s.

Pathophysiology

The most commonly accepted theory of the pathogenesis of appendicitis is that it results from obstruction followed by infection.[2] The lumen of the appendix becomes obstructed by hyperplasia of submucosal lymphoid follicles, a fecalith, tumor, or other pathologic condition. Once the lumen of the appendix is obstructed, the sequence of events leading to acute appendicitis is probably as follows: Mucus accumulates within the lumen of the appendix, and pressure within the organ increases. Virulent bacteria convert the accumulated mucus into pus. Continued secretion combined with the relative inelasticity of the serosa leads to a further rise in pressure within the lumen. This results in obstruction of the lymphatic drainage, leading to edema of the appendix, diapedesis of bacteria, and the appearance of mucosal ulcers. At this stage, the disease is still localized to the appendix; therefore, the pain perceived by the patient is visceral and is localized to the epigastrium or periumbilical area.

Continued secretion into the lumen and increasing edema bring about a further rise in intraluminal and tissue pressure, resulting in venous obstruction and ischemia of the appendix. Bacteria spread into and through the wall of the appendix, and acute suppurative appendicitis ensues. Somatic pain occurs when the inflamed serosa of the appendix comes in contact with the parietal peritoneum and results in the classic shift of pain to the right lower quadrant.

As this pathologic process continues, venous and arterial thromboses occur in the wall of the appendix, resulting in gangrenous appendicitis. At this stage, small infarcts occur, permitting escape of bacteria and contamination of the peritoneal cavity. The final stage in the progression of acute appendicitis is perforation through a gangrenous infarct and the spilling of accumulated pus. Perforating appendicitis is now present, and morbidity and mortality increase.

Symptoms

The symptomatic history in acute appendicitis may vary, but cardinal symptoms are usually present.[1,3] The history usually begins with abdominal pain often localized to the epigastrium or the periumbilical area, followed by anorexia and nausea. Vomiting, if it occurs, appears next. After a variable period, usually about 8 hours, the pain shifts to the right side and usually into the right lower quadrant. At the time of presentation, the duration of pain is less than 24 hours in 75% of patients.

Pain

The typical pain of acute appendicitis initially consists of diffuse, central, minimally severe visceral pain, which is followed by somatic pain that is more severe and usually well localized to the right lower quadrant. Failure to follow the classic visceral-somatic sequence is common in acute appendicitis, occurring in up to 45% of patients who are proved subsequently to have appendicitis. Atypical pain may be somatic and localized to the right lower quadrant from its initiation. Conversely, the pain may remain diffuse and may never become localized. In older patients, atypical pain patterns occur more frequently.

Patients with high retrocecal appendicitis may present with only diffuse pain in the right flank. Similarly, patients in whom the entire appendix is within the true

pelvis may never experience somatic pain and, instead, may have tenesmus and vague discomfort in the suprapubic area.

Anorexia, Nausea, and Vomiting

Anorexia and nausea are present in almost all patients with acute appendicitis, but vomiting occurs in less than 50% of patients. The presence or absence of vomiting is not a criterion for the diagnosis of appendicitis. When vomiting does occur, it is usually not persistent, and most patients vomit only once or twice. If vomiting occurs, it occurs *after* the onset of pain with such regularity that if it precedes pain, the diagnosis of appendicitis should be questioned.

Constipation and Diarrhea

A history of the recent onset of constipation or diarrhea is not helpful in the diagnosis of appendicitis. A greater percentage of patients with appendicitis complain of constipation, but some give a history that defecation relieves the pain.

Physical Examination

Typical physical signs of acute appendicitis include localized tenderness in the right lower quadrant, muscle guarding, and rebound tenderness. Cutaneous hyperesthesia, right-sided pelvic tenderness on rectal examination, and the presence of a psoas or obturator sign occur less frequently and tend to be highly dependent on the examiner. Although often temperature is normal, fever up to 38° C occurs. In the usual case of acute, nonperforated appendicitis, higher fever occurs infrequently.

Tenderness and Muscle Guarding

On routine abdominal examination, an area of maximal tenderness often is elicited in the area of McBurney's point, which is located two thirds of the distance along a line from the umbilicus to the right anterior superior iliac spine. If the appendix is in a high retrocecal position or is entirely within the true pelvis, point tenderness and muscle rigidity might not be elicited. In high retrocecal appendicitis, tenderness may occur over a large area, and there may be no signs of muscle rigidity. In pelvic appendicitis, neither tenderness nor muscle guarding may be present. Both signs are often lacking or only minimally expressed in the aged population.

Signs of peritoneal inflammation or irritation in the right lower quadrant are also helpful in the diagnosis of acute appendicitis and can be demonstrated by many methods. Asking the patient to cough or bounce on the heels elicits this type of pain in 85% of patients. Rebound tenderness is elicited by the sudden release of abdominal palpation pressure. Rovsing's sign—pain elicited in the right lower quadrant with palpation pressure in the left lower quadrant—is a sign of acute appendicitis. Muscle guarding, manifested as resistance to palpation, increases as the severity of inflammation of the parietal peritoneum increases. Initially, there is only voluntary guarding, but this is replaced by reflex involuntary rigidity.

Abdominal Mass

As the disease process progresses, it may be possible to palpate a tender mass in the right lower quadrant. Although the mass may be caused by an abscess, it can also result from adherence of the omentum and loops of intestine to an inflamed appendix. When appendicitis becomes advanced enough that there is a large, inflamed mass and the anterior abdominal wall is involved, the patient often avoids sudden movements that can cause pain.

Psoas Sign

The right hip is often kept in slight flexion to keep the iliopsoas muscle relaxed. Stretching the muscle by extension of the hip or further flexion against resistance can initiate a positive psoas sign, indicating irritation of the muscle by an inflamed appendix. A psoas sign is seldom seen in early appendicitis and can be elicited in patients without any pathologic condition.

Rectal Examination

Rectal examination, although essential in all patients with suspected appendicitis, is helpful in only a few of them. In patients with an uncomplicated appendicitis, the finger of the examiner cannot reach high enough to elicit pain on rectal examination.

If the appendix ruptures, the physical examination will change. If the infection is contained, a tender mass will often develop in the right lower quadrant, and the area of tenderness will now encompass the entire right lower quadrant. Involuntary guarding becomes evident and rebound tenderness more marked. The patient's temperature will be more like that seen with abscess formation and may rise to 39° C with a corresponding tachycardia.

If appendiceal rupture fails to localize, signs and symptoms of diffuse peritonitis will develop. Tenderness and guarding become generalized, the temperature remains higher than 38° C with spikes to 40° C, and the pulse rate increases to more than 100 beats/min.

Laboratory Tests

In the early diagnosis of acute appendicitis, laboratory tests are of little value. Up to one third of patients, particularly older patients,[4] have a normal total leukocyte count with acute appendicitis,[1,5] and more than half have, at most, a mild elevation. Even when the total leukocyte count and the differential white blood cell (WBC) count are abnormal, the degree of abnormality does not correlate well with the degree of appendiceal

inflammation.[6] Even when the total WBC count is normal, the differential WBC count often reveals a shift to the left with an increase in the percentage of polymorphonuclear neutrophils.[5] Less than 4% of patients have both a normal total WBC count and a normal differential count. The most important fact to remember when considering the diagnosis of appendicitis is that the clinical findings take precedence over the WBC count when they are at variance.

Urinalysis is helpful in the differential diagnosis of patients with lower abdominal pain only when it reveals significant numbers of red blood cells, WBCs, or bacteria. Minimal numbers of red blood cells, WBCs, and bacteria are seen in normal patients as well as in patients with appendicitis.

Patients with advanced appendicitis and abscess formation or generalized peritonitis may have abnormalities in liver function tests that mimic obstructive jaundice, biliary stasis, or other primary liver problems.

Radiographic Examination

With rare exceptions, plain roentgenologic examination of the abdomen is of little help in the differential diagnosis of acute appendicitis. The exceptions are when a fecalith is demonstrated and when other diagnoses such as acute cholecystitis, perforating duodenal ulcer, perforating colon cancer, acute diverticulitis, and pyelonephritis are being excluded.

It is not unusual to see cecal distention or a sentinel loop of distended small intestine in the right lower quadrant in patients with acute appendicitis. In late appendicitis with perforation and abscess formation, a mass can often be demonstrated that is extrinsic to the cecum. There may be scoliosis to the right, lack of the right psoas shadow, lack of small bowel gas in the right lower quadrant with abundant gas elsewhere in the small bowel, and signs of edema of the abdominal wall. With late appendicitis and generalized peritonitis, there is an ileus pattern with generalized gas throughout the small and large intestine.

Barium enema (BE) examination was recommended in the past in young women in whom the diagnosis was still in question after hours of observation and in patients with a debilitating systemic disease, such as leukemia, in whom the operative risk is markedly increased.[7] The findings of significance on BE include lack of filling or partial filling of the appendix and an extrinsic pressure defect on the cecum (the "reverse 3" sign).[8] Computed tomography (CT) and ultrasonography (US) are now preferred to BE in these circumstances.

As demonstrated in many studies, an experienced radiologist is able to diagnose acute appendicitis using US with an accuracy of greater than 90%.[9-11] Appendicitis is diagnosed if the maximal cross-sectional diameter of appendix exceeds 6 mm, if it is noncompressible, if an appendolith is present, or if a complex mass is demonstrated.[12] There are other criteria that are not universally agreed on, such as rigidity and nonmobility. Nonvisualization of the appendix is not a criterion for appendicitis. US can also be helpful in the diagnosis of perforated appendicitis with abscess formation. Studies that compared US and CT have demonstrated CT to be more accurate than US in the diagnosis of appendicitis in clinically equivocal cases.[3] Therefore, US should be used only when an experienced radiologist with an interest in appendicitis is available.

Although more expensive, CT has also been demonstrated to be of benefit in the diagnosis of acute appendicitis and has an accuracy of greater than 94%.[13,14] The cost can be reduced with no significant loss in diagnostic accuracy by performing a limited, unenhanced CT.[15] Appendicitis is diagnosed when the appendix is thickened with a diameter greater than 6 mm; a phlegmon, fluid, or abscess is present; there is an appendolith; and there are inflammatory changes in the periappendiceal fat (streaking and poorly defined increased attenuation).[13,14] The presence of pericecal inflammation without the presence of an inflamed appendix or an appendolith without the presence of periappendiceal inflammation are both insufficient to diagnose acute appendicitis.

An important consideration for CT in the diagnosis of acute appendicitis is when to use it. In one study, CT scanning excluded appendicitis in almost half of the patients in the study and identified an alternative diagnosis in 51% of those patients. The authors stated that the routine use of CT in patients with suspected appendicitis avoids unnecessary appendectomies and unnecessary delays before surgical treatment and saves money.[16] CT is not indicated in patients with an unequivocal diagnosis of appendicitis or in patients with a low risk of the diagnosis. In menstruating women and any patient with an equivocal diagnosis, a CT scan is probably indicated. An added benefit of the use of CT is that an identified abscess can be percutaneously drained during the same procedure.[17]

Acute Appendicitis in Infants and Young Children

The diagnosis of acute appendicitis is difficult in infants and young children for many reasons. The patient is unable to give an accurate history, and although appendicitis is infrequent, acute nonspecific abdominal pain is common in infants and children. Because of such factors, the diagnosis and treatment are often delayed, and complications develop.[18,19]

The clinical presentation of appendicitis in children can be quite similar to nonspecific gastroenteritis; thus, the suspicion of appendicitis often is not entertained until the appendix has ruptured and the child is obviously ill.[20] Two thirds of young children with appendicitis have had symptoms for more than 3 days before appendectomy.[19] Because children often cannot give an accurate history of their pain, the physical examination and other aspects of the history must be relied on to make the diagnosis. Vomiting, fever, irritability, flexing of the thighs, and diarrhea are likely early complaints. Abdominal distention is the most consistent physical finding. As in adults, the total leukocyte count is not a reliable test.

The incidence of perforation in infants younger than 1 year of age is almost 100%, and although it decreases with age, it is still 50% at 5 years of age. The mortality rate in this age group remains as high as 5%. In one series, nearly 40% of children with complicated appendicitis had been seen previously by a physician who failed to make the diagnosis of appendicitis.[19]

Appendicitis in Young Women

Although the overall incidence of negative laparotomy in patients suspected of having appendicitis is as high as 20%, the incidence in women younger than 30 years of age is as high as 45%. Pain associated with ovulation; diseases of the ovaries, fallopian tubes, and uterus; and urinary tract infections (cystitis) account for most of the misdiagnoses. If a young woman has atypical pain; no muscular guarding in the right lower quadrant; and no fever, leukocytosis, or leftward shift in the differential WBC count, it is best to observe the patient with frequent re-examinations. If after several hours the patient's signs and symptoms remain stable, it is appropriate to perform a CT scan.

Appendicitis During Pregnancy

The risk of appendicitis during pregnancy is the same as it is in nonpregnant women of the same age; the incidence is 1 in 2000 pregnancies. Appendicitis occurs more frequently during the first two trimesters, and during this period the symptoms of appendicitis are similar to those seen in nonpregnant women.[21] Surgery should be performed during pregnancy when appendicitis is suspected, just as it would be in a nonpregnant woman. As in the nonpregnant patient, the effects of a laparotomy that produces no findings are minor, whereas the effects of ruptured appendicitis can be catastrophic. Recent studies indicate that there is no increase in morbidity and mortality with laparoscopic appendectomy versus open appendectomy for the patient or the fetus.

During the third trimester of pregnancy, the cecum and appendix are displaced laterally and are rotated by the enlarged uterus. This results in localization of pain either more cephalad or laterally in the flank, leading to delay in diagnosis and an increased incidence of perforation. Factors such as displacement of the omentum by the uterus also impair localization of the inflamed appendix and result in diffuse peritonitis. In cases of uncomplicated appendicitis, the prognosis for the infant following appendectomy is directly related to the infant's birth weight. If peritonitis and sepsis ensue, infant mortality increases because of prematurity and the effects of sepsis.

Acute appendicitis can be confused with pyelitis and torsion of an ovarian cyst. However, death from appendicitis during pregnancy is mainly caused by a delay in diagnosis. In the final analysis, early appendectomy is the appropriate therapy in suspected appendicitis during all stages of pregnancy.[21]

Appendicitis in the Elderly Population

Appendicitis has a much greater mortality rate among elderly persons when compared with young adults. The increased risk of mortality appears to result from both delay in seeking medical care and delay in making the diagnosis.[22] The presence of other diseases associated with aging contributes to mortality, but the major reason for the increased mortality of appendicitis in the aged is delay in treatment. Classic symptoms are present in elderly persons but are often less pronounced. Right lower quadrant pain localizes later and may be milder in elderly persons. On initial physical examination, the findings are often minimal, although right lower quadrant tenderness will eventually be present in most patients.[23] Distention of the abdomen and a clinical picture suggesting small bowel obstruction are commonly seen.

More than 30% of elderly patients will have a ruptured appendix at the time of operation.[23] Although other factors play a role, delay in seeking care and in making the diagnosis are the major reasons for perforation. It is imperative, therefore, that once the diagnosis of acute appendicitis is made, an urgent operation must be advised.

Differential Diagnosis

The differential diagnosis of abdominal pain is a stimulating exercise. When the classic symptoms of appendicitis are present, the diagnosis of appendicitis is usually easily made and is seldom missed. When the diagnosis is not obvious, knowledge of the differential diagnosis becomes important. Most of the entities in the differential diagnosis of appendicitis also require operative therapy or are usually not made worse by an exploratory laparotomy. Therefore, it is essential that one eliminate those diseases that do not require operative therapy and can be made worse by operation, such as pancreatitis, myocardial infarction, and basilar pneumonia.

The diseases in young children that are most frequently mistaken for acute appendicitis are gastroenteritis, mesenteric lymphadenitis, Meckel's diverticulum, pyelitis, small intestinal intussusception, enteric duplication, and basilar pneumonia. In mesenteric lymphadenitis, an upper respiratory infection is often present or has recently subsided. Acute gastroenteritis is usually associated with crampy abdominal pain and watery diarrhea. Intestinal intussusception occurs most frequently in children younger than 2 years of age, an age at which appendicitis is uncommon. With intussusception, a sausage-shaped mass is frequently palpable in the right lower quadrant. The preferred diagnostic procedure is a gentle BE, which, in addition to making the diagnosis, usually reduces the intussusception.

In teenagers and young adults, the differential diagnosis is different in men and women. In young women, the differential diagnosis includes ruptured ectopic pregnancy, mittelschmerz, endometriosis, and salpingitis.[24] Chronic constipation also needs to be considered in young women. The symptoms that accompany the acute

onset of regional enteritis can mimic acute appendicitis, but a history of cramps and diarrhea and the lack of an appropriate history for appendicitis are hints that the diagnosis is regional enteritis.

In young men, the potential list of differential diagnoses is smaller and includes the acute onset of regional enteritis, right-sided renal or ureteral calculus, torsion of the testes, and acute epididymitis.

In older patients, the differential diagnosis of acute appendicitis includes diverticulitis, a perforated peptic ulcer, acute cholecystitis, acute pancreatitis, intestinal obstruction, perforated cecal carcinoma, mesenteric vascular occlusion, rupturing aortic aneurysm, and the disease entities already mentioned for young adults.

Treatment

Preoperative Preparation

It is not necessary to rush a patient with a presumed diagnosis of acute appendicitis directly to the operating room. All patients, especially those with a presumed diagnosis of peritonitis, should be adequately prepared before being taken to the operating room. Selected patients with a palpable right lower quadrant mass may be initially managed without operation.[25]

Intravenous fluid replacement should be initiated and the patient resuscitated as rapidly as possible, especially when peritonitis is suspected. Once the patient has a good urinary output, it can be assumed that resuscitation is complete. Nasogastric suction is especially helpful in patients with peritonitis and profound ileus. If the patient's body temperature is higher than 39° C, appropriate measures should be taken to reduce fever prior to beginning an operation.

A broad-spectrum antibiotic, such as cefoxitin, should be administered preoperatively to help control sepsis and to reduce the incidence of postoperative wound infections. If, at the time of operation, the patient has early appendicitis, antibiotic administration can be stopped after one postoperative dose. Antibiotics should be continued as clinically indicated in patients who have gangrenous or ruptured appendicitis with localized or generalized peritonitis.

Examination Under Anesthesia

After the induction of anesthesia, the patient's abdomen should be systematically palpated. Such an examination may, on occasion, demonstrate another pathologic condition to be the cause of the patient's symptoms, such as acute cholecystitis. It also may be possible to palpate an appendiceal mass that will confirm the suspected diagnosis.

Uncomplicated Appendicitis Without a Palpable Mass

In this circumstance, when the diagnosis of acute appendicitis has been made and there is no reason to suspect that the appendix has ruptured, an appendectomy should be performed. The earlier the diagnosis is made and the sooner the appendectomy is performed, the better the prognosis. As stated earlier, if there is any doubt about whether the appendix has ruptured, the operation should be performed at once, because the morbidity of a perforated appendix is 100-fold greater than that of an uncomplicated appendectomy. The latter procedure should have a surgical mortality rate of less than 0.1%, whereas in contrast, the mortality rate of a ruptured appendix can be as high as 10%.

One recommended incision for a routine appendectomy is a transverse one (i.e., Rockey-Davis, Fowler-Weir-Mitchell incisions). The incision is made in a transverse direction, 1 to 3 cm below the umbilicus, and is centered on the midclavicular line. The length of the incision should be approximately 1 cm longer than the breadth of the surgeon's hand. The aponeurosis and muscles of the abdominal wall are split or incised in the direction of their fibers (Fig. 154–1). Exposure of the appendix through this incision is better when compared with that obtained through the classic McBurney incision, particularly in patients with a retrocecal appendix and in those who are obese.

The other recommended incision, the gridiron, or muscle-splitting one (McBurney incision), can be used. This is the most widely used incision in uncomplicated appendicitis. The skin incision is made through a point one third of the way along a line from the anterosuperior spine of the ileum to the umbilicus. The incision is made obliquely, beginning inferiorly and medially, and extending laterally and superiorly. It should be 8 to 10 cm in length, with its most medial extent being the lateral edge of the rectus muscle. The aponeurosis and muscles of the abdominal wall are split or incised in the direction of their fibers in such a manner that the entire skin incision can be used for exposure. After entering the peritoneum, the appendix is found as described for the transverse incision. The exposure through a McBurney incision, especially for a retrocecal appendix, can be awkward unless the appendix lies immediately below the incision. If necessary, the incision can be extended medially, partially transecting the rectus sheath, but this maneuver is usually helpful only in a pelvic appendicitis.

If there is doubt about the diagnosis of acute appendicitis and an exploratory laparotomy is indicated, a vertical midline incision is more appropriate. An appendectomy can be performed with little difficulty through such an incision.

After the peritoneum is opened, the appendix is identified by following the anterior cecal taenia to the base of the appendix. The inflamed appendix is coaxed into the wound by gentle traction and the transection of adhesions, if present. If the appendix is retrocecal or retroperitoneal, or if the local inflammation and edema are intense, exposure is improved by dividing the lateral peritoneal reflection of the cecum. At the end of this maneuver, the cecum should lie within the wound and the appendix should be at the level of the anterior abdominal wall so that continuing vigorous retraction is unnecessary while removing the appendix (see Fig. 154–1).

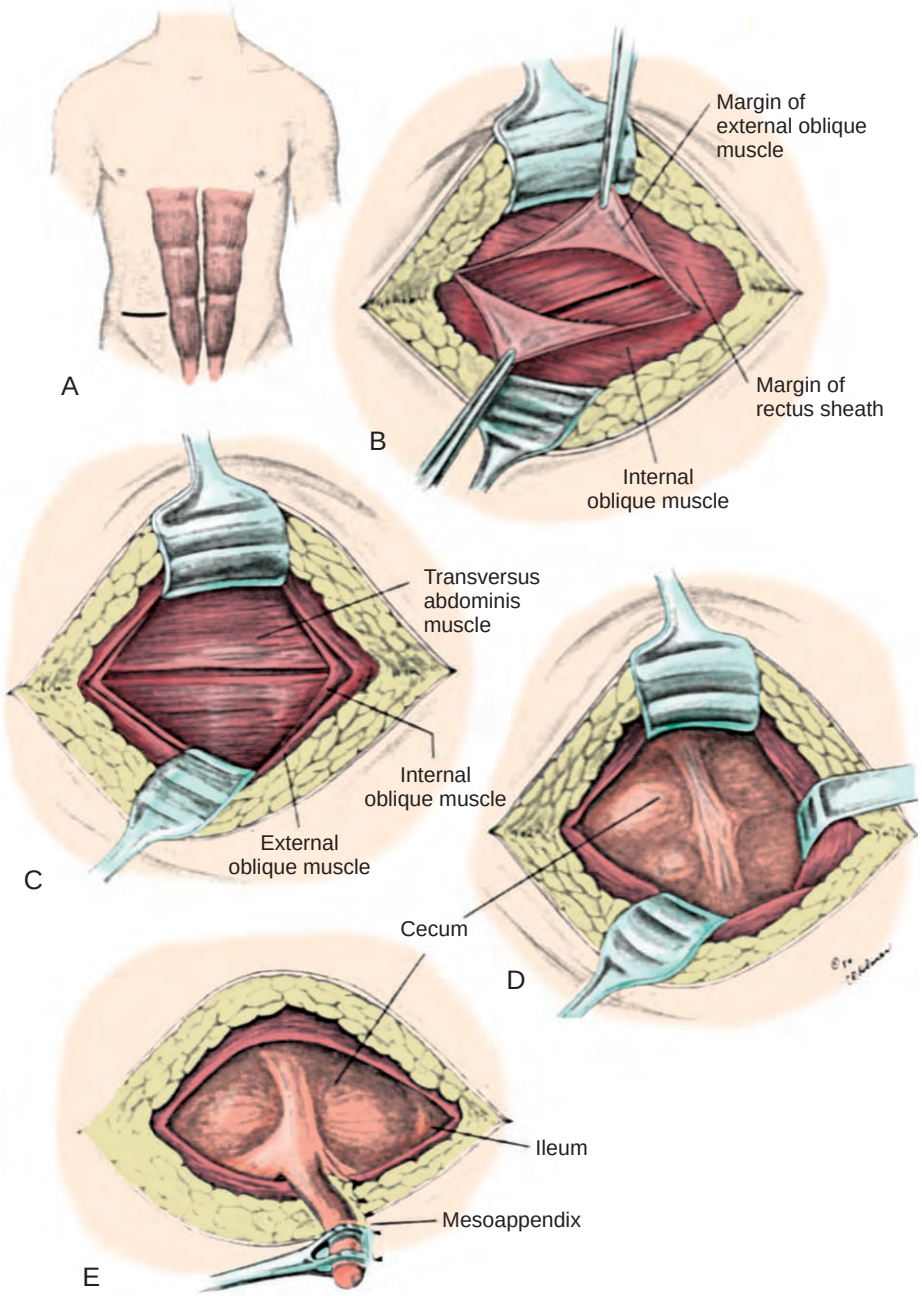

Figure 154–1. Steps in exposing the appendix for an appendectomy through a transverse incision. **A,** Placement of the skin incision. **B** and **C,** External and internal oblique and transversus abdominis muscles are divided in the direction of their fibers. **D,** After incision of the peritoneum, the cecum is exposed and the appendix is located by following the anterior cecal taenia inferiorly. **E,** The cecum is mobilized into the wound through incision of its lateral peritoneal reflections. (**A-E,** From Moody FG, Carey L, Jones RS, et al: Surgical Treatment of Digestive Diseases. Chicago, Year Book, 1986.)

If the appendix is not adherent, its base can be easily identified because the entire appendix often pops into the operative field. If the appendix is adherent, however, its base may be difficult to recognize. Aids in recognition include the following:

1. All three taeniae lead to and end at the base of the appendix.
2. The ileocecal junction can usually be identified, just below which is the base of the appendix.

If the appendix does not come into the wound but the base has been identified, an Allis clamp can be placed around but not on the appendix for traction. An effort is made to deliver the tip of the appendix into the operative field. If the appendix is not adherent to surrounding tissues, traction on the Allis clamp is usually successful in delivering the appendix.

Once the appendix has been freed up, the mesoappendix is transected beginning at its free border, taking small bites of the mesoappendix between pairs of hemostats placed approximately 1 cm from and parallel to the appendix. This process should be repeated until the base of the appendix is reached. If exposure of a long, adherent appendix is difficult, the mesoappendix can be transected in a retrograde manner beginning at the base of the appendix.

There are three ways to handle the appendiceal stump: simple ligation, inversion, and a combination of ligation and inversion. Either simple ligation or inversion

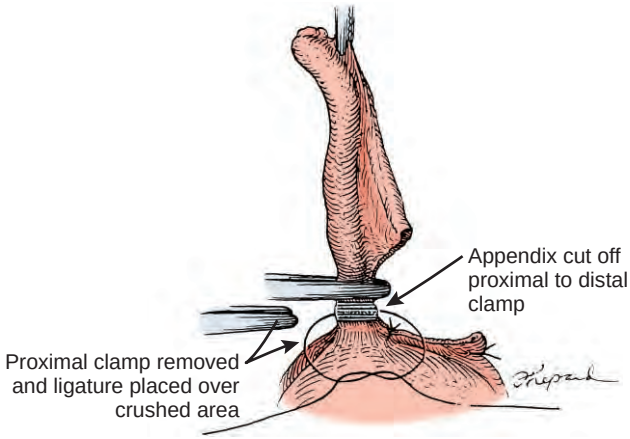

Figure 154–2. Ligation of the stump of the appendix in the groove formed by a crushing clamp. (From Partipilo AV: Surgical Technique and Principles of Operative Surgery, 4th ed. Philadelphia, Lea & Febiger, 1949.)

is acceptable and has a comparable incidence of complications. The combination of ligation and inversion is not recommended, because it does not reduce the risk of septic complications, but it does create conditions conducive to the development of an intramural abscess or mucocele. Also, the ligated and inverted appendiceal stump may later appear on a subsequent BE as a cecal "tumor" and be a source of diagnostic difficulties.[26]

Simple ligature of the appendiceal stump is accomplished by crushing the appendix at its base with a hemostat, then moving the hemostat and replacing it on the appendix just distal to the crushed line. A ligature of monofilament suture is placed in the groove caused by the crushing clamp and is tied tightly (Fig. 154–2). The appendix is transected just proximal to the hemostat and removed. Inversion of an unligated stump using a Z-stitch (Fig. 154–3), rather than the more conventional pursestring suture, is preferred. The upper level of the Z-stitch is placed as a Lembert suture in the cecum, just distal to the base of the appendix. The suture is then brought around the base of the appendix and continued as a second Lembert suture beneath the base of the appendix. The appendix is then transected between clamps, the stump is inverted into the cecum, the proximal clamp is removed, and the ends of the Z-stitch are tied over the stump of the appendix. The appendiceal stump is not ligated. If the appendiceal stump is unsuitable for inversion because of edema, it should simply be ligated and not inverted.

Laparoscopic Appendectomy

Laparoscopic and minimal access surgery continues to expand in the field of general surgery, and diagnostic laparoscopy and laparoscopic appendectomy have become accepted procedures in many surgeons' practices. The early use of diagnostic laparoscopy in patients with right lower quadrant abdominal pain and suspected appendicitis reduces the risk of appendiceal perforation and the negative appendectomy rate to less than 10%.[27] Diagnostic laparoscopy is particularly useful in women of reproductive age and in the obese. In the former, frequently confounding gynecologic disorders can be well visualized to provide the diagnosis, and in the latter, laparoscopy can eliminate the morbidity risks of a large incision. In addition, it is safe to not proceed with appendectomy if the appendix appears normal.[28,29]

Conversion of diagnostic laparoscopy to therapeutic laparoscopy is easily accomplished by the addition of other ports. Trocar placement for laparoscopic appendectomy is a matter of surgeon choice with consideration of the triangle rule for port placement. Diagnostic laparoscopy is usually performed through a periumbilical port, with a 10/11-mm port added midway between the umbilicus and pubis and a 5-mm port placed over the appendix or the right midlateral abdomen if appendectomy is performed (Fig. 154–4). Once the diagnosis is confirmed, the mesoappendix can be taken down with either hemoclips or the harmonic scalpel. The appendix is amputated from the cecum between endoloops or with an endo-GIA stapler (Fig. 154–5). The appendix can then be removed from the abdomen with a specimen pouch or withdrawn into the 10/11-mm port. Care should be taken to prevent contact of the appendix or its contents with the wound edges.

There is general agreement that patients undergoing laparoscopic appendectomy have less postoperative pain, a lower rate of wound infection, a lower overall complication rate, a more rapid return to diet, a shorter hospital stay, a longer operative time, and more equipment charges in the operating room.[30-33] In contrast, a more rapid return to work and a lower complication rate are more controversial claims because prospective studies show differing results.[34,35] Laparoscopic appendectomy results in a lower wound infection rate compared with an open procedure but has a higher intra-abdominal abscess rate if the appendix is perforated. Appendicitis with abscess should not be addressed laparoscopically because the pneumoperitoneum can disrupt the abscess cavity with soilage of the abdomen. Dissection of the abscess laparoscopically carries an undue risk of injury to the bowel and mesentery. Other relative contraindications to laparoscopic appendectomy include previous abdominal surgery precluding safe trocar placement, uncontrolled coagulopathy, and significant portal hypertension.

Laparoscopic appendectomy appears to be safe and efficacious. It provides a rapid diagnosis and a significant reduction in negative appendectomy rate in females of child-bearing age with suspected appendicitis. Minimal access surgery reduces the morbidly risk in obese patients who require an appendectomy.

Perforated or Gangrenous Appendicitis with a Periappendiceal Mass

When a mass is detected by examination under anesthesia, a transverse incision is made over the most prominent portion of the mass. The muscles and aponeuroses are split along their lines of cleavage in gridiron fashion.

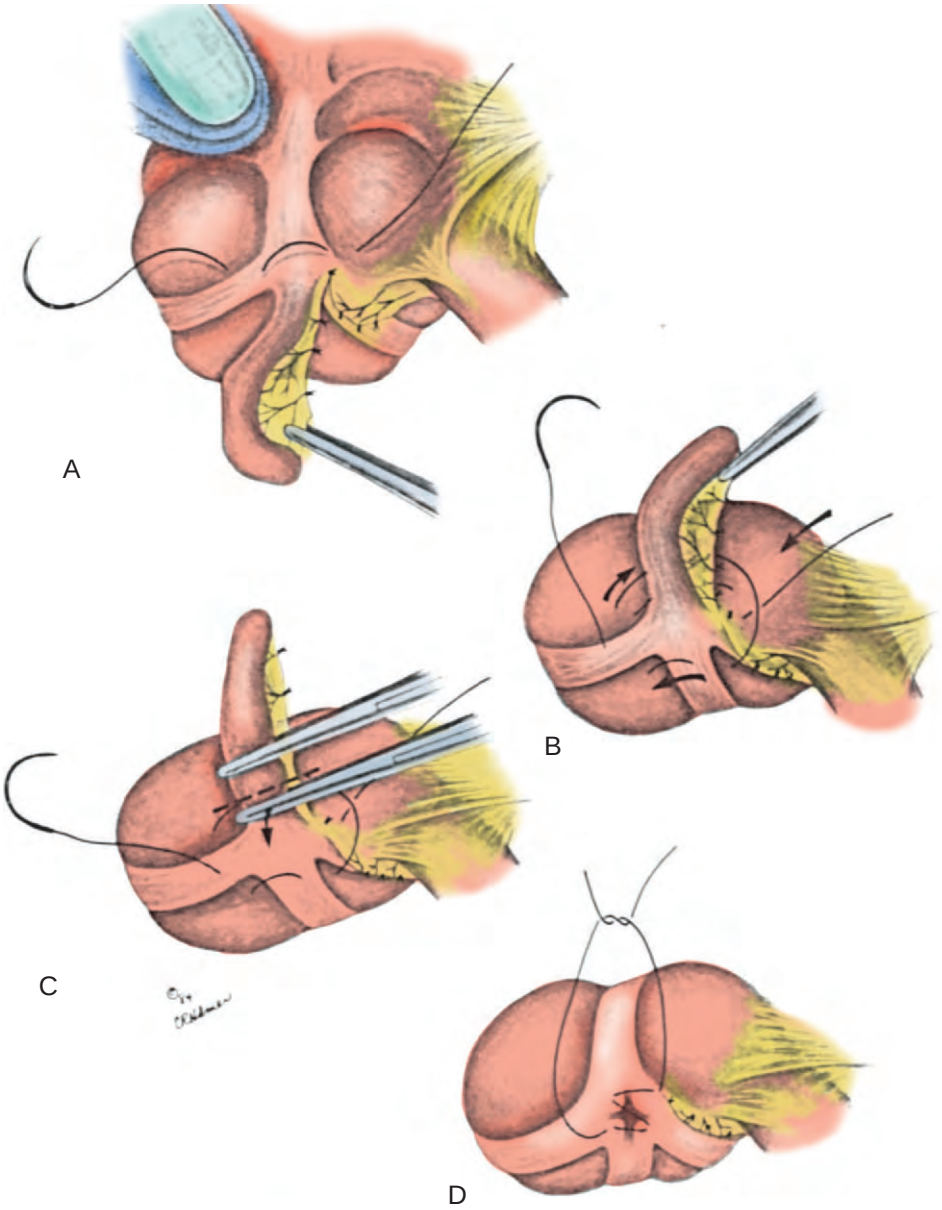

Figure 154–3. Use of a Z-stitch to invert the unligated appendiceal stump. **A,** Two bites of the suture are placed in the cecum 1 cm distal to the base of the appendix. **B,** The suture is then brought around the appendix medially and two additional bites are placed beneath the base of the appendix. **C,** The appendix is then transected. **D,** The stump of the appendix is inverted into the cecum and the clamp is removed as the suture is tightened. (**A-D,** From Adams JT: Z-stitch suture for inversion of the appendiceal stump. Surg Gynecol Obstet 127:1321, 1968.)

After entering the peritoneal cavity, the wound should be packed immediately to prevent contamination of the abdominal cavity. As mentioned earlier, the mass may be made up of omentum and loops of small intestine adherent to the inflamed appendix, and an abscess may not be present. If feasible, an appendectomy is then performed; usually it will not be possible to invert the stump, so simple ligation is preferred.

It is not necessary to place a subfascial drain in a patient with a gangrenous appendix and minimal or no periappendiceal pus. If there is a periappendiceal abscess and the tissues are fixed so as to create a dead space, the cavity should be drained with one or more closed-suction drains brought out through a separate stab incision.

Before fascial closure, the right iliac fossa and the wound should be liberally irrigated. Muscles and aponeuroses should be closed with interrupted nonabsorbable sutures. The skin should be left open, to be closed with adhesive paper tapes on the 5th or 6th postoperative day. Parenteral antibiotics should be continued for 5 days after operation or until clinical signs indicate no infection.

Perforated Appendicitis with Localized Abscess Formation

If, at the time of initial physical examination, a well-localized periappendiceal mass is found and the patient's symptoms are improving, it is acceptable in healthy adults to initiate parenteral antibiotic treatment and to follow the patient expectantly.[36] This form of therapy is not appropriate in children, pregnant women, or elderly patients. In these groups, an emergency operation is indi-

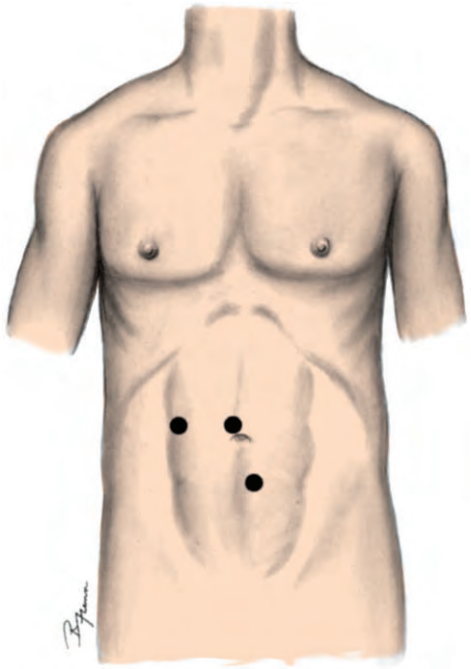

Figure 154–4. Trocar placement for laparoscopic appendectomy. Additional trocars can be placed in the right upper or left lower quadrants. (From Frantzides CT: Laparoscopic and Thoracoscopic Surgery. St. Louis, Mosby–Year Book, 1994, p 66.)

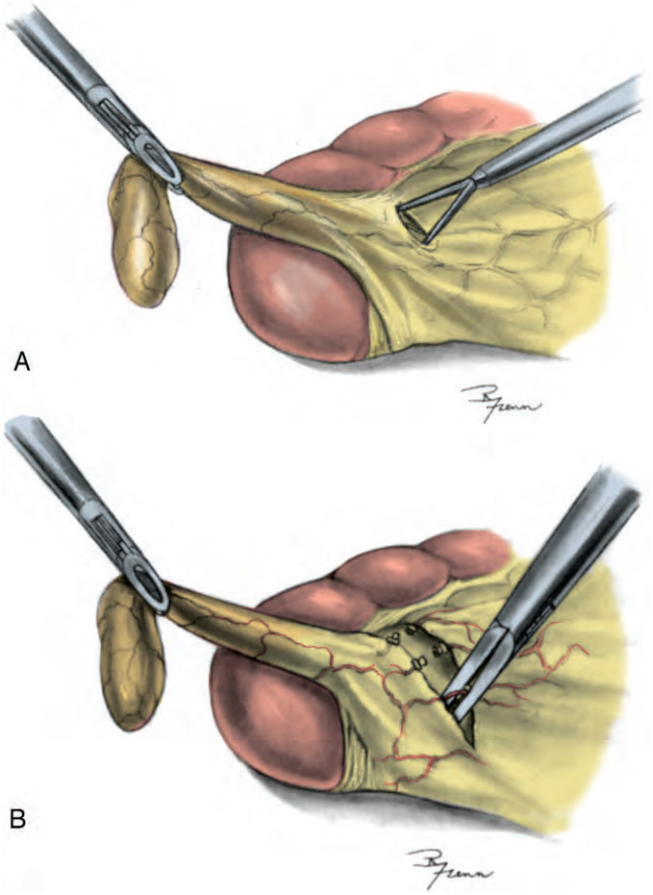

Figure 154–5. Technique for laparoscopic appendectomy. **A,** The appendix is grasped and retracted toward the pelvis, thus exposing the mesoappendix. **B,** The mesoappendix is divided using individually placed clips. (**A** and **B,** From Frantzides CT: Laparoscopic and Thoracoscopic Surgery. St. Louis, Mosby–Year Book, 1994, p 67.)

cated. In two thirds of patients, expectant treatment of an appendiceal mass succeeds, and an interval appendectomy can be performed at a later date. In one third of patients, symptoms do not subside and an emergency CT scan should be performed. If an abscess is identified on CT scan an attempt should be made to drain the abscess percutaneously under CT or US guidance.[17] If not successful, the abscess should be drained surgically.

The skin incision for drainage of a periappendiceal abscess is made just medial to the crest of the ilium at the level of the abscess. Using a muscle-splitting technique, the lateral edge of the peritoneum is exposed and pushed medially so that the abscess is approached from its lateral aspect. Once the abscess is entered, a finger should be used to break up the loculations. If the appendix can be freed up without breaking down adhesions, an appendectomy should be performed. If an appendectomy is not performed, an interval appendectomy can be done 3 to 6 months after drainage from the abscess has ceased and the wound has completely healed.

After the wound has been thoroughly irrigated with normal saline, a closed-suction drain should be inserted into the abscess cavity and brought out through a separate stab wound in the flank. The muscles and aponeuroses are closed with interrupted nonabsorbable sutures, and the skin and subcutaneous tissues are packed open with saline-soaked gauze. The drain should be left in place until it is draining less than 50 ml/day and then advanced progressively until removed.

Systemic antibiotics should be continued for 5 days postoperatively or until signs of sepsis have cleared. A daily rectal examination should be done to detect pelvic abscess. The patient may be discharged from the hospital when there is no fever 48 hours after the discontinuation of antibiotic therapy.

Perforated Appendicitis with Diffuse Peritonitis

The major cause of mortality from appendicitis is generalized peritonitis. Therefore, immediate exploration is indicated in a patient with a diagnosis of acute appendicitis in whom the physical findings are consistent with diffuse peritonitis. If a perforated appendix and diffuse peritonitis are documented at operation, an appendectomy should be performed and the abdomen thoroughly irrigated. The use of drains in diffuse peritonitis is not recommended unless there are localized abscesses requiring drainage.[37] The wound and postoperative care should be handled as described in a patient with a periappendiceal abscess.

Normal Appendix When Appendicitis Is Suspected

If a patient undergoes exploratory laparotomy (especially through a right lower quadrant incision) for suspected acute appendicitis, and a normal appendix is subsequently found, a careful search for another pathologic condition should be made and an appendectomy performed. The abdomen should not be closed until the cause of the symptoms has been identified and treated or the surgeon is sure that no lesion requiring treatment is present. The normal appendix is *removed* to obviate diagnostic confusion in the future.

If the history and physical examination were appropriate for the diagnosis of acute appendicitis, it is not an error to perform an exploratory laparotomy and remove what appears to be a normal appendix. A policy of early surgical intervention on the basis of clinical suspicion has been demonstrated overall to reduce both the morbidity and mortality of acute appendicitis.

In the past, a negative appendectomy rate of 20% was acceptable.[38] Studies have suggested that rates of 10% to 15% and lower are feasible without an unacceptably high rate of perforated appendicitis.[39-41]

Complications

Postoperative complications occur in 5% of patients with an unperforated appendix but in more than 30% of patients with a gangrenous or perforated appendix. The most frequent complications after appendectomy are wound infection, intra-abdominal abscess, fecal fistula, pylephlebitis, and intestinal obstruction.

Subcutaneous tissue infection is the most common complication after appendectomy. The organisms most frequently cultured are anaerobic *Bacteroides* species and the aerobes *Klebsiella, Enterobacter,* and *Escherichia coli.*[42] When early signs of wound infection (undue pain and edema) are present, the skin and subcutaneous tissue should be opened. The wound should be packed with saline-soaked gauze and reclosed with Steri-Strips in 4 to 5 days.

Pelvic, subphrenic, or other intra-abdominal abscesses occur in up to 20% of patients with a gangrenous or perforated appendicitis. They are accompanied by recurrent fever, malaise, and anorexia of insidious onset. CT scanning is of great help in making the diagnosis of intra-abdominal abscess. When an abscess is diagnosed, it should be drained either operatively or percutaneously.

Some fecal fistulas close spontaneously, provided that there is no anatomic reason for the fistula remaining open. Those that do not close spontaneously obviously require operation. Pylephlebitis, or portal pyemia, is characterized by jaundice, chills, and high fever. It is a serious illness that frequently leads to multiple liver abscesses. The infecting organism is usually *E. coli.* This complication has become rare with the routine use of antibiotics in complicated appendicitis. Although not frequent, true mechanical bowel obstruction may occur as a complication of acute appendicitis. As with any other mechanical small bowel obstruction, operative therapy is indicated.

CHRONIC AND RECURRENT APPENDICITIS

There are occasional patients who have had one or more attacks of what appears to be acute appendicitis. Between attacks, these patients are free of symptoms and the physical examination is normal. In such patients, if a fecalith is present on abdominal radiograph, if a BE demonstrates no filling of the appendix, or if repeated examinations during an attack provide evidence of recurrent appendicitis, elective appendectomy should be undertaken.[43] To sustain a diagnosis of chronic appendicitis, the resected appendix must demonstrate fibrosis in the appendiceal wall, partial to complete obstruction of the lumen, evidence of old mucosal ulceration and scarring, and infiltration of the wall of the appendix with chronic inflammatory cells.

MUCINOUS CYSTADENOMA AND CYSTADENOCARCINOMA

Distention of the lumen of the appendix by the mucus secreted by proliferating tumor cells can occur with both mucinous cystadenoma and cystadenocarcinoma. Because it is difficult to distinguish between benign and malignant tumors, a right hemicolectomy should be performed, since appendectomy is not curative in the usual circumstance. When there are numerous peritoneal implants of a mucinous-like substance, a diagnosis of pseudomyxoma peritonei is appropriate. Within these gelatinous masses are nests of tumor cells attached to the peritoneum.

TUMORS OF THE APPENDIX

Neoplasms of the appendix are rare. The two most frequently observed are carcinoid tumor and adenocarcinoma. The appendix is the most common site of carcinoid tumor, and carcinoid is the most common neoplasm of the appendix. It is found in approximately 0.1% of all surgically removed appendices. The only setting in which the diagnosis is suspected preoperatively is in the rare patient with symptoms of the carcinoid syndrome. This syndrome is characterized by flushing, diarrhea, and asthma-like symptoms. If a carcinoid tumor is in the mid or distal appendix and is less than 1 cm in diameter, a simple appendectomy is adequate therapy. If the tumor is greater than 1 cm in diameter or is in the base of the appendix or if there is evidence of nodal metastases, a right hemicolectomy is recommended.[44]

Adenocarcinoma of the appendix may appear as either a well-differentiated mucus-producing tumor or as a poorly differentiated adenocarcinoma that appears as a solid mass. Both types of adenocarcinoma of the appendix have been reported to metastasize to regional lymph nodes, although malignant mucocele has been considered clinically to be less virulent. If an adenocarcinoma of the appendix is confined to the mucosa (carcinoma in situ), there is no difference in survival between simple appendectomy and appendectomy com-

bined with right hemicolectomy. If the tumor is invasive, however, the prognosis is improved by right hemicolectomy, so the more extensive operation is recommended for most cases.[45]

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Part

4

Neoplastic Disease

Chapter

155

Colorectal Polyps, Polyposis Syndromes, and Hereditary Nonpolyposis Colorectal Cancer

David B. Chessin · José G. Guillem

POLYPS OF THE COLON AND RECTUM

Definitions and Classification

The word *polyp* derives from Latin and Greek root words meaning "many feet" and is defined as a mass that protrudes into the lumen of the bowel.[1] It is believed that most polyps originate as *sessile* lesions, defined grossly by their broad base without a stalk. Traction on the polyp can lead to a *pedunculated* polyp with a stalk.

Several histologic types of colorectal polyps have been described and can be broadly classified into neoplastic polyps and non-neoplastic polyps based on their malignant potential (Table 155–1). The most common neoplastic polyp is the adenoma, which harbors malignant potential. Other, less common neoplastic polypoid lesions include carcinoid tumor, melanoma, lymphoma, and rare mesenchymal tumors such as gastrointestinal stromal tumor and Kaposi's sarcoma.

The most common non-neoplastic polyp of the colorectum is the hyperplastic polyp. Other non-neoplastic polyps include hamartomatous polyps (such as those seen in juvenile polyposis syndrome [JPS] and Peutz-Jeghers syndrome [PJS]) and inflammatory polyps. Submucosal lesions that resemble polyps include lymphoid polyps, lipomas, leiomyomas, neuromas, and angiomas.

Adenomatous Polyps

Up to 66% of adenomatous polyps are asymptomatic and are discovered during screening or surveillance.[2] However, when symptoms do occur, they are most commonly rectal bleeding, a change in bowel habits, mucus discharge, and nonspecific abdominal pain. In addition, large distal rectal adenomas have been reported to produce watery diarrhea or form the lead point for a colocolonic intussusception. Colorectal adenomas are uncommon prior to age 50 years and may be more frequent in men.

Adenomas vary from 1 mm up to several centimeters. They arise as a result of epithelial proliferative dysplasia. The nuclei of adenomatous cells appear hyperchromatic and cigar-shaped in a palisading pattern.[1,3] Grossly, they may appear sessile or pedunculated. Most small adenomas have a smooth surface but develop nodularity and superficial clefts as they increase in size.

Table 155–1 Histologic Classification of Colorectal Polyps

Neoplastic	Non-neoplastic
Adenoma	Hyperplastic
Tubular	Hamartoma
Tubulovillous	Juvenile
Villous	Peutz-Jeghers
Rare malignant lesions	Inflammatory
Carcinoid tumor	Submucosal lesions
Melanoma	Lymphoid
Lymphoma	Lipoma
Mesenchymal tumors	Leiomyoma
	Neuroma
	Angioma

Histologically, adenomas are classified as tubular (85% to 90%), tubulovillous (5% to 10%), or villous (1%) (Fig. 155–1).[1] Tubular adenomas are characterized by closely packed straight or branching tubules extending into a normal-appearing lamina propria. Villous adenomas are characterized by finger-like processes made up of a core of lamina propria enveloped by adenomatous epithelium. The tall columnar cells become mucin depleted with basally located oval nuclei. As the adenoma develops dysplasia, nuclear atypia, mitotic figures, and loss of polarity become evident.

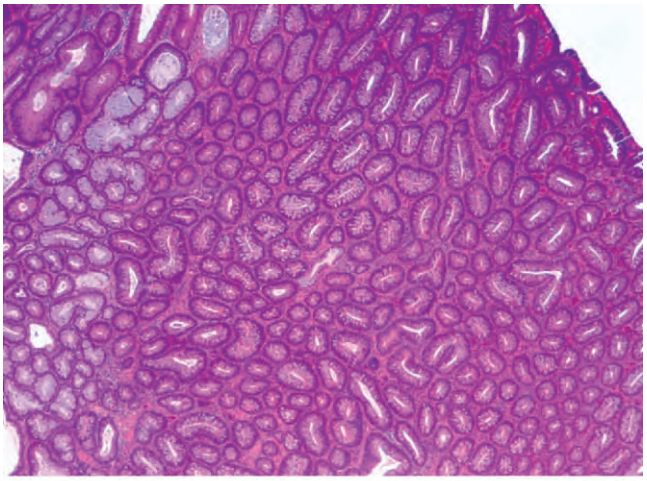
Adenoma to Carcinoma Sequence

The major clinical importance an adenomatous polyp is its malignant potential because most, if not all, colorectal cancer (CRC) arises from an adenomatous polyp. The risk of malignancy in an adenomatous polyp is related to its size, histologic appearance, and severity of dysplasia. The interval between formation of a colorectal adenoma and development of CRC varies, but the average is from 8 to 10 years. However, most colorectal adenomas do not progress to cancer.[4,5] In fact, the cumulative risk of CRC at the site of an adenomatous polyp is approximately 2.5% at 5 years, 8% at 10 years, and 24% at 20 years.[6]

Several lines of evidence support the adenoma to carcinoma concept, including the observation that up to one third of resected CRC specimens contain synchronous adenomas,[5,7] the parallel increase in risk of CRC with increasing number of adenomas,[8] the inevitable development of CRC in patients with familial adenomatous polyposis (FAP),[9] and the high rate of development of CRC in patients who refuse removal of adenomas.[6] In addition, molecular and genetic evidence has emerged to further support the adenoma-to-carcinoma sequence.[10-13]

Screening for Adenomatous Polyps

CRC is the second most common cause of cancer mortality in the United States.[14] However, colonoscopic



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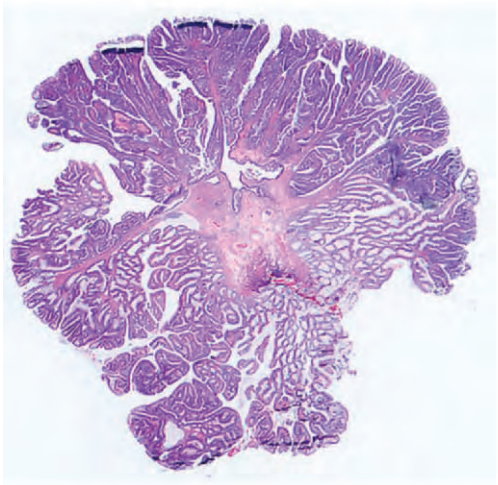

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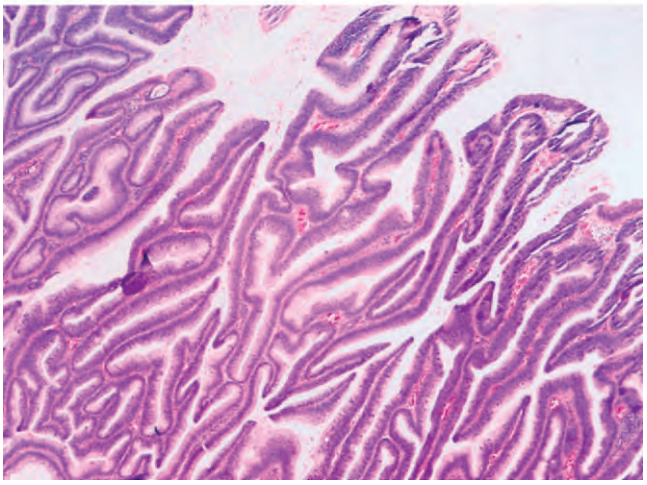

C

Figure 155–1. **A,** Tubular adenoma. **B,** Tubulovillous adenoma. **C,** Villous adenoma. (**A-C,** Courtesy of Jinru Shia, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

Table 155–2 Guidelines for Screening of Colorectal Neoplasms Based on AGA, ACS, and ASCRS Recommendations

Risk Category	Recommendations	Age to Begin, yr	Interval
Average Risk			
Patients ≥ 50 yr who do not meet criteria for moderate or high risk	One of the following:		
	FOBT or FIT	50	Every yr
	Flexible sigmoidoscopy	50	Every 5 yr
	FOBT or FIT plus flexible sigmoidoscopy	50	Every 5 yr
	DCBE	50	Every 5 yr
	Colonoscopy	50	Every 10 yr
Moderate Risk			
Personal history of colorectal adenoma	Colonoscopy	At polyp diagnosis	Within 3 yr (5 yr for patients with complete removal of 1 or 2 small adenomas)
Personal history of resected CRC	TCE	At CRC resection	Within 1 yr (then every 3 to 5 yr if normal)
CRC or adenoma in first-degree relative <60 yr of age at diagnosis	TCE	40, or 10 yr before the youngest familial CRC	Every 5 yr
CRC in ≥ 2 first-degree relatives	TCE	40, or 10 yr before the youngest familial CRC	Every 5 yr
High Risk			
Family history of FAP	Flexible sigmoidoscopy	10-12	Every 1 to 2 yr
Family history of HNPCC	Colonoscopy	20-25, or 10 yr earlier than youngest familial CRC	Every 2 yr until age 40, then every yr
Personal history of IBD	Colonoscopy with biopsies	8-10 yr after onset of colitis	Every 1 to 2 yr

ACS, American Cancer Society; AGA, American Gastroenterological Association; ASCRS, American Society of Colon and Rectal Surgeons; FAP, familial adenomatous polyposis; FOBT, fecal occult blood test; FIT, fecal immunochemical test; DCBE, double-contrast barium enema; HNPCC, hereditary nonpolyposis colorectal cancer; IBD, inflammatory bowel disease (ulcerative colitis and Crohn's disease); TCE, total colorectal examination (colonoscopy or DCBE and flexible sigmoidoscopy).

detection and treatment of adenomatous polyps, prior to the development of invasive cancer, has led to a decrease in the incidence of CRC.[15] The relative lack of signs and symptoms of colorectal adenomas and the potential benefit of their early diagnosis and treatment provide the rationale for screening of the general population. Regardless of the screening regimen chosen, a positive screening test should be followed by a diagnostic colonoscopy with surgical resection when clinically appropriate and follow-up surveillance for adenomas treated with polypectomy alone.[16]

The American Cancer Society recommends an average risk individual begin CRC screening at 50 years of age with one of the following five options: (1) annual fecal occult blood test or fecal immunochemical test; (2) flexible sigmoidoscopy every 5 years; (3) annual fecal occult blood test or fecal immunochemical test plus flexible sigmoidoscopy every 5 years; (4) double-contrast barium enema (DCBE) every 5 years; or (5) colonoscopy every 10 years (Table 155–2).[17] These recommendations are similar to those of the American Gastroenterological Association, American Society of Colon and Rectal Surgeons (ASCRS), and the U.S. Preventive Services Task Force (USPSTF).[16,18,19]

It is important to stratify patients into moderate- or high-risk categories for colorectal adenomas or CRC, as these patients are screened with colonoscopy or a combination of flexible sigmoidoscopy and DCBE (see Table 155–2). Moderate-risk patients include those with a personal history of a colorectal adenoma or resected CRC, a CRC or adenoma diagnosed in a first-degree relative before 60 years of age, or CRC in two or more first-degree relatives. High-risk patients include those with a family history of FAP or HNPCC or a personal history of inflammatory bowel disease (ulcerative colitis or Crohn's disease). The presence of a rectosigmoid polyp is an indication for colonoscopy, because 30% to 50% of patients have at least one synchronous colon lesion.[7,20,21] Others have reported that patients with distal rectal adenomas have a twofold to threefold increased risk of advanced

adenomas of the proximal colon.[22] For patients with untreated polyps of the proximal colon, the risk of CRC doubles.[23]

The standard flexible colonoscope, which is 160 cm long, is the most accurate method of detecting colorectal polyps less than 1 cm in diameter. It can be used to visualize the mucosa of the entire colon and rectum as well as the terminal ileum. When colorectal lesions are detected, polypectomy, biopsies, and brushings for tissue diagnosis can be achieved through the colonoscope. The diagnostic accuracy of colonoscopy is as high as 94% for polyps of 1 cm or greater but falls to 73% for polyps less than 6 mm.[24] Complications from colonoscopy occur in 0.4% of cases, the most common being bleeding and perforation.[25] Colonoscopic visualization of polyps is more challenging in areas of acute angulation (i.e., sigmoid colon and hepatic flexure), behind the ileocecal valve, in regions with colonic spasm or acute inflammation (i.e., diverticulitis), or when the bowel preparation is poor. Good bowel preparation and patient compliance are essential for a complete colonoscopic examination. In addition, endoscopy units should be properly equipped and staffed for the administration of monitored sedation. Despite optimal conditions, in approximately 5% of cases the endoscopist cannot reach the cecum.[26] In these cases, a DCBE is recommended to evaluate the unexamined colon. In addition, virtual colonoscopy may be used to complete the colonic evaluation, although we await more data before its role in this setting can be completely defined.

Current recommendations state that flexible sigmoidoscopy combined with a high-quality DCBE is an acceptable alternative to colonoscopy in average risk patients.[17] It is estimated that 35% of colonic adenomas are proximal to the reach of the flexible sigmoidoscope. In addition, although DCBE is less sensitive than colonoscopy for polyps less than 1 cm and exposes the patient to 0.03 Gy of radiation, it has the advantages that it is less expensive, does not require sedation, and is associated with fewer complications. However, if a lesion is diagnosed by DCBE, a colonoscopy is required for tissue diagnosis.

Practice parameters for antibiotic prophylaxis to prevent endocarditis or infection of prosthetic material during colorectal endoscopy have been developed by the ASCRS in conjunction with the American Heart Association.[27] The ASCRS parameters state that antibiotic prophylaxis be used only for patients at high risk for bacterial endocarditis. These patients include those with prosthetic cardiac valves, a history of endocarditis, surgically constructed systemic pulmonary shunts, complex cyanotic congenital heart disease, and vascular grafts that have been implanted in the prior 6 months.[27] Antibiotic regimens for these patients include (1) ampicillin, gentamicin, and amoxicillin, (2) vancomycin and gentamicin, or (3) amoxicillin or ampicillin alone, but these regimens are not all inclusive and must be tailored to the individual patient.[27] Bacterial endocarditis is a moderate risk in patients with most congenital cardiac malformations, rheumatic and other acquired valvular dysfunction, idiopathic subaortic stenosis, and mitral valve prolapse with insufficiency. Antibiotic prophylaxis is currently not recommended for patients with these moderate-risk conditions.[27]

Initial Management of Adenomatous Polyps

All polyps detected by endoscopy should be removed because it is not possible to accurately determine whether a polyp is premalignant or malignant by visual inspection and size criteria. It is important to record polyp size, morphology, and location in the colon. The endoscopist should make all efforts to completely excise the polyp and properly orient it to allow the pathologist to provide a precise histologic evaluation. Pathologic evaluation should include determination of tubular or villous architecture, low-grade or high-grade dysplasia, and if invasive cancer is present. In the case of invasive cancer (malignant polyp), the pathology report should include whether the resection margins are involved with malignant or adenomatous cells, grade (differentiation), and the presence of lymphovascular or perineural invasion. Randomized, controlled studies have documented a significant reduction in subsequent colorectal adenoma formation in patients treated with aspirin who have a personal history of resected CRC[28] or colorectal adenomas.[29] Its use may be recommended in these cases, but the risks of aspirin require individualized use based on each patient's overall medical condition.

Small Polyps The management of colorectal polyps less than 6 mm in diameter is not well established. The clinical significance and management of these lesions are controversial, because they may confer a low risk of malignant degeneration.[30] In addition, it is uncertain whether biopsy alone is adequate therapy for these lesions. A study of 5137 adenomas less than 5 mm in diameter reported no invasive carcinoma.[30] However, another review of 2064 colorectal adenomas less than 6 mm in diameter determined that 4% contained high-risk features (>25% villous architecture or severe dysplasia) and 0.1% contained invasive cancer.[31] Therefore, colorectal polyps less than 6 mm should be endoscopically treated when clinically appropriate, given their potential for high-risk features and malignancy.

Techniques available for the management of small colorectal polyps include biopsy, ablation (using hot biopsy forceps, bipolar forceps, heater probe, or laser), and removal with a snare (cold snare). The complication rate for colonoscopic treatment of colorectal polyps less than 6 mm has been reported to be as low as 0.15%.[31] The risk of bleeding and perforation using the hot biopsy forceps technique, particularly in the thin-walled right colon, and the associated tissue damage from coagulation necrosis suggest this technique may be suboptimal for the management of small colorectal polyps.[32] The cold-snare technique appears to safely remove these lesions while preserving the architecture of the specimen for pathologic examination.[33]

Pedunculated Polyps Colonoscopic polypectomy is the best treatment for most pedunculated polyps. The cautery snare is placed around the polyp stalk at a point to adequately remove the polyp with a margin of normal

tissue while avoiding thermal injury to the bowel wall at the base of the stalk. Caution should be taken to avoid transmission of electric current through the head of the polyp to the opposite wall.

Sessile Polyps Sessile polyps less than 2 cm in diameter can often be treated endoscopically. However, barring medical contraindications, a bowel resection is indicated for polyps that cannot be completely excised endoscopically or any polyp containing invasive cancer. Large sessile polyps (>2 cm) often require surgical excision or resection, due to their increased incidence of malignancy (5% to 15%),[34-36] increased incidence of complications following endoscopic treatment, and requirement for piecemeal excision in many cases. In select benign-appearing cases, piecemeal excision may be an appropriate initial therapy. Small bites of 0.5 to 1.5 cm are taken with the cautery snare, using a lower current to avoid injury to the bowel wall. The goal is to achieve subtotal resection of the polyp head until the base is reached. Injection of saline in the submucosa below the polyp to elevate the adenomatous tissue has been used successfully to facilitate piecemeal excision.[35] All excised tissue should be retrieved for pathologic analysis, and extraction baskets and bags are commercially available for this purpose. For incomplete piecemeal excision, fulguration of the polypectomy site with the argon plasma coagulator may decrease adenoma recurrence.[34,36] It is important to mark the area with a 0.1-ml submucosal injection of India ink or other agent for colorectal wall "tattooing." This mark may be used for localization of the polypectomy site if subsequent surgery is indicated, such as for positive margins or detection of invasive cancer. Follow-up colonoscopy 3 to 6 months after treatment is necessary to determine if excision was complete and to treat any retained or recurrent adenomatous tissue. Disadvantages of piecemeal excision include lack of pathologic orientation of the specimen and difficulty determining margin status when the polyp is treated with fulguration.

Malignant Polyps A malignant polyp is defined as a polyp containing invasive cancer that has invaded across the muscularis mucosa.[37] They are diagnosed in 2% to 12% of polyps removed endoscopically.[37-39] Colonoscopic polypectomy may be appropriate for small pedunculated invasive cancers with favorable criteria because the risk of residual cancer or lymph node metastases is minimal (0.3% to 1.5%). However, the decision for further treatment with surgical resection is based on the risk of lymph node metastases and the general medical condition of the patient.[37] The finding of lymphovascular invasion, poor differentiation, cancer within 2 mm of the resection margin, flat or ulcerated lesion, or cancer invasion into the lower third of the submucosa indicate the need for colonic resection.[40-42] Follow-up colonoscopy and surveillance of the polypectomy site are recommended 3 to 6 months following therapeutic endoscopy to assess for retained or recurrent neoplastic tissue.

The most significant risk factor for lymph node invasion in patients with a malignant polyp is depth of invasion in the bowel wall. In 1985, Haggitt et al. introduced an anatomic classification system for malignant polyps that helps guide subsequent therapy. Pedunculated polyps with carcinoma in situ or those with invasive cancer limited to the polyp head, neck, or stalk may be treated with endoscopic polypectomy and close surveillance (Fig. 155–2).[43] The risk of lymph node metastases

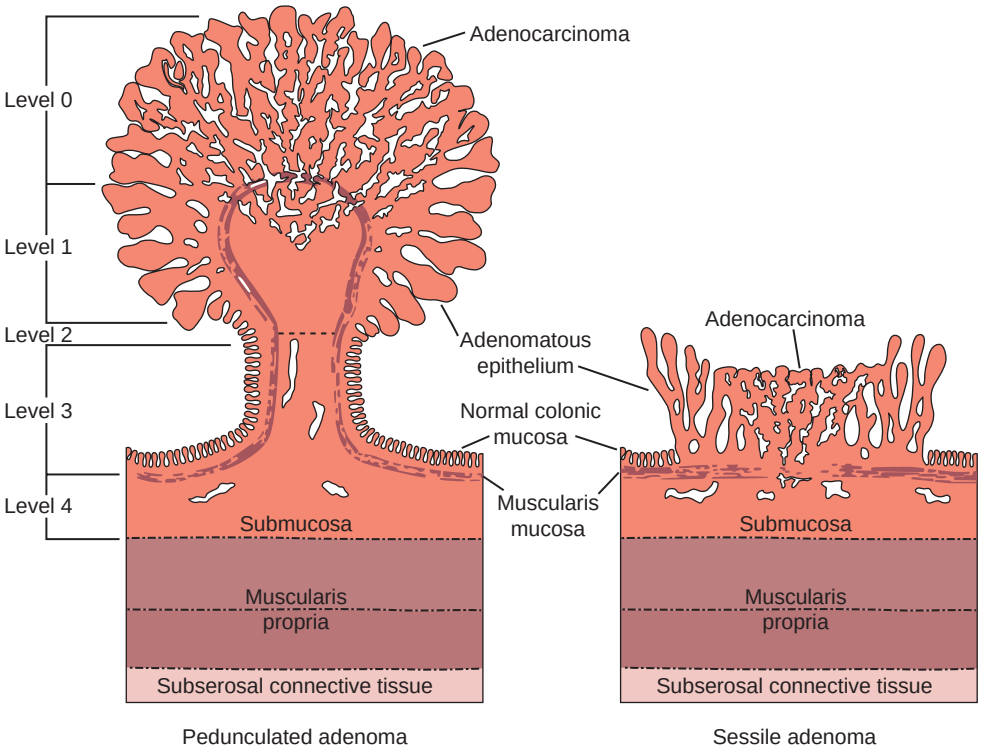

Figure 155–2. Haggitt's classification for anatomic landmarks to guide the management of malignant colorectal polyps.[43]

from these lesions is less than 1%.[43-45] However, once carcinoma invades the submucosa of the bowel wall, surgical resection is recommended for patients who are medically appropriate. The risk of lymph node metastases for these lesions has been reported from 12% to 25%.[40,46,47] By definition, a sessile polyp has no stalk, and the submucosa is immediately adjacent to the muscularis mucosa. Therefore, a sessile polyp containing invasive cancer is optimally treated with formal bowel resection. The decision to proceed with colectomy is based on the risk of residual cancer and lymph node metastases as predicted by pathologic determinants balanced against operative morbidity and mortality risks and the life expectancy of the patient. Prior to radical resection, it is important to clearly inform the patient that there is a potential for no viable cancer to be detected in the bowel wall or lymph nodes on pathologic analysis.

Complications of Therapeutic Colonoscopy The overall rate of serious complications following colonoscopy is 0.6%.[25] The most common complications associated with the procedure are perforation and bleeding. Perforation has been reported in 0 to 2% of cases, and is seen more commonly following a cautery burn or full-thickness snare of the bowel wall and after treatment of a villous lesion.[25,48-50] A small perforation in a patient with a complete bowel preparation and minimal contamination may be treated conservatively with intravenous antibiotics and close observation. However, if signs of sepsis or peritonitis develop, operative intervention is indicated.

The most frequent site of bleeding is the stalk after polypectomy. Bleeding can be divided into two categories: (1) early bleeding, which is diagnosed at the time of endoscopy; and (2) late bleeding, which becomes clinically apparent following completion of endoscopy. Early bleeding has been reported as high as 13% to 22% of cases, the majority of which are self-limited or controlled endoscopically.[48,51] Late bleeding, which may require intervention, has been reported in 0.4% to 3% of cases.[25,48,51] Recauterization by colonoscopy may be required, but uncontrolled hemorrhage may require colectomy to remove the site of bleeding.

Follow-up Surveillance

The basis for surveillance colonoscopy is the increased risk of metachronous neoplasms, which occur at a rate of 29% to 60% following polypectomy of an adenoma, depending on the interval of follow-up.[20,52,53] The risk is higher for patients older than 60 years of age and those with multiple or large adenomas.[21] Other risk factors for metachronous neoplasia may include increasing dysplasia and villous architecture. Due to the finding that colonoscopic polypectomy and subsequent surveillance reduces CRC incidence,[15,54] patients with a personal history of adenomatous colorectal polyps should be offered follow-up surveillance with colonoscopy.[16] Flexible sigmoidoscopy with DCBE may be an acceptable alternative if colonoscopy is not available.[16]

The recommended surveillance interval following removal of an adenomatous colorectal polyp varies depending on the findings of the index colonoscopy. In patients with an incomplete index examination, a repeat colonoscopy should be performed within 3 months. Patients with advanced or multiple (≥3) adenomas should have follow-up colonoscopy within 3 years because there is evidence from a randomized trial that a follow-up interval of 3 years is comparable to an interval of 1 year at detecting advanced adenomas.[15,16] Patients with one or two tubular adenomas less than 1 cm in diameter may wait 5 years for follow-up colonoscopy, because these patients are at low risk for developing advanced adenomas.[16,55] However, as with all screening and surveillance recommendations, management should be individualized with consideration given to comorbid illnesses and the concerns of the patient.

Hamartomatous Polyps

A *hamartomatous polyp* is a localized overgrowth of normal, mature intestinal epithelial cells.[1] They are usually lined with normal epithelium over a submucosal core. Juvenile polyps are the most common type of colorectal hamartomas and occur most commonly in children younger than 5 years of age 5. Up to 80% of juvenile polyps occur as a single lesion of the rectum, but they have been described throughout the colon.[1] Typical symptoms are rectal bleeding, mucus discharge, diarrhea, and abdominal pain. Intussusception through the rectum has also been described. Grossly, a juvenile polyp is a pedunculated, bright red to brown, spherical polyp 1 to 3 cm in diameter that has a friable, granular surface (Fig. 155–3). Microscopically, they contain abundant stroma, most of which is lamina propria, separating tubules of cystically dilated glands (Fig. 155–4).[1] Juvenile polyps are also called *retention polyps* due to the inflammatory obstruction of the crypt necks that leads to cystic dilation of the mucus-filled glands. In general, they do not carry an increased risk of cancer; however, the autosomal dominant JPS, characterized by 50 to 100 juvenile polyps in the gastrointestinal tract, is associated with an increased risk of CRC.[1]

The autosomal dominant–inherited PJS is also characterized by hamartomatous polyps. These lesions are

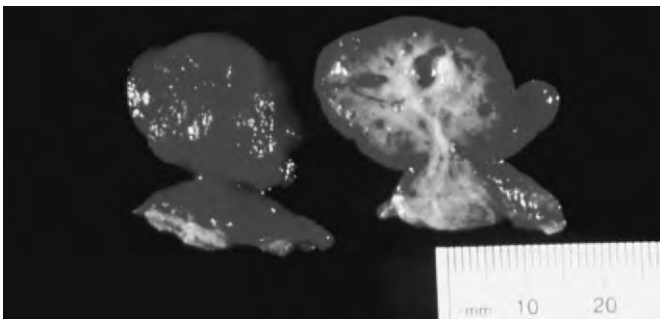

Figure 155–3. Gross appearance of a juvenile polyp. (Courtesy of Stephen S. Sternberg, MD, and Satish Tickoo, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

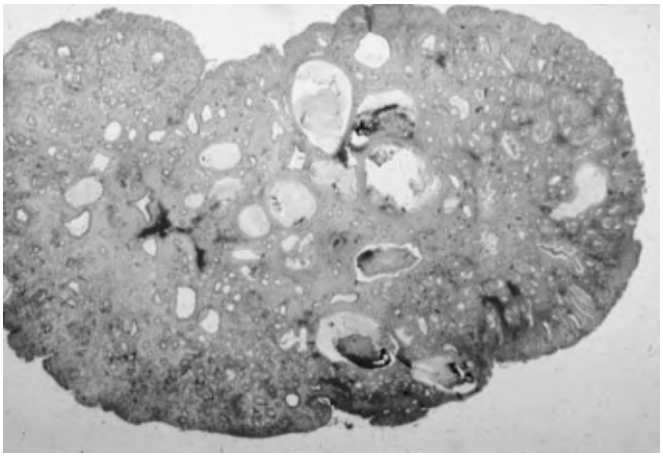

Figure 155–4. Microscopic appearance of a juvenile polyp. (Courtesy of Stephen S. Sternberg, MD, and Satish Tickoo, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

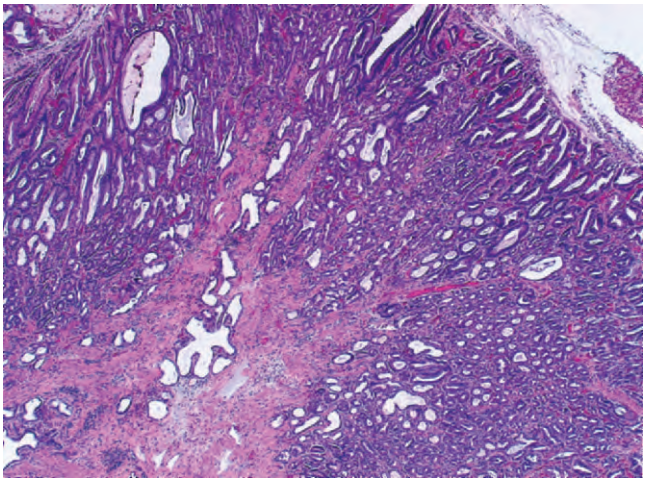

Figure 155–5. Microscopic appearance of a Peutz-Jeghers polyp. (Courtesy of Jinru Shia, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

hemispheric or finger-like protrusions ranging in size from 0.1 to 10 mm, although they may grow to 4 cm. PJS hamartomas are characterized by hypertrophy or hyperplasia of the smooth muscle of the intestinal wall, which can extend into the superficial epithelial layer in a "tree-like" manner, a process that has been termed *arborization* (Fig. 155–5). As the smooth muscle extends upward and invaginates the superficial layers of the bowel wall, epithelial cells can become trapped within the muscle layer, which may be confused with malignant transformation.[56] Mucus-filled cysts in the mucosa are commonly present. Normal columnar epithelium usually covers the polyps, but a small proportion of polyps contain mixed adenomatous/hamartomatous elements.

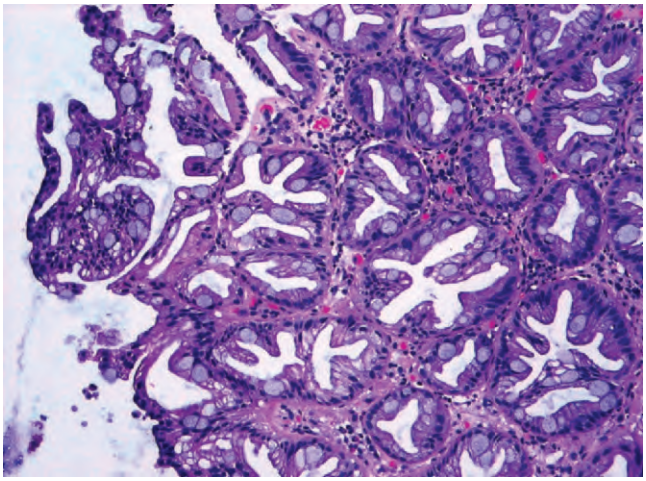

Figure 155–6. Microscopic appearance of a hyperplastic polyp. (Courtesy of Jinru Shia, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

Hyperplastic Polyps

Hyperplastic polyps account for more than 90% of all colorectal polyps.[1] They are found in the rectosigmoid in more than 50% of cases and are diagnosed most commonly after age 50 years. They are usually less than 5 mm in diameter at diagnosis and appear grossly as pale, broadly based, flat, smooth nodules. Hyperplastic polyps arise from faulty epithelial maturation, characterized microscopically as elongated nonbranching mucosal crypts and hyperplasia without atypia (Fig. 155–6). It is generally accepted that hyperplastic polyps have no premalignant potential, but adenomatous change has been described on histologic examination of otherwise typical hyperplastic polyps.[57] These "serrated" or mixed polyps have been associated with the development of carcinoma.[58,59] In addition, recent evidence suggests that patients with hyperplastic polyposis (>20 hyperplastic polyps) may be at increased risk of developing CRC.[60]

Inflammatory Polyps

Inflammatory polyps, also known as *pseudopolyps,* arise from mucosal ulceration and repair. They occur most frequently in the setting of chronic ulcerative colitis but are also seen in Crohn's disease. Inflammatory polyps are uniform in width from the base to the head and consist of islands of inflamed regenerating mucosa surrounded by ulceration (Fig. 155–7).[1] Patients with inflammatory polyps usually require no treatment other than that for the underlying colitis, but the possibility of neoplastic disease should be excluded.

POLYPOSIS SYNDROMES

Gastrointestinal polyposis syndromes include a variety of entities characterized by the number and histologic type of colorectal polyps, as well as polyposis of the upper

Table 155–3 Summary of Gastrointestinal Polyposis Syndromes

Polyp Histology	Syndrome	Genetic Basis	Gene Locus
Adenomatous	FAP*	Germline *APC* mutations	5q21
	aFAP*	Germline *APC* mutations	5q21
	MYH polyposis	Biallelic germline *MYH* mutations	1p34.3-p32.1
	HNPCC*	Germline *MMR* mutations (*hMLH1, hMSH2, hMSH6, hPMS1, hPMS2*)	*hMLH1*: 3p21 *hMSH2*: 2p16 *hMSH6*: 2p16 *hPMS1*: 7p22 *hPMS2*: 7p22 *hMLH3*: 14q24
	Muir-Torre syndrome*	Germline *MMR* mutation (*BTP1*)	
	Turcot's syndrome*	Germline APC mutations (*BTP2*)	
Hamartomatous	JPS*	Germline *SMAD4* mutations	*SMAD4*: 18q21.1
		Germline *BMPR1A* mutations?	*BMPR1A*: 10q21-22
	PJS*	Germline *LKB1/STK11* mutations	19p13.3
	Cronkhite-Canada syndrome*	N/A	N/A
	Cowden's disease	Germline *PTEN* mutations	10q23.3
	Ruvalcaba-Myhre-Smith syndrome	Germline *PTEN* mutations	10q23.3
	Neurofibromatosis		
Other	Hereditary mixed polyposis syndrome	Germline *CRAC1* mutation?	15q13-14
	Hyperplastic polyposis syndrome*	MSI pathway?	
	Inflammatory polyposis	N/A	N/A
	Lipomatous polyposis	N/A	N/A

*Increased risk of CRC.
CRC, colorectal cancer; FAP, familial adenomatous polyposis; aFAP, attenuated FAP; HNPCC, hereditary nonpolyposis CRC; N/A, not applicable.

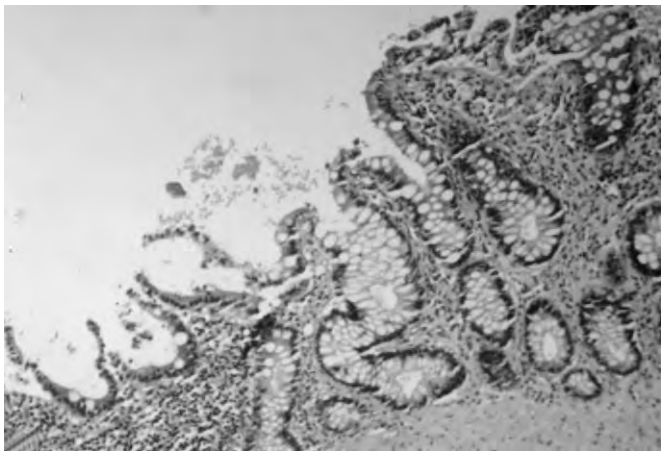

Figure 155–7. Microscopic appearance of an inflammatory polyp. (Courtesy of Stephen S. Sternberg, MD, and Satish Tickoo, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

gastrointestinal tract and specific extraintestinal manifestations (Table 155–3). Adenomatous polyposis syndromes are characterized by adenomas of the gastrointestinal tract and include FAP and hereditary nonpolyposis CRC (HNPCC). Hamartomatous polyposis syndromes are characterized by gastrointestinal hamartomas, or an overgrowth of cells native to the area in which they normally grow, and include JPS, PJS, Cowden's disease, Ruvalcaba-Myhre-Smith syndrome, and Cronkhite-Canada syndrome.[61] Hereditary mixed polyposis syndrome is a variant of JPS that is characterized by both hamartomatous and adenomatous polyps of the gastrointestinal tract.[61]

Familial Adenomatous Polyposis

Clinical Considerations

FAP is an autosomal dominant disease with nearly 100% penetrance characterized by the development of many (usually >100) adenomatous polyps of the colon and rectum.[62] The genetic etiology of the disease is a germline mutation of the APC gene, located on chromosome 5q21.[63] Up to 80% of patients have a family history of FAP, but 10% to 30% of cases represent new mutations. The disease has an incidence of 1 in 5000 to 10,000 live births and accounts for less than 1% of all cases of CRC.[62,64] Almost all patients develop CRC by 40 years of age if colectomy is not performed, usually within 10 to 15 years of diagnosis. Extraintestinal manifestations are common in FAP and include desmoid tumors,

duodenal and periampullary adenomas, gastric fundic gland polyps, thyroid and brain tumors, and congenital hypertrophy of the retinal pigmented epithelium (CHRPE). The combination of FAP with desmoid tumors, osteomas, and sebaceous cysts is known as *Gardner's syndrome.*[65] FAP in association with brain tumors (particularly glioblastoma) is known as *Turcot's syndrome.*

The average age of adenoma development in FAP is 15 years, with approximately 15% manifesting polyps by 10 years, 75% by 20 years, and 90% by 30 years of age.[66] At-risk individuals participating in a screening program are usually diagnosed with FAP by the age of 22 years, whereas the average age at diagnosis in patients presenting with symptoms ranges from 34.5 to 43 years.[67] The average age of development of CRC is 35 to 39 years.[67] The relatively long interval between polyp and cancer development reflects the relatively slow process of FAP CRC tumorigenesis. This slow progression is further substantiated by the observation that only a small number of adenomatous polyps, among the hundreds to thousands in patients with FAP, ultimately develop into invasive cancer.

The polyps in FAP may carpet the entire surface of the colorectal epithelium or spare portions of the epithelial lining (Figs. 155–8 and 155–9). The adenomas may be pedunculated or sessile and have tubular, tubulovillous, or villous histology.[1,67] Most grossly visible adenomas are 5 to 10 mm in diameter. In addition, innumerable microadenomas, which may be limited to one crypt on grossly normal mucosa, are often identified on microscopy. The finding of at least one polyp more than 1 cm is associated with a 47% risk of CRC, whereas polyps greater than 2 to 3 cm usually contain invasive cancer.[68] Most patients with FAP present with distal, left-sided CRC that is similar in anatomic distribution to sporadic CRC. Patients with FAP are at substantial risk for synchronous and metachronous CRC, which emphasizes the need for treatment with total colectomy.

Extracolonic Manifestations

Extracolonic manifestations reflect the systemic growth regulation disorder that afflicts patients with FAP. They usually become clinically evident after colorectal polyposis, but there are reports of FAP presenting with extracolonic manifestations.[68] Benign extracolonic manifestations include CHRPE,[69] osteomas,[70] dental odontomas,[71] and epidermoid cysts.[72] The incidence of these lesions is unclear because they are not a part of routine screening and often require special studies to identify. The value of these benign lesions lies in their ability to screen family members or identify patients with de novo mutations as most are not of major clinical consequence. For example, CHRPEs are asymptomatic and have no malignant potential but may be useful in determining carrier status in asymptomatic individuals. CHRPE in patients with FAP are significantly larger, multiple, bilateral, and with mixed pigment than sporadic CHRPE.[69] Osteomas are benign, slow growing neoplasms of the bone. They occur in more than 50% of patients with FAP, are typically found in the skull and mandible, and are a constituent of Gardner's syndrome, where their presence may precede that of gastrointestinal polyposis.[70] Benign dental abnormalities, diagnosed in up to 70% of patients with FAP, include supernumerary or missing teeth and fused roots of molar teeth and are diagnosed by physical examination and panoramic dental radiographs.[73] Epidermoid cysts are commonly diagnosed in the mid to late teenage years, are often multiple, and occur in atypical locations (face, scalp, and extremities).[74]

After CRC, the most common malignancy diagnosed in patients with FAP is periampullary adenocarcinoma of the duodenum.[75,76] Other malignancies associated with FAP include tumors of the thyroid, brain, pancreas, biliary tree, stomach, small intestine, and adrenal gland. Hepatoblastoma, a rare embryonal tumor of the liver, affects children with FAP at a much higher rate than expected in the general population.[77] Because desmoids

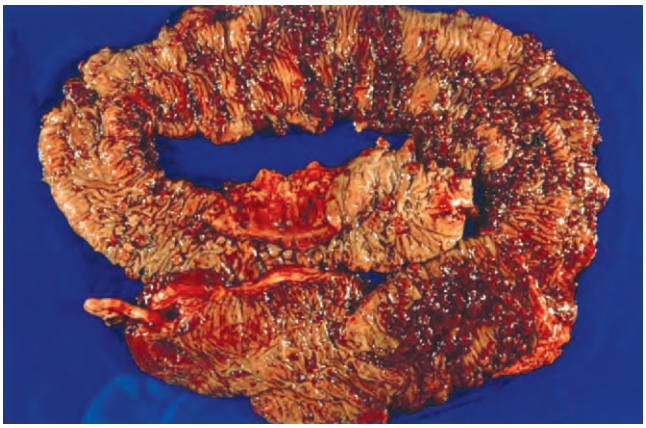

Figure 155–8. Gross appearance of the colon of a patient with familial adenomatous polyposis. (Courtesy of Jinru Shia, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

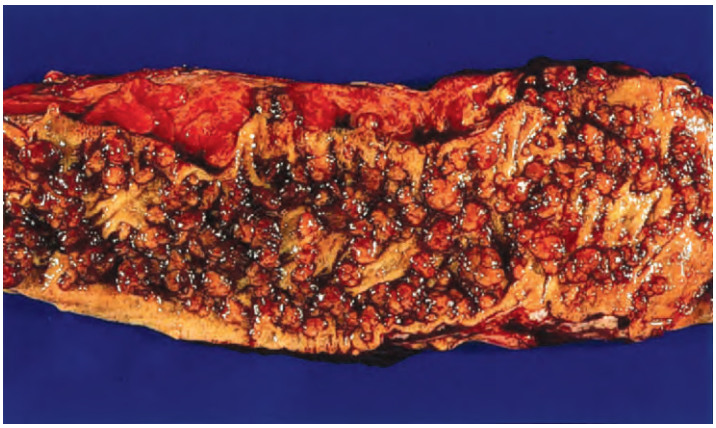

Figure 155–9. Close-up image of colonic mucosa in a specimen from a patient with familial adenomatous polyposis. (Courtesy of Jinru Shia, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York.)

and upper gastrointestinal tract neoplasia represent major management issues in patients with FAP, they are discussed individually.

Desmoids Desmoids are slow-growing, benign mesenchymal tumors characterized by mature, highly differentiated fibroblasts and myofibroblasts with abundant collagen matrix.[78] It has been estimated that between 8% and 17% of patients with FAP develop desmoids, and they are diagnosed at a rate of almost 1000 times that in the general population.[79] Although sporadic desmoids are more common in women,[80] this gender difference is less apparent in patients with FAP and may even be reversed.[81] They do not metastasize, but are locally aggressive, tend to infiltrate surrounding tissues, and have a high recurrence rate following surgical therapy. Desmoids can be fatal, related in large part to their aggressive local growth with compression of surrounding organs (intestine, ureter, and vessels), erosion of adjacent structures, and interference with surgical therapy. In patients with FAP, up to 80% of desmoids are observed in the small intestinal mesentery and 20% to 30% are diagnosed in the abdominal wall or extremities.[67,82] Early desmoids, which have been termed *desmoid precursor lesion* or *desmoid reaction,* appear as flat, white plaques.[83] Larger lesions tend to form nonencapsulated, lobulated masses. Desmoids can become massive and occupy a large portion of the abdomen or pelvis. Clinical presentation ranges from asymptomatic plaques or masses discovered incidentally on imaging or during prophylactic surgery to many nonspecific symptoms. Symptomatic desmoids may cause abdominal pain, bowel obstruction or ischemia, deep venous thrombosis from venous compression, sensory and motor deficits from nerve compression, ureteric obstruction, sepsis from enteric fistula, upper gastrointestinal hemorrhage, and pouch failure.[67,84]

Surgical trauma is a major risk factor for the development of intra-abdominal and abdominal wall desmoid tumors.[85] The interval between surgery and the diagnosis of desmoid tumors is usually less than 5 years but may extend well beyond this interval.[85,86] Estrogens have been implicated in the stimulation of desmoid growth, because they often develop in women of reproductive age and growth is often temporally related to pregnancy or the use of oral contraceptives.[87] In addition, regression has been reported following natural or surgical menopause. Genotype-phenotype correlations have been suggested, as mutations toward the 3′ end of the APC gene may be more likely to be identified in FAP kindreds that have a high incidence of desmoids.[88,89] A genetic predisposition to the development of desmoids, independent of the APC gene, has also been suggested.[90]

Currently, the most useful imaging modality for the preoperative evaluation of desmoids in patients with FAP is contrast-enhanced computed tomography (CT). Mesenteric fibrosis and desmoid precursor lesions have been identified on preoperative CT in up to 20% of patients with FAP.[91] Although CT findings correlate poorly with symptoms, poor prognostic features include size greater than 10 cm, multiple lesions, bilateral hydronephrosis, and extensive small bowel involvement. In addition, a CT scoring system has been introduced that may predict the clinical course of desmoid precursor lesions.[92] Magnetic resonance imaging is most useful for extremity and abdominal wall desmoids but can also be used to evaluate intra-abdominal lesions. High signal intensity on T2-weighted images has been suggested to correlate with active growth.[93] Radionuclide scans may have some use in differentiating scar from recurrent desmoid tumor during postresection follow-up examination.

Treatment of desmoids may be broadly categorized into nonsurgical and surgical approaches, although there is no singularly affective therapy. Because failure with one treatment does not preclude successful therapy with a different approach, clinicians should explore all options in resistant or recurrent cases. Both cytotoxic and noncytotoxic pharmacologic agents have been used, with variable success, in the treatment of desmoid tumors.[94] Nonsteroidal anti-inflammatory drugs (NSAIDs) and antiestrogens are frequently used agents.[87,94,95] In addition, modifiers of cyclic adenosine monophosphate metabolism (ascorbic acid, theophylline, testolactone, and chlorothiazide), corticosteroids, colchicine, interferon-alpha, and warfarin have all been used. NSAIDs (sulindac and indomethacin) are considered first line therapy for desmoids, resulting in response rates of up to 57%.[96] Most patients respond to NSAIDs within 3 months, but delayed response over 24 months has been reported.[94] Antiestrogens, primarily tamoxifen,[95] raloxifene,[87] and toremifene,[97] have been reported to produce response rates comparable to those of NSAIDs, but there are no randomized studies documenting their efficacy. Recently, combination regimens containing both NSAIDs and tamoxifen have been reported to result in improved response rates, a finding that awaits confirmation by larger trials.[95] There are limited data on the use of interferons in the treatment of desmoids, and currently their use is most appropriate in clinical trials.

The most commonly used and successful cytotoxic chemotherapy regimens in the treatment of desmoids are combinations of antisarcoma agents, usually doxorubicin with dacarbazine or cyclophosphamide and vincristine.[98] Reported response rates range from 17% to 100%, with a median of 50%.[94] However, severe early and late toxicity are major concerns with cytotoxic therapy, which limits its use to extensive life-threatening disease that is resistant to other therapy or when alternative approaches are contraindicated. Regional chemotherapy with isolated limb perfusion for extremity desmoids has been reported with encouraging results from small series, but larger studies are required before definitive recommendations can be made.[99] In addition, radiation therapy in doses of 36 to 65 Gy may provide acceptable local control following surgical resection (80%) and as primary therapy for unresectable tumors (81%).[100] Although early in its development, preclinical research with gene transfer to treat patients with FAP and desmoids has been reported.[101]

Surgery for intra-abdominal desmoids should be reserved for select cases of symptomatic disease given their often unresectable nature due to their common

location in the root of the mesentery and their high recurrence rates following resection. Often, their characteristic infiltrating growth pattern makes complete resection impossible without extensive small bowel resection. Local control rates following resection with positive and negative margins are reported as 41% and 72%, respectively.[102] The addition of postoperative radiation therapy, when clinically feasible, can improve local control to as high as 94% when negative pathologic margins are achieved.[102] Bypass procedures are controversial but may be required to treat select cases of nonresolving bowel obstruction. Major complications have been reported in up to 50% of patients with intra-abdominal desmoids treated with surgical resection. In addition, extensive resection may lead to short bowel syndrome and its associated difficult management. Another difficult issue associated with the surgical treatment of intra-abdominal desmoids is the high recurrence rate (up to 85% in some series). Given these limitations, surgery should be reserved for symptomatic patients or those with complications. Abdominal wall desmoids may be treated with surgical resection, with margins of 2 cm. Reconstruction with prosthetic mesh or a myocutaneous flap may be required when large lesions are treated. Extra-abdominal desmoids may be treated with surgical resection, with reported 10-year disease-free rates of 76% for primary tumors and 59% for recurrent tumors.[103]

A reasonable approach to desmoids may be to begin with NSAIDs such as sulindac (150 mg twice per day) as first-line therapy. If the tumor does not respond or progresses following 6 or more months of therapy, an antiestrogen such as tamoxifen (starting at 30 mg per day, with a slow increase up to 120 mg per day) or raloxifene (60 mg twice a day) may be added. If the tumor responds, therapy can be gradually withdrawn over 6 months. Cytotoxic chemotherapy with a doxorubicin-based regimen should be reserved for extensive or life-threatening tumors that do not respond to noncytotoxic pharmacologic regimens and are not amenable to surgery. Surgery should be reserved for localized desmoids of the limbs or abdominal wall or intra-abdominal desmoids causing symptoms or complications.

Upper Gastrointestinal Neoplasia Upper gastrointestinal polyps in patients with FAP may be non-neoplastic, as is the case for most gastric polyps, or neoplastic, which is typical of duodenal or periampullary polyps. Gastric polyps, which are also called *fundic gland polyps,* are benign hamartomas, are diagnosed in 13% to 84% of cases of FAP, and were believed to have a very low malignant potential.[104] However, recent data suggest that fundic gland polyps may be associated with an increased risk for adenomas[105] and high-grade dysplasia.[106] In patients with FAP, duodenal and periampullary polyps usually harbor dysplasia and are premalignant. Duodenal polyps are observed in 65% of patients at first endoscopy and eventually develop in 90% to 100% of patients with FAP, although they usually appear 10 to 20 years after colorectal polyp formation.[76] In contrast with the near-ubiquitous finding of duodenal adenomatosis, the reported incidence of duodenal cancer ranges from 0 to 5%.[75,76,107] Upper gastrointestinal polyps are usually asymptomatic, with symptoms suggesting invasive cancer.

Table 155–4 Modified Spigelman Classification for Staging Duodenal Polyposis in Patients with FAP*

	Grade of Duodenal Disease (points)		
Variable	*1*	*2*	*3*
Polyp number	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Low grade	—	High grade

*Stage 0 (no polyps) = 0 points; Stage I = 1-4 points; Stage II = 5 or 6 points; Stage III = 7 or 8 points; Stage IV = 9-12 points. Data from Spigelman AD, Williams CB, Talbot IC, et al: Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 2:783-785, 1989.

Upper gastrointestinal surveillance is recommended with the goal of early detection and treatment of suspicious, premalignant polyps.[75,76,107] Spigelman's criteria have been developed to predict the malignant risk of duodenal polyposis in patients with FAP and guide surveillance and management. Spigelman's criteria is determined by duodenal polyp number, size, histology, and dysplasia (Table 155–4).[108] Using these features, patients are stratified into a low-risk group (stages 0, I, and II) in whom screening endoscopy is recommended every 2 to 3 years and a high-risk group (stages III and IV) in whom endoscopy with biopsy is recommended every 6 to 12 months. In addition, surgical intervention is justified in advanced duodenal polyposis (Spigelman stage IV and select stage III). The cumulative risk of developing stage IV duodenal polyposis has been estimated at 40% by age 60 years and 50% by age 70 years.[107]

Because clinically significant issues from upper gastrointestinal polyposis are rare before the diagnosis of colorectal disease, upper gastrointestinal screening is initiated at the time of FAP diagnosis. Symptoms of unexplained epigastric pain, weight loss, jaundice, anemia, melena, or vomiting should prompt evaluation with endoscopy, abdominal ultrasound, and CT scan. Imaging findings are used to plan subsequent therapy, including surgical resection when indicated.

Management of duodenal polyps in patients with FAP includes medical intervention (with NSAIDs such as sulindac), endoscopic polyp ablation, and surgical resection. Sulindac has been used because of its potential to stabilize, and in some cases reverse, the development of gastrointestinal neoplasia, especially colorectal adenomas. Sulindac is most successful in the treatment of small (<1 cm) duodenal polyps, whereas large polyps do not respond well and progression to adenocarcinoma has been reported in patients during sulindac treatment. In addition, data to support its benefit are largely derived

from retrospective case series.[109] Endoscopic techniques to treat duodenal polyps include polypectomy; snare ampullectomy; and laser, thermal, and photodynamic ablation. Endoscopic approaches are limited because they cannot definitively treat duodenal polyposis despite multiple interventions and morbidity is a major concern for procedures performed near the duodenal ampulla.

Surgical therapy is reserved for patients at a high risk for cancer, including those with extensive duodenal polyposis, rapid polyp growth, villous lesions with high-grade dysplasia, and suspicious endoscopic features (i.e., induration). In addition, patients with Spigelman IV polyposis have a high risk of harboring or developing duodenal cancer (reported as up to 36%), and surgical resection should be strongly considered in these patients.[75] Operative intervention should be individualized and alternatives include local resection, ampullectomy, pancreas-sparing duodenectomy, and pancreaticoduodenectomy. Local resection is a less attractive option because it has a high failure rate owing to difficulty in complete eradication of duodenal polyps, it makes subsequent surgical resection difficult, and it is associated with a significant morbidity from postoperative duodenal leaks.[110] Pancreaticoduodenectomy is indicated for cancer and large, rapidly growing adenomas with severe dysplasia and may be performed with acceptable morbidity and limited mortality.[111]

Genetics

Adenomatous Polyposis Coli Gene Mutations in the adenomatous polyposis coli *(APC)* gene, located on chromosome 5q21, are responsible for FAP.[63] The *APC* gene consists of 15 exons and 2843 codons and functions as a tumor suppressor gene via its 300-kD protein product. Individuals affected with FAP have a germline mutation in one of their two copies (alleles) of the *APC* gene. When a somatic mutation in the second APC allele occurs, the FAP phenotype develops. Germline mutations have been reported throughout the *APC* gene, with more than 90% resulting in a premature stop codon and a truncated protein product.[12,62] More than 300 different mutations in the *APC* gene have been reported, including insertions, deletions, and nonsense mutations that lead to a truncated protein.[112] The truncated protein may have impaired function, as well as interact with the wild-type protein product of the normal APC allele to cause its inactivation through a dominant negative mechanism.[62,113]

The normal APC protein product is involved in inhibition of the Wnt signaling pathway.[114] The APC protein functions by binding to β-catenin, a cytoskeletal protein and activator of growth regulatory genes. When normal APC is bound, β-catenin is targeted for degradation and cell growth is down-regulated. When APC is mutated, its interaction with β-catenin is impaired, and β-catenin accumulates in the nucleus where it simulates cell growth in an unregulated manner, ultimately leading to polyp and cancer development.[62]

APC Genotype-FAP Phenotype Correlation Correlations have been made between the site of mutation on the *APC* gene and the phenotypic expression of FAP, although these genotype-phenotype correlations are complex and their clinical utility is uncertain (Fig. 155–10).[89] Mutations in the *mutation cluster region* on exon 15 of the *APC* gene (codons 1250 to 1400) have been associated with classic FAP and severe, diffuse polyposis.[115] In addition, patients with a mutation at codon 1309 have been reported to have early-onset, severe polyposis, and death 10 years younger than untreated patients with FAP caused by mutations at other loci on the *APC* gene.[89,115,116] Mutations at the 3′ or 5′ ends of the *APC* gene may be associated with late-onset, mild polyposis and the syndrome of attenuated FAP.[117-119]

Several mutations in the *APC* gene have been correlated with an increased incidence of extracolonic manifestations of FAP. Gardner's syndrome most commonly occurs in patients with mutations distal to codon 1403.[112] In addition, desmoid tumors have been reported in higher incidence in patients with a mutation between codons 1445 and 1580.[120] CHRPE has been reported most commonly when the mutation is between codons

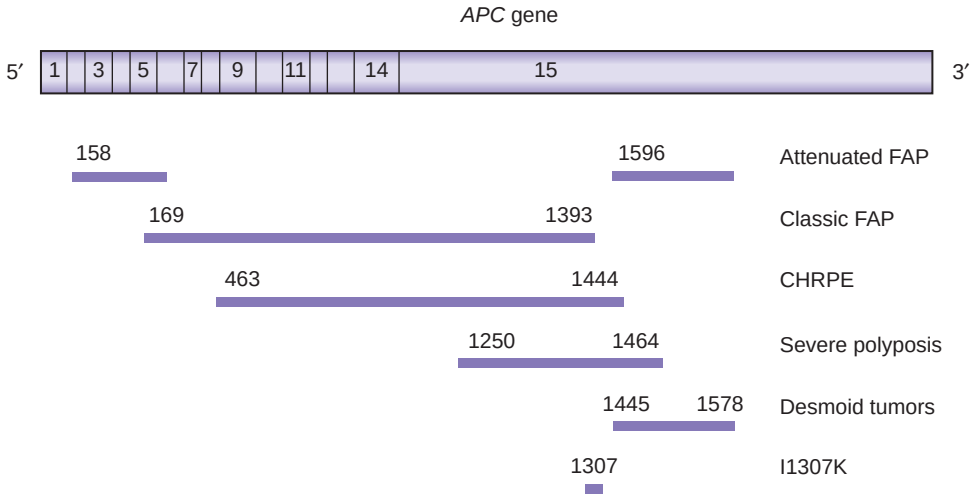

Figure 155–10. Genotype-phenotype correlations between the *APC* gene and familial adenomatous polyposis (FAP). CHRPE, congenital hypertrophy of the retinal pigmented epithelium. (From Jo WS, Chung DC: Genetics of hereditary colorectal cancer. Semin Oncol 32:11-23, 2005.)

457 and 1444.[121] Genotype-phenotype correlations for other extracolonic manifestations are less clearly defined.[89] In addition, it must be emphasized that genotype-phenotype correlations are variable within and between families with identical mutations, likely due to the complex interaction of the type of mutation, impact of the mutation on wild-type APC protein expression, modifying genes (e.g., secretory phospholipase A_2 and DNA methyltransferase), and environmental factors.[122] Currently, the clinical impact of genotype-phenotype correlations in FAP is limited to predictive genetic testing for early diagnosis and the research setting.[89]

Diagnosis

Clinical Diagnosis FAP should be suspected when hundreds to thousands of adenomatous colorectal polyps are diagnosed. Current criteria for the clinical diagnosis of FAP include more than 100 colorectal adenomas or multiple adenomas in a patient with a first-degree relative with FAP. However, the attenuated FAP phenotype presents with less than 100 proximal, flat colorectal polyps and a spared rectum, although the risk of CRC remains high.[119]

Molecular Diagnosis Individuals with a documented mutation in the *APC* gene almost certainly develop FAP, whereas the absence of a mutation in an asymptomatic individual from a family with a known *APC* mutation excludes disease.[123] The identification of gene carriers in presymptomatic at-risk members of an FAP kindred may be achieved using clinically available tests, including linkage analysis, protein truncation testing, confirmation strand gel electrophoresis, and sequencing of the entire gene.[124] Accuracy of linkage analysis has been reported as high as 80% but is limited in some individuals because markers associated with the APC allele may not be informative.[125] Also, DNA is required from family members, and this may be cumbersome to obtain. Finally, gene recombination, although rare, may segregate the linkage marker away from the disease-causing APC allele.

The most common method used to screen for *APC* mutations is the protein truncation test (also known as the *in vitro synthesized protein assay*), which recognizes the smaller protein transcribed from a disease-causing APC allele secondary to a premature stop codon. The protein truncation test alone detects up to 80% of disease-causing APC mutations but does not detect missense mutations.[126] However, the combination of the protein truncation test and strand gel electrophoresis is commercially available and has a mutation detection rate of up to 90%.[124,125] Other screening tests that recognize a premature stop codon include polymerase chain reaction (PCR), single-stranded conformation polymorphism, and denaturing gradient gel electrophoresis.

Direct DNA sequencing is the most accurate method of detecting *APC* mutations, with detection rates reported as high as 95%, and overcomes many of the limitations of linkage analysis.[125] If a disease-causing mutation is documented in a family, the accuracy of the test for other at-risk family members is almost 100%.[124] However, some difficulty with this method is derived from the large APC coding region and the fact that most APC mutations are small insertions, deletions, or substitutions. Also, interpretation of direct DNA sequencing is complicated by the detection of amino acid alterations of uncertain significance.[124]

A positive screening test should be confirmed with a diagnostic modality able to identify the abnormal nucleotide sequence in the disease-causing APC allele. These confirmatory tests include direct DNA sequencing, allele-specific oligonucleotide hybridization (ASO hybridization), ASO amplification (ASO-PCR), restriction fragment length polymorphisms, and ligase chain reaction.

Genetic Testing and Counseling—Implications for Screening and Surveillance

The surveillance of patients at-risk for FAP includes a detailed personal and family history, thorough physical examination, and biannual flexible sigmoidoscopy beginning at age 10 to 12 years.[123-125,127] Once the diagnosis of FAP is made, a full colonoscopy should be performed to evaluate disease severity (CRC, polyp burden, large polyps, or atypia) and to decide appropriate timing for prophylactic colectomy.

Clinical criteria for offering genetic testing to an individual include a newly recognized FAP phenotype (>100 adenomas), clinical suspicion of attenuated FAP (onset of CRC in the 50s to 60s with <100 adenomas or >20 cumulative colorectal adenomas), FAP-associated extracolonic manifestations with any number of colorectal adenomas, first-degree relative with documented FAP or attenuated FAP, or any relative with documented FAP and any number of colorectal adenomas.[123,124] The protein truncation test is the most commonly used initial genetic test. However, this test does not detect missense mutations, and false-negative tests result when there is a previously unrecognized truncating mutation. Therefore, in families in which the protein truncation test does not provide informative results, individuals should be evaluated with linkage analysis or undergo the recommended clinical surveillance regimen. In families with an informative protein truncation test, at-risk relatives should have genetic testing at age 10 to 12 years, and family members with a negative test can be discharged from further screening with almost 100% certainty.[128] However, these patients should resume screening for CRC at 50 years of age, as currently recommended for average-risk individuals.[16-19] In the setting of a positive protein truncation test, patients require genetic counseling and intensive endoscopic surveillance for early recognition of colorectal polyposis.[129] Surveillance should include annual sigmoidoscopy until adenomas are diagnosed, even beyond the age of 40 years, when the probability of developing classic FAP is low. Guidelines for testing, interpretation of results, and management of related psychosocial issues have been established by several medical societies.[123-125]

Genetic counseling is imperative prior to and after genetic testing for FAP. Pretest counseling should include discussion of the test being offered (cost, proce-

dure, risks and benefits) and the implications of a positive, negative, and uninformative result. Other important issues to be discussed include the risk of passing a mutation to children, privacy issues, and emotional distress associated with genetic testing. Post-test counseling should include interpretation of test results, concerns about decreased life expectancy, stigmatization, discrimination by insurance companies and employers, and options for future surveillance and surgery. In patients with a negative genetic test for FAP, emotional relief is common, but survivor guilt may arise due to the identification of an *APC* mutation in family members.[123-125]

Surgical Management

Prophylactic proctocolectomy is recommended for patients with FAP, given the near 100% risk of early-onset CRC. Patients with FAP who present for surgical management may be stratified into two major groups: (1) asymptomatic members of a known FAP kindred with an *APC* mutation detected by screening and (2) symptomatic patients, of whom approximately 30% have no family history of FAP.[123,130] Symptoms from FAP are attributed to CRC in up to 66% of cases. In asymptomatic patients, surveillance endoscopy may be continued when polyps are small (<6 mm) and there is no evidence of dysplasia or cancer.[128] Proctocolectomy is commonly deferred in these patients until after the high school years, due to patient and parental wishes. However, it should not be deferred after the early 20s because the risk of CRC is substantial in untreated patients.[128]

Surgical Options The ideal operative management of the colon and rectum in patients with FAP should satisfy the following three criteria:

1. Removal of all at-risk colorectal mucosa
2. Maintenance of continence with transanal evacuation and low frequency of bowel movement
3. Association with minimal operative complications

Surgical options for patients with FAP include total proctocolectomy with end ileostomy, colectomy with ileorectal anastomosis (IRA), and total proctocolectomy with ileal pouch–anal anastomosis (IPAA). Another alternative, although rarely used, is total proctocolectomy with continent ileostomy (Kock pouch) (Tables 155–5 and 155–6). The anastomosis in IPAA may be performed hand-sewn, where a mucosectomy is done to remove all at-risk rectal mucosa or stapled, where the mucosectomy is deferred and some at-risk mucosa may be left in situ. The most important consideration in choosing an operation for FAP is its effectiveness for prophylaxis against the development of CRC. However, these procedures are often performed in asymptomatic, young patients who perceive the operation as preventive rather than as therapeutic, so issues such as operative morbidity, functional results, and patient acceptability are important variables. Although IPAA meets the goals of surgical therapy in most patients, there remains a defined role for IRA[131] and total proctocolectomy with end ileostomy in specific clinical scenarios.

A total proctocolectomy with either a continent ileostomy (Kock pouch) or end ileostomy eliminates the

Table 155–5 Surgical Options for Management of Colorectal Polyposis in Patients with FAP

Procedure	Indications	Advantages	Disadvantages
TPC	Cancer of lower rectum at diagnosis	Eradicates all at-risk mucosa	Pelvic and perineal dissection (nerve injury, wound healing issues) Permanent ileostomy
IRA	Spared rectum Metastatic cancer	Improved function and continence Simpler operation (one stage, no pelvic dissection, no stoma)	Risk of rectal cancer requires lifelong surveillance
IPAA with mucosectomy	Uncontrollable rectal adenomas Poor compliance to follow-up	Eradicates all at-risk mucosa Acceptable function and continence May be performed in one stage	Pelvic dissection (nerve injury) Mucosectomy may impair continence
IPAA without mucosectomy	Spared rectum	Acceptable function Near-normal continence May be performed in one stage	Retained at-risk mucosa requires surveillance Pelvic dissection (nerve injury)

FAP, familial adenomatous polyposis; IPAA, ileal pouch–anal anastomosis; IRA, colectomy with ileorectal anastomosis; TPC, total proctocolectomy with end ileostomy.

Table 155–6 Surgical Options for Management of Colorectal Disease in the Colorectal Polyposis Syndromes and HNPCC

Syndrome	Surgical Options
FAP	Total proctocolectomy with end ileostomy
	Colectomy with ileorectal anastomosis (IRA)*
	Total proctocolectomy with ileal pouch–anal anastomosis (IPAA)
	Hand-sewn (with mucosectomy)
	Stapled (without mucosectomy)
aFAP	Colectomy with IRA*
MYH polyposis‡	Colectomy with IRA*
	Total proctocolectomy with IPAA
HNPCC	Colectomy with IRA*
	Total proctocolectomy with IPAA†
JPS‡	Colectomy with IRA*
	Total proctocolectomy with IPAA
PJS‡	Intraoperative endoscopy with polypectomy
	Segmental colectomy
Cronkhite-Canada syndrome‡	Segmental colectomy
Cowden's Disease‡	Segmental colectomy
Ruvalcaba-Myhre-Smith syndrome‡	Segmental colectomy
Hereditary mixed polyposis syndrome‡	Colectomy with IRA*

*IRA may be used when there is relative rectal sparing and close endoscopic surveillance of the rectal remnant is possible.
†IPAA may be used when there is rectal cancer or when close postoperative endoscopic surveillance of the rectal remnant is not possible.
‡Surgical intervention is indicated for CRC, large polyp burden, or complications of polyposis.
See Table 155–5 for more details concerning the surgical options for FAP.
FAP, familial adenomatous polyposis; aFAP, attenuated FAP; HNPCC, hereditary nonpolyposis colorectal cancer; JPS, juvenile polyposis syndrome; PJS, Peutz-Jeghers syndrome.

risk of subsequent development of CRC by removing all at-risk mucosa. However, the permanent ileostomy associated with these procedures is often unacceptable to young patients with FAP because of its perceived restriction on social, athletic, and sexual activities. In addition, creation of a Kock pouch is technically difficult and is associated with an early postoperative complication rate of 15%, a mortality rate of 2.2%, and continent valve-related complications that require reoperative intervention in more than 20% of patients.[132] Because the postoperative functional results in a patient with FAP are likely to be observed by family members in need of prophylactic surgery, poor functional outcome and patient dissatisfaction may deter at-risk family members from undergoing appropriate screening, surveillance, and surgical management. Total proctocolectomy is appropriate for patients with an established distal rectal cancer in whom a sphincter-preserving resection would be oncologically suboptimal. In the absence of rectal cancer, the perineal dissection can be performed in the intersphincteric plane to reduce perineal wound healing problems.

IRA with close postoperative follow-up and endoscopic ablation of rectal polyps is an option for patients with rectal sparing and acceptable rectal compliance who are reliable and willing to undergo regular endoscopic surveillance and accept the 8% to 37% risk of subsequent development of rectal cancer.[133-137] Postoperative morbidity following IRA occurs in approximately 25% of patients, with small bowel obstruction being the most common complication.[138] In addition, recent evidence suggests the risk of rectal cancer may be lower than reported in historical series, as more stringent criteria have been developed for selecting patients for IRA following the introduction of IPAA.[136] Advantages of this approach include improved postoperative bowel function, less complexity in performing the procedure, and avoidance of a permanent ileostomy.[137] However, following IRA in patients with FAP, endoscopic follow-up and ablation of residual and new rectal polyps should be performed in 6-month intervals.[128,131]

A combination of IRA and endoscopic rectal surveillance with ablation of polyps may delay the development of rectal cancer by as much as 10 years. If rectal polyps cannot be adequately managed endoscopically, a trial of sulindac can be considered. However, strong consideration should be given to converting the IRA to an IPAA. Significant rectal polyposis (>100 polyps), a long retained rectal segment, inadequate or unreliable follow-up, specific mutation loci on the *APC* gene, and the presence of colon cancer at the time of colectomy have been associated with an increased risk of developing rectal cancer following IRA.[139,140] Historical data, much of which was collected prior to the availability of IPAA as a surgical option, suggest that 16% to 32% of patients with FAP treated with IRA ultimately require proctec-

tomy.[136,141] However, when data are limited to the IPAA era, the rate of proctectomy is reported as low as 2% following IRA, likely due to limitation of IRA to patients with rectal sparing and patients with severe disease undergoing rectal excision at their initial surgery.[136] Reasons for proctectomy following IRA include metachronous rectal cancer, large adenomas, severe dysplasia, rectal strictures, incontinence, or high polyp density that prohibits adequate endoscopic surveillance. Although an IRA improves survival by 30 years in patients with FAP, overall survival remains 10 years less than that for the general population.[142]

IPAA for FAP is commonly performed in two stages. Resection of the entire colon and rectum followed by an IPAA with or without a protecting loop ileostomy is the first operation. When the anastomosis is performed hand-sewn, a mucosectomy is performed, involving the distal anorectal mucosa from the dentate line cephalad approximately 5 cm. During the mucosectomy, care is taken to preserve the internal and external anal sphincters. A reservoir is constructed from the terminal ileum, which requires mobilization of the small bowel mesentery up to the level of the duodenum and uncinate process of the pancreas as well as mesenteric-lengthening maneuvers. The second operation, performed 2 to 3 months later, consists of reversal of the ileostomy. Closure of the ileostomy is preceded by a water-soluble contrast enema to exclude pouch leaks and confirm sacralization of the pouch. Some perform IPAA as a one-stage operation, without a protective ileostomy. However, this approach is controversial because of the potential for an increase in clinically significant anastomotic leaks and pouch failure. The morbidity of the single-stage approach must be balanced against ileostomy-related complications from the two-stage procedure, which may lead to pouch failure and permanent ileostomy. Recently, small series have reported the feasibility of laparoscopic IPAA in patients with FAP.[143]

IPAA should eliminate any future risk of CRC. However, it is unclear whether an IPAA, by virtue of removal of all at-risk mucosa, can push the survival curve of patients with FAP closer to that of the general population. A stapled IPAA without mucosectomy leaves a small ring of rectal mucosa, even when performed close to the dentate line. Similarly, a hand-sewn IPAA with mucosectomy can leave small areas of rectal mucosa between the rectal cuff and serosa of the pouch, a location that is difficult to palpate and visualize endoscopically. There are reports of adenomatous polyps (up to 57% of patients) and adenocarcinomas of the ileal pouch or distal to the anastomosis, a finding that was associated with increasing length of time from IPAA surgery but not with severity of colorectal polyposis.[144] These findings emphasize the need for endoscopic surveillance of the pouch, with biopsy of suspicious lesions.

Mortality following IPAA for FAP is less than 1% and complications occur in 20% to 28% of patients, with small bowel obstruction being most common.[145,146] Postoperative fecal frequency and incontinence are important considerations in patients undergoing IPAA. Patients average between four and six bowel movements per day, with 53% to 78% with perfect continence during the day and 50% to 69% continent at night.[147] Although functional results after IPAA for FAP continue to improve with surgeon experience, the results after IRA may be better.[148] In addition, postoperative recovery, rehabilitation, and complication rates may be better when patients treated with IRA are compared to those treated with IPAA.[146,149] However, with experience, a hand-sewn or stapled IPAA can be performed with low mortality rates, acceptable morbidity rates, and long-term functional results approximating that of IRA.[150]

Issues That Modify Surgical Therapy When CRC is present, stage and location, presence of symptoms, overall patient status, and the extent and location of benign polyp disease are important considerations in planning the extent of surgical resection. If incurable metastatic disease is diagnosed, surgery should be palliative. However, if metastatic disease is resectable, a curative total colectomy with IRA should be performed in patients with colon cancer and limited rectal polyposis. Some suggest that patients with FAP and colon cancer can safely undergo IPAA, but it may be prudent to perform a colectomy and delay IPAA until after definitive pathologic and radiographic staging of the colon cancer, adjuvant treatment is completed, and a period of recovery and observation. In addition, when unsuspected colon cancer is discovered on pathologic examination following IPAA, a period of observation may be warranted before ileostomy closure because adjuvant chemotherapy may worsen anal incontinence and frequency of bowel movements. For upper rectal cancer in the setting of FAP, a staged rectal resection and subsequent IPAA may be considered. However, when the rectal cancer involves the anal sphincters, a total proctocolectomy with ileostomy is required.

A preoperative CT is helpful in the identification of desmoids, as they may influence the surgical approach. Patients with a personal or family history of desmoids are at particular risk and should have an IPAA as an initial procedure because future attempts at proctectomy may be impossible due to dense desmoid fibrosis. However, patients with extensive mesenteric desmoids at initial operation may be poor candidates for IPAA because a shortened mesentery may prohibit the terminal ileal pouch from reaching the anal canal. In addition, desmoids may cause subsequent pouch-related complications such as ulceration, bleeding, or dysfunction from pressure effects.

In women of childbearing age, postoperative fecundity is an issue to consider when planning surgical therapy for FAP. Some data suggest that women treated with IPAA may have a significantly higher infertility rate following surgery.[151,152] It has been hypothesized that pelvic adhesions, which may be significant following IPAA, contribute to postoperative infertility. Suturing the ovaries to the pelvic brim and use of antiadhesion barriers has been suggested following IPAA in women of childbearing age, but there are limited data to conclude that these measures improve postoperative fertility. Therefore, it is important to discuss the potential for impaired postoperative fertility with women of childbearing age considering an IPAA.

An alternative option for women of childbearing age who desire to become pregnant following surgery for FAP may be colectomy with IRA. Some data suggest that the postoperative fecundity of women with FAP who have an IRA is similar to that of the general population.[152] However, in most cases IRA is reserved for those with relative rectal sparing and who are willing to undergo close postoperative endoscopic surveillance of the rectal remnant.

Conclusions When deciding the colorectal operation to offer a patient with FAP, two important points should be considered: (1) colorectal surgery is usually prophylactic and performed in asymptomatic, young patients who are concerned about postoperative restrictions on social, athletic, and sexual activities; and (2) regardless of the type of surgery performed, patients with FAP will likely not have a normal life expectancy because of the morbidity and mortality associated with other manifestations of the syndrome, especially duodenal periampullary neoplasia and desmoid disease.[145] Nevertheless, IPAA is the operation of choice for most patients with FAP because it nearly eliminates the risk of CRC while maintaining transanal fecal evacuation. In a carefully selected subset of patients, IRA with close postoperative endoscopic surveillance and excision or ablation of rectal polyps is an option, recognizing that IRA is associated with somewhat better functional results and lower morbidity. Given the substantial risk of cancer developing in the rectal remnant, IRA is contraindicated in patients who are unable to comply with intensive endoscopic surveillance.

Attenuated Familial Adenomatous Polyposis

Attenuated FAP is diagnosed in a subset of patients with germline APC mutations who present with fewer colorectal polyps (<100), later age of onset of polyps (mean at age 44 years) and cancer (mean at age 56 years), and increased rate of proximal colon involvement.[119] It is inherited in an autosomal dominant fashion, and genotype-phenotype correlations between the mutated *APC* gene locus and clinical presentation of attenuated FAP have been reported.[153] In some cases it is difficult to distinguish attenuated FAP from HNPCC and sporadic colorectal adenomas or carcinomas, with further complexity added by variable patient presentation within the same kindred.[118,154] Extracolonic manifestations of FAP, such as gastric and duodenal polyps, are commonly observed in patients with attenuated FAP. However, patients with attenuated FAP rarely are diagnosed with CHRPE, desmoids, and osteomas.[119]

In asymptomatic patients belonging to an FAP or attenuated FAP kindred, the syndrome is commonly diagnosed using genetic testing. Endoscopic screening and surveillance in these patients must include colonoscopy, given the proximal location of most colonic neoplasia in patients with attenuated FAP. The diagnosis should be considered in patients with multiple colorectal polyps or characteristic extracolonic manifestations, even without a positive family history. Prophylactic surgery in these patients may be guided by the extent of colorectal polyposis. Surgical resection can be deferred in reliable patients willing to undergo close endoscopic surveillance when there are few adenomas that are adequately treated with colonoscopic polypectomy.[119] However, when there are multiple polyps or if the patient is unreliable or unwilling to undergo surveillance, prophylactic colectomy may be prudent (see Table 155–6).

MYH Polyposis

Recently, an autosomal recessive syndrome called *MYH polyposis,* characterized by multiple colorectal adenomas and CRC, has been described that has phenotypic similarities to attenuated FAP or FAP. The initial description of MYH polyposis was in a kindred with an excess of oxidative damage to the *APC* gene resulting in the substitution of thymine-adenine for guanine-cytosine.[155] Later work determined that the oxidative damage was due to missense mutations in the base excision repair gene MYH, most commonly at the loci Y165C and G382D.[156] It is this unrepaired oxidative damage to the *APC* gene that is believed to result in the increased incidence of colorectal adenomas and CRC in these patients.[155,157]

Patients with biallelic mutations in the *MYH* gene usually present with multiple (3 to 100) colorectal adenomas at a median age of 47 to 56 years.[156-158] Patients with hundreds of polyps have been described, although homozygous MYH mutations are rare in those with more than 1000 colorectal polyps.[157-159] The polyps are most commonly tubular or tubulovillous adenomas, with some displaying dysplasia.[157] In addition, these patients have microadenomas similar to those observed in patients with FAP.[158] Although not completely characterized, there have been reports of extraintestinal manifestations such as duodenal polyposis and CHRPE associated with MYH polyposis.[157]

Diagnosis of MYH polyposis requires clinical suspicion in patients with multiple colorectal adenomas, those with suspected FAP and no mutation in the *APC* gene, and those with CRC diagnosed prior to age 50.[156] Furthermore, the syndrome should be considered in patients with a family history consistent with an autosomal recessive inheritance pattern of colorectal adenomas or CRC. Homozygous *MYH* mutations are rare in patients with less than 3 colorectal adenomas, although up to 33% of patients with more than 15 adenomas may have biallelic mutations in the *MYH* gene.[156,157] In addition, in patients with a classic FAP phenotype and no mutation in the *APC* gene, up to 8% with have biallelic mutations in the *MYH* gene. It has been estimated that homozygous mutations in the *MYH* gene are responsible for 1% to 3% of cases of CRC.[160,161] Genetic testing for a known *MYH* mutation may be performed using probe-based PCR.[156] Alternatively, the entire *MYH* gene may be sequenced.[162] As for all genetic testing, pretest and post-test genetic counseling are required.

Although there are no large studies to guide the treatment approach, given the increased risk of CRC throughout the colon it is reasonable to offer patients with MYH polyposis total proctocolectomy with IPAA. Alternatively, patients with relative rectal sparing may be treated with total abdominal colectomy and IRA with close post-

operative surveillance of the remaining rectum to diagnose and treat metachronous adenomas (see Table 155–6). In select cases of MYH polyposis, colorectal adenomas may be controlled with endoscopic polypectomy and colectomy may be avoided.[156,157] The interval of colonoscopic surveillance in patients homozygous for *MYH* mutations remains to be determined, although current recommendations are similar to those for classic FAP.[156] In addition, upper gastrointestinal endoscopy is recommended for patients with homozygous *MYH* mutations.[156,157]

Hereditary Nonpolyposis Colorectal Cancer

Clinical Considerations

HNPCC is an autosomal dominant familial CRC syndrome characterized by familial clustering of early age-of-onset CRC (average age, 40 to 48 years). It is estimated to be responsible for 3% to 5% of all cases of CRC. Other prominent features of HNPCC include a predominance of right-sided colon cancer (60% to 80% proximal to the splenic flexure), an increased incidence of synchronous and metachronous CRC (up to 45% of patients), and an increased incidence of specific extracolonic cancers (endometrial, ovarian, renal pelvis, ureteral, small bowel, and gastric).[163] The first description of this syndrome was by Aldred Warthin in 1913, who reported a kindred known as "Family G" with an increased incidence of colon, gastric, and endometrial cancer.[164] However, the significance of the familial clustering of these malignancies was not fully appreciated until 1966, when Henry Lynch and colleagues reported two large families with the "cancer family syndrome."[165] In 1984, further observation led to the description of two patterns of disease presentation, termed *Lynch syndrome I* (CRC only) and *Lynch syndrome II* (CRC and associated malignancies).[166] Due to the subsequent difficulty in differentiating these two patterns of disease, the term *HNPCC* was given to this syndrome. In 1991, the International Collaborative Group on HNPCC (ICG-HNPCC) published clinical guidelines to standardize diagnosis and facilitate performance of large, cooperative studies. These studies ultimately contributed to the definition of surveillance and treatment protocols and identification of the genetic basis for the syndrome.[167]

The term *nonpolyposis* is often confusing, because patients with HNPCC do have colorectal polyps, although they do not have florid polyposis as is observed in patients with FAP. The incidence of adenomas in patients with HNPCC and CRC is similar to that of the general population with sporadic CRC. However, adenomas in patients with HNPCC have a higher incidence of high-grade dysplasia and villous architecture. In addition, polyps in patients with HNPCC develop at a younger age, tend to be larger than those in the general population, and are distributed equally throughout the colon. Adenomas in HNPCC are thought to be precancerous lesions, similar to the adenoma-to-carcinoma sequence seen in the development of sporadic CRC. However, an accelerated transition from adenoma to carcinoma has been reported in patients with HNPCC.[168]

HNPCC is inherited in an autosomal dominant fashion with 80% penetrance. Therefore, the lifetime risk of CRC is 80%, 60% of which will be diagnosed by age 60 years. CRC in these patients is more likely to be poorly differentiated and mucinous and have signet ring histology.[169] In addition, colorectal neoplasia in patients with HNPCC is more likely to demonstrate medullary growth with cribriform patterns, and a "Crohn's like" pattern of tumor-infiltrating lymphocytes.[169] Despite these normally poor prognostic features, patients with HNPCC have survival that is equivalent, if not better, than patients with sporadic CRC of similar stage.[170]

Extracolonic Cancers

Although CRC is the most common malignancy in HNPCC, several other cancers occur with increased frequency in these patients. The most common extracolonic malignancy is endometrial cancer, diagnosed in 39% to 60% of women with HNPCC by age 70 years.[125,171] Women with HNPCC also have an increased risk of ovarian cancer. Other malignancies that have been associated with HNPCC include cancers of the stomach, transitional cell epithelium of the urinary tract (renal pelvic, ureter, bladder), small bowel, and hepatobiliary system.[172] The estimated cumulative lifetime risk of developing cancers of the stomach is 13% to 19%, urinary tract is up to 4% to 7%, and hepatobiliary system is 2% to 4%.[62,171] HNPCC associated with tumors of the central nervous system (primarily glioblastoma) has been termed *Turcot's syndrome,* whereas association with benign and malignant tumors of the sebaceous glands and keratoacanthomas has been termed *Muir-Torre syndrome.*

Genetics

The genetic etiology of cancer predisposition in patients with HNPCC is a germline mutation in a mismatch repair *(MMR)* gene, which recognizes and repairs mismatched nucleotides during DNA replication.[62] When the *MMR* genes function properly, DNA nucleotides that are mismatched during replication are excised and replaced with the correct bases. Patients with mutations in an *MMR* gene lack appropriate repair of mismatched DNA and express the "mutator phenotype." Cancer develops in these patients due to failure of repair of replication errors and the ultimate dysfunction of tumor suppressor genes and oncogenes involved in tumorigenesis.

When there is a mutated *MMR* gene, the number of base pairs in known microsatellites can increase or decrease. This phenomenon, known as *microsatellite instability* (MSI), is an expression and marker of a mutated *MMR* gene. A germline mutation in one allele of an *MMR* gene along with a somatic mutation of the second allele of the same gene is required to produce MSI. MSI was initially described in unicellular organisms, such as the bacteria *Escherichia coli,* where the role of MMR genes was defined. The detection of MSI in HNPCC tumors led to the hypothesis that HNPCC was due to the mutations in human homologues of the bacterial MMR genes *MutS* and *MutL.* This led to the description of the human MMR genes human MutL homologue *(hMLH)* and

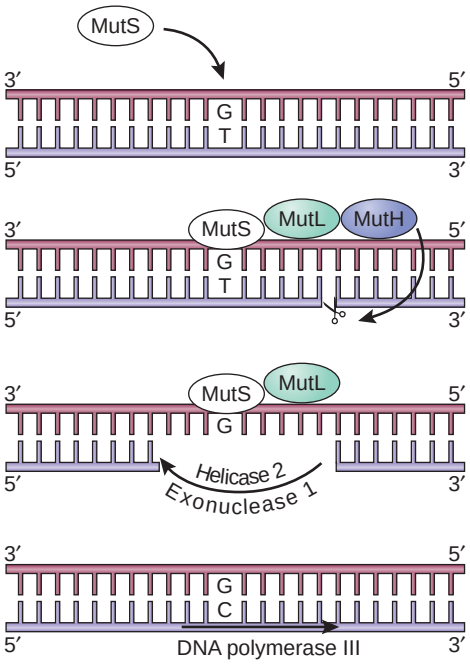

Figure 155–11. Enzymes involved in the recognition, excision, and repair of mismatched nucleotides during DNA replication. (From Service RF: Stalking the start of colon cancer. Science 263:1559-1560, 1994.)

human MutS homologue *(hMSH)* as the genetic etiology of HNPCC (Fig. 155–11).

Mismatch Repair Genes Seven mismatch repair genes have been associated with HNPCC, including four from the mutL family *(hMLH1, hMLH3, hPMS1, hPMS2)* and three from the mutS family *(hMSH2, hMSH3, hMSH6).*[62,173] However, more than 90% of cases of HNPCC are due to mutations in *hMLH1* or *hMSH2.*[174] *hMSH6* mutations are associated with atypical HNPCC, characterized by later onset of CRC, low-level MSI, and increased incidence of endometrial cancer.[175] HNPCC caused by germline mutations in *hMLH3, hPMS1,* and *hPMS2* is rare, and routine evaluation of these genes is not currently recommended.[176] A number of different types of mutations have been described, including truncating, missense, and frameshift mutations.[62] The incidence of *MMR* gene mutations in the general population ranges from 1 in 200 to 1 in 2000, with a penetrance of 80%. In kindreds with a clinical diagnosis of HNPCC, the incidence of a documented germline mutation in an *MMR* gene ranges from 15% to 86%.[177,178]

Microsatellite Instability Phenotype In 1993, DNA replication errors were described in both sporadic[179] and familial[180] CRC. Linkage of the germline etiology of HNPCC to chromosome 2, without increased *K-ras, p53,* and *APC* mutations, led to the hypothesis that CRC in HNPCC develops via a mechanism distinct from the classic pathways of loss of heterozygosity in tumor suppressor genes and oncogenes. The genetic lesions responsible for CRC via tumor suppressor genes and oncogenes are characterized by gross chromosomal abnormalities, whereas mutations in *MMR* genes are characterized by a more subtle genetic alteration, namely MSI.

There are more than 100,000 microsatellites observed throughout the human genome. In HNPCC-associated CRC, the most commonly affected microsatellites are those containing mononucleotide repeats (particularly $[A]_n$. Dinucleotide (particularly $[CA]_n$), trinucleotide, tetranucleotide, and pentanucleotide repeats are less frequently affected by MSI, demonstrating that the simpler the microsatellite sequence, the higher probability of developing instability at that locus when an *MMR* gene is mutated.[181] Most MSI-positive tumors accumulate mutations in short mononucleotide sequence near or within the coding regions of growth regulatory genes. These genes include growth factor receptors (transforming growth factor-β receptor II, insulin-like growth factor receptor II), regulators of the cell cycle, regulators of apoptosis, immune surveillance, and the MMR genes *hMSH6* and *hMSH3.*[62,173]

In 1996, the National Cancer Institute sponsored a workshop on MSI in hereditary CRC and recommended that a series of five microsatellite markers be tested to determine the MSI status of a tumor. DNA is amplified using PCR followed by microdissection, and the lengths of specific microsatellites are compared between tumor and normal tissue of the same individual.[182] When a microsatellite locus of tumor and normal tissue are of different length, that marker is considered to have MSI at that locus. When two or more loci display MSI, the tumor has high-level MSI (MSI-H). When one loci displays MSI, the tumor has low level MSI (MSI-L), and when none of the markers display MSI, the tumor is microsatellite stable (MSS).[181] In patients with MSI-L tumors, an additional panel of five MSI markers is recommended to confirm the MSI status. The MSI-H phenotype is observed in more than 90% of CRCs in patients with HNPCC, whereas it is observed in only 10% to 15% of sporadic CRCs.[173] However, it must be emphasized that MSI in HNPCC is caused by a germline mutation in an *MMR* gene, whereas MSI in sporadic CRC is most commonly due to hypermethylation (and silencing) of the *hMLH1* promoter.[183]

Despite the different mechanism underlying MSI in HNPCC and sporadic CRC, it appears that they have similar pathologic and clinical features. Sporadic MSI-H CRC of the proximal colon have an increased incidence of poorly differentiated, mucinous histology, solid cribriform growth pattern, fewer lymph node metastases, DNA diploidy, and Crohn's-like lymphoid infiltration when compared with sporadic MSS tumors.[173,184] Because these features are typical of HNPCC-associated CRC, it appears that MSI-H CRC may be characterized by distinct clinicopathologic features, regardless of family cancer history. Similar to adenocarcinoma, colorectal adenomas in patients with HNPCC have a significantly increased incidence of MSI than sporadic adenomas (57% to 90% versus 3%).[185-188] MSI-H and MSS adenomas can coexist in the same patient with a germline MMR gene mutation.[187]

Genotype-Phenotype Correlations MMR gene mutations have been evaluated for correlation with a specific clinical presentation of HNPCC. Patients with HNPCC due to a mutation in *hMSH2* may develop CRC at a later age (>40 years) and have a higher incidence of extracolonic cancer, whereas those with a mutation in *hMLH1* present with CRC at an earlier age (<35 years), have relatively fewer extracolonic cancers, and have a higher incidence of rectal cancer.[189] In addition, patients with *hMSH6* mutations may have "atypical" HNPCC, with MSI-L status, lower incidence and later onset (55 years versus 44 years) of CRC, and higher incidence of endometrial cancer and transitional cell cancer of the urinary tract.[175] Gender may affect phenotypic expression among patients with *hMSH2* mutations, because men may have a higher incidence of CRC and death from cancer, whereas women may have more extracolonic malignancies, primarily due to the increased risk of endometrial and ovarian cancer.[190,191] Others have reported a correlation between mutation of *hMSH2* and Muir-Torre syndrome.[192] Although these potential relationships may have implications for screening, surveillance, and treatment, large-scale studies with precise clinical and molecular data are still needed to establish more accurate genotype-phenotype correlations.

Diagnosis

The gold standard for diagnosis of HNPCC is the detection of a germline mutation in an *MMR* gene. In the absence of distinct phenotypic features, the clinical diagnosis of HNPCC is based on family history. The diagnosis should be considered in patients with early age-of-onset CRC, because up to 20% of patients younger than 40 to 45 years at diagnosis of CRC will have HNPCC.[193] However, a family cancer history during the initial consultation of patients with early age-of-onset CRC may be limited in its ability to detect hereditary CRC syndromes, and more extensive follow-up interviews are recommended.[194]

In 1991, the ICG-HNPCC established the Amsterdam Criteria to standardize the clinical diagnostic criteria for HNPCC (Box 155–1).[167] The Amsterdam Criteria are sensitive for the detection of HNPCC but are limited in small families, kindreds where extracolonic cancers are prominent, and in de novo cases of germline *MMR* gene mutations. In response to these concerns, less strict criteria were suggested to include other well-recognized clinical features of HNPCC, such as right-sided CRC, synchronous and metachronous CRC, associated extracolonic cancers, colorectal polyps, and familial aggregation of early age-of-onset CRC. In 1998, the ICG-HNPCC developed a revised set of clinical criteria (Amsterdam Criteria II) that includes many of these associated clinical features (Box 155–2).[195] Furthermore, in 1996 the Bethesda Guidelines were established to direct patient selection for MSI testing (Box 155–3).[182] These guidelines were revised in 2002 (Box 155–4).[196]

Box 155–1 Amsterdam Criteria for the Clinical Diagnosis of HNPCC

- CRC in three relatives, one a first-degree relative of the other two
- At least two successive generations affected
- At least one CRC diagnosed before age 50 years
- FAP is excluded

CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer.
Data from Vasen HF, Mecklin JP, Khan PM, Lynch HT: The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 34:424-425, 1991.

Genetic Testing and Counseling—Implications for Screening and Surveillance

Genetic testing provides the potential for the identification of *MMR* gene mutation carriers prior to the development of cancer. At-risk family members may benefit from detection of a recognized, specific *MMR* gene mutation in their kindred. An optimal strategy to enhance detection of HNPCC should incorporate clinical evaluation, including the Amsterdam II Criteria and Revised Bethesda Guidelines. Prior to genetic testing, individuals should be referred for pretest genetic counseling. The molecular genetic studies available include MSI testing, immunohistochemistry for expression of MMR proteins, and germline sequencing. Initial genetic testing may include MSI or immunohistochemistry for *hMLH1* and *hMSH2,* since these genes are responsible for more than 90% of HNPCC cases. However, if the genetic locus responsible for HNPCC in a particular kindred is known, targeted testing may be performed.

Recommendations for genetic testing and surveillance of patients with a known *MMR* gene mutation have been developed by various expert societies. These recom-

Box 155–2 Amsterdam Criteria II for the Clinical Diagnosis of HNPCC

- HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis) in three relatives, one a first-degree relative of the other two
- At least two successive generations affected
- At least one HNPCC-associated cancer diagnosed before age 50 years
- FAP is excluded (in cases of CRC)

CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer.
Data from Vasen HF, Watson P, Mecklin JP, Lynch HT: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology 116:1453-1456, 1999.

Box 155–3 **Bethesda Guidelines for Selecting Patients with CRC for MSI Testing**

Tumors from individuals should be tested for MSI in the following situations:

1. Individuals with cancer in families that meet the Amsterdam Criteria
2. Individuals with two HNPCC-related cancers, including synchronous and metachronous CRC or associated extracolonic cancers
3. Individuals with CRC and a first-degree relative with CRC and/or and HNPCC-related extracolonic cancer* and/or a colorectal adenoma; one of the cancers diagnosed before age 45 years or the adenoma diagnosed before age 40 years
4. Individuals with CRC or endometrial cancer diagnosed before age 45 years
5. Individuals with right-sided colon cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed before age 45 years
6. Individuals with signet ring cell–type CRC diagnosed before age 45 years
7. Individuals with colorectal adenomas diagnosed before age 40 years

*HNPCC-related extracolonic cancer = endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell (renal pelvis or ureteral) cancer.
CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer; MSI, microsatellite instability.
Data from Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al: A National Cancer Institute workshop on hereditary nonpolyposis colorectal cancer syndrome: Meeting highlights and Bethesda Guidelines. J Natl Cancer Inst 89:1758-1762, 1997.

Box 155–4 **Revised Bethesda Guidelines for Selecting Patients with CRC for MSI Testing**

Tumors from individuals should be tested for MSI in the following situations:

1. CRC diagnosed in an individual who is younger than age 50 years
2. Presence of synchronous or metachronous colorectal or other HNPCC-associated cancers,* regardless of age
3. CRC with the MSI-H histology† diagnosed in an individual who is younger than age 60 years
4. CRC diagnosed in one or more first-degree relatives with an HNPCC-associated cancer, with one of the cancers being diagnosed before age 50 years
5. CRC diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

*Colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain cancers and sebaceous gland adenomas and keratoacanthomas.
†Tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous or signet ring differentiation, or medullary growth pattern. Microsatellite instability–high (MSI-H) in tumors refers to changes in ≥ 2 of the panel of five National Cancer Institute-recommended microsatellite markers.
CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer.
Data from Umar A, Boland CR, Terdiman JP, et al: Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96:261-268, 2004.

mendations may also be appropriate for nontested individuals in a mutation-positive kindred, as well as for individuals who belong to a family with a suspected autosomal dominant predisposition to CRC. Full colonoscopy to the cecum with the removal of adenomatous polyps is recommended to commence at the age of 20 to 25 years and be repeated every 1 to 2 years thereafter for the remainder of the patient's life.[16,17] Although there are no randomized, controlled trials to fully quantify the benefit of colonoscopic polypectomy in *MMR* gene mutation carriers, colonoscopic polypectomies of adenomas have reduced the incidence of CRC in at-risk individuals.[197] Screening for endometrial cancer is recommended to begin at 25 to 35 years of age and be repeated every 1 to 2 years. Options for screening for endometrial cancer include endometrial aspirate/biopsy and transvaginal ultrasound.[198] There is insufficient evidence to make definitive recommendations for the other HNPCC-associated cancers, namely stomach, renal pelvis, ureter, hepatobiliary tract, and ovaries. However, screening is recommended when these cancers occur in an affected individual's family. Methods for ovarian cancer screening include serum CA-125 and transvaginal ultrasound, for gastric cancer include upper gastrointestinal endoscopy, and for genitourinary cancer include abdominopelvic ultrasound and urine cytology.

Surgical Treatment

A total abdominal colectomy with IRA is recommended for individuals with an *MMR* gene mutation who develop CRC, because of the high lifetime risk of metachronous CRC and predilection for developing proximal colon cancer (see Table 155–6). However, there is up to a 12% risk of rectal cancer 10 to 12 years after total abdominal colectomy, so aggressive lifelong surveillance of the remaining rectum should be pursued.[199] In patients who present with rectal cancer, total proctocolectomy with IPAA may be offered, given the 17% to 45% rate of metachronous colon cancer in the remnant colon following segmental resection of rectal cancer in these patients.[198,200] A prophylactic total abdominal colectomy

is also recommended as an alternative to lifelong endoscopic surveillance for selected patients with an *MMR* gene mutation and colorectal adenomas. Prophylactic colectomy should be considered on an individual basis, with special consideration given to patients in whom colonoscopy is technically difficult, patients with lesions not amenable to endoscopic polypectomy, and patients who are not likely to be compliant with aggressive endoscopic surveillance. Prophylactic colectomy for individuals with an *MMR* gene mutation but no evidence of colonic neoplasia remains controversial, because as many as 20% will not manifest the disease and therefore will not benefit from the operation.[129]

Although there are no definitive data to support prophylactic hysterectomy or bilateral salpingo-oophorectomy in *MMR* gene mutation carriers, patients may be offered the procedure. In general, female patients with HNPCC who undergo CRC surgery may be advised to consider resection of the uterus and ovaries, particularly if they are postmenopausal.[198] In premenopausal women, counseling should focus on childbearing plans, the long-term effects of prolonged estrogen replacement therapy, and the risk of metachronous endometrial and ovarian cancers. The patient should be advised of the alternatives of annual gynecologic surveillance and prophylactic surgery in the future.

Other Polyposis Syndromes

Juvenile Polyposis Syndrome

Juvenile polyps, the most common gastrointestinal polyp in children, are often encountered as a single colonic lesion in children younger than 10 years of age and are likely not inherited. However, JPS is a rare autosomal dominantly inherited genetic disorder that must be considered in patients with (1) three or more juvenile polyps, (2) any number of juvenile polyps in a patient with a family history of JPS, or (3) any patient with a first-degree relative with JPS.[124] Three clinical variants of this syndrome have been described. *JPS of infancy* is an autosomal recessive disease characterized by failure to thrive, susceptibility to infection, protein-losing enteropathy, gastrointestinal bleeding, diarrhea, intussusception, rectal prolapse, and death by 2 years of age in severe cases. *Generalized JPS* presents in the 1st decade of life and is characterized by juvenile polyps throughout the gastrointestinal tract. *JPS of the colon* is the most common presentation of the syndrome and is characterized by juvenile polyps limited to the large intestine. The most common presentation is chronic anemia, followed by acute gastrointestinal bleeding, per-anal prolapse of the polyp, protein-losing enteropathy, and intussusception with or without obstruction.[127]

The most common site of polyps in JPS is the colon and rectum, although they have been described throughout the gastrointestinal tract.[127,201] Juvenile polyps appear grossly as smooth, reddish brown, pedunculated lesions with lobulated or spherical heads, and superficial ulceration. Histologically, they are characterized by an inflammatory stroma with abundant lamina propria and cystically dilated, mucus-filled glands lined with columnar epithelium. Notably, the polyps do not contain smooth muscle. In addition, foci of adenomatous tissue within a juvenile polyp have been described and may provide the basis for progression of the polyp to invasive cancer.[202]

Patients with JPS have a 10% to 38% lifetime risk of developing CRC and 68% of patients who reach age 60 years develop the malignancy.[203] CRC in patients with JPS is more likely to be distally located, poorly differentiated, have a mucinous histology, and carry a poor prognosis.[203] In addition, 15% to 21% of patients develop gastroduodenal cancer.[202] Gastric cancer is believed to progress from adenomatous foci in hamartomatous polyps, analogous to that in the colon. In addition to gastrointestinal cancers, pancreatic cancer in association with JPS has been reported.[202]

Congenital anomalies of multiple organ systems have been associated with 15% of patients with JPS.[204] Malformations of the gastrointestinal system (malrotation, mesenteric lymphangiomas, vitellointestinal duct abnormalities), genitourinary system (renal structural abnormalities, glomerulonephritis, cryptorchidism, bifid uterus and vagina), heart and vascular system (ventricular septal defect, patent ductus arteriosus, arteriovenous malformation), nervous system (hydrocephalus), and the soft tissue all have been described in these patients.[205] Other associated extraintestinal abnormalities include nail clubbing, hypertrophic pulmonary osteoarthropathy, macrocephaly, alopecia, bony swellings, and cleft lip and palate. Juvenile polyposis is also a feature of Cowden's syndrome, Cronkhite-Canada syndrome, Ruvalcaba-Myhre-Smith syndrome, and Gorlin's syndrome (nevoid basal cell carcinomas, odontogenic keratocysts, skeletal abnormalities, and intracranial calcification).

A family history of JPS is present in 20% to 50% of patients.[206] The syndrome is inherited in an autosomal dominant manner and a germline mutation of the *SMAD4* gene on chromosome 18q21.1 and the *BMPR1A* gene of chromosome 10q21-22 have been linked to the disease.[207] *SMAD4* mutations have been associated with some cases of sporadic CRC and may be a major factor in the increased risk of CRC in patients with JPS.[208] Commercial genetic testing for JPS is available and may be offered to patients meeting the clinical criteria for the syndrome and their family members.[124] As with all genetic testing, counseling is required before the test is performed.

Patients with clinically severe disease who present with gastrointestinal bleeding, anemia, diarrhea, or protein-losing enteropathy should initially be treated with fluid and electrolyte replacement, transfusion, and nutritional supplementation. These patients may be candidates for surgical treatment with total abdominal colectomy and IRA or total proctocolectomy and IPAA (see Table 155–6).[127,201] Surgical resection is also an option for patients with a large polyp burden or suspicion of CRC. Following surgical treatment of colonic disease, surveillance endoscopy of the remaining rectum or pouch and upper gastrointestinal tract is mandatory.[201] Gastric resection is indicated for patients with symptomatic polyps,

dysplasia, or cancer.[201,209] In addition, investigators have evaluated the role of cyclooxygenase inhibitors (i.e., sulindac, celecoxib) to control polyps in this syndrome.[201,210] However, given the limited experience with the use of these medications for JPS and lack of any clinical trial, it is not possible to make definitive recommendations regarding their clinical utility.

Patients who present with less severe disease should be followed with surveillance colonoscopy, esophagogastroduodenoscopy, and small bowel series. Colonoscopy is recommended every 2 years, with excision of polyps and random biopsies to detect adenomatous change and dysplasia.[127] The interval for upper gastrointestinal tract surveillance is less well defined.

Screening of family members involves a careful history, colonoscopy of potentially affected family members, and surveillance colonoscopy in patients in whom polyps have been identified and removed. Surveillance colonoscopy and esophagogastroduodenoscopy are recommended for first-degree relatives of patients with JPS starting at 12 years of age, with repeated examination every 3 years.[127] Evaluation by small bowel contrast studies is of limited value in asymptomatic patients because cancer is rare in this portion of the intestine.[68]

Peutz-Jeghers Syndrome

PJS is a rare syndrome characterized by gastrointestinal tract hamartomatous polyps (usually <100) and mucocutaneous melanin pigmentation. It is the second most common hereditary gastrointestinal hamartoma syndrome, with an incidence of approximately 1 in 120,000 to 1 in 200,000.[211,212] The hypermelanotic macules most commonly involve the perioral region, buccal mucosa, digits of the hands and feet, and perianal and genital regions. In addition to the gastrointestinal tract, hamartomas have been described in the upper respiratory tract, biliary tract, and urinary tract. Patients may present with symptoms of obstruction from large hamartomatous polyps, as well as intussusception and rectal bleeding (acute and chronic). Biliary obstruction and gastric outlet obstruction are unusual presentations of PJS.

Gastrointestinal hamartomas can occur throughout the gastrointestinal tract and range in size from less than 1 mm to more than 4 cm in diameter.[213] They are most commonly seen in the small intestine, where they appear in up to 90% of cases.[214] In the small bowel, the most common location is the jejunum. The next most common gastrointestinal site is the colon, appearing in 50% of cases, followed by the stomach. Histologically, the polyps in PJS are hamartomas, characterized by hypertrophy or hyperplasia of the smooth muscle of the intestinal wall. The smooth muscle can extend into the superficial epithelial layer in a "treelike" manner, a process that has been termed *arborization.* The histologic term for epithelial cell trapping is *pseudoinvasion,* which has been noted in up to 10% of polyps greater than 3 cm. Given the pathologic phenomena of arborization and pseudoinvasion, the diagnosis of malignancy in a Peutz-Jeghers polyp must include documentation of cellular atypia or an elevated mitotic rate. Normal columnar epithelium usually covers the polyps and mucus-filled cysts in the mucosa are common. However, instances of mixed adenomatous/hamartomatous elements and pure adenomas have been described.

Mucocutaneous pigmentation usually appears during infancy and is most commonly noted in the perioral and buccal regions, where it is seen in up to 95% of cases.[213,215,216] Melanin pigmentation may also be seen in the periorbital and facial areas, as well as the acral areas of the body, such as the hands and feet. The genital region may also be affected. Macules are most commonly 1 to 12 mm in diameter, but the size of the lesions can vary.[213,217]

Pigment spots usually appear in the first few years of life, reach a maximal level in early adolescence, and can fade in adulthood.[218] However, since pigmentation on the buccal mucosa usually remains throughout the life of the patient, buccal examinations are imperative in an adult patient suspected of having PJS.[215,216] It is important to distinguish melanin deposits from common freckles, which are absent at birth, scarce near the lips, and absent on the buccal mucosa. Histologically, the areas of cutaneous pigmentation reveal increased melanocytes at the dermal-epidermal junction, with increased melanin in the basal cells.[219] Of note, the pigmented macules of PJS do not appear to have a malignant potential.[220,221]

Although hamartomas are considered benign lesions, patients with PJS have a substantially increased risk of intestinal and extraintestinal malignancy.[221-224] In addition, malignancy developing in a hamartomatous polyp in PJS has been reported.[225] Patients with PJS have up to a 15.2 relative risk of developing at least one malignancy compared to the general population.[221] In addition, the cumulative risk for developing any cancer between 15 and 64 years of age is estimated at 93%, with the first malignancy detected at an average age of 42.9 years.[221]

The syndrome has been linked to an increased risk of developing adenocarcinoma of the esophagus, stomach, small intestine, and large intestine. There is also an increased risk for extraintestinal cancer of the thyroid, breast (which can be bilateral), lung, pancreas, gallbladder, and biliary tree (cholangiocarcinoma). Women with PJS have an increased risk of gynecologic malignancies of the ovary (bilateral sex cord tumors with annular features) and uterus (well-differentiated adenocarcinoma of the cervix, known as *adenoma malignum* [minimal deviation adenocarcinoma]). In men, there is an increased risk of feminizing Sertoli cell tumors of the testis.

PJS exhibits autosomal dominant inheritance with variable penetrance. Currently, about 50% of cases appear to have a familial component, whereas 50% appear to be due to new sporadic genetic mutations.[226] The putative genetic locus was mapped to a multifunctional serine-threonine kinase named *LKB1* (also known as *STK11*) on 19p13.3.[227,228] Although the exact function of the LKB1/STK11 protein kinase product is unknown, the gene is believed to be a tumor suppressor gene involved in the early stages of tumorigenesis by inducing G_1 cell-cycle arrest.[229-232] It has been hypothesized that an initial germline mutation of the *LKB1/STK11* gene

followed by a somatic mutation of the normal allele leads to the development of the disease.

Genetic testing can be used to screen at-risk individuals and confirm the diagnosis of PJS in patients with a characteristic clinical presentation.[130] Determination of a specific mutation may be possible in as few as 60% of families.[233] However, if a specific mutation can be found, genetic testing of other family members is accurate in up to 95% of cases.[130] If a mutation is not known in a particular patient or family, genetic testing is carried out using gene sequencing for the known mutations in PJS.

Patients typically enter a screening and surveillance program following discovery of the characteristic mucocutaneous melanin pigmentation, a known family history, or the development of symptoms from the disease. An annual serum hemoglobin level and esophagogastroduodenoscopy with removal of polyps every 2 to 3 years beginning at age 10 to 25 years has been recommended.[128,130,212,218,226,234] Routine screening of the remainder of the small bowel is generally accomplished by contrast radiographic techniques, beginning at age 10 years and repeated every 2 to 3 years.[226] Recent advances in capsule endoscopy may provide an additional modality for small bowel screening in the future. Colonoscopic screening with polypectomy is recommended to begin in the late teenage years to age 25 years, with repeat examinations every 2 to 3 years.[218,226,234,235] These recommendations are subject to change based on individual patient preference, symptoms, and clinical presentation.

In females with PJS, annual physician-based breast examination and biannual mammography should commence at 25 years of age.[130,218,226,234] Gynecologic screening should begin by age 20 years and should include annual pelvic examination and pelvic ultrasound and a Papanicolaou smear every 1 to 3 years.[235] Some authors suggest endometrial biopsy on a yearly basis starting at 20 years of age, to screen for endometrial malignancy.[130,218,226,235] In male patients, annual clinical testicular examination starting at age 10 years is recommended.[130,234,235] A testicular ultrasound can be performed if the patient has symptoms of precocious puberty or feminization or if a mass is palpated.[211,218,226,234]

Surgical intervention in patients with PJS is indicated for symptomatic lesions, complications related to polyposis, or cancer (see Table 155–6). Aggressive endoscopic polypectomy may limit the need for operative intervention or increase the interval between surgical interventions. When endoscopic techniques are unable to adequately resect a lesion, intraoperative endoscopy and polypectomy may be indicated.[236] Removal of polyps greater than 1.5 cm in diameter is attempted because these are most likely to produce symptoms or complications. The introduction of laparoscopic-assisted endoscopic polyp clearance in PJS may further reduce morbidity and improve management of these patients. Indications for bowel resection include the detection of adenomatous changes in an incompletely removed polyp, as well as patients presenting with intussusception, obstruction, or gastrointestinal bleeding. Prophylactic colectomy cannot be recommended because of the relatively low incidence of CRC.

Cowden's Disease

Cowden's disease is a rare condition characterized by multiple benign hamartomas and malignant tumors of the breast, thyroid, uterus, brain, and mucocutaneous tissue (including the gastrointestinal tract). It has also been called the *multiple hamartoma syndrome* and has been estimated to occur in 1 in 200,000 individuals.[237] The lesions arise from all germ cell layers, including the endoderm, ectoderm, and mesoderm. Diagnostic criteria for Cowden's disease were established by the International Cowden Syndrome Consortium in 1995 and revised in 2000.[237]

Gastrointestinal polyposis is not as prominent a clinical feature as mucocutaneous lesions, developmental anomalies, and breast and thyroid neoplasia. Eighty percent to 100% of patients present with dermatologic manifestations of this disease, the most common being trichilemmoma, a benign tumor of the hair shaft.[68,238] Other dermatologic signs include multiple smooth facial and oral mucosal papules and acral keratoses.[238] The second most commonly involved organ site is the central nervous system. Cowden's disease associated with cerebellar gangliocytomatosis, megalocephaly, ataxia, and epilepsy is known by the eponym *Lhermitte-Duclos syndrome*.[239] Nonspecific clinical findings include lipomas, hemangiomas, neuromas, and pigmentary disorders. Facial developmental disorders described in patients with Cowden's disease include a high arched palate, adenoid faces, prominent forehead, and hypoplastic mandible.[234] Gastrointestinal polyps are diagnosed in 35% of patients. The polyps are most commonly hamartomas (resembling juvenile polyps), but lipomas, ganglioneuromas, and inflammatory polyps have been described. Polyps are typically small and occur in the gastrointestinal tract from mouth to anus but are observed most commonly in the colon.

Benign thyroid and breast disease are prominent features of Cowden's disease. Thyroid pathology includes benign goiter, adenoma, and follicular thyroid carcinoma. Breast disease may be bilateral and includes fibrocystic disease and adenocarcinoma (both ductal and lobular).[240] The estimated lifetime risk of thyroid cancer is 10%, and that for breast cancer is 30% to 50%.[68] Other malignant diseases described in these patients include carcinomas of the endometrium, cervix, kidney, bladder, lung, and colon. In addition, there have been reports of liposarcoma, malignant melanoma, and squamous cell carcinoma of the skin.[234]

Cowden's disease is transmitted in an autosomal dominant fashion, with near-complete penetrance by the age of 20 years.[241,242] Eighty percent of patient have an identifiable germline mutation in the *PTEN* gene located at 10q23.3.[243] The *PTEN* gene is a lipid phosphatase that acts as a tumor suppressor gene via its impact on gastrointestinal cell cycle arrest and apoptosis.[244] It has been implicated in related gastrointestinal hamartomatous polyposis syndromes (Lhermitte-Duclos and Ruvalcaba-Myhre-Smith syndromes), as well as in familial thyroid cancer,[245,246] inherited breast cancer,[247] prostate cancer,[247] and malignant melanoma.[248] Recent data suggest that the etiology of Cowden's disease in patients without a

germline mutation in *PTEN* may have a mutation in the promoter region of the gene.[234,249] A genotype-phenotype correlation between germline *PTEN* mutations and breast disease has been suggested.[247]

Management of Cowden's disease is based on its accurate diagnosis and careful search for associated malignancy. The dermatologist most commonly makes the diagnosis, as the prominent clinical presentation of Cowden's disease is related to its distinct cutaneous manifestations. Gastrointestinal polyposis is treated with endoscopic surveillance and removal of polyps. Bowel resection is unnecessary because the malignant potential in the polyps is negligible. Given the relatively rare nature of the disease, there are no randomized trials evaluating appropriate screening and surveillance examinations and intervals. However, it is reasonable to recommend monthly self–breast examination and annual clinical breast examination beginning in the teenage years.[234,249] Mammography is recommended to begin at age 25 years and be repeated at least every 3 years.[238,249] Annual clinical thyroid examination is recommended, beginning in the teenage years, supplemented by thyroid ultrasound every 1 to 2 years after 18 years of age.[68] Clinical gynecologic examination and urinalysis have been suggested to screen for uterine and renal disease, respectively.[243]

Ruvalcaba-Myhre-Smith Syndrome

The features of Ruvalcaba-Myhre-Smith syndrome (also referred to as *Bannayan-Zonana syndrome, Ruvalcaba-Riley-Smith syndrome,* and *Bannayan-Riley-Ruvalcaba syndrome*) include gastrointestinal hamartomatous polyposis, developmental abnormalities (mental retardation, delayed psychomotor development), macrocephaly, ocular abnormalities, lipomas, vascular malformations, Hashimoto's thyroiditis, and hyperpigmentation of the penis.[250] It is a rare autosomal dominantly inherited disorder.[61] Ruvalcaba-Myhre-Smith syndrome is believed to be related to Cowden's disease, given that up to 60% of patients have an identifiable germline mutation in the *PTEN* gene.[243] This finding has led some to suggest reclassifying patients with Cowden's disease and Ruvalcaba-Myhre-Smith syndrome into a single entity termed the *PTEN hamartoma syndrome*. It is unclear whether the 40% of patients with Ruvalcaba-Myhre-Smith syndrome without an identifiable germline mutation of the *PTEN* gene have inactivation of the gene by other mechanisms or if other genes are involved in the phenotypic expression of the syndrome. As with Cowden's disease, the increased risk of gastrointestinal cancer is believed to be small. The treatment considerations for Ruvalcaba-Myhre-Smith syndrome are the same as Cowden's disease, with endoscopic removal of symptomatic polyps and screening of family members important considerations.

Cronkhite-Canada Syndrome

Cronkhite-Canada syndrome is a rare acquired gastrointestinal polyposis syndrome characterized by hamartomatous polyps (similar to juvenile polyps) and other epidermal changes. It involves tissues arising from the ectodermal germ cell layer but does not appear to be an inherited disorder. Most cases have been reported from Japan,[251,252] and its similarity to Ménétrier's disease have led some to conclude that the two conditions are related. The etiology of Cronkhite-Canada syndrome is unclear, although infection, toxins, nutritional deficiency, and mental and physical stress all have been suspected as risk factors.

Patients typically present in the 6th decade of life with cutaneous or gastrointestinal manifestations. In addition, watery diarrhea associated with dysgeusia (loss of taste or metallic taste), anorexia, weight loss, peripheral edema, and hypoproteinemia are characteristically observed in patients with Cronkhite-Canada syndrome.[251] Cutaneous manifestations include alopecia, macular pigmentation, patchy vitiligo and onychodystrophy and other nail changes, and skin hyperpigmentation.[253] Polyps are found throughout the gastrointestinal tract, with characteristic sparing of the esophagus.[254,255] The most common site of gastrointestinal involvement is the stomach, although the small and large bowel are also affected.[251,256]

Complications of Cronkhite-Canada syndrome are often severe and include mucosal ulceration, gastrointestinal bleeding, infection, and malnutrition. Severe intestinal polyposis can cause profound metabolic and electrolyte disturbances. In addition, intussusception and rectal prolapse has been described in these patients. There is a marginally increased risk of cancer of the stomach and colorectum.[68,256] However, the mortality from the syndrome, estimated as high as 60%, is due in large part to the associated nonmalignant complications.[256]

Management of patients with Cronkhite-Canada syndrome is multifocal. Given the increased risk of cancer of the stomach, colon, and rectum, endoscopic surveillance has been recommended, as often as on a yearly basis. Supportive care, with management of fluids, electrolytes, nutrition, and anemia, is an important consideration. Corticosteroids, antibiotics, anabolic steroids, cromolyn sodium, histamine receptor antagonists, and proton pump inhibitors have been used for therapy with variable success.[256] Medical management is usually required for 6 to 12 months, and corticosteroids have been used with success for disease recurrence.[257] Surgical management may be indicated if the stomach, colon, or rectum is the source of excessive bleeding, bowel obstruction, or cancer (see Table 155–6). However, case reports suggest that surgical management of Cronkhite-Canada syndrome may be associated with a high perioperative morbidity.[251]

Hereditary Mixed Polyposis Syndrome

Hereditary mixed polyposis syndrome is an autosomal dominant inherited polyposis syndrome characterized by colon polyps of varied histology, increased risk of CRC, and no extraintestinal manifestations.[258] The colon lesions include hamartomas, adenomas, and hyperplastic polyps. The hamartomas are similar to those seen in juvenile polyposis, and the adenomas may be tubular, villous, or flat.[259] Hyperplastic polyps with areas of

dysplasia (serrated adenomas) have also been described in patients with this syndrome.[260,261] Hereditary mixed polyposis syndrome is associated with early age-of-onset CRC, believed to develop through a hyperplastic/juvenile polyp to a mixed/serrated adenoma to carcinoma pathway.[260] There is no evidence that patients with this syndrome are at increased risk of any other type of cancer.

The number of polyps in hereditary mixed polyposis syndrome are spread evenly throughout the colon and usually number less than 15. The colon appears to be the only affected organ system, with no extraintestinal manifestations yet described.[260] Although the putative genetic locus was initially linked to 6q16-21, later data demonstrated this to be incorrect.[258] Evaluation of a large kindred with hereditary mixed polyposis syndrome allowed mapping of the etiologic gene to 15q13-14.[258] Subsequent analysis has suggested that the colorectal adenoma and carcinoma *(CRAC1)* gene may be the gene responsible for this syndrome.[258]

Because phenotypic heterogeneity is common among the gastrointestinal polyposis syndromes, clinical distinction of the hereditary mixed polyposis syndrome from FAP, HNPCC, juvenile polyposis, and PJS may initially be difficult. However, patients with hereditary mixed polyposis syndrome do not display the characteristic extracolonic features of FAP and PJS, and patients with HNPCC do not have juvenile polyps. It is more difficult to distinguish hereditary mixed polyposis syndrome from juvenile polyposis. However, pure adenomas are rare in juvenile polyposis. In addition, patients with juvenile polyposis usually have more extensive polyposis and tend to be diagnosed with polyps and cancer at an earlier age than patients with hereditary mixed polyposis syndrome.

Due to the rarity of this syndrome, definitive management recommendations have yet to be established. However, because polyps have been detected as early as 18 years of age and can develop within a 2-year interval, screening colonoscopy should begin at age 18 to 20 years and be repeated every 1 to 2 years. Total abdominal colectomy with ileorectal anastomosis is an option for selected individuals and should be the treatment of choice for patients who develop CRC (see Table 155–6). In these circumstances, close postoperative surveillance following surgery is mandatory because cancer may develop in the rectal remnant.

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Chapter

156

Adenocarcinoma of the Colon and Rectum

Martin R. Weiser · Mitchell C. Posner · Leonard B. Saltz

Colorectal cancer remains one of the most dynamic fields in oncology, both in the laboratory and in the clinic. The molecular events associated with cellular transformation were reported more than 15 years ago, and mechanisms of carcinogenesis and tumor progression continue to be intensely studied. Recently, molecularly based therapies directed against the epidermal growth factor receptor (EGFR) and against vascular endothelial growth factor (VEGF) have proven useful, and may be the harbingers of more elegant, tumor-specific colorectal cancer therapy. Clinically colorectal cancer is a diverse disease, requiring individually based treatment strategies. This chapter reviews the most current data available regarding epidemiology, screening, diagnosis, staging, and multimodal treatment of colorectal cancer.

INCIDENCE AND EPIDEMIOLOGIC ASSOCIATIONS

Colorectal cancer ranks third (behind prostate and lung cancer in men, and behind breast and lung cancer in women) as the most common malignancy in the United States and represents the second leading cause of cancer-related mortality. Approximately 147,000 patients are diagnosed with colorectal cancer each year, and 57,000 deaths are attributed to this disease.[1] The probability of colorectal cancer developing during a lifetime is approximately 6%. In contrast to the three previous decades, however, the overall incidence and mortality rate for colorectal cancer has declined for both men and women (Fig. 156–1). Age-adjusted incidence and mortality rates are associated with race and ethnicity. For example, blacks have an overall worse outcome; however, this may represent a comparative lack of access to care rather than differences in biologic aggressiveness of the individual cancers.[2]

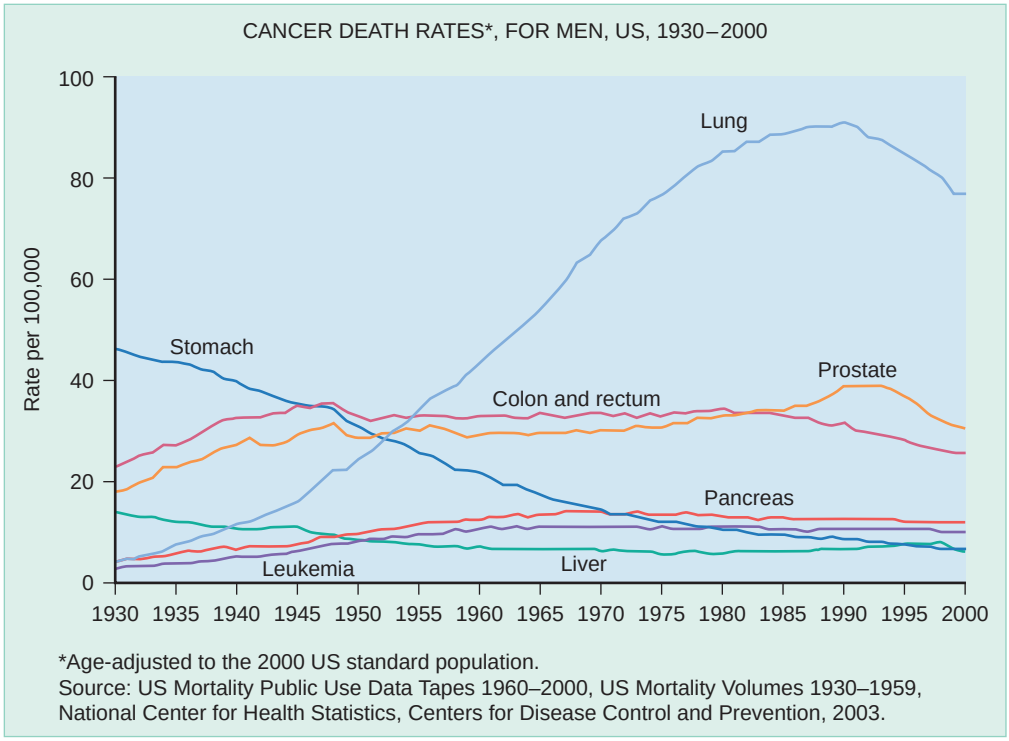
Worldwide, an estimated 1,023,152 patients were diagnosed with colorectal cancer in 2002, with 528,978 associated deaths.[3] The highest rates of colorectal carcinoma predominate in the more industrialized countries. Lower rates are found in Eastern Europe, Asia, Africa, and South America.[4] Studies of Japanese migration to the United States, Asiatic Jewish migration to Israel, and eastern European migration to Australia have shown that migrants acquire the high rates of colorectal cancers prevalent in their adopted countries. There is little question that environmental factors, most likely dietary, account for the rise in cancer rates.

Colon cancer is three times more common than rectal cancer. Epidemiologic studies indicate a rising proportion of right-sided colon lesions. The proximal migration of colon cancer may relate to changing environmental factors; however, there is no doubt that increased colon screening results in detection of early lesions in an aging population.[5]

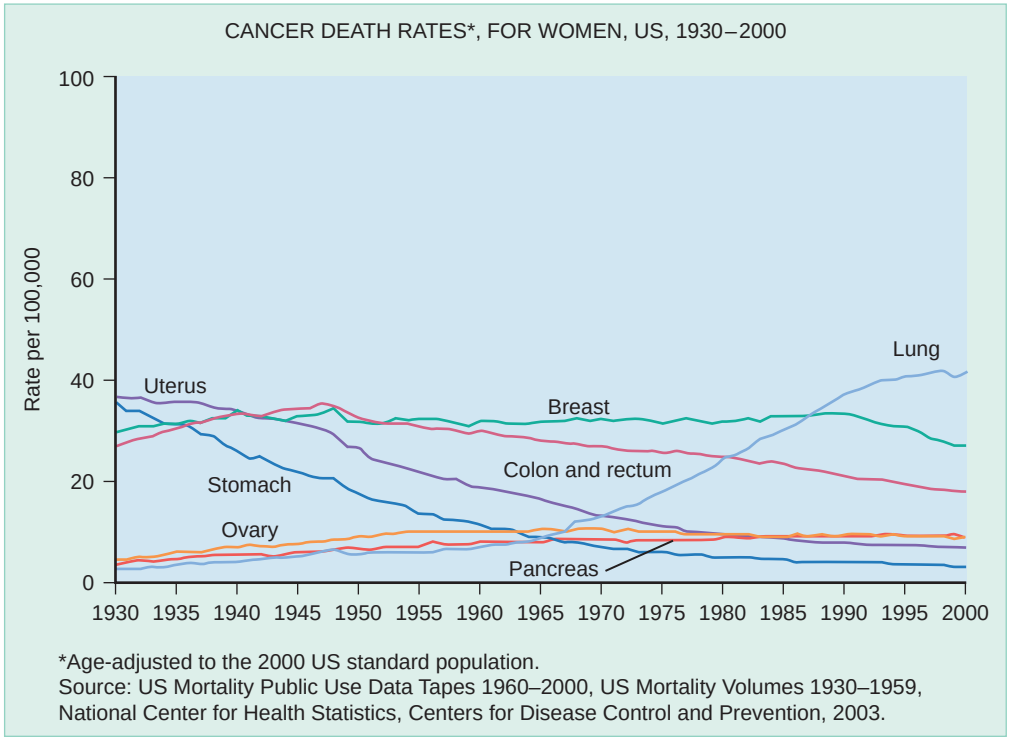
GENETIC PATHWAYS TO COLORECTAL CANCER

Cancer cells are characterized by uncontrolled growth, a capacity to avoid normal senescence and death, and the ability to invade and metastasize. Alterations in genes, oncogenes, and the tumor suppressor genes that normally control these functions result in cellular transformation. This is referred to as the *adenoma-carcinoma cascade* and was first described in relation to colorectal cancer by Fearon and Vogelstein[6] more than 15 years ago.

There are at least two well-described genetic pathways leading to the development of colorectal adenocarcinoma. The chromosomal instability (CIN) pathway is the result of an accumulation of inactivated tumor suppressor genes and overactive protooncogenes. Tumors developing along this pathway are characterized by mutations of the *APC, p53,* and K-*ras* genes, allelic loss of 18q, and aneuploidy. The *APC* gene plays a pivotal role in tumorigenesis, as 100% of familial adenomatous polyposis

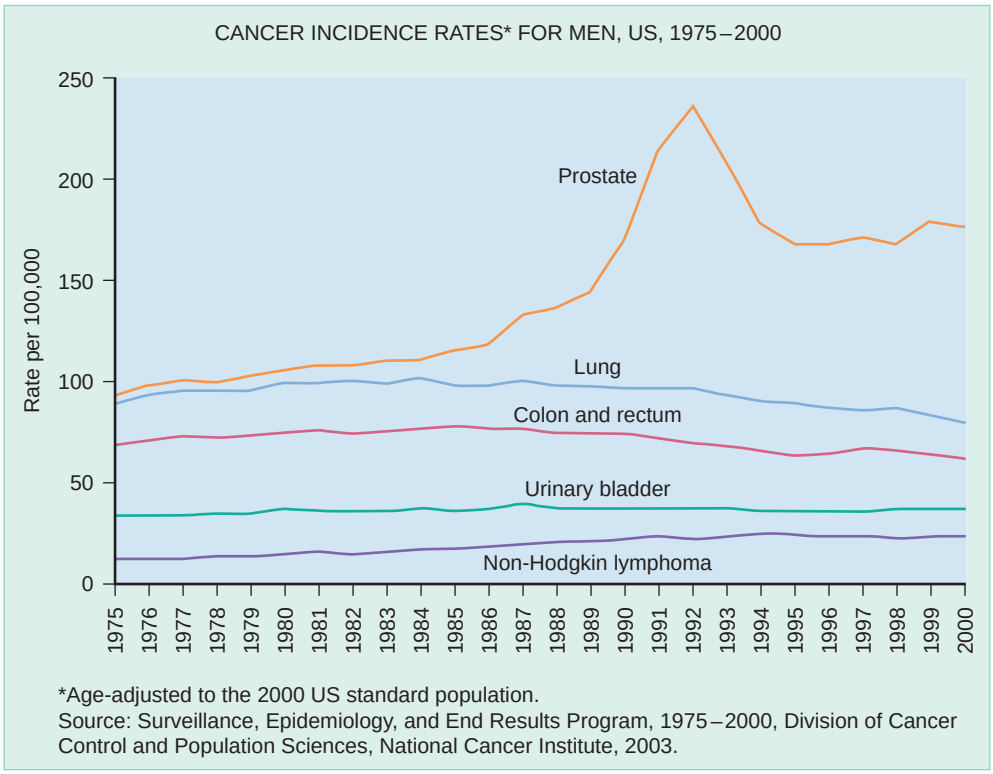


A



B

Figure 156–1. Cancer incidence and mortality trends over time, in men (**A** and **C**) and women (**B** and **D**). (© American Cancer Society. www.cancer.org.)



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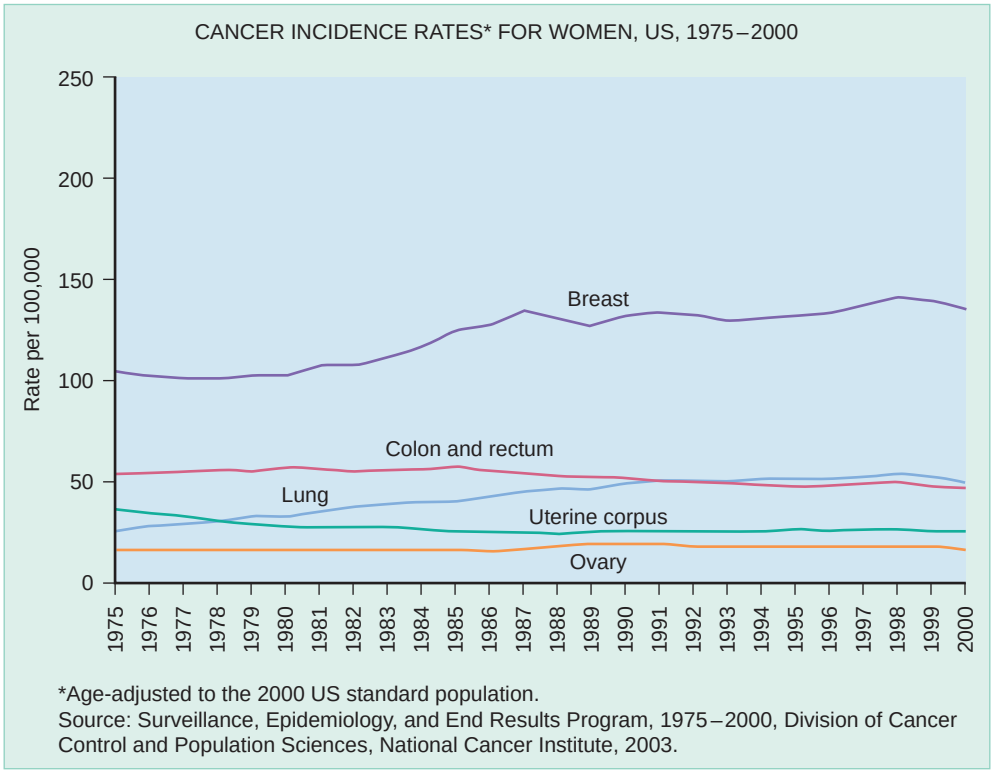

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Figure 156–1, cont'd.

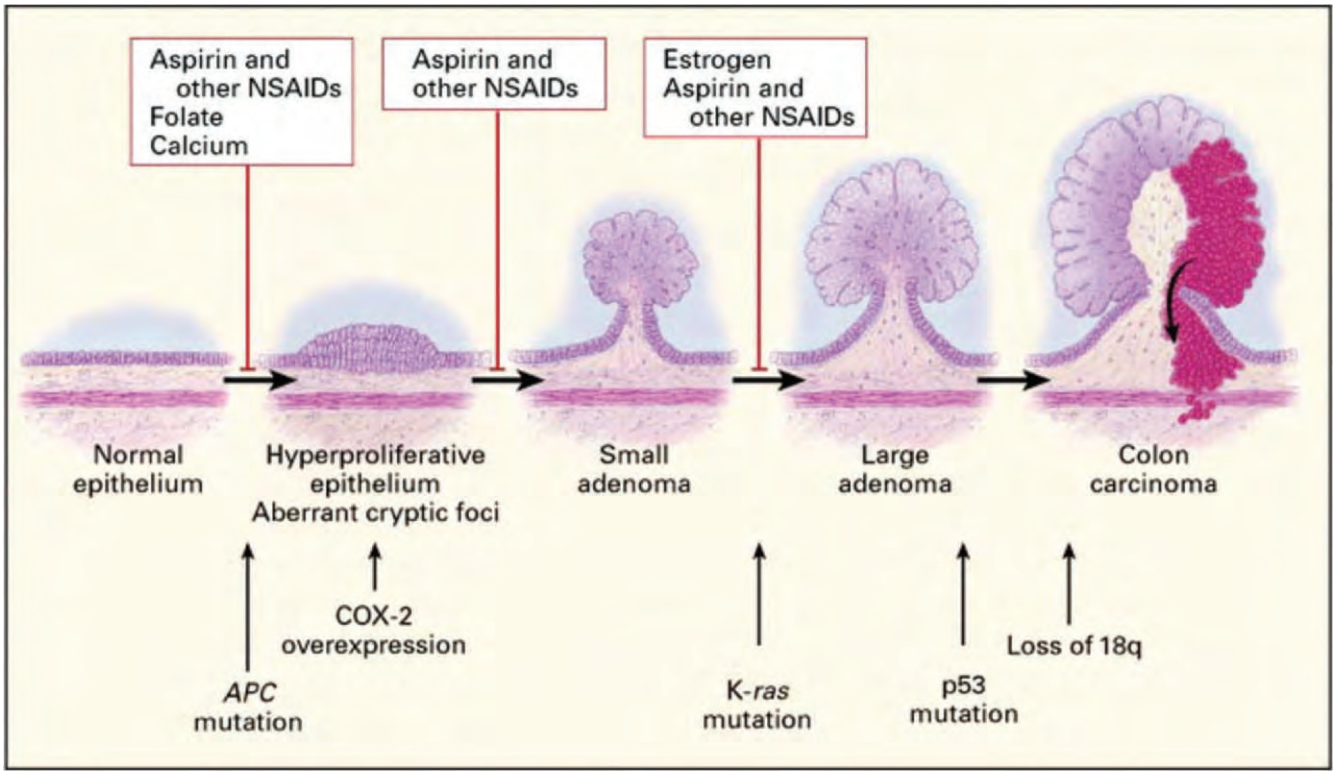


Figure 156–2. Colon carcinogenesis and the effects of chemopreventive agents. NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase. (From Janne PA, Mayer RJ: Chemoprevention of colorectal cancer. N Engl J Med 342:1960-1968, 2000.)

(FAP) patients, who carry this mutation, develop colorectal cancer if prophylactic surgery is not performed. Up to 80% of tumors develop along the CIN pathway.

The microsatellite instability (MIN) pathway is the other well-described genetic cascade implicated in the development of colorectal cancer. These tumors have aberrant DNA mismatch repair, a near-diploid karyotype, and lower levels of *p53, SMAD4,* and K-*ras* mutations but higher frequencies of *BAX, TGF-BIIR,* and *BRAF* mutation. These tumors generally develop proximal to the splenic flexure and carry a better prognosis than those developing by the CIN pathway. Patients with heredity nonpolyposis colon cancer develop malignancy along the MIN pathway, with loss of genes involved in DNA-mismatch repair. This pathway is also referred to as the *replication error* (RER) pathway and is responsible for approximately 20% of carcinomas.

Some tumors do not fall into either category, indicating that other genetic pathways exist.[7] Further study of molecular events will undoubtedly lead to a better understanding of multistep carcinogenesis, molecular staging, and tumor-specific therapy. Figure 156–2 outlines the genetic pathway of colorectal cancer and the potential prophylactic role for chemopreventive agents.

COLORECTAL CANCER RISK FACTORS

Clearly, the development of colorectal malignancy involves interplay between genetic and environmental influences. The most easily identified risk factors include age older than 50 years, a personal or family history of colorectal cancer or adenoma, and a personal history of long-standing inflammatory bowel disease (IBD). Colorectal cancers that develop in individuals without hereditary links are referred to as "sporadic" and account for 75% of all such cancers. A potential genetic influence is identified in the remaining 25% of patients, including family history (15% to 20%); hereditary nonpolyposis colon cancer (HNPCC) (5%); and FAP (<1%).

Age

Age is the most common risk factor. The incidence of colorectal cancer increases from the 4th decade to 8th decade of life.[8] Most individuals present with disease after age 60 years, and only 10% of cancers occur in individuals younger than 40 years. A personal history of colorectal polyps is also a significant risk factor, and cancer can present within the polyp or at another site in the colon. The risk of a polyp harboring invasive disease is related to the size, morphology, and histology of the lesion. Polyps can be classified as tubular, villous, or tubulovillous. Large villous lesions are most likely to harbor malignancy, with about 50% of villous polyps larger than 2 cm containing cancer. Approximately 40% of patients are noted to have multiple adenomatous polyps, and these individual are at highest risk for having or developing subsequent invasive cancer.[9] Individuals previously diagnosed and treated for colorectal cancer are at significant risk for developing metachronous

disease. Approximately 40% of patients treated for sporadic colorectal cancer develop metachronous polyps, and at least 6% develop a second colorectal cancer while under surveillance.[10,11]

Inflammatory Bowel Disease

Patients with the medical condition IBD are at significantly increased risk for developing colorectal cancer; the risk is proportional to the extent and duration of disease. This has been extensively studied in ulcerative colitis patients, where the risk of cancer appears to begin after 8 to 10 years of disease and increases at a rate of about 0.5% to 1% per year. Institutional and population-based studies report the absolute risk to be 2% to 5% at 10 years, 8% to 10% at 20 years, and 20% to 30% at 30 years.[12] The risk is highest in patients with pancolitis (disease extending proximal to the splenic flexure), disease diagnosed at a young age (see Fig. 156–2),[13] and colitis-associated sclerosing cholangitis. Cancer that occurs in patients with ulcerative colitis can arise in any portion of the large bowel, usually presents in the 4th decade of life, and appears to carry the same prognosis as colon cancer in general.[14] However, disease in these patients often presents at a late stage, since endoscopic identification of a malignancy in the setting of active colitis is quite difficult. Since all currently available screening tests (including repetitive biopsies linking dysplasia and bowel mucosa transformation to cancer) are problematic,[15] most patients with long-standing colitis will probably benefit at some point from prophylactic proctocolectomy. The risk of colorectal cancer is also increased in long-standing Crohn's colitis, which until recently has been underappreciated. Currently it is believed that the cancer risk is equivalent for both Crohn's and ulcerative colitis patients who have disease of similar duration and extent.[16]

Familial Colorectal Cancer

Familial factors are associated with 25% of colorectal cancer cases. Individuals with a first-degree relative affected by colorectal cancer have twice the risk of developing the disease themselves. This risk is nearly threefold for individuals with two or more affected first-degree relatives. Not surprisingly, a positive family history is associated with younger age of diagnosis, and this finding implies a genetic predisposition.[17] Currently, the highest risk patients are those that carry the genetic mutations associated with FAP and HNPCC (Fig. 156–3). Nearly

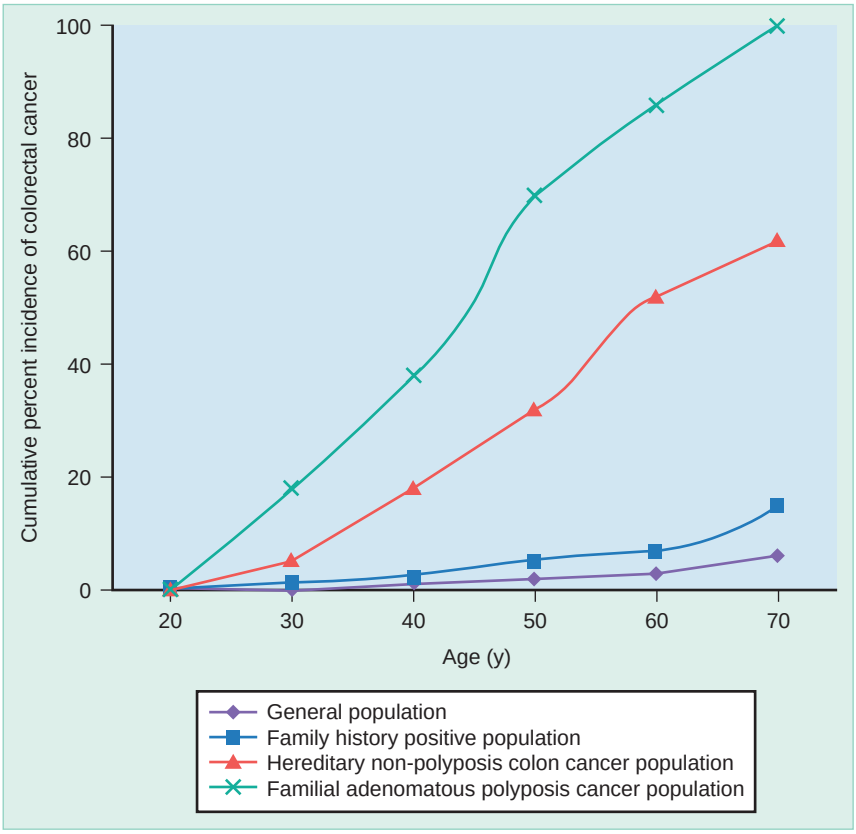


Figure 156–3. Colorectal cancer risk.

100% of patients with FAP and 80% of HNPCC patients develop colorectal cancer in their lifetime.

Familial Adenomatous Polyposis

The FAP syndromes account for 1% of all colorectal cancers and are characterized by early onset of hundreds to thousands of polyps throughout the colon. Adenomas typically begin to present early in the 2nd decade of life, with cancer inevitably developing by the 4th to 5th decade if colectomy is not performed. These syndromes affect approximately 1:8,000 to 10,000 persons; 10% to 20% of cases represent de novo mutations with no apparent family history.[18,19] The disease is inherited as an autosomal dominant trait; therefore, 50% of offspring from an affected individual develop polyposis coli. The gene that causes FAP (*APC* gene) resides on chromosome 5 (5q21). The most common genetic abnormality results in the generation of a premature stop codon, resulting in a truncated and nonfunctional protein.[20] This finding is the basis for a commonly used screening procedure in which the truncated protein is identified in vitro, thereby confirming the diagnosis.

In addition to colonic polyps, FAP patients commonly develop periampullary cancers, gastric fundic gland polyps, and intra-abdominal desmoid tumors. After the colorectal cancer is eliminated by surgery, periampullary tumors are the most frequent cause of death among individuals with FAP.[21] A variant of FAP includes Gardner's syndrome, characterized by colorectal adenomas and extraintestinal manifestations, including osteomas (mainly of the mandible and skull), soft tissue tumors (e.g., lipomas, fibromas, and epidermoid and sebaceous cysts), supernumerary teeth, desmoid tumors, mesenteric fibromatosis, and congenital hypertrophy of the retinal pigmentation epithelium. Turcot's syndrome is another variant of FAP in which colorectal adenomas are associated with brain tumors. Attenuated FAP syndrome is characterized by the development of fewer polyps, more likely in the right colon and later in life.[22] This can make clinical diagnosis of attenuated FAP versus HNPCC quite difficult. The various FAP phenotypes appear to be related to the site of mutation on the *APC* gene.[22] For example, gene mutation in attenuated FAP is usually located more proximal or distal in the *APC* gene than it is in the more common FAP syndrome.

Hereditary Nonpolyposis Colon Cancer

HNPCC is a familial disorder characterized by a high incidence of colon cancer without the excessive polyps identified in classic FAP and accounts for 5% to 6% of colorectal cancers.[23,24] Its phenotypic features include early-onset colorectal cancer with a mean age of 46 years; synchronous or metachronous colorectal cancers (noted in 35% of cases); and a proclivity for right-sided tumors.[25] There is an association with early onset of adenocarcinoma of the ovary, pancreas, breast, bile duct, endometrium, stomach, genitourinary tract, and small bowel.[26] *Lynch II* refers to the cohort of patients with colorectal cancer and an associated other adenocarcinoma, whereas *Lynch I* refers to the cohort with colorectal cancer only. Muir-Torre syndrome is a HNPCC variant associated with sebaceous gland adenomas and carcinoma.[27]

Box 156–1 Amsterdam II Criteria

- At least three relatives with an HNPCC-associated cancer (colorectal, endometrium, small bowel, ureter, or renal pelvis). One affected relative should be a first-degree relative of the other two.
- At least two successive generations should be affected.
- At least one relative should have been diagnosed before age 50 years.
- Familial adenomatous polyposis should be excluded.

Tumors should be verified by pathologic examination.
HNPCC, hereditary nonpolyposis colon cancer.

The molecular genetic marker reflective of HNPCC is MIN, which is a consequence of mutations in DNA mismatch repair genes (*hMSH2, hMLH1, hPMS1,* and *hPMS2*). Diagnostic criteria for identifying individuals with HNPCC have been established. In 1991, at a consensus conference in Amsterdam, criteria were developed to help identify and categorize patients with familial history of colorectal cancer.[25] The initial criteria, referred to as *Amsterdam Criteria I,* requires (1) three relatives with colorectal cancer, one being a first-degree relative of the other two; (2) two successive generations afflicted with colorectal cancer; or (3) one family member who developed colorectal cancer younger than 50 years of age. Furthermore, FAP must be excluded and all cancers verified pathologically. However, these criteria tend to underestimate HNPCC in some family pedigrees.[23] Therefore, *Amsterdam Criteria II* was developed to include extracolonic tumors. The accepted HNPCC-associated cancers include colorectal, endometrial, small bowel, ureteral, or renal pelvic cancers (Box 156–1).

HNPCC cancers have a characteristic histologic appearance. Adenomas tend to have a villous component with more dysplasia than typically seen in sporadic cases. Cancers commonly have signet-ring histology with poor differentiation and inflammatory cell infiltrate.[23,28] In spite of the aggressive histologic appearance, stage-for-stage survival for colorectal cancer patients with HNPCC is better than that for patients with sporadic cancers.[26] Colorectal neoplasms appear to develop more rapidly in patients with HNPCC,[24] which affects their follow-up regimen.

Genetic Syndromes

Peutz-Jeghers and familial juvenile polyposis are genetic syndromes associated with an increased incidence of colorectal cancer. These are autosomal dominant syndromes characterized by hamartomatous polyposis. The

histology of intestinal hamartomas consists of an overgrowth of cells or tissues native to the area in which they normally occur.[29] The molecular mechanisms of these syndromes are currently under study, and specific mutations have been described.[30]

Peutz-Jeghers syndrome is characterized by multiple gastrointestinal hamartomatous polyps associated with mucocutaneous melanin pigmentation. Patients can present with impending obstruction, with polyp intussusception or anemia from gastrointestinal blood loss. The polyps are generally non-neoplastic with a characteristic branching muscular framework, but they can contain carcinoma. Peutz-Jeghers patients are at increased risk for developing both gastrointestinal and extraintestinal carcinomas (e.g., pancreatic, breast, ovarian, testicular and uterine); therefore, prophylactic colectomy is usually not indicated.[31] Polyps are usually managed endoscopically, whereas surgery is reserved for large and symptomatic lesions or those with neoplastic appearance.

Familial juvenile polyposis syndrome is characterized by multiple (often 50 to 200) juvenile polyps throughout the gastrointestinal tract, often associated with other congential anomalies including cardiac and genitourinary. Patients can present in childhood with anemia caused by chronic gastrointestinal blood loss, crampy abdominal pain associated with intussusception, a protein-losing enteropathy, or frank rectal bleeding. (Patients who present with the often self-limited, solitary juvenile polyp are not included within this definition.) Individuals with this syndrome are at an increased risk for developing both upper and lower gastrointestinal cancers.[32] These polyps are generally controlled endoscopically, and total abdominal colectomy with ileal pouch-anal anastomosis is reserved for patients with large and numerous polyps or invasive malignancy.[33]

Additional Risk Factors

Recent research has identified additional genetic risk factors associated with colorectal cancer. A polymorphism in the *APC* gene has been associated with development of colorectal neoplasms in decedents of Eastern European (Ashkenazi) Jews. This population is noted to have the highest colorectal cancer incidence of any Israeli ethnic group. Studies have reported that 6% of unselected Ashkenazi Jews and 28% of those with a family history of colorectal cancer carry an *APC* missense mutation (referred to as I 1307 K). These patients do not have the typical phenotype seen with FAP, but rather the polymorphism creates a hypermutable region of the *APC* gene, which causes a predisposition to colorectal cancer.[34] This translates into a high frequency of synchronous cancer in patients with polyps: 13% of individuals carrying this polymorphism and identified adenomatous polyps harbor an invasive cancer.[35,36] Another relatively new syndrome has been described, involving mutation in the exon-excision-repair gene *MYH*. Individuals carrying this mutation can present with either the FAP or HNPCC phenotype.[37] Finally, an association between hyperplastic polyposis, defined as greater than 20 hyperplastic polyps (of at least 1 cm in size) in sites other than the rectosigmoid, and colorectal adenomas and carcinomas, has recently been described.[38] These cancers are associated with methylation silencing of mismatch repair genes and HPP1 and are referred to as *sporadic MIS tumors*. Ultimately, further identification and characterization of the various molecular pathways of carcinogenesis may lead to tumor-specific therapy.

There is no doubt that environmental factors play a critical role in the development of colorectal cancer. However, the association between dietary and lifestyle factors and development of colorectal neoplasms is extraordinarily complex. The largest body of epidemiologic data is based on case-controlled studies limited by significant recall bias. Prospective cohort studies avoid limitations in patient recollection but may be inadequate, since the food frequency questionnaires are rarely validated. Clinical trials in which nutrient supplementations are given as interventions are similarly limited, because colorectal carcinogenesis has a relatively long latency. Given the limitations of current studies, Table 156–1[39] delineates our current best knowledge regarding dietary and lifestyle risk factors for colorectal cancer.

Table 156–1 Dietary and Lifestyle Risk Factors for Colon and Rectal Cancer

Likelihood of Association	Decreased Risk	Increased Risk
Probable	Physical activity, folate, vegetables	Obesity, smoking, red meat
Possible	Fruit, calcium, vitamin D, methionine	Alcohol, processed meat, heavily cooked meat, iron
Unknown	Fiber supplement	—

COLORECTAL CANCER SCREENING

Goals

The goals of screening asymptomatic patients are to find and remove premalignant adenomatous polyps and identify early malignancies. Polyps most likely to contain invasive disease include those that are sessile rather than pedunculated, villous rather than tubular, and large (>1.5 cm) rather than small. The National Polyp Study confirmed that colonoscopic polypectomy reduces colon cancer mortality. In this study, patients whose adenomas were removed endoscopically had lower probability of developing colorectal cancer, compared with a reference group of individuals whose polyps had not been removed and individuals in a population-based registry (Surveillance, Epidemiology, and End Results [SEER]), most of whom did not have polyps.[40] In essence, this study validated the colorectal adenoma-to-adenocarcinoma

Table 156–2 Screening Guidelines for Average-Risk Individuals

Test	Internal (beginning at age 50 yr)	Comment
FOBT and flexible sigmoidoscopy	FOBT annually and flexible sigmoidoscopy every 5 yr	Flexible sigmoidoscopy together with FOBT is preferred compared with FOBT or flexible sigmoidoscopy alone All positive tests should be followed up with colonoscopy
Flexible sigmoidoscopy	Every 5 yr	All positive tests should be followed up with colonoscopy
FOBTs	Annually	The recommended take-home multiple-sample method should be used All positive tests should be followed up with colonoscopy
Colonoscopy	Every 10 yr	Colonoscopy provides an opportunity to visualize, sample, and/or remove significant lesions
Double-contrast barium enema	Every 5 yr	All positive tests should be followed by colonoscopy

FOBT, fecal occult blood test.

sequence and reinforced the importance of screening. When an adenomatous polyp is detected, the entire large bowel should be visualized endoscopically because synchronous lesions are found 35% to 40% of the time.

The specifics of colorectal cancer screening rely on an understanding of patient risk (Tables 156–2 and 156–3). Asymptomatic, average-risk individuals are candidates for routine screening, whereas those at increased risk as a result of a personal or family history of colorectal cancer or adenoma, IBD, or a hereditary colon cancer syndrome require more individualized screening and surveillance programs.[10]

Low and Average Risk

Average-risk men and women should begin routine colorectal cancer screening at age 50 years (see Table 156–2). Several options exist. The first approach includes stool occult blood test annually and flexible sigmoidoscopy every 5 years. If a positive stool blood test is detected, the patient should undergo a complete colonoscopy to evaluate the entire colon mucosa. On screening sigmoidoscopy, single small lesions should be biopsied and additional treatment predicated on histology. If the lesion is an adenomatous polyp, a colonoscopy should be performed for complete polypectomy and assessment of the proximal colon for synchronous lesions. If the polyp is a benign hyperplastic polyp, no additional test is necessary. If, however, screening sigmoidoscopy reveals either a large polyp or multiple polyps, then initial biopsy is not necessary and the patient should undergo complete colonoscopy with biopsy. The second approach to screening the average-risk individual is complete colonoscopy, repeated at 10-year intervals if negative for neoplasia. This is the preferred screening method. The third and least common screening option includes double-contrast barium enema plus flexible sigmoidoscopy every 5 to 10 years. Any positive test should be followed up by a colonoscopy.

High Risk

High-risk individuals include those with a personal history of adenomas or cancers, family history or genetic syndrome, or predisposing medical condition such as IBD (see Table 156–3). Patients with a history of colorectal adenoma require increased surveillance for metachronous polyps or missed small synchronous polyps that can occur in 15% of cases.[41] Based on the findings of the National Polyp Study, a repeat examination can be performed 3 years after polypectomy.[40] A shorter follow-up interval may be necessary after removal of multiple adenomas, excision of an adenoma with invasive cancer, incomplete or piecemeal removal of a large sessile adenoma, or suboptimal examination because of poor colonic preparation. On the other hand, if the 3-year follow-up colonoscopy is clear, the surveillance interval can be increased to every 5 years.[42]

Previous Colorectal Cancer and Family History of Colorectal Cancer

Patients with a personal history of colorectal cancer required increased surveillance for metachronous disease. In general, the first surveillance colonoscopy should be performed 1 year following cancer resection. If the colon was not fully evaluated prior to surgery, the first examination should be performed within 3 months of surgery. If the first postresection colonoscopy is normal, the interval can be increased to 3 years. However, if additional disease is noted on postoperative colonoscopy, more frequent examinations are warranted.

Patients with a family history of colorectal cancer or adenoma, including affected first-degree relatives, also

Table 156–3 Screening Guidelines for High-Risk Individuals

Risk Category	Age to Begin	Recommendation	Comment
Increased Risk			
Patient with a single small (<1 cm) adenoma	3-6 yr after the initial polypectomy	Colonoscopy	If examination is normal, they can thereafter be screened as per average-risk guidelines
Patient with a large (>1 cm) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change	Within 3 yr after the initial polypectomy	Colonoscopy	If normal, repeat examination in 3 yr; if normal then, the patient can thereafter be screened as per average-risk guidelines
Personal history of curative-intent resection of colorectal cancer	Within 1 yr after cancer resection	Colonoscopy	If normal, repeat examination in 3 yr; if normal then, repeat examination every 5 yr
Either colorectal cancer or adenomatous polyps, in any first-degree relative before age 60 yr, or in ≥2 first-degree relatives at any age (if not a hereditary syndrome)	Age 40 yr, or 10 yr before the youngest case in the immediate family	Colonoscopy	Every 5-10 yr Colorectal cancer in relatives more distant than first-degree does not increase risk substantially above the average-risk group
High Risk			
Family history of familial adenomatous polyposis (FAP)	Puberty	Early surveillance with endoscopy, and counseling to consider genetic testing	If the genetic test is positive, colectomy is indicated These patients are best referred to a center with experience in the management of FAP
Family history of hereditary nonpolyposis colon cancer (HNPCC)	Age 21 yr	Colonoscopy and counseling to consider genetic testing	If the genetic test is positive or if the patient has not had genetic testing, every 1-2 yr until 40 yr of age, then annually These patients are best referred to a center with experience in the management of HNPCC
Inflammatory bowel disease Chronic ulcerative colitis Crohn's disease	Cancer risks begin to be significant 8 yr after the onset of pancolitis or 12-15 yr after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia	Every 1-2 yr These patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease

require more aggressive surveillance. These individuals should undergo screening with colonoscopy beginning at 40 years of age or earlier, when they are 10 years younger than their affected family member(s) were at age of initial diagnosis.

Patients with long-standing IBD are at increased risk of colorectal cancer and should undergo routine surveillance examinations. The cancer risk in chronic Crohn's disease appears to be the same as that in ulcerative colitis; therefore, these patients should be approached similarly. In patients with pancolitis, typically defined as disease extending proximal to the splenic flexure, surveillance colonoscopy should begin after 8 years of symptoms. Surveillance can start later in those patients with left-sided colitis, generally after 12 to 15 years of disease. Colonoscopy should be performed every 1 to 2 years. During each examination, biopsies should be routinely taken at 10- to 12-cm intervals throughout the colon, from grossly normal and diseased-appearing mucosa. Colectomy is indicated for low- or high-grade dysplasia, for patients with difficult-to-control colitis, and for those patients who cannot comply with routine surveillance.

Patients from FAP families who have not been tested for an *APC* mutation should begin routine screening at puberty with annual flexible sigmoidoscopy. If polyps are

not identified by age 40 years, then the frequency of examinations can be decreased to every 3 years. On the other hand, individuals who express the phenotype require upper endoscopy to examine the periampullary region. Patients with a known genetic mutation or members of an FAP kindred should undergo colectomy when they develop polyps, because stage-specific survival of colorectal cancer appears to be the same for polyposis patients as for those who have sporadic bowel cancers.

Colorectal screening for patients with HNPCC should be performed with full colonoscopy, since these individuals have a propensity for developing proximal colon lesions. The adenoma-to-carcinoma sequence appears to be more rapid in this patient cohort, and endoscopy should thus be performed every 1 to 2 years. For individuals with known mutations or family history consistent with the Amsterdam Criteria, screening should begin at 21 years of age.[1,10] Screening for extracolonic disease should be performed as well, including urine cytology, pelvic ultrasound, and periodic endometrial biopsy.

COLORECTAL CANCER STAGING

The prognosis for patients with colorectal cancer is related to the stage of disease at diagnosis and tumor histology, including differentiation, lymphatic invasion, and extent of tumor-free surgical resection margins. Molecular genetic markers may, in the future, define subsets of patients either more or less likely to develop tumor recurrence and so lead to more rational application of adjuvant multimodality treatment.[43,44] However, at the time of this writing use of such molecular markers remains investigational.

The tumor, node, and metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) is the standard colorectal cancer staging system. The sixth edition was published in 2002 and is outlined in Box 156–2 and Table 156–4. The symbols "c" and "p" are used as prescripts to denote clinical and pathologic staging, respectively. The prescript "y" is used to denote post-treatment staging of a tumor (e.g., ypT2N1M0 represents a pathologically staged tumor extending into the muscularis propria, with metastases noted in one to three regional lymph nodes, in a patient who received preoperative treatment).

For colorectal carcinomas, the staging category pTis (carcinoma in situ) denotes either malignant cells confined by glandular basement membrane (intraepithelial carcinoma) or those invading beyond the basement membrane into the mucosal lamina propria (intramucosal carcinoma). The terms *high-grade dysplasia* and *intraepithelial carcinoma* are often used synonymously. The definition of invasive colorectal cancer (i.e., pT1) includes tumor cell invasion through the muscularis mucosa and into the submucosa, where abundant lymphatics are located. This is in contrast to the definition of other gastrointestinal and solid tumors, in which invasion below the lamina propria constitutes malignancy.

There are a few other nuances and subtle aspects to the TNM staging system. Extramural tumor nodules discontinuous from the primary tumor mass, that are irregular in shape, are included in the T category as pT3. If such nodules have smooth contours, they are classified by convention as replaced lymph nodes. *pT4* refers to extension into adjacent organs or structures, penetration of the parietal peritoneum with or without involvement of an adjacent structure, or free perforation into the peritoneal cavity.

As is true for most epithelial cancers, the presence of metastases in regional lymph nodes has a significant impact on survival. Proper staging and treatment of colorectal cancer require adequate lymphadenectomy. Goldstein et al.[45] illustrated the relationship between staging accuracy and lymphadenectomy. In this study of T3 tumors, lymph node metastases were noted in 85% of cases when 15 or more nodes were recovered but in only 22% of cases when fewer than 15 were identified in the specimen. Furthermore, within the cohort of patients who did not show nodal metastases, survival was greatest in the subgroup with high lymph node recovery.

Box 156–2 **American Joint Committee on Cancer–Union Internationale Contre le Cancer Tumor, Node, Metastasis Stage Grouping**

Primary Tumor (T)

TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor
Tis:	Carcinoma in situ intraepithelial or invasion of lamina propria
T1:	Tumor invades submucosa
T2:	Tumor invades muscularis propria
T3:	Tumor invades into through muscularis propria into submucosa, or into nonperitonealized pericolic or perirectal tissues
T4:	Tumor directly invades other organs or structures, and/or perforates visceral peritoneum

Regional Lymph Nodes (N)

NX:	Regional lymph nodes cannot be assessed
N0:	No regional lymph nodes metastasis
N1:	Metastasis in 1 to 3 regional lymph nodes
N2:	Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)

MX:	Distant metastasis cannot be assessed
M0:	No distant metastasis
M1:	Distant metastasis

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer, 2002.

Table 156–4 American Joint Committee on Cancer–Union Internationale Contre le Cancer Tumor, Node, Metastasis Staging of Colon and Rectal Cancer

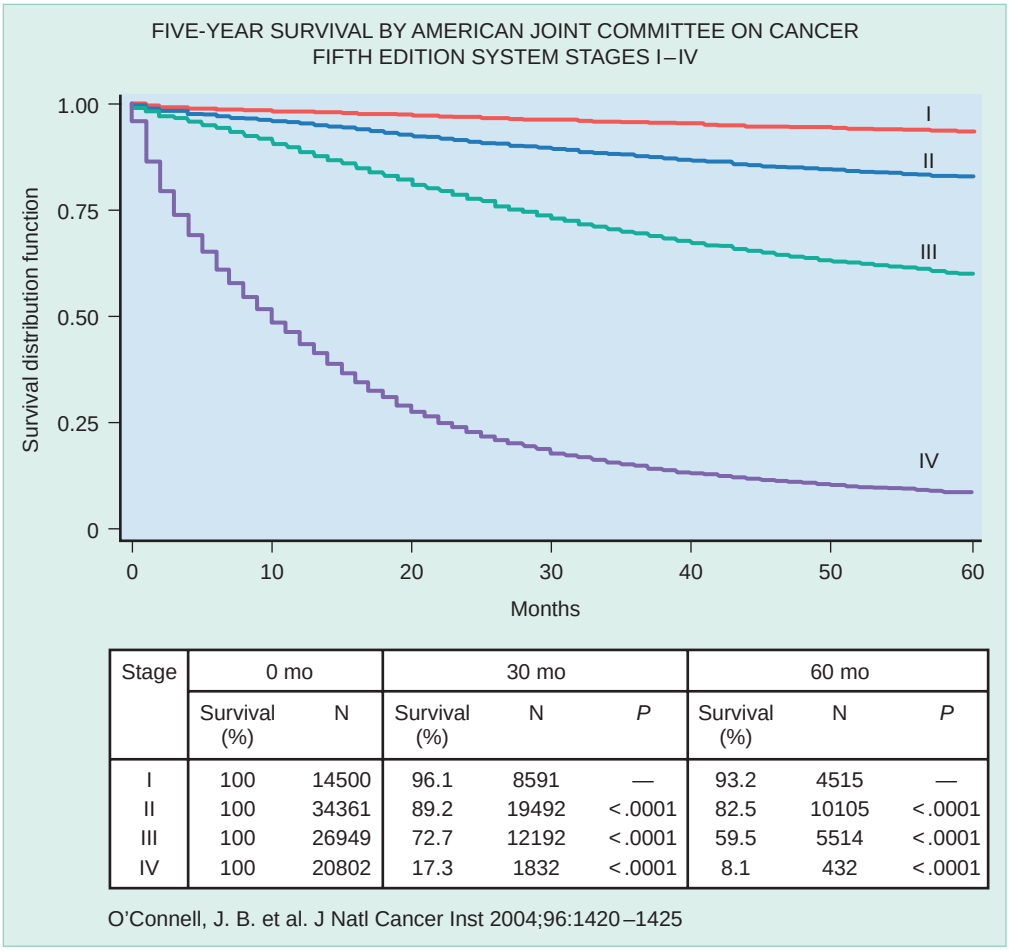
Stage	Tumor (T)	Lymph Nodes (N)	Metastasis (M)
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	T1-T2	N1	M0
IIIB	T3-T4	N1	M0
IIIC	Any T	N2	M0
IV	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer, 2002.

Although there are many factors related to the number of nodes examined, including extent of resection and diligence of the pathologist, these data support the concept that proper oncologic resection is associated with improved outcome. Based on this study and others, it has been recommended that at least 12 lymph nodes be examined to accurately stage colorectal cancer patients.[46]

Alternative methods for detecting very small amounts of metastatic disease have been developed, including molecular biology–based techniques and immunohistochemistry. The biologic significance and clinical impact of minute amounts of tumor detected in metastatic sites are currently unclear, and the sixth edition of the AJCC/UICC TNM staging guide does not classify such disease as N1. Further studies are needed for us to fully understand the significance of micrometastatic nodal disease in colorectal cancer. The use of sentinel node biopsy for intestinal malignancy[47] remains controversial, with at least one large prospective, randomized study showing that this technique may not be valid for colorectal cancer.[48]

The relationship between pathologic stage of disease and outcome is depicted in Figure 156–4.[49] Other pathologic features that have been demonstrated to predict



Stage	0 mo		30 mo			60 mo		
	Survival (%)	N	Survival (%)	N	*P*	Survival (%)	N	*P*
I	100	14500	96.1	8591	—	93.2	4515	—
II	100	34361	89.2	19492	<.0001	82.5	10105	<.0001
III	100	26949	72.7	12192	<.0001	59.5	5514	<.0001
IV	100	20802	17.3	1832	<.0001	8.1	432	<.0001

O'Connell, J. B. et al. J Natl Cancer Inst 2004;96:1420–1425

Figure 156–4. Outcome of colorectal cancer by stage. (From O'Connell JB, Maggard MA, Ko CY: Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst 96:1420-1425, 2004.)

Box 156–3 Selected Pathologic Prognostic Factors in Colorectal Cancer

- Adjacent organ involvement (colon)
- Radial margin (rectum)
- Degree of differentiation
- Blood vessel invasion
- Lymphatic vessel invasion
- Perineural invasion
- Immune response
- DNA content
- Proliferative index
- Allelic loss of chromosome 18q (DCC)

outcome, in addition to bowel wall penetration and lymph node status, are listed in Box 156–3. Lymphovascular invasion is associated with nodal and distant disease as well as independent predictors of survival.[50,51] In contrast to many other solid tumors, if data are corrected for nodal involvement and histologic differentiation, prognosis in patients with colorectal cancer is not influenced by the size of the primary lesion.

TREATMENT OF PRIMARY COLON AND RECTAL CARCINOMA

The mainstay of therapy for locoregional colon and rectal carcinoma is surgery. In colon cancer adjuvant chemotherapy is administered to reduce the risk of recurrence, which is usually distant failure. In rectal cancer neoadjuvant combined-modality therapy, including chemotherapy and radiation, is administered to improve resectability, aid in sphincter preservation, and reduce local as well as distant recurrence. Adjuvant chemotherapy is administered primarily to reduce the risk of distant recurrence.

Critical in the treatment of colorectal cancer is the understanding that the role of surgery for the primary tumor is limited to those patients for whom cure is realistically possible or to those patients with symptomatic lesions resulting in acute obstruction or clinically significant bleeding. For patients who present with synchronous primary and incurable metastatic disease, resection of the primary is not routinely indicated. Advances in systemic chemotherapy (outlined later) have greatly increased the likelihood of tumor control via medical management, and chemotherapy can be routinely started with an asymptomatic or minimally symptomatic primary in place. There is no need to "prepare such a patient for chemotherapy" by performing palliative resection of a primary that does not actively require palliation. In fact, resection of the primary lesion in the setting of metastatic disease has a significant associated morbidity and mortality. In a large review of Medicare/SEER data for patients 65 years of age and older, resection of a synchronous primary tumor was associated with a 10% 30-day postoperative mortality.[52]

Surgery

The basic tenet of colorectal cancer surgery with curative intent is removal of the primary lesion with adequate margins and removal of regional lymph nodes. Determining the extent of lymphadenectomy is one of the most challenging aspects of cancer surgery and is based on a thorough understanding of anatomy and lymphatic spread of intestinal cancer.

The regional lymphatics of the colon have been well described.[53] Abundant lymphatic capillaries are found in the submucosa, and efferent vessels proceed peripherally through the circular and longitudinal layers of the muscularis propria and communicate with a clearly defined subserosal plexus. Lymphatic flow in the subserosal network is principally circumferential. Longitudinal intramural lymphatic spread is generally limited to 2 cm, which explains the general rule of obtaining a 5-cm proximal and distal intestinal margin at time of surgery. Most subserosal lymphatics pass into the mesentery to reach the paracolic lymph nodes. Under normal circumstances, lymph flow within the colon mesentery proceeds centrally, in an orderly fashion, from smaller to larger collecting lymphatics and eventually leads to the root of the mesentery. Lymphatic vessels are in close association with the blood vascular pedicles, and the centrally directed flow proceeds along the nearest or most immediately accessible route to the apex of the mesentery. Thus we can conveniently describe the pathways of lymphatic flow by the appropriate vascular pedicle, including the ileocolic, right colic, and mid colic routes of the superior mesenteric system and the left colic, sigmoidal and superior rectal routes of the inferior mesenteric system.

Although there are many variations in the arrangement of lymph nodes along the pathways of flow, the following three roughly separable groups can be identified:

- First-echelon lymph nodes are paracolic, associated with the marginal vessel of Drummond. These nodes are the most numerous and have the greatest importance in surgical therapy.
- Second-echelon, or intermediate, lymph nodes are located in the mesentery at the level of division of mainstem blood vessels into peripheral branches.
- Third-echelon nodes, represented by the central or principal nodes, are closest to the root of the mesentery and associated with takeoff of the major vascular pedicles.

Cancer emboli generally take the most direct route to regional lymph nodes, and there is a stepwise progression centrally from the paracolic nodes adjacent to tumor, to the intermediate nodes along the most contiguous mesenteric vascular pedicle, and finally to the main or principal lymph nodes at the apex of the mesentery. However, variations and "skip metastases" exist. These unusually situated metastases represent retrograde lymphatic flow secondary to tumor blockage of the main

efferent lymphatic channels. Common atypical sites of lymph node metastases include the gastrocolic omentum, related to transverse colon lesions and paracolic lymph nodes noted at a distance from the primary tumor. In general, skip metastases are associated with a poor prognosis, due to the extensive nature of nodal disease.[53]

In the rectum, at about 7 to 8 cm above the anal verge and at the approximate level of the middle valve of Houston, a so-called lymphatic watershed exists: all lymph from the rectum above this point drains upward along the superior hemorrhoidal vessels, but below this level there is a dual drainage. Although flow remains predominately superior in direction, there may be independent or association drainage laterally along the middle hemorrhoid vessels to the internal iliac chain of lymph nodes, and from there by retroperitoneal vessels to the para-aortic nodes. Very distal lesions can drain along the superficial perineal lymphatics, with flow directed toward the superficial inguinal lymph nodes.

Regardless of the geographic location of the primary tumor, the goal of surgery is removal of the primary lesion with adequate intestinal margin en bloc with regional lymph nodes. As noted, longitudinal spread along the colon rarely extends beyond 2 cm; this has been the rationale for resecting 5 cm of normal intestine proximal and distal to the lesion. In practicality, however, the length of intestinal resection is generally determined by devascularization from lymphadenectomy. The lymph nodes at risk for metastases include those along the primary vascular pedicle, closest to the tumor as well as adjacent vessels. These secondary routes have been well described[53] and are summarized in Figure 156–5. There is a tendency to extrapolate from these studies and perform radical or extended lymph node resections, with hopes of improving patient outcome; however, this is not borne out in practice. For example, "high ligation" of the inferior mesenteric artery at its takeoff from the aorta has not been shown to improve outcome[54,55] but is instead associated with increased perioperative morbidity, including autonomic nerve injury and associated sexual and bladder dysfunction. Operative strategies and lymphadenectomy for colorectal cancer are outlined in Figure 156–6.

The widespread application of sphincter-sparing techniques, including low anterior resection with coloanal anastomosis, especially in combination with combined-modality therapy (chemoradiation), allows most patients to avoid abdominoperineal resection and permanent colostomy. Intersphincteric dissection is a technique increasingly used to gain distal margin and avoid a permanent colostomy. The internal sphincter (which is a continuation of the rectal muscularis propria) is resected with the rectum, allowing for an additional 1 cm of distal margin (Fig. 156–7). Following this procedure, patients rely on the external sphincter for continence. These technical advances allow sphincter preservation for the majority of rectal cancer patients, reserving abdominoperineal resection for those patients with poor preoperative function and those with tumors extending into the external sphincter complex.[56] The functional sequelae and quality of life associated with ultralow coloanal anastomosis has become the center of research.[57] Creation of a reservoir such as a colonic J-pouch or coloplasty is advocated, when technically feasible, as it appears to improve short-term and possibly long-term function.[58]

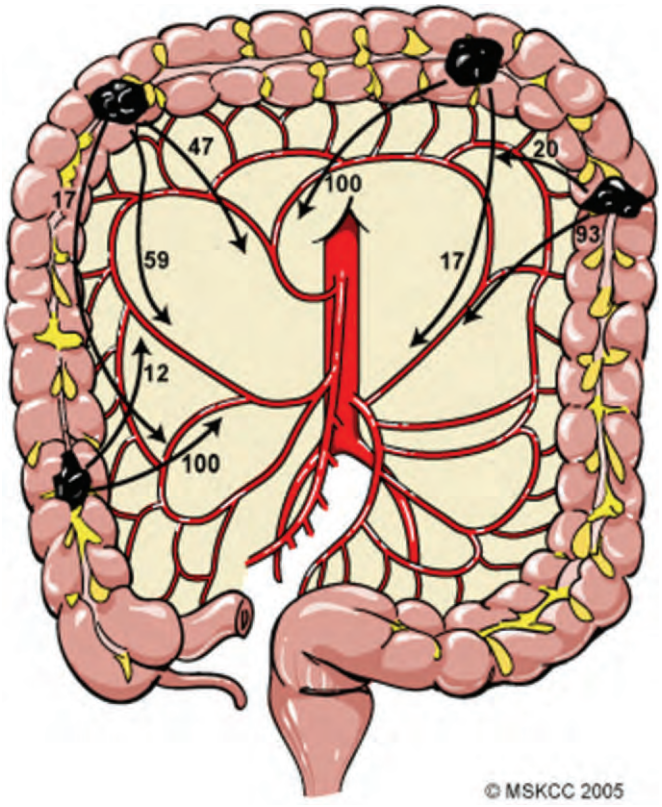


Figure 156–5. Lymphatic drainage for colon cancer. The numbers signify the percentage of metastasizing carcinoma with nodal disease along the outlined vascular pedicle. For example, node-positive tumors lying between the ileocolic and right colic arcades metastasize along the ileocolic pedicle in 100% of cases and along the right colon pedicle in 12% of cases. (© 2005, Memorial Sloan-Kettering Cancer Center, New York.)

The increasing application of these sphincter-saving techniques has renewed interest in defining the necessary length of distal bowel margin. Although 5 cm of distal rectum was originally thought to be necessary,[59] it is now widely accepted that 2 cm is sufficient.[60] More recent studies have indicated that shorter margins may be adequate, especially in the setting of significant tumor regression in response to combined-modality therapy.[61] Possibly more important than length of distal intestine removed beyond tumor is the status of the lateral and circumferential resection margin. Clearly these margins have been overlooked in the past and are as critical as distal margin with regard to tumor recurrence.[62]

It is not surprising that studies have shown a relationship between quality of surgical technique and outcome. Blunt pelvic dissection can result in local recurrence rates as high as 25%. Conversely, appropriate mesorectal

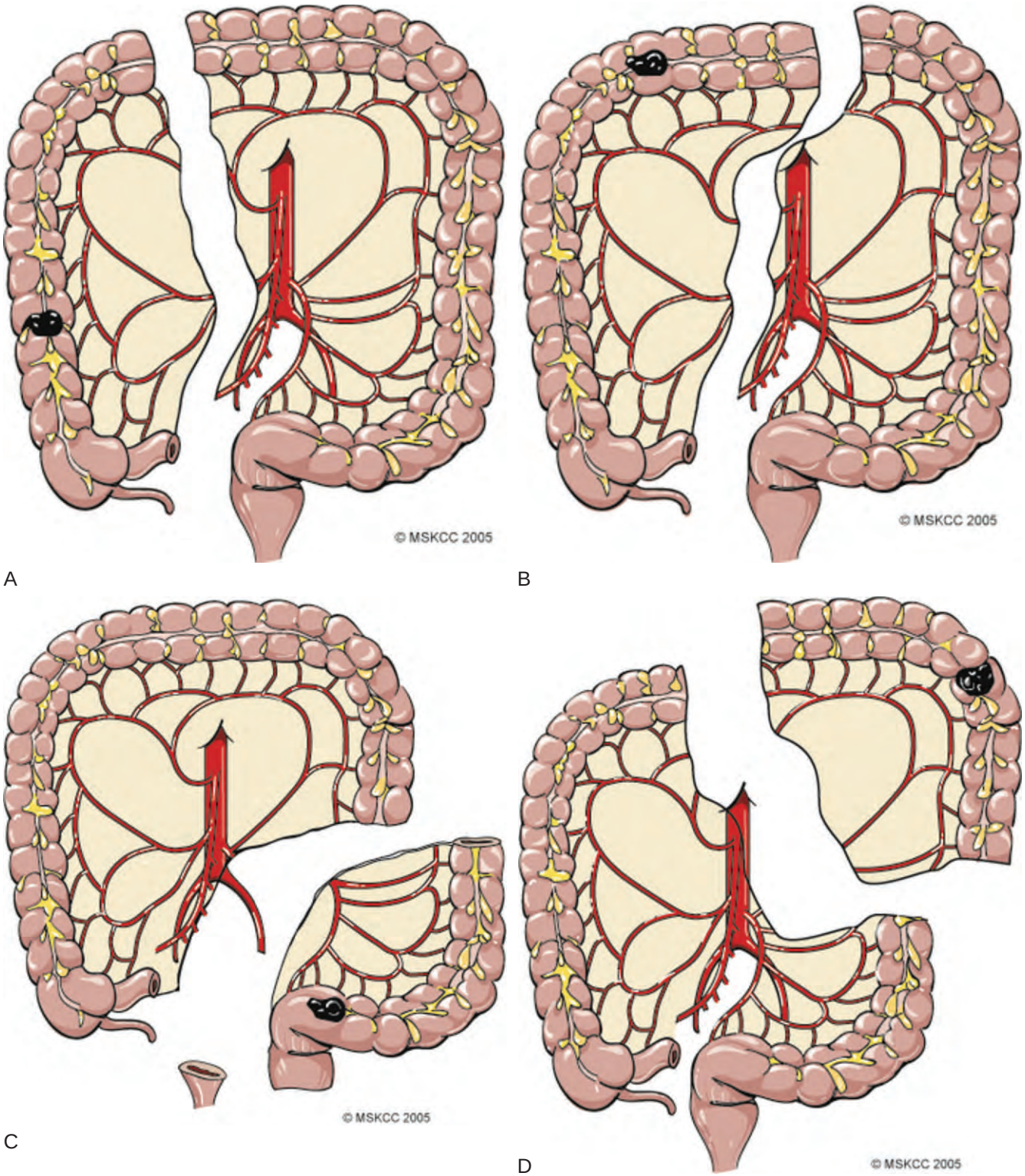


Figure 156–6. **A** to **D,** Operative strategies for colorectal cancer. (**A-D,** © 2005, Memorial Sloan-Kettering Cancer Center, New York.)

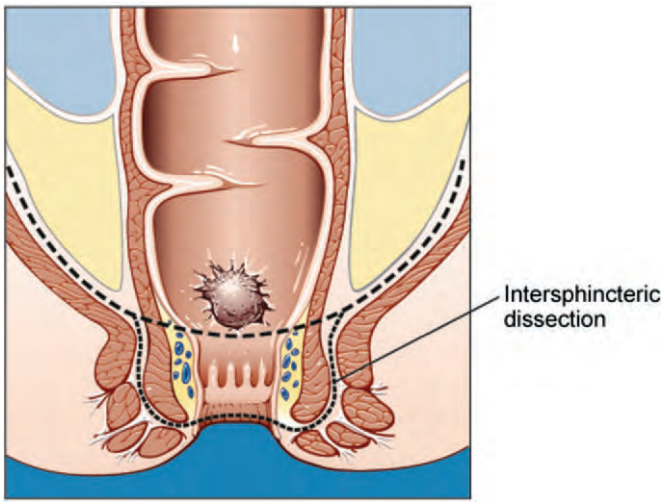


Figure 156–7. The technique of intersphincteric resection allows for additional distal margin for tumors located at the anorectal ring. (From Rullier E, Laurent C, Bretagnol F, et al: Sphincter-saving resection for all rectal carcinomas: The end of the 2-cm rule. Ann Surg 241:465-469, 2005.)

excision (mesorectal excision at least 4 cm to 5 cm below the tumor for high rectal lesions, and total mesorectal excision for middle-to-low rectal cancers) is associated with local failure rates in the 5% to 10% range.[63,64] Appropriate attention must be given to all margins, including the circumferential resection margin.[62] As might be expected, surgeon and hospital volume appear to influence outcome of colorectal cancer surgery.[65,66]

SPECIAL CIRCUMSTANCES

Surgical Treatment of Hereditary Bowel Cancer

Surgical options for patients with hereditary colorectal cancer syndromes include both therapeutic and prophylactic procedures. In patients with FAP, the most common procedures include total abdominal colectomy with ileorectal anastomosis, and total proctocolectomy with either ileal pouch-anal anastomosis or end ileostomy. Total abdominal colectomy with ileorectal anastomosis is reserved for those individuals with minimal disease in the rectum that can be controlled endoscopically. The advantage of ileorectal anastomosis includes relatively normal bowel function, less complex surgical procedure, and preserved bladder and sexual function. However, the remaining rectum requires frequent surveillance, as the risk of developing rectal cancer ranges from 10% to 50%,[67] with 40% to 75% of patients eventually requiring rectal resection. The advantages of total proctocolectomy with ileopouch anal anastomosis include elimination of the colorectal mucosa at risk. However, this is a more complex procedure, with an associated risk for bladder and sexual dysfunction as well as worse (but generally acceptable) bowel function. Total proctocolectomy with end ileostomy is usually reserved for patients who present with advanced rectal cancer or individuals unwilling and unable to undergo an ileopouch-anal anastomosis.

The surgical management of HNPCC patients depends on initial presentation. HNPCC patients who present with cancer or polyps not amenable to endoscopic removal should be considered for total abdominal colectomy with ileorectal anastomosis. Other options include segmental resection with frequent endoscopic surveillance, and enrollment in chemoprevention trial. Women, especially those who have completed childbearing, should be considered for total abdominal hysterectomy and bilateral salpingo-oophorectomy. HNPCC patients who present with rectal cancer should be considered for total proctocolectomy with ileopouch-anal anastomosis. Less preferred options that may be appropriate for select patients include segmental rectal resection with frequent endoscopic surveillance. At-risk individuals showing no colonic manifestations should be monitored with close endoscopic surveillance, since penetrance is only 80%, and up to 20% of individuals will not develop the phenotype. In select circumstances, prophylactic total abdominal colectomy may be reasonable.

Surgery for Malignant Polyps

The treatment of superficial carcinomas or malignant polyps depends on tumor location, depth of bowel invasion if a focus of carcinoma is found, and amenability of the entire tumor to endoscopic removal. Patients whose pedunculated polyps are completely removed for whom histologic examination reveals superficial carcinoma with clear margins and no high-risk pathologic features can often be closely observed, without formal colectomy. On the other hand, medically fit patients with completely resected superficial tumors or polyps that have positive margins or evidence of high-grade pathologic features such as lymphovascular/perineural invasion, poor differentiation, or single cell infiltrate are at increased risk for regional nodal metastases, and formal intestinal resection is warranted.

Local Excision of Rectal Cancer

The use of local excision of rectal cancers has recently gained popularity, although more recent data suggest that extreme caution, careful patient selection, and a full discussion of potential risks and benefits are warranted before embarking on this approach. The appeal is considerable, including rapid surgical recovery, minimal morbidity, and preservation of bowel function. Generally this is reserved for patients who have superficial rectal adenocarcinoma (T1 and T2) occupying less than one third of the bowel circumference, no palpable or radiologically documented perirectal nodes, and located within 10 cm of the anal verge. Although early results of local excision were encouraging, more recent studies with long-term follow-up data consistently show high recurrence rates and lower survival than would be expected in the setting of early rectal cancer.[68] This is

exemplified in a report of 125 patients treated with local excision. Local recurrence rates were 17% and 28% for T1 and T2 rectal lesions, respectively; much higher than reported for radical resection of stage I rectal cancer.[69] The explanation for high relapse rates following local excision is multifactorial but is clearly related to the issue of unaddressed regional lymph nodes: Local excision does not remove, pathologically assess, or treat these potential lymph nodes metastases. Although patients are screened prior to local excision with endorectal ultrasound or magnetic resonance imaging (MRI) with rectal coil, a recent report has demonstrated that nodal metastases from superficial rectal lesions (T1 and T2) are generally small and difficult to detect preoperatively.[70] Of even more concern are recent reports noting that local recurrence is not uniformly amenable to salvage surgery.[71] In fact, the two largest series of salvage surgery for recurrent rectal cancer following local excision show that relapse is generally diagnosed when disease is advanced, at which time extended multiorgan resection is usually required. Overall, postsalvage survival is disappointingly low, considering the early stage of the initial lesion.[71] Improved staging modalities are clearly needed to identify those patients who are optimal candidates for local excision. Until then, patients should be fully informed of the current limitations of local excision.

Minimally Invasive Surgery for Colorectal Cancer

Minimally invasive techniques have been successfully used in the treatment of colorectal cancer. In prospective, randomized series, laparoscopic colectomy for cancer has proven oncologically equivalent to open surgery, with the advantages of smaller incisions, less discomfort, and quicker recovery. Milsom et al.[72] reported the first randomized study of 109 laparoscopic versus conventional colectomies, noting that the minimally invasive procedure was safe, not different from conventional colectomy with regard to lymph nodes or length of intestine resected, and associated with quicker recovery. Lacy et al.[73] reported the first series of 219 randomized patients in whom recurrence and survival were the primary endpoints. Once again, recovery was quicker and morbidity lower in the laparoscopic colectomy group. Unexpectedly, cancer-related survival was higher in the laparoscopy group, without a clear explanation. In addition, the improved outcome was largely due to differences in patients with stage III tumors. Leung et al.[74] reported a randomized trial of 403 patients with rectosigmoid cancer, indicating that laparoscopic colectomy was equivalent to open colectomy. The first multiinstitutional prospective, randomized trial was recently reported by the Clinical Outcomes of Surgery Therapy (COST) Study Group. In an evaluation of 872 randomized colon cancer patients,[75] this study confirmed the oncologic equivalence of conventional and laparoscopic resection as measured by recurrence and survival. Similar to all other laparoscopy studies, laparoscopy for colorectal cancer is associated with a longer operation. Overall, these studies support the use of minimally invasive surgery for colon cancer. However, it should be stressed that all reports include surgeons with extensive experience with laparoscopic colectomy. There are some data available regarding the "learning curve" for laparoscopic colectomy, indicating that a surgeon needs to perform 30 to 50 cases to achieve proficiency with regard to complications, conversion, and operating time.[76,77] These data stress the importance of a mentored learning relationship or use of laparoscopic-assisted procedures, such as hand-assisted surgery, to gain the experience necessary to perform these procedures.

There are considerably less data available regarding laparoscopic rectal resection for cancer. Laparoscopic total mesorectal excision has been described; however, this is a technically more demanding procedure, due to the confines of the bony pelvis and limitations of current stapling technology when considering sphincter preservation.[78,79] As the field advances, the potential for minimally invasive rectal resection should be realized.

CHEMOTHERAPY

Adjuvant Chemotherapy for Stages II and III Disease

Adjuvant chemotherapy for stage III colon carcinoma is considered standard treatment, based on the results of numerous large, multi-institution, prospective, randomized trials demonstrating a disease-free and overall survival benefit for patients who receive 5-fluorouracil (FU)-based chemotherapy (5-FU and levamisole or 5-FU and leucovorin [also known as folinic acid]), compared with concurrent controls who receive no adjuvant therapy.[80-85] Initial studies used 5-FU plus levamisole. It is now widely accepted that levamisole is essentially inactive, and this drug therefore has no role in the management of colorectal cancer or any other human cancer at this time. Until recently, the standard of care has been to treat with 6 to 8 months of a 5-FU plus leucovorin (folinic acid) regimen, with chemotherapy optimally beginning between 3 and 6 weeks after operation (depending on the patient's postoperative recovery).

Recently the role of more aggressive therapies, such as irinotecan (Camptosar)- or oxaliplatin (Eloxatin)-containing regimens, has been addressed. A National Cancer Institute intergroup trial reported by Saltz et al.[86] showed the combination of irinotecan and weekly bolus 5-FU to have no therapeutic benefit over weekly 5-FU/leucovorin, with the irinotecan-containing regimen showing higher toxicity. Subsequent reports of the use of irinotecan with infusional 5-FU have also been disappointing, with the Action to Control Cardiovascular Risk in Diabetes (ACCORD) II trial being overtly negative, and the Pan-European Trial in Adjuvant Colon Cancer (PETACC) IIII trial showing some suggestion of benefit for the addition of irinotecan, but being negative for its prespecified primary endpoint.[87,88]

The Xeloda in Adjuvant Colon Cancer Trial (X-ACT), reported in abstract form, randomized patients with stage III disease to 6 months of 5-FU/leucovorin versus 6 months of oral capecitabine (Xeloda). The

capecitabine had a lower toxicity profile with at least as good efficacy parameters.[89] Thus, capecitabine can be considered as a standard adjuvant treatment option for locoregionally advanced colon cancer. It should be recalled that the trial demonstrating safety and efficacy of capecitabine in this setting was done in Europe, and that European patients appear to tolerate capecitabine better than American patients (possibly due to supplementation of folic acid in American grain products). As such, more toxicity and a greater need for dose attenuations may be expected in the United States.

A large randomized trial known as the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial investigated a biweekly (every other week) 2-day infusion of 5-FU and leucovorin ± a 2-hour infusion of oxaliplatin.[90] This trial included more than 2000 patients, of whom 60% were stage III and 40% were stage II. The oxaliplatin plus infusional 5-FU/leucovorin regimen, known as *FOLFOX,* was shown to be superior in terms of disease-free survival at 3 years and at 4 years. Overall survival at 4 years did not show a significant difference[91]; however, given advances in the management of recurrent disease, it is likely that the overall advantage will take longer to become apparent. Based on the compelling disease-free survival advantage, the FOLFOX combination (for 12 treatments over 24 weeks) is now widely viewed as an appropriate treatment option for most stage III colon cancer patients.

Data from the National Surgical Adjuvant Breast and Bowel Project protocol C-07 trial assessing the usefulness of oxaliplatin plus weekly bolus 5-FU (the FLOX regimen) have recently been reported in abstract form. The 3-year disease-free survival improvement seen with FLOX appears similar to that seen with FOLFOX, suggesting that either FLOX or FOLFOX could be considered acceptable for routine adjuvant treatment; however, the serious diarrhea rate with FLOX (38% grade 3 to 4) could be of significant concern.[92]

The newer agents cetuximab (Erbitux) and bevacizumab (Avastin) (see later) are currently being studied in the adjuvant setting; however, their safety and efficacy in stage II or III colorectal cancer have not been established at this time, and their use should be restricted to the investigational setting.

The usefulness of adjuvant chemotherapy in patients with stage II colon cancer remains controversial (see Fig. 156–7).[93-95] Definitive trials of adjuvant therapy for stage II colon cancer patients are difficult to accomplish due to the very large numbers of patients that would be needed to show a benefit in this population with a relatively good prognosis. The preponderance of data suggests that if there is a survival advantage in stage II patients overall, it is in the 2% to 4% range. It is a matter of some subjectivity as to whether treatment of stage II patients is warranted. Although routine treatment of all medically fit stage II patients has not been widely recommended, it is the general consensus of the academic chemotherapy community that all stage II patients deserve a medical oncology discussion of the relative pros and cons of postsurgical chemotherapy. Those patients with higher risk tumors, such as those with perforated or obstructing primaries, perivascular invasion, or poorly differentiated histology, appear to be at higher risk for recurrence and would logically be more appropriate candidates for consideration of chemotherapy using one of the regimens outlined as an option for stage III patients.

Combined Chemoradiation Therapy

Several well-done prospective, randomized, multiinstitution trials have shown that patients with rectal adenocarcinoma (stage II or III) at high risk for local and systemic failure will benefit from external-beam irradiation and chemotherapy either before or after curative surgery. Adjuvant 5-FU–based chemotherapy plus radiation therapy should be considered the conventional therapy for patients with high-risk rectal carcinoma.[96-99]

In patients with bulky or fixed rectal carcinoma, defined on digital examination under anesthesia, preoperative external-beam radiation therapy with or without chemotherapy has proved to be beneficial.[100-102] If such patients respond to 45 to 50.4 Gy and are found on subsequent digital examination to have mobile tumors, they should undergo resection (either low anterior resection with coloanal anastomosis, or abdominoperineal resection). Barring strong contraindications, it is recommended that patients receive four to six additional cycles of systemic 5-FU–based chemotherapy in the adjuvant (postoperative) setting.

Most preoperative and postoperative trials of radiation therapy alone have demonstrated a reduction in the rate of local relapse.[103] Although many single-institution studies of preoperative radiation therapy have implied increased survival in irradiated versus nonirradiated rectal cancer patients, only one prospective, randomized trial has shown survival benefit with preoperative radiation therapy compared with surgery alone.[104] The radiation doses and techniques (short, intensive course) used in the Swedish trial are associated with significant morbidity rates and are not commonly used by radiation oncologists in the United States. Preoperative irradiation is, therefore, applicable only for patients who are diagnosed as having bulky or fixed rectal carcinomas. Preoperative combined chemotherapy and radiation is being applied with ever-increasing frequency and is touted as resulting in improved bowel function and sphincter preservation compared with postoperative adjuvant therapy,[105,106] More recently, a large (>800-patient) German trial has demonstrated superior results with a preoperative radiation approach in terms of superior local control and a more favorable toxicity profile, albeit with no overall survival difference.[107]

Modern management of rectal carcinoma should include preoperative staging with an endorectal ultrasound or endorectal MRI. Those tumors found by this preoperative assessment to be T3 or T4 lesions are most appropriately treated with preoperative radiation therapy plus 5-FU–based chemotherapy.

A treatment plan that includes preoperative pelvic radiation therapy plus chemotherapy includes a plan for postoperative chemotherapy, beginning 4 to 6 weeks

after surgery and lasting approximately 4 months. It is imperative to note, and to discuss in advance with the patient, that there is absolutely no finding at operation that will lead to a lack of need for follow-up chemotherapy. Even if a pathologic complete response is noted at operation, postoperative chemotherapy must be given as initially planned. The pathologic complete response is an indication of the results of radiation plus chemotherapy. It says nothing about the effect of chemotherapy on micrometastatic disease. To fully minimize the chance of death from distant metastatic disease, the full planned course of postoperative chemotherapy must be given, regardless of the effectiveness of preoperative chemotherapy plus radiation therapy.

Survival

With conventional surgery as described for resectable colon and rectal carcinoma, approximately 50% of all patients with colon cancer and approximately 45% of all patients with rectal cancer will be alive after 5 years.[108] This expected survival rate has not changed in 4 decades. Recurrence patterns have not changed either. In cases of rectal cancer, trials have shown the possibility of increasing the patient's disease-free and overall survival rates when both external-beam irradiation and combination chemotherapy are administered, after adequate surgery, to patients with the highest-risk cancers. Initial publication by the Gastrointestinal Tumor Study Group of disease-free survival benefit in patients treated with adjuvant radiation and chemotherapy after either low anterior resection or abdominoperineal resection of Dukes-Kirklin B2, C1, and C2 rectal cancers was subsequently extended to demonstrate overall survival benefit in those same patients. Completed adjuvant therapy trials demonstrated the synergistic benefit of external-beam irradiation and chemotherapy. An Intergroup trial confirmed that continuous infusion of 5-FU is superior to bolus infusion[99]; however, a subsequent trial failed to confirm this observation.[109]

COLORECTAL CANCER POSTRESECTION FOLLOW-UP

Of patients who have recurrences after curative resection of colon and rectal carcinomas, 80% do so within 3 years. Therefore, any post-treatment plan should include a higher frequency of follow-up during these 3 years, with decreasing frequency thereafter, although data supporting intense follow-up are limited. A prospective, randomized trial conducted in Australia randomly assigned patients after curative resection of colorectal cancer to routine follow-up (history and physical examination every 3 months for 2 years and then every 6 months for a total of 5 years) and to intense follow-up consisting of yearly colonoscopy, computed tomography (CT) scan of the liver, and chest radiography in addition to the standard follow-up. No improvement in survival was noted with the intense follow-up regimen.[110] The American Society of Clinical Oncology (ASCO) has recommended a postoperative monitoring strategy for the detection of recurrent colon and rectal cancer.[111] In general, if a patient would be a candidate for resection of recurrent disease (e.g., hepatic resection), serum carcinoembryonic antigen (CEA) testing should be performed every 3 to 4 months for 2 to 3 years after resection of the primary tumor. Routine liver function tests, fecal occult blood tests, CT scanning, and chest radiography are not recommended in these ASCO guidelines for surveillance of colorectal cancer recurrence.

The rationale for colonoscopy as part of perioperative staging and follow-up is not to define recurrent cancer. The yield in the diagnosis of isolated suture line recurrence by either endoscopy or guaiac testing of the stool is low. The major rationale for colonoscopy is to define synchronous or metachronous bowel tumors, usually polyps. As patients are exposed more uniformly to follow-up endoscopy subsequent to primary colorectal cancer resection, the incidence of metachronous lesions seems to be increasing.[112-114] Whatever the ultimate incidence of metachronous bowel lesions, there is no question that patients with sentinel colorectal carcinomas are at a significant risk for the development of metachronous polyps. If these polyps are discovered and removed, the risk of subsequent development of colon and rectal cancer decreases. Adequate screening at the time of primary surgery or later, to rule out synchronous lesions, and serial follow-up every 3 to 5 years to ensure a cancer- and polyp-free colon, should be a mandatory part of any good postoperative surveillance program for colorectal cancer patients.

TUMOR MARKERS AND SURVEILLANCE

CEA remains the prototypical solid tumor marker. Despite its lack of specificity, if used correctly CEA determination is a valuable addition to clinical decision-making in patients who have been diagnosed with colon or rectal carcinoma. CEA is not an appropriate screening test. Whether sampled once or serially, CEA cannot be used to help in the differential diagnosis of an unknown suspected bowel problem or malignancy. When CEA concentrations are determined before primary tumor resection, they may provide additional prognostic value, particularly for patients who have stage II disease, in whom the poor prognostic marker of an elevated preoperative CEA may influence the choice of whether or not to administer adjuvant chemotherapy.

Serial CEA values obtained postoperatively offer a potentially effective means of monitoring response to therapy. A postoperative CEA titer serves as a measure of the completeness of tumor resection. It should be recalled, however, that the half-life of CEA is 7 to 14 days, so postoperative baselines are best established several weeks after resection. If a preoperative elevated CEA value does not fall to normal within 2 to 3 weeks after surgery, the resection was most likely incomplete or occult metastases are present. A rising trend in serial CEA values from a normal postoperative baseline

(<5 ng/ml) may predate any other clinical or laboratory evidence of recurrent disease by 6 to 9 months.

Serial CEA values tend to roughly parallel either tumor regression or tumor progression during treatment for metastatic disease.[115] However, the actual utility of these measurements is extremely limited, as decisions to continue or discontinue a chemotherapy regimen should rarely, if ever, be made on the basis of a rising CEA alone. Most patients who respond to treatment demonstrate a decline in CEA levels. Rising CEA values are usually incompatible with tumor regression.[116]

There are no data to outline an optimal schedule of CEA monitoring after potentially curative resection. A reasonable strategy is to obtain CEA levels every 3 to 4 months and then every 6 months for the next 3 years. Data do not suggest that continued oncologic monitoring with CEA screening after 5 years is of significant benefit. Colonoscopy is recommended at 1 year after resection, and every 3 years thereafter. Routine CT scans and chest radiographs have not been shown to contribute to survival, so formal, evidence-based recommendations cannot be made.

A newly elevated CEA should first be repeated to confirm the finding and rule out a laboratory error. A confirmed new elevation should be evaluated with a full-body CT scan and, if this is negative, a colonoscopy.

In considering work-up of an elevated CEA, it is important to keep in mind that the goals of this screening are to identify *potentially curable* patients, that is, patients who have surgically resectable metastatic disease. Isolated liver, lung, or ovarian metastases are potentially curable with surgery, as are some local anastomotic recurrences. Identification of asymptomatic but incurable disease, such as peritoneal metastases or retroperitoneal lymph nodes, is of essentially no benefit and does not contribute to the patient's overall well-being. There is no evidence that early initiation of systemic chemotherapy for incurable metastatic disease will yield a better outcome. Thus, the role of CEA monitoring and postoperative imaging is to attempt to identify those patients with resectable, and therefore curable, disease.

"Second-look" surgery in the absence of an identified curable lesion on imaging studies is no longer recommended, since this is extremely unlikely to identify curable disease.[117] In later applications of radioimmunologic scanning techniques using either external or intraoperative gamma scanning,[118] the weak link will still be lack of an effective systemic therapy, even when diffuse disease recurrence is found early.

When liver or lung is the first or only site of recurrence, serial CEA rise will show the steepest slope. Specific diagnostic tests to confirm recurrence in the liver or lung are now preferable to so-called blind CEA-directed second-look procedures.[119] At present, only patients who have recurrence of colorectal carcinoma with defined isolated liver, lung, ovarian, or anastomotic metastases should undergo surgery. Therefore, it is recommended that postoperative monitoring of CEA be reserved for patients who would be candidates for resection of these potentially curable metastases if they occur. As with other follow-up testing, the optimal frequency of serial CEA monitoring has not been established.[111]

Positron emission tomography (PET) scanning has been recommended by some as a tool for work-up of an elevated CEA. However, identification of asymptomatic, unresectable disease is unlikely to be of benefit to the patient in terms of long-term outcome and may actually increase anxiety. Most surgeons would be reluctant to operate on the basis of a positive PET with negative good-quality, current CT and/or MRI scans. As such, the true contribution of PET to the management of an elevated postresection CEA is questionable.

TREATMENT OF SYSTEMIC METASTATIC (STAGE IV) DISEASE

There have been substantial and dramatic changes in chemotherapy for metastatic colorectal cancer over the past decade. Whereas only one drug, fluorouracil (5-FU), was approved for the treatment of colorectal cancer through 1995, in 2005 no fewer than six drugs have received U.S. Food and Drug Administration approval for treatment of this disease. With the greater number of active drugs comes substantially more options and more effective treatments but also far greater complexity (Fig. 156–8).

Although 5-FU remains an important part of many treatment regimens, single-agent fluorouracil (with or without the biomodulation agent leucovorin) is rarely the regimen of choice for first-line management of metastatic colorectal cancer. Irinotecan[120-122] and oxaliplatin[123] are two newer cytotoxic agents that are now routinely combined with fluorouracil and leucovorin to create more active regimens. Two studies combining irinotecan plus either bolus[124] or infusional[125] 5-FU/leucovorin demonstrated a survival advantage over fluorouracil/leucovorin alone. Infusional 5-FU demonstrated advantages over bolus administration, both in terms of both efficacy and safety.[126] Subsequently, a randomized intergroup trial (N9741) of irinotecan plus bolus 5-FU/leucovorin (IFL), versus oxaliplatin plus infusional 5-FU (FOLFOX), showed a higher response rate and longer time to tumor progression for FOLFOX.[127] Survival on the FOLFOX arm was superior; however, the meaning of these survival data is difficult to interpret, since second-line irinotecan was widely available to the FOLFOX patients, whereas second-line oxaliplatin was not widely available to the IFL patients because oxaliplatin was not available in the United States at that time. Second-line irinotecan has been shown to confer a survival advantage,[121] and survival has been correlated with availability of all active drugs.[128] Another randomized study comparing first-line FOLFOX versus FOLFIRI suggested that response rate, time to tumor progression, and overall survival were virtually the same regardless of which regimen was used first (Fig. 156–9).[129] As an aggregate result of these aggregate trials, the most commonly used cytotoxic regimens in the United States and in much of Europe are the combination of leucovorin

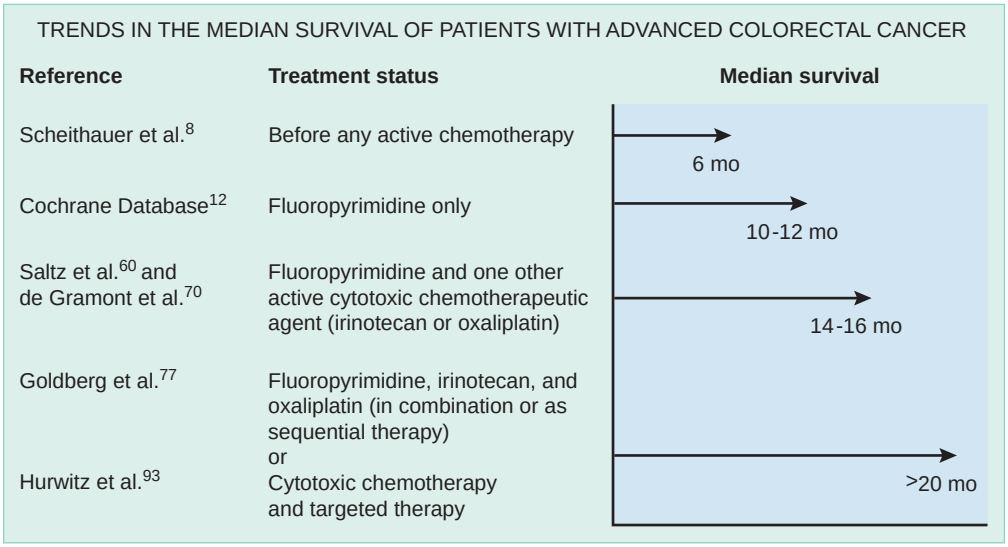


Figure 156–8. Trends in improved survival in stage IV colorectal cancer with more effective systemic chemotherapy. The references cited appear in the original source article. (From Meyerhardt JA, Mayer RJ: Systemic therapy for colorectal cancer. N Engl J Med 352:476-487, 2005.)

Figure 156–9. Survival following treatment with FOLFOX versus FOLFIRI. (From Tournigand C, Andre T, Achille E, et al: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 22:229-237, 2004.)

(FOLinic acid), a two-day infusion of Fluorouracil, and Oxaliplatin, known colloquially as FOLFOX), and the same schedule with IRInotecan substituted for oxaliplatin known as FOLFIRI.

The oral fluorouracil prodrug capecitabine has also been approved for colorectal cancer management.[83] As a single agent, this drug is getting little play. However, there is considerable interest in the possibility of replacing infusional 5-FU with capecitabine in combination regimens, thereby eliminating the need for infusion pumps. Phase II data have suggested that efficacy will be similar between capecitabine/oxaliplatin and FOLFOX regimens,[130] but randomized data have not yet been presented. A randomized phase III study of FOLFOX versus capecitabine/oxaliplatin has been accrued, and data are maturing. At present, pending availability of randomized data, routine use of capecitabine combinations would appear to be premature. Also, as mentioned previously, tolerability of capecitabine is better in European patients than in North American patients, so published toxicity and dosing data from European trials will have to be applied to American patients with caution.

Perhaps the most important changes in chemotherapy for colorectal cancer have been brought about by the recent availability of two monoclonal antibodies, bevacizumab and cetuximab. Unlike the cytotoxic chemotherapy agents discussed earlier, these agents are targeted biologic agents that exploit recent advances in the understanding of tumor biology. Bevacizumab is a monoclonal antibody that targets VEGF, a pivotal growth factor in the process of angiogenesis, or new blood vessel formation.[131] Cetuximab is a monoclonal antibody that targets and blocks the binding site of the EGFR, thereby blocking activation of this important signaling pathway.[132]

In a double-blind randomized trial of more than 800 colorectal patients treated first-line with the IFL chemotherapy regimen plus either bevacizumab or placebo, the group receiving bevacizumab had a superior response rate, longer time to tumor progression, and a substantial median survival advantage of almost 5 months (Fig. 156–10).[133] A study of FOLFOX versus FOLFOX plus bevacizumab in second-line treatment of patients who had not received previous bevacizumab also showed a survival advantage for the FOLFOX plus bevacizumab group.[134] These data have been widely extrapolated, such that in the absence of a significant contraindication it is now general practice to include bevacizumab with all front-line chemotherapy regimens.

The most common complication of bevacizumab is hypertension, requiring treatment (with routine oral antihypertensives) in approximately 10% of patients. Of more serious concern are two rare but serious complica-

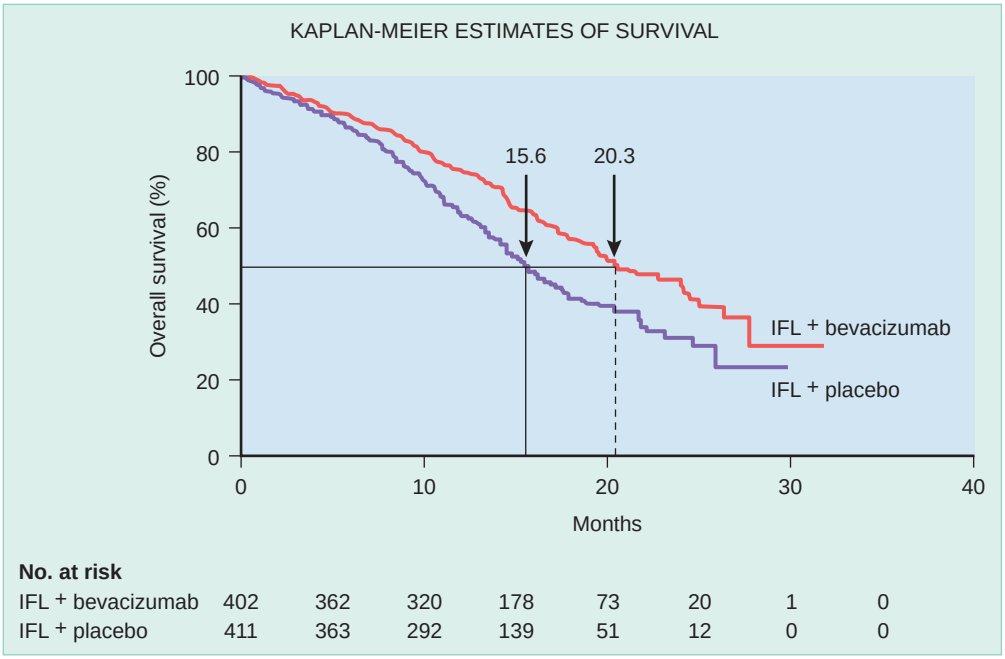


Figure 156–10. Survival advantage of irinotecan plus bolus 5-FU/leucovorin (IFL) + bevacizumab versus IFL + placebo. (From Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004.)

tions: gastrointestinal perforation and arterial thromboses. Overall, 1.5% of patients receiving bevacizumab experienced a perforation in the gastrointestinal tract. There was no consistency to the nature of the perforation, with gastric ulcers, small bowel, and large bowel perforations being reported. At present the primary site, whether resected or not, does not appear to be at increased risk for perforation. The nature of these perforations is not well understood, although they presumably represent some sort of ischemic event.

In terms of arterial thrombotic events, four events combined to obtain this statistic: myocardial infarctions, cerebral vascular accidents, transient ischemic attacks, and angina. Altogether there was a 2.5% combined incidence of these events in the control (chemotherapy only) group and 5% in the chemotherapy plus bevacizumab group. Bevacizumab would be expected to potentially interfere with wound healing, and its long half-life of approximately 3 weeks should be respected in planning preoperative or postoperative chemotherapy treatments.

Cetuximab has demonstrated a high degree of antitumor activity in colorectal cancer patients whose tumors have progressed despite standard chemotherapy. Two studies confirmed a 23% response rate when cetuximab plus irinotecan is given to patients whose tumors have grown despite irinotecan.[135,136] No randomized studies have been done to evaluate the effect of cetuximab on survival, so we simply do not know at this time whether or not a survival advantage is conferred by this drug. The major side effects of cetuximab are an acneiform rash, occurring to some degree in the majority of patients treated, and an approximately 3% risk of serious allergic reaction which, if present, usually occurs with the first dose and is managed with standard supportive measures as with other chemotherapy-induced allergic reactions. No randomized data are available on the benefit, or lack thereof, of cetuximab in front-line chemotherapy combinations, and at present clinical use of cetuximab in first-line treatment of metastatic disease should be regarded as investigational. A common misperception exists regarding the need for immunohistochemical testing of a tissue sample for use of cetuximab. Although the registered indication for cetuximab currently is for EGFR-positive colorectal cancer, the assumption that EGFR-negative tumors could not respond has been solidly disproved.[137,138] At present, it appears that currently available EGFR immunohistochemical testing has no predictive significance in terms of cetuximab activity, and EGFR testing by currently available techniques should not be used to select either for or against cetuximab therapy.

Surgery for Metastatic Disease

In numerous single-institution studies, as well as in a retrospective registry, it becomes clear that only 2000 to 4000 patients each year will have resectable, isolated liver metastases. These patients should undergo resection. The expected 5- and 10-year disease-free survival rates in these patients will be 20% to 30%, exceeding that for any other form of treatment.[139-147] No adequately powered trials of adjuvant therapy after liver resection have been or will ever be done. It is therefore not correct to say that chemotherapy after such a resection is of no use. In this situation, it is reasonable to extrapolate from the experience with stage III patients. It should be noted that

patients with so-called stage III disease who ultimately die of colorectal cancer do not die of the disease that was resected. Rather, they had unsuspected or undetected microscopic stage IV disease all along, and it is these occult micrometastases that are either cured or not cured by systemic adjuvant chemotherapy. Assuming that adjuvant therapy can cure the microscopic metastatic disease of some presumed stage III patients (which it can, otherwise all adjuvant therapy trials would be negative), then it is quite reasonable to assume, in the absence of data to the contrary (and there are none), that adjuvant chemotherapy could be expected to confer similar benefits, for similar reasons, in resected stage IV patients. It is therefore de facto routine practice to administer chemotherapy, if a potentially active regimen remains available, after resection of stage IV disease. Extrapolating from stage III data, such treatments usually start approximately 6 weeks after liver resection and continue for 6 months.

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Chapter

157

Local Excision of Rectal Cancer

Jacob A. Greenberg · Ronald Bleday

Despite recent improvements in patient awareness and compliance with screening modalities, rectal cancer continues to be a significant medical and social problem worldwide. In 2003, approximately 42,000 new cases of rectal cancer were diagnosed, and 57,000 deaths were attributed to the disease in the United States alone. Abdominoperineal resection (APR) has been the traditional treatment for *distal* rectal adenocarcinomas and continues to be the standard to which all other operations for the treatment of rectal cancer must be compared. This procedure involves the en bloc removal of the tumor, rectum, sphincter complex, and surrounding lymph nodes, leaving the patient with a permanent colostomy. The 5-year survival rates after an APR by stage range from 78% to 100% for stage I, 45% to 73% for stage II, and 22% to 66% for stage III.[1-4] Despite radical resection of both the tumor and surrounding tissue, local recurrence rates remain roughly 20%, ranging from 8.5% for stage I disease to 28.6% for stage III disease with surgery alone.[5] These variations in recurrence rates can be attributed to such variables as tumor location within the rectum, surgical technique, and the addition of adjuvant therapy.

While APR is the mainstay of therapy for distal rectal cancer, it is associated with significant morbidity and mortality. A recent review of the literature showed that mortality rates for APR range from 0% to 6.3%,[6,7] with some studies having a 61% incidence of postoperative complications.[3] The majority of these complications are urinary and perineal wound infections with rates as high as 50% and 16% respectively.[8] APR also leads to a significant change in body image and social habits. In a patient survey performed in 1983 by Williams and Johnston,[9] 66% of patients complained of significant leaks from their stoma appliances, 67% experienced sexual dysfunction, and only 40% of patients who were working pre-operatively returned to their jobs following their operation. These complications, coupled with improvements in patient selection secondary to innovations in pre-operative imaging modalities such as endorectal MRI and ultrasound, have led to a renewed interest in local treatment of rectal cancers with the hope of achieving similar survival rates with less morbidity and mortality when compared to APR.

PREOPERATIVE EVALUATION

Proper patient selection remains the key to successful local excision of rectal cancers. The retrospective literature shows that there is a direct correlation between local recurrence and specific pathologic tumor features including depth of invasion, lymphatic invasion, histologic grade, and most importantly negative margins at the time of resection. In the past, preoperative evaluation relied solely on a digital rectal examination, which was found to demonstrate depth of invasion with some degree of accuracy.[10,11] More recent studies have refuted this evidence.[12] Today imaging studies can more accurately predict preoperative stage of rectal cancers and these techniques include endorectal ultrasound (ERUS) and endorectal magnetic resonance imaging (eMRI).

Preoperative evaluation begins with a thorough history and physical, taking care to note sphincter function, as local excision in the setting of poor preoperative sphincter function may be inappropriate. A digital rectal exam should be performed in order to assess the distance of the tumor from the anal verge, as well as its size and mobility. Tumors amenable to local excision should be less than 4 cm in diameter and occupy less than 40% of the bowel circumference (Box 157–1). The distance of the tumor from the dentate line is crucially important to judge resectability: tumors less than 5 cm from the dentate are amenable to tranansal resection, while tumors in the middle third of the rectum may require a transcoccygeal approach or transanal endoscopic microsurgery (TEM). Immobile tumors are likely transmural, and thus, not amenable to local excision. The overall health of the patient must be taken into account, as patients who are considered medically unfit for a major resection are often good candidates for local excision.

Box 157–1 Properties of Distal Rectal Adenocarcinoma Amenable to Local Excision for Curative Intent

- Physical features
  - Tumors <4 cm in diameter
  - Tumor <40% of bowel circumference
  - Tumor within 10 cm of dentate line
  - Tumor freely mobile on digital rectal exam
- Endorectal US
  - T1, T2 lesions
  - No regional lymph node involvement

ERUS AND eMRI

ERUS was introduced as a means of preoperatively staging small rectal cancers during the 1990s. ERUS remains very operator dependent, and there is a significant learning curve, but in experienced hands ERUS can determine depth of tumor invasion reliably. In 1993, Solomon reported a sensitivity of 97% and a specificity of 87% in determining the depth of invasion with ERUS.[13] Garcia-Aguilar et al. found that ERUS was not as useful for determining exact stage, with an overall accuracy of only 59%. However, ERUS was very useful for differentiating tumors localized within the rectal wall, which are amenable to local excision, from those that extend into the peri-rectal fat, which require radical resection and adjuvant chemoradiation.[14] Garcia-Aguilar et al. also found that the accuracy of ERUS in detecting lymph node metastases ranged from 60% to 80%.[14]

Endorectal MRI is also being used to determine the depth of invasion of the primary rectal tumor and is the preferred preoperative evaluation method at our institution. As with ERUS, there is a significant learning curve in performing and reading eMRI.[15] Kim et al. found that the overall accuracy of eMRI for staging depth of invasion and nodal metastases was 81% and 63% respectively.[16] They also found eMRI to have a sensitivity of 78.5% and a specificity of 41.9% making it more sensitive but less specific than ERUS in their study.[16]

Computed tomography (CT) has also been used to evaluate small rectal cancers, however, it is not as accurate as ERUS or eMRI in evaluating the depth of invasion. Thus, the use of CT is not recommended for the evaluation of the primary tumor. CT is still valuable in the initial evaluation of the patient with low rectal cancer due to its ability to detect evidence of distant metastases. Posteroanterior and lateral chest radiographs are useful for the same reason.

It is our recommendation that each institution select a modality that they prefer and concentrate the experience into one person's or one team's hands so as to maximize accuracy and consistency of results. Proper decision-making and patient selection for the use of local excision or local excision with adjuvant therapy is dependent on reliable and reproducible imaging. We prefer endorectal MRI. In our hands it is less operator dependent than endorectal US and provides us significantly more information on the mesorectal tissues than endorectal US.

TECHNIQUE

Historically, there are three approaches to local excision of rectal cancer: transanal, transcoccygeal, and transsphincteric. The transsphincteric approach has been associated with fecal incontinence secondary to sphincter dysfunction, and thus has fallen out of favor. Recently a newer technique, Transanal Endoscopic Microsurgery (TEM), has provided a minimally invasive option for local excision which also allows the operator to reach lesions that are located more proximally and would have required a transcoccygeal or transsphincteric approach in the past.

Transanal Excision

Local excision is accomplished via a transanal approach in the majority of patients with low rectal cancers. In our prospective study of 48 local excisions for rectal cancer, 33 were performed using a transanal approach.[17] Prior to local excision, all patients receive a full mechanical and antibiotic bowel preparation. After induction of anesthesia, the patient is placed in the prone-jacknife position, with the buttocks taped apart. A pudendal nerve block should then be administered, which aids in the control of post-operative discomfort and more importantly relaxes the sphincter complex. A Pratt bivalve retractor is then used to dilate the anus and expose the lesion. Once adequate visualization has been obtained, traction sutures are placed 1 to 2 cm distal to the tumor, and the limits of dissection are marked on the mucosa using electrocautery. This line of dissection should be approximately 1 to 2 cm from the border of the tumor circumferentially. If visualization is not initially adequate, serial traction sutures are used to prolapse the lesion into the field of view. Next, the electrocautery is used to make a full-thickness incision along the previously marked mucosa (Fig. 157–1). Upon completion of this incision, the peri-rectal fat should be visible beneath the lesion to confirm a full-thickness excision. In anterior lesions, care must be taken not to injure the back wall of the vagina in women, or the prostate in men. The lesion is then excised leaving visible peri-rectal fat at the base of the lesion. The defect in the bowel wall is then closed transversely using interrupted 3-0 Vicryl sutures.

Complications after transanal excisions include urinary retention, urinary tract infections, delayed hemorrhage, infections of the perirectal and ischiorectal space, and fecal impactions. However, the overall incidence of these complications is quite low.[17]

Transcoccygeal Excision

The transcoccygeal approach is used preferentially over the transanal approach for larger more proximal lesions.

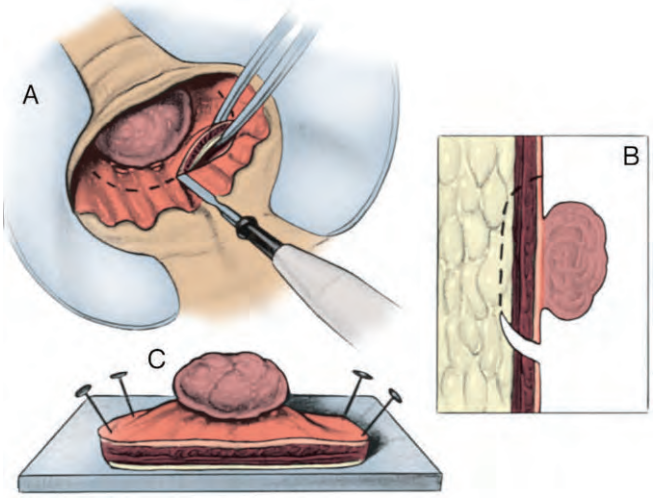

Figure 157–1. **A,** A 1-2 cm margin is marked out circumferentially on the rectal mucosa. **B,** A full thickness excision is carried out with dissection into the perirectal fat. **C,** The specimen is oriented for the pathologist in order to accurately identify all margins.

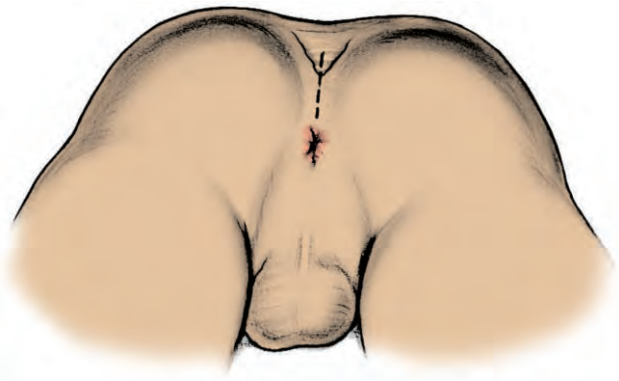

Figure 157–2. Incision line for the transcoccygeal approach.

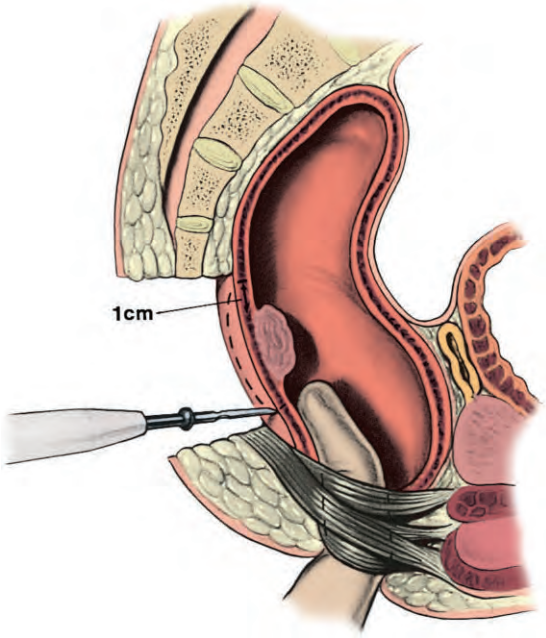

Figure 157–3. For posteriorly based lesions, after the rectum has been exposed, the surgeon can palpate the distal margin of the tumor then choose the dissection margin greater than one centimeter away from the margin for the initial proctotomy. The dissection is then completed under direct vision.

It was originally popularized by Kraske who found it beneficial when operating on lesions within the middle or distal third of the rectum. This approach is especially useful for lesions on the posterior wall of the rectum, but can certainly be used for anterior or lateral lesions as well. In our series, the transcoccygeal approach was used where the distal margin was approximately 4.8 cm from the dentate line as compared to 3.0 cm for the transanal approach.[17]

All patients undergo a full antibiotic and mechanical bowel preparation the day prior to surgery. The patient is placed in the prone-jacknife position with the buttocks taped apart after the induction of general anesthesia. The tape will be released for closure in order to facilitate the approximation of the subcutaneous tissues and skin. An incision is made in the posterior midline adjacent to the sacrum and coccyx down to the upper border of the posterior aspect of the external sphincter (Fig. 157–2). The coccyx, which along with the anal coccygeal ligament lies immediately deep to the skin and subcutaneous tissue, is removed to improve exposure. The levator ani muscles will now be visible at the base of the wound and should separated in the midline, exposing a membrane that resides just outside of the perirectal fat. Division of this membrane allows for complete mobilization of the rectum within the intraperitoneal pelvis.

For posteriorly based lesions, the distal margin of the tumor can be palpated via a rectal examination, and then the mesorectum and rectum are transected at a point 1 to 1.5 cm distal to the tumor (Fig. 157–3). The excision is then completed with a 1 cm margin surrounding the lesion. For posterior lesions, the transcoccygeal approach allows for the removal of perirectal nodes that lie in the surrounding mesorectal tissue. For anterior lesions, a posterior proctotomy is made, and then the lesion is approached under direct vision, again excising the lesion down to the perirectal fat with a 1 cm margin (Figs. 157–4 and 157–5). Following removal, the specimen is re-oriented for the pathologist and all the rectal incisions are closed in a either a longitudinal or transverse manner in order to avoid narrowing of the rectum, using an absorbable suture (Fig. 157–6). An air test should be performed, filling the operative field with sterile saline, and insufflating air in the rectum in order to check for air leaks in the suture line. Once these air leaks are controlled, the levator ani is reapproximated in the midline, and the anal coccygeal ligament is re-attached to the sacrum.

An uncommon but severe complication of this procedure is the development of a fecal fistula that extends

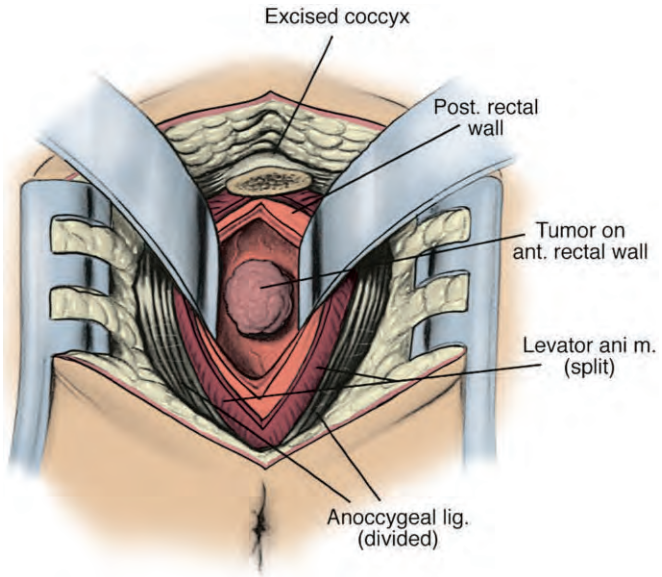

Figure 157–4. The coccyx is excised, the levator split (but not divided) in the midline and rectum is mobilized. After mobilization the posterior wall of the rectum can be opened to expose an anterior lesion.

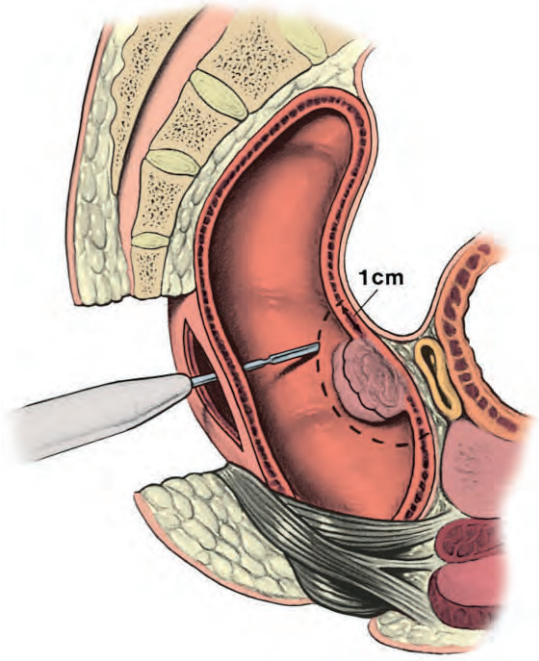

Figure 157–5. For anterior lesions, the posterior rectum is opened and the full-thickness excision is completed through the proctotomy.

from the rectum to the posterior midline incision. The incidence of this complication ranges from 5% to 20%, and most heal after temporary diversion of the fecal stream via a loop ileostomy or colostomy.[17-19]

Although the Kraske technique is rarely used it is important to appreciate the technique. It can be best

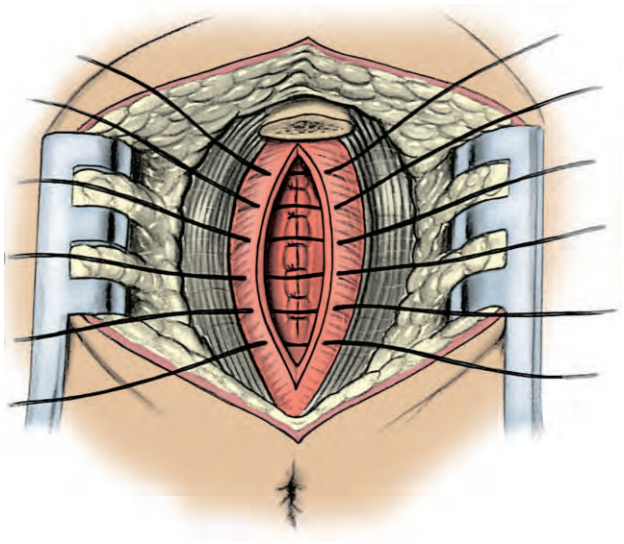

Figure 157–6. The anterior and posterior walls of the rectum are closed in one layer in either a longitudinal or transverse fashion so that the lumen is not significantly narrowed.

applied for small posterior mid rectal cancers. The technique provides a significant amount of mesorectal fat along with the accompanying nodes allowing for accurate staging of most lesions. The approach can also be used for palliation with more advanced lesions and the approach in general can be used to access lesions, both benign and malignant, of the mid rectum. As TEM (see later) becomes widely popular the Kraske approach may become obsolete.

Transsphincteric Excision

The transsphincteric approach developed by York and Mason involves the complete division of the sphincters and the posterior wall of the rectum. The procedure starts similarly to the Kraske transcoccygeal approach; except the levator ani and the external sphincter muscles are divided in the midline. These muscles are carefully tagged so that they can be reapproximated exactly at the end of the procedure. Care must be taken to remain in the midline in order to avoid the nerve supply to the sphincters that lie in a posterolateral position bilaterally. Once the lesion is removed, the rectum, sphincters, and overlying musculature are closed in a careful stepwise manner. This procedure has an increased risk of incontinence secondary to sphincter dysfunction. Since the exposure provided from this approach is similar to that from the Kraske procedure, which carries less of a risk of incontinence, there are very few indications for this technique.

Transanal Endoscopic Microsurgery

TEM was first described in 1984.[20] The surgery is performed with the use of a special resectoscope which is 4 cm in diameter and available in lengths of both 12

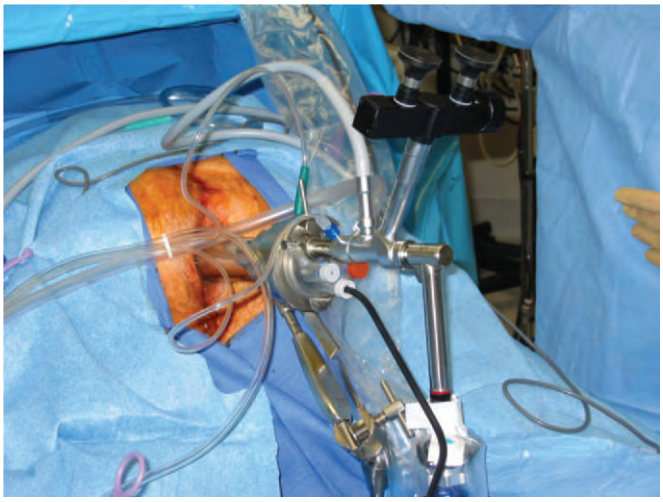

Figure 157–7. Positioning of the resectoscope and operating instruments for TEM. The lesion needs to be in the lower quarter of the field. For anterior lesions the patient is placed in the prone position as shown.

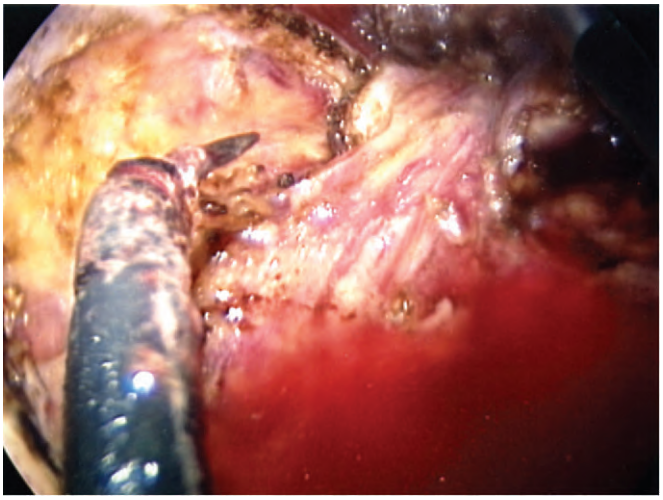

Figure 157–8. TEM as seen under the camera of the resectoscope. A cautery needle tip dissector is used for the excision. Care needs to be taken to recognize whether the peritoneal cavity has been entered.

and 20 cm. The scope is inserted with an obturator in place, which is then removed and replaced with an airtight glass faceplate. The rectum is then manually insufflated, such as in rigid sigmoidoscopy, and the lesion is identified and centered in the field. The scope is then secured in position with the aid of a support arm that is attached to the operating table. The glass faceplate is then removed and replaced with a working adapter that contains four instrument ports and a fifth port for the stereoscope which is connected to a camera and projected onto a monitor. Carbon dioxide is then insufflated at low pressure (10-15 cm H_2O) in order to distend the rectum and allow for visualization of the lesion (Fig. 157–7).[21]

Once set-up is complete, the operation proceeds in a fashion similar to a transanal excision using a variety of special endoscopic instruments, which are introduced through the four ports in the working adapter. We begin with an injection of 1:100,000 solution of epinephrine in the submucosal plane around the lesion to aid with hemostasis. The margin of resection is then marked 1 to 1.5 cm circumferentially around the lesion using electrocautery. The lesion is then grasped and the excision proceeds along the previously marked line through the full-thickness of the rectal wall and into the peri-rectal fat. The specimen is removed by temporarily removing the faceplate after complete excision. The defect is then closed using 3-0 PDS in a continuous or interrupted fashion (Figs. 157–8 and 157–9).[21]

TEM allows for local excision of proximal rectal lesions that are not accessible via the transanal, transsphincteric, or transcoccygeal approaches. Despite favorable results of this relatively new technique, it has not gained widespread popularity secondary to the expense of the equipment, lack of familiarity with the equipment and setup, and complexity of the TEM operating system. However, with the increased frequency of screening colonoscopy, smaller rectal lesions are being

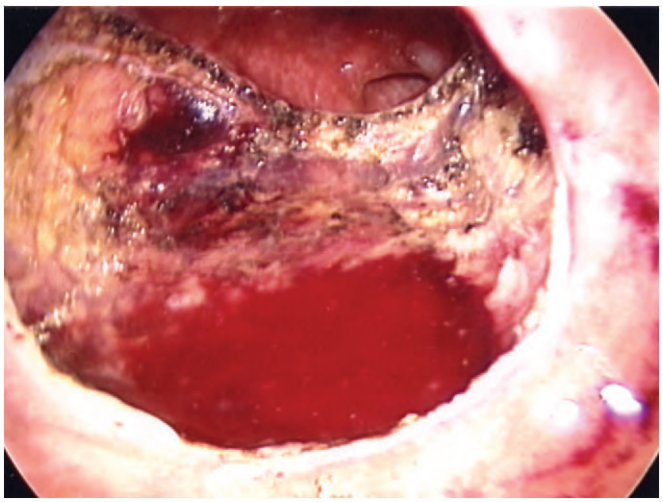

Figure 157–9. A full-thickness excision has been performed into the perirectal fat. The defect can be closed primarily or left open.

detected more frequently. The TEM system allows for a minimally invasive approach for early mid rectal cancers, and its use is likely to increase in the future.

OUTCOMES

When local excisions were initially re-introduced, they were reserved for patients who either refused a colostomy or were deemed medically unfit for a radical operation secondary to any of a number of co-morbidities. Morson et al. published one of the earliest series on local excision of rectal cancer in 1977.[22] In this series he reported 143 cases of low rectal cancers treated via local

excision. At the time of excision, 91 of these lesions were found to have negative margins, and in the patients with negative margins only 2 suffered local recurrence while one had a distal recurrence, yielding a crude 5-year survival of 82%. However, for the 69 patients with positive margins, 13 suffered a local recurrence and there was 1 distant recurrence, yielding a crude 5-year survival of only 60%. Of note, 115 of the 143 carcinomas were noted to be T1 lesions. These results prompted a renewed interest in local excision as they showed that local recurrence and survival rates were similar to those of APR, while the morbidity was greatly reduced.

Retrospective Studies

Most reports of local excision for rectal cancer are small retrospective reviews from single institutions. The results of these studies are difficult to generalize and to interpret. The length of follow-up varies from study to study, and many combine patients with tumors of different depth, positive margins, and different forms of local therapy including snare cautery and fulguration. Multiple retrospective studies, including recently published studies from the University of Minnesota, Mayo Clinic, and Memorial Sloan-Kettering Cancer Center[23-25] have been presented and published with no standard entrance criteria, no standard preoperative imaging criteria, no standards for use of adjuvant therapy, and no standard follow up regimen. The studies also span decades with patients from 20 years ago being evaluated together with patients operated on recently. Therefore, the results and conclusions from such retrospective studies should be looked upon with some skepticism.

A selection of retrospective reviews report a local recurrence rate of 5% to 33% and 5-year survival rates of 57% to 100%.[25-30] For a more detailed description of some of these studies please review Table 157–1. These studies demonstrate that patients with superficial tumors and negative margins at the time of resection have low recurrence rates and a very good prognosis. While these studies are extremely flawed and not conclusive, they do suggest that local excision may provide adequate oncologic control with considerably lower morbidity and mortality rates than APR for select distal rectal cancers. The data seem to support the use of local excision for T1 tumors with good histology. Outcome is best when resection margins are negative for tumor. The data on the use of local excision alone for T2 cancers, even when completely excised and properly staged, demonstrates that local excision alone is inadequate therapy. Controversy remains as to what other therapy should be offered. Some surgeons feel that all T2 patients should proceed to a radical resection while others feel that adjuvant chemoradiation either prior to or after excision will

Table 157–1 Series of Local Excision Alone (Retrospective Series)

Author	No. of Patients	Treatment Arms	Follow-up	Local Recurrence	Survival
Koscinski[29]	58 (26 T1 and 32 T2)	47 TA, 6 TC, 5 TEM	Mean of 48 mos. for Stage I and 59 mos. for Stage II	T1 – 5% T2 – 28%	T1 – 100% T2 – 87.5%
Horn[31]	38 (17 T1, 14 T2, 7 requiring APR after LE)	3 endoscopic polypectomy, 35 TA, 5 salvage APR	Median of 50 mos.	T1 – 0% T2 – 43%	T1 – 100% T2 – 82.6%
Gall[32]	84 (54 T1, 19 T2, 11 T3) via LE 383 APR	16 endoscopic polypectomy, 68 LE, 383 APR	Median of 77.5 mos.	T1 – 11% (LE), 0% (APR) T2 – 22% (LE), 5% (APR)	T1 – 74 +/– 15% (LE), 100–2% (APR) T2 – 68 +/– 24% (LE), 76 +/– 11% (APR)
Morson[22]	143 (115 T1, 20 T2, 7 T3) Only 91 with negative margins	143 LE		2/91 (2%) with neg. margins 13/69 (19%) with pos. margins	Corr. 5-yr. of 100% with neg. margins Corr. 5-yr. of 83-96% with pos. margins
Whiteway[33]	46 (13 T1, 18 T2, 15 T3)	46 TA & TSp 27 for cure, 6 dissem. disease 13 for high risk		Approximately 8 (17%)	Cancer specific survival of 87%

LE, local excision; TA, transanal excision; TC, transcoccygeal excision; TSp, transsphincteric excision; TEM, transanal endoscopic microsurgery.

suffice. Currently a phase II trial is studying the outcome of small distal T2N0Mx patients treated with neoadjuvant therapy and local excision. Results will not be known for several years.

Adjuvant Therapy

Local recurrence continues to be a major source of morbidity and mortality following both local excisions and radical resections for rectal cancer. The major risk factors for recurrence include the depth of invasion of the primary tumor, positive surgical margins, histologic grade of the tumor, and the presence of tumor in the regional lymph nodes. The addition of adjuvant or neoadjuvant radiation has been shown to decrease these local recurrence rates, and there is increasing evidence that chemoradiation may have a beneficial effect on survival. This has led to recommendations by the National Institute of Health stating that all patients with stage II or higher rectal cancer should be treated with adjuvant chemoradiation.

One of the major shortcomings of local excision is the inability to pathologically assess the regional lymph nodes. Microscopic disease can be present in the regional lymph nodes in up to 12% of T1 lesions, 22% of T2 lesions, and 58% of T3 and T4 lesions.[34,35] This microscopic disease may lead to local recurrence if left untreated. These findings have caused many observers to advocate the use of post-operative radiation following local excision in an attempt to eradicate any nodal disease, especially in more aggressive tumors with some of the risk factors previously mentioned. It also further emphasizes the need for pre-operative ERUS or eMRI in order to identify patients with nodal disease who may be inappropriate for local excision.

Unfortunately, most studies involving local excision combined with pre or post-operative chemoradiation are small retrospective single institution studies. The patient population, radiation and chemotherapy protocols, and tumor characteristics are highly variable between these studies (Table 157–2), and thus, 5-year survival rates range from 33% to 100%. However, local recurrence rates are decreased when compared to local excision

Table 157–2 Local Excision Plus XRT (Retrospective Series)

Author	No. of Patients	Treatment Arms	Follow-up	Local Recurrence	Survival
Wong[7]	25	21 TA, 4 endoscopic polypectomy or fulguration, All got 50 Gy XRT postop	Median 72 mos. (minimum of 36 mos.)	6/25 (24%)	Crude 5-yr. survival of 96%
Mendenhall[30]	67 (34 T1, 12 T2, 2 T3)	65 TA, 2 TC 48 received 45-60 Gy XRT postop	Median 65 mos. (6-273 mos.)	T1 = 11% T2-3 = 25%	T1 = 76% T2-3 = 77%
Bailey[36]	63 (35 T1, 18 T2, 10 T3)	63 LE 34 XRT—45-50 Gy	Median 44 mos. (12-130)	4/53 (7.5%)	Crude 5-yrs. survival—74.3%
Chakravarti[27]	99 (58 T1, 41 T2)	52 LE alone 47 LE plus 45-64.8 Gy XRT (45 postop, 2 preop) 33 also had 5-FU	Median 51 mos. (4-162 mos.)	LE alone = 11% T1, 67% T2 LE + CRT = 0% T1, 15% T2	Relapse-free 5-yr. survival LE alone = 80% T1, 33% T2 LE + CRT = 65% T1, 76% T2
Paty[25]	125 (74 T1, 51 T2)	125 LE 31 received 45-54 Gy and 15 of them got 5-FU	Median 80.4 mos	T1 = 17% T2 = 26%	10-yr. survival of 74% for T1 and 72% for T2
Willett et al.[37]	56 (34 T1, 22 T2)	45 TA or TSp, 10 TC, 1 fulgaration. 30 received 45 Gy post-op XRT. Since 1986, received 5-FU	Median 48 mos.	Since 1985, 0/20 patients after chemoradiation	Actuarial 5-yr. recurrence-free survival—72%

LE, local excision; TA, transanal excision; TC, transcoccygeal excision; TSp, transsphincteric excision; CRT, chemoradiation therapy, XRT, radiation therapy.

Table 157–3 Local Excision Plus Adjuvant Therapy—Prospective Series

Author	No. of Patients	Treatment Arms	Follow-up	Local Recurrence	Survival
Ota[38]	46	LE Post-op XRT (53 Gy) 5-FU for 7 T3's, 1 T2	Median 36 months (18-73)	3/46 (6.5%) All T3's	Overall 3-yr. survival—93%
Bleday[17]	48 (21 T1, 21 T2, 6 T3)	Postop XRT 54 Gy & 5-FU/500 mg/M^2 day 1-3, 28-30 for T2, T3 lesions	Mean 40.5 months	4/48 (8%)	Overall 3-yr survival 93.8%
Steele[39]	110 (59 T1, 51 T2)	Postop XRT 54 Gy & 5-FU/500 mg/M^2 day 1-3, 29-31 for T2 lesions	Mean 48 months	T1 – 3/59 (5.1%) T2 – 7/51 (13.7%)	Overall 6-yr survival—85%

alone; ranging from 0% to 15% for T1 and T2 lesions, and 0% to 20% for T3 lesions.

Prospective Studies

Unfortunately, there are very few prospective studies of local excision for distal rectal adenocarcinoma with or without chemoradiotherapy (Table 157–3). We treated 48 patients with rectal adenocarcinoma via local excision, using postoperative chemoradiation for all T2 and T3 lesions. Over a mean follow-up period of 40.5 months we found an overall survival of 93.8%, with recurrence rates by stage of 0% for T0 lesions, 9.5% for T1 lesions, 0% for T2 lesions, and 40% for T3 lesions. Of note, local recurrence was seen in three of five patients with lymphatic invasion and two of two patients with positive margins at the time of local excision. From our results, we concluded that surgery alone was adequate for T1 lesions, while T2 lesions required a combination of surgery and chemoradiation, provided there were negative margins and no lymphatic involvement. If either of these characteristics were present, however, we recommended the addition of chemoradiation for T1 lesions, and radical resection for T2 lesions.

Ota et al. published their results on a study of 46 patients with a median follow-up time of 36 months. In their study, all patients received postoperative radiation, while T3 patients also received chemotherapy in addition to their radiation treatments. Their results were similar to ours, with a 6.5% local recurrence rate and a three-year survival rate of 93%.[38]

Steele et al.[39] published a multicenter, prospective trial of local excision for rectal cancer in 110 patients. All of these patients were thoroughly screened preoperatively to ensure that their tumors were within 10 cm of the dentate line, less than 4 cm in size, and involved less than 40% of the circumference of the bowel wall. Furthermore, all patients had to be N0M0, and statistical analyses were only performed on patients with negative margins at the time of resection. Patients were treated with postoperative chemoradiation only if they had T2 lesions. They published survival rates of 87% and 85% for T1 and T2 lesions respectively, with an overall survival rate of 85%. They also found an overall disease-free survival rate of 78%, with 84% for T1 lesions, and 71% for T2 lesions.[39] This data compares very favorable with APR, with a 5-year survival rate of 70% for stage I disease. Unfortunately, the retrospective APR data is not separated into T1 and T2 lesions, making comparison difficult.

Transanal Endoscopic Microsurgery

As TEM is still a relatively new technique, the data supporting its use is still being compiled. There are a few small, single-institution, retrospective and prospective studies describing the use and outcomes of TEM for the excision of rectal cancer (Table 157–4). In general, these studies show survival and recurrence rates ranging from 83% to 100% and 0% to 27% respectively. These rates are equivalent to those seen for transanal excision, but again comparison is difficult due to the differences in patient population, adjuvant therapy, and tumor characteristics.

ALGORITHM FOR LOCAL EXCISION OF RECTAL CANCER

Patient Selection
- Mobile tumor <4 cm in diameter, <40% of the bowel circumference, within 5 cm of the dentate line (see Box 157–1).
- Significant medical co-morbidities making radical excision unattractive even for patients with T3 lesions.

Preoperative Imaging
- ERUS or eMRI dependent on institutional preference.
- T1 or T2 tumors with no signs of locoregional nodal metastases.
- CT scan to assess for distant metastases.

Table 157–4 Transanal Endoscopic Microsurgery

Author	No. of Patients	Treatment Arms	Follow-up	Local Recurrence	Survival
Lezoche[40]	35 (All T2)	All had preop 50 Gy XRT then TEM	Median 38 mos. (24-96 mos.)	1/35 (2.85%)	Probability of survival at 96 mos. = 83%
Farmer[41]	49 (36 Tis, 10 T1, 3 T2, 1 T3)	All TEM	Median 33 mos. (20-48 mos.)	2/49 (5.6%) 1 patient had a salvage APR	1 death from disseminated cancer. Survival = 97.9%
Azimuddin[21]	21 (7 Tis, 9 T1, 5 T2)	All TEM	Mean 15 mos.	0% for T0 and T1 20% for T2	100% for all grades
de Graaf[42]	76 (32 Tis, 21 T1, 18 T2, 5 T3)	All TEM	Median 10 mos., mean 13.9 mos. (1-52 mos.)	Tis = 0%, T1 = 10%, T2 = 33%, and T3 = 0%	1 patient died yielding overall survival of 98.7%

Table 157–5 Treatment Recommendations Following Initial Resection

T Stage	Low Risk*	High Risk†
T1	No further treatment	Adjuvant chemoradiation
T2	Adjuvant chemoradiation	Radical resection
T3	Radical resection	Radical resection

*Low risk: well or moderately differentiated with no evidence of lymphatic or vascular invasion.
†High risk: poorly differentiated or lymphatic invasion or vascular invasion.

Chemotherapy and Radiation Therapy (Table 157–5)
- T1 lesions completely excised but with unfavorable histology.
- T2 lesions (adjuvant or *neo*-adjuvant chemo-radiotherapy).

Follow-up
- Office visits with physical exam, CEA, and proctoscopy every 3 months for the first 2 years and then every 6 months until 5 years.
- CT scans of the abdomen and pelvis at 6 months and then with an increase in CEA or change in symptoms.
- Colonoscopy at 1 year following surgery and then every 3 to 5 years.
- Radical resection as salvage for any local recurrence.

SUMMARY

Rectal cancer remains a significant cause of morbidity and mortality worldwide. Studies have shown that local excision for favorable T1 cancers, and local excision combined with adjuvant chemoradiation in select T2 cancers can yield similar rates of survival and recurrence when compared with radical resection. This is accomplished with shorter hospital stays, fewer complications, and greater patient satisfaction. Strict selection criteria remains extremely important as local excision should not be offered to patients with transmural lesions or regional nodal involvement. Also, larger tumors, even recurrent disease, may always be treated with salvage APR, but the outcomes of such treatment are not fully known.

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Chapter

158

Operations for Colorectal Cancer: Low Anterior Resection

Alfred M. Cohen

Because 70% to 80% of patients with rectal cancer have disease beyond the rectal wall through either direct extension or lymphatic spread, most require radical resection.[1] Optimal oncologic and functional results require a precise surgical approach, selectively integrated with adjuvant radiotherapy and chemotherapy.

Rectal cancer surgery is a local-regional therapy, but the oncologic efficacy of such surgery is based principally on its rate of local control.[2] The pelvis is a common site of recurrence, which is a major cause of complications and death.[3] Pain secondary to nerve invasion, perineal breakdown, and obstruction, along with bleeding and fistulization, often creates an unmanageable problem. Salvage therapy is limited in most cases and provides incomplete and temporary palliation.[4] The attitude that pelvic recurrence is best prevented should prevail and help guide the choice of operation and conduct of the pelvic dissection.

The major risk factors for relapse, both local and distant, are the number of involved regional lymph nodes, the extent of transmural penetration, and tumor grade.[5,6] Two observations strongly implicate inadequate surgical resection as a major cause of pelvic recurrence. First, involvement of the lateral or circumferential margin of resection strongly correlates with subsequent local recurrence.[7] Conventional resection yields a positive lateral margin in 25% of cases, with local recurrence developing in approximately 80% of these patients. Second, a clear lateral margin on serial section correlates with local control. Studies from the United Kingdom and Germany have demonstrated that the frequency of local recurrence varies among individual surgeons from less than 10% to more than 50%.[8,9] The surgeon's operative technique and ability to achieve a negative circumferential margin are strong determinants of local control.[10]

A common practice in pelvic surgery is "blunt" dissection, which is associated with a high risk for mesorectal or rectal perforation.[11] Heald and colleagues[9,10] advocated total mesorectal excision (TME) in conjunction with low anterior resection (LAR) as the optimal surgical treatment of low rectal cancer. This technique involves removal of the entire rectal mesentery, including that distal to the tumor, as an intact unit. TME requires precise dissection in an areolar plane outside the visceral fascia that envelops the rectum and its mesentery. In contrast to conventional blunt dissection techniques, the envelope that encompasses the pelvic tissue is removed intact, without the risk for mesorectal or rectal perforation that is frequently associated with blunt dissection along the rectosacral fascia. This approach maximizes the likelihood of obtaining a negative lateral or peripheral margin. In addition, TME facilitates nerve preservation, enables complete hemostasis, and emphasizes gentle handling to avoid tearing or disrupting the smooth outer surface of the mesorectum. In a large series of patients treated by rectal resection with TME, MacFarlane et al.[12] reported a 5% local failure rate without the use of radiotherapy. Although such technical strategies are not fully proved, there is increasing evidence to support the conclusion that TME does improve local control. TME has been shown to achieve a negative circumferential margin in 93% of resected specimens.[13] In addition, other surgeons using similar TME techniques have reported local failure rates of less than 10% for transmural or node-positive rectal cancer.[14-16] These data are quite compelling, but all of these reports represent a select group of patients; patients who underwent abdominoperineal resection were excluded, and some patients who received adjuvant radiation therapy were included. Most important, the patients reported are those who have undergone a "potentially curative"

Table 158–1 Results of Total Mesorectal Excision for Rectal Cancer

Series	*N*	Radiation Therapy	Local Failure (%)	Survival (%)
Cawthorne et al.,[13] 1990	122	*n* = 7	7	NS
MacFarlane et al.,[12] 1993	135	None	5	78
Enker and Cranor,[15] 1995	204	≈33%	6	77
Arbman et al.,[16] 1996	128	*n* = 3	7	68
Zaheer et al.,[14] 1998	514	None	7	78

NS, not stated.

operation. Hence, patients with close tangential or lateral margins may be excluded from such reports. Although no randomized trial of TME has been performed, TME has been evaluated prospectively in Sweden, where it has been introduced through a formal preceptorship-based training program. A 5-year prospective audit revealed a local recurrence rate of 7% after the addition of TME as opposed to a historical control rate of 23%.[16] These data are summarized in Table 158–1.

Inherent in reports on TME is the use of sharp mesorectal excision. This technique involves cautery and scissors dissection in the well-defined plane outside the mesorectal visceral fascial lining, which is the "only plane" definable during precise pelvic surgery. I perceive this to be the most important aspect of optimization of pelvic surgery. TME as a component of sharp mesorectal excision may be appropriate for mid and low rectal cancer but not for all rectal cancer. Sharp mesorectal excision is appropriate for all patients.

In the United States, attempts to reduce local recurrence and to improve survival rates have emphasized postoperative adjuvant chemotherapy and radiation therapy. Randomized trials have shown convincingly that for transmural or node-positive rectal cancer treated with conventional surgery, the addition of adjuvant therapy improves outcome. The combination of postoperative chemotherapy and radiation therapy further improves local control and increases overall survival rates.[17,18] In 1991, a National Institutes of Health consensus conference report on rectal cancer recommended combined postoperative chemotherapy and radiation therapy as the standard of care for patients with stage II (*transmural node-negative*) and III (*node-positive*) rectal cancer.[19]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) RO-1 trial compared surgical resection alone with adjuvant chemotherapy or radiation therapy. The data demonstrated a survival benefit with single-modality adjuvant chemotherapy. Current adjuvant therapy trials are testing how to best combine chemotherapy and radiation therapy with regard to drug selection, dose, sequence, and timing to optimize results. The benefits of continuous venous 5-fluorouracil infusion along with leucovorin, levamisole, or both versus the bolus delivery of 5-fluorouracil are under study in separate cooperative group trials in the United States.

Several studies have suggested that postoperative radiation therapy has a considerable long-term detrimental impact on bowel function. With computed tomography or ultrasonography, the presence of extensive hepatic metastases can be excluded preoperatively. In addition, endorectal ultrasound provides objective information with regard to transmural spread. The use of a preoperative chemoradiation strategy is becoming increasingly common. Whether preoperative adjuvant therapy offers better local control, as previously indicated in a trial of preoperative versus postoperative radiotherapy from Sweden,[20,21] was tested by the German cooperative group. They confirmed the efficacy of the preoperative (neoadjuvant) sequence.[21a]

Left unanswered is whether adjuvant local-regional radiotherapy is necessary in the setting of optimal resective surgery. A two-arm randomized study of TME with or without *short-course, high-fraction (25 Gy in five fractions)* preoperative radiotherapy for resectable rectal cancer was performed in the Netherlands.[22] Participation in this trial was limited to surgeons trained in TME who have performed five operations with a member of the monitoring committee. Preoperative radiation reduced local failure by one-half, despite TME. The greatest benefit was in the node-positive patients.

With increasing emphasis on cost-effectiveness and quality-of-life issues, the incremental, but costly benefit of adjuvant radiation therapy in patients undergoing optimal resection will have to be clearly redefined. Data are persuasive that the use of postoperative chemoradiation after conventional resection has a profound negative impact on late bowel function.[23] There are few data regarding the impact of preoperative irradiation on late bowel function, particularly at the most common U.S. doses and fractions.

GOALS AND TERMINOLOGY

The goals of operative treatment of patients with rectal cancer are to cure cancer locally (within the pelvis) and to minimize risk with regard to sphincter loss and bowel, bladder, and sexual dysfunction. Many of the aspects of surgical resection that are described later will affect the success of all of these goals. The issues related to conduct of rectal cancer resection and the risk for local recurrence apply primarily to patients with mid and low rectal

cancer. That is, cancers at or below the peritoneal reflection. The upper third of the rectum, commonly from 11 to 15 cm from the anal verge, is at considerably reduced risk for local recurrence. Patients with cancer of the upper part of the rectum or rectosigmoid are generally treated initially by surgical resection, and adjuvant therapy follows the colon cancer postoperative paradigm. Sphincter-preserving resections of the rectum are referred to as *anterior resection*, *low anterior resection* (LAR), or *low anterior resection with coloanal reconstruction*. In general, anterior resection refers to resection of the sigmoid or rectosigmoid and may involve mobilization of the presacral plane and the anterior plane. LAR is used to refer to anterior resection combined with complete clearance of the pelvic side walls. In this chapter the technique refers only to patients undergoing LAR with a sutured or, more commonly, a stapled reconstruction in the low pelvis. Reconstruction involving a coloanal anastomosis is discussed in Chapter 160. A stapled reconstruction at the pelvic floor should not be referred to as a *coloanal anastomosis*.

PATIENT SELECTION

In the selection of patients suitable for a sphincter-preserving approach, tumor size, differentiation, and location are all taken into account. Low-lying anaplastic or poorly differentiated cancers generally require abdominoperineal resection and chemoradiation therapy. Bulky transmural tumors just above the anorectal ring also frequently require complete proctectomy. The location of the tumor is determined by digital rectal examination and visualization with a rigid sigmoidoscope, usually with the patient in the left lateral decubitus position. The distance from the anal verge or the dentate line is determined. The most important distance is that related to the upper portion of the anal canal, generally referred to as the *anorectal ring*. In a slender patient, particularly a woman, a cancer that is easily palpable but several centimeters above the anorectal ring may be amenable to LAR with a stapled reconstruction. In other patients, as discussed later, this technique is not feasible. An additional tumor feature that determines the likelihood for sphincter preservation is its circumferential location. A tumor 2 to 3 cm above the anorectal ring posteriorly, after total mesorectal mobilization, will frequently be 5 to 6 cm above the anorectal ring when traction is applied. However, an anteriorly located tumor has very little cephalad mobility after mesorectal mobilization.

In addition to these tumor factors involved in allowing a sphincter-preserving approach, there are a number of aspects related to the individual patient. Body habitus and gender are pivotal. A slender woman is the ideal patient. Sphincter preservation in a heavy man with a large prostate and an anterior-based tumor is always problematic, even with cancer in the midrectum. For many such patients, bowel continuity is best restored by coloanal reconstruction. Sphincter preservation is generally precluded in men with a history of prostate cancer treated by either external-beam radiation therapy, brachytherapy seed implantation, or radical prostatectomy.

Patients with extensive diverticulosis or previous left colectomy may not be amenable to LAR and restoration of bowel continuity because of inadequate length of good-quality proximal bowel. There are also rare patients with an incomplete marginal artery. However, most often an inadequate marginal artery represents an iatrogenic intraoperative complication from excess tension on the bowel. Finally, patients should not undergo very low reconstruction in the presence of poor resting and squeezing anal canal pressure.

PREOPERATIVE RADIATION THERAPY

Patients with locally advanced transmural rectal cancer that is tethered or fixed should be evaluated for preoperative radiation therapy. This is usually combined with 5-fluorouracil–based concurrent chemotherapy, both as a radiosensitizer and as an adjuvant for disseminated disease. In addition, there is a subset of patients with relatively early, but very low cancer in whom preoperative radiation therapy is used to facilitate sphincter preservation. The appropriate adequate distal margin to achieve an excellent clinical response remains unclear in a patient with an early cancer who receives preoperative radiation therapy; 5 mm may be acceptable. However, it is completely unacceptable to divide through cancer in an unrealistic attempt at sphincter preservation. Frozen section control of the distal and lateral specimen margins is important before proceeding with restoration of bowel continuity. An incisional biopsy at the start of the operation does not provide adequate data for determination of the ability to achieve tumor clearance.

MANAGEMENT OF OBSTRUCTING CANCER

There are many patients with radiologic or even endoscopic confirmation of obstruction by an upper rectal or rectosigmoid cancer that clinically causes little interference with bowel function. Such patients may undergo elective resection. In the presence of a locally advanced rectal cancer with symptomatic obstruction, patients should undergo a preliminary diversion, receive chemoradiation therapy, and then undergo rectal resection. All such patients should be extensively evaluated preoperatively with chest radiography and computed tomography or ultrasonography, or both, of the liver. A stoma can be created laparoscopically or with a limited laparotomy. A low sigmoid loop colostomy is advantageous in that it will be outside the radiation field and can permit a two-stage operation with resection of the colostomy as part of LAR after the completion of radiation therapy. A left-sided transverse colostomy is to be avoided because of the potential for interference with colon mobilization for reconstruction. If a right-sided transverse colostomy is performed, care must be taken to

not damage the middle colic vessels, which are necessary for the reconstruction. Distal loop ileostomy is also acceptable. Finally, laser ablation with endoscopically placed endoluminal stents that traverse the tumor can facilitate emptying of the bowel and subsequent bowel cleansing in preparation for later excision.

EXTENT-OF-RESECTION ISSUES

Distal Mural Margins

For many decades, a 5-cm distal mucosal/mural margin was recommended, but a considerable body of data do not support this rule.[24] Distal spread may occur by direct submucosal extension or, less likely, via intramural lymphatics. Serial histologic sections of the bowel wall distal to resected specimens reveal that a large majority of patients have no distal spread. Only 2.5% of patients will have spread of more than 2 cm, and such spread almost always occurs in patients with anaplastic or poorly differentiated node-positive cancer. There appears to be no correlation between the risk for local recurrence and a distal margin in excess of 2 cm. Much of these data refer to pathologic and not surgical distances. Aggressive stretch on the specimen can double the pathologic length. As a general rule, in the presence of a moderately well-differentiated cancer, the surgical goal should be to obtain a 2-cm distal mural margin. A 5-mm to 1-cm margin may be adequate in patients who have had an excellent response to preoperative chemoradiation therapy.

Distal Mesorectal Margin

The information provided earlier concerning TME focused on intact removal of the lymph node packet and is based on data showing distal spread of positive lymph nodes beyond the gross tumor.[25] As with distal mural spread, such extension is relatively uncommon but occurs more frequently with high-grade tumors associated with multiple positive lymph nodes. In patients with upper rectal cancer, TME is not appropriate because the risk for lymph node metastasis in the low mesorectum is extremely low and TME may result in a relatively ischemic rectal stump. For such patients, a 5-cm clearance of mesorectum below the gross tumor is adequate. The mesorectum must be divided at a right angle to the point below the tumor selected for bowel division. Most patients with midrectal cancer will have the entire lymph node packet removed through complete mesorectal excision, which facilitates lateral margin clearance and sphincter reconstruction by clearing the distal muscular tube.

Proximal Vascular Ligation

The oncologic benefits of inferior mesenteric artery ligation with clearance of the high lymph node and periaortic lymph nodes are minimal or nil.[26,27] In the series reported by Grinnell,[26] there were no 5-year survivors in patients with positive nodes along the inferior mesenteric artery. However, "high ligation" is frequently necessary for adequate colon mobilization in patients undergoing restorative procedures, as discussed later.

Lateral Mesorectal Margins

The issue of sharp mesorectal excision was discussed previously. The lateral margins, which involve the posterior and anterior planes of the coronal dissection, as well as the lateral planes of the sagittal dissection, are under the control of the operating surgeon. Tumors that are tethered to a side wall require much more extensive lateral dissection, as discussed in sections that follow.

Lateral Pelvic Lymph Nodes

A few groups remove the internal iliac or lateral pelvic lymph nodes, particularly in patients with locally advanced cancer, because of data supporting the occurrence of lateral lymph node spread in a small subset of patients. However, the impact of such extended lateral dissection on local control and survival is unclear. Lateral dissection is frequently associated with increased sexual and bladder dysfunction. It is unlikely that such lateral lymph nodes truly represent "regional" lymph nodes, and in general they should not be included as part of the standard technique of LAR.

SYNCHRONOUS ORGAN RESECTION

Bilateral salpingo-oophorectomy to remove occult ovarian metastases and to prevent primary ovarian cancer remains controversial. Approximately 3% to 5% of patients with colorectal cancer will have synchronous ovarian metastases and will benefit by resection. The benefit associated with the removal of grossly normal ovaries is small at best.

Management of patients with a large fibroid uterus remains problematic. Routine total abdominal hysterectomy under such circumstances should be avoided because of the increased risk for a rectovaginal fistula. Data suggest that a considerable number of subclinical anastomotic leaks occur after LAR, and in the presence of vaginal closure, some of these leaks will become clinically apparent with the development of a rectovaginal fistula, which is a serious problem, particularly in an irradiated patient. An alternative to total abdominal hysterectomy in such women is supracervical hysterectomy.

In women with anteriorly based cancer that is tethered to the posterior aspect of the vagina, a concurrent posterior vaginectomy is appropriate. The surgeon should not feel compelled to routinely perform total abdominal hysterectomy with the posterior vaginectomy. High rectal cancer with transmural involvement in the cul-de-sac may require posterior pelvic exenteration, which involves clearing both ureters, extensively mobilizing the bladder,

and taking all lateral and posterior tissues with the uterus, cervix, and upper part of the vagina. This procedure is equivalent to "radical hysterectomy" with rectal resection and is the only way to completely surgically excise the cul-de-sac. Rectal reconstruction is certainly feasible in many such patients, and abdominoperineal resection may not add anything to the oncologic cure.

In irradiated patients or those undergoing sphincter reconstruction, any vaginal defect must be closed. Such closure is most easily performed with either an omental flap or, more commonly, a rectus abdominis flap. Except in very young women, the rectus flap may exclude skin. The anterior fascia is left intact, and the muscle and peritoneum are taken over the full length of the muscle. This flap is very durable and is based on the inferior epigastric vessels. The flap is rotated 180 degrees, and the peritoneum is sewn to the vaginal defect through a perineal approach. In younger women, a formal myocutaneous flap is used.

Concomitant Hepatobiliary Surgery

In patients with symptomatic gallstones, cholecystectomy at completion of the rectal reconstruction is appropriate. If the splenic flexure has been mobilized, the cholecystectomy can be performed without extending the incision and with very little incremental complication. Resection of hepatic metastasis is appropriate only in selected patients and in general only if it involves minimal surgery. A wedge or segmental resection may be appropriate. Major anatomic resections of the liver are best done as a staged procedure through a more appropriate incision.

RELEVANT PELVIC ANATOMY

The essence of performing an optimal operation for mid or low rectal cancer is to dissect sharply with scissors, cautery, or both in defined anatomic planes. The *mesorectum* is not a true mesentery, but it is the common terminology used to describe the node-bearing fatty tissue that surrounds the extraperitoneal rectum. It is covered by a visceral fascia. Between this visceral fascia and the lateral pelvic wall is an areolar plane, identification of which is essential for sharp mesorectal excision. Posteriorly, the visceral and lateral or parietal fasciae fuse into the "rectosacral fascia." This fascia tethers the posterior aspect of the rectum into the sacral hollow, and division of this structure is required for LAR. Anteriorly, the perirectal fat abuts Denonvilliers' fascia. Denonvilliers' fascia envelops the seminal vesicles and fuses with the prostate fascia. In women, the perirectal fat abuts the rectovaginal septum.

In the upper part of the pelvis posterior to the superior hemorrhoidal vessel is nerve-bearing tissue located within Waldeyer's fascia. The sympathetic nerve trunks reside within this plane. The main parasympathetic nerve trunk necessary for erection and orgasm is S3. This nerve exits in the midpelvis just distal to the piriformis muscle in the horizontal portion of the sacrum and lies just medial to the parietal pelvic fascia. The parasympathetic and sympathetic nerves fuse into a plexus along the pelvic side wall and then extend anterolaterally into the seminal vesicles, prostate, and the vaginal or penile structures.

GENERAL ISSUES RELATED TO LOW ANTERIOR RESECTION

Bowel Preparation

In the absence of high-grade obstruction, full mechanical and oral antibiotic preparation is necessary to reduce the risk for postoperative wound infection. Such preparation is routinely done on an outpatient basis, except in the elderly or in patients with obstruction. Bowel cleansing is performed by restricting patients to a clear liquid diet for 36 hours and the use of cathartics. Oral antibiotics are administered the afternoon and evening before surgery. Intravenous antibiotics are administered approximately 30 minutes before making the skin incision.

Open or Laparoscopic Surgery

The general standard of care for rectal resection involves laparotomy and general exploration, mobilization, and resection, followed by reconstruction. The role of laparoscopically assisted surgery is still being defined (see Chapter 168).

Initial Exploration

As a routine, careful evaluation of the liver, gallbladder, stomach, colon, and peritoneal surfaces is performed. In women, careful assessment of the ovaries and uterus is appropriate. The exact local-regional extent of disease is now determined. The high iliac nodes, inferior mesenteric artery nodes, and periaortic nodes are clinically evaluated.

Pelvic Dissection

The conduct and sequence of the operation are described later. However, adequate positioning of the patient, appropriate instruments, and the use of self-retaining retractors and a fiberoptic headlight are important elements in performing optimal pelvic surgery.

OPERATIVE TACTICS

Patient Position

The patient is placed in the modified lithotomy position (Fig. 158–1), with the thigh in approximately 15% flexion. Care should be taken to avoid the development of peroneal palsy as a result of the stirrups or leg compression boots. In general, a special support under the sacrum is not necessary unless coloanal reconstruction or abdominoperineal resection is being contemplated. The

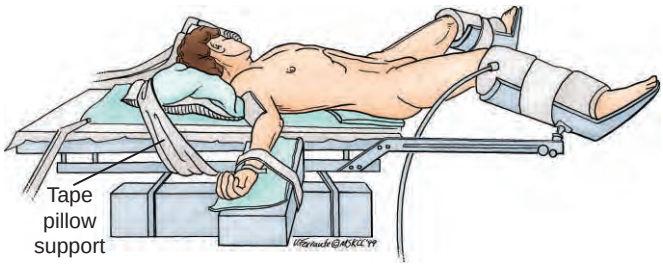

Figure 158–1. Appropriate patient position for low anterior resection. To prevent patient slippage when in the Trendelenburg position, a pillow is placed under the nape of the neck. Shoulder supports are not required. Care must be taken to avoid arm hyperextension.

rectum is suctioned, and a urinary catheter is placed and draped either over or under the leg. In women, complete vaginal irrigation and preparation are necessary.

Traditionally, pelvic surgery has been performed with the patient in a steep Trendelenburg position. With the use of appropriate self-retaining retractors, however, such positioning is no longer necessary and is frequently counterproductive. The Trendelenburg position may be helpful for the initial pelvic dissection, but for the distal dissection, the reverse Trendelenburg position is preferable.

Sagittal Anatomy

In the pelvis, the sympathetic nerves lie posterior to the mesorectal visceral fascia (Fig. 158–2). However, at the level of the aortic bifurcation and above, the nerves are perilously close to the inferior mesenteric artery. They must be sharply separated and pushed posteriorly to avoid nerve damage.

The rectosacral fascia represents a well-defined fusion of the parietal and visceral fasciae in the midpelvis. During LAR, this fascia, which frequently extends between S3 and S5, must be sharply separated with scissors and cautery to allow full clearance of the pelvic floor to the level of the anorectal ring posteriorly.

In men, Denonvilliers' fascia is a crucial anterior anatomic structure. It envelops the seminal vesicles, extends along the prostate, and fuses with the lowermost portion of the prostatic capsule. It can be quite dense and protects the prostate from direct invasion by anteriorly based cancer. The anterior dissection in men should be performed anterior to Denonvilliers' fascia. As with the rectosacral fascia posteriorly, separation of the prostatic capsule and Denonvilliers' fascia requires sharp dissection.

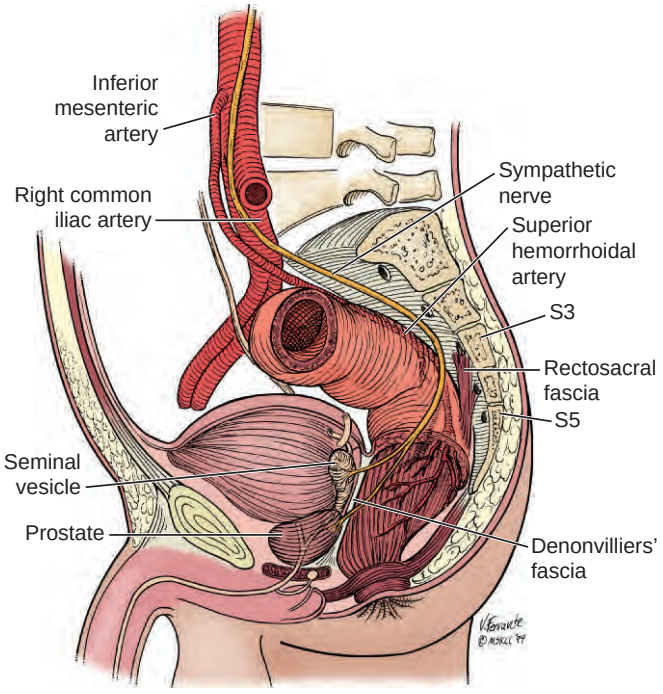

Figure 158–2. Sagittal pelvic anatomy in a man.

Transverse Midpelvic Anatomy

Denonvilliers' fascia is shown lifted from the rectum and overlying the seminal vesicles in Figure 158–3. The S3 nerve roots, which are usually just distal to the piriformis muscle, may lie along the parietal pelvic fascia or be separate and more medial. Merging of the sympathetic and parasympathetic nerves is demonstrated.

Vascular Supply to the Rectum and Left Colon

The left colic branch arises 3 to 4 cm from the origin of the inferior mesenteric artery, then gives off sigmoid branches, and finally continues as the superior hemorrhoidal artery, as illustrated in Figure 158–4. Not shown in this figure are the middle hemorrhoidal arteries, which are small branches that arise from the internal iliac (hypogastric) artery at the level of the S3 nerves. There are important additional collateral vessels via the inferior hemorrhoidal artery that pass from the levatores cephalad along the distal aspect of the rectum. These vessels support the distal portion of the bowel after LAR.

The arch of Riolan is a common variant that represents an ascending branch of the inferior mesenteric artery (see Fig. 158–4). Most commonly, it does not join the proximal middle colic but passes to the marginal artery at the splenic flexure. It may replace the left colic artery. When mobilizing the left colon, such an ascending vessel should not be divided unless absolutely necessary for colon length.

Sympathetic Nerves

The sympathetic nerves are necessary for antegrade ejaculation. As mentioned, they lie in a plane posterior to the lymphatic and nodal pedicle. At the sacral promontory, left and right trunks separate and pass along the high

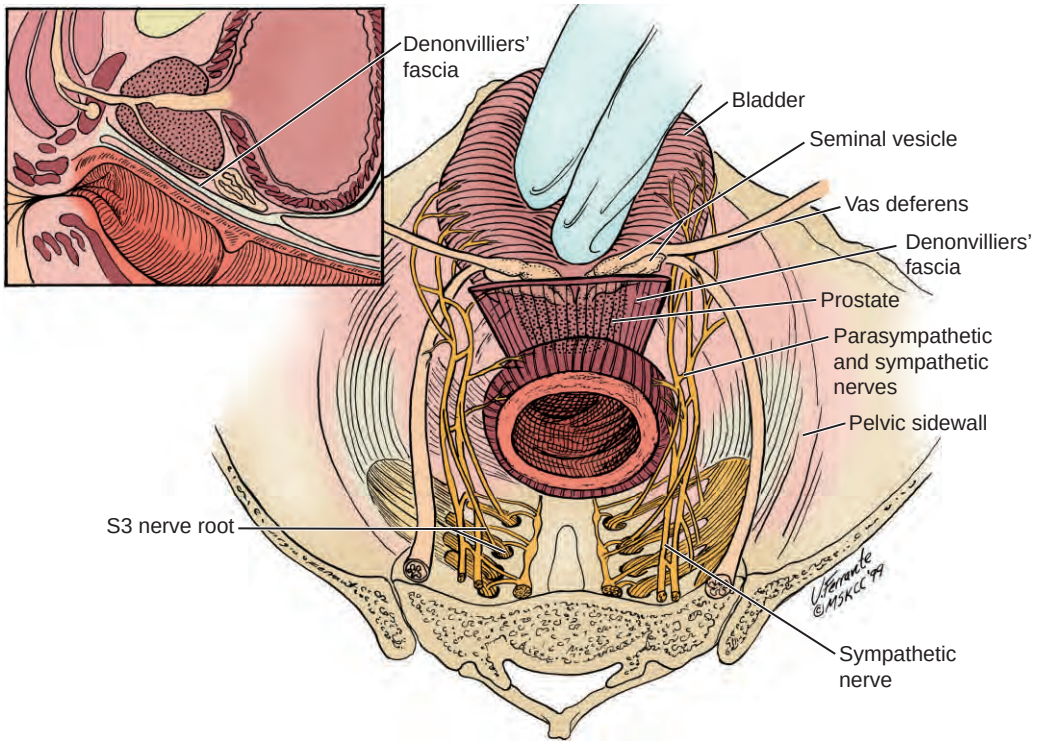

Figure 158–3. Transverse midpelvic anatomy in a man.

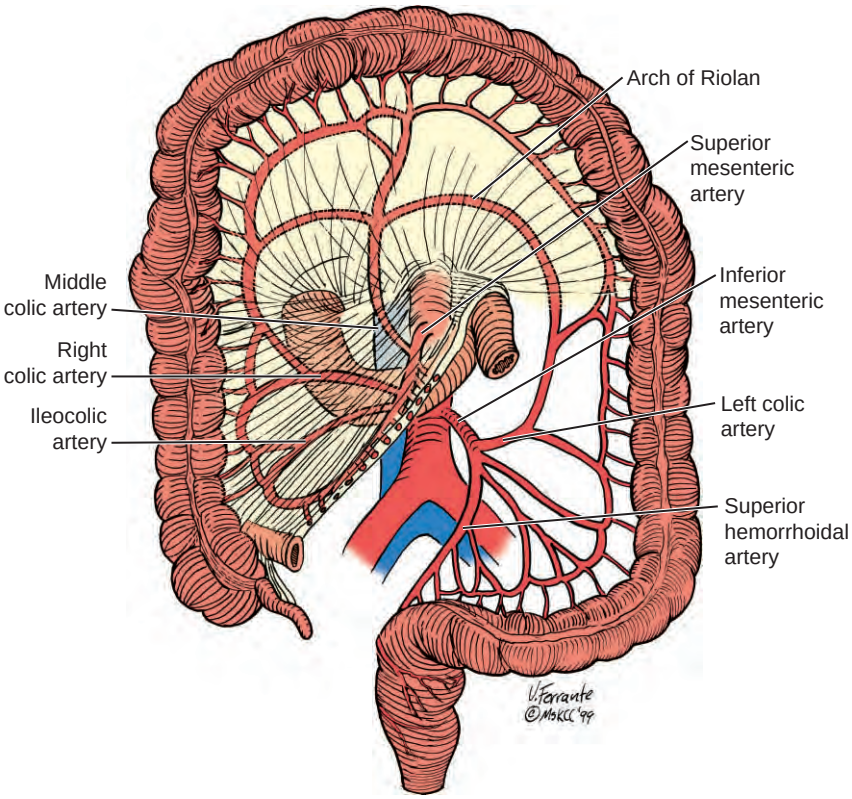

Figure 158–4. Arterial supply to the rectum and colon.

pelvic side wall. Patients with high rectal cancer and extensive lateral spread may require resection of the sympathetic nerves along the pelvic side wall to obtain adequate clearance.

Sigmoid Mobilization from the Left

After completion of routine exploration, placement of the retractors, and packing of the bowels (or my preference, evisceration of the small bowel over the right hypochondrium), the initial dissection involves sigmoid mobilization on the left (Fig. 158–5). The apex of the sigmoid is frequently tethered near the internal ring. The sigmoid is fully mobilized to its apex, and the lower portion of the left colon is mobilized. With retraction anteriorly and to the right, tissue overlying the left common iliac artery is opened, and the opening is extended down into the pelvis. Care should be taken to incise only the peritoneum at this point in the procedure. The ureter is now identified. The peritoneal opening is extended further into the pelvis. At this point the sigmoid is aggressively pulled anteriorly and to the right, and the soft tissue between the superior hemorrhoidal vessels and Waldeyer's fascia is separated. Clearance along the bony sacrum at the level of the promontory will divide the sympathetic nerves. The appropriate plane is more anterior and just posterior to the superior hemorrhoid vessels, which arch over the anterior aspect of the sacrum when the sigmoid is placed at appropriate tension.

Sigmoid Mobilization from the Right

The sigmoid colon is now lifted anteriorly and to the left, and the retroperitoneum is inspected to identify the right ureter (Fig. 158–6). Cautery is used to incise the

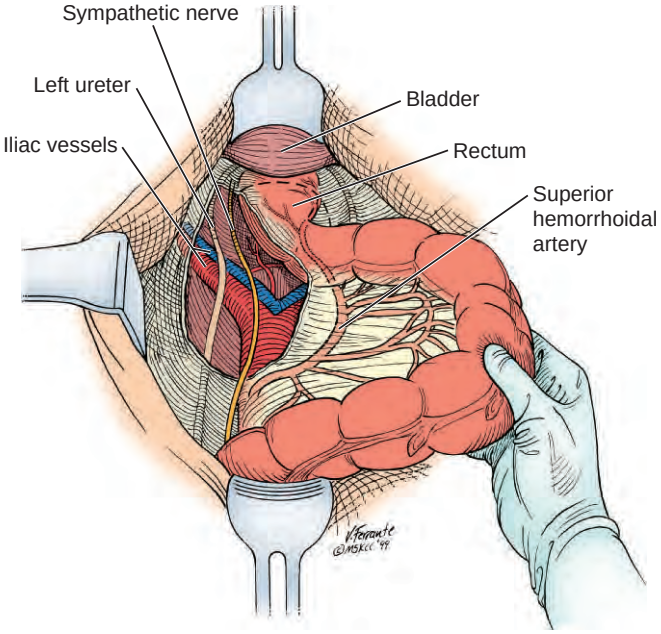

Figure 158–5. Mobilization of the sigmoid colon from the left.

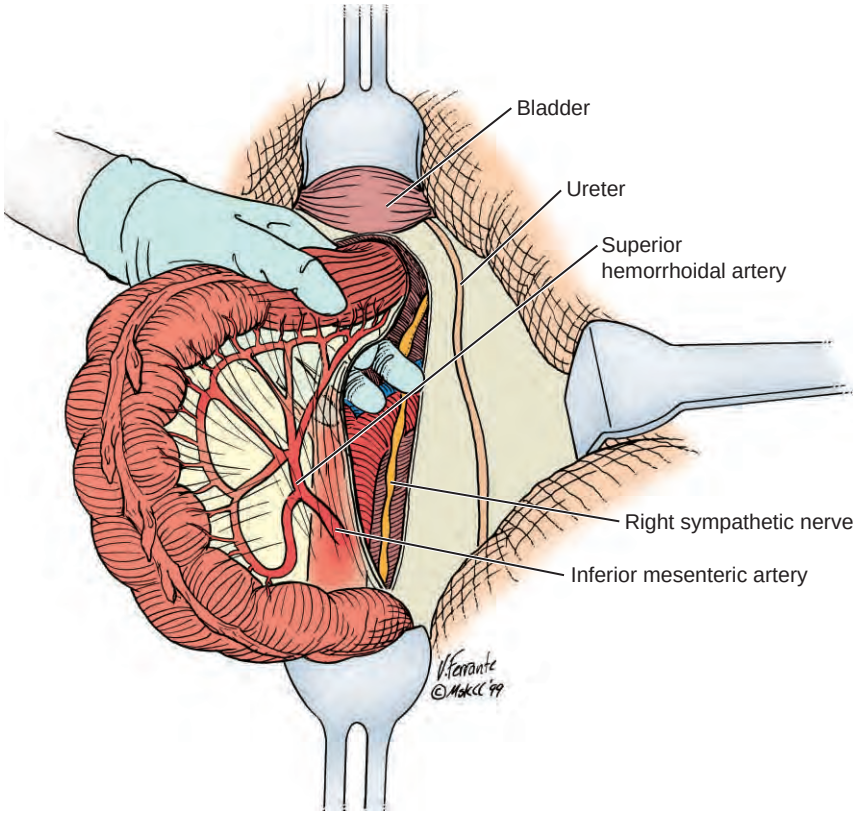

Figure 158–6. Mobilization of the sigmoid colon from the right.

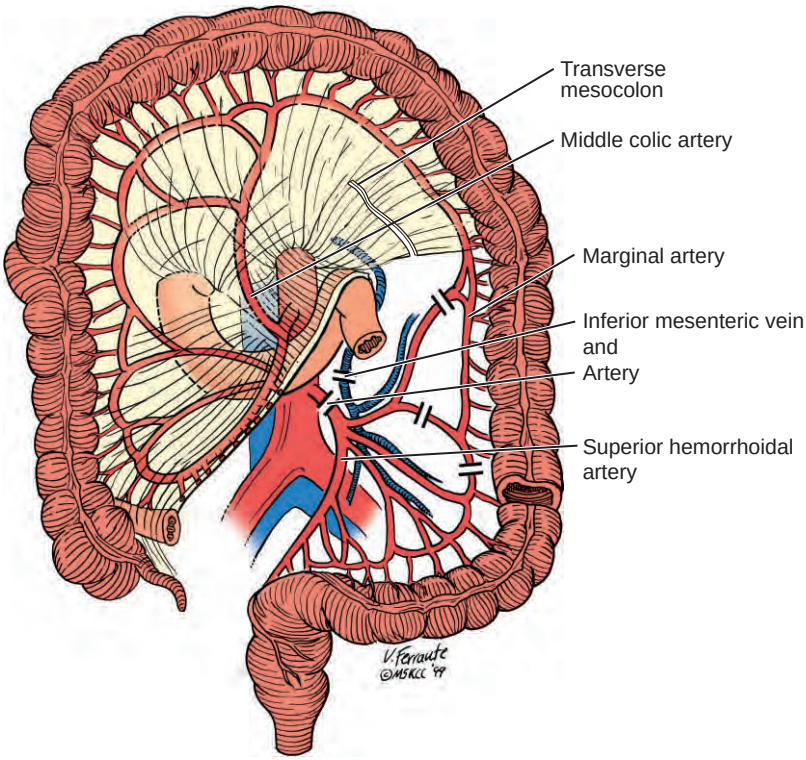

Figure 158–7. Vascular division to obtain maximum proximal colon length. The marginal artery is present in almost all patients. Loss of this artery is usually iatrogenic as a result of aggressive traction on the bowel.

peritoneum near the right common iliac artery, and the incision is extended down the right pelvic side wall medial to the ureter. At this point the correct depth of dissection is unclear. If the left-sided mobilization has proceeded to the midline, the operating surgeon can place a hand beneath the superior hemorrhoidal from the left. The sigmoid colon and the superior hemorrhoidal vessels are encompassed by the index and middle fingers and the thumb, and the vascular pedicle is lifted away from Waldeyer's fascia. Cautery is carried out from the right until tissue over the sacral promontory is exposed. At this point the sympathetic nerves remain posterior. No further pelvic dissection should be performed until the proximal portion of the colon is divided.

Left Colon Mobilization with Strong Traction on the Left Colon

The entire left colon is now mobilized. A common mistake is to extend the dissection superiorly along the "white line of Toldt" to the level of the spleen. An initial dissection along this line should proceed more medially, directly over the midpoint of the kidney, and then around the splenic flexure. Essential to facilitate this dissection is identification of Gerota's fascia. It is quite apparent when one has transgressed this fascia because perinephric fat will be poking through the fascia.

The extent of colonic mobilization depends on the quality and redundancy of the left and sigmoid colon and the length and location of the rectum and the rectal tumor. It is always best to err on the side of full mobilization rather than having to reposition all the retractors at the end of the operation to gain additional length. There are three components entailed in mobilization of the left colon and splenic flexure. The initial component involves lifting the left colon from Gerota's fascia and mobilizing the bowel via retroperitoneal and splenic flexure mobilization. The second component is actual division of the vessels. Ligation of the inferior mesenteric artery and inferior mesenteric vein will gain considerable additional length. The third component is division of the transverse colon mesentery as it runs underneath the pancreas. This step provides complete mobilization of the colon to the level of the middle colic artery (Fig. 158–7). Although this technique affords the operating surgeon a more capacious descending colon for reconstruction, such extensive mobilization may result in autonomic denervation of the bowel with subsequent spasm and bowel dysfunction.

Bowel Division and Distal Traction

After mobilization of the splenic flexure, the bowel and blood supply to the rectosigmoid should be divided before any pelvic dissection commences. With care being taken in regard to the sympathetic nerves, either the superior hemorrhoidal or the inferior mesenteric artery is ligated and divided. The proximal sigmoid or the junction of the descending colon and sigmoid is then divided. If a lengthy pelvic dissection is likely, it is best to divide the bowel with a stapler and worry about the reconstruction at a later time. For routine midrectal cancer that is going to be stapled, a purse-string clamp

or a purse-string stapler can be placed proximally, and a clamp or staple line can be placed distally. If a side-to-end or a pouch reconstruction is under consideration, then again, just a linear staple line is placed. The bowel is divided. For the pelvic dissection, more important than retractors is anterior traction with a clamp on the bowel and the mesorectum.

Initial Posterior Dissection

With aggressive traction on the bowel and its mesentery, the sympathetic nerves will be apparent and can be cleared along their length by either spreading with scissors or the use of cautery. The nerves should be separated from the mesorectum laterally. The pelvis is then entered with spreading of scissors between the sympathetic nerves passing through Waldeyer's fascia and through the areolar tissue until the bony pelvis is identified. The operation then proceeds in the 4 to 5 cm along the sacrum posteriorly to the level of the rectosacral fascia. No attempt at side wall dissection or anterior dissection is made at this time. By sweeping the ureters and the sympathetic nerves laterally, the fascia overlying the piriformis is identified. This should be the limit of the lateral dissection at this time. With spreading of scissors in this very easily separable areolar plane between the visceral fascia overlying the mesorectum and the bony pelvis posteriorly, dissection proceeds rather briskly at this point in the operation (Fig. 158–8). Appropriate retraction on the rectal specimen and the use of a St. Marks Parks retractor and a fiberoptic headlight facilitate this dissection. Care is always taken with regard to the sacral vessels, which may be in the midline or slightly off midline and have a tendency to be tented up into this areolar tissue.

Division of the Rectosacral Fascia

At the level of S3-5, multiple slips of thin fascia pass from the parietal fascia posteriorly into the visceral mesorectal fascia. These are the rectosacral fascia fibers. At this point, further spreading with scissors will identify the levatores. This is best accomplished approximately 1 to 2 cm off midline. The patient should be placed in a neutral or reverse Trendelenburg position. The levatores are now cleared on both sides while staying on the surface of the levator fascia. The midline raphe is divided with cautery. Care must be taken to not enter the rectum at this stage. Unless the entire rectum is mobilized to the anus, a very low reconstruction will not be feasible.

At this point, the main parasympathetic nerves should be identified and dissected anteriorly (Fig. 158–9). By sweeping up the side walls with heavy closed scissors in a "wiping motion," the main S3 nerve trunks become quite apparent. Traction on the mesorectum anteriorly after exposure of the levators distal to these nerves facilitates such identification. Cautery and scissors are used to clear these nerves for approximately two thirds of their length

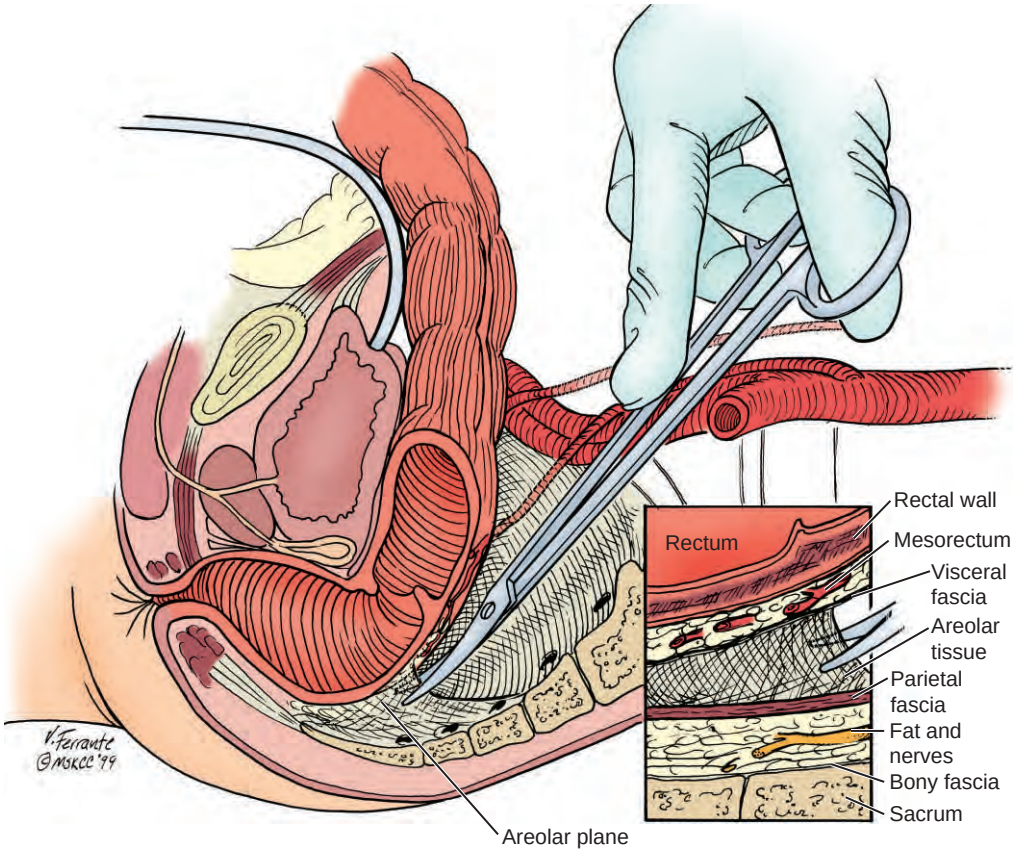

Figure 158–8. Sharp dissection in the areolar plane outside the mesorectal envelope.

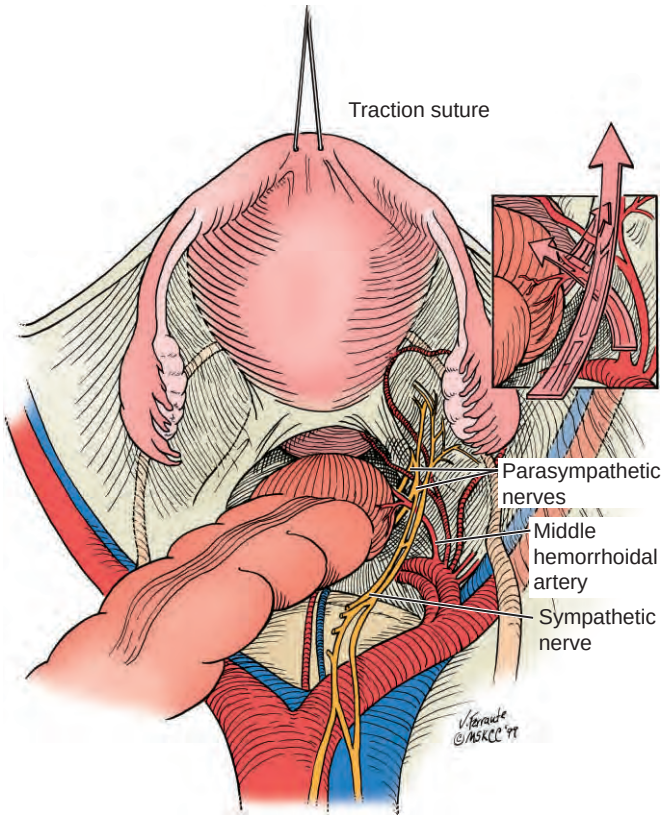

Figure 158–9. Pelvic anatomy in a woman.

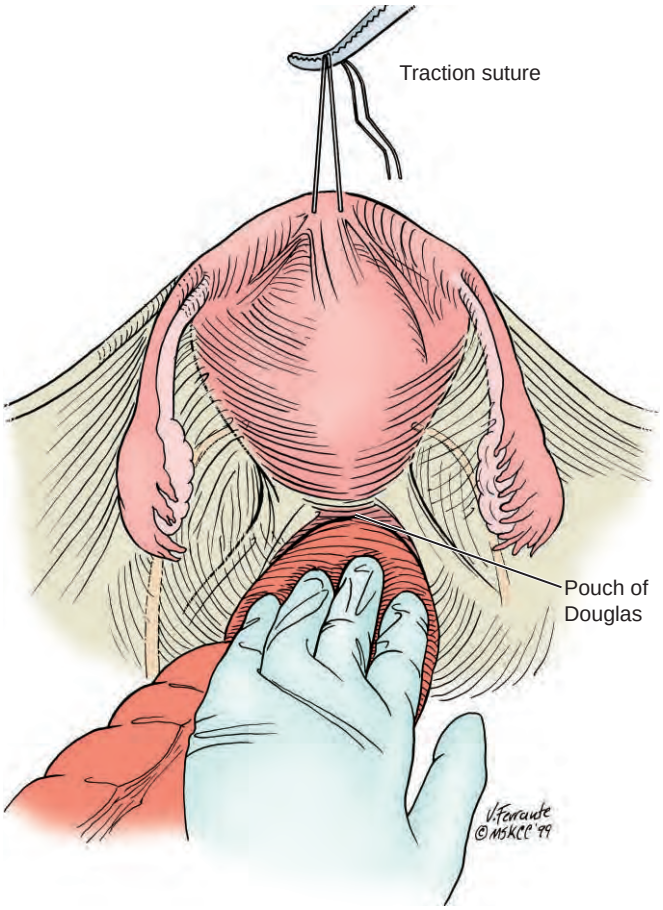

Figure 158–10. Anterior exposure in a woman.

anteriorly. Small branches will be seen and can be clipped and divided or gently cauterized. The full side wall dissection is not completed until the anterior dissection has been accomplished.

Anterior Dissection in Women

The most important aspect of the anterior dissection in a woman who has not previously undergone hysterectomy is traction on the fundus of the uterus (Fig. 158–10). The assistant standing between the patient's legs lifts the uterus anteriorly and inferiorly. Traction is then placed on the rectal specimen superiorly. A hand is pressed posteriorly on the upper part of the rectum, and this defines the peritoneum in the pouch of Douglas. Cautery is used to help open this plane. The dissection proceeds along the length of the vagina. Meticulous dissection is required at this point to avoid damage to the very thin-walled posterior vagina. In a woman who has previously undergone hysterectomy, two fingers are placed in the apex of the vagina to help define the appropriate plane along the posterior rectovaginal septum. In a woman with a lengthy vagina, a gauze pad on a clamp will be helpful. This dissection should proceed under direct vision with cautery and scissors to at least 90% of the length of the vagina. With large, lengthy scissors, the fatty tissue anterolateral to the rectum is cleared so that the levators are exposed both anteriorly and posteriorly. Only after this portion is completed will the pelvic side walls be dissected. At this point the rectum will have been totally mobilized down to the pelvic floor anteriorly and posteriorly, and the levators will be visible completely around the mesorectum.

Anterior Dissection in Men

Anterior dissection in men is much more problematic and prone to serious technical error. A St. Marks or similar retractor is used on the bladder. The fold in the anterior cul-de-sac is identified, and cautery is performed approximately 5 mm anterior to this fold. The seminal vesicles will then be exposed. Scissors and cautery are used to clear the seminal vesicles. At this point the anterior surface of Denonvilliers' fascia will be quite clear. The patient should be placed in the reverse Trendelenburg position to facilitate access to the plane of dissection, and the St. Marks retractor is used to lift the seminal vesicles while the operator assistant's hand pushes posteriorly on the upper part of the rectum. Bleeding from this area is controlled with either a lengthy ball-tipped coagulator or argon beam coagulation. Further separation of Denonvilliers' fascia from the prostatic capsule is best accomplished with scissors dissection (Fig. 158–11). Lengthy scissors with the fingers as a fulcrum are used to

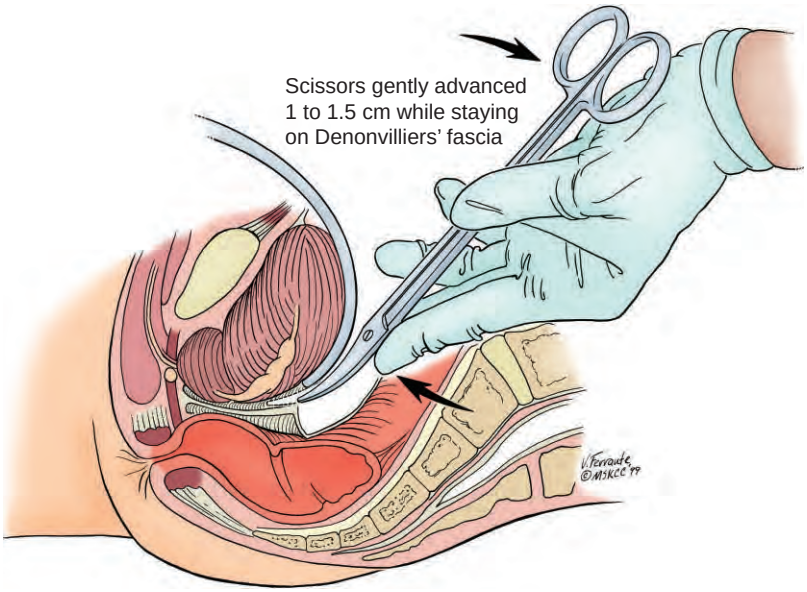

Figure 158–11. Anterior dissection in a man, with Denonvilliers' fascia separated from the prostatic capsule.

actually press aggressively against the prostate. Despite leading to certain anxiety on the part of the operating surgeon, it is actually the safest maneuver. The tips of the scissors are gently advanced 1 to 1.5 cm while staying anterior (dorsal) to Denonvilliers' fascia along the prostate capsule. A finger is used to identify the smooth prostatic capsule. Scissors are then pushed further at this point, and by spreading, the entire prostate will be cleared. While staying 1 cm off midline, the scissors are pushed further past the prostate to break the attachment of Denonvilliers' fascia with the prostatic capsule. This should not be done bluntly. At this point a finger can be used to confirm that the distal end of the urethra with the palpable catheter has been cleared. As in women, spreading with the scissors in the anterolateral plane will identify the levators anteriorly and combine it with the posterior dissection.

Defining and Dividing the Lateral Attachments

Based on the extent and laterality of the tumor, multiple sagittal planes for the lateral dissection are possible (Fig. 158–12). The most conservative involves moving medially to within the visceral fascia of the mesorectum. This is appropriate in a young man with a small superficial tumor on the opposite side. It will be the safest way to protect the sympathetic and parasympathetic nerves but is inadequate for most cancer patients. The most common dissection is along the parietal fascia, which is directly on the medial portion of the S3 nerve. For bulky tumors adherent to the side wall in which sympathetic and parasympathetic nerve trunks are intentionally sacrificed, the plane of dissection is along the vascular adventitia of the internal iliac vessels. On rare occasion, most commonly for recurrent cancer, the plane lateral to the vessels is used.

The main S3 nerve trunks are generally quite easy to identify in the first 2 to 3 cm as they exit the sacrum and,

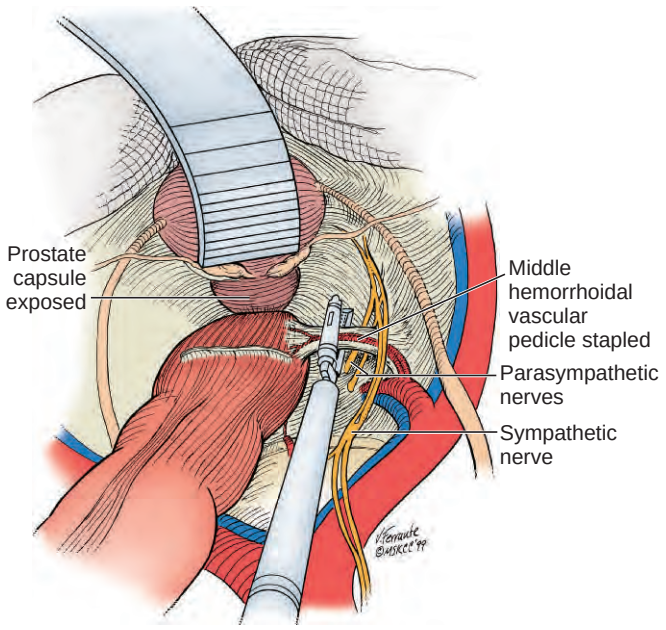

Figure 158–12. Division of the "lateral ligaments" (neurovascular pedicle) with a laparoscopic vascular stapler while protecting the autonomic nerves.

hence, easy to protect. The problematic area is the point where these autonomic trunks merge with the sympathetic nerves and then sweep anterolaterally toward the seminal vesicles. Hence, the strategy used is posterior dissection followed by anterior dissection, which leaves just the side wall under direct vision to allow clearance of these nerves. The options at this point are gentle cautery clearance, clips, and (my preference) placement of multiple vascular staples with a laparoscopic instrument, which provides bidirectional hemostasis between six rows of fine vascular staples (see Fig. 158–12).

Level of Distal Transection

At this point the rectum will be fully mobilized from the posterior, anterior, and lateral attachments. A decision where to divide the bowel and mesentery is made at this time. These are two separate issues that were discussed previously. Whichever is chosen for the individual patient, the bowel cannot be divided until it is clear of all fatty tissue. If TME has been performed, the distal 4 to 5 cm of rectum is already entirely clear and is just a muscular tube. Management of the distal portion of the bowel will then depend on whether one is going to hand-sew, staple, or perform a coloanal reconstruction. If staple reconstruction is going to be performed, a decision regarding a purse-string or "double-staple" technique[28] will have to be made. If an upper rectal cancer is being resected, some mesentery will be left. The distal part of the bowel must be clear in all patients before division.

In dealing with an early cancer, a cancer within an adenoma, or an irradiated patient who has had a complete or nearly complete response, sigmoidoscopic assessment of the actual location of the tumor should be performed at this time to clearly identify the appropriate level of transection.

Technique of Distal Bowel Management

If at all possible, before bowel division the distal part of the rectum may be irrigated free of cancer cells. There are considerable general oncologic principles to support this approach, but no randomized clinical data. Irrigation is probably less important when the patient has received full-dose preoperative radiation therapy. Before bowel division, it is important to place either a right-angle clamp or a staple line on the rectum. One should irrigate distally at that point and then place another staple line or purse-string clamp suture below this initial clamp. It serves no purpose to place a staple line or a right-angle clamp, irrigate the rectum, and then divide *above* this clamp because tumor cells will almost certainly be entrapped at the clamp or staple line. Whether saline, water, or a cytotoxic agent is used for irrigation is probably a personal preference. I use nothing more than saline to dilute out any tumor cells by irrigating with 50 ml six to eight times. Division of the distal portion of the bowel is then performed, as discussed in the next section. For surgeons who do not perform this operation on a daily basis, placement of a linear staple line across the bowel and then proceeding with the double-staple technique is probably the most reliable method. A high-quality linear stapling device that allows the pin to be placed before firing the stapler must be used (Fig. 158–13). The pin allows the stapler to be pushed aggressively down into the pelvis without the rectum slipping out the open end of the stapler. For a very low staple line, the assistant may use a fist in the perineum to push from below.

Colorectal Reconstruction

The rectum may be reconstructed with sutures or staples and with an end-to-end, side-to-end, or a colon J-pouch side-to-end technique. If suturing is performed, a Baker

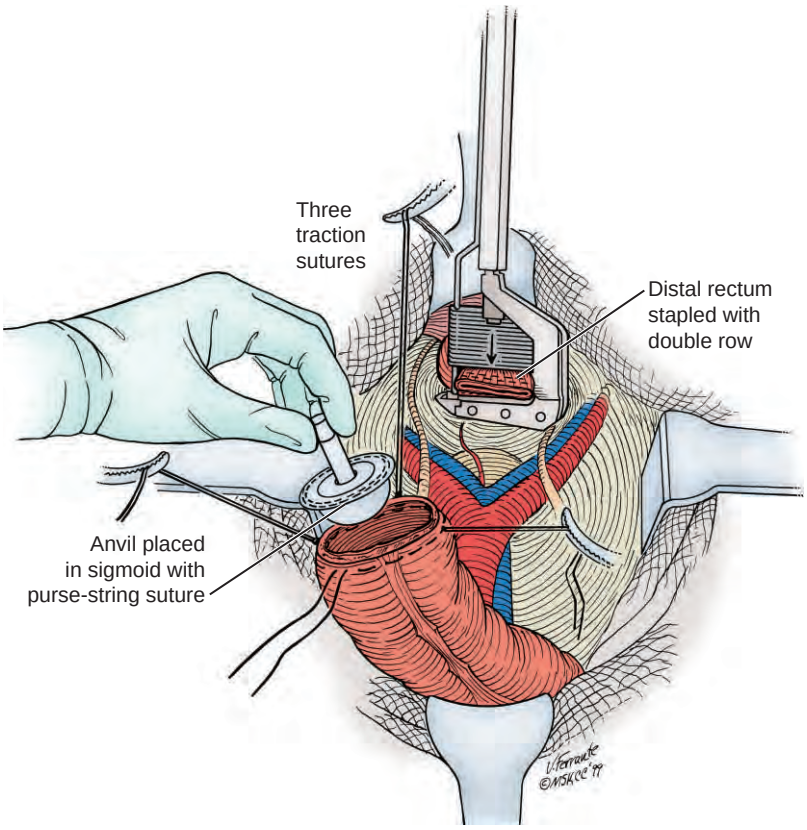

Figure 158–13. The "double-staple" technique.

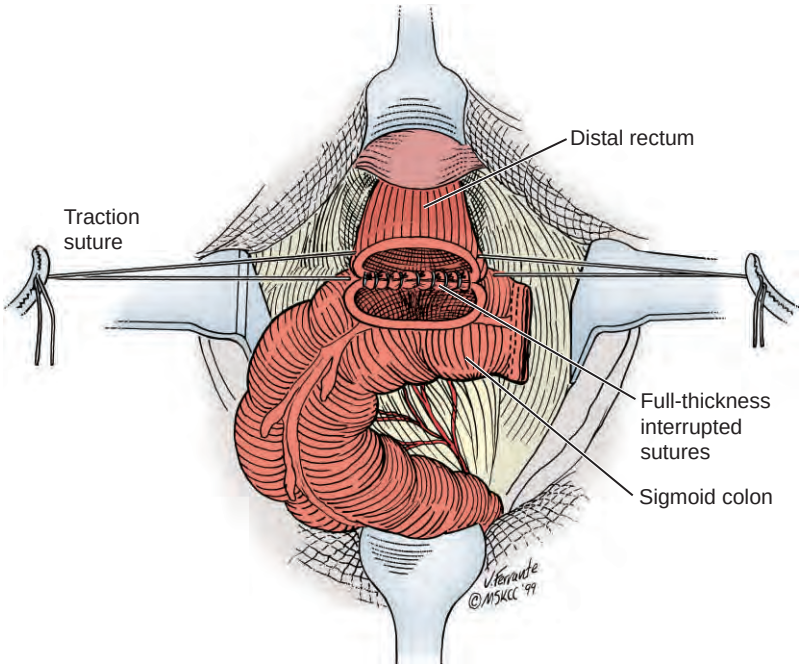

Figure 158–14. Sutured side-to-end anastomosis. This approach obviates problems with size discrepancy between the colon and midrectum.

anastomosis using a side-to-end technique is most reliable (Fig. 158–14). Below a right-angle clamp, the posterior aspect of the rectum is opened and a single layer of interrupted sutures is then placed, facilitated by a fiberoptic headlight. The bowel is then divided anteriorly, and a single layer of anterior sutures is placed. This was a traditional approach for reconstruction for many years before the advent of surgical staples, and it is highly effective with adequate visualization. The side-to-end technique obviates the size discrepancy issue. Surgical stapling with intraluminal circular staples has become the standard for most LAR procedures. If at all possible, perianal placement of the stapler is most appropriate. The preferred approach is the double-staple technique, which is described extensively in the next section.

In the absence of diverticular disease and a capacious left colon, an end-to-end technique is quite satisfactory. The largest intraluminal stapler that will comfortably fit is appropriate. It is important to determine ahead of time what the anus will accept. Although the colon may be capacious, the patient may have had an anal stricture that prohibits placement of a large stapler per anus. For patients with diverticulosis, a side-to-end technique is preferable. An increasing body of data support the use of a 6- to 8-cm colon J pouch in patients undergoing a very low reconstruction or a coloanal reconstruction. Construction of such a J pouch is described in the section on coloanal reconstruction. If low rectal reconstruction with a stapled pouch is performed, the anvil is sewn into the apex of the J, identical to a standard side-to-end approach.

Double-Staple Technique

The double-staple technique for most surgeons solves the fecal contamination problem and the size discrepancy issues associated with an end-to-end double–purse-string approach. Once the staple line has been placed across the rectum, confirmation of hemostasis is obtained, and a moist pack is left in the pelvis. The anvil is removed from the appropriately sized stapler and placed into the distal end of the bowel (see Fig. 158–13). Whether using a purse-string stapling device or a hand-sewn purse-string technique, it is important that the bowel be cleared over the edge of the anvil to avoid stapling through any vascular appendices epiploicae. Hemostasis in the pelvis is now confirmed, and the stapler is placed per rectum. The pin is opened and positioned so that it peaks out just anterior or posterior to the staple line (Fig. 158–15). Every effort should be made to avoid coming directly through the staple line because it will tear as the staples catch on the plastic bar. A long electrosurgical tip in cutting mode is used to allow the stapler pin to be advanced. The pointed pin is removed, with care taken to not puncture a sacral vein. A long Kelly clamp is used to hold the anvil pin and insert it into the stapler cartridge. Before closure of the stapler, the proximal part of the bowel is checked for the correct 360-degree rotation, and the prostate/vagina and proximal colonic appendices epiploicae are confirmed to be away from the staple line. The stapler is tightened completely, fired, and then gently removed. Figure 158–16 demonstrates the double-staple technique for a side-to-end reconstruction.

The presence of two intact “doughnuts” is confirmed. It is important to not start “spinning” the anvil because

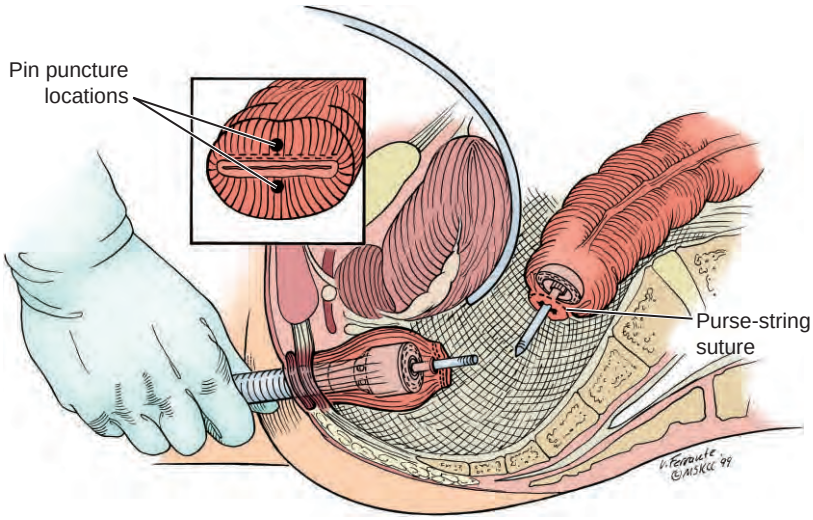

Figure 158–15. The "double-staple" technique.

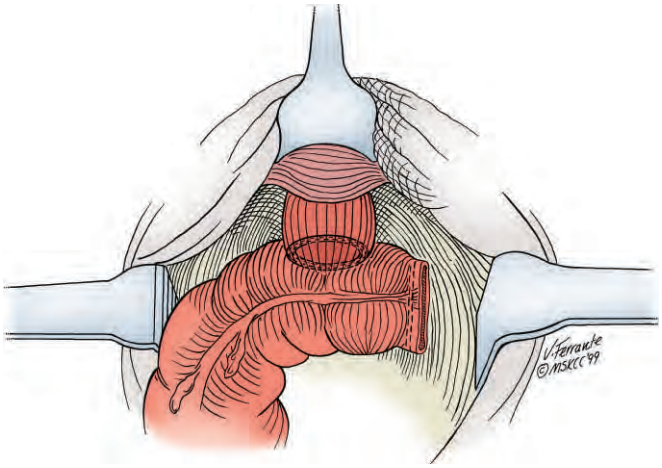

Figure 158–16. Stapled side-to-end anastomosis. The anvil is placed out the side of the proximal part of the bowel, after which the end is stapled closed. The circular staple line and the linear closure line should be approximately 2 cm apart to avoid ischemia of intervening tissue.

if there is an incomplete doughnut, one cannot identify the 360-degree location of the defect. The absence of a complete doughnut does not mandate a diversion; it is possible to have stapled with an incomplete doughnut. The reverse is also true. The anastomosis should be palpated from below and then air injected into the pelvis with saline to look for an air leak. Frequently, bubbles are trapped in the pelvis, so before injecting air into the rectum, the saline in the pelvis should be jostled to try to break up any air pockets. The operating surgeon pinches the bowel proximally to avoid filling the colon with air during this process while making sure that sufficient distention is present. If a minor air leak is noted, the test should be repeated, and if confirmed, the patient can undergo sigmoidoscopy. If there is only a minimal defect in nonirradiated patients with good bowel preparation, it is usually adequate to just temporarily divert with an ileostomy or a colostomy. Of course, if at all possible, a few sutures should be placed, but this may not be feasible. The use of excess traction on these stapled anastomoses to try to identify a defect is frequently very disruptive and could destroy the entire anastomosis. One must judge how aggressively to pursue trying to actually suture the leak. A large leak requires the placement of sutures or complete revision of the anastomosis.

A policy of routine diversion with either colostomy or loop ileostomy is not recommended. Even with the increasing use of TME, routine diversion for a low anastomosis is uncommon. At the Memorial Sloan-Kettering Cancer Center, we have a leak rate of 4% and an overall mortality rate of 0.6% with the selective use of diversion.[29] The leak rate is identical in irradiated and nonirradiated patients.

I prefer to place a closed-suction drain in the pelvis in all patients. Randomized data do not demonstrate a reduction in pelvic abscess rates, but the numbers of LAR patients in these studies are too few to reach a definitive conclusion.

POSTOPERATIVE MANAGEMENT

Routine nasogastric suction is not required. However, persistent nausea and vomiting requiring nasogastric tube placement will develop in approximately 10% of patients 2 to 3 days after surgery. In the absence of major intestinal distress, a clear liquid diet is begun on the third postoperative day, with advancement to a low-fat, low-fiber diet over the next 2 days. The pelvic drain is removed after 3 to 4 days. If daily drainage exceeds several hundred milliliters, a sample should be sent for determination of creatinine in the fluid to rule out a bladder or ureteral leak before drain removal. The urinary catheter is removed on the fifth or sixth postoperative day. Most patients are ready for discharge on the sixth or seventh day.

When a diverting stoma is present, the patient should be educated regarding management, and home nursing care every few days for the first few weeks should be

arranged. If postoperative adjuvant therapy is not required, a water-soluble contrast enema is performed before the stoma is closed at 6 to 8 weeks. If adjuvant therapy is used, closure is generally deferred.

Bowel function is frequently problematic after LAR. Cluster bowel movements are probably related to the denervation associated with mobilization of the colon and division of the inferior mesenteric artery. Frequency and urgency may be due to anastomotic stricture, neorectal spasm, or the effect of radiation. Gentle fiber supplementation after meals and antispasmodic medication before meals may be required for many months. After all chemotherapy is complete, patients should begin a low-fat, high-fiber diet. Lactose intolerance is frequently worse after surgery and chemotherapy. Perineal burning is related to fecal contamination. The use of soothing "baby wipes" after each bowel movement is crucial to avoid skin irritation. Early staple line strictures are aggressively dilated with digital examination 3 to 4 weeks after surgery and repeated monthly as needed. Late, persistent strictures may require intraluminal cautery strictureplasty; if more than 10 cm from the anus, balloon dilatation is effective. A high-fiber diet is essential after stricture dilation to maintain the lumen.

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Chapter

159

Abdominoperineal Resection of the Rectum for Cancer

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Abdominoperineal resection (APR) of the rectum, first introduced by Miles, has undergone progressive anatomic changes to evolve into the present operation.[1-3] From the original Miles resection, which probably was the equivalent of the present resection for inflammatory bowel disease, to the en bloc radical pelvic lymphadenectomy, various surgical investigators have designed operations intended to circumvent all of the local and regional (i.e., pelvic) spread that may be associated with primary rectal cancer. The operation that we describe is an APR performed according to the dissection principles of total mesorectal excision (TME) with autonomic nerve preservation (ANP).[4] Recent advances in minimally invasive surgery have allowed the greater implementation of laparoscopy to colon and rectal surgery.

INDICATIONS FOR THE OPERATION

APR is the procedure of choice for invasive carcinomas of the distal rectum, for persistent or recurrent epidermoid carcinomas of the anal canal (after initial chemotherapy and radiation), for rare lesions of the anorectum (e.g., melanoma), for sarcomas that arise from the levator ani and involve the anal canal, for locally advanced (i.e., bulky rectal tumors), for some chordomas, and for most resectable patients with recurrent rectal carcinoma. Where indicated, as in some anal and low rectal cancers, some surgeons may add either an en bloc or a separate pelvic lymphadenectomy.

PREPARATION OF THE PATIENT

Staging

It is important to stage the patient as accurately as possible. Preoperative staging should include a physical examination, flexible sigmoidoscopy documentation of the location of the tumor as measured in centimeters proximal to the anal verge by rigid proctoscopy, and other features such as the configuration of the tumor (sessile, ulcerated, exophytic, circumferential), its location along the rectal circumference, the presence or absence of extramural palpable disease (i.e., mesorectal nodes), attachment to the vagina or prostate, and whether there was prior pelvic surgery or radiation therapy. Preoperative colonoscopy or double-contrast barium enema is indicated to rule out synchronous cancers.

Additional elements of staging (e.g., complete blood cell count, liver function tests, and carcinoembryonic antigen values) and chest radiography are indicated. A computed tomography (CT) scan of the abdomen and pelvis is vital and assists in documenting the presence of distant metastases or evaluating the local extent of disease. Local CT findings or endorectal ultrasound may supplement clinical judgment in determining the use of preoperative radiation or radiation and chemotherapy.

Recent findings suggest that high-definition or high-resolution magnetic resonance imaging may be useful in defining locoregional disease prior to neoadjuvant radiation and chemotherapy and in the evaluation of treatment prior to surgery. Such studies are particularly adept at defining the relationship of direct extension or of nodal disease to the endopelvic fascia.

Preoperative Consultation with the Patient and Family

The surgeon should confer with the patient and family to explain issues such as the rationale in support of the operation, the role of APR versus sphincter preservation, the use of adjuvant therapy, the risks of surgery, and potential benefits. The patient should have a thorough understanding of the long-term consequences of APR (i.e., the nature of a colostomy) and of the possibilities

of changes or losses in both sexual and urinary function, particularly in older patients. Providing patients with appropriate reading materials and supportive consultations with enterostomal nurses or with other patients who have undergone an APR proved most helpful to their preparation. Other patient and family concerns, such as the average length of stay, home care after discharge, dietary preparation, avoidance of aspirin, and other issues, are reviewed, and written perioperative information is provided to the patient. In the age group of patients with rectal cancer, a complete preoperative medical evaluation is often necessary due to coexisting medical conditions such as heart disease, hypertension, and diabetes, among others. Autologous or family blood and sperm donations are considered elective choices, as appropriate.

Prior to operation, patients are taught coughing, deep breathing, incentive spirometry, splinting of wounds, methods of analgesia, leg exercises, and upright positioning in bed in an ongoing effort to minimize complications that can include atelectasis, pneumonia, and deep vein thrombophlebitis.

Preoperative Bowel Preparation

Mechanical bowel preparation is accomplished in the elective, unobstructed patient. A low-fiber diet is maintained for several preoperative days, and a 48-hour mechanical preparation includes the use of citrate of magnesia and bisacodyl tablets on day 2 before surgery and either a sodium phosphate solution or one-half gallon of polyethylene glycol solution with bisacodyl tablets on the day before surgery. Partially obstructed patients may benefit from longer and gentler preparation, including greater reliance on enemas. The occasional older, infirm, or obstructed patient may require hospitalization. Prophylactic cefoxitin is administered intravenously just before the incision and is repeated after 3 hours of surgery. Postoperative doses are avoided.

Position of the Patient

The operation is performed with the patient in the lithotomy-Trendelenburg position with the legs supported on Allen hydraulic stirrups, with sacral and lumbar support provided by a gel pad.[5] The popliteal fossae and the tibial tuberosities are supported and padded to avoid peroneal or tibial nerve palsies and compartment syndromes. Sequential compression boots are helpful in preventing deep vein thrombophlebitis. The perineum is draped into the sterile field, but it is kept separate from the abdominal field by a supplementary drape that may be removed intraoperatively. The anus is closed with a watertight suture to minimize contamination. The bladder is catheterized within the sterile field. If the patient has a locally advanced primary tumor (i.e., marginally respectable or adjacent organ invasion) or a recurrent tumor in the pelvis and/or has undergone extensive preoperative radiation and/or prior pelvic surgery, indwelling ureteral catheters are considered helpful during the dissection. They are not used except for the specific indications cited. In cases of recurrent or locally advanced disease requiring lengthy dissections, consideration may be given to leaving the patient in a supine position, shifting to stirrups only when necessary, to avoid compartment syndromes.

ABDOMINOPERINEAL RESECTION FOR ADENOCARCINOMA OF THE RECTUM

APR is thought of by most surgeons as the operation performed when there simply is no sphincter-preserving option available due to distal location of the primary tumor. Evidence suggests that in most instances, APR is the appropriate operation for distal rectal cancer and is not just an amputation of the rectum as a last resort. During the 1990s, sufficient evidence accrued to suggest that low rectal cancer (0 to 5 cm from the anal verge) represents a biologically more aggressive disease than cancer of the mid rectum.[4] It has been repeatedly demonstrated in the surgical literature that the 5-year survival rate of patients requiring an APR is significantly less than the survival rate of patients who can be treated with sphincter preservation.[4,5] Clinicopathologic findings support these observations. Owing to access to the systemic circulation (via the internal iliac vessels), the incidence of pulmonary and other systemic metastases can significantly outweigh the incidence of liver metastases.[4]

Lymph node clearing studies demonstrate that compared with patients with mid rectal cancers, patients with low rectal cancer have a higher incidence of positive mesorectal lymph nodes, a higher incidence of lateral pelvic node involvement, a higher overall incidence of pelvic recurrence in Dukes' B and C cases, and a lower 5-year survival rate.[6] A higher incidence of pulmonary metastases and a proportionately lower incidence of liver metastases are observed than are seen in cases of mid rectal cancer, indicating a higher likelihood of low rectal cancer spreading systemically via the internal iliac vessels, as opposed to the liver via the inferior mesenteric circulation.[4] Adverse pathologic findings (e.g., poor differentiation, lymphatic vascular invasion, perineural invasion, and non-nodal implants) are also more common in the mesorectum of patients with low rectal cancers.[7] Thus, in patients with low rectal cancers, APR may prove to be the best means of clearing the pelvis of all regional cancer specifically and not just an amputation that is based on the inability to perform a low anterior resection (LAR). Other pathologic observations of the contents of the mesorectum support complete removal of the mesorectum, for at least 5 cm beyond the distal edge of the primary tumor in conjunction with any rectal excision, regardless of the height of the lesion.[6] Careful attention to the issues that govern the complete resection of all pelvic disease is warranted by these observations.

Hida et al. have demonstrated that 20% of patient's with T3 lesions harbor lymph node metastases as far as 4 cm distal to the lowest palpable edge of the tumor.[8]

PRINCIPLES OF TOTAL MESORECTAL EXCISION WITH AUTONOMIC NERVE PRESERVATION

The principles of TME have been extensively reviewed elsewhere.[5,9,10] The overwhelming majority of regional disease related to the spread of rectal cancer is contained within the mesorectum,[5-8] which is defined by the boundaries of the visceral layer of the pelvic fascia.[7] The goal of surgery for rectal cancer, *whether sphincter preserving or not,* is the resection of the rectum and the mesorectum as a single unit, contained within the visceral layer of the pelvic fascia, with intact circumferential margins uninvolved by cancer. Although there has been professional interest in the extent of resection for years, including issues such as high ligation and the question of pelvic lymphadenectomy, the most important focus of surgical standards in rectal cancer is the need to adopt a uniform, standardized extent of pelvic dissection necessary to accomplish a resection of all regional disease encompassed within negative or uninvolved circumferential margins, an R0 resection. The more experience that is gained worldwide, the clearer will be the evidence that the results of TME as a standardized operation for rectal cancer contrast sharply with those of nonstandardized operations. In a multisurgeon series[11] from the University of Leyden that involved consecutive, unselected patients with Dukes' B or C rectal cancers, TME was associated with a 69% 5-year survival rate versus 42% for nonstandardized resections, and the 5-year incidence of pelvic failure after TME was 8% versus 40% after nonstandardized operations. Other studies have produced similar results.[5,12,13]

To accomplish this goal, the surgeon must become familiar with a precise sharp dissection along the plane that separates the *visceral* from the *parietal* layers of the pelvic fasciae, producing the specimen of rectum and mesorectum with an intact and uninvolved visceral layer of the fascia, a dissection that preserves the autonomic nervous structures of the pelvis. Some have referred to this plane using descriptive adjectives, such as the "holy plane" (Heald) or the "extrafascial plane" (Hill), but in view of the fact that it is the *only* pelvic areolar plane that separates visceral from parietal structures, we prefer to describe this plane as the concentric areolar tissue plane that is found outside of the contours of the visceral layer and medial to the parietal layers of the pelvic fascial planes that cover the autonomic nerves plexuses (Fig. 159–1). In a cross-sectional schematic view of the pelvis, this plane is the equivalent of one of the rings in a target, with the rectum and mesorectum located centrally.

There are several key technical points associated with the successful accomplishment of this dissection, as listed here and discussed in the following sections:

1. Initial entry into the retrorectal space
2. Identification of the hypogastric nerves and the pelvic autonomic nerve plexuses (PANPs)
3. Separation of the posterior visceral compartment from the anterior visceral compartment (e.g., the rectovaginal septum in the female and Denonvilliers' fascia in the male)[14]
4. The "lateral ligaments" and the pelvic splanchnic or sacral parasympathetic nerves
5. Mobilization of the distal rectum in relation to the levator ani (i.e., complete mobilization of the rectum)
6. In the case of APR, the perineal dissection

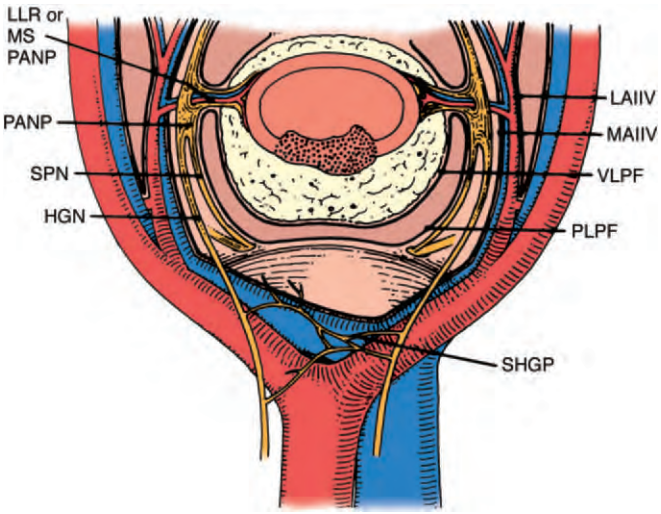

Figure 159–1. A cross section of the rectum through the mid pelvis outlining the various layers of the pelvic fasciae. VLPF and PLPF, visceral and parietal layers of the pelvic fascia, respectively; MAIIV and LAIIV, medial and lateral adventitiae of the internal iliac vessels, respectively; LLR or MS PANP, so-called lateral ligament of the rectum, or the medial segment of the pelvic autonomic nerve plexus (PANP); SPN, sacral parasympathetic nerves; HGN, hypogastric nerves; SHGP, superior hypogastric plexus. (From Enker WE, Kafka NJ, Martz J: Planes of sharp dissection for primary, locally advanced, or recurrent rectal cancer. Semin Surg Oncol 18:19, 2000.)

Initial Entry into the Retrorectal Space

The inferior mesenteric artery (IMA), the sigmoid mesentery, and the sigmoid colon have been divided, and the "rectal" specimen is held upward and forward under traction. Just posterior to the superior rectal veins and artery, the plane between the hypogastric nerves and the outer edge of the mesorectum is entered, separating retroperitoneal from mesenteric structures at the level of the sacral promontory. From here distally, the pelvic dissection is in progress and is performed entirely using sharp technique, along with traction and countertraction at all levels of the dissection, until the anal hiatus of the levator ani is reached. The sine qua non of rectal cancer surgery is complete mobilization of the rectum. The mesorectum and the hypogastric nerves are separated from each other, circumferentially (Fig. 159–2). Dissection with a medium-length pair of Metzenbaum scissors is most expedient, although in the teaching setting, dissection with a right-angle clamp and cauterization of all small branches of the hypogastric nerves leading from

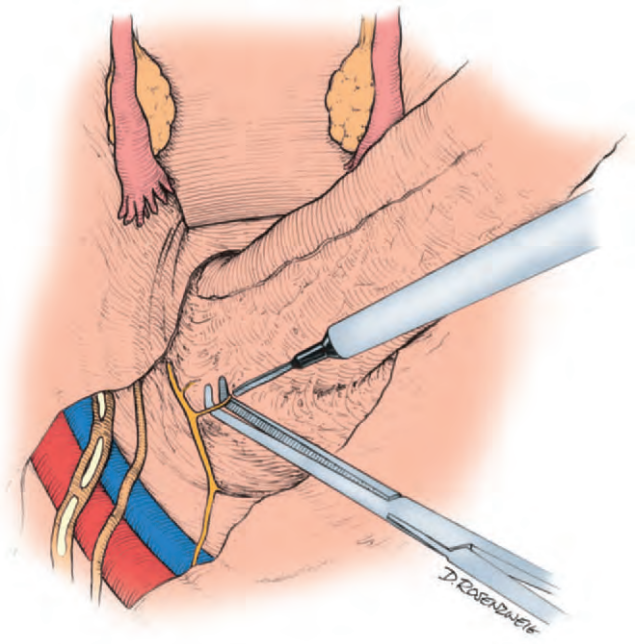

Figure 159–2. Dissection between the left hypogastric nerve and the visceral layer of the pelvic fascia. Separation of these structures allows one to enter the plane between the visceral and the parietal layers of the pelvic fascia, proceeding caudad. (From Enker WE: Total mesorectal excision with sphincter and autonomic nerve preservation in the treatment of rectal cancer. Curr Tech Gen Surg 5:1, 1996.)

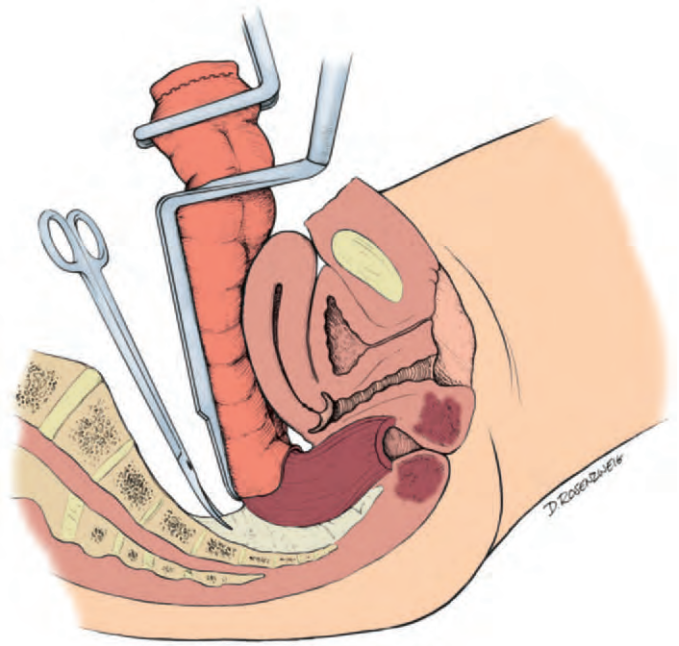

Figure 159–3. The rectosacral ligament is found midway down along the curvature of the sacrum. When sharply divided, the integral mesorectum and the rectum remain intact, and the node-bearing fat is not violated. Once the ligament is sharply divided, the distal pelvis is much easier to dissect sharply. (From Enker WE: Total mesorectal excision with sphincter and autonomic nerve preservation in the treatment of rectal cancer. Curr Tech Gen Surg 5:1, 1996.)

the main trunk to the mesorectum are commonly practiced. To avoid injury to the hypogastric nerves, the surgeon must appreciate that these nerves routinely enter the outermost layer of the visceral fascia at the level of the rectosigmoid, only to diverge laterally again toward the pelvic side wall.[15] The dissection continues, distally, with a deep St. Mark's retractor holding the rear of the mesorectum forward, while the assistant simultaneously maintains upward traction on the specimen.

At this point, the retrorectal space is open between the lateral ligaments. At or slightly above the level of S3, in the midline, one encounters the rectosacral ligament. This structure is divided sharply (Fig. 159–3). This important act constitutes one of the major differences between TME and conventional surgery, as the surgeon performing a conventional resection is dissecting down the retrorectal plane bluntly and encounters the rectosacral ligament as an obstruction to further progress. To avoid disrupting the presacral venous plexuses, a surgeon moves the bluntly dissecting hand forward, often rupturing instead, into the mesorectum just where positive nodes or other pathologic findings are most likely to be found: parallel to or proximal to the level of the primary tumor in the rectum.[7] A portion of the violated mesorectum remains, attached to the sacrum, and constitutes the nidus for persistent (i.e., "recurrent") cancer that presents as a local recurrence, clinically within 2 years.[16] By contrast, in TME, all dissection is performed sharply, and the sharp division of the rectosacral ligament ensures that the mesorectal specimen remains intact as well as surrounded by the visceral layer of the pelvic fascia as one passes this point in the dissection. After the rectosacral ligament is divided, the pelvis opens widely to view distally, and further elements of dissection become possible under direct vision. Dissection is facilitated by a deep St. Mark's retractor. In cases where a sphincter-preserving operation was advisable, this same hindrance to further blunt dissection at the level of the rectosacral ligament frequently prompts a decision to perform an APR, whereas further sharp dissection down the presacral plane would have mobilized the rectum sufficiently to perform the sphincter-preserving operation. The TME dissection is much easier and more open to view in the gynecoid pelvis.

The Hypogastric Nerves and PANPs

As the nerves are dissected away from the mesorectum, the complete course of the hypogastric nerves becomes evident, leading to the PANP, the so-called lateral ligament (Fig. 159–4). As the posterior dissection reaches the level of S3, one may observe the first views of the anterior nerve roots of the parasympathetic nerves as they exit from the sacral foramina, bilaterally. Particularly in the gynecoid pelvis, an antegrade dissection of these nerves anterolaterally to the PANPs may be possible and expedient. More commonly, particularly in the male

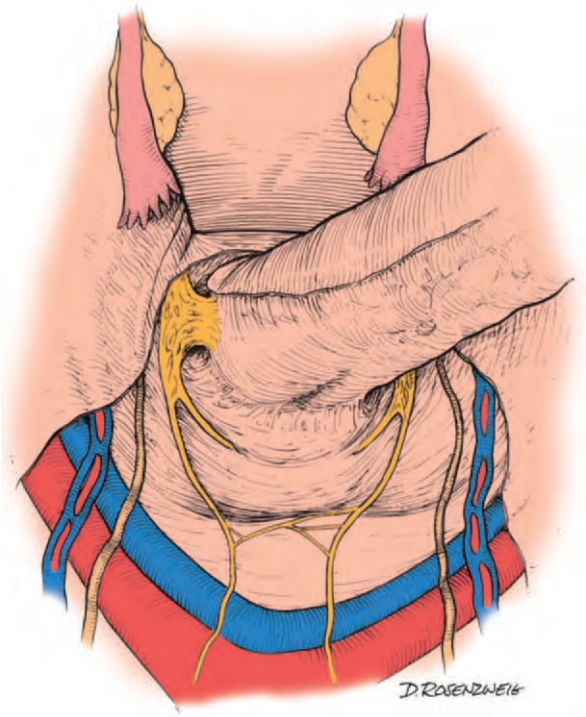

Figure 159–4. Circumferential sharp dissection frees the visceral from the parietal layers of the pelvic fascia. Included within the most medial layer of the parietal fascia are the pelvic autonomic nerves and the plexuses. The medial segment of the plexus is a neurovascular bundle to the rectum, the so-called lateral ligament. This may be divided sharply along the outer edge of the mesorectum, preserving the autonomic nerves and sexual and urinary functions. (From Enker WE: Total mesorectal excision with sphincter and autonomic nerve preservation in the treatment of rectal cancer. Curr Tech Gen Surg 5:1, 1996.)

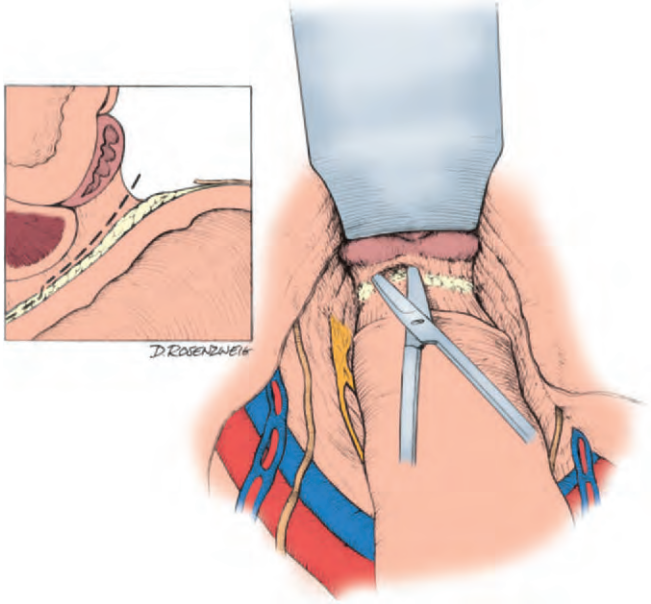

Figure 159–5. The anterior dissection in the pelvis of a male is facilitated by a St. Mark's retractor. The dissection begins between the seminal vesicles and the Denonvilliers' fascia *(inset)* and returns to the rectoprostatic space, distal to the junction of Denonvilliers' fascia and the prostatic capsule. (From Enker WE: Total mesorectal excision with sphincter and autonomic nerve preservation in the treatment of rectal cancer. Curr Tech Gen Surg 5:1, 1996.)

pelvis, one must first shift to the anterior dissection between rectum and seminal vesicles, to surround the rectum/mesorectum with dissected spaces and leave the dissection of the sacral nerves and the so-called lateral ligaments (i.e., the PANP) to a later point.

Separation of Anterior and Posterior Compartments

Forward or anterior traction is now applied to the genitourinary tract. Often, the hand-held St. Mark's retractor proves to be superior to the self-retaining retractor at this point in the dissection, providing both upward and forward retraction. In women, upward traction on the uterus or gently held Allis clamps on the vagina may also help define the rectovaginal septum.

Countertraction is maintained by downward (i.e., posterior) pressure on the anterior rectum and anterior traction on the vagina, seminal vesicles, and so on. For optimum benefit, the fingertips provide countertraction within millimeters of the site to be sharply dissected. If the peritoneum of the cul-de-sac has not been fully incised, it is completely incised now. The plane between the rectum and the genitourinary tract is developed sharply. In the case of the female pelvis, sharp dissection leaves a nonviolated full-thickness wall of the vagina with intact blood supply. Unless the vagina needs to be sacrificed as an involved adjacent organ, the vascularity of the posterior vaginal wall must not be disturbed by an ill-conceived sense of radicality, namely, dissection within the wall of the vagina to obtain a "wide" anterior margin. A late fistula may occur due to necrosis. The dissection continues down to the pelvic floor or the vaginal hiatus in the levator ani.

In the male patient, the technique of dissection continues in the same manner. The anterior plane is begun by incising the cul-de-sac, and after both seminal vesicles are outlined, the plane of dissection shifts anteriorly to encompass Denonvilliers' fascia until the junction of Denonvilliers' fascia and the prostatic capsule. Further dissection continues distally between the mesorectal fat and the prostate capsule, staying as wide as possible anteriorly (Fig. 159–5).

"Lateral Ligaments"

After the anterior and posterior dissections are completed, the remaining dissections are lateral and anterolateral. The retraction is changed to provide the surgeon with the optimal view of the lateral pelvic side wall.

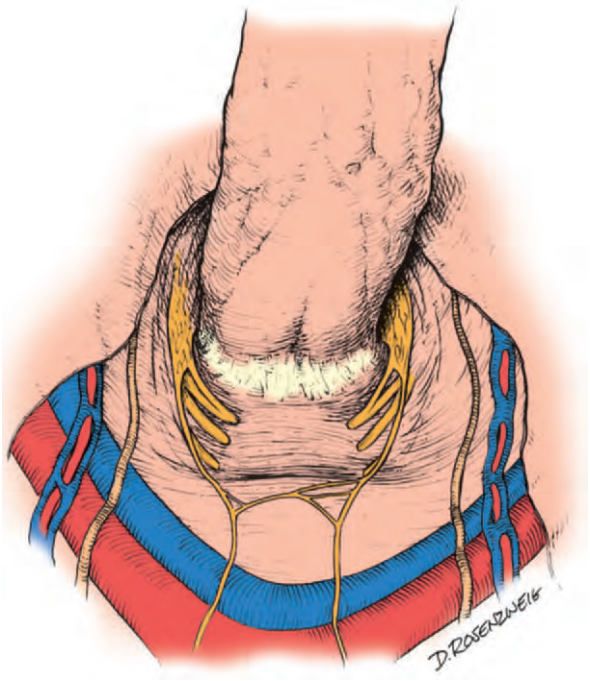

Figure 159–6. The neurovascular bundle to the rectum has been divided, the visceral layer of the fascia is intact overlying the back wall of the mesorectum, and the pelvic autonomic plexuses remain intact. (From Enker WE: Total mesorectal excision with sphincter and autonomic nerve preservation in the treatment of rectal cancer. Curr Tech Gen Surg 5:1, 1996.)

Excellent lighting is needed, as are extra-long instruments, including suction cannulas (e.g., Cooley), DeBakey forceps, and dissecting instruments. The rectum is retracted medially by the first assistant. On either side of the table, the surgeon (who is ipsilateral) dissects, while the assistant retracts toward himself or herself, providing visibility of the edge of the mesorectum and the dissection plane. All dissection is performed sharply, under direct vision, with careful hemostasis. The dissection is performed between the lateral edge of the mesorectum and the medial edge of the PANP, preserving the intact plexus. The goal is to identify both the medial segment of the lateral ligament and from the lateral segment, dividing only the medial segment containing the neurovascular branches of the PANP and the middle rectal artery, which are the only structures headed directly to the rectum. This dissection preserves the lateral portion of the PANP that is integrating the fibers of the pelvic autonomic nervous system into functional bundles. These bundles head anteriorly to supply the genitourinary system for both sexual and urinary functions (Fig. 159–6).[17] As the dissection continues, the middle rectal artery is often encountered where it penetrates through the PANP. The sacral parasympathetic nerve or nerves may be observed leading directly from the sacral foramen of S3 to the PANP along the pelvic side wall and should be preserved unless there is a need to take the nerves to achieve a tumor-free margin. Once the dissection has separated the edge of the mesorectum from the PANP, the levator ani become visible, approximately 3 to 4 cm distally. The same dissection is completed on the opposite side of the pelvis, optimally by switching who dissects and who retracts, before finalizing the pelvic or abdominal side of the procedure with complete mobilization to the pelvic floor.

Distal Rectal Mobilization

At this point, the rectum, which has been circumferentially dissected down to the levator ani, may be elevated out of the pelvis. It assumes a completely straight line from the anal opening to the sigmoid colon. The final attachments of the mesorectum to the levator ani, particularly in the lower midline posteriorly, are divided sharply. An occasional bleeder may be grasped with forceps and cauterized, where the visceral and parietal layers of the pelvic fascia seem to fuse in the midline. This fusion plane is the only known remnant of Waldeyer's fascia, as used in current nomenclature.[15,18] In the patient with a mid rectal cancer, which is treatable by low anterior resection, the rectum is divided at this point in the operation. In the patient with a low rectal cancer, the abdominopelvic portion of the operation ends here, and the surgeon proceeds with the perineal phase of the operation. Some technical aspects of the perineal dissection (see later), such as handling the specimen as a guide to dissection, do not apply where a two-team approach is used.

The Laparoscopic Abdominoperineal Resection

Advances in minimally invasive surgery have allowed the application of the laparoscopic approach to distal rectal cancers and recurrent anal canal lesions that require an APR. The extraperitoneal location of the rectum and the need for minimal manipulation of the tumor via the abdomen, the absence of an anastomosis, and the increased visualization of the pelvic dissection are potential advantages of the laparoscopic approach. Patients with recurrent rectal cancer or adjacent organ involvement should be excluded from this technique.

The safety of this technique has been studied. Overall survival, isolated recurrence rate, and disease-free survival rates have been similar. No differences in distance to lateral margin and the number of lymph nodes harvested have been seen. Advantages observed include shorter length of stay, decreased time to ambulation, and earlier return to normal activities of daily living for patients undergoing laparoscopic colorectal surgery.[19,20] Complication rates involving the laparoscopic technique involve increased perineal wound infections rates have been observed.

Technique The patient is positioned in the lithotomy position in Allen, or "yellow fin," stirrups. These allow for the maximal versatility in leg position. The procedure begins with the knee height in the maximal downward position. The abdomen is entered via a sub umbilical 10-mm trocar. A 5-mm trocar is placed in the left lower quadrant two fingerbreadths superior and medial to the

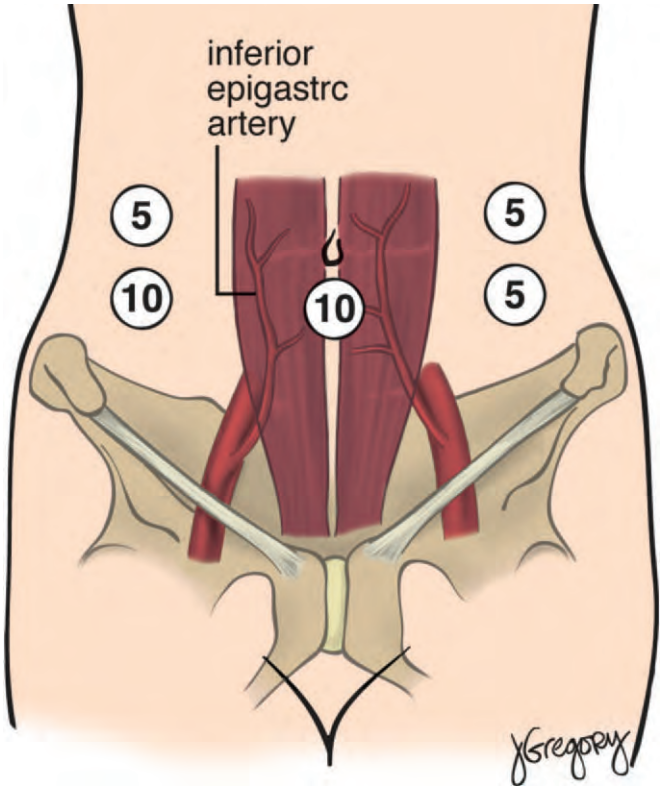

Figure 159–7. Trocar placement for the laparoscopic abdominal perineal resection. The inferior trocar is placed two fingerbreadths superior and medial to the anterior iliac spine.

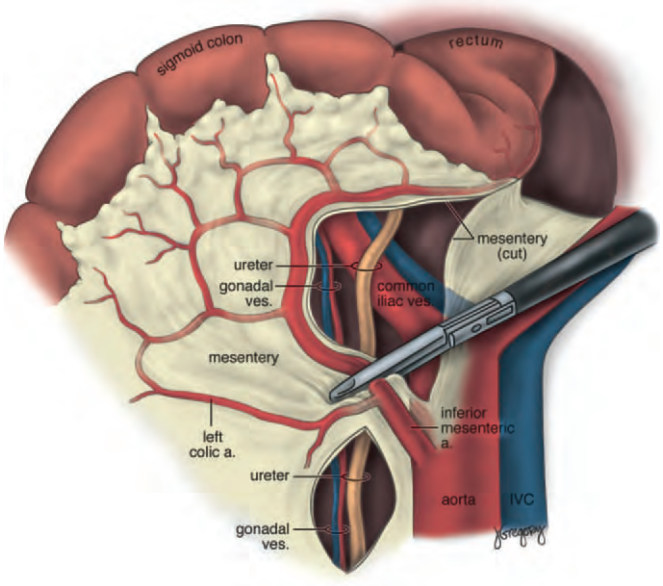

Figure 159–8. The division of the vascular pedicle is performed about 2 cm distal to the origin of the inferior mesenteric artery. The vascular pedicle may be divided with the LigaSure device or Endo GIA vascular staplers. VC, vena cava.

anterior iliac spine. This is to avoid injury to the inferior epigastric vessels. In the obese patient with a widened distance between the iliac crests the trocar benefits from a slightly increase in medial position. An additional 5-mm trocar is placed four fingerbreadths superior. In the right lower quadrant a 12-mm trocar is placed two fingerbreadths superior and medial to the anterior iliac spine, with an additional 5-mm trocar placed superior to this (Fig. 159–7).

The procedure begins with a thorough inspection of the abdomen for evidence of metastatic disease. The peritoneal surfaces, liver, and pelvic sidewall are inspected. The steps of the procedure can be outlined as follows:

1. Vascular division of the inferior mesenteric vessels
2. Division of the sigmoid colon
3. TME of the rectum
4. Creation of the colostomy
5. Completion of the proctectomy via the perineum

The initial dissection begins with the ventral and lateral traction of the sigmoid colon with a bowel grasper and the identification of the IMA. The overlying peritoneum should be scored with the mesentery separated off the retroperitoneum from the level of the sacral promontory. The left ureter and gonadal vessels are identified. Their identification can be facilitated by lighted ureteral stents in one's early experience with the medial-to-lateral dissection approach. The division of the vascular pedicle is performed about 2 cm distal to the origin of the IMA. The vascular pedicle may be divided with the LigaSure device or Endo GIA vascular staplers (Fig. 159–8). The inferior mesenteric vein is similarly identified in the medial-to-lateral mobilization of the sigmoid mesentery and divided at the corresponding level.

The second stage of the operation involves the division of the sigmoid colon. After dividing the vascular pedicle, the remaining mesentery is mobilized to the white line of Toldt. The white line is incised and the remaining left colon is mobilized. The site of division is identified and a window is created posterior to the colon wall. The bowel is divided with the Endo GIA stapler. The remaining mesentery is then divided.

The peritoneal attachments of the rectum are incised circumferentially. This includes the anterior dissection between the Denovilliers' fascia in males and the posterior wall of the vagina in females. The rectum is then mobilized along the areolar tissue plane that is found outside of the contours of the visceral layer and medial to the autonomic nerves plexuses within the parietal layers of the pelvic fascial planes as described previously. The laparoscopic technique allows for enhanced visibility of these vital structures. Additional retraction may be obtained via the placement of an extracorporeal Prolene suture into the pelvis or by the use of a fan retractor. This Prolene suture is placed with a Keith needle via a suprapubic puncture site. This may be useful in securing a large uterus, providing enhanced anterior retraction of the rectum. The pelvic dissection may be facilitated by a Pfannenstiel incision in larger tumors and in the difficult android pelvis. This allows for the preservation of much

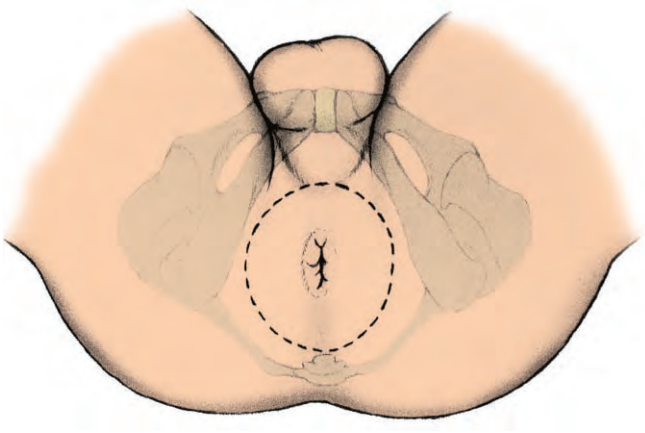

Figure 159–9. The topographic landmarks for the perineal dissection (see text). (Adapted from Enker WE: Cancer of the rectum: Operative management and adjuvant therapy. In Fazio VW [ed]: Current Therapy in Colon and Rectal Therapy. Ontario, BC Decker, 1990, pp 120-130.)

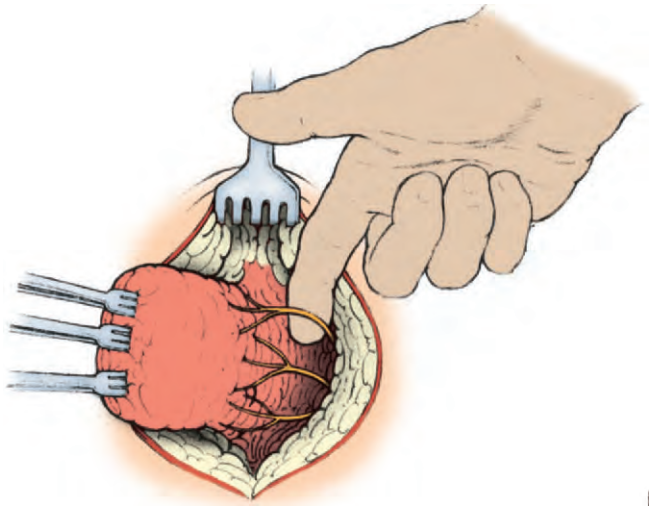

Figure 159–10. The radial branches of the pudendal nerves are located running toward the rectum across the ischiorectal space. They may be appreciated as violin strings by palpation between thumb and index finger. (Adapted from Enker WE: Cancer of the rectum: Operative management and adjuvant therapy. In Fazio VW [ed]: Current Therapy in Colon and Rectal Therapy. Ontario, BC Decker, 1990, pp 120-130.)

of the advantages of the laparoscopic procedure while ensuring an adequate mesorectal dissection.

After completion of the abdominal portion of the procedure, the colostomy may be created via a separate circular incision in the left rectus sheath. Prior to violation of the peritoneum the distal colon should be grasped using a right-sided bowel grasper and delivered into the stoma site incision. The colon should not be matured until the completion of the procedure. The pneumoperitoneum should be re-established and may require the placement of Vaselinized packing at the stoma site to prevent excessive air leakage. The perineal operator can then complete the proctectomy and delivery of the specimen.

The Perineal Dissection

The perineal dissection is based on several goals: the complete resection of the rectum and the mesorectum, the complete resection of the surrounding fat of the ischiorectal space, and the most lateral (i.e., widest) circumferential resection of the levator muscles possible in the particular patient. Learning or performing a proper perineal dissection can be a daunting chore in the android pelvis.

The perineal phase begins with an outline of the cutaneous incision. The landmarks for complete resection are the perineal body anteriorly, the *palpable* tip of the coccyx posteriorly, and the medial *palpable* edges of the ischial tuberosities laterally (Fig. 159–9). The entire dissection may be performed using the cautery device, and few if any sutures are used for hemostasis, except in relation to the puborectalis muscles or the prostate capsule. The incision is made in the skin and deepened to the subcutaneous fat, circumferentially. The two posterior quadrants are incised first, so minor blood loss from the upper half of the incision does not obscure the field. The skin edges of the specimen are grasped in the midline with Lahey clamps, which may be tied together with a sponge or an umbilical tape.

Self-retaining retractors or skin-retracting sutures are used where possible. A T-shaped prototype of a self-retaining retractor for the perineal dissection has been used in conjunction with the Thompson retractor system. Alternatively, widely placed sutures retract the skin and subcutaneous tissues radially.

The dissection is deepened until the puborectalis muscles are noted. The transverse perineus muscle is superficial. The ischiorectal fat is entered with a clamp just below the puborectalis muscles until the levator ani are reached. A finger follows this path and then curls dorsally, toward the coccyx. Anterior to the finger, strong bands, or "violin strings," may be felt traversing the ischiorectal space bilaterally (Fig. 159–10); these represent the radial branches of the pudendal nerves, whose fibers are going to the anal sphincter. Each nerve is accompanied by its blood supply, and when cut, bleeding from these vessels can suffuse through the fat and obscure the field. A clamp is passed under each of these vessels, identifying it and separating it from the surrounding fat. The vessel and nerve are grasped in another clamp and cauterized and divided medial to the prominent eschar (Fig. 159–11). When all of the branches have been divided circumferentially, the levators may be exposed and the dissection proceeds to the next step.

The anococcygeal raphe is divided, and the anococcygeal ligament is dissected to the coccyx. The levator attachment to the coccyx is divided sharply, and the pelvis is entered, signaled by a small collection of blood or fluid. The levators are swept over the index finger and

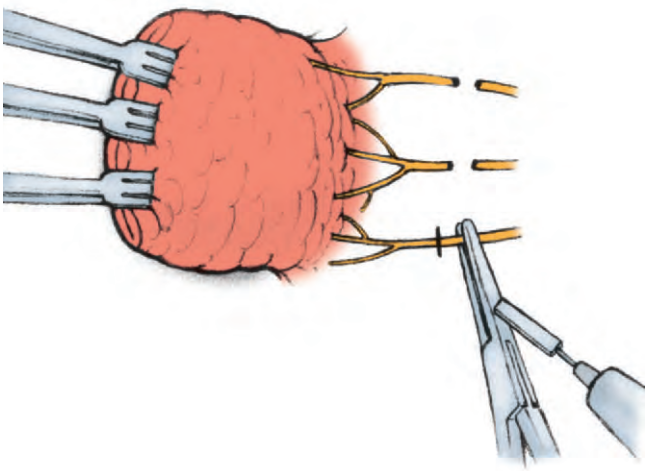

Figure 159–11. The radial branches of the pudendal nerves are isolated and cauterized, avoiding the usual step of ligation of the ischiorectal fat. (Adapted from Enker WE: Cancer of the rectum: Operative management and adjuvant therapy. In Fazio VW [ed]: Current Therapy in Colon and Rectal Therapy. Ontario, BC Decker, 1990, pp 120-130.)

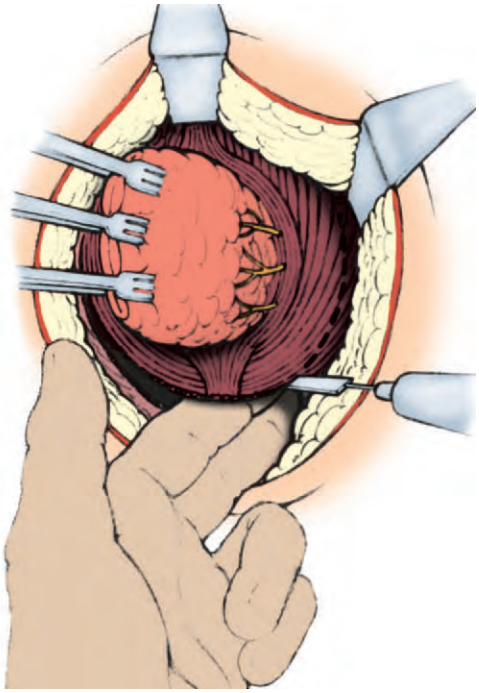

Figure 159–12. The levator ani muscles are divided with a finger inside the pelvis. The levators are divided from the 2 o'clock to the 10 o'clock position as widely as the pelvis will allow. The defect should not be small enough to close by approximating the levator muscles. (Adapted from Enker WE: Cancer of the rectum: Operative management and adjuvant therapy. In Fazio VW [ed]: Current Therapy in Colon and Rectal Therapy. Ontario, BC Decker, 1990, pp 120-130.)

divided as close to the pelvic side wall as possible (Fig. 159–12). Although the levators may be preserved for pelvic floor closure in surgery for inflammatory bowel disease, in cancer surgery they are divided widely and should not be available for pelvic floor closure. The levator ani are a presumed pathway for lymphatic spread for rectal carcinomas to the iliac lymph node chain. Once the levators have been divided from the 2 o'clock to the 10 o'clock position, the retrorectal space is open. The specimen may now be passed from the abdominal to the perineal dissector via the posterior opening. The dissection continues anteriorly, guided by the easier handling that the delivered specimen allows. If possible, the rectum and the prostate are separated in the midline using a blunt instrument such as a Kelly clamp. The final attachments of the rectum to the perineum are the puborectalis muscles, which are the medial fascicles of the pelvic diaphragm (Fig. 159–13). While they are coronally oriented in the intact pelvis, they are obliquely situated in the perineum, when the specimen is passed to the perineum. The puborectalis muscles may be divided with the cautery, or with clamps, and if needed, heavy absorbable sutures may be used to each of four puborectalis heads.

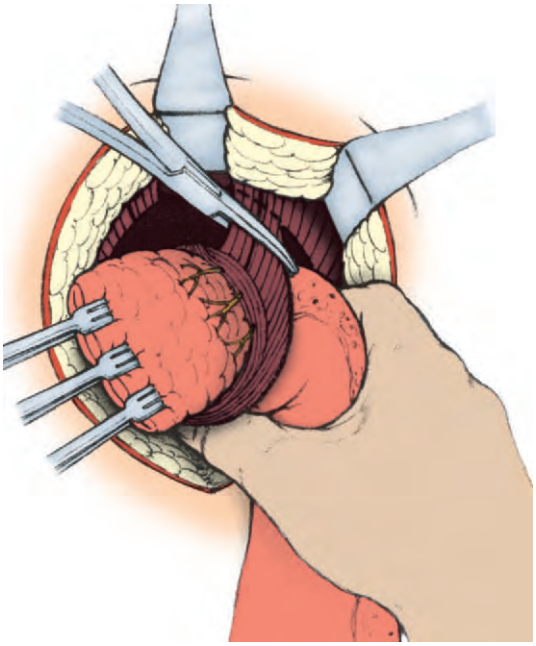

Figure 159–13. The puborectalis muscles are divided, and the specimen can be removed. (Adapted from Enker WE: Cancer of the rectum: Operative management and adjuvant therapy. In Fazio VW [ed]: Current Therapy in Colon and Rectal Therapy. Ontario, BC Decker, 1990, pp 120-130.)

Colostomy

The end sigmoid colostomy is constructed using a transrectus defect in the abdominal wall. The skin opening of the colostomy has been optimally chosen and marked by the surgeon before the operation with the patient sitting upright to avoid skin folds. A superior method for avoiding parastomal hernia is the extraperitoneal colostomy, ascribed to Goligher, in which the sigmoid colon is tunneled out to the abdominal defect extraperitoneally. The skin and subcutaneous tissues are excised

as usual, and the anterior rectus sheath is either excised or cut in the cruciate fashion. The rectus muscle is split, and the posterolateral corner of the rectus fascia is identified. The edge of the rectus sheath is opened gently and carefully by spreading with a clamp, and a plane is created between the transversalis fascia and the peritoneum. If a defect is created in the peritoneum, it may be repaired. The colon is "tunneled" out through this channel, and the peritoneum is sutured to the psoas fascia. The colostomy is brought out so that it rests on the abdominal wall with no tension. The mucocutaneous junction is matured at the end of the case, after skin closure. If an extraperitoneal colostomy is not possible, the lateral defect is closed securely to avoid an interval peristomal hernia.

Closure of the Pelvic Floor and Biologic Spacers

After hemostasis and irrigation, the perineal floor is closed in two layers—one of Scarpa's fascia and the other of dermis or dermis and skin—using absorbable sutures. Particularly in the irradiated pelvis and perineum, an attempt is made to fill the pelvis with an omental pedicle, importing neovasculature or fresh blood supply to promote healing in the irradiated field. The cecum may be used frequently to fill the pelvis excluding the small bowel. In the nonirradiated field, a rectus muscle flap is becoming increasingly useful as a biologic spacer before postoperative irradiation. In the irradiated patient or in the patient who is undergoing intraoperative irradiation, a rectus muscle or myocutaneous flap serves as a means of excluding the small bowel from the pelvis and as a source of neovasculature as well. In cases requiring resection of the posterior wall of the vagina, reconstruction by a rectus myocutaneous flap also provides a functional vaginal reconstruction as well as perineal closure, with dramatic healing results. Closed-suction drainage is achieved by leaving round Silastic drains in the pelvis, which are brought out along the lower abdominal wall. In the absence of new blood supply, healing of the irradiated perineum remains a problem, with breakdown of the wound being a common event. Healing, however, does take place eventually and does not interfere with the resumption of systemic chemotherapy. Unlike the persistent perineal wound healing problems associated with Crohn's disease, these wounds do heal, but they may represent a continuing problem of an uncomfortable, open wound for several months.

Adjacent Organ Involvement

About 10% of rectal cancers exhibit some form of adjacent organ invasion, involvement, or adherence, which is sufficient to raise concerns about the circumferential margins. Resection along the standard planes could cut across tumor, violating all principles of curative therapy. This event has a catastrophic outcome, significantly raising the local recurrence rates and dramatically reducing the chances of survival to about one fourth of the survival rate that would be predicted by stage alone.

Proper management of adjacent organ involvement requires en bloc resection of the adjacent organ and reconstruction, wherever possible. Although the entire subject is beyond the scope of this chapter, examples of this approach include the en bloc posterior vaginectomy and reconstruction of the posterior vaginal wall and perineum and the varying degrees of pelvic exenteration. Reconstruction is successfully accomplished by the use of a rectus myocutaneous flap.

SUMMARY

APR of the rectum performed in accordance with the principles of TME and autonomic nerve preservation is the operation of choice for low-lying primary rectal cancers that do not meet the criteria for local therapy, for pelvic recurrences of rectal cancers, and for a variety of other malignant anorectal diseases. Modern concepts have reduced both the morbidity and the mortality rates of the procedure since its introduction in the early part of the 20th century. Recent advances in minimally invasive surgery have further improved quality of life outcomes without affecting oncologic results.

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Chapter

160

Coloanal Anastomosis

Gerald Isenberg · Christophe Penna · Rolland Parc

The goal of coloanal anastomosis (CAA) is to preserve the anal sphincter and restore bowel continuity after total removal of the rectum. This operation was originally described for rectal cancer,[1] but it has since been widely used not only for malignant and benign tumors of the rectum but also for complex rectovaginal fistulas, hemangiomas, and radiation proctitis.

Because tumor deposits or metastatic nodes can be found in the mesorectum for 2 to 5 cm (very rare) below the lower edge of the tumor,[2] the necessity of performing total mesorectal excision is widely accepted for the treatment of cancers of the *lower* rectum. Distal intramural spread of rectal cancer rarely exceeds 1 cm. In patients in whom the spread exceeds 1 cm, advanced disease commonly occurs, with multiple positive lymph nodes and distant metastases.[3] Importantly, anterior resection with a margin of 2 cm distal to the tumor is associated with 5-year survival and local recurrence rates similar to those for abdominoperineal resection (APR).[4] Therefore, for the surgical treatment of cancer of the lower portion of the rectum, a distal margin of 2 cm is sufficient, provided that all of the mesorectum has been removed. For some cancers of the distal third of the rectum, a 2-cm margin can be obtained below the lower edge of the tumor, but the level of bowel transection renders intrapelvic anastomosis technically difficult or impossible. In these situations, bowel continuity can be restored with CAA. In other situations, the rectum is transected a few centimeters above the level of the levator ani muscles, and a double-stapled low colorectal anastomosis is technically feasible. Although preservation of any length of distal rectum after total mesorectal excision leaves a potentially ischemic rectal stump, leak rates are low and long-term functional and oncologic outcomes are quite good. However, some surgeons advocate both total mesorectal and total rectal excision with CAA for the treatment of all low rectal cancers. After total rectal resection and straight CAA, the concomitant loss of rectal reservoir function results in increased frequency, urgency, and fecal incontinence.[5] As we[6] (C.P. and R.P.) and Lazorthes et al.[7] suggested and as was demonstrated in several comparative studies,[8-13] the frequency of these troublesome symptoms can be decreased by adding a colonic pouch anastomosed directly to the anal canal.

In this chapter we describe the technical aspects of hand-sewn and stapled colonic pouch–anal anastomosis and provide data about the oncologic and functional results of these procedures.

OPERATIVE TECHNIQUE

Preparation for Coloanal Anastomosis

Preoperative Preparation

A mechanical bowel preparation is performed the day before surgery, and systemic antibiotics are administered within 1 hour before the incision. Appropriate deep venous thrombosis prophylaxis is recommended.

The patient is positioned to allow a combined abdominal and perineal approach. The legs are placed in Lloyd-Davis stirrups, and the hips are flexed 30 degrees. A Foley catheter is placed in the bladder.

Incision and Abdominal Exploration

The abdomen is opened through a midline incision that extends to the pubic symphysis. The abdominal cavity is explored in a search for ascitic fluid, invasion of mesenteric or para-aortic lymph nodes, peritoneal carcinomatosis, resectability of the tumor, and liver metastasis.

Division of the Inferior Mesenteric Vessels and Colon Mobilization

The inferior mesenteric artery (IMA) is ligated and divided about 2 cm from the aorta to preserve the autonomic nerves, which split around its origin. If the decision to perform APR can be made only intraoperatively, the rectal dissection is performed first and mobilization of the left colon is performed later. If, however, CAA is planned, the inferior mesenteric vein is transected at its termination, below the body of the pancreas near the

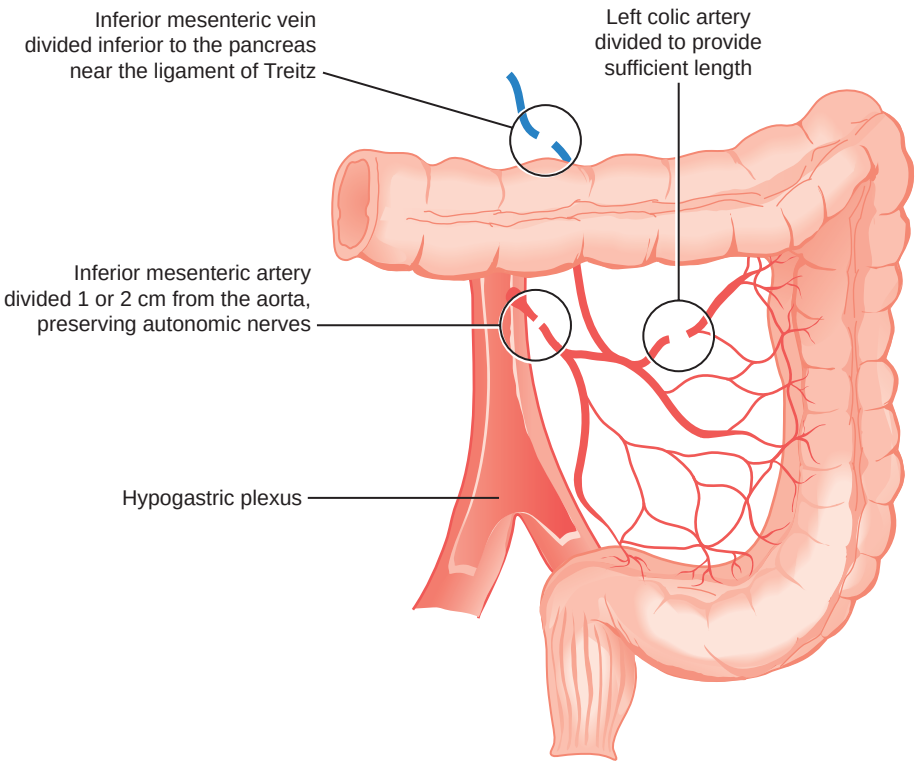

Figure 160–1. Division of the inferior mesenteric vessels.

ligament of Treitz, because this provides the greatest amount of mobility of the splenic flexure. It is helpful for the surgeon to be positioned between the patient's legs to take down the splenic flexure. Complete mobilization of the left colon is performed to ensure adequate length of viable bowel and to avoid any traction on the anastomosis. The descending colon, the splenic flexure, and the left portion of the transverse colon are mobilized, and the superior left colic artery is divided to provide further length (Fig. 160–1). The left ureter is identified by locating the intersigmoidal fossa at the root of the sigmoid mesentery; it is dissected laterally away from the origin of the IMA.

Total Mesorectal Excision

The sigmoid colon is lifted anteriorly to allow visualization of the IMA as it becomes the superior hemorrhoidal artery. The tissue just posterior to the vessel contains the hypogastric nerves. Sharp dissection allows preservation of these nerves and entrance into the perfect presacral plane for total mesorectal excision. Sharp dissection is extended downward around the curve of the sacrum in the midline, past the coccyx, and forward in front of the anococcygeal raphe. The lateral attachments are mobilized by extending the plane of dissection forward from the posterior midline around the side walls of the pelvis. The inferior hypogastric plexuses, which curve tangentially around the surface of the mesorectum in close proximity to it, are identified and preserved. The nervi erigentes lie more posteriorly in the same plane as the presacral nerves and then curve forward from the sacral foramina and converge to join the presacral nerves and form the neurovascular bundles at the outer edge of Denonvilliers' fascia. They must be identified and preserved, especially in the anterolateral position just behind the lateral edges of the seminal vesicles, where they are in danger of trauma. As the dissection moves deeper into the pelvis, one or two tiny branches of the middle rectal vessels may be divided, generally with the use of diathermy coagulation. In men, anterior dissection begins with a transverse incision through the peritoneum anterior to the peritoneal reflection to descend straight to the superior aspect of the seminal vesicles. The dissection moves along in front of Denonvilliers' fascia and is extended laterally to meet the lateral dissection. Denonvilliers' fascia is divided at its bottom where it fuses with the posterior fascia of the prostate and contact is made with the anterior wall of the last centimeter of the rectum before it enters the levator ani muscle. In women, anterior dissection begins with a transverse incision at the bottom of the peritoneal reflection and moves along the posterior face of the cervix and the vagina down to the level of the levator ani.

Choosing the Type of Anastomosis

At this stage, the whole mesorectum has been fully mobilized (Fig. 160–2). If the tumor extends through the bowel wall into the levator ani or if a "sufficient" margin cannot be obtained between the distal edge of the tumor and the dentate line, abdominoperineal excision must be performed. On the other hand, if a right-angled rectal clamp can be applied below the lower border of the tumor, a sphincter-saving operation can probably be considered. If section of the rectum 2 cm below the edge of

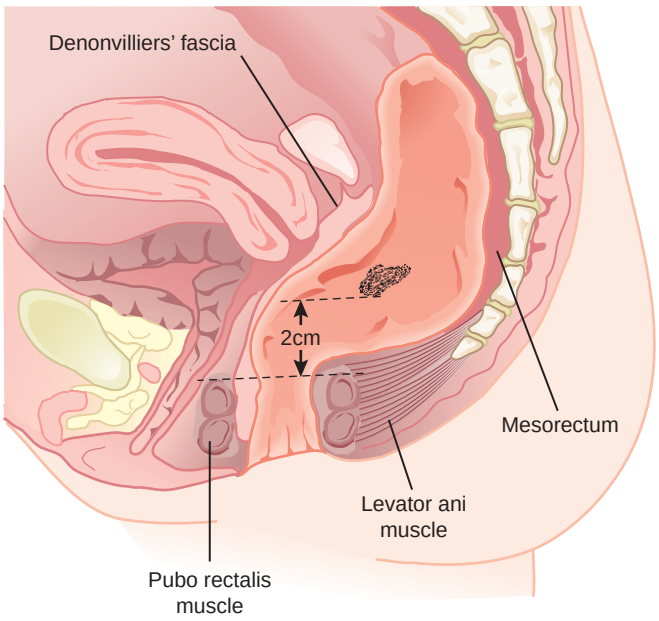

Figure 160–2. Choosing the type of anastomosis after total mesorectal excision.

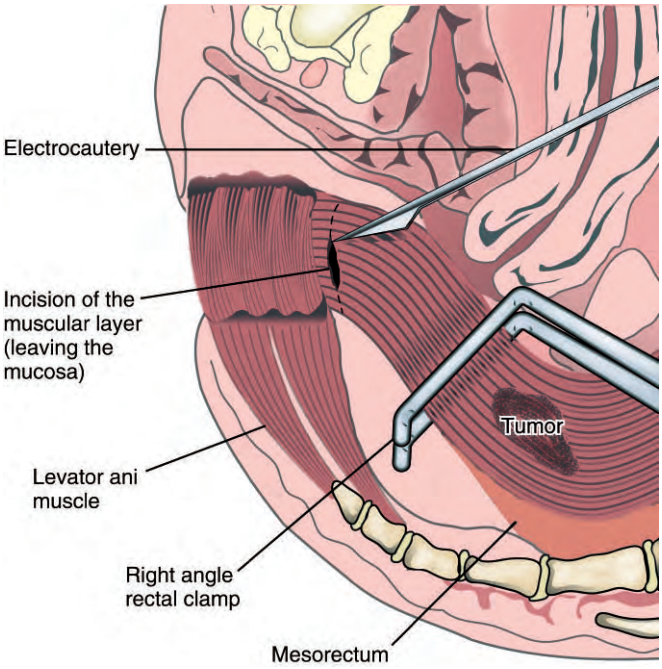

Figure 160–3. Hand-sewn coloanal anastomosis showing incision of the muscular layer of the rectum at the level of the levator ani muscle.

the tumor leaves 1 cm or more of rectum above the levator ani, a stapled anastomosis (colorectal or coloanal) is feasible. A hand-sewn CAA will be used if the distance between the level of resection and the upper border of the anal sphincter does not allow the use of a stapling device. This is the case for very low rectal tumors when the remaining anal canal is too short after rectal resection to admit the circular stapler or when a TA stapler cannot be safely applied 2 cm below the tumor.

An alternative method of sphincter preservation for very distal lesions is to approach the tumor from the perineum first. This technique allows complete mobilization of distal perirectal tissues without the "cone-down effect" that can occur when working in the distal pelvis via the abdomen (see the non-mucosectomy technique later).

Hand-Sewn Colonic Pouch–Anal Anastomosis

Mucosectomy of the Rectal Stump

If it is technically feasible, after full mobilization of the rectum and mesorectum, the muscular wall of the rectum is transected circumferentially at the level of the anorectal ring (Fig. 160–3). The mucosa is visible but should not be incised. If impossible, this will be performed via a perineal approach.

Transanal exposure is obtained with two Gelpi retractors applied perpendicular to each other on the external sphincter or with a Lone Star retractor (Lone Star Medical Products, Houston). A solution of saline with epinephrine (1:1,000,000) is injected into the submucosa to balloon it up and float the mucosa away from the underlying muscle. A circumferential mucosectomy is then carried out from the dentate line up to the stapled-over end of the rectum (Fig. 160–4). The specimen is exteriorized. Hemostasis of the muscular stump and the lower portion of the pelvis is easily achieved when the specimen has been removed and after irrigation with warm saline.

Non-Mucosectomy Technique

The patient is put in the prone jackknife position and a Lone Star retractor is placed. The tumor or residual ulceration (after chemoradiotherapy) is palpated and a margin 2 cm distal to this point is marked with the cautery circumferentially. The most distal position that can be used is the dentate line. A full-thickness incision is made with the cautery through the internal sphincter into the intersphincteric plane and advanced circumferentially. The edges of the rectum (specimen side) are grasped with wide-mouthed Allis clamps. The dissection is continued proximally with blunt and sharp dissection in the intersphincteric plane to the distal part of the rectum with the help of small Deaver retractors (Fig. 160–5). Once maximal length is achieved, the specimen side of the rectum is oversewn to prevent spillage of the tumor and stool. A sponge is inserted in the anal canal and the patient is placed in the lithotomy position for the abdominal procedure.

Preparation and Division of the Colon

A suitable site for division of the colon is chosen to ensure a good blood supply and a tension-free anastomosis. The apex of the pouch should reach the

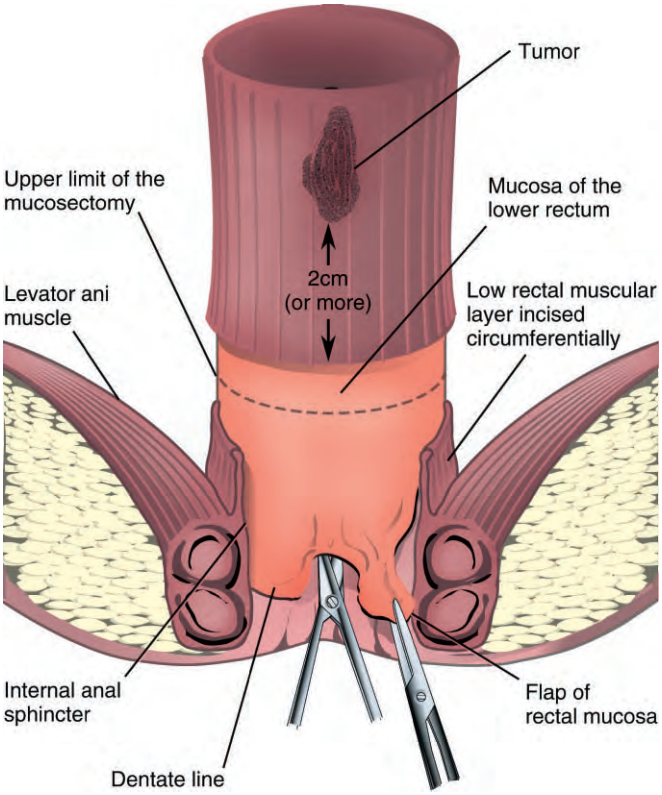

Figure 160–4. Mucosectomy of the rectal stump.

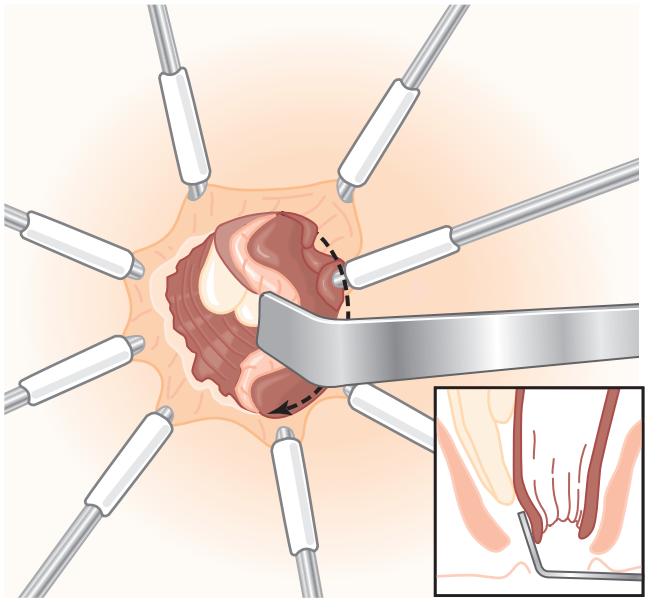

Figure 160–5. Preparation of the "intersphincteric space" is facilitated by assistance from the "abdominal surgeon." (From Schiessel R, Novi G, Holzer B, et al: Technique and long-term results of intersphincteric resection for low rectal cancer. Dis Colon Rectum 48:1858, 2005.)

level of the lower border of the pubic symphysis very easily without traction. The usual site for division is the descending colon just proximal to the sigmoid. Use of the sigmoid colon to construct the pouch may contribute to evacuatory problems because of the severe motility dysfunction of a pouched sigmoid segment in comparison to a descending colonic pouch.[14] Moreover, in Western societies, the sigmoid is often affected by diverticular disease or surrounded by fatty epiploic appendices, which may complicate pouch construction. In addition, the sigmoid colon may have been in the radiation field and therefore not be optimal for anastomosis; always try to use *nonirradiated* descending colon instead. The colon is divided after the application of a TA 55 stapling device, and the stapled end is underrun with continuous 4-0 suture. The specimen is removed from the operative field, and the distance between the lower border of the tumor and the level of muscular division is measured.

Construction of the Colonic Pouch

The colonic pouch for CAA is J shaped, principally because it is easy to perform. The optimal size for a colonic reservoir is not known. However, these reservoirs should be small, with each limb of the pouch being no more than 9 cm in length; otherwise, difficulty in evacuation and sometimes constipation occur. In a prospective randomized study, similar clinical results were obtained at 1 year with a small (5 cm) or a large (10 cm) pouch, but with long-term follow-up, constipation and evacuation problems were more likely in the group with a large reservoir.[15]

The distal 15 cm of the colon is brought together in a J-shaped manner to construct the pouch. Each limb measures 6 to 8 cm. The descending limb is positioned on the left and the efferent limb is positioned on the right, with the mesentery placed behind. A pair of Allis forceps is applied on the antimesenteric border of the colon at the apex of the future pouch, and two additional Allis forceps are placed at the base of the pouch: one on the stapled end of the colon and the other on the descending limb of the pouch (Fig. 160–6). Two adjacent holes are made by stab puncture on the antimesenteric border of each limb of the pouch at an equal distance from the top, close to the Allis forceps. The two forks of a GIA stapler (50 or 90) are introduced into the lumen of the colon, each through one hole, toward the apex of the pouch (Fig. 160–7). Before firing, it is necessary to check that the mesentery of the pouch is away from the stapler. The bowel is then everted to expose the remaining bridge, which is sectioned by application of a GIA 50 stapler. The pouch is inverted, the Allis forceps are removed, and the hole is closed with continuous 4-0 polyglycolic acid suture. In this manner, the pouch is totally closed with no risk for septic contamination of the pelvis during its descent to the anal canal. Moreover, the size of the hole that will be made at the apex of the pouch for the anastomosis will be chosen to exactly fit the diameter of the anal canal.

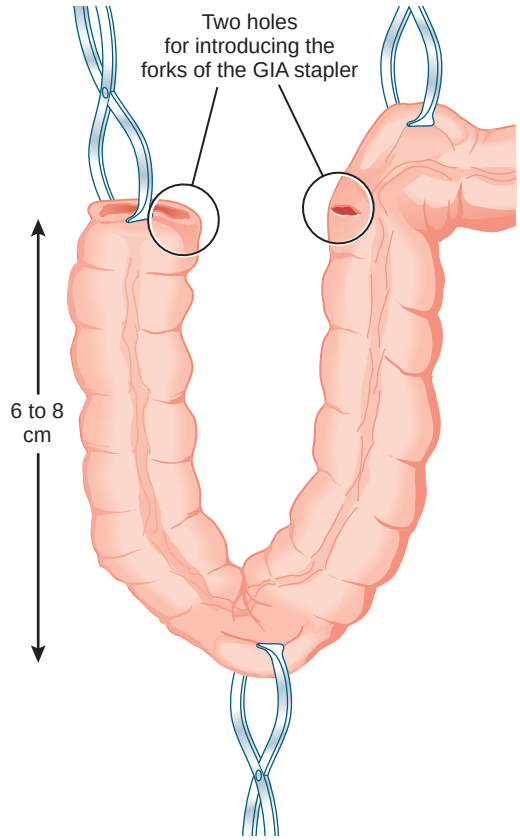

Figure 160–6. Preparation of the colonic reservoir for a hand-sewn coloanal anastomosis.

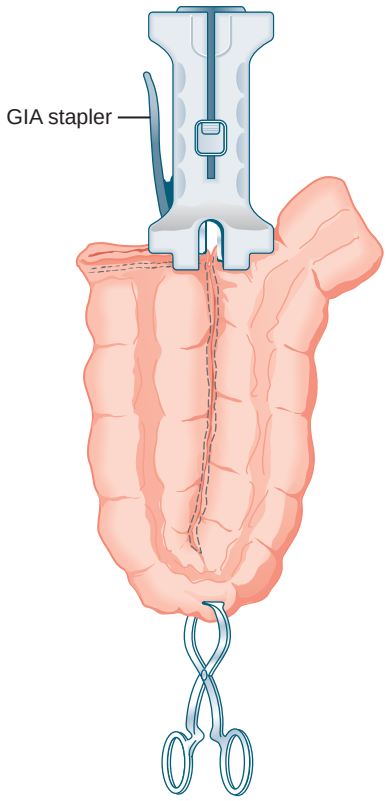

Figure 160–7. Creation of colonic J pouch without apical colotomy.

Coloanal Anastomosis

The apex of the pouch is brought to the anus with Babcock forceps introduced through the anal stump (Fig. 160–8). During this maneuver, care should be taken to not twist the colon around its mesentery. To facilitate descent of the pouch, the genitourinary organs should be lifted with a hand or retractor, and the pouch should be gently pushed from above. The pouch is then anchored to the anal sphincter with four stitches of resorbable suture, each at one cardinal point just above the mucosal section. The apex of the pouch is then opened, and the mucosa of the anal canal is anastomosed to the full thickness of the colon with the use of interrupted 4-0 polyglycolic acid suture (Fig. 160–9). Four stitches are initially placed at 3, 6, 9, and 12 o'clock, and then an additional one or two stitches are added to each of the quadrants thus formed. The perianal retractors are removed, and a small drain is inserted through the anastomosis into the reservoir and will be left in place for 24 to 48 hours to reveal any bleeding in the pouch, obviate the risk for pouch distention by blood clots, and facilitate treatment of such hemorrhage by saline irrigation.

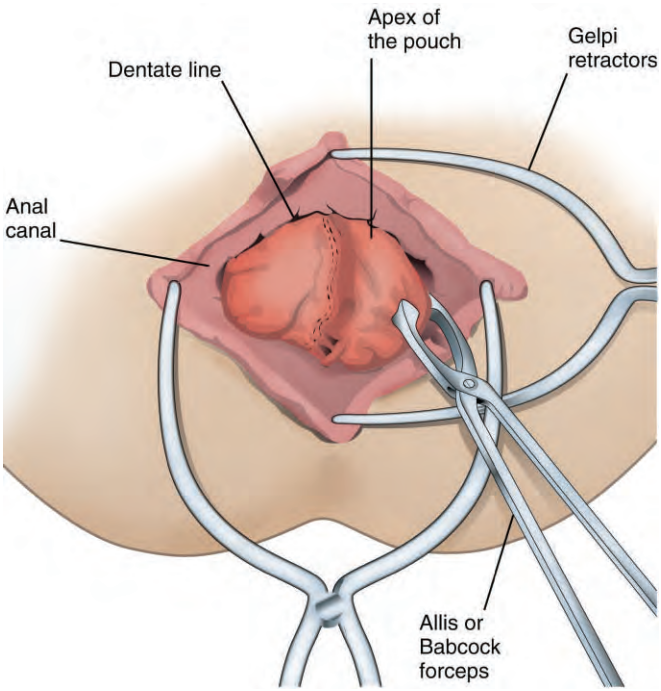

Figure 160–8. The apex of the pouch is drawn through the anus.

Drainage, Loop Stoma, and Postoperative Care

Two multiperforated suction drains are usually placed in the pelvis posterior and anterior to the pouch. We strongly advocate routine construction of a diverting stoma simply

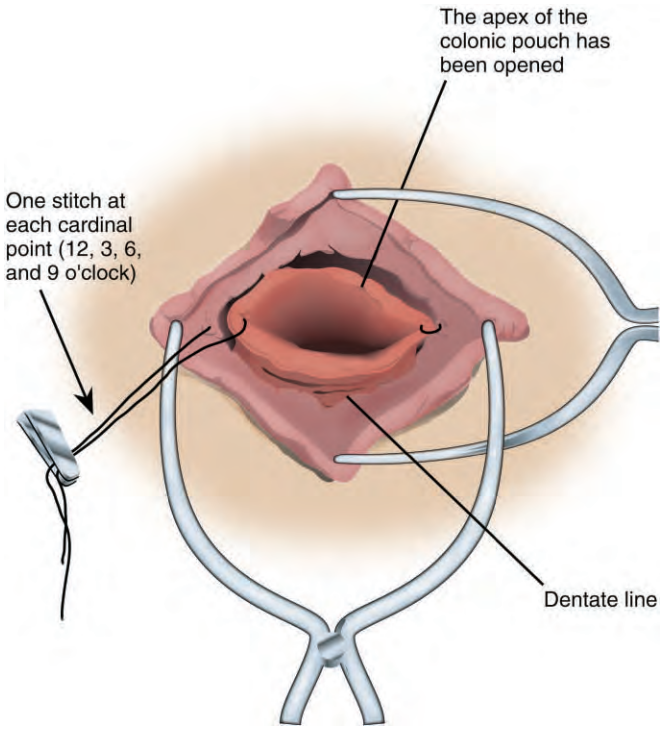

Figure 160–9. Hand-sewn coloanal anastomosis.

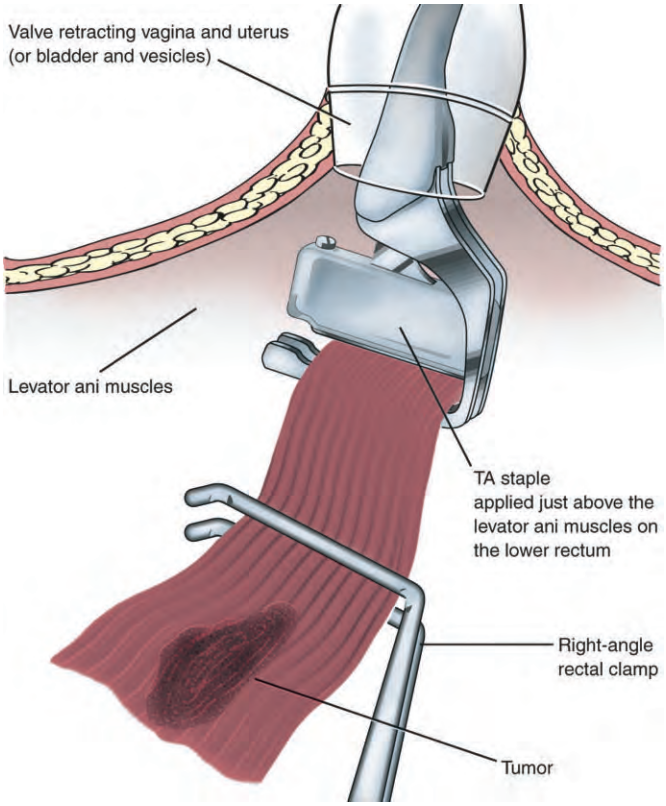

Figure 160–10. Double-stapled coloanal anastomosis. A TA stapler is applied at least 2 cm below the lower edge of the tumor, at the level of the levator ani muscle.

because anastomotic leakage after total mesorectal excision and an ultralow anastomosis causes dramatic complications.[12,16] We usually prefer a loop ileostomy over a colostomy because there is no risk of traction on the anastomosis and the blood supply to the descending colon is not compromised. However, some surgeons (including one of the authors [G.I.]) prefer a loop proximal transverse colostomy because the distal ileum may have been exposed to radiation during preoperative therapy. If the mobilized colon and mesocolon compress the duodenojejunal junction, the ligament of Treitz should be divided to avoid postoperative small bowel obstruction.

One to two doses of antibiotics are usually administered postoperatively. The nasogastric tube is removed at the end of the procedure or the next morning, depending on how much dissection was performed near the stomach. Appropriate deep venous thrombosis prophylaxis should be maintained until the patient is fully ambulatory. The urinary catheter is generally removed on the third postoperative day. The pelvic suction drains are removed 24 to 48 hours after surgery.

The stoma is closed in 6 to 8 weeks and after a water-soluble contrast study performed through the efferent limb of the stoma has shown satisfactory healing of the pouch and the anastomosis. If a leak is observed, the stoma should be left in place for an additional few weeks and the contrast study repeated.

Stapled Colonic Pouch–Anal Anastomosis

After total mesorectal excision, if a TA stapler can be applied between a rectal clamp positioned 1 or 2 cm below the lower edge of the tumor and the levator ani, a double-stapled anastomosis is possible. On the other hand, if the length of the rectal stump is more than 3 cm above the anal sphincter, the functional outcome after low colorectal anastomosis will be acceptable, but the incidence of anastomotic leakage reaches 10% to 15% in most series,[16,17] probably because the anastomosis is performed on a devascularized rectum. For this reason, fecal diversion is usually warranted.

Section of the Rectum

A right-angled rectal clamp is applied below the lower edge of the tumor (Fig. 160–10). The lower portion of the rectum is washed with a povidone-iodine solution. Though not proven, this may be helpful in decreasing the risk for anastomotic recurrence as a result of viable tumor cells being trapped within the stapled line. The rectal clamp is used to horizontally align the rectum and facilitate positioning of a terminal anastomosis stapling device (TA 30 or 55, Roticulator 55 or 30) or linear stapler (Tx or Contour) on the lower part of the rectum at the level of the levator ani. On closing the instrument before firing, care must be taken to include only the rectum (and nothing else) within the stapler. After firing, the rectum is divided, the specimen is removed from the pelvis, and the distal margin is assessed.

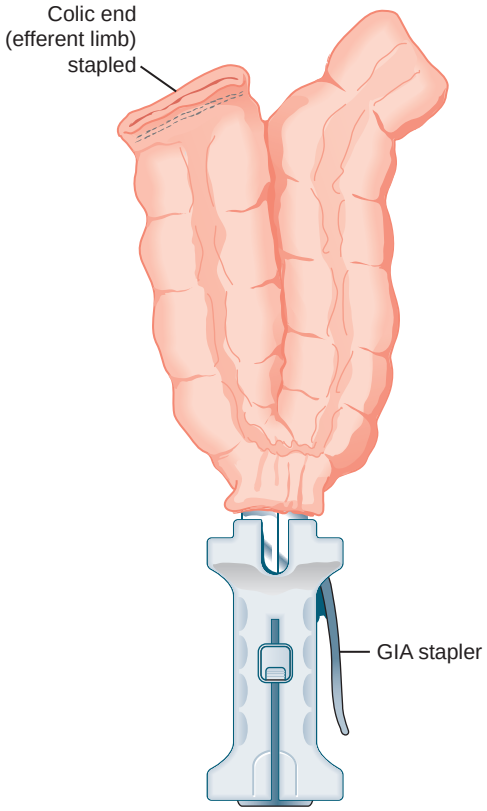

Figure 160–11. Double-stapled coloanal anastomosis: preparation of the colonic pouch.

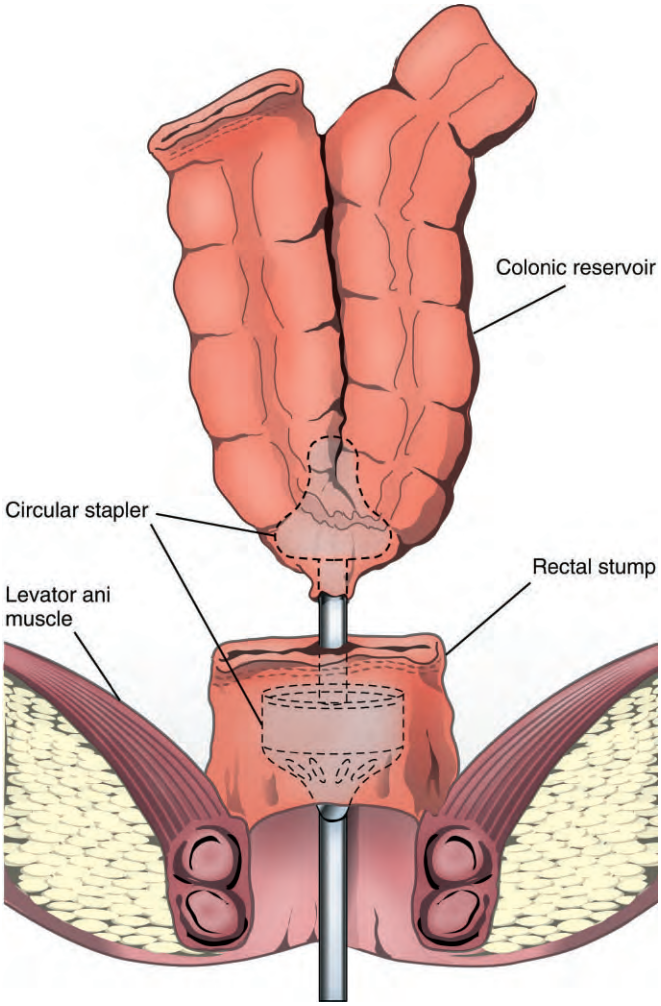

Figure 160–12. Double-stapled coloanal anastomosis with a colonic pouch.

Construction of the Pouch

The colon is divided at the junction of the descending and sigmoid colon after the application of a TA 55 stapling device, and the stapled end is underrun with continuous 4-0 suture. Six to 9 cm from the colonic section, a 1-cm opening is created on the antimesenteric border of the colon. The forks of a GIA 50 or 90 stapler are inserted into each limb, and a side-to-side anastomosis is performed between the two limbs to create the pouch (Fig. 160–11). A simple over-and-over continuous purse-string suture of 0 nylon or polypropylene (Prolene) is placed around the hole where the GIA stapler was inserted. The anvil of a circular stapler (EEA 28/31 or ILS 29/33) is disconnected from the stapler and introduced into the hole, and the purse-string suture is tightened.

Coloanal Anastomosis

The body of the circular stapler is introduced into the anus, aided by lubricant and the assistant's fingers. The spindle is slowly advanced and should perforate the rectal wall just behind the linear TA stapled line. The two halves of the stapler are fixed together (Fig. 160–12) and the instrument is closed, with great care taken to not catch adjacent structures such as the posterior wall of the vagina or vesicles. The gun is fired when the gap is within the recommendations. The stapler is removed and the rings are checked. They should be identified from both the rectal and the colonic sides. The distal (anorectal) ring should be sent for pathologic examination. If both anastomotic rings are intact, it is not necessary to test the anastomosis because it will be diverted regardless. If either ring is incomplete, proctoscopy should be performed to determine whether sutures are required to close a significant defect.

Drainage, stoma, and postoperative care are similar to those for a hand-sewn anastomosis.

Transverse Coloplasty

There are several circumstances in which a colonic pouch can not be constructed, including a narrow pelvis, severe diverticulosis, inadequate colonic length, and sometimes metastatic disease or other technical problems.[18] An alternative method was devised by Fazio et al.[19] in which a reservoir is created just proximal to the anastomosis by adapting the Heineke-Mikulicz strictureplasty technique used for the small bowel

(Fig. 160–13). The colotomy can be closed with either sutures or a stapler. Functional results have been similar to those of the colonic J pouch.[20,21] Technically, the "pouch" is easier to construct and is less bulky than the colonic J pouch.

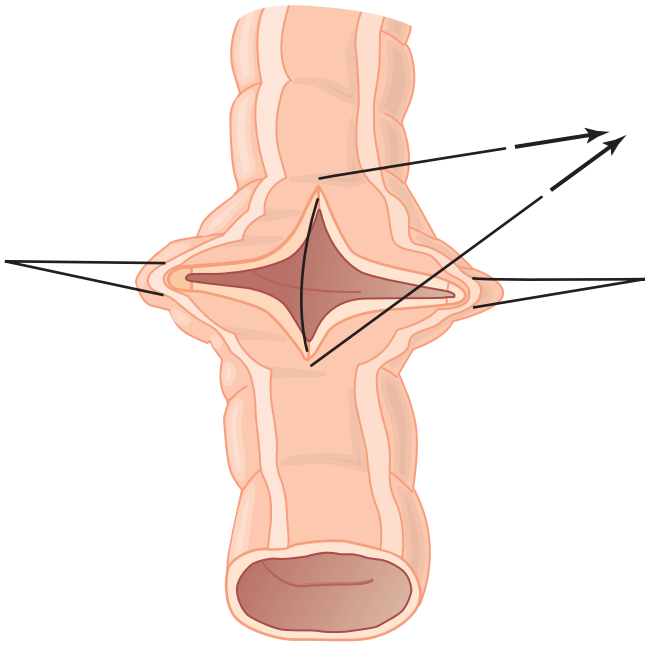

Figure 160–13. Stay sutures are placed midway between the colotomy on each side so that the longitudinal opening can be closed in transverse fashion. The next suture is a seromuscular stitch placed in the middle to line up the closure. This middle suture is not tied until the remainder of the row is placed. Next, starting at each end and working toward the middle, seromuscular sutures of 2-0 polyglycolic acid are placed to close the colotomy. (From Fazio VW, Mantyh CR, Hull TL: Colonic "coloplasty": Novel technique to enhance low colorectal or coloanal anastomosis. Dis Colon Rectum 43:1448, 2000.)

Laparoscopy

Laparoscopic surgery for colon cancer is now gaining acceptance among U.S. surgeons. It has been embraced by European surgeons for the past decade. A randomized study by the Clinical Outcomes of Surgical Therapy Study Group published in the *New England Journal of Medicine*[22] showed the safety and efficacy of laparoscopic *colectomy*. Although a number of studies have reported that laparoscopic proctectomy is safe and even provides good functional and oncologic results,[23-26] the American Society of Colon and Rectal Surgeons in its recently revised practice parameters[27] has not endorsed the use of laparoscopy for rectal cancer at this time.

ONCOLOGIC RESULTS

Results after low anterior resection and CAA have been reported and are presented in Table 160–1. These series are retrospective, nonrandomized, and quite heterogeneous in the distribution of Dukes' classification, level of tumor, and the use of adjuvant radiation therapy. However, the rate of local recurrence is usually less than 10% and the 5-year actuarial survival rate ranges from 69% to 81%, similar to results reported after low anterior resection and colorectal anastomosis or APR. In a retrospective study of 564 patients with rectal cancer treated by surgery alone, the local recurrence and 5-year disease-free survival rates were 7% and 78%, respectively, after anterior resection; 6% and 83%, respectively, after CAA; and 4% and 80%, respectively, after abdominoperineal excision.[34] In our series (R.P.) of 162 patients operated on between 1984 and 1990,[35] including 14 in stage A, 79 in stage B, 53 in stage C, 8 in stage D, and 8 patients in whom cancer had previously been treated by local resection, radiation therapy, or colorectal anastomosis, local recurrence developed in 12 patients (7%) at a mean time of 22 months after surgery. In an update of this series, 154 patients had been monitored for a minimum of 5 years, and the 5-year survival rate was 70%. Twenty patients (13%) were found to have locoregional recurrence at an average of 31 months after

Table 160–1 Oncologic Results After Low Anterior Resection and Coloanal Anastomosis for Rectal Cancer

Study	No. of Patients	Local Recurrence Rate (%)	5-Year Survival (Actuarial) Rate (%)
Cavaliere et al.[28]	117	7	69
Berger et al.[29]	162	7*	79
Paty et al.[30]	134	11*	73
Lazorthes et al.[7]	65	6	72
MacAvena et al.[31]	81	3.5	81
Nakagoe et al.[32]	112	9.8	76
Schiessel et al.[33]	117	5.3	77

*Five-year actuarial rate.

surgery. In 11 patients (7%), the local recurrence was isolated, and half of the patients were treated with curative surgery.[29]

Risk factors for pelvic recurrence after low anterior resection and CAA are the degree of transmural penetration of tumor, lymph node metastases, poorly differentiated tumors, perineural or vascular invasion, and mesorectal implants. In the series of Paty et al.,[30] short distal resection margins were not significantly associated with pelvic recurrence. The crude rate of local control was 94% in patients who underwent resection with short distal margins (<2 cm) versus a crude rate of 89% in those with longer margins. The low rate of recurrence after CAA may be explained by total excision of the mesorectum.[29] Chemoradiation therapy may also help prevent local recurrence and allow sphincter preservation, even with very distal tumors.[36-38]

FUNCTIONAL RESULTS

Complete rectal excision followed by reconstruction with an ultralow colorectal anastomosis or a straight CAA results in greatly reduced reservoir capacity and an alteration in the continence mechanism. The association of increased bowel frequency, urgency of defecation, and minor fecal leakage (the so-called anterior resection syndrome) is seen in 5% to 60% of patients.[5,39-41] The mechanism underlying this dysfunction is complex but involves a decrease in internal anal sphincter tone secondary to the trauma of pelvic dissection and anal dilatation and a loss of the rectal reservoir. A colonic pouch may increase reservoir capacity and act as a pressure relief in which the high intraluminal pressure generated within the relatively noncompliant colon is dissipated before it reaches the anal canal.

The functional outcome after a colon pouch–anal anastomosis is superior to that of a straight CAA or an ultralow CAA. This was obvious from the earliest reports[6,7] and confirmed in randomized trials.[9,12,13] A recent meta-analysis has compared the functional results of 2240 patients from the collected series (Table 160–2).[42] A reduction in bowel frequency and a decreased incidence of urgency are observed in all studies. The functional results of colon pouch–anal anastomosis are comparable to those obtained with a low colorectal anastomosis.[43,44] The functional superiority of the colonic J-pouch is greatest within the first year after surgery[45] but is still sustained over the long term.[43,46]

The major drawback of the pouch is fecal retention secondary to poor evacuation. In our series,[7,35] this was observed in 20% of patients; these patients required enemas or suppositories to defecate. The combination of smaller J pouches (5 rather than 10 cm long) constructed from the descending rather than the sigmoid colon may help overcome these problems.[15]

CONCLUSION

Low anterior resection with total mesorectal excision and CAA can eradicate low rectal cancers while preserving sphincter function and providing oncologic results similar to those of APR and low anterior colorectal anastomosis. The functional results of straight CAA are far from perfect, particularly in terms of bowel frequency and urgency. The addition of a colonic reservoir or coloplasty markedly decreases the frequency of defecation without increasing morbidity and should therefore be the option of choice. The long-term results of colon pouch–anal anastomosis are good, but spontaneous evacuation continues to be a problem that may alter quality of life.

Table 160–2 Results of Meta-analysis of Colonic Reservoirs Versus Straight Coloanal Anastomosis

No. of studies	35
No. of patients	2240
Straight coloanal (SCA)	1066
J pouch (JP)	1050
Coloplasty (CP)	124
Complications	No difference
No. less frequent BM/24 hr (JP + CP versus SCA)	
6 month	1.88
1 year	1.35
2 year	0.74
Fecal urgency (JP + CP versus SCA)	Less prevalent

BM, bowel movement.
From Heriot AG, Tekkis PP, Constantinides V, et al: Meta-analysis of colonic reservoirs versus straight coloanal anastomosis after anterior resection. Br J Surg 93:19, 2006.

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Chapter

161

Recurrent and Metastatic Colorectal Cancer

Luca Stocchi ▪ Heidi Nelson

The primary goal in the management of primary colon and rectal cancers is to minimize the risk of development of locally recurrent or metastatic disease. This is best achieved using proper aggressive surgical techniques and appropriate adjuvant therapies at the time of primary tumor presentation.[1,2] Despite best efforts, relapse of disease still occurs in significant numbers. In the not-so-distant past, the presence of either locally recurrent or metastatic disease signified an incurable condition. Increasingly, it is recognized that focal relapses can be managed surgically with curative intent. Early detection of disease relapse with appropriate postoperative surveillance programs aimed at sites where recurrences can be treated with curative intent would increase the salvage rates. Of these, the lung, liver, and locoregional recurrences are those most frequently involved with disease relapse and have the greatest potential for cure if localized and of limited extent at the time of presentation. The discussion of the management of liver metastases from colorectal cancer is outlined in Chapter 162. Therefore, the focus of this chapter is on locoregional recurrences such as in the pelvis after the treatment of primary rectal cancer and on the management of pulmonary metastases.

TUMOR RELAPSE

Incidence

The combined rate of locoregional and distant recurrence after resection of colorectal cancer with curative intent is reported to be approximately 30%.[3,4] The incidence of relapse depends in part on the length and intensity of follow-up and on whether early, first site of relapse, late, or all sites of relapse are reported. Of these, the most important is the first site of relapse because curative attempts would be favorably influenced by efforts directed at detecting early relapse. First sites of relapse most often develop in the liver, locoregional sites, or lungs (Fig. 161–1). Less commonly, sites such as the ovaries, bone, anastomosis, or brain may be affected.

Risk Factors

Assessment of the risk of relapse of a particular tumor allows a focused surveillance effort and therefore early detection of curable disease. A large number of risk factors have been associated with relapse of colorectal cancer,[5] including tumor-related and technical factors (Boxes 161–1 and 161–2).

Tumor-Related Factors

These fall into two broad categories: biologic factors and anatomic factors. Certain histologic features have been correlated with aggressive behavior, including poor tumor differentiation,[6] mucin production, and venous or lymphatic invasion.[6,7] Molecular markers have also been found to predict aggressive tumor behavior; these include aneuploidy,[8-10] the presence of mutant p53,[11,12] and low rate of proliferation marker Ki-67.[10] A number of recent studies seem to indicate that high microsatellite instability phenotype, which is present in approximately 10% to 15% of colorectal carcinomas, is associated with improved prognosis.[13-16] Conversely, the presence of low microsatellite instability could be associated with a worse prognosis.[17]

Although in the future the prediction of tumor behavior using biologic molecular markers may be possible, the extent of disease, or stage, is to date the single most important factor that predicts relapse. The risk of local recurrence is increased when the tumor has invaded beyond the confines of the bowel wall or involves nodes and is highest in patients with both (see Box 161–1).[18-20] There is recent evidence suggesting that circumferential margins of resection are prognostic factors in both rectal and colon carcinoma.[7] Other anatomic risk indicators

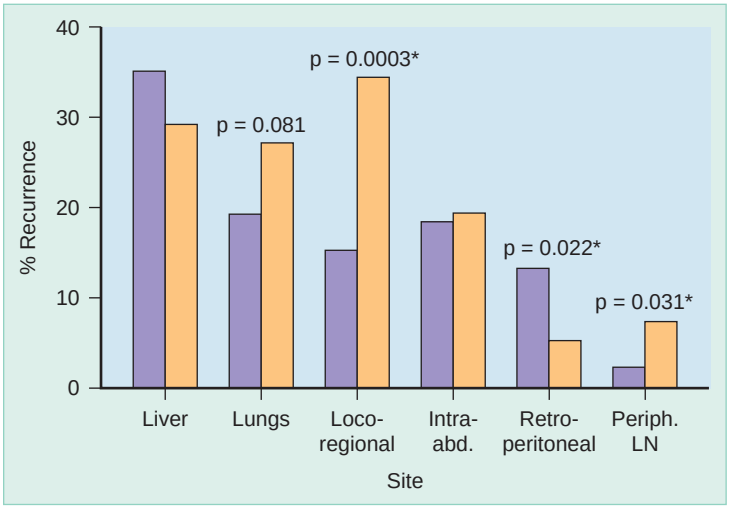

Figure 161–1. Sites of first recurrence in colon *(purple bars)* and rectal cancer *(orange bars).* Significant differences between colon and rectal tumors are indicated by an asterisk. LN, lymph node. (From Galandiuk S, Wieand HS, Moertel CG, et al: Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet 174:27, 1992.)

include bowel obstruction, perforation,[7,21] and local organ adherence.

Technical Factors

Although tumor-related factors remain the main determinants of prognosis for colon carcinoma, technical factors influence both local recurrence and overall survival in rectal carcinoma. Local recurrence rates after rectal cancer resections range from 4% to 40%,[22] which is at least partially dependent on the individual operating surgeon.[21-23] Some authors have not detected significant prognostic differences according to the location in the rectum,[6] but others have pointed out increased local recurrence rates in tumors in the distal rectum, possibly related to increased technical difficulty.[24] At a minimum, it is evident that wide anatomic resection of the tumor—in all dimensions, including mesorectal,[25,26] radial, distal bowel, and en bloc resection of adherent organs—is critical. Most surgeons accept a distal margin of more than 2 cm as ideal and a margin of more than 1 cm as acceptable where the tumor is not locally advanced and abdominoperineal resection (APR) is the only alternative.[27] Although the importance of adequate resection margins is clear, extended lymphadenectomy has been fraught by increased morbidity rates not offset by measurable survival benefits.[28] Similarly, high-level ligation of the inferior mesenteric artery and vein has failed to demonstrate a survival advantage[29] while associated with increased morbidity.[30] Of all the surgical techniques reviewed and considered significant, none has received more attention than the concept of mesorectal clearance.[31,32] In Scandinavian countries, the implementation of appropriate mesenteric clearance referred to as *total mesorectal excision* has reduced local recurrence rates and improved survival.[33,34] In all cases, sharp dissection should be performed in the areolar tissue behind the mesentery, just in front of the sacrum and particularly at the level of Waldeyer's fascia. The fascia propria should be removed intact with proper rectal dissection.[35] Therefore, a total mesorectal excision is advised for all cancers of the distal rectum for which APR or low anterior resection and coloanal anastomosis are planned. In the management of more proximal rectal cancers it seems reasonable to use a margin of approximately 4 cm of distal mesorectum as a benchmark, since tumor deposits in the mesorectum are rarely reported 4 cm beyond the tumor.[36] Despite optimization of surgical techniques, adjuvant radiation treatment remains an independent factor reducing the incidence of local relapse.[37]

DETECTION OF RELAPSES

Surveillance

The principal aim of postoperative surveillance is early detection, because it is at this stage that there is the greatest possibility of a cure. The first stage in the evaluation of disease relapse is detection of clinically unsuspected disease through routine surveillance. Once relapse is detected, confirmatory tests are used to delineate the extent of disease. Single-site locoregional recurrence or focal metastatic disease may be amenable to resection with curative intent; however, diffuse or unresectable disease unfortunately mandates treatment for palliation only. The algorithm in Figure 161–2 summarizes our clinical approach to disease recurrence.

Although all surveillance programs are targeted at early detection of relapse, there is, unfortunately, no agreement on which programs are most effective. Some of the most commonly performed surveillance tests are outlined in Box 161–2. At least six randomized trials have been conducted to investigate the impact of intensive surveillance strategies.[38-43] In five of six trials a more intensive surveillance allowed for more frequent operations with curative intent on recurrent disease detected at an earlier stage. In addition, in two of six trials more intensive surveillance was associated with survival benefits. Meta-analyses of these trials have confirmed reduc-

Box 161–1 Pathologic TNM Staging Nomenclature

Primary Tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria to the subserosa, or into the non-peritonealized pericolic/perirectal tissues
T4	Tumor directly invades other organs or structures, and/or perforates

Regional Lymph Nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)

Mx	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

AJCC Stage Groupings

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
	T2, N0, M0
Stage IIA	T3, N0, M0
Stage IIB	T4, N0, M0
Stage IIIA	T1, N1, M0
	T2, N1, M0
Stage IIIB	T3, N1, M0
	T4, N1, M0
Stage IIIC	Any T, N2, M0
Stage IV	Any T, Any N, M1

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the Cancer Staging Manual, Sixth Edition (2002) published by Springer-New York, www.springeronline.com.

Box 161–2 Factors Associated with a High Risk of Relapse for Colorectal Cancer

Tumor Factors

- Disease stage
- High-grade tumor (poorly differentiated)
- Tumor location
- Obstruction/perforation
- Venous invasion
- Perineural invasion
- Mucin production
- Diminished stromal immune reaction
- Aneuploidy
- Mutant *p53* gene expression
- Low microsatellite instability

Technical Factors

- Inadequate resection margins (radial, distal, mesorectal)
- Implantation of exfoliated cells
- Tumor location (pelvis and splenic flexure is anatomically and technically more difficult)

tion in death rates and in some cases cost-effectiveness of intensive surveillance strategies.[44-46] Unfortunately, it is not clear what specific area of the proposed surveillance programs is actually responsible for improving survival, and none of the studies mentioned was conducted in the United States. Designing and implementing a prospective study to test the efficacy of follow-up represents a significant challenge. It is doubtful that consensus on cost-effective surveillance will be reached soon; perhaps it is most reasonable to focus resources on sites that are both frequently affected and amenable to curative resection. With this concept in mind, the lung, liver, and locoregional sites should be primary areas for the detection of asymptomatic lesions, so these could be the basis of a site-directed approach to surveillance (i.e., only find what you can fix).

History and Physical Examination

Symptoms of recurrence might include abdominal, pelvic, perineal, or sciatic pain; change in bowel habits; obstruction; anorexia; weight loss; malaise; and rectal bleeding or discharge. Unfortunately, when symptoms arise, the relapse is often at a late stage and beyond the hope of cure. Furthermore, these symptoms often present in the interval between routine follow-up appointments. Physical examination is of little value in most asymptomatic patients. Occasionally, it may reveal the presence of advanced disease, such as the presence of a mass on abdominal, rectal, vaginal, or perineal examination or the presence of a supraclavicular node. It does, however, provide valuable information on the general health status of the patient, which is vital in determining the suitability of aggressive resection. Follow-up visits can also be important in counseling patients regarding increased cancer risk in family members and the need for cancer screening.

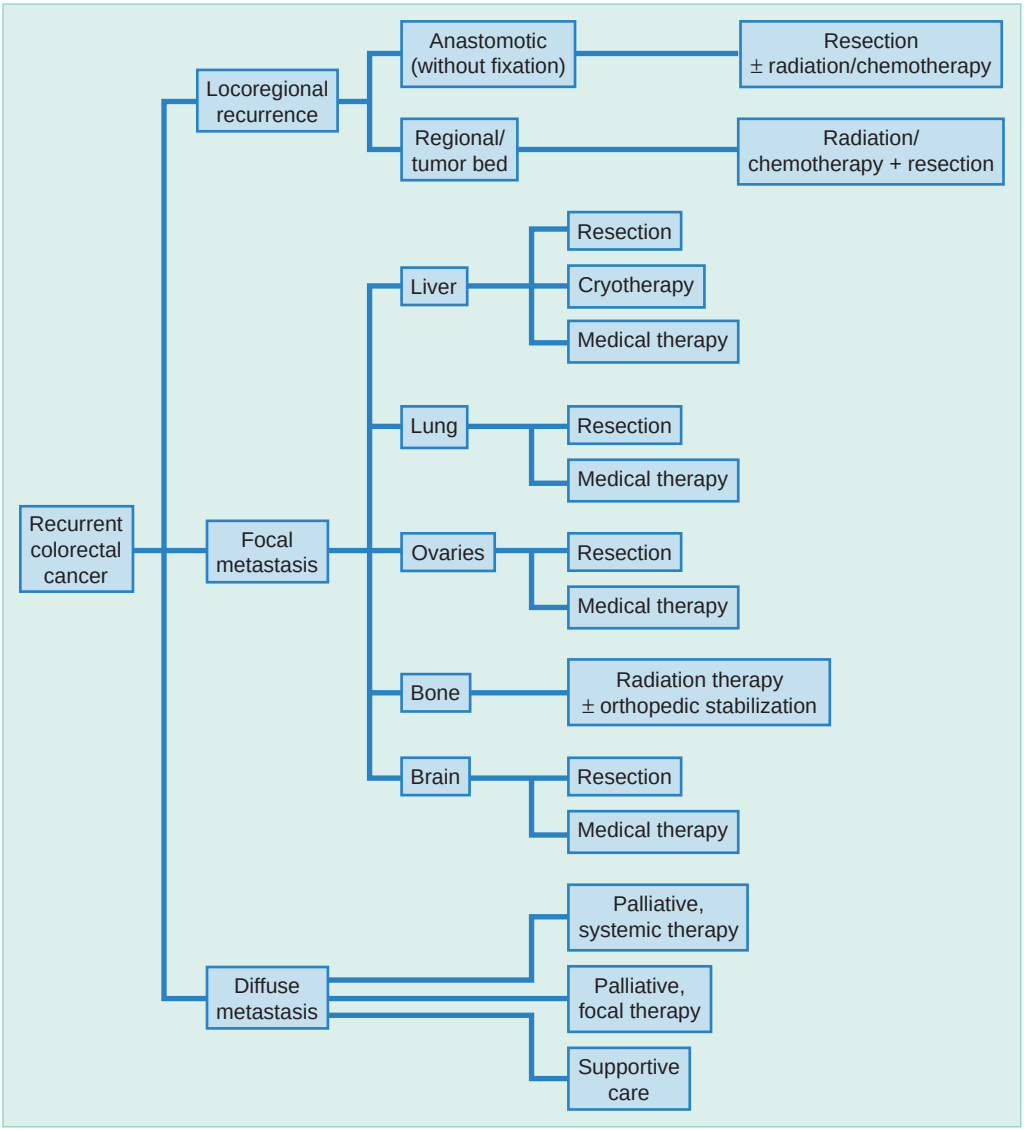

Figure 161–2. Flow chart of therapeutic options for recurrent colorectal cancer. (From Frizelle F, Nelson H: Recurrent colon cancer. In Wexner SD, Vernava AM [eds]: Clinical Decision Making in Colorectal Surgery. New York, Igaku-Shoin, 1995, p 390.)

Laboratory and Imaging Studies

Of all of the available tests, the chest film would seem to be the most rational because it is inexpensive and has the potential to detect asymptomatic but resectable lesions. However, the impact of surveillance chest radiograms on survival has been limited when tested in prospective studies.[38,47]

Routine blood cell counts and chemistries are almost useless except for the rare occasion when anemia indicates a new primary or disease relapse. The liver function tests, on the other hand, are rarely abnormal, and when they are, this often indicates the presence of extensive, unresectable disease. For patients at high risk for local or regional relapse, it may be reasonable to obtain a computed tomography (CT) scan of the abdomen and pelvis 6 months after surgery to serve as a baseline study and then repeat the CT scan at 6- to 12-month intervals for 2 to 3 years.

Endoscopy

The aim of endoscopy is the detection of anastomotic recurrences and metachronous lesions,[48] the latter being more common. To detect metachronous lesions requires full colonoscopy. Since metachronous tumors are 1.5 to 3 times more likely to occur after sporadic colorectal carcinoma, it is considered appropriate to perform frequent follow-up examinations. The frequency of surveillance colonoscopies remains the subject of debate. It is influenced by variables such as age of onset, genetic predisposition, and other risk factors. For average-risk patients a colonoscopy at 1 and 5 years seems the most common

practice. For patients with genetic susceptibilities, the interval should be 1 to 2 years depending on the certainty and magnitude of the risk. For patients treated for more high-risk tumors, especially of the rectum, it is reasonable to perform more frequent examinations using flexible sigmoidoscopy. For rectal cancers it may be possible to identify the rare anastomotic recurrence or even the more frequently occurring extrarectal recurrence. Extraluminal recurrences from residual lymphatic tissue represent the apparent origins of most locoregional pelvic recurrences.

Carcinoembryonic Antigen Test

When the carcinoembryonic antigen (CEA) test was first introduced, it received a great deal of attention because of its simplicity. Frequent monitoring of CEA levels was advocated and found to be effective in detecting the presence of local and liver recurrence 6 and 3.5 months, respectively, before becoming clinically apparent.[39,41,47,49]

The CEA story, however, has another side that deserves mention. Although rising CEA levels have a sensitivity between 86 and 94%,[50,51] normal CEA levels are not reassuring because the specificity is only between 58% and 66%.[49,51] A normal CEA level often only provides false reassurance. In a study on 1216 patients with resected colon carcinomas, 59% of the 417 patients who suffered recurrences had a preceding CEA elevation. On the other hand, 38 of 417 patients with recurrence treated with curative intent had normal CEA values.[52] In addition, once relapse is detected, whether CEA monitoring significantly affects survival is still a subject of considerable debate. In the study mentioned earlier, the 1-year disease-free survival rates were 2.3% versus 2.0% for CEA-monitored versus non–CEA-monitored patients, respectively.[52] Another report confirming the limitation of CEA in the follow-up of colorectal carcinoma comes from the United Kingdom, where a multicenter trial accrued 216 patients who underwent frequent CEA measurements as part of their follow-up after resection of colorectal carcinoma with curative intent. One half of the patients were randomized to receive aggressive work-up in case of asymptomatic CEA rise that culminated in second-look laparotomy in 62% of cases. In the remaining 108 patients, clinicians were blind to the CEA measurements and decided for second-look laparotomy in 23%. Five-year survival was 20.4% in patients undergoing "aggressive" work-up and 22% after "conventional" work-up, a difference which was not statistically significant.[53]

Positron Emission Tomography

Positron emission tomography (PET) is an imaging modality that is based on the detection of 2-(^{18}F)-fluoro-2-deoxyglucose, a glucose metabolite that is abnormally elevated in most tumor cells. Several reports have shown promise in the detection of recurrent colorectal carcinoma. This might be particularly useful following surgical resection for rectal carcinoma, where the postoperative scar tissue or postradiation changes can often be difficult to differentiate from recurrent neoplasm. Contemporary series report a sensitivity to detect local recurrences at the primary colorectal resection site up to more than 90%[54,55] and even an increased ability of PET to predict resectability of the recurrence when compared to conventional CT-based imaging.[56] In addition, a recent report suggests that PET can be 87% accurate in detecting locally recurrent rectal carcinoma even in a previously irradiated field.[57] However, PET is expensive and is still fraught with accuracy limitations, especially with regard to possible false-positive interpretations. In a report on 62 patients the accuracy of PET alone was 74%, with most false-positive results related to physiologic uptake of fluoro-deoxyglucose in displaced pelvic organs. When PET was combined with CT, the accuracy increased to 93%.[55] This can be useful for verifying the presence of a recurrence.

PET can provide important clinical information; however, its role as a surveillance strategy following curative treatment of colorectal carcinoma is evolving and cannot yet be recommended as a standard of care as a surveillance tool.

Conclusion

The aim of any postoperative follow-up strategy should be early detection of resectable disease. These efforts should be focused on identifying (1) tumors of favorable prognosis (i.e., slow growing); (2) sites of disease amenable to resection for cure (i.e., locoregional, hepatic, and pulmonary); and (3) patients who are a good risk, vigorous, and motivated who would be suitable for extensive resection.

LOCOREGIONAL RECURRENCE

Single-site locoregional recurrences account for 5% to 19% of colon cancer and 7% to 33% of rectal cancer relapses.[49,58,59] Of these, between 7% and 20% are resectable with a curative intent.[58] As discussed later, local recurrences are more likely to follow resections of rectal cancers compared with those of the colon. This section therefore focuses on locally recurrent *rectal* cancer, because most of the strategies for diagnosis and therapy can be similarly applied to locally recurrent colon cancers.

Patients with untreated locally recurrent rectal cancer live a median of 7 months. Survival up to 5 years has been reported with pelvic irradiation with or without chemotherapy but is rare (0 to 7%).[60] Radiation therapy alone is rarely, if ever, curative; it provides a 6-month symptom-free period[61] and prolongs the survival to a median of 10 to 17 months. In contrast, complete resection of locally recurrent disease can be accomplished in some patients with mean survival times of 33 to 59 months and a long-term 5-year survival rate of up to 30%.[62,63]

The patient who presents with only locally recurrent rectal cancer and no demonstrable extrapelvic disease is the ultimate challenge in the management of rectal cancers. This is because it is difficult to achieve adequate exposure and surgical access in the pelvis. Furthermore, these recurrences typically involve multiple organs and

structures, which often require extensive resection in the attempt to achieve histologically negative margins. Whether extensive surgery is possible or even reasonable requires judgment on the part of the surgeon. A number of factors should be carefully considered, including the overall health status of the patient, the status of extrapelvic disease, and the extent of local pelvic disease.

Preoperative Evaluation and Patient Selection

General Health

In the approach to repeat resection, it is imperative that the patient and physician understand the extent and magnitude of the endeavor. The ideal patient should be in good health; such extended resection in combination with preoperative chemoradiotherapy is not appropriate for patients who are in poor health, with American Society of Anesthesiology classification IV to V for certain and most patients with classification III.

Exclusion of Extrapelvic Disease

Once it is determined that the patient is suitable for surgery, the next step is to confirm that the locoregional recurrence is *isolated*. In addition to physical examination and standard surveillance tests outlined (see Box 161–2), a CT scan of the abdomen and pelvis will assess the presence of extrapelvic disease. Evaluation of the liver can be further supplemented by hepatic ultrasound or magnetic resonance imaging (MRI). This can be useful when the CT scan detects a suspicious but nondiagnostic finding. In cases of a borderline chest film, a chest CT scan should be obtained. CT scanning of the thorax is not useful as a screening tool because it is too sensitive. The identification of small indeterminate nodules is common and problematic. PET, often used in combination with CT scan, can be useful especially in patients at high risk for peritoneal spread or distant metastases. These tests for metastatic disease are usually performed before preoperative radiation and chemotherapy and again just before surgery. This provides additional reassurance that patients with aggressive disease that may have metastasized in the interim will be identified, thus avoiding noncurative surgery.

Evaluation of the Presence and Extent of Local Disease

It may be particularly challenging to prove resectability of a lesion because it is often difficult to differentiate between recurrent tumor and postoperative changes. Evaluation begins with a physical examination of the rectum and vagina. Next, endoscopy and CT with or without MRI are performed. There are generally three ways of differentiating postoperative changes from recurrent tumor. The first is to document a change in the lesion, such as increase in size, over time; the second is invasion of the adjacent organs; and finally, the third is histologic evidence obtained from CT-guided biopsies. Histology may also be obtained from a luminal or mucosal aspect of the recurrence, although this presentation is least common. Extraluminal lesions that are palpable via the perineum or per rectum or vagina may also be biopsied transrectally or transvaginally. Those not amenable to endoscopic or transluminal biopsy can almost always be sampled for biopsy using CT guidance. Histologic diagnosis can usually be obtained with these methods. Occasionally, pelvic disease is suspected due to a rising CEA level. In such situations, histologic proof should be sought. Exploratory pelvic surgery should be discouraged in the absence of imaging findings because the CEA elevation could be due to extrapelvic disease. Furthermore, the only way to exclude a pelvic recurrence is to explore the entire pelvis down to the level of the pelvic floor. This is often an extraordinary task. Even if this was done, it is often difficult to distinguish scar from tumor even at surgery, including frozen section histology. Some tumors produce nodular or discrete recurrences, whereas others can have ill-defined limits and be infiltrative or sheet-like in nature; the determination of borders and resectability can, accordingly, be difficult. Histological evidence of recurrence and radiographic imaging suitable for defining the extent and boundaries of a pelvic recurrence are almost essential.

Resectability

Locoregional recurrences can extend anteriorly, posteriorly, laterally, or in a combination of directions. In addition, any of the organs in and around the pelvis may be involved, including intestinal, urologic, gynecologic, bone, and vascular structures. When assessing locoregional recurrences, two factors are important: fixation and anatomic location. The combination of these two factors determines the resectability (Fig. 161–3). Suzuki and colleagues[64] originally categorized the extent of local recurrence based on the degree of fixation (with F0 indicating no fixation and F1 to F3 indicating one to three sites of fixation, respectively). We have modified this scheme for F0 to indicate when the tumor is not fixed, FR to indicate when the tumor is fixed but resectable, and FNR to indicate when the tumor is fixed and not resectable. FR is further subdivided by noting the anatomic extent of the fixation (anterior, posterior, and lateral) because this allows the determination of the extent of resection that will be required. Thus, anteriorly fixed lesions may require a hysterectomy or a partial or complete cystectomy, or both, and in lesions with posterior fixation, a sacrectomy may be necessary (see Fig. 161–3).

Despite this classification, it is not always possible to predict resectability before surgery. Some indicators predict that curative surgery with negative resection margins is not likely to be possible (Boxes 161–3 and 161–4). For example, unless there is infiltration of the trigone of the bladder at the insertion of the ureters to the bladder, bilateral ureteric obstruction usually indicates a bulky tumor that has invaded the lateral pelvic side walls. This means that the disease is present at the level of the pelvic inlet. In this regard, extensive disease at the pelvic inlet strongly suggests circumferential disease, and by and large circumferential tumor that

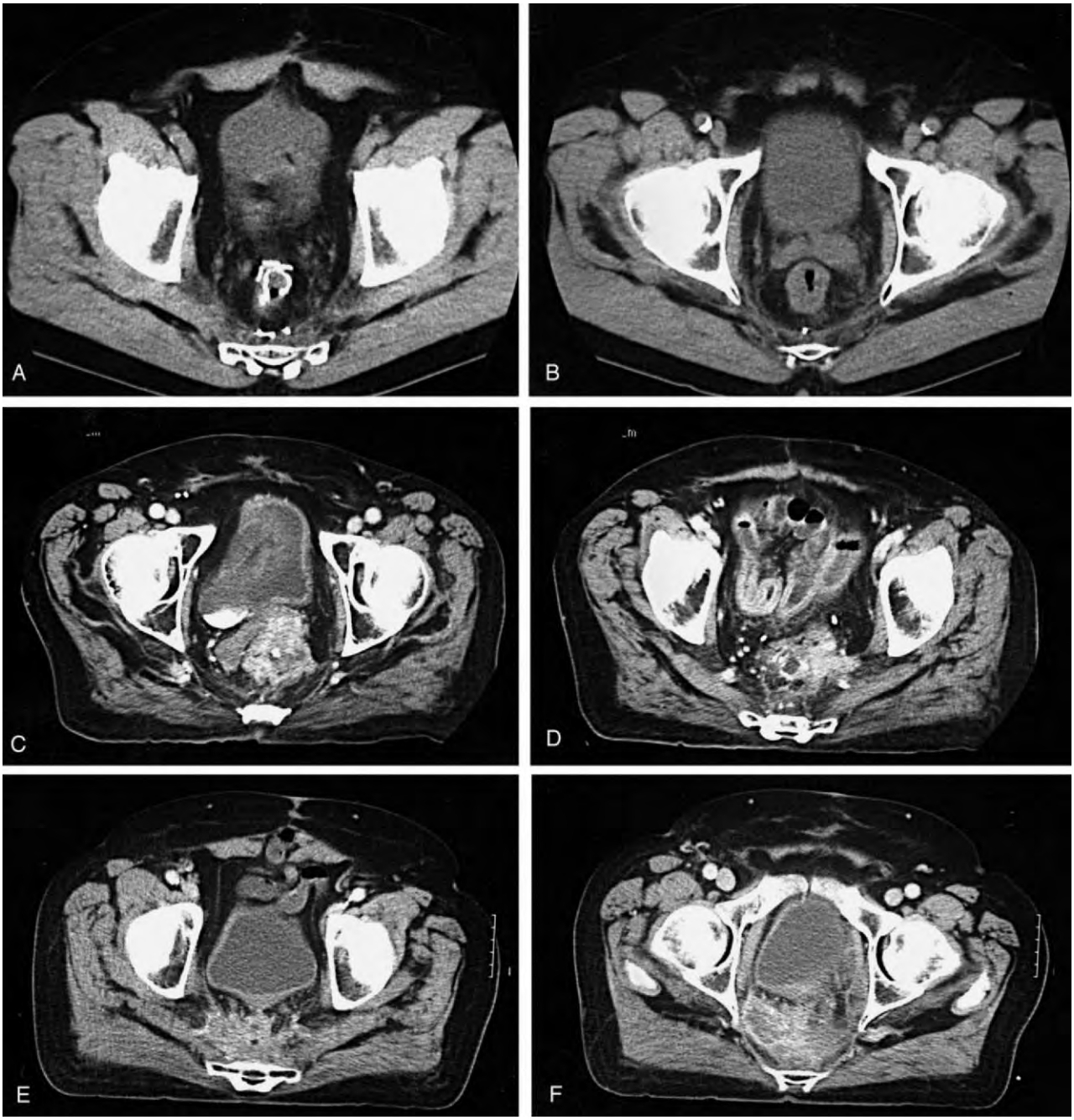

Figure 161–3. Classification of local recurrence according to fixation. **A** and **B** are examples of no fixation (F0). **A,** The stapled low anterior anastomosis is easily visualized on CT scan. **B,** Distal to the anastomosis is a perianastomotic recurrence; there is no evidence of fixation to local organs or structures. Complete resection with negative margins would be anticipated. **C** and **D** are examples of fixed resectable (FR). **C,** Single-site fixation to anterior structures such as the bladder, as illustrated, or gynecologic structures can typically be resected with negative margins. **D,** Lateral pelvic side wall fixation can be resected, but margins will often be close or microscopically positive. **E** and **F** are examples of fixed, not resectable (FNR). **E** and **F,** Two images from the same patient illustrate posterior fixation **(E)** and anterior fixation **(F)** in addition to lateral side wall involvement, rendering this recurrence unresectable.

extends to the pelvic sidewall should be considered unresectable. For relapses that involve the sacrum, lesions that are central and distal to S2 can be removed with a distal sacrectomy. Nerve root involvement of S1 or S2 or evidence of invasion of the sacral bone at the level of S1 and S2 typically indicates unresectable disease. Sacrectomy proximal to S2 results in sacroiliac joint instability, and although it is technically feasible to internally fix this, it is not warranted for cases of locally recurrent rectal cancer. Lesions above S2 and unilateral can occasionally

Box 161–3 Detection and Confirmation of Recurrent Colorectal Cancer*

Studies Advised for Surveillance

- History and physical examination (abdomen, nodes, rectum, and vagina)
- Complete blood cell counts
- Chemistries (liver function tests and lactate dehydrogenase)
- Endoscopy
- Carcinoembryonic antigen
- Chest radiography
- CT scan
- PET scan
- Hepatic ultrasonography

Studies to Confirm Relapse

- Locoregional recurrence
  - CT scan of abdomen/pelvis
  - Biopsy: CT guided, endoscopic, transrectal, or transvaginal
  - Endorectal ultrasonography
  - PET scan
  - MRI (pelvis)
- Hepatic metastases
  - CT scan of abdomen
  - Hepatic ultrasonography
  - Intraoperative ultrasonography
- Pulmonary metastases
  - CT scan of chest

Under Investigation

- Radiolabeled antitumor antibody scan
- Endorectal coil MRI

*See text for discussion.
PET, positron emission tomography.
Modified from Nyam D, Nelson H: Recurrent colorectal cancer. In Nicholls RJ, Dozois RR (eds): Surgery of the Colon and Rectum. New York, Churchill-Livingstone, 1997.

be treated with resection of the anterior sacral table. Any tumor with a component of bone involvement both above and below S2 is not resectable.

Pain from nerve root tumor involvement occasionally has to be differentiated from sciatic nerve involvement that is due to nerve compression rather than invasion, because in the latter instance, complete resolution of pain may follow the initiation of irradiation plus concomitant chemotherapy. Buttock and perineal pain, on the other hand, are usually a result of tumor expansion and are less ominous.

Box 161–4 Contraindications to Resection of Locally Recurrent Rectal Cancer

- Extrapelvic disease
- Sciatic pain
- Bilateral ureteral obstruction
- Circumferential or extensive pelvic side wall involvement
- S1 or S2 involvement (bony or neural)
- Poor general condition and surgical risk (ASA classifications IV or V, rare ASA III)

ASA, American Society of Anesthesiologists.
From Nyam D, Nelson H: Recurrent colorectal cancer. In Nicholls RJ, Dozois RR (eds): Surgery of the Colon and Rectum. New York, Churchill-Livingstone, 1997.

Trimodality Therapy

The cornerstone of treatment for locally recurrent rectal cancer with a curative intent must be surgery. However, surgery alone results in a high local and systemic failure rate. This has been the rationale for a multimodality approach to the treatment using preoperative irradiation plus concomitant chemotherapy and maximal resection for local control and chemotherapy to address the possibility of systemic failure.

Preoperative Irradiation Therapy and Chemotherapy

Although it provides symptomatic relief, irradiation therapy alone does not result in any significant chance of cure; furthermore, as stated earlier, surgery alone in cases of locally advanced rectal cancer gives rise to high relapse rates. When combined, irradiation and surgery reduce local recurrence rates and increase resectability.[6,37] Similarly, when used in the scenario of locally recurrent cancer, irradiation has been shown to improve results. In addition, the demonstration that combined fluorouracil-based chemoradiotherapy further improves results for primary rectal cancer prompted us to use a similar regimen to reduce local and systemic failures in patients with local or regional relapse. As an added modality to avoid or reduce dose-related toxicity while improving local control, we combine external beam irradiation therapy (EBRT) plus chemotherapy with intraoperative electron radiation therapy (IOERT). IOERT offers the advantages of localized tumor-directed therapy with limited normal tissue exposure, single-fraction, high biologic equivalence with improved local control in high-risk sites, as discussed later.

A full course of external beam radiation (5040 cGy) with protracted venous infusion 5-fluorouracil (5-FU) chemotherapy (225 mg/m^2/24 hr) is administered preoperatively to patients who have not had previous pelvic irradiation. Patients who have received previous adjuvant radiotherapy in the treatment of their primary tumor are treated with 1000 to 3000 cGy preoperative

radiation plus 5-FU–based chemotherapy, when possible. Maximum synergy between full-dose preoperative external beam and intraoperative radiation occurs if the two are completed within a 4- to 8-week interval. For patients receiving a full course of treatment with doses of approximately 5040 cGy, a 3- to 5-week rest period before surgery and IOERT is standard. Restaging is performed before the procedure is undertaken. When low-dose irradiation plus protracted venous infusion 5-FU is given before surgery, surgery can be scheduled without delay because continuous-infusion 5-FU rarely depresses white blood cell counts to unacceptable levels.

Operative Procedures

It is imperative that the first step in planning for surgery of this magnitude includes an extensive discussion and explanation of the planned procedure with the patient and relatives. Sphincter-saving surgery is most often not indicated in cases of local recurrence. Therefore, within the discussion must be the acceptance of a permanent colostomy. In addition, an ileal conduit or a sacrectomy in situations of anterior or posterior fixation (or both) may be required.

Patients undergo a mechanical and antibiotic bowel preparation the night before surgery. At our institution, all patients with locally recurrent rectal cancers are scheduled for surgery in a dedicated IOERT suite. This suite within the operating room complex houses the standard operating room equipment, a linear accelerator, and special anesthetic equipment that allows movement of the anesthetized patient from operating to radiating stations (Fig. 161–4). In addition, remote controls allow monitoring of the patient outside the suite in a lead-shielded room while radiation is delivered.

The patient is placed in the combined position. Special care is taken to ensure that the calves are not resting on the stirrups because prolonged operating times can result in compartment syndrome[65] or venous thrombosis. Nearly all patients receive ureteral stents. The 0-degree cystoscope is used to instrument the bladder, and the 70-degree scope is used to inspect the bladder for mucosal or extrinsic abnormalities. On occasion, direct bladder invasion is detected cystoscopically; this information can help guide the extent of surgery. No. 5 French ureteral stents are inserted using the 30-degree cystoscope, and these are secured to a Foley catheter.

A lower midline incision is used to provide optimal pelvic exposure, as well as to facilitate the possible use of rectus abdominis myocutaneous flap. Care is exercised to preserve the inferior epigastric vessels when it is anticipated that a transpelvic rectus abdominis flap may be used. Exploration includes an examination of the liver, peritoneum, omentum, ovaries, retroperitoneum, and wound to confirm the absence of extrapelvic disease because this would contraindicate radical resection. Very rarely, exceptions may be made in very young patients

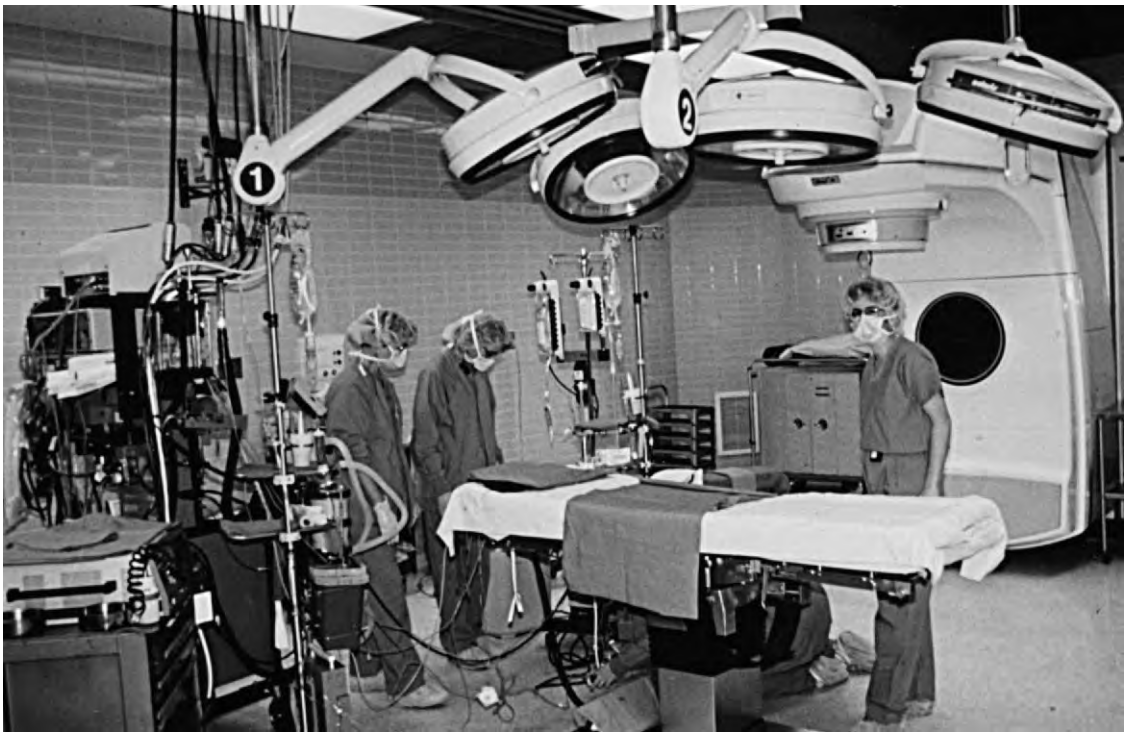

Figure 161–4. The intraoperative electron radiation therapy suite, showing the equipment, operating room table, and linear accelerator. (From Nyam D, Nelson H: Recurrent colorectal cancer. In Nicholls RJ, Dozois RR [eds]: Surgery of the Colon and Rectum. New York, Churchill-Livingstone, 1997, pp 505-523.)

who have limited pelvic and liver disease where the pelvic recurrence and liver metastases are each synchronously resected for curative potential.

We use a self-retaining ring retractor. The small bowel is packed superiorly for pelvic exposure. Because these operations are lengthy, care must be taken to avoid pressure from a retractor on the retroperitoneal/pelvic tissues; femoral nerve injuries have been described, implicating prolonged retractor pressure as causative. Because pelvic fibrosis is the rule, the dissection starts at the bifurcation of the aorta so a safe fascial plane is found to guide the posterior dissection down to the pelvic floor (Fig. 161–5A). The iliac arteries and veins are coursed from the aorta and cava to the branching of the internal and external branches. Below the common and external branches of the iliac arteries, the vessels can be ligated without concern for ischemia. Knowledge of the location of these vessels prevents most of the risk for exsanguination and the need for vascular bypass surgery; at the same time, it facilitates identification of the safest posterior and lateral planes. In the same way, the ureters are identified from the pelvic brim and followed by anterior

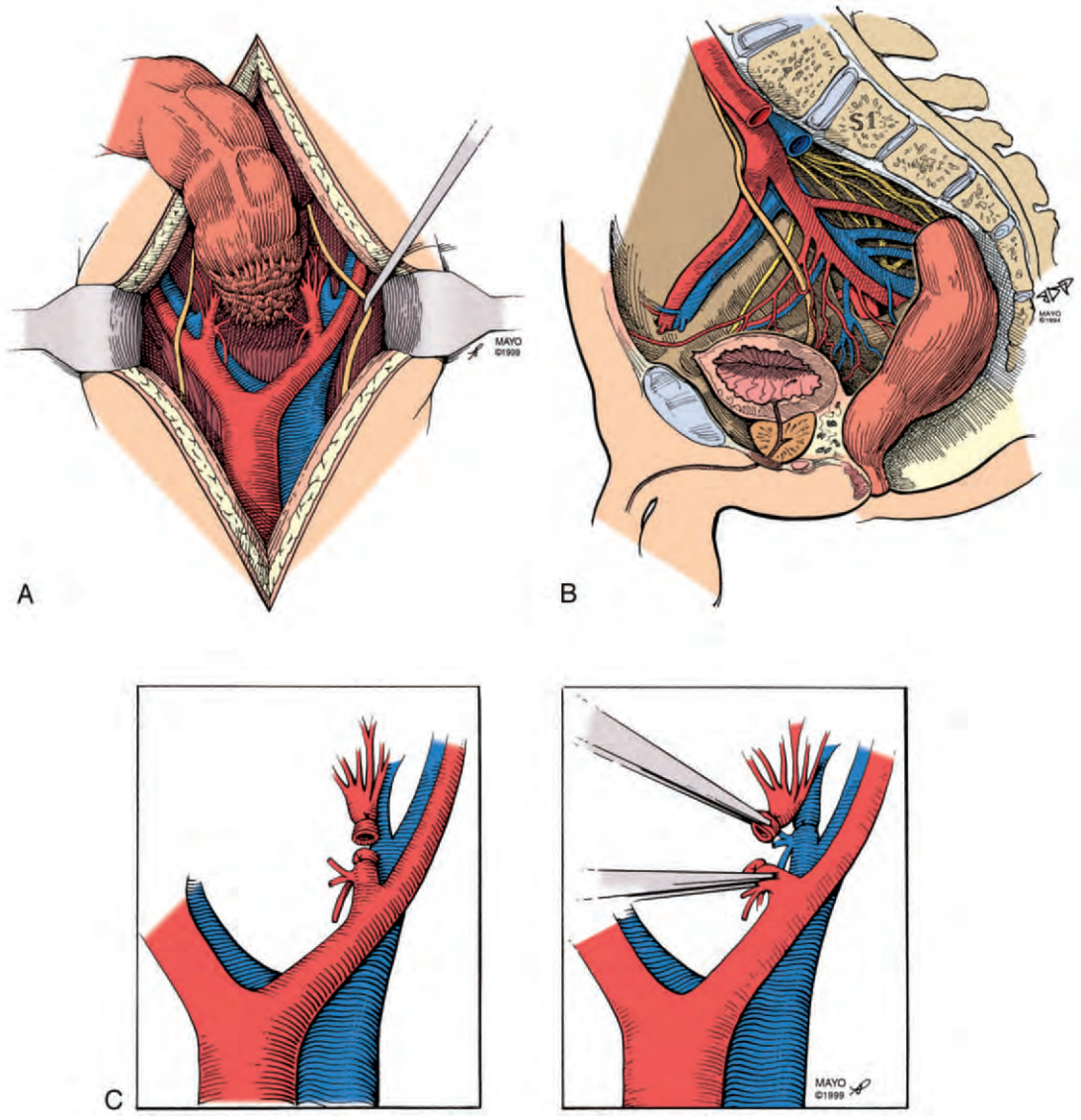

Figure 161–5. **A,** Broad view of pelvic dissection. The iliac vessels are dissected from the level of the aortic bifurcation to at least the origin of the internal iliac branches. The ureters are located and followed from the pelvic brim to their insertion into the bladder. Once the vessels and ureters are located, it is safe to proceed with the posterior dissection, commencing at the sacral promontory. **B,** Anterior approach (operative anatomy of pelvic structures). The anterior procedure provides assurance that no extrapelvic disease is present and provides several preparatory steps for the sacral resection, including anterior and lateral dissection, proximal sacral margin delineation, parasacral vascular ligation, gastrointestinal and/or urinary stoma formation, and omental or rectus abdominis flap creation. **C,** Bilateral internal iliac artery and vein ligation is performed if sacral transection proximal to S3-4 is expected. The artery typically must be ligated and divided to provide exposure to the internal iliac vein. The vein can be ligated without transection. (**A-C,** © Mayo Foundation, 1999.)

dissection to the level of their insertion into the bladder. It is usually necessary to trace the ureters right to their insertion into the bladder so the lateral dissection can be performed safely. Ureter dissection is more extensive when a cystectomy or sacrectomy is contemplated; it is essential for the construction of an ileal conduit and for the prevention of injury during the posterior dissection, respectively.

Nonfixed Lesions

The recurrence of F0 lesions after local excisions or low anterior resection may require nothing more than a simple completion APR. The main difference between this and the standard APR is the added difficulty in dissection due to fibrosis and changes in anatomy due to the original surgery. Distinction between fibrosis and tumor infiltration is very difficult at best. In such circumstances, particularly when it occurs outside the realm of planned resection, such as the sacral promontory and lateral pelvic walls, frozen section should be obtained. If tumor cells are seen within the samples of diffuse or extensive "fibrosis," complete resection with negative margins is not feasible.

Fixed-Resectable, Anterior Lesions

Anterior lesions demonstrate the greatest diversity between men and women. In women, anterior fixation may require little more than en bloc resection of the rectum, uterus, and posterior wall of the vagina. In contrast, anterior fixation in a narrow male pelvis is more likely to require cystectomy or cystoprostatectomy. Caution should be exercised for lesions that are directly invading the trigone or prostate because these are often circumferential and "after the fact" are found not to be completely resectable. It is perhaps the tissue planes at and below the seminal vesicles that allow for ease of circumferential tumor spread. Pelvic MRI or CT/PET fusion studies show promise for better delineation of tumor extent in these cases.

For anterior lesions, partial cystectomy may be sufficient in some cases to accomplish negative margins. However, it may be preferable to perform total cystectomy and ileal conduit for heavily radiated bladders where tissues are unlikely to allow for proper healing and acceptable postoperative functional results.

Fixed-Resectable, Posterior Lesions

The ideal procedure for tumors with posterior fixation and bone involvement is a distal sacrectomy. If sacral resection is considered it should be distal to S2-3. Having said that, true sacral invasion is uncommon and sacral resection is rarely indicated. A resection more proximal than S2 may require stabilization of the sacroiliac joints with internal fixation and other reconstructive methods and is not indicated. Furthermore, by limiting the resection to the S2-3 level, the preservation of one S3 root is generally possible. This is usually sufficient to preserve bladder function. Best results in terms of margins and risk of recurrence can be expected for central lesions, that is, those without a pelvic side wall component.

Distal sacrectomy consists of four stages: (1) the anterior resection procedures, (2) the posterior resection procedures, (3) IOERT, and (4) pelvic reconstruction. Anterior procedures are performed with the patient in the legs-up position. The abdominal cavity is explored before pelvic dissection. As described earlier, to minimize the risk of inadvertent injury due to anatomic displacement, dissection of the ureters and iliac vessels begins at the level of the aortic bifurcation (see Fig. 161–5A and B) and progresses deep into the pelvis. The posterior plane is generally the safest place to begin but is limited to the level of the tumor. Anterior and lateral resection planes are dissected with adherent organs, and structures are removed en bloc with the posterior-based tumor. A frozen-section biopsy at the level of posterior fixation ensures that a negative sacral margin is achievable. In addition, the top of the sacral resection margin is scored, a maneuver that facilitates identification of the posterior sacral transection.

With resectability established, the remainder of the anterior and lateral dissections are completed, leaving the tumor attached only to the sacrum posteriorly. The internal iliac artery and veins are ligated bilaterally if sacral transection proximal to S3-4 is anticipated (see Fig. 161–5C); this reduces blood loss during sacrectomy. Either an omental or a rectus abdominis flap (Fig. 161–6) is mobilized and transposed into the pelvis for subsequent retrieval and reconstruction during the posterior procedure. The gastrointestinal or urinary stomas are fashioned before closure of the abdomen. This completes the anterior procedures.

The patient is repositioned prone, and a posterior midline incision is made over the lower lumbars and sacrum to coccyx. If sacrectomy is performed simultaneous with APR en bloc, then the elliptical anal excision is incorporated with the proximal sacrum incision. The gluteus is dissected to expose the entire sacrum. This exposure facilitates the division of the sacrotuberous and sacrospinous ligaments (Fig. 161–7A). With care taken to protect the sciatic and pudendal nerves, the piriformis muscle is divided (see Fig. 161–7B). Division of this muscle allows the endopelvic fascia to be entered. Once the pelvic floor is opened, palpation from behind allows identification of the level of sacral transection as previously determined by frozen sections that confirmed the absence of tumor. The orthopedic surgeon next performs the laminectomy, dural sac ligation, and bony transection. The pelvic surgeon assists in completing the lateral pelvic side wall dissection, taking care to protect the ureters, bladder, and urethra. Intraoperative irradiation, as described later, is performed next, followed by wound closure with or without flap reconstruction.

Intraoperative Delivery of Electron Beam Radiation Therapy

Once the specimen is resected, it is reviewed by the pathologist, surgeon, and radiation oncologist to determine margins and the need for IOERT. As indicated,

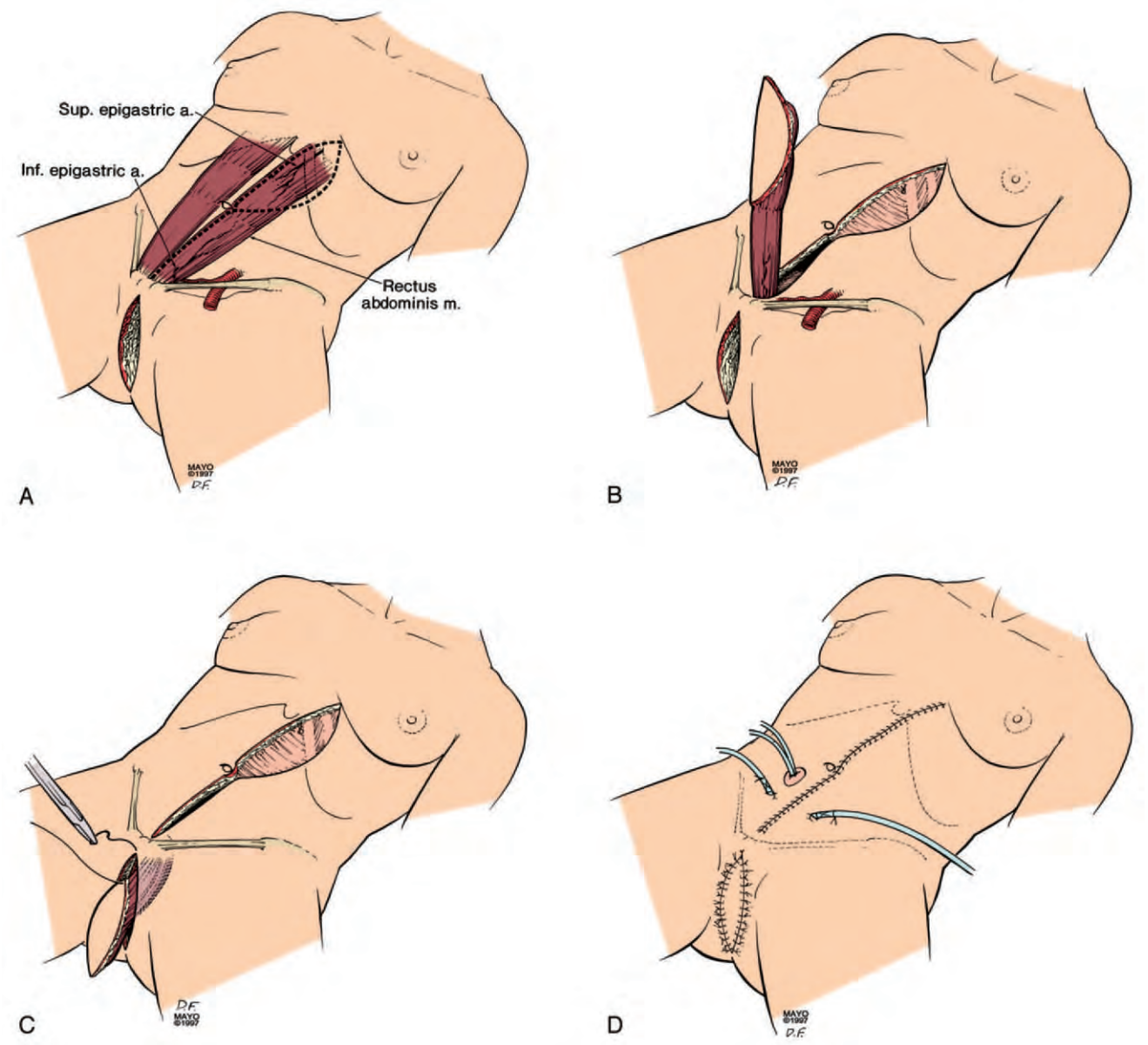

Figure 161–6. Rectus abdominis myocutaneous flap pelvic closure. This series of drawings illustrates the perineal positioning of a rectus flap. The same technique is used for sacrectomy wounds only that the flap is left in the pelvis at the end of the anterior (abdominal) procedures and pulled through the posterior defect and sutured after the sacrectomy and intraoperative electron radiation therapy are completed. **A,** Once perineal resection is complete, the skin paddle is designed to match the size of the defect. The harvest site for the skin paddle is determined based on the direct perforators from the underlying rectus abdominis muscle. **B,** The myocutaneous flap and associated skin paddle are raised and include the anterior fascia of the rectus sheath. The blood supply is provided by the inferior epigastric artery. **C,** The flap is delivered through the pelvis to the perineal defect. Care is taken to avoid stretching or torsion on the inferior epigastric blood supply. **D,** The skin paddle is secured with interrupted sutures, and the abdominal fascia and skin are reapproximated. (**A-D**, © Mayo Foundation, 1997.)

additional biopsies may be required to define sites of marginal resection. When IOERT is required, a Lucite applicator is positioned in the pelvis to target the tissues at risk (Fig. 161–8). The applicator is selected for size (typically 5 to 8 cm in diameter) and shape (typically circular and 30 degrees beveled). The patient is then positioned under the linear accelerator. Between 1000 to 2000 cGy is usually delivered depending on the extent of margin involvement and the dose of preoperative EBRT. If full-dose preoperative EBRT is feasible to 5040 cGy, a dose of 1000 to 1250 cGy is recommended for less than or equal to microscopic residual disease; 1500 to 1750 cGy for gross residual disease less than 2 cm in size; and 2000 cGy is reserved for unresected or gross residual disease of more than 2 cm in size. These single-dose radiation treatments are biologically equivalent to 1.5 to 2.5 times the same quantity of EBRT fractions.[22,24] If the preoperative EBRT dose has to be limited to 2000 to

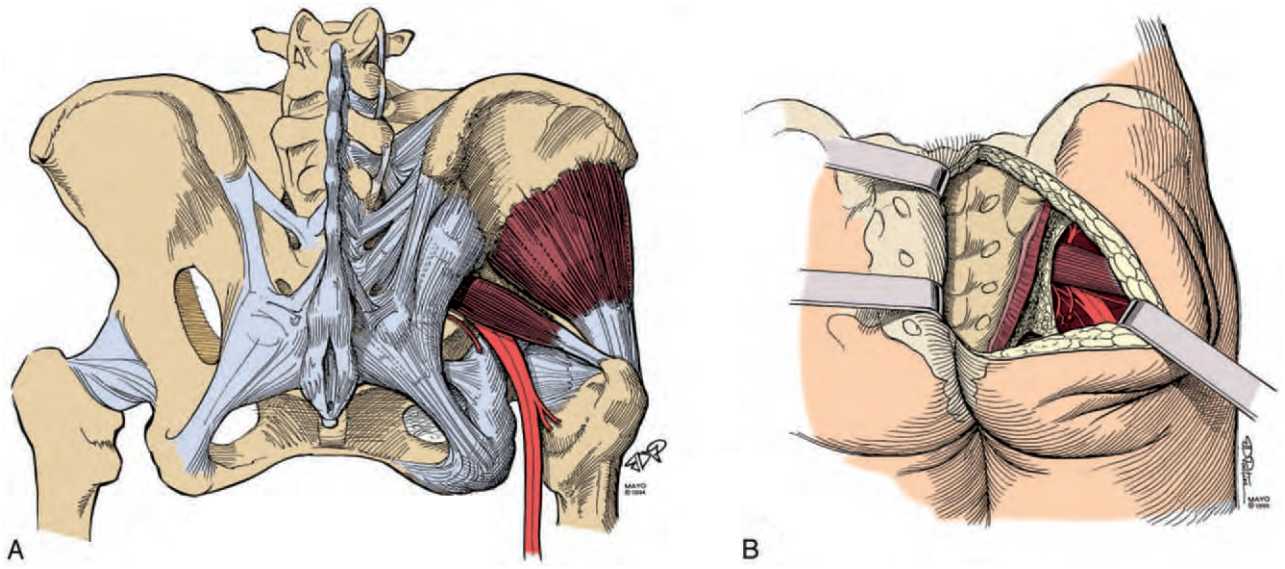

Figure 161–7. Operative techniques, posterior approach showing anatomic relationships **(A)** and operative anatomy **(B).** To remove the sacral tumor posteriorly, the gluteus must be dissected from the sacrum, and the sciatic nerve identified. The sacrotuberous and sacrospinous ligaments, pyriformis muscle, and endopelvic fascia are divided, and then the dural sac is ligated and sacrum transected. (**A** and **B,** © Mayo Foundation, 1994.)

3000 cGy due to prior EBRT, the IOERT dose ranges from 1500 to 2000 cGy because it has to account for some of the dose that could not be delivered with EBRT. IOERT doses of less than 1250 cGy are less likely to cause long-term side effects such as motor and sensory neuropathies but usually are not feasible in retreatment situations.

Perineal Wound Closure

Because the residual defects are generally sizable and the tissue quality poor due to prior irradiation, flaps are often used to partition the pelvis, obliterate the dead space, and deliver nonirradiated vascularized well-oxygenated tissues to the area. If the omentum is not of suitable size or consistency, the rectus abdominis flap is preferred especially for sacrectomy wounds (see Fig. 161–6).[66] In addition, the rectus is versatile and can be used to reconstruct a narrowed or shortened vagina after extensive resection. A vaginal tube can be constructed from a spiral configuration of the rectus attached to a short cuff at the introitus or from a folded flap reconstructing the anterior or posterior defects.[67] Sexual function can be acceptable after flap-vaginal reconstruction.

An alternative option to the creation of a flap is the application of a vacuum-assisted closure device which can also be used to treat perineal wound complications.[68]

Results of Trimodality Treatment for Locally Recurrent Disease

In the largest experience with long-term follow-up reported to date, 429 patients with locally recurrent rectal cancers were treated with the multimodality approach between 1981 and 1996.[63] After preoperative chemoradiation and restaging at 3 to 5 weeks after completion of treatment, 35 patients demonstrated evidence of extrapelvic disease and became unsuitable for surgery. That leaves 394 individuals who underwent exploratory laparotomy with the intent of removal of gross disease. Unfortunately, 90 of these patients had intraoperative evidence of unresectable or extrapelvic disease. Therefore, the 304 remaining patients underwent maximal resection, which was histologically confirmed as curative in intent in 138 cases. The remaining 166 patients had a palliative procedure because of either gross or microscopic residual disease in the pelvis, which occurred in 139 and 27 cases, respectively. Follow-up was complete for 5 years or until death in 95% of the 304 patients analyzed.

At multivariate analysis the number of sites of tumor fixation predicted palliative versus curative resection. Gender, age, probability of sphincter preservation and presence of symptoms did not vary significantly between palliative procedures versus procedures with curative intent.

Performed procedures included low anterior resection with primary anastomosis in only 5% of cases. Among the remaining patients, 41% underwent APR, wide local resection of the recurrent mass (25%), or Hartmann's procedure (7%). An additional 9% was treated with major radical resection (sacrectomy, pelvic exenteration, and total cystectomy with ileal conduit). A total of 5% of patients had no detectable tumor cells in their specimen despite preoperative histological evidence of recurrent carcinoma.

Morbidity

Mortality was 0.3% and was related to one patient with uncontrollable hemorrhage. Overall morbidity was 26%.

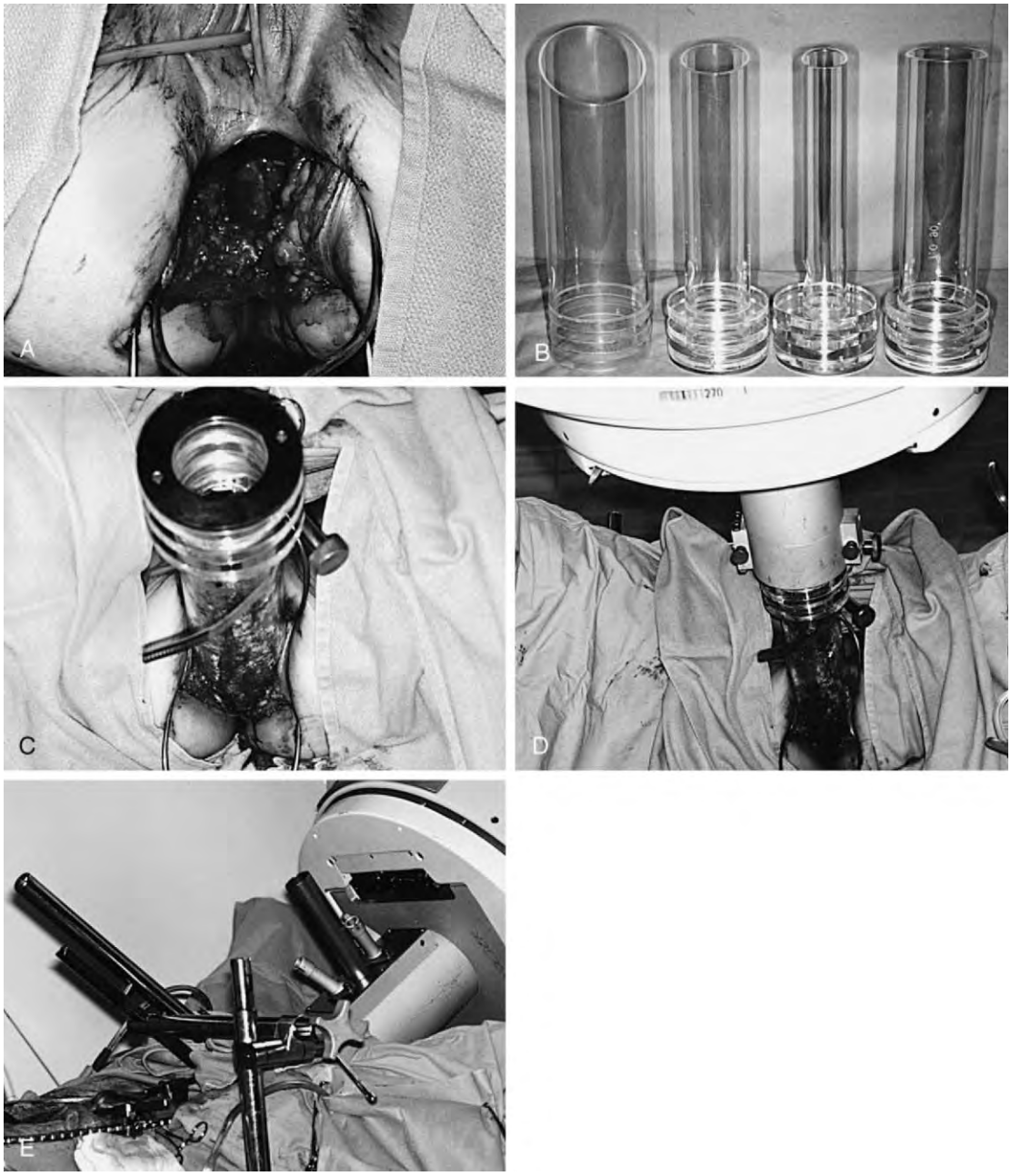

Figure 161–8. Intraoperative delivery of radiation therapy. **A,** Once the tumor is resected, the pathologist, surgeon, and radiation oncologist examine the closest margins and determine the site and extent of tumor bed risk. Sites of recurrence deep in the pelvis are often best approached with a perineal port for radiation therapy. **B,** A Lucite applicator is selected to fit the surgical field at risk for failure of local control. Several sizes and shapes are available with varying degrees of bevel to accommodate the field of radiation. **C** to **E,** The applicator is placed into the field, stabilized to the operating table, and connected to the linear accelerator.

The most frequent causes of morbidity were pelvic abscesses (7%), bowel obstruction and perineal wound problems (5% each), fistula (4%) and cardiovascular complications (1%). Predictors of increased morbidity were extended resections (32% versus 21%, $P = .04$) and two or more fixed pelvic recurrence sites (20% for = 1 fixed site of recurrence versus 35% for 2 fixations and 32% for three or more fixations, $P = .05$). Morbidity and mean length of hospital stay were similar between patients undergoing surgical procedures with palliative (16.4 days) versus curative intent (15.7 days).

In the subset of patients undergoing sacrectomy ($n = 16$), the complication rate was as high as 50%, with most complications related to the posterior wound.[69] In response to the high wound complication rate for posterior (sacrectomy) and perineal (APR) cases, we now

encourage the use of a primary rectus abdominis myocutaneous flap.[66]

Cancer Outcomes

Patients undergoing potentially curative resection had longer 5-year overall survival compared with patients with residual disease (37% versus 16%, $P < .001$). Among patients with a palliative resection, overall survival was non-significantly related to the amount of residual disease (22% for microscopic disease versus 14% for gross disease, $P = .1$). Factors predictive of decreased 5-year overall survival were number of fixed pelvic recurrence sites (37% if no fixation, no survivors if 3 or more fixation sites, $P < .001$), pain as a symptom of recurrent disease (39% for painless recurrences versus 18% for patients with pain, $P < .001$). IORT was selectively administered in 52% of patients who underwent palliative procedures and in 33% of patients operated with curative intent. Although the select use of IORT precludes definitive conclusions regarding its specific contribution to cancer outcomes, the encouraging cancer outcomes in this series of patients support its continued use.

The role of multimodality and repeat resective therapy in controlling and relieving disabling symptoms of pain, bleeding, tenesmus, and bowel and bladder dysfunction should be mentioned. Although we are not proposing this line of management for lesions that are preoperatively considered unresectable, the curative intent of surgery often secondarily results in significant palliation. Long-term survival is rare (less than 5% for patients with gross residual without IOERT and 0 to 18% of those with IOERT), but median survival times are long enough that palliation becomes a significant issue. It is difficult to conclusively demonstrate the effect of multimodality therapy on long-term palliation, but at least in the sacrectomy group, one report describes patient benefits from the relief of symptoms. In a questionnaire survey, eight of nine long-term survivors who had undergone a sacrectomy reported a reduction in pain and improved quality of life, with six of the eight returning to work.[69] This is impressive considering the extensiveness of the procedure and the frequency of morbidities. More sophisticated quality-of-life evaluations will be useful to provide more definitive evidence of the value of multimodality therapy for long-term palliation.

Locally Recurrent Colon Carcinoma

It is estimated that approximately 10-20% of patients presents with an isolated locoregional recurrence amenable to surgical resection. The role of multimodality treatment for this specific indication is not considered as standard of care. However, 73 patients with locally recurrent colon carcinoma treated with a combination of chemotherapy, EBRT, and surgical excision followed by IORT had a 5-year survival of 24.7%. More specifically, the 5-year survival rate in the subset of 38 patients having their disease completely resected was 37.4%.[70] While this specific treatment strategy and in particular the use of IORT cannot be easily applied on widespread basis, this data demonstrates once more the validity of an aggressive approach to treat locally recurrent colorectal carcinoma in select patients.

Summary

Patients who otherwise enjoy good health and who present with isolated locally recurrent tumors may be candidates for trimodality therapy with EBRT, chemotherapy (preferably concomitant with EBRT and maintenance), repeat resection, and IOERT. The possibility of cure and the extent of resection, including anterior and posterior exenteration, are determined by the anatomic location and degree of tumor fixation. When achievable with negative margins or microscopic residual disease, the use of resection and trimodality therapy that includes IOERT is associated with acceptable 5-year survival rates and nerve tolerance. Nerve intolerance is higher in patients with gross residual because larger IOERT doses are necessary.

PULMONARY METASTASIS

It is generally accepted that less than 10% of patients with pulmonary metastases have not any additional recurrence sites and only 2% of patients with colorectal lung metastases are candidate for metastasectomy. This holds true for hepatic and pulmonary metastases even though the former are more common than the latter. Because hepatic metastases are covered in a separate chapter, this section focuses exclusively on the management of pulmonary metastases. The basic management in terms of therapeutic modalities available, results, and controversial issues is essentially similar between hepatic and pulmonary metastases. In general, favorable outcomes may be anticipated when lesions are isolated or in only one lung lobe and can be completely resected in an otherwise healthy individual.

Patient Selection

No formal guidelines exist with regard to pulmonary surveillance after resection of colorectal carcinoma. Most lung secondary tumors are seen on plain chest films. Once detected, a CT scan of the thorax is necessary to evaluate the resectability of the lesion and to detect other smaller lesions. At the same time, a metastatic work-up should be done to exclude extrathoracic lesions in the manner as outlined earlier. General guidelines for pulmonary resection for metastatic disease closely parallel those for hepatic disease (i.e., disease should be limited, preferably three or fewer lesions, all disease must be amenable to resection, and patients must be in good health with good pulmonary function and pulmonary reserve).

Results of Pulmonary Resection

Pulmonary resection for metastasis can be performed with low mortality and high success rates with contem-

porary 5-year survival rates in the range of 27 to 41% in recent series.[71-74] Analogous to hepatic metastases, there is an inverse relationship between the number of metastases and survival outcomes. Other prognostic factors include size of the lesion, lymph node involvement, presence of additional metastatic sites and in some series prethoracotomy CEA level.[72] In the Mayo Clinic series of 139 patients, 71% had solitary lesions. The authors reported an operative mortality rate of 1.4%, a 5-year survival rate of 31%, and a 20-year survival rate of 16%.[75] Interestingly, neither primary disease-free survival nor primary colorectal cancer stage significantly affect survival rates after thoracotomy.[76] The role of adjuvant therapy after resection of pulmonary secondary tumors is not established, because there is no evidence that systemic therapies reduce the high risk of subsequent relapse in these patients. Repeat resection of recurrent pulmonary metastasis has been described, with survival being very similar to that for the first resection.[76]

Summary

Although pulmonary metastases are less common than hepatic secondary tumors, it is worthwhile identifying isolated pulmonary lesions amenable to resection. In addition, not only do first resections have a reasonable 5-year survival outcome, but repeat resections for recurrent lesions are also associated with a reasonable chance for cure. The most important criterion for good outcomes is patient selection. Isolated resectable lesions in patients with good health and good pulmonary reserve are key to this outcome.

ISOLATED METASTASES—OTHER SITES

The ovaries, bone, and brain are much less often involved with focal lesions. Although ovarian relapse is often considered to indicate a peritoneal process, in the absence of extrapelvic disease, a curative approach with resection and irradiation would be appropriate. Prophylactic oophorectomy has been recommended at the time of primary surgery typically for postmenopausal women.[77,78] However, prospective evaluation of the resected ovaries seems to indicate the number of ovarian secondary tumors removed is negligible, and the only value of such a procedure, if any, was in the detection and treatment of early ovarian neoplasms.[79] The potential advantages of oophorectomy may be negated by the risk of dysfunctional uterine bleeding when the uterus is not removed (even in postmenopausal women) and by the risk of complications when the uterus is removed.

Bone and brain lesions typically manifest in the setting of diffuse disease and are rare sources of curable disease. Bone metastases are usually treated with internal fixation as required for stabilization and irradiation for palliation and to control disease.[80] In cases of solitary brain metastases in a nonvital region, resection and postoperative irradiation are reasonable. When surgical resection is not indicated, steroids plus irradiation serve to palliate the process.

DIFFUSE METASTASES

In the presence of diffuse disease, no curative options are available. However, the importance and complexity of palliative therapies should not be overlooked or underestimated. Because the practice of managing focal metastatic disease generates a group of patients with diffuse disease, a few words on this topic are included.

The goals in management should be refocused away from the pursuit of cure and toward the short-term goals of improving quality of life and prolonging life where appropriate. Toward the end of the natural history of events, the physician should facilitate the family and individual in coping with chronic illness and the concept of death while at the same time alleviating disabling symptoms.

Chemotherapy Agents

5-Fluorouracil has been the mainstay of palliative chemotherapy for many years and has resulted in a overall survival averaging 12 months. However, in the past few years newer agents have demonstrated activity against metastatic colorectal carcinoma in a number of phase III trials, namely irinotecan and oxaliplatin. The addition of irinotecan to the standard regimen of 5-fluorouracil and leucovorin, referred to as IFL, has resulted in a statistically significant survival benefit when compared to the standard treatment alone.[81,82] Similarly, the addition of oxaliplatin (FOLFOX regimen) improved survival over 5-fluorouracil and leucovorin alone.[83] Efforts to optimize chemotherapy doses, schedules and combination treatments are currently underway. A phase III European trial has shown that the sequence of folinic acid, fluorouracil and irinotecan followed by folinic acid, fluorouracil and oxaliplatin was associated with a median overall survival of 21.5 months.[84] In addition, an analysis based on data from 7 recently published phase III trials in metastatic colorectal carcinoma indicated that the use of all 3 active drugs (fluorouracil-leucovorin, irinotecan, oxaliplatin) in advanced colorectal cancer maximizes overall survival. The prevailing standard of care in the advanced disease setting is currently the FOLFOX regimen, which offers decreased toxicity and possibly survival benefits when compared to the IFL regimen.[85] However, this area of investigation is rapidly evolving as monoclonal antibodies are being tested in combination with more traditional chemotherapeutic agents.

Biologic Response Modifiers

Monoclonal antibodies have been used in combination with chemotherapy agents to improve control of metastatic disease. Bevacizumab is a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF) ligand. The addition of bevacizumab to both irinotecan and oxaliplatin regimens has shown survival benefits. In a recent trial on 813 patients with previously untreated metastatic colorectal carcinoma, the median overall survival in the subgroup treated with irinotecan, bolus fluorouracil/leucovorin,

and bevacizumab was 20.3 months as compared with 15.6 months in the group treated with IFL regimen only.[86] In a smaller group of previously treated patients with advanced colorectal cancer the addition of bevacizumab to FOLFOX increased the median overall survival from 10.7 to 12.5 months.[87] Other anti-VEGF agents in clinical development include vatalanib (PTK787/ZK), also a selective tyrosinase inhibitor, and angiozyme, which catalyzes the mRNA encoding the VEGF receptors.

Cetuximab (C 225) is an FDA-approved chimeric antibody directed against the endothelial growth factor (EGFR) receptor which has been studied mainly in phase II trials. A group of 329 patients with EGFR-positive metastatic colorectal carcinoma refractory to irinotecan was randomized to receive a combination of irinotecan and cetuximab versus cetuximab alone. Response rate and time to progression were significantly greater in the combination arm while no survival benefits were noted, possibly related to a crossover treatment in patients treated with cetuximab alone.[88] Other EGFR-inhibitors currently under investigation include panitumumab (ABX-EGF), gefitinib (ZD 1839) and erlotinib (OSI 774).

Recent innovations in the medical treatment of metastatic colorectal carcinoma have already significantly improved the survival of this patient population. As several new agents are being developed and tested, further improvements and establishment of newer standards of care are anticipated.

Other Palliative Treatments

Later in the course of the disease, palliation is focused entirely on relieving symptoms, either surgically or medically. Surgery has been historically the mainstay of treatment to relieve bowel obstruction. However, in recent years self-expanding metal stents have been increasingly used as an alternative to emergent surgery. A recent analysis of 54 different studies based on a total of 1198 patients showed a technical and clinical success of 94% and 91%, respectively. Major complications included perforation (4%), stent migration (12%) and reobstruction (7%) with a stent-related mortality of 0.6%.[89] While stents have been often used to allow colonic decompression and bowel preparation followed by surgery, their use to palliate symptoms and avoid colostomy has been proven effective.[90] A small randomized trial comparing stoma creation with metallic stent placement suggests that both approaches carry similar morbidity and mortality but stent placement allowed for faster resumption of oral intake and reduced hospital stay.[91] The use of stents to promptly resolve colorectal obstruction and allow a more rapid initiation of chemotherapy is also attractive although data on this approach are still limited. One of the drawbacks of self-expandable metallic stents is their inability to control bleeding. With this regard, endoscopic laser ablation is an alternative modality which can only temporarily relieve obstruction but has greater efficacy in the treatment of rectal bleeding from advanced unresectable disease.[92,93] Medical therapies, including narcotic agents, antidepressants, local nerve blocks, and epidural analgesic pumps, can be used in a stepwise manner to relieve pain and improve coping abilities. Finally, patients and family often need reassurance and assistance with end-of-life issues; they must never feel abandoned.

CONCLUSION

Colorectal cancer relapse, although often complex in presentation, can best be considered and categorized as resectable for possible cure or not. Where the former is possible and long-term survival can be achieved, specifically for isolated lesions in the liver, lungs, and locoregional sites, is encouraging. For relapses in local and regional sites, results appear to be improved with the use of multimodality therapy, including EBRT plus concomitant 5-FU–based chemotherapy, in addition to maximal resection and IOERT. These results may be further enhanced by the introduction of new systemic adjuvant therapies with different mechanisms of actions that are aimed at reducing the risk of systemic failure. In the meantime, a focus of efforts on surveillance and early detection of high-risk but resectable sites may improve outcomes for locally recurrent or metastatic disease. When presented with cases of diffuse disease, clinical efforts should not be abandoned but rather refocused on improving quality of life.

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Chapter

162

Resection and Ablation of Metastatic Colorectal Cancer to the Liver

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In this chapter, we address the management of hepatic metastases from colorectal cancer. Our primary aim is to provide a practical algorithm of treatment options for various clinical situations encountered by surgeons. Within this overview, the advantages and disadvantages of therapeutic alternatives are presented in some detail to facilitate management of these often complex clinical situations and, more important, to benefit the patient's care.

Metastatic colorectal carcinoma in the liver is a significant clinical problem. Nearly 70% of the approximate 150,000 persons who develop colorectal carcinoma yearly in the United States will harbor hepatic metastases *eventually*. Approximately 25% of these patients have metastases that are recognized at the initial clinical presentation of the primary tumor, and in another 45% of the patients, metastases are diagnosed subsequently. Nearly 50% of the patients with hepatic metastases harbor disease in the liver only, and these patients are the focus for hepatic resection. Currently, hepatic resection of colorectal metastases is the treatment of choice for patients with resected or resectable primary and regional disease if all gross liver disease can be excised. However, ablation of hepatic metastases has evolved as either an alternative or adjunct to re-resection if primary and regional disease as well as all gross liver disease can be excised.

PATIENT SELECTION

The selection of patients with colorectal metastases for hepatic resection is influenced by several factors, including (1) the stage of primary tumor, (2) the extent of the hepatic metastases, (3) the intent of the resection (curative vs. palliative), and (4) response to neoadjuvant chemotherapy. Assumedly, the clinical performance status of the patient and the comorbidities of major organ systems permit resection with an expected operative risk of less than 5%. Temporally, colorectal metastases present in three clinical situations: (1) synchronously with the primary cancer, (2) metachronously after resection of the primary cancer, and (3) metachronously after previous hepatic (or pulmonary) resection of colorectal metastases. Undertaking concurrent resection of the primary colorectal cancer and hepatic metastases resection requires thorough preoperative hepatic imaging. If resections are undertaken concurrently, gross total resection of the primary tumor with all regional disease is required. If these caveats are fulfilled, then resection can be undertaken with the same expected outcome and similar mortality and morbidity as staged resections.

The stage of the primary cancer clearly affects the decision to resect the hepatic metastases. Candidates for hepatic resection must have had complete excision of the primary cancer without gross residual (macroscopic) extrahepatic metastatic disease. If the primary cancer is not controllable, resection of metastatic colorectal cancer is not indicated. Standard resection of the primary cancer with gross tumor-free margins of resection and appropriate regional lymphadenectomy is the goal of the colonic or rectal resection. Confirmation of an adequate locoregional resection allows a surgeon who is considering reoperation to focus on an evaluation of the metastases and not the primary cancer. If objective documentation of an adequate resection of the primary cancer is lacking, further evaluation of the site of the origin of the primary cancer is performed. Although an inadequate resection of the primary cancer does not exclude reoperation for metastatic disease, the patient must be informed of potentially decreased survival caused by residual primary disease. Indeed, the surgeon who is undertaking hepatic resection must stress that

re-excision of the residual primary cancer may be required or that resection of metastases may be aborted because unresectable residual primary cancer may be found at exploration, even if the hepatic metastases themselves *are* resectable. Surgeons to whom patients are referred for resection of hepatic metastases must be cognizant of the possibility that an inadequate resection of the primary cancer has been performed and act accordingly.

Assessment of the adequacy of the primary operation depends on the origin of the primary colorectal tumor. In brief, the risk of locoregional recurrence of primary colorectal carcinoma correlates with the tumor, node, metastasis (TMN) stage. Risk of locoregional recurrence is greatest for advanced T and N stage. Careful imaging evaluation of the primary and regional tumor site is indicated in patients who have had locally advanced stage cancers.

Additional primary tumor factors that may be relevant to patient selection for the resection of hepatic metastases are the intraoperative features of the primary tumor and the operative technique used to resect the tumor. For example, patients with large colorectal tumors with invasion into or adherence to adjacent structures or colorectal tumors that are "peeled off" from adjacent pelvic structures or major vascular structures with tumor extending to the microscopic margins may benefit from postoperative adjuvant irradiation and chemotherapy in an attempt to gain optimal local control. In general, such adjuvant treatment precedes surgery for hepatic metastases and subsequent restaging before hepatic resection inclusive of positron emission scintigraphy or positron emission tomographic scanning is performed. Other factors that warrant consideration in patient selection for reoperation are factors that predispose the patient to progression of peritoneal disease, such as division of adhesions between the primary tumor and adjacent structures, fracture of the tumor during resection, and incisional or wedge biopsy of hepatic metastases. Gross spillage of tumor during resection of the primary cancer usually dictates a longer period of observation before reoperation for hepatic metastases to allow detection of intraperitoneal disease progression. Finally, hepatic resection for metastases should rarely be undertaken if any extrahepatic metastases exist, exclusive of regional lymph node or limited pulmonary metastases.

Operative intent also influences patient selection. Resection of hepatic metastases is undertaken primarily for cure. Such intent implies removal of all metastases without additional therapy. Adjuvant chemotherapy with regional hepatic arterial infusion or floxuridine and systemic fluorouracil has improved survival that is free of hepatic progression after hepatic resection of metastatic colorectal cancer.[1] Palliative resection may be effective for patients with refractory pain or infected, necrotic metastases.

The extent of hepatic metastatic disease affects patient selection for liver resection. In brief, adequate hepatic reserve in patients without chronic liver disease can be assumed if only two anatomically adjacent segments are preserved after resection. If cirrhosis is present, the extent of resection is reduced, and ablation necessarily assumes a larger therapeutic role. Extensive hepatic steatosis without cirrhosis also limits the extent of hepatic resection. Portal vein embolization (PVE) of the lobe of anticipated resection to induce hypertrophy of the planned remnant is indicated when initial remnant volume is marginal.

GENERAL PRINCIPLES AND PREPARATION

Resection or ablation of metastases should never put the liver at risk for irreversible dysfunction. The extent of resection depends on the size of the metastases, the intrahepatic site, and the relationship of the tumor to major afferent and efferent vasculature and bile ducts. In patients with deeply seated metastases, formal anatomic resections are indicated. Moreover, metastatic disease manifesting indistinct margins mandates formal resection. A 1- to 2-cm margin is considered appropriate to reduce the risk of intrahepatic recurrence at the margins of resection. However, margins of resection should never risk damage to major hepatic vasculature. The afferent and efferent vasculature of the liver remnant must be protected scrupulously.

The liver parenchyma can be transected by a variety of methods: compression (finger fracture or digitoclasia, clamp fracture or kellyclasia, or staples), contact (Cavitron Ultrasonic Aspirator), or thermal (electrocautery, laser, radiofrequency ablation [RFA]). Each approach has advantages and disadvantages. Most methods disrupt parenchyma to expose vessels and bile ducts for ligation. A new method (TissueLink and Harmonic Scalpel) fuses small vessels and ducts. Although the extent of parenchymal necrosis adjacent to the transection plane varies among techniques, such devitalized parenchyma is not clinically significant. Vessels or ducts greater than 2 mm generally require ligation with suture or clips. Major hepatic or portal veins are best occluded securely with the use of vascular staples or alternatively a running monofilament permanent suture.

ANATOMY

Safe hepatic resection depends on a clear understanding of the hepatic anatomy. Although hepatic regenerative capacity and metabolic reserve permit many types of resections, resection based on preservation of residual anatomic integrity best reduces the operative risk and optimizes function. Couinaud's[2] description of hepatic anatomy highlights the anatomic features of the liver relevant to resection and in adults provides anatomic terminology that is clinically useful. Although the regenerative capacities and metabolic reserve of the liver are great, hepatic resection based on anatomic considerations reduces operative risk and optimizes postoperative liver function. In general, anatomic resections are preferable oncologically to ensure cancer-free margins and potential sites for intrahepatic spread. The major anatomic features of the liver relevant to resection have been detailed elsewhere.[2]

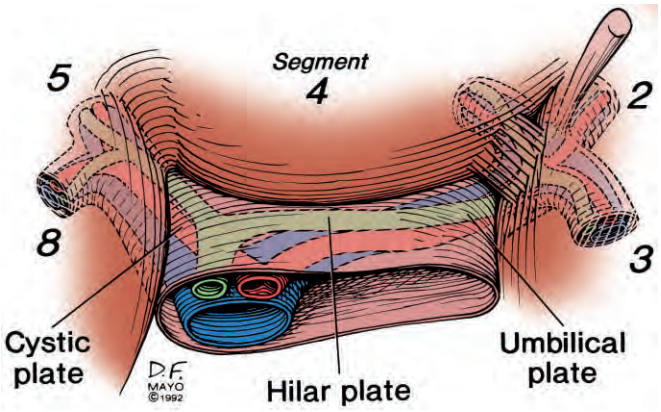

Figure 162–1. The fascial plates of the liver hilus, which represent a fusion of endoabdominal fascia around the portal structures. The fascial plate at the liver base is formed by three plates—cystic, hilar, and umbilical—that fuse with ill-defined boundaries. The numbers refer to the hepatic segments. (©1992, Mayo Foundation.)

The hilar plate is the extension of a vasobiliary sheath that is particularly relevant to hepatic resection (Fig. 162–1). The vasobiliary sheath represents a fusion of the endoabdominal fascia around the bile ducts, portal vein, and hepatic artery at the porta hepatis. These fibrous sheaths invest the components of the pedicles from the portal vein bifurcation to the sinusoids. By contrast, the hepatic veins lack endoabdominal fascial investment and, consequently, are more fragile than their portal counterparts. The density of the vasculobiliary sheaths decreases as the pedicles extend intrahepatically. At the hepatic hilus, these sheaths fuse to form plates that surround the portal pedicles, both anteriorly and posteriorly. Three primary hepatic plates are recognized: the cystic, the hilar, and the umbilical plates (see Fig. 162–1). Recognition of the vasculobiliary sheaths and the hepatic plates facilitates precise access to the hilar structures. Division of these plates is required to expose and mobilize the portal pedicle during resection.

PREOPERATIVE CARE

The preoperative preparation for patients undergoing hepatic resection is similar to that undertaken for any major pancreaticobiliary procedure. Coagulation profiles are corrected and prophylactic antibiotics directed at upper gastrointestinal tract flora are administered. If jaundice or cholangitis and bile duct obstruction are present, biliary decompression by endoscopic or percutaneous intubation is preferred to improve hepatic function and control infection. Biliary drainage is established for the anticipated hepatic remnant. In general, major hepatic resection is not undertaken unless the total serum bilirubin is nearly normal and clinical infection is controlled.

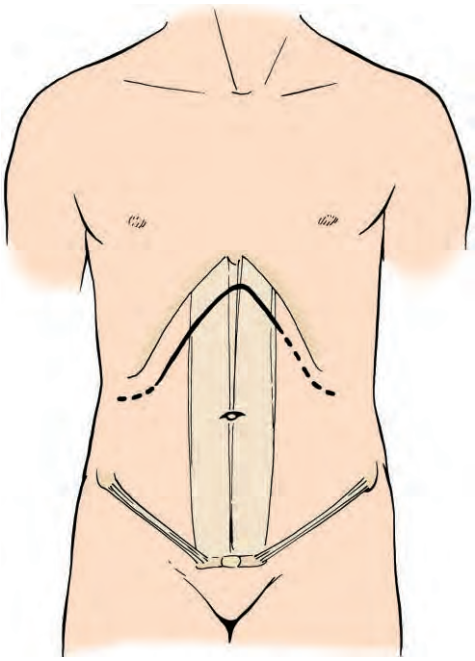

Figure 162–2. The standard subcostal incision extending to the anterior axillary lines bilaterally. (Courtesy of the Mayo Foundation.)

A major complement to the safety of hepatic resection is anesthetic management. The maintenance of low central venous pressure (5 to 7 mm Hg) reduces parenchymal blood loss via small hepatic veins. Large-bore intravenous access for rapid transfusion is also essential.

The major pitfalls or danger points with hepatic resection include hemorrhage from hepatic or portal veins or hepatic arteries; air embolism from hepatic venous injury; injury to the biliary ductal system with postoperative obstruction or fistula formation; portal or hepatic vein compromise with subsequent ischemia or postsinusoidal portal hypertension, respectively; prolonged vascular inflow occlusion leading to refractory hepatic ischemia or hepatic injury; and injury to the diaphragm, inferior vena cava, or intestine.

SURGICAL TECHNIQUE

Incision and Exposure

A bilateral subcostal incision or a right subcostal incision with a vertical extension to the xiphoid process affords wide exposure for any hepatic resection (Fig. 162–2). A long midline incision provides a satisfactory alternative, particularly for limited resections of segments II through VI or if the patient has a narrow or acute costal angle. Tumors that involve segments VII or VIII or extended lobar resections are approached more safely through a bilateral subcostal incision, which permits better

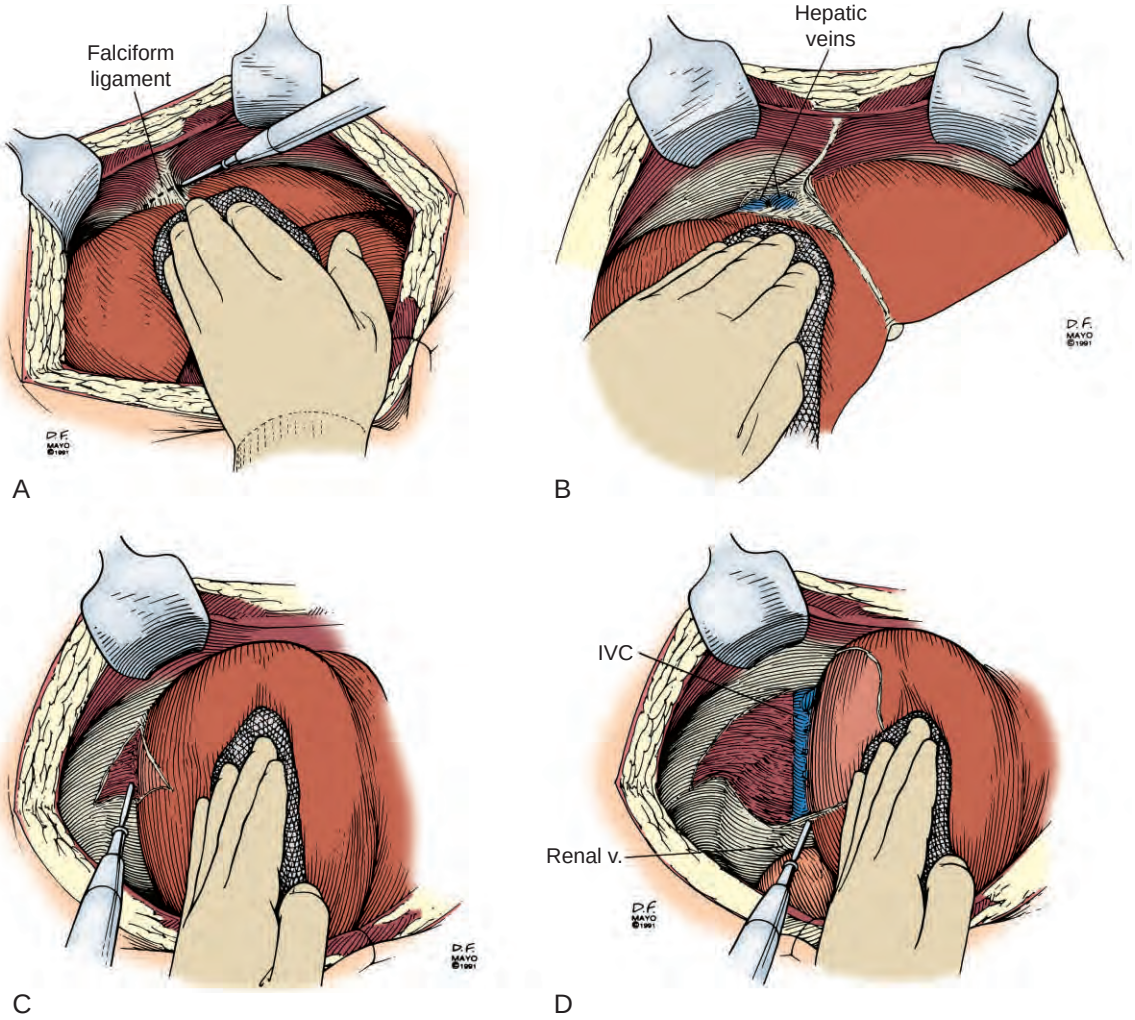

Figure 162–3. **A,** Mobilization of the liver is initiated by dividing the falciform ligament. **B,** Division of the falciform ligament is extended to the hepatic veins posteriorly. **C,** The liver is rotated medially to divide the right coronary and triangular ligaments, exposing the bare area of the liver. **D,** Complete division of the right coronary and triangular ligaments exposes the right lateral aspect of the inferior vena cava (IVC). Multiple short hepatic veins are visible after complete exposure. (**A-D,** ©1991, Mayo Foundation.)

exposure and control of the hepatic vein/inferior vena cava junction. Rarely, a right thoracic extension (thoracoabdominal incision) may be necessary for safe exposure of large bulky tumors that involve segments VII and VIII or those that require inferior caval reconstruction. All perihepatic adhesions are divided. Adherent diaphragm is excised with the metastasis. The liver is mobilized by complete division of its ligamentous attachments (i.e., coronary, falciform, and triangular ligaments) (Fig. 162–3). The thin gastrohepatic omentum is incised adjacent to the hepatoduodenal ligament. The foramen of Winslow is opened in anticipation of subsequent inflow vascular occlusion. An upper hand or chain retractor should be used to elevate the rib cage anteriorly and cephalad. Additional retractors may be used to retract the remaining viscera caudally.

Parenchymal Transection

The hepatic parenchyma is transected by the method of personal preference. Each method disrupts the parenchyma to expose vessels or ducts for ligation or cauterization. Hemorrhage is reduced by digital compression of the liver on each side of the transection plane. Both the surgeon and the assistant compress the parenchyma on opposing sides of the transection plane (Fig. 162–4). Typically, the assistant surgeon maintains hemostasis by electrocautery or clips. An additional assistant maintains field exposure by suctioning bile or blood from the transection interface. Bile ducts or vessels greater than 2 mm are clamped with metal clips or ligated with suture. Suture-ligation of remnant vessels or ducts reduces artifacts during postoperative imaging. After local hemostasis

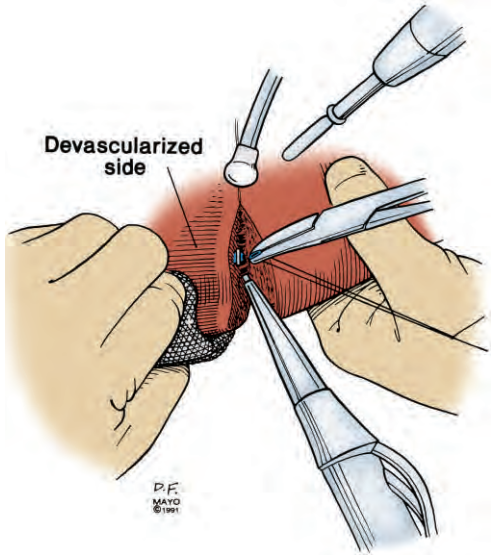

Figure 162–4. Parenchymal transection of the liver. The hepatic parenchyma is transected in the standard fashion with compression of the parenchyma manually along both sides of the planned transection plane. The parenchyma may be divided with an ultrasonic aspirator (as shown here) or by other methods. Vessels and bile ducts along the devascularized side or specimen side of the liver are clipped. The vessel and bile duct along the opposite side (the patient's side) of the liver are suture-ligated for permanent and secure closure and to avoid artifact on postresection liver imaging. (©1991, Mayo Foundation.)

and bile stasis are obtained, the abdomen is closed. Closed low-pressure suction drainage is optional.

TYPES OF SURGICAL TREATMENT OF HEPATIC METASTASES

Multiple terms have been used to describe various hepatic resections. The current recommendations for formal terminology have been proposed and are referenced for review.[3]

Wedge Resections

Wedge resections (i.e., nonanatomic resections) are performed without reference to segmental or sectoral anatomy. Wedge resections typically are subsegmental and frequently cross intersegmental planes and are well tolerated by the liver because they are used for small peripheral, nonhilar tumors. Wedge resections are usually performed with a minimum of blood loss, even without inflow vascular occlusion.

Anatomic Unisegmental and Polysegmental Resections

Anatomic resections of a single liver segment or multiple contiguous liver segments require identification and ligation of the segmental vascular biliary pedicles for accurate anatomic demarcation of the segment or segments. Portal and segmental pedicles are best approached by dissection from the hilus to the appropriate pedicle or by direct rapid parenchymal transection along an estimated intersegmental plane with ultrasound guidance. Dissection from the hilum is most applicable for anterior liver segments. Dissection along an intersegmental plane is more appropriate for ligation of the posterior hepatic segments II, VII, and VIII. Both approaches are facilitated by temporary inflow vascular occlusion to reduce hemorrhage and by the use of the ultrasonic aspirator to rapidly expose the pedicles through the intervening parenchyma. Alternatively, methylene blue may be injected into the segmental or portal pedicle using ultrasound guidance, which provides visual identification of the anatomic segmental or sectoral anatomy. Total vascular isolation of the liver may be required rarely for large tumors. If so, the infrahepatic suprarenal and suprahepatic inferior vena cava are excluded to permit occlusion by vascular clamps or tapes.

Lobar Resections

Lobar resections actually are polysegmental resections based on the primary right and left portal pedicles. The risk of blood loss is reduced significantly by ligation of the appropriate lobar hepatic arterial and portal venous branches before parenchymal transection. In addition, ligation of the corresponding hepatic vein before parenchymal transection further reduces blood loss. Major lobar resections can be extended either anatomically or nonanatomically. Anatomic extensions are performed by resecting the involved liver segments adjacent to the principal plane and nonanatomic extensions by subsegmentectomy.

The liver is mobilized fully for all lobar resections. Cholecystectomy is performed either en bloc with the resected lobe (if adherent to the tumor) or before parenchymal transection to facilitate exposure of the hilar structures. The lobar hepatic artery is ligated initially. The right hepatic artery generally traverses the triangle of Calot. Pericholedochal lymph nodes are excised to further expose the bile duct, portal vein, and hepatic artery and for staging. For a right lobectomy, the right lateral aspect of the hepatoduodenal ligament is incised longitudinally just posterior to the bile duct (Fig. 162–5). The right hepatic arteries, regardless of their origin, are always found lateral to the common hepatic duct or inferior to the right main hepatic duct, where they enter the liver parenchyma.

The left hepatic artery is approached through the lesser sac through the left lateral aspect of the hepatoduodenal ligament after division of the gastrohepatic omentum. The main left hepatic artery is generally found just inferior to the base of the round ligament as it enters the left lobe between segments III and IV anterior to segment I (Fig. 162–6). When present, an accessory left hepatic artery arising from the left gastric artery courses through the gastrohepatic omentum and is often divided during division of the gastrohepatic omentum

for resections of the left lobe. Lymphatic vessels around the hepatic arteries are ligated before division to reduce postoperative lymphatic drainage. Regardless of the type of lobectomy performed, the artery that supplies the lobe of the resection is occluded temporarily, whereas the artery to the opposite lobe is palpated to ensure patency of the arterial supply to the hepatic remnant. After blood flow to the hepatic remnant is appropriately confirmed, the lobar artery is doubly ligated with heavy silk and divided.

A similar approach is used for right hepatic artery ligation, although the right hepatic artery is exposed to the right aspect of the hepatoduodenal ligament (Fig. 162–7). The bile duct is retracted anteriorly with a vein retractor to expose portal venous bifurcation. Again, the right portal vein is exposed to the right of the hepatoduodenal ligament, and the left portal vein is exposed to the left of the hepatoduodenal ligament. The main left portal vein branch always bifurcates from the right main branch at an approximately 90-degree angle and courses anterolaterally.

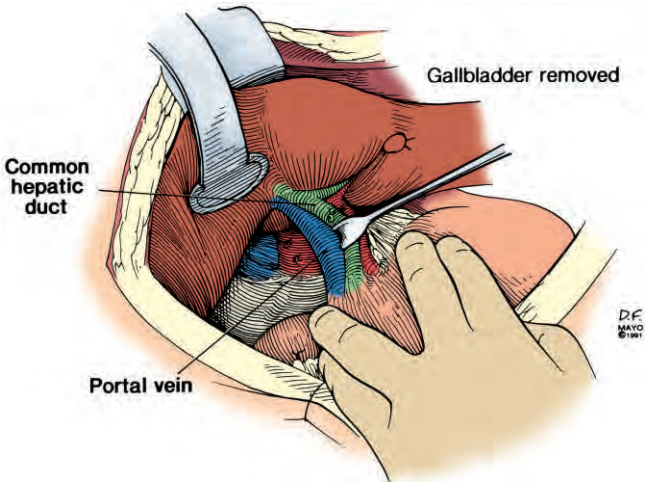

Figure 162–5. Exposure of the hepatic hilus for vascular control before major hepatic resection. Cholecystectomy facilitates exposure of the major vessels of the liver at its hilus. The peritoneum along the right lateral aspect of the hepatoduodenal ligament is incised, and the bile duct is retracted medially and superiorly using a vein retractor. The major portal vessels can then be identified. (©1991, Mayo Foundation.)

Occasionally, two major branches of the right portal vein—anterior and posterior—may arise separately without a common trunk, resulting in a portal vein trifurcation. The appropriate lobar portal vein branch is freed from the surrounding lymphoareolar tissue and is ligated with a vascular stapler or a running vascular suture after division between clamps (see Figs. 162–6 and 162–7). A simple suture ligature is not used on the portal vein because ligature dislodgment can result in immediate life-threatening hemorrhage. After division of the lobar blood supply, a clear line of vascular demarcation along the principal hepatic plane between the lobes confirms appropriate and complete lobar vascular ligation (Fig. 162–8). Parenchymal transection can be initiated at this time or after ligation of the hepatic vein (depending on the size of the tumor and the tumor-hepatic vein relationship). After the blood supply to the liver has been controlled, the hepatic veins may be approached safely.

During a right lobectomy, multiple short hepatic veins between the inferior vena cava and the paracaval segments are ligated to prevent avulsion during anterior retraction of the liver. Ligation starts caudally and proceeds cephalad. Occasionally, a large right inferior hepatic vein enters the inferior vena cava from the posterior aspect of segment VI. Either staples or a running suture closure for secure ligation of this vein is preferred to simple ligature. To expose the main right hepatic vein, the hepatocaval ligament bridging segments I and VII is divided (Fig. 162–9). A moderate-sized vein frequently traverses this ligament, and its presence should be anticipated before division. The main right hepatic vein, which has an extra hepatic component of 1 to 2 cm, is dissected from the inferior vena cava and the overlying liver. Unless large metastases preclude access, the right

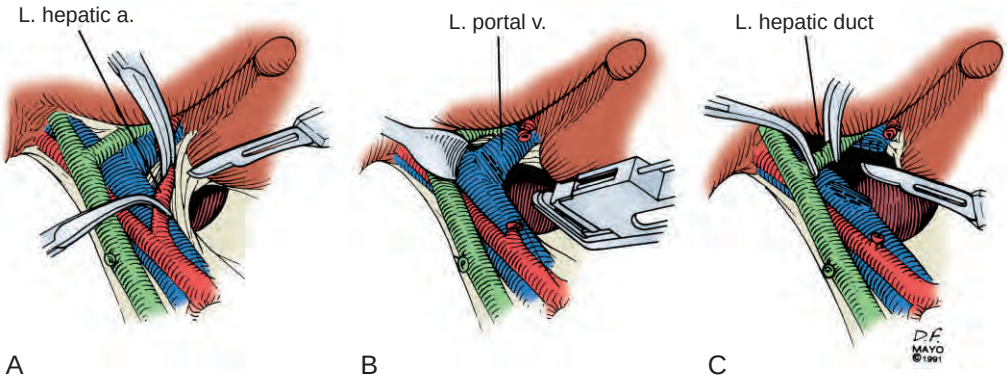

Figure 162–6. Vascular and biliary control before left hepatectomy is best obtained through the gastrohepatic omentum along the left lateral aspect of the hepatoduodenal ligament. Initially, the left hepatic artery is ligated at its origin. **A,** The left main artery enters the liver just below the falciform ligament. **B,** The left main portal vein, which courses toward the left shoulder, is transected with a vascular stapler. **C,** Finally, the left main bile duct is transected and ligated. a, artery; L, left; v, vein. (**A-C,** ©1991, Mayo Foundation.)

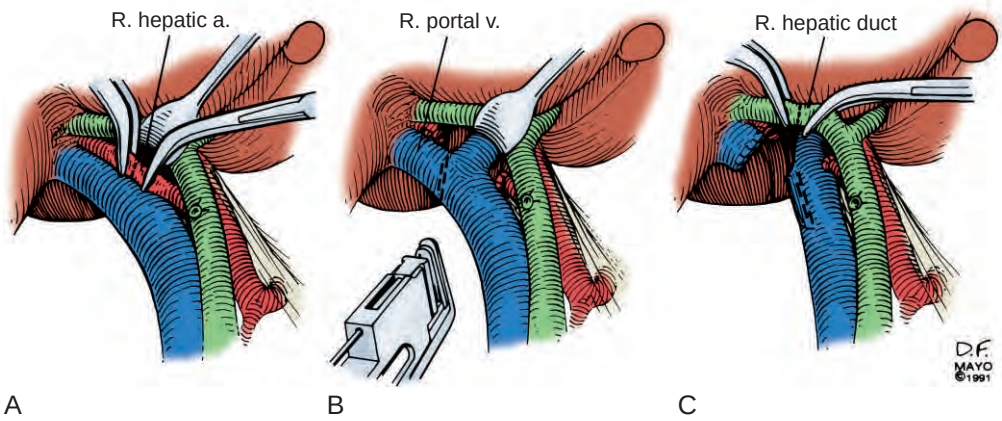

Figure 162–7. Exposure of the right hepatic artery and right main portal vein branch is best obtained through the right lateral aspect of the hepatoduodenal ligament. The bile duct is retracted medially and superiorly with a vein retractor. **A,** The right main hepatic artery is identified and divided between clamps. **B,** The right main portal vein branch is exposed and transected with a vascular stapler. **C,** After clear identification, the right main bile duct is divided. a, artery; R, right; v, vein. (**A-C,** ©1991, Mayo Foundation.)

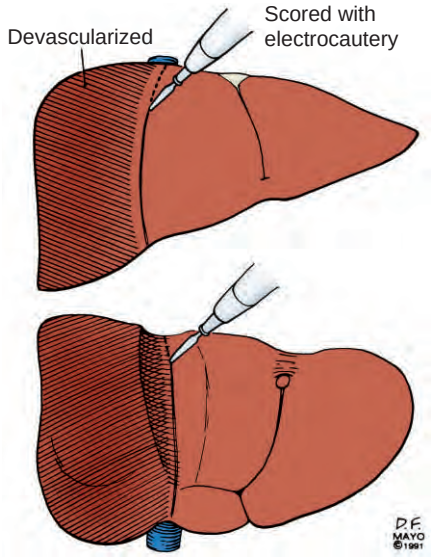

Figure 162–8. After completion of hilar ligation of the major lobar hepatic vessels, the interface between the vascularized and devascularized portions of the liver is evident. The planned transection plane is marked with cautery immediately adjacent to the devascularized portion of the liver. (©1991, Mayo Foundation.)

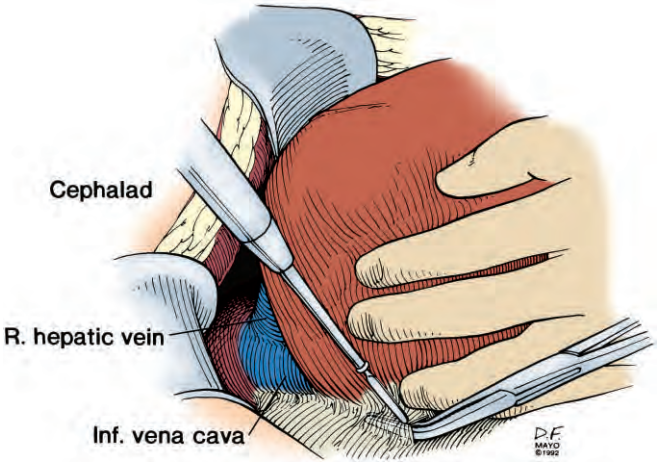

Figure 162–9. Transection of the right main hepatic vein. Access to the right main hepatic vein extrahepatically can best be achieved only after full mobilization of the right lobe. Frequently, a thick band of tissue extends from the caudate lobe to segment VII, just inferior to the right hepatic vein. Complete division of the retrocaval ligament is required for adequate extrahepatic exposure of the main right hepatic vein in its junction with the inferior vena cava. Inf, inferior; R, right. (©1992, Mayo Foundation.)

hepatic vein can almost always be transected with a vascular stapler before parenchymal transection. After division, the parenchymal side is ligated with a running vascular suture before parenchymal transection.

During left lobectomy, ligation of the main left hepatic vein, which usually joins the middle hepatic vein before entering the vena cava, can be deferred until parenchymal transection is complete because extrahepatic exposure is technically more difficult. Although the middle hepatic vein can be ligated during either right or left lobectomy, preservation reduces postoperative hepatic congestion and the volume of postoperative serous drainage. Alternatively, compression of the left hepatic vein at the confluence of the middle and left hepatic veins by a vascular clamp can be used to reduce hemorrhage from the hepatic venous branches along the interface of the liver during transection.

The parenchymal transection is guided by the zone of vascular demarcation and intraoperative ultrasonography. Parenchyma is transected by the surgeon's method of choice (Fig. 162–10). Major bile ducts are ligated with permanent suture. Injection of the cystic duct stump or

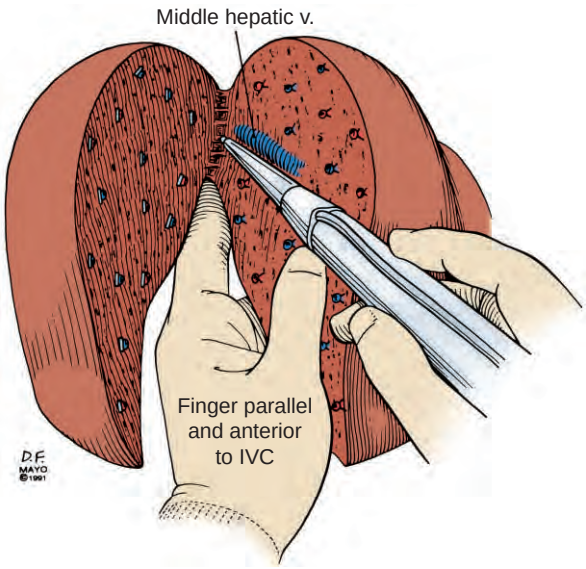

Figure 162–10. Parenchymal transection is continued throughout the liver with vascular and biliary structures ligated as necessary. The surgeon's orientation for appropriate parenchymal transection can be maintained by using the index finger as a guide. IVC, inferior vena cava; v, vein. (©1991, Mayo Foundation.)

main bile duct can be performed with saline or a dilute methylene blue solution to exclude occult bile leaks along the transection interface. Leaks are closed with sutures or clips. After parenchymal transection, topical hemostatic agents are used as needed. In general, persistent, diffuse interface hemorrhage or oozing results from elevated central venous pressure due to excessive intraoperative crystalloid, colloid, and blood product transfusion or, rarely, due to various causes of right heart failure. Compression of the transection interface and reduction in the central venous pressure by vasodilators or by decreasing the rate of fluid infusion and diuresis will reduce such hemorrhage. Development of a coagulopathy requires blood component therapy, liver packing, and normothermia. If preferred, a suction drain or drains are placed adjacent to the transected hepatic surface and brought out dependently and laterally through the flank. The divided falciform ligament may be reapproximated to prevent torsion of a small left lobe hepatic remnant and postoperative vascular compression of the left hepatic vein. The omentum is not attached to the parenchyma. The abdomen is closed in a standard fashion.

POSTOPERATIVE CARE

Postoperative care generally involves appropriate fluid administration. The addition of albumin to standard crystalloid solutions reduces postoperative weight gain and maintains adequate urine output. Most hepatic resections are associated with a mild acidosis and coagulation abnormalities in the immediate postoperative period. Neither acid-base abnormalities nor coagulation deficits are corrected postoperatively unless they are clinically significant. Urinary output is monitored until hemodynamic stability has been maintained for 24 hours. Postoperative epidural analgesia markedly improves pulmonary function and pain control.

COMPLICATIONS OF HEPATIC RESECTION AND THEIR MANAGEMENT

Intraoperative Complications

Hemorrhage is the most common intraoperative complication. It results from major vessel trauma along the transection interface or from coagulopathy. Inflow occlusion or total hepatic vascular isolation has dramatically reduced abrupt life-threatening hemorrhage from trauma to the major hepatic vasculature. A simple Pringle maneuver with an appropriate-sized vascular clamp or loop snare easily controls hemorrhage from either the portal vein or the hepatic arteries. Traumatic injury to the extrahepatic bile duct from a vasculature clamp is rare. The noncirrhotic liver tolerates warm ischemia periods for more than 1 hour without permanent long-term consequence. Ischemia/reperfusion injury may be reduced by intermittent occlusion. Although ischemic hepatic injury is reflected by elevations of serum aspartate transaminase and bilirubin and prolongation of the prothrombin time, these changes reverse to normal within 7 to 10 days.

Diffuse hemorrhage from the transection interface usually results from elevation of the central venous pressure to greater than 12 to 15 mm Hg. Continuous intraoperative monitoring of the central venous pressure and volume replacement to maintain central venous pressures between 5 and 8 mm Hg reduces this operative risk of hemorrhage but allows the maintenance of adequate systemic hemodynamics. Vasodilators may also be required. Persistent interface hemorrhage is treated best by coagulation with electrocautery, the argon beam coagulator, TissueLink, or by compression with laparotomy pads and topical hemostatic agents. Should interface bleeding persist after the use of these techniques, intraoperative evaluation for coagulopathy must be undertaken. An intraoperative thromboelastogram should be obtained, and abnormal coagulation profiles should be corrected with blood products as indicated.

The last significant intraoperative complication is air embolus from hepatic vein damage. Although a potentially life-threatening source of cardiac arrhythmias and ventilation/perfusion defects, early recognition is possible through careful anesthetic monitoring. The techniques for anesthetic monitoring for venous air embolism include precordial Doppler sonography, right heart catheterization, capnography from mass spectroscopy, transcutaneous oxygen probes, and transesophageal echocardiography. Doppler sonography and transesophageal echocardiography are the most sensitive; abnormalities of capnographic mass spectrometry provide the most practical recognition of venous air embolism. With an increasing volume of air embolism, initial gas exchange abnormalities are supplanted by

deteriorating systemic hemodynamics. Venous air embolism should be suspected initially by a decrease in arterial oxygen tension, transcutaneous oxygen pressure, fractional end-tidal concentrations of carbon dioxide, and an increase in fractional end-tidal concentration of nitrogen. If undetected, the arterial carbon dioxide tension and transcutaneous carbon dioxide pressures will increase rapidly. Advanced signs include a precordial machinery murmur, visible air in the hepatic vein or inferior vena cava, and decreases in cardiac output and blood pressure. Treatment consists of placing the patient in a Trendelenburg position, suture closure of the hepatic vein, and aspiration of the intracardiac air through a central venous pressure catheter with positive pressure ventilation.

Postoperative Complications

Postoperative hemorrhage usually arises from displaced vascular clips or ligatures. Recognition should be obvious by depressed hemodynamics or bloody abdominal drainage. Any concurrent coagulopathy should be at least partially corrected before reoperation for control of hemorrhage.

Serosanguineous drainage through intra-abdominal drains is expected postoperatively. The volume of drainage may vary widely. Large-volume drainage may require isotonic fluid replacement to maintain fluid and electrolyte balance in the postoperative period. In general, abdominal drains can be removed safely regardless of the volume unless the drainage is bilious. Usually, even high-output drainage volumes are resorbed rapidly through the peritoneum without the formation of focal fluid collections or ascites. In patients with cirrhosis, drains should be avoided after hepatic resection because of protracted ascitic fluid drainage. Moreover, secondary infection of the ascites, which is associated with prolonged drainage, will be avoided.

Bilious drainage through the intra-abdominal drains or after puncture of loculated perihepatic fluid collections is indicative of a biliary injury. Most injuries are best managed conservatively by continuous close-suction drainage until they resolve. Minor fistulas (<100 ml/day) usually resolve with continuous suction drainage. Major fistulas (>200 ml/day) warrant cholangiographic evaluation and biliary stenting to speed resolution. Major fistulas may require Roux-en-Y hepaticojejunostomy for definitive repair. Reoperation for repair of biliary fistula is indicated rarely unless there has been complete disruption of the major bile duct from the remnant liver and a complete absence of bilioenteric bile flow.

A perihepatic intra-abdominal abscess may occur after any hepatic resection. Careful hemostasis and bile stasis after resection reduce perihepatic fluid accumulation and the risk of infection. Percutaneous drainage of abscesses is the treatment of choice.

Finally, hepatic insufficiency or failure can occur after hepatic resection. Hepatic failure usually occurs in patients with chronic hepatic diseases and cirrhosis or after extended polysegmental resection. The most common cause of hepatic insufficiency after hepatic resection is inadequate residual functional reserve. The treatment of this cause of hepatic failure is simply supportive. Preoperative PVE is indicated in patients in whom small hepatic remnants are anticipated. Orthotopic liver transplantation provides the only curative solution for refractory postoperative hepatic failure caused by inadequate reserve. However, even in selected patients, the risk associated with orthotopic liver transplantation for the salvage of hepatic failure induced by resection is exceedingly high and contraindicated in the presence of metastatic cancer, albeit resected.

Correctable causes of hepatic insufficiency should be sought postoperatively. Correctable causes of hepatic failure postoperatively include major bile duct obstruction and efferent or afferent vascular compromise as a result of venous thrombosis or vessel narrowing. Bile duct obstruction should be suspected by steadily increasing total and direct serum bilirubin levels. Endoscopic retrograde or magnetic resonance cholangiography best defines the location and extent of the injury, but only the former technique permits therapeutic intervention. Percutaneous transhepatic cholangiography is less useful postoperatively because of delayed proximal bile duct dilation and altered hepatic position after resection. Potentially correctable major hepatic vasculature injuries include portal and hepatic vein thromboses. Color-flow Doppler ultrasonography is the best screening technique if suspected. Definitive imaging by angiography, magnetic resonance imaging, or computed tomographic angiography further defines the extent and vascular damage caused by thrombus. Once thromboses are recognized, reoperation for thrombectomy and repair of the venous damage that precipitated the thrombus are indicated. Systemic thrombolytic agents are contraindicated because of recent operative intervention. Anticoagulants (heparin and warfarin) are useful to prevent recurrent thrombosis.

NONRESECTIONAL SURGERY FOR HEPATIC METASTASES

Hepatic Artery Infusion

Hepatic artery infusional chemotherapy has been used for unresectable hepatic metastases for colorectal carcinoma and as adjuvant therapy after hepatic resection. Although combination systemic chemotherapy has produced objective responses in only a minority of patients and has had significantly improved patient survival rates compared with no therapy or single-agent chemotherapy, systemic chemotherapy remains primarily palliative. Alternatively, regional chemotherapy for unresectable metastases has proved to be more effective. The theoretical rationale for regional or hepatic artery infusional chemotherapy is based on the nearly exclusive arterial blood supply of the metastases from the hepatic artery and first-past drug clearance kinetics, which support high local hepatic concentrations of the drug with reduced systemic toxicity. Multiple studies have compared the use of regional hepatic arterial infusion of 5-fluorodeoxyuridine (5-FUDR) with systemic 5-fluorouracil (5-FU).

Meta-analyses of these trials have shown that (1) objective tumor response rates are significantly greater for regional 5-FUDR than systemic 5-FU treatment[4] and (2) there is minimal or no improvement in overall survival. The use of regional infusional chemotherapy improved median survival times by only 3.2 months compared with systemic chemotherapy. The data from individual trials may bias outcomes because many patients randomized to regional therapy did not complete therapy due to technical problems with the infusion pump or toxicity. Subset analyses of the patients who actually received regional therapy suggests improved survival compared with those treated systemically. Further trials of regional infusion of 5-FUDR are being carried out in an attempt to reduce associated toxicity and to address the role of concurrent systemic chemotherapy as an adjunct after the resection of metastases.

Complications of intrahepatic arterial chemotherapy can be divided into two broad groups: (1) pump-related (technical) complications and (2) chemotherapy-related complications.[5] Pump-related complications of intrahepatic arterial chemotherapy include pump malfunctions, pump site infections, and chemotherapy-related complications, including hematologic and gastrointestinal toxicities. Gastrointestinal toxicity includes nausea, vomiting, and diarrhea, which occur infrequently with hepatic artery infusion of 5-FUDR. When diarrhea does occur, misperfusion of chemotherapy to the gastrointestinal tract through an improperly placed catheter or hepatic arterial collateral vessels should be suspected. The most common problems of hepatic artery infusion therapy are gastroduodenal ulceration and hepatotoxicity. Ulcer disease usually results from misperfusion of the stomach and duodenum via small collateral branches of the hepatic artery or the right gastric artery and are preventable by careful division of these collateral vessels during pump placement. Hepatobiliary toxicity is the most problematic toxicity. The bile ducts are particularly sensitive to regional chemoperfusion because like the hepatic metastases, bile ducts derive their blood supply almost exclusively from the hepatic artery. Clinically, biliary toxicities manifest as an elevation in the aspartate aminotransferase, alkaline phosphatase, and bilirubin levels and cholangiographic biliary sclerosis mimicking sclerosing cholangitis. Hepatotoxicity is manifested by hepatitis. Dose reduction of 5-FUDR and concurrent corticosteroid perfusion through the pump reduce hepatobiliary toxicity.

Cryoablation

Frequently, either the extent or location of hepatic metastases precludes safe resection. Cryoablation offers a technically sound and biologically rational approach for the treatment of such liver metastases.[6,7] The reputed advantages of cryoablation versus resection of hepatic metastases are the avoidance of the inherent risks of resection over the technical ease and safety of the cryoablation with its potentially similar efficacy. Cryosurgery is an ablative procedure based primarily on the chemicophysiologic sequelae of rapid freeze-thaw cycles on cellular membranes. To achieve a total cell kill, tissue temperatures of −50° C or below are required. Repetitive freeze-thaw cycles increase the probability of complete tissue destruction. Thawing should be completed before the onset of the next freeze cycle for maximum cytotoxic potential. Various cryounits are commercially available and differ primarily by type of cryogen and probes and rapidity of freeze-thaw cycles. In brief, the technique for cryoablation is simple. The liver is mobilized, and the metastases are located. Depending on the size of the metastases, an appropriate-sized cryoprobe is placed through the metastases, and cryoablation is initiated under ultrasonographic guidance. The cryoprobe is removed, and the cryotract is packed with a hemostatic agent.

Intraoperative ultrasonography is essential for effective cryoablation. Ultrasonography provides (1) accurate positioning of cryoprobes within the metastases to avoid injury to major bile ducts and vessels, (2) accurate monitoring of freeze-thaw process with a clear demonstration of the freeze-front, and (3) detection of occult hepatic metastases. For large tumors, multiple concurrent probes speed treatment.

Potential intraoperative complications of hepatic cryosurgery include accidental freezing of adjacent tissues, cracking of the liver parenchyma, bleeding due to the introduction of Trotter probes, hypothermia and related cardiac arrhythmias, nitrogen embolism, bile duct or major vascular injury, and renal failure from myoglobinuria. Insulation of the diaphragm, bowel, and skin from the liver with laparotomy packs prevents accidental cryoinjury to adjacent structures. Bleeding from the probe tract is rarely a problem and can be easily controlled by packing the cryotract with hemostatic material. Large vessels tolerate cryotherapy extremely well without rupture or occlusion due to the continued dissipation of thermal energy by the flow of blood. In contrast, large bile ducts are extremely vulnerable to cryoinjury, and caution should be exercised in treating tumors located near the hilum. After cryosurgery, a transient elevation of liver enzymes and a mild leukocytosis may occur, but they should normalize within 1 week. Carcinoembryonic antigen levels will remain elevated for approximately 6 weeks. Patients are commonly febrile for 3 to 4 days after cryoablation but respond promptly to treatment with indomethacin. Pleural effusions, subphrenic abscesses, or bile collections occur rarely.

Survival rates after cryoablation for unresectable metastases approaches 60% at 2 years with median survival times of 25 to 32 months.[6-8] To date, the outcome of cryoablation alone for hepatic metastases from colorectal carcinoma has been promising. Survival rates have ranged from 15% to 35% at 5 years. Whether survival after cryoablation will be equivalent to resection is yet undetermined. No randomized, controlled trials have been performed to compare these treatments. Adjuvant chemotherapy (regional or systemic) has been used frequently with cryoablation in an effort to improve outcome. Adjuvant cryoablation has been used concurrently with resection for the treatment of small, deep-seated hepatic metastases during major hepatectomy and consequently has extended the role of resection in some patients who were otherwise unresectable.

Hyperthermia

In contrast with cryoablation (freezing), focal hyperthermia also has tumor ablative potential. The technology for focal delivery of hyperthermic temperatures capable of tumor destruction has been developed using microwave, radiofrequency, and laser techniques. The general technique of hyperthermic ablation is similar to cryoablation. An applicator or probe is inserted into the tumor guided by ultrasound imaging. Ablation cycles are usually not repeated. Monitoring of the destruction zone by ultrasound is less accurate than for cryoablation for some of these modalities because echogenicity changes minimally with heat. Interstitial laser ablation has involved the use of the Nd:YAG laser, primarily due to its light emission wavelength. Biologic response depends on wavelength, intensity, and exposure time and absorption characteristics of the tissue. The current major advantages of hyperthermic ablation include ease of application, both percutaneous and open applicability, accuracy, retreatment potential, and decreased hospitalization time. Disadvantages include delivery unit expense, variable reaction time monitoring, and size of maximum destruction zones.

The use of RFA, as either a primary or adjunct modality, has proven the most versatile of ablative techniques[9] and is currently the most widely used by surgeons and interventional radiologists.

The advantages of RFA

1. Tumor necrosis for metastases adjacent to vasculature that, if resected, would jeopardize postresection function
2. Tumor necrosis for deep, small (≤3 cm) metastases that, if resected, would require removal of significant tissue volume and jeopardize function
3. Tumor necrosis of metastases (3 to 5 cm) in patients with underlying chronic liver diseases or cirrhosis
4. Enlargement of postresection margins

The disadvantages of RFA

1. High recurrence rate for large tumors (>5 cm)
2. Necrosis of adjacent structures—major bile ducts, stomach, duodenum, colon, diaphragm
3. Delayed tumor recurrence on late (>3 years) follow-up[10]
4. Metastases must be clearly visible by imaging

RFA can be performed percutaneously or at laparoscopy or laparotomy. RFA generally is associated with minimal morbidity and rarely with mortality. Currently, RFA is used primarily as an adjunct to resection or as primary therapy when resection is precluded regardless of cause. Although initial outcomes with RFA (<3 years) were similar to those of resection in patients with similar primary and metastatic cancer characteristics, late outcomes (5 years) are unknown and evidence-based data are unavailable.

PROGNOSTIC DETERMINANTS

Hepatic resection of metastatic colorectal cancer to the liver has become the treatment of choice for selected patients. Overall 5-year survival rates consistently range between 25% and 40%.[11-14] Operative mortality rates are usually 4% or less. Perioperative morbidity rates range from 15% to 20%. Indications for resection of hepatic metastases include any hepatic metastases that can be resected with cancer-free margins provided that a functional hepatic remnant can be maintained. Concurrent resections are now indicated provided surgical expertise for both colorectal and hepatic surgery is available, all other resectability criteria are fulfilled, and the patient's intraoperative condition permits extending the operation for hepatic resection. The only outcome difference overall is the negative impact of "synchronous" metastases. Such resections are favored when encountered to allow prompt initiation of the potent chemotherapy now available.

Focal extrahepatic disease that is concurrently resectable is currently considered only a relative contraindication to resection. Concurrent contraindications to resection of hepatic metastases include distant metastases (including peritoneal carcinomatosis, osseous or brain metastases, extra-abdominal lymph node metastases, and multiple, unresectable pulmonary metastases), extensive liver metastases (multiple, bilobar metastases, metastatic involvement of both the afferent and efferent vasculature, and medically unresponsive metastases), and prohibitive comorbidity inclusive of hepatic insufficiency.

Many surgeons have postulated that patient overall survival rates for patients with hepatic metastases for colorectal cancer could be increased by refining patient selection for resection or by neoadjuvant chemotherapy leading to resection of initially unresectable metastases. If clinical factors with consistent prognostic value were identifiable, resection should be encouraged for patients with a high probability of survival. Moreover, if effective adjuvant chemotherapy after hepatic resection becomes established, the treatment of hepatic metastases could be further stratified by survival risk based on these prognostic factors and response to adjuvant therapy. Potential prognostic factors have been culled from various patient, primary tumor, and metastatic disease characteristics from literature reports. In addition, the relationship of survival to medical and surgical intervention has been examined. Associations between potential prognostic factors and survival have been based on the analysis of overall or disease-free survival data.[15] Factors that have a statistical correlation to survival are shown in Table 162–1. Because Table 162–1 is simply a tabulation of prognostic factors abstracted from individual reports, the strength of survival correlation varied among factors. There was no single factor other than incomplete resection that absolutely and reliably precluded survival. Hepatic resection of metastatic colorectal cancer should be the primary treatment approach unless all gross disease is not resectable. Current risk scoring systems permit stratification of expected outcomes and identify patients with low probability of survival. However, these systems do not identify patients whose survival is certain and do not preclude consideration for adjuvant therapy.

Table 162–1 Clinicopathologic Factors Adversely Associated with Survival in Patients Who Underwent Hepatic Resection for Metastatic Colorectal Cancer

Patient Clinical Findings	Primary Colorectal Cancer	Pathologic Findings Metastatic Colorectal Cancer	Interventional Findings
Age ≥70 yr	TNM stage 3	Percent replacement (extent) ≥50%	Margins of resections ≤1 cm
Male gender	Histologic grade: high to undifferentiated	Bilobar distributions	Nonanatomic hepatic resection
Symptoms: jaundice, pain	Primary site: rectum	Number ≥4	Perioperative blood transfusions
Performance status <50%	Colorectal venous invasion	Satellite configuration	
	Tumor DNA aneuploidy	Size ≥1 cm	
		Perihepatic lymphatic metastases	
		Extrahepatic metastases	
		Serum carcinoembryonic antigen level ≥30 ng/ml	
		Tumor DNA aneuploidy	
		Intrahepatic vascular invasion	
		Intrahepatic biliary invasion	
		Synchronous recognition ≤1 yr from primary	

RECURRENCE AND REPEAT HEPATIC RESECTION

Recurrence (or reappearance) of tumor after potentially curative liver resection usually involves the liver, lungs, and peritoneal cavity. In the French multicenter study,[16] 1013 (65%) of 1569 patients with accessible follow-up data developed clinically recurrent disease. The liver was involved in 63% of patients with recurrences, which included nearly 47% of patients with recurrent disease limited to the liver. Metastatic disease after hepatectomy occurred in 70% of the 607 patients from the U.S. Registry of Hepatic Metastases.[9] Three hundred sixteen patients had recurrence in a single organ: 149 (47%) in the liver, 73 (23%) in the lung, 30 (10%) local, and 61 (19%) in other sites. These patterns of recurrence after hepatic resection for metastatic colorectal cancer have been confirmed repeatedly. Given the frequency of isolated hepatic progression, repeat hepatic resection has been used.[17,18] Reports have consistently shown that survival after repeat resection is equal to that after the initial hepatic resection, and predictors of survival are similar to those for the first hepatic operation. In other words, a 5-year survival rate of 25% to 30% can be expected after repeat hepatic resection. These findings warrant assessment for resection in all patients with recurrent hepatic metastases after hepatic resection.

Salvage Hepatectomy

The main cause of unresectability is achieving a balance between resection of the entire tumor burden while leaving sufficient residual functional liver parenchyma (at least 30% of initial liver parenchyma) for survival. The definition of unresectability depends on many factors, not the least of which is the surgical expertise and support care at the medical facility. Theoretical prognostic factors and technical factors of unresectability of hepatic metastases are essentially determined by factors which affect the amount of post-resection functional hepatic mass; the most important of these are tumor location, number of metastases, and bilobar disease.

Prognostic Factors Influencing Resectability

Some subgroups of patients with negative prognostic factors such as lymph node involvement, large numbers of the tumors (>4), and large size of metastases (>10 cm), or extrahepatic disease have been historically considered unresectable. However, recent studies suggest that all of these criteria treated with newer chemotherapy protocols that are improving long-term survival are also able to downstage patients to allow for an attempt at curative resection. Historically, 1- to 2-cm margins are still considered the gold standard for resection of hepatic metastases. Recent study has examined the relationship of measured margins of hepatic resection for colorectal metastases to survival and local recurrence[19] and suggested a smaller margin (2 mm) may be as effective. Histopathology of resected specimens showed that micrometastases in the surrounding liver were present in 2% of patients and were found within 4 mm of the margin. The incidence of definitive recurrence at the surgical margin was 13.3%, 2.8%, and 0% if the margin was less than 2 mm, 2 to 4 mm, and 5 mm or wider, respectively. Resective margins can be extended with the use of RFA or cryoablation provided the ablation zone does not affect major ducts or vessels. In general, at least a 1-cm margin is preferred.

Finally, extrahepatic disease is usually associated with poorer survival. Nevertheless, long-term survival is

reported in a significant number of patients when complete resection of extrahepatic disease is achieved, particularly with pulmonary metastases.[20,21] With control of the primary disease prior to pulmonary resection, 5- and 10-year survival rates of 30% and 16%, respectively, can be expected.[20] Similarly, although long-term prognosis in patients with metastases to lymph nodes is unfavorable, hepatic resection combined with lymphadenectomy may be beneficial in occasional patients whose disease has been downstaged or completely eliminated clinically by chemotherapy and can be resected completely.[19]

Strategies for Improving Resectability

Strategies for improving resectability are based on clinical response to neoadjuvant chemotherapy to downstage disease stage and increase postresection hepatic reserve in combination with cytodestructive modalities such as RFA. Novel chemotherapeutic regimens combining 5-FU, folinic acid, and oxaliplatin or irinotecan with or without bevacizumab (Avastin) have been proven to increase both patient survival and quality of life. In fact, response to chemotherapy before hepatic resection may become a major selection factor for resection. A recent study,[22] demonstrated that patients with tumor progression on chemotherapy had a poorer outcome, even after potentially curative hepatectomy. Tumor stabilization or a decrease in tumor burden during chemotherapy was associated with long-term survival. Five-year survival was 37%, 30%, and 8% for patients with objective tumor response, tumor stabilization, and tumor progression, respectively. Control of metastatic disease prior to surgery may be crucial for a chance of prolonged remission in patients at high risk for progression after resection (see Prognostic Scores).[15]

If the anticipated functional hepatic volume after hepatic resection is considered marginal, strategies using hepatic regeneration can transform some patients from unresectable to resectable. PVE and staged resection are two such treatment modalities. PVE of the planned hepatic resection allows hypertrophy of the remnant liver and has been demonstrated to allow more patients with previously unresectable liver tumors to undergo successful resection.[23] PVE is indicated when the functional liver remnant is estimated at less than 30% of initial functional hepatic volume in which hepatic failure is a leading cause of postoperative death. PVE of the resection volume induces contralateral compensatory hypertrophy of the hepatic remnant, thus decreasing the risk of postoperative liver failure. Once hypertrophy of the remnant liver volume has reached a plateau, usually 4 to 6 weeks postprocedure, hepatic resection can be performed. Preresectional selective PVE may increase the rate of resection in such patients by 20%.[23] Their 5-year survival is 40%, similar to the survival rate of patients who did not require selective PVE. Tumor volume may also increase to a similar extent as the remnant, which emphasizes that PVE must be used selectively.[24] Finally, cryotherapy and RFA can be used efficiently during operation for resection to recruit patients to treatment that would not be resected otherwise. Initial treatment outcomes and complication rates were similar for either ablative technique, but local recurrence was higher for cryoablation.[25] Currently, ablation is limited by large size of metastases, proximity to major vessels and bile ducts, and loss of tumor definition by chemotherapy. Thus, RFA can be used in conjunction with resection for multiple metastases to allow selection of patients with otherwise unresectable lesions.

Two-stage hepatectomy consists of sequentially resecting hepatic metastases in patients that would otherwise be unresectable. This option is usually reserved for patients with multiple bilobar metastases responsive to chemotherapy. The initial hepatic resection for metastases is performed on the planned remnant liver, which allows it to hypertrophy in the absence of metastasis. The second hepatic resection for metastases is performed after restaging to exclude interim progression and is intended to be curative. After the initial liver resection, chemotherapy is deferred for a minimum of at least 3 weeks to allow the early regeneration of the remnant liver. Postoperative chemotherapy, consisting of the same proven chemotherapy that the patient responded to previously, is continued for further response. The second hepatectomy should only be performed if there is no interim tumor progression and significant hepatoxicity from chemotherapy has not occurred. Clinical data suggest that disease-free survival can be achieved in some patients.[26]

The usefulness of aggressive multimodality therapy including neoadjuvant combination chemotherapy to downstage hepatic metastases and techniques to increase postresection hepatic reserve (selective PVE, second resection, and ablation) to allow salvage of patients otherwise considered unresectable is best shown by the studies from the Paul Brousse Hospital.[27] A group of 1104 (77%) of 1439 patients with colorectal metastases who were initially unresectable were treated with combination chemotherapy consisting of 5-FU and leucovorin combined with oxaliplatin, irinotecan, or both. Responses of the nonresectable patients were assessed after every four courses for resection. Of the 1104 patients treated, 138 patients (12.5%) were considered "good responders" and underwent hepatic resection after an average of 10 cycles. Liver resection was combined with portal embolization, ablative treatment or second-stage hepatectomy in 42 patients (30%) and resection of extrahepatic disease in 41 patients (30%). Operative mortality was less than 1% and after a mean follow-up of 48.7 months, 111 (80%) of the 138 patients developed tumor recurrence. Some patients developed recurrence in the liver (29%), extrahepatic sites (9%), or both hepatic and extrahepatic sites (43%) and underwent further therapy. Hepatic only recurrence was treated by repeat hepatectomy (52 patients) and by extrahepatic resection (42 patients). Survival in these two groups was 33% and 23% at 5 and 10 years, respectively. Disease-free survival was 22% and 17% at 5 and 10 years, respectively. Patients whose hepatic metastases were initially resectable had 5- and 10-year survival rates of 48% and 30%, respectively.

In conclusion, improvements in combination chemotherapy leading to downstaging of metastatic disease and modalities to induce selective hypertrophy

of the remnant liver in patients who would otherwise not be candidates for hepatic resection can now permit hepatic resection with curative intent in selective responsive patients.

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Chapter

163

Neoplasms of the Anus

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The variety of histologic cell types within the anal canal leads to a diverse spectrum of possible malignancies. Squamous cell carcinoma, however, is by far the most common. Management of squamous lesions of the anus changed dramatically in 1974, when Dr. Norman Nigro demonstrated significant improvement in the survival of patients treated with chemoradiation therapy as opposed to radiation therapy alone.[1] Currently, the majority of anal canal squamous lesions are treated with chemoradiation therapy, thus avoiding the morbidity associated with abdominoperineal resection (APR).

This chapter reviews the anatomy of the anal canal, followed by an examination of the various neoplasms based on their histologic cells types. This is followed by a review of precancerous conditions and how infection with human immunodeficiency virus (HIV) has affected the management of precancerous and cancerous lesions of the anal canal and margin.

ANATOMY

The anatomic extent of the anus has been defined and clarified by the American Joint Committee on Cancer[2] and by the World Health Organization.[3] The anus is composed of the anal canal and the anal margin. Two definitions of the anal canal exist: the anatomic anal canal and the surgical anal canal. The anatomic canal extends from the dentate line distally to the anal verge. The surgical anal canal is defined as extending the length of the internal sphincter, from the pelvic floor (i.e., the anorectal ring) to the anal verge. The surgical anal canal best defines the physiologic boundaries of the anal canal and is therefore used within this chapter. The length of the canal varies between men (3 to 6 cm) and women (2 to 4 cm). The anal margin is the perianal skin that extends radially from the anal verge approximately 5 to 6 cm.[4] The anal verge is the junction of the specialized anoderm of the distal anal canal with the normal squamous epithelium of the anal margin, which contains the normal structures of the epidermis and is generally 2 cm distal to the dentate line. The anal verge defines the physiologic base of the anal canal and is therefore important in defining whether tumors can be excised without injury to the sphincter complex.

There are three types of epithelium within the anal complex. The anal margin consists of squamous keratinized epithelium containing all the structures of normal skin. The anoderm is a modified squamous epithelium without epidermal appendages and extends from the anal verge to the dentate line. Close to the dentate line, the anoderm merges with the transition zone, which is composed of distal rectal transitional and squamous epithelium. The transition zone extends up approximately 2 to 3 cm from the dentate line, where it merges into rectal columnar epithelium.

The lymphatic drainage of the anal canal is threefold. Above the dentate line the lymphatics follow the superior hemorrhoidal artery to the pre-aortic and para-aortic nodes. The area directly around the dentate line drains through the internal pudendal, hypogastric, and obturator nodes. Distal to the dentate line, drainage is via the inferior hemorrhoidal vessels terminating at the inguinal nodes.[5] This trimodal drainage of the anal canal requires close monitoring of both the visceral and somatic lymph drainage sites in patients with anal canal carcinoma. Thus, physical examination includes palpation of the inguinal lymph nodes. Surveillance computed tomography (CT) scanning after treatment may indicate nodal areas of relapse within the pelvis.

HISTOLOGY OF ANAL NEOPLASMS

The confluence of epithelial types in the relatively small area of the anal canal and margin accounts for the multitude of malignancies that arise in the region. The epithelium of the anal canal may give rise to epidermoid cancers, including squamous, cloacogenic, transitional, basaloid, mucoepidermoid, and round cell carcinoma. Epidermoid cancers tend to have similar responses to therapy and therefore have a similar prognosis. The anal canal also gives rise to adenocarcinomas and melanomas, although they are much rarer.

The anal margin, consisting of normal skin, gives rise to cancers seen elsewhere in the skin, with squamous cell

carcinoma being the most common. Basal cell carcinoma and melanoma, common in other areas of skin, are very rare in the anal margin. Anal intraepithelial neoplasia (AIN) is believed to be a preinvasive form of squamous cell carcinoma. AIN may arise from anoderm or perianal skin and thus may occur anywhere from the dentate line distally onto the anal margin. The classification scheme for AIN is complex and will be described later. It is, however, worth stating here that before defining AIN, the disorder was referred to as Bowen's disease. Currently, this term is best avoided because it is not as specific as the AIN classification scheme and can create confusion. Paget's disease is another rare intraepithelial neoplasm (intraepithelial adenocarcinoma) that may occur in the anal margin.

INCIDENCE

Anal cancer is relatively uncommon and accounts for 3% to 5% of all large bowel malignancies. The National Cancer Data Base, which collects information voluntarily submitted by hospital cancer registries, reported 1050 cases of anal cancer in 1988, 1289 cases in 1993, and 2970 cases in 2002.[6,7] The incidence may be underestimated because of misdiagnosis of some anal cancers as rectal tumors or misclassification of anal margin cancers as squamous cell skin cancers. In the past, anal canal lesions were thought to be more common in women.[6]

Recent data published by Johnson et al. looked at the incidence of anal cancer from 1973 until 2000 and showed equivalent incidence when comparing women and men.[8] They used the Surveillance, Epidemiology, and End Results (SEER) program, which is a system of tumor registries within the United States that are population based. They found a significant increase in the incidence of anal cancer in both men and women when comparing the time period 1973 to 1979 with the period 1994 to 2000. The increase, however, was greater in men than women (an increase from 1.06 to 2.04 per 100,000 for men versus 1.39 to 2.06 per 100,000 for women). They also found that black men had a higher incidence than did other race- or gender-specific groups (2.71/100,000). The incidence of anal cancer increases with age. Squamous cell carcinoma is by far the most common histologic cell type (0.92 per 100,000 in men and 1.05 per 100,000 in women), with cloacogenic being next most frequent (0.22 per 100,000 in men and 0.43 per 100,000 in women) and adenocarcinoma being the least described histologic cell type (0.37 per 100,000 in men and 0.25 per 100,000 in women).[8] The significant increase in anal cancer in men may be attributed to the prevalence of HIV-infected men engaging in anorectal receptive intercourse.

ANAL INTRAEPITHELIAL NEOPLASIA

AIN is a rare condition that is thought to be a precursor of squamous cell carcinoma of the anus. Its incidence is increasing, especially in patients infected with HIV and those with a history of anal condyloma. Indeed, infection with human papilloma virus (HPV) is a significant risk factor for the development of AIN.[9]

AIN is graded pathologically from 1 to 3 according to nuclear abnormalities seen in the epithelium, as originally described by Fenger and Nielsen.[10,11] Grade 1 AIN refers to nuclear changes seen only in the lower third of the epithelium, grade 2 is defined as changes in the lower two thirds of the epithelium, and grade 3 describes changes throughout the epitheilium.[12] AIN 1 may also be described by pathologists as low-grade AIN, whereas high-grade AIN generally correlates with AIN 2 and 3. Bowen's disease is thought to correlate with grade 3 AIN. There is confusion regarding the best classification scheme, and indeed, pathologic intraobserver interpretation of AIN may vary significantly.[13,14] Standardization of the grading of AIN by strictly adhering to the 1 to 3 scale and avoiding the terms low-grade dysplasia, high-grade dysplasia, and Bowen's disease should decrease confusion.

The incidence of AIN in HIV-positive males who engage in anal receptive intercourse has been documented to be as high as 52% in some series.[15] Indeed, the overall incidence of AIN in males engaging in anal receptive intercourse is thought to be 35 per 100,000, and this figure doubles in the same population that is also HIV positive.[16,17] A recent study by Palefsky et al. found that in patients who are HIV positive, engage in anoreceptive intercourse, and are taking highly active antiviral therapy, 81% had some form of anal dysplasia and 52% had AIN 2 or 3.[16]

The clinical features of AIN are not well defined, and most patients are asymptomatic. The rate of detection of AIN in patients who undergo resection of anal condyloma ranges from 28% to 35%. This figure can rise as high as 60% in HIV-positive individuals.[17-21] The most common initial symptom is pruritus ani, and when examined, these patients may have some discoloration of the perianal skin (Fig. 163–1). Evidence of skin breakdown or ulceration in a patient with a known history of AIN requires biopsy because it may represent progression to squamous cell carcinoma.

Novel screening techniques, such as anal cytology and anal colposcopy, have been investigated over the past 10 years in high-risk populations. Such screening has been prompted by the high incidence of AIN in HIV-positive patients and the fact that AIN is essentially asymptomatic. Anal cytologic examination uses techniques similar to cervical smears and requires brushing of the anal canal and verge. Palefsky and colleagues demonstrated a 69% sensitivity of detecting dysplasia in HIV-positive patients versus a 47% sensitivity in HIV-negative patients. Increasing the number of visits and screening procedures enhanced the sensitivity of the test.[22] Anal colposcopy has also been advocated as a screening tool for AIN, but patient discomfort and difficulty learning the technique have limited its use.[23] Anal colposcopy or high-resolution anoscopy requires coating the anus with 3% acetic acid for 1 minute and then examining the area with a colposcope for coarse punctation and mosaicism.[24] Biopsy is then performed on suspicious lesions.

Management of AIN after the diagnosis is made requires perianal mapping to localize the extent and

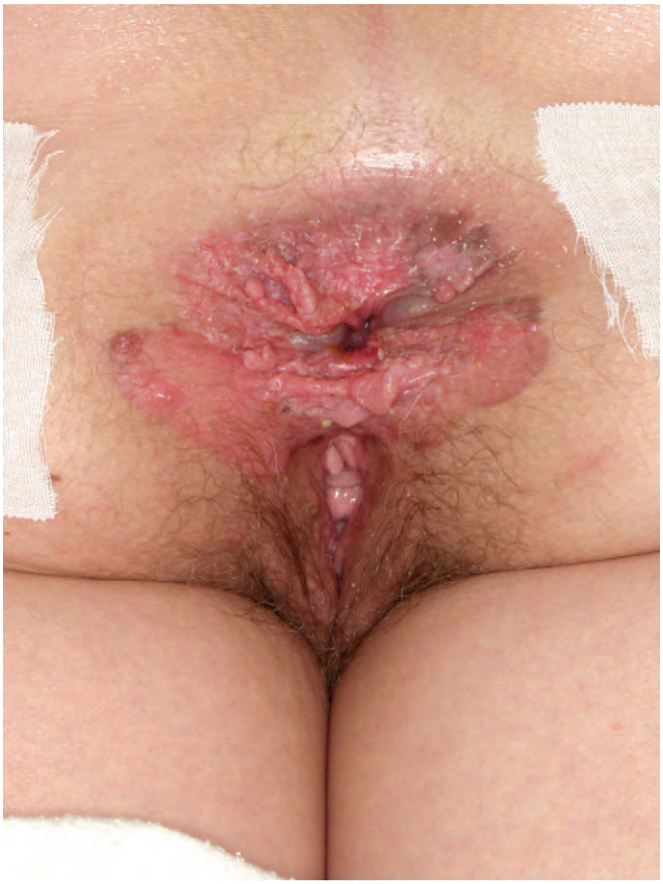

Figure 163–1. Patient with circumferential anal intraepithelial neoplasia and anal condyloma.

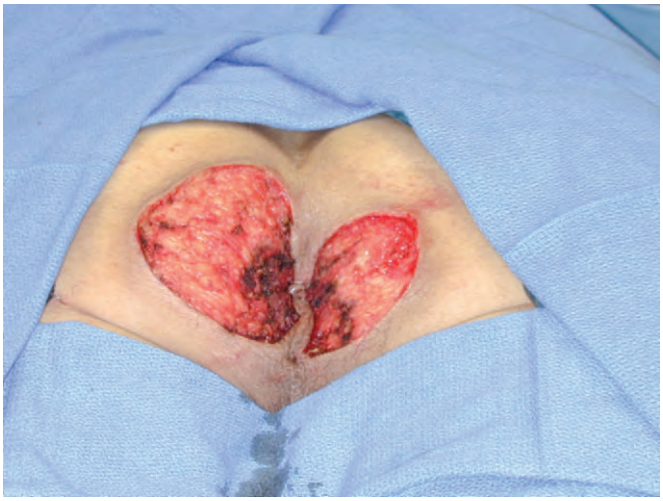

Figure 163–2. Status after wide excision of perianal intraepithelial neoplasia.

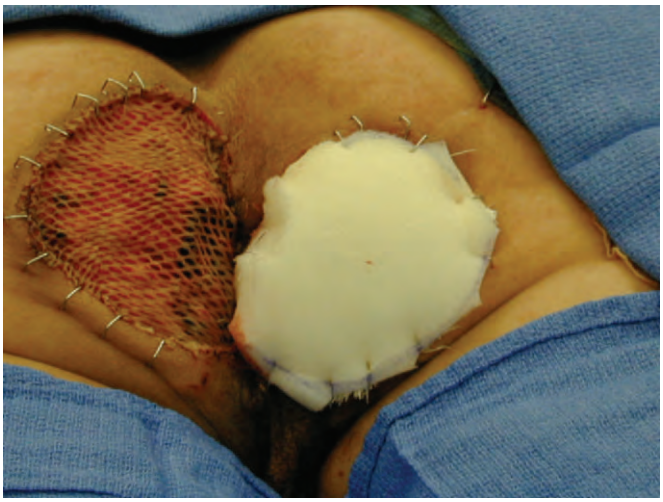

Figure 163–3. Skin grafting of the resected areas.

location of grade 3 disease. Punch biopsies are performed circumferentially around the anus at the level of the dentate line and anal verge and within the anal margin. These biopsy sites are them "mapped" to define the extent of the disease. Once the areas have been identified, wide excision with skin grafting or flap reconstruction may be performed (Figs. 163–2 and 163–3). Reported recurrence rates after wide local excision of AIN with reconstruction range from 0% to 36% with an average of 26%.[25-29]

Other managements options for AIN include immunomodulation and photodynamic therapy.[12] Little has been written on the use of immunotherapy, which involves the application of 5% imiquimod (Aldara) cream, topical 5% 5-fluorouracil (5-FU), or a combination of the two to the anal area. Imiquimod is an immunomodulator that enhances interferon's activity. Several case reports have documented complete resolution of grade 3 AIN when treated with imiquimod cream or both imiquimod and 5-FU.[30,31] A typical regimen is to apply the cream to the affected perianal skin three times a week for 10 hours at a time and then wash it off, for a total treatment time of 4 to 5 months. Kreuter and colleagues reported on 10 HIV-positive patients who were also infected with HPV serotype 16, had various grades of AIN, and were treated with 5% imiquimod cream. The cream was applied three times a week for 4 months; side effects included erythema and burning at the initiation of therapy. Most patients had complete resolution or downgrading of the AIN.[32] Graham et al. treated eight patients with grade 3 AIN with 5% 5-FU for 16 weeks. Seven of the eight patients had a complete response to the topical therapy and were AIN-free at 1 year.[33]

Photodynamic therapy has only rarely been described for the management of AIN. Photodynamic therapy involves the use of a photosensitizing agent that is injected 1 to 2 days before therapy, followed by treatment with an activating light source. Webber and Fromm treated five HIV-positive AIN patients with photodynamic therapy. After 5 months of follow-up, they confirmed downgrading or elimination of the AIN in all patients. Side effects were minor, without any evidence of stenosis.[34]

Although the effectiveness of both of these therapies has been reported only in small pilot studies, the relatively high recurrence rate and morbidity associated with radical surgical excision make these less invasive options appealing. More work is required to clearly define the roles of immunomodulation and photodynamic therapy in the treatment of AIN. Indeed, the natural history of AIN has not been well defined. Progression of AIN from type 1 to type 2 or 3 has been established.[16,35] The two studies that have performed long-term follow-up (20 years) on grade 3 AIN lesions found a malignant transformation rate of 5%.[29,36] This begs the question whether any intervention is required or whether close observation plus follow-up is adequate. Certainly, this lower rate of progression makes less invasive treatment far more attractive than wide excision.

ANAL NEOPLASMS

Squamous Cell Carcinoma

As noted in the introduction, management of anal squamous cell carcinoma is dependent on its location with respect to the anal sphincter complex. Small lesions that are separate from the anal sphincters and without evidence of spread are typically excised. These lesions are generally found in the anal margin. In contrast, anal canal tumors tend to be larger, involve the anal musculature, and are therefore typically initially treated with chemoradiation therapy. The actual approach (surgical versus chemoradiation) is determined more by the size of the lesion, its histology, the relationship of the lesion to the sphincter, and evidence of nodal spread than by whether it resides in the canal or the anal margin.

Clinical Features

The most common initial symptoms of anal canal tumors are bleeding, pruritus, discharge, and pain. Unfortunately, these are also nonspecific symptoms of common benign entities such as hemorrhoids and anal fissures. This common symptomatology, in conjunction with a patient's reluctance to seek medical attention for these complaints, often results in delay in diagnosis. Even when patients seek medical attention, 80% of anal cancers are initially diagnosed as benign conditions.[37,38]

Additional symptoms such as incontinence, change in bowel habits, pelvic pain, and rectovaginal or rectovesical fistulas are ominous. These symptoms suggest advanced malignancy with infiltration into the sphincters or penetration into rectal wall.[39,40] A Mayo Clinic series of 188 patients demonstrated tumor invasion past the mucosa in 88% of such patients.[41]

Physical Examination

Physical examination for anal carcinoma is geared toward confirming the diagnosis, establishing its stage, and determining therapy. A complete physical examination in which specific note is made of the status of the inguinal lymph nodes is essential. Detailed anorectal examination is the keystone to determining therapy. Assessment includes digital examination to evaluate the size and mobility of the mass, invasion of the sphincters or adjacent structures, and the presence of palpable pararectal lymph nodes. If the patient has excessive pain on examination in the office secondary to sphincter invasion and spasm, adequate examination under anesthesia in the operating room with biopsy is required. If adequate examination can be obtained in the office, biopsy of the lesion with local anesthetic should be performed to confirm the diagnosis.

Staging

After adequate examination has been performed, further investigations are directed toward staging the primary lesion and excluding metastatic disease. CT scanning and a chest radiograph are the primary investigations for determining metastatic disease. Endoanal ultrasound (which may require sedation) helps determine the depth of invasion of anal cancers and provides some data on perirectal lymph node status.[42-45] The role of assimilated CT/positron emission tomography (PET) scans in pretherapy staging of anal squamous cell cancer has yet to be determined. One role for CT/PET scans may be to help determine metastatic spread to the inguinal lymph nodes. The presence of metastatic disease in the inguinal region on initial evaluation requires alteration of radiation or surgical therapy to the lymph node basin involved. Magnetic resonance imaging (MRI) is also being used to stage anal cancer. Specific studies looking at the accuracy of MRI in anal tumor staging are rare, although some preliminary work has shown poor results.[46]

The TNM staging of anal canal and anal margin tumors is listed in Box 163–1. It is based on the size of the tumor; perirectal, unilateral, or bilateral inguinal lymph node involvement; and the presence of distant metastatic disease.

Therapy

Primary Surgical Management Primary surgical management of anal cancer was the optimal therapy before the 1970s, and APR was the usual operation performed. Reported 5-year survival rates with radical surgery alone ranged from 30% to 71%, with the local recurrence rate varying from 18% to 45%.[47] In a Mayo Clinic series of 188 patients treated for anal cancer between 1950 and 1976, APR was performed in 118 of these patients. Their 5-year survival rate was 71%.[41] Few tumors in the series were 2 cm or less, but excellent results were achieved with local excision alone. Workers at St. Mark's Hospital reported on 83 patients with anal margin tumors.[48] Two thirds underwent local excision with a 5-year survival rate of 65%. The 11 patients who underwent APR for cure had a disappointing 5-year survival rate of 36%.

Currently, primary surgical management is reserved for select cases. Small tumors (<2 cm in size) that are in the anal margin or do not involve the anal musculature may be amenable to wide local excision. Studies have

Box 163–1 American Joint Committee on Cancer/Union Internationale Contre le Cancer Staging System for Carcinoma of the Anal Canal and Anal Margin

Primary Tumor (T)

Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 ≤2 cm in greatest dimension
T2 >2 cm but ≤5 cm in greatest dimension
T3 >5 cm in greatest dimension

Anal Canal

T4 Invading adjacent structures: vagina, urethra, or bladder (involvement of the sphincter muscle alone is not classified as T4)

Anal Margin

T4 Invading deep extradermal structure: skeletal muscle or bone

Regional Lymph Node Involvement (N)

Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node involvement

Anal Canal

N1 Metastases to perirectal lymph nodes
N2 Metastases to unilateral internal iliac and/or unilateral inguinal lymph nodes
N3 Metastases to perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or bilateral inguinal lymph nodes

Anal Margin

N1 Metastases to ipsilateral inguinal lymph nodes

Distant Metastases (M)

Mx Distant metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases present

Staging

Stage 0	Tis	N0	M0
Stage I	TI	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Anal Canal			
Stage IIIA	T4	N0	M0
	T1-3	N1	M0
Stage IIIB	T4	N1	M0
	Any T	N2,3	M0
Anal Margin			
Stage III	T4	N0	M0
	Any T	N1	M0
Both			
Stage IV	Any T	Any N	M1

demonstrated that patients with tumors less than 2 cm in size treated by local excision have a 5-year survival rate of 60% to 70%.[47-50] Small tumors still have an 8% to 11% risk of lymph node metastasis, and therefore consideration should still be given to the use of chemoradiation therapy, even for small tumors. Surgical management may also be considered for a bulky tumor that has invaded a large portion of the sphincter. Regression with chemoradiation therapy will probably render the patient incontinent. Multimodality therapy should still be pursued even if considering extirpative surgical resection, given the high risk for nodal relapse or local recurrence with surgical therapy alone.

Combined Chemotherapy and Radiation Therapy In 1974, Nigro described the use of relatively low-dose radiotherapy (30 Gy over a 3-week period) in combination with low-dose 5-FU and mitomycin C (MMC) (5-FU infused for 4 days during the first week of radiation therapy and MMC given as a bolus dose on day 1) in an attempt to render three unresectable tumors amenable to resection. All three patients obtained complete remission, and in the two who accepted APR 6 weeks later, no residual tumor was found.[1] The technique was refined over the next 10 years, and routine radical surgery gave way to excision of the primary site after completion of combined-modality therapy (CMT).[50-52]

Subsequent modifications have centered on optimizing the components of CMT. The dose of radiation has increased from 30 Gy to 45 to 50 Gy. 5-FU was used at the beginning and end of the first radiotherapy course, with a single dose of MMC administered on the first day. Some studies have investigated the use of cisplatinum as opposed to MMC with 5-FU.[53,54] Numerous retrospective and prospective studies have been performed to look at the efficacy of CMT, with overwhelming evidence demonstrating that CMT should be initiated as the primary therapy for all anal squamous cell carcinomas. Complete tumor response has been reported in 68% to 100% of patients, with 5-year survival rates ranging from 65.5%

Table 163–1 Trials on Combined-Modality Therapy for Anal Canal Squamous Cell Carcinoma

Author	Year	*N*	Complete Response Rate (%)	Five-Year Survival Rate (%)
Cummings et al.[55]	1984	30	98	70
Greenall et al.[56]	1985	18	72	78
Sischy[57]	1985	29	89.6	81
Meeker et al.[58]	1986	19	88	87.5
Nigro[59]	1987	104	91	81
Tviet et al.[60]	1989	24	87.5	58
Sischy et al.[61]	1989	79	90	73
Cummings et al.[62]	1991	57 RT only	56	61
		66 RT + 5-FU	60	62 (disease-free)
		69 CMT	86	55
Lopez et al.[63]	1991	33	88	79
Tanum et al.[64]	1991	106	84	72
Rich et al.[53]	1993	58	89	94
Allal et al.[65]	1993	68	67.5	65.5
Smith et al.[66]	1994	42	73.8	90
Martenson et al.[67]	1995	52	74	58
Doci et al.[54]	1996	35	94	94
Martenson et al.[68]	1996	19	68	NR
Arnott et al.[69]	1996	279 RT only	30	58 (3 year)
		238 CMT	39	65 (3 year)
Flam et al.[70]	1996	145 RT + 5-FU	86	51 (disease-free)
		146 CMT	92.2	73 (disease-free)
Bartelink et al.[71]	1997	52 RT only	54	40
		51 CMT	80	60
Ceresoli et al.[72]	1998	35	100	71

CMT, combined radiation therapy and chemotherapy with 5-fluorouracil (5-FU) and mitomycin C (MMC); RT, radiation therapy.
Adapted from Sato H, Koh K, Bartolo DCC: Management of anal canal cancer. Dis Colon Rectum 48:1301-1315, 2005.

to 94%.[47] Table 163–1 lists the relevant studies and results.[55-72] The rate of salvage surgery required in these trials has ranged from 9% to 38% and is dependent on the rate of complete response.[47]

Prospective randomized trials have attempted to answer whether radiation therapy alone is sufficient to treat anal canal tumors, thereby avoiding the toxicity associated with chemotherapy. These studies showed no difference in the overall survival of patients at either 3- or 5-year follow-up, but they did demonstrate a significantly higher local response rate with fewer salvage surgeries when combined therapy was used.[62,69-71] CMT with both 5-FU and MMC, regardless of tumor stage, provides better local control and response rates than does just radiotherapy or combined therapy with only 5-FU. Although acute toxicity is higher with both 5-FU and MMC, when both are given together with radiation therapy, there is significant improvement in survival, local control, and colostomy-free survival.[47,55,70] The use of cisplatin as a substitute for MMC was shown to be as effective as MMC in three separate series.[68,73,74] Current recommendations are therefore initial therapy with 45 Gy of radiation with concomitant 5-FU and either MMC or cisplatin. Six to 8 weeks after completion of therapy, repeat physical examination is performed, and biopsy of the area where the cancer was located may be considered. Routine biopsy is not considered necessary in the absence of suspicious findings. Residual scaring or ulceration may be noted, and biopsy is often withheld because the effects of CMT may continue. Residual subtle changes should prompt further examination in a month rather than biopsy.

Salvage Surgery As shown in Table 163–1, complete response rates have varied among studies. Residual tumor is currently treated by either radical surgery or further CMT. The best timing for biopsy of apparent residual disease after CMT has not been well defined. If biopsy is performed at 6 weeks and residual disease is present but a response has been seen, current recommendations call for observation and repeat biopsy at 6-week intervals.[47] If there is continued response, continued observation is called for. If there is no regression, salvage therapy with either further CMT or APR is required.

A phase III intergroup study performed in 1996 evaluated CMT therapy for residual tumor.[70] Twenty-four patients who were found to have residual disease after

initial CMT were given a radiation boost with 9.0 Gy to the tumor bed and repeat infusion of 5-FU and cisplatin. In follow-up, 50% of the patients showed a complete response and were disease-free.

Initial studies of the role of salvage APR for anal carcinoma that has failed CMT have not demonstrated excellent long-term survival, with 3-year survival rates of less than 40%.[75-76] A recent report by Ghouti et al. examined their success in 36 patients who underwent salvage APR after either failure of CMT or local recurrence of anal epidermoid cancer.[77] The 5-year survival rate in the immediate failure group was 60.7%, with a 71.5% rate in the recurrence group. The 5-year disease-free survival rates were 31.1% and 48.2%, respectively. Of note, some form of recurrence developed in 64% of the patients at 30 months. The perineal wound complication rate in this study was 70%, which corresponds with other studies that have shown an increase in the wound complication rate with the use of neoadjuvant chemoradiation therapy.[78,79] Consequently, some authors are advocating primary closure of APR defects with rectus flap reconstruction. Chessin et al. performed a case-control series comparing perineal wound closure performed primarily or with rectus abdominis flaps. The wound complication rate was significantly higher in the primary closure group (44.1% versus 15.8%).[80] The gracilis muscles can also be used as reconstruction flaps for large perineal wounds. Figure 163–4 illustrates the reconstruction of a large perineal defect after APR and neoadjuvant chemoradiation therapy.

No randomized trials have compared salvage CMT with local resection or APR. Salvage CMT provides the same benefits as primary CMT, namely, sphincter preservation. The results of subsequent APR after salvage CMT have not been examined, but serious consideration should be given to primary wound closure with a muscle flap in view of the significant risk for perineal wound breakdown.

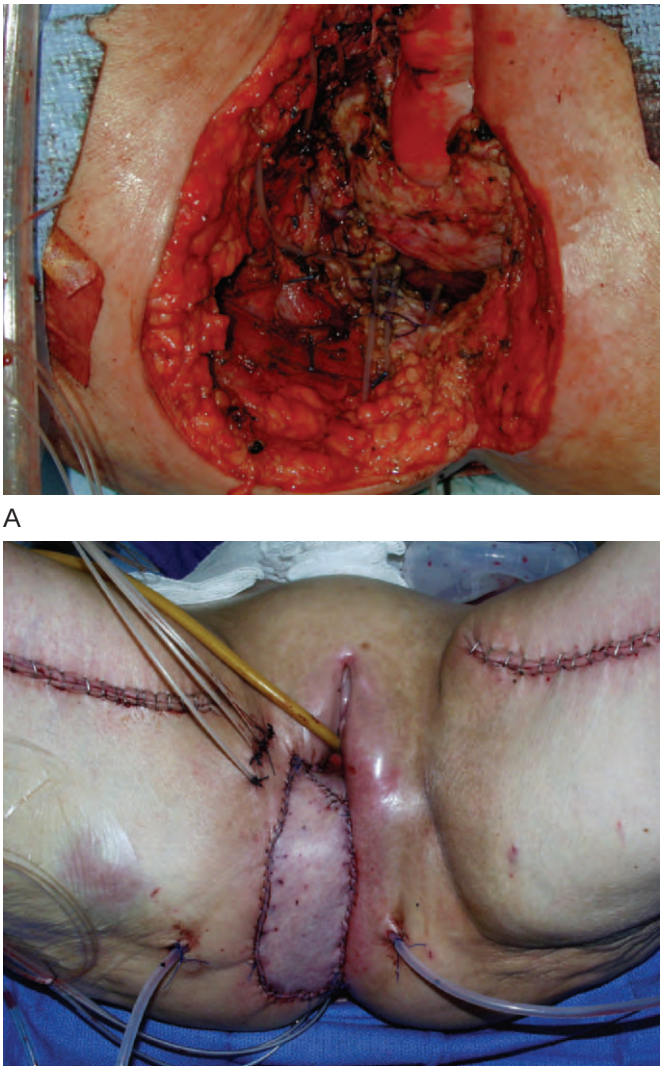

Figure 163–4. Abdominoperineal resection with wide excision and posterior vaginectomy after neoadjuvant therapy **(A)** and then reconstruction with bilateral gracilis flaps **(B)**.

Inguinal and Pelvic Lymph Node Metastases

The inguinal lymph nodes are palpable in 10% to 25% of patients at initial evaluation. Clinically positive inguinal lymph nodes should be evaluated by needle aspiration cytology as part of appropriate staging, with subsequent open biopsy if the result is benign. Cutaneous metastasis can also occur and may be found in locations around the perineum (Fig. 163–5). Formal node dissection is considered unnecessary because it delays therapy and increases the risk for leg edema. In the presence of histologically proven positive lymph nodes in the inguinal region, radiation doses of 45 to 50 Gy are administered to the groin. The pelvic nodes are always included in the radiation field with CMT.

The presence of either inguinal or pelvic lymph node metastasis significantly decreases the 5-year survival of the patient. Frost et al. examined 192 patients with anal carcinoma and found the 5-year survival rate in node-negative patients to be 74%, as opposed to 44% in node-positive patients.[49] Klotz et al. examined 221 patients and also found a significant difference in survival rates when comparing node-negative and node-positive patients (63.3% versus 24%).[81]

Rare Anal Neoplasms

Paget's Disease

Patients with this extremely rare lesion of the perianal skin commonly complain of pruritus and, occasionally, bleeding, a palpable lump, soiling, or a change in bowel habits. Examination usually reveals an erythematous, scaling, rash-like lesion with well-demarcated edges, frequently with an appearance similar to psoriasis. The disease generally occurs in patients older than 60 years and is found equally in men and women. Paget cells are the characteristic finding on histologic examination.

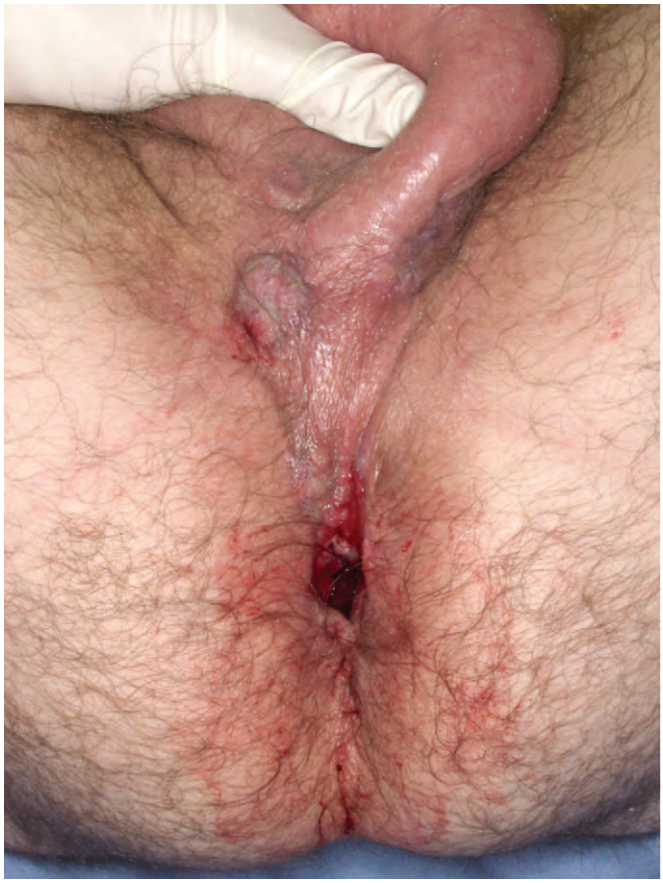

Figure 163–5. Male patient with cutaneous and lymph node metastasis from poorly differentiated squamous cell carcinoma of the anus.

These epithelial cells are large and rounded, with abundant pale cytoplasm and a large peripheral nucleus. The cells may resemble signet-ring cells but have less mucus and a different staining pattern. Paget cells are thought to be of apocrine origin. In the absence of an associated adenocarcinoma, perianal Paget's disease is usually a low-grade malignant lesion. If the staining pattern is different from usual (i.e., if there are no apocrine markers), the lesion is more likely to be associated with an underlying malignancy.[82]

Management begins with biopsy of the perianal skin lesion to establish the diagnosis. Therapy is determined on the basis of the local extent of the lesion and whether an associated adenocarcinoma is present. The true extent of the lesion may not be obvious macroscopically, and it is therefore necessary to take skin biopsy specimens at various distances around the periphery of the visible lesion, either at a preliminary planning operation or at one sitting if accurate intraoperative frozen section is available. Work-up for associated colorectal malignancy should include colonoscopy, although an article by Sarmiento et al.[83] in which 13 patients with anal Paget's disease were described revealed that even though 4 had associated malignancies, none of them were visceral. (In a similar series of 18 patients with grade 3 AIN who underwent colonoscopy, Sarmiento et al. found that none had internal tumors.[28]) If the Paget's lesion is isolated, wide local excision with skin graft or advancement flap reconstruction is performed. The deep margins of excision are the sphincter muscle and, proximally, the dentate line within the anal canal. An associated rectal cancer mandates APR regardless of the level of the lesion in the rectum. Recent success has been obtained with imiquimod cream.

Melanoma

Anal melanoma is a rare tumor that accounts for 1% of malignant anal lesions. It is found more commonly in females and is usually seen in 50- to 60-year-olds.[84,85] Bleeding is the most common symptom, and the lesions are often mistaken for thrombosed external hemorrhoids. Thibault et al. found 5-year and disease-free survival rates of 22% and 16%, respectively, in 50 patients who were retrospectively reviewed.[85] They also found that patients continued to die of their disease up to 11 years after diagnosis and therapy. Patients treated with curative intent were compared, but no survival benefit was found between those who underwent APR (19% disease-free at 66 months to 20 years) and those who were treated by local excision (18% disease-free with a follow-up of 66 months to 44 years). Ballo et al. recently reported on 23 patients treated by local excision with or without regional lymph node dissection and adjuvant radiation therapy.[86] Fifteen patients had died and 15 had relapsed after 32 months of follow-up with an actuarial 5-year survival rate of 31%. None, however, had evidence of local recurrence, and the authors concluded that local excision with radiation therapy is adequate to achieve local control of this disease.

One series from the Memorial Sloan-Kettering Cancer Center demonstrated increased survival in patients who undergo radical excision (APR) as opposed to local excision.[84] This finding is in contradiction to the experience at St. Mark's Hospital and Sweden.[87,88] Our practice is to consider melanoma a systemic disease at initial evaluation and to perform local excision for small lesions and APR for advanced lesions for local control or palliation. However, in a young patient, radical excision of a small lesion may be considered worthwhile for potential chance of cure. Immunotherapy may be considered in these patients as one would for cutaneous melanoma.

Basal Cell Carcinoma

Whereas basal cell carcinoma is the most common cutaneous malignancy in sun-exposed areas, reports of this lesion in unexposed areas are relatively uncommon. Lesions in the perianal area are very rare. It is important to obtain histologic conformation to distinguish these lesions from a basaloid or subtype of cloacogenic carcinoma (squamous cell carcinoma). Although early reports suggested that perianal basal cell carcinoma may behave more aggressively than lesions in other parts of the body, this was not borne out by a more recent series

of 19 patients.[89] All patients underwent either local excision, Mohs' surgery, or electrodessication with no recurrences. Eighty percent of the patients were men with a mean age of 67 years, and 60% had basal cell lesions at other sites.

Adenocarcinoma

Adenocarcinoma of the anus is a very rare entity. It is often difficult to determine whether tumors have grown from the rectum and extended down toward the anus or whether they have indeed originated from the anus. The anal glands may undergo malignant change and produce a flat submucosal tumor. Patients with Crohn's disease and long-standing anal fistulas may undergo malignant transformation within the tracts.[90]

Management of anal adenocarcinoma is undergoing evolution. Originally, APR was touted as the preferred definitive therapy. Investigators are starting to examine CMT alone or in conjunction with surgery as a therapeutic option. Papagikos et al. compared patients with adenocarcinoma of the anus treated by chemoradiation therapy and patients with epidermoid cancer treated by CMT.[91] Seven of 16 (44%) patients with adenocarcinoma had local recurrence as compared with 16 of 92 (17%) with epidermoid cancer. The authors therefore recommended neoadjuvant therapy with chemoradiation therapy followed by APR for adenocarcinoma of the anus. The Rare Cancer Network performed a multicenter retrospective study of 82 patients who underwent treatment of adenocarcinoma of the anus.[92] They differentiated three treatment groups—radiotherapy and surgery, CMT, and surgery alone—and found that the actuarial locoregional recurrence rate at 5 years for the three groups was 37%, 36%, and 20%, respectively. The 5-year survival rate in each group was 29%, 58%, and 21%, respectively. From these data and multivariate analysis they concluded that CMT was associated with better survival than surgery was and that APR should be reserved for salvage therapy. Further studies are required to make firm conclusions regarding the feasibility of CMT as the sole management of anal adenocarcinoma.

CONCLUSIONS

The variety of anal neoplasms found in the anal canal results in diverse approaches to therapy. Squamous cell carcinoma of the anal canal, by far the most common, is best initially treated in most cases with CMT regardless of the tumor stage at diagnosis. Extensive surgery should be reserved for patients who fail to respond to CMT. When performing APR for recurrent or residual disease, thought should be given to primary reconstruction with muscle interposition flaps to reduce wound complication rates. Topical therapies are becoming more accepted for precancerous anal canal and margin disorders such as AIN and may replace wide excision as the mainstay of therapy. Other rarer malignancies require individualized therapy based on the principles of maximizing cure while minimizing sphincter dysfunction.

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Chapter

164

Retrorectal Tumors

Tonia M. Young-Fadok · Eric J. Dozois

The retrorectal (presacral) space is the anatomic harbor for a spectrum of rare tumors ranging from simple, benign cystic lesions that may be approached by a single surgeon familiar with pelvic and rectal anatomy to complex malignant masses involving multiple pelvic structures. Improvements in imaging modalities, coupled with neoadjuvant chemoradiation, and the realization that true multidisciplinary teams are required for optimal management have allowed a more aggressive surgical approach to these latter tumors.

ANATOMIC CONSIDERATIONS

Given the bony confines of the pelvis, within which the retrorectal space is almost centrally located, tumors arising in this space are in close proximity to multiple other structures. Thus, appropriate evaluation plus management of presacral tumors requires an understanding of the anatomic relationships of the pelvic soft tissues and neurologic and osseous structures, as well as assembly of a multidisciplinary team of surgeons if required. The retrorectal space is actually a potential space, identical to the presacral plane. The posterior wall of the rectum or, more accurately, the mesorectum, forms the anterior boundary of the space, and the anterior aspect of the sacrum forms the posterior border. Superiorly, the space extends to the peritoneal reflection and inferiorly to the rectosacral fascia.[1] Below this is the U-shaped supralevator space. The lateral boundaries are demarcated by the lateral ligaments, the ureters, and the iliac vessels.

The retrorectal space itself contains few structures: loose connective tissue, the middle sacral artery, superior hemorrhoidal vessels, and branches of sympathetic and parasympathetic nerves. The vast spectrum of rare tumors that may occur in this location is a consequence of the multitude of adjacent tissue types that preferentially extend into this area. Vascular and neural structures originate or traverse in close proximity to this area and may give rise to or be involved in retrorectal tumors.

Knowledge of sacral root function is of particular importance to adequately counsel patients regarding potential functional sequelae. Even if all sacral roots on one side of the sacrum are sacrificed, normal anorectal function is preserved, and sphincter-sparing operations may be considered if oncologically appropriate. Likewise, if only the upper three sacral roots remain intact on either side of the sacrum, the patient will still exhibit spontaneous defecation and control of anorectal contents. If both S3 roots are destroyed, however, anal incontinence and difficult defecation will result,[2] and a permanent colostomy is usually indicated. The need for sacrectomy has additional ramifications besides neurologic sacrifice. The surgical team must be familiar with the anatomy of the thecal sac, sacral nerve roots, sciatic nerve, piriformis muscle, and sacrotuberous and sacrospinous ligaments. Our practice has been to incorporate the skills of both an oncologic orthopedic surgeon and a spine surgeon to achieve these aims. Technically, it is feasible to resect the majority of the sacrum inasmuch as pelvic stability is maintained if more than half of the S1 vertebral body is preserved. Because stress fractures may occur in this remnant if preoperative radiation therapy has been used, preservation of spinopelvic stability may require fusion. Resection of more complex malignant tumors often leaves a large soft tissue or bony defect (or both), frequently within an irradiated field. Reconstruction plus closure requires the talents of a plastic surgeon familiar with muscle and soft tissue flaps.

Patients require careful, but frank, preoperative counseling to allow appropriate decision making once they have been informed of the potential neuromuscular and gastrointestinal/genitourinary changes that may radically affect function and thus quality of life.

INCIDENCE

Retrorectal tumors are rare. One report of 20,851 proctosigmoidoscopies described three presacral cysts,[3] and another older study reported one presacral tumor in

40,000 hospitalizations,[4] for an incidence of 0.0025% to 0.014%.

CLASSIFICATION

Any tissue type within or adjacent to the retrorectal space may give rise to benign or malignant lesions. The most comprehensive classification of retrorectal masses considers each potential cell line (Box 164–1).[5] A simpler way of classifying these unusual tumors is to consider that two thirds are congenital in origin, of which a further two thirds are developmental cysts, and the next most common masses are neurogenic tumors.[6] Developmental cysts may originate from any of the three germ layers[7] and include epidermoid and dermoid cysts, enterogenous cysts, tailgut cysts (TGCs), and teratomas. Teratomas are the most common presacral tumor in children.

An alternative classification divides the lesions into cystic and solid based on preoperative investigations because this information guides the diagnostic approach. Cystic lesions are seen most commonly in women,[6] and most solid lesions are chordomas. Overall, malignancy is more common in men, even though most retrorectal tumors occur in women, possibly because benign lesions are often asymptomatic but are detected in women during routine gynecologic and prenatal examinations.

CLINICAL FINDINGS AND DIAGNOSIS: GENERAL

History and Physical Examination

Symptoms are frequently absent or nonspecific. In the absence of symptoms, retrorectal tumors may be discovered incidentally on routine pelvic or rectal examination. Pain, if present, is typically vague and of long duration and occurs in the perineum, lower part of the back, or both. Classically, this pain is aggravated by sitting and ameliorated by standing or walking. Pain is an ominous sign in that it is present more commonly when the lesion is malignant than benign (88% versus 39%).[6] All patients with osseous tumors in one series complained of low back or perineal pain.[6] The vague nature of the pain may even have eluded diagnosis to the point that the patient has been referred to a psychiatrist. Constipation, urinary and fecal incontinence, and sexual dysfunction are usually symptoms of advanced tumors with sacral nerve involvement.

Box 164–1 Classification of Presacral Cysts and Tumors

I. Congenital
  A. Developmental cysts
    1. Epidermoid
    2. Dermoid
    3. Mucus secreting
    4. Teratomas
  B. Teratocarcinoma
  C. Chordoma
  D. Anterior sacral meningocele

II. Nerve
  A. Ganglioneuroma
  B. Ependymoma
  C. Neurilemmoma
  D. Neurofibroma
  E. Neurofibrosarcoma

III. Cartilage, bone, and muscle
  A. Benign
    1. Osteoma
    2. Osseous cyst (simple or aneurysmal)
    3. Chondroma
    4. Leiomyoma
  B. Malignant
    1. Osteogenic sarcoma
    2. Ewing's tumor
    3. Chondrosarcoma
    4. Giant cell tumor
    5. Leiomyosarcoma

IV. Adipose, fibrous, and endothelial
  A. Lipoma and liposarcoma
  B. Fibroma and fibrosarcoma
  C. Endothelioma and hemangioendothelial sarcoma
  D. Myelolipoma

V. Hematologic and lymphatic
  A. Lymphangioma and lymphangiosarcoma
  B. Plasmacytoma
  C. Hemangioma and hemangiosarcoma
  D. Pericytoma
  E. Lymphoma

VI. Traumatic and inflammatory
  A. Hematoma
  B. Abscess (perineal/pelvic/perirectal/enteric with fistula)
  C. Granuloma

VII. Miscellaneous
  A. Desmoid
  B. Endometrioma
  C. Mesenchymoma
  D. Metastatic carcinoma
  E. Recurrent pelvic carcinoma

Modified from Uhlig BE, Johnson RL: Presacral tumors and cysts in adults. Dis Colon Rectum 18:581, 1975, with permission.

Occasionally, patients complain of persistent perianal discharge. Their symptoms may have previously been attributed to a perianal fistula or pilonidal disease. Several circumstances should alert the examiner to the possibility of a retrorectal cystic lesion: repeated operations for "anal fistula," inability to uncover a primary source of infection at the dentate line, recurrent infection of the retrorectal space without an obvious cause, presence of a postanal dimple, and fullness and fixation of the precoccygeal area.[1]

A careful physical examination should focus on the perineum and rectum. Evidence of a postanal dimple should be sought. In almost all patients, a digital rectal examination will reveal the presence of an extrarectal mass displacing the rectum anteriorly. In a series from the Mayo Clinic, 97% of tumors were palpable on digital rectal examination.[6] The overlying mucosa is usually smooth and mobile; absence of this feature overlying the mass is suggestive of previous infection of a cystic lesion that has discharged through the rectum or an advanced malignancy. The rectal examination is also important in evaluating for fixation and determining the level of the tumor in relation to the coccyx and other structures such as the prostate. Neurologic evaluation focused on the sacral nerves and musculoskeletal reflexes may indicate the presence of sacral nerve involvement.

Investigations

Presacral masses may be evaluated with plain radiographs of the sacrum, computed tomography (CT), endoanal ultrasound (EUS), and magnetic resonance imaging (MRI). Simple anteroposterior and lateral radiographs of the sacrum will identify bone expansion and destruction, calcification, and soft tissue–occupying masses, but these findings are not pathognomonic of a specific tumor type. These features are commonly seen with chordoma inasmuch as bone destruction is present in a third of patients with chordoma, and in more than two thirds of these patients the lesion is malignant. Bone destruction, however, may also be seen with benign tumors such as giant cell tumors, neurilemoma, aneurysmal bone cysts, and osteochondroma.[6] A "scimitar" sign on sacral views is a classic feature seen in association with anterior sacral meningocele, a diagnosis that should be confirmed with myelography or MRI with gadolinium enhancement.

Imaging with CT or MRI has become the preferred approach in establishing a diagnosis for these lesions, and these studies often provide complementary information. CT can distinguish between cystic, solid, and mixed tumors and can also be used to determine whether other pelvic structures such as the bladder, uterus, ureters, or rectum are involved. Cortical bone destruction is likewise demonstrated by CT, whereas MRI is superior in the evaluation of marrow involvement. The improved soft tissue resolution of MRI is helpful in planning the extent of resection of adjacent structures. Spinal imaging is best performed by MRI, which may demonstrate meningocele, nerve root and foraminal involvement by tumor, and thecal sac compression.[8] Magnetic resonance angiography or venography may add additional information regarding vascular involvement and indicate the need for a vascular surgeon to be a member of the multidisciplinary surgical team. Importantly, sagittal views on either CT or MRI help delineate the relationship of the tumor to the sacrum, particularly upper extension of the tumor, which determines the appropriate operative approach.

In patients with a chronically draining sinus associated with a presacral cystic mass, sinography may be useful in defining the lesion. EUS may be helpful in determining the relationship of a retrorectal mass to the wall of the rectum.[9] Many of these lesions are completely separate from the rectum, which may thus be preserved, but infection of a cystic lesion or malignancy may result in involvement of the rectal wall.

Role of Preoperative Biopsy

Whether to biopsy a presacral mass has previously been a hotly debated topic, fueled by the lack of information available on these rare tumors. Some authors have opined that preoperative biopsy is contraindicated in the case of any presacral tumor considered resectable,[6,10-12] whereas others have stated that all solid tumors should be biopsied before surgical intervention.[13] Advances in preoperative imaging techniques and neoadjuvant therapy have clarified the issue. The need for biopsy is predicated on whether the result will change operative management and probable benefit to the patient.

Simple cystic lesions do not usually need to undergo biopsy because the results will not alter management. The situation may be very different, however, for solid and heterogeneously cystic lesions. Patients with tumors that respond to neoadjuvant chemoradiation, such as Ewing's sarcoma, osteogenic sarcoma, and neurofibrosarcoma, will obviously benefit from biopsy and appropriate preoperative therapy. Tumors that may attain very large proportions, such as desmoid tumors, may be more readily excised if some degree of tumor regression is obtained with radiation.

If biopsy is to be performed, it must be performed correctly. Transrectal (or transvaginal) biopsy should always be avoided for two reasons. If malignancy is present, excision of the rectum is then mandated, whereas if it were not directly involved by tumor, it could otherwise have been preserved. Second, in the presence of a cystic lesion, transrectal biopsy introduces the risk of infection, thus rendering subsequent attempts at excision more difficult and enhancing the risk for recurrence. Inadvertent biopsy of a meningocele may result in the disastrous complications of meningitis and death. If tissue diagnosis of a retrorectal mass is required, a needle biopsy may be performed within the field of the proposed area of resection so that the needle tract may be excised en bloc with the specimen at the time of surgery.[14] Either the transperineal or parasacral approach may be considered, depending on the anticipated field of resection. It is helpful to discuss the case with a radiologist familiar with evaluation of pelvic

tumors and with an appreciation of the intended operative approach.

CLINICAL FINDINGS AND DIAGNOSIS: TUMOR SPECIFIC

Developmental Cysts

Epidermoid and Dermoid Cysts

These cysts result from abnormal closure of the ectodermal tube of the fetus, which is thought to be caused by local failure of separation of cutaneous ectoderm from neural ectoderm (Table 164–1).[15] Epidermoid and dermoid cysts and sinuses both exhibit keratinizing stratified squamous epithelium, but whereas epidermoid cysts bear no skin appendages, dermoid cysts may exhibit characteristic sweat glands, hair follicles, or sebaceous cysts.[16] They may be extraspinal, intraspinal, or both. Although those in the postsacral position may have an intraspinal component or connection in up to 69% of pediatric patients,[16] presacral dermoids are rare in pediatric patients, and communication with the spinal canal does not appear to be a factor in presacral dermoids in adults.

Dermoid and epidermoid cysts exhibit the classic features of retrorectal cysts. They are more common in women and may be associated with a postanal dimple or sinus. An infection rate of up to 30% has been noted, in which case the cysts are manifested as retrorectal or perirectal abscesses. Communication between an abscess and a postanal dimple may result in a false diagnosis of perianal fistula. A recurrently infected cyst has been associated with squamous carcinoma in middle age.[3]

Enterogenous Cysts

Enterogenous cysts (duplication cysts of the rectum) are thought to result from sequestration of the developing hindgut.[17] They may be lined by squamous epithelium (like dermoid and epidermoid cysts) or columnar epithelium (like TGCs). They differ from these other entities by having a well-defined muscular wall with a myenteric plexus.[18] Villi or crypts are also commonly found in intestinal duplications, but not in TGCs.[18] Enterogenous cysts, like other presacral cysts, have a tendency to become infected, and there is a female preponderance. Malignant change has been reported.[19]

Tailgut Cysts

Multiple terms have been used to describe TGCs, including retrorectal cyst hamartoma and postanal gut cyst. These retrorectal cysts are thought to originate from remnants of the embryonic primitive gut that extend into the transient true tail, which develops in the human embryo between 35 and 56 days of gestation before regressing.[18]

Despite their rare nature, the pathologic features of TGCs have been well described. The masses are multicystic and multilocular (Figs. 164–1 and 164–2). The cysts

Table 164–1 Features of Retrorectal Cysts

Cyst Type	Tissue Type	Distinguishing Features	Mechanism of Formation	Female-Male Ratio
Dermoid cyst	Keratinizing stratified squamous epithelium	With or without sweat glands, hair follicles, sebaceous cysts	Failure of separation of cutaneous ectoderm from neural ectoderm	F > M
Epidermoid cyst	Keratinizing stratified squamous epithelium	No skin appendages	Failure of separation of cutaneous ectoderm from neural ectoderm	F > M
Enterogenous cyst (duplication cyst)	Squamous or columnar epithelium	Well-defined muscular wall with myenteric plexus; with or without villi or crypts	Sequestration of the developing hindgut	F > M
Tailgut cyst	Squamous or glandular columnar, transitional, or mixture	Smooth muscle may be present, but not well defined; no myenteric plexus	Remnants of embryonic primitive gut	3:1
Teratoma	Contains tissue from each of the germ layers	May contain hair, bone, teeth		F > M

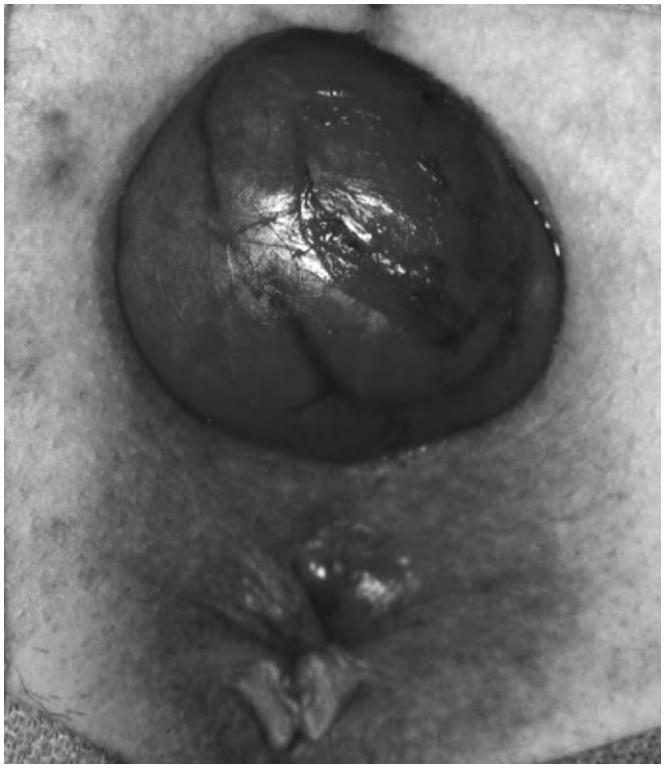

Figure 164–1. Small, distal tailgut cyst exposed through a paracoccygeal incision.

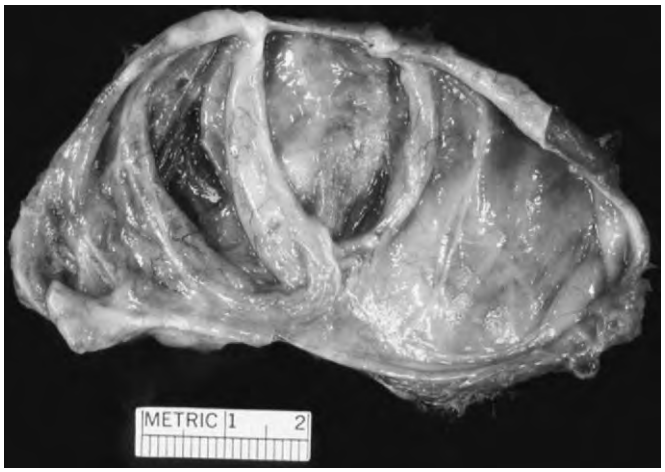

Figure 164–2. Gross pathologic specimen of a tailgut cyst revealing a multicystic, multiloculated appearance.

are lined by squamous, glandular columnar, or transitional epithelium, all three of which may be present in the same specimen.[20] The presence of the latter two epithelial types excludes the diagnoses of dermoid and epidermoid cysts, which contain squamous epithelium only. Although smooth muscle may be identified in the specimen, a well-defined muscular wall with a myenteric plexus should be absent to exclude the possibility of a

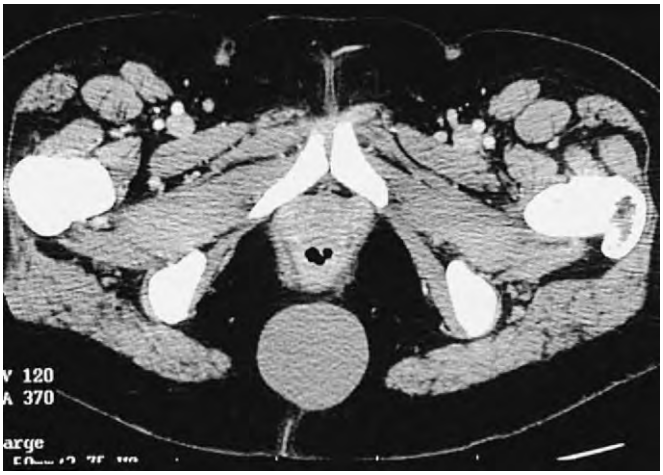

Figure 164–3. Typical computed tomography appearance of a tailgut cyst.

duplication cyst.[18] Glomus bodies have also been identified in a subset of these cysts.[18]

TGCs are detected more frequently in females at a ratio of approximately 3:1.[18] The age range spans birth to old age, which is somewhat unusual given the presumed congenital nature of this entity. Nonetheless, the majority have been reported in adults, with few reports of these lesions being detected in neonates.[21,22] A cystic, extrarectal mass can almost always be detected on physical examination, which may also reveal the presence of a postanal funnel-shaped dimple.[18] Sinus tracts in patients without previous surgical procedures are unusual and occurred in only 2 of 45 patients who had not previously undergone anorectal operations.

Radiographic studies are helpful in establishing a preoperative diagnosis. Barium enema will suggest an extrinsic retrorectal mass in 50% of patients.[18] CT scan reveals the multicystic nature of the lesion. The presence of calcification is common in teratomas and generally eliminates the diagnosis of TGC, but it may be seen in lesions with malignant degeneration.[18] CT reveals a well-defined homogeneous mass with preservation of adjacent fat planes and often keratinous debris within the cysts (Fig. 164–3).[23] The rectum is smoothly indented, and although sacral abnormalities may be noted,[18] sacral destruction is absent.[23] Characteristic MRI findings are low signal on T1-weighted images with a homogeneously intense signal on T2-weighted sequences.[24] Irregular wall thickening with intermediate signal intensity on both T1- and T2-weighted images has been noted with malignant degeneration.[20] MRI may be helpful in confirming the presence of a sinus tract if there has been a history of previous drainage.

Malignant degeneration has been described in TGCs, although the risk is difficult to calculate given the rarity of this lesion. The majority of reported malignancies have been adenocarcinomas.[18,20,24-28] One study reported two adenocarcinomas that stained positive for p53, both within the area of carcinoma and in surrounding dysplastic tissue, thus raising the possibility of a dysplasia-

carcinoma sequence comparable to colon cancer.[29] Presacral carcinoid tumors have also been described in association with TGCs,[30,31] which has led to speculation that these carcinoids arise from neuroendocrine cells in presacral hindgut rests, regardless of whether they are associated with identifiable TGCs.[32] This would be supported by the description of glomus bodies in TGCs.[18,33]

TGCs are usually low-lying masses within the presacral space, although they have been described adjacent to the kidney in the retroperitoneum.[34] TGCs are often excised via a parasacral approach. One author (TY-F) has, however, performed laparoscopic resection of one such lesion in conjunction with laparoscopic cholecystectomy after the incidental finding of a retrorectal cystic mass in an elderly woman with cholelithiasis.

Neurogenic Tumors

Neurogenic tumors are the second most common form of retrorectal tumor after congenital cysts. They account for 12% of presacral lesions, and again there is a female preponderance.[6] They represent peripheral nerve tumors, two thirds of which are benign.[6] However, neurogenic tumors also account for 15% of malignant retrorectal masses.[35] Even with a benign lesion, these tumors may be associated with sacral bone destruction, possibly as a result of pressure erosion because these masses tend to be large (mean size, 7 cm).[6] In our experience, one distinguishing feature is the typical dumbbell shape of these solid lesions, which may be helpful in distinguishing them from other solid retrorectal masses.

Sacrococcygeal Chordomas

Even though they are extremely rare, sacrococcygeal chordomas are the most frequently encountered malignant tumors of the retrorectal space. They are believed to originate from primitive notochordal tissue, either from the nuclei pulposi or from abnormal rests.[14] This explains their location anywhere along the spinal column with a predilection for its two extremities, the spheno-occipital and the retrorectal regions (Fig. 164–4). Half of the lesions are located in the sacral area.[36-38]

Chordomas are seen mostly in men[39,40] and rarely before the age of 30 years. Patients may be asymptomatic or have a long-standing history of vague pain,[37,41-43] mostly in the perineal area and characteristically aggravated by sitting and ameliorated by standing or walking.[14] Because of the frequent inability of the clinician to ascertain the cause of this chronic ill-defined pain, such patients are often seen by many different physicians, including pain clinic specialists and psychiatrists. Advanced, large tumors may cause constipation, rectal and urinary incontinence, and sexual dysfunction.[40]

The diagnosis is based on a high index of clinical suspicion and suggestive findings on digital rectal examination and radiography. In nearly all patients, digital examination will reveal a posteriorly located, extrarectal mass that displaces the rectum anteriorly.

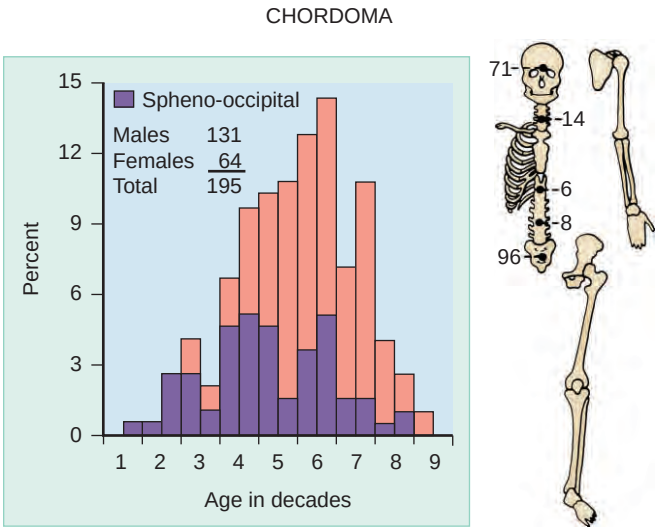

Figure 164–4. Distribution of chordomas showing a predilection for sacrococcygeal and spheno-occipital sites. (From Dahlin DC: Bone Tumors: General Aspects and Data on 6,221 Cases, 3rd ed. 1978. Courtesy of Charles C Thomas, Publisher, Ltd., Springfield, Illinois.)

Anterior and lateral views of the sacrum demonstrate bone destruction (Figs. 164–5 and 164–6) and a soft tissue–occupying mass. Other tumors less likely to cause bony destruction include giant cell tumors, neurolemmomas, aneurysmal bone cysts, and osteochondromas. Imaging of the sacral area by CT[44] and MRI helps distinguish between cystic, semisolid, or solid tumors and delineate the upper level of the tumor, which in turn determines the most appropriate surgical approach.[14]

Biopsy may be considered in order to ascertain the diagnosis and to decide whether patients require preoperative adjuvant therapy either because of the nature of the tumor or to facilitate future extirpation by reducing its large size (Figs. 164–7 to 164–9). Transrectal biopsies should be avoided because curability may be compromised.[45] If the diagnosis remains unclear after plain films and other imaging, a transperineal or parasacral biopsy within the field of impending surgical resection is indicated.[14]

Biopsies of sacrococcygeal chordoma reveal rounded or polygonal cells arranged in cords and syncytial clumps amid abundant mucinous matrix. These cells are often heavily vacuolated, which gives them a "bubbly" appearance from the intracytoplasmic mucin, and are referred to as physaliphorous cells.[46] Diagnosis of chordoma is possible from a fine-needle aspiration biopsy specimen.[46,47]

Teratoma and Teratocarcinoma

Presacral teratoma is the most common teratoma seen in infancy, the vast majority occur in infants, and they are rare beyond the second decade.[48] These teratomas are detected more commonly in females than males.[48,49]

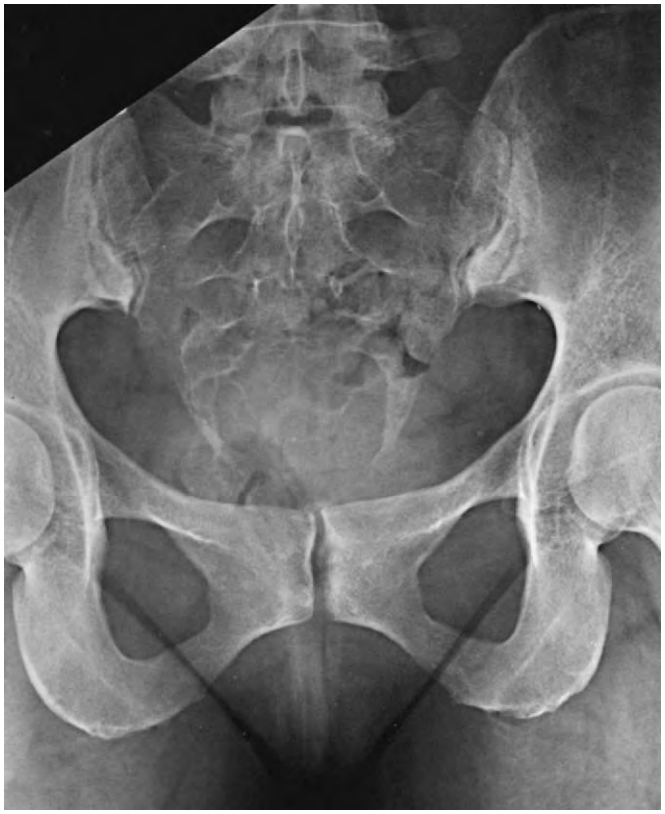

Figure 164–5. A radiograph of sacral bone destruction secondary to chordoma reveals a characteristic "fang" appearance of the distal portion of the sacrum. (From Dozois RR: Retrorectal tumors: Spectrum of disease, diagnosis and surgical management. Perspect Colon Rectal Surg 3:241-255, 1990. Courtesy of Thieme [prior copyright held by Quality Medical Publishing], publisher, New York.)

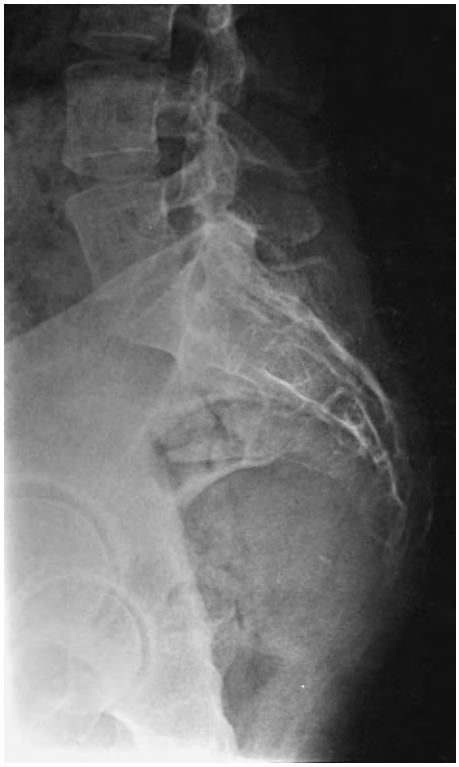

Figure 164–6. Lateral view of the sacrum with bone destruction secondary to a presacral chordoma. (From Dozois RR: Retrorectal tumors: Spectrum of disease, diagnosis and surgical management. Perspect Colon Rectal Surg 3:241-255, 1990. Courtesy of Thieme [prior copyright held by Quality Medical Publishing], publisher, New York.)

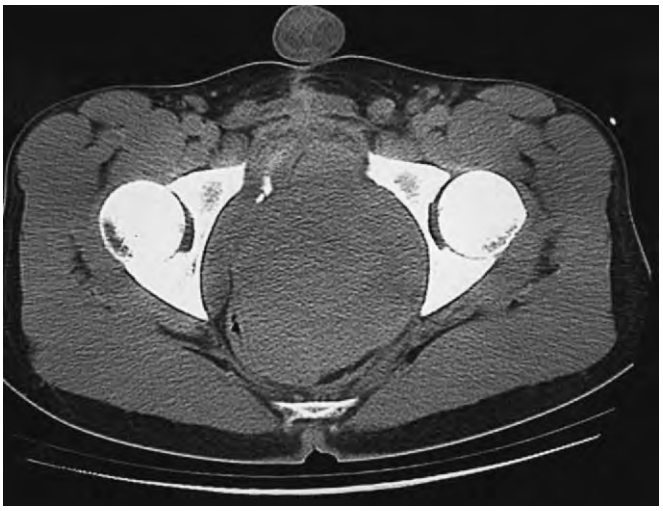

Figure 164–7. Large presacral desmoid.

Presacral teratomas typically contain tissue from each germ layer, although the degree of differentiation may vary. The more well-differentiated the elements, with recognizable hair, bone, or teeth, for example, the more likely that the tumor is benign. As with other retrorectal masses, benign lesions are usually cystic, whereas malignant degeneration appears to occur in solid components.[50]

Teratomas may be confined to the pelvis or may extend superiorly into the presacral space or downward with an externally visible component. Altman and colleagues classified these tumors in infants into four types depending on the relative representation of external and intrapelvic components.[48] For example, type IV tumors are entirely presacral with no external component. These differences explain why teratomas were diagnosed on the day of birth in more than 50% of infants in a series from 1974 and 18% were not diagnosed within the first 6 months of life. This has a significant impact on the rate of malignancy at diagnosis because the development of malignancy correlates strongly with age in infants; only 7% of girls and 10% of boys were found to have malignancy before 2 months of age, but these rates rose to 48% and 67%, respectively, after 2 months.[48] The current trend toward widespread use of ultrasound monitoring during pregnancy would be anticipated to greatly increase the rate of prenatal diagnosis and reduce the risk for malignancy. In presacral tumors found in adulthood, the risk for malignancy appears to be low.[49]

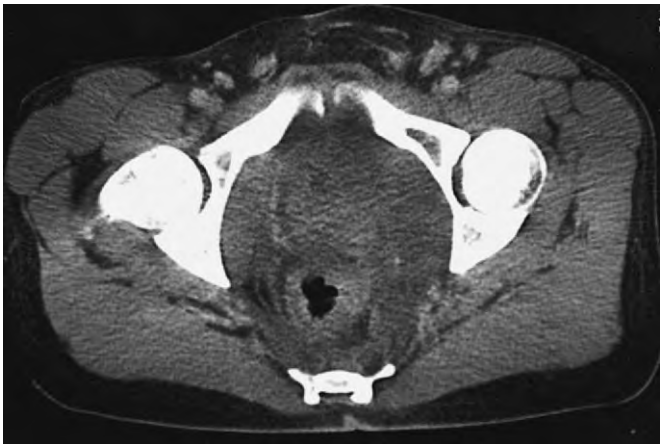

Figure 164–8. Appearance of a presacral desmoid after preoperative radiation therapy.

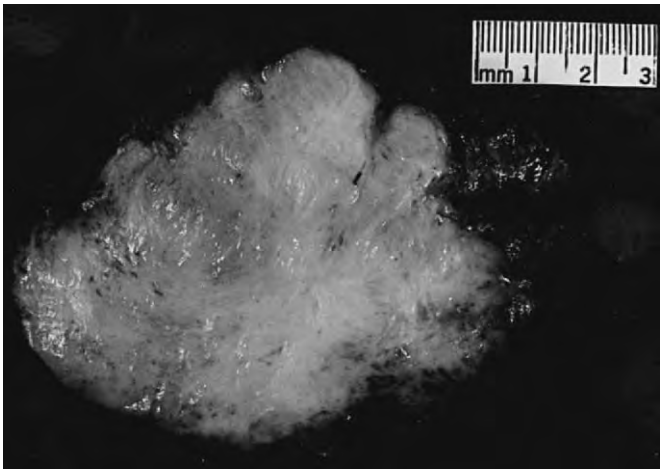

Figure 164–9. Desmoid specimen after excision.

Osseous Lesions

Primary osseous lesions are less common than metastatic ones, but they are the next most common retrorectal mass after neurogenic tumors and account for 11% of these lesions. There is a male preponderance of 2:1,[6] and half of these masses are malignant: Ewing's sarcoma, myeloma, and osteogenic sarcoma. Benign lesions are represented by tumors such as giant cell tumor, aneurysmal bone cyst, and osteochondroma.[6] Bone destruction is a frequent associated feature of such tumors, even those that are benign,[6] and they are often accompanied by pain.

Miscellaneous Lesions

This group encompasses a spectrum of rare tumors. Malignant lesions accounted for half of this group in one series[6]: lymphoma, fibrosarcoma, and sarcoma. Benign masses are represented by such entities as lipoma, leiomyoma, fibroma, and hemangioma.

SURGICAL THERAPY

Rationale

Once diagnosed, retrorectal tumors should be treated aggressively. The rationale for such treatment is based on several observations.[1,6] First, the lesion may already be malignant. In patients with teratomas, especially children, the risk for malignant degeneration is significant and increases with delay. An anterior sacral meningocele may become infected and result in meningitis if left untreated. Cystic lesions are also at risk of becoming infected, which renders subsequent excision more difficult and increases the risk for recurrence. Retrorectal masses in young women may continue to grow and result in dystocia.

There are several issues that may result in less than optimal management of these tumors. Sadly, given the vague symptoms that often accompany these tumors, patients may initially be seen with advanced disease, with a large mass affecting multiple pelvic structures. This scenario is not uncommon with chordomas. Many surgeons are reluctant to approach such rare and complex lesions with which they have little experience, and others may not be familiar with the techniques that allow for complete resection. Some may be aware of older data describing poor outcomes after resection of chordomas and thus adopt a defeatist attitude and not be familiar with the improved outcomes that may be attained with an aggressive surgical approach. The outcome may be compromised preoperatively by obtaining biopsy specimens via an inappropriate approach. Intraoperatively, the desire to avoid injury to the rectal wall or to neurovascular structures results in a misguided attempt to limit the extent of resection, which compromises oncologic outcomes.

Oncologic and functional outcomes can be optimized, however, if an experienced, multidisciplinary team approaches these tumors, especially complex malignant lesions.

The Multidisciplinary Team

The most important principle is assembly of the appropriate multidisciplinary team. Preoperatively, members will include an experienced radiologist, medical oncologist, radiation oncologist (plus consideration of intraoperative radiation therapy), and anesthesiologist. The surgical team must be appropriate for the intended resection. Many smaller lesions are comfortably dealt with by colorectal surgeons alone. Suspected osseous and neurogenic lesions and larger tumors, especially those extending to the upper half of the sacrum, should be approached by a multidisciplinary team consisting of a colorectal surgeon, an orthopedic oncologic surgeon, and a spine surgeon/neurosurgeon. Additional expertise may be required of colleagues in vascular surgery, urology, and plastic surgery. Postoperatively, the team may also require the skills of a rehabilitation therapist.

Surgical Approach

There are three possible approaches for resection of a retrorectal tumor: anterior approach (transabdominal), posterior approach (perineal), or combined abdominoperineal approach. Accurate preoperative imaging (and reimaging after neoadjuvant therapy if it has been used) is vital in defining the relationship of the tumor to the sacrum and the margins of resection. Small, low-lying lesions below S3 may be removed transperineally through a parasacral/paracoccygeal incision. Tumors extending above S3 should be approached either from the abdomen alone or via a combined anterior and posterior approach, depending on the need for concomitant sacrococcygeal resection.

The approach used determines patient positioning and preparation. Another factor to be considered is the need for reconstruction and soft tissue coverage, for which the plastic surgeon plays a vital role. Although a transabdominal rectus abdominis myocutaneous (TRAM) flap is often the flap of choice, occasionally a gracilis flap may be used, and the patient's skin preparation should be planned accordingly.

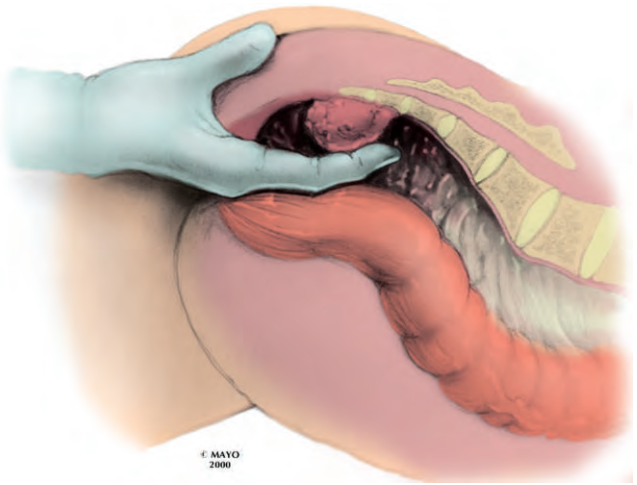

Figure 164–10. Separation of a distal presacral lesion from the rectum. (Redrawn from MacCarthy CS, Waugh JM, Mayo CW, Coventry MB: The surgical treatment of presacral tumors: A combined problem. Proc Staff Meet Mayo Clin 27:73-83, 1952.)

Preoperative Planning

Careful planning and forethought are required for resection of a complex presacral mass. The importance of preoperative imaging has been underscored in terms of choosing an operative approach and assembling a team of surgeons capable of resecting pelvic structures affected by the tumor and reconstructing the resultant defect. Attention must be paid to correcting nutritional impairments, which are frequently present in these oft-debilitated patients, with total parenteral nutrition or tube feeding. A temporary vena cava filter is considered when prolonged operative time and significant postoperative debilitation are anticipated, given the significant risk for deep venous thrombosis and pulmonary embolism in a setting in which postoperative anticoagulation may be contraindicated. The team members should meet to coordinate strategy and timing of the various steps of the operation. The discussion should also include the anesthesiologist, who must have the experience and the equipment to handle the potentially massive transfusion requirements that can accompany resection of the bony components of the pelvis.

Tumors Located Below S3—The Posterior Approach

The patient is placed in the prone jackknife position and the buttocks are taped apart. An incision is made over the lower part of the sacrum and coccyx down to the anoderm while being cautious to avoid damage to the external sphincter. Transection of the anococcygeal ligament facilitates exposure of the tumor and separation of the lesion from retrorectal fat. The lesion can then be dissected from surrounding tissues, including the rectal wall, which is frequently not involved, especially in benign tumors, in a plane between the retrorectal fat and the tumor itself (Fig. 164–10). In the case of very small lesions, especially if cystic, the surgeon may double-glove the nondominant hand and, with the index finger in the anal canal and lower part of the rectum, push the lesion outward, away from the depths of the wound. This technique facilitates dissection of the lesion away from the wall of the rectum without entry into the rectal lumen. Previous infection of a cystic lesion may obliterate the plane between the cyst wall and rectum. A portion of the rectal wall may be excised with the specimen and the defect closed in two layers. The lower sacrum and coccyx can then be excised en bloc with the tumor, if indicated. Performing this step early during the procedure, if excision is warranted, may facilitate exposure.

Combined Abdominoperineal Approach

If the upper extension of the tumor is above the S3 level, an anterior-posterior approach is preferred. The patient is usually positioned in the supine position. If resection of the rectum is to be combined with re-establishment of bowel continuity, a carefully padded, combined synchronous (modified dorsal lithotomy) position is used. Other positions, such as the "sloppy lateral" position, have also been described to facilitate a two-team approach to the combined anterior and posterior resection.[51] Cystoscopy with bilateral stent placement facilitates intraoperative identification of the ureters, particularly in a patient who has received neoadjuvant radiation therapy or has a bulky tumor.

The abdominal cavity is entered through a lower midline incision, and the peritoneal cavity is carefully explored to rule out disseminated disease. After mobilization of the lower sigmoid, the presacral space is entered just below the promontory and the posterior mesorectum dissected off the sacral fascia down to the level of the upper extension of the tumor. The lateral stalks are also separated from the tumor. If the tumor can

be safely separated from the posterior aspect of the rectum, the lesion is dissected free in a plane anterior to the mass between its capsule and the mesorectum. Posterior to the tumor, if a plane exists between the lesion and the sacrum, this too is carefully developed. Isolated tumors, without invasion of adjacent organs, may be dissected free circumferentially in this manner and removed. If the tumor is bulky, it may compress and displace the rectum, and attempts at dissection between the tumor and the rectum risk entering the rectal lumen. In this event, we favor excision of the rectum en bloc with the tumor. If the lesion is benign or if it is considered to have a low risk for recurrence despite being malignant, re-establishment of bowel continuity may be considered, along with a protective diverting loop ileostomy if indicated by a low-level anastomosis and preoperative irradiation. If the tumor extends high on the sacrum, with evidence of invasion so that both S3 roots and even the S2 nerve roots will need to be sacrificed, excision of the rectum en bloc with the mass may facilitate resection, avoids tumor cell spillage, and is appropriate in a patient who will be rendered incontinent. In this situation, the upper part of the rectum is transected above the level of the tumor with a cutting stapler, and distally its anterior and lateral attachments are completely freed to the level of the pelvic floor. An end sigmoid colostomy is established.

Resection of large complex tumors may result in substantial loss of blood from friable, irradiated pelvic vessels or from the sacrectomy itself. Thus, when a major sacrectomy is contemplated, ligation of the middle sacral artery and the internal iliac vessels and their branches helps reduce blood loss. Preservation of the anterior division of the internal iliac artery, which gives off the inferior gluteal artery, reduces the risk for perineal necrosis. The assistance of a vascular surgeon is invaluable for this step, especially in the presence of an irradiated field. It is helpful to mobilize the ureters, together with supporting tissues, and suspend them laterally away from the planned margin of the sacrectomy by placing fine absorbable suture through the paraureteral tissues.

With extended sacral excision, especially when radiation is an integral part of the treatment, a well-vascularized musculocutaneous flap derived from the rectus abdominis can be used to close the perineum.[52] The flap can be mobilized at this point in the procedure and placed in the deep pelvis to be accessed later via the perineal wound and used for closure. To protect both the flap and other vital structures during the perineal portion of the procedure, a barrier of thick plastic sheeting or laparotomy pads is placed immediately in front of the sacrum, to be removed after resection of the sacrum.

After closure of the abdominal incision and creation of the stoma, the patient is moved into the prone position. A midline incision is made over the sacrum and coccyx down to the anus, and the anococcygeal ligament is transected and the levators retracted bilaterally. If the rectum is to be preserved, its posterior aspect is separated from the tumor. The orthopedic surgeon can then proceed with dissection of the gluteus maximus muscles on both sides, transection of the sacrospinous and sacrotuberous ligaments (Figs. 164–11 and 164–12), and

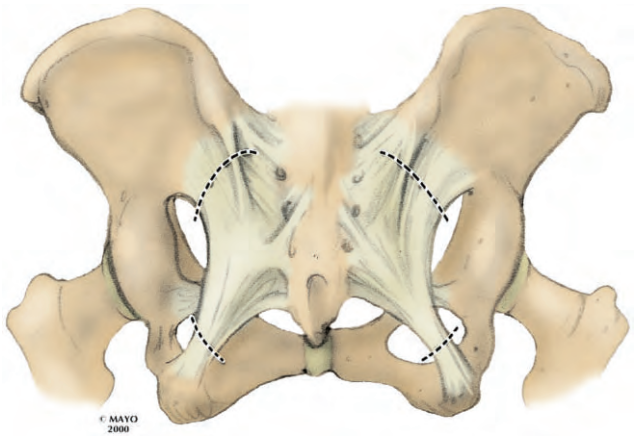

Figure 164–11. Division of the sacrospinous and sacrotuberous ligaments (posterior view). (Redrawn from Dozois RR: Retrorectal tumors. In Mazier WP, Levien DH, Luchtefeld MA, Senagore AM [eds]: Surgery of the Colon, Rectum, and Anus. Philadelphia, WB Saunders, 1995.)

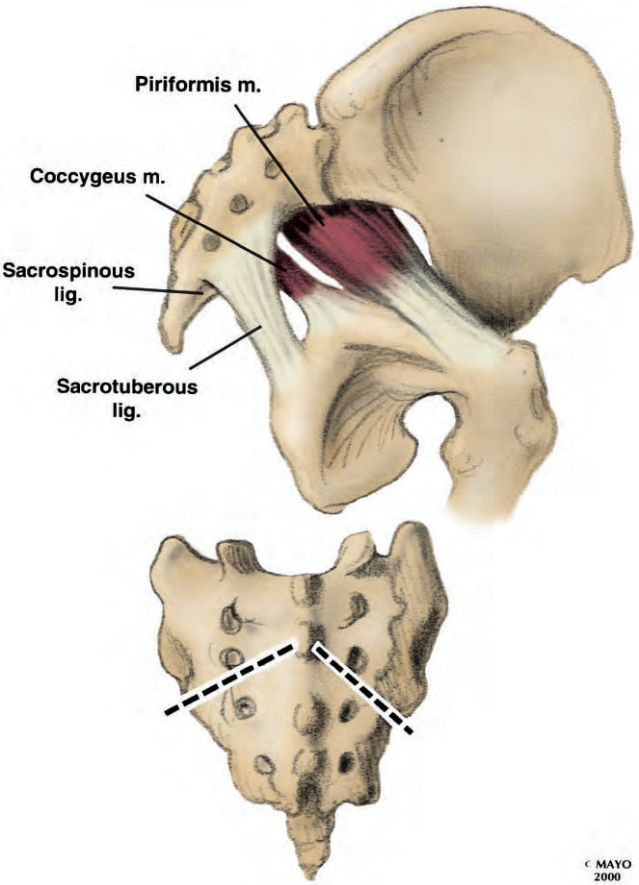

Figure 164–12. Division of the sacrospinous and sacrotuberous ligaments (lateral view) with osteotomy at the S2-3 level and distal sacrectomy. (Redrawn from MacCarthy CS, Waugh JM, Mayo CW, Coventry MB: The surgical treatment of presacral tumors: A combined problem. Proc Staff Meet Mayo Clin 27:73-83, 1952.)

division of the piriformis muscles to expose the sciatic nerves. An osteotomy is then carried out at the S3 level or even higher after exposing and preserving at least one S3 nerve root if at all possible. The neural sac may need to be ligated. In this fashion, the tumor can be removed en bloc with the attached sacrum, coccyx, and involved sacral nerve roots, with or without the rectum. The wound is closed over drains, with a musculocutaneous flap used as deemed necessary, especially for large perineal defects and particularly if preoperative irradiation has been used.

Results

Malignant Tumors

Oncologic outcomes after resection of malignant retrorectal tumors are widely variable. Conclusions are limited by small series of these rare tumors and the heterogeneity of the malignancies reported. In general, the malignant retrorectal tumors reported in the literature have had poor outcomes, but in such cases the completeness of resection is either uncertain or the tumor is excised piecemeal, thus breaking oncologic principles. Kaiser et al. found that the rate of local recurrence increased from 28% to 64% if the tumor was violated perioperatively.[45] Accordingly, one must question poor outcomes in series in which the extent of resection is unclear and a multidisciplinary team has not been involved to allow for complete resection with negative margins.

The prognosis of patients with the most common malignant retrorectal tumor, chordoma, has varied greatly, with some authors[39] reporting an almost inevitable risk of local recurrence and others reporting 10-year survival rates ranging from 15% to 76%. At the Mayo Clinic, the 5-year survival rate for patients with sacrococcygeal chordomas was reported to be 75% in 1985.[6] More recently, we have found the likelihood of surviving 5 and 10 years after surgery to be 80% and 56%, respectively (unpublished data, Chiu LK, Dozois RR). Isolated metastatic tumors to the lungs, ribs, spine, and long bones can be excised successfully to provide patients with symptomatic relief and more prolonged survival. The prognosis for retrorectal malignancies other than chordoma was more grim, with a 5-year survival rate of 17%.[51] Three patients, with neuroblastoma, neurofibrosarcoma, and Ewing's sarcoma, were alive without recurrence at 3, 5, and 7 years, respectively. Even the more recent of these analyses, however, was without the benefit of current thoughts regarding preoperative biopsy and neoadjuvant therapy.

Others have reported small series. Lev-Chelouche et al. described 21 patients with malignant retrorectal tumors, nine of which were chordomas.[10] No preoperative biopsy was performed, and only 15 lesions were considered to be completely excised. Most recurrences occurred after incomplete resection, and half of these patients died of recurrent or progressive disease. Wang et al. described 22 patients with malignant retrorectal tumors: five were chordomas, and seven were leiomyosarcomas.[53] Again, no patient underwent preoperative biopsy, and only five patients had complete resections, with a 5-year survival rate of 41%. Postoperative chemoradiotherapy was used in selected patients. Bohm et al. described 24 patients, but only 4 had chordomas and 20 had developmental cysts.[12] Three chordomas recurred at 25, 32, and 55 months. In contrast, in only 3 of 20 patients did cystic lesions recur, and re-excision was successful in all.

Patients with gross residual chordoma after resection have been treated with high-dose radiation therapy. One series of 25 patients from the Royal Marsden Hospital showed that the median duration of freedom from local progression was 32 months after radiation therapy and that all patients in whom pain was a major symptom experienced relief.[54] Doses higher than 55 Gy appeared to produce more prolonged freedom from progression.

Benign Tumors

Low-lying cystic lesions can be completely excised via a posterior approach in many cases. Larger cystic lesions that extend higher into the pelvis should be excised via a combined abdominal and perineal approach. One author (TY-F) has also performed laparoscopic excision of a TGC in a patient who required concomitant cholecystectomy (Fig. 164–13).

The requirement for coccygectomy in conjunction with resection of a congenital cystic lesion is debatable.[55] Whereas some believe that the coccyx may harbor totipotential cells that will lead to recurrence if not excised,[56] other series have not demonstrated a high recurrence rate in the absence of coccygectomy. In addition, although one review reported that 10% to 38% of cystic lesions harbor a malignancy,[34] malignant degeneration is usually considered to be rare, especially in simple cysts. In the Mayo series, only 3 teratocarcinomas were noted among 49 congenital cystic lesions (which included 15 epidermoid cysts, 16 mucus-secreting cysts, 15 teratomas, and 2 meningoceles).[6]

Lev-Chelouche et al. described complete excision of 21 benign presacral lesions, with no recurrence during a 10-year follow-up.[10] Singer et al. reported on seven patients with presacral cysts (six females, one male).[55] All patients had been subject to misdiagnosis and had undergone an average of 4.1 previous operative procedures in which they were treated for pilonidal cysts, perirectal abscesses, fistula in ano, psychogenic disorders, proctalgia fugax, and post-traumatic or postpartum pain before the correct diagnosis was made. All lesions were successfully resected via a parasacrococcygeal approach after the correct diagnosis was made with a CT fistulogram.

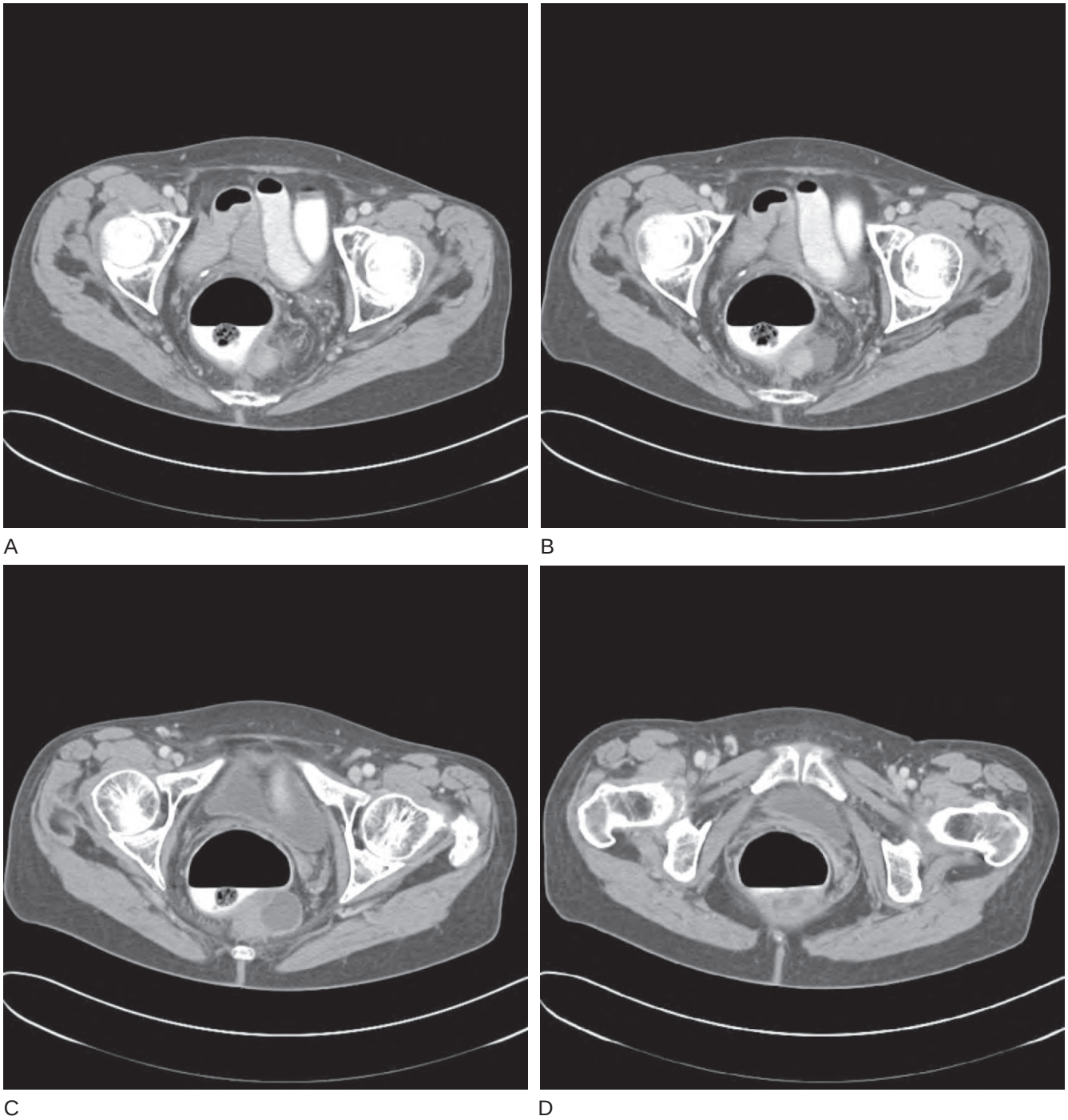

Figure 164–13. Computed tomography scan of a 74-year-old woman with a complex cystic left retrorectal mass. This tailgut cyst was approached laparoscopically during concomitant cholecystectomy.

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Chapter

165

Rare Colorectal Malignancies

Paul J. McMurrick · Peter W. G. Carne · Michael Johnston

More than 90% of all malignancies of the large bowel are derived from surface epithelial cells, predominantly adenocarcinoma. Other extrarectal malignancies of the pelvis, retrorectal tumors, and squamous cell carcinoma of the anal canal are discussed in other chapters. This chapter deals with those lesions derived from other structural tissues of the large bowel and surrounding structures, as well as the more common metastases. These lesions frequently represent a diagnostic and management challenge. They are rarely seen by individual medical practitioners and are often of miserable prognosis. Owing to the uncommon nature of these lesions, most of the literature supporting therapeutic strategies is based on experience of small case series.

Classically, rare colorectal malignant lesions are classified by the tissue of origin (Table 165–1).

CARCINOID TUMORS OF THE COLON AND RECTUM

Carcinoid tumors of the colon and rectum are rare tumors of neuroendocrine cell origin. Colonic carcinoids account for 3% to 10% of all carcinoids and 0.3% of all colon cancers. Rectal carcinoids represent 19.6% to 27.4% of gastrointestinal carcinoids and account for around 1% of all rectal tumors. Recent population data suggest that the incidence of rectal carcinoids may be increasing.[1] Surgery represents the primary curative modality for these tumors.

Carcinoids usually have positive reactions to immunohistochemical markers of neuroendocrine cells, including neurone specific enolase, chromogranin, and synaptophysin. Secretory granules seen at electron microscopy may contain a variety of hormones and biogenic amines, serotonin being one of the best characterized. However, colorectal carcinoids are much less likely to produce such substances than are carcinoids found in other locations.

The carcinoid syndrome occurs primarily in the setting of liver metastases because hepatic metabolism of neuroendocrine products usually prevents the syndrome from occurring. Rarely, when venous blood from the tumors directly enters the systemic circulation, the carcinoid syndrome may occur in the absence of liver metastases.

Patients with colorectal carcinoids are at a significant risk of both synchronous and metachronous cancers. The synchronous cancers appear to be most frequently located in the gastrointestinal tract and occur at a rate of 8% to 40%. The 20-year metachronous cancer rate is reported at 22.6%, these tumors often being outside the gastrointestinal tract (lung/bronchus, urinary tract, and prostate). Overall, the risk of a second cancer is about 31%.[2]

Colonic Carcinoids

Colonic carcinoids frequently present at an advanced stage, with nodal or distant metastases. They are more frequently found in the proximal colon and are often large at the time of diagnosis. Presentation is often in the 7th decade of life and may be with an abdominal mass, large bowel obstruction, rectal bleeding, or with other nonspecific symptoms. Carcinoid syndrome is only rarely seen.

Segmental resection forms the mainstay of management of this rare tumor, similar to the management of colonic adenocarcinomas. Five-year survival rates range from 70% in the setting of localized disease to 44% and 20% in patients with regional or metastatic disease, respectively.

Synchronous carcinoid tumors are rare; however, second primary malignancies occur at a rate of 25% to 40%.

Table 165–1 Classification of Rare Tumors of the Large Intestine

Primary Tumors
Epithelial origin
Carcinoid
Neuroendocrine carcinoma
Squamous cell carcinoma
Lymphoid
Lymphoma
Plasmacytoma
Mesenchymal
Malignant gastrointestinal stromal
Liposarcoma
Leiomyosarcoma
Rhabdomyosarcoma
Malignant fibrous histiocytoma
Fibrosarcoma
Other
Schwannoma
Kaposi's sarcoma
Secondary Tumors
Breast
Lung
Kidney
Melanoma
Bladder

Adapted from Corman ML: Colon and Rectal Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 1998.

Rectal Carcinoids

Rectal carcinoid tumors are more common than colonic carcinoids. Presenting symptoms include rectal bleeding, constipation, pain, and tenesmus. They may also be found incidentally. Peak incidence is in the 5th to 7th decades of life. Carcinoid syndrome is essentially unknown with rectal carcinoids.

The risk of metastatic disease is related to the size of the primary tumor and therefore influences surgical management. Tumors of 1 cm or smaller have a very low (~3%) risk of nodal metastases, whereas metastases occur at a rate of around 11% in tumors between 1 and 2 cm. Rectal carcinoids larger than 2 cm are found to have metastasized in around 74% of cases.

Tumors of 1 cm or less can therefore be treated successfully with curative intent by local excision. Those greater than 2 cm should undergo an oncologic resection (anterior or abdominoperineal resection). Tumors between 1 and 2 cm can be treated with either radical resection or local excision. If there is evidence of invasion into the muscularis propria, radical excision is preferable. Endorectal ultrasound may be useful for the assessment of local invasion. If local excision is performed, then careful follow-up is necessary. Clearly an individualized approach to patients with carcinoids of 1.1 to 2 cm is required, taking into consideration the position of the tumor and the patient's fitness for surgery.

Surgery remains the only curative therapeutic modality for rectal carcinoids. Adjuvant chemotherapy and radiotherapy are not curative and should not be administered outside of a clinical trial. In the absence of metastatic disease a 92% 5-year survival rate is reported; this is reduced to 44% with nodal metastases and 7% with distant metastases.

As the course of patients with regional or distant metastatic disease may be indolent, attempts should be made to resect all of the tumor if possible. Even in the setting of incurable disease, palliative bypass or resection should be considered.

Compared to colonic carcinoids, multiple tumors occur less commonly (0 to 3%) and second malignancies are found at a rate of 7% to 32%.

NEUROENDOCRINE CARCINOMAS OF THE COLON AND RECTUM

Neuroendocrine carcinomas are high-grade tumors of the neuroendocrine cells within the colon and rectum. These tumors are rare and highly aggressive. They have been reported to represent between 0.1% and 4% of colorectal malignancies. A single, large, tertiary referral center recently reported 38 cases of neuroendocrine carcinoma over a 23-year period.[3] These carcinomas are found most commonly in the rectum and caecum.

Presentation is often with advanced disease, with up to 65% to 85% of cases presenting in this manner. Consequently prognosis is poor, with a series from Memorial Sloan-Kettering reporting a median survival of 10.4 months.[3]

Treatment of this uncommon tumor is not clearly established. Surgery is the primary curative therapy, with the use of adjuvant chemotherapy and radiotherapy also reported. Cisplatin-based chemotherapy appears to have a role; however, this approach requires further investigation.

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma of the colon and rectum is extremely rare. To make the diagnosis it is necessary to exclude (1) cranially extending anal canal squamous cell carcinoma, (2) squamous cell carcinoma in a fistulous tract, and (3) metastatic squamous cell carcinoma. The cause of squamous cell carcinoma of the colon and rectum and the etiologic role of human papillomavirus (HPV) are unclear. These tumors are found most commonly in the right colon. Presenting symptoms are similar to those of colorectal adenocarcinomas.

Resection would appear to be the predominant curative treatment modality. Adjuvant radiation and chemotherapy have also been used in various combinations. The prognosis of this tumor is similarly difficult to comment on due to the limited number of cases available. It does appear to be poor when compared to adenocarcinoma; however, long-term survivors have been reported.

PRIMARY LYMPHOMA OF THE COLON AND RECTUM

Extranodal lymphoma, although rare, is most frequently found in the gastrointestinal tract. The large intestine is the site of around 10% to 20% of these tumors, with the cecum and rectum the most common locations. Surgery, radiation therapy, and chemotherapy all play roles in the management of this condition; however there is a paucity of quality evidence to guide therapy and certainly no randomized trials.

Primary rectal lymphoma accounts for between 0.19% and 1.3% of rectal neoplasms. Presentation includes the usual symptoms associated with rectal tumors. Macroscopically the tumor may be submucosal or ulcerated. Treatment of primary rectal lymphoma includes chemotherapy, resection, and radiation therapy, the most appropriate combination of therapies determined by the nature of the tumor and the presenting symptoms.

Primary colonic lymphoma accounts for around 0.65% of colonic neoplasms. As for rectal lymphoma, presenting symptoms are similar to those of other colonic tumors. Resection is often required, as is chemotherapy.

MESENCHYMAL TUMORS OF THE RECTUM

Tumors of the mesenchyme of the rectum are rare, with the most common being a gastrointestinal stromal tumor (GIST). Originally, leiomyomas and leiomyosarcoma were reported as more common, but recent advances in immunohistochemistry techniques have allowed for better classification. Rarer tumors include malignant fibrous histiocytoma, liposarcoma, malignant schwannoma, hemangiopericytoma, and rhabdomyosarcoma. The interstitial mesenchymal stem cells may differentiate into smooth muscle cells and, when mutated, give rise to a GIST, leiomyoma, or sarcoma. Most mesenchymal tumors present incidentally or with a mass effect. They rarely cause bleeding but may be found incidentally with hemorrhoids or similar perianal conditions.

All rectal tumors should be biopsied because treatment modalities differ. The biopsy site and direction of the incision should always be planned with future resection in mind.

Mesenchymal tumors are well imaged in the pelvis with magnetic resonance imaging (MRI). Endorectal ultrasound may be useful for demonstrating invasion if the tumor is appropriately located. Malignant tumors are generally positron emission tomographic (PET) avid and are well staged using this modality in combination with computed tomographic (CT) scanning.

Gastrointestinal Stromal Tumors

GISTs were originally mistakenly classified as leiomyomas, leiomyosarcomas, or smooth muscle tumors arising from the mesenchyme of the gut and divided with some difficulty histologically into benign and malignant tumors.

GISTs are now thought to arise from the interstitial cells of Cajal (ICC) or their precursors—the interstitial mesenchymal cells. Generating electrical slow waves, the interstitial cells of Cajal are intercalated between the intramural neurons and the effector smooth muscular cells to form a gastroenteric pacemaker system.

Epidemiology

GISTs are around 10 times more common than true leiomyomas and sarcomas but still in the largest population study to date occur in 0.68/100,000 people per annum. These tumors arise in men slightly more commonly than women, and the incidence is higher in blacks than other races. Eighty percent are diagnosed in individuals older than 50 years of age. They are most commonly seen in the stomach and small intestine, with the colon making up 7% tumors and the rectum 5%.

Pathophysiology and Pathology

The interstitial cells of Cajal express CD117, which is a product of the c-*kit* protooncogene (Figs. 165–1 and 165–2). This gene encodes a tyrosine kinase receptor that is involved in cell proliferation, and mutations of this oncogene may result in a GIST. Mutation resulting in activation of the tyrosine kinase receptor complex without any ligand result in a malignant GIST.

Ten percent to 30% of GISTs are malignant, and differentiation from benign tumors is made either with the diagnosis of metastases or demonstration of invasion on clinical presentation, imaging, or pathology.

Immunohistochemistry is the mainstay of diagnosis at present, with expression of CD117 and CD34 the most helpful distinguishing stains. The differential diagnosis includes schwannoma and leiomyoma, which stain more for the smooth muscle marker SMA and with desmin. Differentiating a GIST from a subclass called gastrointestinal autonomic nerve (GAN) tumors can be achieved by staining for neuron-specific enolase and skenoid

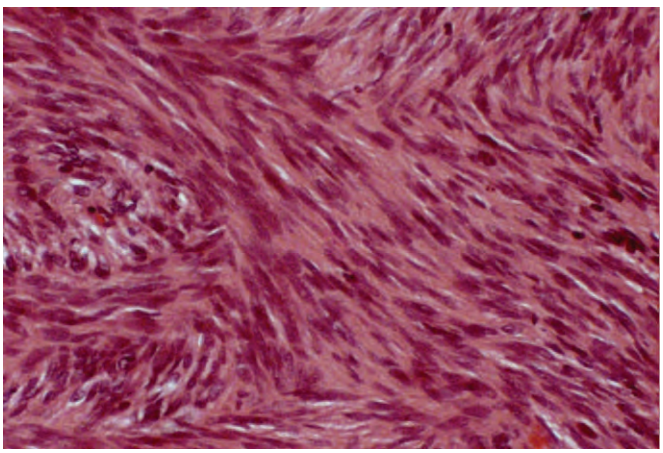

Figure 165–1. High-power histology of a gastrointestinal stromal tumor showing a spindle cell arrangement similar in appearance to a leiomyoma and schwannoma.

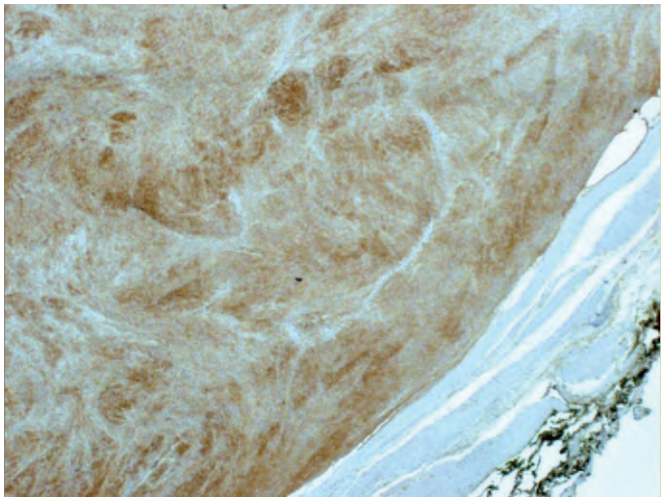

Figure 165–2. Immunostain for c-*kit* showing positive staining consistent with gastrointestinal stromal tumor. Note the pushing but not invasive margin, suggesting that this tumor is benign.

fibers. Electron microscopy show the neurosecretory granules present within gastrointestinal autonomic nerve tumors.

Presentation

GISTs of the colon and rectum, although rare, usually present incidentally or with mass effect. They have been seen presenting with pain in the perineum or tenesmus as well as with focal ulceration into the lumen of the intestine with resultant haemorrhage.[4]

Of malignant GISTs, 20% present with distant metastases, 20% with regional metastases, and the remaining 60% with localized disease. Survival is most related to age, stage, and treatment.

Investigation

Diagnosis can generally be suggested by imaging, particularly CT scan and MRI (Fig. 165–3). GISTs can be characterized on T2-weighted by homogenous isointensity masses without necrosis or hemorrhage and by enhancement with gadolinium. MRI also allows for planning of surgery with good definition of tumor margins seen. Differentiation from leiomyomas and sarcomas may be difficult, and primary excision is recommended for intraperitoneal GISTs, with resection of the colon involved. If abdominoperineal excision is required for resection of a tumor around the anorectum, then biopsy through skin to be excised should be performed. Preoperative biopsies may be useful as sarcomas of the anorectum may be treated with preoperative radiation therapy, the use of which has been associated with worse prognosis in GISTs.

Most GISTs are PET avid, and this modality may be useful in assessing for metastatic disease as well as response to medical therapy.

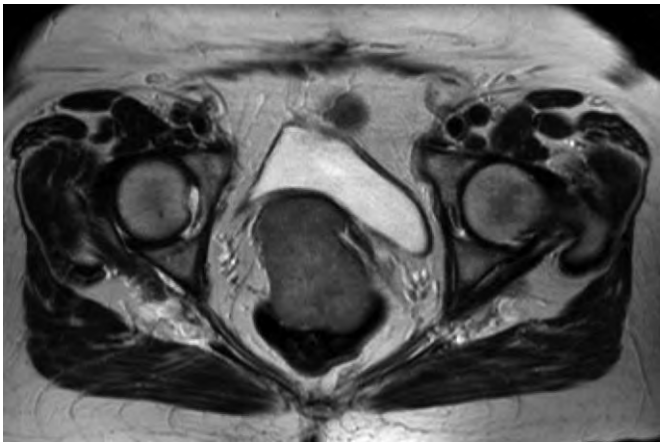

Figure 165–3. Moderate-sized rectal gastrointestinal stromal tumor on T2-weighted MRI showing homogenous texture and pushing margin.

Management

Medical Therapy In recent years, specific therapy aimed at inhibiting the tyrosine kinase receptor on GISTs has been developed. Phase III trials of STI571 or imatinib mesylate have shown regression of tumor and improved survival. Treatment arrests growth and may result in subsequent regression but is not directly tumoricidal; 65% of malignant tumors respond, but subsequent resistance to therapy is not uncommon. Complications of therapy include cerebral edema, retinal changes, pleural and pericardial effusions, and bone marrow suppression.

Radiation therapy is not effective in the treatment of GISTs.

Surgery Surgery remains the mainstay of treatment for localized disease. Differentiation between malignant and benign GISTs intraoperatively can be difficult unless invasion is noted. If malignancy is confirmed or suspected, a 2-cm margin of normal tissue is regarded as adequate by most authors. In the pelvis, however, this 2-cm margin may require exenterative surgery, which has a significant impact on morbidity and quality of life. There is little evidence beyond anecdotal experience that this 2-cm margin improves survival, but it allows for good clearance without encountering tumor during surgery.

There is some suggestion now that neoadjuvant treatment with imatinib may result in malignant tumor shrinkage that would allow for less morbid surgery, with margins not necessarily as wide as originally required.[5] It is advised, however, that organs obviously invaded on pretreatment imaging should be included in the resection regardless of post-treatment imaging outcome. Similarly, localized recurrent disease may be pretreated before attempting further radical surgery.

Resection should include the adjacent colon or rectum and recurrence is related to positive margins, so clearance should be obtained in length of colon or rectum as well as radially, with consideration given to the associated morbidity. Care must be taken not to enter or

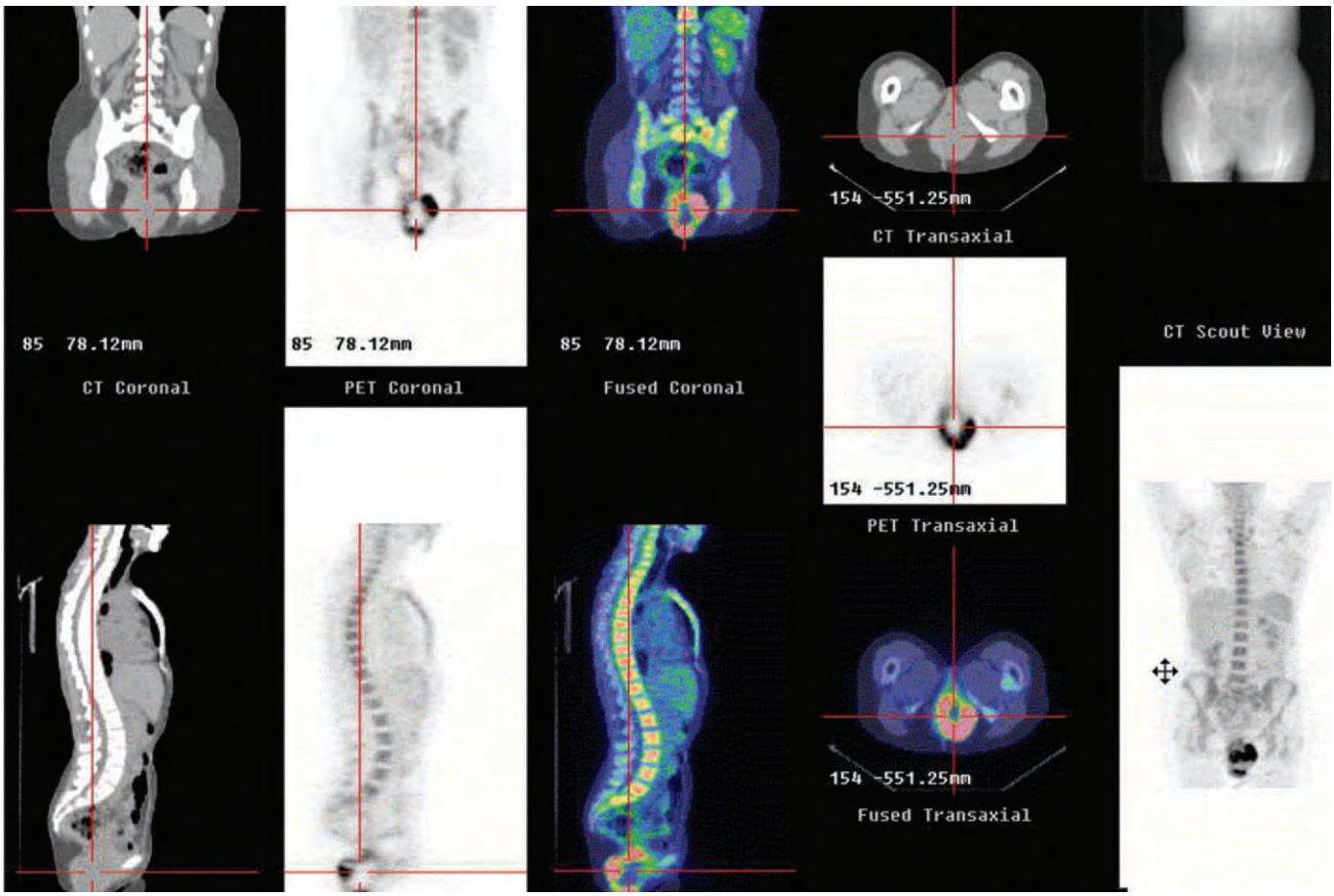

Figure 165–4. FDG PET CT fusion showing rectal leiomyosarcoma with central inactive core (likely necrosis) and no evidence of metastatic disease.

rupture the tumor itself because contamination almost certainly results in implantation and dissemination of malignant tumors.

A small benign tumor of the rectum, with no evidence of invasion on MRI, can be excised locally without radical surgery unless subsequent pathology shows high-grade malignancy.

Prognosis

Without evidence of invasion or high-grade activity, those GISTs designated as benign have a good prognosis with little recurrence reported with local excision.

Malignant GISTs have an overall 5-year survival of 45% in population-based studies. Good prognosis can be predicted by (1) the grade of tumor (<5 mitoses per high-power field); (2) the presence of skenoid fibers; and (3) size smaller 5 cm.

Leiomyoma and Leiomyosarcoma

Leiomyoma and leiomyosarcoma (Figs. 165–4 and 165–5) are rare tumors that comprise less than 0.1% of all rectal malignancies. Unlike GISTs they are moderately

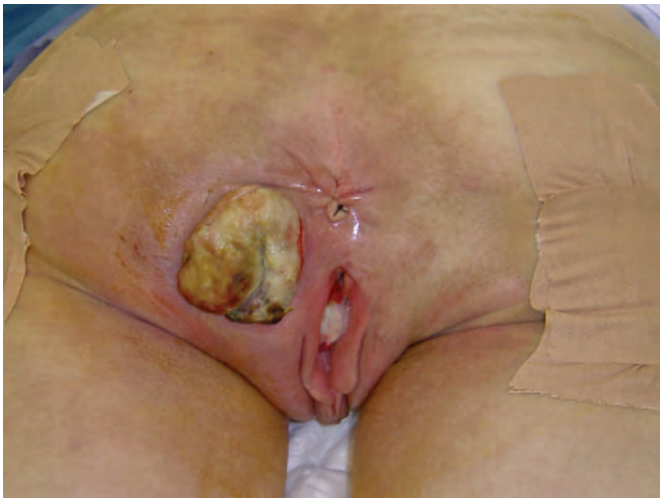

Figure 165–5. Necrotic leiomyosarcoma of the rectum after neoadjuvant radiation, invading the skin and vagina.

radiosensitive, and malignancy may be suspected on endorectal ultrasound by irregularity and mixed echogenicity with cystic spaces and echogenic foci.

Malignancy is more likely with larger tumors and biopsy will show the absence of CD34 staining and positive staining for actin and desmin. Leiomyosarcomas can be staged as described earlier. Grading is based on the number of mitoses present in 50 high-power fields and large size of tumor, and the presence of necrosis indicates a poorer prognosis.

Benign tumors can be excised locally. Low-grade malignant tumors may be excised with a margin of 1 cm of normal tissue. Good survival has also been obtained for small malignant tumors(<5 cm) with local resection and postoperative brachytherapy. High-grade leiomyosarcomas are best resected with a 4-cm margin, although a smaller margin may be adequate after neoadjuvant radiotherapy. This is preferable in the pelvis because a 4-cm margin will often require exenteration, but the dose to sterilize sarcomas is usually in the order of 60 Gy, a toxic dose to both the rectum and small bowel. However, most irradiated tissue is removed with the resection. As with the treatment of rectal cancer, there is a significant leak rate after radiation for restorative surgery and wound problems are common with abdominoperineal resection, so preemptive flap closures should be considered.

Chemotherapy has been used for metastatic disease with a 15% to 20% response rate, the most active agents being ifosfamide and doxorubicin. There is little evidence to suggest that adjuvant therapy postoperatively confers any benefit.

Overall survival for small reported series of rectal leiomyosarcomas is in the vicinity of 50% to 70% at 3 years for those tumors presenting without metastases.

Malignant Fibrous Histiocytoma

The cell of origin of these tumor is thought to be the fibroblast and tumors previously characterized as fibrosarcoma have been included in this group. Controversy still surrounds the classification of these tumors with the World Health Organization now designating them a subclass of pleomorphic sarcomas.

Occurrence in the rectum is rare, and tumors arising in the bony pelvis adjacent to the rectum are more common. Malignant fibrous histiocytomas are moderately sensitive to radiation therapy and should be managed in a multidisciplinary setting. Neoadjuvant radiation allows for a safe smaller margin (3 to 5 mm), which in the pelvis is important for limitation of morbidity. Total dose is usually in the order of 60 Gy with 45 Gy given before surgery and the remainder as a boost after surgery.

Chemotherapy is of little benefit, although imatinib, used in the treatment of malignant GISTs, has been shown to be effective in animal models. Prognosis generally reflects histologic grade. Patients treated without metastases with low-grade tumors have 5-year survival rates in excess of 60%, whereas high-grade tumors have a 20% to 25% survival.

Liposarcoma

Liposarcomas are exceedingly rare, and there are few reports of their occurrence. Its clinical and pathologic behavior can be predicted only by comparison with the behavior of liposarcoma in other parts of the body. Malignancy is suspected by size and fixation and should prompt biopsy. They have been excised with small (<1 cm) margins without reports of recurrence. Metastatic disease is rare, but multicentricity is not uncommon so other lesions should be sought using clinical examination and CT scan, particularly to look at the retroperitoneum where large tumors can be present asymptomatically. Limited success has been achieved with chemotherapy using anthracycline (e.g., doxorubicin) and ifosfamide for metastatic disease.

Rhabdomyosarcoma

Rhabdomyosarcomas of the rectum and perianal region are extremely rare tumors in children but even rarer in adults. The median age of presentation is 4 years with usual clinical features involving a mass or suspected perianal abscess. They are more common in individuals affected by Li Fraumeni syndrome and neurofibromatosis type I.

Tumors are well imaged by MRI and staged with CT and clinical examination. PET scanning has a high sensitivity for metastases, and in combination with CT a reduced false-positive rate. Lymph node metastases occur in approximately 10% patients without metastatic disease.

Rhabdomyosarcomas should be managed in a multidisciplinary setting because surgery is not always required. All tumors should undergo biopsy and diagnosis is made with immunohistochemistry or electron microscopy.

These tumors are moderately radiation sensitive, requiring high doses for effective tumor kill, but this dose can be reduced with combination chemotherapy. Multiple agents have been shown to be effective with the most common regimen used being vincristine, actinomycin D, and cyclophosphamide.

Surgery is often morbid, with wide excision margins required to prevent recurrence. More recently, reports of the use of radiofrequency ablation in combination with neoadjuvant therapy have emerged, but this has not been explored well in the pelvis.

Overall prognosis is poor, with lesions arising in the pelvis and particularly from mucosal sites having survival figures of less than 50%.

OTHER MISCELLANEOUS TUMORS

Primary and Secondary Melanoma of the Large Intestine

Melanoma is an uncommon condition that has been rarely reported and is associated with a poor prognosis. It has been hypothesized that most reported cases of primary melanoma in fact represent metastatic spread in

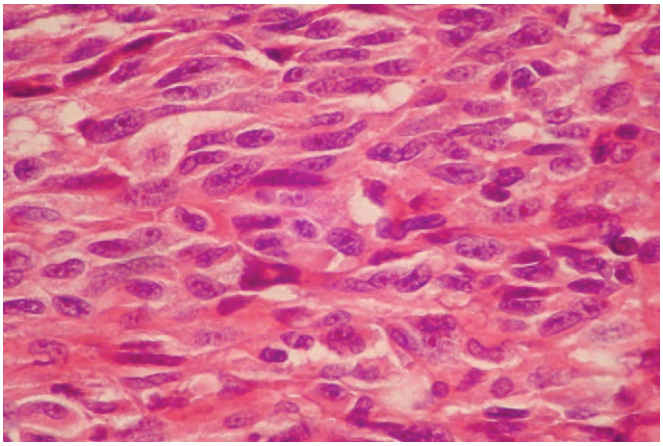

Figure 165–6. Hematoxylin-eosin stain of primary rectal melanoma.

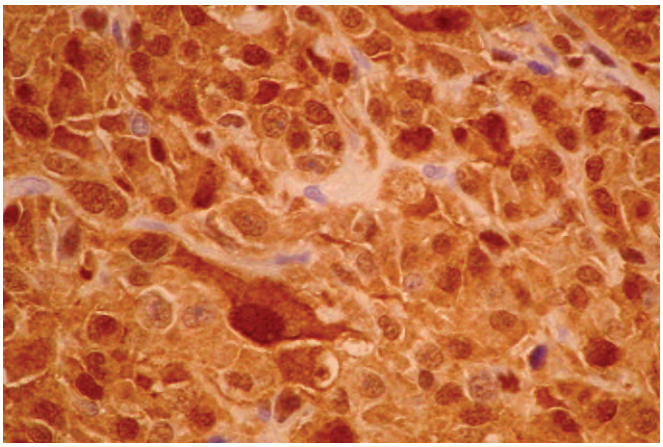

Figure 165–7. S 100 stain of primary rectal melanoma.

patients in whom the primary lesion has never been identified or has spontaneously regressed, although a small number of cases seem to demonstrate indication of primary growth in the large bowel. Histopathologic and tissue staining is typical of melanoma (Figs. 165–6 and 165–7). Treatment of primary anorectal melanoma is usually by standard radical anatomic resection, after exclusion of metastatic disease (Fig. 165–8); however, local resection is at times indicated.

A detailed review of literature relating to melanoma metastatic to the colon from the Mayo Clinic[6] indicated less than 100 cases of isolated metastases have been reported in the literature. The average interval between primary presentation and the development of a clinically significant colonic secondary lesion was more than 7 years. One- and 5-year survival rates were 37% and 21%, respectively, for resected patients. Nodal status and presentation with either bowel obstruction or perforation were associated with a reduction in survival time.

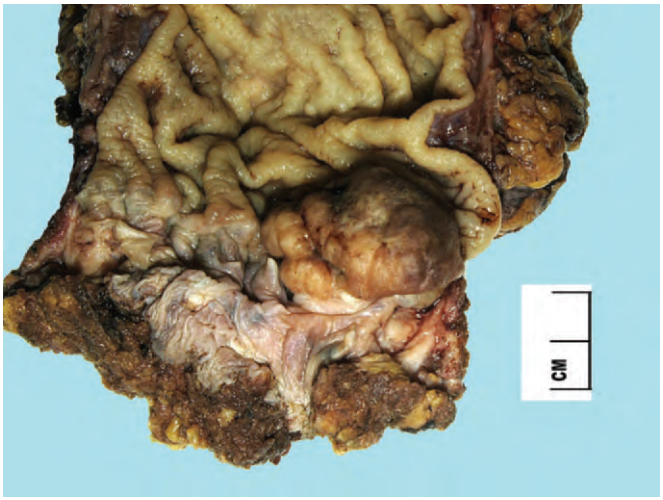

Figure 165-8. Abdominoperineal resection specimen of primary melanoma of the lower one third of the rectum. Macroscopically, the lesion appeared indistinguishable from adenocarcinoma of the rectum. Preoperative ultrasound demonstrated T3 penetration.

Bowen's Disease

Intraepithelial squamous cell carcinoma tends to affect the anogenital region and progresses to invasive squamous cell carcinoma in up to 30% of patients. It is a rare condition that is treated definitively by excision with clear margins. This may be facilitated by *lesion mapping*, where examination under general anesthesia is combined with frozen section pathology of multiple points around the lesion to determine the microscopic margins. Advancement flap or even skin grafting may be required to achieve complete excision

Buschke-Lowenstein Tumors

Buschke-Lowenstein tumors have been reported fewer than 50 times. First described in 1925, the term refers to a locally invasive, rapidly growing variant of condylomata acuminata, with deep penetration of local tissues. They are associated with HPV-6 and HPV-11.[7] The histology is similar to that of simple condylomata acuminata with an orderly arrangement of the epithelial layers. The basement is maintained intact, and cell polarity is preserved. The major difference between condylomata acuminata and the Buschke-Lowenstein tumor lies in the tendency of the latter to downward growth, simulating malignant invasion. Cure is obtained by early and radical excision; radiation therapy may assist in local control.

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Chapter

166

Radiation Injuries of the Rectum

Matthew L. Lynch ▪ Theodore J. Saclarides

The benefits of pelvic radiation for prostate, endocervical, and anorectal malignancies have been well established; however, many patients experience distressing side effects of radiation therapy. The rectum is the most frequently injured organ due to its fixed position within the pelvis and its close proximity to the irradiated area. Injuries to the rectum include rectovaginal fistulas, anorectal strictures, and hemorrhagic proctitis. Although the treatment of rectovaginal fistulas is covered in detail elsewhere within this text, the principles of the surgeries are discussed here as well. The small bowel may also be injured by pelvic irradiation. Since modifications of the radiation therapy method can be implemented to reduce the incidence of small bowel injury, this occurs much less frequently than injuries to the rectum. Small bowel injuries may be manifested as obstruction, diarrhea and malabsorption, or fistulas to other organs; small bowel injuries are not discussed here.

Whether the injured rectum can be salvaged depends on which specific complication is being addressed as well as the presence of certain patient-specific factors such as age, the presence of comorbid conditions making restorative surgery more complicated, preexisting bowel dysfunction, the ability of the rectum to serve as a suitable reservoir, and anal sphincter impairment. Proctectomy within an irradiated pelvis is a technically demanding procedure that may be accompanied by significant blood loss. Thus, proper patient selection is a must. For elderly or infirm patients, a well-constructed colostomy may be preferable to misguided efforts to repair the irradiated rectum. This would certainly be the case for a patient with significant anal sphincter dysfunction unrelated to the effects of radiation.

INCIDENCE OF COMPLICATIONS

During radiation therapy, almost all patients experience some alteration of gastrointestinal function. Symptoms include tenesmus, urgency, bleeding, diarrhea, and incontinence. These symptoms generally resolve within 2 to 3 months after completion of radiation. Rarely is aggressive therapy required because most patients respond to measures such as temporary cessation of radiation therapy, fluid resuscitation, diet modification, and antidiarrheal medications. Fortunately, only a small percentage of patients develop chronic problems. After radiation for prostate cancer, the incidence of moderate proctitis is 5%, enteritis is 1%, and anorectal stricture or fibrosis is 1%. The incidence of severe complications is less than 1%. Most injuries become manifest within 2 to 5 years.[1] Moore et al. demonstrated that although 80% of patients treated with radiation for prostate cancer developed rectal bleeding within 3 years, only 8% of these patients required chronic treatment.[2]

Risk factors for the development of radiation-induced injuries include widening of the radiation field to include pelvic lymph nodes in addition to the prostate, a history of diabetes and prior pelvic surgery, age less than 60 years, and the use of split course rather than a continuous course of treatment.[3] After radiation for cervical cancer, approximately 30% of patients developed some form of late rectal complication, but only 3.5% of patients had severe complications such as bleeding requiring transfusion or fistula requiring surgery. If high-dose intercavitary radiation is administered, the rate of rectal complications is higher.[4] Rectal injuries are also common after radiation therapy for endometrial cancer. Huguenin et al. showed an actuarial rate of 7% for grade 3/4 complications at 3 years following curative radiation therapy for endometrial cancer.[5] For anal cancer, radiation and chemotherapy have become the mainstay of treatment, and most patients can be rendered tumor free while preserving the anus. The risk of severe late complications following radiation for anal cancer is approximately 15% after 10 years of follow-up.[6] Complications are more likely to occur if both the anal canal and anal margin are involved, if radiation doses exceeding 39.6 Gy

are used, and if local excision of tumor was performed before radiation. Overall, sphincter preservation is possible in 85% of patients with anal cancer treated with multimodality therapy.[7]

MEDICAL TREATMENT OF THE INJURED RECTUM

Because a standard universally accepted protocol for rectal radioprotection is not available, injuries will continue to occur and require treatment. As mentioned previously, the treatment of acute radiation proctitis is supportive and elaborate diagnostic tests are unnecessary in most patients. Topical butyrate versus saline in a randomized, crossover trial has been shown to be an effective treatment for acute radiation proctitis. Twenty patients were randomized to either daily saline enemas for 3 weeks or daily enemas with 80 ml of 80 mmol/L of sodium butyrate. After 3 weeks, the treatment regimens were switched. Nine patients completed each arm of the study. The group first treated with sodium butyrate all experienced remission in symptoms, whereas none of the saline-treated group experienced remission. During the second half of the study, 8 of the 9 patients previously treated with saline experienced remission with sodium butyrate treatment, and 3 of the patients switched to saline treatment experienced a relapse in their symptoms.[8] In a double-blind, randomized trial, oral sucralfate was used as prophylaxis for acute radiation proctitis, and the study showed no difference in symptoms compared to placebo and may in fact increase the incidence of rectal bleeding after pelvic irradiation.[9] Hendrickson et al. showed that oral sucralfate given 2 to 8 weeks after radiation improved the frequency and consistency of bowel movements and patients required less antidiarrheal medicines.[10]

Hemorrhagic Proctitis

Chronic hemorrhagic proctitis presents a therapeutic challenge for the treating physician. Diverting the fecal stream with colostomy has been tried with mixed results. Complete cessation of bleeding is infrequently achieved, although Ayerdi et al. were able to show resolution of bleeding in 8 of 9 patients treated with diverting loop colostomy.[11] Of paramount importance in the evaluation of the chronically bleeding patient is the exclusion of recurrent cancer as the cause. Symptoms of tenesmus, urgency, and bleeding that occur several months after completion of radiation may be due to chronic proctitis, but a thorough endoscopic evaluation of the rectum and sigmoid is mandatory. Endoscopically, the chronically injured rectal mucosa appears diffusely telangiectatic with contact friability, especially if external-beam radiation was given. Focal, rather than diffuse, erythema and telangiectasias may be seen with focused radiation techniques such as brachytherapy.

Chronic hemorrhagic proctitis has been historically treated with a variety of methods, most of which have been unsuccessful or anecdotally effective. These treatments include anti-inflammatory agents, topical steroid preparations, cautery, and laser ablation. In a prospective, randomized, double-blind trial, 5 weeks of short-chain fatty acid enemas versus placebo significantly decreased the number of days per week with rectal bleeding and significantly increased hemoglobin in patients treated for chronic radiation proctitis.[12] Sucralfate enemas have been shown to reduce symptoms from chronic radiation proctitis and may be useful as a first-line agent for treatment of chronic radiation proctitis.[13] In a study of a simple oral treatment for chronic radiation proctitis, one group showed a lifestyle improvement in 13 of 20 consecutive patients treated with vitamins C and E three times daily for a minimum of 4 weeks.[14] With regard to laser treatment, multiple endoscopic treatments are frequently necessary to produce a significant reduction in the frequency of bleeding, increase in hematocrit level, and improvement in activities of daily life.[15]

MEDICAL MANAGEMENT FOR CHRONIC RADIATION PROCTITIS

In the past several years, three medical treatments for chronic radiation proctitis have been extensively studied. Depending on the availability of treatment facilities and equipment, formalin instillation, hyperbaric oxygen, and argon plasma coagulation (APC) have become widely used treatments for chronic radiation-induced proctitis resistant to more conservative medical therapies.

Formalin Instillation

Of the three, formalin instillation via proctoscope or formalin dab with a cotton pledget is probably the cheapest, easiest, and most effective treatment modality. Initially used as a treatment for hemorrhagic cystitis, formalin instillation has become one of the treatments of choice for hemorrhagic proctitis. Parikh et al. reviewed their database of patients undergoing formalin treatment and found that 88% of their patients had improvement or cessation in bleeding following an average of 3.4 applications of a 4% formalin-soaked pledget.[16] Ismail and Qureshi noted 90% of their patients respond to one or two 2-minute applications of a 4% formalin-soaked cotton pledget. Two of their patients with torrential bleeding did not respond to formalin therapy and required surgical excision of the rectum.[17] A group from Mexico instilled 50-ml aliquots of 4% formalin and found that 85% of patients had immediate cessation of bleeding.[18] In a report of 16 patients with radiation-induced hemorrhagic proctitis, Saclarides et al. instilled a 500-ml solution of 4% formalin in 30- to 50-ml aliquots; each aliquot was kept in contact with the rectal mucosa for 60 seconds, after which the formalin was withdrawn and the rectum was flushed with saline. The treatments were performed in the operating room under light sedation in most cases. The bleeding stopped after a single treatment in 12 patients; in 3 patients, the bleeding continued sporadically, but no further transfusions were required. One

patient required three treatments before bleeding stopped. The only complication noted was anal fissures in 4 patients: two healed within 1 month, one healed slowly, and one persisted until the patient's death from disseminated prostate cancer. Administering the formalin through a rigid proctoscope has reduced the incidence of anal fissures, rather than through a bivalve retractor, which may have traumatized the anal canal.[19]

Hyperbaric Oxygen

Although not widely available, hyperbaric oxygen has been successfully used for the treatment of radiation-induced injuries. Hyperbaric oxygen is used to overcome the chronic tissue hypoxia present in radiation-damaged tissues. Repetitive sessions gradually induce regrowth of fibrous tissue, capillaries, and epithelium. Hyperbaric oxygen therapy is generally well tolerated, with claustrophobia being the only major complaint. The treatment regimen is 60 minutes daily with 100% oxygen at 2.2 to 2.4 atmospheres. In one study, 5 of 5 patients with grade 2 to 3 rectal bleeding stopped bleeding after multiple (18 to 60) treatments; improvement persisted during the follow-up period (range 5 to 52 months).[20] Kitta et al. reported a series of 4 patients who underwent hyperbaric oxygen therapy. All 4 patients had significant improvement in rectal bleeding, but one recurred after only 3 months and another continues to have minor rectal bleeding.[21]

Argon Plasma Coagulation

APC has been used in the treatment of chronic radiation-induced proctitis, and this modality has shown great promise. In a study of 40 patients with refractory hemorrhagic proctitis, APC was successful in 39 patients after one or two treatments. Follow-up was from 3 to 30 months, and success was defined as the absence of significant bleeding, no symptomatic anemia, and a hemoglobin higher than 9 g/dl. The one failure responded to 4% formalin instillation. The study group of patients included 4 patients that had failed treatment with Nd:YAG laser ablation. All 4 of these patients were successfully treated with APC. No patient in the treatment group required surgery. Complications were limited to 2 patients with low-grade fever, 1 with urinary retention, and 1 with bleeding. Most patients still experienced small amounts of bleeding.[22] Another study of 16 patients showed improvement in all patients with an average of 3.7 APC treatments. At a mean follow-up of 10.7 months, 7 did not have recurrent bleeding, and the other 9 had only negligible occasional spotting. None of the treated patients required transfusion after treatment, and 1 patient required two additional sessions for recurrent bleeding.[23] In a study from Australia of 15 patients treated with APC, 2 patients developed rectal strictures that responded to dilatation.[24] Tjandra et al. treated 12 patients that had failed formalin therapy with APC. Of the 12, 6 patients had complete cessation of bleeding and 4 others had symptomatic improvement. The 2 other patients had radiation-induced sigmoiditis that caused continued but reduced bleeding. None of the 12 suffered any significant side effects or complications from the therapy.[25] With regard to laser treatment, multiple endoscopic sessions are frequently necessary to produce any significant change. Nd:YAG and argon lasers have been used, and although they may seem attractive as a means to avoid surgery, they are unlikely to stop bleeding with a single treatment.[26,27]

Summary

Formalin, APC, and hyperbaric oxygen therapy represent three effective treatments for chronic hemorrhagic radiation proctitis. Formalin and APC have both been used to treat bleeding that has failed to respond to other treatments. Formalin therapy via instillation or cotton applicator is more likely to gain widespread acceptance due to the ease of treatment and need for only a rigid proctoscope. If the equipment is available, APC does seem to be a viable alternative to formalin, but it is more expensive and is less likely to be effective with one treatment session. Of the three, hyperbaric oxygen is the least likely to gain widespread use due to expense, limited facilities available for treatment, and the high number of sessions required to affect a response.

There is no perfect treatment for hemorrhagic radiation-induced proctitis. All of the treatments are aimed at relieving bleeding once damage has occurred. With respect to prophylaxis, a recent study looked at the use of misoprostol suppositories during radiation therapy. In this small prospective, randomized, placebo-controlled, double-blinded study of 16 patients, mean radiation proctitis symptom scores were significantly reduced at 4, 8, 12, and 36 weeks in the nine patients treated with misoprostol suppositories.[28] This is one small study, but it is intriguing because prevention of this disease would certainly be more cost-effective than multiple treatment sessions with frequently unsuccessful therapies.

RECONSTRUCTIVE OPERATIONS FOR RECTAL INJURIES

The treatment of radiation-induced rectovaginal fistulas and rectal strictures is individualized. Suitability for major pelvic surgery must be determined, as well as the presence of locally recurrent or widely disseminated cancer. Anal manometry may provide useful insight as to whether the native rectum can adequately function as a storage reservoir. Compliance is measured by instilling sequential volumes of air into a balloon placed in the rectal vault while assessing intrarectal pressure and patient sensation. Most normal patients are able to feel as little as 15 to 30 ml of air within the rectum and can tolerate up to 200 ml without having excessive discomfort. The urge to defecate usually occurs at 90 ml of air. The noncompliant irradiated rectum cannot accommodate increasing volumes of air without substantial and inappropriate rises in intrarectal pressure. Furthermore, the patient may experience significant discomfort shortly after the threshold sensation for bowel movement is

reached. The presence of a noncompliant rectum may argue for resectional procedures rather than local repair of rectovaginal fistulas or strictures. The benefit gained from a resectional procedure is correction of the underlying problem and improvement in quality of life (i.e., increased compliance and storage capacity of the neorectum). The cost is a procedure with significant risk of major blood loss and accompanying morbidities such as genitourinary dysfunction and anastomotic leak.

TRANSABDOMINAL APPROACHES FOR RADIATION INJURY

A transabdominal approach is required for high rectovaginal fistulas and high-grade rectal strictures accompanied by loss of rectal compliance. Surgical options include low anterior resection with descending colorectal anastomosis, low anterior resection with coloanal anastomosis with or without colonic reservoir, and the proximal sigmoid on-lay patch popularized by Bricker and Johnston.[29] In preparation for laparotomy, patients must receive a thorough bowel cleansing with cathartics, enemas, or oral lavage solutions. However, Jimenez and Wilson in reviewing the literature since 1966 have found credible clinical trial data suggesting that mechanical bowel preparation prior to elective colorectal surgery may not be essential.[30] Nonabsorbable oral and, frequently, intravenous antibiotics are administered. The appropriate sites on the abdominal wall are marked for either a loop transverse colostomy or a loop ileostomy. Patients should receive prophylaxis for deep venous thromboses. Due to the lengthy nature of these operations, a Foley catheter should be inserted, and thought must be given to placement of ureteral stents to assist in identification of the ureters during the dissection.

Bricker-Johnston Technique

The Bricker-Johnston technique is mentioned for historical interest because its use has been made somewhat obsolete by the colonic reservoir performed during proctectomy. Theoretical advantages of the on-lay method include the avoidance of proctectomy and possible blood loss and the construction of a loop of sigmoid colon that can potentially serve as a reservoir. It does not totally obviate the need for pelvic dissection because the anterior dissection must be continued caudally until either the stricture or fistula has been identified and isolated. Compared with posterior dissection along the presacral space, this anterior dissection between the rectum and vagina is more technically challenging. Thus, little is gained with this approach. The essential feature consists of division of the rectosigmoid junction followed by suturing of the open end of the sigmoid colon to the débrided edges of the rectal fistula or stricture. A loop is thereby created to which the proximal colon is anastomosed. Temporary fecal diversion is generally required. The disadvantage of the Bricker-Johnston technique is that unhealthy and diseased rectum is left in place and is at risk for anastomotic leak, bleeding, and stenosis. Experience is limited, and it may not confer any advantage over the coloanal anastomosis with or without construction of a colonic J-pouch.[29,31]

Low Anterior Resection

The technique of low anterior resection is familiar to most general surgeons. Functional results and healing are probably improved using healthy, compliant, nonirradiated bowel as the proximal limb of the anastomosis. Stapling devices have greatly facilitated performing anastomoses deep in the pelvis. To gain a sufficient length of bowel, it is usually necessary to mobilize the left colon and splenic flexure with ligation of the left colic artery and inferior mesenteric vein at the border of the pancreas. It is important to be certain that the blood supply to the left colon is preserved, and this can be verified by checking capillary refill at the cut edge. If there is any doubt, the distal transverse colon should be used as the proximal limb. If the colonic anastomosis and the vaginal closure are in close proximity to each other, it is advisable to fashion a tongue of omentum for interposition between the two viscera. As long as the proximal limb is healthy nonirradiated bowel, normal healing can be anticipated. If there is any concern, temporary fecal diversion is justified.

Coloanal Anastomosis

Complete, rather than partial, proctectomy and advancement of the proximal colon to the anus and construction of a coloanal anastomosis was popularized by Turnbull and Cuthbertson.[32] The sigmoid and descending colon are mobilized in the usual manner, the rectum is resected down to the pelvic floor, and dissection within the rectovaginal septum is undertaken to separate the vagina from the rectum. In Turnbull's original operation, the rectum was everted and severed 1 cm above the dentate line. The abdominal colon was then gently advanced through the everted rectal stump, amputated 5 cm external to the anus, and then wrapped in gauze. The coloanal anastomosis was then completed around the 10th postoperative day.[32] Kirwan et al. performed this operation on 84 cancer patients and found that 26% had perfect bowel function; 36% needed an occasional enema or could not hold gas; and 35% needed daily enemas, wore pads, or complained of fecal soilage.[33] In a modification of this approach, following proctectomy, Parks et al. performed a transanal mucosectomy of the rectal remnant after which the proximal colon was stapled or hand-sewn to the dentate line. Usually, an ileostomy or colostomy was created. They reported complications of impaired continence, increased stool frequency, fecal urgency, pelvic abscess, and anastomotic fistula or stenosis.[34] Because of these complications, up to one third of patients may require permanent colostomies.

Concern about less than perfect functional results has stimulated further modifications. A group from Switzerland reported the construction of an ileocecal reservoir for rectal replacement. In this procedure, an ileocecal segment is isolated on its lymphovascular pedicle, rotated

counterclockwise, and anastomosed to the dentate line. This provides a neorectal segment with an intact lymphovascular supply. Observations in two patients so treated showed good quality defecation with good tolerance volumes, compliance, and anal manometry.[35] Additionally, this same group demonstrated in 12 patients so treated that gastric emptying rates, small bowel transit times, and colonic transit times were similar in patients with ileocecal reservoir reconstruction and in a sex- and age-matched group of healthy controls.[36] Soave's procedure has also been used as a sphincter-preserving solution for radiation-induced rectal pathology. Faucheron et al. performed this procedure on 30 patients and noted complications of postoperative hemorrhage, small bowel obstruction, pelvic or perianal sepsis, and anastomotic strictures; of 23 evaluable patients, continence was described as normal in 19.[37]

Colopouch Anal Anastomosis

The addition of a colonic J-pouch after proctectomy can improve functional results due to the increased storage capacity provided by the neorectum. In a prospective comparison of 40 patients randomized to either colonic J-pouch or straight coloanal anastomosis, Lazorthes et al. showed that there was no significant difference in the complication rate between the two groups, but the reservoir group showed a significant improvement in frequency of defecation at 3, 12, and 24 months. There was significantly less clustering of stools at 3 and 12 months and less frequent incontinence in the first year.[38] The colonic J-pouch is constructed in a manner analogous to the ileal J-pouch procedure performed for inflammatory bowel disease and familial polyposis. Proctectomy is carried out in the usual manner with full mobilization of the splenic flexure and left colon. Stapling devices are used to create the colonic reservoir from 5- to 6-cm segments of the colon; larger pouches may be associated with defecatory dysfunction. The pouch is either hand-sewn or stapled to the anus and protected with temporary fecal diversion. The stoma may be closed in approximately 3 months once satisfactory healing of the reservoir has been demonstrated with contrast studies.

Coloplasty

In 2000, Fazio et al. introduced colonic coloplasty as an alternative to J-pouch construction to augment reservoir function of the neorectum and reduce bowel frequency and dysfunction. With this new technique, rectal resection follows conventional principles with mobilization of the splenic flexure and high ligation of the inferior mesenteric vessels. The construction of the coloplasty begins with an 8- to 10-cm longitudinal colotomy between the taenia approximately 4 to 6 cm from the distal cut end of the colon. This colotomy is then closed in a transverse fashion using a single layer of interrupted 2-0 polyglycolic acid sutures. After construction of the coloplasty, the colon can be anastomosed to the anus in either a hand-sewn or stapled fashion.[39] Since its introduction, several studies have been conducted to compare the coloplasty pouch with straight anatomosis and colonic J-pouch. In 2001, the group at the Cleveland Clinic compared the functional results in 20 patients with coloplasty with 16 patients who had colonic J-pouch and 17 patients who had straight coloanal anastomoses. This study showed a similar complication rate in all three groups. The coloplasty group had on average 2.6 bowel movements per day compared to 3.1 for J-pouch patients and 4.5 for patients with straight coloanal anastomosis. Additionally, the coloplasty and J-pouch groups had greater tolerated volume and compliance with anal manometry compared to the straight coloanal anastomosis group.[40] A group from Germany randomized 40 consecutive patients to receive either coloplasty or J-pouch following low anterior resection. The patients in each group had similar rates of complications, resting and squeeze pressure, and neorectum volumes. The coloplasty group had increased neorectal sensitivity. Functionally, the coloplasty group had on average 2 bowel movements per day, and the J-pouch group had 2.75 bowel movements per day.[41] This new technique offers an alternative to J-pouch construction in patients with a narrow pelvis that may not accommodate a J-pouch, and the functional results are similar to those observed with colonic J-pouch construction.

LOCAL REPAIRS OF DISTAL RECTOVAGINAL FISTULAS

Rectovaginal fistulas arising in the distal rectum or anal canal are best treated with local perineal approaches; these operations are discussed in detail in other areas of this text. Operative choices include transanal, transvaginal, and transperineal routes. The basic principles of repair are mentioned and include (1) exclusion of recurrent cancer as the cause of the fistula; (2) allowance of acute radiation changes to subside before repair; (3) excision of the fistula tract; (4) interposition of relatively healthy tissue between the vagina and the rectum; and (5) consideration given to temporary fecal diversion in selected cases, such as large fistulas and/or failed previous repairs. If the fistula arises in a severely stenotic or noncompliant rectum, permanent fecal diversion may be the best option.

The *transanal* technique is performed with the patient in the prone position. A trapezoid flap of mucosa, submucosa, and circular muscle is mobilized for several centimeters above the fistula. The width of the base of the flap should be two to four times the width of the flap apex to ensure adequate blood supply to the tissue. After the rectal opening of the fistula is excised and the edges are débrided, the rectal wall is closed with monofilament suture. The flap is then advanced to cover the closure. The vaginal side of the fistula is left open.[42,43] Some advocate the use of a labial fat pad transposition to improve the healing of the advancement flap. Recently, a group form the Netherlands demonstrated no improvement in healing by the addition of the labial fat pad transposition to the transanal advancement flap.[44] For severe, complex fistulas, Marchesa et al. advocated the use of a transanal sleeve advancement flap. The principles of the surgery

are similar to the flap advancement, except that a circumferential sleeve of rectum is advanced to cover the defect after excision of the fistulous tract.[45] Simmang et al. have used this rectal sleeve advancement technique to repair fistulas in association with anorectal stricturing, which provides repair of the fistula and stricture while maintaining continence.[46]

Transvaginal repairs are performed in the lithotomy position. The vaginal mucosa is incised and mobilized in all directions around the fistula. The fistula is then itself excised and débrided. Using a series of purse-string sutures, the fistula is inverted into the rectum and the vaginal mucosa is then closed.[47] A *transperineal* approach follows the same principles: excision of the fistula tract, closure of the defect in layers without tension, and possible inclusion of well-vascularized tissue into the repair. This can be accomplished with transfer of a portion of bulbocavernosus muscle, an island of vulvar skin and adipose tissue, or gracilis muscle flap maintained on its vascular pedicle.[48] The transperineal approach is similar to repair of a fourth-degree perineal obstetrical injury. Although it provides improved exposure compared to the transanal or transvaginal approaches, one must be concerned about the healing of previously irradiated tissues. There have been no randomized studies to compare these different approaches. The choice of technique should be dictated by the skill, experience, and familiarity of the surgeon.

SUMMARY

Because adequate means to protect the rectum during radiation therapy have not been developed, rectal injuries will continue to plague patients. Fortunately, most injuries occur in the acute period and chronic problems are rarely seen. Chronic radiation-induced hemorrhagic proctitis can be adequately managed with endoscopic APC or formalin pledgets or instillation. For patients with high rectovaginal fistulas or stricturing arising within a noncompliant rectum, transabdominal approaches incorporating proctectomy may be undertaken. However, these procedures are technically demanding and potentially morbid. Low rectovaginal fistulas can be repaired with transanal, transvaginal, or transperineal approaches, depending on the particular expertise of the surgeon. For elderly or infirm patients, the best treatment option may simply be a well-constructed diverting colostomy as the only treatment.

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Part

5

Techniques and Pearls

Chapter

167

Antibiotics, Approaches, Strategy, and Anastomoses

Jan Rakinic

GENERAL CONSIDERATIONS

The successful outcome of any surgical intervention depends on careful planning, appropriate assessment of the patient's history and performance status, and a thorough understanding of the technical aspects of the anticipated procedure and associated risks. The information gained from performance of indicated endoscopic and imaging studies minimizes intraoperative surprises, events that every surgeon prefers to avoid.

Operative risks should be detailed to the patient clearly and completely. The possibility of infection, hemorrhage, anastomotic dehiscence, disease recurrence, degree of alteration in bodily function or appearance, injury to or involvement of adjacent structures, and possible nerve damage resulting in weakness, paralysis, or genitourinary dysfunction must be explained.

Up to 10% of patients undergoing colorectal surgery suffer venous thromboembolic events (VTE).[1] Patients with cancer or inflammatory bowel disease are at particular risk, as are those with a previous history of VTE.[2] Additional parameters associated with increased risks of embolic events are many, including prolonged operative time, multiple preoperative blood transfusions, preoperative hospitalization, and obesity (Table 167–1).[3] The incidence of postoperative VTE is decreased by 50% or more when appropriate prophylactic measures are instituted preoperatively[4]; the initiation of prophylaxis *postoperatively* is far less effective. Accepted methods of prophylaxis include graded compression stockings, intermittent pneumatic compression devices, standard low-dose subcutaneous heparin, and low-molecular-weight heparin. A risk of postoperative bleeding is inherent with unfractionated or low-molecular-weight heparin prophylaxis, but most studies show this is outweighed by the concomitant decrease in VTEs. Epidural anesthesia is valuable postoperatively by decreasing need for systemic opiates and also by promoting better immediate postoperative pulmonary toilet. However, the use of VTE prophylaxis is altered when employing epidural anesthesia. Guidelines such as those developed by the American Society of Regional Anesthesia must be strictly adhered to for patient safety.[5]

ANTIBIOTICS AND BOWEL PREPARATION

Opening the colon during an operation significantly increases the risk of postoperative infectious complications. This risk is least in *clean-contaminated* cases, where division of the colon is performed in a highly controlled setting, higher in *contaminated* cases with a minimum of inadvertent fecal spillage, and quite high with gross fecal soilage (so-called dirty cases). Surgeons have therefore pursued methods to lower the risk of postoperative infection. Mechanical bowel preparation alone has been

Table 167–1 VTE Risk Factors and Estimated Relative Risk

VTE Risk Factor	Estimated Relative Risk
Major surgery or major trauma	5-200
History of VTE	50
Age >50 yr	5
Age >70 yr	10
Cancer	5
Hospitalization for major medical illness	5
Antiphospholipid antibodies	2-10
Pregnancy	7
Estrogen therapy	2-5
Estrogen receptor modulators	3-5
Obesity	1-3
Antithrombin deficiency	25
Protein C or S deficiency	10
Factor V Leiden mutation	5-50

VTE, venous thromboembolism.
Adapted from Bates SM, Ginsberg JS: Treatment of deep vein thrombosis. N Engl J Med 351:268, 2004.

shown to significantly decrease postoperative infectious complications.[6] Poorly absorbed oral antibiotics enhance this effect.[7] The most widely used bowel preparation regimen in the United States combines a mechanical washout of fecal material with the administration of parenteral, and often oral, antibiotics.[8,9] However, the alternative of omitting a preoperative mechanical washout of the colon has again become a hotly debated topic.

Mechanical Preparation

Bowel preparation regimens that require 18 to 24 hours, and produce completely satisfactory washout, are commonly used in both the outpatient and inpatient setting. Nonabsorbable polyethylene glycol (CoLyte, GoLYTELY) is used widely, as are combinations of laxatives and purgatives. Enemas can be used to facilitate emptying of the rectum. Clinically significant electrolyte disturbances occur infrequently with these regimens. The most common side effect is mild dehydration caused by inadequate oral fluid replacement. Use of carbohydrate-electrolyte rehydration solutions can diminish this transient intravascular volume contraction.[10]

Mannitol was historically used for colonic lavage. However, colonic bacteria metabolize mannitol, producing hydrogen gas, and explosions were reported during both open and endoscopic procedures. The simultaneous administration of antibiotic with the ingestion of mannitol appears to reduce this risk, but mannitol is now used rarely for bowel preparation.

Reports appear periodically that describe the outcomes of colon surgery performed without preoperative mechanical preparation.[11-13] The morbidity and mortality rates are reported to be the same in patients who did as in those who did not undergo a mechanical preparation preoperatively. Proponents of this approach claim that mechanical preparation provides no additional benefit when accompanied by appropriate parenteral prophylaxis. A number of authors have suggested that mechanical preparation may be associated with an increased number of wound infections and anastomotic dehiscences.[11,14-16] Most of the work reporting the safety of unprepped colon resection has come from Europe and Latin America. Nearly all American surgeons continue to use a mechanical bowel preparation in addition to antibiotic prophylaxis in elective situations, in part due to medicolegal concerns. However, American prospective randomized studies of mechanical bowel preparation versus none are underway.

Oral Antibiotics

The use of nonabsorbable oral antibiotics in addition to a mechanical bowel preparation started in the 1970s. At that time, they were administered for as long as 96 hours before surgery, prompting the emergence of resistant organisms and the overgrowth of pathologic species.[17] The ideal oral antibiotic should have a rapid onset of bactericidal activity directed at the enteric bacterial population, possess low toxicity, and demonstrate limited absorption. The combination used most often is erythromycin (effective against aerobes) and either neomycin or metronidazole (for anaerobic coverage), administered 19, 18, and 9 hours before the start of surgery, with no oral antibiotics administered postoperatively. This abbreviated course of antibiotics has not been associated with an increased microbial resistance or the overgrowth of pathogens.[6] However, many American surgeons have begun omitting preoperative oral antibiotics, believing they offer no additional benefit.[9]

Parenteral Antibiotics

The preoperative administration of parenteral antibiotics has been shown to decrease the incidence of wound infections following elective colon surgery. This can be achieved without the use of additional oral antibiotics. However, these benefits disappear if parenteral antibiotics are administered *after* surgery has begun.[18] This implies that therapeutic tissue levels must be achieved before making the incision. The ideal prophylactic parenteral antibiotic should possess a broad spectrum of activity against colonic flora, rapid tissue distribution with acceptable duration of activity, and low toxicity. The use of second-generation cephalosporins with activity against both aerobic and anaerobic coliform bacteria is the most popular choice. Metronidazole is sometimes added to extend anaerobic coverage. Infectious complications increase when the operative time exceeds 3 hours or the anastomosis is in the extraperitoneal rectum. Many surgeons continue parenteral antibiotics postoperatively for 24 hours, although there are no data to suggest that this has any beneficial effect. Multiple drug-resistant strains of *Enterococcus* have received attention

in the medical literature.[19-21] The significance of these organisms on the use of bowel preparation, as well as the significance of bowel preparation on the emergence of these organisms, is not yet clear.

Topical Antibiotics and Antiseptics

Topical antibiotics, which include intraperitoneal irrigation with kanamycin and direct application of ampicillin to the wound, have been recommended periodically as a method to prevent wound infection. Whether there is any real benefit of such topical antibiotic application is difficult to determine because parenteral antibiotics are always administered in these studies.[22] Povidone-iodine has been instilled into the colonic lumen as a topical instant bowel preparation,[23] but this technique is not popular in the United States.

Summary and Current Practice

Although the ideal bowel preparation, in terms of patient acceptance, utility, efficacy, and cost, remains unclear, the most common practice in the United States continues to be mechanical fecal washout (usually adding poorly absorbed oral antibiotics for colonic lumen sterilization), and a total of 24 hours of perioperative prophylactic antibiotics, begun preoperatively.[8,9,24]

Special Considerations

There is a distinct difference between *prophylactic* and *therapeutic* antibiotic use. The goal of prophylaxis is to reduce the risk of operatively induced infectious complications. Broad-spectrum nontoxic antibiotics are administered for a brief but critical period, so as to minimize the emergence of disease-causing or antibiotic-resistant organisms. Therapeutic antibiotics, on the other hand, are directed at a specific infection-causing organism.

The prophylactic use of antibiotics is not without risk. A well-recognized complication associated with prophylactic antibiotics is *Clostridium difficile* colitis, which was first associated with clindamycin use, but is now more commonly associated with cephalosporins and has been reported following administration of virtually every antibiotic currently in use. The incidence of *C. difficile* colitis after elective gastrointestinal surgery has been estimated to be as high as 4%.[25] *C. difficile* elaborates an enterotoxin that causes the symptoms. Diagnosis can be elusive, with as many as 15% to 20% of patients testing negative for the toxin in stool. Treatment consists of appropriate supportive care, the discontinuation (if possible) of all other antibiotics, and the administration of oral metronidazole. (The parenteral route is less effective here.) Oral vancomycin, with its increased risk and expense, is indicated for patients who do not respond to metronidazole or who are extremely ill. Recurrence is common, requiring retreatment in as many as 25% of patients.

INCISIONS

A vertical midline incision through the linea alba is the incision of choice for colorectal surgery because it is easily and swiftly made, provides unlimited access to the abdominal cavity, may be easily extended upward or downward, and is rapidly and safely closed. The main disadvantage of the midline approach is a 5% to 10% incidence of incisional hernia.[26] Transverse incisions have a lower incidence of incisional hernia, but access to the peritoneal cavity is limited by incision placement.[27,28] Oblique incisions in the lower quadrants provide reasonably good exposure of the appendix and proximal right colon on the right and of the sigmoid and rectosigmoid colon on the left. Right hemicolectomy can often be easily accomplished through a transverse incision in the right mid-abdomen, particularly when the abdominal wall has some laxity. Low anterior resection can be performed through a Pfannenstiel incision when the patient's body habitus permits. However, this incision affords limited access to the remainder of the peritoneal cavity.

Paramedian incisions were popular in the past, probably because the incidence of ventral herniation seemed lower than that after a midline incision. However, the hernia incidence increases as distance from the midline decreases. Drawbacks of the paramedian approach include more time to enter the peritoneal cavity, more blood loss while the incision is being made, and longer time for the layered closure.

Closure of abdominal incisions should follow the surgical principles of gentle tissue handling and proper hemostasis. Results from studies using human cadaveric fascia in suture pullout tests suggest that sutures used to close the abdominal wound should optimally be spaced 10 to 15 mm apart.[29] The peritoneum does not require separate closure. Fascial closure with running rapidly absorbable suture results in significantly more incisional hernias than closure with running slowly absorbable or nonabsorbable suture.[30] A higher incidence of incisional hernia is also seen after fascial closure with braided absorbable suture.[31] Several studies have found increased incisional pain and formation of suture sinuses with nonabsorbable suture.[30,31] Divided muscle should not be reapproximated.

RESECTIONS

Extent

When the colon is resected for inflammatory bowel disease, diverticulitis, or other benign conditions, the resection encompasses all the involved bowel but much less mesentery than when operating for colon or rectal cancer. However, when resecting the colon or rectum for carcinoma, the mesentery supporting the pathway of lymphatic drainage is excised en bloc. The main vascular supply of the cancer-bearing segment is divided at or close to its origin, which by definition devascularizes a larger portion of the bowel, above and below the site of the tumor.

Pelvic malignancies often occur with contiguous involvement of adjacent structures, necessitating en bloc removal of disease, even if a resection may be palliative. The simplest case is rectal cancer that involves one or more loops of small bowel. For patients with more complex involvement, such as bladder, vagina, pelvic side wall, sacrum, prostate, or pelvic vasculature, preoperative planning for a team approach incorporates specialists in urology, gynecologic oncology, orthopedic or neurosurgery, plastic surgery, and vascular surgery.

In contrast, a less extensive resection may be indicated in a patient with a bleeding or obstructing lesion and metastatic disease. If the cancer is not resectable, alternatives include laser therapy, stent placement, and bypass (see "Palliative Treatment").

THE PATIENT WITH COLON OBSTRUCTION

Acute obstruction of the colon is associated with significant complications and requires prompt relief. Sequelae include colonic perforation and sepsis. Normal small bowel may be dilated if the colonic obstruction is chronic and the ileocecal valve is incompetent. Large-volume third-space fluid losses occur, resulting in hypovolemia and electrolyte imbalances. Progressive abdominal distention provokes respiratory embarrassment. In patients with colonic obstruction, distention is associated with increased intraluminal pressure,[32] which decreases colonic wall blood flow and shunts blood preferentially to the muscularis propria and away from the mucosa, compromising mucosal integrity.[33,34]

The goal of intervention in patients with colonic obstruction is relief of the obstruction and treatment of the underlying cause, if clinically indicated at the same operation. Management of the obstructed colon depends on both the cause and the location of the obstruction. Peritonitis requires urgent exploration regardless of the cause. A sigmoid or cecal colonic volvulus may be reduced by sigmoidoscopy or colonoscopy, permitting an elective approach for definitive therapy. Inflammatory lesions, such as diverticulitis and Crohn's disease, often improve with intensive medical therapy, bowel rest, and nutritional support, allowing resection on an elective basis. This is especially true if the obstruction is only partial.

Right colonic obstruction may present clinically as a small bowel obstruction. The colon distal to the obstruction may be in large part empty. Ideally, management consists of right colectomy with primary ileocolonic anastomosis. Morbidity rates are quite acceptable. The remainder of the colon must be evaluated for synchronous lesions.

For left-sided obstruction, the historical approach included three stages. The initial step was performance of a colostomy for fecal diversion and relief of obstruction. A closed-loop obstruction resulted from use of an ileostomy in the patient with a competent ileocecal valve. Interval resection of the lesion followed when clinically indicated. Lastly, the stoma was closed. This three-stage approach is associated with excessive morbidity and mortality rates and is rarely indicated today.

The approach currently most favored is resection of the obstructing lesion, with performance of an end stoma or immediate anastomosis with or without a proximal stoma. Total abdominal colectomy with either ileostomy or ileorectal anastomosis may also be performed in this setting. The advantages of the last approach include removal of the disease process, no need for a bowel preparation or investigation for synchronous lesions, easy irrigation of the rectum prior to anastomosis if one is performed, and avoidance of a stoma if ileoproctostomy is performed. This approach does require an absence of rectal involvement and resectability of the obstructing lesion. Most studies show acceptable rates of morbidity and mortality, even in elderly patients.[35-37] However, some patients tolerate poorly the postoperative bowel alterations caused by an ileostomy or an ileorectal anastomosis.

A decompressing colostomy may be considered for patients with several severe comorbid conditions or those with the rectum as the site of obstruction. This approach facilitates investigation and preparation of the bowel, with the expectation that a resection more limited than a total abdominal colectomy will follow. Advantages include a limited resection with resulting better postoperative bowel function. A competent ileocecal valve precludes an ileostomy from decompressing a colonic obstruction.

Resection and an end sigmoid stoma, or *Hartmann's procedure,* is frequently used for the management of left-sided obstructing as well as perforating lesions. The perioperative morbidity rate is quite low. The main drawback is that a formal laparotomy is required to reestablish intestinal continuity. The percentage of patients in whom a so-called Hartmann stoma is never closed is variably reported to be between 20% and 65%.[38]

Intraoperative colonic lavage followed by resection and anastomosis has been reported on extensively, but the results vary considerably. Some report that morbidity rates are significantly higher than those after either a formal three-stage approach or a subtotal or total abdominal colectomy.[37,39-41] One recurring problem is hypothermia: the lavage fluid must be warmed to 37° C to avoid this potentially dangerous complication. However, a prospective, randomized trial that compared subtotal colectomy with intraoperative lavage, segmental resection, and primary anastomosis found that the morbidity and mortality rates were similar but that postoperative stool frequency was higher among the subtotal colectomy patients.[41] A 2002 study from Taiwan also reported that wound infections after intraoperative lavage and reanastomosis were nearly three times that after subtotal colectomy and ileorectal anastomosis.[42] Intraoperative colonic lavage also prolongs the operation and requires the presence of operating room personnel experienced in the technique.

PALLIATIVE TREATMENT

Diversion alone is often used for the 20% to 30% of patients who present with locally extensive, unresectable cancer. However, diversion alone does little to alleviate

associated bleeding and pain. The obstructing lesion can be bypassed. Although this spares the patient a stoma, bowel habits are frequently altered. Complications other than obstruction are also not addressed. The anastomosis must be made in fairly normal bowel. If the ileocecal valve is present, it is necessary to perform a colocolostomy. An ileocolostomy will not relieve the obstruction of the colon proximal to the lesion.

Surgical resection, when possible, is reported to produce results superior to bypass alone in patients with incurable disease and a limited life expectancy yet fit enough to tolerate surgery. However, as more experience is gained with nonoperative methodology, surgical palliation has come under close scrutiny. Radiation, delivered via external beam or an intracavitary approach, palliates symptoms of bleeding and pain from bulky, unresectable rectal carcinomas and can produce dramatic improvement of impending obstruction. There are side effects of radiation to consider, and radiation tolerance is markedly less in the abdomen than in the pelvis. Increasingly, endoscopic palliation is a reasonable alternative to surgical palliation. Nd:YAG laser energy is useful to recanalize obstructing lesions and to treat bleeding. Large series have shown this approach to be safe, effective, and less costly than standard palliative surgical treatment.[43] Some authors suggest, however, that pain due to sacral plexus involvement, tumor encroachment on the anal canal, and/or sphincter dysfunction from tumor invasion should be considered relative contraindications to the use of laser therapy as the only treatment modality.[44] In addition, patients who survive longer than 24 months after the first laser treatment are more likely to require palliative surgery.[45]

The colonoscope can also be used to position a stent across a narrowed area for palliative treatment of impending malignant obstruction. This may be preceded, when necessary, with preliminary laser therapy for recanalization or treatment of bleeding. Several types of stent have been used; the most common is the self-expanding mesh stent. Morbidity rates are acceptably low in most reported series, consisting mostly of stent dislodgment, reobstruction from tumor ingrowth during the patient's remaining lifespan, and bowel perforation.[46,47] Intraluminal stents have also been used successfully to temporarily relieve obstructions caused by rectal cancer, permitting subsequent resection with curative intent.

ANASTOMOSES

Intestinal anastomoses are fashioned in a variety of ways, with the specific technique used being in large part a function of surgeon preference. Hand-sewn anastomoses have become less common after the introduction of intestinal stapling devices. However, a knowledge of the techniques for fashioning a hand-sewn anastomosis remains a key part of surgical education. Sutureless anastomotic techniques have not gained wide acceptance in the United States despite favorable reports.

Sutured Anastomoses

Many types of absorbable and nonabsorbable suture material have been used in intestinal anastomoses. More important than the choice of suture material is good surgical technique, including gentle handling of the bowel, adequate hemostasis, meticulous approximation of well-vascularized bowel, and a tension-free anastomosis.

Many surgeons favor two-layer anastomoses, and the technique varies. Commonly, the inner layer is an absorbable 3-0 or 4-0 running full-thickness stitch, and the outer layer is an inverting, usually 3-0, seromuscular stitch, which may be running or interrupted, absorbable or nonabsorbable. The outer posterior row is placed first (Fig. 167–1). The inner row is then placed, posterior wall first, followed by the anterior wall. The anterior outer row is the last completed.

One-layer anastomoses are also favored by many surgeons. A full-thickness technique, interrupted (Fig. 167–2A) or running (see Fig. 167–2B), with absorbable or nonabsorbable suture is common for hand-sewn colorectal anastomoses. An interrupted inverting seromuscular technique can also be used for small bowel and

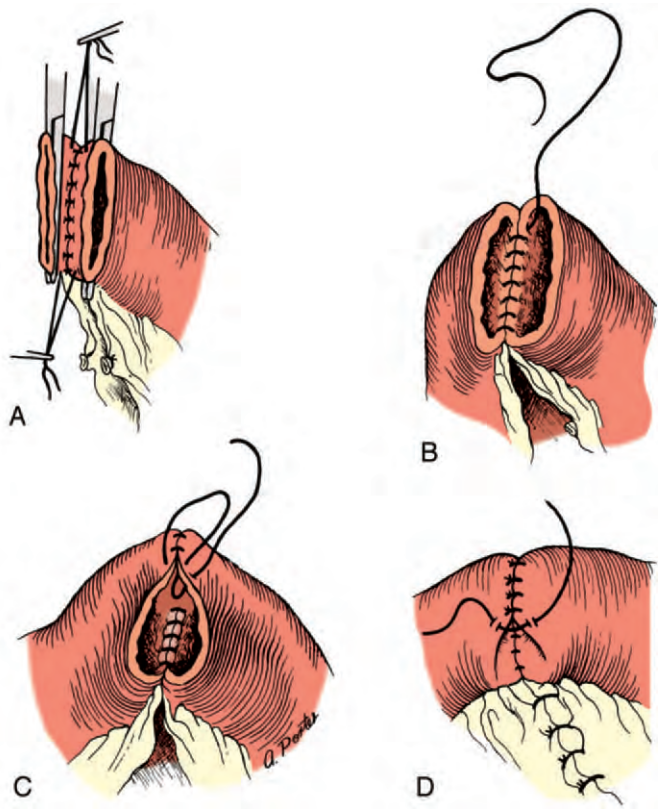

Figure 167–1. Two-layer, hand-sewn, end-to-end anastomosis. **A,** Placement of posterior outer layer of Lembert stitches. **B,** Inner posterior layer, shown as continuous, but may also be interrupted. **C,** Inner anterior layer, shown here as Connell stitch. **D,** Outer anterior layer of Lembert seromuscular stitches. (**A-D,** From Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations, 10th ed. Stamford, Appleton & Lange, 1997.)

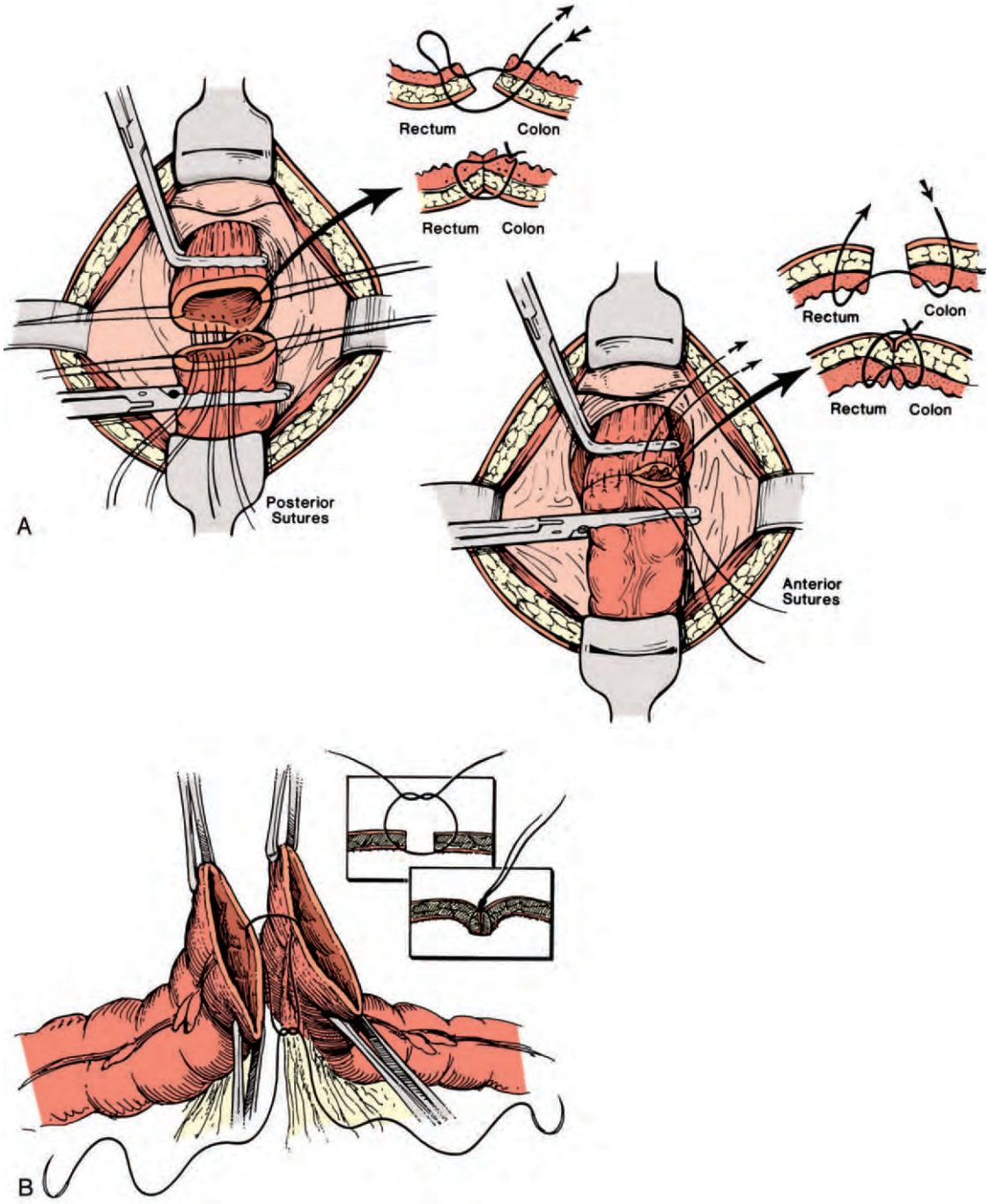

Figure 167–2. One-layer, full-thickness, end-to-end, hand-sewn low anterior anastomosis. **A,** Interrupted technique. The posterior row is placed first, with knots tied on the mucosal side. The anterior row is then placed. Knots may be tied on the mucosal or serosal side. **B,** Continuous technique. The suture is begun on the posterior wall, with the knot tied on the serosal side. The suture is continued in a running fashion. (**B,** From Max E, Sweeney WB, Bailey HR, et al: Results of 1,000 single-layer continuous polypropylene intestinal anastomoses. Am J Surg 162:461-467, 1991.)

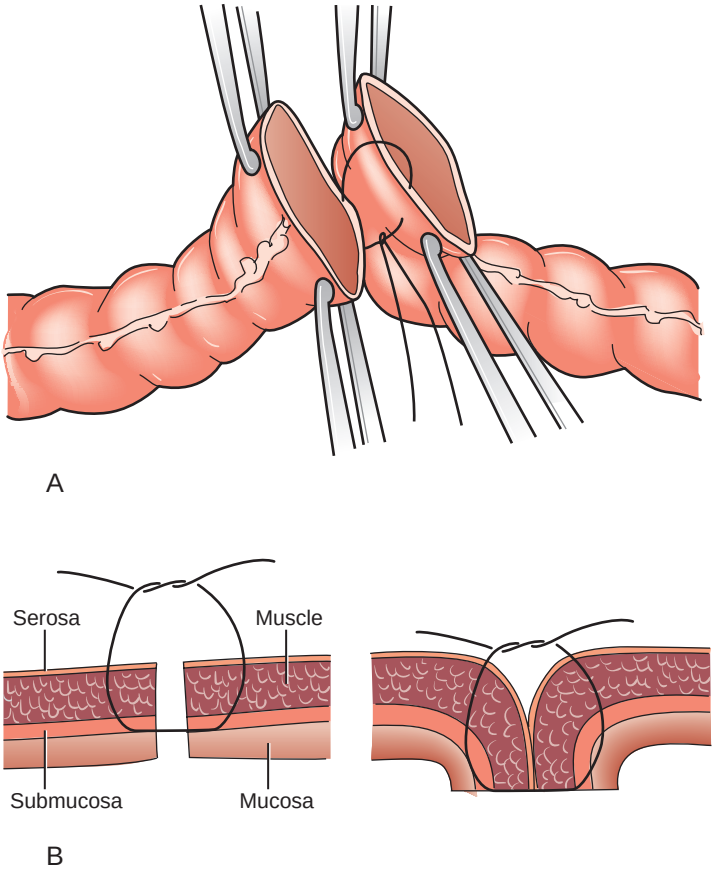

Figure 167–3. One-layer seromuscular anastomosis. **A,** Operative appearance. The posterior row is placed first. **B,** Detail of stitch placement. Care is taken to invert the mucosa, which is not incorporated into the suture.

colon anastomoses, with either braided silk or polyglycolic or polyglycolitic acid (Vicryl or Dexon), size 3-0 or 4-0 (Fig. 167–3). The single-layer full-thickness and seromuscular methods produce secure anastomoses with rates of stricture and leak comparable to those of the two-layer technique. Hand-sewn coloanal or ileal pouch–anal anastomoses are usually fashioned with one layer of interrupted absorbable sutures, with each suture incorporating the full thickness of both components of the anastomosis.

Stapled Anastomoses

The surgical staplers now widely used evolved from 1950s-era Russian prototypes. Many modifications have been made, but the theory and basic technique for construction of the anastomosis remain constant.

The linear-cutting stapling devices place two double-linear rows of staggered staples and divide the tissue between the rows. The staplers are available in several lengths (50 to 100 mm) and two staple heights. These staplers are used to divide the bowel and to simultaneously close both sides. Alternatively, this device can be used to fashion a side-to-side (functional end-to-end) anastomosis (Fig. 167–4).

Circular staplers are used to construct end-to-end or end-to-side anastomoses. The stapler (Fig. 167–5) consists of a tubular body and a detachable anvil. The body of the stapler is usually passed per anus to the end of the rectal stump, which has been closed with a pursestring stitch (Fig. 167–6) or a linear stapler (Fig. 167–7). The anvil is secured within the proximal bowel with the connecting end protruding. The two parts are joined and the stapler is fired, producing a circular anastomosis of two concentric rows of staggered staples. The stapler contains a circular knife that excises the excess tissue. Low anterior and ileal pouch–anal anastomoses may be controlled with this stapling technique.

Results of stapled anastomoses have been examined extensively. Anastomotic leak and stenosis compare favorably with those of hand-sewn techniques.[48,49] Moreover, anastomotic recurrence is not more common after a stapled anastomosis than after a hand-sewn anastomosis.

Sutureless Intestinal Anastomosis

Sutureless intestinal anastomosis is a type of anastomosis that is produced with compression devices, tissue or synthetic glues, or laser welding. Tissue glues have been studied in animal models, and safety is not yet acceptable; although there is significantly less inflammation and edema at the anastomotic site, bursting strength is also less than with conventionally performed anastomoses.[50,51] A synthetic glue, 2-cyanoacrylate (Dermabond) has been studied in rats, with bursting pressures equal to that of

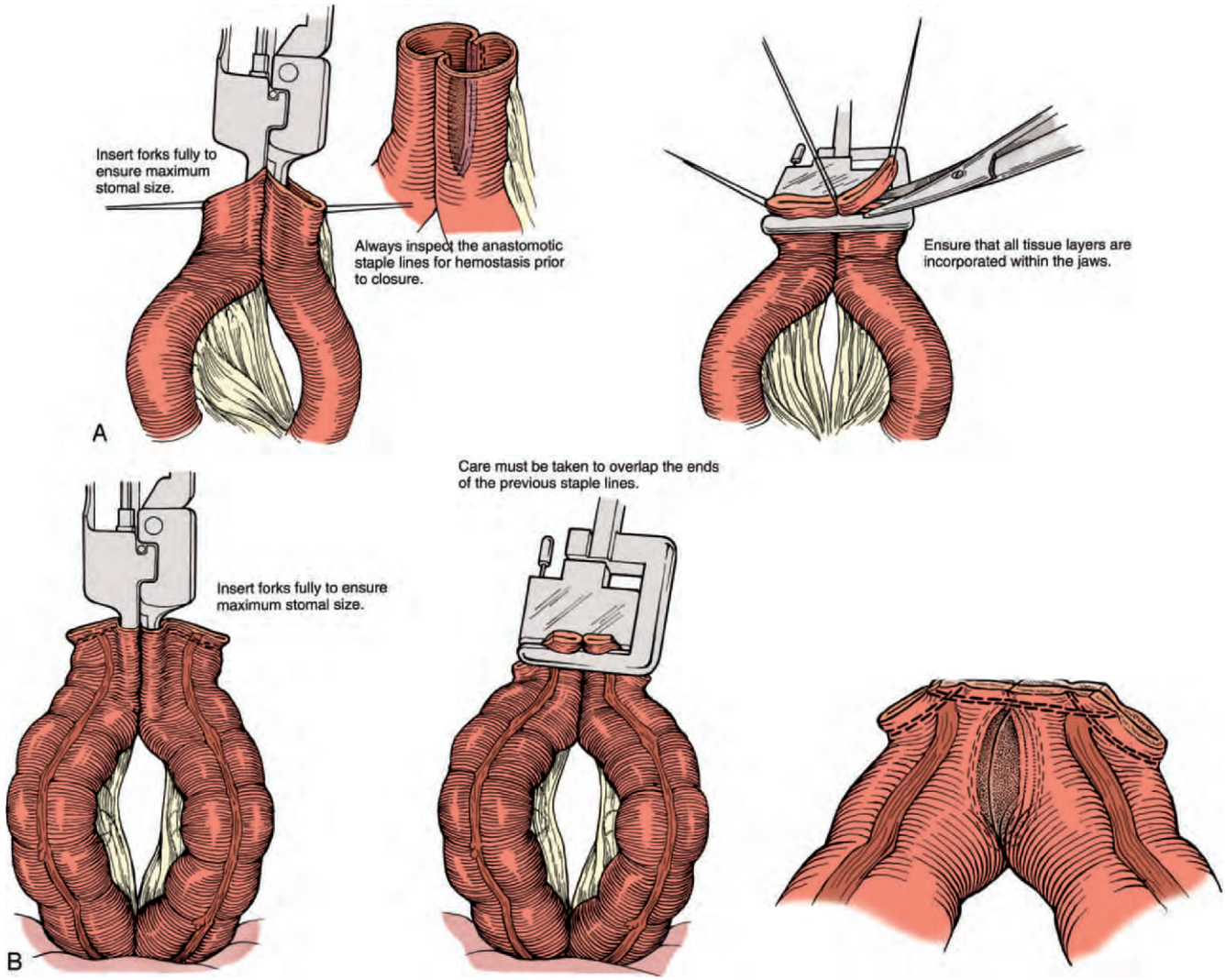

Figure 167–4. **A,** Side-to-side (functional end-to-end) small bowel anastomosis performed with the linear-cutting stapler. The enterotomy is closed with a linear stapler. **B,** Side-to-side (functional end-to-end) colonic anastomosis done with the linear-cutting stapler. The enterotomy is closed with a linear-type stapler. (**A** and **B,** From Zinner MJ, Schwartz SI, Ellis H [eds]: Maingot's Abdominal Operations, 10th ed. Stamford, Appleton & Lange, 1997.)

sutured anastomoses. There was, however, more adhesion formation noted.[52] Laser-welded anastomoses have shown some promise in experimental studies, and further investigation is ongoing.

The earliest reported compression device for bowel anastomosis was the Murphy button of the 1920s. More modern biofragmentable devices have facilitated renewed interest in this compression anastomosis, but this has occurred mainly in Europe and Asia.[53-55]

Colonic J-Pouch

Studies have found that early postoperative bowel function after very low anterior resection or coloanal anastomosis is improved if a colonic pouch is constructed. The pouch is constructed in a manner similar to that of the ileoanal J-pouch. Pouch size is important—a 5- to 8-cm pouch produces better function than does a pouch of 10 cm or longer, as large pouches are associated with difficulty in evacuation.[56,57] The pouch confers no added benefit, however, if the anastomosis is more than 8 cm above the dentate line.[58,59] Functional benefits include better continence, less urgency, and fewer stools. Patients benefit most in the first year after surgery, but after that the function of a straight coloanal anastomosis is similar to that provided by the J-pouch. Some authors have reported improved function for up to 5 years.[60] The colonic J-pouch can be technically difficult to construct and may be too bulky to fit into a narrow pelvis. An alternative is the transverse coloplasty, which avoids the fit problem in a narrow pelvis and provides good functional results and fewer stool evacuation problems.[61]

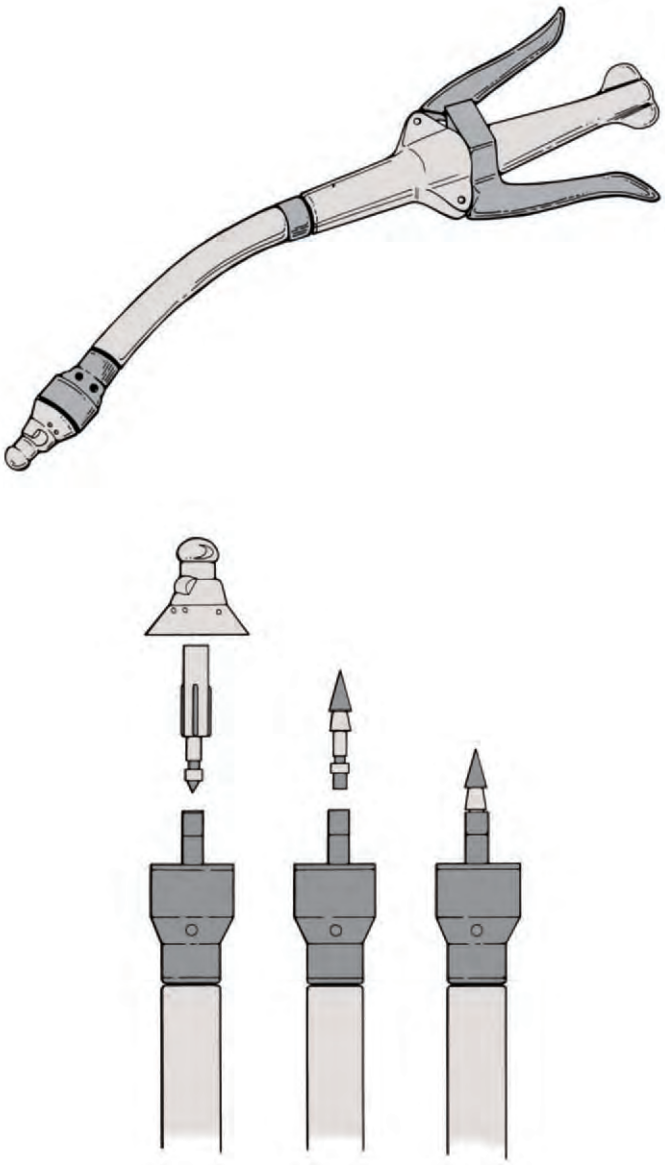

Figure 167–5. Circular-type staplers. Note detachable anvil and snap-on trocar.

Restorative Proctocolectomy for Familial Adenomatous Polyposis or Ulcerative Colitis with Dysplasia or Cancer

Although a double-stapled ileal pouch–anal anastomosis has become the most common technique used in restorative proctocolectomy, two situations exist that favor a rectal mucosectomy with per-anal hand-sewn ileal pouch–anal anastomosis: the patient with familial adenomatous polyposis and the patient with ulcerative colitis in whom the indication for restorative proctocolectomy is dysplasia or cancer. In both situations, the rectal mucosa remaining after stapling of the anastomosis may carry an increased risk of future neoplastic change. More extensive discussion can be found in the chapters dealing with ulcerative colitis (see Chapter 152) and familial adenomatous polyposis (see Chapter 155).

ANASTOMOSIS OR STOMA?

A satisfactory anastomosis is likely to result if all of the following questions can be answered in the affirmative regardless of the anastomotic technique used. Is the patient stable? Is the resection complete? Is hemostasis satisfactory? Has all debris been removed from the proposed anastomotic site? Are both ends of the intestine healthy and well vascularized? Will the proposed anastomosis be tension free? Leak rates of 2% to 5% after intraperitoneal colonic anastomoses and 5% to 10% after colorectal anastomoses are expected. However, if the patient becomes unstable intraoperatively, diversion quickly performed is indicated. Continuity can be reestablished at a subsequent appropriate time.

In the event of peritonitis with fecal or purulent soilage of the peritoneal cavity, resection of the diseased segment with fecal diversion remains the standard of care. The risk factors for poor outcome—unprepared bowel, peritonitis, emergency operation, and septic patient—should overrule the desire to spare the patient from the difficulty of living with a stoma, even temporarily.

Although chronic partial obstruction may allow the bowel to be prepared satisfactorily, the anastomosis can be a challenge because the proximal and distal bowel diameters are different. If the proximal bowel is not able to hold sutures or staples, diversion is necessary. Sometimes, although a conventional end-to-end anastomosis may not be feasible, other options exist for the construction of a secure anastomosis. A side-to-side anastomosis (functional end-to-end) is often performed in this setting (see Fig. 167–4). An anastomosis can also be constructed by approximating the end of the dilated segment to the side of the normal segment of bowel. A Cheatle cut may also be used along the antimesenteric border of the normal-sized intestine, which allows conformation of bowel diameter for anastomosis.

Furthermore, there are situations in which an anastomosis should be protected by a proximal stoma. In the absence of an anastomotic leak, the mortality rate after colorectal resection is 2%; with a leak, the mortality rate rises to 10%.[62] When the chance of anastomotic leak is high and the patient would be unlikely to survive such a complication, it is logical to construct an end stoma or, alternately, to anastomose the bowel but to protect it with a proximal stoma. If the patient is unlikely to improve sufficiently to allow an anastomosis to be considered in the future, the patient will be best served by a well-planned end stoma. However, if the patient's clinical situation can logically be expected to improve, anastomosis with proximal diversion is a valid option. This is commonly performed for patients undergoing proctocolectomy with restorative ileal pouch–anal anastomosis. Patients who have undergone neoadjuvant chemoradiation for rectal cancer, followed by sphincter-sparing resections, also are most often managed in this way. Because the risk of anastomotic leak after

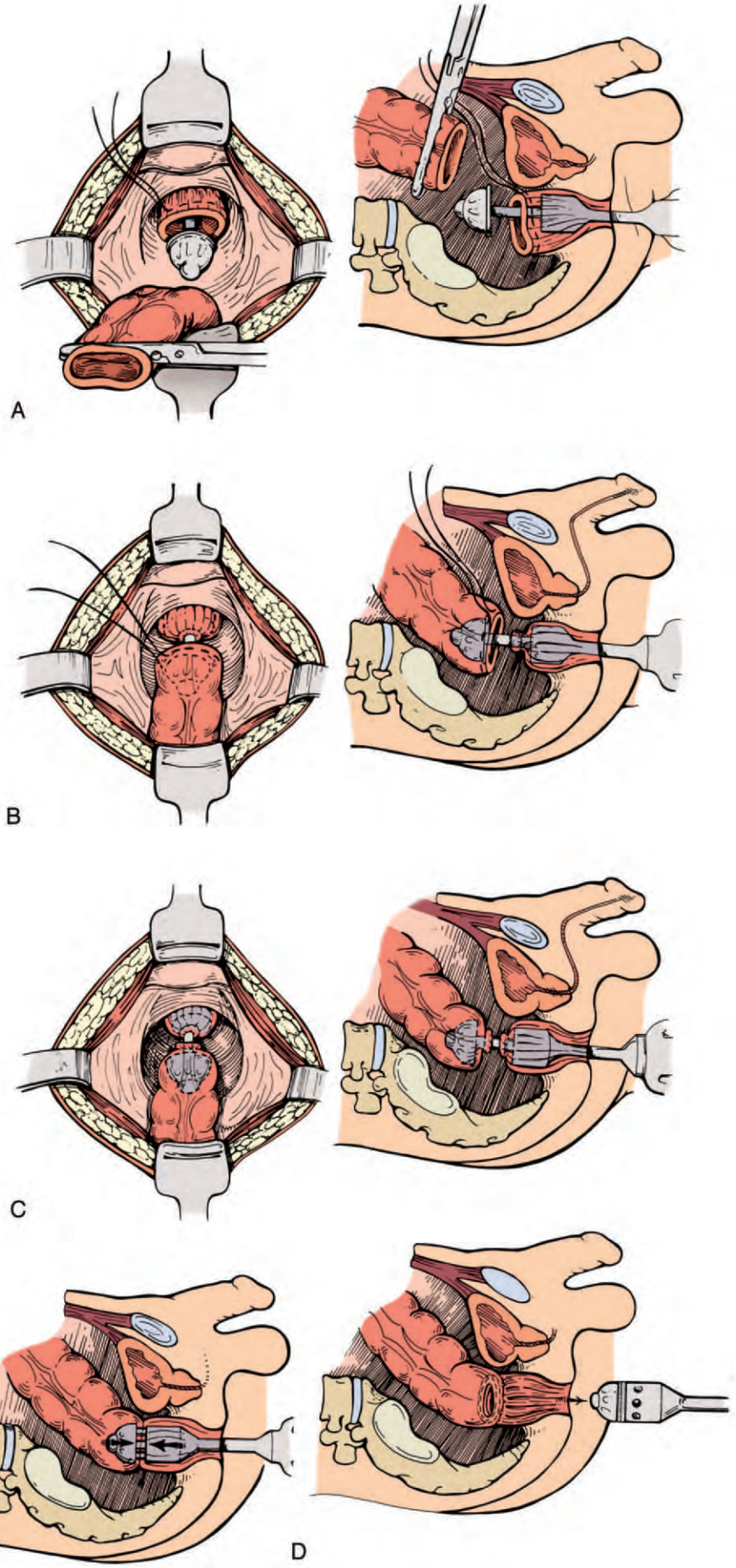

Figure 167–6. Stapled low anterior resection with proximal and distal pursestring sutures. **A,** The stapler is passed gently transanally until the anvil protrudes from the sectioned edge of the rectum. The distal pursestring is secured around the inferior edge of the anvil shaft. **B,** The proximal colon is placed onto the anvil. **C,** The proximal pursestring is tied around the upper end of the anvil shaft. **D,** The stapler is closed to the desired degree and fired, completing the anastomosis. The stapler is then gently withdrawn.

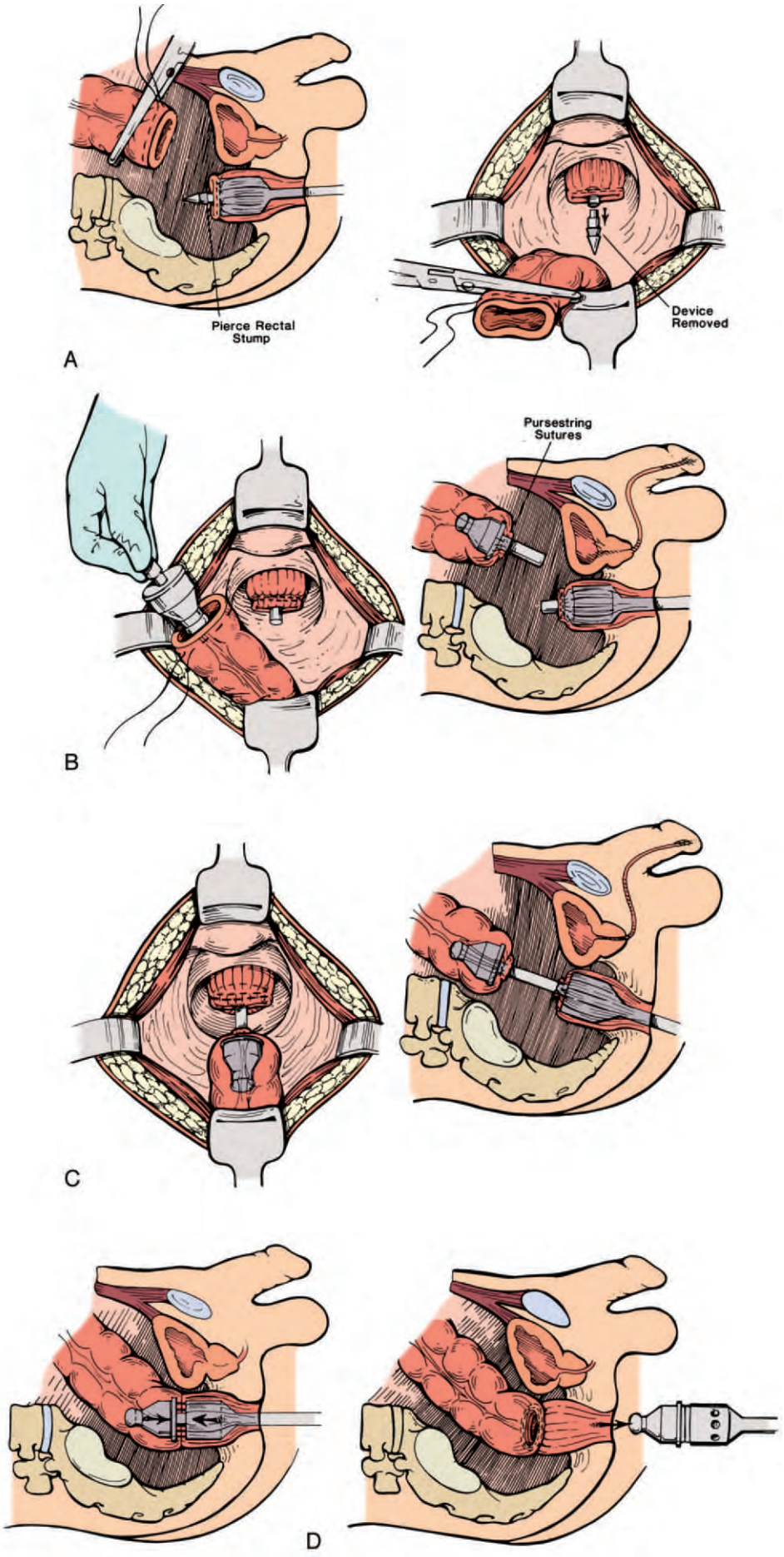

Figure 167–7. Stapled low anterior anastomosis performed with double-stapled technique. **A,** The stapler is passed transanally to the end of the rectal stump. The instrument is slowly opened; the trocar pierces the end of the stump, which has been closed by an application of the linear stapler. **B,** The anvil is placed into the proximal bowel and tied into place with a pursestring suture. **C,** The anvil is snapped onto the shaft of the stapler. **D,** The stapler is closed to the desired degree and fired, completing the anastomosis. The stapler is then gently withdrawn.

chemoradiation is elevated,[63,64] a diverting loop stoma is constructed and the low anastomosis is allowed to heal. The stoma is subsequently closed (usually about 10 to 12 weeks after the initial procedure). Finally, there are some patients who never progress to stoma closure. This underscores the importance of meticulous planning for every stoma, because some intended to be temporary will become lifelong.

SPECIAL APPROACHES

Several specialized approaches deserve mention. *Laparoscopic colon resection,* with intracorporeal or extracorporeal anastomosis, is discussed at length in Chapter 168.

Transanal excision of rectal tumors, although simple in concept, is often quite difficult in practice. This approach has the potential to avoid subjecting patients to the greater complications of transabdominal surgery. However, the caveats are numerous. The anus is unavoidably stretched to some degree; this can produce alterations in continence, which are sometimes persistent. Exposure and visibility are limited, making access to lesions that are more than 4 to 6 cm from the dentate line difficult. Whether transanal excision of rectal cancer is oncologically sound is debatable. Most agree, however, that histologically proven T1 carcinomas with an absence of poor prognostic indicators, such as lymphovascular invasion, poor differentiation on histopathology, aneuploidy, or evidence of lymph node involvement on physical examination or imaging, can be treated safely by local excision with an acceptable rate of local recurrence.[65,66] This approach is also discussed at length in Chapter 157.

Transanal endoscopic microsurgery (TEM) extends the boundaries of the classic transanal approach by using a 40-mm-diameter operating rectoscope with sixfold magnification and ports for the manipulation of laparoscopic-type instruments. This technique has been used extensively in Europe to resect benign rectal lesions as high as 24 cm from the anal verge, with acceptable morbidity and mortality.[67] The main drawbacks of TEM are the cost and complexity of the equipment. There also are postoperative alterations in anorectal physiology that appear to persist. However, adequate continence is satisfactorily preserved in most patients.[68,69]

The role of TEM in local excision of early rectal carcinomas is being evaluated.[70-72] The indications currently parallel those of classic transanal excision of rectal cancers, specifically that TEM is best suited for histologically proven T1 carcinomas with an absence of poor prognostic indicators. The adjunct roles of radiation and chemotherapy remain controversial (see also Chapter 157).

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Chapter

168

Laparoscopic Colorectal Surgery

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BACKGROUND

Laparoscopic colorectal surgery finally came of age in 2004, after more than a decade of controversy that was resolved with the publication of results of randomized controlled trials. The current era of minimally invasive surgery began with the introduction of laparoscopic cholecystectomy in 1987 in France[1] and in 1988 in the United States by Reddick and Olsen.[2] The success and rapid acceptance of laparoscopic cholecystectomy led naturally to the application of minimally invasive techniques to other intra-abdominal organs, and the first report of laparoscopically assisted colectomy was by Jacobs et al. in 1991.[3] Initially used for procedures such as simple mobilization and colotomy to remove benign lesions, laparoscopic techniques subsequently were applied to the full spectrum of colorectal procedures, with varying degrees of success. By early 2004, however, fewer than 5% of resections for colon and rectal cancer were being performed laparoscopically. (For purposes of comparison, in 2003, approximately 105,500 new cases of colon cancer and 42,000 new cases of rectal cancer occurred in the United States.[4]) This decline in laparoscopic procedures was the result of controversy related to the phenomenon of wound implants, or cancer recurrence at incision sites. Although a single-institution, randomized controlled trial from Spain already had suggested that the laparoscopic approach did not adversely affect oncologic outcomes,[5] the United States was awaiting the results of its own multicenter study. The results of the landmark COST (Clinical Outcomes of Surgical Therapy) trial were published in spring 2004.[6] Data from that and more recent randomized controlled trials (Table 168–1) have laid to rest the controversial aspects of the minimally invasive approach for colon cancer, and with more widespread adoption of these techniques, laparoscopic colectomy is currently taught at more than 75% of the colorectal fellowship training programs compared with fewer than 25% before 2004.

It is important that laparoscopic surgery be recognized for what it really is—a technique, and not a therapy. Laparoscopic surgery does not represent a new operation, but rather a different approach to obtain the same end result. Laparoscopy is more "minimal access" surgery than "minimally invasive" surgery because within the peritoneal cavity, the same procedure and same extent of dissection is performed. Generally, the *indications* for operative intervention are the same, but the *technique* differs. The indications for surgery may be modified in some disease processes (e.g., resection for limited Crohn's disease) because some patients may find operative intervention by a minimally invasive approach an acceptable alternative to the risks and side effects of long-term medical care, such as the long-term use of steroids or immunosuppressive agents. Laparoscopy in colorectal surgery has been more slowly adopted, however, than for other abdominal procedures (e.g., cholecystectomy and bariatric operations). The extent to which laparoscopy has been used has been determined by the balance between advantages that drive it and concerns and challenges that limit it.

OUTCOMES OF MINIMAL ACCESS TECHNIQUES

In general, the introduction of new techniques such as laparoscopy should produce equivalent, if not better, clinical results than conventional techniques to become an acceptable alternative. Most surgeons familiar with laparoscopic colorectal surgery would concur that the approach results in patient benefits, such as reduced postoperative pain, a shorter period of convalescence, and the potential for financial savings (as a result of fewer hospital days). There is still dissent, however, regarding the existence of benefits—primarily from surgeons who have resisted learning the technique.

Early reports of laparoscopic-assisted colectomy did not consistently show advantages,[7,8] and this was an initial

Table 168–1 Prospective Randomized Trials Comparing Laparoscopic and Conventional Surgery for Colorectal Cancer

	Lacy (2002)[5]—Laparoscopic Versus Open	COST (2004)[6]—Laparoscopic Versus Open	CLASICC (2005)[12]—Laparoscopic Versus Open
Baseline Characteristics			
No. assigned	111:108	435:437	526:268
No. completed	105:101	435:428	452:231
(dead or no data)			74:37
Age	68:71	70:69	69:69
Gender (F)	55:58	49%:51%	44%:46%
Previous surgery	40:47	43%:46%	
Operative Findings			
Procedure			
Right	49:49	54%:54%	24%:24%
Left	4:1	7%:7%	7%:9%
Sigmoid	52:46	38%:38%	13%:12%
AR/LAR	3:9		37%:36%/12%:13%
Other	3:3		4%:3%
TNM stage			Not given
0		5%:8%	
I	27:18	35%:26%	
II	42:48	31%:34%	
III	37:36	26%:28%	
IV	5:6	4%:2%	
No. lymph nodes	11.1:11.1	12:12	12:13.5
Conversion	12 (11%):NA	21%:NA	29%:NA
Operating room time (min)	142:118*	150:95*	180:135 (anesthesia time)
Incision length (cm)	—	6:18*	10:22
Short-Term Outcomes			
Oral intake	54:85* (hr)	—	6:6 (days)
Hospital stay (days)	5.2:7.9*	5:6*	9:11
30-day mortality	—	<1%:1%	4%:5%
Postoperative complications	12:31*	19%:19%	33%:32%
Wound infection	8:18	—	5%:5% (colon); 13%:12% (rectum)
Pneumonia	0:0	—	7%:4% (colon); 10%:4% (rectum)
Ileus	3:9	—	—
Leak	0:2	—	2%:0% (colon); 10%:7% (rectum)
Duration of oral analgesics (days)	—	1:2*	—
Duration of parenteral analgesics (days)	—	3:4*	—
Cancer Outcomes			
Tumor recurrence	18:28	76:84	—
Distant	7:9	—	—
Locoregional	7:14	—	—
Peritoneal seeding	3:5	—	—
Port site	1:0	2:1	—
5-yr overall survival†	82%:74%	79%:78%	—
I	85%:94%	84%:94%	—
II	75%:77%	78%:81%	—
III	72%:45%	60%:63%	—

Table 168–1 Prospective Randomized Trials Comparing Laparoscopic and Conventional Surgery for Colorectal Cancer—cont'd

	Lacy (2002)[5]— Laparoscopic Versus Open	COST (2004)[6]— Laparoscopic Versus Open	CLASICC (2005)[12]— Laparoscopic Versus Open
5-yr disease-free survival†	—	78%:80%	—
I	90%:88%	92%:96%	—
II	80%:76%	82%:88%	—
III	70%:45%	62%:60%	—
Cancer-related survival†	91%:79%*	—	—
I	100 %:99%	—	—
II	88%:85%	—	—
III	84%:50%*	—	—

*$P < .05$

†Extrapolated from graphs in original articles.

AR, anterior resection; LAR, low anterior resection; NA, not available.

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cause of concern. Reasons for this lack of advantages are apparent in hindsight. Early reports of experience with laparoscopic colectomy often included a spectrum of colorectal procedures, from stoma creation to various segmental resections and extended colectomies, to report adequate case numbers. In addition, patient populations were heterogeneous, as were the underlying disease processes. These studies were performed when the authors were still developing the technique,[9,10] so conversion rates were high, and operative times were long. It may be more accurate to describe these first series as showing a "development curve," rather than a learning curve.[11] A "learning curve" is perhaps better defined as the number of cases required for a surgeon with existing laparoscopic skills to become adept at a procedure when taught by an experienced mentor, as is the case in residency and fellowship programs. In contrast, when homogeneous populations, procedures, and indications are reported, laparoscopic procedures seem to be more "patient friendly" than standard laparotomy.

The potential benefits of laparoscopic colectomy include shorter duration of postoperative ileus, reduced incisional pain and less need for analgesics, earlier introduction of diet, shorter length of hospital stay, and improved cosmetic appearance. Not obvious to patients is the possible preservation of immune function. These benefits are countered by longer operative times, expensive laparoscopic equipment, and a long learning curve. In reports other than those of randomized controlled trials, there is probably a selection bias when comparing conventional and laparoscopic cases. More challenging cases usually are not considered for a minimally invasive approach. As an additional confounding factor, few studies, other than prospective randomized studies, include "converted" cases in the laparoscopic group as part of the "intention-to-treat" analysis.

Although patient benefits have been evaluated in the published randomized trials, these outcomes were secondary to the analysis of oncologic outcomes. Some of these trials have not shown the same degree of benefits that were expected based on nonrandomized case-matched or case-controlled comparative studies. Some authors have considered the results of these trials to indicate that the true benefits are less than many expected, whereas others consider that the focus on oncologic results resulted in less thorough evaluation of outcomes that were considered less important in the face of the focus on cancer survival. The conclusions regarding patient benefits must be derived from the overwhelming repetitiveness of the results favoring laparoscopic techniques from multiple study types and multiple institutions.

Operative Time

Operative time may variably be defined as the time between making an incision and closing it versus "anesthesia time," in which patient preparation and draping also are included. Times often cannot be compared across institutions and studies. Also, there may be different groups of surgeons performing the laparoscopic and open procedures. Frequently, multiple types of procedures are included in a mean operative time for all procedures, losing the ability to discern that more complex procedures are more likely to have a bigger discrepancy in operative times when comparing the two approaches. In general, most studies report longer operative times for the laparoscopic procedure. In prospective randomized trials, this difference has ranged from 20 to 60 minutes[5,6,12,13] longer in the laparoscopic arm. With experience, operative times do decrease[14] and may become comparable, particularly in the more simple segmental colectomies, such as right and sigmoid resections.

Return of Bowel Activity and Resumption of Diet

After most colorectal operations, length of hospital stay is governed by duration of postoperative ileus. Earlier resolution of ileus is a major advantage of laparoscopic techniques. Most studies describe a statistically significant reduction in the time to passage of flatus and stool, favoring the laparoscopic approach. In most series, this is a 1- to 2-day improvement. Hospital stay was 5 days versus 6 days (laparoscopic versus open) in the COST randomized trial,[6] 5.2 days versus 7.9 days in Lacy's study,[5] and 9 days versus 11 days in the CLASICC (*C*onventional versus *L*aparoscopic-*A*ssisted *S*urgery *I*n *C*olorectal *C*ancer) trial.[12] The reduction in duration of ileus is likely multifactorial, resulting from less intraoperative bowel manipulation, reduced exposure of the peritoneal cavity to air, less requirement for narcotics, and other unidentified factors. The shorter period of ileus noted in randomized controlled trials reproduces findings from earlier retrospective studies.[15-24]

Although patients in clinical trials are subject to biases engendered by higher expectations of the laparoscopic approach, animal studies, which are free of this subjective bias, also confirm more rapid return of bowel activity. More rapid return of intestinal myoelectric activity and return to preoperative motility has been shown in canine and porcine models after laparoscopic intervention.[25-27]

The shorter duration of postoperative ileus seems to translate into earlier introduction of liquids and solid food after laparoscopic colectomy. Tolerance of diet varies from 2 to 7 days, with this range likely determined by postoperative feeding practices, as the benefit of the laparoscopic group is fairly consistently 1 to 2 days sooner than the comparative open group. Oral intake was not addressed in the COST study,[6] favored the laparoscopic arm in Lacy's study[5] (54 hours versus 84 hours; $P < .05$), and was not significantly different in the CLASICC trial.[12] The preponderance of reproducible data, reported in retrospective and prospective trials, shows shorter postoperative ileus and earlier tolerance of diet.

Postoperative Pain and Recovery of Pulmonary Function

Postoperative pain, as a subjective symptom, is notoriously difficult to standardize and measure. Most studies have measured narcotic requirements, measured duration of narcotic use, or employed an analogue pain scale. Although physician bias and the placebo effect may introduce bias, most studies have reported a reduction in postoperative pain associated with the laparoscopic approach. Early, single-institution randomized trials evaluated this feature and reported reduced narcotic use in the minimally invasive group.[28-30] In the COST study, the laparoscopic arm required fewer days of intravenous analgesics (3 days versus 4 days; $P < .05$) and oral analgesics (1 day versus 2 days), although the latter may have been governed by the shorter hospital stay noted.[6,31] This finding is consistently reported in nonrandomized studies.[15,16]

Compromise of pulmonary function is a well-recognized phenomenon postoperatively, and the degree of compromise is related closely to the severity of postoperative pain. Appropriate pain control permits deep breathing and use of incentive spirometry devices. In a randomized trial of patients undergoing laparoscopic colectomy ($n = 55$) and open colectomy ($n = 54$) for cancer or polyps, spirometry was performed every 12 hours to determine 80% recovery of baseline forced vital capacity and forced expiratory volume in 1 second.[28] The laparoscopic group showed significantly more rapid recovery of pulmonary function. Other authors have confirmed this finding.[30]

Length of Stay

Earlier resolution of ileus and resumption of diet, combined with reduced postoperative narcotic use, seems to produce a shorter length of hospital stay for patients undergoing laparoscopic colectomy compared with open procedures. In most reports, length of stay is 1 to 6 days shorter for laparoscopic colectomy. Critics of the laparoscopic approach have pointed to reduced hospital stay produced by early feeding practices, minilaparotomy, and fast-track patient care protocols. Experience gained with laparoscopic procedures has indicated that it is not necessary to wait for bowel function, in the form of passage of gas or stool, to introduce oral intake. Early feeding after *laparotomy* has been shown in randomized prospective trials to result in earlier tolerance, but this did not translate into reduced hospital stay.[32] The benefits of minilaparotomy have been evaluated alongside laparoscopic procedures. Fleshman et al.[33] compared minilaparotomy in 35 patients (mean incision length 12 cm) with 54 laparoscopic patients. In an intent-to-treat analysis, the length of stay was not statistically different (6.9 days minilaparotomy versus 6 days laparoscopic). The results were "diluted," however, by a conversion rate of 25% in the laparoscopic group. In the nonconverted group, the length of stay was 5.3 days, which was statistically different from the minilaparotomy group. Fast-track protocols after open colectomy produce results more similar to the results of laparoscopic approaches, but fast-track protocols after minimally invasive procedures produce additional gains.[34,35]

Quality of Life

One would expect that reduced postoperative pain and faster recovery after laparoscopic colectomy would translate into improved quality of life in the postoperative period. Assessments of quality of life were included in the COST study, using three instruments: patient self-reported symptoms, patient self-reported functional status, and a measurement scale of compliance to treatment referred to as *Q-TWiST* (quality-adjusted time without symptoms of disease and toxicity of treatment).[31] Many investigators were surprised by the lack of significant differences between open and laparoscopic colectomy with the exception of a global rating score 2 weeks

after surgery. Closer inspection of the results revealed a trend toward improved quality of life in laparoscopic patients in every category. The high conversion rate of 26% has been blamed for minimizing potential benefits in the intent-to-treat analysis, but although there were greater differences when comparing laparoscopic-completed patients with either open or laparoscopic-converted patients, the difference was still small and not significant. The lack of expected benefits may be a true result or a consequence of the nature of the quality-of-life instruments used. The questionnaires employed were carefully chosen and well validated, but they were validated in cancer patients and designed to detect differences in quality of life when such patients are experiencing changes in their quality of life (e.g., during chemotherapy or radiation therapy or as a result of cancer recurrence). They were not specifically designed to detect differences in postoperative patients.

Nonrandomized studies also have attempted to address this issue. The SF-36 scale has been used in a prospective study to evaluate quality of life at 2 and 4 months after laparoscopic and open colectomy.[36] In six of eight subscales, laparoscopic colectomy resulted in less impact on quality of life, a finding that persisted at 4 months, although it was less noticeable. Hand grip strength, as an indicator of protein loss, returned earlier in the laparoscopic group.

Cosmetic outcome is less important than other clinical parameters, particularly in the setting of cancer, but because it is related to the overall quality of life, it should not be entirely discounted. A report described improved patient assessment of cosmetic results after laparoscopic procedures for Crohn's disease compared with standard approaches.[37] Finally, a case-control study of laparoscopic colorectal surgery in elderly patients revealed an unexpected benefit: More elderly patients in the laparoscopic group retained their independent status on discharge from the hospital, being able to return home rather than being admitted to a nursing home.[38]

Hospital Costs

Laparoscopic colectomy is associated with higher costs for the procedure itself, as a result of longer operative times, disposable instruments, and depreciation of expensive laparoscopic equipment. Having a positive impact on costs are the reduced length of hospital stay and shorter period for which intravenous medications are required. The balance of these two sets of opposing forces likely differs by institution, procedure performed, underlying disease process, and patient factors because results in the surgical literature have varied. A case-matched study from the Mayo Clinic detailed a formal analysis of costs (not charges) after laparoscopic and open ileocolic resection for Crohn's disease.[15] Thirty-three patients in each group were well matched. Of particular note, there was no significant difference in operative times between the two groups. In the laparoscopic group, patients required narcotics for a shorter period, tolerated a regular diet earlier, and were hospitalized for fewer days (4 versus 7 days). Although operative costs were greater in the laparoscopic group, the overall mean costs were $3273 less as a result of reduced costs for room and board and for medications. Although bias likely was introduced by different surgeons performing the laparoscopic and open procedures, the study was completed while all surgeons were exposed to the current climate of cost containment. Duepree et al.[39] and Shore et al.[40] also reported similar findings, notably in a similar patient population, with a mean reduction of $438 in costs and $7465 in hospital charges in laparoscopic versus open ileocolic resection. The results also have been reproduced for elective sigmoid resection for diverticular disease.[41] These studies reveal the potential to minimize costs by improving operative times and minimizing use of expensive disposable instruments.

Complications

Data on complication rates were confusing in early series, likely a consequence of the impact of the learning curve. Laparoscopic colectomy currently is performed with intraoperative complication rates similar to the rates reported for open surgery. Early experience resulted in reports of injury to the intestine, ureteral injury, vascular injury, delay in recognition of intraoperative complications, and poor outcome after the treatment of colorectal cancer. These problems seemed to be caused by lack of familiarity with the operation. With increased experience, intraoperative technical problems during laparoscopic colectomy have become rare. Data suggest that complications are similar or less frequent after open colectomy. The COST study[6] and the CLASICC trial[12] showed similar rates of complications in both arms of the trial. Lacy's study reported significantly fewer complications in the laparoscopic arm (12 of 111 in the laparoscopic group versus 31 of 108 in the open arm; $P < .05$), with most of the difference related to lower wound infection rates.[5] These results mirror the similar or reduced rate of complications previously noted in retrospective and nonrandomized prospective studies.[14,21,23,42-44] Decreased wound infection rates also were an unexpected finding in several retrospective series.[23,42]

Laparoscopy also may have the potential to reduce the incidence of other complications. Minimally invasive techniques may reduce the incidence and extent of adhesions.[45,46] This has two possible implications: The incidence of small bowel obstruction may be reduced,[38,42,43] and subsequent abdominal procedures may be made easier. This is an important consideration in patients who are at high risk for reoperation, such as patients with Crohn's disease.

CHALLENGES

The acceptance of laparoscopy in colorectal surgery has occurred much more slowly, a consequence of the spectrum of complexity of typical cases that resulted in long learning curves and high conversion rates and the need to adhere to oncologic principles.

Anatomic Challenges

Laparoscopic colorectal procedures present challenges not encountered with laparoscopic cholecystectomy. The term *laparoscopic colectomy* does not apply to a single procedure, but to a spectrum of procedures of varying complexity ranging from simple stoma creation to small bowel resection and segmental colectomies to total abdominal colectomy with ileorectal anastomosis and proctocolectomy with ileal pouch–anal reconstruction. The colon is a bulky specimen, and its mobilization usually requires operating across more than one quadrant of the abdomen. This factor makes robotic devices tedious to use given the time consumed by repositioning the equipment. The specimen must be retrieved intact, and cannot be morcellated, at least in the case of cancer, because staging information would be lost. Most cases require intestinal continuity to be re-established. Resections for colorectal cancer additionally require adherence to oncologic principles, such as avoidance of tumor handling, proximal vascular pedicle ligation, and adequate lymphadenectomy. Operations for rectal cancer introduce an additional level of complexity given the difficulties of operating within the confines of the bony pelvis, particularly in men and obese patients, and the need to obtain adequate radial and distal margins.

Colorectal operations may be performed using entirely intracorporeal laparoscopic techniques or, more commonly, a laparoscopically assisted approach, in which a part of the procedure (e.g., anastomosis in right colectomy) is performed extracorporeally through a small incision. A completely intracorporeal approach is often time-consuming because creation of an intracorporeal anastomosis is more technically demanding and is unnecessary because removal of a specimen for pathologic examination usually requires that an incision be made. Although this requirement may change if tumor markers prove to be more accurate indicators of prognosis than tumor stage and lymph node status, to date there has been no study that confirmed any advantage for a completely intracorporeal approach compared with a laparoscopically assisted technique.

Learning Curve

The complexity of laparoscopic colectomy has resulted in recognition of a long learning curve. This curve applies not only to the surgeon, but also to the entire operating room team, including cameraperson, assistant, scrub nurse or technician, and circulating nurse. The anesthetic team also must be aware of certain demands and peculiarities of the procedures, such as ventilatory changes prompted by the pneumoperitoneum, steep positional changes, and the varying requirements for paralyzing agents at different stages of the operation. Hence the need to perform many cases before the surgeon and surgical team become proficient. Initial estimates placed the learning curve at 20 cases, but as more complex procedures and disease processes have been addressed, many experienced laparoscopic surgeons consider that ascent of the curve requires closer to 50 cases.[10,14,47] There does seem to be a gradation of difficulty, however, with the skills necessary for procedures such as right hemicolectomy being more rapidly acquired than the skills for more complex procedures.[48,49] The recognition of stepwise approaches to the acquisition of skills may shorten the learning curve.

The COST study required participating surgeons to provide evidence of having completed 20 laparoscopic cases.[6] At the time, many participating surgeons considered this to be reasonably extensive experience. The COST study had an overall conversion rate of 21% (26% in the interim quality-of-life analysis), a rate that many experienced surgeons now would consider unacceptable in their own practices. In the similar CLASICC trial, a prospective randomized controlled trial of laparoscopy for colorectal cancer in the United Kingdom, there was also a requirement for 20 laparoscopic resections for surgeons to participate.[12] Over the course of the study (1996 to 2002), the rate of conversion decreased from 38% to 16%, suggesting that 20 cases are insufficient to ascend the plateau of the learning curve. In the European COLOR (*CO*lon carcinoma *L*aparoscopic or *O*pen *R*eduction) trial,[13] hospital case volumes were related to operative and postoperative outcomes. High-volume (>10 cases/year) hospitals versus low-volume (<5 cases/year) hospitals had a median operative time of 188 minutes versus 241 minutes and conversion rates of 9% versus 24%. High-volume hospitals also were associated with a greater lymph node harvest, decreased complications, and shorter length of stay. Based on results from randomized controlled trials, the learning curve requires more than 20 cases.

Many surgeons may not have adequate annual case volumes to ascend the learning curve within a reasonable time. Among 2434 surgeons sitting for the recertification examination for the American Board of Surgery, most performed fewer than 20 colon resections in 1 year; the mean number was 11.[50] Assuming that half of presenting cases are even amenable to a laparoscopic approach, and reducing the learning curve to 40 rather than 50 cases, it would still require 8 years to ascend the learning curve, making an additional assumption that the learning curve retains the same characteristics despite the paucity of cases. This situation prompts the call for means of shortening the learning curve (e.g., simplified step-by-step approaches or hand-assisted approaches) or careful credentialing procedures for surgeons who perform these operations.

Conversions

Conversion rates depend on surgeon experience and case complexity. The rates of conversion vary in the literature, ranging from 0% to 48%. Most conversion rates fall within the range of 10% to 25% of cases. Although experience reduces the conversion rate, this is counterbalanced by the ability to attempt more complex cases. An early study by Senagore et al. indicated that conversion rates were high initially in the authors' experience; as experience was gained, conversion rates, operative times, and complications decreased.[14] Factors such as obesity, prior abdominal surgery, acuity of inflammation (i.e.,

abscess and fistula formation), tumor bulk or contiguous involvement, and disease location and extent also affect the rate of conversion. Obesity (body mass index >30 kg/m^2) is a relative contraindication for laparoscopic colectomy by inexperienced surgeons, but obesity may not be a contraindication for an experienced surgeon.[51-53] The degree of difficulty may depend not only on experience, but also on the actual procedure (e.g., right colectomy being less affected by obesity than a procedure requiring dissection in the pelvis). In Crohn's disease and diverticulitis, with associated inflammation and a bulky specimen, conversion occurred in 50% of early series.[54,55] More recently, enteric fistulas prompt a reduced conversion rate of 25% to 35%, as surgeons have learned that enteroenteric fistulas may be exteriorized en bloc via the planned extraction incision and may be controlled intracorporeally by stapling.[56-58] Identification of a fistula or abscess preoperatively is not a contraindication to a laparoscopic approach, but should prompt counseling of the patient that the risk of conversion is higher. Perhaps most importantly, conversion to an open resection should not be viewed as a failure by the surgeon or the patient, but as a sign of mature judgment. Patients accept that their safety is more important than the size of the incision if appropriately counseled before their operation. Mature intraoperative decision making allows for an initial laparoscopic assessment of the complexity of the operation and an expeditious decision that an open approach is more appropriate, wasting little time or additional costs. Although initial reports suggested increased complications and even worse oncologic outcomes for patients undergoing conversion, an analysis of the COST trial results has suggested conversion results in equivalent oncologic outcomes to open surgery.[59,60] The goal is to convert before persistent attempts at completing a laparoscopic procedure result in intraoperative complications.

DISEASE-RELATED OUTCOMES AND TECHNICAL POINTS

Colorectal Cancer Outcomes

After the adoption of laparoscopic cholecystectomy, reports of minimally invasive colon resections soon appeared.[61] The phenomenon of wound implants, or recurrence of cancer in the laparoscopic incisions, was reported soon after.[62] With hindsight, it would seem that in the initial attempts to provide patients with the benefits of laparoscopy, standard oncologic principles were not followed, resulting in tumor implants in the incisions. Although a large series presenting the initial experience of the COST study group did not indicate an excessive incidence of implants,[63] the damage was done. The result was essentially a moratorium on laparoscopic colectomy for colon cancer from 1994 to 2004, with the exception of approved trials.[64] The issues that surround laparoscopic resection of colorectal cancer provide an interesting dichotomy.[65] On the one hand, concerns regarding anatomic adequacy of the procedure have acted to slow its acceptance, whereas on the other hand, these same concerns have prompted well-designed randomized prospective trials on a scale rarely seen for the evaluation of surgical procedures. To justify laparoscopic resection of colorectal cancer, oncologic outcomes cannot be compromised. Tumor implants prompted multiple randomized controlled trials[6,12,13,28-31,66,67] and a new field of tumor and immunology research.

Historical Retrospective Data

The authors of the first large-scale report that quantified the incidence of port site recurrences were the surgeons who initiated the COST Study Group. They analyzed their own results from laparoscopic procedures performed for colorectal cancer in 372 patients from 1991 through 1995.[63] With a mean follow-up of 22.6 months, Kaplan-Meier survival curves by tumor TNM stage were similar to those reported for open colectomy by the National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) Program. There were four wound implants, for an overall incidence of 1.08%, or an incidence of 4 of 304 (1.3%) potentially curable patients. Three of the four implants (in patients with Dukes' A and B disease) were amenable to local resection, rendering the patients without evidence of disease. The fourth patient had stage D disease initially.

Historical Prospective Data

In a prospective nonrandomized trial of laparoscopic versus open colectomy for cancer, Franklin et al.[42] analyzed results from 415 patients (191 laparoscopic). Patients with disease stages I through III had median follow-up ranging from 31 to 37 months for the laparoscopic group and 22 to 28 months for the open group. Despite the longer follow-up in the laparoscopic patients, the 13% recurrence rate was less for these patients than for the open group (19%). There were no wound implants in this series.

Lacy et al.[67] reported on 71 patients undergoing surgery for cure, with a mean follow-up of 21.4 months. There were no wound implants in the laparoscopic arm, and the recurrence rate was not statistically different between the two groups. The study was not sufficiently powered to detect differences that would be clinically relevant, however, because there were only 31 patients in the laparoscopic arm. A similar study was reported in which 80 patients with colon or rectal cancer underwent open (38 patients) or laparoscopic (42 patients) resection.[28] All patients underwent diagnostic laparoscopy to exclude conditions that would preclude a laparoscopic procedure and were randomly assigned to laparoscopic or open treatment arms. This differs from standard convention, in which the decision regarding the operative approach is made preoperatively, and outcomes are analyzed on an intent-to-treat basis. Median follow-up was 1.5 years in the laparoscopic group and 1.7 years in the open arm. The laparoscopic group had no wound implants, but two incisional recurrences were noted in the open group, both in the setting of disseminated disease. The

study was underpowered, and the short period of follow-up precluded definitive conclusions regarding safety of the laparoscopic approach in cancer surgery.

Randomized Trials

The results of the first large single-center randomized controlled trial were presented by Lacy et al. in 2002.[5] After a median follow-up of 39 months, there was improved overall cancer-related survival for the laparoscopic arm (see Table 168–1). This benefit seemed to be attributable to improved survival in stage III cancers. Specifically, there was no difference between laparoscopic and open approaches in stage II cancers, but improved survival for the laparoscopic arm in stage III cancers. In this latter group of patients, the outcomes were so good that they were similar to stage II patients. This finding has been criticized because it was not an *a priori* hypothesis, but the result of subset analysis of a small group of patients. It does raise interesting questions, however, regarding the impact of the reduced immunologic insult associated with laparoscopy.

The results of the large multicenter COST study group were published in 2004.[6] Results of 872 patients randomly assigned to the open or the laparoscopic arm of the study revealed no differences in overall survival or disease-free survival (see Table 168–1). This was true for all stages. No benefit of the laparoscopic approach was seen in stage III cancers. Further reassurance regarding oncologic outcomes was provided by the low rate of wound recurrences, with only two wound recurrences in the laparoscopic group and one in the open arm. Actual values for the survival curves are strikingly absent from the published texts of the two aforementioned trials, and the values in Table 168–1 have been extrapolated from the published graphs and have an unknown margin of error dependent on the accuracy of the graph.

The United Kingdom's CLASICC trial[12] and the European COLOR trial[13] have supported the short-term benefits of laparoscopic resection for colon cancer (see Table 168–1). Mature oncologic data are still pending from these two more recently closed trials.

Colorectal Cancer Technical Points

Careful attention to technical detail is considered to be the most important factor in avoiding the complication of wound implants. Technical ability and experience are considered so important that the American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Endoscopic and Gastrointestinal Surgeons (SAGES) have jointly endorsed credentialing recommendations,[68,69] and SAGES has published "Guidelines for Laparoscopic Resection of Curable Colon and Rectal Cancer" (www.sages.org).

General Considerations

Preoperative evaluation includes staging, assessment of comorbidities, and decision regarding the operative approach, whether laparoscopic or open. This decision depends on tumor location (e.g., segmental resections for colon cancer are simpler procedures than procedures requiring dissection in the pelvis), evidence of extensive adhesions (prior surgery does not exclude a laparoscopic approach), and other factors such as obesity, although the distribution of abdominal fat relative to the breadth of the pelvis is more important than the absolute body mass index (i.e., the combination of obesity and the narrow male pelvis is more important than the body mass index alone). Counseling should cover laparoscopic and open approaches and the potential for conversion.

Tumor Localization

The exact site of the cancer must be confirmed, and synchronous tumors must be excluded.[70,71] Early cancers may not be detectable from the serosal surface during a laparoscopic approach, so accurate localization is important to avoid resection of the wrong segment of colon.[72] Colonoscopy is limited by the "sameness" of the endoscopic appearance so that only lesions in the rectum and cecum are accurately localized, with inaccurate localization elsewhere in the colon in 14% of cases.[73]

Several methods are employed to identify the tumor site, including colonoscopic tattooing or placement of metallic clips, barium enema, or intraoperative endoscopy. Clips, although used infrequently, are useful if an immediate abdominal radiograph is taken. Colonoscopic tattooing is helpful if performed correctly.[74,75] India ink or alternative dye must be injected into the submucosa in three or four quadrants around the lesion to avoid the site of tattooing being obscured by the mesentery or attachments to the retroperitoneum. Intraoperative endoscopy is best avoided because of associated bowel distention, although colonoscopy using carbon dioxide may minimize this issue.[76]

Preoperative Staging

Because the liver cannot be palpated intraoperatively during a laparoscopic colon resection, there should be appropriate preoperative liver evaluation, which may use computed tomography (CT), ultrasound, or magnetic resonance imaging. Alternatively, intraoperative laparoscopic ultrasonography offers the ability to evaluate the liver fully at the time of colorectal resection. Preoperative CT or ultrasound was part of the protocol for the COST study, and as stage IV disease was evenly represented in each arm, this suggests preoperative liver imaging was equivalent to intraoperative palpation.[6] For rectal cancer, CT scan of the abdomen and pelvis and transanal rectal ultrasound are routine staging studies anyway.[77,78]

Operative Techniques for the Colon

An appropriate oncologic resection for colon cancer includes proximal and distal resection margins, mesenteric lymph node harvest of at least 12 lymph nodes (although this number is in flux), proximal ligation of the vascular pedicle, and en bloc resection of locally advanced adherent colorectal tumors.[79] The randomized trials followed these principles[5,6,12] and showed

equivalent bowel margins, lymph nodes, and, in the COST study, perpendicular mesenteric length (a surrogate for proximal ligation of the vascular pedicle).[6] These principles, particularly proximal vascular pedicle ligation, determine which steps may be performed intracorporeally or extracorporeally. Division of the origin of the ileocolic pedicle may be performed extracorporeally via a periumbilical incision in a slim patient, but all other pedicles require intracorporeal ligation in the presence of cancer. En bloc resection of a T4 tumor invasive into an adjacent organ may be attempted by an experienced surgeon, but in less experienced hands should prompt an open approach if discovered on preoperative imaging and indicate conversion if found intraoperatively.

Operative Techniques for the Rectum

Published guidelines exist for open rectal cancer surgery.[77,78] These include a distal margin of 1 to 2 cm and mesorectal excision with radial clearance. Laparoscopic resection of rectal cancer has not been evaluated in a multicenter trial except as a subset of patients included in the CLASICC trial.[12] Although prospective nonrandomized[80,81] and retrospective[82,83] case series indicate that laparoscopic rectal resection is possible in selected patients, the CLASICC trial results were concerning for positive radial margins in 16% of patients undergoing laparoscopic resection. Even more concerning, however, regarding the quality of surgical intervention, was the positive margin rate of 14% in the open group. These alarming results have contributed to the call for a randomized trial of laparoscopic techniques for rectal cancer in the United States. Compared with colon cancer, laparoscopic resection for rectal cancer introduces additional technical challenges: tumor factors, such as bulkiness and proximal or distal location, and patient factors, such as width of the pelvis, obesity, a bulky uterus, and obscuration of tissue planes by prior radiation.

Prevention of Wound Implants

Wound implants have occurred at extraction and trocar site incisions,[62,84] and careful technique is considered to keep these at a rate of 1% or less. Basic science studies, rather than clinical practice, have generated most recommendations for avoidance of wound implants. Gasless laparoscopy,[85-88] level of insufflation pressure,[89] and wound excision[90,91] have not shown sufficiently consistent results to recommend changes. Carbon dioxide is associated with increased tumor implantation and growth,[92] but is clinically the safest and most widely used gas. Helium decreases tumor implants[92-94] in contrast to carbon dioxide,[92] but carbon dioxide's safety profile is superior, and it is more widely used. Evacuation of the pneumoperitoneum via the ports rather than via the incision is widely performed,[95] although the significance of aerosolization of tumor cells is unclear.[96,97] Similarly, some surgeons fix the trocars to prevent slippage because gas leakage alongside loose ports ("chimney effect") has been associated with wound implants in experimental models.[98] Irrigation of laparoscopic incisions with a multitude of substances (e.g., povidone-iodine, heparin, methotrexate, cyclophosphamide, taurolidine, and 5-fluorouracil) has decreased incisional recurrences in animal models and is widely used.[88,92,99-104] Protection of the extraction site or extraction of the specimen in a bag is almost universally practiced.[95]

Most important in the prevention of cancer implants is experience and proper oncologic technique. Despite concerns regarding early implant rates of 2% to 21%,[62,84] experienced surgeons report rates of 1% or less,[5,6,63] which is similar to the incidence of incisional recurrence after laparotomy for colorectal cancer.[105] The COST Study Group reported implants in 2 of 435 patients in the laparoscopic arm (0.5%) and in 1 of 428 patients in the open arm (0.2%; $P = .50$).[6] Lacy's study found 1 implant in 111 patients (0.9%).[5]

Oncologic principles must be followed laparoscopically. Box 168–1 (Figs. 168–1 to 168–6) and Box 168–2 (Figs. 168–7 to 168–12) outline oncologically appropriate approaches to right hemicolectomy and anterior resection. The avoidance of direct tumor handling is probably important, and for this reason, we try to avoid handling of the bowel at all, preferring to grasp the cut peritoneal edge to manipulate the bowel. The same proximal vessel ligation and bowel margins must be obtained. We evacuate the pneumoperitoneum through the trocars, rather than removing the trocars and allowing

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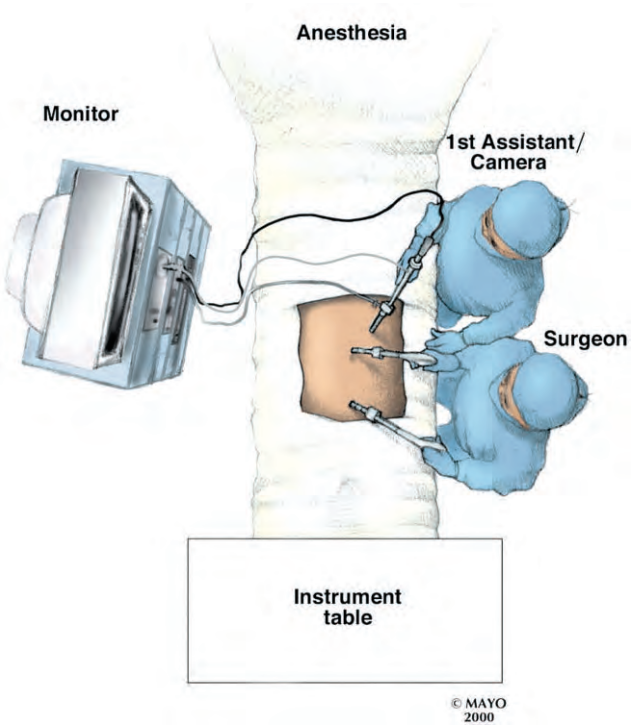

Figure 168–1. Patient and staff positioning and trocar placement for right hemicolectomy. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

Box 168–1 Steps for a Right Colon Resection

1. Equipment: three 35-mm trocars and one 12-mm trocar, 30-degree or flexible scope, endoscopic Babcock clamps, electrocautery scissors, or Harmonic scalpel
2. Positioning: supine or lithotomy, beanbag secured to bed for steep airplaning/Trendelenburg, sequential compression devices
3. Port placement: three trocars (supraumbilical, suprapubic, left upper quadrant), four trocars (anchor shape) (see Fig. 168–1)
4. In Trendelenburg, right side up: retract small bowel out of pelvis to patient's head and to the left
5. Elevate cecum to anterior abdominal wall, and incise peritoneum around base of cecum and medial aspect of small bowel mesentery from pelvic brim to aortic bifurcation (see Fig. 168–2); identify and protect the right ureter; this enters the avascular retroperitoneal plane, which can be followed superiorly to the third portion of the duodenum
6. Retract cecum to the left and incise the right lateral peritoneal reflection to the hepatic flexure (see Fig. 168–3)
7. Divide the hepatocolic attachments from lateral to medial, while placing tension toward the feet on the flexure and transverse colon (see Fig. 168–4)
8. If performing intracorporeal vessel division, the ileocolic pedicle is identified in the right colon mesentery with a mesenteric window on either side; traction is placed upward on the vascular pedicle with a Babcock clamp; the vessels are dissected, clipped, and transected; the right branch of the middle colic artery and the terminal branch of the superior mesenteric artery also can be transected
9. The supraumbilical port site incision is extended around the umbilicus to 4 to 6 cm (see Fig. 168–5); a ring drape or other form of wound protection is used for cancer cases; the terminal ileum and right colon are exteriorized, and resection and anastomosis are performed (see Fig. 168–6)
10. Any 10-mm ports and the periumbilical incision are closed

Modified from Morales Conde S, Fleshman JW: Laparoscopic colon resection. In Cameron JL (ed): Current Surgical Therapy, 6th ed. St Louis, Mosby, 1998, pp 1195-1201.

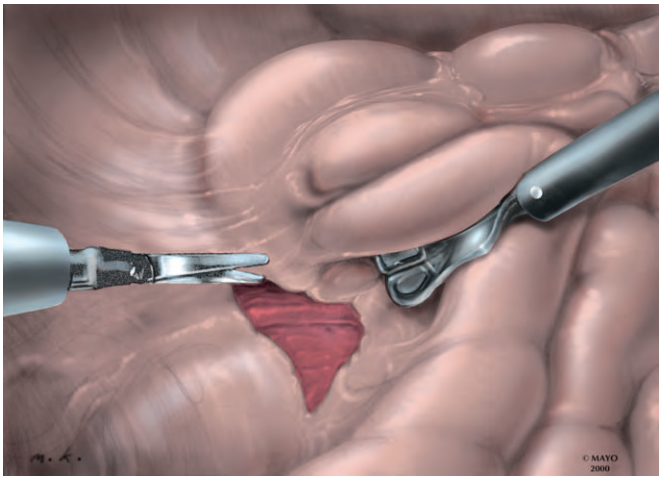

Figure 168–2. Retraction of cecum and terminal ileum cephalad while opening peritoneum in "groove" at base of small bowel mesentery. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

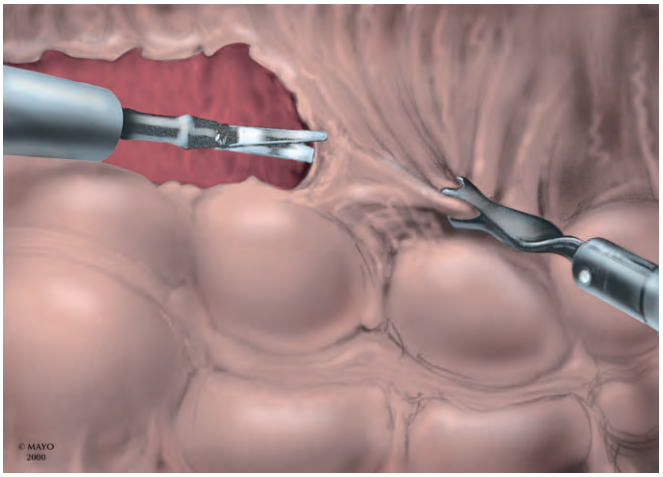

Figure 168–3. Retraction of ascending colon medially and opening of right lateral peritoneal reflection. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

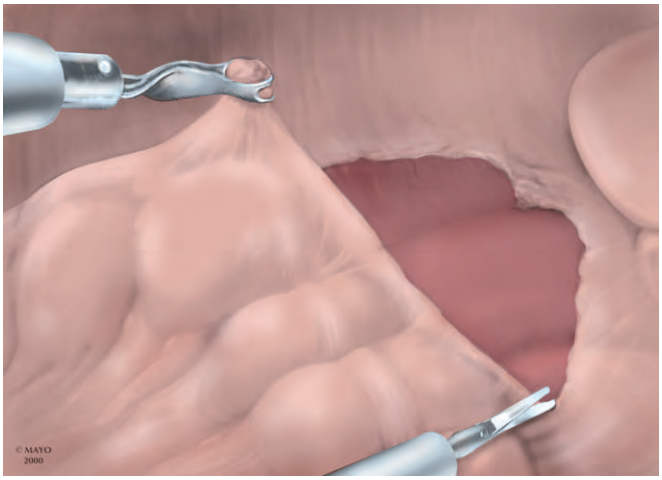

Figure 168–4. Elevation of hepatic flexure obliquely toward feet and anterior abdominal wall to expose correct retroperitoneal plane and the duodenum. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

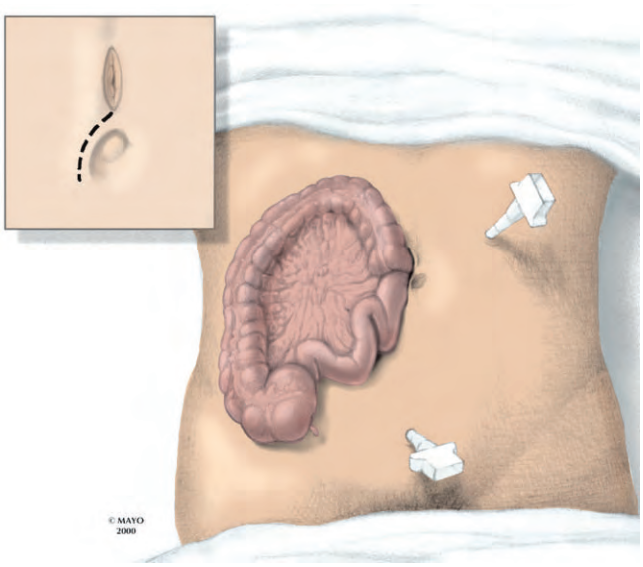

Figure 168–5. Enlargement of supraumbilical port site incision around umbilicus to allow exteriorization of whole right colon from terminal ileum to mid transverse colon. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

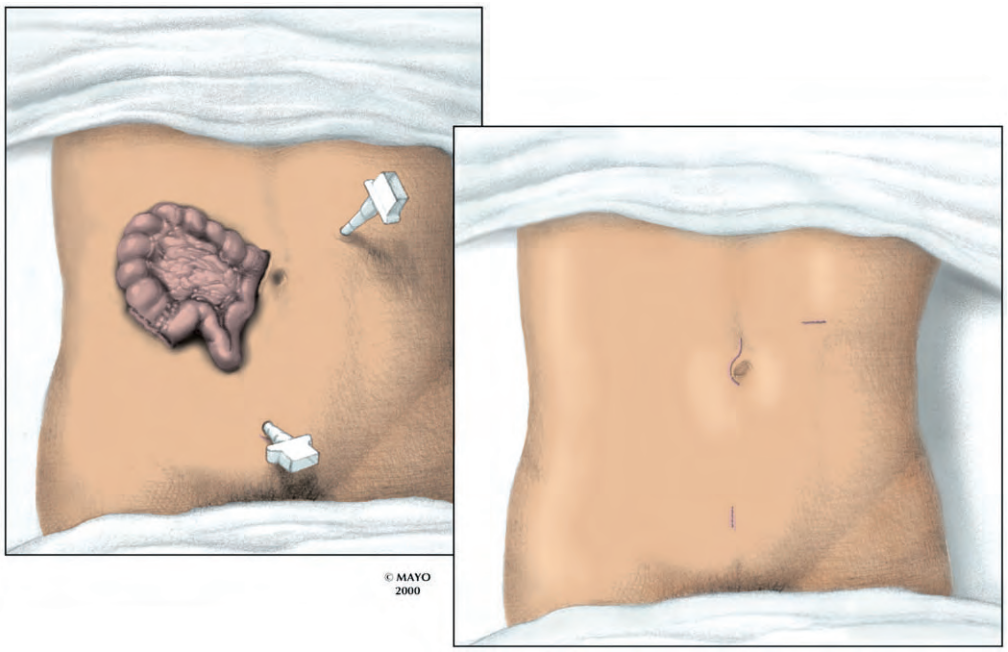

Figure 168–6. Extracorporeal creation of side-to-side stapled anastomosis and return to the abdominal cavity with closure of incisions. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

Box 168–2 Steps for a Low Anterior Resection

1. Equipment: two 12-mm trocars and 25-mm trocars, 30-degree or flexible scope, endoscopic Babcock clamps, electrocautery scissors, or Harmonic scalpel
2. Positioning: lithotomy, beanbag secured to bed for steep airplaning/Trendelenburg, sequential compression devices
3. Port placement: four trocars (anchor shape) (see Fig. 168–7)
4. In Trendelenburg, left side up: retract small bowel out of pelvis to patient's head and to the right. Retract sigmoid to right, divide left lateral peritoneal reflection, and remain in the avascular plane to identify and protect the left ureter; mobilize sigmoid and descending colon in the avascular plane between the left colon mesentery and retroperitoneum all the way from the splenic flexure superiorly to the aortic bifurcation medially
5. In reverse Trendelenburg, free the splenic flexure; for a left colectomy for cancer, the omentum should be removed with the appropriate part of transverse colon, and the splenocolic attachments can be divided and the splenic flexure and omentum swept off the retroperitoneum; for a low anterior resection, if merely mobilization of the flexure is required, the transverse colon is retracted caudally, and the adhesion of the omentum to the colon is divided
6. The plane behind the superior hemorrhoidal artery is entered by pulling up on the sigmoid and scoring the pararectal peritoneum bilaterally, starting from the right side (see Fig. 168–8); the window behind the artery, anterior to the aorta, is developed from the sacral promontory to the inferior mesenteric artery; the left gutter is joined by the dissection from the right
7. A Babcock clamp is placed to lift the sigmoid and left colon; the inferior mesenteric artery is cleared of fat, clipped, and divided; the inferior mesenteric vein is encountered cephalad and divided in similar fashion
8. The rectum is pulled or lifted up toward the pubis, and dissection proceeds in the presacral space (see Fig. 168–9); performing the posterior dissection first places tension on lateral tissues, followed by dissection anteriorly
9. In the case of cancer, intraoperative endoscopy may be required to mark the distal edge; the mesorectum is cleared at the chosen level with clips and scissors or Harmonic scalpel; the rectum may be transected with a laparoscopic linear stapler; articulated staplers assist with stapling low in the pelvis (see Fig. 168–10)
10. The specimen is exteriorized via a 4- to 6-cm periumbilical, suprapubic, or left lower quadrant incision (see Fig. 168–11); the remaining proximal sigmoid mesentery and proximal division of the bowel can be performed extracorporeally; a purse-string suture is placed on the proximal margin, securing the head of a circular stapler
11. The proximal bowel is returned to the abdominal cavity, the incision is closed, and pneumoperitoneum is re-established; the head of the stapler is docked onto the handle inserted via the anus in standard manner (see Fig. 168–12)
12. All port sites are closed with fascial sutures

Modified from Morales Conde S, Fleshman JW: Laparoscopic colon resection. In Cameron JL (ed): Current Surgical Therapy, 6th ed. St Louis, Mosby, 1998, pp 1195-1201.

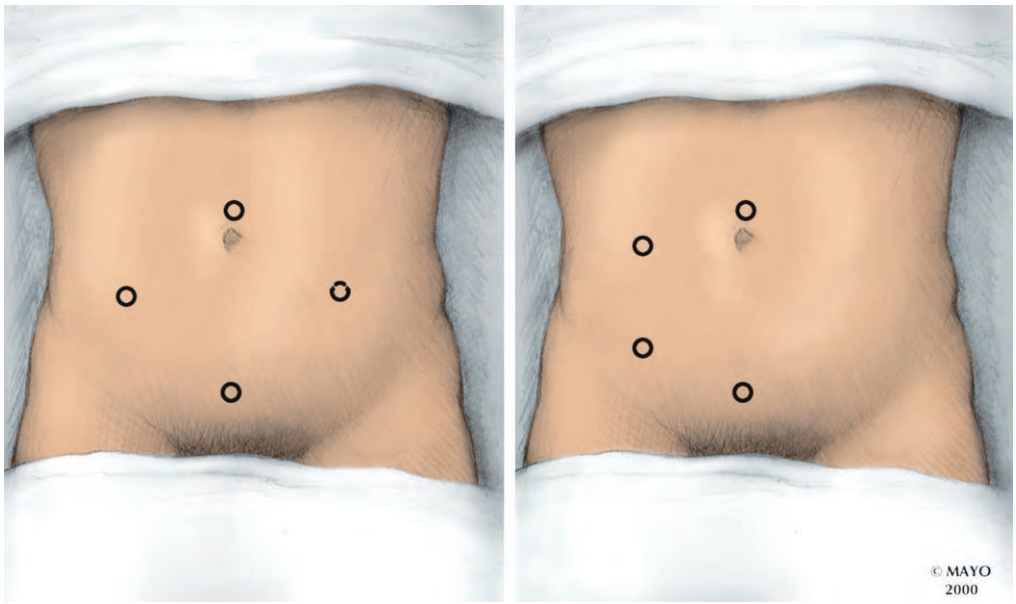

Figure 168–7. Two common patterns of port site placement for low anterior resection. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

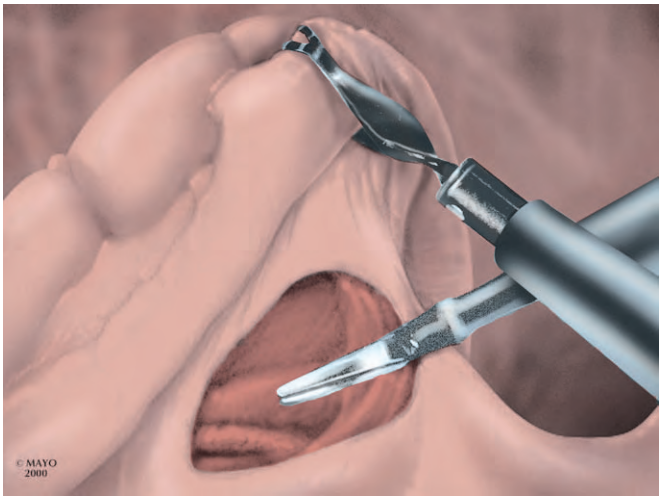

Figure 168–8. Entry into superior portion of presacral space from the right side of the rectum, joining prior dissection from left side. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

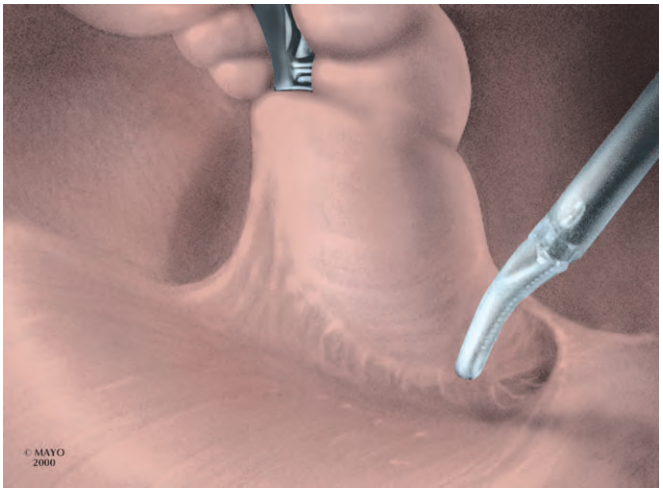

Figure 168–9. Dissection in presacral space with retraction of rectum anterosuperiorly. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

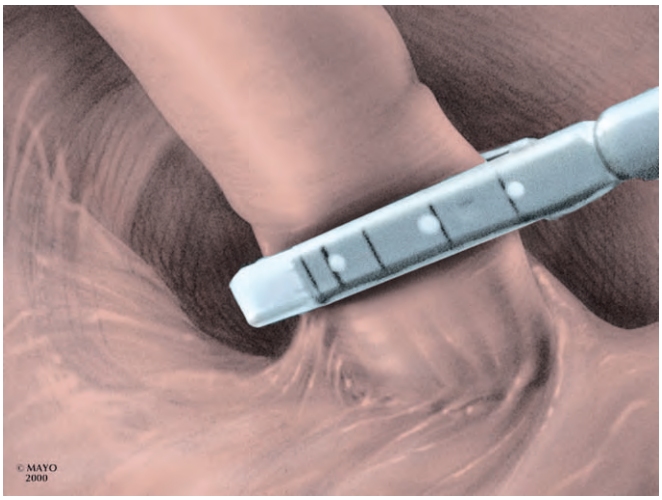

Figure 168–10. Transection of rectum with laparoscopic linear stapler. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

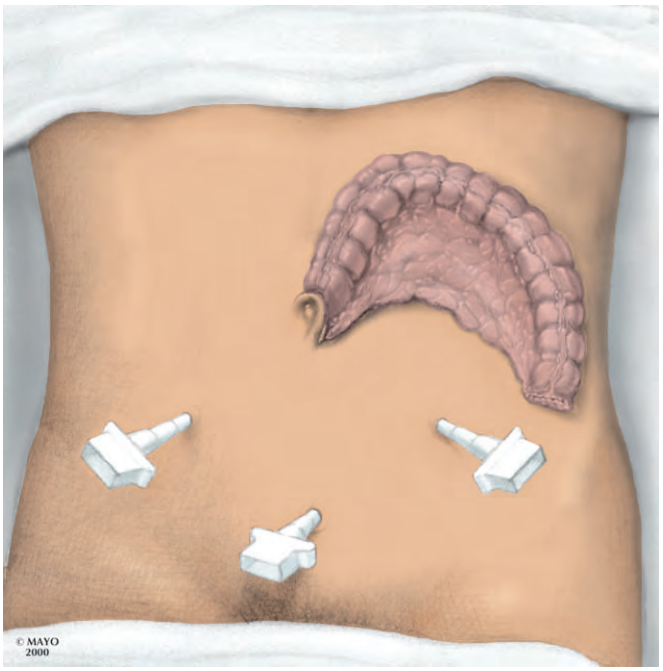

Figure 168–11. Exteriorization of the mobilized/transected sigmoid colon and proximal rectum. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

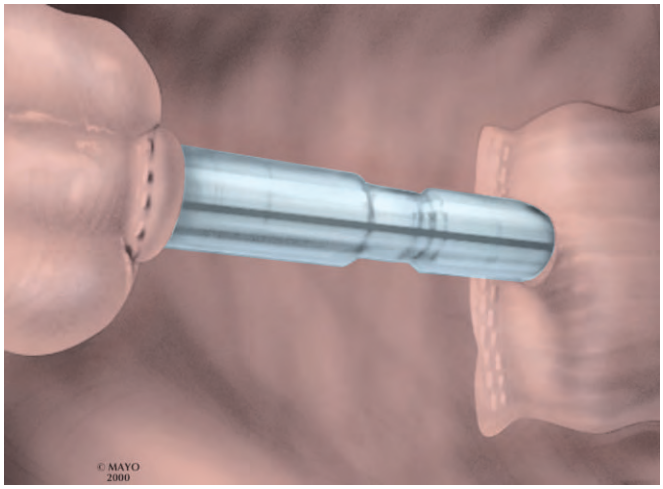

Figure 168–12. Docking of anvil of stapler onto handle. (From Young-Fadok TM, Nelson H: Laparoscopic colectomy. In Baker RJ, Fischer JE [eds]: Mastery of Surgery, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 1581–1588. © Mayo Foundation.)

the gas to escape through the port site incisions. Gauze sponges or sterilized plastic bags are used to protect the extraction incision. The extraction incision and the port site incisions are treated with a dilute solution (1:5 to 1:10) of povidone-iodine.[100,106]

Training and Credentialing in Laparoscopic Colorectal Surgery

Laparoscopic colon and particularly rectal operations are technically challenging operations. Initial reports suggested the learning curve for laparoscopic colectomy was 20 to 50 cases.[10,14,47] The COST study[6] and the CLASICC trial[12] required participating surgeons to have performed 20 cases. An approved statement from ASCRS[68] and endorsed by SAGES[69] specified a minimum experience of 20 cases for benign disease or metastatic disease before attempting laparoscopic resection of curable colorectal cancer. Given the high conversion rates in both studies, there are many surgeons in this field who believe the number may be higher to gain sufficient experience.

Hand-assisted techniques have been promoted as an alternative to straight laparoscopic techniques. Use of the hand in the abdomen during laparoscopy may restore proprioception, particularly for surgeons without extensive prior laparoscopic experience. Because an extraction incision usually is required for specimen retrieval, supporters of this approach believe a hand may be deployed through that incision to assist. Critics note that the incision used for a hand device is often more than twice the size of the incision necessary for a pure laparoscopic approach, and because the devices are expensive they should show savings in operative time for their use to be justified.

Several randomized and nonrandomized studies have evaluated hand-assisted techniques for colectomy. In one case-control series, compared with open colectomy, hand-assisted approaches resulted in longer operative times, but a reduction in hospital stay from 8.3 days to 5.6 days.[107] In a randomized comparison of hand-assisted versus open colectomy, the former resulted in decreased postoperative ileus, shorter length of stay, and smaller incisions with no difference in operative time or complications.[108] Randomized trials comparing hand-assisted with straight laparoscopic techniques found similar functional results with fewer conversions in the former group.[109-111] By allowing surgeons without extensive laparoscopic experience to perform laparoscopic colectomy, it has been suggested that a hand-assisted approach may be more readily learned than a straight laparoscopic approach.[108,112]

Polyps

Outcomes

Occasionally, benign colorectal polyps are not amenable to colonoscopic resection and require surgery for removal. The most widely accepted method is to perform a segmental colonic resection. Such a resection can be achieved with laparoscopic techniques and has been shown to result in less need for narcotics, shorter ileus, and reduced hospital stay.[113,114]

In most patients, segmental colectomy is the preferred approach. In more highly selected cases, laparoscopically assisted colonoscopic polypectomy may be useful for large benign polyps in the thin-walled right colon. This is inappropriate if there is any suspicion that the polyp may harbor carcinoma. Likewise, colotomy and polypectomy with laparoscopic mobilization, which allows extraction through a small port site, are to be condemned because this essentially converts an early-stage carcinoma, if present, to a perforated carcinoma. This approach has been implicated as a cause of some of the early incisional recurrences seen with laparoscopic colectomy.

Technical Points

At the time of endoscopy, a biopsy should be performed to rule out malignancy. The site should be marked with India ink. If the site is not tattooed, another form of localization or intraoperative colonoscopy is often necessary because the site of the polyp may not be apparent from the serosal aspect of the bowel. The latter has the disadvantage of distending the colon, which compromises exposure.

Diverticular Disease

Outcomes

Laparoscopic sigmoid resection is the most common indication for laparoscopic colon resection for benign disease. Laparoscopy may have a role in several different facets of diverticular disease,[115] including diagnosis, control of sepsis, diversion, resection of the affected segment of colon, and restoration of colonic continuity

(as a staged procedure or primarily). Free perforation and fecal peritonitis or extensive purulent peritonitis are absolute contraindications to laparoscopy; complete exploration and clearance of contaminated material are not possible.

Although fibrotic changes are frequently encountered, with experience more complex cases involving abscesses and fistulas have been successfully completed laparoscopically. After early reports showing feasibility,[116-118] further series compared laparoscopic and open techniques (Table 168–2).[41,119-125] Most series describe an operative time of 2 to 3 hours with a conversion rate of 10% to 20%. A large German multi-institutional study of 1545 patients accumulated over 7 years at 52 institutions showed low complication rates and a conversion rate of 6.1%.[125] As experience increased, more complex cases were attempted without altering the morbidity or rate of conversion.

Nearly all series show a shorter period of ileus and shorter length of stay, but longer operative time. Early reports were inconclusive regarding costs, but more recent studies (see Table 168–2) have suggested a cost saving with the laparoscopic approach, at least for uncomplicated cases.

Technical Points

Resolution of the inflammatory component facilitates a successful laparoscopic approach in most patients.[115] The presence of a colovesical, colovaginal, or coloenteric fistula reduces the chances of completing the procedure laparoscopically. Sometimes the bladder side of a colovesical fistula requires nothing more than pinching off the fibrous fistula tract and leaving the bladder decompressed with catheter drainage. Ureteral stents may be helpful. Lighted stents are unnecessary because the firm tubular structure of the stent in the retroperitoneum usually can be detected at laparoscopy, but some surgeons prefer them. It is helpful to approach a mass in the sigmoid colon from cephalad and caudad directions, having identified normal tissue planes away from the phlegmon. A combination of lateral-to-medial and medial-to-lateral techniques also may be helpful. A low threshold for conversion should be maintained, however, to avoid damage to vessels and the ureter. The same extent of resection should be accomplished laparoscopically—proximal resection of the sigmoid back to soft, pliable tissue and distal resection to a point where the taeniae have coalesced, usually requiring resection to a point below the sacral promontory. Limitation of the resection to the part of the sigmoid colon that can be mobilized as a loop through the left lower quadrant, allowing extracorporeal resection and anastomosis, is inadequate; appropriate resection almost always requires intracorporeal division of the bowel and stapled anastomosis.

The treatment of colonic diverticular bleeding by resection of an identified source is relatively straightforward. The difficulty arises from identifying the segment that contains the bleeding. If this is initially identified through colonoscopy, the site of bleeding is tattooed with the injection of 0.1 ml of India ink into the submucosa. This should be performed in at least three positions around the circumference to avoid mesenteric fat from obscuring the site of the tattoo.

Crohn's Disease

Outcomes

Laparoscopic resection for Crohn's disease has been surprisingly successful despite the challenges posed by this disease. These patients are frequently immunosuppressed and are malnourished. In addition, the tissue involved is frequently densely inflamed, thick, and fragile. It is common to see adjacent loops of small bowel adherent to each other, with interloop abscesses and enteroenteric fistulas. Fistulas to other organs or the abdominal wall also may be present.

Given the frequent coexistence of fistula, abscess, or phlegmon, it was thought initially that laparoscopic resection of Crohn's disease would be impossible. The results of several series have suggested, however, that fistulas, abscesses, and prior resection do not preclude a successful laparoscopic approach.[126] One multicenter study had an overall conversion rate of only 16%.[127] In the absence of preoperatively identified fistula, abscess, or phlegmon, the conversion rate was only 4%. Even the incidental finding of an abscess or a fistula or a history of prior surgery resulted in successful completion of the procedure in 75% to 85% of patients. The preoperative presence of a palpable phlegmon increased the conversion rate to approximately 50%.

Significant benefits of laparoscopic resection of Crohn's disease have been documented by several groups. Laparoscopy is the preferred method of resection for isolated ileocolic disease. A case-matched series of laparoscopic versus open ileocolostomy for Crohn's disease showed that mean length of stay was 4.1 days for laparoscopy patients compared with 6.7 days for open procedure patients; the operative times were the same, and laparoscopy resulted in reduced costs.[15]

Early reports of laparoscopic ileocolic resection showed it to be feasible and safe, but were typically small nonrandomized uncontrolled studies. Although most studies are retrospective (Table 168–3),[15,39,40,128-134] most consistently report quicker return of bowel function, earlier tolerance of oral diet, and reduced postoperative pain, which combine to produce a shorter length of stay compared with traditional open procedures. The rate of conversion ranges from 10% to 20% with the proportion of complex cases (abscess, fistula, or reoperative surgery) ranging from 40% to 50%.

In a prospective randomized trial, 60 patients were assigned to conventional or laparoscopic resection, although study design was unconventional because randomization occurred after an initial diagnostic laparoscopy to assess feasibility of a laparoscopic resection.[131] The laparoscopic arm showed benefits in terms of restoration of pulmonary function, morbidity, and length of stay. Oral intake was not started for 3 days to evaluate nutritional parameters and likely obviated any potential differences in length of stay between laparoscopic and open groups (5 days versus 6 days; not significant).

Table 168–2 Laparoscopic Resection for Diverticulitis

Study	Year	No. Patients —Open Versus Laparoscopic	Mortality (%)—Open Versus Laparoscopic	Morbidity (%)—Open Versus Laparoscopic	Convert (%)	OR time (min)* —Open Versus Laparoscopic	Resume diet (days)* —Open Versus Laparoscopic	Flatus/BM (days)* —Open Versus Laparoscopic	LOS (days)* —Open Versus Laparoscopic	Total Costs*— Open Versus Laparoscopic
Liberman[119]	1996	14:14	0:0	14:14	0	182:192	6.1:2.9†	NA	9.2:6.3†	P 13,400:11,500
Bruce[120]	1996	17:25	0:0	23:16	12	115:397†	5.7:3.2†	NA	6.8:4.2†	$7068:$10,230†
Kohler[121]	1998	34:27	0:0	61:15	7	121:165†	5.8:4.1†	5.3:3.7†	14.3:7.9†	DM 8975:7185†
Senagore[41]	2002	71:61	0:1.6	30:8†	7	101:107	NA	NA	6.8:3.1†	$4321:$3458†
Dwivedi[124]	2002	88:66	0:0	24:18	20	143:212†	4.9:2.9†	NA	8.8:4.8†	$14,863:13,953†
Lawrence[122]	2003	215:5600	1.6:1	27:9†	7	140:170†	NA	NA	9.1:4.1†	$25,700:$17,414†
Gonzalez[123]	2004	80:95	4:1	31:19†	NA	156:170	NA	3.7:2.8	12:7†	NA
Schneidbach[125]	2004	—:1545	—:0.4	—:17	6	—:169	NA	NA	NA	NA

*Median or mean values listed.
†Statistically significant difference.
BM, bowel movement; DM, Deutsch marks; LOS, length of stay; NA, not available; OR, operating room; P, pounds.
Modified from Marcello PW, Young-Fadok TM: Laparoscopy. In Fleshman JW, Wolff BG, Beck DE, et al (eds): The ASCRS Textbook of Colon and Rectal Surgery. New York, Springer Science+Business Media, in press.

Table 168–3 Laparoscopic Resection for Crohn's Disease: Ileocolic Resection

Author	Year	No. Patients		Operative Time (min)		LOS (days)		Morbidity (%)	
		LAP	*Open*	*LAP*	*Open*	*LAP*	*Open*	*LAP*	*Open*
Alabaz[128]	2000	26	48	150	90	7	9.6	—	—
Bemelman[129]	2000	30	48	138	104	5.7	10.2	15	10
Young-Fadok[15]	2001	33	33	147	124	4	7	—	—
Schmidt[130]	2001	46	—	207	—	5.7	—	—	—
Milsom[131]	2001	31	29	140	85	5	6	16	28
Evans[132]	2002	84	—	145	—	5.6	—	11	—
Dupree[39]	2002	21	24	75	98	3	5	14	16
Shore[40]	2003	20	20	145	133	4.3	8.2	—	—
Benoist[133]	2003	24	32	179	198	7.7	8.0	20	10
Bergamaschi[134]	2003	39	53	185	105	5.6	11.2	9	10

LAP, laparoscopic; LOS, length of stay.
Modified from Marcello PW, Young-Fadok TM: Laparoscopy. In Fleshman JW, Wolff BG, Beck DE, et al (eds): The ASCRS Textbook of Colon and Rectal Surgery. New York, Springer Science+Business Media, in press.

One concern regarding laparoscopic surgery has been the potential to miss more proximal areas of small bowel disease. This concern was raised by the observation that many laparoscopic surgeons were examining the proximal small bowel by performing an "instrument-over-instrument" inspection, passing the small bowel between two instruments while inspecting it. Tactile feedback regarding subtle lesions was missing. Several longer term studies have shown no excess incidence of recurrent disease in laparoscopic cases. In one series with mean long-term follow-up of 39 months, 32 patients undergoing laparoscopic ileocolic resection were compared with 29 patients undergoing open resection.[135] The incidence of recurrent Crohn's disease was high but similar in both groups (48% laparoscopic, 44% conventional). In another series of 39 laparoscopic and 53 open ileocolic resections with 5-year follow-up, recurrence was detected in 27% versus 29% of patients.[134] A study comparing 63 laparoscopic ileocolic resections with 50 open procedures showed surgical recurrence in 9.5% of the laparoscopic group at a mean follow-up of 63 months versus 24% in the open group at a mean follow-up of 82 months. Median times to recurrence were 60 months and 62 months.[136] An unexpected finding was that the incidence of small bowel obstruction was less in the laparoscopic group (11% versus 35%; $P = .02$), possibly from reduced adhesions.

Isolated ileocolic Crohn's disease is perhaps an ideal model for laparoscopic techniques. For a surgeon with limited experience, an uncomplicated ileocolic resection requires only intracorporeal mobilization, with or without vascular pedicle division, and the resection and anastomosis are performed extracorporeally. Patients are typically young, motivated, Internet-savvy, and interested in techniques that minimize scarring. Also, because many patients undergo reoperation over their lifetime, this may be facilitated by a laparoscopic approach, as this has been associated with a reduced incidence of adhesion formation.

Technical Points

Preoperative evaluation involves a standard small bowel series, CT scan, or both to indicate the extent of small bowel disease. Colonoscopy is used to rule out concomitant colonic disease. If a phlegmon is palpable, conversion rates may increase, but conversion is not inevitable. At the beginning of the procedure, it is helpful to ensure that all of the loops of small bowel can be swept out of the pelvis before further mobilization is started because a loop of terminal ileum stuck in the pelvis would preclude later exteriorization.[137] Mobilization of the entire right colon, even if only the cecum is affected, permits easier exteriorization and facilitates a wide side-to-side stapled anastomosis if that is the surgeon's preference. The use of a small periumbilical incision as the extraction site allows for easy extraction of the mobilized bowel because it overlies the ileocolic pedicle. In addition, use of this incision allowed us to address concerns regarding more proximal disease: The entire small bowel may be exteriorized and palpated exactly as one would in an open case.

Ulcerative Colitis

Outcomes

Laparoscopic resection for ulcerative colitis requires advanced laparoscopic skills. The combination of complexity and unfavorable early reports has likely contributed to slow acceptance of a laparoscopic approach for proctocolectomy and ileal pouch–anal anastomosis. Only retrospective and prospective nonrandomized studies are available, with the largest study describing

Table 168–4 Results of Laparoscopy for Rectal Prolapse

Study	Year	No. Patients	Follow-up (mo)	Procedure	Operative Time (min)—LR/LRR	LOS (days)	Recurrence
Himpens[149]	1999	37	6-48	LR	130	7	0%
Bruch[150]	1999	57	30	LR/LRR	227/257	15	0%
Kessler[151]	1999	32	33	LR/LRR	150	5	FT 6.2%
Kellokumpu[152]	2000	34	24	LR/LRR	150/255	5	7%
Benoist[153]	2001	48	20-47	LR/LRR	—	—	MP 8%
Solomon[154]	2002	20	24	LR	153	3.9	0%
Kairiluoma[155]	2003	53	12	LR/LRR	127/210	5	6%
D'Hoore[156]	2004	42	61	LR	NS	NS	FT 4.8%
Lechaux[157]	2005	48	36	LR/LRR	193	4-7	MP 4.2%
Ashari[158]	2005	117	62	LRR	110-180	5	FT 2.5%; MP 18%

AR, anterior resection; FRM, full rectal mobilization without fixation; FT, full thickness; LR, laparoscopic rectopexy; LRR, laparoscopic resection rectopexy; MP, mucosal prolapse; NS, not specified; PFR, pelvic floor repair; RR, resection rectopexy.
Modified from Marcello PW, Young-Fadok TM: Laparoscopy. In Fleshman JW, Wolff BG, Beck DE, et al (eds): The ASCRS Textbook of Colon and Rectal Surgery. New York, Springer Science+Business Media, in press.

only 59 patients.[138-147] Initial reports in the early 1990s from Cleveland Clinic Florida showed longer operative times and higher blood loss than matched open procedures with no benefits.[138,139] Although the study showed feasibility, which was the stated aim, minimally invasive techniques for total colectomy were discouraged. Next, a series from Marcello et al.[140] continued to report longer operative times, but for the first time a 1-day reduction in length of stay was noted. This prompted continued study of this technique, and subsequent series have shown than laparoscopic proctocolectomy with and without ileal pouch–anal anastomosis is feasible and shows the expected benefits of minimally invasive surgery. Elective and emergent laparoscopic proctocolectomy have been reported. In an attempt to improve operative times that remain considerably longer than for the open approach, hand-assisted techniques have been employed, resulting in a reduction in operative time of approximately 50 minutes (247 minutes versus 300 minutes for hand-assisted versus laparoscopic).[147,148]

Technical Points

After initial reports suggested no benefit compared with open procedures, we re-evaluated the technique described. The authors used seven incisions: five port sites; a separate site for the diverting loop ileostomy; and a transverse suprapubic (Pfannenstiel) incision for completion of the rectal dissection, specimen extraction, and pouch creation.[138] We have attempted to simplify the procedure by using a four-incision technique, including intracorporeal pelvic dissection and transection of the rectum at the pelvic floor. Patients are discharged in 3 to 4 days. Although operative times remain in the 3- to 4-hour range, in patients with optimal body mass index the times have been less than 2.5 hours, and patients with increasing body mass index are now being offered this procedure.

Rectal Prolapse

Outcomes

Countless operations are described for rectal prolapse. In patients in whom an abdominal approach is preferred, laparoscopy permits resection and rectopexy or either component alone. Rectopexy alone has the advantage of not requiring an extraction incision. The application of laparoscopic techniques to transabdominal procedures for rectal prolapse has resulted in expected benefits (Table 168–4).[149-158] Operative times are longer, length of stay is shorter, and there seems to be a relatively low conversion rate of less than 10%. In a well-designed prospective randomized study of 40 patients with full-thickness rectal prolapse, patients were assigned to laparoscopic and open arms.[154] The operative time was longer in the laparoscopic group (153 minutes versus 102 minutes; $P < .01$). The average hospital stay was shorter (3.9 days versus 6.6 days; $P < .01$), and 75% of the laparoscopic group were able to adhere to the goals of a clinical pathway versus only 37% in the open group. A mean cost savings of £357 per patient was subsequently shown in the laparoscopic group.[159] Assessment of the laparoscopic approach is limited by the period of follow-up because a major concern after correction of prolapse is the problem of recurrence. In a large series of 117 patients with a mean follow-up of 62 months, the rate of recurrent full-thickness prolapse was only 2.5%, although there was an 18% rate of mucosal prolapse.[158]

Technical Issues

Mobilization of the rectum for rectal prolapse is an ideal procedure in which to learn the laparoscopic technique of rectal mobilization, which may be applied to other procedures, such as laparoscopic proctocolectomy or total mesorectal excision for rectal cancer. If rectopexy is

performed, intracorporeal suturing may be employed to affix the lateral rectal peritoneum to the sacrum; alternatively, this step has been simplified further by the availability of laparoscopic tacking devices, which are effective at securing the pararectal tissues to the sacral promontory.

Miscellaneous

Laparoscopy has been performed for other, less common benign indications, such as colonic inertia, endometriosis, volvulus, fecal diversion (for anal incontinence or perineal sepsis), and localized perforation arising from trauma or colonoscopic injury. We have found the technique to be particularly useful in patients who require abdominal colectomy and ileorectal anastomosis for colonic inertia because they are frequently slim. In addition, they often have an altered perception of abdominal pain and seem to benefit significantly from the smaller incisions.

SUMMARY

Evidence has accumulated that the laparoscopic approach is an acceptable alternative for many colorectal procedures and may be preferable for selected indications and individuals. For benign diseases, such as polyps, diverticulitis, and Crohn's disease, it is a part of the colorectal surgeon's armamentarium. Many of the initial concerns regarding laparoscopy for colorectal cancer, particularly with regard to trocar site recurrences, have been allayed as experience has accumulated, and the reassuring results from randomized trials have provided the impetus for greater numbers of surgeons to learn and implement these techniques. Just as the procedure is not suitable for every indication or every patient, it also may not be suited to all surgeons. More complex procedures, such as total colectomy for colonic inertia and proctocolectomy and ileal pouch–anal anastomosis, are likely to remain the province of centers with advanced laparoscopic experience.

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Chapter

169

Ostomy Management

Peter Cataldo · Neil H. Hyman

More than 1 million individuals in the United States and Canada live with some type of intestinal stoma. These stomas are typically constructed as one of the last components of a long and challenging surgical procedure. Although created in only a few short minutes, permanent stomas must function for the remainder of the ostomate's lifetime.

The creation of a stoma is a technical exercise. Like most undertakings, if done correctly, the stoma will usually function well with minimal complications for the remainder of the ostomate's life. Conversely, if created poorly, stoma complications are common and can lead to years of misery. Intestinal stomas are in fact enterocutaneous anastomoses, and all the principles that apply to creation of any anastomosis (i.e., using healthy intestine, avoiding ischemia and undue tension) are important in stoma creation.

INDICATIONS

Stomas are created either as a temporary means of fecal diversion when an anastomosis is unsafe or unwise or as permanent orifices for the passage of excrement (stool or urine) when surgical resection prohibits the body's normal orifices from accomplishing these tasks. In this chapter we discuss the creation of ileostomies and colostomies.

Permanent colostomies are nearly always created from the sigmoid or descending colon, usually in association with distal bowel resection. Colostomies proximal to the splenic flexure typically function poorly, are often placed in locations difficult for ostomates to manage, and are at high risk for complications. If a permanent colostomy is contemplated using the transverse or ascending colon, the surgeon should strongly consider resecting the remaining large bowel and creating an end ileostomy. Common indications for a colostomy are listed in Box 169–1.

With the development and general acceptance of the ileal pouch–anal anastomosis, permanent ileostomies are far less common than they were 25 years ago. Nonetheless, permanent ileostomies are often created for inflammatory bowel disease, familial adenomatous polyposis, multiple synchronous colorectal cancers, and a variety of other miscellaneous disorders. Poor anal function, comorbid diseases, or quality of life considerations may make an ileostomy preferable to more complex reconstructive options in selected patients.

Temporary diverting stomas are usually created in association with distal bowel resections when anastomosis is unsafe or to protect a distal anastomosis when operative conditions or comorbidities make proximal diversion of the fecal stream prudent.

Traditionally three types of diverting stomas predominate: end sigmoid colostomy, transverse loop colostomy, and loop ileostomy.

PREOPERATIVE CONSIDERATIONS

Patients undergoing either elective or emergency surgery in which the creation of an abdominal stoma is a possibility should be adequately prepared preoperatively. Emergent surgery dictates a more rapid preparation than elective surgery, but stoma considerations must not be neglected.

Many patients are unsure as to what a colostomy or ileostomy is. A few minutes of preoperative education by the surgeon combined with printed material is helpful. In addition, if available, all patients should meet with an enterostomal therapist (ET). The ET can provide specific information regarding stoma appliances, dietary and clothing alterations, and pouch management. Most important, the ET will help select the appropriate abdominal wall site for the future stoma. Appropriate stoma placement decreases postoperative complications and may improve the ostomate's well-being for years following surgery. Bass et al. showed that preoperative counseling and marking by an ET prior to surgery improve postoperative quality of life.[1]

In addition to meeting with an ET, patients scheduled for stomal surgery often benefit from the opportunity to meet with other ostomates. Prior patients now well adjusted to life with a stoma provide an excellent so-called nonmedical source of information and are often

glad to share their experience with new ostomates. In addition, local chapters of the United Ostomy Association and the Crohn's and Colitis Foundation may be of benefit in this area.

Patients should be marked prior to surgery. An abdominal surgeon should be able to locate and mark stoma sites. In most circumstances, marking is simple, straightforward, and requires only a few minutes. Three abdominal wall landmarks outline the *ostomy triangle* (Fig. 169–1): the anterosuperior iliac spine, the pubic tubercle, and the umbilicus. The stoma should lie within this triangle overlying the rectus muscle, generally at the site of an infraumbilical bulge in the abdominal wall. A site should be located on a flat segment of the abdominal wall 5 cm away from bony prominences, the umbilicus, prior surgical scars, or skin folds. Once the site has been selected and marked, the patient should sit up to ensure that any new skin folds do not interfere with the stoma site. The patient's beltline should be identified and avoided if possible because this decreases postoperative clothing restrictions.

Special circumstances may require additional consideration. In obese individuals, a large pannus may preclude stoma placement below the umbilicus. The pannus is often thicker in this area and may also hide the stoma from the patient's vision, making management difficult. Patients confined to a wheelchair should be marked while in their chair to avoid unanticipated postoperative difficulties. As mentioned, despite these restrictions, the stoma should pass through the rectus abdominal muscle to decrease the complications of parastomal hernia and stomal prolapse. In complex cases, a stoma site can be marked and the stoma appliance left in place for 24 hours to determine the accuracy of preoperative placement.

Box 169–1 Common Indications for Permanent Colostomy

- Rectal cancer
- Radiation proctopathy
- Incontinence
- Refractory anorectal infection
- Ischemia
- Crohn's disease
- Diverticular disease
- Sacral decubitus

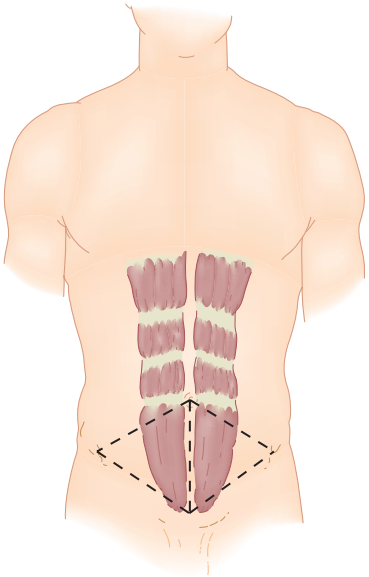

Figure 169–1. The ostomy triangle is defined by the anterior superior iliac spine, the umbilicus, and the pubic tubercle on the right and left sides of the abdominal wall for ileostomy and colostomy placement, respectively.

TYPES OF OSTOMIES

End Ileostomy

End ileostomies are routinely performed in association with either partial or total colorectal resections. Exposure is generally through a midline incision, and the stoma is created after performing the indicated bowel resection. The premarked stoma site (usually in the right lower quadrant) is excised (Fig. 169–2). A skin disk the size of a quarter is removed, sparing all subcutaneous fat,

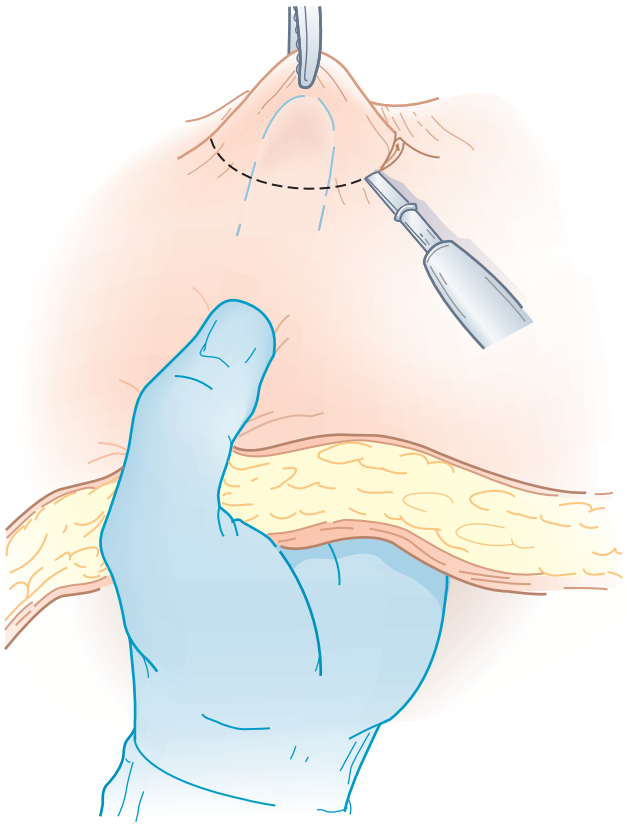

Figure 169–2. A disk of skin is excised at the stoma site.

because this fat is helpful to support the stoma in the postoperative period. The fat is then separated with scissors or cautery to expose the anterior rectus sheath. The sheath is incised vertically with a curved Mayo scissors for 3 to 4 cm (Fig. 169–3). The incision can then be extended in a cruciate fashion laterally for 1 cm if desired. Medial extension should be avoided because this brings the stoma incision in close proximity with the midline incision and may make the midline closure more difficult. The rectus abdominis muscle is split in the direction of its fibers to expose the posterior sheath. With the nondominant hand protecting the underlying viscera, the posterior sheath is bluntly opened with the Mayo scissors and the defect is enlarged to admit two fingers (Fig. 169–4).

After the abdominal wall defect has been created, the ileum is prepared. Any residual retroperitoneal attachments are divided to facilitate passage of the bowel through the abdominal wall without tension. The mesentery may be cleared from the terminal 5 to 6 cm of the ileum. Care is taken to leave a 1-cm strip of mesentery with the ileum because this generally carries a vessel paralleling the ileal wall and prevents stomal ischemia (Fig. 169–5). The ileum is then oriented with the cut mesenteric edge cephalad and passed through the previously created defect in the abdominal wall. The ileum should protrude 5 to 6 cm beyond skin level and appear pink and well perfused. The lateral ileal gutter may be closed if desired to prevent small bowel obstruction secondary to small bowel rotating around the ileostomy. This is done by suturing the free edge of the ileal mesentery (taking care to avoid blood vessels feeding the stoma) to the abdominal wall lateral to the midline incision up to the falciform ligament. There is no need to suture the ileum to the posterior fascia of the abdominal wall because this has not been shown to decrease the risk of prolapse or hernia. The abdominal incision is then closed in routine fashion, including the skin.

The incision is protected to prevent contamination with intestinal contents and the staple line removed from the ileum. Ileostomies must be everted and matured to prevent serositis and skin irritation due to the caustic nature of the ileal effluent. This is accomplished by so-called tripartite sutures containing dermis, the seromuscular layer of the bowel at the fascial level, and full-thickness bites of the cut edge of the ileum (Fig. 169–6). Three or four of these sutures are placed without tying. After all the everting sutures have been placed, they are tied while general traction is placed within the lumen of the ileum by an Allis clamp to facilitate eversion. After the stoma has been everted, the enterocutaneous anastomosis is completed with sutures between the cut edge of the ileum and dermis. The bowel should appear pink and protrude 2 to 3 cm beyond the abdominal skin.

End Colostomy

As previously discussed, left-sided end colostomies are usually created in association with distal colorectal resection. The lateral attachments of the colon are transected

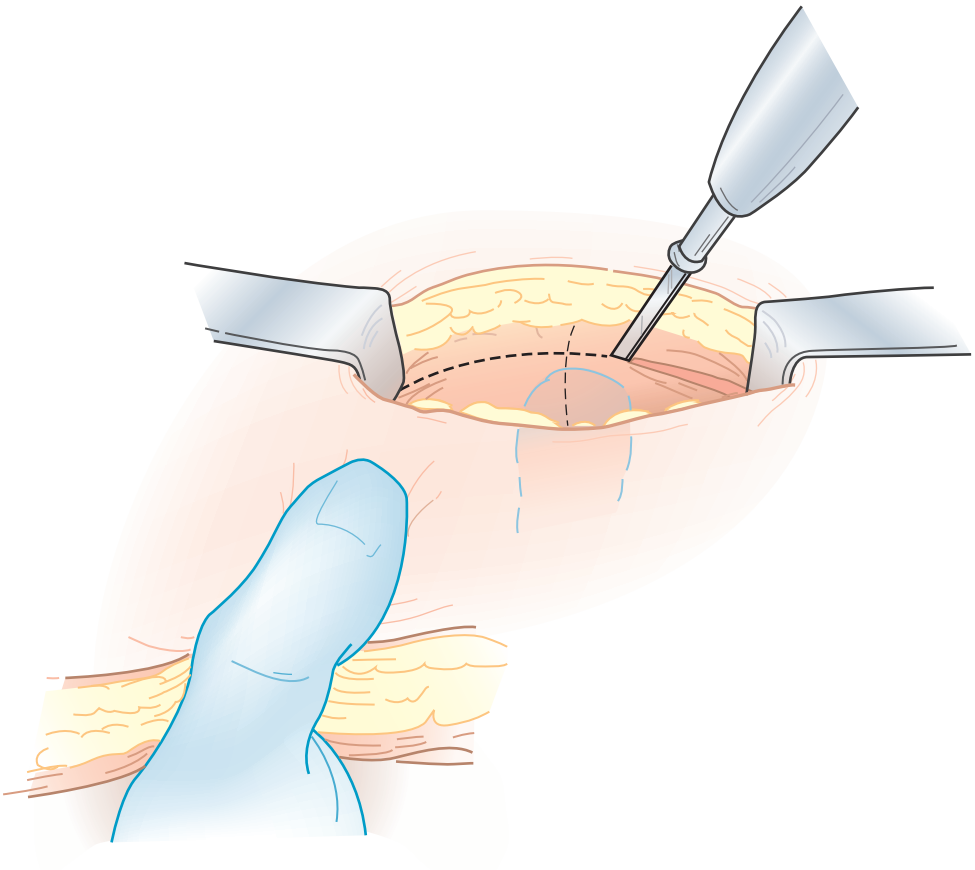

Figure 169–3. The anterior rectus sheath is opened vertically. It may be "T-ed" laterally if desired. Medial extension should be avoided.

along the white line of Toldt until sufficient colon is mobilized to create a colostomy that protrudes from the abdominal wall and can be matured without tension. Once the colon has been sufficiently mobilized, the stoma site is prepared and the abdominal wall defect created similar to that described for end ileostomy. The only differences are that the premarked stoma site is usually in the lower left quadrant and the cutaneous and fascial openings may need to be slightly larger to facilitate unrestricted passage of the colon through the abdominal wall.

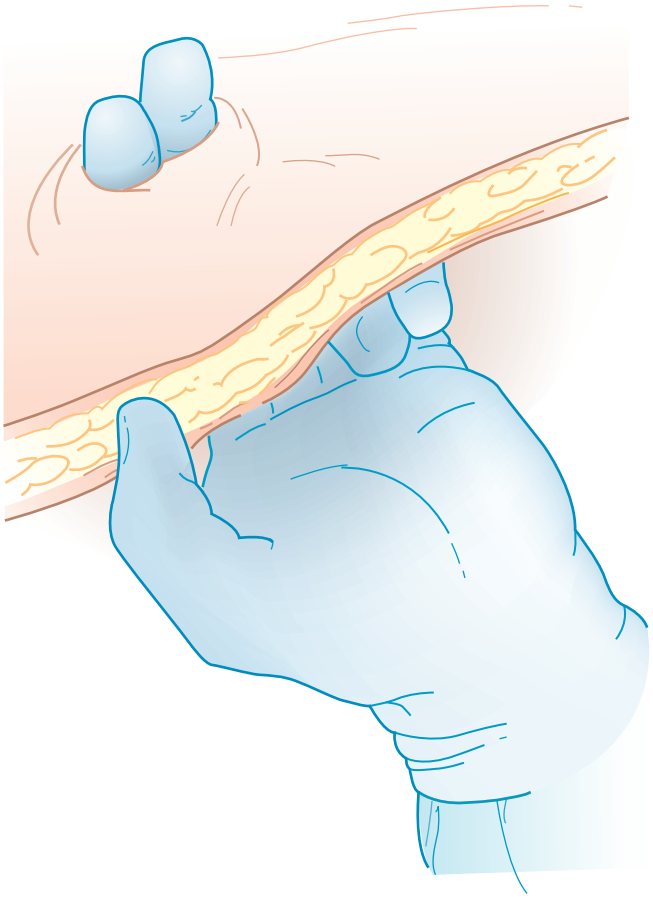

Figure 169–4. The stoma site admits two fingers.

After the trephine site has been successfully created, the colon is oriented without twisting and passed through the abdominal wall. Again, the colon should protrude beyond the abdominal skin and appear well perfused. There is no need to close the lateral gutter or to suture the colon to the posterior abdominal fascia as neither of these maneuvers have been shown to prevent parastomal hernia or prolapse. Alternatively, a retroperitoneal colostomy can be created by tunneling the colon under the posterolateral peritoneum and exiting through the previously created stoma site. This has been associated with decreased rates of parastomal herniation and prolapse but increased technical demands with its creation have limited its utility.

Once the abdominal incision has been closed and protected, the colostomy can be matured. Colostomies may be sutured without eversion because distal colonic contents are not irritating to the surrounding skin.

Diverting Stomas

As previously mentioned, diverting stomas are created to divert the fecal stream away from the downstream intestine. Diverting stomas consist of three types: loop ileostomy, loop colostomy, and end-loop stomas. In the past, the most common loop stoma created was the transverse-loop colostomy, popularized for the treatment of complicated diverticular disease and for protection of distal anastomoses. The transverse-loop colostomy is often a poorly tolerated stoma with high complication rates and therefore has largely been replaced by the loop ileostomy. Additionally, anywhere a loop ileostomy or a loop colostomy is planned, an end-loop ileostomy or end-loop colostomy can be performed at the surgeon's discretion.

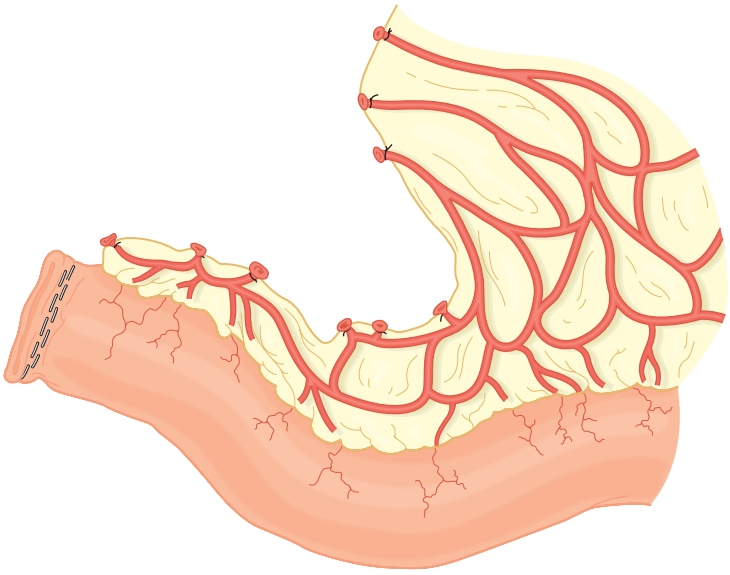

Figure 169–5. The ileum is prepared for ileostomy creation.

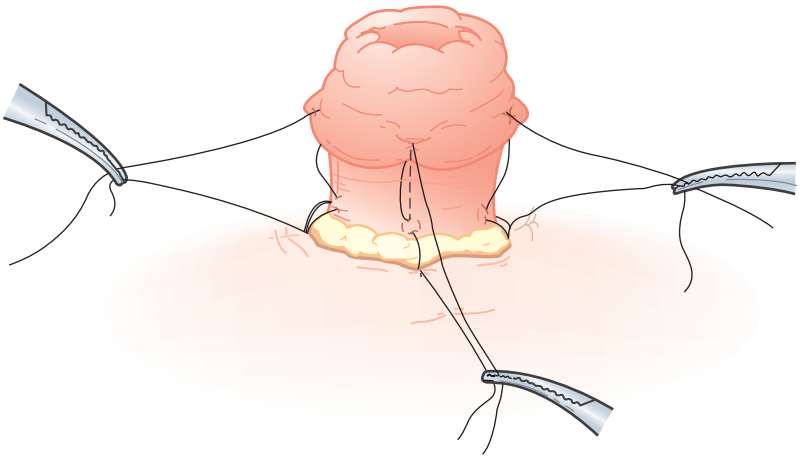

Figure 169–6. Tripartite bites consisting of the dermis, the seromuscular layer of the bowel wall at the fascial level, and full thickness of the cut edge evert the stoma.

Loop Ileostomy

The loop ileostomy is generally created in association with distal bowel resection. After the resection and/or anastomosis have been completed, a segment of terminal ileum is selected. The most distal segment of the terminal ileum that will reach the abdominal wall without tension is selected. This generally corresponds to a segment 20 to 30 cm proximal to the ileocecal valve or from an ileoanal reservoir. The ileum is encircled with a Penrose drain or umbilical tape after its mobility has been ensured.

An abdominal wall defect is created as previously describe for an end ileostomy. The defect may need to be slightly larger to accommodate both loops of bowel that, by necessity, pass through the abdominal wall in a loop stoma. Prior to passing the ileum through the abdominal wall, proper orientation is ensured and the distal end is marked with a suture to prevent maturation of the incorrect segment after the abdominal incision has been closed. The ileal loop is passed through the abdominal wall without twisting and should protrude 4 to 5 cm beyond the abdominal skin. The midline incision is closed appropriately and protected with a cutaneous drape. The distal aspect of the ileum just above the abdominal wall is transected along approximately 80% of its circumference (from mesentery to mesentery). The distal end is then matured with simple sutures between the full-thickness terminal bowel and dermis. These sutures are placed close to one another to reserve most of the stoma site for the functional, proximal stoma.

Once the distal end has been sewn to the abdominal skin, the proximal end is everted. Three tripartite bites are taken between the dermis, the seromuscular layer of the ileum 5 cm proximal to the transected end, and a full-thickness bite of the open end of the ileum. Once the three sutures have been placed, they are tied with gentle traction applied to an Allis clamp within the lumen to facilitate eversion. Maturation is completed with two additional sutures between the dermis and the full thickness of the terminal ileum (Fig. 169–7). The loop stoma should protrude adequately, with its functional end occupying approximately 80% of the trephine circumference. Unless undue tension is present, a support rod is generally not necessary.

Loop Colostomy

A loop sigmoid colostomy may be created to prevent the fecal stream from reaching the rectum and anus in cases of incontinence and severe anorectal infection or for proximal protection after complex anal reconstruction. This stoma is essentially created in identical fashion to that of a loop ileostomy, with the exception that the stoma is commonly placed in the left lower quadrant. Eversion is not strictly necessary due to the noncaustic nature of the effluent from the left colon. However, in many circumstances, an end-loop stoma as described in the following section is easier to create and functions better than the standard-loop colostomy.[2]

End-Loop Stomas

There are three types of end-loop stomas: end-loop ileostomy, end-loop colostomy, and end-loop ileocolostomy. These stomas have three main benefits: (1) they often make stoma management easier in the postoperative period because they appear similar to end stomas; (2) they can be created with remote sections of the intestine such as an end-loop ileotransverse colostomy; and (3) they do not require formal laparotomy for stoma takedown. The end-loop ileostomy and end-loop colostomy can be created in any situation where a standard-loop ileostomy or loop colostomy might be performed. End-loop ileocolostomies can be created in association with intestinal resection. For example, a right colectomy may be performed for right colonic trauma or for right colon ischemia, and an anastomosis is deemed unwise. In this situation, the ileostomy and the transected edge of the proximal transverse colon can be brought through one single stoma site, avoiding the need for a second stoma and laparotomy at the time of stoma takedown.

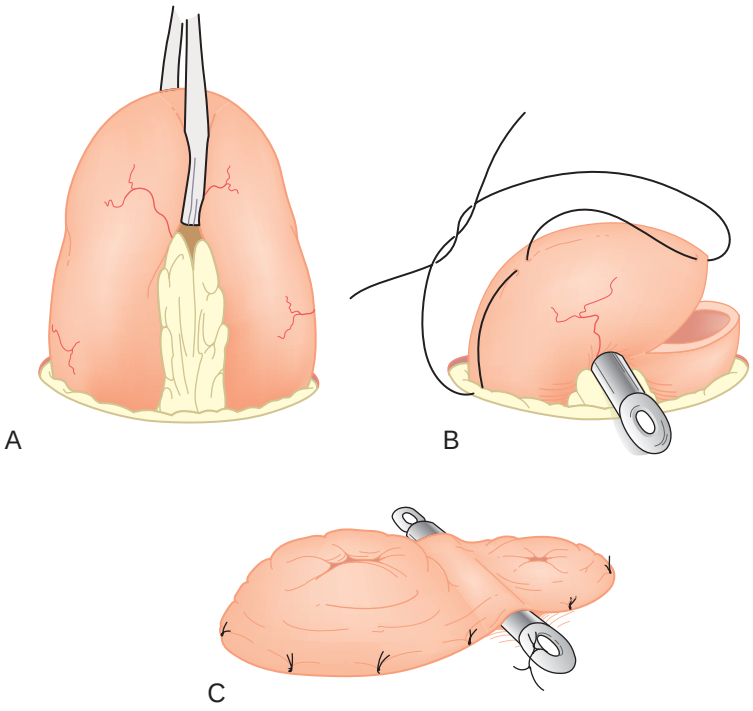

Figure 169–7. **A** to **C,** Creation of a loop ileostomy.

End-Loop Ileostomy

Following intestinal resection and creation of an appropriate abdominal wall defect, the end-loop ileostomy is created as follows: A small defect is created in the mesentery at the preselected ileal stomal site. The bowel is then transected with a linear stapling device. The proximal or functional end of the ileostomy is brought through the abdominal wall as for a standard end ileostomy. The antimesenteric corner of the distal, nonfunctional segment is brought through the same stoma site. The incision is closed appropriately. The antimesenteric corner of the distal staple line is transected and the small opening in the distal bowel is matured to the abdominal wall without eversion. The remainder of the staple line lies buried in the subcutaneous tissue. The proximal bowel is then everted and matured in a similar fashion to any end ileostomy (Fig. 169–8). A single suture between the proximal end ileostomy and the distally matured segment connects the two and completes the maturation. These stomas completely divert the fecal stream and appear almost identical to end ileostomies.

End-Loop Colostomy

The end-loop colostomy is created with a preselected segment of the sigmoid colon. It is mobilized appropriately and passed through the previously created abdominal wall defect similar to that of an end-loop ileostomy. The abdominal incision is closed appropriately. The end colostomy is matured in a similar fashion to that of the end-loop ileostomy. As previously mentioned for loop colostomies, the proximal end may be everted but a flush colostomy may also be created.

End-Loop Ileocolostomy

End-loop ileocolostomy can be performed in association with resection of the right colon when an anastomosis is unsafe. Following resection, the terminal ileum is prepared as for any routine end ileostomy. Often a stoma site will have to be created in the right upper quadrant to facilitate passage of the ileostomy and the distal transverse colon through the same abdominal aperture. Once the stoma site has been created, the terminal ileum is brought through the abdominal wall similar to an end ileostomy. The stapled-off end of the proximal transverse colon is brought through the abdominal wall defect. The mesenteric defect can be closed as with any standard colon resection.

Following this, the abdominal incision is closed in routine fashion. The antimesenteric corner of the transverse colon staple line is then transected and matured without eversion to the abdominal wall stoma site. Cutaneous sutures should be placed in close proximity to save most of the stoma site for the ileostomy. Once this has been completed, the staple line is resected from the terminal ileum and the ileum matured as for a standard end ileostomy (Fig. 169–9). The final suture between transverse colon and the ileum is placed to complete the maturation.

This stoma has the previously mentioned advantages of avoiding a second stoma site for a mucous fistula. In addition, since the terminal ileum and transverse colon

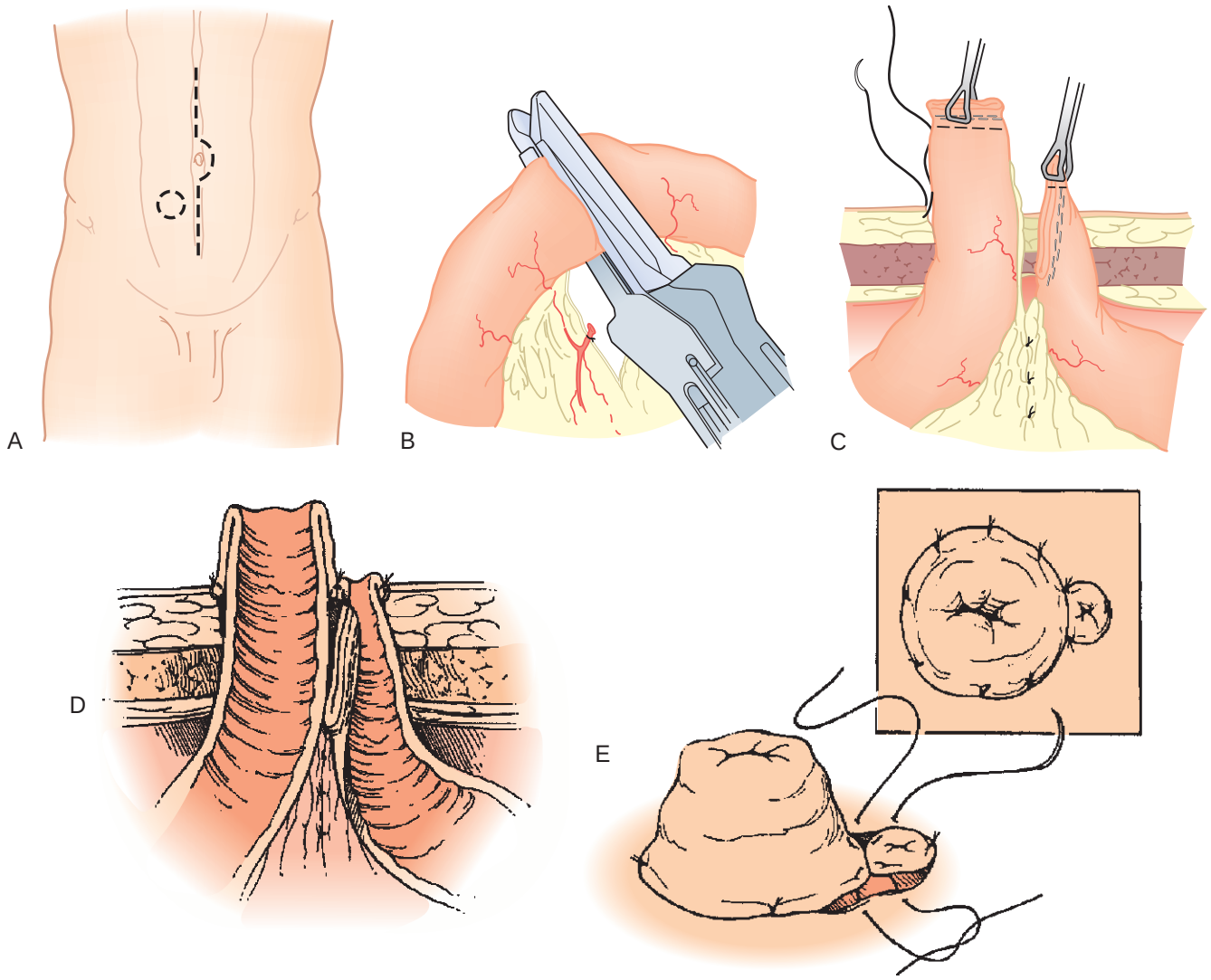

Figure 169–8. **A** to **E,** Creation of an end-loop ileostomy.

are in close approximation through the same stoma site, stoma takedown can be later performed directly through a parastomal incision without the need for a formal laparotomy. This may significantly decrease subsequent morbidity and recovery time after the subsequent stoma takedown.

Enterostomal Therapy

Dedicated ETs' contributions to the long-term quality of life of an ostomate is simply immeasurable. They provide preoperative counseling, early postoperative education, and guidance and act as a long-term resource for individuals with stomas. They supply information on appliance choices and local support groups such as the United Ostomy Association and the Crohn's and Colitis Foundation; suggest dietary or clothing modifications that may alleviate stoma-related problems; and aid in the management of skin problems, parastomal hernias, prolapse, and other complications. In most situations, an ET or surgical nurse will detail postoperative education for a new ostomate. However, if this support is unavailable, it is the surgeon's responsibility to ensure the patient is educated in appliance management.

The appliance must be emptied frequently enough to avoid overfilling and dislodgement of the pouch. This is determined by the location of the stoma and the patient's natural bowel pattern. Ileostomies are usually emptied four to six times per day, with colostomies emptied once or twice per day or even once every other day. The entire appliance only needs to be changed every 4 to 7 days. The exact details vary from individual to individual, but a common technique for changing a typical one-piece system is included in Box 169–2.

Appliances should generally be changed when the stoma is least active, which is often after a period of fasting. The time varies from individual to individual, but

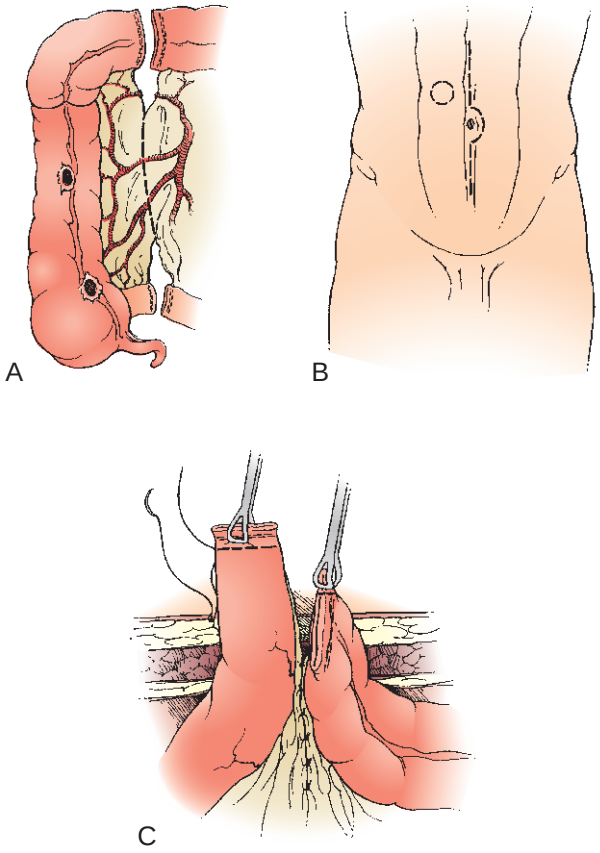

Figure 169–9 **A** to **C,** Creation of an end-loop ileocolostomy.

changing the appliance when the stoma is less active avoids the need to control fresh output during the procedure.

The noise and odor of gas emitted from a stoma are a major concern to most ostomates. Anything that causes gas before creation of the stoma is likely to create gas following its construction. Gas comes from two sources: swallowed air and bacterial breakdown of ingested foodstuffs, particularly carbohydrates. The amount of swallowed air can be minimized by avoiding the use of straws, excessive talking while eating, chewing gum, and smoking. Each individual can best identify which foods lead to gas production, but beans, broccoli, onions, brussel sprouts, beer, and dairy products in lactose-deficient individuals are common culprits. Avoiding these foods is a personal choice but will decrease the quantity and odor of stomal flatus. Yogurt, parsley, and orange juice have been associated with decreased odor. Odor-proof pouches, charcoal filters, and pouch deodorants (e.g., commercial deodorants, mouthwash, and perineal deodorants) may also help. Orally ingested deodorants are also available and include bismuth subgallate and chlorophyllin complex. However, the most important key to preventing odor is good peristomal hygiene and creating a leak-proof seal at the time of appliance change.

A period of adjustment occurs in all ostomates, but attention to detail at the time of appliance change

Box 169–2 Stoma Care

1. Gather all supplies.
2. Gently remove the soiled pouch by pushing down on the skin while lifting up on the pouch. Discard the soiled pouch in an odor-proof plastic bag. *Save the tail closure.*
3. Clean the stoma and peristomal skin with water; pat dry. *If indicated,* shave or clip peristomal hair.
4. Use a stoma-measuring guide or established pattern to determine the size of the stoma. *Pre-sized pouch:* Check to be sure the pouch opening is the correct size. Order new supplies if indicated. *Cut-to-fit pouch:* Trace a correctly sized pattern onto the back of the barrier or pouch surface and cut the stomal opening to match the pattern. Once stomal shrinkage is complete, this step may be omitted and preparation of the clean pouch may be completed before the soiled pouch is removed.
5. Apply skin barrier paste around the stoma. (*Tip:* wet finger to facilitate paste application.) An alternative approach is to apply skin barrier paste to the aperture in the prepared pouch or barrier. Allow paste to dry. *Optional:* Apply skin sealant to skin that will be covered by tape. Allow to dry.
6. Remove paper backing from the pouch or barrier to expose adhesive surface; center the pouch opening over stoma and press into place. Attach closure. *Optional:* Apply tape strips to "picture frame" the pouch-skin junction.

From Erwin-Toth P, Doughty DB: Principles and procedures of stomal management. In Hampton BG, Bryant RA (eds): Ostomies and Continent Diversions. St. Louis, Mosby-Year Book, 1992, p 59.

combined with minor dietary and clothing modifications should make a stoma completely unnoticeable to all except the ostomate's closest acquaintances. In addition, abdominal stomas should not preclude participation in almost any physical activity.

COMPLICATIONS

Despite modest advances in surgical technique and enterostomal therapy, complications after stoma creation remain extremely common. The rate of stoma-specific complications in the literature varies quite widely, ranging from 10% to 70% depending on the methodology of the study, the length of follow-up, and the definition of a complication.[3-7] For example, virtually all ostomates have at least transient episodes of minor peristomal irritation, and skin irritation is often the most commonly reported stoma complication. Studies only reporting problems that require revisional surgery obviously indicate a much lower rate of complications. As such, the relative incidence and frequency of the specific complications varies substantially from series to series.

Stoma-related complications may be classified as those that occur early (within 1 month of surgery) or late (>1 month postoperatively). The most common early complications are peristomal skin irritation, leakage, high output, and ischemia. The most commonly reported late complications include parastomal hernia, prolapse, obstruction, and stenosis.

Incidence

There are no universally accepted criteria for what constitutes a complication. As such, adverse events associated with stoma creation may be quite mild, such as transient skin irritation or leakage, or require major revisional surgery as may be the case for parastomal hernia or necrosis. In a 20-year retrospective review of 1616 patients in the Cook County Hospital database, Park et al. reported a 34% incidence of complications, 28% being early and 6% classified as late.[3] The most common early complications were skin irritation (12%), pain associated with poor stoma location (7%), and partial necrosis (5%), and the most common late complications were also skin irritation (6%), prolapse (2%), and stenosis (2%). Of note, complications varied greatly by service with ostomies created by general surgeons associated with a 47% complication rate, whereas the complication rate for colorectal surgeons was 32%. Duchesne et al. retrospectively reviewed 164 ostomates cared for at Charity Hospital in New Orleans.[4] The overall complication rate was 25%; 38% of the complications were early; and 62% were late. As is typically the case, ileostomies were associated with a higher complication rate than colostomies. The most common complications were necrosis (22%), prolapse (22%), skin irritation (17%), and stenosis (17%). Risk factors for complications included inflammatory bowel disease, ischemic colitis, and increased body-mass index. As others have observed,[5] obesity markedly increased the risk of skin irritation. Of particular note was the sixfold decrease in stoma complications when an ET was involved in the patient's care.

Saghir et al. retrospectively reviewed 121 stoma patients and reported a 67.5% complication rate, 41% of which were considered minor, and 26% were considered major.[6] Nine of the patients (7%) required revisional surgery. Complications were associated with older age, increased medical comorbidities, and an ostomy created by other than a colorectal surgeon.

Life table analyses have been performed both for patients undergoing ileostomies[8] and colostomies.[9] The cumulative probability of a complication after creation of an end ileostomy in 150 patients was 68% at 20 years. There was a 34% cumulative risk of skin problems that tended to diminish over time. Twenty-three percent of patients developed a bowel obstruction. Of note, in this series, patients undergoing an ileostomy for ulcerative colitis had a higher risk of complications than those undergoing an ileostomy for Crohn's disease. Most other studies find the opposite to be true. The actuarial risk of a colostomy complication was 58.1% at 13 years.[9] The cumulative probability of revisional surgery was 17% at 11 years. The most common complications were hernia (36.7%), obstruction (13.7%), prolapse (12%), and stenosis (7%).

Both patient-specific and technical factors contribute to stoma complications. Preoperative consultation with an ET, or at least preoperative stoma marking, reduces the incidence of stoma-related complications.[1]

Skin Irritation and Leakage

Skin irritation is common among patients with a stoma. In a review of 610 patients, it was by far the most common early local complication.[5] The problem is far more commonly seen in patients with an ileostomy owing to the liquid, caustic effluent.[10] This highlights the need for proper technique when an ileostomy is created. Nugent et al. described the results of a study using quality-of-life questionnaires in 391 ostomates.[11] Fifty-one percent reported problems with a rash, and 36% had experienced leakage, both of which were much more commonly seen with ileostomies than colostomies. Thirty percent of patients with a colostomy and 55% with an ileostomy had experienced a reaction to the adhesive. However, only 8% of ostomates reported a substantial degree of difficulty associated with skin irritation.

Although a minor degree of skin irritation on occasion is probably inevitable, most significant cases of skin irritation are potentially preventable. Preoperative marking by an ET can help ensure proper siting and a secure fit. Appropriate location and careful appliance fitting minimize the noxious, irritating effect that can be associated with leakage or unprotected peristomal skin (Fig. 169–10). Patients also need to be monitored for allergic reactions to the components of the appliance.

Particular attention must be paid to older patients who may have limitations in eyesight or dexterity. Patients with a high-output stoma are at particular risk for skin irritation and ulceration if they do not have an appropriately fitted appliance. Obesity has been frequently reported to be associated with an increased risk

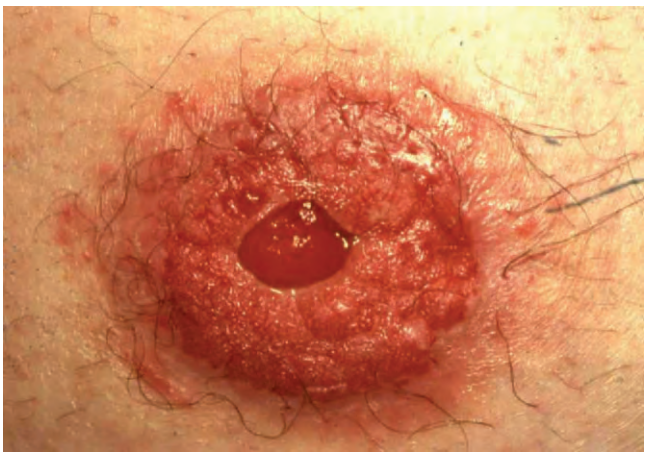

Figure 169–10. Skin irritation around the stoma site from a poorly fitting appliance.

of skin irritation, likely owing to technical problems with stoma construction.[12] Consideration should be given to placing the stoma in the upper abdomen where there is typically much less subcutaneous fat and the patient can see it much more readily.

The patient should be instructed to avoid creams or ointments that may interfere with the adherence of their appliance. In the postoperative period, a stoma tends to become less edematous and the abdomen becomes less distended. As such, it is quite common to need to downsize the appliance at the first postoperative visit to minimize exposed skin. Changing a stoma too frequently may lead to excessive wear and tear on the parastomal skin; on the other hand, too long an interval between changing the appliance may be associated with erosion of the protective barrier.

Even with the help of an excellent ET, specific skin infections may occur. Fungal overgrowth is evident when there is a bright red rash around the stoma with associated satellite lesions. This is typically easily treated by dusting the parastomal skin with an appropriate antifungal powder. If the dermatitis conforms precisely to the outline of the stoma appliance, then an allergic reaction to the wafer or other component of the appliance is likely the culprit. Peristomal skin irritation may also be associated with reactivation of inflammatory bowel disease.

Fortunately, most cases of skin irritation and leakage are readily managed by conservative means. However, a redundant pannus, surgical scars or creases with poor stoma siting may result in the need for revisional surgery. Stoma resiting or combined abdominal wall recontouring and stoma revision may be necessary.[13]

High-Output Stomas

For obvious reasons, a high-output state is typically described in association with an ileostomy rather than a colostomy. Marked diarrhea and dehydration occur in 5% to 20% of ileostomy patients, with the greatest risk occurring in the early postoperative period. An ileostomy usually functions by the third or fourth postoperative day.[14] The output typically peaks on the fourth postoperative day, with an output of up to 3.2 L reported. Since the ostomy effluent is rich in sodium, hyponatremia can be a problem. The particular window of vulnerability for dehydration appears to be between the third and eighth postoperative day. In time, the small bowel typically adapts with mucosal hyperplasia and there is a steady decrease in ostomy output. However, patients with an ileostomy, particularly those who have had concomitant small bowel resection, are at risk to become dehydrated. Most often, this is easily managed by oral rehydration with one of the commonly available sports drinks. However, patients who have lost considerable absorptive surface owing to previous bowel resection and/or those with recurrent/residual Crohn's disease are at particular risk. In addition to the loss of absorptive surface area, ileal resection also removes the fat or complex carbohydrate stimulation of the so-called ileal brake that slows gastric emptying and small bowel transit.[15] Fluid and electrolyte maintenance in these patients may require a period of parenteral hydration and nutrition.

Ileostomy diarrhea may be treated in its milder forms with fiber supplements or cholestyramine, which can thicken secretions. Histamine H_2 receptor antagonists or proton pump inhibitors are often useful in reducing gastric fluid secretion, especially in the first 6 months after surgery when hypergastrinemia is most severe.[16] Often, antimotility agents (e.g., loperamide or diphenoxylate) or opiates (e.g., codeine or tincture of opium) may be required to slow intestinal transit. In refractory cases, somatostatin analogue has been used with some success. Somatostatin reduces salt and water excretion and slows gastrointestinal tract motility. However, its clinical usage has met with variable results.[17,18] Special mention is made of patients with a high-output ostomy required to treat complications of an anastomotic leak. Good results have been reported with exteriorizing the leak and reinfusing the ostomy effluent into the downstream limb until gastrointestinal continuity can be restored. This has led to weaning parenteral nutrition in a substantial number of patients.[19]

A related problem in patients with an ileostomy is the development of urinary stones. The obligatory loss of fecal water, sodium, and bicarbonate reduces urinary pH and volume.[20] Whereas approximately 4% of the general population develop urinary stones, the incidence in patients with an ileostomy is approximately twice that. Whereas uric acid stones comprise less than 10% of the calculi in the general population, they comprise 60% of stones in ileostomy patients. There is also an increase in the incidence of calcium oxalate stones.[21]

Bowel Obstruction

Life table analyses suggest that bowel obstruction is a rather common complication of ostomy creation. Twenty-three percent of patients with an ileostomy ultimately develop bowel obstruction.[8] Adhesions are probably the most common cause, but small bowel volvulus or internal hernia may be the culprit. Although it is frequently mentioned that suture of the mesentery to the lateral abdominal wall may prevent volvulus or obstruction, retrospective analyses have not shown any benefit to this maneuver.[8,9] Treatment is not dissimilar to other patients presenting with a mechanical small bowel obstruction.

However, special note must be made of food bolus obstruction. Many patients with an ileostomy develop signs and symptoms of bowel obstruction owing to the accumulation of poorly digested food stuffs (e.g., popcorn, peanuts, fresh fruits and vegetables). A careful history may reveal dietary indiscretions. Further, the possibility of a food bolus obstruction should be considered in any patient with an ileostomy who has radiologic evidence of a distal obstruction. A red rubber catheter may be inserted gently into the ostomy and saline irrigation initiated. If suspicious concretions begin to pass into the stoma, the irrigations may be carefully repeated until the obstruction is relieved.

Ischemia

Edema and venous congestion are common after stoma creation owing to mechanical trauma and compression of the small mesenteric venules as they traverse the abdominal wall. This is typically self-limiting and requires no treatment. However, ischemia may be related to tension on the mesentery or excessive mesenteric division, particularly in obese patients or those undergoing emergency surgery. A common error is dividing the sigmoidal vessels to obtain the length to allow a colostomy to reach the skin. In these cases, the inferior mesenteric vessels should instead be divided proximally and/or the splenic flexure mobilized, preserving the sigmoid arcades.

If ischemia becomes apparent, a glass test tube or flexible endoscope may be inserted into the stoma. If the stoma is viable at fascial level, then the patient may be carefully observed. However, if there is question about the viability of the stoma at fascial level, immediate laparotomy and stoma revision are required. Early ischemia is seen in 1% to 10% of colostomies and 1% to 5% of ileostomies.[22]

Parastomal Hernia

Parastomal hernia is probably the most common stoma complication requiring operative intervention (Fig. 169–11). A parastomal hernia develops in 1.8% to 28.3% of patients with an end ileostomy and 4% to 48.1% with an end colostomy.[23] The occurrence of these hernias increases with time[24]; as such, the reported incidence depends greatly on the length of follow-up. Most patients with a parastomal hernia can be managed expectantly or with a belted appliance; however, patients with pain, obstruction, or difficulty maintaining an appliance generally require surgical repair.

Patient-specific factors such as obesity, advanced age, and chronic obstructive pulmonary disease appear to increase the risk of parastomal herniation.[25] From the technical standpoint, making the smallest possible opening in the abdominal wall without making the stoma ischemic seems prudent. However, many of the other preventive measures such as lateral space closure, fascial fixation, or stoma placement through the rectus muscle appear to have no effect on the incidence of these hernias. A recent randomized trial suggested that using prosthetic mesh prophylactically markedly reduces the risk of parastomal herniation.[26]

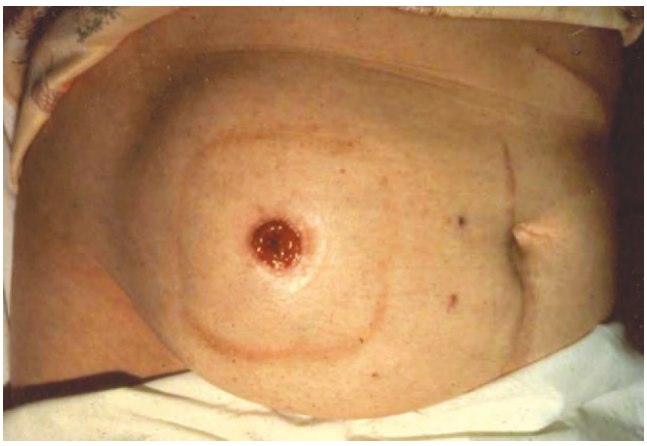

Figure 169–11. Large parastomal hernia.

Unfortunately, the results of surgical correction have historically been poor. In one of the largest reported series, 63% of patients developed a recurrent hernia and 63% had at least one complication.[27] The most commonly described techniques are direct repair, stoma relocation, and mesh repair. The recurrence rate with mesh repairs (0% to 33%) clearly appears to be lower than that of direct repair (46% to 100%), or stoma relocation (0% to 76.2%).[23,28-30]

A wide of variety of mesh repairs have been used without strong evidence to prefer one technique over another. The intraperitoneal mesh repair, championed by Sugarbaker, has been associated with encouraging results, but reported series are typically small and follow-up rather short.[31,32] One benefit of the intraperitoneal technique is that a concomitant incisional hernia may be repaired at the same time. More recently, laparoscopic approaches have been successfully utilized for intraperitoneal mesh placement.[33,34] Concerns have been expressed about the long-term risk of mesh erosion.

Mesh may also be placed using an extraperitoneal fascial on-lay technique.[35,36] A curvilinear lateral incision is made outside the outline of the stoma wafer. The hernia sack is entered and omentum and bowel are reduced. An on-lay mesh is secured to the fascial defect. The advantage of this technique is that it avoids a major laparotomy; possible disadvantages include the risk of contamination by stomal contents and the inability to repair an associated incisional hernia.

Stenosis

Stoma stenosis may result from ischemia, excessive tension, retraction, or recurrent inflammatory bowel disease. The reported incidence is typically less than 10%.[9] Mild asymptomatic stenoses do not require any treatment. Skin level stenoses are readily treated with local procedures such as a Z-plasty, whereas those associated with Crohn's disease usually require formal bowel resection.

Prolapse

The risk of stoma prolapse has been reported to be 11.8% at 13 years.[9] Transverse-loop colostomies are especially notorious for prolapse (Fig. 169–12); the efferent limb is virtually always the offending cause. Although somewhat controversial,[37-39] this is a primary reason why loop ileostomy is commonly preferred to loop colostomy for temporary fecal diversion.[40-42] Although often advocated, mesenteric fixation or lateral space closure does not appear to reduce the incidence of stoma prolapse.

Although the prolapse is often unsettling to the patient or health care providers, asymptomatic prolapse

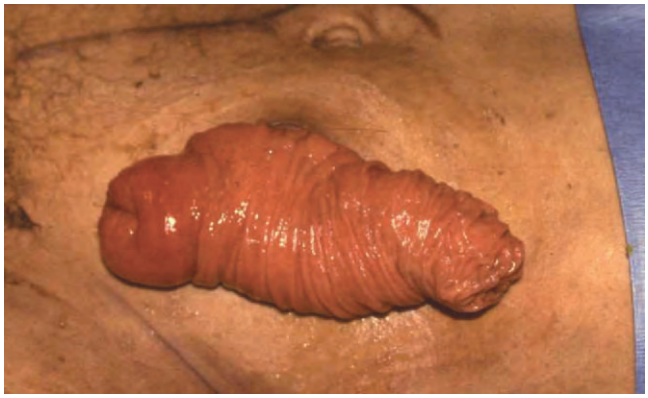

Figure 169–12. Large prolapse of a transverse-loop colostomy.

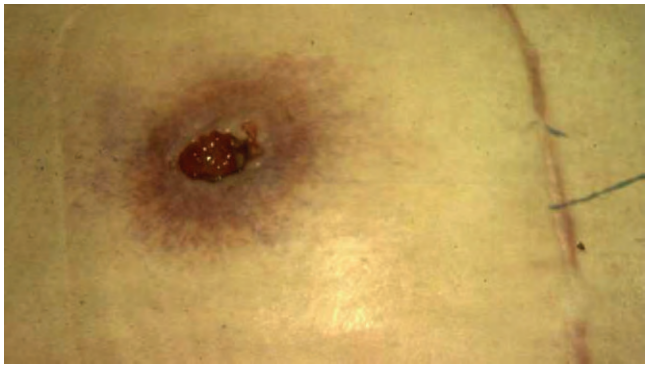

Figure 169–13. The characteristic blue hue of peristomal varices is visible only after removing the stoma appliance.

requires no treatment, especially if the stoma is temporary. When the prolapse causes ischemia, obstruction, or pouching problems, surgical intervention is warranted and usually straightforward. The stoma is freed up from the abdominal wall and the bowel delivered until taut. The redundant bowel is amputated and the mucocutaneous border is reestablished.

Peristomal Varices

Stomal varices may cause life-threatening hemorrhage. The varices occur at the level of the mucocutaneous border of the ostomy secondary to the anastomoses between the high-pressure portal venous system and low-pressure subcutaneous veins of the abdominal wall.[43,44] The diagnosis is suspected in ostomates with serious liver disease and confirmed by the typical purplish hue, or caput medusae, in the peristomal skin. Common scenarios include extensive liver metastases after abdominoperineal resection for rectal cancer or sclerosing cholangitis in a patient who has undergone total proctocolectomy with ileostomy for ulcerative colitis. A high index of suspicion is critical, and the stoma wafer must be removed to allow for skin inspection (Fig. 169–13).

Patients with short life expectancies (e.g., extensive liver metastases) may be treated by mucocutaneous disconnection; the stoma is freed up to the level of fascia, thereby dividing the portosystemic connections. Since these anastomoses typically reform within 1 year, more definitive solutions are required in most patients. More durable options include surgical shunts, transjugular intrahepatic portosystemic shunts, or liver transplantation, based on life expectancy and the status of the associated liver disease.[45]

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Chapter

170

Surgery in the Immunocompromised Patient

George J. Chang ▪ Mark L. Welton

The immunocompromised state is characterized by defects in the system of defense against infections and malignancy and is classified as primary (as in immunodeficiency syndromes) or secondary (as in acquired states). Impaired immune function may thus result from genetic disorders, malnutrition, injury, disease, cancer therapy, inflammatory diseases, or pharmacologic manipulation. Advances in transplantation, oncology, and the treatment of acquired immunodeficiency syndrome (AIDS) have increased the life expectancy of these patients, and thus the population of patients with impaired immunologic function has enlarged. Immunocompromised patients who have problems that require surgical attention are more likely to experience a delay in diagnosis and an increased mortality rate compared with patients without immune defects. Because an increasing number of surgical patients are immunocompromised, it is important to recognize and to understand the immunocompromised state to properly manage these patients.

MECHANISMS OF IMMUNODEFICIENCY

Host defense mechanisms are broadly characterized as local and systemic. Local defenses include skin and mucosal barriers. Systemic defenses include cell-mediated and humoral immunity and nonspecific, complement-mediated mechanisms. Primary and acquired defects in these defenses may occur.

Table 170–1 lists the most common primary immunodeficiencies and their sequelae. Patients with primary immune defects are more likely to have infectious complications that require medical, rather than surgical, treatment compared with patients with acquired deficiencies. With combined cellular and humoral defects, severe, life-threatening infections with opportunistic organisms such as cytomegalovirus (CMV), *Pneumocystis carinii,* or *Candida* may occur. Secondary immunodeficiency is caused by immunosuppressive medication administered to patients after transplantation, with inflammatory bowel disease (IBD), cancer, cancer therapies, injury, or malnutrition. Common causes of acquired immunodeficiency in surgical patients are summarized in Box 170–1.

Pharmacologic Therapy

One of the most common causes of immunosuppression in surgical patients occurs when immunosuppressive drug therapy is administered to patients for transplantation and IBD. Other diseases that are treated with pharmacologic immunosuppression include autoimmune disorders such as rheumatoid arthritis and scleroderma. Immunosuppressive regimens generally involve combinations of corticosteroids, T-cell inhibitors (e.g., cyclosporine, tacrolimus, OKT-3, antithymocyte globulin, anti-CD25 monoclonal antibodies), antimetabolites (methotrexate, 6-mercaptopurine, azathioprine, mycophenolate mofetil), and cytokine regulators (infliximab). Immunosuppressive drugs commonly used for solid organ transplantation and IBD, along with their mechanisms of action, are listed in Table 170–2. The net effect is down-regulation of the cellular immune response with a resultant increased susceptibility to bacterial infection, impairment of wound healing, and increased risk for some malignancies. Furthermore, these immunosuppressive agents cause hepatotoxicity, nephrotoxicity, and bone marrow suppression, which pose additional problems for the management of these patients. Drug-induced immunosuppression may increase the cumulative risk for the development of

Table 170–1 Common Causes of Primary Immunodeficiency

Defect	Sequelae
IgA or IgM deficiency syndromes	Bacterial infections
Hypogammaglobulinemia	Staphylococcal and encapsulated bacterial infections; increased risk for lymphoma, leukemia, and gastric carcinoma
Complement defects	Bacterial infections and increased risk for death from sepsis
T-cell defects	Fungal and viral infections
Natural killer cell defects	Viral infections
Combined cellular/humoral deficiency	Fungal, viral, opportunistic infections; graft-versus-host disease
Leukocyte adhesion molecule defects	Bacterial infections, abnormal antibody responses to infection
Phagocytic dysfunction	Bacterial and fungal infections

Box 170–1 Common Causes of Acquired Immunodeficiency in Surgical Patients

- Diabetes mellitus
- Age
- Cancer
- Chemotherapy
- Diabetes mellitus
- Inflammatory bowel disease
- Liver disease
- Malnutrition
- Radiation
- Renal failure
- Thermal injury
- Transplantation
- Splenectomy

certain malignancies (e.g., skin cancers, cervical and anal cancers, and non-Hodgkin's lymphomas).

Cancer and Cancer Therapy

Defects in both T- and B-cell–mediated immunity are associated with advanced cancer. This occurs primarily as a result of the malignancy and secondarily as a result of the oncologic therapy. Tumorigenesis may be associated with impaired cytokine production and lymphokine-activated killer cell development. The secondary causes of immunosuppression include the effects of chemotherapy and radiation therapy on the bone marrow and intestinal mucosa. These therapies cause bone marrow suppression with neutropenia or pancytopenia and can result in profoundly impaired immune function. Lymphocytes are the most radiosensitive immune cells. Thus, irradiation is associated with lymphocyte dysfunction and resultant defects in humoral and cell-mediated immunity.

Chemotherapy and radiation also have deleterious effects on barrier defenses. Both radiation and chemotherapy can cause mucosal sloughing or ulceration in the gastrointestinal tract, leading to weakened barrier defenses and an increased risk for bacterial transmigration. Finally, these immunosuppressed patients with cancer often have indwelling catheters through which chemotherapy is delivered and that allow bacterial access through the skin.

Malnutrition and Injury

Prolonged starvation is associated with both humoral and cellular immune defects with reduced immunoglobulin production and T-cell proliferation in response to immunogens. Macrophage and neutrophil defects may also occur. Wound healing is impaired. Trauma and injury cause similar immune defects, especially in cellular immunity.

Burns are among the injuries that cause the most dramatic immunosuppression. They cause defects in humoral and cellular immunity similar to traumatic injury and cause loss of the skin/mucosal barrier. In severe burns, immunoglobulin levels reach their nadir on the second to third day, and depletion of IgG, an important opsonizing antibody, correlates with septic complications.[1] As a result, approximately 50% of the deaths of patients in burn units are from infection.

Acquired Immunodeficiency Syndrome

The pathogenesis of AIDS immunosuppression begins with the binding of the human immunodeficiency virus (HIV) virions to the CD4 lymphocytes (also known as helper T cells) via an interaction between the gp120 viral envelope protein and the CD4 cell surface molecule. The viral core components, consisting of a single-stranded RNA particle and the reverse transcriptase, become internalized in the target CD4 cell. Within the cell, the single-stranded viral RNA becomes transcribed into double-stranded DNA, which incorporates into the host

Table 170–2 Commonly Encountered Immunosuppressive Drugs in Transplantation and Inflammatory Bowel Disease

Agent	Route	Mechanism of Action
Corticosteroids	PO/IV/PR	Inhibit cytokine production and secretion, particularly IL-2 by T cells; may also have other effects
Cyclosporine	PO/IV	Binds to cyclophilin, thus inhibiting calcineurin-mediated gene activation; results in decreased IL-2 production and T-cell proliferation
Tacrolimus	PO/IV	Binds to FK-binding protein, causing inhibition of calcineurin
Sirolimus	PO	Binds to nuclear FK-binding protein, inhibits T-cell cycle progression
Azathioprine	PO/IV	Antimetabolite
Mycophenolate mofetil	PO/IV	Inhibits purine synthesis
OKT3	IV	Murine monoclonal anti-human antibody to $CD3^+$ T cells; targets T-cell proliferation
ALG/ATG	IV	Polyclonal antilymphocyte or antithymocyte globulin; targets T-cell proliferation
Basiliximab, daclizumab	IV	Monoclonal antibodies to CD25 (high-affinity IL-2 receptors expressed on activated T lymphocytes); targets T-cell activation and proliferation
Infliximab	IV	Chimeric monoclonal antibody to TNF-α
Experimental		
Anti–IL-12	SC	Inhibits Th1 response
Adalimumab	IV	Humanized monoclonal antibody to TNF-α
Fontolizumab	IV	Anti–interferon-γ monoclonal antibody
Natalizumab	IV	Anti–α-4-integrin monoclonal antibody, inhibits leukocyte migration
Visilizumab	IV	Anti-CD3 monoclonal antibody

IL, interleukin; IV, intravenous; PO, oral; PR, per rectum; SC, subcutaneous; TNF, tumor necrosis factor.

genome and is subsequently expressed to yield infectious viral progeny that are released with cell lysis. In progressive HIV infection, the amount of virus increases and the number of CD4 cells decreases. CD4 lymphocytes are important in the host cellular immune system. The depletion of these cells results in the impairment of cytotoxic lymphocyte and natural killer cell responses.

Infection with HIV results in a broad spectrum of immunocompromise from mild to severe. Because of the progressive nature of their disease, patients with AIDS (CD4 count <200, or history of opportunistic infections), in contrast with other immunocompromised patients, become more immunosuppressed with time. In patients with AIDS, the absolute CD4 lymphocyte count has been considered to be the best marker for the degree of immunodeficiency. However, significant progress has been made in the quantitative diagnosis of HIV. The HIV viral RNA load can be quantified, and it may be a more sensitive indicator of HIV progression and predictor of death than is the CD4 count.

THERAPEUTIC APPROACH TO IMMUNOCOMPROMISED PATIENTS

Steroids

Since 1949, when Hench and coworkers first described the beneficial effects of cortisone in patients with rheumatoid arthritis, hundreds of indications for the use of steroid therapy have been described.[2] These include the treatment of inflammatory conditions such as ulcerative colitis and Crohn's disease, the treatment and prevention of graft rejection in organ transplantation, the treatment of chronic obstructive pulmonary disease, and the treatment of collagen vascular diseases. Administration of steroids has effects on immune defenses and the hypothalamic-pituitary-adrenal (HPA) axis that are now well established. Steroid therapy is a common reason for immunocompromise in surgical patients. It is thus important to identify patients who receive or have received steroid therapy and to understand how this may affect their perioperative management.

Immunosuppression

Corticosteroids have many anti-inflammatory effects that make them potent immunosuppressants. These anti-inflammatory effects are also the mechanisms through which the complications of steroid therapy occur. Much of their activity is initiated at the molecular level via binding to cytoplasmic hormone receptors. The steroid-receptor complex migrates to the nucleus, where it acts by affecting gene transcription. The net effects are inhibition of cytokine gene transcription and secretion, particularly interleukin (IL)-1, IL-6, and tumor necrosis factor by macrophages and IL-2 by T cells. Furthermore, macrophage activation and mobilization are inhibited, as is endothelial adhesion molecule expression.

Steroids increase exposure to pathogens by diminishing the barrier function of the gut mucosa through decreased mucosal turnover and regeneration. They also cause atrophy of the gut lymphoid elements and thinning of the bowel wall.[3]

Impaired Wound Healing

The inhibitory effects of corticosteroids on wound healing were first described in 1950,[4] but the cellular events were not known until the 1960s.[5] The anti-inflammatory steroids have two major effects on wound repair: (1) inhibition of initial inflammation and (2) diminution of collagen synthesis. These effects are seen clinically as increased rates of postoperative complications in patients who receive corticosteroids. In one review dehiscence or incisional hernia after intraperitoneal surgery in steroid-treated patients was reported as 13% versus 2% for non-steroid-treated patients.[6] In another review of 658 intestinal anastomoses in 429 operations for Crohn's disease, the postoperative complication rate was significantly higher in the group treated for the long term with steroids.[7] Furthermore, in an animal model of chronic steroid use, a significant decrease was found in the bursting strength of colonic anastomoses with steroid therapy.[8]

Despite these studies, controversy persists over the effects of steroid administration on clinical outcomes after bowel surgery and the need for protective fecal diversion. A review of 692 patients at the Cleveland Clinic found no difference in septic complications in patients receiving corticosteroids compared with those not receiving steroids if a protective loop ileostomy was created at the time of ileal pouch–anal anastomosis. However, the authors did note a significant increase in septic complications in the steroid group compared with the non-steroid group when the fecal stream was not diverted.[9] In contrast, Schrock et al.[10] reported no difference in the clinically detectable rate of leakage after colonic anastomoses in patients who had received steroids. Furthermore, a more recent review at the same authors' institution confirmed the observation that there was no increase in morbidity rate associated with primary anastomosis in a selected group of patients receiving less than 40 mg of prednisone per day.[11] However, high-dose steroids do appear to have significant adverse effects on bowel anastomoses. Our preferred technique is to reserve primary anastomosis for patients who have a technically uncomplicated operation and are on limited doses of steroids. Diversion is performed in those with technical complications and in those who have had significant steroid exposure.

Altered Hormonal Response to Stress

Increased secretion of cortisol from the zona fasciculata of the adrenal cortex in response to adrenocorticotropic hormone (ACTH) released from the anterior pituitary gland is an essential component of the surgical stress response. The nonstressed human adrenal gland secretes approximately 25 to 30 mg of cortisol per day. After major surgery, the stressed adrenal gland secretes 75 to 100 mg of cortisol during the first 24 hours. It has since been demonstrated that hormonal responses to graded surgical stress reflect the degree of surgical stress and that the effects are transient; hormone levels return to normal within 24 hours.[12]

The most accurate way to evaluate the capacity of the adrenal cortex to respond to stress is the rapid ACTH stimulation test. After a baseline cortisol level is obtained, 25 units (250 μg) of synthetic ACTH (Cosyntropin, Cortrosyn) is administered intravenously, and serial plasma cortisol determinations are made at 30 and 60 minutes. A normal response is an increase in the plasma cortisol level of at least 7 μg/dl above baseline or an absolute ACTH-induced rise in plasma cortisol to more than 20 μg/dl.

Stress-Dose Steroids

In 1952, Fraser et al.[13] first reported a case of postoperative hypotension and death caused by perioperative withdrawal from glucocorticoid therapy. This was followed by a similar report by Lewis in 1953, which also gave recommendations for perioperative glucocorticoid treatment for patients on chronic steroid therapy. Those recommendations, a roughly fourfold increase in glucocorticoid dosage, became the standard of therapy until recently. Adrenal insufficiency in a patient on chronic steroids usually manifests as hypotension, abdominal pain, nausea, vomiting, fever, and dehydration and can progress to hypovolemic shock. Concomitant electrolyte abnormalities, caused by mineralocorticoid insufficiency, are unusual. Adrenal insufficiency is an uncommon complication after surgery in patients on chronic steroid therapy.[14]

Despite the low incidence of secondary adrenal insufficiency, some authors have advocated the use of screening tests for adrenocorticoid insufficiency, such as the synthetic ACTH stimulation test, to determine the need for perioperative so-called stress-dose steroids in surgical patients.[15] This would apply to any patient who has received corticosteroid therapy within the year before surgery, because recovery of the HPA axis may take up to 1 year after steroid withdrawal.[16] Recommendations for patients with HPA axis dysfunction are summarized in Table 170–3.

Over the past 20 years, understanding of adrenal cortical responses to surgery and anesthesia has improved, and an increasing body of evidence challenges the standard recommendations for perioperative corticosteroid coverage in patients on chronic steroid therapy. Udelsman et al.[17] studied the effect of surgical stress in adrenalectomized monkeys when adrenalectomy was followed by replacement corticosteroids for 4 months and subsequent cholecystectomy. There was no difference between animals receiving only physiologic doses of steroids and those receiving supraphysiologic stress-dose steroids. However, an increased mortality rate was associated with subphysiologic steroid replacement. In a study of 40 renal transplant patients admitted to the hospital with significant physiologic stress such as sepsis or surgery, there was no increase in mortality rate, hospital stay, or

Table 170–3 Recommendations for Perioperative Steroid Replacement Therapy

Degree of Surgical Stress	Steroid Dose
Minor	25 mg hydrocortisone or equivalent, then resume normal dose
Moderate	50–75 mg/day hydrocortisone or equivalent for 1 to 2 days, then resume usual dose as clinical course dictates
Major	100–150 mg/day hydrocortisone or equivalent for 2 to 3 days, then resume usual dose as clinical course dictates

eosinophilia associated with simple replacement steroid therapy without stress-dose therapy. In this group, the synthetic ACTH stimulation test overestimated the incidence and degree of clinically significant adrenal dysfunction compared with other biochemical determinants, such as serum ACTH, urinary free cortisol, or serum cortisol.[18] Similar findings were reported in a double-blinded study of stress-dose steroids in patients with abnormal Cosyntropin stimulation tests with hemodynamic parameters as end points.[19] Together, these studies suggest that supraphysiologic steroid supplementation in surgical patients is unnecessary and that physiologic cortisol replacement may be sufficient even for patients undergoing major procedures.

Despite these data, a survey of practice patterns among fellows of the American Society of Colon and Rectal Surgeons demonstrated that the majority (84% of 307 survey responders) of surgeons still administer perioperative stress-doses of steroids. This is partly due to the difficulty in applying the limited data to the spectrum of patients that include those on low-dose steroids such as for transplantation and those on very high anti-inflammatory doses of steroids such as for IBD. It is our practice to administer a perioperative steroid bolus for patients on long-term chronic steroid therapy, followed by a rapid taper. Patients on low doses of short duration or those undergoing minor operations (i.e., takedown-loop ileostomy) receive their usual replacement dose. Although a complete discussion of this subject is beyond the scope of this chapter, Box 170–2 lists some of the common physiologic and metabolic effects of acute adrenal insufficiency.

Box 170–2 Common Manifestations of Acute Adrenal Insufficiency

- Pyrexia (fever)
- Tachycardia
- Hypotension
- Hyponatremia
- Hyperkalemia
- Elevated urinary sodium
- Decreased urinary potassium

Immunosuppression for Transplantation

Generalized T-cell immunosuppression remains the mainstay of post-transplantation immunosuppression. Agents are directed at various steps in T-cell activation, including gene transcription, DNA synthesis, cell cycling, and T-cell receptor function. Most current immunosuppressive regimens involve triple therapy with corticosteroids, cyclosporine or tacrolimus, and azathioprine or mycophenolate mofetil. The detrimental effects of corticosteroids on wound healing are well known. No demonstrable effect on wound healing, however, has been shown with cyclosporine or azathioprine.[20] Furthermore, no clear evidence suggests that impaired wound healing occurs with the newer agents such as tacrolimus and mycophenolate mofetil.

Transplantation immunosuppression is directed at the cellular immune response and results in a significant impairment in the host's ability to fight bacterial and viral infections. From 50% to 75% of transplant recipients have one or more episodes of bacterial infection, and 30% to 60% have one or more serious viral infections after transplantation.[21] Most common infectious complications, such as bronchitis after lung transplantation and urinary tract infection after renal transplantation, can be treated medically. However, transplant patients may be more likely to develop serious perioperative infectious complications that require reoperation. Appropriate perioperative antibiotic prophylaxis should be administered, and steroid prophylaxis should be given as previously outlined.

During the perioperative period, maintenance immunosuppression should be continued. If the patient does not have a functioning gastrointestinal tract, intravenous preparations may be administered, but the transplant pharmacist should be consulted to determine equivalent dosing based on bioavailability. Daily monitoring of serum trough levels of agents such as cyclosporine and tacrolimus is necessary to prevent inadequate immunosuppression or drug toxicity.

Immunosuppression for Inflammatory Bowel Disease

IBD is a common reason for pharmacologic immunocompromise in patients seen by general and colorectal surgeons. Often these patients have medically refractory disease or fulminant colitis associated with high-dose steroids, other immunosuppressive agents, and malnutrition at the time of evaluation by the surgeon. A

complete discussion of the evaluation and management of patients with IBD occurs in Chapter 151. As with immunosuppression for transplantation, perioperative steroid replacement needs should be considered when operating on patients with IBD. Surgical interventions in patients with IBD are broadly categorized based on the indication as emergent or elective. In the emergent setting the goal of treatment is life saving and may be in the setting of fulminant colitis with chronic ulcerative colitis or acute bowel obstruction or perforation with Crohn's disease. Priorities in the management of these patients are the same as for those without immunocompromise for IBD—patients should be thoroughly evaluated for a medical cause of their acute abdominal symptoms (e.g., acute CMV or *Clostridium difficile* colitis in a patient with chronic ulcerative colitis) while undergoing resuscitation. Surgical therapy should not be unnecessarily delayed and should be directed at treating the acute problem. In the elective setting treatment can be definitive. Of concern is the potential risk for increased perioperative morbidity in these patients. However, even restorative proctocolectomy with ileal pouch–anal reconstruction has been shown to be safely performed in patients on immunosuppressive therapy for IBD.[22]

Cancer Immunosuppression

Malignancy may cause or be a result of immunosuppression. Advanced malignancies are associated with defects in T- and B-cell function. Drug toxicities, tumor burden, and cytokine release cause malnutrition, which further suppresses the patient. There are additional direct immunosuppressive effects of cancer therapies. Whole-body radiation may result in profound immunosuppression from bone marrow depression and resultant pancytopenia. It also has local effects on barrier defenses such as the skin or intestinal mucosa. The majority of chemotherapeutic agents also cause some degree of myelosuppression that may respond poorly to granulocyte-colony-stimulating factor (G-CSF). The resultant pancytopenia renders the cancer patient markedly susceptible to opportunistic infections, particularly during chemotherapy administration, when bone marrow suppression is the greatest.

Severe neutropenia is defined as an absolute neutrophil count less than 500/mm^3 and is associated with severe immunosuppression. The magnitude of the neutropenia is directly related to the patient's risk for infection and mortality.[23] An important consideration in the evaluation of patients with chemotherapy-induced myelosuppression is the timing of the nadir of the leukocyte count. Most myelotoxic chemotherapeutic agents result in the nadir of neutropenia at approximately 10 to 14 days following drug administration. Approaching this nadir, the patient is at the highest risk for perioperative complications; however, when the counts have begun to recover, the patient's risk may improve. Further consideration can be given to the velocity of the rise in counts. In selected circumstances it may be possible to provide supportive care through this severely neutropenic state and delay surgical intervention until the neutrophil count has recovered to be greater than 500/mm^3.

Neutrophil count recovery may be accelerated by the use of G-CSF (filgrastim, pegfilgrastim), which has been shown to decrease the duration and severity of neutropenia, the incidence of infections and febrile neutropenia, the duration of neutropenia-related hospitalization, and antibiotic use.[24] The role of colony-stimulating factors in the management of surgical disease in the setting of neutropenia is unclear; however, improved outcome has been demonstrated for patients with pneumonia, cellulitis, abscess, or sinusitis.[25]

Surgical Risk Assessment in Patients with Acquired Immunodeficiency

As the understanding of HIV infection and its treatment has improved, the complication rates in patients with HIV who undergo surgery have decreased. More recently the introduction of highly active antiretroviral therapy (HAART) has revolutionized the management of HIV-infected individuals. HAART regimens use combinations of three or more antiretroviral agents and result in maintenance of immunologic function and reduce morbidity and mortality in HIV-infected patients.[26] However, the exact surgical risks associated with HIV infection are unknown because HIV infection exists as a spectrum or continuum. For example, during the early stages of HIV infection, the helper T-cell (CD4) level may be near normal, and the patient therefore has a relatively intact immune system. Later, as the disease progresses and the CD4 cell count falls below 300 cells/mm^3, patients may experience self-limited illnesses such as mild to moderate skin and respiratory tract infections. Patients with AIDS as defined by the Centers for Disease Control and Prevention (CD4 cell counts <200 cells/mm^3) may experience opportunistic and uncommon infections that present in unusual manners. This last group of patients experienced the greatest surgical morbidity rates, and it was this group that was first reported to experience high surgical complication rates.[27] However, later literature contradicts those earlier findings.[28] The reasons for this are multifactorial but appear to be associated with improved control of viral replication and improved functional status of the patients.

Harris and Schecter observed that the presence of AIDS-related abdominal pathology conferred a threefold to fourfold increased operative morbidity risk and increased the associated average mortality rate from 15% to 44%.[28] The best predictor of increased operative risk in these patients is the patient's cardiopulmonary, renal, endocrine, and nutritional reserve status and not the absolute CD4 T-cell count. Other poor prognostic factors included an active opportunistic infection, serum albumin level of less than 2.5 g/dl, and the presence of concurrent organ failure. Although the literature regarding surgical complications in HIV-infected patients is largely retrospective, descriptive, and based on small numbers of patients, there is general agreement that HIV infection by itself is not the determinant risk factor;

rather, the overall clinical status of the patient determines the surgical risk.

SPECIFIC SURGICAL PROBLEMS IN IMMUNOCOMPROMISED PATIENTS

Acute abdominal pain in the immunocompromised patient presents a particular challenge to the surgeon. In addition to the myriad conditions affecting immunocompetent patients in general, these patients are also susceptible to conditions such as opportunistic or drug-related gastroenteritis, gastrointestinal lymphoma, and neutropenic enterocolitis. The work-up is frequently made more difficult by the lack of specific inflammatory responses; clues such as pyrexia, leukocytosis, and abdominal tenderness may be absent or diminished because of myelosuppression or decreased inflammatory responses.[29]

The initial evaluation and care of the immunocompromised patient (airway, breathing, and circulation) are no different than those of the immunocompetent patient in this regard. Once the patient has been adequately resuscitated, a careful history should be taken, and a careful physical examination should be performed. The severity of symptoms and signs in immunocompromised patients who present with catastrophic complications is completely unimpressive. A full laboratory work-up, including a complete blood cell count, urinalysis, plain radiographs of the chest and abdomen, electrocardiogram, blood cultures, and CMV serology, should be obtained. A chemistry panel that includes liver function tests and amylase should be obtained as indicated. Computed tomography (CT) should be liberally used as a part of the diagnostic work-up because the physical examination and laboratory data are often unreliable. Despite these measures, uncertainty about the diagnosis is common. The decision for surgical treatment depends on the underlying diagnosis. In general, the indications for acute surgical interventions in the immunocompromised patient are no different than for those patients with an intact immune system, with few exceptions (e.g., neutropenic typhlitis). Therefore, the surgeon must have a high degree of clinical suspicion for significant pathology despite seemingly minimal physical findings.

Acute Appendicitis

Acute appendicitis is a common abdominal surgical problem in both immunocompromised and immunocompetent patients. The evaluation of an immunocompromised patient in whom acute appendicitis is suspected proceeds as it would for an immunocompetent patient. A high index of suspicion and the liberal use of radiographic imaging may help to avoid delays in diagnosis. The safety of emergency surgery for acute appendicitis in severely immunocompromised patients has been described with a mortality rate less than 10%.[30,31] However, the pediatric surgical literature has reported success with initial nonoperative management of acute appendicitis in selected patients.[32] A similar approach with close observation and intravenous antibiotics may be possible in highly selected patients with severe neutropenia, early signs of acute appendicitis without any evidence of systemic sepsis, and in whom recovery of the neutropenia is anticipated during the following 24 to 48 hours. Few differences are observed in clinical findings and perioperative morbidity and mortality rates between non-HIV and HIV patients without AIDS.

Colonic Complications

Colonic complications that lead to perforation in the immunocompromised patient are catastrophic and often fatal.[33,34] Common causes of colon perforation include diverticulitis, infectious colitides, malignancy, foreign body, and trauma. Less common causes include neutropenic enteritis and a unique syndrome of spontaneous perforation that occurs in steroid-treated patients and in post-kidney transplantation or chronic hemodialysis patients.[35]

Diverticular Disease

Patients who are immunocompromised are at a high risk for complications associated with diverticulitis.[36] However, the literature supporting these views is contradictory, so the actual risk is unclear.[37,38] Kidney transplant recipients have been considered to be at a particular risk because of an association between polycystic kidney disease and diverticulosis.[39] Because of this association, pretransplantation screening for diverticulosis in patients should be performed.[37,40] Indeed, some authors have even suggested that patients with an antecedent history of diverticulitis undergo a pretransplantation colectomy.[41,42] Immunosuppression does make the abdominal examination less reliable, confounding the assessment and resulting in reports of increased morbidity and mortality rates with conservative management. Moreover, the disease could be advanced at presentation. Some have used this information as a basis for the advising of early surgical intervention.[34] We suggest an aggressive approach that recognizes the limitations of the physical examination and uses early CT scanning rather than prophylactic colectomy or urgent laparotomy. As with immunocompetent patients, the immunocompromised patient with a pericolic abscess is better treated with CT-guided drainage, bowel preparation, resection, and primary anastomosis than with urgent exploration, colectomy, and stoma formation.

Infectious Colitis

Immunocompromised patients are susceptible to the same range of infectious diseases of the gastrointestinal tract as immunocompetent patients. However, management of infectious diseases in this population is often complicated by delayed or late presentation. In addition, opportunistic pathogens, such as *Clostridium difficile, Cryptosporidia,* and CMV can supervene. Infections of the large bowel usually cause diarrhea, which may be bloody

or contain mucus, and can produce fever or abdominal pain. In transplant recipients, mycophenolate mofetil can cause severe diarrhea and abdominal pain, mimicking infectious enterocolitis. The work-up of a patient with suspected infectious colitis should include a complete history, especially recent travel, unusual ingestions suspect for food poisoning, similar illnesses among family members, recent hospitalizations, and treatment with antibiotics. It should also include testing for fecal leukocytes, *C. difficile* toxin, CMV culture, and stool cultures for bacteria, ova, and parasites. Selective endoscopic evaluation may be useful to obtain tissue or cultures and to establish the extent of colonic involvement. Radiographic imaging may be necessary to assess the degree of colonic involvement and to examine for evidence of necrosis or perforation. Regardless of the cause of the enteritis, early diagnosis and institution of medical therapy or surgical intervention are critical to prevent progression to necrosis or perforation.

CMV is the most common infectious complication of solid-organ transplantation or HIV infection.[43] It is also a common pathogen in patients with IBD. Symptoms include fever, weight loss, diarrhea, and hematochezia or melena. Endoscopic examination reveals patches of characteristic ulcers that mimic mucosal ulcerative colitis. CMV infection can cause a severe vasculitis that results in bowel wall ischemia and perforation. Medical therapy for CMV enteritis includes high-dose ganciclovir (5 mg/kg every 12 hours, usually for 14 days).

C. difficile infection occurs in relationship with antibiotic use and results from a proliferation of the toxin-producing strains of *C. difficile,* a gram-positive anaerobic organism. The toxins produce mucosal damage and inflammation. Patients present with watery diarrhea, fever, and leukocytosis. Abdominal pain and tenderness are also common. Some patients develop toxic megacolon. Symptoms can occur both during antibiotic administration or weeks to months after the cessation of treatment. The diagnosis is made by rapid immunoassays that test for antigens or toxins in the stool. These tests are inexpensive and easy to perform. If confirmation is needed, tissue culture assay can be performed with biopsy samples from a sigmoidoscopic or colonoscopic examination. When the toxin binds to the bowel wall, it affects the mucosa, creating the inflammation and plaque-like membranes seen endoscopically. This has led to the name *pseudomembranous colitis.* Fecal leukocytes, although not specific for *C. difficile* colitis, are present about 50% of the time.

The mainstay of therapy involves cessation of the offending antibiotics, supportive care, and the administration of oral vancomycin or metronidazole, which are highly effective against *C. difficile.* Metronidazole (250 mg four times a day) administered for 10 days is the first line of therapy because it is less expensive and resistant organisms are uncommon. Vancomycin (125 mg four times a day) or even bacitracin (25,000 U four times a day) can be administered if treatment with metronidazole fails. For patients who are unable to tolerate an oral dose because of abdominal surgery or ileus, intravenous metronidazole is effective with bactericidal levels of the drug in the stool. Cholestyramine to bind the bacterial toxin or vancomycin enemas have both been reported in the treatment of refractory *C. difficile* colitis.

Cryptosporidiosis is a common cause of diarrhea in immunosuppressed patients and health care workers. Trophozoites attach firmly to the mucosa, causing an inflammatory cell infiltrate in the lamina propria. Patients present with fever, abdominal pain, and watery diarrhea. Colonic biopsy or acid-fast staining of the stool reveals oocysts. The disease is self-limiting, lasting about 2 weeks. The treatment is supportive with rehydration. No medication is known to be effective.

Steroid-Induced Gastrointestinal Perforation

First reported by Beck et al. in 1950, acute gastrointestinal perforation is a well-documented complication of chronic steroid therapy.[44] In these patients, the lesions are often in unusual locations or result in perforation in an otherwise normal colon.[45] Mortality rates have been reported to be as high as 85% to 100%. Delay in treatment is an important reason for the high mortality rates and is associated with steroid doses of more than 20 mg of prednisone per day.[46] The inhibition of the inflammatory response results in a decreased tendency to wall off perforating lesions. These factors lead to a greater frequency of free perforation as well as a reduced peritoneal protective response to soilage in patients who receive chronic corticosteroid therapy. Furthermore, steroids may impair mucosal regeneration and cause atrophy of the lymphoid elements with thinning of the bowel wall.[3]

Neutropenic Enteritis

Neutropenic enteritis (typhlitis or neutropenic enteropathy) is a potentially life-threatening complication in patients receiving cytotoxic chemotherapy and in patients with aplastic anemia or cyclic neutropenia. It is a disease typically of the cecum, ascending colon, and terminal ileum and associated with varying degrees of mucosal and submucosal necrosis, hemorrhage, and ulceration. Originally described by Wagner and associates as a complication of childhood leukemia, neutropenic enteritis occurs most commonly in patients receiving high-dose chemotherapy for either hematologic or solid-organ malignancies.[47] An increased association with cytosine arabinoside has been observed, but high doses of virtually any myelotoxic regimen can cause neutropenic enteritis. The clinical presentation usually consists of the triad of fever, abdominal pain, and diarrhea in a neutropenic patient. Other symptoms include nausea, vomiting, hematochezia, and abdominal distention. Symptoms generally occur approximately 7 to 9 days after the onset of neutropenia. A rapid course suggests a more virulent form of the disease.[48,49] The differential diagnosis includes other causes of acute abdominal pain, such as appendicitis, diverticulitis, ischemic colitis, pseudomembranous colitis, and chemotherapy-induced gastroenteritis.

Laboratory studies are generally not useful in making the diagnosis, although positive blood cultures with a variety of gram-positive and -negative species have been

reported in 21% to 82% of patients.[48,49] Plain radiographs may show a paucity of gas in the right lower quadrant with dilated small bowel loops, thumbprinting, pneumatosis intestinalis, or free air. However, plain radiographs may be completely normal in mild cases. Ultrasound and CT are significantly more sensitive than plain radiographs in establishing the diagnosis. Findings include bowel wall thickening, ascites, a peri-intestinal inflammatory mass, pneumatosis, or free air. CT is particularly useful in the follow-up evaluation of the patient whose clinical condition has not improved despite the resolution of neutropenia; occult retroperitoneal perforation or advanced bowel necrosis may be identified.

The optimal treatment of neutropenic enteritis is aggressive medical therapy consisting of bowel rest, hydration, broad-spectrum intravenous antibiotics, and close observation. In general, the clinical course does not improve until after the neutrophil count begins to recover. Close observation with CT scanning is important if the patient's clinical course is not improving. Shamberger et al.[50] proposed the following objective criteria for emergency surgical intervention: (1) free intraperitoneal perforation, (2) persistent intestinal bleeding despite resolution of neutropenia and coagulopathy, and (3) clinical deterioration despite maximal medical care, suggesting uncontrolled sepsis.

Anorectal Complications

Anorectal problems are challenging clinical dilemmas in immunocompromised patients, particularly in those who are neutropenic or have AIDS. Symptoms usually include pain, ulceration, discharge, incontinence, bleeding, mass, or tenesmus. Both benign and malignant pathologic processes cause these symptoms. Common communicable anorectal pathogens are similar to those occurring in immunocompetent patients (Table 170–4). Other noncommunicable causes of anal disease include abscess, fistula, perirectal infections, hemorrhoids, fissures, ulcers, and tumors. These lesions are significant problems in the neutropenic patient but may occur in patients with less severe immunocompromise and in patients who are immunocompetent. The work-up for anorectal lesions should include a thorough history, inspection, digital rectal examination, anoscopy, and proctoscopy with biopsy samples because immunocompromised patients are at an increased risk for developing both rectal and anal cancers.

Suppurative anal disease in immunocompromised patients requires incision and drainage. In cases of deep perirectal infections, after a thorough examination under anesthesia that includes anoscopy and rigid proctosigmoidoscopy, a CT scan may help to delineate the extension of the abscess and identify the presence of any undrained pus if there is clinical suspicion. Perianal sepsis in immunocompromised patients may have little or no purulent drainage because the patient's immune system is unable to mount a significant inflammatory response.

Malignancies in the Immunocompromised Patient

An increased incidence of squamous cell carcinoma of the skin, non-Hodgkin's lymphoma, Kaposi's sarcoma, cervical carcinoma in situ, carcinoma of the anogenital region, and hepatobiliary carcinoma occurs in post-transplantation immunosuppressed patients.[51] In addition, similar neoplasms occur in patients who are immunocompromised for other reasons. In the general population, the most common malignancies are carcinomas of the lung, prostate, colon and rectum, and female breast and invasive cervical and pancreatic carcinomas. Moreover, there has been an increase in the incidence of lymphomas in the postcyclosporine era compared with the precyclosporine era.[52] Two factors—immunosuppression and oncogenic viruses—appear to be important in the pathogenesis of many malignancies in immunosuppressed patients (e.g., Epstein-Barr virus for lymphomas and human papilloma virus [HPV] for anal and cervical

Table 170–4 Common Anorectal Infections in the Immunocompromised Patient

Causative Organism or Condition	Manifestations
Neisseria gonorrhoeae	Nonulcerating proctitis with a mucopurulent discharge
Syphilis	Primary chancre may be single or multiple, painful or painless; may be confused with fissures; immunocompromised patients may have a prolonged interval between acute infection and seroconversion
Chlamydia proctitis and lymphogranuloma venereum (LGV)	Severe proctitis with ulceration may result from LGV; serologic responses may be impaired in immunocompromise, so tests should be performed on rectal swabs or mucosal biopsy samples
Herpes simplex virus	Perianal clusters of vesicles coalesce and ulcerate; may develop into a persistent ulcerative lesion
Human papilloma virus (HPV)	Multiple types, associated with "benign" genital warts (HPV-6, -11, -42) or with the development of high-grade dysplasia and anal cancer (HPV-16, -18, -33); may result in condylomatous, papular, or keratotic lesions; intra-anal disease is common, so proctoscopy is essential

squamous cell carcinomas). Because these malignancies occur at an average of 5 years after the initiation of immunosuppression for transplantation, the surgeon may be asked to evaluate a patient with abdominal complications of lymphoma or with anogenital or hepatobiliary lesions. The appropriate transplant physician should be consulted, and reduction in or cessation of immunosuppression should be considered.

Adverse immunologic effects also occur with cancer chemotherapy, malnutrition, and acquired immunodeficiency. In addition, some of the genetic factors that predispose a patient to a primary malignancy may play a role in the development of a secondary malignancy. Radiation therapy is another important contributor to secondary carcinogenesis. Leukemias and lymphomas are common secondary malignancies, followed by carcinomas of the thyroid, breast, lung, and stomach and sarcomas of soft tissue and bone.[53]

In transplant recipients, carcinomas of the skin and lips are the most common and are 38% of all malignancies in the Cincinnati Transplant Tumor Registry.[52] Compared with the frequencies of these cancers in the general population, the incidence was increased 4-fold to 7-fold in low sun–exposure areas and more than 20-fold in high sun–exposure areas. The lesions were more likely to be multiple in location and aggressive; these were mostly squamous cell carcinomas. In the general population, basal cell carcinomas are more common. The affected patients were on average 30 years younger than their counterparts in the general population. Kaposi's sarcoma is the most common malignant tumor in patients with AIDS. Gastrointestinal tract lesions are usually asymptomatic but can cause bleeding, obstruction, perforation, intussusception, or protein-losing enteropathy. The lesions look similar to Crohn's disease on endoscopy but are located in the submucosa. A higher mortality rate has been observed in AIDS patients with Kaposi's sarcoma of the gastrointestinal tract in comparison with those with only cutaneous lesions.[54]

Anal neoplasms are more common in immunocompromised patients. Overall, anal cancers occur in 7 per 1 million men and 9 per 1 million women. In HIV-negative men who have sex with men, the rate is estimated at 35/100,000. In immunocompromised groups (e.g., transplant, HIV), this risk is considerably higher.[55] In the HIV-positive men who have sex with men, the rate approaches 70/100,000. There is a high incidence of anal dysplasia (15%) in HIV-positive patients, and the rate of anal cancers may increase as lives are prolonged with highly active retroviral therapies.[56]

Prediction of the biology and planning for the treatment of tumors of the perianal region is dependent on precise localization of the tumor with respect to anal landmarks such as the dentate line, the anal verge, and the anal sphincters. These landmarks define two classes of perianal neoplasms: tumors of the anal margin and tumors of the anal canal. The Histologic Typing of Intestinal Tumors (adopted by the World Health Organization) defines the anal canal as extending from the upper to the lower border of the internal anal sphincter (from the pelvic floor to the anal verge). The American Joint Committee on Cancer agrees with this classification, and efforts are under way to classify tumors in this manner. The anal margin extends from the anal verge (the junction of the highly specialized epithelium of the anoderm with the hair-bearing perianal skin) to 5 to 6 cm from this point.[57] Squamous cell tumors of the anal margin are well-differentiated, keratinizing tumors that behave similarly to squamous cell tumors of the skin elsewhere. Tumors of the anal canal are aggressive high-grade tumors with significant risk for metastasis.

HPV has been implicated as a causative agent in the development of anal cancer. As in the cervix, HPV types 16 and 18 appear to be causally related to the development of high-grade dysplasia and anal cancer, whereas types 6 and 11 cause common genital warts and low-grade dysplasia.[58]

These parallels to cervical disease have led investigators to explore the use of anal Papanicolaou smears and high-resolution anoscopy (magnified examination of the anus with a culposcope or operating microscope) as a method of detecting and destroying high-grade lesions in high-risk patients before the development of cancer.[59,60] If high-grade disease is found, we have recommended referral for surgical excision or ablation. The anal canal is painted with acetic acid and examined circumferentially with an operating microscope or culposcope. Vascular changes characteristic of severe dysplasia are noted, and the anus is mapped as to the distribution of this disease. The anal canal is next painted with Lugol's solution and mapped again. (Lugol's solution is a concentrated [10%] iodine solution that stains glycogen stores in nondysplastic tissues a dark brown/black. Low-grade dysplasia stains partially, and high-grade disease does not take up the solution, leaving it mahogany in color). Representative biopsy samples are taken from the areas of severe dysplasia, and the surrounding severely dysplastic disease is destroyed with electrocautery.[61]

SUMMARY

Advances in the medical care of the immunocompromised patient have increased life expectancies and therefore increased the likelihood that they will require intervention by a general surgeon. The management of the acutely ill immunocompromised patient should first include the standard survey of the airway, breathing, and circulation before an exhaustive effort is undertaken to establish a diagnosis. Immunocompromised patients are susceptible to the same diseases that occur in immunocompetent patients but are also susceptible to opportunistic diseases. The surgeon must maintain a high index of suspicion and realize that the physical examination and laboratory studies may be unreliable or misleading. However, it should be emphasized that the immunocompromised state in and of itself is rarely a contraindication to a necessary surgical procedure; rather, the overall clinical presentation should be considered on an individual basis, and the therapy should be tailored to each patient.

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Chapter

171

Anorectal Anomalies

Scott A. Engum · Jay L. Grosfeld

Anorectal malformations (ARMs) are relatively common congenital anomalies. The first report of surgical correction by performance of an anoplasty was by Amussat in 1835. Stephens performed the first objective studies with ARM and proposed an initial approach to separate the rectum and urinary system in 1953.[1] Several surgical techniques have been proposed since this time, with the main objective to protect and use the puborectalis sling. In 1982, deVries and Peña described a new operative approach—posterior sagittal anorectoplasty (PSARP).[2,3] With this approach it became possible to correlate the external appearance of the perineum with the operative findings and subsequent clinical outcome.

The cause of ARM is unknown. The vast majority of experience in the management of these problems has been obtained at specialized children's hospitals that deal with disorders of the newborn. The reported incidence of anorectal anomalies ranges from 1:3500 to 1:5000 live births. Some families have a genetic predisposition, with ARMs noted in succeeding generations. The estimated risk for a couple having a second child with an ARM is approximately 1%.[4] Malformations occur more commonly in boys than girls (1.4:1 to 1.6:1)[5,6]; however, this may vary according to the level of the defect because the majority of females have low (rectovestibular fistula)[7] rather than high lesions.

EMBRYOLOGY

The gastrointestinal tract develops from the embryonic gut, which is composed of an epithelium of endodermal origin surrounded by cells of the mesoderm. Cell signaling between these two tissue layers appears to play a critical role in coordinating patterning and organogenesis of the gut and its derivatives. Studies have shown that sonic hedgehog signals are essential for organogenesis of the mammalian gastrointestinal tract and suggest that mutating members of this signaling pathway may be involved in the occurrence of human gastrointestinal malformations.[8-11]

Although numerous efforts have been made to understand the abnormal processes that produce ARMs, neither the normal nor the abnormal development of the hindgut and cloaca is fully understood. Most theories to explain the disturbance in embryogenesis resulting in ARMs are mainly speculative. There is general agreement that the cloaca is seen in the 12- to 15-day embryo. The *cloacal membrane* is defined as that area between the primitive streak and the body stalk where endoderm and ectoderm fuse without intervening mesoderm. The allantois is an extension of gut endoderm that becomes part of the bladder and extends up to the amnion. The allantois marks the ventrocephalic limits of the cloaca. Cloacal folds (or genital folds) are mesoblastic proliferations that surround the cloacal membrane.

The mesonephric ducts join the superior lateral wall of the cloaca just inside the cloacal membrane at 28 days of gestation. The cloaca is now a large chamber into which the hindgut enters superiorly and the tailgut exists inferiorly. Just in front of the hindgut, the allantois projects ventrally and superiorly. The ventral body wall develops and displaces the upper end of the cloaca. Anal tubercles (mesoblastic structures) form on both sides of the cloaca at its junction with the tailgut and impinge on the lumen at this junction. The anal tubercles fuse centrally, displacing the cloacal orifice of the involuting tailgut dorsally away from the cloacal membrane.[12]

The urorectal septum descends to demarcate the cloaca into a ventral urogenital sinus and a dorsal hindgut. Recent investigations utilizing the Carnegie Embryological Collection and three-dimensional modeling have suggested that the urogenital sinus and anorectum form early and are separated by the urorectal septum as a passive structure. There does not seem to be septation or differentiation of the cloaca itself.[13,14] Others have illustrated that a delay of tailgut regression, an abnormal and massive apoptotic cell death involving the posterior cloacal wall, and underdevelopment of the dorsal aspect of the cloaca and its membrane may also contribute to a culmination of aberrations that result in a spectrum of ARMs.[15] By the middle of the 7th week of

gestation, the anus and rectum are completely divided from the urogenital tract. The anal membrane then involutes and becomes perforate. The mesodermal perineal body extends to the level of the anal folds (hillocks). The cloaca completely divides, and no external cloaca exists. The anal tubercles unite behind the cloaca and form a U-shaped fold dorsally and laterally between the tail and the anus. The dorsal cloacal wall evaginates just above the level where the anal tubercle impinges on the lumen at the future site of the crypts and columns of Morgagni. The anorectal musculature becomes defined and arises from the third sacral to the first coccygeal myotonic hypomeres, starting at the 8th week of gestation.[16] The anal portion of the rectum is initially long and is of endodermal origin (hindgut origin). In the 9th week of gestation, the external sphincter, levator ani (particularly the puborectalis muscle), and even the ganglia and plexuses of the rectum are well defined.

In the 55-mm fetus, the anal portion of the rectum is reduced in length and gradually becomes shorter and broader. According to studies of human embryos in the Carnegie collection by deVries and Friedland,[12] no proctodeum is observed. This finding contradicts the time-honored role of the anal pit (or proctodeum of ectodermal origin) in the development of the anal canal as demonstrated in other mammalian species (e.g., chick embryo). Furthermore, it brings into question the theory that ARMs are the result of a failure of the anal pit (proctodeum) to become continuous with the hindgut cavity. Additional studies in human embryos are required to further elucidate the exact cause of the myriad of anorectal anomalies.

CLASSIFICATION

ARMs are classified according to their anatomic level of presentation and gender. Ladd and Gross proposed the original types I through IV malformation classification system in 1934. Several modifications of this system were subsequently proposed, in large part based on embryologic observations. Smith[17] in addition to Stephens and Smith[18] developed an important classification at an international workshop on ARMs in 1970 (Table 171–1). This system was based on whether the lesions were located low (translevator), at an intermediate level, high (supralevator), or whether it was a miscellaneous type. This culminated in 11 different lesions noted in males and 16 in females. Although this classification was used extensively (particularly in Australia and New Zealand), it was considered too complex and detailed by many pediatric surgeons.

In 1984, Stephens and Smith[19] and others developed the Wingspread classification to address only commonly observed anorectal anomalies (Table 171–2). The newer classification used similar terms and was based on

Table 171–1 International Classification of Anorectal Anomalies (1970)

Level	Male	Female
High Deformities (Supralevator)		
Anorectal agenesis	Without fistula	Without fistula
	With fistula	With fistula
	Rectovesical	Rectovesical
	Rectourethral	Rectovaginal (high)
		Rectocloacal
Rectal atresia, male and female		
Intermediate Deformities (Supralevator and Translevator)		
Anal agenesis	Without fistula	Without fistula
	With fistula	With fistula
	Rectobulbar	Rectovaginal (low)
		Rectovestibular
Anorectal stenosis, male and female		
Low Deformities (Infralevator)		
At normal anal site, male and female		
Covered anus: complete		
Anal stenosis		
At perineal site	Anterior perineal anus	Anterior perineal anus
	Anocutaneous fistula	Anocutaneous fistula
	(Covered anus: incomplete)	(Covered anus: incomplete)
At vulvar site	Nil	Vulvar anus
		Anovulvar fistula
		Anovestibular fistula

Data from Stephens FD, Smith ED: Anorectal Malformations in Children. Chicago, Year Book, 1971.

Table 171–2 Wingspread Classification of Anorectal Anomalies (1984)

Level	Male	Female
High	Anorectal agenesis	Anorectal agenesis
	With rectoprostatitis	With rectovaginal fistula
	Without fistula	Without fistula
	Rectal atresia	Rectal atresia
Intermediate	Rectobulbar urethral fistula	Rectovestibular fistula
		Rectovaginal fistula
	Anal agenesis without a fistula	Anal agenesis without a fistula
Low	Anocutaneous fistula	Anovestibular fistula
	Anal stenosis*	Anocutaneous fistula
		Anal stenosis*
		Cloacal malformations
	Rare malformations	Rare malformations

*Previously called *covered anus*.
Developed by Stephens FD, et al: Symposium on Anorectal Abnormalities, Wingspread Report, Racine, Wisconsin, 1984.

Table 171–3 Peña's Classification of Anorectal Malformations

Category	Criteria
Males	
No colostomy	Perineal fistula
Colostomy	Rectourethral fistula
	Bulbar
	Prostatic
	Rectovesical fistula (bladder neck)
	Imperforate anus without fistula
	Rectal atresia
Females	
No colostomy	Perineal fistula
Colostomy	Vestibular fistula
	Persistent cloaca (<3 cm or >3 cm common channel)
	Imperforate anus without fistula
	Rectal atresia

From Peña A: Anorectal malformations. Semin Pediatr Surg 4:35, 1995.

anatomic levels but excluded other important anomalies such as a rectocloacal defects and anterior ectopic anus. There were 7 different lesions in males and 10 in females, with the cloacal malformations listed separately under the new classification system.

Peña[20] proposed a more recent classification system in which the lesions are grouped according to gender and whether a colostomy is indicated in the management (Table 171–3). This system further classifies the anomalies according to the differences in treatment and prognosis.

Regardless of the classification system used, lesions are characterized as to whether they occur as high-lying, intermediate, or low-lying anomalies with or without an associated fistula from the hindgut. High-lying lesions indicate that the end of the rectal atresia is located in a supralevator location above the pubococcygeal line. Intermediate lesions indicate that the end is in a translevator position between the pubococcygeal line and the lower sacrum. Low-lying (infralevator) lesions indicate that the end of the rectal atresia has passed beyond the level of the levator (through the puborectalis) to a position below the lowest portion of the ischium (Fig. 171–1).

Using the Wingspread Classification System, Holschneider et al.[6] found that 47% of anorectal defects were low, 14% were intermediate, 36% were high, and 1% of patients had cloacal anomalies. More than 80% of patients have a fistulous connection to the genitourinary tract or perineum (Fig. 171–2). Eighty percent of boys with high rectal atresia have a fistula to the urethra at the level of the verumontanum, and 6% have fistula to the bladder.[21] In instances of imperforate anus with a rectourethral fistula, the fistula opens in the lower posterior urethra (bulbar portion) or in the upper posterior urethra (prostatic portion). Those with a bulbar fistula typically have well-functioning sphincters and an intact sacrum, whereas those with a prostatic fistula experience a higher incidence of sacral anomalies and poorly functioning sphincter mechanisms. In boys with a low-lying lesion, 70% have an anocutaneous fistula that presents anterior to the external sphincter along the midline raphe of the perineal body as it extends up to the scrotum (Fig. 171–3).

In girls, the easiest way to clinically assess the anatomy is by direct visualization during physical examination of the perineum in the lithotomy position. Girls present with variants of the normal three perineal orifices: (1) urethra, vagina, and a third opening that represents an imperforate anus with associated perineal or

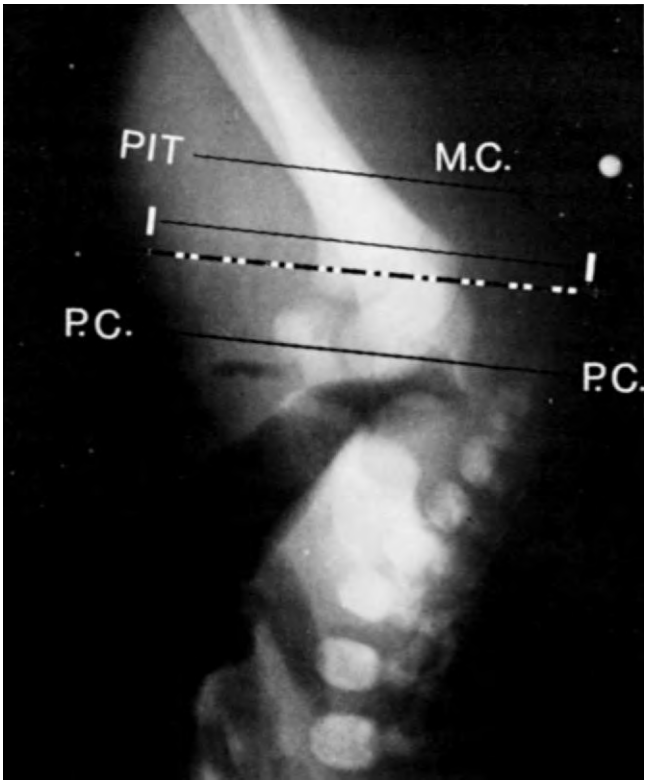


Figure 171–1. Lateral invertogram in a patient with anorectal agenesis and a rectourethral fistula. Air shadow is above the pubococcygeal line (PC). Air is noted anteriorly in bladder. I is the line of the ischial ossification site (the level of translevator lesion), whereas MC is the mucocutaneous line, the level of low (infralevator) lesions. PIT indicates the anal dimple. (From deVries PA: The surgery of anorectal anomalies: Its evolution with evaluations of procedures. Curr Probl Surg 21:1, 1984.)

rectofourchette/vestibular fistula (Fig. 171–4); (2) two openings (the urethra and vagina) with an imperforate anus and a rectovaginal fistula; and (3) one perineal opening, an imperforate anus with a cloaca, and associated vesicocloacal and rectocloacal fistulas (Fig. 171–5). Of the girls with high anomalies, 80% have an associated fistula (usually to the lower third of the vagina), whereas more than 93% with low rectal atresia have a fistula. In females, a rectovestibular fistula is quite common and is located where the rectum opens in the vestibule of the genitalia. These patients typically have a normal sacrum and well-developed sphincteric mechanism. A *persistent cloaca* is defined as a defect in which the rectum, vagina, and urethra enter into one common channel that opens into the perineum as a single orifice. Peña[20] described two cloacal groups: those that have a common channel shorter than 3 cm or and the other with a common channel longer than 3 cm. Patients with a channel shorter than 3 cm can usually be repaired via a posterior sagittal approach, whereas a defect with a longer channel presents a more complex anomaly that typically requires a laparotomy and posterior sagittal approach.

Imperforate anus without a fistula in either sex is unusual and accounts for approximately 5% of the entire group. In this instance, the atretic rectum is typically located within 2 cm of the skin of the perineum. These infants usually have a good sacrum and muscle complex. Instances of low imperforate anus in infants with Down syndrome (trisomy 21) are less likely to have an associated fistula. Rectal atresia and stenosis represent a unique defect in which the infant has an intact anal canal with normal sphincter and sacral development along with normal external anatomy; however, when a tube is passed into the rectum, an obstruction is identified that is related to an atresia noted between the anal canal and the rectum.

ASSOCIATED ANOMALIES

Genitourinary Types

The association between imperforate anus and abnormalities of the genitourinary system is well recognized. The incidence of genitourinary lesions increases as the level of rectal descent decreases; that is, high imperforate anus is associated with the greatest number of abnormalities. Urologic malformations are present in 40% to 52% of males with high anomalies and in 48% of females with high anomalies.[5,22] For the low and intermediate groups, the incidence of urinary malformations was 21% and 14%, respectively[5]; however, females with cloacal malformations may have genitourinary anomalies in 81% of cases.[23]

The most common anomaly noted is an absent kidney, followed by vesicoureteric reflux. An accurate and thorough investigation must be completed using an abdominal ultrasound and voiding cystourethrogram (VCUG) to minimize long-term morbidity.

Sacral and Spinal Types

The coexistence of spinal and sacral abnormalities in patients with imperforate anus has been well established. Segmentation anomalies, sacral agenesis, or both may occur. In addition, the underlying spinal cord may contain occult dysraphic lesions. The overall incidence of lumbosacral anomalies (noted on plain radiograph) in patients with imperforate anus ranges from 30% to 44% but is more common in high lesions (48% to 54%) than in low lesions (15% to 27%).[24-26] Spinal cord abnormalities, including a low-lying conus medullaris, a thickened fatty filum terminale, and a cord lipoma, have been observed in 18% to 50% of patients.[24,26-28] Typically, the incidence of spinal lesions is somewhat higher in cases of high rectal atresia and high-lying imperforate anus (44 vs. 27%).[29] There is a correlation between the degree of sacral development and the final functional prognosis.

Other Anomalies

In addition to the well-known urologic and spinal anomalies, cardiac lesions coexist in 8% of patients with ARMs, esophageal atresia and/or tracheoesophageal fistula

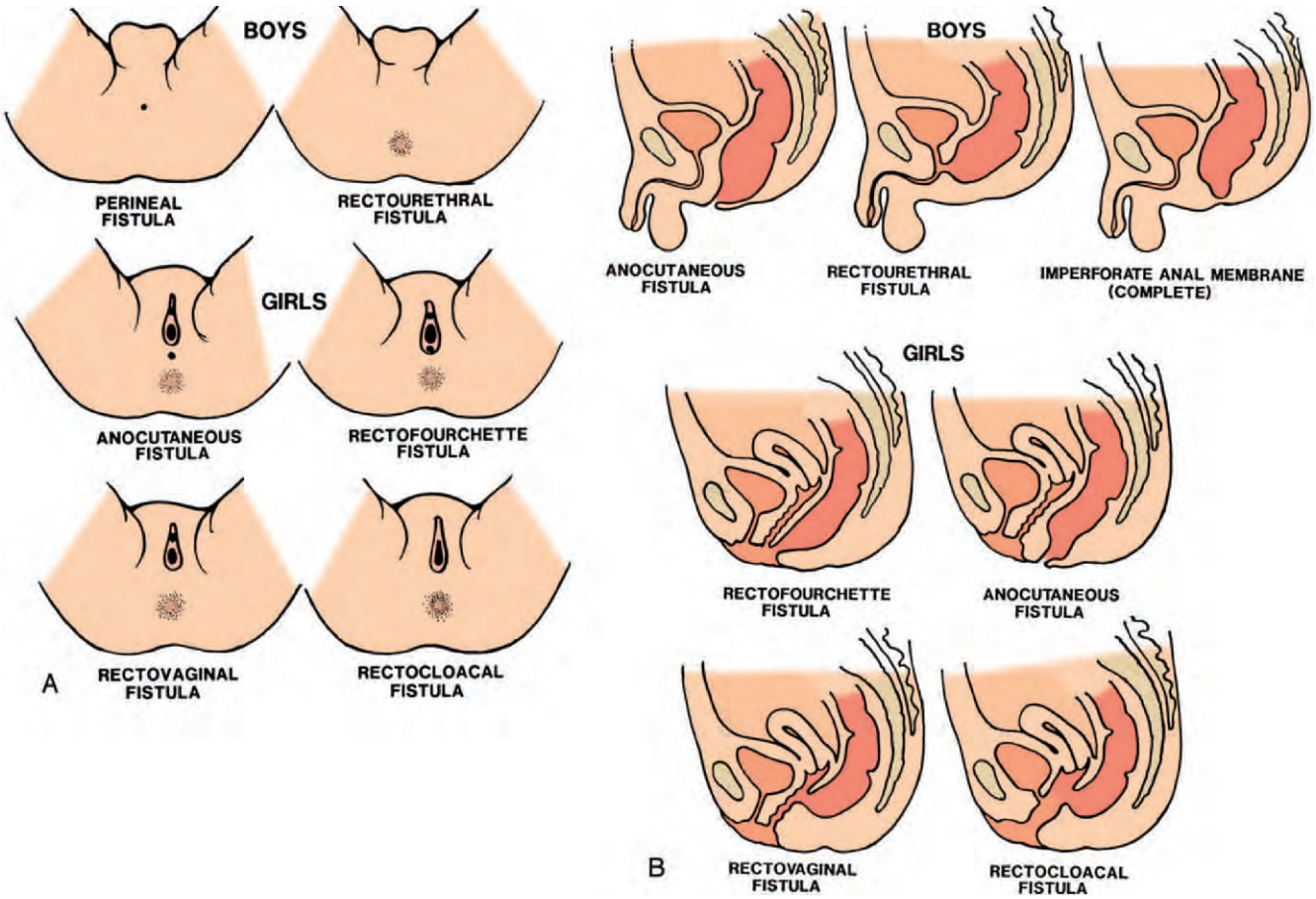


Figure 171–2. **A,** Perineal appearance of anorectal anomalies in boys and girls. **B,** The lateral view of the same defects.

occurs in 6%, and abdominal wall defects are noted in 2%.[30,31] The tendency for some of these lesions to occur concurrently is represented by the acronym VACTERL association (i.e., *v*ertebral, *a*nal, *c*ardiac, *t*racheo-esophageal, *r*enal, and *l*imb anomalies).[32] An imperforate anus may also be associated with duodenal atresia and, rarely, coexist with aganglionic megacolon; presacral lesions (i.e., Currarino's syndrome, teratomas, anterior meningocele)[33-35]; chromosomal syndromes,[36,37] including trisomy 13 to 15, trisomy 16 to 18, Down syndrome (trisomy 21)[38,39]; intestinal atresias[40,41]; congenital short colon (pouch colon syndrome)[42]; and cat-eye syndrome (otic atresia and colobomas).

PELVIC MUSCULAR ANATOMY AND THE PHYSIOLOGY OF CONTINENCE

We briefly review the normal anatomy of the rectum and pelvic musculature and mechanisms of continence as they are related to congenital disorders to further understand the reconstruction of complex anorectal anomalies. The normal rectum is divided at its angulation by the contraction of the puborectalis muscle into an ampulla above and an anal canal below. The posterior rectal wall is acutely indented by the anterior pull of the puborectalis muscle and overhangs the remainder of the levator diaphragm. The anal canal is surrounded by sphincter muscles and is tethered to a concentrically arranged internal (involuntary) sphincter and an external (voluntary) sphincter. The skin-lined anal canal has intrinsic sensory receptors with conventional nerve endings that detect pain, touch, temperature, tension, and friction. There are no sensory receptors per se in the ampulla, but it is sensitive to distention (stretch). The puborectalis muscle is the key sensor mechanism at the entry of the anal canal from the ampulla.[19] This governs both unconscious and conscious opening and closing of the anal canal and provides warning of impending defecation.

Continence is maintained normally through a combination of resting tone in all the sphincters and both reflex and voluntary contraction of the puborectalis muscle and deep external anal sphincter. The resting tone in the internal sphincter occludes the lumen of the perineal part of the anal canal but relaxes just ahead of the peristaltic contraction in the adjoining ampulla and pelvic portion of the anal canal. As an increase in the intraluminal pressure in the rectum rises to the level of the resting pressure of the anal canal, the spinal reflex operates to maintain closure through contraction of the

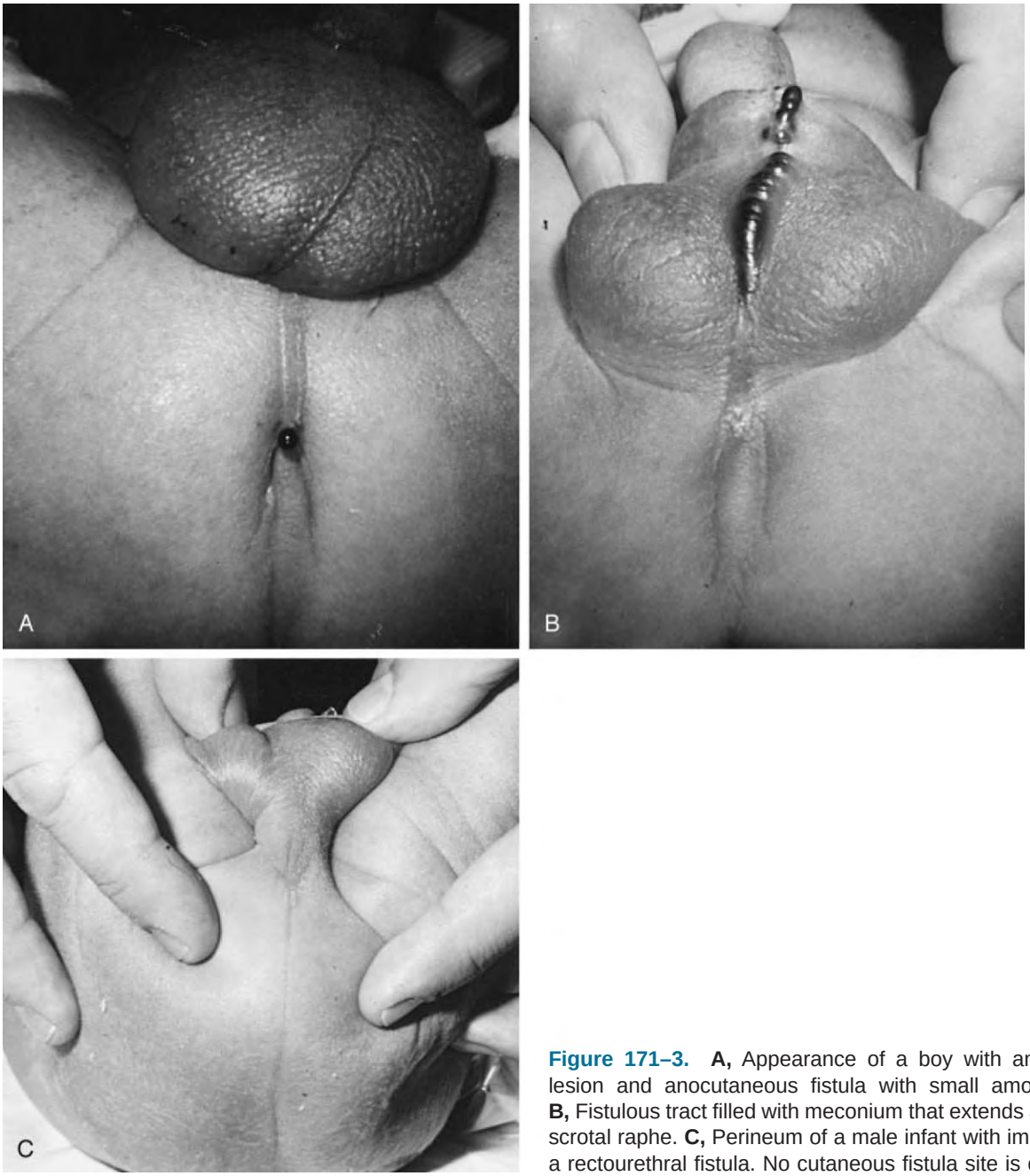
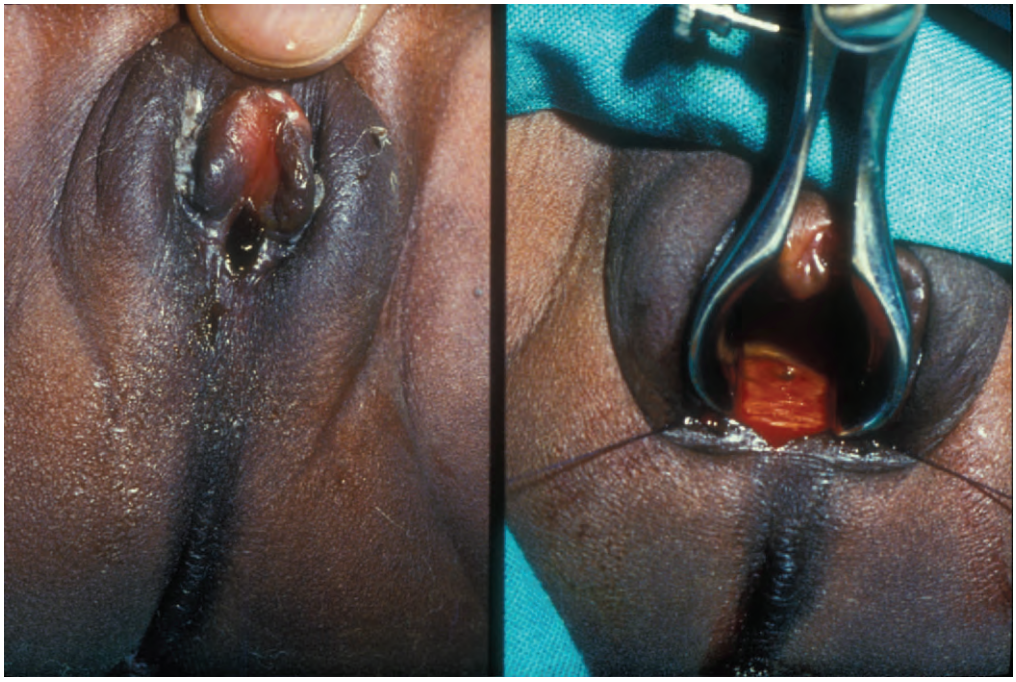


Figure 171–3. **A,** Appearance of a boy with an infralevator (low) lesion and anocutaneous fistula with small amount of meconium. **B,** Fistulous tract filled with meconium that extends anteriorly along the scrotal raphe. **C,** Perineum of a male infant with imperforate anus and a rectourethral fistula. No cutaneous fistula site is observed.

puborectalis sling and maintains continence during the relaxation phase.[31] Higher propulsion pressure waves in the rectum force the entrance of stool into the anal canal. This activates stretch receptors of the puborectalis and initiates an afferent impulse to the spinal and cortical centers and an awareness of rectal distention. The voluntary sphincters and regulation of anorectal continence are then under conscious control.

The relaxation of the internal sphincter in response to rectal distention in normal patients is referred to as the *rectoanal reflex* and is lacking in patients with Hirschsprung's disease. The internal sphincter is under control of the parasympathetic nervous system through the spinal arc at S2, S3, and S4, which contains nerve centers that coordinate rectal peristaltic activity and involuntary (unconscious) sphincter control. The pudendal nerve supplies the sympathetic stimulus that causes constant contraction of the internal sphincter and produces the so-called continent slit shape of the anus. This cortical arc is called into play when increased intraluminal pressure exceeds the resting pressure. The afferent pathway is via the pudendal nerve to the spinal center and cerebral endings in the cortex that activate the efferent pathway that controls the voluntary muscle sphincters.

The entire length of the anal canal is surrounded by voluntary muscles. The funnel-shaped musculature compresses the upper anal canal on three sides by the



A B

Figure 171–4. Perineal examinations in two different girls show the presence of imperforate anus with a rectofourchette fistula **(A)**, and a rectovaginal fistula **(B)**.

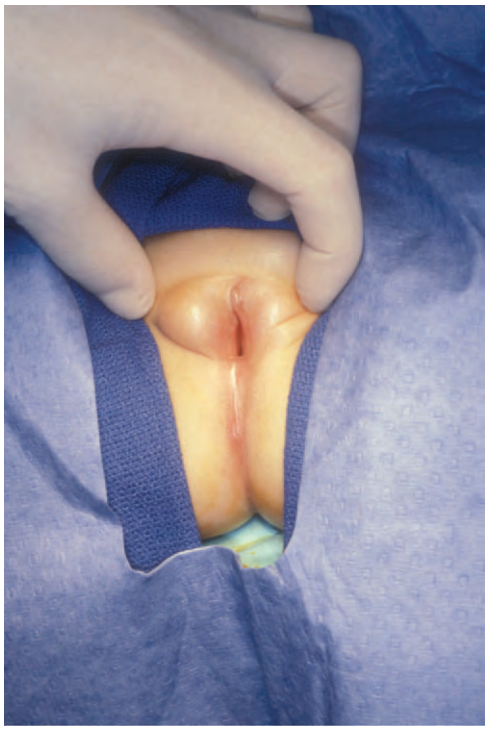


Figure 171–5. Female perineum showing a cloaca.

anterior pull of the puborectalis sling, whereas the barrel-shaped external sphincter squeezes the lower skin-lined aspect of the anal canal. The levator ani muscle complex is composed of four muscles (pubococcygeus, iliococcygeus, puborectalis, and coccygeus). These structures form the complete muscle floor of the pelvis, provide a portal of exit from the anal canal, and prevent herniation of the pelvic contents alongside the canal by blending with the smooth muscle coats of the rectum.

The external sphincter is a barrel-shaped muscle that lies outside the internal sphincter in continuity with the puborectalis sling and surrounds the anal canal from the pectinate line to the anal orifice. Although Stephens and Smith[18] stressed the importance of the puborectalis muscle in regard to the development of continence in patients with imperforate anus, they also considered the internal and external sphincter muscles to be of minimal value. They theorized that the puborectalis provided the main sphincter mechanism available for continence in these cases. deVries and Peña,[2] however, demonstrated that the external sphincter played an important role in the development of fecal continence. In their careful dissections during the performance of posterior sagittal anoplasty for imperforate anus, they failed to detect an isolated puborectalis muscle but referred to a striated muscle complex that represents a fusion of the puborectalis portion of the levator ani and the external sphincter muscle (particularly the deep portion). They further stated that dorsal to the muscle complex are the superficial and subcutaneous external sphincter muscles

that extend up to the coccyx as a separate layer of longitudinal muscle fibers. The point at which the external sphincter muscle fuses with the levator muscle marks the beginning of the striated muscle complex.

Many patients with imperforate anus have problems with continence. There is great variability in the presence of striated muscle from patient to patient. Some patients have weak musculature, whereas some have nearly normal muscle. The presence or lack of underlying sacral and neurologic abnormalities also plays a role in the success or failure in any specific case. In addition, a major problem in many cases (particularly in infants with high imperforate anus) is the lack of internal sphincter muscle. The internal sphincter can be identified in some instances of low imperforate anus with an anterior ectopic opening or perineal fistula. When the location of the rectal atresia associated with imperforate anus is higher, however, the important so-called message center for the rectoanal reflex is lacking, leading to the frequent complaint among some of these patients that they are unaware of the presence of feces in the anus, which results in soiling. Sections taken through the site of a rectourethral fistula indicate that the remnant of the internal sphincter muscle may be within the fistula itself. Because most surgical procedures for imperforate anus leave this area in place to reduce the chance of injury to the urethra, the internal sphincter in these cases is often not of use to the patient. In addition, Holschneider et al.[43] have noted abnormal innervation patterns in 96% of specimens (fistula/rectal pouch). Of interest was that all fistula tracts were found to be aganglionic including the adjacent part of the rectum involving the internal sphincter equivalent. It was concluded that partial denervation of the rectum may not be the only cause of stooling abnormalities after definitive repair. In patients with high imperforate anus, the goal is to perform a procedure as carefully as possible to preserve whatever sphincter and levator muscles are available and to place the rectum within the muscle complex to allow the best opportunity for the development of socially acceptable continence.

INITIAL MANAGEMENT OF THE NEWBORN

Male Infant

In male infants with low lesions, increases in rectal intraluminal pressure may not occur for up to 24 hours after birth. Because this is a low-lying cause of neonatal intestinal obstruction, the physician can safely wait 18 to 24 hours to observe for a bulging anal membrane and possible darkening by meconium. One may also note the presentation of an anocutaneous fistula or find meconium present in the median raphe of the scrotum. Remaining patient during the evaluation may minimize subjecting the neonate to an unnecessary preliminary colostomy. Decompression of the stomach with an orogastric tube limits distal bowel distention and may reduce the ability to make an appropriate clinical decision. Similarly, if the level of descent of bowel gas relative to the anterior inferior edge of the ischium and pubococcygeal line is to be relied on as a guide to determine the level of rectal atresia, one must wait until the rectum is sufficiently distended with air. Because of the contraction of the levator muscle complex that surrounds the rectum, radiographs obtained in normal newborns may suggest a bowel gas appearance consistent with a high supralevator rectal atresia before intraluminal pressure increases sufficiently to force open the distal rectal lumen. All boys with a perineal fistula, bucket handle abnormality, or median raphe fistula are treated with a cutback or anterior perineal anorectoplasty.

If meconium is noted in the urine (Fig. 171–6) but is not visible at the perineum, the patient has a flat-appearing bottom with little or no buttock crease, and anal skin features are absent, one can presume there is an associated sacral defect (dysgenesis or agenesis), and the presence of a high anorectal lesion with a rectourinary fistula is almost certain. Because sacral nerve branches S1, S2, and S3 are necessary for anal continence, patients with sacral agenesis unfortunately have little chance to achieve typical fecal continence. A colostomy is the initial surgical management in cases with high or intermediate imperforate anus.

Female Infant

In the female patient, an anocutaneous or anovestibular fistula to the posterior fourchette of the vagina is almost always visible in low types of lesions on physical examination. If the opening of the bowel cannot be seen, or there is meconium observed coming from the vagina, it is likely there is a high rectovaginal fistula, which requires

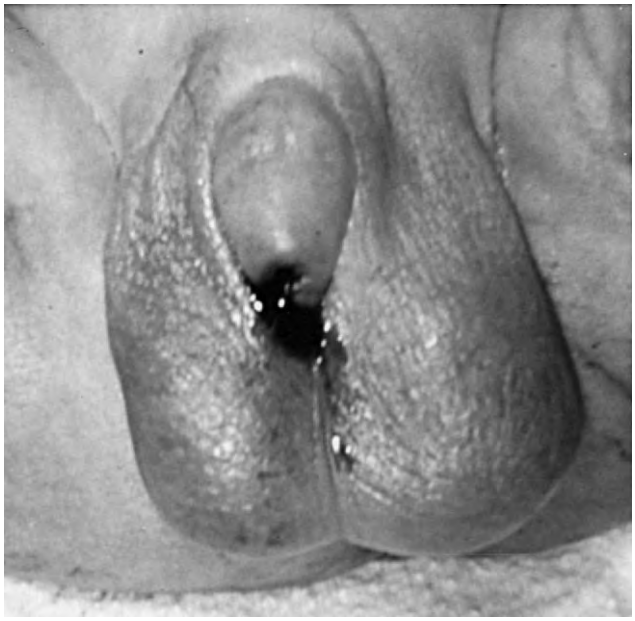


Figure 171–6. Meconium is seen coming from the penile urethral orifice. This is consistent with a rectourethral fistula.

a temporary diverting colostomy and formal reconstruction later. The presence of a single perineal orifice indicates the presence of a cloaca. In the event of a cloaca a screening abdominal ultrasound is performed. It is important to understand the status of the urologic system prior to colostomy in these patients because it may be necessary to divert the urinary tract.

All Infants

Unfortunately, a physical examination does not always provide the definitive answer as to which patients require a colostomy. Imaging studies have been used to assist in making this decision, including the invertogram[44]; however, as an alternative to holding the infant upside down, a prone cross-table lateral view can be obtained.[45] With this technique, a radiopaque perineal skin marker is taped in place to aid in determining the distance between the end of the rectum and the anal skin site. Other imaging modalities include ultrasonography, magnetic resonance (MR) imaging, VCUG, and lumbosacral radiography. These modalities have been used to determine the level of the distal rectal pouch, to identify the presence of a fistula, and to diagnose any associated congenital anomalies. In the neonate, ultrasound examination of the lumbosacral spine is useful in identifying spinal cord lesions. The puborectalis muscle is a landmark used to distinguish the level of the defect. MR imaging can demonstrate the presence of muscle preoperatively; however, MR may have some limitations in demonstrating the relationship of the distal rectal pouch to the puborectalis muscle and may require sedation and/or a general anesthetic to accomplish in the newborn phase.[46,47] Infracoccygeal ultrasound, on the other hand, can directly demonstrate the puborectalis muscle in neonates[48] without sedation. It is difficult to accurately depict the puborectalis sling using conventional transperineal ultrasound because this study relies on indirect measurements to reach a conclusion.

In older infants, MR imaging studies are of great value in detecting spine abnormalities. Lumbosacral radiographs are obtained to evaluate the sacral anatomy. Obtaining a renal ultrasound is also useful in detecting associated urinary tract anomalies. A retrograde cystourethrogram is an accurate method of delineating an associated rectourethral fistula in boys. Diagnostic endoscopic evaluation in girls with a cloacal defect is essential before any definitive repair. It demonstrates instances of vaginal septation, vaginal atresia, and duplex uterus and separates high from low cloacal anomalies.

Operative Technique

As a general rule, infants born with low anomalies are treated definitively in the neonatal period. Infants with a complete atretic anal membrane are managed by incising the skin covering (usually seen bulging with meconium behind it) to relieve the obstruction. Anal dilations (using Hegar dilators) for 3 to 6 months result in adequate anal orifice without stenosis. The passage of more-formed stools in later infancy maintains the opening.

LOW IMPERFORATE ANUS

Cutback Anoplasty

Infants with an anocutaneous fistula undergo a cutback perineal anoplasty (Fig. 171–7). A Y-V technique that creates a U-shaped superficial external sphincter and widened skin orifice is used. The puborectalis and deep external sphincter muscles are carefully identified through electrostimulation and are preserved. A portion of the posterior fistula wall is incised and sutured to the skin edges with interrupted 4-0 absorbable suture. The new anoplasty site should be sized to a No. 10 Hegar dilator. Postoperatively, bowel contents are gently dabbed from the perianal skin with moist cotton balls. Vigorous wiping techniques should be avoided in the first week. Gentle tepid water irrigation can be used after 48 to 72 hours to clean the perineal skin. Daily dilation with a No. 10 Hegar dilator is initiated approximately 10 to 14 days after the procedure and continued for a 6-month period. The dilator size is gradually increased to a No. 13 or 14 dilator.

Although Smith[19] suggested a cutback anoplasty for girls with an anovestibular fistula to the extravaginal

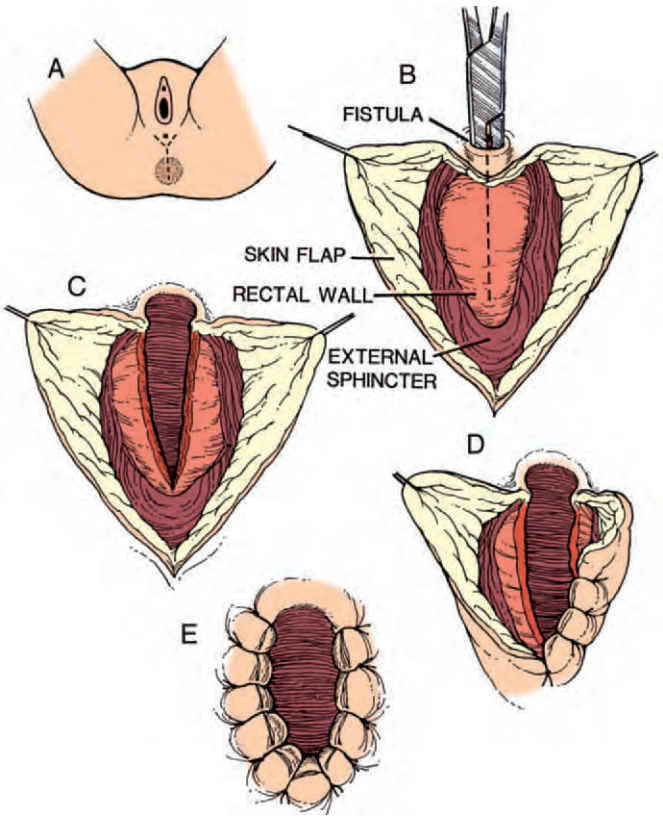


Figure 171–7. Y-V cutback anoplasty for anal atresia with anocutaneous fistula. After Y incision **(A),** skin flaps are carefully raised, and the sphincter is identified and preserved **(B).** The rectal pouch is incised **(C),** and the edges of the rectum are sutured (full-thickness) to the skin edges **(D** and **E)**.

fourchette, we believe these patients require either a transplant anoplasty or a minimal PSARP to preserve the perineal body and adequately separate the vaginal and anal orifices as described by Potts and associates.[49] Fecal content is passed through the rectofourchette fistula aided by daily dilation, and definitive operative repair can be delayed until the perineal and vaginal tissues become more sturdy. Accurate diagnosis of the level of the rectal atresia is important, because an intermediate-level rectovestibular fistula in a girl is similar to a rectourethral fistula at the level of the verumontanum in a boy and would require a preliminary colostomy. Proponents of anterior sagittal anorectoplasty argue that anal transplantation is performed without the clear identification of muscular anatomy that this procedure provides.[50] However, there are no randomized prospective studies that directly compare the two techniques, and it has been our practice to individualize therapy based on the location of the fistula.

Transplant Anoplasty

Transplant anoplasty is initiated by placing a series of 4-0 silk traction sutures at the 12-, 3-, 6-, and 9-o'clock positions of the fistula opening (Fig. 171–8). Using fine curved tenotomy scissors, or electrocautery, the fistula is carefully dissected free close to its wall (in all four quadrants). The anterior dissection in the common wall between the fistula and posterior vaginal wall is usually quite tedious. A fine-tip electrocoagulator, wide-angled magnifying loupes, and small aspirator are useful adjuncts. Once above the level of the fistula site, the anterior and lateral dissection is more easily accomplished. Posteriorly, careful perineal dissection is also required to prevent injury to the striated muscle complex. The superior extent of the posterior dissection is continued superiorly within the puborectalis–deep external sphincter muscular sling. The site of the new anal orifice is identified by electrical muscle mapping to demonstrate maximum contraction at the pucker site. A skin incision is made at this point, and to join the posterior dissection of the fistula tract within the muscular sling, careful dissection through the center of the subcutaneous and superficial external sphincter muscle is performed. The opening is progressively dilated with Nos. 7, 8, and 9 Hegar dilators. The fistula is then transplanted to the new anal orifice site using the previously placed traction sutures. The fistula site is usually narrow enough to enter this area without tapering. The posterior smooth muscle rectal wall 2.0 cm above the orifice is sutured to the muscle complex with interrupted absorbable sutures to prevent prolapse. Suturing the anal orifice (full thickness) to the edges of the anal skin with interrupted 4-0 absorbable suture completes the anoplasty. The previous fistula site at the fourchette is closed, and an indwelling Foley catheter is left in place for approximately 72 hours to prevent urine from bathing the new suture lines. Alternately, Peña and others approach this lesion by performing a posterior sagittal anoplasty and proximal diverting colostomy in each instance.

Anterior Perineal Anorectoplasty

The PSARP has been the mainstay treatment for ARM; however, the anterior perineal anorectoplasty may offer similar outcomes in selected cases. Rectovestibular fistula is the most common form of anorectal anomaly in female patients and the lithotomy position is chosen. The rectal fistula is dissected free and released from the posterior vaginal wall and the anterior portion of the sphincter muscle is divided through a median perineal skin incision. The rectal fistula is then pulled posteriorly to the center of the sphincter muscle and sutured into place with absorbable interrupted sutures.[50,51] This technique has also been employed for higher lesions but requires considerably more expertise.[52]

HIGH IMPERFORATE ANUS

ARM is one of the major indications for a colostomy in a newborn infant.[53,54] In most patients, colostomy is performed as a temporary procedure before definitive surgical correction of the malformation is completed. A colostomy is recommended in the neonatal period for both boys and girls with anorectal anomalies excluding those with perineal fistula. The colostomy often permits a better radiologic definition of the malformation (i.e., loopography), continued growth of the child while waiting for the definitive procedure, and protection of the operative anoplasty site when a corrective procedure has been performed.

Construction of a Colostomy

Infants with intermediate or high anorectal agenesis or rectal atresia, with or without a fistula to the genitourinary tract, and all patients with cloacal anomalies require an initial colostomy. Most surgeons prefer a sigmoid colostomy for these anomalies as recommended by Wilkins and Peña[55] at the junction of the descending and the sigmoid colon, but some surgeons recommend a right transverse colostomy for infants with a cloacal anomaly. A sigmoid stoma is smaller and more manageable with a decreased tendency to prolapse and more formed stool; it eliminates distal loop fecal impaction; it allows sufficient length of colon distal to the stoma so that subsequent pull-through procedure can be carried out without tension; and it may reduce the risk of urinary tract infections. Most surgeons recommend a divided colostomy to ensure complete fecal diversion to avoid potential contamination of the urinary tract and vagina due to spillover of fecal material into the efferent limb and the rectal fistula. Patwardhan and colleagues have recently shown that the incidence of urinary tract infections was 28% in patients with loop colostomy compared to 30% in patients with divided colostomy. A skin gap between the two ends of the divided colostomy did not seem to prevent the development of urinary tract infections.[56] In agreement with the findings of Wiener and Kiesewetter,[57] the incidence of associated urologic anomalies in the patients that had a urinary tract infection was

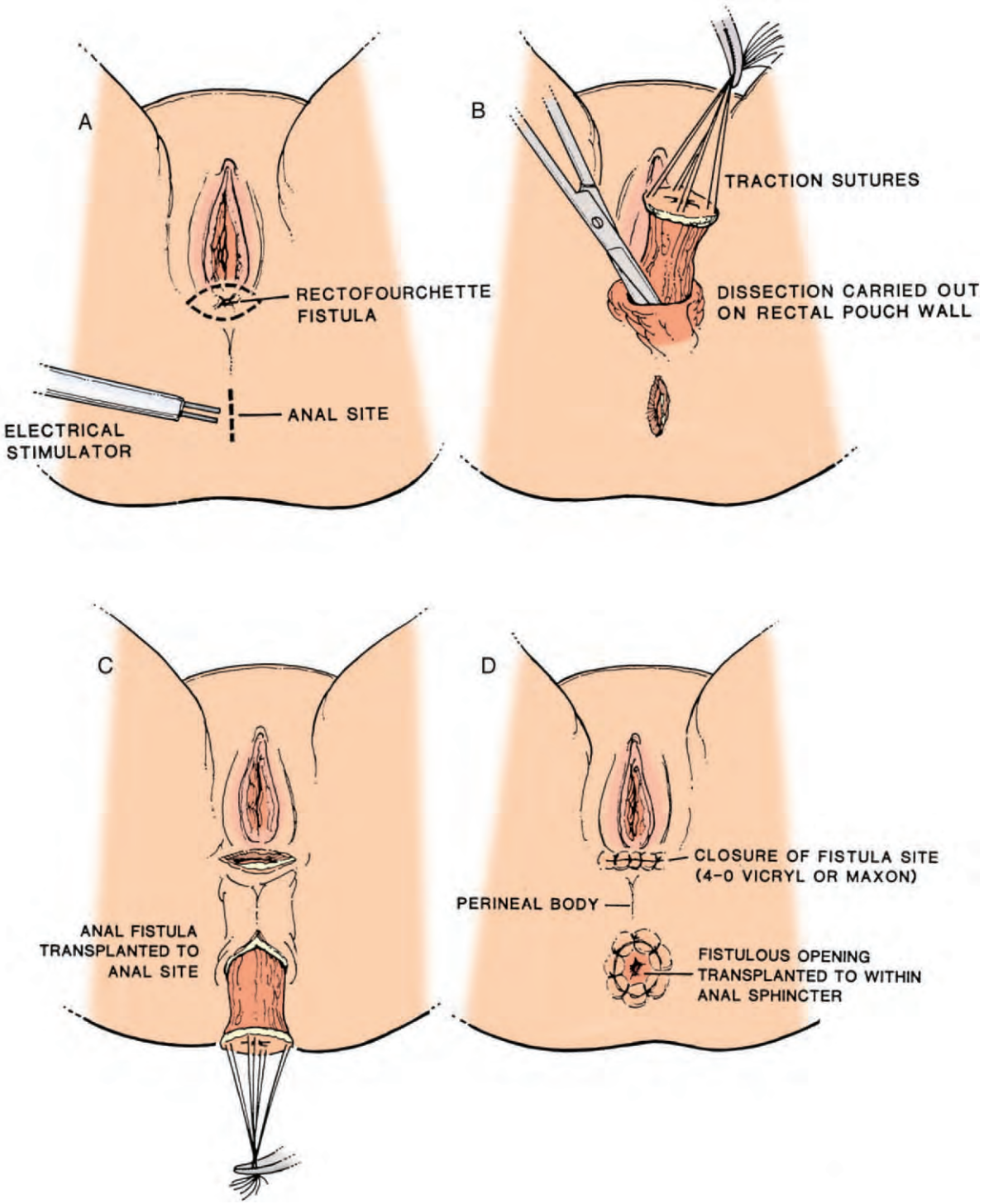


Figure 171–8. Correction of imperforate anus with rectofourchette fistula. The anal site is selected with the aid of an electrical stimulator **(A).** Traction sutures are placed. The fistula is carefully dissected free with tenotomy scissors **(B).** The traction sutures are used to guide the opening to a transplanted anal location within the sphincter complex. Interrupted 4-0 absorbable sutures are used **(C).** The fistulous site is closed with interrupted 4-0 suture. Note the preservation of the perineal body **(D).**

particularly high (71%) and prophylactic antibiotics did not prevent the infections.[56]

Even if the sigmoid stoma is maintained as a loop colostomy, the relatively shorter distal segment allows for irrigation of the distal colon and avoids the occurrence of hyperchloremic acidosis. This electrolyte abnormality is occasionally seen in patients with a transverse colostomy and is caused by the absorption of potentially infected urine from the mucosa of a long segment of unused distal colon.[21] Infants with a fistula to the urinary tract may benefit from urinary tract prophylaxis with oral trimethoprim-sulfamethoxazole. The colostomy is left in place until the time of definitive repair.

Prior to the definitive anorectal procedure, a distal colostogram can be carried out. Peña suggests this is the single most valuable method to accurately study an ARM. This study will demonstrate the location of the blind rectum and identify the site of the rectourinary fistula. Peña recommends the colostogram be done using considerable hydrostatic pressure and fluoroscopic control to minimize the false impression of a very high defect or pure rectal atresia without a fistula. With this knowledge in hand, the surgeon can determine whether an exploratory laparotomy is necessary.

Correction of High and Intermediate Malformation

A number of techniques have been advocated for the modern operative correction of high and intermediate anorectal anomalies, including (1) the abdominoperineal pull-through procedure[58]; (2) a sacroperineal or sacroabdominoperineal pull-through procedure (as advocated by Stephens and Smith),[18] which delineates the puborectalis muscle and divides the rectourethral fistula from within the rectal atresia; and (3) in the 1960s, modifications of the Stephens procedure were reported by Kiesewetter[59] and by Rehbein,[60,61] using a submucosal resection that left leaves a muscular sleeve from the original rectal atresia in place through which an abdominoperineal pull-through procedure is performed. In 1975, Mollard and associates[62,63] advocated the use of an anterior transperineal approach to identify the puborectalis sling and the fistula and then used Kiesewetter's technique to complete the procedure. In 1982, deVries and Peña[2] described the PSARP, a procedure that divides each of the striated muscles in the posterior midline sagittal plane, divides the fistula from within the atretic rectal lumen, and tapers the distal bowel to fit snugly within the muscle complex, which is then reconstituted around the rectum and anoplasty site. More recent innovations by Yokoyama et al.[64] and modifications by Smith[19] combine the excellent exposure afforded by the Peña and deVries[3] sagittal anorectoplasty (which avoids laparotomy and gains excellent exposure to divide the fistula) but keeps the combined puborectalis, pubococcygeus, and deep external sphincter intact and minimally tapers the bowel. The Peña procedure (PSARP) is the most popular operation for intermediate and high anorectal lesions and all ARMs can be corrected by this approach. We present the Peña operation (PSARP) and Smith's modifications in detail.

PSARP can be performed at all ages. The distal bowel segment is prepared by mechanical irrigation with 0.25% neomycin solution and perioperative systemic antibiotics. Care must be taken to alert the anesthesiologist to the fact that muscle stimulation is necessary and paralysis is not desired during the procedure. A urinary catheter is placed, and in 25% of cases, the catheter may pass through the fistula into the rectum rather than into the bladder. The infant is placed in a prone jackknife position with careful padding of the knees, groin, and chest. The operative field is prepared with an iodophor solution, and appropriate sterile drapes and linens are applied. The proposed anal site is determined by electrical muscle stimulation and marked.

A midline sagittal incision is placed on the lower sacrum just above the coccyx and is carried inferiorly to the anticipated anal site; all of the levator ani and sphincter muscles are divided posteriorly in the midline, including the puborectalis and deep external sphincter (Fig. 171–9). Smith[19] modified this procedure by dividing the superficial and subcutaneous parts of the external sphincter and the diaphragmatic portion of the levator (iliococcygeus, ischiococcygeus) muscles sagittally but does not divide the puborectalis, pubococcygeus, and deep external sphincter muscles, which are kept intact. The higher the malformation, the deeper the levator muscle.

The atretic rectal pouch is identified and carefully mobilized circumferentially above the fistula site by blunt and sharp dissection close to the bowel wall to avoid injury to neural structures and the prostatic plexus. An umbilical tape or a small Penrose drain is passed around the rectal atresia. The distal rectal pouch is entered, and the fistula identified from within the lumen. A submucosal plane is developed around the fistula to avoid injury to the seminal vesicles and prostate. The fistula is closed with interrupted 4-0 absorbable sutures. If able, closing additional tissue over the urethral fistula site may minimize the risk of postoperative complications. The atretic rectal pouch is then carefully mobilized, keeping the dissection in the plane of the bowel wall and using a fine-tip electrocoagulator to cauterize multiple vessels (from the middle hemorrhoidal artery) just beyond the rectal wall. In most cases, rectal mobilization is more than adequate through the sacroperineal approach, and a laparotomy is unnecessary.

Once the rectum is fully mobilized, a decision is made concerning the need to taper the rectum. If tapered, the distal bowel is narrowed to comfortably fit within the reconstituted muscle complex without causing injury to the essential muscles. Tapering is accomplished by excising a V-shaped wedge of the posterior wall of the rectal atretic segment and using a two-layered inverting closure with interrupted 4-0 absorbable sutures in the inner and outer layer. It is important to avoid excessive tapering, which may result in a severe stricture. We usually perform the tapering over a No. 12 Hegar dilator.

The tapered rectum is then placed within the divided muscular complex, which is reconstituted around the rectum with fine interrupted absorbable sutures. The

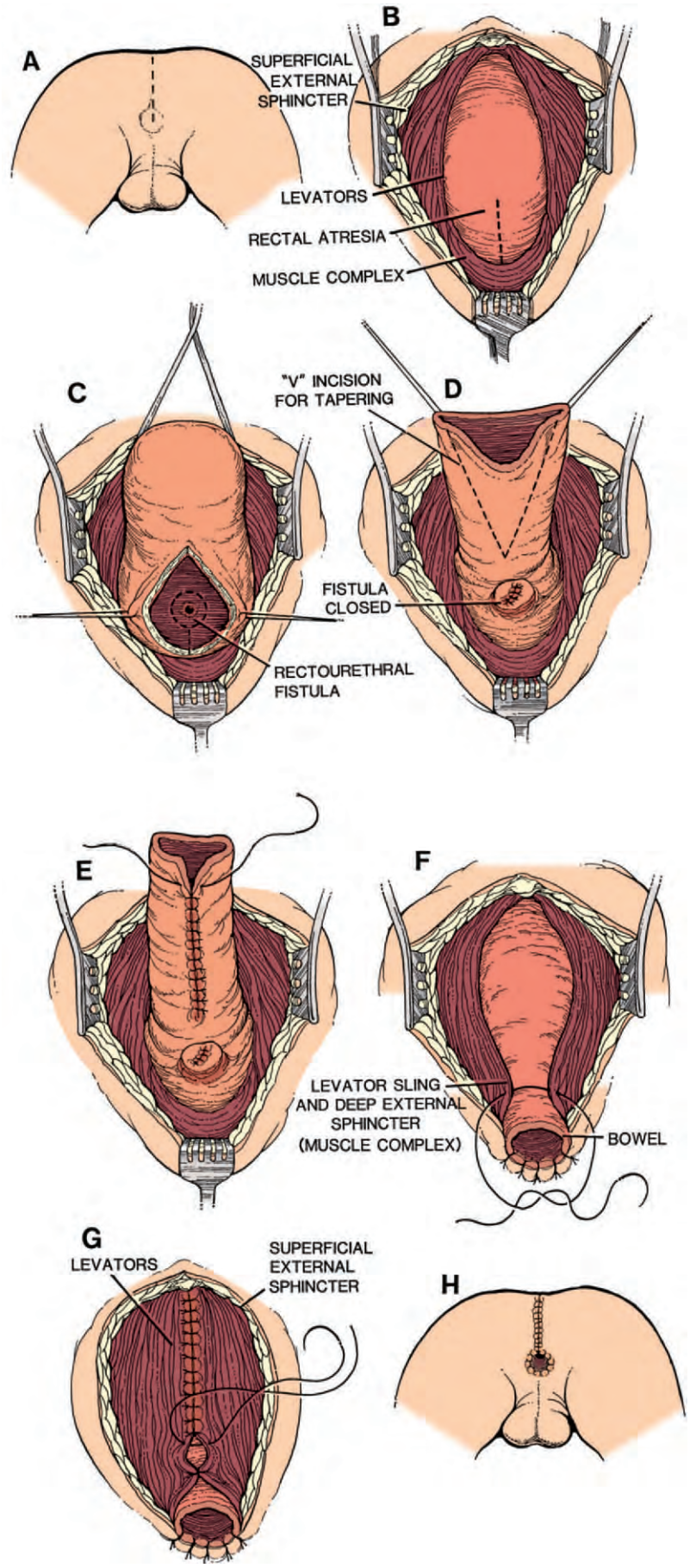


Figure 171–9. Posterior sagittal anorectoplasty. In the prone position, an incision is made in the midline from the lower sacrum to the selected anal site **(A).** The levator and sphincter muscles are divided posteriorly in the midline. The rectal pouch is identified **(B).** The pouch is opened, and the rectourethral fistula is identified within the rectal lumen **(C).** Submucosal resection frees the bowel from the fistula, which is closed with interrupted sutures **(D).** The bowel is tapered to a No. 12 Hegar size **(E).** The muscle complex is reconstituted starting at the deepest portion of the puborectalis muscle and the deep external sphincter **(F).** Levators and superficial external sphincters are then reapproximated with interrupted sutures **(G).** The tapered anoplasty is sutured to the skin with interrupted 4-0 absorbable suture **(H).**

deepest suture begins where the distal portion of the levator ani joins the external sphincter layers, bringing the rectum close to the urethra or vagina. Electrical muscle stimulation is used to identify the structures. The wall of the rectum is tacked to the muscle complex in a few places in an attempt to reincorporate the longitudinal smooth muscle of the rectum with the striated muscle complex, causing a tethering effect. The proximal margins of the levators are closed with interrupted suture. The course of the tapered anoplasty then passes more posteriorly to the site of the new anal opening. The anoplasty is completed by securing the end of the tapered bowel (full thickness) to the skin exit with interrupted 4-0 sutures, incorporating the subcutaneous sphincter in the bites. Performing the procedure with slight tension on the anoplasty avoids postoperative prolapse.

In Smith's modification of the Peña procedure, a Penrose drain is passed through the sling below the fistula site, and the tapered bowel is then passed through the sling anterior to the drain with the aid of traction sutures. The distal bowel is placed within the divided levator muscles and superficial and subcutaneous external sphincter muscles, which are accurately reconstituted around the bowel with interrupted 4-0 absorbable sutures. The anoplasty Smith advocated is a skin-lined tract originally credited to H. H. Nixon of London[65,66] that avoids anocutaneous stenosis. Skin closure of the main wound in both techniques is accomplished with subcuticular absorbable sutures and Steri-Strips.

The colostomy is left in place for approximately 2 to 3 months to allow complete healing and adequate dilation of the new anoplasty site. Daily dilations are started at 10 to 14 days after the procedure using Nos. 8, 9, and 10 Hegar dilators initially and then advancing to larger dilators with time (up to a maximum of No. 13 or 14 Hegar size). The parents must be carefully instructed regarding the importance of the dilations, which must be performed on a daily basis at home to avoid stenosis. Frequent follow-up visits to the surgeon's office after the procedure is necessary to monitor progress, because dilations may be necessary for 6 to 12 months postoperatively.

Neonatal Pull-Through Procedures

The traditional surgical correction of a high or intermediate imperforate anus in the male infant has typically been a three-stage process. Despite performing a technically perfect operation, there are subsets of children that require significant lifelong bowel management for constipation or incontinence.[7,67] It is unlikely that much can be done to improve the outcome for children with poor prognostic factors (abnormal sacrum, poor perineal musculature, colonic dysmotility, and deficient pelvic innervation).[68] The theoretical basis for early restoration of gastrointestinal continuity stems from the belief that the neuronal framework for normal bladder and bowel function exists at the time of birth.[69,70] Because neonates are incontinent of urine and feces, there is a learning period in which long-lasting activity-driven neuronal changes take place during neuronal circuitry development.[71] Theoretically, by delaying the repair of the anorectal anomaly, critical time may be lost in which neuronal networks and synapses would have formed resulting in normal or near-normal anorectal function.[72]

Unfortunately, most studies at this time have limited follow-up due to the fact that it takes a few years to develop continence. The following advantages of a definitive neonatal procedure are highlighted: (1) there is only a single operation; (2) urinary tract colonization through the fistula is avoided; (3) the potential morbidity of a colostomy is avoided; and (4) the fistula can be documented by cystoscopy, thus avoiding other imaging studies.[68] The advantage of avoiding a colostomy especially in developing countries may be an attractive alternative due to the fact that a colostomy is socially unacceptable, colostomy bags are expensive and difficult to locate, many of the parents are illiterate and cannot manage the colostomy, and these environments usually have no stomal therapists available.[73]

Peña cautioned that some of the most devastating complications that he has seen after a posterior sagittal exploration occurred in patients that underwent posterior sagittal exploration without a precise diagnosis obtained by a distal colostogram. The worst morbidity was observed in instances of high defects (rectal–bladder neck fistulas) while looking for an atretic rectum that could only be found at laparotomy. Peña suggested that those surgeons who want to attempt to repair these anomalies in a single-stage approach should develop their own learning curve. Perhaps the first cases that are performed should be relatively low-lying lesions noted on a simple cross-table radiograph taken in the prone position rather than attempting repair of a possible higher lesion that carries higher risks.[68]

Minimally Invasive Repair of High Imperforate Anus

Minimal access surgery has revolutionized the field of surgery in the past decade. The laparoscopically assisted anorectal pull-through (LAARP) for high ARM uses fundamental concepts learned from decades of experience with high ARM repair and additionally incorporates modern technologic advancements in surgical instrumentation and technique.[74] LAARP combines extraordinary anatomic exposure of an infant's deep pelvis with a reconstruction technique that minimizes trauma to important surrounding structures. The advantages (improved visualization, relatively atraumatic proper placement of the pull-through bowel without division of the muscle complex, preservation of the internal anal sphincter fibers within the fistula) essentially allow the surgeon to treat a high lesion similar to a low lesion, are associated with decreased postoperative pain, and potentially reduce the incidence of perineal wound complications.[75]

The infant is positioned horizontally and supine on the operating room table to allow the surgeon and assistant to stand at the patient's head, and, if present, a second surgeon can work at the feet. A total-body sterile

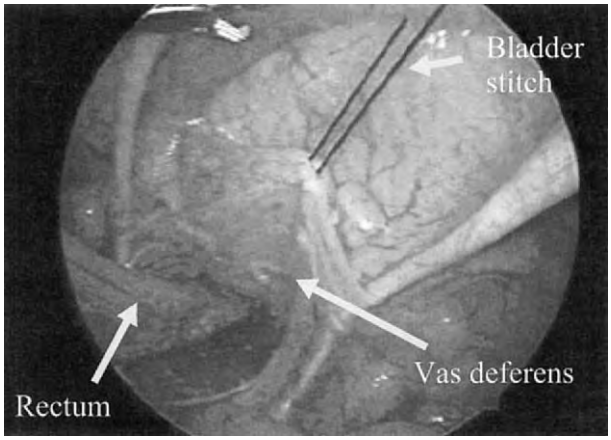


Figure 171–10. Although decompressed, the floppy bladder still needs to be retracted anteriorly. In this figure, a percutaneously placed U-stitch is placed through the bladder and is used for retraction, thereby allowing exposure of the deep pelvic structures. (From Sydorak RM, Albanese CT: Laparoscopic repair of high imperforate anus. Semin Pediatr Surg 11:217-225, 2002.)

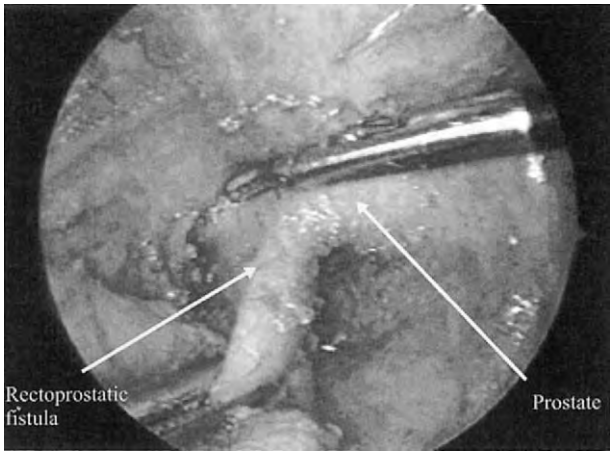


Figure 171–11. The completed dissection of the rectoprostatic fistula before division is shown. The upper instrument is pushing up on the prostate and bladder, and the lower instrument is grasping the rectum. (From Sydorak RM, Albanese CT: Laparoscopic repair of high imperforate anus. Semin Pediatr Surg 11:217-225, 2002.)

preparation is employed from the nipple line to the toes. Preoperative cystoscopy may be helpful in identifying the level of the fistula if not known previously. An indwelling Foley catheter is placed. Local anesthetic may be infiltrated into the subcutaneous tissue around the laparoscopic port sites either preemptively or at the completion of the case. Using an umbilical trocar for camera visualization has not been optimal.[75] Thus the ideal position for the camera port is just to the right of the midline below the liver edge. A 5-mm cannula is introduced 3.0 cm to the right and above the umbilicus. A 30-degree scope is utilized because this provides excellent visualization of the deep pelvic structures and allows several views of the same structure. Surgeons have utilized either a three- or four-port method using either 3- or 5-mm trocars.

Dissection begins at the level of the peritoneal reflection, and the blood supply to the sigmoid and rectum is preserved. Too high a dissection and sacrifice of these vascular structures may result in ischemia of the distal bowel. In addition, the dissection remains adjacent to the wall of the colon to minimize potential damage to the vas deferens, ureter, urethra, prostate, and pelvic nerves. The bladder despite being decompressed requires retraction (Fig. 171–10). Some have used a trocar site for retraction, whereas others have used a transcutaneous bladder stitch that is inserted through the abdominal wall.[75] Once the dissection has reached the level of the bladder neck (Fig. 171–11), a bipolar scissors is used to minimize lateral damage to the pelvic nerves. The distal colon is dissected circumferentially leaving only the fistulous tract connection. The harmonic scalpel or endoscopic clips have been used to divide the fistula tract.[74,75] Some surgeons have been concerned that complications related to these methods may result in urethral stricture or recurrent fistula and advocate division and direct suturing of the fistula tract.[75]

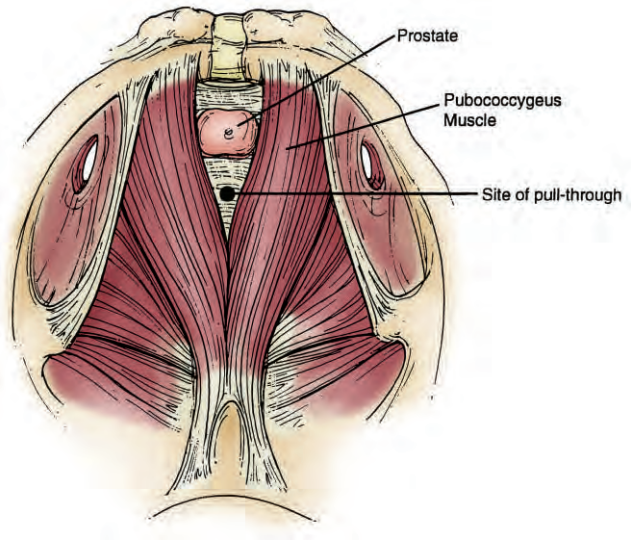


Figure 171–12. Laparoscopic visualization of the pelvis after dissection of the rectum out of the pelvis in a typical boy with high imperforate anus and rectourethral fistula. (From Georgeson KE, Inge TH, Albanese CT: Laparoscopically assisted anorectal pull-through for high imperforate anus: A new technique. J Pediatr Surg 35:927-931, 2000.)

Once the rectum and the fistula are free, the pelvic musculature can be identified. The classic anatomic arrangement of the puborectalis, resembling a sling-shot, can often be appreciated (Fig. 171–12). An assistant can now use a perineal muscle stimulator to identify the location of the central portion of the anorectal muscular complex, and this is marked. Some surgeons have used a laparoscopic muscle stimulator as well to identify the

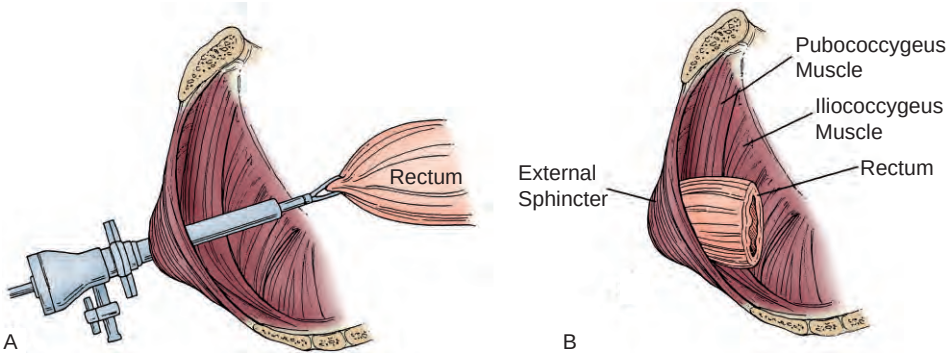


Figure 171–13. **A,** Sagittal view of the trocar through the external sphincter and levator ani and pull-through of the rectum. **B,** Position of the rectum after pull-through to the perineal wound. (**A** and **B,** From Georgeson KE, Inge TH, Albanese CT: Laparoscopically assisted anorectal pull-through for high imperforate anus: A new technique. J Pediatr Surg 35:927-931, 2000.)

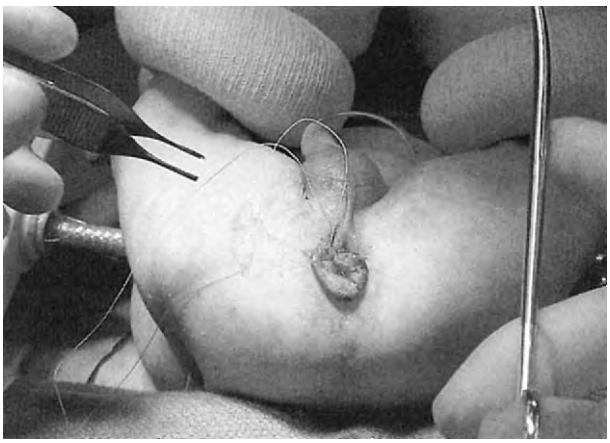


Figure 171–14. The pull-through is completed, and the anorectoplasty is being performed. (From Sydorak RM, Albanese CT: Laparoscopic repair of high imperforate anus. Semin Pediatr Surg 11: 217-225, 2002.)

exact position for the pull-through within the abdomen.[76,77] In essence, one identifies a direct line between the centers of the internal sphincter (external stimulator) and the levator ani (internal stimulator), thus creating an anatomically correct position of the anorectum through the external anal sphincter. The assistant then places a Veress needle/trocar system transcutaneously through the two slings and the sheath of the Veress needle is dilated sequentially from a 5- to 12-mm size depending on the size of the bowel and age of the infant. An endo-Babcock is then introduced into the abdomen and the rectum secured and the bowel is then brought out through the pelvic musculature and out onto the perineum (Fig. 171–13). The anoplasty is then completed with interrupted absorbable sutures (Fig. 171–14). Several rectum-to–presacral fascia sutures can be placed to increase the length of the skin-lined anal canal and to minimize the risk of prolapse.

Surgery for Cloacal Malformation

The initial treatment of a neonate with a cloacal malformation is to provide drainage of the urinary tract and the colon (colostomy). Intermittent catheterization usually can empty the distended vagina and bladder. Infants with a cloacal anomaly do not require an extensive pelvic laparotomy to assess the anatomy. This assessment can be done endoscopically and radiologically. MR imaging of the spinal canal should be performed because a third of these patients have a tethered spinal cord.[78-80] Cloacal reconstruction can be a long and difficult procedure and goes beyond the scope of this chapter, but it is usually deferred until the patient is approximately 1 year old. The pelvis is approached through a long midsagittal incision and down into the single perineal opening. The rectum or vagina is opened. The goal of this procedure is to separate the rectum from the vagina and, subsequently, the vagina from the urinary tract. The rectum and vagina have a common wall, and the separation of these structures requires a meticulous and time-consuming effort, but this dissection is usually easier than separation of the vagina from the urinary tract. The urogenital sinus (common channel) must be reconstructed to become the new urethra by tubularizing the tissue (Fig. 171–15). If the length of the vagina is inadequate to reach the perineum, some form of vaginal augmentation will be necessary. The vaginal orifice is sutured to the perineal skin immediately behind the urethra. The perineal body is then reconstructed to the anterior component of the external sphincter. The rectum is then reconstructed as previously described for the PSARP procedure.[81]

POSTOPERATIVE COMPLICATIONS

Although deVries and Peña[2] reported only minor postoperative complications, some authors have described a number of serious complications after the PSARP procedure. Others[82] have reported major complications in 26% of cases, including sacral wound dehiscence and/or infection, ureteric injury, neurogenic bladder, femoral nerve palsy, leak from the tapered rectoplasty, recurrent urethral fistula, multiple rectocutaneous fistulas, and a supralevator fistula. Most of these complications, however, were related to technical errors and are probably avoidable. Genitourinary complications, including neurogenic bladder, urethral stricture, and urethral diverticulum, have also been observed and may be related to technical errors at the time of the PSARP procedure.

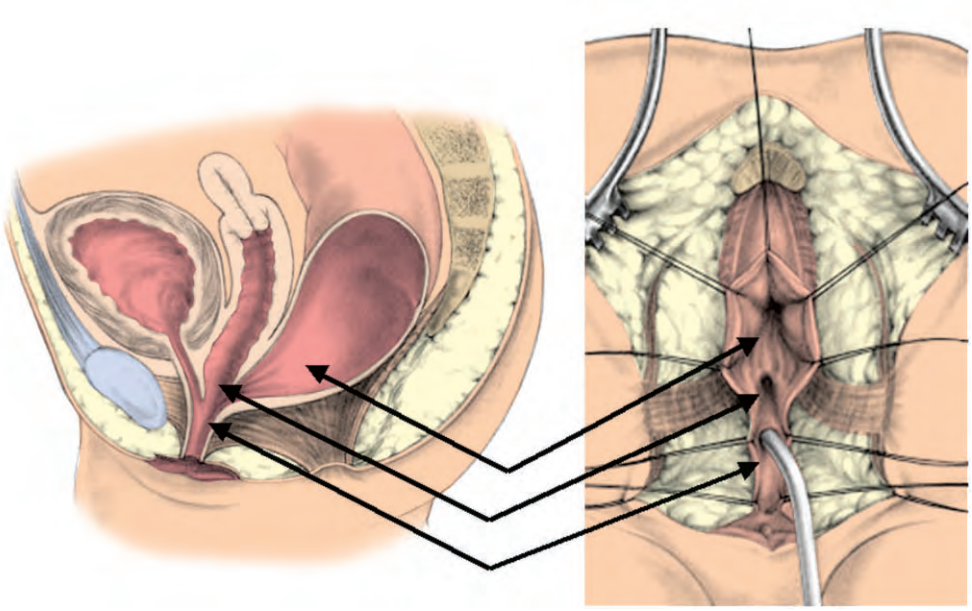


Figure 171–15. Female cloaca. *Arrows* indicate common channel, vagina, and distal rectum. The rectum and vagina will be separated, followed by tubularization and reconstruction of urethra, vagina, and rectum. (From Peña A, Levitt MA: Anorectal malformations. In Grosfeld JL, O'Neill JA, Coran AG, Fonkalsrud EW [eds]: Pediatric Surgery, 6th ed. Philadelphia, Mosby, 2006.)

Previous clinical practice has included evaluation for the presence of a tethered cord in those children who have imperforate anus with a high lesion. In a retrospective study, Golonka and colleagues noted that 34.9% of their patients had evidence of a tethered cord. Twenty-six percent of patients had a high lesion compared to 50% having a low lesion. Forty-five percent of the patients with low lesions and a tethered cord had no other lumbosacral anomalies. Thus, early evaluation for tethered cord is advocated for all children with ARM.[83]

Reoperative Surgery

Reoperation may be considered for a number of reasons, including to achieve improved functional results following a primary procedure, improve pain and discomfort, recurrent fistula, wound dehiscence, persistent anorectal stricture, or fecal incontinence. The number of patients that require a reoperation for fecal incontinence has decreased over the years and coincides with the use of the posterior sagittal approach.[84] The most rewarding group of patients to treat are those with previous catastrophic complications, because they enjoy the greatest benefit.

Based on Peña's anatomic findings,[84] he speculated that retraction, dehiscence, and acquired rectal atresia were most likely caused by technical errors. In addition, rectal strictures are most likely caused by ischemia of the distal part of the rectum. Some surgeons follow a protocol to dilate the rectum in the operating room rather than have the patient's family perform this at home on a daily basis. This may actually provoke a rectal laceration with further healing with a scar and possible intractable ring of fibrosis. If necessary, revision anoplasty (Y-V, Nixon, diamond flap, and three-flap techniques) can be used.[85,86]

Persistent rectourethral fistulas occur because the repair probably did not address the fistula initially, most likely using a perineal approach rather than a PSARP. Recurrent rectourethral/rectovaginal fistula may result if the fistula is closed but the rectum is not mobilized adequately, resulting in tension on the anterior wall of the rectum.

Posterior urethral diverticulum is typically present when the patient has a transabdominal procedure and the surgeon was unable to reach the fistula. The patient may suffer from passing mucous though the urethra, orchiepididymitis, urinary tract infection, or urinary pseudoincontinence.[84]

Misdiagnosis of a cloaca as a rectovaginal fistula and then repairing only the rectal component of the defect create significant long-term difficulties for subsequent reconstruction. A true congenital rectovaginal fistula is an extremely unusual defect.[20] An acquired vaginal atresia may occur as a result of devascularization of the vagina during separation from the urethra during a cloacal repair. With the use of total urogenital mobilization, the risk of this complication has been reduced.

FUNCTIONAL RESULTS

Because of variability in anatomy and sacral deformity, the wide spectrum of anorectal disorders managed by different surgical techniques, and dissimilar criteria for success, the results are difficult to interpret and compare. As a general rule, fecal continence rate after the correction of low anomalies is quite good. The anal canal is in its normal anatomic position, and a simple cutback or transplant anoplasty for a low fistula usually results in a good outcome. Unfortunately, the higher the rectal atresia/fistula, typically the worse the functional outcome. In some reports, girls have better fecal continence results than boys. This is possibly due to the increased incidence of low- and intermediate-level anomalies in girls.

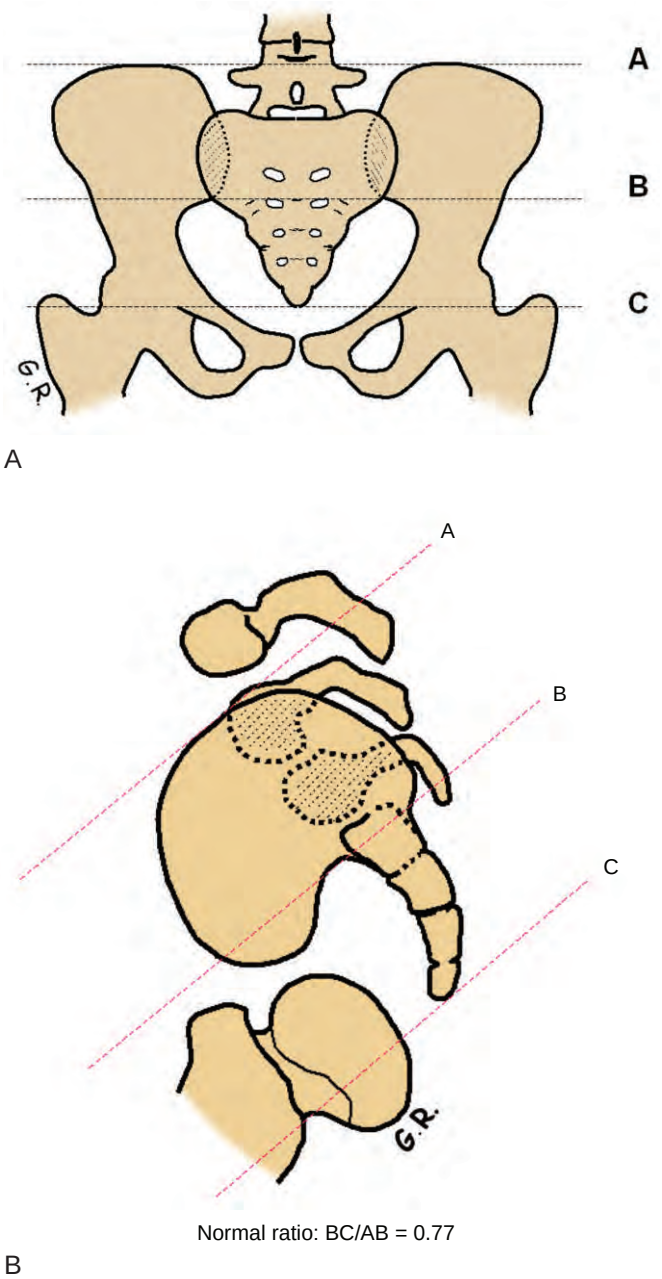


Figure 171–16. Anteroposterior **(A)** and lateral **(B)** illustration showing sacral ratio measurement (dashed lines A, B, and C are shown). (**A** and **B,** From Peña A, Levitt MA: Anorectal malformations. In Grosfeld JL, O'Neill JA, Coran AG, Fonkalsrud EW [eds]: Pediatric Surgery, 6th ed. Philadelphia, Mosby, 2006.)

The sacral ratio proposed as a method to evaluate the sacrum in patients with imperforate anus is useful in estimating the functional prognosis (Fig. 171–16). In general, ratios lower than 0.500 significantly decrease the chance of achieving good bowel function. The measurement of the sacrum is easy to accomplish and eliminates the difficulty frequently experienced in trying to count the number of sacral vertebrae. In addition, by using sacral measurements, one can detect abnormal sacra, which are quite short despite the fact that they may have the normal number of vertebrae.[20] A recent evaluation to test the repeatability and validity of the sacral ratio measurement as a method for detecting sacral abnormalities showed that the sacral ratio has good interobserver and intraobserver repeatability. The mean value for a normal anteroposterior ratio concurred with that described previously by Peña, but the variability of values among similar patients was wide, suggesting this single measure is of limited value in discriminating a normal from an abnormal sacrum.[87]

Assessment of Continence

A number of methods to assess continence have been developed and include subjective (e.g., good, fair, poor), numerical (e.g., the Kelly score based on fecal leakage, sensation, and contrast enema findings),[88] and a variety of physiologic evaluations, including balloon anorectal manometry, electrical sphincter muscle mapping, and anorectal angulation. Despite numerous technical advances in the surgical repair of ARM, a significant number of children have long-term problems with fecal continence. Little is known about the psychosocial consequences of this chronic disability, although there is extensive anecdotal evidence that fecal incontinence is the cause of distress to both the child and the family. A long-term evaluation of children with anorectal anomalies by Ludman and Spitz[89] demonstrated that (1) children/adolescents with incontinence are not less well adjusted than those with good bowel control; (2) in children with continence, those with frequent soiling accidents were more likely to be recognized as emotionally disturbed; (3) young girls with incontinence showed significantly more behavioral and internalized problems; (4) parental factors were strongly associated with outcome; (5) incontinent adolescents were not more emotionally disturbed than those with good bowel control; and (6) parental perception of how others would react to a child with fecal incontinence influenced the child's coping behaviors.[89]

Outcome in Patients with High Imperforate Anus

Long-term results for patients with high imperforate anus indicate that an excellent to good result is obtained in approximately 50% of patients,[21,59] whereas the remaining half will have a fair or poor (incontinent) outcome. Mollard et al.[62] reported the best results with 80% of patients being continent. However, this study included only 15 patients. The results of studies suggest that the short-term functional results after the Peña procedure and its modifications have been encouraging, in that good results have been achieved in 70% of patients.[21,90,91] Clinical studies show that biofeedback is effective in improving the outcome in those with constipation and fecal soiling. This technique, however, must be used in concert with other methods and requires patient motivation and compliance. The advent of

cutaneous electromyography electrodes and computer-assessed games allows better compliance and acceptance in children. A child must undergo a careful preassessment to ensure the patient and therapist of proper expectations.[92]

Constipation

Constipation is one of the most frequent sequelae seen in children with imperforate anus. More important, the frequency of constipation does not coincide with the frequency of fecal incontinence. Children with low lesions have a better prognosis in regard to continence but often have a higher incidence of significant constipation than those with high defects. Peña[20] noted that 61.4% of patients with vestibular fistula had constipation, whereas 41.4% of patients with a prostatic fistula and 18.1% with an associated bladder neck fistula had this problem. Some suggest that dissection of the rectal pouch may provoke some degree of denervation of the rectum, decreasing motility, and may contribute to the occurrence of severe constipation (low, 35.7% occurrence; high, 72% occurrence)[93]; however, Peña supported the concept that the degree of rectal ectasia that the patient has initially in the atretic rectal segment predicts the most severe constipation, as may be the case in instances of rectovestibular fistulas. Most of the patients that experience soiling are exhibiting signs of overflow pseudoincontinence (encopresis), provoked by severe constipation. If this is ignored, a megasigmoid may develop, which is associated with a vicious cycle of further constipation and colon enlargement. Aggressive treatment of constipation is warranted, and, if necessary, sigmoid resection may be necessary to eliminate the chronic impaction and cure the overflow pseudoincontinence.

Treatment of Postoperative Fecal Incontinence

Patients with ARM frequently experience fecal incontinence despite the vigorous efforts of pediatric surgeons to perform a precise anatomic repair. At least 25% of all patients treated with a PSARP procedure still suffer from fecal incontinence.[20] Treatment with enemas, laxatives, and medications are often prescribed by clinicians in an indiscriminate manner and without a demonstrated benefit. Peña et al.[94] have shown that this indiscriminate use of therapy not only failed to keep the patient clean but also may actually worsen the patient's condition. Peña has advocated an organized plan for bowel management therapy.

Others have shown that somatic and behavioral factors contribute to the persistence of chronic defecation problems. Treatment of these problems in patients with anal atresia should also include behavioral modification techniques.[95,96] Patients that remain incontinent beyond the age of 5 or 6 years should be evaluated for additional procedures. Careful study of the pelvic musculature and sacral anatomy, the urinary tract, and electrical sphincter mapping should be done before reoperation. These patients typically have an abnormal sacrum, flat perineum, and poor sphincters. There usually is evidence that they were born with a high ARM or cloaca with a common channel longer than 3.0 cm. Their sacral ratio is almost always less than 0.4. Reoperative procedures are most useful for instances of missed muscle complex or a misplaced anal orifice in patients with a good sacrum; however, with the poor prognostic factors noted, reoperation will not improve their situation. The Peña PSARP and the Mollard anterior perineal procedure have been used successfully (in 33% of patients) as secondary operations with good pelvic musculature.[17] It is wise to protect a secondary anoplasty procedure with a proximal diverting colostomy to ensure healing without fecal contamination.[3] Another reason not to reoperate on patients with fecal incontinence is the problem of short colon and, therefore, an incapacity to form solid stool, because these patients often do not gain bowel control regardless of how well their sphincters function. It had previously been believed that children with anorectal disorders would gradually improve their bowel habits with time. However, new data indicate as the patients grow older, they likely implement their own bowel management programs and do not actually acquire improved bowel function.[20]

In instances of incontinence that occur despite a proper pull-through procedure, a gracilis muscle sling operation may prove useful in achieving voluntary muscle tone and improved control. This latter procedure is useful in 60% to 70% of cases; nevertheless, it is difficult to know exactly when to recommend this type of surgery. Newer options include the artificial bowel sphincter and electrostimulated gracilis neosphincter. At the present time these surgical options are under investigation in children, and long-term morbidity and outcomes are not yet available.[97-99]

Enemas are often required to ensure complete fecal evacuation after the sling and sphincter procedures. In some instances in which incontinence is inevitable (e.g., sacral agenesis, failure of previous surgical procedures, and reoperation), an end colostomy may be the most appropriate long-term procedure to achieve a socially acceptable status. The Malone antegrade colonic enema (MACE) procedure, in which the appendix,[100] cecal flap, cecostomy tube,[101-103] or a sigmoid irrigation tube[104] is used as a continent stoma to deliver antegrade enemas, has become a popular alternative to evacuate the colon and to promote cleanliness.[105] When used in patients, the antegrade colonic enema procedure has been one of the most effective means the pediatric surgeon has to achieve socially acceptable continence status. However, this also carries with it some morbidity—especially stomal stenosis, which may occur in 25% to 30% of cases. The MACE procedure is successful in achieving cleanliness in more than 70% of cases.

Genitourinary Tract

Most patients with an ARM and concomitant sacral agenesis have vesicourethral as well as anorectal dysfunction and have both urinary and fecal incontinence.[7,106]

However, in contrast to vesicourethral dysfunction, anorectal dysfunction does not cause functional deterioration of other organs. Significant long-term sequelae can arise from neurogenic lower urinary tract dysfunction, including recurrent urinary tract infection, vesicoureteral reflux (VUR), impaired renal function, and urinary incontinence. Moreover, other problems that can arise from impaired genitourinary innervation include ejaculatory and erectile dysfunction. Operative dissection during surgical treatment of ARM gets perilously close to the ejaculatory system, especially when a rectourethral fistula is present. Therefore, in addition to reconstructing the anorectal anomaly, other major goals in the management of these patients are preservation of renal function, prevention of urinary tract infections, maintenance of sexual function, and treatment of urinary incontinence.[107] Some children do not receive appropriate early urologic treatment; therefore, screening all newborns with ARMs for associated lower urinary tract anomalies and dysfunction along with appropriate urological management is necessary to prevent urinary tract deterioration.

Spinal dysraphism and neurovesical dysfunction (NVD) frequently are associated in children with ARMs. A significant proportion of these patients also have associated urologic abnormalities, which include VUR, hydronephrosis, or renal agensis.[108] Renal insufficiency and renal failure remain the most significant causes of morbidity and mortality in patients with ARMs.[109] As such, prevention of renal damage remains a high priority. This has led to a recognition of sacral or spinal cord data to predict the risk of urologic problems in patients that demonstrate vertebral anomalies.[110] NVD involves an impaired innervation to the lower urinary tract, which affects both the filling and emptying functions. During the filling phase detrusor pressure may be increased and the detrusor may be overactive, together with sphincter disturbance and detrusor-sphincter dyssynergy. This may result in incomplete bladder emptying that in turn may be associated with urinary tract infections and subsequent renal damage.[111,112] NVD was seen in 24% of 90 patients with ARM in one series[106] and 18% in another.[113] Among these cases were some patients with a normal sacrum, leading the authors to conclude that a normal radiograph does not exclude the risk of NVD.

Outcome of Cloacal Surgery

Cloaca, which occurs in approximately 1 of 50,000 births, is the most complex of ARMs with confluence of the rectum, vagina, and bladder in a urogenital sinus. Functional results for the bowel, the genital tract, and the urinary tract have been uniformly poor. In the current era, a reasonable lifestyle can be accomplished for most of these children with comprehensive surgical planning.[81]

The results of cloacal reconstruction are satisfactory for most patients. Sixty-two percent void spontaneously, 88% are socially clean with bowel control, and 89% have described normal coitus, with six women reported having children.[114] The best results have been achieved in centers where the surgeon has a special interest in this very complex reconstructive surgery and large operative volume.

SUMMARY

In spite of the technical advances in the surgical repair of ARM, the management of patients with variants of imperforate anus is difficult and carries a significant degree of physician responsibility, often requiring long-term follow-up into adulthood. A concise understanding of the anatomy and the surgical techniques is essential. These are procedures that should not be attempted by the occasional surgeon who rarely deals with neonatal anomalies. Unfortunately, there remain a significant number of patients who undergo attempted anorectal repairs with catastrophic complications. Many of these complications are preventable. One must have a thorough understanding of these malformations and the first operation performed well by an experienced pediatric surgeon most often allows the child the best chance for successful bowel control.

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Chapter

172

Reoperative Pelvic Surgery

M. Jonathan Worsey · Victor W. Fazio

Reoperation in the pelvis may be required under a number of different circumstances ranging in complexity from reversal of a Hartmann procedure to resection of a recurrent rectal cancer with a sacral resection and pelvic exenteration. This chapter discusses the applied anatomy of the pelvis as it pertains to reoperative surgery, preoperative work-up, and planning, though the main focus examines technical and practical aspects of these operations. The discussion is in the context of gastrointestinal surgery, although these principles can be equally applied to urologic or gynecologic surgery.

APPLIED ANATOMY

There are a number of anatomic and pathophysiologic factors that contribute to the difficulty of pelvic reoperation (Box 172–1). In the anatomic position, the pelvis resembles a forward-tilted basin composed of bone covered with muscle and lined with fascia. This forward angulation of the pelvis limits visualization of the anterior pelvic surface, especially deep in the pelvis, and the unyielding bony margins of the pelvis limit exposure that can be obtained with retraction.

Important urologic, vascular, and nervous structures course within the pelvis and are at risk of damage during pelvic reoperation. The distal half of the ureter lies within the pelvis, crossing the pelvic brim at the iliac artery bifurcation and then coursing downward along the lateral pelvic side wall before turning upward and medially to enter the base of the bladder at the pelvic floor. After pelvic surgery, especially where the rectum is mobilized, the ureters may assume a much more variable course. At the pelvic brim, it is not unusual for the ureters to assume a much more medial position, sometimes even being fused to the mesorectum or a rectal stump. Likewise, after previous resection of the colon, the abdominal portions of the ureters can be encountered surprisingly quickly during lateral abdominal dissection. They may be closely related to the small bowel as it fuses to the retroperitoneum and remnant of the mesocolon.

The pelvic organs are covered with visceral pelvic fascia, which is an extension of the parietal fascia lining the pelvis. The presacral fascia is a condensation of the parietal endopelvic fascia, and breach of this layer may lead to, at best, troublesome bleeding and, at worst, catastrophic bleeding. This is in part due to the avalvular presacral veins that communicate directly with the basivertebral veins. The pelvic sympathetic nerves run downward and laterally over this fascia to join the pelvic plexus on the lateral side wall and then supply the anal and urinary sphincters. Initial posterior rectal dissection, if performed sharply and in the right plane, allows relatively easy separation of the fascia propria of the rectum from presacral fascia. In reoperative cases, this plane is much less well defined or even obliterated, leading to inadvertent dissection through the presacral fascia, with hemorrhage being the likely result. Likewise, the sympathetic nerves are at great risk of division or damage if this plane is not developed correctly.

GENERAL MEASURES

Decide on Timing of Reoperation

If at all possible, 3 or preferably even 6 months should be allowed before reoperative pelvic surgery is attempted, in cases of benign disease an even longer interval may be useful, whereas in the case of malignant disease this may not be practical. It is hoped that waiting will reduce the difficulty and potential complications attributable to adhesions. Should early reoperative pelvic surgery be required, as in the case of an anastomotic leak or obstruction, there is a window of about 10 to 14 days before the adhesions reach their worst when reexploration may perhaps be undertaken safely. After this, there is a significant risk of iatrogenic injury, and alternative approaches such as percutaneous abscess drainage, proximal fecal diversion, or parenteral nutrition should be contemplated to buy time. Factors that may make adhesions worse include sepsis and irradiation; in the

Box 172–1 Factors Contributing to Difficulty of Reoperative Pelvic Surgery

Anatomic Factors

- Orientation and angulation of pelvis
- Unyielding bony margins that cannot be retracted
- Narrow male pelvis (android)
- Course and relationships of vascular, neural, and urologic structures
- Vascular anatomy of sacrum

Pathophysiologic Factors

- Tendency of small bowel to fill and become fixed in pelvis postoperatively
- Potential for ectopic position of ureters in postoperative pelvis
- Tendency of bowel anastomosis or rectal stump to fuse to surrounding structures

presence of these factors, if the patient can wait, at least 6 months and perhaps longer should be allowed.

Prepare the Patient

Pelvic reoperation may necessitate prolonged surgery and anesthesia, and careful preoperative patient preparation may help reduce general postoperative complications. The nutritional status of the patient should be addressed with protein and calorie deficiencies corrected, preferably via the enteral route but parenterally if needed. In older patients, particular attention to cardiopulmonary status is important because bleeding may cause intraoperative blood pressure fluctuations and prolonged anesthetic times, and large incisions may predispose the patient to pulmonary problems. Reoperative pelvic surgery also carries a very high risk of pelvic and lower extremity thromboembolic problems. Appropriate prophylaxis must be used especially in the elderly, those with malignancy, and other risk factors. Compression stockings are important, though the additional use of pharmacologic anticoagulation is often warranted despite concerns regarding perioperative or postoperative bleeding. The preoperative placement of a caval filter should be considered in those at highest risk or where heparin cannot be given. Mechanical bowel preparation and appropriate preoperative antibiotics should be administered even if entering the bowel lumen is not planned, as this may nevertheless occur.

Preoperative Imaging Studies

The purposes of these are really twofold. First, in the case of malignant disease, to exclude locally irresectable disease or distant metastatic disease that would preclude a curative resection. Second, providing a preoperative plan of attack, by detailing the pelvic anatomy.

Determining resectability of malignant pelvic disease can be unreliable on clinicopathologic grounds and is improved by using either computed tomographic (CT) scanning and/or magnetic resonance (MR) scanning. In a series of 119 patients from Memorial Sloan-Kettering undergoing reoperation for pelvic recurrence of colon and rectal cancer,[1] only the presence of pelvic sidewall involvement and ureteric obstruction were associated with a statistically significantly smaller chance of a complete resection.[1] Conversely, anastomotic and anterior pelvic recurrence proved particularly amenable to curative resections. Positron emission tomographic (PET) scanning should also be routinely performed in the case of malignant pelvic recurrence. This technique relies on the preferential uptake of the glucose analogue ^{18}F-fluorodeoxyglucose by malignant cells and then detection of these sites using PET scanning. It is a sensitive and specific technique for colon and rectal cancer,[2] especially when the size of recurrence is greater than 1 cm. Liver or lung metastases that are not amenable to resection may discourage a now palliative pelvic operation. PET scanning is also useful in distinguishing postoperative changes from locally recurrent malignant disease in the pelvis and the advent of the PET-CT fusion scanner that can superimpose their images may make this even more accurate. CT scanning and MR imaging may also provide a road map of pelvic anatomy when the initial operation was performed elsewhere or there has been a significant interval change due to an abscess or anastomotic leak. Contrast studies may better define a rectal stump, an anastomotic stricture, or an enterocutaneous fistula.

Anticipate Bleeding

Blood should be cross-matched, and if clinically indicated, coagulation parameters should be checked. The use of a cell saver in certain circumstances where fecal contamination is not anticipated may be of use. The availability at short notice of other clotting agents, such as platelets, fresh frozen plasma, and cryoprecipitate, is also advisable in case massive transfusion is required. Recently the use of recombinant factor VIIa has been described in cases of life-threatening hemorrhage complicated by massive blood product replacement or underlying coagulopathy; this may be particularly useful if a sacral resection is anticipated or planned.

Anticipate a Long, Difficult Case and the Need for Other Specialists

Schedule the case first and do not plan other equally difficult cases to follow. Use the most senior help available as assistants rather than a new house officer. Forewarn urologic, gynecologic, and other specialists of the possible need for intraoperative assistance. Give the anesthetist advance notice of the potential for blood loss, and allow time for the placement of appropriate lines and

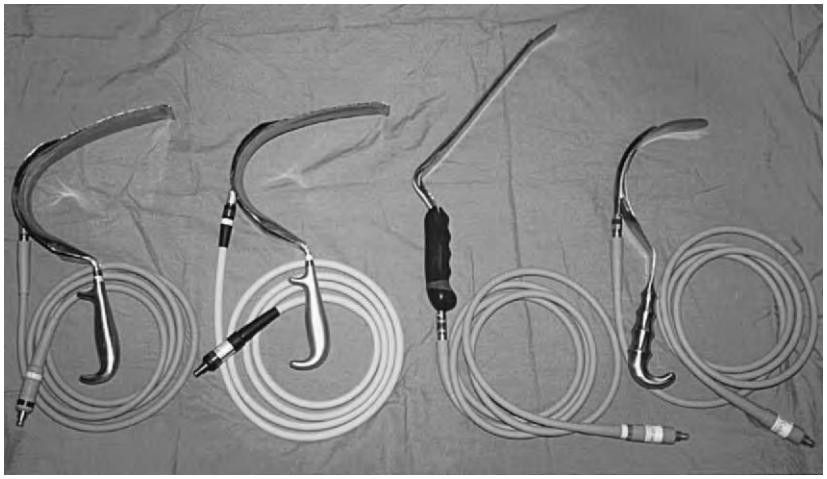

Figure 172–1. Commonly used lighted retractors in pelvic surgery. *Left to right:* standard-width deep pelvic retractor, narrow-width deep pelvic retractor, straight-blade retractor (BrightTrack), and lighted Deaver retractor.

monitoring devices. Epidural or other neuraxial anesthesia may be helpful in early postoperative pain management and promoting early ambulation and effective pulmonary toilet. Perioperative anticoagulation must be taken in to account with these techniques because of the risk of epidural bleeding.

SPECIFIC MEASURES

Patient Positioning

We place the patient on a beanbag that can be molded to fit the patient and then fixed in position when the air is evacuated. This is especially useful because it stops the patient from slipping down the table when steep Trendelenburg position is applied. Do not let the anesthetist talk you into leaving an arm out from the side for better vascular access; allow the time needed before final positioning to place the appropriate lines. Tuck both arms securely at the patient's side even if the patient is obese; otherwise, room to obtain adequate visualization of and access to the pelvis is jeopardized. In addition, the risk of brachial plexus stretch injury exists in these long operations. The legs are placed in carefully positioned and padded Lloyd-Davies or Allen stirrups; the right hip is not overflexed because this will interfere with a self-retaining retractor placed in the most distal aspect of the wound. The patient is prepared from the nipples to the perineum and draped so that access to the perineum can be obtained without contaminating the abdominal field.

Optimizing Visibility and Exposure

Long midline incisions are routinely used, with the distal end carried on to the pubis and the proximal incision as far as needed; it may be necessary to gain safe entry to the abdomen above the umbilicus in the case of dense adhesions or fistulas. Enterocutaneous fistulas are left in place until the bowel around them is fully mobilized to avoid injury to noninvolved bowel. A self-retaining retractor is used, and a C-arm is attached to this to retract the viscera into the upper abdomen. A bladder blade also

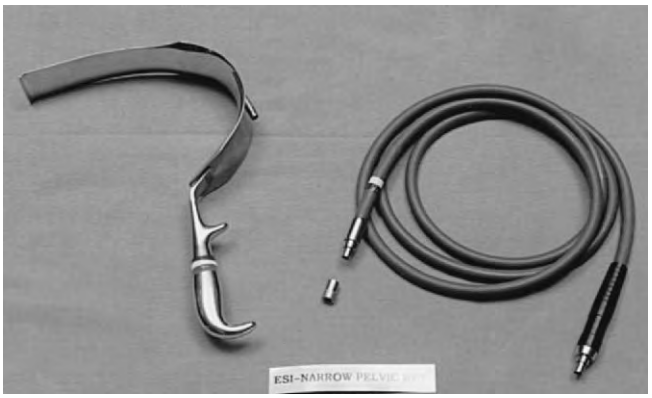

Figure 172–2. Close view of narrow pelvic retractor. Unlike the lighted Goligher straight-blade retractor, this allows for vigorous elevation of the prostate and bladder base away from the rectum or the low rectum and mesorectum from the sacrum. (This is the senior author's preferred retractor.)

attaches to the self-retaining retractor, and if properly placed, it should sit snugly against the pubic bone. A large chromic suture is often placed in the dome of the uterus and then tied around the bladder blade to pull the uterus up out of the pelvis. Once the small bowel has been brought up out of the pelvis, placing the patient in Trendelenburg position will help keep the pelvic field clear.

A headlight can be useful, especially with the newer lightweight models using more powerful light sources. In addition, lighted retractors (Figs. 172–1 and 172–2) and occasionally the free light cord are most helpful deep in the pelvis. The first instrument to be used is often the lighted Deaver retractor. This has a relatively shallow curve and is a short instrument that is ideal for the early part of the posterior rectal dissection, when a broad instrument is of value. It is also of value for the early anterior rectal and bladder exposure and dissection and may be used to good effect with a high splenic flexure mobilization. As the rectal dissection progresses, longer instru-

ments are used, especially in the case of the narrower male pelvis; two additional types of retractors are then used. The Bright-Track instrument is 15 inches long and 1.5 inches wide and is used with the fiberoptic light source. It is ideal for anterolateral retraction of the seminal vesicles and prostate or vagina, deep in the pelvis when bleeding occurs, and the most inferior part of the posterior rectal dissection. The final retractor that is used is a longer and much more curved retractor, with wide- and narrow-blade types. This is especially useful in lifting the rectum forward with some degree of force to accentuate the correct plane of dissection behind the rectum. In addition, it can be used to retract the bladder and prostate or vagina forward to assist with dissection or subsequent hemostasis. Because the light source can get very hot, care must be taken to avoid burning the drapes or even worse the patient or surgeon.

Conducting the Operation

Adhesions are taken down carefully, with the preferred technique being to mobilize matted loops of bowel into the wound and then to separate the individual loops. This is not usually possible when a loop or loops of small bowel descend into the pelvis and are fused to the vagina, levators, or anterior sacrum. In this instance, it is best to try to identify the afferent and efferent loops descending into the pelvis and, with a sponge in the nondominant hand, to gently retract the apex of the loop caudad. Sharp dissection is performed close to the bowel wall, and the loop is separated from the dense fibrous adhesions. Enterotomies or myotomies may be unavoidable and should be repaired or resected as appropriate. Once the loops of bowel are delivered into the wound, their separation is not usually too difficult.

On occasion, dissection may be exceedingly difficult owing to grade IV adhesions that fuse the bowel together or to the abdominal wall or owing to the presence of an enterocutaneous fistula. In the case of a fistula to the abdominal wall, the bowel should be mobilized around this, leaving the fistulous connection for last and then detaching it sharply. Dissection of the most dense adhesions may be facilitated by infiltrating the fused area with saline using a small-gauge needle *(hydrodissection)*. This preferentially expands the correct plane for dissection and reduces the likelihood of bowel injury and contamination of the field. Sometimes even this cannot overcome the fusion between bowel and the abdominal wall, and here, if a relatively small area is involved, it may be circumvented by leaving the abdominal fascia attached to the bowel. The dissection is carried outside the fascia, returning to the abdominal cavity beyond the area of fusion. Hydrodissection may also be of value in finding a plane between the vagina and the previously mobilized rectum (Fig. 172–3).

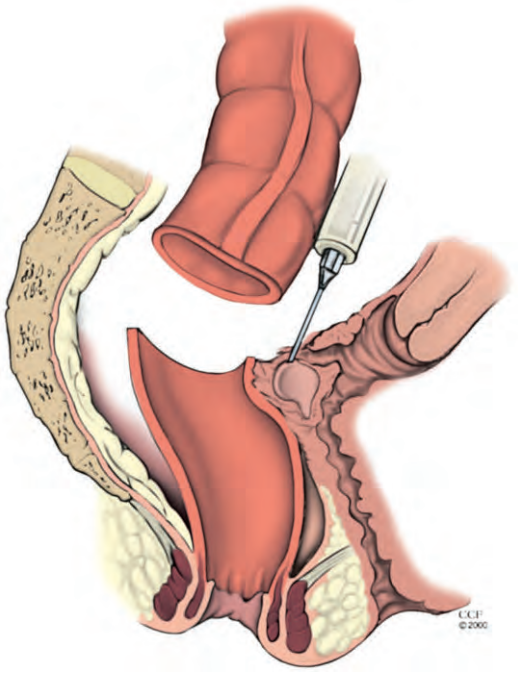

Figure 172–3. Schematic showing injection of saline into the scar between rectum-rectal stump and posterior vagina, which may be fused inseparably. A 1- to 2-mm-thick septum can be made into a 7- to 10-mm septum, allowing some cushion against inadvertent rectal or vaginal injury. (©2000, Cleveland Clinic Foundation.)

Identification of Pelvic Structures

During reoperation, identifying specific anatomic structures is indeed difficult. If a scarred obliterated pelvis becomes reperitonealized, it may appear at first glance that the entire rectum, bladder, and uterus have been removed because of the deceptive smooth concavity of the pelvis. This may be especially so after the effects of external-beam irradiation. However, there are specific ways to help identify important pelvic structures.

Ureters

Identification of the ureters may be facilitated by preoperative ureteric stent placement, which we perform frequently for reoperative pelvic surgery. Unfortunately, in the most difficult cases, where the ureter may be kinked or angulated because of adhesions or inflammation, stent placement sometimes cannot be safely undertaken. Furthermore, dense adhesions may make palpation of even stented ureters difficult.

Early identification, with or without stenting, is the key to avoiding ureteric injury. In the densely scarred pelvis, the ureters are found proximally and traced to the pelvis. They may be marked by loosely placed encircling ligatures, and then are constantly referred back to during the conduct of the dissection. Critics of stenting cite increased cost and time and that stents have not been proved to reduce the rates of ureteric injury. However, one of the great disasters of pelvic surgery is the missed ureteric injury, and this is rarely the case with stented ureters, where injury is much more obvious and readily identified.

Bladder

There usually is not much difficulty in identifying the bladder, but a couple of points are worthy of mention. If the previous abdominal incision was taken down to the pubis for maximal exposure and the bladder likewise mobilized to allow its anterior retraction, the bladder may be densely adhered beneath the midline fascia in the lower part of the wound. Care is necessary in reentering the abdomen to avoid inadvertent injury to the bladder at this point. After irradiation, there may be a tight restrictive crescent moon–shaped band in the deep pelvis corresponding to a fibrous bladder base, which will adversely affect exposure of the lower rectum. This is improved by placing superficial cautery incisions in the bladder base, with the entrance of the ureters taken into account, and then stretching this narrow entrance.

Rectal Stump

Depending on the previous operation, this may be conveniently sitting in the lower aspect of the abdominal wound (really the distal sigmoid), out of sight in the depths of the pelvis below a reperitonealized pelvic floor, or anywhere in between. If divided at or just below the sacral promontory, which is commonly done, the stump may be adherent to the presacral fascia, the great vessels, or the ureters, with all being at risk of damage. In this situation, it often is best to begin the rectal dissection lateral to the mid rectum in so-called virgin tissue and to develop the plane of the mesorectum. Once the peritoneum has been incised, this is facilitated by retracting the rectum medially using the lighted Deaver retractor and then using electrocautery to follow the mesorectum posteriorly to the presacral space, which can more readily be found with this approach. The proximal part of the rectal stump is then mobilized by sharp dissection or electrocautery exactly in the midline over a 1- to 2-cm area to allow development of the plane between the posterior mesorectum and the presacral fascia. The dissection is then kept on the posterior wall of the mesorectum, and attached ureters or vessels are dissected free. Using the appropriate narrow retractors, the plane is developed to meet the presacral dissection beginning laterally, and this is carried caudad as far as needed. The remainder of the lateral attachments and lateral stalks can then be divided if necessary.

Should there be only a short, nearly invisible rectal stump, its initial identification and subsequent mobilization can be facilitated by placing a large bougie or proctoscope in the rectum. This should be done with some care because it is not uncommon for a stricture to develop in a defunctionalized rectum. With a very low rectal stump, bimanual palpation is a useful technique not only to identify the rectum but also to accurately assess the level of the dissection in relation to the sphincters. Here, an additional sleeve and glove are donned to allow the placement of a finger through the anus into the distal rectum, which is then palpated from above with the other hand (Figs. 172–4 and 172–5).

Before any anastomosis is attempted to a defunctionalized rectum, the presence of an occult stricture must

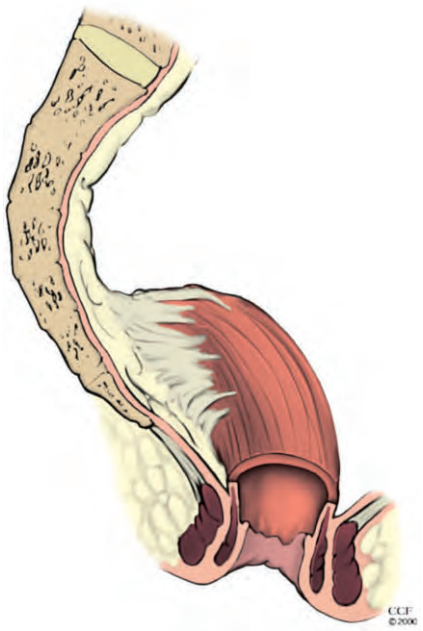

Figure 172–4. The difficult (short) rectal stump. Stump length of less than 10 to 12 cm usually means a difficult dissection. Fusion of the stump apex to the low sacrum requires several alternative or composite procedures for safe mobilization. Stump apex leak caused by radiation with chronic sepsis makes for extra difficulty. (©2000, Cleveland Clinic Foundation.)

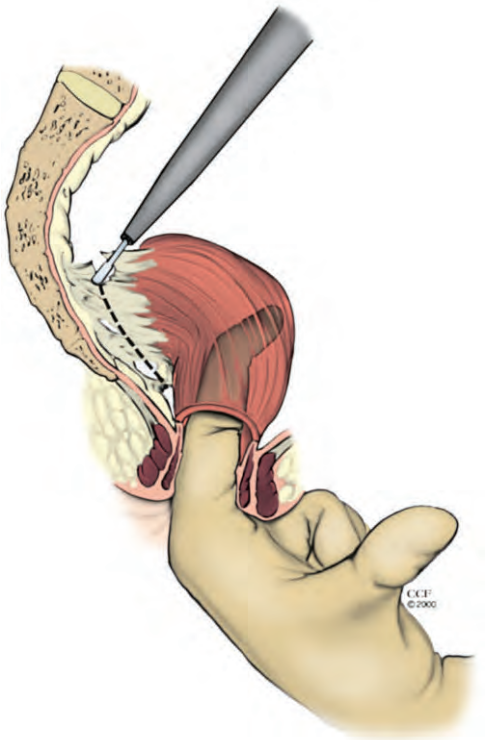

Figure 172–5. Electrocautery is kept exactly in the midline and over a short distance of 2 to 3 cm. Bimanual examination with a double-gloved index finger in the rectum may help guide the surgeon in rectal mobilization. (©2000, Cleveland Clinic Foundation.)

be excluded. This can be done either preoperatively or intraoperatively.

Vagina

In reoperative operations, the vagina should always be prepped with povidone-iodine in case it is inadvertently entered. Similar to the rectal dissection, the use of an obturator or a bougie may be extremely helpful in the identification and prevention of injury. The use of hydrodissection in the case of an obliterated rectovaginal plane has been discussed. Occasionally, bimanual palpation with one finger in the rectum and one in the vagina facilitates the separation of the most distal aspects of the rectum and vagina.

Control of Bleeding

The anticipation of significant bleeding and appropriate preoperative cross-matching of blood are essential. Those at risk of clotting disorders should be identified, and appropriate clotting factors should be administered or made available for intraoperative use. The benefits of perioperative heparin must be weighed against the potential for bleeding as mentioned earlier.

The common sites at which pelvic bleeding is encountered are as follows:

1. Presacral and lateral sacral veins: Premature, inadvertent breaching of the presacral or Waldeyer's fascia occurs above the S3-4 level. This is usually caused by blunt dissection in the presacral space, although it may also occur when the fascia is deliberately incised to gain access to presacral masses or occasionally to excise recurrent rectal cancer. Another situation in which this happens is with synchronous abdominal and perineal dissections. If the perineal operator gets ahead of the abdominal operator and breaks through the anococcygeal ligament too posteriorly, the dissection may proceed beneath the rectosacral fascia, shearing the basivertebral branches of the lateral sacral veins.
2. Internal iliac vein: The internal iliac vein is injured if tearing or shearing of branches from the main trunk occurs. Also, in the irradiated pelvis, vascular structures may be covered by such dense indurated and adherent scar tissue that exploratory incisions may lacerate the internal or external iliac veins.
3. Rectovaginal, retroprostatic, and paravesical veins: Bleeding may occur anterolaterally.
4. Pelvis: Arterial bleeding may occur from any of the arterial structures in the pelvis.
5. Sacrum or presacral artery: Bleeding may occur from the cut end of the sacrum or presacral artery if hemisacrectomy is performed.

When significant bleeding occurs, there are a number of general and specific measures that should be initiated depending on the site of bleeding. In general, good lighting, more than one suction, and good exposure are the keys to identifying the source of the bleeding. If the bowel lumen has not been entered, then the cell saver can be used to scavenge shed blood. In extreme cases, the rapid infusion system may be used, although such precipitous bleeding that cannot at least be slowed by packing is unusual.

When bleeding is encountered, the following steps should be taken. If the point of bleeding cannot be identified quickly, use an index finger to apply pressure. Should this fail to stop the bleeding, place packs, inform the anesthetists of the problem, and allow them to catch up with blood loss and send for blood. Optimize light, suction, and exposure and then gently tease out the packs until the bleeding site is seen. If the bleeding site is seen, use a sponge or small cotton pledget on an instrument to control the bleeding because this will allow more room to perform measures to stop the bleeding than if a finger is used. If bleeding occurs from the presacral area, such a maneuver will sufficiently control the bleeding to facilitate more definitive maneuvers. These are the following:

- Apply a suture using a $^{3}/_{4}$-circle needle (e.g., 2-0 Vicryl on a UR6 needle) if the bleeding is localized and there is sufficient intact fascia on either side to provide tamponade.
- If there is insufficient intact fascia, use a sterile thumbtack with or without some Surgicel secured beneath it. The thumbtack is best driven home using the flat part of a heavy pair of scissors.
- A roll of Surgicel or a 1-cm cube of rectus muscle may be sewn over the bleeding point again using a stout $^{3}/_{4}$-circle needle.
- If this does not work, then pack the pelvis after applying Surgicel to the bleeding area.

At this point, proceed with the remainder of the operation, returning to check hemostasis in 30 to 60 minutes. If this is satisfactory, suction drains will be left in the pelvis and an omental pedicle brought down to fill the dead space. If there is continued bleeding, additional packs are placed, and the abdomen is closed with the intent of returning to the operating room within 48 hours to remove the packs. Recurrent bleeding after such packing is rare.

If the bleeding cannot be readily controlled, the key to packing is to pack early before there has been massive blood loss and the vicious downward spiral of coagulopathy and hypothermia has begun. Packs should be firmly placed at the site of bleeding and not roughly stuffed into the pelvis so as to cause shearing of small veins and compound the problem. If a pelvic anastomosis is to be created and the packs need to be left for 24 to 48 hours, the anastomosis should be left until the packs are removed, because a tightly packed pelvis may compromise the blood supply of the proximal bowel and put tension on the newly created anastomosis. Stapling or oversewing of the cut end of bowel and leaving it in the pelvis provide the safest alternative. For less severe bleeding, we have used packing in the presence of an anastomosis without untoward complications such as dehiscence.

Ligation of the internal iliac vein in the case of bleeding from its more distal branches is rarely helpful because of the rich collateral network. Direct injuries to

the vein can be managed with ligation above and below the injury. However, in the frozen, irradiated pelvis mobilization, isolation and ligation of the vein may be impossible, and either repair with a fine vascular suture or oversewing may be required. To obtain visualization of the injury, pressure may need to be applied above and below the venous injury using a peanut or small swab on an instrument.

Arterial injuries may be treated by ligation or oversewing if bleeding is from small distal branches. Likewise, a single internal iliac artery can usually be ligated without untoward effects. In the case of injury to the external iliac artery, repair must be undertaken. Direct repair with fine vascular sutures can be undertaken with proximal and distal control. Short segments of more significant damage can be excised and the mobilized ends can be reanastomosed safely, but the need for more extensive reconstruction with prosthetic graft creates problems. Because there is likely to be contamination from either intestinal lumen or a focus of infection, anatomic placement of a vascular graft is inadvisable and an extra-anatomic graft may be required (usually a femorofemoral crossover graft).

Drainage

We routinely drain the reoperative pelvis. If there has been minimal bleeding and this has been readily controlled, a single Jackson-Pratt or Atraum suction drain will suffice. If, however, there has been significant blood loss, fecal contamination, or both, then sump drains are used and brought out through a separate stab incision rather than the wound. These can be irrigated with normal saline and are usually removed on postoperative day 3.

The omentum is routinely mobilized and brought down the left gutter to fill any dead space in the pelvis or to wrap around or isolate an anastomosis. It is not usually necessary to mobilize the omentum inside the epiploic arcade unless it is short or has been partially removed at a prior operation. One or two sutures are used to hold the omentum in the pelvis; otherwise, cephalad migration may occur. Perineal drains are rarely used.

SPECIFIC CLINICAL PROBLEMS

Benign

Reversal of Hartmann's Procedure

Anastomosis to an oversewn out-of-circuit rectum, as in the second stage of a Hartmann's procedure, may pose a couple of common problems (Fig. 172–6A). First, there may be a midrectal stricture, which makes passage of the stapler impossible. Usually, the serial passage of dilators per rectum remedies this, but occasionally, further rectal resection to healthy rectum is needed. Second, it is tempting to pass the cartridge of the stapler without the anvil per rectum and to drive the trocar through the presumed end of the rectum. However, if the oversewn end of rectum has much scarring around it, the distal donut may be excessively large and cause tearing of the anastomosis on withdrawal. Similarly, if the trocar is brought through the rectum close to but not at the end, ischemia may develop between the anastomosis and the oversewn end of the rectum, with a risk of subsequent perforation. The variation of technical problems in the fashioning of an anastomosis deep in the pelvis calls for some ingenuity, and no one technique will always be the best. In general, the prevailing principle applies of ensuring good blood supply to both ends of bowel. Thus, if the distal rectum is too contracted to allow for a stapled anastomosis with introduction of the cartridge component per anum, then a handsewn anastomosis is perhaps the safest way to go. This is appropriate if the rectum has been out of circuit for many months or years. One variation is the side-to-end anastomosis, in which the stapler head is passed through the open end of the distal colon, punching the trocar through the antimesenteric colon wall 5 to 7 cm from the open colonic end. The anvil is inserted into the opened distal rectum, which previously had a purse-string suture placed, and the stapled anastomosis is completed (see Fig. 172–6B and C). On withdrawal of the circular stapler, the opened colon end is closed with a linear stapler, the tissue rings are checked, and anastomotic integrity is confirmed by transanal insufflation of dilute povidone-iodine.

In case of apparent inadequate colon length due to previous resection and previous splenic flexure mobilization, a few crucial inches of length can be obtained by mobilizing the colon to the hepatic flexure and passing the colon through a mesenteric window between the ileocolic and superior mesenteric vessels. Thus, a retroileocolonic low rectal anastomosis is made.

Redo Pelvic Pouch Procedure

The redo pelvic pouch procedure perhaps epitomizes the difficulties encountered in benign reoperative pelvic surgery. Not only has there been extensive pelvic dissection with removal of the entire rectum but also a neorectum has been placed into the pelvis whose blood supply is dependent on a single posterior blood vessel—the superior mesenteric artery. The successful performance of this procedure emphasizes the principles discussed earlier. Careful positioning is required to allow initial perineal access to disconnect the pouch-anal anastomosis; then the abdominal phase of the operation and finally reanastomosis to the anal canal below the dentate line are undertaken. Ureteric stents are routinely placed to reduce the chance of inadvertent injury. The pelvic dissection requires sharp mobilization of the pouch, which is usually fused to the presacral fascia, obliterating the anatomic dissection plane. Particular care is required with the posterior dissection to avoid injury to the superior mesenteric artery, which is the major blood supply. Adhesion of the pouch deep within the pelvis requires the careful use of retractors and lighting to allow safe mobilization under direct vision. Bleeding is sometimes a problem, necessitating the maneuvers described earlier. Drainage with either sump or passive drains is combined with mobilization and placement of the

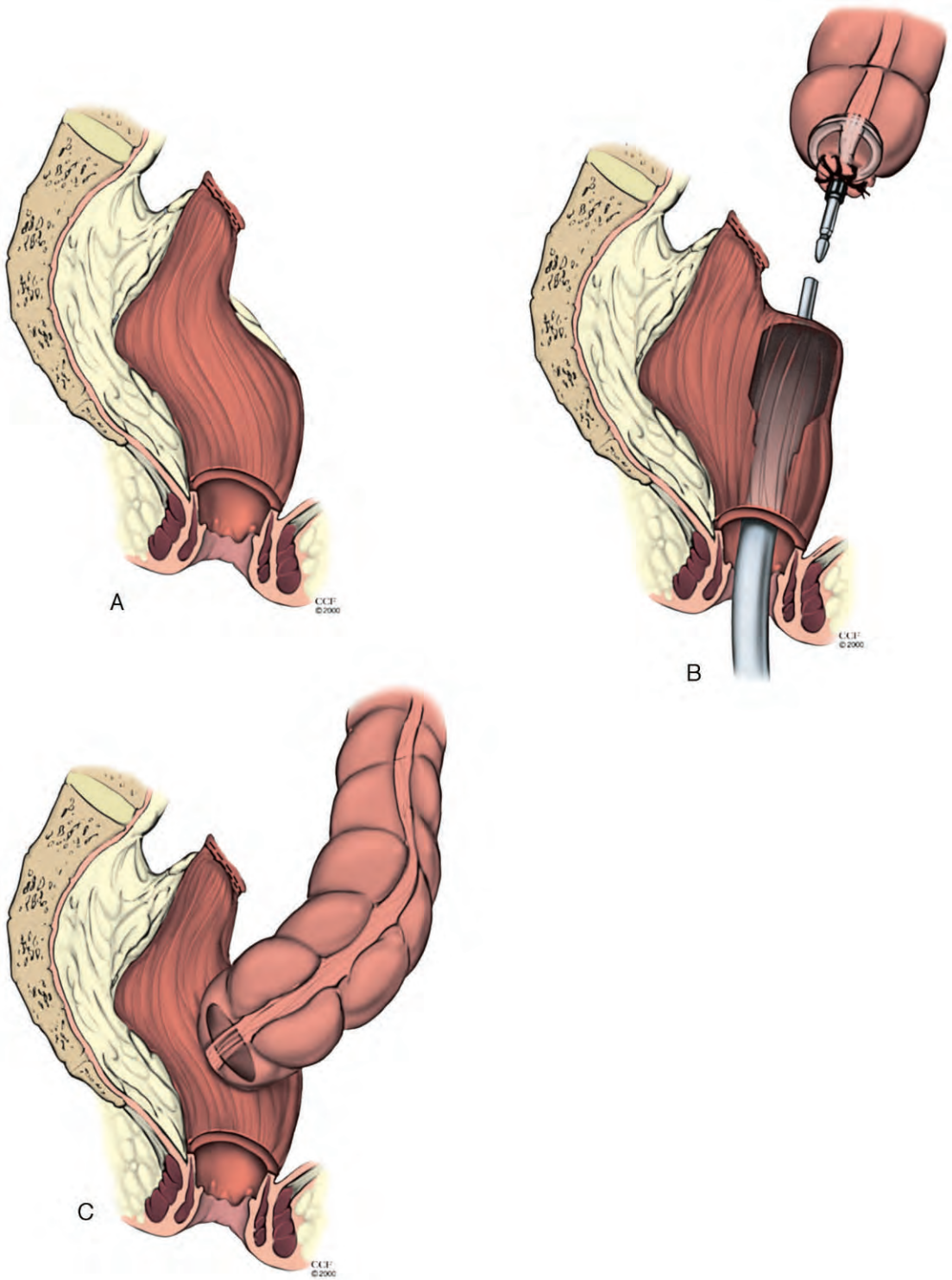

Figure 172–6. Reversal of Hartmann's operation. A problem with double-stapled operations is that the apex of the stump is scarred and narrowed and tends to "concertina" on the cartridge component **(A).** This leads to incomplete tissue rings and dehiscence of the anastomosis. The solution is removal of the narrowed apex with anastomosis **(B)** or end colon–to–side of rectum anastomosis **(C).** (**A-C,** ©2000, Cleveland Clinic Foundation.)

omentum deep within the pelvis. Surprisingly, obtaining a tension-free anastomosis is rarely a problem.

The results of a series of redo pelvic pouches at our institution highlight some of the problems that can be encountered with such surgery, yet at the same time illustrate the success that can be achieved with experience and a well-organized approach to the reoperative pelvis.[1]

Experience with Redo Pelvic Pouch Operations We reviewed the medical records of 1680 patients who underwent restorative proctocolectomy between 1983 and March 1998.[3] Of these patients, 13 required complex salvage surgery for failure of restorative proctocolectomy; this consisted of abdominoanal disconnection of the ileo pouch–anal anastomosis (IPAA), resection of distal pouch and neo-pouch–anal anastomosis with mucosectomy (if not already performed), and (usually) temporary ileostomy. An additional 33 patients were referred from outside institutions with a major septic complication of the pelvic pouch surgery and underwent redo IPAA. The origin of the sepsis invariably was an anastomotic defect at the IPAA with (usually) a pelvic abscess.

Although the posterior pelvic mobilization was often difficult with inadvertent pouch enterotomy being common, this was easily repaired. The early concerns involved attaining sufficient extra length (pouch reach) of the ileum to allow for a tension-free neo-IPAA.

This proved to be an unfounded concern. Thirty-five patients were followed in the long term. Thirty (86%) had a functioning pouch 6 months after redo IPAA. Four of 10 patients with Crohn's disease in the study required pouch excision or diversion. One of 22 patients with ulcerative colitis declined closure of the temporary ileostomy. The other 21 all had a functioning pouch at 6 months or later after stoma closure. The main concerns with the operation were the temporary incontinence or decreased continence as a result of remanipulation of the anal canal. This improved, however, and all patients said they would undergo repeat IPAA again if presented with the same complication.[1]

Malignant

Although the general operative principles discussed earlier apply to surgery for recurrent malignancy, more emphasis must be placed on weighing the benefits of surgery against the potential for complications or death. Preoperative imaging and staging are essential to avoid an unnecessary and unhelpful operation. As discussed earlier, PET scanning has become useful in this respect,[2] and the pattern of recurrence in the pelvis may also be predictive of the chance of a complete resection.[1] Palliative resections of recurrent rectal, gynecologic, or urologic carcinomas in the pelvis have been rarely indicated, since control of symptoms is low with morbidity being high and long-term survival being poor. However, with the advent of newer biologic chemotherapeutic agents directed against angiogenesis or growth factors, survival with metastatic colon and rectal cancer may be prolonged from historical expectations and the role of palliative surgery may need to be reevaluated. Preoperative chemotherapy and radiation (if not received earlier) should be considered as it would be for primary rectal cancers, the indications being bulky or advanced disease. As with primary rectal cancer, waiting 4 to 6 weeks before subsequent surgery is recommended.

Reoperation for recurrent rectal cancer is almost always a difficult undertaking. Landmarks may be absent owing to pelvic fibrosis and scarring. Ureteric stents may be impalpable. Distinction between postoperative scarring and radiation effect from recurrent cancer may be difficult. Certain landmarks include the promontory of the sacrum, aorta, aortic bifurcation, and iliac vessels. If some mobility can be imparted to the matted scar around a previous colorectal anastomosis, one is encouraged to go forward. Trial dissection of the presacral space may come to a halt when real or apparent fusion of a mid sacral level colorectal anastomosis—the site of recurrence to the sacrum—is encountered. In such cases, if a sense of partial fusion is obtained, the surgeon may choose to dissect posterior to Waldeyer's fascia. This is a bold step, because shearing of the basivertebral veins from the sacrum may occur, especially if an osteotome is used. However, the surgeon may be rewarded by finding a plane in which a fibrous layer of thickened membrane—or periosteum—is anterior to the sacrum. Bleeding may be dealt with by one of the methods described earlier. It is important to identify situations where such efforts are beyond the capacity to perform a curative operation; these include preoperative sciatic pain, lower limb lymphedema, bilateral ureteric obstruction, retroperitoneal paraortic lymph node involvement by cancer, and especially fixation of the pelvic mass to the side walls of the pelvis. Although an anastomosis may occasionally be possible, usually distal transection and stapling of the lower rectum or abdominoperineal resection is required.

Radical resection, including exenteration and/or sacral resection, is sometimes indicated in experienced hands at centers with appropriate anesthesia and intensive care support. A series from Japan[4] reported 64 patients undergoing exenteration and/or sacrectomy (all S3 or below) for advanced primary rectal tumors or recurrent rectal tumors over a 12-year period. Two thirds of patients had recurrent cancer, and in this group, although morbidity was reported at 60%, perioperative mortality and reoperation were only 2.4% each. In those in whom a curative resection was performed 5-year survival was 23%, whereas it was 0% if a palliative resection was performed. A series from the Netherlands[5] reported 26 sacral resections, with or without concurrent exenterations for isolated pelvic malignancy in 24 patients over an $8^1/_2$-year period. Using a standardized approach, median operative times were 6 hours and median blood loss 3.6 L; omental flaps, rectus flaps, and nonabsorbable mesh were commonly used to reconstruct the pelvic defect. One patient died in the perioperative period, but at a median follow-up of 14 months, 16 of 19 surviving patients were disease-free.

Intraoperative radiation therapy (IORT) is advocated by some to further improve local control of completely resected recurrent cancer or to treat microscopic or macroscopically positive margins. A dedicated operating

room necessary for this will only be feasible at tertiary care centers. In the earlier referenced series of patients from Memorial Sloan-Kettering,[1] 101 of 119 received IORT in a dedicated operating room from a shielded ^{192}Ir source. Doses of 1500 cGy were given with a negative margin, and 1750 cGy was given with a positive margin.

Our experience with reoperation for selected recurrent rectal cancer justifies our approach and relies on accurate preoperative staging and a familiarity with the reoperative pelvis.

OPERATIVE MEASURES TO MAKE SUBSEQUENT PLANNED OR UNPLANNED PELVIC SURGERY EASIER AND SAFER

Although it is rare to perform a planned second operation in the pelvis, the one instance where difficulty can be minimized is in the performance of a Hartmann procedure when a subsequent colorectal anastomosis is planned. Leaving the rectal stump long by essentially dividing the distal sigmoid and not entering the pelvis prevents a potentially difficult pelvic dissection. If the distal sigmoid is diseased and there are concerns as to so-called stump blowout, it can be left long enough to suture it above the fascia in the lowermost portion of the wound. Any breakdown here would be in the subcutaneous tissues rather than the peritoneal cavity and easily managed by opening the skin.

Much of the difficulty in reoperative pelvic surgery is the mobilization of small bowel out of the pelvis. Almost any operation in the pelvis allows small bowel to become adherent to the site of surgery, and this is particularly pronounced when a large space is created such as in the case of an abdominoperineal resection. Inflammation due to infection, bleeding, or irradiation is also likely to make the small bowel more firmly adherent. Routine use of an omental pedicle to fill the potential space may reduce this. Further, the liberal use of drains with or without irrigation may lessen the inflammation that promotes adhesions. Seprafilm placed beneath the abdominal wall and even in the pelvis may also help to reduce adhesions.

CONCLUSION

Reoperative pelvic surgery may be one of the most challenging procedures that a surgeon can face. However, careful preoperative planning and patient preparation combined with a well-practiced, methodical intraoperative approach may yield rewarding results with acceptable complications.

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Index

Note: Page numbers followed by b refer to boxed material; those followed by f refer to figures; those followed by t refer to tables.

A

Abdomen
  anatomy of, 16
  "frozen," 1148
  hostile, 1147–1148, 1148b
Abdominal abscesses, percutaneous drainage of, duodenal perforation due to, 1095
Abdominal aortic surgery, colonic ischemia complicating, management of, 2006, 2008f, 2008–2009, 2009f
Abdominal distention
  differential diagnosis of, 1884
  in small bowel obstruction, 1028
Abdominal examination, for small bowel obstruction, 1028
Abdominal exploration, in Crohn's disease, 1057–1058, 1058f
Abdominal incisions, for Crohn's disease, 1056–1057, 1057f
Abdominal masses, in appendicitis, 2142
Abdominal pain
  in appendicitis, 2141–2142
  in Crohn's disease, 1045
  differential diagnosis of, 1884
  in mesenteric ischemia, chronic, 1257
  with pancreatic pseudocysts, 1330
  in pancreatitis, chronic, 1344–1345
  in small bowel obstruction, 1028
Abdominal plain films
  with colon, rectal, and anal disorders, 1891
  in colonic volvulus, 1981
  in duodenal injury, 765
  with hepatic abscesses
    amebic, 1654
    pyogenic, 1646
  in mesenteric ischemia, 1252
  in mesenteric venous thrombosis, 1256
  of obturator hernias, 693, 694f
  in small bowel obstruction, 1029, 1029f
  in small bowel volvulus, 1036
  in small intestinal atresia, 1219, 1221f
Abdominal trauma, in pediatric patients, evaluation of, 1806–1808, 1807f, 1808t, 1809f, 1810f, 1811t
Abdominal wall
  abnormalities of, with gastrointestinal fistulas, 1098
  anterior, anatomy of, 636–640, 640f
Abdominal wall *(Continued)*
  of muscles, ligaments, and aponeurosis, 636–639, 637f–639f
  of skin, fascia, vessels, and nerves, 636
  innervation of, 641–642
  vasculature of, 642, 642f
Abdominoperineal approach, for retrorectal tumors, 2307–2309, 2308f
Abdominoperineal resection, of rectum. *See* Rectum, abdominoperineal resection of.
Abhandlung von den Bruchen (Richter), 632
Ablative therapies
  cryoablation as
    for Barrett's esophagus, 371
    hepatic, external biliary fistulas following, etiology and prevention of, 1540
    for hepatocellular carcinoma, 1738
    for metastatic colorectal cancer, 2283
  laser, for Barrett's esophagus, 370–371
  radiofrequency
    circumferential balloon-based, for Barrett's esophagus, 367–370, 368f, 369f
    for hepatocellular carcinoma, 1737–1738, 1738
    transarterial, hepatic abscesses following, pyogenic, 1642
Abscesses
  abdominal, percutaneous drainage of, duodenal perforation due to, 1095
  anastomotic cuff, following ileal pouch–anal anastomosis, 2111
  anorectal. *See* Anorectal abscesses.
  in Crohn's disease, 1065
  hepatic. *See* Liver abscesses.
  intra-abdominal
    with appendicitis, 2150
    following ileal pouch–anal anastomosis, 2111
    management of, 1101–1103, 1103f, 1104f
  liver. *See* Liver abscesses.
  pancreatic, 1329
    definition of, 1296
    with pancreatic pseudocysts, 1342–1343, 1343f
    with trauma, 1405
  pelvic, with appendicitis, 2150
Abscesses *(Continued)*
  perianal, in Crohn's disease, surgical treatment of, 2135, 2136f
  periappendiceal, 2148–2149
  pericolic, in colonic diverticular disease, 2016–2017
  pilonidal. *See* Pilonidal disease.
  splenic, 1818–1820
    characteristics of, 1819
    diagnosis of, 1818, 1819f
    image-guided interventional therapy for, 1795, 1795f
    management of, 1820
    presenting signs and symptoms of, 1818
    splenectomy for, 1833
  subphrenic, with appendicitis, 2150
Absorption
  duodenal, 978–980
    of calcium, 979
    of iron, 979–980, 980f
  of energy, in ultrasonography, 111
  enteral, of nutrients, maximizing in short-bowel syndrome, 1165–1166, 1166b
  by gallbladder, 1456, 1457f, 1458
  small intestinal. *See* Small intestinal epithelium, digestion and absorption and.
Acarbose, for dumping syndrome, 871
Accessory hemiazygos vein, 22
Acetaminophen
  fulminant liver failure due to, 1703
  hepatotoxicity of, 1720
Acetic acid, for hepatocellular carcinoma, 1738
Achalasia, 405–409, 411–417
  Chagas' disease and, 406–407
  classic, imaging in, 71–72, 72f
  clinical features of, 407
  complications of, 409
  cricopharyngeal, 427. *See also* Zenker's diverticulum.
  diagnosis of, 407, 408f, 408t, 411–412, 412f
  dilation therapy for, esophageal perforation following, 538
  early (mild), imaging in, 72
  endoscopic ultrasonography in, 124–125
  epidemiology of, 405, 406f
  esophageal carcinoma and, 466

Achalasia *(Continued)*
esophageal replacement for, 294f, 294–296, 295f
esophagomyotomy for, complications of, 619–620
Heller myotomy with, 416
historical background of, 411
imaging in, 71–74, 72f
medical therapy for, 412
botulinum toxin for, 412
pharmacologic, 412
pneumatic dilatation for, 412
pathogenesis of, 136, 405–407, 406f
secondary, 407–409
radiographic appearance of, 76, 77f
surgical therapy for, 413–417. *See also* Heller myotomy, laparoscopic.
early development of, 5
vigorous, imaging in, 72, 73f
Acid ingestion, gastric injury due to, 762
Acid perfusion test, esophageal, 164, 165t
for esophageal motility disorders, 159–160
Acid reflux test, standard, 164, 165t
Acid secretion, basal, in esophageal disease, 195
Acidosis, metabolic, in short-bowel syndrome, 1166
Acinar cell(s), 1291, 1291f
injury of, 1296–1297
Acinar cell carcinoma, 1432, 1433f, 1434
Acoustic impedance, in ultrasonography, 111
Acquired immunodeficiency syndrome. *See also* Human immunodeficiency virus infection.
anal fissures in, 2038
immunosuppression due to, 2376–2377
surgical risk assessment in, 2380–2381
Acute Physiology and Chronic Health Evaluation-II scoring system, for pancreatitis, acute, 1300, 1301b, 1302
Adalimumab
for inflammatory bowel disease, 2093
mechanism of action of, 2377t
Adenocarcinoma. *See specific site, e.g.* Esophageal adenocarcinoma.
Adenoma(s)
bile duct, 1526, 1729
flat
gastric, 885
small intestinal, in hereditary flat adenoma syndrome polyposis, 894t, 896
gastric, 884
hepatic, 1729
diagnosis of, 1729, 1730f
drug-induced, 1723
etiology of, 1729
treatment of, 1729, 1730f
pancreatic. *See* Mucinous cystic neoplasms, pancreatic; Serous cystic neoplasms, pancreatic.
papillary, gastric, 885
tubular, small intestinal, 891–892
villous, small intestinal, 892–893
Adenoma-carcinoma cascade, 2183
Adenomatosis, 1729
Adenomatous polyps
colorectal. *See* Colorectal polyps, adenomatous.
endoscopic appearance of, 740, 741f
Adenomyomas, gastric, 884
Adhesiolysis, for small bowel obstruction, open vs. laparoscopic, 1032–1033
Adhesions
with laparoscopic surgery, 1135
lysis of
with hostile abdomen, 1148
with ventral herniorrhaphy, 681
prevention of, 1033
reoperative surgery and, 1135
small bowel obstruction due to, 1027
Advancement flaps
for anal stenosis, 2063, 2063f
anorectal, for anorectal fistulas, 2056, 2056f
mucosal, for anal stenosis, 2063
sleeve, for rectovaginal fistulas, 1951, 1951f
Y-V, for anal stenosis, 2063, 2063f
Aerophagia, partial fundoplication for, 279
Afferent loop obstruction
following gastrectomy, 809, 877–879, 879f
reoperative surgery for, 1147
Age. *See also* Elderly people; Pediatric patients.
Barrett's esophagus and, 342
drug-induced liver disease and, 1717
esophageal cancer and, 442, 442f
ileal pouch–anal anastomosis outcome and, 2118
AIDS. *See also* Human immunodeficiency virus infection.
anal fissures in, 2038
immunosuppression due to, 2376–2377
surgical risk assessment in, 2380–2381
Alagille's syndrome, 1546
diagnosis of, 1546
Alanine aminotransferase, elevated, 1611b, 1611–1612
Albumin, elevated, patient approach for, 1615–1616
Alcohol ingestion
abuse and
esophageal motility disorders in, 140
pancreatitis and, acute, 1298
esophageal cancer and, 444, 466
pruritus ani associated with, 2069
Alcohol sclerotherapy
for esophageal cancer, 488, 489t
for hepatocellular carcinoma, 1737
Alcoholic liver disease
end-stage liver disease due to, 1687
hepatic laboratory tests in, 1612
Alemtuzumab, for islet transplantation, 1428
Alfa-fetoprotein, in hepatocellular carcinoma, 1734
Alkaline phosphatase, elevated, patient approach for, 1614–1615
Alkaline reflux gastritis. *See* Bile reflux gastritis.
Alkalosis, metabolic, in short-bowel syndrome, 1166
Allergic dermatitis, pruritus ani associated with, 2069
Allis forceps, 633
Allison, Phillip, 5, 6
Allison repair, 228
Allison's membrane. *See* Phrenoesophageal membrane.
AlloDerm, for ventral herniorrhaphy, 676
Altemeier procedure, for rectal prolapse, 1962, 1964t
Amanita mushrooms, hepatotoxicity of, 1720
Amebiasis. *See* Liver abscesses, amebic.
Amifostine, for radiation enteritis prevention, 1155
Amiloride, for ascites, 1764
5-Aminosalicylates, for Crohn's disease, 1052, 1053
Amiodarone, hepatotoxicity of, 1720
Amoxicillin
hepatotoxicity of, 1723
for lymphoma, 1209t
Ampullary balloon dilation, 1484–1485, 1485f
Amrinone, mesenteric blood flow and, 1243t
Amsterdam Criteria, for hereditary nonpolyposis colorectal cancer, 2171, 2171b, 2188
Amsterdam Criteria II, for hereditary nonpolyposis colorectal cancer, 2171, 2171b
Amylase, serum
in pancreatic trauma, 1401
in pancreatitis, 1299, 1300b
Amyloidosis
esophageal motility disorders in, 140
splenectomy for, 1835
Anabolic steroids, hepatotoxicity of, 1723
Anal adenocarcinoma, 2296
Anal anastomosis, colopouch, for rectal radiation injury, 2324
Anal canal
lesions of, in Crohn's disease, 2088
neoplasms of, 1912–1913, 1913f, 1913t
ultrasound of. *See* Endoanal ultrasound.
Anal carcinoma
adenocarcinoma as, 2296
squamous cell, 2291–2294
clinical features of, 2291
physical examination of, 2291
staging of, 2291, 2292f
therapy of, 2291–2294
combined chemotherapy and radiation therapy for, 2292–2293, 2293t
salvage surgery as, 2293–2294, 2294f
surgical, primary, 2291–2292
Anal disorders
diagnosis of, 1883–1897
examination for, 1885–1888
with anorectal pain or swelling, 1887
for bleeding, 1887
for constipation, 1888
general principles of, 1885–1886

Anal disorders *(Continued)*
inspection and palpation in, 1886–1887
positioning for, 1886, 1886f
for urgency and incontinence, 1888
history in, 1883
investigation for, 1888–1897
blood and stool testing in, 1888–1889
endoscopy in, 1889f, 1889–1891, 1890f
radiologic tests in, 1891f, 1891–1897, 1892f, 1894f–1897f
symptoms in, 1883–1885
abdominal pain and distention as, 1884
anorectal pain, itching and swelling as, 1884
bleeding as, 1883–1884
constipation as, 1884–1885
diarrhea as, 1885
urgency and incontinence as, 1885
ultrasound in. *See* Endoanal ultrasound.
Anal encirclement, 1923
for rectal prolapse, 1964f, 1964t, 1964–1965
Anal fissures, 2038–2043, 2039f
diagnosis of, 2039, 2039f
etiology of, 2038–2039
examination for, 1887
nonsurgical management of, 2039–2040
botulinum toxin for, 2040
calcium-channel blockers for, 2040
general approaches for, 2039–2040
topical nitroglycerin for, 2040
surgical treatment of, 2041, 2041f, 2042f, 2042t
treatment algorithm for, 2042f, 2043
Anal fistulas
chronic, malignant transformation in, 2058
classification of, 2045, 2047f, 2048t
in Crohn's disease, 2057–2058, 2088
diagnosis of, 2049–2051
colonoscopy in, 2049
computed tomography in, 2051
fistulography in, 2049
fistuloscopy in, 2051
history in, 2049
magnetic resonance imaging in, 2051
manometry in, 2051
physical examination in, 2049, 2050f
sigmoidoscopy in, 2049
ultrasonography in, 2049–2051, 2050f–2052f
endoanal ultrasound in, 1911–1912, 1912f
etiology of, 2045
in infancy, 2058
recurrent, 2057
treatment of
anorectal advancement flaps for, 2056, 2056f
complications of, 2057
fibrin glue for, 2056–2057
fistulotomy for, 2055
Anal fistulas *(Continued)*
postoperative care for, 2057
seton management for, 2055f, 2055–2056
Anal infections, in immunocompromised patients, 2383, 2383t
Anal neoplasms, 2288–2296
adenocarcinoma as, 2296
anal intraepithelial neoplasia as, 2289–2291, 2290f
anatomy and, 2288
basal cell carcinoma as, 2295–2296
histology of, 2288–2289
in immunocompromised patients, 2384
incidence of, 2289
inguinal and pelvic lymph node metastasis and, 2294, 2295f
melanoma as, 2295
in Paget's disease, 2294–2295
Anal sphincter, artificial, 1924, 1924f
Anal sphincter defects, endoanal ultrasound in, 1910–1911, 1911f
Anal sphincter reconstruction, 1922f, 1922–1923
Anal sphincterotomy
internal, partial, for anal fissures, 2041, 2041f, 2042f
lateral, for anal fissures, 2041, 2042t
Anal stenosis, 2062–2065
medical therapy for, 2062
surgical therapy for, 2062–2065
advancement flaps as, 2063, 2063f
island flaps as, 2063f, 2063–2064, 2064f
rotational flaps as, 2064–2065, 2065f
Anal wipes, pruritus ani associated with, 2069
Analgesia
for pancreatitis
acute, mild, 1302
severe, necrotizing, 1303
patient controlled, following bariatric surgery, 937
Anastomotic complications, of esophagectomy, 481
Anastomotic cuff abscesses, following ileal pouch–anal anastomosis, 2111
Anastomotic leaks
with esophageal and tracheoesophageal atresia repair, 569–570
esophagogastric, following esophageal surgery, 599
following esophageal resection with visceral esophageal substitution, 611–613, 612f
Anastomotic stricture
with esophageal and tracheoesophageal atresia repair, 570
following esophageal resection with visceral esophageal substitution, 613
Androgen(s), hepatotoxicity of, 1722, 1723
Androgenic metabolic steroids, hepatotoxicity of, 1724
Anemia
following gastrectomy, 873
with gastrointestinal fistulas, 1098
Anemia *(Continued)*
iron deficiency
in Crohn's disease, 1054
following gastrectomy, 873
splenectomy for hematologic disorders causing, 1825–1827
hemolytic, acquired anemia and, 1826–1827
hereditary anemia and, 1825–1826
Anesthesia
in biliary disease, 1626
for groin hernia surgery, 646
in liver disease, 1626
Anesthesiologists, on portal hypertension multidisciplinary team, 1767
Aneurysm(s). *See also* Pseudoaneurysms.
celiac artery, 1279–1280
clinical findings in, 1279
diagnosis of, 1279
incidence of, 1279
pathogenesis of, 1279
treatment of, 1279–1280
colic artery, 1282f, 1283
gastric artery, 1282
gastroduodenal artery, 1280f, 1280–1282
gastroepiploic artery, 1282
hepatic artery, 1277–1278, 1711–1712, 1712f
arteriography in, 1278
clinical findings in, 1278
diagnosis of, 1278
false, 1277
incidence of, 1277
pathogenesis of, 1277
treatment of, 1278
ileal artery, 1282f, 1283
inferior mesenteric artery, 1280
pancreatic artery, 1280–1282
pancreaticoduodenal artery, 1280–1282, 1281f
splenic artery, 1274–1277
clinical findings in, 1275
diagnosis of, 1275, 1276f
incidence of, 1274
pathogenesis of, 1274–1275
splenectomy for, 1833–1834
treatment of, 1275, 1277
superior mesenteric artery, 1278–1279
clinical findings in, 1278
diagnosis of, 1278–1279
incidence of, 1278
pathogenesis of, 1278
treatment of, 1279
Aneurysmorrhaphy
for splenic artery aneurysms, 1275, 1277
for superior mesenteric artery aneurysms, 1279
Angiodysplasia
gastric, 887
endoscopic appearance of, 739
signs and symptoms of, 887
treatment of, 887
small intestinal, 898
Angiography
in aortoenteric fistulas, 1271
calcium, for insulinoma localization, 1378
with colonic vascular ectasias, 1993

Angiography *(Continued)*
with duodenal diverticula, 779, 780f
mesenteric, with colon, rectal, and anal disorders, 1896–1897, 1897f
Angiomyolipomas, hepatic, 1730
Angiosarcomas, hepatic, 1747–1748, 1748f
drug-induced, 1724
end-stage liver disease due to, 1687
Angiozyme, for colorectal cancer metastases, 2271
Anismus, surgical treatment of, 1936–1938, 1939f, 1940f, 1941t
Ann Arbor staging system with Cotswold modification, 1827, 1828t
Annular pancreas, 1407–1408, 1408f
Anocutaneous reflex, 1918
Anoplasty
cutback, for low imperforate anus, 2394f, 2395–2396
Martin, for anal stenosis, 2063
transplant, for low imperforate anus, 2396, 2397f
Anorectal abscesses
classification of, 2045, 2046f, 2048t
diagnosis of, 2045, 2048–2049
history in, 2045, 2048
magnetic resonance imaging in, 2051
physical examination in, 2048–2049
ultrasonography in, 2049–2051, 2050f–2052f
etiology of, 2045
horseshoe extension and
diagnosis of, 2049
treatment of, 2053–2054, 2054f
in human immunodeficiency virus disease, 2058
intersphincteric
diagnosis of, 2048
treatment of, 2053
ischiorectal
diagnosis of, 2048
treatment of, 2053
in leukemia, 2058
management of, 2057–2058
perianal
diagnosis of, 2048
treatment of, 2052–2053, 2053f
postanal
diagnosis of, 2049
treatment of, 2053–2054, 2054f
submucosal
diagnosis of, 2048
treatment of, 2053
supralevator
diagnosis of, 2048–2049
treatment of, 2053, 2053f
treatment of, 2051–2055
complications of, 2057
for horseshoe extension, 2053–2054, 2054f
for intersphincteric abscesses, 2053
for ischiorectal abscesses, 2053
for perianal abscesses, 2052–2053, 2053f
for postanal abscesses, 2053–2054, 2054f
postoperative care for, 2057
Anorectal abscesses *(Continued)*
primary versus delayed fistulotomy for, 2054–2055
for submucosal abscesses, 2053
for supralevator abscesses, 2053, 2053f
Anorectal advancement flaps, for anorectal fistulas, 2056, 2056f
Anorectal anomalies, 2387–2406
associations among, 2390–2391
genitourinary types of, 2390
sacral and spinal types of, 2390
classification of, 2388t, 2388–2390, 2389t, 2390f–2393f
embryology of, 2387–2388
initial management of newborn with, 2394–2395
in all infants, 2395
in female infant, 2394–2395
in male infant, 2394, 2394f
operative technique for, 2395
pelvic muscular anatomy and physiology of continence and, 2391–2394
surgical management of, 2395–2406
functional results of, 2403–2406, 2404f
with cloacal surgery, 2406
constipation as, 2405
continence and, 2404
genitourinary, 2405–2406
with high imperforate anus, 2404–2405
treatment of incontinence and, 2405
for high imperforate anus, 2396, 2398–2402, 2399f
with cloacal malformation, 2402, 2403f
colostomy construction and, 2396, 2398f
minimally invasive repair as, 2400–2402, 2401f, 2402f
neonatal pull-through procedures for, 2400
for low imperforate anus, 2395–2396
anterior perineal anorectoplasty as, 2396, 2397f
cutback anoplasty as, 2395f, 2395–2396
transplant anoplasty as, 2396, 2397f
postoperative complications of, 2402–2403
reoperative surgery for, 2403
Anorectal disorders. *See also specific disorders.*
abscesses as. *See* Anorectal abscesses.
congenital. *See* Anorectal anomalies.
in Crohn's disease
abscesses as, 2057–2058
fistulas as, 2057
surgical treatment of, 2135
itching as, differential diagnosis of, 1884
swelling as
differential diagnosis of, 1884
examination for, 1887
ultrasound in. *See* Endoanal ultrasound; Endorectal ultrasound.
Anorectal injury, 1977–1978
Anorectal mucosectomy, with muscular plication, for rectal prolapse, 1962, 1962f–1964f, 1964, 1964t
Anorectal pain
differential diagnosis of, 1884
examination for, 1887
Anorectal pull-through
for high or intermediate imperforate anus, 2400
laparoscopically assisted, for high imperforate anus, 2400–2402, 2401f, 2402f
Anorectal ring, 2220
Anorectoplasty
perineal, anterior, for low imperforate anus, 2396
sagittal, posterior, 2387, 2398, 2399f, 2400
Anorexia, in appendicitis, 2142
Anoscopy, 1889, 1889f
Anovaginal fistulas, 1946
Antacids, for gastroesophageal reflux disease, 253
Antibiotics
for asplenia, in pediatric patients, 1811
for cholangitis prophylaxis, 1550t
for cholangitis treatment, with primary sclerosing cholangitis, 1588
for hepatic abscesses, pyogenic, 1648–1649
for inflammatory bowel disease, 1052, 2090–2091, 2128
for intra-abdominal abscesses, 1102
for pancreatitis
acute, mild, 1302
severe, necrotizing, 1303, 1304t
preoperative
for colorectal surgery, 2328–2329
oral, 2328
parenteral, 2328–2329
prophylactic
for cholangitis, 1550t
for overwhelming postsplenectomy infection, 1838
prophylactic vs. therapeutic use of, 2329
for splenic abscesses, 1820
Antibodies
anti-*Saccharomyces cerevisae,* in Crohn's disease, 1046
cytoplasmic, perinuclear antineutrophil, in Crohn's disease, 1046
hOKT3-γ1-ala-ala, for islet transplantation, 1428
for pancreas transplantation, 1419
Anticoagulation
for mesenteric ischemia, 1255
for mesenteric venous thrombosis, 1256–1257
Antidiarrheal agents, for fecal incontinence, 1921
Antiemetic agents, for gastroparesis, 921
Antiestrogens, for desmoids, in familial adenomatous polyposis, 2161, 2162
Antifungals, hepatotoxicity of, 1722
Antihistamines, for gastroparesis, 921

Anti-inflammatory drugs, nonsteroidal
for Barrett's esophagus, 258
for desmoids, in familial adenomatous polyposis, 2161, 2162
esophageal cancer and, 445
Anti-interleukin-12, mechanism of action of, 2377t
Antilymphocyte globulin, mechanism of action of, 2377t
Antireflux procedures. *See also specific procedures.*
for Barrett's esophagus, 354–363
dysplastic
high-grade, 361–363, 362f
low-grade, 360–361, 361b
impact on metaplasia-dysplasia-carcinoma sequence, 358–359
regression of Barrett's esophagus and, 358–359, 359f, 360f
outcome of, 355–357
choice of operation and, 356
objective measures of reflux control and, 357
symptomatic, 356–357, 357f
rationale for, 354–355, 355t, 356t
chylothorax following, 609
contraindications to, in severe gastroesophageal reflux disease, 267
early development of, 6–7
endoscopic, 306–331
endoluminal gastroplasty as, 309–314
physiologic/anatomic mechanisms of, 328–329, 330f
Enteryx for, 320–323
physiologic/anatomic mechanisms of, 330–331
Gatekeeper for, 323–325, 326t, 327t
physiologic/anatomic mechanisms of, 330–331
historical background of, 307–308, 308b
NDO plicator for, 308b, 314–316
complications of, 316
efficacy of, 315–316, 316t
physiologic/anatomic mechanisms of, 329–330, 330f
procedure for, 314f, 314–315, 315f
physiologic/anatomic mechanisms of, 326, 328–331
for endoluminal gastroplasty, 328–329, 330f
for Enteryx, 330–331
for Gatekeeper, 330–331
for NDO plicator, 329–330, 330f
for Stretta procedure, 330–331
Plexiglas for, 325
reflux pathophysiology and, 306–307
selection criteria for, 308f, 308–309
Stretta procedure for, 317–320, 325, 326t, 327t
physiologic/anatomic mechanisms of, 330–331
Syntheon device for, 316f, 316–317
endoscopic evaluation following, 106, 108, 108f
Antireflux procedures *(Continued)*
esophageal imaging following, 85, 86f
with esophagomyotomy, controversy about, 620
failure of
barium examination for, 70
reoperative surgery for, 1141–1143
technical aspects of, 1143, 1143b
with Heller myotomy, for achalasia, 416
hemorrhage following, 609–610
with intraoperative stricture dilatation for esophageal strictures, 241–248
laparoscopic, complications of, 610–611
predischarge barium swallow study for, 610, 610f
retrosternal dysphagia following, low, 609
Anti-*Saccharomyces cerevisae* antibodies, in Crohn's disease, 1046
Antiserotoninergics, for gastroparesis, 921
Antithymocyte globulin
for islet transplantation, 1428
mechanism of action of, 2377t
Antral hypomotility, detection by antroduodenal manometry, 188
Antral webs, endoscopic appearance of, 738
Antrectomy
for caustic injury, gastric, 763
with long-limb Roux-en-Y gastric bypass, for Barrett's esophagus, 303–304
with vagotomy
for duodenal ulcers, 796, 798t
for gastric outlet obstruction, in peptic ulcer disease, 826
Antroduodenal manometry, delayed gastric emptying and, 186–188, 188f, 188t, 189f, 190, 190t
Anus
coloanal anastomosis and. *See* Coloanal anastomosis.
imperforate. *See* Anorectal anomalies; Imperforate anus.
Anxiety, with levator spasm, 2075
Aortoduodenal fistulas, 1095
Aortoenteric fistulas, 1269–1274
classification of, 1269
clinical features of, 1270–1271
diagnosis of, 1271f, 1271–1272
graft-enteric erosion and, 1269, 1270
graft-enteric fistula and, 1269, 1270
pathogenesis of, 1269–1270
treatment of, 1114
endovascular, 1273–1274
results with, 1274
surgical, 1272–1273
for primary aortoenteric fistula, 1272
for secondary aortoenteric fistula, 1273
Aortography
with aortoenteric fistulas, 1115
in mesenteric ischemia, chronic, 1258
Aortomesenteric bypass, for mesenteric revascularization, 1258–1260, 1260f
APACHE-II scoring system, for pancreatitis, acute, 1300, 1301b, 1302
APC gene
familial adenomatous polyposis and, 2163
screening for mutations in, 2164
Aphthous ulcers, in Crohn's disease, 1043
Aponeurotic arch, 638, 638f
Appendiceal distention, with mucinous cystadenoma and cystadenocarcinoma, 2150
Appendiceal orifice, on colonoscopy, 1867
Appendiceal tumors, 2150–2151
carcinoid, 1182
treatment of, 1185
Appendices epiploicae, 1845
Appendicitis
acute, 2141–2150
differential diagnosis of, 2144–2145
in elderly people, 2144
in immunocompromised patients, 2381
in infants and young children, 2143–2144
laboratory tests in, 2142–2143
pathophysiology of, 2141
physical examination in, 2142
during pregnancy, 2144
radiographic examination in, 2143
symptoms of, 2141–2142
treatment of, 2145–2150
complications of, 2150
examination under anesthesia and, 2145
laparoscopic appendectomy for, 2147, 2149f
for normal appendix when appendicitis is suspected, 2150
for perforated appendicitis with diffuse peritonitis, 2149
for perforated appendicitis with localized abscess formation, 2148–2149
for perforated or gangrenous appendicitis with a periappendiceal mass, 2147–2148
preoperative preparation for, 2145
for uncomplicated appendicitis without a palpable mass, 2145–2147, 2146f–2148f
in young women, 2144
chronic and recurrent, 2150
Aprepitant, for gastroparesis, 921
Arch of Riolan, 1239
Arch of Treves, 1239
Argon beam coagulation, for esophageal cancer, 489t, 492
Argon plasma coagulation
for Barrett's esophagus, 371
for gastric bleeding, 741–742, 742f
for watermelon stomach, 740
Aristotle, 632, 1813
Arrhythmias, with inguinal herniorrhaphy, laparoscopic, 667
Arsenic, hepatotoxicity of, 1723, 1724
Arteries. *See specific arteries.*

Arteriography
with diverticular hemorrhage, 2016, 2017f
for esophageal reconstruction, 581–582, 582f
in hepatic artery aneurysms, 1278
mesenteric, preoperative, for esophageal replacement, 287–288, 288f
in mesenteric ischemia, 1253f, 1253–1254, 1254f
in mesenteric venous thrombosis, 1256, 1256f
in portal hypertension, 1757
Arterioles, mesenteric, 1240, 1241
Arteriomesenteric duodenal
ileus/compression, 974–975, 975f, 976f
Arterioportal shunts, hepatic, 1713f, 1713–1714
Arteriovenous malformations
colonic, congenital, 1997, 1998f
gastric
congenital, 740, 740f, 886–887
symptoms and diagnosis of, 887
treatment of, 887
endoscopic appearance of, 739, 739f
small bowel, capsule endoscopy of, 746f
Arteriovenous shunts, hepatic, 1713f, 1713–1714
Artery of Drummond, 1239
Artificial anal sphincter, 1924, 1924f
Artificial liver support systems, 1704–1708
biologic, 1706–1707, 1707f
future of, 1707–1708, 1708f
need for, 1705
nonbiologic, 1705–1706
Ascites, 1751, 1755–1756
in cirrhosis, 1624–1625
pancreatic, 1349–1352, 1350f–1352f
in chronic pancreatitis, 1312
in portal hypertension, 1755–1756, 1763–1765
diagnosis of, 1764
management of, 1764–1765, 1765f
pathophysiology of, 1763–1764, 1764f
refractory, 1765
Ascorbic acid, small intestinal absorption of, 1006, 1007t
Aspartate aminotransferase, elevated, 1611, 1611b
Aspergillus, splenic abscess due to, 1819
Aspiration
in achalasia, 407
closed, for hepatic abscesses, pyogenic, 1649
following esophageal surgery, 599
of hepatic cysts, in polycystic liver disease, 1634–1635
percutaneous, of pancreatic pseudocysts, 1333
Asplenia, prophylaxis for, in pediatric patients, 1811–1812
Asthma, gastroesophageal reflux disease associated with
diagnosis of, 171, 172f
medical therapy for, 258, 259f, 260f
Atheroembolism, peripheral, following esophageal resection with visceral esophageal substitution, 615
Atherosclerosis
celiac artery aneurysms due to, 1278
superior mesenteric artery aneurysms due to, 1278
Atlanta Classification, 1296
Atopic eczema, pruritus ani associated with, 2070
Attenuated familial adenomatous polyposis, small intestinal, 894t, 896
Attenuation, in ultrasonography, 112
Auerbach's plexus, 26, 720
Aureobasidum pullulans, splenic abscess due to, 1819
Autoimmune hepatitis, hepatic laboratory tests in, 1613
Autoimmune neutropenia, splenectomy for, 1827
Autonomic nerve plexuses, pelvic, total mesorectal excision with autonomic nerve preservation and, 2237–2238, 2238f
Autoregulation, splanchnic, 1243
Azathioprine
for Crohn's disease, 1053, 2128
for gastrointestinal fistulas, 1105
hepatotoxicity of, 1723
for inflammatory bowel disease, 2091–2092
mechanism of action of, 2377t
Azygos vein, 15f, 22

B

Baker tubes, 750, 751f
Balloon catheters
for bile duct stone removal, 1494, 1495f
biliary, 1484
Balloon dilation
of bile duct strictures, 1588
of biliary sphincter, for stone removal, 1496–1497
of superior mesenteric artery, 1261, 1264t
Balloon expulsion, in obstructed defecation, 1879b
Balsalazide, for inflammatory bowel disease, 2090
Band ligation, endoscopic, for gastric bleeding, 743, 743f
Bannayan-Zonana (Bannayan-Riley-Ruvalcaba) syndrome, 894t, 897, 2159t, 2176
Barbette, Paul, 1229
Barcelona Chronic Liver Cancer staging system, 1735
Bariatric surgery
amelioration of obesity-related diseases and, 938–939
biliopancreatic diversion for, 936, 936f
dietary management following, 938
fistulas following, 1093
follow-up for, 938
gastric banding for, 934–935, 935f
gastric restrictive operations for, 930–931, 931f
indications for, 929–930
jejunoileal bypass for, 930, 930f
Bariatric surgery *(Continued)*
perioperative care for, 937–938
revision operations and, 936–937, 1143–1146
for failed laparoscopic adjustable gastric banding, 1145
for failed malabsorptive procedures, 1146
for failed Roux-en-Y gastric bypass, 1145–1146
for failed vertical banded gastroplasty, 1144–1145
patient selection for, 1144
Roux-en-Y gastric bypass for, 931–934, 932f, 933t
Barium burger studies, radiographic, for gastric emptying assessment, 190
Barium examination
barium enema as
in appendicitis, 2142–2143
with colon, rectal, and anal disorders, 1891–1892, 1892f
in colonic volvulus, 1981, 1982f
in constipation, 1929–1930, 1931f
double-contrast
with colon, rectal, and anal disorders, 1892f, 1892–1893
screening for adenomatous polyps with, 2157
in small bowel obstruction, 1030, 1030f
barium swallow as
in achalasia, 411, 412f
in epiphrenic diverticulum, 432f, 433f, 433–434
with paraesophageal hernia, 552, 553f
for staging of esophageal cancer, 455, 456f
with carcinoid tumors, 1183, 1183f
esophageal, 64
air-contrast technique for, 64, 64f, 65f
in esophageal carcinoma, 75f–79f, 75–76
for staging, 77
in esophageal motility disorders, 68, 71
esophagography as, 164, 165t
in esophageal carcinoma, 469, 469f
for esophageal reconstruction, 582
esophagoscopy as, with leiomyoma, 517, 517f
full-column technique for, 64, 65f, 66f
in gastroesophageal reflux disease, 68–70
to detect esophageal injury, 68–69, 69f, 70f
to detect gastroesophageal reflux, 68
to evaluate esophageal clearance, 68
to exclude motility disorder, 68
for postoperative complication evaluation, 70

Barium examination *(Continued)*
for preoperative planning, 70, 71f
single- or double-contrast technique for, in esophageal carcinoma, 75
with varices, 95, 97f
Barostat system, 1874
Barostat test, in esophageal disease, 195
Barrett, Norman, 5, 7, 336f, 336–337, 341
Barrett's esophagus, 341–351
ablation therapy for, 360, 361, 362
endoscopic, 365–372
argon plasma coagulation for, 371
cryotherapy for, 371
laser, 370–371
mucosal resection for, 370
multipolar electrocoagulation for, 371
photodynamic, 370
radiofrequency, circumferential balloon-based, 367–370, 368f, 369f
rationale for, 367
adenocarcinoma and, 445
invasive, 219, 219f
bile acid injury to esophageal mucosa and, 232
classification systems for, 103–104
columnar epithelium in, detection of, barium examination for, 69, 70f
definition of, 334, 341–342
diagnosis of, 215f, 218f, 218–219, 219f
endoscopic
conventional, 102–104, 103f, 104f
specialized techniques for, 104, 105f
duodenogastroesophageal reflux associated with, 190
dysplastic, 347–348, 349t, 359–363, 360t, 361t
high-grade, 219, 219f
surgical treatment of, 361–363, 362f
low-grade, surgical treatment of, 360–361, 361b
endoscopic examination in, 108, 109f
epidemiology of, 342
gastroesophageal reflux disease and, 200, 203
goblet cells in, 215f, 218
hiatal hernia and, 60
historical background of, 334–338, 336f, 338f
ideal end point of treatment for, 60
length of, 335, 341
long-segment, 335, 346
malignant transformation in, 347–348, 349t
medical treatment of, 60–61, 257–258
microscopic stage of, 218, 218f, 219f
natural history of, 348, 350
nondysplastic, risk of progression to dysplasia and adenocarcinoma, 365, 366t
pathophysiology of, 343–347
intestinalization of cardiac mucosa and, 345f, 345–347
metastatic columnarization with cardiac mucosa and, 343–345
Barrett's esophagus *(Continued)*
patient approach for, 60–61
prevention of, 358–359, 360f
progression to colorectal cancer, risk of, 366
refluxate in, 60
regression of, after antireflux procedures, 358–359, 359f, 360f
reversibility of, 358
risk for, 348
biomarkers for stratifying, 348
risk factors and, 342–343
screening for, 350
short-segment, 335, 346
surgical treatment of, 354–363
for dysplastic Barrett's esophagus
high-grade, 361–363, 362f
low-grade, 360–361, 361b
esophagectomy as, 248
impact on metaplasia-dysplasia-carcinoma sequence, 358–359
regression of Barrett's esophagus and, 358–359, 359f, 360f
outcome of, 355–357
choice of operation and, 356
objective measures of reflux control and, 357
symptomatic, 356–357, 357f
rationale for, 354–355, 355t, 356t
surveillance for, 350–351
treatment goals for, 354
ultrashort, 335
vagotomy and antrectomy for, with long-limb Roux-en-Y gastric bypass, 303–304
Barrett's mucosa, esophageal adenocarcinoma and, 468, 468f
Basal cell carcinoma, anal, 2295–2296
Basiliximab, mechanism of action of, 2377t
Baskets, for bile duct stone removal, 1494
Bassini, Edoardo, 632–633
Bassini hernia repair, 648
Bear claw defect, 1660
Beck, Claude, 4
Beger procedure, for pancreatitis, chronic, 1314, 1315
Belching, gastroesophageal reflux disease and, 227–228
Bell, Charles, 5
Belsey, Ronald, 6
Belsey fundoplication, for esophageal strictures, 241–242
Belsey Mark IV procedure, 276, 277f
Collis gastroplasty with, for esophageal strictures, 242, 243f
early development of, 6
for esophageal strictures, 241
imaging following, 85
recurrent reflux following, 598
results with, 283, 283t
transthoracic, 282f, 282–283
Benzimidazoles, substituted, gastric acid secretion and, 727
Bernstein test, 164, 165t
Bethanechol, for gastroesophageal reflux disease, 253, 254
Bethesda Guidelines, for hereditary nonpolyposis colorectal cancer, 2171, 2172b
Bevacizumab
for metastatic colorectal cancer, 2202, 2270–2271
palliative, for esophageal cancer, 496
Bezoars, 943–945, 944t
clinical features and diagnosis of, in pediatric patients, 959
definition and types of, in pediatric patients, 959
diagnosis of, 944f, 944–945, 945f
management of, 945
in pediatric patients, 959–960, 960f
in pediatric patients, 959–960
clinical features and diagnosis of, 959
definition and types of, 959
management of, 959–960, 960f
signs and symptoms of, 944
types of, 943–944, 944t
Bianchi procedure, for short-bowel syndrome, 1171, 1172f, 1173
Bicarbonate, gastric secretion of, 728–729
Bilayer hernia repair, 653
Bile
bilirubin metabolism and, 1454
cholesterol in, 1452–1453, 1455f, 1456f
composition of, 1455, 1455t
enterohepatic circulation and, 1453–1454, 1457f
flow of, 1454–1455
formation of, 1451–1452, 1608
Bile acids
Barrett's esophagus and, 346
esophageal mucosal injury due to, mechanism of, 231–232
Bile duct(s). *See also* Biliary *entries;* Common bile duct; Cystic duct; Hepatic ducts.
adenomas of, 1526, 1729
cancer of, after cyst excision, 1556
staging of, 1529b
common. *See* Common bile duct.
cysts of, classification of, 1552
extrahepatic, anatomy and embryology of, 1441, 1442f, 1443
intrahepatic, anatomy and embryology of, 1440–1441, 1442f
obstruction of, malignant, biliary drainage procedures for, 1505–1508, 1506f
perforation of, spontaneous, with choledochal cysts, 1554
Bile duct stones. *See* Biliary stones.
Bile duct strictures. *See* Biliary strictures.
Bile leaks, liver transplantation and, 1698
Bile reflux gastritis
following gastrectomy, 875–877, 876f–878f
reoperative surgery for, 1146f, 1146–1147, 1147f
Bile salts, small intestinal absorption of, 1007t, 1008
Biliary atresia, 1545
classification of, 1546, 1547f
diagnosis of, 1545
etiology of, 1546
management of
liver transplantation for, 1550–1551
operative, 1546, 1548, 1549f
outcome of, 1550
postoperative care and, 1550, 1550t

Biliary balloon catheters, 1484
Biliary bypass, for pancreatitis, chronic, with bile duct stricture, 1347–1348
Biliary cystadenocarcinoma, end-stage liver disease due to, 1687
Biliary cystadenomas, 1526, 1636
Biliary decompression, for cholangiocarcinoma, 1531
Biliary disease. *See also specific conditions.*
  anesthesia in, 1626
  with duodenal diverticula, 780–781
  hepatic abscesses due to, pyogenic, 1641–1642
  operative considerations in, 1626–1627
  perioperative management for, 1622
  postoperative management in, 1627–1628
Biliary drainage, 1500–1509
  for benign biliary strictures, 1500–1503
    distal, secondary to chronic pancreatitis, 1501, 1502f, 1502t, 1503
    postoperative, 1500f, 1500–1501
  for biliary fistulas, 1504–1505
  for choledochal cysts and anomalous pancreaticobiliary union, 1508–1509
  for malignant bile duct obstruction, 1505–1508, 1506f
    tissue sampling at endoscopic retrograde cholangiopancreatography and, 1507–1508
  for primary sclerosing cholangitis, 1503f, 1503–1504
  for sump syndrome, 1508
Biliary fistulas
  biliary drainage procedures for, 1504–1505
  drainage procedures for, 1504–1505
  external, 1537–1543
    clinical presentation of, 1541, 1541f
    diagnosis of, 1541–1542
    etiology and prevention of, 1537–1541
      of fistulas after gastrectomy, 1540
      of fistulas after invasive radiologic procedures, 1540–1541
      of fistulas after liver injury, 1539, 1539f
      of fistulas after liver surgery, 1539–1540
      of fistulas after liver transplantation, 1540
      of fistulas following biliary-intestinal anastomosis, 1538–1539
      of fistulas following cholecystectomy, 1537, 1538, 1539f
      of fistulas following common duct exploration, 1537–1538
      hydatid disease of liver and, 1540, 1540f
    pathophysiologic consequences of, 1541
    treatment of, 1542–1543
      initial, 1542
Biliary hamartomas, 1729–1730, 1730f
Biliary hypoplasia, 1545
  diagnosis of, 1545
  etiology of, 1546
Biliary neoplasms. *See also specific neoplasms.*
  benign, 1526
  malignant, percutaneous image-guided therapy of, 1466–1468
Biliary obstruction, with pancreatic pseudocysts, 1344
Biliary reconstruction
  liver transplantation and, 1696–1697
  for primary sclerosing cholangitis, 1568–1569
Biliary stents, percutaneous, duodenal perforation due to, 1095
Biliary stones, 1494–1500
  cholangitis and, acute, 1499–1500
  endoscopic retrograde cholangiopancreatography/laparoscopic cholecystectomy interface and, 1497, 1498f
  extraction of, 1494–1497
    dissolution therapy for, 1495–1496
    endoscopic balloon dilation for, 1496–1497
    lithotripsy techniques for, 1494–1495
    standard method for, 1494, 1495f
    stents and nasobiliary tubes for, 1496, 1496f
  gallstone pancreatitis and, acute, 1497–1499
  percutaneous management of, 1466
Biliary strictures
  benign
    biliary drainage procedures for, 1500–1503
      for distal common bile duct strictures secondary to chronic pancreatitis, 1501, 1502f, 1502t, 1503
      for postoperative strictures, 1500f, 1500–1501
    dilation of, technique of, 1464–1466
  dominant, with primary sclerosing cholangitis, 1565
    treatment of, 1567
  liver transplantation and, 1698
  postoperative, 1573–1579
    clinical presentation of, 1577f, 1577–1578
    imaging of, 1578f, 1578–1579, 1579f
    laboratory studies with, 1578
    pathogenesis of, 1573–1574, 1575f–1577f, 1576–1577
    surgical management of, 1579–1585
      elective repair for, 1580, 1581f, 1582f, 1582–1583
      immediate repair for, 1579–1580, 1580f
      long-term results with, 1583t, 1583–1585, 1584f, 1584t, 1585f
      nonsurgical repair compared with, 1585–1586
      postoperative complications and death and, 1583
Biliary surgery. *See also specific procedures.*
  transfusion therapy with, 1619–1620
Biliary tract, 1659, 1661f. *See also* Bile duct *entries;* Hepatobiliary *entries.*
  anatomy and embryology of, 1440–1447, 1441f
    of extrahepatic ducts, 1441, 1442f, 1443
    of gallbladder and cystic duct, 1443f, 1443–1444, 1444f
    of intrahepatic ducts, 1440–1441, 1442f
    lymphatic, 1446–1447
    neural, 1447, 1447f
    of sphincter of Oddi, 1444–1445, 1445f
    vascular, 1445f, 1445–1446, 1446f
  anomalies of, 1447–1451
    of biliary ducts, 1447–1448, 1448f, 1449f
    of gallbladder, 1448–1451, 1449b, 1451f–1453f
    vascular, 1451, 1454f
  imaging modalities for, 1460–1462
    computed tomography as, 1461f, 1461–1462
    magnetic resonance imaging as, 1462, 1462f
    nuclear medicine as, 1462, 1463f
    ultrasonography as, 1460–1461, 1461f
  interventional radiology for, 1462–1469
    for benign biliary disease, 1468
    complications of, 1468–1469
    image-guided therapy of malignant biliary disease and, 1466–1468
    percutaneous transhepatic cholangiography and percutaneous biliary drainage and, 1464–1466
    radiologist's role in, 1462–1464, 1463f–1465f
    for stone management, 1466
  physiology of, 1451–1459
    bile composition and, 1455, 1455t
    bile flow and, 1454–1455
    bile production and, 1451–1454
    gallbladder function and, 1455–1458
    of sphincter of Oddi, 1458f, 1458–1459
  trauma to. *See* Hepatobiliary trauma.
Biliary-enteric bypass, pancreatic ductal drainage with, with common bile duct strictures, 1348
Biliary-intestinal anastomosis, external biliary fistulas following, etiology and prevention of, 1538–1539
Biliopancreatic diversion
  failed, revision surgery for, 1146
  for obesity, 936, 936f
Bilirubin
  in bile, 1452
  metabolism of, 1454
  serum, elevated, patient approach for, 1613–1614, 1614f
  24-hour ambulatory detection of, 168–169
    Bilitec probe for, 168–169, 169f
    clinical use of, 169–173
    test performance and, 169, 170b, 170f

Bilirubin *(Continued)*
24-hour monitoring of, for duodenogastroesophageal reflux, 193–195, 194f, 194t
Bilitec probe, 168–169, 169f, 193
Billroth I gastroduodenostomy
for caustic injury, gastric, 763
for duodenal ulcers, 795, 796, 796f, 797f
following gastrectomy, 911
Billroth II gastrojejunostomy
bile reflux gastritis following. *See* Bile reflux gastritis.
for caustic injury, gastric, 763
for duodenal ulcers, 795, 796, 796f, 797f
following gastrectomy, 911
gastroparesis following, 923
revision of, for bile reflux gastritis, 877, 878f
Bioartificial liver support system, 1706, 1707
Biofeedback
for constipation, 1938
for fecal incontinence, 1921–1922
for perineal pain syndromes, 2074–2075
Biofragmentable anastomosis ring, 1089–1090, 1090f
Biologic therapies
for carcinoid tumors, 1186, 1187
for colorectal cancer metastases, 2270–2271
for inflammatory bowel disease, 2092–2093
Biomaterials, injectable, for fecal incontinence, 1925–1926
Biotin, small intestinal absorption of, 1006, 1007t
Bipolar electrocoagulation, for esophageal cancer, 489t, 492
"Bird's beak" appearance
in colonic volvulus, 1981, 1982f
in malrotation, 1216, 1217f
Bismuth, for lymphoma, 1209t
Bladder
identification of, 2413
injury of
with hernia repair, 654
with inguinal herniorrhaphy, laparoscopic, 666
Blastomyces dermatitidis, splenic abscess due to, 1819
Bleeding. *See also* Hemorrhage.
control of, with reoperative pelvic surgery, 2414–2415
in Crohn's disease, 1045
ectasias and, colonic. *See* Colon, vascular ectasias of.
with esophageal stricture dilatation, 240–241
in fulminant hepatic failure, management of, 1704
gastric, endoscopic management of, 741–745, 742f–744f
with hepatobiliary trauma, control of, 1664f, 1664–1665
herald (sentinel), with aortoenteric fistulas, 1114
lower gastrointestinal, in diverticular disease, surgical treatment of, 2026–2027
Bleeding *(Continued)*
with Nissen fundoplication, 274
with paraesophageal hernia, 552
rectal, 1883–1884
examination for, 1887
in ulcerative colitis, 2085
with reoperative pelvic surgery, anticipation of, 2410
of ulcers
emergency surgery for, 802t, 802–804, 803f, 804f
for gastric ulcers, 804
in pediatric patients, 962
vagotomy and drainage for, 824–825, 825f
variceal. *See* Esophageal varices, bleeding.
Bleeding scans, with diverticular hemorrhage, 2016, 2017f
Blind probe(s), radial mechanical, 113, 113f
Blood loss
control of
in biliary disease, 1627
in liver disease, 1627
intraoperative, with splenic vein thrombosis, 1353
Bloodless fold of Treves, 1862
Blue rubber bleb syndrome, colonic hemangiomas in, 1997
Blumer's shelf nodes, 906, 1361
B-mode ultrasonography, 112
Bochdalek, foramen of, 36
Bochdalek hernias, 561
"Body packers," 943, 943f
Body position, in gastroesophageal reflux disease, 252–253
Boerhaave, Hermann, 528
Boerhaave's syndrome, 91, 93, 528, 529, 530f, 530–531. *See also* Esophageal perforation.
Bone
colorectal cancer metastases to, 2270
disease of, following gastrectomy, 873
hepatic osteodystrophy and
in end-stage liver disease, 1693
with primary sclerosing cholangitis, treatment of, 1568
retrorectal osseous lesions and, 2306
Borrke ileostomy, 1070
Botulinum toxin
for achalasia, 412
for anal fissures, 2040
for constipation, 1938–1939
for gastric bleeding, 743
for gastroparesis, 921
for perineal pain syndromes, 2075
Bougienage, for esophageal cancer, 488–489, 489t
Bougies, for esophageal stricture dilatation, 237, 238f, 239f, 240
Bowditch, Henry Ingersoll, 6
Bowel activity, return of, following laparoscopic colorectal surgery, 2343
Bowel injury
with hernia repair, 654
with inguinal herniorrhaphy, laparoscopic, 665–666
during laparoscopic enteroclysis, 1136
Bowel preparation
for abdominoperineal resection of rectum, 2235
antibiotics with, 2328–2329
for gastric resection and reconstruction, 831
for low anterior colorectal resection, 2222
mannitol for, 2328
mechanical, 2328
polyethylene glycol for, 831, 2328
Bowel resection. *See also* Colon resection; Colorectal resection.
for Crohn's disease, stricturoplasty vs., 1058–1059
duodenal, for duodenal adenocarcinoma, 915
ileal, diarrhea following, 1880
for mesenteric ischemia, 1254–1255
short-bowel syndrome following. *See* Short-bowel syndrome.
of small bowel
for Crohn's disease, 2132, 2133f
for intestinal dysmotility, 927
Bowen's disease
anorectal, 1887
colorectal, 2318
pruritus ani and, 2068
Brain, colorectal cancer metastases to, 2270
Braun enteroenterostomy, for bile reflux gastritis, 877, 878f, 1146, 1146f
Bravo probe, 167–168, 168f, 266
Breath hydrogen test, in constipation, 1932
Bricker-Johnston technique, 2323
Bronchial artery, 20, 20f
Bronchogenic carcinoma, esophageal endoscopic ultrasonography in, 125
Bronchogenic cysts, esophageal, 525, 525f
Bronchoscopy
in esophageal carcinoma, 471
for staging of esophageal cancer, 456
Bronchospasm, in carcinoid syndrome, 1182
Brooke, Bryan N., 1070
Brunner's gland polyps, 884
Brush cytology, in malignant bile duct obstruction, 1507–1508
Budd-Chiari syndrome, 1714f, 1714–1715, 1757
Budesonide
for Crohn's disease, 1052, 2128
for inflammatory bowel disease, 2090
Burchardt's triad, 550–551
Burkitt's lymphoma, pathology of, 1204, 1204f
Burns, immunosuppression due to, 2376
Buschke-Lowenstein tumors, colorectal, 2318
Busulfan, hepatotoxicity of, 1723
Button batteries, ingested, 942–943

C

"C and M" classification system, for Barrett's esophagus, 104
^{13}C breathing test, for delayed gastric emptying, 185–186

CA 19-9
in pancreatic and periampullary adenocarcinomas, 1361
pancreatic pseudocysts and, 1332
CA-125, pancreatic pseudocysts and, 1331–1332
"-Caines," pruritus ani associated with, 2069
Calcium
deficiency of, in Crohn's disease, 1054
duodenal absorption of, 979
small intestinal absorption of, 1007t, 1008
Calcium angiography, for insulinoma localization, 1378
Calcium-channel blockers
for anal fissures, 2040
hepatotoxicity of, 1721
Calot's triangle, 1444, 1444f, 1473, 1474
Camper's fascia, 636
Cancer. *See* Malignancies; Metastases; *specific cancers.*
Cancer antigen 125, pancreatic pseudocysts and, 1331–1332
Cancer of the Liver Italian Program, 1736
Candida infection
pruritus ani associated with, 2070
splenic abscess due to, 1819
Cantlie's line, 1673, 1673f
Cantor tubes, 750, 751f
Capecitabine, for metastatic colorectal cancer, 2202
Capillaries, mesenteric, 1241
Capsule endoscopy
in Crohn's disease, 1051f, 1051–1052
of small bowel, 745–746, 746f
Carbohydrate(s)
duodenal absorption of, 980
small intestinal absorption of, 1002, 1002f, 1003f, 1003t
Carbohydrate antigen 19-9
in pancreatic and periampullary adenocarcinomas, 1361
pancreatic pseudocysts and, 1332
Carbon monoxide, gastric innervation and, 720
Carbon tetrachloride, hepatotoxicity of, 1719
Carcinoembryonic antigen
colorectal cancer and, 1888, 2200, 2201
to detect tumor relapse, of colorectal cancer, 2259
in pancreatic and periampullary adenocarcinomas, 1361
pancreatic pseudocysts and, 1331t, 1331–1332
Carcinoid syndrome, 1182
atypical (variant), 1182
diarrhea in, 1880
Carcinoid tumors, 1179–1187
appendiceal, 1182
treatment of, 1185
appendiceal distention by, 2150
clinical features of, 1180–1182, 1181f
colonic, 2312
treatment of, 1185
diagnosis of, 1182–1184
imaging in, 1183f, 1183–1184, 1184f
laboratory studies in, 1182–1183
Carcinoid tumors *(Continued)*
duodenal, 1181
treatment of, 1185
epidemiology of, 1179
future directions for, 1187
gastric, 1181
treatment of, 1185
ileal, treatment of, 1185
incidence of, 1179
jejunal, treatment of, 1185
midgut, 1181, 1181f
pathology of, 1179–1180, 1180f
rectal, 2313
treatment of, 1185
treatment and outcome with, 1184–1187
for locoregional disease, 1185
for metastatic disease, 1185–1187
medical therapy and, 1186–1187
surgical therapy and, 1185–1186
Carcinomatosis, with hostile abdomen, 1147–1148
Cardia
anchorage of, 12–14, 14f
prenatal development of, 34, 34f
spastic, surgery for, early development of, 5
Cardiac complications, of esophagectomy, 480
Cardiac mucosa, 335–336
development of, 229, 344
distal extent of, 207–210, 209f, 210b, 210f
esophageal, 213–215, 215f
etiology of, 41–42
goblet cell acquisition by, 347
with intestinal metaplasia, 335
intestinalization of, 345f, 345–347
Cardiologists, on portal hypertension multidisciplinary team, 1767
Cardiomyotomy, esophageal imaging following, 85, 86f
Cardioplasty, early development of, 5
Cardiopulmonary assessment, preoperative, for esophageal replacement, 287
Cardiopulmonary disorders, in cirrhosis, 1623–1624
Cardiovascular disorders
with immunosuppressive therapy, following liver transplantation, 1700
with inguinal herniorrhaphy, laparoscopic, 667
obesity and, bariatric surgery and, 938
Carditis, reflux, 213f, 213–215. *See also* Cardiac mucosa.
evolution of, 215, 215f
Carmustine, hepatotoxicity of, 1723
Caroli's disease, 1546, 1557–1558, 1558f
Carrell patch, 2008
Cast syndrome, 974–975, 975f, 976f
Catecholamines, splanchnic circulation and, 1243t, 1243–1244, 1244f, 1244t
Catgut, chromic, for bowel anastomoses, 1083, 1084
Cattell-Braasch maneuver, in duodenal injury, 766, 767f
Caustic ingestions
esophageal injury due to, 540–547
in children, 540
Caustic ingestions *(Continued)*
clinical features of, 541
endoscopic assessment of, 542, 542b
esophageal carcinoma and, 466
historical background of, 540
imaging of, 91
long-term consequences of, 547
management of
chronic dilation for, 544
in chronic phase, 544–547
emergency department, 542
esophageal substitutes for, 545
in-patient, 543–544
for intractable strictures, 544–545
for oropharyngeal strictures, 546f, 546–547
principles of, 541–542
for strictures in cervical esophagus and below, 545–546, 546f
pathophysiology of, 540–541
pH and, 541
phases of injury and, 541
gastric injury due to, 762
diagnosis of, 763
treatment of, 763
Cavernous hemangiomas, rectal, 1996
CEA. *See* Carcinoembryonic antigen.
Cecal volvulus, 1984–1985
etiology and pathophysiology of, 1984
treatment of, 1984–1985
outcomes following, 1985
Cecorectal anastomosis, for colonic inertia, 1934
Cecum
anatomy of, 1845–1846, 1862
diverticulitis of, 2019, 2020f
Celiac artery, 1292, 1293f
anatomy of, 1236f, 1236–1237, 1237f
aneurysms of, 1279–1280
clinical findings in, 1279
diagnosis of, 1279
incidence of, 1279
pathogenesis of, 1279
treatment of, 1279–1280
stenosis of, identification of, 1258
Celiac axis
anatomy of, 1236f, 1236–1237, 1237f
in mesenteric ischemia, 1247, 1248f. *See also* Mesenteric ischemia.
superior mesenteric artery communications with, 1238–1239, 1239f
Celiac nerve, alcohol block of, for pain palliation, in pancreatic and periampullary carcinoma, 1367, 1367f
Celiac plexus, 1447, 1447f
anatomy of, 720
Cell membrane, pancreatic, function of, 1292
Certolizumab, for inflammatory bowel disease, 2093
Cetuximab, for metastatic colorectal cancer, 2202, 2203, 2203f, 2271
Chagas' disease
achalasia and, 406–407
esophageal motility disorders in, 140
imaging in, 74

Change agent, as clinical nurse specialist role, in palliative treatment, for esophageal cancer, 498
Charcoal hemoperfusion, for liver failure, acute, 1706
CHARGE association, with esophageal and tracheoesophageal atresia, 564
Chauliac, Guy de, 623
Chemoradiotherapy
  for colorectal cancer, 2199–2200
  for esophageal cancer
    in multimodality therapy, 505–508
      as definitive therapy, 505t, 505–506
      postoperative, 509
      preoperative, 506–508, 507t
    neoadjuvant, 482–483
    palliative, 495
  for gastric adenocarcinoma
    adjuvant, 912
    neoadjuvant, 913–914
  for pancreatic and periampullary carcinoma, 1372
  radiation enteritis and, 1156
Chemotherapy. *See also* Chemoradiotherapy.
  for anal squamous cell carcinoma, 2292–2293, 2293t
  for carcinoid tumors, 1186
  for colorectal cancer
    adjuvant, 2198–2199
    locally recurrent, preoperative, 2262–2263
    metastases of, 2270
  for desmoids, in familial adenomatous polyposis, 2161
  for esophageal cancer
    in multimodality therapy, 502–505
      postoperative, 504t, 504–505
      preoperative, 502–504, 503t
    palliative, 495–496
      combination therapy for, 495–496
      new agents for, 496
      patient selection for, 495
      response to, 495
      single-agent therapy for, 495
  for gallbladder cancer, 1524
  for gastric adenocarcinoma
    adjuvant, 912
    neoadjuvant, 913
    palliative, 914
  for hepatocellular carcinoma, 1736
  immunosuppression due to, 2376
  for lymphoma, 1209
  for pancreatic and periampullary carcinoma, 1372
    palliative, 1372–1373
Chest, anatomy of, 15f, 15–16
Chest pain
  in achalasia, 407
  in esophageal disease, 57
  in esophageal motility disorders, 71
  gastroesophageal reflux disease associated with, diagnosis of, 171
Chest radiography
  with colon, rectal, and anal disorders, 1891, 1891f
  in colonic volvulus, 1981, 1982f
  in esophageal carcinoma, 469
Chest radiography *(Continued)*
  in esophageal perforation, 93, 95f, 531
  with hepatic abscesses, pyogenic, 1646
  with liver abscesses, amebic, 1654
  with paraesophageal hernia, 552, 553f
  postoperative, following esophageal surgery, 83
  with splenic abscesses, 1818
Chiari's triad, with aortoenteric fistulas, 1271
Child-Pugh score, 1674, 1674t
  in portal hypertension, 1758, 1758t
Children. *See* Pediatric patients.
Child-Turcotte-Pugh system, 1691, 1691t
Chlamydia proctitis, in immunocompromised patients, 2383t
Chloride
  colonic absorption of, 1872
  small intestinal secretion of, 1008–1009, 1010f
Chlorpromazine, hepatotoxicity of, 1722–1723
Cholangiocarcinoma, 1526–1534
  adjuvant therapy for, 1531
  diagnosis of, 1527–1528
    of distal cholangiocarcinoma, 1528
    of hilar cholangiocarcinoma, 1528, 1528f
    of intrahepatic cholangiocarcinoma, 1527–1528, 1528f
  distal
    diagnosis of, 1528
    practical management of, 1531–1532
    surgical treatment of, 1530
  epidemiology of, 1526–1527
  hepatocellular carcinoma and, 1534
  hilar
    diagnosis of, 1528, 1528f
    practical management of, 1531–1532
      surgical technique for, 1532, 1533f–1534f, 1534
    surgical treatment of, 1529–1530
  intrahepatic, 1743–1745, 1745f
    diagnosis of, 1527–1528, 1528f
    practical management of, 1531
    surgical treatment of, 1529
  palliation for, 1531
  pathology of, 1527
  practical management of, 1531–1532
    for distal cholangiocarcinoma, 1531–1532
    for hilar cholangiocarcinoma, 1531–1532
      surgical technique for, 1532, 1533f–1534f, 1534
    for intrahepatic cholangiocarcinoma, 1531
  presentation of, 1527
  with primary sclerosing cholangitis, 1565–1566
    treatment of, 1570
  in primary sclerosing cholangitis, treatment of, 1588
  staging of, 1529, 1529t, 1530t
  surgical treatment of, 1529–1531
    for distal cholangiocarcinoma, 1530
    for hilar cholangiocarcinoma, 1529–1530, 1532, 1533f–1534f, 1534
Cholangiocarcinoma *(Continued)*
    for intrahepatic cholangiocarcinoma, 1529
    liver transplantation as, 1530–1531
Cholangiography, 1493, 1493f
  in biliary atresia, 1548
  with biliary strictures, benign, 1500, 1500f
  with hepatic abscesses, pyogenic, 1646, 1646f
  operative, with bile duct strictures, 1576
  in pancreatitis
    acute, mild, 1302
    chronic, 1347
  retrograde, endoscopic, with biliary fistulas, 1542
  transhepatic, percutaneous
    with bile duct strictures, 1578–1579
    with biliary fistulas, 1542
    complications of, 1468–1469
    indications for, 1463–1464
    in periampullary carcinoma, 1363, 1364f
    technique of, 1464–1466
  tube, with biliary fistulas, 1542
Cholangiohepatocellular carcinoma, mixed, 1745–1746, 1746f
Cholangiopancreatography. *See also* Endoscopic retrograde cholangiopancreatography.
  with bile duct strictures, 1578f
Cholangiopathy, human immunodeficiency virus, 1615
Cholangitis
  acute, treatment of, 1499–1500
  fibro-obliterative, in primary sclerosing cholangitis, 1562
  liver transplantation and, 1694
  in pancreatitis, chronic, 1347
  postoperative, prevention of, 1550, 1550t
  primary sclerosing. *See* Primary sclerosing cholangitis.
  recurrent, bacterial, with primary sclerosing cholangitis, treatment of, 1567
Cholecystectomy
  anatomic considerations for, 1473f, 1473–1474
  external biliary fistulas following, etiology and prevention of, 1537
  for gallbladder cancer, 1521, 1523f, 1523–1524
  gastroparesis following, 923
  hepatectomy and, 1678
  indications for, 1471, 1472b
  laparoscopic
    for bile duct strictures, 1574, 1575f, 1576
    duodenal injury due to, 1094
    endoscopic retrograde cholangiopancreatography, 1497, 1498f
    external biliary fistulas following, etiology and prevention of, 1538, 1539f
    gallbladder cancer diagnosed incidentally after, 1525

Cholecystectomy *(Continued)*
minicholecystectomy as, 1477
morbidity and mortality with, 1479f, 1479–1480
open
external biliary fistulas following, etiology and prevention of, 1537
technique for, 1474–1477
fundus-down approach and, 1476–1477, 1477f, 1478f
neck-toward-fundus approach and, 1474f–1476f, 1474–1475
for pancreatitis
acute, mild, 1302
severe, necrotizing, 1303
partial, 1477–1478, 1478f
prophylactic, 1471, 1472b
timing of, 1473
Cholecystectomy triangle, 1444, 1444f, 1473, 1474
Cholecystitis, 1472–1473
cholecystostomy for, 1478–1479, 1479f
Cholecystokinin
duodenal function and, 980–981, 981t
pancreatic cell function and, 1292
small intestinal neuroendocrine function and, 1018
Cholecystostomy, 1478–1479, 1479f
Choledochal cysts, 1545, 1552–1556, 1553f
classification of, 1546, 1547f
complications of, 1554, 1554f
diagnosis of, 1545–1546, 1553–1554
etiology of, 1546
signs and symptoms of, 1553
surgical treatment of, 1508–1509, 1548, 1554–1556
operative technique for, 1555, 1555f, 1556f
outcome of, 1550
postoperative care and, 1550
postoperative complications of, 1555–1556
preoperative care for, 1554–1555
Choledochocele, 1556–1557, 1557f
Choledochoduodenostomy
external biliary fistulas following, etiology and prevention of, 1538–1539
for pancreatitis, chronic, with bile duct stricture, 1348
side-to-side, sump syndrome as complication of, 1508
Choledochoenterostomy, for common bile duct stones, 1594
Choledochojejunostomy
external biliary fistulas following, etiology and prevention of, 1538–1539
with liver transplantation, 1551
for pancreatitis, chronic, with bile duct stricture, 1348
Roux-en-Y, for duodenal diverticula, 782–783, 784f
Choledocholithiasis, 1590–1594, 1591f
common bile duct exploration and laparoscopic, 1590, 1592–1593, 1593f
open, 1594
detection of, 1590
Choledocholithiasis *(Continued)*
endoscopic therapy for
postoperative, 1590, 1593–1594
preoperative, 1590–1591
intraoperative diagnosis and treatment of, 1591–1592
laparoscopic management of, 1482–1488
ampullary balloon dilation as, 1484–1485, 1485f
antegrade sphincterotomy as, 1485
biliary balloon catheter as, 1484
choledochoscopy for, 1482–1484, 1483f, 1484f, 1484t
choledochotomy as, 1485–1487, 1486f, 1487f, 1487t, 1488t
cystic duct catheter technique as, 1485
fluoroscopic wire basket stone retrieval as, 1484
transcystic common bile duct exploration or choledochotomy for, 1482, 1483t
in pancreatitis, acute, mild, 1302
with primary sclerosing cholangitis, 1565
treatment of, 1567
Choledochoscopy, 1482–1484, 1483f, 1484f, 1484t
with choledochal cysts, 1555
Choledochotomy
indications for, 1482, 1483t
laparoscopic, 1485–1487, 1486f, 1487f, 1487t, 1488t
Cholelithiasis, 1471–1480
asymptomatic, 1471–1472, 1472b
cholecystectomy for. *See* Cholecystectomy.
cholecystitis secondary to, 1472–1473
with choledochal cysts, 1554
following gastrectomy, 875
following ileostomy, 1071
with primary sclerosing cholangitis, 1565
treatment of, 1567
in short-bowel syndrome, 1167
stone erosion and, fistulas due to, 1094–1095
Cholestasis
canalicular, in primary sclerosing cholangitis, 1562
drug-induced, 1722–1723
canalicular, 1722
hepatocanalicular, 1722–1723
Cholestatic liver disease. *See* Primary biliary cirrhosis; Primary sclerosing cholangitis.
Cholesterol, 1452–1453, 1455f, 1456f
small intestinal absorption of, 1004–1006, 1005f, 1006f
Cholestyramine
hepatotoxicity of, 1722
for pruritus
in primary sclerosing cholangitis, 1567, 1588
for steatorrhea, following ileal resection, 1880
Chordomas, sacrococcygeal, 2304, 2304f–2306f
Chromoendoscopy, in Barrett's esophagus, 104
Chromogranin, carcinoid tumors and, 1183
Chronic lymphocytic leukemia, splenectomy for, 1830t, 1830–1831, 1831t
Chronic myelogenous leukemia, splenectomy for, 1831
Chylomicrons, 1005, 1006f
Chylothorax
after antireflux procedures, 609
following esophageal resection with visceral esophageal substitution, 614–615
Cicatricial pemphigoid, esophageal strictures in, 89, 92f
Cigarette smoking
cessation of, for gastroesophageal reflux disease, 253
esophageal cancer and, 444, 466
pancreatic adenocarcinoma and, 1359
Cimetidine, 255. *See also* Histamine$_2$ receptor antagonists.
for peptic ulcer disease, 870
Cinedefecography
in perineal pain syndromes, 2074
in rectal prolapse, 1959
Ciprofloxacin, for inflammatory bowel disease, 1052, 2091, 2128
Circular staplers, 1087
Cirrhosis, 1623f, 1623–1626
ascites in, 1624–1625
cardiopulmonary disorders in, 1623–1624
coagulopathy in, 1625–1626
decompensated, with primary sclerosing cholangitis, treatment of, 1568
drug-induced, 1719t, 1720–1721
gastrointestinal disorders in, 1625
hemodynamics in, 1623, 1692–1693
hepatic encephalopathy in, 1625
hepatocellular carcinoma and, 1732, 1733f
infectious diseases in, 1626
metabolic abnormalities in, 1625
pathophysiology of, 1618–1619
portal hypertension in, 1624, 1624t
pulmonary disorders in, 1693, 1693b
pyogenic hepatic abscesses associated with, 1643
renal dysfunction in, 1625
Cisapride. *See also* Prokinetic agents.
for gastroesophageal reflux disease, 253
for gastroparesis, 921
Clarithromycin, for lymphoma, 1209t
Claudication, esophageal, 138–139
Claudins, 999
Clavulanic acid, hepatotoxicity of, 1723
Clean-contaminated cases, 2327
Cleft lip technique, for pilonidal disease, 1969, 1970f
Clinical expert, as clinical nurse specialist role, in palliative treatment, for esophageal cancer, 497–498
Clinical nurse specialist, role of, in palliative treatment, for esophageal cancer, 497–498
Cloaca, 2390, 2393f
malformation of, surgical treatment of, 2402, 2403f
Cloacal membrane, 2387

Cloacal surgery, outcome of, 2406
Clonidine, for diarrhea, in diabetic neuropathy, 1880
Cloquet's node, 641
Clostridium difficile colitis
  antibiotics and, 2329
  in immunocompromised patients, 2382
Coagulation testing
  in biliary tract disease, 1620
  in liver disease, 1620
Coagulopathy, in cirrhosis, 1625–1626
Cobalamin. *See* Vitamin B_{12}.
Coccygectomy, for benign tumors, 2309
Coccygodynia, 2071, 2072
  idiopathic, 2074
Coelom, development of, 31
Coiled spring sign, 765–766
Colchicine, pruritus ani associated with, 2069
Colectomy
  with ileorectal anastomosis
    for familial adenomatous polyposis, 2165, 2165t, 2166t, 2166–2167, 2168
    for ulcerative colitis, 2122
  with ileorectostomy, for intractable constipation, 1880
  laparoscopic, 2345
  subtotal, with ileorectal anastomosis, for colonic inertia, 1934, 1935t, 1936
Colic arteries, 1849–1850, 1851f, 1852f
  anatomy of, 1867–1868
    variations in, 1868–1869
  aneurysms of, 1282f, 1283
  middle, accessory, 1239
  middle-left collateral, 1239
Colitis
  Clostridium difficile (pseudomembranous)
    antibiotics and, 2329
    in immunocompromised patients, 2382
  granulomatous. *See* Crohn's disease.
  indeterminate, 2086
  infectious, in immunocompromised patients, 2381–2382
  ulcerative. *See* Ulcerative colitis.
  universal, fulminating, colonic ischemia complicating, management of, 2009
Colitis cystica profunda, 2075–2076
  diagnosis of, 2075–2076, 2076f
  endoanal ultrasound in, 1913–1914, 1914f
  treatment of, 2075–2076
Collagen vascular disorders, superior mesenteric artery aneurysms due to, 1278
Colles' fascia, 636
Collis, Lee, 6–7
Collis gastropexy, 599
Collis gastroplasty
  with Belsey repair, for esophageal strictures, 242, 243f
  laparoscopic, for esophageal strictures, 247f, 247–248, 248f
  with Nissen fundoplication, for esophageal strictures, 244f, 244–245, 246f–248f, 247–248
  for short esophagus, acquired, 272f, 272–273, 273f
Coloanal anastomosis, 2245–2253
  functional results with, 2253, 2253t
  oncologic results with, 2252t, 2252–2253
  operative technique for, 2245–2252
    for hand-sewn colonic pouch-anal anastomosis, 2247–2250
    anastomosis and, 2249, 2249f, 2250f
    colon preparation and division for, 2247–2248
    colonic pouch construction for, 2248, 2249f
    drainage, loop stoma, and postoperative care for, 2249–2250
    mucosectomy of rectal stump and, 2247, 2247f, 2248f
    non-mucosectomy technique for, 2247, 2248f
  incision and abdominal exploration and, 2245
  inferior mesenteric vessel division and colon mobilization and, 2245–2246, 2246f
  laparoscopy and, 2252
  preoperative preparation and, 2245
  for stapled colonic pouch-anal anastomosis, 2250–2252
    anastomosis and, 2251, 2251f
    pouch construction for, 2251, 2251f
    section of rectum for, 2250, 2250f
    transverse coloplasty and, 2251–2252, 2252f
  total mesorectal excision and, 2246
  type of anastomosis and, 2246–2247, 2247f
for rectal radiation injury, 2323–2324
for rectovaginal fistulas, 1952, 1954
Colocolostomy, for colorectal cancer, 2331
Colocutaneous fistulas, in colonic diverticular disease, 2018
Colon
  anatomy of, 1236, 1845–1856, 1846f, 1861–1870, 1863f, 1864f, 1871–1872
    arterial, 1849–1851, 1850f–1853f, 1867–1868
      variations in, 1868–1869
    of ascending colon, 1846–1847, 1848f, 1863, 1865f
    of cecum, 1845–1846, 1862
    on colonoscopy, 1866–1867
    of descending colon, 1848–1849, 1866
    of ileocecal valve, 1846
    lymphatic, 1854f, 1854–1855, 1869, 1869f
    neural, 1855f, 1855–1856, 1869–1870, 1870f, 1871–1872
    of sigmoid colon, 1849, 1866, 1867f, 1868f
    surface, 1845, 1847f
    of transverse colon, 1847–1848, 1848f, 1849f, 1864, 1866, 1866f
    venous, 1851, 1853f, 1854, 1869
    of vermiform appendix, 1846, 1863, 1864f
Colon *(Continued)*
  arteriovenous malformations of, congenital, 1997, 1998f
  ascending, anatomy of, 1846–1847, 1848f, 1863, 1865f
  cancer of. *See* Colon carcinoma; Colorectal adenocarcinoma; Colorectal cancer; Colorectal carcinoma.
  Crohn's disease in, surgical treatment of, 2130, 2133, 2135
  descending, anatomy of, 1848–1849, 1866
  duplication of, 1858, 1860–1861, 1862f
  embryology of, 1857–1861, 1858f–1860f
  as esophageal substitute, 579
    esophagocoloplasty and, 588b, 588–592
      abdominal team and, 589–591, 590f
      cervical team and, 591
      operative technique for, 589–591
      preoperative preparation for, 589
      results with, 591t, 591–592, 592t
    short-segment colon interposition and, 596–597
      results of, 596t, 596–597
  fixation of, anomalies of, 1858, 1861f
  function of, 1872–1881
    colonic metabolism and, 1873
    colonic sensation as, 1876–1878, 1877f, 1877t
    defecation as, 1876, 1876f
    fluid and electrolyte transport as, 1872
    motor, 1873–1876
    perturbation of, in disease states, 1878–1880
    regional heterogeneity in, 1872
    surgical implications of, 1880–1881
  intussusception of, 1980, 1981f
  juvenile polyposis syndrome in, 2173
  in Klippel-Trénaunay-Weber syndrome, 1999
  left, vascular supply to, 2223, 2224f
  lymphatics of, regional, 2194–2195, 2195f, 2196f
  motor response of, to eating, 1875
  sigmoid
    anatomy of, 1849, 1866, 1867f, 1868f
    mobilization of, for low anterior resection, 2225f, 2225–2226
    torsion of, 1983
  telangiectasias of, 1997, 1999
  transverse, anatomy of, 1847–1848, 1848f, 1849f, 1864, 1866, 1866f
  varices of, 1997
  vascular ectasias of, 1987–1995
    clinical aspects of, 1988–1989
    diagnosis of, 1989, 1991, 1992f, 1993–1995
      with active major bleeding, 1993, 1994f
      with major bleeding, 1991, 1993
      with major bleeding that has ceased, 1993–1994
      with nonmajor bleeding, 1994–1995

Colon *(Continued)*
incidence and pathophysiology of, 1987–1988, 1989f–1991f
treatment of, 1995
for control of acute hemorrhage, 1995
definitive, 1995
Colon carcinoma. *See also* Colorectal adenocarcinoma; Colorectal carcinoma.
colitis associated with, in colonic ischemia, management of, 2010
lesions mimicking, in colonic ischemia, management of, 2009–2010
locally recurrent, trimodality therapy for, results with, 2269
ulcerative colitis with, surgical management of, restorative proctocolectomy for, 2335
Colon diversion, for colorectal cancer, 2330–2331
Colon interposition
for caustic ingestions, 545
for foregut reconstruction for benign disease, 295, 295f, 296–299, 297f–299f
short-segment, 596–597
results of, 596t, 596–597
Colon resection
for colorectal cancer, 2331
with end sigmoid stoma, for colonic obstruction, 2330
extent of, 2329–2330
laparoscopic, 2338
right, steps for, 2349b, 2349f, 2350f
Colonic atresia, 1858
Colonic carcinoid tumors, treatment of, 1185
Colonic circulation, 1999–2000
Colonic disorders. *See also specific disorders.*
diagnosis of, 1883–1897
examination for, 1885–1888
with anorectal pain or swelling, 1887
for bleeding, 1887
for constipation, 1888
general principles of, 1885–1886
inspection and palpation in, 1886–1887
positioning for, 1886, 1886f
for urgency and incontinence, 1888
history in, 1883
investigation for, 1888–1897
blood and stool testing in, 1888–1889
endoscopy in, 1889f, 1889–1891, 1890f
radiologic tests in, 1891f, 1891–1897, 1892f, 1894f–1897f
symptoms in, 1883–1885
abdominal pain and distention as, 1884
anorectal pain, itching and swelling as, 1884
bleeding as, 1883–1884
constipation as, 1884–1885
diarrhea as, 1885
urgency and incontinence as, 1885
Colonic hemangiomas, 1995–1997, 1996f
in blue rubber bleb syndrome, 1997
cavernous, rectal, 1996
in diffuse intestinal hemangiomatosis, 1997
Colonic inertia, surgical treatment of, 1934, 1935t, 1936
Colonic interposition, gastroparesis following, 923
Colonic ischemia, 1999–2010, 2000f
colonic circulation and, 1999–2000
demographics of, 2001
diagnosis of, 2003, 2004f
distribution of, 2001f, 2001–2002
management of, 2003, 2005–2010
with abdominal aortic surgery, 2006, 2008f, 2008–2009, 2009f
in acute mesenteric ischemia, 2010
of colitis associated with colon carcinoma, 2010
in fulminating universal colitis, 2009
general principles of, 2003, 2005
of irreversible lesions, 2005
of ischemic strictures, 2006, 2007f
of late manifestations, 2005–2007, 2006f
of lesions mimicking colon carcinoma, 2009–2010
of reversible lesions, 2005
natural history of, 2002, 2002f
pathophysiology of, 2000, 2000b
symptoms of, 2001
Colonic J pouch, 2104–2105, 2334
Colonic lavage, intraoperative, for colonic obstruction, 2330
Colonic motility, 1873–1876
assessment of, 1873–1874
radiopaque marker methods for, 1873, 1873f
recording techniques for, 1874, 1874f
scintigraphic techniques for, 1873f, 1873–1874
cellular basis for, 1875, 1875f
normal, 1875–1876, 1876f
peristalsis and, 1874f, 1874–1875
Colonic obstruction
in colonic diverticulitis, 2018–2019
in diverticular disease, surgical treatment of, 2025–2026, 2026f
as emergency surgical indication, 2102
left-sided, 2330
right-sided, 2330
treatment of, 2330
Colonic pain, referral of, 1856
Colonic perforation
as emergency surgical indication, 2102
in immunocompromised patients, 2381
Colonic pseudo-obstruction, acute, 1879
Colonic sensation, 1876–1878, 1877f, 1877t
Colonic strictures, ischemic, management of, 2006, 2007f
Colonic transit
in constipation, 1931–1932, 1932f
in rectal prolapse, 1959
Colonic volvulus, 1980–1985, 1982f, 1983f
cecal, 1984–1985
etiology and pathophysiology of, 1984
outcomes following treatment of, 1985
treatment of, 1984–1985
ileosigmoid knot and, 1984
sigmoid, 1981, 1983–1984
etiology and pathophysiology of, 1981, 1983
outcomes following treatment of, 1984
treatment of, 1983–1984
transverse colon and splenic flexure, 1985
etiology and pathophysiology of, 1985
outcomes following treatment of, 1985
treatment of, 1985
Colonoscopic polypectomy, 2157
complications of, 2157
for malignant polyps, 2156f, 2156–2157
for pedunculated polyps, 2155–2156
for sessile polyps, 2156
Colonoscopy, 1890–1891
with anorectal fistulas, 2049
colonic anatomy and, 1866–1867
with colonic vascular ectasias, 1993
in constipation, 1929–1930
in Crohn's disease, 2088
with diverticular hemorrhage, 2016, 2016f
preoperative, for esophageal replacement, 287
risks of, 1891
screening with
for adenomatous polyps, 2153–2155, 2154t
for colorectal carcinoma, 1888, 2189–2192
goals of, 2189–2190, 2190t, 2191t
with high risk, 2190
with low and average risk, 2190
with previous colorectal cancer and family history of colorectal cancer, 2190–2192
stent positioning using, 2331
surveillance, for adenomatous polyps, 2157
total, with small intestinal tumors, benign, 890
Coloplasty
for rectal radiation injury, 2324
transverse, 2251–2252, 2252f
Colopouch anal anastomosis, for rectal radiation injury, 2324
Colorectal adenocarcinoma, 2183–2204
chemotherapy for, 2198–2200
adjuvant, for stages II and III disease, 2198–2199
combined chemoradiation therapy and, 2199–2200
survival and, 2200, 2200f, 2201f
genetic pathways to, 2183, 2186, 2186f
incidence and epidemiology of, 2183, 2183f–2185f

Colorectal adenocarcinoma *(Continued)*
metastatic, treatment of, 2201–2204, 2203f
chemotherapy for, 2201–2202, 2203f
surgical, 2203–2204
risk factors for, 2186–2189
age as, 2186–2187
familial adenomatous polyposis as, 2188
familial colorectal cancer as, 2187f, 2187–2188
familial juvenile polyposis as, 2188–2189
hereditary nonpolyposis colorectal cancer as, 2188, 2188b
inflammatory bowel disease as, 2187
Peutz-Jeghers syndrome as, 2188–2189
screening for, 2189–2192
goals of, 2189–2190, 2190t, 2191t
high risk and, 2190
low and average risk and, 2190
previous colorectal cancer and family history of colorectal cancer and, 2190–2192
staging of, 2192b, 2192–2194, 2193f, 2193t, 2194b
surgical treatment of
of hereditary bowel cancer, 2197
local excision of rectal cancer and, 2197–2198
for malignant polyps, 2197
for metastatic cancer, 2203–2204
minimally invasive, 2198
postresection follow-up for, 2200
for primary cancers, 2194–2195, 2195f–2197f, 2197
surveillance for, 2200–2201
tumor markers for, 2200–2201
Colorectal cancer, 2312–2318. *See also* Colon carcinoma; Colorectal adenocarcinoma; Colorectal carcinoma; Rectal cancer.
adenoma to carcinoma sequence and, 2153
in Bowen's disease, 2318
Buschke-Lowenstein tumors as, 2318
carcinoid tumors as, 2312–2313
colonic, 2312
rectal, 2313
in Crohn's disease, 2089
gastrointestinal stromal tumors as, 2314–2317
epidemiology of, 2314
investigation of, 2315, 2315f
management of, 2315–2316
pathophysiology and pathology of, 2314f, 2314–2315, 2315f
presentation of, 2315
prognosis of, 2316
laparoscopic surgery for. *See* Laparoscopic colorectal surgery, for cancer.
leiomyomas as, 2316–2317
leiomyosarcomas as, 2316f, 2316–2317
liposarcoma as, 2317
lymphoma as, 2314
malignant fibrous histiocytoma as, 2317
melanoma as, 2317–2318, 2318f
Colorectal cancer *(Continued)*
metastases of
to bone, 2270
to brain, 2270
diffuse, 2270–2271
biologic response modifiers for, 2270–2271
chemotherapy for, 2270
palliative treatments for, 2271
hepatic. *See* Hepatic metastases, of colorectal cancer.
ovarian, 2270
pulmonary, management of, 2269–2270
patient selection for, 2269
pulmonary resection results and, 2269–2270
systemic, treatment of, 2201–2204, 2203f
neuroendocrine carcinomas as, 2313
nonpolyposis, hereditary, 2159t, 2169–2173
clinical considerations in, 2169
as colorectal cancer risk factor, 2188, 2188b
diagnosis of, 2171, 2171b, 2172b
extracolonic cancers and, 2169
genetic testing and counseling and, 2171–2172
genetics of, 2169–2171, 2170f
surgical treatment of, 2172–2173
recurrent, 2255–2269
detection of, 2256–2259
carcinoembryonic antigen for, 2259
endoscopy for, 2258–2259
history and physical examination for, 2257
laboratory and imaging studies for, 2258
positron-emission tomography for, 2259
surveillance for, 2256–2259, 2258f
incidence of, 2255, 2256f
locoregional, 2259–2269
preoperative evaluation and patient selection for, 2260–2262, 2261f, 2262b
trimodality therapy for, 2262–2269
risk factors for, 2255–2256, 2257b
technical, 2256
tumor-related, 2255–2256
trimodality therapy for, 2262–2269
with fixed-resectable, anterior lesions, 2265
with fixed-resectable, posterior lesions, 2265, 2266f, 2267f
intraoperative delivery of electron beam radiation therapy and, 2265–2267, 2268f
with nonfixed lesions, 2265
operative procedures for, 2263f, 2263–2265, 2264f
perineal wound closure and, 2267
preoperative irradiation therapy and chemotherapy and, 2262–2263
Colorectal cancer *(Continued)*
results for locally recurrent disease, 2267–2269
rhabdomyosarcoma as, 2317
squamous cell carcinoma as, 2313
surgical treatment of, 2330–2331
low anterior resection for. *See* Colorectal resection, low anterior.
in ulcerative colitis, 2082–2084
Colorectal carcinoma. *See also* Colon carcinoma; Colorectal adenocarcinoma; Colorectal cancer.
blood and stool testing for, 1888–1889
prevention of, 366–367
risk of, in Barrett's esophagus, 366
surgical intervention for, 366
Colorectal polyps, 2152–2158. *See also* Polyposis syndromes; *specific polyposis syndromes.*
adenomatous, 2152–2157, 2153f
adenoma to carcinoma sequence and, 2153
follow-up surveillance for, 2157
initial management of, 2155–2157
complications of therapeutic colonoscopy and, 2157
for malignant polyps, 2156f, 2156–2157
for pedunculated polyps, 2155–2156
for sessile polyps, 2156
for small polyps, 2155
screening for, 2153–2155, 2154t
definitions and classification of, 2152, 2153t
hamartomatous, 2157f, 2157–2158, 2158f
hyperplastic, 2158, 2158f
inflammatory, 2158, 2159f
laparoscopic surgery for
outcomes of, 2353
technical points for, 2353
malignant, surgical treatment of, 2197
pedunculated, 2152
retention, 2157
Colorectal reconstruction, 2230–2231, 2231f
Colorectal resection
low anterior, 2218–2233, 2219t
anterior, 2228–2229
in men, 2228–2229, 2229f
in women, 2228, 2228f
bowel division and distal traction for, 2226–2227
bowel preparation for, 2222
colorectal reconstruction and, 2230–2231, 2231f
defining and dividing lateral attachments for, 2229, 2229f
distal bowel management technique for, 2230, 2230f
distal mural margins and extent of, 2221
distal mesorectal margin and, 2221
lateral mesorectal margins and, 2221
lateral pelvic lymph nodes and, 2221
proximal vascular ligation and, 2221

Colorectal resection *(Continued)*
double-staple technique for, 2231–2232, 2232f
extent of, 2221
goals and terminology for, 2219–2220
initial exploration for, 2222
initial posterior dissection for, 2227, 2227f
left colon mobilization for, 2226, 2226f
level of distal transection for, 2230
for obstructing cancer, 2220–2221
open vs. laparoscopic, 2222
patient position for, 2222–2223, 2223f
patient selection for, 2220
pelvic anatomy relevant for, 2222
pelvic dissection for, 2222
postoperative management with, 2232–2233
preoperative radiation therapy with, 2220
for rectal radiation injury, 2323
retrosacral fascia division for, 2227–2228, 2228f
sagittal anatomy and, 2223, 2223f
sigmoid mobilization for, 2225–2226
from left, 2225, 2225f
from right, 2225f, 2225–2226
steps for, 2351b, 2351f–2353f
sympathetic nerves and, 2223, 2225
synchronous organ resection and, 2221–2222
transverse midpelvic anatomy and, 2223, 2224f
vascular supply to rectum and left colon and, 2223, 2224f
for rectal prolapse, 1961, 1964t
with rectopexy, for rectal prolapse, 1961, 1961f, 1964t
Colorectal surgery. *See also specific procedures.*
colonic physiology and, 1880–1881
laparoscopic. *See* Laparoscopic colorectal surgery.
Colorectal trauma, 1972–1977, 1973t, 1974t
diagnosis of, special problems in, 1975
foreign bodies causing, 1977
iatrogenic, 1976–1977
initial resuscitation and assessment of, 1973–1975
intraoperative management of, 1976, 1977f, 1977t
postoperative complications of, 1978, 1978t
preoperative management of, 1975–1976, 1976t
Colostomy
abdominoperineal resection and, 2242–2243
decompressing, for colonic obstruction, 2330
end, 2364–2365
end-loop, 2367
following colorectal trauma, 1978, 1978t
for high imperforate anus, 2396, 2398
loop, 2366
permanent, indications for, 2362, 2363b
Colovesical fistulas, in colonic diverticular disease, 2017–2018, 2018f
Columnar transformation, esophageal
Barrett's esophagus and, 343–345
gastroesophageal reflux and, 212, 212f, 230
short esophagus and, 234
Combination tubes, 756–757
Comfrey, hepatotoxicity of, 1723
Common bile duct, 1442f, 1444
anomalies of, 1448
cysts of
classification of, 1552
congenital. *See* Choledochal cysts.
diverticulum of, congenital, 1556, 1556f
obstruction of, in pancreatitis, chronic, 1345–1348, 1346f
stenosis of, in pancreatitis, chronic, 1311
strictures of, in pancreatitis, chronic, 1345–1347, 1346f
distal, biliary drainage procedures for, 1501, 1502f, 1502t, 1503
Common bile duct exploration
external biliary fistulas following, etiology and prevention of, 1537–1538
transcystic
choledochoscopic, 1482–1484, 1483f, 1484f, 1484t
laparoscopic techniques of, contraindications to, 1482, 1483t
Common bile duct stones. *See* Choledocholithiasis.
Compartments, esophageal, anatomy of, 11–12
Components separation techniques, for hernia repair, 682–683, 683f
Composite mesh, for ventral herniorrhaphy, 676
Computed tomography
in abdominal trauma, in pediatric patients, 1807, 1807f
with aortoenteric fistulas, 1114–1115, 1115f
in appendicitis, 2142–2143
of carcinoid tumors, 1183
with choledochal cysts, 1553–1554
with colon, rectal, and anal disorders, 1893–1894, 1894f
in colorectal trauma, 1974
in Crohn's disease, 1047–1048, 1048f, 1049f
in diverticular disease, colonic, 2014b, 2014f, 2014–2015
in duodenal injury, 766, 766f
of echinococcal cysts, 1637, 1638f
in esophageal cancer
abdominal imaging and, 471
chest imaging and, 471
for staging, 77, 80f, 457, 457f
therapy monitoring and, 461
in esophageal perforation, 93–94, 531, 532f
following esophageal surgery, 84
in gastric adenocarcinoma, 907
in gastric blunt trauma, 762
in gastroduodenal artery aneurysms, 1280, 1280f
Computed tomography *(Continued)*
of gastrointestinal stromal tumors, 1195
of hepatic abscesses, pyogenic, 1646–1647, 1647f
of hepatic cysts, solitary, 1630–1631
in hepatocellular carcinoma, 1734–1735, 1735f
for insulinoma localization, 1377, 1377f
with intra-abdominal abscesses, 1102, 1104f
in jaundice, obstructive, 1461f, 1461–1462
with liver abscesses, amebic, 1654
in mesenteric ischemia, 1252t, 1252–1253
in mesenteric venous thrombosis, 1256
of obturator hernias, 693, 693f
in pancreatic and periampullary carcinoma, for preoperative staging, 1365
with pancreatic cystic neoplasms, 1393f–1395f, 1393–1394
with pancreatic pseudocysts, 1332–1333
in pancreatic trauma, 1401, 1401f
in pancreaticoduodenal artery aneurysms, 1280, 1281f
in pancreatitis
acute, 1299–1300, 1300f, 1302f
chronic, 1347
with paraesophageal hernia, 552, 553f
in periampullary carcinoma, 1361–1362, 1362f
in perineal pain syndromes, 2074
in portal hypertension, 1757
with retrorectal tumors, 2301
in small bowel injury, 771–772, 772f
in small bowel obstruction, 1030–1032, 1031f
in small bowel volvulus, 1036, 1036f
with splenic abscesses, 1818, 1819f
in splenic artery aneurysms, 1275, 1276f
in splenic trauma, 1799
in Zollinger-Ellison syndrome, 863
Computed tomography enteroclysis, in small bowel obstruction, 1031
Computed tomography enterography, 1894, 1895f
Condylomata acuminata, pruritus ani associated with, 2070
Congenital diaphragmatic hernias, 36–37
Congenital disorders. *See also specific disorders.*
esophageal, 32–33
gastric, 35
in pediatric patients. *See* Anorectal anomalies; Pediatric patients, congenital disorders in.
Congenital membranous web/diaphragm, 573
Conjoint tendon, 638, 638f
Connell suture, 1085
Constipation, 1878, 1878f, 1884–1885, 1929–1941
in appendicitis, 2142
botulinum toxin for, 1938–1939
etiology of, 1929, 1930b
evaluation of, 1929–1934
clinical approach and, 1930–1931, 1931b

Constipation *(Continued)*
diagnostic studies in, 1929–1930
history and physical examination in, 1929
Minnesota Multiphasic Personality Inventory in, 1934
physiologic studies in, 1931–1934
of colonic transit, 1931–1932, 1932f
defecography as, 1933
electromyography and pudendal nerve terminal motor latency as, 1933–1934
manometry as, 1932–1933
of small bowel transit, 1932
results of, interpretation of, 1934
examination for, 1888
following surgery for anorectal anomalies, 2405
rectal prolapse due to, 1958
treatment of, 1934–1939
pelvic floor retraining and biofeedback for, 1938–1939
surgical, 1934–1938
for colonic inertia, 1934, 1935t, 1936
for paradoxical puborectalis contraction, 1936–1938, 1939f, 1940f, 1941t
for pelvic outlet obstruction, 1936, 1937f, 1938f
Contact dermatitis, pruritus ani associated with, 2069
Contaminated cases, 2327
Continence. *See* Fecal continence; Fecal incontinence.
Cooper, Astley, 632
Cooper's ligament, 636
Copper salts, hepatotoxicity of, 1724
Corkscrew configuration, of small intestine, 1216, 1217f
"Corkscrew" esophagus, 419, 420f
Corticosteroids
altered hormonal response to stress and, 2378
for Crohn's disease, 1052, 2128
in immunocompromised patients, 2377–2379
immunosuppression induced by, 2377–2378
impaired wound healing associated with, 2378
for inflammatory bowel disease, 2090
mechanism of action of, 2377t
stress-dose, 2378–2379, 2379b, 2379t
Corticotropin-producing tumor, 1382–1383
diagnosis of, 1383
therapy for, 1383
Corynebacterium minutissimum infection, pruritus ani associated with, 2070
Costs, of obesity-related treatments, 929
Cough
chronic, in gastroesophageal reflux disease, medical therapy for, 258–259
gastroesophageal reflux disease associated with, diagnosis of, 171, 172f
in tracheomalacia, 570
Counseling, for reoperative surgery, 1134
Courvoisier's sign, 1361
Cowden's disease, 894t, 897, 2159t, 2175–2176
COX-2
bile acid injury to esophageal mucosa and, 232
cancer and, 348
esophageal cancer and, 445
COX-2 inhibitors
for Barrett's esophagus, 258
for esophageal cancer, 509–510
Cranial nerves, prenatal development of, 44
"Creeping fat," in Crohn's disease, 1058, 1058f
Cricopharyngeal achalasia, 427. *See also* Zenker's diverticulum.
Cricopharyngeal dysfunction, swallowing disorders caused by, 134
Cricopharyngeal myotomy. *See* Myotomy, cricopharyngeal.
Critical care physicians, on portal hypertension multidisciplinary team, 1767
Critical illness, gastric dysmotility in, 730
Crohn's disease, 1041–1067. *See also* Inflammatory bowel disease.
abscesses in, 1065
anorectal, 2057–2058
anal fissures in, 2038
anorectal, surgical treatment of, 2135
capsule endoscopy of, 746f
chronic, cancer risk in, 2191
classification of, 1044
clinical features of, 1044–1045, 2087–2088
colonic, surgical treatment of, 2133, 2135
colorectal cancer and, 2089
diagnosis of, 2088f, 2088–2089
diverticulitis vs., 2015
duodenal, 1066, 1066f
epidemiology of, 1041, 2085–2086
esophageal, 91, 94f
etiopathogenesis of, 2085–2086
fistulas in, 1063–1065, 1094
anorectal, 2057
endoanal ultrasound in, 1912
enterocutaneous, 1065
enteroenteric, 1064
enterogenital, 1065
enterovesical and enteroureteral, 1064
ileosigmoid, 1064
treatment of, 1104–1105, 1110, 1111
free perforation in, 1066
ileal pouch–anal anastomosis failure in, 2121–2122
imaging in, 1046–1049
cross-sectional, 1047–1048, 1048f, 1049f
endoscopy as, 1049–1052
small bowel follow-through and enteroclysis as, 1046–1047, 1047f
ultrasound, 1048–1049
Crohn's disease *(Continued)*
laboratory findings in, 1045–1046
laparoscopic surgery for
outcomes of, 2354, 2356, 2356t
technical points for, 2356
medical treatment of, 1052f–1055, 2089–2093, 2127–2128
5-aminosalicylic acid compounds in, 2089–2090
antibiotics in, 2090–2091
biological therapies in, 2092–2093
corticosteroids in, 2090
immunosuppressive agents in, 2091–2092
to induce remission of active disease, 1052–1053
to maintain remission, 1053
nutrition in, 1053–1055
sulfasalazine in, 2089
natural history of, 1042
pathology of, 1043–1044, 2086f, 2086–2087, 2087f
gross features and, 1043, 1043f
microscopic features and, 1043–1044, 1044f
perianal, 2087–2088
quality of life in, 2096
risk factors and pathogenesis of, 1042–1043
environmental factors in, 1042
genetic factors in, 1042–1043
of small bowel
complicated, treatment of, 1063
treatment of, 2132
surgical treatment of, 1055–1067, 2094–2096, 2127, 2128–2138
abdominal exploration and disease segment identification in, 1057–1058, 1058f
abdominal incision for, 1056–1057, 1057f
for anorectal disease, 2135
bowel resection and anastomotic techniques for, 1059–1060
bowel resection vs. stricturoplasty for, 1058–1059
bypass procedures for, 1063
for colonic disease, 2130, 2133, 2135
for fistulas, 2135–2136, 2137f–2138f
ileal pouch–anal anastomosis for, 2130, 2132
indications for, 1055b, 1055–1056, 2127
laparoscopic, 1063
laparoscopy-assisted, 2132
operative concerns for, 2128–2130
anastomotic technique as, 2129
recurrence as, 2129
resection margin as, 2129–2130
for perianal abscesses, 2135, 2136f
postoperative care for, 1066–1067
preoperative evaluation and preparation for, 1056, 1056f, 2128
for rectovaginal fistulas, 2136, 2138
resection as, 2132, 2133f
for small bowel, 2132
stoma formation and, 1060, 1062–1063

Crohn's disease *(Continued)*
stricturoplasty as, 2132, 2134f–2135f
techniques for, 1059, 1059f–1062f
ulcerative colitis differentiated from, 1050, 1050f
ureteral obstruction in, 1065–1066
Crohn's Disease Endoscopic Index of Severity, 1051
Cronkhite-Canada syndrome, 884, 2159t, 2176
small intestinal, 894t, 898
Crural repair, anterior, for gastric volvulus, 950
Cryoablation
for Barrett's esophagus, 371
hepatic, external biliary fistulas following, etiology and prevention of, 1540
for hepatocellular carcinoma, 1738
for metastatic colorectal cancer, 2283
Cryptococcus neoformans, splenic abscess due to, 1819
Cryptosporidiosis, diarrhea due to, in immunocompromised patients, 2382
Cullen's sign, 1299
Curling's ulcers, in pediatric patients, 961
"Cushing ulcers," in pediatric patients, 961
Cutaneous flushing, in carcinoid syndrome, 1182
Cyclooxygenase-2
bile acid injury to esophageal mucosa and, 232
cancer and, 348
esophageal cancer and, 445
Cyclooxygenase-2 inhibitors
for Barrett's esophagus, 258
for esophageal cancer, 509–510
Cyclophosphamide, hepatotoxicity of, 1723
Cyclosporine
for gastrointestinal fistulas, 1104–1105
hepatotoxicity of, 1722
for inflammatory bowel disease, 2092
mechanism of action of, 2377t
Cyst(s)
bronchogenic, esophageal, 525, 525f
choledochal. *See* Choledochal cysts.
dermoid, retrorectal, 2302, 2302t
duplication
esophageal, 570–572
evaluation of, 572, 572f
imaging of, 82–83
treatment of, 572, 573f
gastric, 888
small intestinal, 901, 1221–1223, 1222f
enterogenous, retrorectal, 2302, 2302t
epidermoid, retrorectal, 2302, 2302t
esophageal, 524b, 524–525, 525f
endoscopic ultrasonography in, 123–124, 124f
gastric, esophageal, 525, 525f
glandular, gastric, 884
hepatic, 1630–1638
cystic neoplasms and, 1636, 1636f, 1637f
echinococcal, 1636–1638, 1638f
in polycystic liver disease, 1634–1635, 1635f
solitary, 1630–1633, 1631f–1634f
Cyst(s) *(Continued)*
inclusion, esophageal, 525
mesenteric, 1860
neuroenteric, esophageal, 525
pancreatic. *See* Pancreatic cystic neoplasms.
small intestinal, in pediatric patients, 1221–1223, 1222f, 1223f
splenic, 1813–1815
nonparasitic
congenital, 1814
secondary (false), 1813, 1814
parasitic, 1813–1814
true, 1813
tailgut, retrorectal, 2302t, 2302–2304, 2303f
Cyst fenestration, for hepatic cysts
in polycystic liver disease, 1635
solitary, 1632–1633
Cystadenocarcinoma
biliary, 1534, 1636
end-stage liver disease due to, 1687
mucinous, 1391
appendiceal distention by, 2150–2151
Cystadenomas
biliary, 1526, 1636, 1636f, 1637f
mucinous, 1390
appendiceal distention by, 2150
Cystic artery, 1445, 1445f, 1446, 1446f
Cystic duct
anatomy and embryology of, 1443, 1444
anomalies of, 1448
Cystic duct artery, 1445
Cystic duct catheter technique, 1485
Cystic fibrosis, jejunoileal atresia associated with, 1219
Cystic veins, 1603
Cystoduodenostomy
for choledochal cysts, 1554
for pancreatic pseudocysts, 1339, 1342f
Cystoenterostomy, for choledochal cysts, 1554
Cystogastrostomy
for pancreatic ductal disruption, 1352
for pancreatic pseudocysts, 1335, 1339, 1340f–1341f
Cystohepatic ducts, 1603
Cystojejunostomy
laparoscopic, 1339, 1342f
for pancreatic pseudocysts, 1335, 1335f–1339f
Cytologic analysis, in gastric adenocarcinoma, 908
Cytomegalovirus infection, colitis due to, in immunocompromised patients, 2382

D

Daclizumab
for islet transplantation, 1424
mechanism of action of, 2377t
Dallemagne, Bernard, 7
Danazol, hepatotoxicity of, 1723
Dantrolene, hepatotoxicity of, 1722
Débridement, with hepatobiliary trauma, 1666
Decompression, long-tube, for small bowel obstruction, 1032
Deep vein thrombosis, with inguinal herniorrhaphy, laparoscopic, 667
Defecation, 1876, 1876f
obstructed, 1879, 1879b
Defecography
with colon, rectal, and anal disorders, 1893
in constipation, 1933
in fecal incontinence, 1920
in obstructed defecation, 1879b
Deglutitive inhibition, 52–53, 54f
Deglutitive lower esophageal sphincter relaxation, 54
DeLorme procedure
for rectal prolapse, 1962, 1962f–1964f, 1964, 1964t
for solitary rectal ulcer syndrome, 2076
Delta agents. *See* Hepatitis D.
Denk, Wolfgang, 4
Dental caries, gastroesophageal reflux disease associated with, diagnosis of, 171
Depression, with levator spasm, 2075
Dermatitis, pruritus ani associated with, 2069
Dermatologic conditions, pruritus ani associated with, 2069–2070
Dermatomyositis, esophageal motility disorders in, 140
Dermoid cysts, retrorectal, 2302, 2302t
Deroofing, of hepatic cysts, in polycystic liver disease, 1635
Desmoid(s)
in familial adenomatous polyposis, 2161
recurrent, reoperative surgery for, 1141
Desmoid precursor lesions, 2161
Desmoid reaction, 2161
Devascularization procedures, for bleeding varices, 1763
Dextropropoxyphene, hepatotoxicity of, 1723
DGER. *See* Duodenogastroesophageal reflux.
Diabetes mellitus
esophageal motility disorders in, 140
islet transplantation for. *See* Islet transplantation.
obesity and, bariatric surgery and, 938
in pancreatitis, chronic, 1345
type 1, pancreas transplantation for. *See* Pancreas transplantation.
Diabetic neuropathy, diarrhea in, 1880
Diagnostic peritoneal lavage
in abdominal trauma, in pediatric patients, 1807–1808
in colorectal trauma, 1974
in gastric trauma, 762–763
Diamond-shaped island flaps, for anal stenosis, 2064, 2064f
Diaphragm
dysfunction of, with inguinal herniorrhaphy, laparoscopic, 667
pelvic, perineal pain and, 2072
prenatal development of, 35–36, 37f

Diaphragmatic hernias, 549–561
congenital, 36–37, 560–561
Bochdalek, 561
Morgagni, 560
paraesophageal. *See* Paraesophageal hernias.
parahiatal, 560
postoperative, 560
recurrent, reoperative surgery for, 1141–1142
traumatic, 560
Diaphragmatic hiatus, 100
Diarrhea, 1885
in afferent loop syndrome, 878
in appendicitis, 2142
in carcinoid syndrome, 1182
in Crohn's disease, 1045
following gastrectomy, 873–874, 874f
reoperative surgery for, 1138–1139
following vagotomy, 809
functional, 1879–1880
with gastrointestinal fistulas, 1098
with ileostomy, 1081
in pancreatitis, chronic, 1345
pruritus ani and, 2068
in short-bowel syndrome, controlling, 1165
Diathermy, bipolar, for hemorrhoids, 2031, 2031f, 2033
Diazepam, for endoscopic retrograde cholangiopancreatography, 1491
Diclofenac, hepatotoxicity of, 1722
Didanosine, hepatotoxicity of, 1720
Diet. *See also* Nutrition.
Barrett's esophagus and, 343
esophageal cancer and, 443, 445
for fecal incontinence, 1921
following bariatric surgery, 938
gastroesophageal reflux disease and, 200, 252
pancreatic adenocarcinoma and, 1359
pruritus ani and, 2068
resumption of, following laparoscopic colorectal surgery, 2343
Dieulafoy's lesions, 886–887
endoscopic appearance of, 740, 740f
symptoms and diagnosis of, 887
treatment of, 887
Diffuse esophageal spasm, 139–140, 419–421
examinations in, 419–421
historical background of, 419
imaging in, 73, 73f
manometric features of, 419–420, 420t, 421f
treatment of, 421
Diffuse gastrointestinal hemangiomatosis, 887
Diffuse large B-cell lymphoma, pathology of, 1200, 1202f, 1203
Digestion
duodenal, 978–980
mesenteric circulation and, 1242–1243
small intestinal. *See* Small intestinal epithelium, digestion and absorption and.
Digestive system, embryonic development of, 31, 32f
Dilators, for esophageal stricture dilatation, 237, 238f, 239f
Diloxanide furoate, for liver abscesses, amebic, 1655
Dissolution therapy, for bile duct stones, 1495–1496
Distal splenorenal shunt, for bleeding varices, 1762–1763
follow-up for, 1762–1763
management of, 1762
procedure for, 1762, 1762f
Disulfiram, hepatotoxicity of, 1721
Diverticula. *See also* Diverticulitis; Diverticulosis.
cervical, lateral (Killian-Jamison), 95
colonic, 2012, 2013f
giant, 2019–2020, 2021f
of common bile duct, congenital, 1556, 1556f
epiphrenic, 433–437
diagnosis of, 433f, 433–434
pathophysiology of, 433
symptoms of, 433
treatment of, 434–435
surgical, methods and results of, 434f–437f, 435–437
esophageal
imaging of, 94–95, 96f
midesophageal, 437–438, 438f, 439f
pulsion, 94, 96f
Zenker's, 94–95, 96f
of gallbladder, 1449–1450, 1451f
periampullary, 780
pharyngoesophageal. *See* Zenker's diverticulum.
small bowel. *See* Duodenal diverticula; Jejunoileal diverticula; Meckel's diverticula.
"tenting" of, 94, 96f
Zenker's. *See* Zenker's diverticulum.
Diverticular disease. *See also* Diverticula; Diverticulitis; Diverticulosis.
colonic, 2012–2027
clinical features of, 2015–2021
atypical, 2021, 2021t
in cecal diverticulitis, 2019, 2020f
diseases confused with diverticulitis and, 2015f, 2015–2016
with diverticular hemorrhage, 2016, 2016f, 2017f
diverticulitis and, 2015
with fistulas, 2017–2018, 2018f
with generalized peritonitis, 2018, 2019f
with giant diverticula, 2019–2020, 2021f
in immunocompromised patients, 2020
with intestinal obstruction, 2018–2019
with pericolic abscess, 2016–2017
in subacute diverticulitis, 2016
in young patients, 2021
diagnostic modalities for, 2012–2015, 2013f, 2014b, 2014f, 2014t
Diverticular disease *(Continued)*
laparoscopic surgery for
outcomes of, 2353–2354, 2355t
technical points for, 2354
medical management of, 2022
pathophysiology and epidemiology of, 2012, 2013f
surgical management of, 2022–2027
with bleeding, 2026–2027
elective resection as, 2022–2024, 2023f, 2024f
emergency surgery for, 2024–2025, 2025f
for obstruction, 2025–2026, 2026f
for postresection diverticulitis, 2027
in immunocompromised patients, 2381
Diverticular hemorrhage, colonic, 2016, 2016f, 2017f
Diverticular resection
colonic, postresection diverticulitis following, 2027
elective, for colonic diverticular disease, 2022–2023, 2023f, 2024f
Diverticulectomy
early development of, 5–6
epiphrenic, for epiphrenic diverticulum, 435, 435f, 436f
esophageal, complications of, 618f, 618–619, 619f
with esophagomyotomy, for epiphrenic diverticulum, 435
incidental, for Meckel's diverticulum, 787
for Meckel's diverticulum, 788–789
pharyngoesophageal, for Zenker's diverticulum, methods and results of, 430–431
for Zenker's diverticulum, 396
Diverticulitis. *See also* Diverticula.
colonic
clinical features of, 2015
Crohn's disease vs., 2015
diseases confused with, 2015f, 2015–2016
postresection, surgical treatment of, 2027
subacute (persistent), 2016
Meckel's, 787, 789f
Diverticulization, duodenal, 768
Diverticulopexy
early development of, 6
for Zenker's diverticulum, 396
Diverticulosis. *See also* Diverticula.
colonic, 1880
painful, 2016
Diverticulum hepatis, 1598
Diverting stomas, 2365
Dobbhoff tube, 750, 751f
Dobutamine, mesenteric blood flow and, 1243t
Domperidone
for gastroesophageal reflux disease, 253
for gastroparesis, 921
Dopamine, mesenteric blood flow and, 1243, 1243t
Dor fundoplication, 276, 277f
for achalasia, 416
for esophageal perforation, 417

Dor fundoplication *(Continued)*
laparoscopic
for epiphrenic diverticulum, 435–437, 437f
surgical technique for, 282
results with, 283
"Downhill" varices, 95, 97f
Doxorubicin, esophageal malformations due to, 564
Drainage
external, of pancreatic pseudocysts, 1341–1342
internal, of pancreatic pseudocysts, 1335, 1335f–1342f, 1339
laparoscopic, 1339, 1342f
laparoscopic, for splenic abscesses, 1820
for pancreatitis, chronic, 1314–1315
"extended" procedures for, rationale for, 1314–1315, 1315f–1317f
indications for, 1316–1317, 1318f
rationale for, 1314
percutaneous
for hepatic abscesses, pyogenic, 1649
for liver abscesses, amebic, 1656
of pancreatic pseudocysts, 1333–1334
for splenic abscesses, 1820
surgical
for hepatic abscesses, pyogenic, 1649–1650
for liver abscesses, amebic, 1656
Droperidol, for endoscopic retrograde cholangiopancreatography, 1491
Drug(s), illicit, ingested packages of, 943, 943f
Drug therapy. *See also specific drugs and drug types.*
for bleeding varices, 1624
immunosuppression due to, 2375–2376, 2377t
pancreatitis due to, 1299
pharmacobezoars and, 943, 944, 944t
pruritus ani associated with, 2069
Drug-induced liver disease, 1717–1724
alternative remedies and, 1724
conditions associated with, 1719–1724
cholestasis as, 1722–1723
cirrhosis as, 1719t, 1720–1721
hepatic tumors as, 1719t, 1723–1724
hepatitis as, 1719t, 1720–1721
acute, 1721
chronic, 1722
hepatocellular zone 1 necrosis as, 1719t, 1720
hepatocellular zone 3 necrosis as, 1719t, 1719–1720
immunoallergy as, 1721
metabolic idiosyncrasy and, 1722
mitochondrial cytopathies as, 1719t, 1720
steatohepatitis as, 1719t, 1720–1721
vascular toxicity as, 1723
diagnosis and treatment of, 1718, 1719t
environmental agents and, 1724
epidemiology of, 1717
fulminant liver failure as, 1703
hepatotoxic reactions to, 1615
mechanisms of liver injury and, 1718
Drug-induced liver disease *(Continued)*
pathophysiology of, 1717–1718
recreational drugs and, 1724
Drummond, artery of, 1239
DualMesh, for ventral herniorrhaphy, 676, 676f
Ductal epithelial cells, pancreatic, 1290f, 1290–1291, 1291f
Ducts of Luschka, 1444
Ductus venosus, 1598
Dumping syndrome
following gastrectomy, 809, 870–873, 872f
following gastric bypass, 934
reoperative surgery for, 1138–1139
Duodenal adenocarcinoma, 915–916
Duodenal cap, 964, 966f
Duodenal carcinoids, 1181
treatment of, 1185
Duodenal diverticula, 775–783, 776f, 777f, 977
complications of, 779–781
biliary-pancreatic, 780–781
hemorrhage as, 780
obstruction as, 779
perforation as, 779
diagnosis of, 777–779, 778f–780f
disease associated with, 776–777
management of, 781–783
nonoperative, 781
operative, 781f–784f, 781–783
pathogenesis of, 775–776
symptoms of, 777
Duodenal fistulas
with duodenal injuries, 768
etiology of, 1093–1096
treatment of, 1110
Duodenal function, gastrin and, 985
Duodenal injury, 764–770
anatomy and, 764
with biliary stent placement, 1095
diagnosis of, 765–766, 766f
historical background of, 764
with laparoscopic cholecystectomy, 1094
management of, 766, 767f, 768–770, 769f
mechanisms of, 765
morbidity and mortality with, 770
with percutaneous transhepatic wire placement, 1095
physiology and, 764–765
Duodenal motility, intrinsic and extrinsic control of, 985
Duodenal obstruction
with duodenal diverticula, 779
in pancreatic and periampullary carcinoma
nonoperative palliation of, 1365–1366
operative palliation of, 1366–1367
with pancreatic pseudocysts, 1344
in pancreatitis, chronic, 1311, 1348–1349, 1349f
in pediatric patients, 952–954
clinical features and diagnosis of, 953, 953f, 954f
embryology and etiology of, 952
incidence and epidemiology of, 952
management of, 953–954, 955f
Duodenal perforation
with duodenal diverticula, 779
treatment of, 1108–1110
Duodenal reflux, esophageal mucosal injury and, 230–232
animal studies of, 230
human studies of, 230–231
mechanism of, 231–232
Duodenal resection, for duodenal adenocarcinoma, 915
Duodenal stump fistulas, treatment of, 1110
Duodenal stump leakage, 1093–1094
Duodenal switch operation
for bile reflux gastritis, 1146–1147, 1147f
failed, revision surgery for, 1146
Duodenal ulcers
intractable, elective surgery for, 792–798
choice of operation for, 796–798, 798f, 798t
drainage procedures as, 794–795
gastric resection procedures as, 795–796, 796f–798f
laparoscopic, 798, 799f
for recurrent ulcers, 798
vagotomy as, 792–794
pathogenesis of, 811–812
perforated, emergency surgery for, 805, 806f, 807f
surgery for, gastric outlet obstruction following, reoperation for, 1136–1137
Duodenocolic fistulas, in Crohn's disease, 1094
Duodenocolic ligament, 1863
Duodenocutaneous fistulas, in Crohn's disease, 1094
Duodenoduodenostomy, for annular pancreas, 1407–1408, 1408f
Duodenogastric reflux, 185
Duodenogastroesophageal reflux, 185, 190–195
assessment of, 191–195
Barostat test for, 195
basal acid secretion for, 195
electrogastrography for, 195
gastric acid secretion for, 195
impedance measurement for, 195
24-hour bilirubin monitoring for, 193–195, 194f, 194t
24-hour gastric pH monitoring for, 191f–193f, 191–193, 192t
with Barrett's esophagus, 190
diagnosis of, 168–169
with gastroesophageal reflux disease, 194
with postgastrectomy syndrome, 190
Duodenojejunostomy
for duodenal injury, 768
Roux-en-Y
for duodenal diverticula, 782, 783f
for gastroduodenal fistulas, 1110
for superior mesenteric artery syndrome, 975, 975f
Duodenostomy
for gastroduodenal fistulas, 1110
tube, for duodenal stump fistulas, 1110

Duodenotomy
for bleeding ulcers, 824–825, 825f
with inversion and mucosal excision, for duodenal diverticula, 781
in Zollinger-Ellison syndrome, 865, 865f, 868
Duodenum. *See also* Small intestine.
anatomy of, 964, 965f–967f, 968, 969f, 970f, 971–977
adult abnormalities of, 971, 974–977
arterial, 968, 971f
histology and, 971, 973f
innervation and, 971, 974f
lymphatic, 968
venous, 968, 972f
Crohn's disease of, 1066, 1066f
embryology of, 947
pathophysiologic aspects of, in esophageal disease, 184–185
physiology of, 977–985
absorption and digestion and, 978–980
of calcium, 979
of iron, 979–980, 980f
of macronutrients, 980
endocrine, 980–985, 981t
cholecystokinin and, 980–981, 981t
endorphins and, 984
enkephalins and, 984
gastric inhibitory polypeptide and, 981t, 981–982
gastrin and, 981t, 985
gastrin-releasing peptide and, 981t, 984
ghrelin and, 981t, 984
melatonin and, 981t, 985
motilin and, 981t, 982
neuropeptide Y and, 981t
neurotensin and, 981t, 983
nitric oxide and, 981t, 983
opioids and, 981t
pancreatic polypeptide and, 981t, 984
peptide YY and, 981t, 984–985
secretin and, 980, 981t
serotonin and, 981t, 982–983
somatostatin and, 981t, 982
substance P and, 981t, 983–984
vasoactive intestinal peptide and, 981t, 983
in esophageal disease, 184–185
exocrine, 977–978, 978f, 979f
prenatal development of, 34
Duplications
cystic
esophageal, 570–572
evaluation of, 572, 572f
imaging of, 82–83
treatment of, 572, 573f
gastric, 888
small intestinal, 901, 1221–1223, 1222f
esophageal, 524b, 524–525, 525f
small intestinal, in pediatric patients, 1221–1223, 1222f, 1223f
tubular, of small intestine, 1221, 1223f
Duval procedure, in pediatric patients, 1410
Dynamic myoplasty, for fecal incontinence, 1923–1924
Dysejaculation syndrome, following hernia surgery, 654
Dysphagia
in achalasia, 407, 411
with epiphrenic diverticulum, 433
in esophageal cancer, 61
esophageal carcinoma and, 468, 469t
in esophageal disease, 57
in esophageal motility disorders, 71
following esophagomyotomy, for achalasia, 620
following fundoplication, 611
following Heller myotomy, 417
imaging in, gastric, 66
myogenic, cricopharyngeal myotomy for, 384, 386, 386f, 387f, 388
neurologic, cricopharyngeal myotomy for, 382, 384, 385f–386f
oropharyngeal, 374
assessment of, 377–378, 378t
causes of, 374, 375b
surgical management of, 378–390
cricopharyngeal myotomy for, 379–384
for idiopathic upper esophageal sphincter dysfunction, 388, 389f
indications for, 378–379
for myogenic dysphagia, 384, 386, 386f, 387f, 388
after neck surgery, 388, 390
operative technique for, 379f–382f, 379–380
partial fundoplication for, 278–279
patient approach for, 61
retrosternal, low, after antireflux procedures, 609
Dysplasia
Barrett's esophagus and
ablation of, rationale for, 367
classification of, 359
development of, incidence of, 360
grading of, 347–348
high-grade, 219, 219f
adenocarcinoma distinguished from, 359–360
prevention of, 366–367
risk of, 366
surgical management of, 361–363, 362f
low-grade
prevalence of, 360, 361t
surgical management of, 360–361, 361b
high-grade
Barrett's esophagus and, 219, 219f
adenocarcinoma distinguished from, 359–360
prevention of, 366–367
risk of, 366
surgical management of, 361–363, 362f
colorectal cancer and, 2192
prevention of, 366–367
low-grade, Barrett's esophagus and
prevalence of, 360, 361t
Dysplasia *(Continued)*
surgical management of, 360–361, 361b
in residual rectal mucosa, following ileal pouch–anal anastomosis, 2112
ulcerative colitis with, 2082–2084
surgical management of, restorative proctocolectomy for, 2335
Dysrhythmias, with inguinal herniorrhaphy, laparoscopic, 667

E

Eating, colonic motor response to, 1875
Echinococcal cysts
hepatic, 1636–1638, 1638f
splenic, 1832
Echoendoscopes, electronic, curvilinear, 113–114, 115f
Ectopic rests, congenital, esophageal, 522
Ectopic tissue polyps, small intestinal, 892–893
Ectropion, 2062
Eczema, atopic, pruritus ani associated with, 2070
Edmonton Protocol, 1426, 1427
Edrophonium test, for esophageal motility disorders, 160
Educator, as clinical nurse specialist role, in palliative treatment, for esophageal cancer, 497
EEA staplers, 1087
Efferent loop obstruction, following gastrectomy, 809, 877, 878
Elderly people, appendicitis in, 2144
Electrical hazard zone, 639–640
Electrocoagulation, bipolar, for esophageal cancer, 489t, 492
Electrogalvanic muscle stimulation, for perineal pain syndromes, 2074
Electrogastrography, in esophageal disease, 195
Electrohydraulic lithotripsy, for bile duct stones, 1495
Electromyography
anal sphincter, in obstructed defecation, 1879b
in constipation, 1933
in perineal pain syndromes, 2074
Embolization
for celiac artery aneurysms, 1278–1279
radiographic, of injured spleens, in pediatric patients, 1808, 1810f
for splenic artery aneurysms, 1277
transarterial, hepatic abscesses following, pyogenic, 1642
transcatheter
for mesenteric artery branch aneurysms, 1281–1282
for superior mesenteric artery aneurysms, 1279
Emphysema
preperitoneal, with inguinal herniorrhaphy, laparoscopic, 667
subcutaneous, with inguinal herniorrhaphy, laparoscopic, 667

En bloc esophagectomy, for localized esophageal cancer, 477–478
Encephalopathy, hepatic
in end-stage liver disease, 1694, 1694b
portal hypertension, 1756
Endarterectomy, mesenteric artery, 1258, 1259f
End-loop stomas, 2366–2368
colostomy and, 2367
ileocolostomy and, 2367–2368, 2369f
ileostomy and, 2367, 2368f
Endoanal ultrasound, 1909–1914
with anal canal neoplasms, 1912–1913, 1913f, 1913t
with retrorectal tumors, 1913, 1914f
with anal sphincter defects and fecal incontinence, 1910–1911, 1911f
in fecal incontinence, 1920, 1920f
normal anatomy on, 1909–1910, 1910f
in perianal sepsis and fistula-in-ano, 1911–1912, 1912f
with rectovaginal fistulas, 1912
in solitary rectal ulcer syndrome and colitis cystica profunda, 1913–1914, 1914f
Endobiliary forceps biopsy, in malignant bile duct obstruction, 1508
EndoCinch therapy. *See* Gastroplasty, endoluminal.
Endocrine disorders, intestinal motility and, 926
Endometriosis, small intestinal, 893
Endorectal magnetic resonance imaging, in rectal cancer, 2209
Endorectal ultrasound, 1899–1909
with colon, rectal, and anal disorders, 1893, 1894f
limitations of, 1907
after neoadjuvant therapy, accuracy of, 1908
normal anatomy on, 1900, 1901f
for postoperative follow-up, 1908–1909, 1909f
in rectal cancer, 1900–1909, 2209
staging and
accuracy for, 1900–1903, 1903t
depth of invasion and, 1904t, 1904–1906
modification of staging system and, 1907, 1907t
nodal involvement and, 1906f, 1906–1907
uT0 lesions and, 1904, 1904f
uT1 lesions and, 1904, 1905f
uT2 lesions and, 1905, 1905f
uT3 lesions and, 1905f, 1905–1906
uT4 lesions and, 1906, 1906f
technique of, 1899–1900, 1900f
three-dimensional, 1909
Endorphins, duodenal function and, 981t, 984
Endoscopes
electronic, 113–114, 115f
standard, for endoscopic ultrasonography, 113, 113f
ultrasound, radial mechanical, 112f, 112–113
Endoscopic balloon dilation, for gastric bleeding, 743
Endoscopic band ligation, for gastric bleeding, 743, 743f
Endoscopic clips, for gastric bleeding, 743, 743f
Endoscopic examination. *See also specific techniques, e.g.* Colonoscopy.
in achalasia, 407, 411–412
anorectal, 1889–1891
capsule
in Crohn's disease, 1051f, 1051–1052
of small bowel, 745–746, 746f
in caustic ingestions, 542, 542b
chromoendoscopy as, in Barrett's esophagus, 104
with colonic vascular ectasias, 1991
complications of, esophageal perforation as, 529
in Crohn's disease, 1049–1052
capsule endoscopy as, 1051f, 1051–1052
push endoscopy as, 1050f, 1050–1051
to detect tumor relapse, of colorectal cancer, 2258–2259
with duodenal diverticula, 779, 779f
esophageal, 100–109
in Barrett's esophagus
conventional technique for, 102–104, 103f, 104f
specialized techniques for, 104, 105f
in esophageal cancer, 108–109, 109f
in esophageal carcinoma, 469–470
esophageal perforation due to, 529
for esophageal reconstruction, 581
in esophageal spasm, 419
following antireflux surgery, 106, 108, 108f
of gastroesophageal junction, 100–102, 101f, 102f
in gastroesophageal reflux disease, 59–60
normal appearance on, 100, 101f, 207–210, 208b, 208f–210f, 210b
in nutcracker esophagus, 422
in reflux esophagitis, 105–106, 106t, 107f
for staging of esophageal cancer, 455–456
for structural abnormality detection, 143
surveillance, for Barrett's esophagus, 350
of swallowing, 378
gastric, 733–741
in gastric adenocarcinoma, 907
indications for, 733
instrumentation for, 733–734
pathology on, 736–741, 737f–741f
patient preparation for, 734
technique for, 734f–736f, 734–736
with gastrointestinal fistulas, 1106
with leiomyoma, 517, 518f
magnification, in Barrett's esophagus, 104, 105f
with pancreatic tumors, unusual, 1432
with paraesophageal hernia, 552
Endoscopic examination *(Continued)*
in periampullary carcinoma, 1363
in portal hypertension, 1757
push, in Crohn's disease, 1050f, 1050–1051
screening, for Barrett's esophagus, 350
of small bowel, 745f–747f, 745–747
with benign tumors, 890
double-balloon, 747
Endoscopic gastrostomy, percutaneous, in pediatric patients, 960
Endoscopic mucosal resection, for Barrett's esophagus, 370
Endoscopic polypectomy, fistulas due to, 1095
Endoscopic retrograde cholangiography
with bile duct strictures, 1578, 1578f
with biliary fistulas, 1542
Endoscopic retrograde cholangiopancreatography, 1490–1513
with alkaline phosphatase elevation, 1615
cannulation success rates with, 1494
cholangiography and, 1493, 1493f
in cholangitis, acute, 1499–1500
cholecystectomy and, laparoscopic, 1497, 1498f
with choledochal cysts, 1553
anomalous pancreaticobiliary union and, 1508–1509
complications of, 1494
fistulas as, 1095
gastroduodenal perforations as, 1108–1110
in gallstone pancreatitis, acute, 1497–1499, 1498–1499
indications for, 1463, 1490
laparoscopic cholecystectomy and, 1497, 1498f
in malignant bile duct obstruction, tissue sampling and, 1507–1508
with pancreatic cystic neoplasms, 1394, 1395f
with pancreatic pseudocysts, 1332, 1332f
with pancreaticoduodenal injury, 769
in pancreatitis
acute, 1300
mild, 1302
chronic, 1347
severe, necrotizing, 1303
pancreatitis following, 1298
pancreatography and, 1493, 1493f
in pediatric patients, 1412–1413
in periampullary carcinoma, 1362–1363, 1363f
preparation for, 1490–1491, 1492t
in primary sclerosing cholangitis, 1503, 1503f, 1503–1504, 1504, 1561, 1562f
technique for, 1491–1493
Endoscopic sphincterotomy, 1493
complications of, 1494
Endoscopic therapy. *See also specific procedures.*
for achalasia, 409
for bezoars, 945
for bleeding, gastric, 741–745, 742f–744f
for bleeding varices, 1624

Endoscopic therapy *(Continued)*
for chronic pancreatitis, 1321–1327, 1322f, 1322t
results after endotherapy for stones, 1324, 1324f
results after endotherapy for stricture without stones, 1323
results after head resection with pylorus-preserving pancreaticoduodenectomy, 1325–1327
surgical resection techniques and, 1324, 1325f, 1326f
techniques for, 1323
for common bile duct stones
postoperative, 1593–1594
preoperative, 1590–1591
for duodenal diverticula, 781
for gastric cancer, 744–745
palliative, 914
for gastric volvulus, 1038–1039
mucosal reconstruction as, for gastric adenocarcinoma, 909
transgastric surgery as, 745
for variceal bleeding, 1759, 1760f
for Zenker's diverticulum, 397–398, 398f, 429
methods and results of, 431–433, 432f
Endoscopic transgastric surgery, 745
Endoscopic ultrasonography
esophageal, 111–125
in achalasia, 124–125
of benign tumors, 122–123, 123t
of cysts, 123–124, 124f
of esophageal carcinoma, 116–122, 117b, 470f, 470–471
during clinical stage, 117–121, 118f–122f
during re-treatment stage, 121–122
esophageal wall and, 114–116, 115f, 116f
instruments and techniques for, 112–114, 112f–115f
in paraesophageal diseases, 125
for staging of esophageal cancer, 457–458, 458f
therapy monitoring and, 461
for structural abnormality detection, 143
ultrasonography fundamentals and, 111–112
of varices, 124, 125f
in gastric adenocarcinoma, 907
for insulinoma localization, 1378, 1378f
with leiomyoma, 517–519, 518f, 518t
in pancreatic and periampullary carcinoma, for preoperative staging, 1365
in pancreatic carcinoma, 1354
with pancreatic cystic neoplasms, 1396
in periampullary carcinoma, 1363, 1364f
with small intestinal tumors, benign, 890
in Zollinger-Ellison syndrome, 864–865
Endoscopists, on portal hypertension multidisciplinary team, 1767
Endovascular mesenteric revascularization, 1260–1261, 1263t, 1264t, 1265f
Endovascular therapy
for aortoenteric fistulas, 1273–1274
for celiac artery aneurysms, 1278–1279
for hepatic artery aneurysms, 1278
Enkephalins, duodenal function and, 984
Entamoeba infection, liver abscesses due to. *See* Liver abscesses, amebic.
Enteral nutrition
for biliary surgery, 1622
for liver surgery, 1622
Enteric feeding, 753–755, 754f
gastric access for, 754–755
Enteric fistulas, 1096
congenital, 1096
in Crohn's disease, 1063–1065
enterocutaneous, 1065
enteroenteric, 1064
enterogenital, 1065
enterovesical and enteroureteral, 1064
ileosigmoid, 1064
treatment of, 1104–1105, 1110, 1111
infection causing, 1096
inflammatory causes of, 1096–1097
radiation-induced, 1097
traumatic, 1096
tumors causing, 1097
Enteritis
ischemic, on push enteroscopy, 745f
neutropenic, in immunocompromised patients, 2382–2383
radiation. *See* Radiation enteritis.
Enterobius vermicularis infection, pruritus ani associated with, 2070
Enterocervical fistulas, treatment of, 1114
Enterochromaffin cells, 1179, 1182
Enteroclysis
computed tomography, in small bowel obstruction, 1031
laparoscopic, bowel injury during, 1136
small bowel, in Crohn's disease, 1046–1047, 1047f
in small bowel obstruction, 1030, 1030f
Enterocolitis, necrotizing, in premature infants, 1227–1229, 1228f, 1229f
Enterocutaneous fistulas
in Crohn's disease, 1065
failure to close spontaneously, 1108
following ileal pouch–anal anastomosis, 2112
small intestinal, 1096
treatment of, 1110–1111
Enteroendocrine cells, small intestinal, 998
Enteroenteric fistulas
in Crohn's disease, 1064
treatment of, 1111f, 1111–1112
Enteroenterostomy, Braun, for bile reflux gastritis, 877, 878f, 1146, 1146f
Enterofallopian fistulas, treatment of, 1114
Enterogenital fistulas, in Crohn's disease, 1065
Enterogenous cysts, retrorectal, 2302, 2302t
Enteroglucagon, small intestinal neuroendocrine function and, 1018
Enterohepatic circulation, 1453–1454, 1457f
Enteropathy, neutropenic, in immunocompromised patients, 2382–2383
Enteropathy-type T-cell lymphoma, pathology of, 1205, 1205f, 1206t
Enteroscopy
intraoperative, 746–747
push, 745, 745f
with small intestinal tumors, benign, 890
sonde, push, with small intestinal tumors, 890
Enterotomy, longitudinal, for gastric outlet obstruction, 952
Enteroureteral fistulas, in Crohn's disease, 1064
Enterouterine fistulas, treatment of, 1114
Enterovaginal fistulas, treatment of, 1113–1114
Enterovesical fistulas
in Crohn's disease, 1064
treatment of, 1112f, 1112–1113
Enterra stimulator, 921–923, 922f
Enteryx, for endoscopic antireflux procedures, 320–323, 325, 326t, 327t
complications of, 323
efficacy of, 321–323, 322t, 323f
histologic changes and, 321
patient selection for, 320
physiologic/anatomic mechanisms of, 330–331
precautions recommended with, 323
procedure with, 320–321, 321f
results with, 325, 326t, 327t
Eosinophilic esophagitis, esophageal strictures in, 90, 93f
Epidermal growth factor receptors, for esophageal cancer, 510
Epidermoid cysts, retrorectal, 2302, 2302t
Epidermolysis bullosa, esophageal strictures in, 89
Epidermophyton infection, pruritus ani associated with, 2070
Epigastric artery
inferior, 657, 659f, 673
superior, 673
Epinephrine, mesenteric blood flow and, 1243t
Epiphrenic diverticulum, 433–437
diagnosis of, 433f, 433–434
pathophysiology of, 433
symptoms of, 433
treatment of, 434–435
surgical, methods and results of, 434f–437f, 435–437
Epithelial cells, ductal, pancreatic, 1290f, 1290–1291, 1291f
Epithelioid hemangioendotheliomas, hepatic, 1748–1749
Epithelium. *See* Esophageal epithelium; Small intestinal epithelium.
Erasistratus, 632
Erlotinib, for colorectal cancer metastases, 2271
Erythrasma, pruritus ani associated with, 2070
Erythromycin
for bowel preparation, 831
for gastroparesis, 921
hepatotoxicity of, 1723

Erythromycin *(Continued)*
for intestinal dysmotility, 926
preoperative, 2328
Escherichia coli
hepatic abscesses and, 1644
overwhelming postsplenectomy infection and, 1782
splenic abscess due to, 1819
Esomeprazole. *See also* Proton pump inhibitors.
gastric acid secretion and, 727
Esophageal adenocarcinoma
endoscopic examination in, 108–109, 109f
epidemiology of, 441, 442f
age, sex, and race distribution and, 442f, 442–443
risk factors and, 443–446
alcohol as, 443
Barrett's esophagus as, 445
diet and nutrition as, 443, 445
gastroesophageal reflux disease as, 445
Helicobacter pylori infection as, 445–446
lower sphincter-relaxing medications as, 445
nonsteroidal anti-inflammatory drugs as, 445
obesity as, 443, 443t, 444f
tobacco as, 443
high-grade dysplasia distinguished from, 359–360
invasive, in Barrett's esophagus, 219, 219f
prevention of, 366–367
resection for, extent of, 475–477
risk of nondysplastic Barrett's esophagus progression to, 365, 366t
Esophageal ampulla, radiographic appearance of, 66–67, 67f
Esophageal anastomosis, for short-segment esophagectomy, 291
Esophageal anatomy, 9–27
of esophageal body, muscular, 16, 17f–19f
of innervation, 23, 25–27
extramural, 25–26, 26f, 27f
intramural, 26
lymphatic, 22–23, 24f
macroscopic, 9–16
abdominal anatomy and, 16
anchorage and
of cardia, 12–14, 14f
of esophageal body, 12, 13f
in neck, 12, 13f
chest anatomy and, 15f, 15–16
of compartments, 11–12
diameter of esophagus and, 10–11
of fascial planes, 11
general aspects of, 9–10, 10f, 11f
length of esophagus and, 10
length of orthotopic bypass and, 10
neck anatomy and, 14–15, 15f
of periesophageal tissue, 11
of sphincters, 17–18, 19f
of tissues, 16f, 16–19
tela submucosa as, 16f, 18
tunica adventitia as, 16, 16f
Esophageal anatomy *(Continued)*
tunica mucosa as, 16f, 18–19
tunica muscularis as, 16f, 16–19, 17f–19f
vascular, 20–22
arterial, 20, 20f, 21f
venous, 20–22, 22f, 23f
Esophageal arteries, 20
Esophageal atresia, 563–571
abnormalities associated with, 564, 565f
classification of, 564, 565f
clinical findings and diagnostic evaluation of, 565, 566f
development and, 563–564
development of, 32–33
historical background of, 563
management of, 565–566
complications of, 569–571, 571f
operative, 566–569, 567f–570f
pure, 568–569, 569f, 570f
Esophageal balloon distention, for esophageal motility disorders, 160–161
Esophageal biopsy, mucosal, 165t
Esophageal body
anatomy of, 16f, 16–17
muscle types and, 17, 19f
muscular arrangement and, 17, 17f–19f
"corkscrew" appearance of, 73, 73f
disorganized contractions of, 138–139
motor disorders of, primary, 135–140, 136b, 137t, 138f–140f
"rosary-bead" appearance of, 73, 73f
swallowing and, 129–132, 132f
Esophageal bolus clearance, tests to evaluate, 154–159
ambulatory esophageal impedance and pH monitoring as, 158–159, 159f, 160f
esophageal transit scintigraphy as, 154–155
impedance testing as, 155–156, 157f, 158, 158f
multichannel intraluminal impedance as, 175–183
combined with manometry, 175–176, 178f, 179, 179f
combined with pH monitoring, 180f–183f, 180–181
principles of, 175, 176f–178f
videocineroentgenography as, 154, 155f, 156f
Esophageal bypass, for strictures, intractable, 544–545
Esophageal cancer, 465–483. *See also specific cancers.*
clinical features of, 446, 468, 469t
diagnosis of, 469
epidemiology of, 441–446, 442f, 466
age, sex, and race distribution and, 442f, 442–443
changing, reasons for, 446
mortality/prognosis and, 441–442
risk factors and, 443–445
alcohol as, 443
Barrett's esophagus as, 445
diet and nutrition as, 443, 445
Esophageal cancer *(Continued)*
gastroesophageal reflux disease as, 445
Helicobacter pylori infection as, 445–446
lower sphincter-relaxing medications as, 445
nonsteroidal anti-inflammatory drugs as, 445
obesity as, 443, 443t, 444f
tobacco as, 443
esophageal perforation associated with, 538
etiology of, 466t, 466–467
of adenocarcinoma, 467
of squamous cell carcinoma, 466
evaluation of, 74–81, 469–472
barium esophagography in, 469, 469f
bronchoscopy in, 471
chest radiography in, 469
computed tomography in, 471
endoscopic, 108–109, 109f
endoscopic ultrasonography in, 470f, 470–471
for metastasis detection, 471–472
minimally invasive surgery for staging and, 472
radiologic appearance and, 74–76, 75f–79f
for recurrent esophageal cancer assessment, 79, 81
for staging, 76–78
for treatment evaluation, 79
upper gastrointestinal endoscopy in, 469–470
historical background of, 465–466
localized, en bloc esophagectomy for, 477–478
management of, 474–483
multimodality treatment of, 499–510
chemoradiation in, 505–508
definitive therapy using, 505t, 505–506
preoperative, 506–508, 507t
chemotherapy in, 502–505
postoperative, 504t, 504–505
preoperative, 502–504, 503t
meta-analyses of, 508–509
of postoperative chemoradiation, 509
radiation therapy in, 499–502
postoperative, 501t, 501–502
preoperative, 499–501, 500t
rationale for, 499
neoadjuvant therapy for, 482–483
new treatment modalities for, 509–510
cyclooxygenase-2 inhibitors as, 509–510
epidermal growth factor receptors as, 510
tumor necrosis factor as, 510
palliative treatment of, 487–498
endoscopic methods for, 488–493
alcohol sclerotherapy as, 488, 489t
bougienage as, 488–489, 489t
esophageal prostheses as, 489t, 489–492

Esophageal cancer *(Continued)*
photodynamic, 489t, 493
thermal, 489t, 492–493
oncologic management in, 493–497
chemoradiation for, 495
chemotherapy for, 495–496
options for, 493
with prominent local symptoms, 496, 496f
radiotherapy for, 493–495
with systemic symptoms, 496–497
patient assessment for, 487–488, 488b, 489t
surgical, 497
for terminal patients, 497
upper gastrointestinal clinical nurse specialist's role in, 497–498
pathology of, 467b, 467–468
of adenocarcinoma, 468, 468f
of squamous cell carcinoma, 467–468, 468f
patient approach for, 61, 61f
recurrent, assessment of, 79, 81
squamous cell, association with achalasia, 409
stage-directed treatment of, 461–462
staging methods for, 455–461
barium contrast study as, 455, 456f
bronchoscopy as, 456
computed tomography as, 457, 457f
endoscopic examination as, 455–456
endoscopic ultrasonography as, 457–459, 458f
laparoscopy as, 460
minimally invasive surgery as, 472
percutaneous ultrasonography as, 457
positron-emission tomography as, 459f, 459–460
therapy monitoring and, 460–461
thoracoscopy as, 460
staging systems for, 448–455, 472–474
anatomic subsites and, 448–449, 449f
cancer around gastroesophageal junction and, 450–451, 452f
choice of, 451–455
inadequacies in, 473–474, 474t
nodal metastases and (N stage), 449b, 449–450, 450t, 451f, 452f, 453t–455t
TNM, 472t, 472–473, 473t
TNM residual tumor classification and, 455
tumor infiltration depth and (T stage), 449
surgical treatment of, 475–482
complications of, 480t, 480–481
extent of resection for early adenocarcinoma and, 475–477
extent of resection for localized cancer and, 477t, 477–478
historical background of, 3–5
patient assessment for, 475, 476f
postoperative care for, 480
reconstruction and, 478–479
results with, 481t, 481–482
transhiatal esophagectomy as, 479–480
Esophageal cancer *(Continued)*
TNM classification of, endoscopic ultrasonography for, 116–122, 117b
in clinical state, 117–121, 118f–122f
in re-treatment stage, 121–122
Esophageal claudication, 138–139
Esophageal clearance, evaluation of, barium examination for, 68
Esophageal compression, vascular, 573–574, 574f
Esophageal contraction abnormalities, tests to detect, 143–154
ambulatory 24-hour esophageal manometry as, 152–154
stationary esophageal manometry as, 144–146, 145f–155f, 145t, 150, 152
Esophageal cysts, 524b, 524–525, 525f
Esophageal dilatation
for caustic ingestions, 544
for esophageal strictures, 237, 238f, 239f, 240
fistulas due to, 1095
Esophageal disorders. *See also specific conditions.*
Barrett's esophagus as. *See* Barrett's esophagus.
benign, end-stage
clinical manifestations of, 286b, 286t, 286–287, 287t
esophageal replacement for. *See* Esophageal replacement, for end-stage benign esophageal disease.
congenital, 563–574. *See also specific disorders.*
embryology and anatomic considerations in, 563, 564f
delayed gastric emptying in, 185–190
antroduodenal manometry and, 186–188, 188f, 188t, 189f, 190, 190t
barium burger studies and, 190
^{13}C breathing test for, 185–186
gastric emptying scintigraphy and, 185, 186f, 187f
duodenum in, physiologic and pathophysiologic aspects of, 184–185
gastric function tests in, 184–195
malignant. *See* Esophageal cancer.
motor. *See* Dysphagia; Esophageal dysmotility.
reflux as. *See* Gastroesophageal reflux disease.
stomach in, physiologic and pathophysiologic aspects of, 184–185
symptoms of, 56–57, 57b
mechanisms of, 57–58, 58f
Esophageal diverticula, surgery for, early development of, 5–6
Esophageal duplication cysts, 570–572
evaluation of, 572, 572f
imaging of, 82–83
treatment of, 572, 573f
Esophageal duplications, 524b, 524–525, 525f
Esophageal dysmotility, 134–161. *See also specific disorders.*
barium examination for, 68
Esophageal dysmotility *(Continued)*
esophageal perforation associated with, 538
imaging in, 71–74
nonspecific, 71, 74
partial fundoplication for, 278
pathophysiology of, 134–142
gastroesophageal reflux disease and, 140–142, 141f
obesity and, 142, 142t
of pharyngoesophageal swallowing disorders, 134–135, 135f, 136f
of primary disorders of esophageal body and lower esophageal sphincter, 135–140, 136b, 137t, 138f–140f
of secondary disorders, 140
patient approach for, 61
primary. *See also* Achalasia; Diffuse esophageal spasm; Nutcracker esophagus.
imaging in, 71–74, 72f, 73f
secondary, imaging in, 74
surgery for, early development of, 5
symptoms of, 71
tests for assessment of, 142–161
for esophageal bolus clearance evaluation, 154–159
ambulatory esophageal impedance and pH monitoring as, 158–159, 159f, 160f
esophageal transit scintigraphy as, 154–155
impedance as, 155–156, 157f, 158, 158f
videocineroentgenography as, 154, 155f, 156f
for esophageal contraction abnormality detection, 143–154
ambulatory 24-hour esophageal manometry as, 152–154
stationary esophageal manometry as, 144–146, 145f–155f, 145t, 150, 152
for esophageal structural abnormality detection, 143
esophageal symptom provocation, 159–161
acid perfusion test as, 159–160
edrophonium test as, 160
esophageal balloon distention as, 160–161
for increased esophageal exposure to gastric and duodenal juice detection, 24-hour esophageal pH monitoring as, 161
Esophageal epithelium
columnar
ciliated, prenatal development of, 40–41, 41f
detection of, barium examination for, 69, 70f
squamous, stratified, prenatal development of, 41
vacuolization of, 39–40, 40f
Esophageal impedance, measurement of, in esophageal disease, 195

Esophageal injury, detection of, barium examination for, 68–69, 69f, 70f
Esophageal leiomyosarcoma, imaging in, 81
Esophageal lumen, prenatal development of, 42, 43f
Esophageal lymphoma, imaging in, 81
Esophageal manometry
combined with multichannel intraluminal impedance, 175–176, 178f, 179, 179f
24-hour
ambulatory, 152–154
stationary, 144–146, 145f–155f, 145t, 150, 152
Esophageal melanoma, imaging in, 81
Esophageal motility
disorders of. *See* Esophageal dysmotility.
physiology of, 128–134
esophageal body and, 129–132, 132f
lower esophageal high-pressure zone and, 132–134, 133f
upper esophageal sphincter and, 129, 129f–131f
preoperative studies of, for Nissen fundoplication, 266
Esophageal mucosal injury, duodenal reflux and, 230–232
animal studies of, 230
human studies of, 230–231
mechanism of, 231–232
Esophageal neoplasms. *See also specific neoplasms.*
benign, 513–522
classification of, 514b, 514–515
endoscopic ultrasonography in, 122–123, 123t
historical background of, 514
imaging of, 81–83, 83f
incidence of, 513
intraluminal/mucosal, 522–524
fibrovascular polyps as, 522–523, 523t
squamous papillomas as, 523–524, 524f
intramural/extramucosal
congenital ectopic rests as, 522
gastrointestinal stromal tumor as, 520
granular cell, 520–521, 521f
hemangioma as, 521–522
inflammatory pseudotumors as, 522
leiomyoma as, 515–520, 516f–519f, 516t, 518t
lipomas as, 522
mesenchymal, 515t, 515–520
rhabdomyomas as, 522
schwannoma as, 520
surgical treatment of, 514
symptoms of, 513–514
Esophageal obstruction
following fundoplication, 85
following gastric banding, 935
Esophageal perforation, 528–538
clinical findings in, 529–531, 530f
diagnosis of, 531, 531f, 532f
with dilatation, 240f, 240–241
management of, 532–537, 533f
Esophageal perforation *(Continued)*
with dysmotility, 532–537, 533f
with esophageal cancer, 532–537, 533f
in esophageal disease, 537–538
with esophageal strictures, intractable, 532–537, 533f
during esophageal surgery, 600f, 600–602, 601b
diagnosis of, 601, 602f
treatment of, 601–602, 603f–605f
etiology of, 528–529, 529t
with gastroesophageal reflux, end-stage, 532–537, 533f
with Heller myotomy, 417
historical background of, 528
imaging of, 91, 93–94, 95f
management of, 532–537, 533f
after dilation therapy for achalasia, 532–537, 533f
nonoperative, 532
surgical
of cervical perforation, 533
of intrathoracic and intra-abdominal perforations, 533–537
with Nissen fundoplication, 273
operative, 1094
spontaneous (Boerhaave's syndrome), 91, 93
Esophageal pH monitoring. *See* pH monitoring, esophageal.
Esophageal propulsive force, 53
Esophageal prostheses, for esophageal cancer, 489–492
Esophageal reconstruction, 578–597
conduits for, 249, 578–579
guidelines for choosing, 581
studies useful for decision making about, 581–582
for esophageal strictures, 248–249, 249f
esophagocoloplasty for, 588b, 588–592
operative technique for, 589–591
abdominal team and, 589–591, 590f
cervical team and, 591
postoperative care for, 591
preoperative preparation for, 589
results with, 591t, 591–592, 592t
esophagogastrostomy for, 582–588
anastomosis for, 586–587, 587f, 588
drainage of stomach for, 584–585, 585f
functional results with, 588
lengthening of stomach for, 584, 584f
mobilization of stomach for, 582–584, 583f
transposition of stomach for, 585, 586f
esophagojejunoplasty for, 592–596
free transfer and, 595f, 595–596
interposition and, 593f, 593–594, 594f
results of, 596t, 596–597
Roux-en-Y limb and, 594f, 594–595
for esophageal cancer, 478–479
historical background of, 578
incision placement for, 579–580, 580f
Esophageal reconstruction *(Continued)*
level of anastomosis for, 580–581
route of replacement for, 580
short-segment colon interposition for, 596–597
results of, 596t, 596–597
Esophageal replacement
for end-stage benign esophageal disease, 285–304, 286b
clinical manifestations of disease and, 286b, 286t, 286–287, 287t
conduits for, 289, 289b, 289f, 296–299, 297f–300f
esophagectomy as primary therapy and, 299, 301b, 301–302, 302t
long- vs. short-segment esophagectomy for, 289–291, 290f
operative approach for esophagectomy and foregut reconstruction for, 291–294, 292f–294f
preoperative evaluation for, 287–289, 288f
proximal gastrectomy or gastric bypass for, 302–304, 303f
vagal-sparing vs. standard esophagectomy for, 294f, 294–296, 295f
substernal, complications of, 615, 616f
Esophageal resection
for esophageal cancer. *See* Esophageal cancer, surgical treatment of.
esophageal imaging following, 86, 87f, 88f
for esophageal strictures, 248–249, 249f
for leiomyoma, 519f, 519–520
for strictures, intractable, 544–545
with visceral esophageal substitution, complications of, 611–618
anastomotic leak as, 611–613, 612f
anastomotic stricture as, 613
of bypassing or excluding native esophagus, 616, 617f, 618
chylothorax as, 614–615
diaphragmatic hiatal obstruction or herniation as, 614, 615f
gastric outlet obstruction as, 613–614, 614f
pancreatitis as, 615
peripheral atheroembolism as, 615
pulmonary, 613
splenic injury as, 615
of substernal esophageal replacement, 615, 616f
Esophageal rings, imaging of, 88f, 88–89, 90f, 91f
Esophageal shortening
evaluation of, barium examination for, 70, 71f
with paraesophageal hernia, 558–559
Esophageal spasm
diffuse and segmental, 419–421
examinations in, 419–421
historical background of, 419
treatment of, 421
esophagomyotomy for, complications of, 619–620

Esophageal squamous cell carcinoma, epidemiology of
age, sex, and race distribution and, 443
risk factors and, 443–445
alcohol as, 443
diet and nutrition as, 443, 445
nonsteroidal anti-inflammatory drugs as, 445
obesity as, 443, 443t, 444f
tobacco as, 443
Esophageal squamous epithelium
acid-induced damage to, 210–212, 211f
cardiac mucosa and, 213f, 213–215, 215f
columnar transformation in, 212, 212f, 230
normal appearance of, 208–210, 209f, 210b, 210f
Esophageal stenosis, congenital, 572–573
esophageal strictures in, 90, 90f
Esophageal strictures
anastomotic, following esophageal resection, 86, 88f
in caustic ingestions, development of, 541
in cicatricial pemphigoid, 89, 92f
in congenital esophageal stenosis, 90, 90f
detection of, barium examination for, 69, 69f
in eosinophilic esophagitis, 90, 93f
in epidermolysis bullosa, 89
gastroesophageal reflux causing, 234–249
anatomic variation of, 235, 235f, 236f
classification of, 236–237
evaluation of, 235–236, 236f, 237
medical therapy for, 256–257
short esophagus and, 234. *See also* Short esophagus.
treatment of, 237–249
antireflux surgery with intraoperative stricture dilatation for, 241–248
esophageal resection and reconstruction for, 248–249, 249f
nonoperative, 237, 238f–240f, 240–241
imaging of, 89–91, 92f–94f
intractable
with caustic ingestions, management of, 544–545
esophageal perforation associated with, 538
in lichen planus, 89–90, 92f
midesophageal, 90, 93f
nasogastric intubation causing, 90
oropharyngeal, 546f, 546–547
recurrence of, 241
Esophageal stripping, transhiatal, vagal-sparing, for Barrett's esophagus, 362–363
Esophageal surgeons, 7–8
Esophageal surgery. *See also specific procedures.*
complications of, 598–620
anatomic and physiologic considerations in, 598–599, 599f, 600f
Esophageal surgery *(Continued)*
of esophageal diverticulectomy, 618f, 618–619, 619f
esophageal perforation as, 600f, 600–602, 601b
diagnosis of, 601, 602f
treatment of, 601–602, 603f–605f
of esophageal resection and visceral esophageal substitution, 611–618
of esophagomyotomy, 619–620
of esophagoscopy, 598, 602–604, 606, 606f
of hiatal hernia repair, 606b, 606–607, 607f, 608f, 609–610, 610f
of laparoscopic antireflux/hiatal hernia surgery, 610–611
historical background of, 3–8
Esophageal transit scintigraphy, 154–155
Esophageal varices
bleeding, 1755, 1758–1763
acute, 1759, 1759f, 1760f
in cirrhosis, 1693
decompression for, 1761–1763
distant splenorenal shunt for, 1752f, 1762
surgical stents for, 1762
transjugular intrahepatic portocaval shunt procedures for, 1693, 1761f, 1761–1762
prophylaxis of, 1758f, 1758–1759
recurrent, prevention of, 1759–1760, 1760f
treatment of, 1624, 1624t
decompression for, 1761–1763
devascularization procedures for, 1763
primary therapy for, 1760–1761
"downhill," 95, 97f
endoscopic ultrasonography in, 124, 125f
imaging of, 95, 97f
in pancreatitis, chronic, 1352–1353
"uphill," 95, 97f
Esophageal wall, anatomy of, ultrasound, 114–116, 115f, 116f
Esophageal webs
cervical, imaging of, 89, 91f
esophageal imaging of, 88f, 88–89, 90f, 91f
Esophagectomy
for Barrett's esophagus, 362
mortality and, 363
cervical, esophagogastric anastomotic strictures following, 292, 292f
complications of, 480t, 480–481
atheroembolism as, 615
chylothorax as, 614
pancreatitis as, 615
splenic injury as, 615
conduit for, route of passage for, 292–294, 293f, 294f
early development of, 4
en bloc, for localized esophageal cancer, 477–478
for esophageal cancer, results with, 481–482
for esophageal perforation, 536, 536f
Esophagectomy *(Continued)*
for esophageal strictures, 248–249, 249f
for foregut reconstruction for benign disease
long- vs. short-segment, 289–291, 290f
operative approach to, 291–294, 292f–294f
as primary therapy, 299, 301b, 301–302, 302t
vagal-sparing, 294f, 294–296, 295f
gastroparesis following, 923
imaging following, 86
operative approach to, for foregut reconstruction for benign disease, 291–294, 292f–294f
partial, incision for, 579
postoperative care for, 480
short-segment
advantages of, 290
clinical experience with, 291, 291t
esophageal anastomosis with, 291
gastroesophageal reflux following, 290
limitations of, 290–291
thoracic, total, with cervical esophagogastric anastomosis, 249
transhiatal, 291–292, 292f, 479–480, 579–580, 580f
technique of, 479–480
vagal-sparing, 249, 249f
for adenocarcinoma, 477
for foregut reconstruction for benign disease, 294f, 294–296, 295f
with vein stripper, for caustic ingestions, 544
Esophagitis
achalasia and, 409
caustic, imaging in, 91
classification of, 236
detection of, barium examination for, 69, 69f
eosinophilic, esophageal strictures in, 90, 93f
erosive
natural history of gastroesophageal reflux disease and, 202
prevention prevalence of, 199–200, 200t
in gastroesophageal reflux disease, medical therapy for, 255–256, 256f
Esophagocoloplasty, 588b, 588–592
operative technique for, 589–591
abdominal team and, 589–591, 590f
cervical team and, 591
postoperative care for, 591
preoperative preparation for, 589
results with, 591t, 591–592, 592t
Esophagogastric anastomosis
cervical, for esophageal structure, 249
early development of, 4
intrathoracic, for esophageal structure, 249
Esophagogastric junction, wall structure at, 16f
Esophagogastroduodenoscopy, 165t
for aortoenteric fistulas, 1271
esophageal perforation due to, 529

Esophagogastrostomy, 582–588
anastomosis for, 586–587, 587f, 588
drainage of stomach for, 584–585, 585f
functional results with, 588
imaging following, 86, 87f
intrathoracic
for Barrett's esophagus, 362
early development of, 4
lengthening of stomach for, 584, 584f
mobilization of stomach for, 582–584, 583f
transposition of stomach for, 585, 586f
Esophagography
in achalasia, 407
barium, 164, 165t
in esophageal carcinoma, 469, 469f
for esophageal reconstruction, 582
in esophageal perforation, 93, 95f
postoperative, 83–86
contrast materials for, 84, 84t
following antireflux procedures, 85, 86f
following cardiomyotomy, 85, 86f
following cricopharyngeal myotomy, 84–85, 85f
Esophagojejunoplasty, 592–596
free transfer and, 595f, 595–596
interposition and, 593f, 593–594, 594f
results of, 596t, 596–597
Roux-en-Y limb and, 594f, 594–595
Esophagomyotomy
for achalasia or esophageal spasm, complications of, 619–620
concomitant antireflux procedure with, controversy about, 620
with diverticulectomy, for epiphrenic diverticulum, 434f, 435
Esophagoscopy
barium, with leiomyoma, 517, 517f
complications of, 598, 602–604, 606, 606f
esophageal perforation as, 602–604, 606, 606f
in esophageal perforation, 531, 532f, 601, 602f
with gastric tumors, in pediatric patients, 959, 959f
stricture dilation using, 237, 240, 240f
Esophagus
body of, anchorage of, 12, 13f
caustic injury of. *See* Caustic ingestions.
columnar-lined. *See* Barrett's esophagus.
compression of, with paraesophageal hernia, 551–552
"corkscrew," 419, 420f
Crohn's disease involving, 91, 94f
diameter of, 10–11
endoscopic examination of. *See* Endoscopic examination, esophageal.
exposure to gastric juice, increased, causes of, 141f, 141–142
feline, radiographic appearance of, 67, 67f
function of, 63
imaging of. *See* Imaging, esophageal; *specific imaging modalities.*
Esophagus *(Continued)*
irradiation of, esophageal carcinoma and, 466
length of, 10
metastatic disease to, imaging in, 81, 82f
minor deviations along, 9–10, 10f
native, bypassing or excluding, complications of, 616, 617f, 618
nutcracker, 74, 421–423
examinations in, 422f, 422–423, 423f
manometric features of, 420t, 422f, 422–423, 423f
treatment of, 423
rosary-bead, 419, 420f
scarring of, detection of, barium examination for, 69, 70f
segmental narrowing of, barium examination for, 69
sigmoid shaped, Heller myotomy with, 416
structural abnormalities of, tests to detect, 143
submucosa of, benign tumors of, endoscopic ultrasonography in, 123
swallowing and. *See* Swallowing.
tears of, hiatal herniorrhaphy and, 607, 607f, 608f
"trachealization" of, 90, 93f
Estrogens
hepatotoxicity of, 1722, 1723
synthetic, hepatotoxicity of, 1721
Etanercept, for inflammatory bowel disease, 2093
Ethanol injection
for esophageal cancer, 488, 489t
percutaneous, for hepatocellular carcinoma, 1737, 1738
Ethnicity
Barrett's esophagus and, 342–343
esophageal cancer and, 442–443
Etoposide, hepatotoxicity of, 1723
Etretinate, hepatotoxicity of, 1721, 1722
Evans's syndrome, splenectomy for, 1827
External oblique muscle, anatomy of, 636, 637f
Extracellular matrix, groin hernias and, 635
Extracorporeal liver assist device, 1706
Extracorporeal shock-wave lithotripsy
for bile duct stones, 1494, 1495
for pancreatic duct stones, 1510–1511
Extrahepatic portal hypertension, in pancreatitis, chronic, 1312–1313

F

Falciform ligament, 1598
Familial adenomatous polyposis, 2159t, 2159–2169
attenuated, 2168
small intestinal, 894t, 896
clinical features of, 2159–2160, 2160f
as colorectal cancer risk factor, 2187f, 2187–2188
diagnosis of, 2164
extracolonic manifestations of, 2160–2163
desmoids as, 2161–2162
Familial adenomatous polyposis *(Continued)*
upper gastrointestinal neoplasia as, 2162t, 2162–2163
genetic testing and counseling for, 2164–2165
genetics of, 2163–2164
APC gene and, 2163
APG genotype-FAP phenotype correlation and, 2163f, 2163–2164
MYH polyposis and, 2168–2169
small intestinal, 893f, 893–895, 894t
symptoms and diagnosis of, 894–895
treatment of, 895
surgical management of, 2165–2168
issues modifying, 2167–2168
restorative proctocolectomy for, 2335
surgical options for, 2165t, 2165–2167, 2166t
Famotidine, 255. *See also* Histamine$_2$ receptor antagonists.
gastric acid secretion and, 727
for gastroesophageal reflux disease, 254
Fascial planes, esophageal, anatomy of, 11
FAST. *See* Focused abdominal sonography for trauma.
"Fat wrapping," in Crohn's disease, 1058, 1058f
Fatigue
in Crohn's disease, 1045
with primary sclerosing cholangitis, 1566
Fatty liver
nonalcoholic, hepatic laboratory tests in, 1612–1613
of pregnancy, acute, 1703
Fecal continence. *See also* Fecal incontinence.
following surgery for anorectal anomalies, 2404
pelvic muscular anatomy and, 2391–2394
Fecal diversion
for fecal incontinence, 1926
for rectovaginal fistulas, 1954
Fecal fistulas, with appendicitis, 2150
Fecal incontinence, 1885, 1917–1926
after anorectal surgery, 2057
endoanal ultrasound in, 1910–1911, 1911f
evaluation of, 1917–1921, 1918b
history in, 1917–1918
laboratory assessment in, 1919–1921
benefits and limitations of, 1920–1921
defecography for, 1920
endoanal ultrasound for, 1920, 1920f
manometry for, 1919
pudendal nerve terminal motor latency for, 1919–1920
physical examination in, 1918–1919
examination for, 1888
following surgery for anorectal anomalies, treatment of, 2405
treatment of, 1921–1926
biofeedback for, 1921–1922
following surgery for anorectal anomalies, 2405

Fecal incontinence *(Continued)*
medical, 1921
surgical, 1922–1926
artificial anal sphincter and, 1924, 1924f
dynamic myoplasty as, 1923–1924
fecal diversion as, 1926
injectable biomaterials and, 1925–1926
sacral nerve stimulation and, 1925, 1925f
salvage therapy as, 1923
sphincter reconstruction as, 1922f, 1922–1923
Fecal occult blood testing, 1888–1889
Fecal urgency, 1885
examination for, 1888
Feces, pruritus ani due to, 2066–2067
Feline esophagus, radiographic appearance of, 67, 67f
Felty's syndrome, splenectomy for, 1827
Females
anorectal anomalies in, 2394, 2394f
initial management of newborn with, 2394–2395
fertility in, following ileal pouch–anal anastomosis, 2117, 2167–2168
groin hernias in, 643
low anterior resection in, 2228, 2228f
pregnancy and
acute fatty liver of, 1703
appendicitis during, 2144
gastroesophageal reflux disease and, 200
young, appendicitis in, 2144
Femoral hernias, 623–630, 643, 644
anatomy and, 623, 624f, 625f
in children, 712
diagnosis of, 626
etiology of, 626
historical background of, 623–626
treatment of, 626–629, 627f–629f
femoral approach for, 626–627, 627f
inguinal approach for, 624–625, 627, 627f, 628f
laparoscopic approach for, 625–626, 628–629, 629f
preperitoneal approach for, 625, 627–628, 628f
results with, 629, 629t
Femoral nerve, 657, 658f
Ferguson hemorrhoidectomy, 2033
Fertility, female, following ileal pouch–anal anastomosis, 2117, 2167–2168
Fever, in Crohn's disease, 1045
Fibrin glue
for anorectal fistulas, 2056–2057
autologous, for rectovaginal fistulas, 1952
for bowel anastomoses, 1089
Fibroid polyps, inflammatory, gastric, 884
Fibromas
esophageal, endoscopic ultrasonography in, 123
gastric, 887–888, 888
small intestinal, 901
Fibromuscular hypertrophy, idiopathic, 572
Fibromuscular stenosis, idiopathic, 572
Fibrosarcomas, hepatic, 1747, 1747f
Fibrosis, drug-induced, 1719t, 1720–1721
Fibrovascular polyps, esophageal, 522–523, 523t
Fine-needle aspiration
endoscopic ultrasonography, in bronchogenic carcinoma, 125
with pancreatic cystic neoplasms, 1396
with pancreatic tumors, unusual, 1432
Finney pyloroplasty, 5, 816, 818, 819f
for duodenal ulcers, 795
technique for, 842f
Finney stricturoplasty, for Crohn's disease, 1059, 1061f
Fissure-in-ano. *See* Anal fissures.
Fistulas, 1092–1117
anal. *See* Anal fistulas.
anovaginal, 1946
aortoduodenal, 1095
aortoenteric. *See* Aortoenteric fistulas.
biliary. *See* Biliary fistulas.
colocutaneous, in colonic diverticular disease, 2018
colovesical, in colonic diverticular disease, 2017–2018, 2018f
complications of, 1097–1098
in Crohn's disease, 1063–1065, 1094
enterocutaneous, 1065
enteroenteric, 1064
enterogenital, 1065
enterovesical and enteroureteral, 1064
ileosigmoid, 1064
treatment of, 1104–1105, 2135–2136, 2137f–2138f
diagnosis of, 1097
duodenal
with duodenal injuries, 768, 770
etiology of, 1093–1096
treatment of, 1110
duodenal stump, treatment of, 1110
duodenocolic, in Crohn's disease, 1094
duodenocutaneous, in Crohn's disease, 1094
enterocervical, treatment of, 1114
enterocutaneous
in Crohn's disease, 1065
failure to close spontaneously, 1108
following ileal pouch–anal anastomosis, 2112
small intestinal, 1096
treatment of, 1110–1111
enteroenteric
in Crohn's disease, 1064
treatment of, 1111f, 1111–1112
enterofallopian, treatment of, 1114
enterogenital, in Crohn's disease, 1065
enteroureteral, in Crohn's disease, 1064
enterouterine, treatment of, 1114
enterovaginal, treatment of, 1113–1114
enterovesical, treatment of, 1112f, 1112–1113, 1115
etiology of, 1093–1097
of gastric and duodenal fistulas, 1093–1096
of small intestinal fistulas, 1096–1097
fecal, with appendicitis, 2150
gastric, etiology of, 1093–1096
Fistulas *(Continued)*
gastrocolic, in Crohn's disease, 1094
gastroduodenal, treatment of, 1110
gastrojejunocolic, internal, 1094
ileosigmoid, in Crohn's disease, 1064
intestinal. *See also* Enteric fistulas; *specific sites, e.g.* Anal fistulas.
in Crohn's disease, surgical treatment of, 2095
intra-abdominal, in colonic diverticular disease, 2021
management of, 1098–1117
definitive therapy for, 1108–1117
for aortoenteric fistulas, 1114–1115, 1115f
for enterocervical fistulas, 1114
for enterocutaneous fistulas, 1110–1111
for enteroenteric fistulas, 1111f, 1111–1112
for enterofallopian fistulas, 1114
for enterouterine fistulas, 1114
for enterovaginal fistulas, 1113–1114
for enterovesical fistulas, 1112f, 1112–1113
for gastric and duodenal perforations and fistulas, 1108–1110
general considerations for, 1115–1117, 1116f
healing and, 1117
for nephroenteric fistulas, 1113
investigation in, 1105f, 1105–1106, 1107f
stabilization for, 1099–1105
control of sepsis and, 1101–1103, 1103f, 1104f
nutrition and, 1100–1101
pharmacologic support and, 1103–1105
resuscitation and, 1099–1100
treatment decisions and, 1107–1108
nephroenteric, treatment of, 1113
pancreatic
external, 1352
internal, in pancreatitis, chronic, 1311
management of, 1307–1308
pancreatic drainage procedures for, 1511f, 1511–1513, 1512f
with trauma, 1404
paraprosthetic-enteric, 1114
peri-ileostomy, 1080–1081
pouch-vaginal, following ileal pouch–anal anastomosis, 2112–2113, 2114f
rectourethral, 1954–1955
meconium in urine and, 2394, 2394f
rectovaginal. *See* Rectovaginal fistulas.
renogastric, 1095
small intestinal, 1096
congenital, 1096
infection causing, 1096
inflammatory causes of, 1096–1097
intestinal, of small intestine, 1097
radiation-induced, 1097
traumatic, 1096
tumors causing, 1097

Fistulas *(Continued)*
staging/classification of, 1097
tracheoesophageal, 15
following esophageal resection with visceral esophageal substitution, 613
radiographic appearance of, 76, 78f
Fistulography, 1105f, 1105–1106
with anorectal fistulas, 2049
with biliary fistulas, 1542
contrast, 1893
Fistulotomy
for anorectal abscesses, primary versus delayed, 2054–2055
for anorectal fistulas, 2055
radiofrequency, 2055
for rectovaginal fistulas, 1952
FK506
for inflammatory bowel disease, 2092
for islet transplantation, 1424
mechanism of action of, 2377t
Floating gallbladder, 1450, 1453f
Fluconazole, hepatotoxicity of, 1722
Fluid and electrolyte abnormalities
in biliary tract disease, 1620
in cirrhosis, 1625
with gastrointestinal fistulas, 1098
in liver disease, 1620
Fluid and electrolyte therapy, for pancreatitis
acute, mild, 1302
severe, necrotizing, 1303
Fluid and electrolyte transport, colonic, 1872
Fluid management, in fulminant hepatic failure, 1704
Fluoroscopic wire basket stone retrieval, 1484
5-Fluorouracil
for anal intraepithelial neoplasia, 2290
for metastatic colorectal cancer, 2201, 2202
Focal nodular hyperplasia, 1728–1729
diagnosis of, 1728, 1728f
drug-induced, 1723
etiology of, 1728
treatment of, 1728–1729
Focused abdominal sonography for trauma
in abdominal trauma, in pediatric patients, 1807
in colorectal trauma, 1974–1975
in gastric blunt trauma, 762
in pancreatic trauma, 1401
in small bowel injury, 772
in splenic trauma, 1799
Folate/folic acid
deficiency of, in Crohn's disease, 1054
small intestinal absorption of, 1006, 1007t
Follicular lymphoma, pathology of, 1204
Fontolizumab, mechanism of action of, 2377t
Foods. *See also* Diet; Nutrition.
phytobezoars and, 943, 944, 944t
Foramen of Bochdalek, 36
Foramen of Morgagni, 36–37
Foramen of Winslow, 964, 966f
hernias of, 975, 976, 977f, 1123–1124, 1124f
Foregut. *See also* Esophagus.
cranial segment of
malformations of, 32–33
prenatal development of, 31–33, 33f, 34f
intermediate segment of, prenatal development of, 33–34
prenatal development of, 29t, 29–31
basic tissue and organ development and, 30, 30f, 31f
of cardia, 34f–36f, 34–35
congenital anomalies and. *See* Congenital disorders; *specific anomalies.*
congenital malformations and anomalies and, 30
crown-rump length and, 29
of duodenum, 34f–36f, 34–35
of esophagus, 33–34
of hypopharynx, 31–33, 33f, 34f
intraembryonic body cavity development and, 31
of larynx, 31–33, 33f, 34f
of mediastinum, 35–37, 37f
mesenchymal clefts and, 31
of nervous system, 43–46
of pharynx, 31–33, 33f, 34f
of phrenoesophageal membrane, 36, 36f
of primitive digestive system, 31, 32f
of research system, 31–33, 33f, 34f
of stomach, 34f–36f, 34–35
tissue organization and, 37–46
lamina mucosa, submucosa, and esophageal lumen formation and, 37, 39t, 39–42
muscular, 37, 38f
of trachea, 34f, 35, 39f
vascular, 42–43, 43f, 44f
Foreign body ingestion, 940–945
bezoars and, 943–945, 944t
diagnosis of, 944f, 944–945, 945f
signs and symptoms of, 944
treatment of, 945
diagnosis of, 940–941
duodenal injury due to, 1095
management of, 941–943
for button batteries, 942–943
for illicit drugs, 943, 943f
for sharp/pointed or long foreign bodies, 941–942, 942f
FortaGen, for ventral herniorrhaphy, 676
Fowler-Stevens procedure, 711
Fowler-Weir-Mitchel incision, for appendectomy, 2145, 2146f
Fox's sign, 1299
Frantz tumors, in pediatric patients, 1411
Free perforation, in Crohn's disease, 1066
"French hernia," 688
Frey procedure
Hamburg modification of, for pancreatitis, chronic, 1315
in pediatric patients, 1410
"Frozen" abdomen, 1148
FTY720, for islet transplantation, 1428
Fulminant hepatic failure, 1702. *See also* Liver failure, acute.
Fundic gland polyps (fundic glandular cysts; fundic hyperplasia), 884, 2162
Fundic gland-type polyps, endoscopic appearance of, 740, 741f
Fundoplication
Belsey, for esophageal strictures, 241–242
Dor, 276, 277f
for achalasia, 416
for esophageal perforation, 417
laparoscopic
for epiphrenic diverticulum, 435–437, 437f
surgical technique for, 282
results with, 283
laparoscopic
for esophageal strictures, 245, 247, 247f
gastric perforation due to, 1094
Nissen. *See* Nissen fundoplication.
Toupet. *See* Toupet fundoplication.
Watson, 276, 277f, 278
Fungal infections, splenic abscess due to, 1820
Furosemide, for ascites, 1764–1765
Fuykwan procedure, for rectal prolapse, 1961, 1961f, 1964t

G

Galen, 632, 1771, 1813
Gallbladder
agenesis of, 1450
anatomy and embryology of, 1443f, 1443–1444, 1444f
anomalies of, 1448–1451, 1449b
bilobed, 1449, 1451f
diverticulum of, 1449–1450, 1451f
duplication of, 1450, 1452f
floating, 1450, 1453f
function of, 1455–1458
hourglass, 1449, 1451f
injury of, 1663, 1667
intrahepatic, 1450–1451, 1453f
left-sided, 1451
motility of, 1458
retrodisplaced, 1451
rudimentary, 1450
transverse, 1451
Gallbladder cancer, 1519–1526
adjuvant therapy for, 1524
anatomy of, 1520
diagnosis of, 1520–1521, 1521f
epidemiology of, 1519–1520
palliation for, 1524
pathology of, 1520
practical management of, 1524–1525
for cancer diagnosed incidentally after laparoscopic cholecystectomy, 1525
for cancer presenting as gallbladder mass, 1525
for cancer presenting with obstructive jaundice, 1525
for preoperatively diagnosed radiographically suspicious gallbladder polyps, 1524–1525

Gallbladder cancer *(Continued)*
staging of, 1521, 1522t
surgical treatment of, 1521, 1522f, 1523–1524
technique for, 1525–1526
Gallbladder neoplasms
benign, 1519
malignant. *See* Gallbladder cancer.
Gallbladder polyps
with primary sclerosing cholangitis, 1565
treatment of, 1567
radiographically suspicious, preoperatively diagnosed, 1524–1525
Gallstone(s). *See* Cholelithiasis.
Gallstone pancreatitis, 1298
acute, treatment of, 1497–1499
Ganciclovir, for cytomegalovirus infection, in immunocompromised patients, 2382
Ganglia, of gallbladder, 1444
Ganglioneuromas
gastric, 887–888
small intestinal, 900
Gant-Miwa procedure, for solitary rectal ulcer syndrome, 2076
Gardner's syndrome, 2160
small intestinal, 894t, 895
Garengeot, Rene Jacques Croissant de, 688
Gas embolism, with inguinal herniorrhaphy, laparoscopic, 666
Gastrectomy. *See also* Gastric resection and reconstruction.
for caustic injury, gastric, 763
distal, technique for, 845, 849f–856f
for duodenal ulcers, 795–796, 796f–798f
external biliary fistulas following, etiology and prevention of, 1540
near-total, for gastroparesis, 924, 925
partial
fistulas following, 1093
with Roux-en-Y biliary diversion, for esophageal stricture, 249
postgastrectomy syndromes and. *See* Postgastrectomy syndromes.
proximal, for foregut reconstruction for benign disease, 302–304, 303f
with Roux gastrojejunostomy, for gastroparesis, 925
subtotal, for gastric adenocarcinoma, 909
reconstruction following, 911
total
for gastric adenocarcinoma, 909
technique for, 847f–860f, 857
vertical, for emetogenic injuries, 763–764
Gastric access, for enteric feeding, 754–755
Gastric acid
functions of, 727
hypersecretion of
in short-bowel syndrome, 1168
in Zollinger-Ellison syndrome. *See* Zollinger-Ellison syndrome.
secretion of, 724–727
basal or interprandial, 724
cellular basis of, 725–727
nocturnal, 255
pharmacologic regulation of, 727
stimulated, 724
Gastric adenocarcinoma, 904–915
clinical features of, 906
diagnosis of, 907–908
epidemiology of, 904–905
of gastric remnant, reoperative surgery for, 1140
pathology of, 905, 905b
risk factors for, 905–906, 906b
staging of, 908, 908b
treatment of
adjuvant, 912–913
chemoradiotherapy as, 912
chemotherapy as, 912
intraperitoneal, 912–913
for advanced disease, 914
palliative chemotherapy as, 914
palliative endoscopy as, 914
palliative radiotherapy as, 914
palliative surgery as, 914
neoadjuvant, 913–914
chemoradiotherapy as, 913–914
chemotherapy as, 913
radiotherapy as, 913
surgical, 908–912
for distal tumors, 909
endoscopic mucosal resection as, 909
lymphadenectomy extent and, 909–911, 910f, 910t
for midbody tumors, 909
prognostic factors and patterns of failure and, 911–912
for proximal tumors, 908–909
reconstruction after gastrectomy and, 911
Gastric antral vascular ectasia, 886
endoscopic appearance of, 739–740
symptoms and diagnosis of, 886
treatment of, 740, 886
Gastric arteries, 20, 20f, 718, 719f
anatomy of, 1237
aneurysms of, 1282
Gastric banding
adjustable, 934
failed, revision surgery for, 1145
for obesity, 934–935, 935f
Gastric barrier function, 729
Gastric bypass
for foregut reconstruction for benign disease, 302–304, 303f
internal hernias due to, 1124–1126, 1125f
clinical features of, 1125
diagnosis of, 1125–1126
treatment of, 1126
resection of excluded distal gastric remnant after, 304
Roux-en-Y
failed, revision surgery for, 1145–1146
for obesity, 931–934, 932f, 933t
Gastric cancer. *See also* Gastric adenocarcinoma; Gastric lymphomas.
endoscopic appearance of, 740, 740f
following gastrectomy, 809
treatment of
endoscopic, 744–745
laparoscopic, 745
Gastric carcinoid tumors, 1181
treatment of, 1185
Gastric cysts, esophageal, 525, 525f
Gastric derotation, for gastric volvulus, in pediatric patients, 950
Gastric distention, lower esophageal sphincter and, 227f, 227–229, 228f
Gastric duplication, in pediatric patients, 948
clinical features of, 948
diagnosis of, 948, 950f
incidence and etiology of, 948
management of, 948, 950f
Gastric dysmotility, 730–731
gastroparesis as. *See* Gastroparesis.
reoperative surgery for, 1139–1140
Roux stasis syndrome as, 809, 880, 925
reoperative surgery for, 1140
Gastric electrical stimulation, for gastroparesis, 921–924
Enterra, 921–923, 922f
postsurgical, 923–924
Gastric emptying, delayed, 185–190
assessment of
antroduodenal manometry and, 186–188, 188f, 188t, 189f, 190, 190t
barium burger studies and, 190
^{13}C breathing test for, 185–186
gastric emptying scintigraphy and, 185, 186f, 187f
in gastroparesis. *See* Gastroparesis.
Helicobacter pylori and, 730
reoperative surgery for, 1139–1140
Gastric emptying scintigraphy, 185, 186f, 187f
Gastric fistulas, etiology of, 1093–1096
Gastric foreign bodies. *See* Foreign body ingestion.
Gastric heterotopia, small intestinal, 892
Gastric inhibitory peptide
duodenal function and, 981t, 981–982
small intestinal neuroendocrine function and, 1018
Gastric injuries, 760–764
anatomy and physiology and, 760–761, 761f
blunt, 761–762
diagnosis of, 762–763
treatment of, 763
caustic, 762
diagnosis of, 763
treatment of, 763
complications of, 764
diagnosis of, 762–763
emetogenic, 762
treatment of, 763–764
historical background of, 760
iatrogenic, 762
penetrating, 761
diagnosis of, 762–763
treatment of, 763
treatment of, 763–764
Gastric interposition, for esophageal reconstruction, 249

Gastric juice, 727–728, 728t
  increased esophageal exposure to
    causes of, 141f, 141–142
    tests to detect, 161, 164–168, 165t
      clinical use of, 169–173
      performance of, 165–168
      24-hour esophageal pH monitoring as, 164–168
Gastric lymphomas
  diagnosis of, 1207f, 1207–1208, 1208f
  epidemiology of, 1199, 1200t
  treatment of, 1209, 1209t, 1210f
Gastric motility, 729–731
  fasting, 729–730
  normal, 920
  postprandial, 730
Gastric neoplasms. *See also specific neoplasms.*
  benign
    mesenchymal lesions as, 886–889
    mucosal hypertrophy and hyperplasia as, 882–886
      diffuse, 885–886
      focal, 882–885, 883t
  malignant. *See* Gastric adenocarcinoma; Gastric cancer; Gastric lymphomas.
  in pediatric patients, 958–959
    clinical features and diagnosis of, 958–959
    incidence of, 958
    management of, 959
Gastric outlet obstruction
  following esophageal resection with visceral esophageal substitution, 613–614, 614f
  at gastrojejunostomy site, reoperative surgery for, 1137–1138
  in pancreatitis, chronic, 1348–1349, 1349f
  in pediatric patients, 950–951
    clinical features of, 950–951
    diagnosis of, 951, 951f
    management of, 951–952
    types of, 951, 951f
  in peptic ulcer disease
    emergency surgery for, 806–808
    reoperation for, 1136–1137
    vagotomy and drainage for, 825–826
Gastric perforation
  in laparoscopic fundoplication, 1094
  in neonates, 957–958
    clinical features and diagnosis of, 957–958
    etiology of, 957
    incidence of, 957
    management of, 958
  with Nissen fundoplication, 273
  operative, 1094
  treatment of, 1108–1110
Gastric polyps
  adenomatous or neoplastic, 884–885
  benign, 882–885
    adenomatous or neoplastic, 884–885
      flat adenomas as, 885
      papillary adenomas as, 885
    non-neoplastic, 882–884
      adenomyomas as, 884
      Brunner's gland, 884
Gastric polyps *(Continued)*
      fundic gland, 884
      hamartomatous, 884
      hyperplastic or regenerative, 883–884
      inflammatory, 884
      pancreatic, heterotopic, 884
  non-neoplastic, 882–884
  retention, 884
Gastric pull-up
  for caustic ingestions, 545
  for foregut reconstruction for benign disease, 296, 299
  for gastric adenocarcinoma, 909
Gastric resection. *See* Gastrectomy.
Gastric resection and reconstruction, 831–857
  postoperative management for, 857
  preoperative preparation for, 831
  procedures for, 831–857
    gastrectomy
      distal, 845, 849f–856f
      total, 857, 857f–860f
    gastrojejunostomy, 845, 846f–848f
    gastrostomy, Stamm, 857, 860f, 861f
    pyloroplasty, 831, 841f–845f
    vagotomy
      gastric, proximal, 831, 835f–838f
      highly selective, 831, 838f–840f
      truncal, 831, 832f–835f
Gastric restrictive operations, for obesity, 930–931, 931f
Gastric rotation, development of, 35
Gastric stasis, following vagotomy, 874–875
Gastric ulcers, 820f, 820–822
  classification of, 820f, 820–821
  endoscopic appearance of, 737, 737f, 738f
  intractable, elective surgery for, 798–800, 799f, 799t
    for type I ulcers, 799–800
    for type II ulcers, 800
    for type III ulcers, 800
    for type IV ulcers, 800, 801f
    for type V ulcers, 800, 801f
  pathogenesis of, 812
  perforated, emergency surgery for, 806, 808f
Gastric varices, in pancreatitis, chronic, 1352–1353
Gastric volvulus, 1037–1039
  diagnosis of, 1037–1038, 1038f, 1039f
  etiology of, 1037, 1037f
  in pediatric patients, 950
  treatment of, 1038–1039
Gastrin, 721–722
  hypergastrinemia and, 722
  receptors for, gastric acid secretion and, 725
  synthesis and action of, 721–722
Gastrinoma(s), 1375
  lymph node primary, 863
  secretin infusion for localization of, 865
  in Zollinger-Ellison syndrome, 863–864. *See also* Zollinger-Ellison syndrome.
Gastrinoma triangle, 863
Gastrin-releasing peptide, 723
  duodenal function and, 981t, 984
Gastritis, bile reflux
  following gastrectomy, 875–877, 876f–878f
  reoperative surgery for, 1146f, 1146–1147, 1147f
Gastrocolic fistulas, in Crohn's disease, 1094
Gastrocolic ligament, 717, 717f, 718f
Gastrocolic reflex, 1875
Gastrocolic trunk, 968, 972f
Gastroduodenal anastomosis, longitudinal, for gastric outlet obstruction, 951
Gastroduodenal artery, 964, 968, 971f
  anatomy of, 1237
  aneurysms of, 1280f, 1280–1282
Gastroduodenal fistulas, treatment of, 1110
Gastroduodenal reflux disease, esophageal mucosal injury and, 230–232
  animal studies of, 230
  human studies of, 230–231
  mechanism of, 231–232
Gastroduodenostomy
  Billroth I
    for caustic injury, gastric, 763
    for duodenal ulcers, 795, 796, 796f, 797f
    following gastrectomy, 911
  Jaboulay, for duodenal ulcers, 795
Gastroepiploic arteries, 718, 719f
  aneurysms of, 1282
  right, 1237
Gastroesophageal barrier, 223–229
  anatomic alterations and, 228
  definition of, 223
  gastroesophageal reflux disease pathophysiology and, integrated hypothesis of, 228–229
  lower esophageal sphincter and, 223–226, 224f, 226t
    transient loss of competence of, 226f–228f, 226–228
Gastroesophageal junction, 334
  cancer at. *See also* Esophageal cancer.
    staging systems for, 450–451, 452f
  cardiac mucosa at, 344
  endoscopic evaluation of, 100–102, 101f, 102f
  impedance in, measurement of, in esophageal disease, 195
Gastroesophageal reflux
  amount of, determination of, 206
  detection of, barium examination for, 68
  esophageal strictures resulting from. *See* Esophageal strictures.
  following esophageal surgery, 599
  following Heller myotomy, 417
  multichannel intraluminal impedance for monitoring, 175–183
    combined with manometry, 175–176, 178f, 179, 179f
    combined with pH monitoring, 180f–183f, 180–181
    principles of, 175, 176f–178f
Gastroesophageal reflux disease, 206–221
  adenocarcinoma and, 445, 467
  antireflux surgery for. *See* Antireflux procedures; Nissen fundoplication.
  barium examination in
    to detect esophageal injury, 68–69, 69f, 70f

Gastroesophageal reflux disease *(Continued)*
to detect gastroesophageal reflux, 68
to evaluate esophageal clearance, 68
to exclude motility disorder, 68
for postoperative complication evaluation, 70
for preoperative planning, 70, 71f
Barrett's esophagus and. *See* Barrett's esophagus.
cardiac mucosa in, at gastroesophageal junction, 344
diagnosis of
of atypical disease, 171–172, 172f
bilirubin monitoring for, 168–169
clinical use of, 169–173
endoscopic, 105–106, 106t, 107f
pH monitoring for, 164–168, 165t
clinical use of, 169–173
test performance for, 165–168
24-hour esophageal pH monitoring and, 164–168
of typical disease, 170–171
duodenogastroesophageal reflux associated with, 194
end-stage, esophageal perforation associated with, 538
epidemiology of, 197–202
based on endoscopic assessment, 199–200, 200t
increasing prevalence and, 201–202
population risk factors and, 200–201, 201f
regional variation in prevalence and, 201
of symptoms, 198t, 198–199, 199f
erosive, natural history of, 202–203
esophageal motility disorders in, 140–142, 141f
gastroesophageal barrier and, 223–229
anatomic alterations and, 228
definition of, 223
integrated hypothesis of gastroesophageal reflux disease pathophysiology and, 228–229
lower esophageal sphincter and, 223–226, 224f, 226t
transient loss of competence of, 226f–228f, 226–228
histologic classification of, 219–221, 220b
histologic grading of, 214–215
imaging in
esophageal, 67–70
barium examination for, 68–70, 69f–71f
gastric, 66
medical therapy for, 252–261
antacids in, 253
for complications, 255–258
Barrett's esophagus as, 257–258
esophagitis as, 255–256, 256f
strictures as, 256–257
evaluation of response to, 173
for extraesophageal manifestations, 258–260
asthma as, 258, 259f, 260f
cough as, 258–259
laryngitis as, 259–260, 261f

Gastroesophageal reflux disease *(Continued)*
histamine$_2$ receptor antagonists in, 254
lifestyle modifications in, 252–253
nocturnal acid secretion and, 255
promotility agents in, 253–254
proton pump inhibitors in, 254–255, 255f
natural history of, 202–203
of erosive gastroesophageal reflux disease, 202–203
of nonerosive gastroesophageal reflux disease, 202
nonerosive, 211
epidemiology of, 197
natural history of, 202
normal endoscopy and histology and, 207–210, 208b, 208f–210f, 210b
pathology of, 210–218
acid-induced damage and, 210–211, 211f
esophageal squamous epithelium primed by, 211–212
carcinogenesis in intestinal metaplasia and, 217–218
cardiac mucosa and, 213f, 213–215, 215f
columnar transformation and, 212, 212f
intestinal metaplasia and, 215–216
oxyntocardiac mucosa and, 216–217
reversibility of genetic switches and, 217
pathophysiology of, integrated hypothesis of, 228–229
patient approach for, 58–60
refluxate in, 60, 206–207
surgical treatment of. *See also* Antireflux procedures; Nissen fundoplication.
evaluation of response to, 173
symptoms of, typical vs. atypical, 58–59
without Barrett's esophagus, refluxate in, 60
Gastroesophageal scintiscanning, 165t
Gastrointestinal disorders. *See also specific disorders.*
in cirrhosis, 1625
Gastrointestinal perforation
diagnosis of, 1097
steroid-induced, in immunocompromised patients, 2382
Gastrointestinal stromal tumors, 1189–1197. *See also* Leiomyomas.
adjuvant therapy for, 1196–1197
clinical evaluation of, 1191f, 1191–1192
colorectal, 2314–2317
epidemiology of, 2314
investigation of, 2315, 2315f
management of
medical, 2315
surgical, 2315–2316
pathophysiology and pathology of, 2314f, 2314–2315, 2315f
presentation of, 2315
prognosis of, 2316
esophageal, 520
gastric, endoscopic appearance of, 740–741, 741f

Gastrointestinal stromal tumors *(Continued)*
historical background of, 1189
imaging of, 1195f, 1195–1196
malignant potential of, assessing, 1191
management of
medical, 2315
surgical, 1196, 2315–2316
targeted therapy for, 1193–1195, 1194f
molecular biology of, 1192f, 1192–1193
natural history of, 1189–1190, 1190t
pancreatic, 1359
pathology of, 1190f, 1190–1191, 1191f
Gastrojejunocolic fistulas, internal, 1094
Gastrojejunostomy
Billroth II
bile reflux gastritis following. *See* Bile reflux gastritis.
for caustic injury, gastric, 763
for duodenal ulcers, 795, 796, 796f, 797f
following gastrectomy, 911
gastroparesis following, 923
revision of, for bile reflux gastritis, 877, 878f
for duodenal ulcers, 795
for gastric drainage, 815–816, 817f
gastric outlet obstruction at site of, reoperative surgery for, 1137–1138
technique for, 1138
jejunogastric intussusception following, 879–880
for obesity, 932
pyloric exclusion with, 768–769
for pyloric outflow obstruction, 1137, 1137f
Roux-en-Y
for bile reflux gastritis, 876, 876f
for dumping syndrome, 872f, 872–873
following gastrectomy, 911
technique for, 845, 846f–848f
Gastroparesis, 920–925
postsurgical, 924–925
electrical stimulation for, 923–924
Roux stasis syndrome as, 809, 880, 925
reoperative surgery for, 1140
treatment of
botulinum toxin for, 921
electrical stimulation for, 921–924, 922f
for postsurgical gastroparesis, 923–924
pharmacologic, 921
reoperative surgery for, 1139–1140
surgical, 924
Gastropathy, hypertrophic, 886
Gastropexy
anterior, for gastric volvulus, in pediatric patients, 950
Collis, 599
for gastric volvulus, 1038
Hill
complications of, 598–599
imaging following, 85
for paraesophageal hernia, 559

Gastroplasty
Collis. *See* Collis gastroplasty.
endoluminal, 309–314
advantages of, 313
complications of, 312–313
disadvantages of, 313
efficacy of, 310, 311t, 312, 312f
endoscopic, physiologic/anatomic mechanisms of, 328–329, 330f
failure of, 313
histologic changes and, 310, 310f
historical background of, 309
plication configuration and number and, 312
procedure for, 309, 309f
results with, 325, 326t, 327t
selection criteria for, 312
for obesity, 930–931, 931f
vertical banded
failed, revision surgery for, 1144–1145
for obesity, 931, 931f
Gastroschisis, intestinal atresia with, 1220
Gastrosplenic ligament, 717–718
Gastrostomy, 755–756
for gastroduodenal perforations, 1109
image-guided, percutaneous, 960
Janeway
with hostile abdomen, 1147
in pediatric patients, 960
laparoscopic, 755
laparoscopy-assisted, in pediatric patients, 960
longitudinal, for gastric outlet obstruction, 951
for paraesophageal hernia, 559
in pediatric patients, 960–961
complications of, 960–961
indications for, 960
types of, 960
percutaneous, 755–756, 757f
contraindications to, 750t
endoscopic
fistulas due to, 1095
in pediatric patients, 960
indications for, 750t
Stamm, 755, 756f
contraindications to, 750t
for esophagocoloplasty, 591
with hostile abdomen, 1147
indications for, 750t
in pediatric patients, 960
technique for, 857, 860f, 861f
Witzel, in pediatric patients, 960
Gatekeeper, for endoscopic antireflux procedures, 323–325, 325, 326t, 327t
advantages of, 325
complications of, 325
disadvantages of, 325
efficacy of, 323, 324t, 325
patient selection for, 323
physiologic/anatomic mechanisms of, 330–331
procedure with, 323, 324f
results with, 325, 326t, 327t
Gaucher's disease, splenectomy for, 1835
Gefitinib, for colorectal cancer metastases, 2271
Gemcitabine, for pancreatic and periampullary carcinoma, palliative, 1372–1373
Genetic factors
in Barrett's esophagus, 343, 348, 349t
in Crohn's disease, 1042–1043
gastroesophageal reflux disease and, 200
groin hernias and, 635
Genetic switches, in gastroesophageal reflux disease, 215–218
intestinal metaplasia as, 215–216
irreversible, 217–218
oxyntocardiac mucosa as, 216–217
reversibility of, 217
Genitofemoral nerve, 657, 658f
Genitourinary anomalies, associated with imperforate anus, 2390, 2405–2406
Gentamicin, for cholangitis prophylaxis, 1550t
GERD. *See* Gastroesophageal reflux disease.
Gerlach's valve, 1862
Ghrelin
duodenal function and, 981t, 984
gastric, 723
Ghrelinoma, 1383
GIA staplers, 1086, 1087f
Giant migrating contractions, small intestinal, 1017, 1017f
Gibson, Thomas, 563
Gimbernat's ligament, 636
GISTs. *See* Gastrointestinal stromal tumors.
Glands, esophageal, prenatal development of, 41, 42f
Glandular cysts, fundic, 884, 2162
Glasgow criteria, modified, for pancreatitis, acute, 1300, 1301t
Glisson, Francis, 1751
Glomus tumors, gastric, 887–888
Glucagon-like peptide, small intestinal neuroendocrine function and, 1018
Glucagonoma, 1381–1382
diagnosis of, 1381, 1382f
therapy of, 1382, 1382f
Glucocorticoids, hepatotoxicity of, 1722
Glucose, small intestinal absorption of, 1003t
Glucose-dependent insulinotropic peptide, duodenal function and, 981t, 981–982
Glucose-6-phosphate dehydrogenase deficiency, splenectomy for, 1826
Glycoprotein, secretion of, by gallbladder, 1458
Goblet cells
in Barrett's esophagus, 341–342, 347
development of, 347
intestinalization of cardiac mucosa and, 345, 347
prenatal development of, 40–41, 41f
Goodsall's rule, 2049
Gracilis muscle sling operation, 2405
Graft-versus-host disease, following intestinal transplantation, 1177
Granular cell tumors, esophageal, 520–521, 521f
endoscopic ultrasonography in, 123
Granulomatous colitis. *See* Crohn's disease.
Gray-scale ultrasonography, 112
Great prosthesis for reinforcement of the visceral sac, 652–653
Grey Turner's sign, 1299
GRFoma, 1382
diagnosis of, 1382
therapy, 1382
Gridiron incision, for appendectomy, 2145
Griffith's point, 1239, 1868
Groin hernias, 1471–1493. *See also* Femoral hernias; Inguinal hernias.
anatomy and, 635–642
of anterior abdominal wall, 636–639
muscles, ligaments, and aponeurosis of, 636–639, 637f–639f
skin, fascia, vessels, and nerves of, 636
of inguinal region, laparoscopic, 639–642
of abdominal wall innervation and blood supply, 641–642, 642f
of deep aspects, 639–640, 640f
of Hesselbach's triangle and spermatic cord, 641
or transversalis fascia and its derivatives, 640–641, 641f
classification of, 643–644, 644t, 645f
embryology and, 633–634
in females, 643
femoral, 643
historical background of, 632–633, 633f
incarceration of, 643
incidence of, 634
etiology, biochemical basis, and mechanical stress and, 634–635
indirect, 643
irreducible, 643
natural history of, 634
recurrent, 653–654
sliding, 643
strangulation of, as indication for surgery, 644
surgical treatment of, 644–654
anesthesia for, 646
combined anterior and preperitoneal approaches for, 647t, 653
complications of, 653–654
conventional anterior nonprosthetic approach for, 647t, 647–649
conventional anterior prosthetic approach for, 647t, 649, 650f
conventional preperitoneal prosthetic approach for, 647t, 649, 651–653
indications and alternatives for, 644–645, 646f
preoperative preparation for, 645–646
prosthetic material for, 646b, 646–647
symptoms and diagnosis of, 642–643
Groin pain
following hernia surgery, 653
with inguinal herniorrhaphy, laparoscopic, 668
"Ground glass" appearance, in meconium ileus, 1224, 1224f
Grynfeltt-Lesshaft hernias, 687

Guanylin, small intestinal neuroendocrine function and, 1019
Gut-associated lymphoid tissue, small intestinal immune function and, 1010, 1012f
Gynecologic disorders
following ileal pouch–anal anastomosis, 2117–2118
pruritus ani and, 2068

H

Haemophilus influenzae infection
immunization against
with asplenia, in pediatric patients, 1811
with splenic cysts, 1815
overwhelming postsplenectomy infection and, 1782
Haight, Cameron, 563
Hair, trichobezoars and, 943, 944, 944t
Hairy cell leukemia, splenectomy for, 1831
HALO system, for Barrett's ablation, 367–370, 368f, 369f
Halothane, fulminant liver failure due to, 1703
Halsted suture, 1085
Hamartomas
in Cowden's disease, 894t, 897, 2159t, 2175–2176
in Peutz-Jeghers syndrome, 2174
Hamartomatous polyps
colorectal, 2157f, 2157–2158, 2158f
gastric, 884
Hand-assisted laparoscopic surgery
for colonic diverticular disease, 2023f, 2023–2024
colorectal, 2353
splenectomy as, 1786
for splenic tumors, 1816
Hanley, Patrick H., 2053
Hannington-Kiff sign, 693
Hardy, Thomas G., Jr., 1089
Harmonic scalpel
for hemorrhoidectomy, 2033
hepatic surgery using, external biliary fistulas following, etiology and prevention of, 1540
for splenectomy, partial, 1815
Hartmann procedure, 2330
for colonic diverticular disease, 2025, 2025f
reversal of, 2415, 2416f
Harvey, William, 1751
Hayward, John, 341
Heart. *See also* Cardiovascular disorders.
esophagectomy affecting complications, 480
iron overload and, 1693
Heartburn, in esophageal disease, 56, 57b
achalasia as, 407
motility disorders as, 71
Heineke-Mikulicz cardioplasty, 5
Heineke-Mikulicz pyloroplasty, 816, 818f
for duodenal ulcers, 794–795, 795f
technique for, 841f, 842f
Heineke-Mikulicz stricturoplasty, for Crohn's disease, 1059, 1059f
Heister, valves of, 1444
Helicobacter pylori infection
adenocarcinoma and, 445–446
Barrett's esophagus and, 334–335
gastric, endoscopic appearance of, 737
gastric adenocarcinoma and, 905, 906
gastric dysmotility associated with, 730–731
gastric lymphoma and, treatment and, 1209
gastric polyps associated with, hyperplastic, 883
gastroesophageal reflux disease and, 200–201, 201f
MALT lymphoma associated with, 1203
treatment and, 1208
peptic ulcer disease and, in pediatric patients, 961
reflux carditis and, 213–214
somatostatin and, 722–723
ulcerogenesis and, 811–812
Heliodorus, 632
Heller, Ernst, 5
Heller myotomy, 5
for achalasia, 409
with Dor repair, results with, 283
esophagography following, 85, 86f
laparoscopic
for achalasia, 413–415
antireflux procedure with, 416
complications of, 416–417, 417f
fundoplication technique and, 416
length of myotomy and, 415
operative steps for, 413–414, 414f, 415f
patient positioning and preparation for, 413
port placement for, 413, 413f
postoperative management for, 414–415
with sigmoid-shaped esophagus or megaesophagus, 416
for epiphrenic diverticulum, 435–437, 437f
Hemangioendotheliomas, epithelioid, hepatic, 1748–1749
Hemangiomas
colonic, 1995–1997, 1996f
in blue rubber bleb syndrome, 1997
cavernous, rectal, 1996
in diffuse intestinal hemangiomatosis, 1997
cutaneous, cavernous, 1997
esophageal, 521–522
endoscopic ultrasonography in, 123
gastric, 887
hepatic, 1726–1728
diagnosis of, 1726–1727, 1727f
etiology of, 1726
giant, 1726
treatment of, 1727–1728
intestinal
cavernous, 1997
small intestinal, 899
rectal, cavernous, 1996
Hemangiomas *(Continued)*
small intestinal, 899
splenic, 1815
Hemangiomatosis, gastrointestinal, diffuse, small intestinal, 899
Hemangiosarcomas, splenic, primary, 1815
Hematologic disorders, splenectomy for. *See* Splenectomy, for hematologic disorders.
Hematomas
duodenal, 1095
intramural, 766
Hemiazygos vein, 22
Hemicolectomy, right
for colonic ectasias, 1995
steps for, 2349b, 2349f, 2350f
Hemochromatosis
cardiac iron deposition and, 1693
hepatic laboratory tests in, 1613
Hemodialysis, for liver failure, acute, 1705–1706
Hemofiltration, for liver failure, acute, 1706
Hemoglobinopathies, splenectomy for, 1826
Hemoperfusion, charcoal and resin, for liver failure, acute, 1706
Hemorrhage. *See also* Bleeding.
with aortoenteric fistulas, 1270–1271
colonic
acute, control of, in colonic ectasia, 1995
diverticular, 2016, 2016f, 2017f
diverticular
colonic, 2016, 2016f, 2017f
duodenal, 780
duodenal, diverticular, 780
as emergency surgical indication, 2102
following antireflux procedures, 609–610
following ileal pouch–anal anastomosis, 2111
with gastrointestinal fistulas, 1098
with ileostomy, 1081
with jejunoileal diverticula, 784–785
with Meckel's diverticulum, 787
with pancreatic pseudocysts, 1343–1344
rectal bleeding and, 1883
upper gastrointestinal, with splenic vein thrombosis, 1353
Hemorrhagic proctitis, management of, 2321
Hemorrhoid(s), 2029–2035
anatomy and etiology of, 2029
clinical evaluation of, 2029–2030
external, thrombosed, 1887
treatment of
bipolar diathermy for, 2031, 2031f
excisional hemorrhoidectomy for, 2031–2033, 2032f
hemorrhoidal ligation with rubber bands for, 2031, 2032f
nonexcisional options for, 2030
postoperative management and, 2034
for prolapsing hemorrhoids, 2033–2034, 2035f
rubber band ligation for, 2031, 2032f
sclerotherapy for, 2030f, 2030–2031

Hemorrhoidectomy
excisional, 2031–2033, 2032f
instrumentation for, 2033
nonexcisional, for prolapsing hemorrhoids, 2033–2034, 2035f
postoperative management and, 2034
Hemostasis, with hepatobiliary trauma, 1664f, 1664–1665, 1667
Henle's trunk, 968, 972f
Hepatectomy
general maneuvers for, 1676f, 1676–1677, 1677f
major, 1677–1680
left
extended, 1680, 1682f
with hilar dissection, 1678–1679, 1681f
left lateral sectionectomy and, 1679–1680
right
extended, 1680, 1681f, 1682f
with hilar dissection, 1678, 1679f, 1680f
native, total, 1695
salvage, for metastatic colorectal cancer, 2285
Hepatic adenomas, 1729
diagnosis of, 1729, 1730f
drug-induced, 1723
etiology of, 1729
treatment of, 1729, 1730f
Hepatic angiosarcomas, end-stage liver disease due to, 1687
Hepatic arterioportal shunts, 1713f, 1713–1714
Hepatic arteriovenous shunts, 1713f, 1713–1714
Hepatic artery(ies), 1445, 1445f, 1446, 1600, 1602
anatomy of, 1237, 1237f
anomalies of, 1753, 1754f
common, 1292, 1293f, 1600
absent, 1600
accessory, 1602
left, 1602
replaced, 1600, 1602
right, 1602
hepatocellular carcinoma and, 1732–1733
Hepatic artery aneurysms, 1277–1278, 1711–1712, 1712f
clinical findings in, 1278
diagnosis of, 1278
false, 1277
incidence of, 1277
pathogenesis of, 1277
treatment of, 1278
Hepatic artery arterioportal and arteriovenous shunts, 1713f, 1713–1714
Hepatic artery disorders, 1711–1714. *See also specific disorders.*
Hepatic artery failure, liver transplantation and, 1697
Hepatic artery infusion, for metastatic colorectal cancer, 2282–2283
Hepatic artery injury, 1712
Hepatic artery ligation, liver necrosis following, 1278
Hepatic artery thrombosis, 1712–1713, 1713f
liver transplantation and, 1698
Hepatic blood flow, 1607
Hepatic cryotherapy, external biliary fistulas following, etiology and prevention of, 1540
Hepatic cyst(s), 1630–1638
cystic neoplasms and, 1636, 1636f, 1637f
echinococcal, 1636–1638, 1638f
in polycystic liver disease, 1634–1635, 1635f
solitary, 1630–1633, 1631f–1634f
Hepatic cystadenocarcinomas, 1746–1747
Hepatic ducts, 1602
anomalies of, 1447–1448, 1448f, 1449f
confluence of, 1602
Hepatic encephalopathy
in cirrhosis, 1625
in end-stage liver disease, 1694, 1694b
portal hypertension and, 1756
Hepatic fibrosis, congenital, portal hypertension and, 1757
Hepatic flexure, 1847, 1863, 1865f
Hepatic functional reserve, 1621
Hepatic laboratory tests, abnormal, 1610–1616
albumin and, 1615–1616
in alcoholic liver disease, 1612
alkaline phosphatase elevation as, 1614–1615
aminotransferase elevations as, 1611b, 1611–1612
in autoimmune hepatitis, 1613
in hemochromatosis, 1613
in nonalcoholic fatty liver disease, 1612–1613
percutaneous liver biopsy and, 1616
prothrombin time and, 1615
serum bilirubin elevation as, 1613–1614, 1614f
in viral hepatitis, 1612
in Wilson's disease, 1613
Hepatic lobectomy, for hepatic cysts, solitary, 1633
Hepatic metabolism, 1607–1608
Hepatic metastases, of colorectal cancer, 2274–2287
cryoablation for, 2283
hepatic artery infusion for, 2282–2283
hepatic resection for
anatomic unisegmental and polysegmental, 2278
anatomy and, 2275–2276, 2276f
complications of, 2281–2282
general principles of, 2275
lobar, 2278–2281, 2279f–2281f
patient selection for, 2274–2275
postoperative care for, 2281
preoperative care for, 2276
surgical technique for, 2276f–2278f, 2276–2278
wedge, 2278
hyperthermia for, 2284
prognostic determinants for, 2284, 2285t
recurrent and repeat hepatic resection for, 2285–2287
prognostic factors affecting resectability and, 2285–2286
Hepatic metastases, of colorectal cancer *(Continued)*
salvage hepatectomy and, 2285
strategies for improving resectability and, 2286–2287
Hepatic neoplasms. *See also specific neoplasms.*
benign, 1726–1730
adenoma as, 1729
diagnosis of, 1729, 1730f
etiology of, 1729
treatment of, 1729, 1730f
angiomyolipoma as, 1730
bile duct adenoma as, 1729
biliary hamartoma as, 1729–1730, 1730f
focal nodular hyperplasia as, 1728–1729
diagnosis of, 1728, 1728f
etiology of, 1728
treatment of, 1728–1729
hemangioma as, 1726–1728
diagnosis of, 1726–1727, 1727f
etiology of, 1726
treatment of, 1727–1728
peliosis hepatis as, 1730
malignant, 1743–1749, 1744b, 1744t
epithelial, 1743–1747
hepatic cystadenocarcinoma as, 1746–1747
intrahepatic cholangiocarcinoma as, 1743–1745, 1745f
mixed cholangiohepatocellular carcinoma as, 1745–1746, 1746f
squamous cell carcinoma as, 1747
mesenchymal, 1747
fibrosarcoma as, 1747, 1747f
leiomyosarcoma as, 1747
liposarcoma as, 1747
rhabdomyosarcoma as, 1747
schwannoma as, 1747
vascular, 1747–1749
angiosarcoma as, 1747–1748, 1748f
epithelioid hemangioendothelioma as, 1748–1749
Hepatic osteodystrophy, in end-stage liver disease, 1693
Hepatic resection
for hepatocellular carcinoma, 1738–1739
liver transplantation vs., 1740
operative techniques for, 1739
intraoperative assessment in, 1675f, 1675–1676, 1676f
laparoscopic, for hepatic cysts, solitary, 1633
for metastatic colorectal cancer. *See* Hepatic metastases, of colorectal cancer, hepatic resection for.
oncologic considerations in, 1674–1675
postoperative complications with, 1683
postoperative management of, 1627–1628, 1683
segmental, 1680
wedge, 1683, 1683f

Hepatic reserve, preoperative evaluation of, 1674, 1674t
Hepatic trauma. *See* Hepatobiliary trauma.
Hepatic veins, 1603
  disorders of, Budd-Chiari syndrome as, 1714f, 1714–1715
Hepatic venous pressure gradient, in portal hypertension, 1757–1758
Hepaticojejunostomy
  for biliary atresia, 1548
  for choledochal cysts, 1554–1555
Hepatitis
  autoimmune
    hepatic laboratory tests in, 1613
    in primary sclerosing cholangitis, 1564
  drug-induced
    acute, 1721
    chronic, 1722
  viral, hepatic laboratory tests in, 1612
Hepatitis B
  end-stage liver disease due to, 1686
  fulminant liver failure due to, 1703
  hepatocellular carcinoma and, 1732
Hepatitis C
  end-stage liver disease due to, 1686
  hepatic laboratory tests in, 1612
  hepatocellular carcinoma and, 1732
Hepatitis D, fulminant liver failure due to, 1703
Hepatobiliary cancer
  with choledochal cysts, 1554
  hepatic abscesses associated with, pyogenic, 1642–1643
Hepatobiliary disease. *See also specific disorders.*
  with primary sclerosing cholangitis, treatment of, 1568
Hepatobiliary surgery, with low anterior resection, 2222
Hepatobiliary trauma, 1468, 1659–1668
  biliary system and, 1659, 1661f
  blunt, hepatic, 1662–1663, 1663f
  classification of, 1660, 1662t
  diagnosis of, 1668
  of gallbladder, 1663
  hemostasis and, 1667–1668
  mechanism of injury and, hepatic, 1659–1660
  mobilization of liver and, 1659, 1660f, 1661f
  operative management of, 1664f–1666f, 1664–1667
    for biliary trauma, 1666–1667, 1667f, 1668f
    débridement and, 1666
    for gallbladder injury, 1667
    Gore-Tex grafts for, 1668
    hepatic resection for, total, 1667
  penetrating, diagnostic approach for, 1660, 1662
  shock and, 1668
Hepatoblastoma, in children, alfa-fetoprotein and, 1734
Hepatocellular carcinoma, 1732–1740
  cholangiocarcinoma and, 1534
  clinical presentation of, 1733–1735
    biopsy and, 1734
Hepatocellular carcinoma *(Continued)*
    imaging and, 1734–1735
    laboratory investigation and, 1733–1734
  drug-induced, 1723–1724
  end-stage liver disease due to, 1687
  epidemiology of, 1732, 1733f
  etiology of, 1732
  liver transplantation for, 1692, 1692t
  management of, 1736–1740
    ablative therapies for, 1736–1738
    chemotherapy for, 1736
    resection for, 1738–1739
      transplantation vs. 1740
    transplantation for, 1739–1740
      resection vs., 1740
  pathology of, 1732–1733, 1733f
  risk factors for, 1732, 1733b
  staging of, 1735–1736
    Barcelona Chronic Liver Cancer staging system for, 1735
    Cancer of the Liver Italian Program for, 1736
    Okuda classification for, 1735
    TNM system for, 1735
Hepatocellular necrosis
  zone 1, drug-induced, 1719t, 1720
  zone 3, drug-induced, 1719t, 1719–1720
Hepatoduodenal ligament, 717, 718f
Hepatogastric ligament, 717, 718f
Hepatolithiasis, postoperative, with choledochal cysts, 1555
Hepatologists, on portal hypertension multidisciplinary team, 1767
Hepatoportoenterostomy, for biliary atresia, 1550
Hepatopulmonary syndrome, 1766f, 1766–1767
  clinical presentation of, 1766
  liver transplantation and, 1693
  pathophysiology of, 1766
Hepatorenal syndrome
  in cirrhosis, 1625
  in end-stage liver disease, 1693–1694
Hepatosplenopathy, 1751
Herald bleeding, with aortoenteric fistulas, 1114
Hereditary flat adenoma syndrome, small intestinal, 894t, 896
Hereditary hemorrhagic telangiectasia, colonic, 1999
Hereditary mixed polyposis syndrome, 2159t, 2176–2177
  small intestinal, 894t, 898
Hereditary nonpolyposis colorectal cancer, 2159t, 2169–2173
  clinical considerations in, 2169
  as colorectal cancer risk factor, 2188, 2188b
  diagnosis of, 2171, 2171b, 2172b
  extracolonic cancers and, 2169
  genetic testing and counseling and, 2171–2172
  genetics of, 2169–2171, 2170f
  surgical treatment of, 2172–2173
Hereditary spherocytosis, splenectomy for, 1825–1826, 1826t
Hernias
  diaphragmatic, congenital. *See* Diaphragmatic hernias.
  femoral. *See* Femoral hernias.
  Grynfeltt-Lesshaft, 687
  with ileostomy, 1080–1081
  inguinal, in children, 705–709
    clinical features of, 706
    contralateral inguinal exploration and, 709
    embryology of, 705
    incidence of, 705–706
    indirect, operative management of, 706–708, 707f, 708f
    with undescended testes, 709, 710f
  internal. *See* Internal hernias.
  levator ani, 687
  lumbar, 687–691
    anatomic considerations and, 688, 688f
    classification of, 689–690
    clinical features and diagnosis of, 688–689, 689f
    historical background of, 687–688
    incarceration plus strangulation of, 689
    treatment of, 690f, 690–691
  mesocolic (paraduodenal), 1858, 1861f
  obturator, 691–694
    anatomy and, 691, 692f
    clinical features and diagnosis of, 691, 693, 693f, 694f
    treatment of, 693–694, 694f
  paraesophageal. *See* Paraesophageal hernias.
  parastomal, 2372, 2372f
  perineal (levator), 694–700
    anatomy and, 696, 697f
    classification of, 694–696, 695f, 696f
    clinical features and diagnosis of, 696, 698f, 698–699, 699f
    treatment of, 699–700, 700f–703f
  pudendal, 695, 696f
  sciatic, 700–704
    anatomy and, 701, 703f
    clinical features and diagnosis of, 701–702, 703f
    treatment of, 702–704, 703f
  spigelian, repair of, 682
Herniation, internal, small bowel obstruction due to, 1027
Herniogenetics, 635
Herniorrhaphy
  for groin hernias, 643
  hiatal
    esophageal perforation due to, 606b, 606–607, 607f, 608f, 609–610, 610f
    laparoscopic, complications of, 610–611
  inguinal. *See* Inguinal herniorrhaphy.
  laparoscopic, for umbilical hernias, 681–682
  Lichtenstein, 649, 650f
Herophilus, 632
Herpes simplex virus infection
  achalasia due to, 406
  pruritus ani associated with, 2070

Hesselbach, Franz, 632
Hesselbach's triangle, 641
Heterotropic pancreatic polyps, 884
Hiatal hernias
  Allison repair for, 228
  Barrett's esophagus and, 60
  classification of, 549–550, 550f
  early development of surgery for, 6–7
  evaluation of, barium examination for, 70
  following esophageal resection with visceral esophageal substitution, 614, 615f
  gastric, endoscopic appearance of, 737–738, 738f
  gastroesophageal reflux disease and, 200
  imaging of, 87, 88f, 89f
  lower esophageal sphincter competence and, 228
  paraesophageal. *See* Paraesophageal hernias.
  prevalence of, 550
  short esophagus, imaging of, 87, 89f
  sliding (type I), imaging of, 87, 88f
  type II, imaging of, 87, 89f
Hiatal herniorrhaphy
  esophageal perforation due to, 606b, 606–607, 607f, 608f, 609–610, 610f
  laparoscopic, complications of, 610–611
Hiatal obstruction, following esophageal resection with visceral esophageal substitution, 614, 615f
Hiatus of Schwalbe, 696
Hidradenitis suppurativa, 2076–2078
  clinical presentation of, 2077, 2077f
  pathophysiology of, 2076–2077
  pruritus ani associated with, 2070
  treatment of, 2077–2078
Highly active antiretroviral therapy, 2380
  hepatotoxicity of, 1720
Hilar dissection, hepatectomy with
  left, 1678–1679, 1681f
  right, 1678, 1679f, 1680f
Hilar plate, 1599, 1603
Hill, Lucious, 6
Hill gastropexy
  complications of, 598–599
  imaging following, 85
Hippocrates, 632, 1771
Hirschsprung's disease, 1879, 2392
Histamine, gastric, 723
Histamine$_2$ receptor antagonists
  for esophageal strictures, 256
  for esophagitis, reflux, 255
  gastric acid secretion and, 727
  for gastroesophageal reflux disease, 254
Histamine receptors, gastric acid secretion and, 725
Histiocytoma, malignant fibrous, colorectal, 2317
Hoarseness, gastroesophageal reflux disease associated with, diagnosis of, 171
Hodgkin's disease
  Ann Arbor staging system with Cotswold modification for, 1827, 1828t
  splenectomy for, 1827–1829, 1828f, 1828t
  splenic, 1816
hOKT3-γ1-ala-ala antibody, for islet transplantation, 1428
Horizontal mattress suture, 1085
Hormonal disorders, obesity and, bariatric surgery and, 938
Hormonal therapy, for carcinoid tumors, 1186
Hospital costs, for laparoscopic colorectal surgery, 2344
Hospital stay, length of, for laparoscopic colorectal surgery, 2343
Hostile abdomen, 1147–1148, 1148b
Hourglass gallbladder, 1449, 1451f
Howell-Jolly bodies, 1775
Howship-Romberg sign, 693
Human immunodeficiency virus infection. *See also* Acquired immunodeficiency syndrome.
  anal intraepithelial neoplasia and, 2289
  anorectal fistulas in, 2058
  anorectal sepsis in, 2058
  cholangiopathy and, 1615
  splenectomy for, 1825
Human papillomavirus infection, anal
  anal intraepithelial neoplasia and, 2289
  in immunocompromised patients, 2383t, 2384
Hunter, John, 632, 811
Hunt-Lawrence pouch, for microgastria, 950
Hurst dilators, 5
Hydatid disease of liver, external biliary fistulas associated with, etiology and prevention of, 1540, 1540f
Hydrocarbons, fulminant liver failure due to, 1703
Hydrocele, with inguinal herniorrhaphy, laparoscopic, 668
Hydrocortisone phosphate, pruritus ani associated with, 2069
Hydrodissection, 2412
Hydrogen ions, secretion of, by gallbladder, 1458
Hydropneumothorax, in esophageal perforation, 93, 95f
5-Hydroxyindoleacetic acid, carcinoid tumors and, 1182–1183
5-Hydroxytryptophan. *See* Serotonin.
Hydroxyzine, for pruritus, in primary sclerosing cholangitis, 1567
Hyperamylasemia, pancreatitis associated with, 1299
Hyperbilirubinemia, direct (conjugated) alkaline phosphatase level in, 1614–1615
  in infancy, 1545
Hypercalcemia, pancreatitis associated with, 1299
Hyperemia, intestinal, postprandial, 1242–1243
Hyperfractionation, 1156
Hypergastrinemia, 722
Hyperglycemia, in short-bowel syndrome, 1166
Hyperinsulinism, in pediatric patients, 1408–1409
Hyperlipidemia
  obesity and, bariatric surgery and, 938
  pancreatitis associated with, 1299
Hyperplastic colorectal polyps, 2158, 2158f
Hyper-rotation, duodenal, 1214, 1216f
Hypersplenism, 1777
  partial splenic embolization for, 1793–1795, 1794f, 1795f
Hypertension
  portal, in pancreatitis, chronic, 1312–1313
  portopulmonary, 1767, 1767f
Hyperthermia, for metastatic colorectal cancer, 2284
Hypogastric nerves, total mesorectal excision with autonomic nerve preservation and, 2237–2238, 2238f
Hypoglycemia
  factitious, with insulinoma, 1376
  hyperinsulinemic, of infancy, persistent, 1408–1409
  with insulinoma, management of, 1378
  in short-bowel syndrome, 1166
Hypopharynx, prenatal development of, 31–33, 33f, 34f
Hyposplenism, 1777

I

Icones Herniarum (Camper), 632
Idiopathic thrombocytopenic purpura, splenectomy for, 1822–1824, 1824f
Ileal adenocarcinoma, 916
Ileal artery aneurysms, 1282f, 1283
Ileal atresia, 1219
Ileal carcinoids, treatment of, 1185
Ileal motility, 2105–2106
Ileal pouch–anal anastomosis
  for Crohn's disease, 2130, 2132
    failure of, 2121–2122
  for familial adenomatous polyposis, 2165, 2165t, 2166t, 2167
  redo, 2417
  revision pouch surgery for, 2118–2120, 2120f, 2121f
    alternative techniques for pouch salvage and, 2119–2120, 2120f, 2121f
    surgical technique for, 2118–2119, 2119t
  total proctocolectomy with, for ulcerative colitis, 2093–2094
  for ulcerative colitis, 2102–2122
    alternatives to, 2122
    critical level of, 2109–2110
    ileal pouch design for, 2103f, 2103–2105
      comparative studies of, 2105
      quadruplicated pelvic ileal reservoir (W pouch) as, 2105
      three-limbed pelvic ileal reservoir (S pouch) as, 2104
      two-limbed pelvic ileal reservoir (J pouch) as, 2104–2105
    ileal pouch function and, 2105–2107
      ecology of pouch and, 2107
      efficiency of evacuation and, 2106
      functional outcome and, 2107
      ileal motility and, 2105–2106

Ileal pouch–anal anastomosis *(Continued)*
postprandial pouch tone and, 2106–2107
pouch compliance and capacity and, 2105
ileoanal anastomosis and, 2107–2110
single- or double-stapled technique for, 2108–2109, 2109f
transanal mucosectomy and, 2108, 2108f
laparoscopic, 2102
operative technique for, 2102f, 2102–2103
pouch-specific complications of, 2111–2122
age-related, 2118
anastomotic cuff abscess as, 2111
Crohn's disease as, 2121–2122
dysplasia in residual rectal mucosa as, 2112
enterocutaneous fistulas as, 2112
gynecologic, 2117–2118
intra-abdominal abscess as, 2111
neoplastic, 2116–2117
postoperative hemorrhage as, 2111
pouchitis as, 2113, 2115t, 2115–2116
pouch-vaginal fistulas as, 2112–2113, 2114f
proctitis in residual rectal mucosa as, 2112
quantification of risk of pouch failure and, 2120–2121
revision pouch surgery for, 2118–2120, 2119f–2121f
sexual dysfunction as, male, 2117
small bowel obstruction as, 2111
stricture at anastomosis as, 2112
two vs. one stage, 2110
Ileocecal valve
anatomy of, 1846, 1861, 1862
on colonoscopy, 1867
lipohyperplasia (lipomatous hypertrophy) of, 900–901
Ileocolic artery, 1849, 1851f, 1852f
Ileocolostomy
for colorectal cancer, 2331
end-loop, 2367–2368, 2369f
Ileorectal anastomosis, colectomy with
for familial adenomatous polyposis, 2165, 2165t, 2166t, 2166–2167, 2168
for ulcerative colitis, 2122
Ileorectostomy, colectomy with, for intractable constipation, 1880
Ileosigmoid anastomosis, for colonic inertia, 1934
Ileosigmoid fistulas, in Crohn's disease, 1064
Ileosigmoid knotting, 1984
Ileostomy, 1070–1081
complications of, 1078–1081
bowel obstruction as, 1078–1080
diarrhea as, 1081
hemorrhage and peri-ileostomy varices as, 1081
mucocutaneous separation as, 1080
Ileostomy *(Continued)*
parastomal hernia as, 1080
peri-ileostomy fistula as, 1080–1081
skin problems as, 1081
stoma necrosis as, 1078
stoma prolapse as, 1080
stoma retraction as, 1080
stoma stenosis as, 1080
continent, Kock
for familial adenomatous polyposis, 2165t, 2165–2166, 2166t
for ulcerative colitis, 2122
diverting, for ileal pouch–anal anastomosis, 2110
divided-loop, 1075, 1077f
end, 1071, 1072f–1074f, 1074–1075, 2363–2364, 2363f–2366f
total proctocolectomy with, for familial adenomatous polyposis, 2165, 2165t, 2166t
end-loop, 1075–1076, 1078f, 2367, 2368f
historical background of, 1070
indications for, 1070–1071
loop, 1075, 1076f, 2366, 2367f
closure of, 1076–1078, 1079f
temporary, 1071
panproctocolectomy with, for ulcerative colitis, 2122
physiology and, 1071
preoperative preparation for, 1071
techniques for, 1071
Ileostomy bags, for abscess drainage, 1102, 1103f
Ileus
with inguinal herniorrhaphy, laparoscopic, 667
meconium, 1224f, 1224–1225, 1225f
postoperative, bowel obstruction vs., 1028
Iliac artery, deep circumflex, 673
Iliococcygeus muscle, 696
Iliohypogastric nerve, 656
Ilioinguinal nerve, 656
Iliopectineal arch, 656–657
Iliopubic tract, 657
Iliopubic tract hernia repair, 652
Illicit drugs, ingested packages of, 943, 943f
ILS staplers, 1087
Image-guided interventional therapy, for spleen. *See* Spleen, image-guided interventional therapy for.
Imaging. *See also specific imaging modalities.*
of carcinoid tumors, 1183f, 1183–1184, 1184f
for caustic ingestions, 543
esophageal, 63–95
in caustic injury, 91
of diverticula, 94–95, 96f
of esophageal perforation, 91, 93–94, 95f
of esophageal rings and webs, 88f, 88–89, 90f, 91f
examination techniques for, 64, 64f–66f
in gastroesophageal reflux disease, 67–70
barium examination for, 68–70, 69f–71f
Imaging *(Continued)*
of hiatal hernia, 87, 88f, 89f
in motility disorders, 71–74
primary, 71–74, 72f, 73f
secondary, 74
in neoplastic disease, 74–83
benign, 81–83, 83f
malignant, 74–81, 75f–81f
normal anatomy and function and, 63
normal radiographic appearance and, 64f–66f, 64–66
normal variants and, 66–67, 67f
postoperative, 83–86
following antireflux procedures, 85, 86f
following cardiomyotomy, 85, 86f
following cricopharyngeal myotomy, 84–85, 85f
following esophageal resection, 86, 87f, 88f
goals and techniques of, 83–84, 84t
of strictures, 89–91, 92f–94f
for structural abnormality detection, 143
of varices, 95, 97f
in esophageal spasm, 419, 420f
in hypertensive lower esophageal sphincter, 424
in nutcracker esophagus, 422
preoperative, for reoperative pelvic surgery, 2410
Imatinib mesylate, for gastrointestinal stromal tumors, 1197
^{131}I-metaiodobenzylguanidine scans, of carcinoid tumors, 1184
Imiquimod, for anal intraepithelial neoplasia, 2290
Immune function, in pediatric patients, consequences of splenectomy and, 1806
Immune system, small intestinal, 1009–1012
gut-associated lymphoid tissue and, 1010, 1012f
M cells and, 1010, 1012f
regulation of, 1010
regulation of gut function by, 1011–1012
secretory immunoglobulin A and, 1010, 1011f
Immunoallergy, drug-induced, 1721
Immunocompromised patients, 2375–2384.
See also Acquired immunodeficiency syndrome; Human immunodeficiency virus infection.
colonic diverticular disease in, 2020
mechanisms of immunodeficiency and, 2375–2377, 2376b, 2376t
AIDS as, 2376–2377
cancer and cancer therapy as, 2376
malnutrition and injury as, 2376
pharmacologic, 2375–2376, 2377t
surgical problems in
acute appendicitis as, 2381
anorectal complications as, 2383, 2383t
colonic complications as, 2381
diverticular disease as, 2381
infectious colitis as, 2381–2382

Immunocompromised patients *(Continued)*
malignancies as, 2383–2384
neutropenic enteritis as, 2382–2383
steroid-induced gastrointestinal perforation as, 2382
surgical risk assessment in, 2380–2381
therapeutic approach to, 2377–2381
altered hormonal response to stress and, 2378
immunosuppression and cancer and, 2380
for inflammatory bowel disease, 2379–2380
for transplantation, 2379
immunosuppression in, 2377–2378
impaired wound healing and, 2378
steroids in, 2377
stress-dose steroids and, 2378–2379, 2379b, 2379t
Immunodeficiency. *See also* Acquired immunodeficiency syndrome; Human immunodeficiency virus infection.
mechanisms of, 2375–2377, 2376b, 2376t
AIDS as, 2376–2377
cancer and cancer therapy as, 2376
malnutrition and injury as, 2376
pharmacologic, 2375–2376, 2377t
pruritus ani associated with, 2070
Immunoglobulin A, secretory, small intestinal immune function and, 1010, 1011f
Immunomodulators, for Crohn's disease, 1053
Immunosuppression
for inflammatory bowel disease, 2091–2092
for islet transplantation, 1424, 1428–1429
for pancreas transplantation, 1418–1419
steroid-induced, 2377–2378
Immunotherapy. *See also* Immunosuppression.
for pancreatic and periampullary carcinoma, 1373
Impedance testing
ambulatory, pH monitoring and, for esophageal bolus clearance testing, 158–159, 159f, 160f
of esophageal bolus clearance, 155–156, 157f, 158, 158f
Imperforate anus. *See also* Anorectal anomalies.
anomalies associated with genitourinary, 2390
sacral and spinal, 2390
high, surgical management of, 2396, 2398–2402, 2399f
with cloacal malformation, 2402, 2403f
colostomy construction and, 2396, 2398f
minimally invasive repair as, 2400–2402, 2401f, 2402f
neonatal pull-through procedures for, 2400
low, surgical management of, 2395–2396
anterior perineal anorectoplasty as, 2396, 2397f
Imperforate anus *(Continued)*
cutback anoplasty as, 2395f, 2395–2396
transplant anoplasty as, 2396, 2397f
In vitro synthesized protein assay, for *APC* gene mutation screening, 2164
Incision(s)
abdominal, for Crohn's disease, 1056–1057, 1057f
for appendectomy, 2145, 2146f
closure of, 2329
for colorectal surgery, 2329
for esophageal reconstruction, 579–580, 580f
for liver surgery, 1671–1673
midline, 1671
right thoracoabdominal, 1671, 1673
subcostal, 1671, 1672f
Incisional hernias, repair of, 682–683, 683f
Inclusion cysts, esophageal, 525
Incontinence. *See* Fecal incontinence.
Infants
anorectal fistulas in, 2058
appendicitis in, acute, 2143–2144
juvenile polyposis syndrome in, 2173
newborn. *See* Neonates.
persistent hyperinsulinemic hypoglycemia of infancy and, 1408–1409
Infections. *See also specific infections.*
in cirrhosis, 1626
following intestinal transplantation, 1176
with gastrointestinal fistulas, 1098
hepatic artery aneurysms due to, 1277
with immunosuppressive therapy, following liver transplantation, 1699, 1699t
intra-abdominal, hematogenous spread of, hepatic abscesses due to, pyogenic, 1642
with pancreatic pseudocysts, 1342–1343, 1343f
pruritus ani associated with, 2070
superior mesenteric artery aneurysms due to, 1278
suture material and, 1084
systemic, hepatic abscesses due to, pyogenic, 1642
wound, with herniorrhaphy, 654
inguinal, laparoscopic, 668
Infectious colitis, in immunocompromised patients, 2381–2382
Inferior mesenteric artery
anatomy of, 1238, 1849, 1850, 1851f, 1867, 1868
variations in, 1869
aneurysms of, 1280
embryology of, 1234, 1236f
hypogastric communications of, 1239, 1240f
in mesenteric ischemia, 1247, 1248f. *See also* Mesenteric ischemia.
superior mesenteric artery communications with, 1239
Inferior mesenteric vein, anatomy of, 1869
Infertility
with inguinal herniorrhaphy, laparoscopic, 667
obesity and, bariatric surgery and, 938
Inflammation
cancer and, 348
local, in pancreatitis, acute, 1297–1298
in pancreatitis, chronic, 1345
perineural, in pancreatitis, chronic, 1345
systemic, in pancreatitis, acute, 1298
Inflammatory bowel disease, 2080–2096. *See also* Crohn's disease; Ulcerative colitis.
cancer and, 2380
as colorectal cancer risk factor, 2187
immunosuppression for, 2379–2380
in primary sclerosing cholangitis, 1563–1564
with primary sclerosing cholangitis, 1693
Inflammatory lesions, gastric, benign, 885
Inflammatory polyps, gastric, 884
Inflammatory processes, small bowel obstruction due to, 1027
Inflammatory pseudotumor
esophageal, 522
in pancreatitis, chronic, 1312
Infliximab
for anorectal abscesses, 2057–2058
for Crohn's disease, 1053, 2128
for gastrointestinal fistulas, 1105
for inflammatory bowel disease, 2092–2093
mechanism of action of, 2377t
Infrared coagulation, for hemorrhoids, 2031, 2031f, 2033
Ingelfinger, Franz, 5
Inguinal canal, embryology of, 705
Inguinal hernias, 643–644
in children, 705–709
clinical features of, 706
contralateral inguinal exploration and, 709
embryology of, 705
incidence of, 705–706
indirect, operative management of, 706–708, 707f, 708f
with undescended testes, 709, 710f
recurrence of, postoperative, 667
Inguinal herniorrhaphy, 656–668
anatomy and, 656–657
laparoscopic, 658–668
complications of, 665–668, 666t
associated with hernia repair, 667–668
associated with laparoscopic approach, 665–667
associated with patient, 667
convention herniorrhaphy compared with
operative strategies and, 659, 661–664
patient selection and, 659
conventional herniorrhaphy compared with, 658–659, 660t, 661t, 661–665
Inguinal ligament, 636
Inguinal region, anatomy of, laparoscopic, 639–642
of abdominal wall innervation and blood supply, 641–642, 642f
of deep aspects, 639–640, 640f

Inguinal region, anatomy of, laparoscopic *(Continued)*
of Hesselbach's triangle and spermatic cord, 641
of transversalis fascia and its derivatives, 640–641, 641f
Inhibitory relaxation wave, swallowing and, 53
Insulinomas, 1375, 1376–1379
invasive localization studies for, 1377–1378, 1378f
preoperative localization of, 1377, 1377f
symptoms and diagnosis of, 1376–1377
therapy of, 1378–1379, 1379f
Intensity-modulated radiation therapy, 1155
Intercostal trunk, superior, 22
Interdigestive migrating motor complex, 188, 189f
phasic activity of, disturbance of, detection by antroduodenal manometry, 188
Interferon, for carcinoid tumors, 1186
Internal hernias, 1120–1126
acquired, 1124–1126, 1125f
clinical features of, 1125
diagnosis of, 1125–1126
treatment of, 1126
congenital, 1120–1124
foramen of Winslow, 1123–1124, 1124f
paraduodenal, 1120–1121, 1121f
clinical features of, 1121
diagnosis of, 1121–1122
treatment of, 1122
transmesenteric, 1122f, 1122–1123
clinical features of, 1123
diagnosis of, 1123
treatment of, 1123
transomental, 1123, 1124f
small bowel obstruction due to, 1120
Internal oblique muscle, 636, 637f, 638
Intersigmoid fossa, 1866
Interstitial cells of Cajal, intestinal motility and, 925
Interventional radiology. *See also specific techniques.*
biliary
for benign biliary disease, 1468
complications of, 1468–1469
image-guided therapy of malignant biliary disease and, 1466–1468
percutaneous transhepatic cholangiography and percutaneous biliary drainage and, 1464–1466
radiologist's role in, 1462–1464, 1463f–1465f
for stone management, 1466
Intestinal anastomoses, 1083, 2331–2335
biofragmentable anastomosis ring for, 1089–1090, 1090f
with colonic J-pouch, 2334
inverted vs. everted, 1085–1086, 1086f
with restorative proctocolectomy for familial adenomatous polyposis or ulcerative colitis with dysplasia or cancer, 2335
Intestinal anastomoses *(Continued)*
stapled, 1086f, 1086–1089, 2333, 2334f–2337f
hand-sewn vs., 1088–1089
staplers for, 1086–1087, 1087f
techniques and pitfalls in, 1087–1088
functional end-to-end anastomosis and, 1087, 1088f
stapled end-to-end anastomosis and, 1087–1088, 1088f
stoma vs., 2335, 2338
sutured, 1083–1086, 2331, 2331f–2333f, 2333
hand-sewn vs. stapled anastomoses and, 1088–1089
methods of, 1084–1086
suture material and, 1083–1084
infection and, 1084
tumor cell adherence and, 1084
sutureless, 2333–2334
tissue adhesives for, 1089
Intestinal atresia, in pediatric patients, 1219–1221, 1220f, 1221f
Intestinal bypass, for Crohn's disease, 1063
Intestinal decompression, 750
Intestinal dysmotility, 926–927
diagnosis of, 926
treatment of
pharmacologic, 926
surgical, 926–927
Intestinal failure. *See* Short-bowel syndrome.
Intestinal fistulas. *See also* Enteric fistulas; *specific sites, e.g.* Anal fistulas.
in Crohn's disease, surgical treatment of, 2095
Intestinal fluid, small intestinal secretion of, 1008–1009, 1010f
Intestinal ganglioneuromatosis syndrome, small intestinal, 894t, 898
Intestinal hemangiomatosis, diffuse, colonic hemangiomas in, 1997
Intestinal lymphomas
diagnosis of, 1208, 1208f
epidemiology of, 1199, 1200t
treatment of, 1209, 1211f
Intestinal metaplasia
Barrett's esophagus and, 334–335
in gastroesophageal reflux disease, 215–216, 217–218
Intestinal motility, 925–926. *See also specific regions of intestine, e.g.* Colonic motility.
in short-bowel syndrome, 1163–1164
improving, 1169
Intestinal obstruction. *See also specific regions of intestine, e.g.* Duodenal obstruction.
with groin hernias, as indication for surgery, 644
with ileostomy, 1078–1080
with inguinal herniorrhaphy, laparoscopic, 666
neonatal, 947–948, 1219
clinical features and diagnosis of, 948
with stomas, 2371
Intestinal perforation
colonic
as emergency surgical indication, 2102
Intestinal perforation *(Continued)*
in immunocompromised patients, 2381
duodenal
with duodenal diverticula, 779
treatment of, 1108–1110
prenatal, meconium peritonitis and, 1225
Intestinal polyposis syndromes. *See also* Familial adenomatous polyposis.
small intestinal
attenuated familial adenomatous polyposis as, 894t, 896
Bannayan-Zonana (Bannayan-Ruvalcaba-Riley) syndrome as, 894t, 897
Cowden's disease as, 894t, 897
Cronkhite-Canada syndrome as, 894t, 898
familial adenomatous polyposis as, 893f, 893–895, 894t
Gardner's syndrome as, 894t, 895
hereditary flat adenoma syndrome as, 894t, 896
hereditary mixed polyposis syndrome as, 894t, 898
intestinal ganglioneuromatosis syndrome as, 894t, 898
juvenile polyposis syndrome as, 894t, 896–897
lymphoid polyposis syndrome as, 894t, 898
Muir-Torre syndrome as, 894t, 896
Peutz-Jeghers syndrome as, 894t, 897–898
Turcot's syndrome as, 894t, 895–896
Intestinal tapering and lengthening procedure, for short-bowel syndrome, 1171–1173, 1172f
Intestinal transit
colonic
in constipation, 1931–1932, 1932f
in rectal prolapse, 1959
prolonging, in short-bowel syndrome, 1169–1171, 1170f, 1170t
colon interposition for, 1171
intestinal pacing for, 1171
intestinal segment reversal for, 1169–1171
intestinal valves for, 1171
recirculating loops for, 1171
small bowel transit studies and, in constipation, 1932
Intestinal transplantation
for intestinal dysmotility, 927
for short-bowel syndrome, 1168, 1173–1177
indications for, 1173–1174
operative procedure for, 1174f, 1174–1175
outcome with, 1175f, 1175–1177, 1176f
Intestinal tubes, for nutrition
complications of, 758
management of, 758
Intra-abdominal abscesses
with appendicitis, 2150
following ileal pouch–anal anastomosis, 2111

Intra-abdominal fistulas, in colonic diverticular disease, 2021
Intracranial pressure, elevated, in fulminant hepatic failure, management of, 1704
Intraductal papillary mucinous neoplasms, 1359
pancreatic
clinical presentation of, 1387–1388
diagnosis of, 1393–1394, 1395f
incidence and epidemiology of, 1387
pathology and biologic behavior of, 1391b, 1391–1392, 1392f
treatment of, 1397–1398
Intraepithelial carcinoma, colorectal, 2192
Intrahepatic cholangiocarcinoma, 1743–1745, 1745f
Intraoperative radiation therapy, 1156
for recurrent cancer, 2417–2418
Intraoperative ultrasound, in Zollinger-Ellison syndrome, 865, 865f
Intraperitoneal-only mesh repair, for inguinal hernias, 656, 661, 664, 665t
Intraperitoneal therapy, for gastric adenocarcinoma, adjuvant, 912–913
Intratracheal tubes, development of, 4
Intravenous immunoglobulin, for idiopathic thrombocytopenic purpura, 1824
Intravenous pyelography, with nephroenteric fistulas, 1106
Intrinsic factor, gastric secretion of, 728
Intussusception
colonic, 1980, 1981f
jejunogastric, following gastrectomy, 879–880
in pediatric patients, 1229–1230, 1230f–1232f, 1232
rectal, surgical treatment of, 1936, 1938f
Invasive radiologic procedures, external biliary fistulas following, etiology and prevention of, 1540–1541
Iodoquinol, for liver abscesses, amebic, 1655
Irinotecan, for metastatic colorectal cancer, 2201
Iron absorption
duodenal, 979–980, 980f
small intestinal, 1007t, 1008, 1009f
Iron deficiency anemia
in Crohn's disease, 1054
following gastrectomy, 873
Iron overload, cardiac iron deposition and, 1693
Irritable bowel syndrome, diarrhea-predominant, 1879–1880
Ischemia
colonic. *See* Colonic ischemia.
mesenteric, acute, colonic ischemia as manifestation of, management of, 2010
with stomas, 2372
Ischemic orchitis, following hernia surgery, 654
Island flaps
for anal stenosis, 2063f, 2063–2064, 2064f
diamond-shaped, for anal stenosis, 2064, 2064f
U-shaped, for anal stenosis, 2064
V-Y, for anal stenosis, 2063f, 2063–2064
Islet cell(s), 1289
proliferation of, 1290
Islet cell dysmaturation syndrome, 1408–1409
Islet cell tumors, in Zollinger-Ellison syndrome. *See* Zollinger-Ellison syndrome.
Islet transplantation, 1422–1429
challenges and emerging opportunities in, 1427–1429, 1428f
alloimmune and autoimmune drugs as, 1428–1429
islet protection and regeneration as, 1429
living donor transplantation as, 1427–1428
supply and demand as, 1427
early clinical trials of, 1423–1424
evaluation and risk assessment for, 1424–1425
historical background of, 1422–1423, 1423f
immunosuppression for, 1424
indications for, 1424
islet preparation for, 1424, 1425f
procedure for, 1425
recent advances in, 1425–1427, 1426f
outcomes and, 1426–1427, 1427f
site of, 1423
Isoniazid, hepatotoxicity of, 1722
Isoperistaltic stricturoplasty, side-to-side, for Crohn's disease, 1059, 1062f
Isoproterenol, mesenteric blood flow and, 1243t
Itraconazole, hepatotoxicity of, 1722
Ivor-Lewis esophagogastrectomy, for gastric adenocarcinoma, 909

J

J pouch, 2104–2105, 2334
Jaboulay gastroduodenostomy, for duodenal ulcers, 795
Jaboulay pyloroplasty, 818, 819f
technique for, 844f
Jaboulay stricturoplasty, for Crohn's disease, 1059, 1062f
Jackson's membrane, 1863
Jamaican bush teas, hepatotoxicity of, 1723
Janeway gastrostomy
with hostile abdomen, 1147
in pediatric patients, 960
Japanese Society for Esophageal Diseases staging system, for esophageal cancer, 448, 449, 452f, 453f, 453t, 454t
Jaundice
with cholangiocarcinoma, palliation for, 1531
cholestatic, pruritus ani in, 2067
in newborns, 1545
obstructive
gallbladder cancer presenting with, 1525
in pancreatic and periampullary carcinoma
Jaundice *(Continued)*
nonoperative palliation of, 1365
operative palliation of, 1366, 1366f
pathophysiology of, 1618–1619
patient approach for, 1460
Jejunal adenocarcinoma, 916
Jejunal artery aneurysms, 1283
Jejunal atresia, 1219
Jejunal carcinoids, treatment of, 1185
Jejunal interposition
for bile reflux gastritis, 876–877, 877f
for dumping syndrome, 872, 872f
Jejunal reservoir, for microgastria, 950
Jejunogastric intussusception, following gastrectomy, 879–880
Jejunoileal atresia, in cystic fibrosis, 1219
Jejunoileal bypass, for obesity, 930, 930f
Jejunoileal diverticula, 783–786
complications of, 784–785
hemorrhage as, 784–785
malabsorption as, 785
obstruction as, 785
perforation as, 785
diagnosis of, 784, 785f
diseases associated with, 783
incidence of, 783
management of, 785–786
nonoperative, 785
operative, 785–786
pathogenesis of, 783–784, 784f
symptoms of, 784
Jejunojejunostomy, for obesity, 933
Jejunostomy, 757–758, 758f
contraindications to, 750t
for esophagogastrostomy, 588
feeding, for microgastria, 950
for gastroduodenal perforations, 1109
indications for, 750t
Witzel, 757, 758f
Jejunum. *See also* Small intestine.
as esophageal substitute, 579
esophagojejunoplasty and, 592–596
free transfer and, 595f, 595–596
interposition and, 593f, 593–594, 594f
results of, 596t, 596–597
Roux-en-Y limb and, 594f, 594–595
for foregut reconstruction for benign disease, 298, 299, 300f
JSED staging system, for esophageal cancer, 448, 449, 452f, 453f, 453t, 454t
Judd stricturoplasty, for Crohn's disease, 1059, 1060f
Juvenile polyposis syndrome, 2159t, 2173–2174
of colon, 2173
generalized, 2173
for hereditary nonpolyposis colorectal cancer, 2188
of infancy, 2173
small intestinal, 894t, 896–897
symptoms and diagnosis of, 897
treatment of, 897

K

Kaposi's sarcoma, in immunocompromised patients, 2384
Kasabach-Merritt syndrome, 1726
Kegel exercises
  for constipation, 1938
  for fecal incontinence, 1921–1922
Kelling, G., 4
Ketoconazole, hepatotoxicity of, 1722
Kidney transplantation, with simultaneous pancreas transplantation, 1417f, 1417–1418, 1418f
Killian-Jamison diverticula, 95
Killian's dehiscence, 94
Killian's triangle, 391
KIT molecule, gastrointestinal stromal tumors and, 1192f, 1192–1193
  targeted therapy and, 1193–1195, 1194f
Klebsiella pneumoniae, hepatic abscesses and, 1644, 1645
Klippel-Trénaunay-Weber syndrome, colonic involvement in, 1999
Knee-shoulder position, 1886
Kocher maneuver, 579, 964, 966f
  with duodenal diverticula, 782, 782f
  in duodenal injury, 766, 767f
Kock continent ileostomy
  for familial adenomatous polyposis, 2165t, 2165–2166, 2166t
  for ulcerative colitis, 2122
Krukenberg tumors, 906
Kugel/Ugahary hernia repair, 651f, 652–653
Kulchitsky cells, 1179, 1182

L

Lacey, Paul E., 1423f
Lacteals, small intestinal, 998
Lactobezoars, 943, 944
  in pediatric patients, 960
Lacunar ligament, 636
Ladd, William, 1213
Ladd procedure, 1217, 1218f, 1219f
Ladd's bands, 1214, 1215f, 1857
Laimer's ligament. *See* Phrenoesophageal membrane.
Laird technique, for rectovaginal fistulas, 1948
Lamina mucosa, prenatal development of, 37, 39t, 39–42
  ciliated columnar epithelium and, 40–41, 41f
  epithelial vacuolization and, 39–40, 40f
  goblet cells and, 40–41, 41f
  lumen occlusion secondary to vacuoles and, 40, 42f
  precursor mucosa proliferation and, 37, 39f
  stratified squamous epithelium and, 41
Lamina propria, of gallbladder, 1444
Lamivudine, hepatotoxicity of, 1720
Lanreotide, for carcinoid tumors, 1186
Lansoprazole. *See also* Proton pump inhibitors.
  gastric acid secretion and, 727
  for laryngitis, 260
Laparoscopic abdominoperineal resection, of rectum, 2239–2241
  technique for, 2239–2241, 2240f
Laparoscopic adhesiolysis, for small bowel obstruction, 1032–1033
Laparoscopic appendectomy, 2147, 2149f
Laparoscopic cholecystectomy
  for bile duct strictures, 1574, 1575f, 1576
  endoscopic retrograde cholangiopancreatography, 1497, 1498f
  external biliary fistulas following, etiology and prevention of, 1538, 1539f
  gallbladder cancer diagnosed incidentally after, 1525
Laparoscopic colectomy, 2345
Laparoscopic colon resection, 2338
Laparoscopic colorectal surgery, 2340–2358
  for cancer
    historical data on
      prospective, 2346–2347
      retrospective, 2346
    operative techniques for
      for colon, 2347–2348
      for rectum, 2348
    outcomes with, 2346
    preoperative staging and, 2347
    randomized trials of, 2345–2346
    training and credentialing and, 2353
    tumor localization for, 2347
    wound implant prevention and, 2348, 2348f–2353f, 2349b, 2351b, 2353
  challenges with, 2344–2346
    anatomic, 2345
    conversions and, 2345–2346
    learning curve and, 2345
  for Crohn's disease
    outcomes of, 2354, 2356, 2356t
    technical points for, 2356
  for diverticular disease
    outcomes of, 2353–2354, 2355t
    technical points for, 2354
  historical background of, 2340, 2341t–2342f
  less common indications for, 2358
  outcomes of minimal access techniques and, 2340, 2342–2344
    complications and, 2343–2344
    hospital costs and, 2343–2344
    length of stay and, 2343
    operative rime and, 2342
    postoperative pain and recovery of pulmonary function and, 2343
    quality of life and, 2343–2344
    return of bowel activity and resumption of diet and, 2343
  for polyps
    outcomes of, 2353
    technical points for, 2353
  for rectal prolapse
    outcomes of, 2357, 2357t
    technical points for, 2357
Laparoscopic colorectal surgery *(Continued)*
  for ulcerative colitis
    outcomes of, 2356–2357
    technical points for, 2357
Laparoscopic drainage, for splenic abscesses, 1820
Laparoscopic enteroclysis, bowel injury during, 1136
Laparoscopic examination
  in gastric adenocarcinoma, 907
  in gastric trauma, 763
  of liver, 1670–1671
  in pancreatic and periampullary carcinoma, for preoperative staging, 1365
  small bowel obstruction after, 1027–1028
  during splenectomy, 1785
  for staging of esophageal cancer, 460
Laparoscopic fundoplication
  for esophageal strictures, 245, 247, 247f
  gastric perforation due to, 1094
Laparoscopic hepatic resection, for hepatic cysts, solitary, 1633
Laparoscopic hernia repair
  for lumbar hernias, 691
  for ventral hernias, 678–680, 679f, 680f
Laparoscopic myotomy, 5
  Heller. *See* Heller myotomy, laparoscopic.
Laparoscopic splenectomy, 1777, 1780–1788
  complications of, 1787–1788
  contraindications to, 1781
  hand-assisted, 1786
    for splenic tumors, 1816
  for idiopathic thrombocytopenic purpura, 1823
  indications for
    elective situations as, 1781, 1781b
    emergency situations as, 1780–1781
  operative technique for, 1782–1786
    anatomic considerations for, 1783
    diagnostic laparoscopy and, 1785
    division of remaining attachments and placement of spleen in specimen bag and, 1785–1786
    division of splenic vessels and, 1785
    extraction of spleen from peritoneal cavity and, 1786
    inspection of operative field and, 1786
    mobilization of spleen with dissection of splenic ligaments and, 1785
    positioning and safe access for pneumoperitoneum and, 1783–1785
    preliminary steps in, 1783–1786
    removal of trocars, desufflation, and closure of port site and, 1786
  patient selection for, 1781–1782
  portal and splenic vein thrombosis following, 1838
  postoperative care for, 1787
  preoperative considerations for, 1782
    general considerations as, 1782
    imaging as, 1782

Laparoscopic splenectomy *(Continued)*
immunizations against overwhelming postsplenectomy infection as, 1782
robotic-assisted, 1787
for splenic trauma, 1802
for splenic tumors, 1816
Laparoscopic surgery. *See also specific procedures.*
for colon cancer, 2252
for colonic inertia, 1936
for Crohn's disease, 1063
for duodenal ulcers, 798, 799f
hand-assisted
for colonic diverticular disease, 2023f, 2023–2024
colorectal, 2353
splenectomy as, 1786
for splenic tumors, 1816
for peptic ulcer disease, perforation in, 823–824
reoperative, 1135
technique for, 1135–1136
Laparoscopic therapy
for choledocholithiasis. *See* Choledocholithiasis, laparoscopic management of.
for gastric cancer, 745
for gastric volvulus, 1038–1039
for paraesophageal hernia, 554–557
open repair vs., 558
technique for, 555, 555f–557f, 557
for rectal prolapse, 1961
for undescended testes, 711
Laparoscopic ultrasound, in gastric adenocarcinoma, 907–908
Laparoscopically assisted anorectal pull-through, for high imperforate anus, 2400–2402, 2401f 2402f
Laparoscopic-assisted surgery
for Crohn's disease, 2132
gastrostomy as, in pediatric patients, 960
Laparotomy
for caustic injury, gastric, 763
exploratory, in duodenal injury, 766
for gastric volvulus, 1038
with gastrointestinal fistulas, 1106
small bowel, perforation due to, 770
ventral hernia following, 674
Lap-Band, 934
Large intestine, 1845. *See also* Colon.
Laryngeal nerves
inferior
nonrecurrent, prenatal development of, 45
recurrent, anatomy of, 25–26, 26f, 27f
superior, anatomy of, 25–26
Laryngitis
in gastroesophageal reflux disease, medical therapy for, 258–259
reflux, endoscopic appearance of, 259, 261f
Larynx, prenatal development of, 31–33, 33f, 34f
Laser therapy
ablative, for Barrett's esophagus, 370–371
Laser therapy *(Continued)*
for colonic ectasias, 1995
for hemorrhoids, 2033
lithotripsy as, for bile duct stones, 1495
Nd:YAG, for esophageal cancer, 489t, 492–493
thermotherapy as, for hepatocellular carcinoma, 1738
Lateral decubitus position, 1886, 1886f
Lateral fossa, 639
Leakage
following cardiomyotomy, 85
following cricopharyngeal myotomy, 84–85
following esophagectomy, 86
following esophagogastrostomy, 86
LEA29Y, for islet transplantation, 1428
Lecithin, in bile, 1452
Leiomyomas
colorectal, 2316–2317
esophageal, 515–520, 516f–519f, 516t, 518t
benign, malignant transformation of, 123
endoscopic ultrasonography in, 123, 124f
imaging of, 81, 82, 83f
gastric, 888
endoscopic appearance of, 740–741, 741f
small intestinal, 899–900
Leiomyosarcomas
colorectal, 2316f, 2316–2317
esophageal, imaging in, 81
hepatic, 1747
Lembert suture, 1084, 1085f
Leptin, gastric, 723–724
Lesser omentum, 717
Leucovorin, for metastatic colorectal cancer, 2201
Leukemia
anorectal sepsis in, 2058
splenectomy for, 1830t, 1830–1831
Leukocytosis, following splenectomy, 1777, 1838
Levator ani muscle complex, 696
Levator hernias, 687, 694–700
anatomy and, 696, 697f
classification of, 694–696, 695f, 696f
clinical features and diagnosis of, 696, 698f, 698–699, 699f
treatment of, 699–700, 700f–703f
Levator spasm, 2071
Levator syndrome, 2071
Lewis, double incisions of, 579
Lexipafant, for pancreatitis, severe, necrotizing, 1303–1304
Lhermitte-Duclos syndrome, 2175
Lice, pruritus ani associated with, 2070
Lichen planus, esophageal strictures in, 89–90, 92f
Lichen sclerosus et atrophicus, pruritus ani associated with, 2069–2070
Lichtenstein herniorrhaphy, 649, 650f
Liebermann-Meffert, Dorothea, 7
Lifestyle modifications, for gastroesophageal reflux disease, 252–253
Ligament(s)
anchoring stomach, 717–718, 718f
associated with external oblique muscle, 636, 637f
Ligament of Treitz, 968, 970f, 1864
Ligamentum venosum, 1598
Ligature, for Crohn's disease, 1063
Linea alba, 672, 672f
Linear cutters, 1086, 1087f
Linear staplers, 1086, 1087f
Linitis plastica, 905, 906
Lipase, serum
in pancreatic trauma, 1401
in pancreatitis, 1299, 1300b
Lipids
duodenal absorption of, 980
small intestinal absorption of, 1003t, 1004–1006, 1005f, 1006f
Lipohyperplasia, of ileocecal valve, 900–901
Lipomas
esophageal, 522
endoscopic ultrasonography in, 123
gastric, 887–888, 888
small intestinal, 900
Lipomatous hypertrophy, of ileocecal valve, 900–901
Liposarcomas
colorectal, 2317
hepatic, 1747
Lithotripsy, for bile duct stones, 1494–1495
Littre, Alexis, 632
Liver. *See also* Hepatic *entries;* Hepatobiliary *entries.*
anatomic segments of (Couinaud), 1604–1607, 1673f, 1673–1674
left hemiliver (segments II, III, IV, and I) and, 1604
left lobe (segments II and III) and, 1604–1605
posterior liver (dorsal liver, sector I) and, 1604
right hemiliver (segments V, VI, VII, and VIII) and, 1605f, 1605–1606
right lateral sector (segments VI and VII) and, 1606
right paramedian sector (segments V and VIII) and, 1606
segment IV and, 1605
segment VII and, 1606
segment VIII and, 1607
segments V and VI and, 1606
anatomy of, 2275–2276, 2276f
of cystic veins, 1603
of cystohepatic ducts, 1603
of fissures, 1599f, 1602–1603
functional, 1673f, 1673–1674
of hepatic arteries, 1600, 1602
of hepatic ducts, 1602
of hilar plate, 1599f, 1603
of hilum, 1602
lymphatic, 1607
microscopic, 1607
neural, 1607
of parabiliary venous system, 1603
of portal vein, 1602
segmental, 1753, 1754f
of small ducts, 1603
of sulcus of Rouviere, 1603

Liver *(Continued)*
of vasculobiliary sheaths, 1599–1600
venous, 1603–1604
bile formation and, 1608
colorectal cancer metastases to. *See* Hepatic metastases, of colorectal cancer.
divisions of, 1598–1599
embryology of, 1598
metastases to, carcinoid, 1185–1186
mobilization of, 1659, 1660f, 1661f
morphology of, 1673f, 1673–1674
packing of, to control bleeding, 1664f, 1664–1665
regeneration of, 1608, 1608f
trauma to. *See* Hepatobiliary trauma.
wrapping with absorbable mesh, to control bleeding, 1665, 1665f
Liver abscesses, 1640–1657
amebic, 1650–1657
complications of, 1654–1655
pleuropulmonary, 1655
rupture into pericardium as, 1655
demographics of, 1651
diagnosis of, 1653–1654
computed tomography in, 1654
liver scanning in, 1654
magnetic resonance imaging in, 1654
radiography in, 1654
ultrasonography in, 1654
etiology and pathogenesis of, 1651
incidence of, 1650–1651
location and number of, 1651–1652
outcome and prognostic factors for, 1656–1657
patient presentation and, 1652t, 1652–1653, 1653t
treatment of, 1655–1656
medical, 1655–1656
percutaneous drainage for, 1656
surgical drainage for, 1656
pyogenic, 1640–1650
anatomic considerations with, 1654, 1655t
demographics of, 1640–1641, 1641t
diagnosis of, 1646–1647
cholangiography in, 1646, 1646f
computed tomography in, 1646–1647, 1647f
magnetic resonance imaging in, 1647, 1648f
radiography in, 1646
ultrasonography in, 1646
etiology and pathogenesis of, 1641–1642, 1642t
laboratory analysis for, 1643, 1644t
management of, 1647–1650
antibiotics in, 1648–1649
drainage procedures for, 1649
microbiology of, 1644–1645
outcome with, 1650
presenting signs and symptoms of, 1643, 1643t, 1652t, 1653t
prognostic factors for, 1650
risk factors for, 1642–1643
Liver biopsy, 1670–1671
in hepatocellular carcinoma, 1734
laparoscopic, 1670–1671
open, 1671
percutaneous, 1616, 1670
in primary sclerosing cholangitis, 1561
transjugular, 1670
Liver bud, 1598
Liver disorders. *See also specific disorders.*
anesthesia in, 1626
operative considerations in, 1626–1627
with parenteral nutrition, in short-bowel syndrome, 1165, 1167
perioperative management for, 1618–1622
general assessment and preoperative preparation and, 1619t, 1619–1620, 1620t
hepatic functional reserve and, 1621
nutritional intervention and, 1621–1622
nutritional status and, perioperative management for, 1621
postoperative management in, 1627–1628
vascular, 1711–1715
of hepatic artery, 1711–1714
aneurysms as, 1711–1712, 1712f
arterioportal and arteriovenous shunts as, 1713f, 1713–1714
thrombosis as, 1712–1713, 1713f
traumatic, 1712
of hepatic vein, Budd-Chiari syndrome as, 1714f, 1714–1715
Liver failure
acute, 1702–1704
etiology of, 1702–1703
fulminant, 1702
treatment of, 1703–1704
liver transplantation for, 1704
medical, 1703–1704
in portal hypertension, 1756
Liver function
assessment of, in portal hypertension, 1758
tests of. *See* Hepatic laboratory tests.
Liver injury, external biliary fistulas following, etiology and prevention of, 1539, 1539f
Liver resection, external biliary fistulas following, etiology and prevention of, 1539–1540
Liver scans, with liver abscesses, amebic, 1654
Liver support systems, 1704–1708
biologic, 1706–1707, 1707f
future of, 1707–1708, 1708f
need for, 1705
nonbiologic, 1705–1706
Liver surgery
incisions for, 1671–1673
midline, 1671
right thoracoabdominal, 1671, 1673
subcostal, 1671, 1672f
modern anatomic approach to, 1597, 1599f–1601f
transfusion with, 1619–1620
Liver transplantation, 1685–1700, 1686f
for ascites, 1765
for biliary atresia, 1550–1551
candidacy for, 1688–1694
allocation and, 1691t, 1691–1692, 1692t
associated conditions and special considerations and, 1692–1694
contraindications and, 1688–1691, 1689t, 1690t
indications for transplantation and, 1688
for cholangiocarcinoma, 1530–1531
complications of
early, 1698
biliary, 1698
hepatic artery thrombosis as, 1698
portal vein thrombosis as, 1698
late, 1699–1700
of immunosuppressive medications, 1699–1700
rejection as, 1699
epidemiology of, 1685–1687, 1686t
causes of end-stage liver disease and, 1686–1687
evaluation for, 1687–1688
external biliary fistulas following, etiology and prevention of, 1540
for fulminant liver failure, 1704
future directions for, 1700
for hepatocellular carcinoma, 1739–1740
resection vs., 1740
intraoperative problems and
graft function and primary nonfunction as, 1697–1698
hepatic artery failure as, 1697
portal vein thrombosis as, 1697
split grafts as, 1697
living donor, 1740
adult-to-adult, 1694–1695, 1695f
for metastatic carcinoid, 1186
Milan criteria for, 1739–1740
organ shortage and, 1700, 1700b
for polycystic liver disease, 1635
for primary sclerosing cholangitis, 1569–1570, 1588–1589
procedure for, 1695–1697
for back table preparation of donor organ, 1696
for biliary reconstruction, 1696–1697
for implantation, 1696
reperfusion syndrome and, 1696
for total native hepatectomy, 1695
for venovenous bypass, 1695–1696
split grafts for, 1697
University of California San Francisco criteria for, 1740
Liver–small bowel transplantation, for short-bowel syndrome, 1174f, 1174–1175
Longmire-Traverso procedure, for pancreatitis, chronic, 1314, 1315
Long-tube decompression, for small bowel obstruction, 1032
Loop ileostomy, 2366, 2367f
Loperamide, for fecal incontinence, 1921
Lortat-Jacob, Jean-Louis, 337

Los Angeles classification, for reflux esophagitis, 106, 106t, 107f
Lower esophageal high-pressure zone. *See* Lower esophageal sphincter.
Lower esophageal sphincter, 100
achalasia and, 405–406, 406f. *See also* Achalasia.
anatomy of, 17–18, 19f, 63
failure of, increased esophageal exposure to gastric juice due to, 141, 141f
gastroesophageal barrier and, 223–228, 224f, 226t
hypertensive, 423–426
in achalasia, 407
examination in, 424
manometric features of, 420t
treatment of, 424, 426
incompetent, Nissen fundoplication for. *See* Nissen fundoplication.
length of, 224, 225f
medications relaxing, adenocarcinoma and, 445
nonrelaxing, 138, 140f
permanently defective, 225–226, 226t
position of, 224–225
pressure and, 224, 225f
swallowing and, 53–55, 54t, 132–134, 133f
transient loss of competence of, gastroesophageal barrier and, 226–228, 226f–228f
Lower esophageal sphincter manometry, 165t
Ludlow, Abraham, 5
Lumbar hernias, 687–691
anatomic considerations and, 688, 688f
classification of, 689–690
clinical features and diagnosis of, 688–689, 689f
historical background of, 687–688
incarceration plus strangulation of, 689
treatment of, 690f, 690–691
Lumbar plexus, 657
Lung disease, end-stage, gastroesophageal reflux disease associated with, diagnosis of, 171–172
Lung transplantation, gastroesophageal reflux disease associated with, diagnosis of, 171–172
Luschka, ducts of, 1444
Lyall, Alexander "Sandy," 337
Lye, gastric injury due to, 762
Lymphadenectomy, for gastric adenocarcinoma, extent of, 909–911, 910f, 910t
Lymphangiomas
gastric, 887
small intestinal, 899
splenic, 1815
Lymphocytic leukemia, chronic, splenectomy for, 1830t, 1830–1831, 1831t
Lymphogranuloma venereum, anal, in immunocompromised patients, 2383t
Lymphoid polyposis syndrome, small intestinal, 894t, 898
Lymphoid tumors, splenic, 1815
Lymphomas
colorectal, 2314
Hodgkin's, splenic, 1816
non-Hodgkin's, 1199–1210
clinical features of, 1199–1200, 1201t
diagnosis of, 1206–1208
of gastric lymphoma, 1207f, 1207–1208, 1208f
of intestinal lymphoma, 1208, 1208f
epidemiology of, 1199, 1200t
esophageal, imaging in, 81
gastric, epidemiology of, 1199, 1200t
grading of, 1205–1206
incidence of, 1199
pancreatic, 1434–1436, 1436f
in pediatric patients, 1411
pathology of, 1200, 1201t, 1202t, 1203–1205
of Burkitt's lymphoma, 1204, 1204f
of diffuse large B-cell lymphoma, 1200, 1202f, 1203
of enteropathy-type T-cell lymphoma, 1205, 1205f, 1206t
of follicular lymphoma, 1204
of MALT lymphoma, 1203f, 1203–1204, 1204f
of mantle cell lymphoma, 1204, 1205f
prognosis of, 1210
small intestinal, epidemiology of, 1199, 1200t
splenectomy for, 1829, 1829t, 1830b
splenic, 1816
staging of, 1206, 1206b, 1207b
treatment of, 1208–1209
of gastric lymphoma, 1209, 1209t, 1210f
of intestinal lymphoma, 1209, 1211f
Lymphoplasmacytic sclerosing pancreatitis, 1436–1437, 1437f
Lymphoproliferative disorders, splenectomy for, 1827–1831
for Hodgkin's disease, 1827–1829, 1828f, 1828t
for leukemias, 1830t, 1830–1831
for non-Hodgkin's lymphoma, 1829, 1829t, 1830b
Lynch syndrome I, 2169, 2188
Lynch syndrome II, 2169, 2188

M

M cells, small intestinal immune function and, 1010, 1012f
Macrocystic adenomas. *See* Mucinous cystic neoplasms, pancreatic.
Macronutrients, duodenal absorption of, 980
Magnetic resonance cholangiopancreatography
with alkaline phosphatase elevation, 1615
with bile duct strictures, 1579
with biliary fistulas, 1542
Magnetic resonance cholangiopancreatography *(Continued)*
with choledochal cysts, 1553
in malignant bile duct obstruction, 1506
in pancreatic carcinoma, 1354
with pancreatic cystic neoplasms, 1396
in pancreatitis
acute, 1300
chronic, 1347
Magnetic resonance defecography, in constipation, 1933
Magnetic resonance imaging
with anorectal abscesses, 2051
with anorectal fistulas, 2051
of carcinoid tumors, 1183–1184, 1184f
with colon, rectal, and anal disorders, 1893, 1895, 1895f
in Crohn's disease, 1047–1048, 1048f, 1049f
in gastric adenocarcinoma, 907
with groin hernias, 643
with hepatic abscesses, pyogenic, 1647, 1648f
of hepatic cysts, solitary, 1631, 1632f–1634f
in hepatocellular carcinoma, 1735, 1735f
for insulinoma localization, 1377
in jaundice, obstructive, 1462, 1462f
with liver abscesses, amebic, 1654
in mesenteric ischemia, 1253
in obstructed defecation, 1879
with pancreatic cystic neoplasms, 1393
of pancreatic pseudocysts, 1331
in pancreatitis, chronic, 1347
in periampullary carcinoma, 1362, 1363f
of perineal hernias, 699
in perineal pain syndromes, 2074
in portal hypertension, 1757
in primary sclerosing cholangitis, 1562
with retrorectal tumors, 2301
Magnification endoscopy, in Barrett's esophagus, 104, 105f
Major histocompatibility complex antigens, achalasia due to, 406
Malabsorption, with jejunoileal diverticula, 785
Malago maneuver, 1605
Malaise, in Crohn's disease, 1045
Males
anorectal anomalies in, 2394, 2394f
low anterior resection in, 2228–2229, 2229f
sexual dysfunction in, as ileal pouch–anal anastomosis complication, 2117
Malignancies. *See also* Metastases; *specific malignancies.*
achalasia due to, 408–409
in immunocompromised patients, 2383–2384
immunosuppression due to, 2376
with immunosuppressive therapy, 2380
following liver transplantation, 1699–1700
inflammation and, 348
reoperative pelvic surgery for, 2417–2418
in ulcerative colitis, as surgical indication, 2101

Malignant carcinoid syndrome, 1182
Malignant fibrous histiocytoma, colorectal, 2317
Mallory-Weiss tears, 762
Malnutrition
  with gastrointestinal fistulas, 1098
  immunosuppression due to, 2376
Malone antegrade colonic enema procedure, 2405
Maloney dilators, 5
Malrotation, in pediatric patients, 1213–1214, 1214f–1219f, 1216–1217, 1219
MALT lymphoma, pathology of, 1203f, 1203–1204, 1204f
Mannitol, for bowel preparation, 2328
Manometry
  anal, in fecal incontinence, 1919
  anorectal
    in constipation, 1932–1933
    in obstructed defecation, 1879b
  antroduodenal, delayed gastric emptying and, 186–188, 188f, 188t, 189f, 190, 190t
  esophageal
    in achalasia, 407, 408f, 408t, 411
    combined with multichannel intraluminal impedance, 175–176, 178f, 179, 179f
    in esophageal spasm, 419–420, 420t, 421f
    in hypertensive lower esophageal sphincter, 420t, 424, 424f, 425f
    in nutcracker esophagus, 420t, 422f, 422–423, 423f
    with paraesophageal hernia, 552
    24-hour
      ambulatory, 152–154
      stationary, 144–146, 145f–155f, 145t, 150, 152
  lower esophageal sphincter, 165t
  small bowel, in intestinal dysmotility, 926
  sphincter of Oddi, 1492–1493
  for swallowing evaluation, 378
Mantle cell lymphoma
  pathology of, 1204, 1205f
  splenectomy for, 1829
Marginal artery, 1851, 1853f
Marginal zone B-cell lymphoma, splenectomy for, 1829
Markex, 675
MARS, 1705–1706
Marshall, Samuel, 4
Marsupialization
  for pilonidal disease, 1968
  for splenic cysts, 1815
Martin anoplasty, for anal stenosis, 2063
Matrix metalloproteinases, groin hernias and, 635
Matthias, Nicolaus, 1813
Mattress suture, horizontal, 1085
Mayo, William, 681
Mayo repair, 676–677, 677f, 681
McBurney's point, 1846
  tenderness of, in appendicitis, 2142
McVay Cooper's hernia repair, 648
Meandering mesenteric artery, 1239
Meckel's diverticula, 786–789, 1225, 1227, 1227f
  complications of, 787
    diverticulitis as, 787, 789f
    hemorrhage as, 787
    obstruction as, 787, 788f
    umbilical, 787
  diagnosis of, 786f, 786–787
  incidence of, 786
  management of, operative, 787–789
  pathogenesis of, 786
  symptoms of, 786
Meconium, in urine, 2394, 2394f
Meconium cysts, in utero perforation and, 1225, 1225f
Meconium ileus, 1224f, 1224–1225, 1225f
Meconium peritonitis, 1225
Meconium plug syndrome, 1224, 1224f
Meconium syndromes, 1224f, 1224–1225, 1225f
Medial fossa, 639
Mediastinum, prenatal development of, 34f, 35, 39f
Medications. *See* Drug *entries; specific drugs and drug types.*
Megacolon
  chronic, 1879
  toxic
    as emergency surgical indication, 2101
    in ulcerative colitis, 2084
Megaesophagus. *See* Achalasia.
Meglumine diatrizoate studies, in duodenal injury, 765–766
Meissner's plexus, 720
Melanomas
  anal, 2295
  anorectal, pruritus ani and, 2068
  colorectal, 2317–2318, 2318f
  esophageal, imaging in, 81
Melatonin, duodenal function and, 981t, 985
MELD, 1691t, 1691–1692, 1692t
  in portal hypertension, 1758, 1758b
MELS, 1706–1707
MEN. *See* Multiple endocrine neoplasia; Zollinger-Ellison syndrome.
Ménétrier's disease, 886
Menstrual cycle
  following ileal pouch–anal anastomosis, 2117
  obesity and, bariatric surgery and, 938
Meperidine, for endoscopic retrograde cholangiopancreatography, 1491
6-Mercaptopurine
  for Crohn's disease, 1053, 2128
  for gastrointestinal fistulas, 1105
  for inflammatory bowel disease, 2091–2092
"Mercedes-Benz" sign, 1867
Mesalamine
  for Crohn's disease, 2127
  for inflammatory bowel disease, 2090
Mesenchymal clefts, development of, 31
Mesenteric arteries *See also* Inferior mesenteric artery; Superior mesenteric artery.
  inferior, 1128
  superior
    anatomy of, 1128, 1129f
    injuries to, 1128–1132
      operative exposure and management decisions regarding, 1128–1130, 1129f–1131f
      treatment results with, 1130t, 1130–1132
Mesenteric arteriography, preoperative, for esophageal replacement, 287–288, 288f
Mesenteric artery endarterectomy, 1258, 1259f
Mesenteric circulation, 1234–1245, 1235f. *See also* Inferior mesenteric artery; Superior mesenteric artery.
  autoregulatory escape and, 1243
  catecholamines and, 1243t, 1243–1244, 1244f, 1244t
  collaterals of, clinical correlations of, 1234–1245, 1235f
  control mechanisms of, 1241–1242
    extrinsic control of splanchnic blood flow and, 1241
    intrinsic control of splanchnic blood flow and, 1241–1242, 1242b
  digestion and, 1242–1243
  dopamine and, 1243
  embryology of, 1234, 1235f, 1236f
  physiology of, 1240–1241
  resting state and, 1242
Mesenteric cysts, 1860
Mesenteric ischemia, 1247–1261, 1248f
  acute
    arterial, 1248–1255, 1250f–1251f
    colonic ischemia as manifestation of, management of, 2010
    venous, 1255–1257, 1256f
  arterial, acute, 1248–1255, 1250f–1251f
    diagnosis of, 1251–1254
      arteriography for, 1253f, 1253–1254, 1254, 1254f
      computed tomography for, 1252t, 1252–1253
      magnetic resonance imaging for, 1253
      plain films for, 1252
      ultrasonography for, 1252
    embolic occlusion and, 1249b, 1249–1250
    nonocclusive, 1251
    patient management for, 1254f, 1254–1255
    thrombotic occlusion and, 1250
  chronic, 1257–1261
    clinical features and diagnosis of, 1257–1258
    mesenteric revascularization for, 1258–1261
      endovascular, 1260–1261, 1263t, 1264t, 1265f
      surgical, 1258–1260
  venous, acute, 1255–1257, 1256f

Mesenteric revascularization, 1258–1261
endovascular, 1260–1261, 1263t, 1264t, 1265f
surgical, 1258–1260
aortomesenteric bypass for, 1258–1260, 1260f
mesenteric artery endarterectomy for, 1258, 1259f
retrograde bypass for, 1260, 1261f, 1262f
Mesenteric vein
inferior, anatomy of, 1869
superior, 968, 972f, 1772
anatomy of, 1869
Mesenteric venous thrombosis
acute, ischemia due to, 1255–1257, 1256f
following splenectomy, 1838
Mesh contraction, with inguinal herniorrhaphy, laparoscopic, 668
Mesocolic hernias, 975–976, 976f, 1120–1121, 1121f, 1858, 1861f
clinical features of, 1121
diagnosis of, 1121–1122
treatment of, 1122
Mesomesenteric artery, 1239
Mesorectal excision, total, 2246
with autonomic nerve preservation, 2236f, 2236–2243
distal rectal mobilization and, 2239
hypogastric nerves and pelvic autonomic nerve plexuses and, 2237–2238, 2238f
initial entry into retrorectal space and, 2236–2237, 2237f
"lateral ligaments" and, 2238–2239, 2239f
separation of anterior and posterior compartments and, 2238, 2238f
Metabolic acidosis, in short-bowel syndrome, 1166
Metabolic alkalosis, in short-bowel syndrome, 1166
Metabolic disorders
following gastrectomy, 873
following gastric bypass, 934
Metal biliary endoprostheses, for malignant biliary disease, 1466–1468
Metastases
of anal squamous cell carcinoma, 2294, 2295f
assessment for, in esophageal carcinoma, 471–472
carcinoid, surgical therapy for, 1185–1186
colorectal cancer and. *See* Colorectal cancer, metastases of; Hepatic metastases, of colorectal cancer.
to esophagus, imaging in, 81, 82f
pancreatic, 1437–1439, 1438f, 1439f
splenic, 1816
splenectomy for, 1832
in Zollinger-Ellison syndrome, 868
Methotrexate
for Crohn's disease, 1053, 2128
hepatotoxicity of, 1721, 1723
for inflammatory bowel disease, 2092
Methyldopa, hepatotoxicity of, 1721, 1722
Methylprednisolone
for cholangitis prophylaxis, 1550t
for idiopathic thrombocytopenic purpura, 1824
Metoclopramide. *See also* Prokinetic agents.
for esophageal strictures, 237
for gastroesophageal reflux disease, 253
for gastroparesis, 921
Metronidazole
for anorectal abscesses, 2057
for *Clostridium difficile* colitis, in immunocompromised patients, 2382
for Crohn's disease, 1052, 2128
for inflammatory bowel disease, 2091
for liver abscesses, amebic, 1655–1656
for lymphoma, 1209t
preoperative, 2328
Meyers, Willy, 7
MHC antigens, achalasia due to, 406
Microcystic adenomas. *See* Serous cystic neoplasms, pancreatic.
Microgastria, in pediatric patients, 950
Microsatellite instability, 1360, 2169, 2170–2171
Microsurgery, endoscopic, transanal, for rectal cancer, 2211–2212, 2212f
outcomes with, 2215, 2216t
Microwave thermotherapy, for hepatocellular carcinoma, 1738
Midesophageal diverticulum, 437–438, 438f, 439f
Midline incision, for appendectomy, 2145
Midpelvic anatomy, transverse, low anterior resection and, 2223, 2224f
Migrating myoelectric complex
fasting gastric motility and, 730
gallbladder function and, 1458, 1459
intestinal motility and, 925
in short-bowel syndrome, 1163–1164
small intestinal motility and, 1015f, 1015–1016, 1016f
Milan criteria, for liver transplantation, 1739–1740
Milk, lactobezoars and, 943, 944
Milligan-Morgan hemorrhoidectomy, 2032–2033
Mineral(s), small intestinal absorption of, 1008, 1009f
Mineral oil, pruritus ani associated with, 2069
Minicholecystectomy, 1477
Minnesota Multiphasic Personality Inventory, in constipation, 1934
Minocycline, hepatotoxicity of, 1721, 1722
Mirizzi's syndrome, 1471, 1474, 1526
Mismatch repair gene, 2169–2171, 2170f
Mitochondrial cytopathies, drug-induced, 1719t, 1720
Mixed cholangiohepatocellular carcinoma, 1745–1746, 1746f
Mixed connective tissue disease, esophageal motility disorders in, 140
MMPI, in constipation, 1934
MMR gene, 2169–2171, 2170f
Model for End-Stage Liver Disease, 1691t, 1691–1692, 1692t
in portal hypertension, 1758, 1758b
Modular Extracorporeal Liver System, 1706–1707
Molecular Adsorbent Recycling System, 1705–1706
Mollard procedure, 2405
Moloney darn, 648
Morbid obesity, surgery for. *See* Bariatric surgery.
Morgagni, foramen of, 36–37
Morgagni hernias, 561
Moskel-Walske-Neumayer stricturoplasty, for Crohn's disease, 1059, 1060f
Motilin
duodenal function and, 981t, 982
small intestinal neuroendocrine function and, 1019
Moynihan, Berkeley, 1296
MRCP. *See* Magnetic resonance cholangiopancreatography.
MRI. *See* Magnetic resonance imaging.
Mucinous cystadenocarcinomas, 1391
Mucinous cystadenomas, 1390
Mucinous cystic neoplasms, pancreatic
clinical presentation of, 1387
diagnosis of, 1393, 1394f
incidence and epidemiology of, 1387
pathology and biologic behavior of, 1389f, 1389–1391, 1390f
treatment of, 1397
Mucocutaneous pigmentation, in Peutz-Jeghers syndrome, 2174
Mucocutaneous separation, with ileostomy, 1080
Mucosa
cardiac. *See* Cardiac mucosa.
esophageal
anatomy of, ultrasound, 114–115, 115f
injury of, duodenal reflux and, 230–232
small intestinal, 998
Mucosal resection, endoscopic
for Barrett's esophagus, 370
for gastric adenocarcinoma, 909
Mucosectomy
of rectal stump, for coloanal anastomosis, 2247, 2247f, 2248f
transanal, for ileal pouch–anal anastomosis, 2108, 2108f
Mucus, gastric, 728
Muir-Torre syndrome, 2188
small intestinal, 894t, 896
"Mules," 943, 943f
Multichannel impedance–esophageal manometry, 136–138, 137t, 138f, 139f
Multichannel intraluminal impedance, 175–183
combined with manometry, 175–176, 178f, 179, 179f
combined with pH monitoring, 180–181, 180f–183f
preoperative, for Nissen fundoplication, 266
principles of, 175, 176f–178f
Multilumen tubes, 756
Multiorgan Dysfunction Score, for pancreatitis, acute, 1302

Multiple endocrine neoplasia
surgical management for, 866–867, 867f
type 1, 1379–1380
diagnosis of, 1379–1380
prognosis of, 1380
therapy of, 1380
Zollinger-Ellison syndrome and. *See* Zollinger-Ellison syndrome.
Multiple hamartoma syndrome, 894t, 897, 2159t, 2175–2176
Multiple sclerosis, esophageal motility disorders in, 140
Multipolar electrocoagulation, for Barrett's esophagus, 371
Multislice (multidetector) computed tomography, with pancreatic tumors, unusual, 1431
Multivisceral transplantation, for intestinal dysmotility, 927
Muscarinic receptors, gastric acid secretion and, 725
Muscle(s). *See also specific muscles.*
esophageal
arrangement of, 16, 17f–19f
types of, 17, 19f
foregut, prenatal development of, 37, 38f
Muscle guarding, in appendicitis, 2142
Muscle layer, of gallbladder, 1444
Muscle-splitting incision, for appendectomy, 2145
Muscularis propria
anatomy of, ultrasound, 115f, 115–116
benign tumors of, endoscopic ultrasonography in, 123, 124f
small intestinal, 998
MUSE classification, for reflux esophagitis, 106t
Mushroom poisoning
fulminant liver failure due to, 1703
liver disease due to, 1720
Mutation cluster region, 2163
Mycobacterium infection
M. avium subspecies *paratuberculosis,* in Crohn's disease, 2091
splenic abscess due to, 1819, 1820
Mycophenolate mofetil, mechanism of action of, 2377t
Mycotic infections. *See also specific infections.*
pruritus ani associated with, 2070
Myelofibrosis with myeloid metaplasia, splenectomy for, 1831
Myelogenous leukemia, chronic, splenectomy for, 1831
Myeloproliferative disorders, splenectomy for, 1831–1832
Myenteric plexus, prenatal development of, 46
Myenteric reflex, 1014
MYH polyposis, 2168–2169
Myoblastomas, granular cell, esophageal, 520–521, 521f
Myopectineal orifice, 636
Myoplasty, dynamic, for fecal incontinence, 1923–1924
Myotomy
cricopharyngeal, 378–384
esophageal imaging following, 84–85, 85f
Myotomy *(Continued)*
indications for, 378–379
for myogenic dysphagia, 384, 386, 386f, 387f, 388
for neurologic dysphagia, 382, 384, 385f–386f
operative technique for, 379–380
access to pharyngoesophageal junction and, 379, 380f, 381f
position and incision and, 379, 379f
for oropharyngeal dysphagia, 382f
complications of, 381–382, 384f
drainage and closure for, 381
idiopathic upper esophageal sphincter dysfunction and, 388, 389f
mucosal integrity and, documentation of, 381, 384f
myogenic, 384, 386, 386f, 387f, 388
after neck surgery, 379, 388
postoperative care for, 381
results with, 382, 384, 384b, 385f–386f
Zenker's diverticulum and, 378–379, 381, 383f
for Zenker's diverticulum, 429
methods and results of, 429–431, 430f, 431f
for diffuse esophageal spasm, 421
for esophagogastrostomy, 585
extramucosal, for Zenker's diverticulum, 396–397, 397f, 398f
Heller. *See* Heller myotomy.
for hypertensive lower esophageal sphincter, 424, 426
laparoscopic, 5
for nutcracker esophagus, 423

N

Naltrexone, for pruritus, in primary sclerosing cholangitis, 1567
NANC pathway, 720
Nasobiliary tubes, for bile duct stones, 1496, 1496f
Nasoenteric intubation, 749–753
complications of, 753
contraindications to, 750t, 752
indications for, 750t, 750–752
methods of, 752f, 752–753
tubes for, 749–750, 751f
Nasogastric intubation, 749–753
complications of, 753
contraindications to, 750t, 752
esophageal strictures due to, 90
indications for, 750t, 750–752
methods of, 752f, 752–753
tubes for, 749–750, 751f
Natalizumab
for inflammatory bowel disease, 2093
mechanism of action of, 2377t
Nausea, in appendicitis, 2142
NDO plicator, for endoscopic antireflux procedures, 308b, 314–316
complications of, 316
efficacy of, 315–316, 316t
NDO plicator, for endoscopic antireflux procedures *(Continued)*
physiologic/anatomic mechanisms of, 329–330, 330f
procedure for, 314f, 314–315, 315f
results with, 325, 326t, 327t
Nd:YAG laser therapy, for esophageal cancer, 489t, 492–493
Neck
anatomy of, 14–15, 15f
esophageal anchorage in, 12, 13f
Neck surgery, oropharyngeal dysfunction following, cricopharyngeal myotomy for, 388, 390
Necrolytic migratory erythema, with glucagonoma, 1381
Necrosectomy
gastroduodenal fistulas after, treatment of, 1110
for pancreatitis, severe, necrotizing, 1304–1306, 1305f–1307f, 1305t
Necrotizing enterocolitis, in premature infants, 1227–1229, 1228f, 1229f
Neisseria gonorrhoeae infection, anal, in immunocompromised patients, 2383t
Neisseria meningitidis infection, overwhelming postsplenectomy infection and, 1782
Neomycin
for bowel preparation, 831
preoperative, 2328
Neonates
gastric perforation in, 957–958
clinical features and diagnosis of, 957–958
etiology of, 957
incidence of, 957
management of, 958
hyperbilirubinemia in, 1545
intestinal obstruction in, 947–948, 1219
clinical features and diagnosis of, 948
jaundice in, 1545
Neoplastic disorders. *See also* Malignancies; Metastases; *specific neoplasms and regions, e.g.* Esophageal neoplasms.
in ileal pouches, 2116–2117
perineal pain syndromes due to, 2073–2074
Neovesical dysfunction, associated with imperforate anus, 2406
Nephroenteric fistulas, treatment of, 1113
Nephrolithiasis, in short-bowel syndrome, 1167–1168
Nephrologists, on portal hypertension multidisciplinary team, 1767
Nerve conduction studies, in perineal pain syndromes, 2074
Nervous system, foregut, prenatal development of, 43–46
of cranial nerves, 44
of myenteric plexus, 46
nonrecurrent inferior laryngeal nerve and, 45
of periesophageal nerves, 46
of phrenic nerve, 45–46
of vagus nerve, 44–45, 45f
Nesidioblastosis, 1408–1409

Neuralgia, obturator, 693
Neurilemomas
gastric, 887–888
small intestinal, 900
Neuroblastomas, pancreatic, in pediatric patients, 1411, 1411f
Neuroendocrine carcinomas, colorectal, 2313
Neuroenteric cysts, esophageal, 525
Neurofibromas
esophageal, endoscopic ultrasonography in, 123
gastric, 887–888
Neurogenic tumors
gastric
benign, 888
retrorectal, 2304
Neurologic disease, intestinal motility and, 926
Neuropeptide Y, duodenal function and, 981t
Neurotensin, duodenal function and, 981t, 983
Neurotensinoma, 1383
Neutropenia, autoimmune, splenectomy for, 1827
Neutropenic enteritis, in immunocompromised patients, 2382–2383
Newborns. *See* Neonates.
Nigro, Norman, 2288
Nissen, Rudolf, 7
Nissen fundoplication, 265–274
for Barrett's esophagus, 356
symptomatic outcome with, 356–357, 357f
Collis gastroplasty with, for esophageal strictures, 244f, 244–245, 246f–248f, 247–248
complications of, 598–599, 599f
dysphagia following, 611
early development of, 6, 7
endoscopic examination following, 106, 108, 108f
for esophageal strictures, 241–242
failed, reoperative surgery for, 1141
gastroparesis following, 923
hernias following, 560
historical background of, 265
for hypertensive lower esophageal sphincter, 424
imaging following, 85, 86f
indications for, 266b, 266–267
laparoscopic, 267–271
for Barrett's esophagus, symptomatic outcome with, 367, 367f
crural closure for, 270, 270f
dissection for, 268–270
of crus, 268, 269f
of fundus and greater curve, 269, 269f
of lesser curve, 268
of mediastinal and posterior esophagus, 270, 270f
for esophageal strictures, 245, 247, 247f
exposure for, 268
fundoplication and, 270–271, 271f
Nissen fundoplication *(Continued)*
gastric perforation due to, 1094
open fundoplication vs., 267
partial, 280–281, 281f
surgical technique for, 282, 282f
position and port placement for, 267–268, 268f
"missin'," 106
open, 271
exploration and exposure for, 271
laparoscopic fundoplication vs., 267
repair and fundoplication and, 271, 272f
for paraesophageal hernia, 558
partial, 276–283
contraindications to, 279–280
indications for, 278–279, 279t
mechanism of, 278, 278f, 279f
postoperative care for, 283
preoperative evaluation for, 280, 280t
results with, 283, 283t, 284t
surgical technique for, 280–283, 281f, 281t
for laparoscopic Dor procedure, 282
for laparoscopic Toupet procedure, 282, 282f
for transthoracic Belsey Mark IV repair, 282f, 282–283
types of, 276–278, 277f
patient selection for, 265
postoperative care for, 273
postoperative complications of, 273–274
preoperative evaluation for, 266
results with, 274
with short esophagus, acquired, 272f, 272–273, 273f
slipped, 106, 108f, 242, 242f, 598, 599f
too-generous, 108
Nitric oxide
duodenal function and, 981t, 983
gastric innervation and, 720
Nitrofurantoin, hepatotoxicity of, 1721, 1722
Nitroglycerin
mesenteric blood flow and, 1243t
topical, for anal fissures, 2040
Nitroprusside, mesenteric blood flow and, 1243t
Nixon, H. H., 2400
Nizatidine, 255. *See also* Histamine$_2$ receptor antagonists.
Nociceptive pain, 668
Nodular regenerative hyperplasia, drug-induced, 1723
Nonadrenergic noncholinergic pathway, 720
Nonalcoholic fatty liver disease, hepatic laboratory tests in, 1612–1613
Non-Hodgkin lymphomas. *See* Lymphomas, non-Hodgkin's.
Non-meckelian diverticula. *See* Jejunoileal diverticula.
Nonrotation, 1213–1214, 1215f
Nonsteroidal anti-inflammatory drugs
for Barrett's esophagus, 258
for desmoids, in familial adenomatous polyposis, 2161, 2162
esophageal cancer and, 445
Norepinephrine, mesenteric blood flow and, 1243t
Nuclear medicine. *See* Scintigraphy.
Nutcracker esophagus, 74, 421–423
examinations in, 422f, 422–423, 423f
manometric features of, 420t
treatment of, 423
Nutrient deficiencies, prevention of, in short-bowel syndrome, 1166–1167
Nutrition. *See also* Diet.
in Crohn's disease, 1053–1055
malnutrition and, 1053–1054
as primary therapy, 1054–1055
esophageal cancer and, 443, 445
with gastrointestinal fistulas, 1100–1101
maintenance of, for caustic ingestions, 543–544
for pancreatitis
acute, mild, 1302
severe, necrotizing, 1303
reoperative surgery and, 1136
in short-bowel syndrome, 1165
Nutritional status
biliary surgery and, 1621
liver surgery and, 1621
Nutritional therapy
for biliary surgery, 1621–1622
for liver surgery, 1621–1622
Nyhus/Condon hernia repair, 652

O

Obesity
Barrett's esophagus and, 343
costs associated with, 929
esophageal cancer and, 443, 443t, 444f
esophageal motility disorders associated with, 142, 142t
gastroesophageal reflux disease and, 200, 253
health risk and mortality due to, 928–929, 929f, 929t
prevention of, 928
pruritus ani in, 2067
ventral herniorrhaphy and, 684
Obesity-hypoventilation syndrome, bariatric surgery and, 938
Oblique incision, for colorectal surgery, 2329
Oblique muscle
external, 672–673, 673f
internal, 673, 673f
Obstipation, in small bowel obstruction, 1028
Obturator hernias, 691–694
anatomy and, 691, 692f
clinical features and diagnosis of, 691, 693, 693f, 694f
treatment of, 693–694, 694f
Obturator neuralgia, 693
Occludin, 999
Octreoscan, for insulinoma localization, 1377
Octreotide
for carcinoid tumors, 1186
for dumping syndrome, 871
for gastrointestinal fistulas, 1103–1104

Octreotide *(Continued)*
for intestinal dysmotility, 926
for pancreatic pseudocysts, 1342
for variceal bleeding, 1759
Octyl-2-cyanoacrylate, for bowel anastomoses, 1089
Oddi, sphincter of, 1444–1445, 1445f
function of, 1458f, 1458–1459
Ogilvie's syndrome, 1879
Ohsawa, Tatsuo, 4
OISC, 1799
OKT3, mechanism of action of, 2377t
Okuda classification, 1735
Olsalazine, for inflammatory bowel disease, 2089
Omental cysts, 1223
Omentum, lesser, 717
Omeprazole. *See also* Proton pump inhibitors.
for Barrett's esophagus, 257–258
for esophageal strictures, 237
for esophagitis, reflux, 255–256, 256f
gastric acid secretion and, 727
for lymphoma, 1209t
for Zollinger-Ellison syndrome, 866, 866f
Omphalomesenteric duct remnants, 1225, 1226f, 1227
Meckel's diverticulum as, 1227, 1227f
omphalomesenteric band as, 1227
omphalomesenteric cyst as, 1227
patent omphalomesenteric duct as, 1225, 1227
at umbilicus, 1227
vitelline blood vessel remnants as, 1227
Onlay patch anastomosis, for rectovaginal fistulas, 1954
Opioids, duodenal function and, 981t
Orchitis, ischemic
following hernia surgery, 654
with inguinal herniorrhaphy, laparoscopic, 668
Organ Injury Scaling Committee, 1799
Orthotopic bypass, esophageal, length of, 10
Orthotopic liver transplantation. *See* Liver transplantation.
Osler-Weber-Rendu syndrome, gastric, 887
Osseous lesions, retrorectal, 2306
Osteodystrophy, hepatic
in end-stage liver disease, 1693
with primary sclerosing cholangitis, treatment of, 1568
Ostomies, 2362–2373
complications of, 2369–2373
bowel obstruction as, 2371
high-output state as, 2371
incidence of, 2370
ischemia as, 2372
parastomal hernia as, 2372, 2372f
peristomal varices as, 2373, 2373f
prolapse as, 2372–2373, 2373f
skin irritation and leakage as, 2370f, 2370–2371
stenosis as, 2372
enterostomal therapy for, 2368–2369, 2369b
indications for, 2362, 2363b
Ostomies *(Continued)*
preoperative considerations for, 2362–2363, 2363f
types of, 2363–2368
diverting stomas as, 2365
end colostomy as, 2364–2365
end ileostomy as, 2363f–2366f, 2363–2364
end-loop, 2366–2368
end-loop colostomy as, 2367
end-loop ileocolostomy as, 2367–2368, 2369f
end-loop ileostomy as, 2367, 2368f
loop colostomy as, 2366
loop ileostomy as, 2366, 2367f
Ostomy triangle, 2363, 2363f
Outlet bleeding, 1883
Ovarian metastases, of colorectal cancer, 2270
Overwhelming postsplenectomy infection, 1778, 1838
counseling regarding, 1787
immunizations against, 1782, 1787
prevention of, 1814
Oxaliplatin, for metastatic colorectal cancer, 2201, 2202
Oxyntocardiac mucosa, 216–217

P

PACAP, small intestinal neuroendocrine function and, 1018
Pacemaker region, duodenal, 1013
Paget's disease
anal, 2294–2295
anorectal, 1887
pruritus ani and, 2068
Pain. *See also specific site.*
with groin hernias, 642
nociceptive, 668
in pancreatic and periampullary carcinoma
nonoperative palliation of, 1366
operative palliation of, 1367, 1367f
pancreatic generation of, 1294
Palisade vessels, endoscopic appearance of, 102, 102f
Pancreas
acinar cells of, 1291, 1291f
annular, duodenal obstruction due to, 953
blood supply of, 1292–1293, 1293f
cellular membrane function in, 1292
ductal epithelial cells of, 1290f, 1290–1291, 1291f
dysfunctional cellular changes in, 1291–1292, 1292f
embryology of, 1287–1290
cellular changes and, 1289–1290
early anatomic formations and, 1287–1289, 1288f, 1289f
endocrine, embryology of, 1289
exocrine, embryology of, 1289
innervation of, 1293f, 1293–1294, 1294f
lymphatic system of, 1293
regulation of, 1294–1295
Pancreas divisum, 1299, 1409–1410
management of, 1513
Pancreas transplantation, 1415–1420. *See also* Islet transplantation.
immunosuppression for, 1418–1419
postoperative course with, 1418
rejection and, 1419
results of, 1419–1420, 1420f
with simultaneous kidney transplantation, 1417f, 1417–1418, 1418f
of vascularized pancreas allograft, 1415–1418
cadaveric organ procurement and preservation for, 1416–1417
candidates for, 1415–1416
living-donor transplant and, 1417
surgical techniques for, 1417f, 1417–1418, 1418f
Pancreatectomy
cadaveric, 1416–1417
distal
for living-donor pancreas transplantation, 1417
for pancreatic cancer in body or tail
complications following, 1370–1371, 1371t
technique for, 1370, 1370f
for pancreatic ductal disruption, 1351
near-total, for hyperinsulinism, 1409
Pancreatic abscesses, 1329
definition of, 1296
with pancreatic pseudocysts, 1342–1343, 1343f
with trauma, 1405
Pancreatic adenocarcinoma, 1431
etiology of diet, 1359t, 1359–1360
environmental factors in, 1359–1360
host factors and, 1360
genetic alterations and, 1360
Pancreatic arteries, 1292, 1293f
aneurysms of, 1280–1282
Pancreatic ascites, 1349–1352, 1350f–1352f
in pancreatitis, chronic, 1312
Pancreatic biopsy, in pancreatic and periampullary carcinoma, 1363–1364
Pancreatic carcinoma, 1353t, 1353–1354, 1358–1373. *See also* Pancreatic adenocarcinoma.
adjuvant therapy for, 1372
clinical findings in, 1360–1361
etiology of, 1359t, 1359–1360
genetic alterations and, 1360
host factors and, 1360
gastrointestinal stromal tumors as, 1359
immunotherapy for, 1373
incidence of, 1358
intraductal papillary mucinous neoplasms as, 1359
laboratory findings in, 1361
neoadjuvant therapy for, 1372
palliation for
nonoperative, 1365–1366
chemotherapeutic, 1372–1373
of duodenal obstruction, 1365–1366
of obstructive jaundice, 1365
of pain, 1366

Pancreatic carcinoma *(Continued)*
operative, 1366–1367
of duodenal obstruction, 1366–1367
of obstructive jaundice, 1366, 1366f
for pain, 1367, 1367t
pathology of, 1358–1359
resection of, 1367–1370
pancreatectomy for
for cancer in pancreatic body or tail, 1370, 1370f
complications following, 1370–1371, 1371t
pancreaticoduodenectomy for
complications following, 1370–1371, 1371t
operative technique of, 1367–1370, 1368f, 1369f
staging of
clinicopathologic, 1365
preoperative, 1364–1365
tissue diagnosis of, 1363–1364
Pancreatic cystic neoplasms, 1387–1398
clinical presentation of, 1387–1388
diagnosis of, 1392–1396
cross-sectional imaging in, 1393–1394, 1393f–1395f
endoscopic retrograde cholangiopancreatography in, 1394, 1395f
endoscopic ultrasonography in, 1396
fine-needle aspiration in, 1396
of intraductal papillary mucinous neoplasms, 1393–1394, 1395f
magnetic resonance cholangiography in, 1396
of mucinous cystic neoplasms, 1393, 1394f
of serous cystic neoplasms, 1393, 1393f
incidence and epidemiology of, 1387
pathology and biologic behavior of, 1388b, 1388–1392
of intraductal papillary mucinous neoplasms, 1391b, 1391–1392, 1392f
of mucinous cystic neoplasms, 1389f, 1389–1391, 1390f
of serous cystic neoplasms, 1388–1389, 1389f
prognosis and follow-up of, 1398
treatment of, 1396–1398
of intraductal papillary mucinous neoplasms, 1397–1398
of mucinous cystic neoplasms, 1397
of serous cystic neoplasms, 1396–1397
Pancreatic drainage procedures, 1509–1513
for chronic pancreatitis, 1509
for pancreatic ductal stones, 1510–1511
for pancreatic pseudocysts and fistulas, 1511f, 1511–1513, 1512t
for pancreatic strictures, 1509–1510
Pancreatic duct
disruption of, in pancreatitis, chronic, 1349–1352
Pancreatic duct *(Continued)*
pancreatic ascites and pleural effusions and, 1349–1352, 1350f–1352f
elevated pressure in, in pancreatitis, chronic, 1345
injuries of, in pediatric patients, 1412
Pancreatic duct of Santorini, 964
Pancreatic duct of Wirsung, 964
Pancreatic ductal stones, pancreatic drainage procedures for, 1510–1511
Pancreatic fistulas
external, 1352
internal, in pancreatitis, chronic, 1311
management of, 1307–1308
pancreatic drainage procedures for, 1511f, 1511–1513, 1512f
with trauma, 1404
Pancreatic fluid collections, acute, 1296, 1329
management of, 1307
Pancreatic insufficiency, endocrine and exocrine, management of, 1307
Pancreatic lymphomas, in pediatric patients, 1411
Pancreatic necrosis
definition of, 1296
infected, 1329
management of, 1307
treatment of, 1343, 1343f
Pancreatic neoplasms. *See also specific neoplasms.*
in pediatric patients, 1410–1411
unusual, 1431–1439
acinar cell carcinoma as, 1432, 1433f, 1434
diagnostic imaging of, 1431–1432
lymphoma as, 1434–1436, 1436f
lymphoplasmacytic sclerosing pancreatitis as, 1436–1437, 1437f
metastatic, 1437–1439, 1438f, 1439f
solid pseudopapillary tumor as, 1434, 1435f
Pancreatic neuroblastomas, in pediatric patients, 1411, 1411f
Pancreatic neuroendocrine tumors, 1375–1384, 1376f
classification of, 1376
corticotropin-producing tumor as, 1382–1383
diagnosis of, 1383
therapy for, 1383
diagnosis of, 1381
ghrelinoma as, 1383
glucagonoma as, 1381–1382
diagnosis of, 1381, 1382f
therapy of, 1382, 1382f
GRFoma as, 1382
diagnosis of, 1382
therapy, 1382
insulinoma as, 1376–1379
invasive localization studies for, 1377–1378, 1378f
preoperative localization of, 1377, 1377f
symptoms and diagnosis of, 1376–1377
therapy of, 1378–1379, 1379f
Pancreatic neuroendocrine tumors *(Continued)*
multiple endocrine neoplasia 1 as, 1379–1380
diagnosis of, 1379–1380
prognosis of, 1380
therapy of, 1380
neurotensinoma as, 1383
nonfunctioning, 1383–1384
diagnosis of, 1383
presentation of, 1383, 1384f
prognosis of, 1383–1384
therapy of, 1383
PPoma as, 1383–1384
diagnosis of, 1383
presentation of, 1383, 1384f
prognosis of, 1383–1384
therapy of, 1383
presentation of, 1381
somatostatinoma as, 1380–1381
diagnosis of, 1380
presentation of, 1380
therapy of, 1381
treatment of, 1381
tumor-releasing parathyroid hormone–related protein and, 1383
VIPoma as, 1381
Pancreatic polypeptide, duodenal function and, 981t, 984
Pancreatic polyps, heterotropic, 884
Pancreatic pseudocysts, 1329–1344, 1330b, 1330f
acute, definition of, 1296
clinical features of, 1330–1331
complications of, 1342–1344
hemorrhage as, 1343–1344
infection as, 1342–1343, 1343f
obstruction as, 1344
rupture as, 1344
diagnosis of, 1331t, 1331–1332
etiology of, 1330
management of, 1307, 1307f, 1333b, 1333–1335, 1335f–1342f, 1339, 1341–1342
natural history of, 1332–1333, 1333t
pancreatic drainage procedures for, 1511f, 1511–1513, 1512t
in pediatric patients, drainage of, 1412, 1412f
rupture of
silent, 1344
spontaneous, 1344
terminology for, 1329, 1331f
treatment algorithm for, 1332, 1332f
Pancreatic pseudopseudocysts, 1329
Pancreatic resection
duodenum-preserving, operative modifications of, 1315–1316
for pancreatic pseudocysts, 1339, 1341
reoperative, 1317
Pancreatic rests, endoscopic appearance of, 738, 739f
Pancreatic stones
endotherapy for, results after, 1324
obstructing calculi and, 1322
removal of, 1323

Pancreatic strictures
benign, dilation of, 1323
chronic, pancreatic drainage procedures for, 1509–1510
inflammatory stenoses and, 1322
without stones, endotherapy for, results after, 1323
Pancreatic tissue, ectopic, small intestinal, 892
Pancreatic trauma, 1400–1405
diagnosis of, 1400–1401, 1401f
intraoperative evaluation of, 1401, 1402f
operative treatment of, 1402–1404, 1403f–1405f, 1403t
postoperative considerations with, 1404–1405
Pancreaticobiliary union, anomalous, treatment of, 1508–1509
Pancreaticoduodenal artery, 1445, 1446
aneurysms of, 1280–1282, 1281f
inferior, 968, 971f
superior, 968, 971f, 1237
Pancreaticoduodenal injuries, 769
Pancreaticoduodenal veins
anterior inferior, 968, 972f
posterosuperior, 968, 972f
Pancreaticoduodenectomy, 1341
for duodenal adenocarcinoma, 915
for pancreatic and periampullary carcinoma
complications following, 1370–1371, 1371t
operative technique of, 1367–1370, 1368f, 1369f
for pancreaticoduodenal injury, 769–770
pylorus-preserving, 1321
results after, 1325–1327
results after head resection with, 1325–1327
techniques for, 1324, 1325f, 1326f
Pancreaticojejunostomy
longitudinal, side-to-side, with common bile duct strictures, 1348
Roux-en-Y, for pancreatic ductal disruption, 1351, 1351f
Pancreatitis
acute, 1296–1308
Atlanta Classification for, 1296, 1297f
clinical presentation of, 1299
definition of, 1296
diagnosis of, 1299–1300
etiology of, 1298b, 1298–1299
future directions for, 1308
gallstone, 1298
laboratory studies in, 1299, 1300b
mild
definition of, 1296
management of, 1301–1302
pathogenesis and pathophysiology of, 1296–1298
acinar cell injury in, 1296–1297
local inflammation in, 1297–1298
systemic inflammation and distant organ injury in, 1298
postoperative, 1298
postprocedural, 1298
prognostic indicators for, 1300, 1301b, 1301t, 1302
Pancreatitis *(Continued)*
radiologic studies in, 1299–1300, 1300f, 1302f
sequelae of, management of, 1307–1308
severe, definition of, 1296
severe necrotizing, management of, 1303t, 1303–1306, 1305f–1307f, 1305t
with choledochal cysts, 1554, 1554f
chronic, 1310–1317, 1344–1354
clinical features of, 1344–1345, 1345b
complications of, 1311–1314, 1345–1354
common bile duct obstruction as, 1345–1348, 1346f
common bile duct stenosis as, 1311
duodenal and gastric outlet obstruction as, 1348–1349, 1349f
duodenal obstruction as, 1311
external pancreatic fistula as, 1352
internal pancreatic fistulas as, 1311
pancreatic cancer as, 1353t, 1353–1354
pancreatic ductal disruption as, 1349–1352
splenic vein thrombosis as, 1352–1353
vascular, 1312–1314
distal common bile duct strictures secondary to, biliary drainage procedures for, 1501, 1502f, 1502t, 1503
endoscopic treatment of, 1321–1327, 1322f, 1322t
results after endotherapy for stones, 1324, 1324f
results after endotherapy for stricture without stones, 1323
results after head resection with pylorus-preserving pancreaticoduodenectomy, 1325–1327
surgical resection techniques and, 1324, 1325f, 1326f
techniques for, 1323
hypertension in, ductal and parenchymatous, 1310–1311
natural course of, 1310
pain in, pathogenesis of, 1310
pancreatic drainage procedures for, 1509
in pediatric patients, pancreaticoenteric procedures for, 1410
small duct disease, 1317
surgical treatment of, 1314–1317
indications for drainage procedures and, 1316–1317, 1318f
modifications of duodenum-preserving resectional procedures and, 1315–1316
Pancreatitis *(Continued)*
rationale for drainage procedures and, 1314
rationale for resectional procedures or "extended" drainage procedures and, 1314–1315, 1315f–1317f
salvage procedures and, 1317
following esophageal resection with visceral esophageal substitution, 615
gallstone, 1298, 1303
acute, treatment of, 1497–1499
sclerosing, lymphoplasmacytic, 1436–1437, 1437f
Pancreatitis chronic, recurrence following surgical treatment of, salvage procedures for, 1317
Pancreatoblastoma, in pediatric patients, 1411
Pancreatography, 1493, 1493f
in pancreatic trauma, 1403
with pancreaticoduodenal injury, 769
Pancreozymin, 981
Panitumumab, for colorectal cancer metastases, 2271
Panproctocolectomy, with ileostomy, for ulcerative colitis, 2122
Pantoprazole. *See also* Proton pump inhibitors.
for Zollinger-Ellison syndrome, 866, 866f
Pantothenic acid, small intestinal absorption of, 1006, 1007t
Papaverine
mesenteric blood flow and, 1243t
for mesenteric ischemia, 1254–1255
for mesenteric venous thrombosis, 1257
Papilla of Vater, 964, 965f
Papillary adenomas, gastric, 885
Papillary cystic tumors, 1434, 1435f
in pediatric patients, 1411
Papillomas, squamous, esophageal, 523–524, 524f
Pappenheimer bodies, 1775
Paraduodenal hernias, 975–976, 976f, 1120–1121, 1121f, 1858, 1861f
clinical features of, 1121
diagnosis of, 1121–1122
treatment of, 1122
Paraesophageal diseases, endoscopic ultrasonography in, 125
Paraesophageal hernias, 549–560
classification and pathophysiology of, 549–550, 550f, 551f
diagnosis of, 552
preoperative evaluation of, 552
prevalence of, 550
symptoms of, 550–552, 552t
bleeding as, 552
esophageal or gastric compression as, 551–552
incarceration and strangulation as, 550–551
pulmonary, 552
treatment of, 552, 554–557
esophageal lengthening for, 558–559
fundoplication for, 558
gastropexy and gastrostomy for, 559
indications for, 554

Paraesophageal hernias *(Continued)*
laparoscopic approach for, 554–555
laparoscopic technique for, 555, 555f–557f, 557
outcomes of, 557–558
prosthetic mesh for, 559–560
surgical approach for, 554
Paraesophageal tissue, anatomy of, ultrasound, 116
Parahiatal hernias, 560
Paramedian incision, for colorectal surgery, 2329
Paraprosthetic-enteric fistulas, 1114
Parasitic infections, pruritus ani associated with, 2070
Parastomal hernias, 2372, 2372f
with ileostomy, 1080
Pare, Ambrose, 632
Parent education, for asplenia, in pediatric patients, 1811–1812
Parenteral nutrition, in short-bowel syndrome, 1165
Parietal cell(s), gastric acid secretion by, 725–727, 726f
Parietal cell receptors, gastric acid secretion and, 725
Parks postanal repair, 1923
Paromomycin, for liver abscesses, amebic, 1655
Partial splenic embolization, for hypersplenism, 1793–1795, 1794f, 1795f
Pathologists, on portal hypertension multidisciplinary team, 1767
Patient advocate, as clinical nurse specialist role, in palliative treatment, for esophageal cancer, 497
Patient controlled analgesia, following bariatric surgery, 937
Patient education, for asplenia, in pediatric patients, 1811–1812
Pediatric End-Stage Liver Disease, 1691, 1691t
Pediatric patients. *See also* Infants; Neonates.
annular pancreas in, 1407–1408, 1408f
appendicitis in, acute, 2143–2144
bezoars in, 959–960
clinical features and diagnosis of, 959
management of, 959f, 959–960
types of, 959
caustic ingestions in, 540
chronic pancreatitis in, pancreaticoenteric procedures for, 1410
colonic intussusception in, 1980
congenital disorders in
anorectal. *See* Anorectal anomalies.
duodenal obstruction as, 952–954
clinical features and diagnosis of, 953, 953f, 954f
embryology and etiology of, 952
incidence and epidemiology of, 952
management of, 953–954, 955f
gastric duplication as, 948
clinical features of, 948
diagnosis of, 948, 950f
Pediatric patients *(Continued)*
incidence and etiology of, 948
management of, 948, 950f
gastric outlet obstruction as, 950–951
clinical features of, 950–951
diagnosis of, 951, 951f
management of, 951–952
types of, 951, 951f
gastric volvulus as, 950
intestinal atresia as, 1219–1221, 1220f, 1221f
malrotation as, 1213–1214, 1214f–1219f, 1216–1217, 1219
meconium syndromes as, 1224f, 1224–1225, 1225f
microgastria as, 950
omphalomesenteric duct remnants as, 1225, 1226f, 1227
Meckel's diverticulum as, 1225, 1227, 1227f
omphalomesenteric band as, 1227
omphalomesenteric cyst as, 1227
patent omphalomesenteric duct as, 1225, 1227
at umbilicus, 1227
vitelline blood vessel remnants as, 1227
small intestinal duplications and cysts as, 1221–1223, 1222f, 1223f
diabetes mellitus in, type 1, 1415
pancreas transplantation for. *See* Pancreas transplantation.
endoscopic retrograde cholangiopancreatography in, 1412–1413
femoral hernia in, 712
foreign bodies in, 959, 959f. *See also* Foreign body ingestion.
foreign body ingestion in, 940
gastric perforation in, in neonates, 957–958
clinical features and diagnosis of, 957–958
etiology of, 957
incidence of, 957
management of, 958
gastric tumors in, 958–959
clinical features and diagnosis of, 958–959
incidence of, 958
management of, 959
gastrostomy in, 960–961
complications of, 960–961
indications for, 960
types of, 960
hepatoblastoma in, alfa-fetoprotein and, 1734
hyperinsulinism in, 1408–1409
inguinal hernia in, 705–709
clinical features of, 706
contralateral inguinal exploration and, 709
embryology of, 705
incidence of, 705–706
indirect, operative management of, 706–708, 707f, 708f
with undescended testes, 709, 710f
Pediatric patients *(Continued)*
intestinal obstruction in, in newborn, 947–948
clinical features and diagnosis of, 948
intussusception as, 1229–1230, 1230f–1232f, 1232
Ménétrier's disease in, 886
necrotizing enterocolitis in, 1227–1229, 1228f, 1229f
pancreas divisum in, 1409–1410
pancreatic duct injuries in, 1412
pancreatic pseudocysts in, drainage of, 1412, 1412f
pancreatic tumors in, 1410–1411
peptic ulcer disease in, 961–962
clinical features of, 961
definition and types of, 961
diagnosis of, 961
etiology of, 961
management of, 961–962
polyposis in. *See* Juvenile polyposis syndrome.
pyloric stenosis in, hypertrophic, 954, 956
clinical features of, 954, 956
diagnosis of, 956
etiology and pathogenesis of, 954
incidence and epidemiology of, 954
management, 956, 957f, 958f
splenic trauma in, 1805–1812
asplenia prophylaxis for, 1811–1812
evaluation of, 1806–1808, 1807f, 1808t, 1809f, 1810f, 1811t
historical background of, 1805–1806
immune function and consequences of splenectomy and, 1806
operative management of, 1808, 1811
testicular torsion in, 711–712
operative management of, 711–712
undescended testes in, operative management of, 709–711
Pediculosis pubis, pruritus ani associated with, 2070
PELD, 1691, 1691t
Peliosis hepatis, 1730
drug-induced, 1723
Pelvic abscesses, with appendicitis, 2150
Pelvic anatomy, low anterior resection and, 2222
Pelvic floor, perineal pain and, 2072
Pelvic floor exercises, for fecal incontinence, 1921–1922
Pelvic floor function, tests of, 1897
Pelvic floor retraining, for constipation, 1938
Pelvic girdle disorders, pain associated with, 2072
Pelvic muscles, anatomy of, continence and, 2391–2394
Pelvic organ prolapse, perineal hernias associated with, 695–696
Pelvic outlet obstruction, surgical treatment of, 1936, 1937f, 1938f
Pelvic pain. *See* Perineal pain syndromes.
Pelvic pouch procedure, redo, 2415, 2417

Pelvic splanchnic nerves, 1870
Pelvic surgery
  operative measures to improve ease and safety of, 2418
  perineal pain and, 2072
  reoperative. *See* Reoperative surgery, pelvic.
Peña procedure, 2387, 2398, 2399f, 2400
  fecal incontinence following, 2405
  postoperative complications of, 2402–2403
Penicillin V, for asplenia, in pediatric patients, 1811
Pepsinogen, gastric secretion of, 728
Peptic ulcer disease
  bleeding ulcers and
    emergency surgery for, 802t, 802–804, 803f, 804f
      for gastric ulcers, 804
    in pediatric patients, 962
    vagotomy and drainage for, 824–825, 825f
  duodenal. *See* Duodenal ulcers.
  gastric. *See* Gastric ulcers.
  gastric barrier function and, 729
  intractable, vagotomy and drainage for, 822–823
  pathogenesis of, 811–812
  in pediatric patients, 961–962
    clinical features of, 961
    definition and types of, 961
    diagnosis of, 961
    etiology of, 961
    management of, 961–962
  perforation of, vagotomy and drainage for, 823–824
  recurrent, after vagotomy and drainage, 826–827
  surgery for, 791–809
    complications of, 808–809
    elective, 792–800
      for intractable duodenal ulcer disease, 792–798
      for intractable gastric ulcer disease, 798–800, 799f, 799t
    emergency, 800–808
      bleeding lesions and, 802t, 802–804
      gastric outlet obstruction and, 806–808
      perforation and, 804–806
    gastric outlet obstruction following, reoperation for, 1136–1137
    indications for, 791
    vagotomy and drainage as. *See* Vagotomy, with drainage.
  in Zollinger-Ellison syndrome. *See* Zollinger-Ellison syndrome.
Peptide YY, duodenal function and, 981t, 984–985
Percutaneous aspiration, of pancreatic pseudocysts, 1333
Percutaneous drainage
  biliary
    alkaline phosphatase elevation in, 1615
    complications of, 1468–1469
    technique of, 1464–1466
Percutaneous drainage *(Continued)*
  of pancreatic pseudocysts, 1333–1334
  for splenic abscesses, 1820
Percutaneous endoscopic gastrostomy
  contraindications to, 750t
  fistulas due to, 1095
  indications for, 750t
  in pediatric patients, 960
Percutaneous transhepatic cholangiography
  with bile duct strictures, 1578–1579
  with biliary fistulas, 1542
  complications of, 1468–1469
  indications for, 1463–1464
  in periampullary carcinoma, 1363, 1364f
  technique of, 1464–1466
Perhexiline, hepatotoxicity of, 1721
Periampullary carcinoma, 1358–1373
  adjuvant therapy for, 1372
  clinical findings in, 1360–1361
  etiology of, 1360
  imaging studies in, 1361–1363
    on computed tomography, 1361–1362, 1362f
    on endoscopic retrograde cholangiopancreatography, 1362–1363, 1363f
    on magnetic resonance imaging, 1362, 1363f
    on percutaneous transhepatic cholangiography, 1363, 1364f
    on positron-emission tomography, 1363
    on right upper quadrant ultrasound, 1361
    on upper endoscopy and endoscopic ultrasonography, 1364, 1364f
  immunotherapy for, 1373
  incidence of, 1358
  laboratory findings in, 1361
  neoadjuvant therapy for, 1372
  palliation for
    chemotherapeutic, 1372–1373
    nonoperative, 1365–1366
      of duodenal obstruction, 1365–1366
      of obstructive jaundice, 1365
      of pain, 1366
    operative, 1366–1367
      of duodenal obstruction, 1366–1367
      of obstructive jaundice, 1366, 1366f
      for pain, 1367, 1367t
  pathology of, 1358–1359
  resection of, 1367–1370
    long-term survival after, 1371f, 1371–1372
    pancreatectomy for
      for cancer in pancreatic body or tail, 1370, 1370f
      complications following, 1370–1371, 1371t
    pancreaticoduodenectomy for
      complications following, 1370–1371, 1371t
      operative technique of, 1367–1370, 1368f, 1369f
Periampullary carcinoma *(Continued)*
  staging of
    clinicopathologic, 1365
    preoperative, 1364–1365
  tissue diagnosis of, 1363–1364
Periampullary diverticula, 780
Perianal abscesses, in Crohn's disease, surgical treatment of, 2135, 2136f
Perianal disease, in Crohn's disease, 1045
Perianal lumps, examination of, 1887
Perianal neoplasms, pruritus ani and, 2068
Perianal sepsis, endoanal ultrasound in, 1911
Periappendiceal abscesses, 2148–2149
Peribiliary venous system of Couinaud, 1603
Pericolic abscesses, 2016–2017
Pericysts, echinococcal, 1637, 1638
Periesophageal nerves, prenatal development of, 46
Periesophageal tissue, anatomy of, 11
Peri-ileostomy fistulas, 1080–1081
Perineal abscesses, in Crohn's disease, 2088
Perineal body, 696
Perineal hernias, 694–700
  anatomy and, 696, 697f
  classification of, 694–696, 695f, 696f
  clinical features and diagnosis of, 696, 698f, 698–699, 699f
  treatment of, 699–700, 700f–703f
Perineal pain syndromes, 2071–2075
  anatomy and, 2072
  causes of, 2072–2074, 2073t
    functional, 2074
    inflammatory diseases as, 2072
    mechanical, 2072–2073
    muscular, 2072
    neoplastic, 2073–2074
    neurologic, 2072, 2074
    orthopedic, 2074
    pelvic, 2072
    spinal, 2072
  evaluation of, 2074
  treatment of, 2074–2075, 2075t
Perineoproctectomy, with layered closure, for rectovaginal fistulas, 1952
Perinuclear antineutrophil cytoplasmic antibodies, in Crohn's disease, 1046
Peristalsis
  colonic, 1874f, 1874–1875
  esophageal, 51–53, 52f–54f, 130–132, 132f
    deglutitive inhibition and, 52–53, 54f
    duration response and, 51
    inhibitory relaxation wave and, 53
    primary, 130, 132f
    propulsive force and, 53
  pharyngeal peristaltic contraction and, 49
Peristaltic reflex, 1014
Peritoneal lavage, diagnostic
  in abdominal trauma, in pediatric patients, 1807–1808
  in colorectal trauma, 1974
  in gastric trauma, 762–763
Peritonitis
  in colonic diverticulitis, 2018, 2019f
  diffuse, perforated appendicitis with, 2149

Permacol, for ventral herniorrhaphy, 676
Persistent hyperinsulinemic hypoglycemia of infancy, 1408–1409
PET scans. *See* Positron-emission tomography.
Petit, Jean Louis, 632
Peutz-Jeghers syndrome, 2159t, 2174–2175
as risk factor for colorectal cancer, 2188–2189
small intestinal, 894t, 897–898
small intestinal
symptoms and diagnosis of, 897
treatment of, 898
Pfannensteil incision, for Crohn's disease, 1057, 1057f
pH, of ingested material, in caustic ingestions, 541
pH monitoring
esophageal, 164–169
ambulatory esophageal impedance testing and, for esophageal bolus clearance, 158–159, 159f, 160f
Bravo probe for, 167–168, 168f
combined with multichannel intraluminal impedance, 180–181, 180f–183f
instrumentation for
catheters and probes and, 165, 165f
data-recording devices and, 165
software analysis and, 165–166
integrated ambulatory monitoring and, 173
with paraesophageal hernia, 552
preoperative, for esophageal replacement, 287
protocols for, 166–167
catheter systems and, 166
data analysis and, 166–167, 167f, 167t
diary and, 166
patient preparation and, 166, 166b
24-hour, 161
in esophageal spasm, 420–421
gastric, 24-hour, for duodenogastro-esophageal reflux, 191f–193f, 191–193, 192t
in gastroesophageal reflux disease, 231
in hypertensive lower esophageal sphincter, 424
24-hour
in gastroesophageal reflux disease, 59
preoperative, for Nissen fundoplication, 266
Pharmacobezoars, 943, 944, 944t
Pharyngeal cylinder, valves in, 128–129
Pharyngoesophageal diverticulectomy, for Zenker's diverticulum, methods and results of, 430–431
Pharyngoesophageal diverticulum. *See* Zenker's diverticulum.
Pharyngoesophageal junction, access to, 379, 380f, 381f
Pharyngoesophageal junction disorders, 374–390. *See also* Dysphagia, oropharyngeal.
Pharyngoesophageal transit studies, radionuclide, for swallowing evaluation, 378
Pharynx
peristaltic contraction of, 49
prenatal development of, 31–33, 33f, 34f
Phenobarbital, for pruritus, in primary sclerosing cholangitis, 1567
Phenothiazine derivatives, for gastroparesis, 921
Phenylephrine, mesenteric blood flow and, 1243t
Phenytoin, hepatotoxicity of, 1721
Phospholipids, in bile, 1452
Photodynamic therapy
for anal intraepithelial neoplasia, 2290
for Barrett's esophagus, 370
for esophageal cancer, 489t, 493
for low-grade dysplasia, following antireflux procedures, 360
Phrenic veins, 1604
Phrenoesophageal membrane
anatomy of, 12–14, 14f
prenatal development of, 36, 36f
Phrygian cap, 1449, 1450f
Phytobezoars, 943–944, 944t
in pediatric patients, 960
Pigmentation, mucocutaneous, in Peutz-Jeghers syndrome, 2174
Pilonidal disease, 1966–1970
clinical presentation of, 1966–1967
etiology of, 1966, 1967f
malignant degeneration of, 1969–1970
pathology of, 1966
treatment of, 1967–1969
for acute pilonidal abscess, 1967
drainage technique for, 1967
for chronic disease, 1968–1969
conservative, nonresectional approach for, 1968
excision with or without closure for, 1968–1969
incision and curettage with marsupialization or saucerization for, 1968
midline follicle excision and lateral drainage for, 1968, 1968f
for recurrent or unhealed disease, 1969
cleft lip technique for, 1969, 1970f
Pinworms, pruritus ani associated with, 2070
Piperacillin, for cholangitis prophylaxis, 1550t
Piriformis muscle, sciatic hernias and, 701
Pituitary adenylate cyclase activating polypeptide, small intestinal neuroendocrine function and, 1018
Plain radiographs
abdominal. *See* Abdominal plain films.
chest. *See* Chest radiography.
sacral, with retrorectal tumors, 2301
Plasma exchange, for liver failure, acute, 1705
Pleural effusions, pancreatic, 1349–1352, 1350f–1352f
Plexiglas, for endoscopic antireflux procedures, 325
Pliny the Elder, 1813
Plug and patch hernia repair, 649, 650f, 651f
Pneumatic dilatation, for achalasia, 412
Pneumocystis carinii infection, splenic abscess due to, 1820
Pneumonia, following esophageal surgery, 599
Pneumothorax
following Heller myotomy, 417
with Nissen fundoplication, 273
Polycystic liver disease, 1634–1635, 1635f
Polydioxanone suture material, for bowel anastomoses, 1083, 1084
Polyester, for ventral herniorrhaphy, 676
Polyethylene glycol, for bowel preparation, 831, 2328
Polyfilament, for groin hernia repair, 646
Polyglycolic mesh, for rectovaginal fistulas, 1952
Polyglyconate suture material, for bowel anastomoses, 1083, 1084
Polymyositis, esophageal motility disorders in, 140
Polyp(s)
adenomatous. *See also* Familial adenomatous polyposis.
colorectal. *See* Colorectal polyps, adenomatous.
endoscopic appearance of, 740, 741f
gastric, endoscopic appearance of, 740, 741f
Brunner's gland, 884
colorectal. *See* Colorectal polyps; Polyposis syndromes; *specific polyposis syndromes.*
ectopic tissue, small intestinal, 892–893
esophageal
endoscopic ultrasonography in, 122–123
imaging of, 82, 83f
fibroid, inflammatory, gastric, 884
fibrovascular, esophageal, 522–523, 523t
fundic gland, 2162
fundic gland-type, endoscopic appearance of, 740, 741f
gallbladder, 1519
with primary sclerosing cholangitis, 1565
treatment of, 1567
radiographically suspicious, preoperatively diagnosed, 1524–1525
gastric. *See* Gastric polyps.
hamartomatous
colorectal, 2157f, 2157–2158, 2158f
gastric, 884
inflammatory, gastric, 884
pancreatic, heterotropic, 884
retention, 2157
gastric, 884
small intestinal. *See also* Intestinal polyposis syndromes.
neoplastic, 891–893
Brunner's gland, 892–893
ectopic tissue, 892–893

Polyp(s) *(Continued)*
endometriosis as, 893
tubular adenomas as, 891–892
villous adenomas as, 892–893
non-neoplastic, benign, 891
Polypectomy, colonoscopic, 2157
complications of, 2157
for malignant polyps, 2156f, 2156–2157
for pedunculated polyps, 2155–2156
for sessile polyps, 2156
Polypoid lesions, gastric, endoscopic appearance of, 740, 740f, 741f
Polyposis syndromes, 2158–2177, 2159t
Cowden's disease as, 2159t, 2175–2176
Cronkhite-Canada syndrome as, 2159t, 2176
familial. *See* Familial adenomatous polyposis.
hereditary mixed polyposis syndrome as, 2159t, 2176–2177
hereditary nonpolyposis colorectal cancer as. *See* Hereditary nonpolyposis colorectal cancer.
juvenile, 2159t, 2173–2174
Peutz-Jeghers syndrome as, 2159t, 2174–2175
Ruvalcaba-Myhre-Smith syndrome as, 2159t, 2176
Polypropylene
for groin hernia repair, 646
mesh for ventral herniorrhaphy and, 675, 675f
patches for paraesophageal hernia and, 559–560
Polysplenia, 1777
Polytetrafluoroethylene
expanded
for groin hernia repair, 647
paraesophageal hernia and, 560
for ventral herniorrhaphy, 676, 676f
mesh for paraesophageal hernia and, 559, 560
Porfimer sodium, for Barrett's esophagus, 370
Porphyria cutanea tarda, in primary sclerosing cholangitis, 1562
Porta hepatis, 1602
Portal fissure, main, 1599f, 1602–1603
Portal hypertension, 1751–1767
anatomy and, 1752–1753, 1753f, 1754f
ascites in, 1755–1756, 1763–1765
diagnosis of, 1764
management of, 1764–1765, 1765f
pathophysiology of, 1763–1764, 1764f
in cirrhosis, 1624, 1693
clinical presentation of, 1755–1756
encephalopathy in, 1756
etiology of, 1756b, 1756–1757
evaluation of, 1757b, 1757–1758, 1758b, 1758t
hepatocellular carcinoma in, 1756
historical background of, 1751–1752
intrahepatic, 1756–1757
liver failure in, 1756
multidisciplinary team for, 1767
noncirrhotic, drug-induced, 1723
in pancreatitis, chronic, 1312–1313
Portal hypertension *(Continued)*
pathophysiology of, 1754–1755, 1755f
portopulmonary syndromes in, 1756
posthepatic, 1757
prehepatic, 1756
with primary sclerosing cholangitis, 1566
treatment of, 1568
pulmonary syndromes in, 1766t, 1766–1767
clinical presentation of, 1766
hepatopulmonary syndrome as, 1766f, 1766–1767
pathophysiology of, 1766
portopulmonary hypertension as, 1767, 1767f
splenectomy for, 1834
variceal bleeding in. *See* Esophageal varices, bleeding.
Portal pedicle, 1599
Portal vein, 1602, 1772
anatomy of, 1752–1753, 1753f
anomalies of, 1602
hepatocellular carcinoma and, 1733
preduodenal, 974, 974f
Portal vein thrombosis
with cavernous transformation, in chronic pancreatitis, 1313f, 1313–1314
following splenectomy, 1838
liver transplantation and, 1697, 1698
Portal venous sampling, for insulinoma localization, 1378
Portocaval shunt, intrahepatic, transjugular
for ascites, 1765
for bleeding due to portal hypertension, 1693
for bleeding varices, 1693, 1761–1762
procedure for, 1761f, 1761–1762
for Budd-Chiari syndrome, 1714, 1715
Portopulmonary hypertension, 1767, 1767f
in cirrhosis, 1693, 1693b
clinical presentation of, 1766
pathophysiology of, 1766
Portopulmonary syndromes, in portal hypertension, 1756
Positron-emission tomography
of carcinoid tumors, 1184
with colon, rectal, and anal disorders, 1895, 1896f
to detect colorectal cancer tumor relapse, 2259
in esophageal carcinoma
assessment for metastases using, 471–472
for recurrent cancer assessment, 79, 81
for staging, 77–78, 81f
therapy monitoring and, 461
for treatment selection, 79
FDG, for staging of esophageal cancer, 459f, 459–460
in gastric adenocarcinoma, 907
of gastrointestinal stromal tumors, 1195f, 1195–1196
in pancreatic carcinoma, 1354
in periampullary carcinoma, 1363
Postanal repair, 1923
Posterior sagittal anorectoplasty, 2387, 2398, 2399f, 2400
fecal incontinence following, 2405
postoperative complications of, 2402–2403
Postgastrectomy syndromes, 808–809, 870–880
afferent loop obstruction as, 809, 877–879, 879f
bile reflux gastritis as, 875–877, 876f–878f
diarrhea as, 809, 873–874, 874f
reoperative surgery for, 1138–1139
dumping syndrome as, 809, 870–873, 872f
reoperative surgery for, 1138–1139
duodenogastroesophageal reflux associated with, 190
early satiety as, 808–809
efferent loop obstruction as, 809, 877, 878
gallstones as, 875
gastric cancer as, 809
gastric stasis as, 874–875
jejunogastric intussusception as, 879–880
metabolic aberrations as, 873
reflux gastritis as, alkaline, 809
Roux stasis syndrome as, 809, 880
reoperative surgery for, 1140
Postoperative pain, following laparoscopic colorectal surgery, 2343
Postpolycythemic myeloid metaplasia, splenectomy for, 1831
Post-thrombocytopenic myeloid metaplasia, splenectomy for, 1831
Post-transplant hyperproliferative disease, following intestinal transplantation, 1176–1177
Potassium
absorption of, colonic, 1872
secretion of, colonic, 1872
Pott, Percivall, 632, 633f
Pouchitis, following ileal pouch-anal anastomosis, 2113, 2115t, 2115–2116
anti-tumor necrosis factor and, 2115
morphologic changes in ileal pouch mucosa and, 2116
acute, treatment of, 2116
pathogenesis of, 2115
severe, 2115–2116
Pouch–vaginal fistulas, following ileal pouch–anal anastomosis, 2112–2113, 2114f
PPH staplers, 1087
PPomas, 1383–1384
diagnosis of, 1383
presentation of, 1383, 1384f
prognosis of, 1383–1384
therapy of, 1383
Prednisone
for cholangitis prophylaxis, 1550t
for inflammatory bowel disease, 2090
Pregnancy
acute fatty liver of, 1703
appendicitis during, 2144
gastroesophageal reflux disease and, 200
Prenatal development of, of phrenic nerve, 45–46
Presacral nerve, 1856

Prevertebral ganglia, 1869
Primary biliary cirrhosis, end-stage liver disease due to, 1686–1687
Primary sclerosing cholangitis, 1560–1570, 1586t, 1586–1589
biliary drainage procedures for, 1503f, 1503–1504
biliary tumors vs., 1526
biochemical and serologic abnormalities in, 1561
clinical presentation of, 1560, 1587
complications of, 1564–1565
non-primary sclerosing cholangitis–associated, 1566
primary sclerosing cholangitis–associated, 1565–1566
biliary strictures as, 1565
cholangiocarcinoma as, 1565–1566
choledocholithiasis as, 1565
cholelithiasis as, 1565
gallbladder polyps as, 1565
diagnosis of, 1560–1561, 1561b, 1586–1587, 1587f
diseases associated with, 1563–1564, 1564b
autoimmune hepatitis as, 1564
inflammatory bowel disease as, 1563–1564
end-stage liver disease due to, 1686–1687
epidemiology of, 1560
etiopathogenesis of, 1562–1563
imaging studies in, 1561–1562, 1562f
inflammatory bowel disease with, 1693
natural history of, 1564, 1587
pathogenesis of, 1586
pathology of, 1562, 1563t, 1586
treatment of, 1587–1588
medical, 1567–1568
for hepatobiliary disease, 1568
nonoperative dilation therapy for, 1588
for non-primary sclerosing cholangitis-associated complications, 1567t, 1567–1568, 1568t
for primary sclerosing cholangitis-associated complications, 1567
surgical, 1568–1570, 1588f, 1588–1589
with cholangiocarcinoma, 1570
liver transplantation as, 1569–1570
proctocolectomy as, 1570
reconstructive biliary surgery as, 1568–1569
Primitive neuroectodermal tumors, in pediatric patients, 1411
Pringle maneuver, 1605
for hepatectomy, 1676, 1677
in hepatobiliary trauma, 1664
Procedure for prolapsing hemorrhoids, 2034–2035, 2035f
Processus vaginalis, 633–634
Procidentia. *See* Rectal prolapse.
Proctalgia fugax, 2071
Proctitis
hemorrhagic, management of, 2321
radiation, medical management for, 2321–2322
argon plasma coagulation as, 2322
formalin instillation as, 2321–2322
hyperbaric oxygen as, 2322
in residual rectal mucosa, following ileal pouch–anal anastomosis, 2112
Proctocolectomy
for primary sclerosing cholangitis, 1570
total
with continent ileostomy, for familial adenomatous polyposis, 2165, 2165t, 2166t
with end ileostomy
for familial adenomatous polyposis, 2165, 2165t, 2166t
for ulcerative colitis, 2093
for familial adenomatous polyposis, 1070
with ileal pouch–anal anastomosis, for ulcerative colitis, 2093–2094
for ulcerative colitis, 1070
Proctosigmoidectomy, perineal, for rectal prolapse, 1962, 1964t
Proctosigmoidoscopy
with colonic vascular ectasias, 1991
flexible, 1890, 1890f
rigid, 1889f, 1889–1890
Prokinetic agents
for cough, in gastroesophageal reflux disease, 259
for gastroesophageal reflux disease, 253–254
for gastroparesis, 921
Proliferative mucinous cystic neoplasms, noninvasive, 1390
Prolonged propagated contractions, small intestinal, 1017, 1017f
Promoter of quality care, as clinical nurse specialist role, in palliative treatment, for esophageal cancer, 497–498
Prone jackknife position, 1886, 1886f
Prosthetic materials. *See also specific materials.*
for groin hernia surgery, 646b, 646–647
for hernia repair, complications of, 654
Prosthetic mesh
for paraesophageal hernia, 559–560
for ventral herniorrhaphy, 675f, 675–676, 676f
Proteins
duodenal absorption of, 980
small intestinal absorption of, 1002–1004, 1003t, 1004f
Prothrombin time, increased, patient approach for, 1615
Proton pump inhibitors. *See also specific drugs.*
for asthma, in gastroesophageal reflux disease, 258, 259f, 260f
for Barrett's esophagus, 257–258
for cough, in gastroesophageal reflux disease, 259
for esophageal strictures, 237, 256–257
for esophagitis, reflux, 255–256, 256f
evaluation of patients receiving, pH monitoring for, 173
gastric acid secretion and, 727
Proton pump inhibitors *(Continued)*
for gastroesophageal reflux disease, 254–255, 255f
empirical trials of, 181
for gastrointestinal fistulas, 1104
for laryngitis, reflux, 259–260
maintenance of, 543
Pruritus
in cholestatic liver disease, 1694
with primary sclerosing cholangitis, 1566
treatment of, 1567, 1567t, 1588
Pruritus ani, 1884, 2065–2071
causes of, 2066–2070, 2068t
anatomic compromise as, 2067
dermatologic conditions as, 2069–2070
diarrhea as, 2068
dietary, 2068
drugs as, 2069
gynecologic, 2068
infectious, 2070
neoplastic, 2068
personal hygiene as, 2066–2067
psychological, 2069
radiation as, 2069
systemic diseases as, 2067–2068
history in, 2065
pathophysiology of, 2066
physical examination in, 2066, 2066f
treatment of, 2070–2071
Pseudoachalasia, 408–409
imaging in, 72–73
Pseudoaneurysms
of hepatic artery, 1711
of splenic artery, image-guided interventional therapy for, 1791, 1793, 1793f
Pseudocysts
pancreatic. *See* Pancreatic pseudocysts.
splenic, image-guided interventional therapy for, 1795, 1795f
Pseudoepitheliomatous hyperplasia, 1887
Pseudomembranous colitis
antibiotics and, 2329
in immunocompromised patients, 2382
Pseudomonas infection, hepatic abscesses and, 1645
Pseudopapillary tumors, solid, in pediatric patients, 1411
Pseudopolyps, 2158, 2159f
inflammatory, gastric, 884
Pseudopseudocysts, pancreatic, 1329
Pseudotumors, inflammatory
esophageal, 522
in pancreatitis, chronic, 1312
Psoas sign, in appendicitis, 2142
Psoriasis, perianal, pruritus ani associated with, 2069
Psychological factors, pruritus ani and, 2069
Psychosocial factors, gastroesophageal reflux disease and, 201
PTEN hamartoma syndrome, 2159t, 2176
Pteroylglutamic acid
deficiency of, in Crohn's disease, 1054
small intestinal absorption of, 1006, 1007t

PTFE
expanded
for groin hernia repair, 647
paraesophageal hernia and, 560
for ventral herniorrhaphy, 676, 676f
mesh for paraesophageal hernia and, 559, 560
Pubococcygeus muscle, 696
Puborectalis muscle, 696
paradoxical contraction of, surgical treatment of, 1936–1938, 1939f, 1940f, 1941t
Puborectalis syndrome, surgical treatment of, 1936–1938, 1939f, 1940f, 1941t
Pudendal hernias, 695, 696f
Pudendal nerve terminal motor latency
in constipation, 1933–1934
in fecal incontinence, 1919–1920
Puestow procedure, modified, in pediatric patients, 1410
Pulmonary disorders
in cirrhosis, 1693, 1693b
with paraesophageal hernia, 552
postoperative, following esophageal surgery, 599
esophagectomy as, 480
resection with visceral esophageal substitution as, 613
Pulmonary embolism, following bariatric surgery, 937
Pulmonary function, recovery of, following laparoscopic colorectal surgery, 2343
Pulmonary metastases, of colorectal cancer, management of, 2269–2270
patient selection for, 2269
pulmonary resection results and, 2269–2270
Pulmonologists, on portal hypertension multidisciplinary team, 1767
Pulse-echo technique, 112
Purse-string suture, 1085
Push endoscopy, in Crohn's disease, 1050f, 1050–1051
Pyelography
intravenous, with nephroenteric fistulas, 1106
retrograde, with nephroenteric fistulas, 1106
Pyloric atresia, gastric outlet obstruction and, 950f, 951
Pyloric exclusion
for gastroduodenal perforations, 1110
with gastrojejunostomy, 768–769
Pyloric reconstruction
for dumping syndrome, 871–872
longitudinal, for gastric outlet obstruction, 951
Pyloric stenosis
endoscopic appearance of, 738, 739f
hypertrophic, in pediatric patients, 954, 956
clinical features of, 954, 956
diagnosis of, 956
etiology and pathogenesis of, 954
incidence and epidemiology of, 954
management, 956, 957f, 958f
Pyloric ulcers, surgery for, gastric outlet obstruction following, reoperation for, 1136–1137
Pyloric webs, gastric outlet obstruction and, 951
Pyloromyotomy, for esophagogastrostomy, 585, 585f
Pyloroplasty, 816–818
for duodenal ulcers, 794–795
Finney, 816, 818, 819f
for duodenal ulcers, 795
technique for, 842f
gastroparesis following, 923
Heineke-Mikulicz, 816, 818f
for duodenal ulcers, 794–795, 795f
technique for, 841f, 842f
Jaboulay, 818, 819f
technique for, 844f
longitudinal, for gastric outlet obstruction, 951
technique for, 831, 841f–845f
Pylorus-preserving pancreaticoduodenectomy, 1321
results after, 1325–1327
results after head resection with, 1325–1327
techniques for, 1324, 1325f, 1326f
Pyoderma gangrenosum, in colonic diverticular disease, 2021

Q

Quincke, Heinrich Irenaeus, 3, 6, 337–338, 338f
Quinidine, pruritus ani associated with, 2069

R

Rabeprazole. *See also* Proton pump inhibitors.
gastric acid secretion and, 727
Race, gastroesophageal reflux disease and, 200
Radiation enteritis, 1150–1158
clinical features of, 1153
diagnosis of, 1153–1154
etiology of, 1151
histologic findings in, 1151–1152
early, 1151
late, 1151–1152
historical background of, 1150
incidence of, 1150–1151
management of, 1155–1158
conservative/symptomatic, 1156–1157
novel techniques in radiotherapy and combined radiotherapy/chemotherapy for, 1155–1156
prevention and, 1155
surgical, 1157–1158
microcirculation and
molecular biology of, 1152
radiation and, 1152
molecular biology of, 1152
Radiation enteritis *(Continued)*
natural history of, 1152–1153
predisposing risk factors for, 1151
prognosis of, 1154–1155
Radiofrequency ablation
circumferential balloon-based, for Barrett's esophagus, 367–370, 368f, 369f
for hepatocellular carcinoma, 1737–1738, 1738
transarterial, hepatic abscesses following, pyogenic, 1642
Radiographic embolization, of injured spleens, in pediatric patients, 1808, 1810f
Radioisotope-labeled meal, in constipation, 1932
Radiologists, on portal hypertension multidisciplinary team, 1767
Radiopaque marker method, for colonic transit measurement, 1873, 1873f
Radioprotectant chemicals, 1155
Radiotherapy. *See also* Chemoradiotherapy.
adjuvant, radiation enteritis and, 1156
for anal squamous cell carcinoma, 2292–2293, 2293t
electron beam, intraoperative delivery of, for locally recurrent colorectal cancer, 2265–2267, 2268f
esophageal, esophageal carcinoma and, 466
external beam, for carcinoid tumors, 1187
for gallbladder cancer, 1524
for gastric adenocarcinoma
neoadjuvant, 913
palliative, 914
hormone receptor–mediated, for carcinoid tumors, 1187
hyperfractionated, 1156
immunosuppression due to, 2376
intraoperative, 1156
for recurrent cancer, 2417–2418
for lymphoma, 1209
in multimodality therapy, for esophageal cancer, 499–502
postoperative, 501t, 501–502
preoperative, 499–501, 500t
neoadjuvant, radiation enteritis and, 1156
palliative, for esophageal cancer, 493–495
brachytherapy as, 494
combined radiation therapy as, 494–495
external beam radiotherapy as, 494
patient selection for, 493
preoperative
for locally recurrent colorectal cancer, 2262–2263
with low anterior resection, 2220
pruritus ani due to, 2069
rectal injuries due to. *See* Rectum, radiation injuries of.
total-body, hepatotoxicity of, 1723
Raloxifene, for desmoids, in familial adenomatous polyposis, 2162

Ranitidine, 255. *See also* Histamine$_2$ receptor antagonists.
for esophageal strictures, 237
for gastroesophageal reflux disease, 254
Ranson's criteria, 1300, 1301t
Rapid ACTH stimulation test, for evaluation of response to surgical stress, 2378
Read, Raymond, 674
Read/Rives hernia repair, 651–652
Real-time ultrasonography, 112
Recombinant tissue plasminogen activator, for mesenteric venous thrombosis, 1257
Rectal adenocarcinoma, abdominoperineal resection for, 2235
Rectal bleeding
differential diagnosis of, 1883–1884
examination for, 1887
Rectal cancer. *See also* Colorectal adenocarcinoma; Colorectal cancer; Colorectal carcinoma.
adenocarcinoma as, abdominoperineal resection for, 2235
carcinoids as, treatment of, 1185
local excision of, 2197–2198, 2208–2216
algorithm for, 2215–2216, 2216t
endorectal ultrasound and endorectal magnetic resonance imaging and, 2209
outcomes with, 2212–2215
adjuvant therapy and, 2214t, 2214–2215
prospective studies of, 2215, 2215t
retrospective studies of, 2213t, 2213–2214
with transanal endoscopic microsurgery, 2215, 2216t
preoperative evaluation for, 2208, 2209b
technique for, 2209–2212
transanal, 2209, 2210f
transanal endoscopic microsurgery and, 2211–2212, 2212f
transcoccygeal, 2209–2211, 2210f, 2211f
transsphincteric, 2211
recurrent, reoperative pelvic surgery for, 2417
staging of, endorectal ultrasound for, accuracy of, 1900–1903, 1903t
Rectal carcinoids, treatment of, 1185
Rectal disorders. *See also specific disorders.*
diagnosis of, 1883–1897
examination for, 1885–1888
with anorectal pain or swelling, 1887
for bleeding, 1887
for constipation, 1888
general principles of, 1885–1886
inspection and palpation in, 1886–1887
positioning for, 1886, 1886f
for urgency and incontinence, 1888
history in, 1883
investigation for, 1888–1897
blood and stool testing in, 1888–1889
Rectal disorders *(Continued)*
endoscopy in, 1889f, 1889–1891, 1890f
radiologic tests in, 1891f, 1891–1897, 1892f, 1894f–1897f
symptoms in, 1883–1885
abdominal pain and distention as, 1884
anorectal pain, itching and swelling as, 1884
bleeding as, 1883–1884
constipation as, 1884–1885
diarrhea as, 1885
urgency and incontinence as, 1885
Rectal dyschezia, surgical treatment of, 1936–1938, 1939f, 1940f, 1941t
Rectal examination
in appendicitis, 2142
for small bowel obstruction, 1029
Rectal intussusception, surgical treatment of, 1936, 1938f
Rectal neoplasms. *See also* Colorectal adenocarcinoma; Colorectal cancer; Colorectal carcinoma; Rectal cancer; Retrorectal tumors; *specific neoplasms.*
transanal excision of, 2338
Rectal obstruction, management of, 2220–2221
Rectal pain. *See also* Perineal pain syndromes.
examination for, 1887
idiopathic, chronic, 2071
Rectal prolapse, 1958–1965, 1959f
diagnosis and testing in, 1958–1959
historical background of, 1958
laparoscopic surgery for
outcomes of, 2357, 2357t
technical issues for, 2357
pathophysiology of, 1958
physical examination in, 1918, 1958
treatment of, 1959–1965
acute management for, 1959–1960
results and patient selection for, 1964t, 1965
surgical, 1960–1965
abdominal approaches for, 1960–1961
perineal approaches for, 1961–1965, 1962f
Rectal reconstruction, for radiation injury, 2322–2323
Rectal sensation, determination of, 1919
Rectal stump, identification of, 2413f, 2413–2414
Rectal ulcers
endoanal ultrasound with, 1913–1914, 1914f
solitary, 2075–2076
diagnosis of, 2075–2076, 2076f
treatment of, 2076
Rectoanal inhibitory reflex, 1919
Rectoanal reflex, 2392
Rectocele
repair of, 699, 700f–702f
surgical treatment of, 1936, 1938f
Rectopexy
for rectal prolapse, 1960–1961, 1964t
resection with, for rectal prolapse, 1961, 1961f, 1964t
Rectorectal neoplasms, endoanal ultrasound in, 1913, 1914f
Rectorectal space, initial entry into, for total mesorectal excision with autonomic nerve preservation, 2236–2237, 2237f
Rectourethral fistulas, 1954–1955
meconium in urine and, 2394, 2394f
Rectovaginal fistulas, 1945–1954
clinical presentation of, 1945–1946
in Crohn's disease, 2088
surgical treatment of, 2136, 2138
diagnosis of, 1946
endoanal ultrasound in, 1912
etiology of, 1945
examination of, 1946
local repairs of, 2324–2325
treatment of, 1946–1954, 1947b
abdominal procedures for, 1952, 1954
coloanal anastomosis as, 1952, 1954
diversion and, 1954
onlay patch anastomosis as, 1954
local procedures for
advancement sleeve flap as, 1951, 1951f
autologous fibrin glue for, 1952
fistulotomy as, 1952
perineoproctectomy with layered closure as, 1952
polyglycolic mesh for, 1952
sliding flap repair as, 1947–1950, 1948f–1950f, 1949t
sphincteroplasty as, 1950f, 1950–1951, 1951t
timing of surgery and, 1947
tissue transfer techniques for, 1952
Rectrorectus extraperitoneal repair, for ventral hernias, 677–678, 678f, 679f
Rectum. *See also* Anorectal *entries;* Colorectal *entries;* Rectal *entries.*
abdominoperineal resection of, 2234–2243
for adenocarcinoma of rectum, 2235
adjacent organ involvement and, 2243
closure of pelvic floor and biologic spacers and, 2243
colostomy and, 2242–2243
indications for, 2234
laparoscopic, 2239–2241
technique for, 2239–2241, 2240f
patient preparation for, 2234–2235
bowel preparation and, 2235
consultation with patient and family and, 2234–2235
patient positioning and, 2235
staging and, 2234
perineal dissection and, 2241f, 2241–2243, 2242f
total mesorectal excision with autonomic nerve preservation and, 2236f, 2236–2243
distal rectal mobilization and, 2239

Rectum *(Continued)*
hypogastric nerves and pelvic autonomic nerve plexuses and, 2237–2238, 2238f
initial entry into retrorectal space and, 2236–2237, 2237f
"lateral ligaments" and, 2238–2239, 2239f
separation of anterior and posterior compartments and, 2238, 2238f
cavernous hemangiomas of, 1996
radiation injuries of, 2320–2325
incidence of, 2320–2321
medical treatment of, 2321
proctitis due to, medical management for, 2321–2322
reconstructive surgery for, 2322–2323
rectovaginal fistulas and, local repairs of, 2324–2325
transabdominal approaches for, 2323–2324
Bricker-Johnston, 2323
coloanal anastomosis as, 2323–2324
coloplasty as, 2324
colopouch anal anastomosis as, 2324
low anterior resection as, 2323
vascular supply to, 2223, 2224f
Rectus abdominis muscle, 1290f, 1291–1292
Rectus sheath, 638–639, 639f, 672, 672f
Recurrent laryngeal nerve, injury of, during esophageal surgery, 598
Redo pelvic pouch procedure, 2415, 2417
Reflection, in ultrasonography, 111–112
Reflux carditis, 213f, 213–215. *See also* Cardiac mucosa.
evolution of, 215, 215f
Reflux esophagitis. *See also* Gastroesophageal reflux disease.
classification of, 105–106, 106, 106t, 107f
stricture formation due to, 90
treatment of, 255–256, 256, 256f
Reflux gastritis, alkaline, following gastrectomy, 809
Refraction, in ultrasonography, 112
Regeneration, hepatic, 1608, 1608f
Regurgitation
in achalasia, 407
with epiphrenic diverticulum, 433
in esophageal disease, 56–57
in esophageal motility disorders, 71
following esophagomyotomy, for achalasia, 620
Rejection, of pancreas transplants, 1419
Renal cell carcinoma, metastatic to pancreas, 1437–1439, 1438f, 1439f
Renal dysfunction
in cirrhosis, 1625
in end-stage liver disease, 1693–1694
Renal failure, chronic, pruritus ani in, 2067
Rendu-Osler-Weber disease, 1713
Renogastric fistulas, 1095
Reoperative surgery, 1133–1136, 1134b
for adenocarcinoma, of gastric remnant, 1140
for afferent limb syndrome, 1147
Reoperative surgery *(Continued)*
for anorectal anomalies, 2403
assessment and counseling for, 1134
bariatric, 1143–1146
for failed laparoscopic adjustable gastric banding, 1145
for failed malabsorptive procedures, 1146
for failed Roux-en-Y gastric bypass, 1145–1146
for failed vertical banded gastroplasty, 1144–1145
patient selection for, 1144
for bile reflux gastritis, 1146f, 1146–1147, 1147f
for desmoid tumors, recurrent, 1141
for gastric outlet obstruction
at gastrojejunostomy site, 1137–1138
operative technique for, 1138
after pyloric or duodenal ulcer surgery, 1136–1137
operative technique for, 1137, 1137f
for gastroesophageal reflux disease, 1141–1143
technical aspects of, 1143, 1143b
for gastroparesis, 1139–1140
hostile abdomen and, 1147–1148, 1148b
information preparation for, 1133–1134
laparoscopic, 1135–1136
technique for, 1135–1136
bowel injury during, 1136
nutritional issues and access for, 1136
open, 1134–1135
pelvic, 2409–2418
anatomy and, 2409, 2410b
anticipation of problems with, 2410–2411
conduction of, 2412, 2412f
control of bleeding and, 2414–2415
drainage and, 2415
identification of pelvic structures and, 2412–2414
of bladder, 2413
of rectal stump, 2413f, 2413–2414
of ureters, 2412
of vagina, 2414
for malignancies, 2417–2418
operative measures to make pelvic surgery easier and safer and, 2418
optimizing visibility and exposure for, 2411f, 2411–2412
patient preparation for, 2410, 2411
preoperative imaging studies for, 2410
preparation for bleeding and, 2410
to redo pelvic pouch procedure, 2415, 2417
for reversal of Hartmann's procedure, 2415, 2416f
timing of, 2409–2410
for postgastrectomy dumping and diarrhea, 1138–1139
for Roux limb syndrome, 1140
for stromal cell tumor, recurrent, 1141
Reperfusion syndrome, liver transplantation and, 1696
Researcher, as clinical nurse specialist role, in palliative treatment, for esophageal cancer, 498
Resin hemoperfusion, for liver failure, acute, 1706
Resolution, in ultrasonography, 112
Respiratory insufficiency, following esophageal resection with visceral esophageal substitution, 613
Respiratory system, prenatal development of, 31–33, 33f, 34f
Resuscitation
for caustic ingestions, 543
for gastrointestinal fistulas, 1099–1100
Retention polyps, 2157
gastric, 884
Retroduodenal artery, 1445, 1446
anatomy of, 1237
Retrograde bypass, for mesenteric revascularization, 1260, 1261f, 1262f
Retrograde giant contractions, small intestinal, 1016–1017
Retrograde pyelography, with nephroenteric fistulas, 1106
Retrorectal tumors, 2299–2309
anatomy and, 2299
classification of, 2300, 2300b
clinical findings and diagnosis of, 2300–2302
biopsy in, 2301–2302
of developmental cysts, 2302–2304
enterogenous, 2302, 2302t
epidermoid and dermoid, 2302, 2302t
tailgut, 2302t, 2302–2304, 2303f
history and physical examination in, 2300–2301
investigations in, 2301
of neurogenic tumors, 2304
of osseous lesions, 2306
of sacrococcygeal chordomas, 2304, 2304f–2306f
of teratoma and teratocarcinoma, 2302t, 2304–2305
incidence of, 2299–2300
surgical therapy for, 2306–2309
multidisciplinary team and, 2306
rationale for, 2306
results with, 2309
for benign tumors, 2309, 2310f
for malignant tumors, 2309
surgical approach for, 2307–2309
combined abdominoperineal approach as, 2307–2308, 2308f
preoperative planning and, 2307
for tumors located below S3, 2307, 2307f
Retrosacral fascia, division of, for low anterior resection, 2227–2228, 2228f
Reverse rotation, 1214, 1215f, 1216f
Rex's ramus arcuatus, 1606
Rhabdomyomas, esophageal, 522
Rhabdomyosarcomas
colorectal, 2317
hepatic, 1747
Riboflavin, small intestinal absorption of, 1006, 1007t
Ricordi, Camillo, 1424

Riedel's lobe, 1598
Rifampin, for pruritus, in primary sclerosing cholangitis, 1567
Riolan, arch of, 1239
Ripstein procedure
for rectal prolapse, 1960f, 1960–1961
Well's modification of, for rectal prolapse, 1960, 1960f
Rituxumab, for islet transplantation, 1428
Robotic-assisted laparoscopic splenectomy, 1787
Rockey-Davis incision, for appendectomy, 2145, 2146f
Rokitansky-Aschoff sinuses, 1444
Ronsil, Roland Arnaud de, 688
Rosary-bead esophagus, 419, 420f
Rosetti, Franciscus, 1813
Rotational flaps, for anal stenosis, 2064–2065, 2065f
Rouviere, sulcus of, 1603
Roux, Cesar, 4
Roux gastrojejunostomy, gastrectomy with, for gastroparesis, 925
Roux stasis syndrome
following gastrectomy, 809, 880, 925
reoperative surgery for, 1140
Roux-en-Y biliary diversion, partial gastrectomy with, for esophageal stricture, 249
Roux-en-Y choledochojejunostomy, for duodenal diverticula, 782–783, 784f
Roux-en-Y duodenojejunostomy
for duodenal diverticula, 782, 783f
for gastroduodenal fistulas, 1110
Roux-en-Y gastric bypass
for foregut reconstruction for benign disease, 303, 303f
for obesity, 931–934, 932f, 933t
Roux-en-Y gastrojejunostomy
for bile reflux gastritis, 876, 876f
for dumping syndrome, 872f, 872–873
following gastrectomy, 911
Roux-en-Y reconstruction, for duodenal ulcers, 796, 798f
Rubber bands, hemorrhoidal ligation with, 2031, 2032f
Rutkow hernia repair, 649, 650f, 651f
Ruvalcaba-Myhre-Smith (Ruvalcaba-Riley-Smith) syndrome, 894t, 897, 2159t, 2176

S

S pouch, 2104
Sacral anomalies, associated with imperforate anus, 2390
Sacral nerve stimulation, for fecal incontinence, 1925, 1925f
Sacral plain radiographs, with retrorectal tumors, 2301
Sacrococcygeal chordomas, 2304, 2304f–2306f
Sagittal anatomy, low anterior resection and, 2223, 2223f
"Salem sump" tube, 750, 751f
Salmonella, splenic abscess due to, 1819
Salvage surgery, for anal squamous cell carcinoma, 2293–2294, 2294f
Santorini, pancreatic duct of, 964
Sarcoidosis, splenectomy for, 1835
Sarcoptes scabiei infection, pruritus ani associated with, 2070
Satiety, early, following gastrectomy, 808–809
Saucerization, for pilonidal disease, 1968
Savary Miller classification, for reflux esophagitis, 106t
Scabies, pruritus ani associated with, 2070
Scarpa, Antonio, 632
Scarpa's fascia, 636
Schatzki rings
imaging of, 88, 90f
origin of, 229
Schistosomiasis, portal hypertension and, 1756–1757
Schwannomas
esophageal, 520
hepatic, 1747
small intestinal, 900
Sciatic hernias, 700–704
anatomy and, 701, 703f
clinical features and diagnosis of, 701–702, 703f
treatment of, 702–704, 703f
Scintigraphy
in aortoenteric fistulas, 1271f, 1271–1272
with bile duct strictures, 1578
with colon, rectal, and anal disorders, 1895–1896, 1896f
for colonic transit measurement, 1873f, 1873–1874
with colonic vascular ectasias, 1991, 1993
esophageal transit, 154–155
gastric emptying, 185, 186f, 187f
HIDA, with biliary fistulas, 1542
in jaundice, obstructive, 1462, 1463f
somatostatin receptor-based
of carcinoid tumors, 1184, 1184f
for insulinoma localization, 1377
in Zollinger-Ellison syndrome, 864, 865f
Scleroderma, esophageal motility disorder in, imaging in, 74
Sclerotherapy
alcohol, for esophageal cancer, 488, 489t
for gastric bleeding, 742–743
for hemorrhoids, 2030f, 2030–2031
for hepatic cysts, in polycystic liver disease, 1634–1635
for hepatocellular carcinoma, 1737
Scopolamine, for gastroparesis, 921
Seat belt sign, small bowel perforation and, 770, 771, 771f
Seborrheic dermatitis, pruritus ani associated with, 2069
Second messengers, gastric acid secretion and, 725, 725f
Secretin
duodenal function and, 980, 981t
infusion of, for gastrinoma localization, 865
pancreatic cell function and, 1292
small intestinal neuroendocrine function and, 1018
Sectionectomy, left lateral, 1679–1680
Segmental arteries, 1772
Selenium, deficiency of, in Crohn's disease, 1054
Self-expanding metal stents
for colorectal cancer metastases, 2271
for esophageal cancer, 489–492
placement of, 490, 491f, 492, 492f
special considerations with, 492
for esophageal perforation, 532
for gastric bleeding, 743–744, 744f
Sentinel bleeding, with aortoenteric fistulas, 1114
Sepsis
catheter-related, in short-bowel syndrome, 1167
control of, with gastrointestinal fistulas, 1101–1103, 1103f, 1104f
with gastrointestinal fistulas, 1098
with parenteral nutrition, 1165
perianal, endoanal ultrasound in, 1911
Seromas
with inguinal herniorrhaphy, laparoscopic, 668
with ventral herniorrhaphy, laparoscopic, 681
Seromyotomy, lesser curve, anterior, 815, 822
Serosa, small intestinal, 998
Serosal patching, for short-bowel syndrome, 1168–1169, 1169f
Serotonin
carcinoid tumors and, 1183
duodenal function and, 981t, 982–983
Serotonin receptors, intestinal motility and, 926
Serous cystic neoplasms, pancreatic
clinical presentation of, 1387
diagnosis of, 1393, 1393f
incidence and epidemiology of, 1387
pathology and biologic behavior of, 1388–1389, 1389f
treatment of, 1396–1397
SES-CD, 1051
Setons
for anorectal fistulas, 2055f, 2055–2056
for fistula treatment, in Crohn's disease, 2135–2136, 2137f–2138f
Sex
Barrett's esophagus and, 342
drug-induced liver disease and, 1717
esophageal cancer and, 444
gastroesophageal reflux disease and, 200
Sex hormone–binding globulin, obesity and, bariatric surgery and, 938
Sex hormones, hepatotoxicity of, 1721, 1722, 1723, 1724
Sexual dysfunction, following ileal pouch–anal anastomosis, 2117
Sham feeding, to stimulate postoperative gastrointestinal motility, 1028
Shock, with hepatobiliary trauma, 1668
Short chain fatty acids, metabolism of, colonic, 1873
Short esophagus
acquired, Nissen fundoplication for, 272f, 272–273, 273f
definition of, 234

Short esophagus *(Continued)*
evaluation of, barium examination for, 70, 71f
preoperative assessment of, 237
strictures and. *See* Esophageal strictures.
Short-bowel syndrome, 1162–1177, 1163b
intestinal adaptation and, 1163–1164, 1164b, 1164f
intestinal remnant length and, 1162
medical management of, 1164–1168
maintenance of nutritional status and, 1165
maximization of enteral nutrient absorption and, 1165–1166, 1166b
prevention of complications and, 1166–1168, 1167f
outcome, factors influencing, 1162–1163, 1163t
prevalence of, 1162
site of resection and, 1162
surgical management of, 1168b, 1168t, 1168–1177
to improve intestinal function, 1169–1171
motility and, 1169
prolonging intestinal transit and, 1169–1171, 1170f, 1170t
to increase absorptive area, 1171–1173, 1172f
intestinal transplantation as, 1173–1177
indications for, 1173–1174
operative procedure for, 1174f, 1174–1175
outcome with, 1175f, 1175–1177, 1176f
to preserve and maximize intestinal remnant, 1168–1169, 1169f
Short-segment colon interposition, 596–597
results of, 596t, 596–597
Shoulder pain, with inguinal herniorrhaphy, laparoscopic, 666–667
Shouldice hernia repair, 633, 648–649
Shrock shunt, 1665
Shunts
arterioportal, hepatic, 1713f, 1713–1714
arteriovenous, hepatic, 1713f, 1713–1714
portocaval, intrahepatic, transjugular
for ascites, 1765
for bleeding due to portal hypertension, 1693
for bleeding varices, 1693, 1761–1762
procedure for, 1761f, 1761–1762
for Budd-Chiari syndrome, 1714, 1715
Shrock, 1665
splenorenal, distal, for bleeding varices, 1762–1763
follow-up for, 1762–1763
management of, 1762
procedure for, 1762, 1762f
Sickle-cell disease, splenectomy for, 1826
Siderotic particles, 1775
Side-to-side isoperistaltic stricturoplasty, for Crohn's disease, 1059, 1062f
Sigmoid arteries, 1850–1851, 1851f
Sigmoidocele, surgical treatment of, 1936, 1937f
Sigmoidoscopy
with anorectal fistulas, 2049
flexible, screening with, for colorectal carcinoma, 2191–2192
rigid, with colonic vascular ectasias, 1991
Sildenafil
for achalasia, 412
for nutcracker esophagus, 423
Silk sutures, for bowel anastomoses, 1083–1084
Simonds, Charter, 743
Simplified Endoscopic Activity Score for Crohn's Disease, 1051
Sims' position, 1886, 1886f
Sirolimus
for islet transplantation, 1424
mechanism of action of, 2377t
Sister Mary Joseph's nodule, 906, 1361
Skin problems
in Crohn's disease, 2087
with stomas, 1081, 2370f, 2370–2371
Skip lesions, in Crohn's disease, 1043
Sleep apnea, obesity and, bariatric surgery and, 938
Sliding flap repair
for rectourethral fistulas, 1955
for rectovaginal fistulas, 1947–1950, 1948f–1949f, 1949t
Sliding hernias, 643
Small bowel
Crohn's disease in, surgical treatment of, 2132
diverticula of. *See* Duodenal diverticula; Jejunoileal diverticula; Meckel's diverticula.
endoscopic examination of, 745f–747f, 745–747
Small bowel enteroclysis, in Crohn's disease, 1046–1047, 1047f
Small bowel follow-through, in Crohn's disease, 1046–1047, 1047f
Small bowel injury, 770–773
anatomy and physiology and, 770
diagnosis of, 771f, 771–772, 772f
historical background of, 770
mechanism of, 770–771
operative management of, 772
perforation of, 770
postoperative management of, 772–773
Small bowel motility, obstruction and, 1025
Small bowel obstruction, 1025–1033
classification of, 1025, 1026t
clinical findings in, 1028, 1028t
closed-loop, pathophysiology of, 1026–1027, 1027f
complete, 1025
etiology of, 1027
following ileal pouch–anal anastomosis, 2111
functional, 1025
high grade, 1025
internal hernias as cause of, 1120
with jejunoileal diverticula, 785
laboratory tests in, 1029
low grade, 1025
mechanical, 1025
Small bowel obstruction *(Continued)*
with Meckel's diverticulum, 787, 788f
motility and, 1025
partial, 1025
pathophysiology of, 1025–1027
of closed-loop obstruction, 1026–1027, 1027f
physical examination in, 1028–1029
radiologic investigations in, 1029–1032
computed tomography and, 1030–1032, 1031f
contrast radiographs and, 1030, 1030f
plain radiographs and, 1029, 1029f
risk of, following laparoscopy, 1027–1028
treatment of
medical, 1032
surgical, 1032–1033
adhesion prevention and, 1033
laparoscopic vs. open adhesiolysis for, 1032–1033
operative, 1033
Small bowel resection
for Crohn's disease, 2132, 2133f
for intestinal dysmotility, 927
Small bowel strictures, in Crohn's disease, management of, 1063
Small bowel transit studies, in constipation, 1932
Small bowel transplantation, for intestinal dysmotility, 927
Small bowel volvulus, 1035–1037
diagnosis of, 1036, 1036f
etiology of, 1035–1036, 1036t
treatment of, 1036–1037
Small intestinal adenocarcinoma, 915–916
duodenal, 915–916
ileal, 916
jejunal, 916
pathogenesis of, 915
risk factors for, 915
Small intestinal adenomas
Brunner's gland, 892–893
ectopic tissue, 892–893
Small intestinal cysts, in pediatric patients, 1221–1223, 1222f, 1223f
Small intestinal duplications, in pediatric patients, 1221–1223, 1222f, 1223f
Small intestinal epithelium, 998–1009
architecture of, 998, 999f, 1000f
barrier function of, 998–999, 1000f, 1001
digestion and absorption and, 1001–1008
of bile salts, 1007t, 1008
of carbohydrates, 1002, 1002f, 1003f, 1003t
of lipids and cholesterol, 1003t, 1004–1006, 1005f, 1006f
of minerals, 1008, 1009f
of protein, 1002–1004, 1003t, 1004f
of sodium, 1001–1002, 1002f
of vitamins, 1006–1008, 1007t
of water, 1001, 1001t
intestinal fluid secretion and, 1008–1009, 1010f
Small intestinal fistulas. *See* Enteric fistulas.

Small intestinal immune system, 1009–1012
gut-associated lymphoid tissue and, 1010, 1012f
M cells and, 1010, 1012f
regulation of, 1010
regulation of gut function by, 1011–1012
secretory immunoglobulin A and, 1010, 1011f
Small intestinal lymphomas, epidemiology of, 1199, 1200t
Small intestinal polyps, 891–893
benign, non-neoplastic, 891
fibroid, inflammatory, 891
neoplastic, 891–893
Brunner's gland, 892–893
ectopic tissue, 892–893
endometriosis as, 893
tubular adenomas as, 891–892
villous adenomas as, 892–893
Small intestine. *See also specific parts, e.g.* Duodenum.
anatomy of, 988, 989f, 990, 990f, 1234, 1236f
benign neoplasms of, 889–901, 890t
mesenchymal, 898–901
congenital, 901
leiomyomas as, 899–900
lipomas as, 900–901
vascular, 898–899
mucosal, 891–893
polyposis syndromes and. *See* Intestinal polyposis syndromes.
symptoms and diagnosis of, 889–890, 890t
developmental anomalies of, 994–997
atresia as, 997, 997f
duplications as, 994
internal hernias as, 997
omphalocele as, 994–995, 995f
rotational, 995, 996f, 997
stenosis as, 997
ventral hernias as, 994–995
vitelline duct, 994, 995f
embryology of, 992–993
gastrulation and, 992–993, 993f, 994f
foreign bodies in. *See* Foreign body ingestion.
histology of, 990, 991f
innervation of, 990, 992
lymphoid functions and architecture of, 992
microvasculature, 992
motility of, 1012–1017
intestinal smooth muscle cells and, 1013, 1013f
organization of contractile activity and, 1015b, 1015–1017
individual phasic contractions and, 1015
organized groups of contractions and, 1015f, 1015–1016, 1016f
special propulsive contractions and, 1016–1017
patterns of contractions and, 1013–1015
chemical control and, 1014–1015
myogenic control and, 1013–1014
neural control and, 1014
Small intestine *(Continued)*
neuroendocrine function of, 1017–1019, 1018b
cholecystokinin and, 1018
guanylin and, 1019
motilin and, 1019
secretin and related peptides and, 1018
somatostatin and, 1018–1019
uroguanylin and, 1019
physiology of, 997–998
Small-bowel follow-through, in small bowel obstruction, 1030
Smith-Lortat-Jacob, M., 337
Smoking
cessation of, for gastroesophageal reflux disease, 253
esophageal cancer and, 444, 466
pancreatic adenocarcinoma and, 1359
Smooth muscle cells, intestinal, small intestinal motility and, 1013, 1013f
Smooth muscle disease, intestinal motility and, 925–926
Sodium
absorption of, colonic, 1872
small intestinal absorption of, 1001–1002, 1002f
Sodium butyrate, for rectal radiation injuries, 2321
Solid pseudopapillary tumors, 1434, 1435f
in pediatric patients, 1411
Solitary rectal ulcer syndrome, 2075–2076
diagnosis of, 2075–2076, 2076f
endoanal ultrasound in, 1913–1914, 1914f
treatment of, 2075–2076
Somatostatin
duodenal function and, 981t, 982
gastric, 722–723
Helicobacter pylori effects on, 722–723
synthesis and action of, 722
small intestinal neuroendocrine function and, 1018–1019
for variceal bleeding, 1759
Somatostatin receptor(s), gastric acid secretion and, 725
Somatostatin receptor-based scintigraphy
of carcinoid tumors, 1184, 1184f
for insulinoma localization, 1377
in Zollinger-Ellison syndrome, 864, 865f
Somatostatinoma, 1380–1381
diagnosis of, 1380
presentation of, 1380
therapy of, 1381
Spastic pelvic floor syndrome, surgical treatment of, 1936–1938, 1939f, 1940f, 1941t
Speech, preservation of, with oropharyngeal strictures, 546–547
Spencer, Thomas, 1813
Spermatic cord, 641
Sphincter of Oddi, 1444–1445, 1445f
function of, 1458f, 1458–1459
Sphincter of Oddi manometry, 1492–1493
Sphincteroplasty
for common bile duct stones, 1594
for rectovaginal fistulas, 1950f, 1950–1951, 1951t
Sphincteroplasty *(Continued)*
transduodenal, for duodenal diverticula, 781, 781f, 782f
Sphincterotomy
antegrade, 1485
for common bile duct stones, 1594
endoscopic, 1493
complications of, 1494
Sphincter-sparing techniques, for colorectal cancer, 2195, 2197f
Spiegel, Adriaan van der, 682
Spigelian fascia, 672, 673f
Spigelian hernias, repair of, 682
Spinal anomalies, associated with imperforate anus, 2390
Spinal disorders, pain associated with, 2072
Spinal dysraphism, associated with imperforate anus, 2406
Spinal surgery, gastroparesis following, 923
Spindle cells, gastrointestinal stromal tumors and, 1190, 1190f
Spironolactone
for ascites, 1764
following distal splenorenal shunt procedure, 1762–1763
Splanchnic autoregulatory, 1243
Splanchnic blood flow
extrinsic control of, 1241
intrinsic control of, 1241–1242, 1242b
Splanchnic nerve, 1294
Splanchnicectomy, for pain palliation, in pancreatic and periampullary carcinoma, 1367, 1367f
Spleen
accessory
in idiopathic thrombocytopenic purpura, 1823, 1824f
search for, 1785
anatomy of, 1771–1772
of blood supply, 1772, 1773f
of lymphatic drainage, 1772, 1773f
neural, 1772, 1773f
embryology of, 1772, 1772f
function of, evaluation of, 1775
functions of, 1772–1773
histology and immunophenotype of, 1773–1775, 1774f, 1775t, 1776f
image-guided interventional therapy for, 1788–1795
for hypersplenism, partial splenic embolization as, 1793–1795, 1794f, 1795f
for pseudoaneurysm of splenic artery, 1791, 1793, 1793f
for splenic abscess and pseudocyst, 1795, 1795f
transarterial splenic embolization as, 1788–1790
anatomy and, 1788, 1789f, 1790f
splenic bleeding and, 1790–1791, 1792f
technique for, 1788–1790, 1790f
imaging of, 1775–1776
pathologic findings in, 1776–1777
red pulp of, 1772
white pulp of, 1772

Splenectomy, 1777–1778, 1822–1838
for abscesses, 1833
for amyloidosis, 1835
for bleeding varices, 1353
complications of, 1777–1778
consequences of, in pediatric patients, 1806
for cysts, 1832–1833
nonparasitic, 1833
parasitic, 1832
for Gaucher's disease, 1835
for hematologic disorders, 1822–1827
autoimmune neutropenia as, 1827
causing anemia, 1825–1827
hemolytic, acquired, 1826–1827
hereditary, 1825–1826
causing thrombocytopenia, 1822–1825
human immunodeficiency virus as, 1825
idiopathic thrombocytopenic purpura as, 1822–1824, 1824f
systemic lupus erythematosus as, 1824–1825
thrombotic thrombocytopenic purpura as, 1824
Wiskott-Aldrich syndrome as, 1825
Evans's syndrome as, 1827
Felty's syndrome as, 1827
for iatrogenic injury, 1834–1835
indications for, 1777
for lymphoproliferative disorders, 1827–1831
Hodgkin's disease as, 1827–1829, 1828f, 1828t
leukemias as, 1830t, 1830–1831
non-Hodgkin's lymphoma as, 1829, 1829t, 1830b
for myeloproliferative disorders, 1831–1832
nonsurgical, 1353
operative considerations with, 1835–1837, 1836f, 1837f
partial, 1836
operative considerations for, 1836
for splenic cysts, 1815
for splenic tumors, 1816
postoperative course and complications of, 1837–1838
preoperative preparation for, 1835
for sarcoidosis, 1835
for splenic abscesses, 1820
for splenic cysts, 1815
for splenic trauma, 1801
for tumors, 1832
for vascular disorders, 1833–1834
portal hypertension as, 1834
splenic artery aneurysm as, 1833–1834
splenic vein thrombosis as, 1834
"wandering spleen" and splenic torsion as, 1834
Splenic abscesses, 1818–1820
characteristics of, 1819
diagnosis of, 1818, 1819f
image-guided interventional therapy for, 1795, 1795f
Splenic abscesses *(Continued)*
management of, 1820
presenting signs and symptoms of, 1818
splenectomy for, 1833
Splenic artery, 20, 20f, 21f, 1237, 1292, 1293f
aneurysms of, 1274–1277
clinical findings in, 1275
diagnosis of, 1275, 1276f
incidence of, 1274
pathogenesis of, 1274–1275
splenectomy for, 1833–1834
treatment of, 1275, 1277
pseudoaneurysm of, image-guided interventional therapy for, 1791, 1793, 1793f
Splenic autotransplantation, for splenic trauma
in adults, 1802
in pediatric patients, 1811
Splenic bleeding, transarterial splenic embolization and, 1790–1791, 1792f
Splenic circulation, 1775, 1777f
Splenic cysts, 1813–1815
nonparasitic
congenital, 1814
secondary (false), 1813, 1814
splenectomy for, 1833
parasitic, 1813–1814
splenectomy for, 1832
splenectomy for, 1832–1833
true, 1813
Splenic decapsulization, partial, for splenic cysts, 1815
Splenic embolization
partial, for hypersplenism, 1793–1795, 1794f, 1795f
transarterial, 1788–1790
anatomy and, 1788, 1789f, 1790f
splenic bleeding and, 1790–1791, 1792f
technique for, 1788–1790, 1790f
Splenic flexure, 1847
Splenic flexure volvulus
etiology and pathophysiology of, 1985
treatment of, 1985
outcomes following, 1985
Splenic hypertrophy, 1777
Splenic injury
in adults, 1798–1803
diagnostic modalities for, 1798–1800, 1800t
grading systems for, 1799–1800, 1800t
nonoperative treatment of, 1802–1803
operative treatment of, 1800–1802
autotransplantation as, 1802
general principles of, 1800–1801
laparoscopic splenectomy as, 1802
splenectomy as, 1801
splenorrhaphy as, 1801–1802
rupture following, delayed, 1803
following esophageal resection with visceral esophageal substitution, 615
with Nissen fundoplication, 273
Splenic injury *(Continued)*
in pediatric patients, 1805–1812
asplenia prophylaxis for, 1811–1812
evaluation of, 1806–1808, 1807f, 1808t, 1809f, 1810f, 1811t
historical background of, 1805–1806
immune function and consequences of splenectomy and, 1806
operative management of, 1808, 1811
Splenic neoplasms
benign, splenectomy for, 1832
solid, 1815–1816
splenectomy for, 1832
Splenic nervous plexus, 1772
Splenic pseudocysts, image-guided interventional therapy for, 1795, 1795f
Splenic torsion, splenectomy for, 1834
Splenic vein, 1772
Splenic vein thrombosis
asymptomatic, 1353
following splenectomy, 1838
in pancreatitis, chronic, 1352–1353
splenectomy for, 1834
Splenomegaly, 1777
massive, 1778
with splenic vein thrombosis, 1353
Splenorenal shunt, distal, for bleeding varices, 1762–1763
follow-up for, 1762–1763
management of, 1762
procedure for, 1762, 1762f
Splenorrhaphy, for splenic trauma, 1801–1802
Sporadic MIS tumors, 2189
Squamocolumnar junction, 19
Barrett's esophagus classification and, 103–104
endoscopic appearance of, 101, 101f
in Barrett's esophagus, 103, 103f, 104f
Squamous cell carcinoma
anal, 2291–2294
clinical features of, 2291
physical examination of, 2291
staging of, 2291, 2292f
therapy of, 2291–2294
combined chemotherapy and radiation therapy for, 2292–2293, 2293t
salvage surgery as, 2293–2294, 2294f
surgical, primary, 2291–2292
colorectal, 2313
esophageal, epidemiology of
age, sex, and race distribution and, 443
risk factors and, 443–445
alcohol as, 443
diet and nutrition as, 443, 445
nonsteroidal anti-inflammatory drugs as, 445
obesity as, 443, 443t, 444f
tobacco as, 443
hepatic, 1747
perianal, pruritus ani and, 2068
Squamous papilloma, esophageal, 523–524, 524f
Stacked coin sign, 765–766

Stamm gastrostomy
contraindications to, 750t
for esophagocoloplasty, 591
with hostile abdomen, 1147
indications for, 750t
in pediatric patients, 960
technique for, 857, 860f, 861f
Staphylococcus aureus infection
hepatic abscesses and, 1644–1645
overwhelming postsplenectomy infection and, 1782
splenic abscess due to, 1819
Stapled gastric partitioning, for obesity, 930
Stapled intestinal anastomoses, 2333, 2334f–2337f
Staplers
circular (EEA; ILS; PPH), 1087
GIA, 1086, 1087f
linear, 1086, 1087f
Stapling, for bowel anastomoses, 1086f, 1086–1089
hand-sewn vs. stapled anastomoses and, 1088–1089
staplers for, 1086–1087, 1087f
techniques and pitfalls in, 1087–1088
functional end-to-end anastomosis and, 1087, 1088f
stapled end-to-end anastomosis and, 1087–1088, 1088f
Steatohepatitis, drug-induced, 1719t, 1720–1721
Steatorrhea
following ileal resection, 1880
in pancreatitis, chronic, 1345
with primary sclerosing cholangitis, 1566
treatment of, 1567, 1588
Stents
for bile duct stones, 1496
for caustic ingestions, 543
for celiac artery aneurysms, 1278–1279
for colorectal cancer, colonoscopic positioning of, 2331
for gastric bleeding, 743f, 743–744, 744f
for hepatic artery aneurysms, 1278
for pancreatitis, chronic, with bile duct stricture, 1348
self-expanding
for esophageal cancer, 489–492
placement of, 490, 491f, 492, 492f
special considerations with, 492
for esophageal perforation, 532
metal
for colorectal cancer metastases, 2271
for gastric bleeding, 743–744, 744f
surgical, for bleeding varices, 1762
STEP procedure, for short-bowel syndrome, 1171, 1172f, 1173
Steroids. *See also* Corticosteroids.
anabolic, hepatotoxicity of, 1723
androgenic, hepatotoxicity of, 1724
for caustic ingestions, 543
Stoma(s). *See also* Ostomies; *specific procedures.*
anastomosis vs., 2335, 2338
formation of, for Crohn's disease, 1060, 1062–1063
necrosis of, with ileostomy, 1078
Stoma(s) *(Continued)*
prolapse of, 2372–2373, 2373f
with ileostomy, 1080
retraction of, with ileostomy, 1080
stenosis of, 2372
with ileostomy, 1080
Stomach. *See also* Gastric *entries;* Gastro- *entries.*
anatomy of, 717–721
anatomic relationships and, 717–718, 718f
of divisions, 717, 718f
of glandular organization, 721, 721t, 722f
of innervation, 719–720, 720f
lymphatic, 719
morphology and, 720–721, 721f
vascular, 718, 719f
antrum of, 717, 718f
cardia of, 717, 718f
compression of, with paraesophageal hernia, 551–552
congenital malformation of, 35
decompression of, 750
embryology of, 947
endoscopy of, diagnostic, 733–741
in gastric adenocarcinoma, 907
indications for, 733
instrumentation for, 733–734
pathology on, 736–741, 737f–741f
patient preparation for, 734
technique for, 734f–736f, 734–736
as esophageal substitute, 579
esophagocoloplasty and, postoperative care for, 591
esophagogastrostomy and, 582–588
anastomosis for, 586–587, 587f, 588
drainage of stomach for, 584–585, 585f
functional results with, 588
lengthening of stomach for, 584, 584f
mobilization of stomach for, 582–584, 583f
transposition of stomach for, 585, 586f
foreign bodies in. *See* Foreign body ingestion.
gastric barrier function and, 729
gastric peptides and, 721–724
imaging of
in dysphagia, 66
in gastroesophageal reflux disease, 66
ligaments anchoring, 717–718, 718f
mucosa of, 720–721, 721f
peptic ulcer disease and. *See* Peptic ulcer disease.
physiologic and pathophysiologic aspects of, in esophageal disease, 184–185
prenatal development of, 34–35, 35f, 36f
pylorus of, 717, 718f
secretions of. *See* Gastric acid; Gastric juice.
watermelon, 886
endoscopic appearance of, 739–740
symptoms and diagnosis of, 886
treatment of, 740, 886
Stoppa extraperitoneal repair, for ventral hernias, 677–678, 678f, 679f
Streptococcus infection
group b, overwhelming postsplenectomy infection and, 1782
hepatic abscesses and, 1645
S. milleri, hepatic abscesses and, 1645
S. pneumoniae
immunization against, with splenic cysts, 1815
overwhelming postsplenectomy infection and, 1782
vaccination against, with asplenia, in pediatric patients, 1811
splenic abscess due to, 1819
Stress, surgical, altered hormonal response to, 2378
Stretta procedure, 317–320, 325, 326t, 327t
complications of, 319
efficacy of, 318f, 318–319, 319t
failure of, alternatives after, 319–320
histologic changes and, 318
patient selection for, 317
physiologic/anatomic mechanisms of, 330–331
precautions recommended for, 319
procedure for, 317f, 317–318
results with, 325, 326t, 327t
Strictures. *See also specific sites and conditions, e.g.* Biliary strictures.
following ileal pouch–anal anastomosis, 2112
Stricturoplasty
for Crohn's disease, 2132, 2134f–2135f
bowel resection vs., 1058–1059
techniques for, 1059, 1059f–1062f
Finney, for Crohn's disease, 1059, 1061f
Heineke-Mikulicz, for Crohn's disease, 1059, 1059f
isoperistaltic, side-to-side, for Crohn's disease, 1059, 1062f
Jaboulay, for Crohn's disease, 1059, 1062f
Judd, for Crohn's disease, 1059, 1060f
Moskel-Walske-Neumayer, for Crohn's disease, 1059, 1060f
for short-bowel syndrome, 1168, 1169, 1169f
"String of lakes" appearance, in mesenteric ischemia, 1254
Stromal cell tumor, recurrent, reoperative surgery for, 1141
Stromayr, Casper, 632
Subcutaneous tissue infections, with appendicitis, 2150
Submucosa
esophageal, anatomy of, ultrasound, 115, 115f
small intestinal, 998
Subphrenic abscesses, with appendicitis, 2150
Subserosa, of gallbladder, 1444
Substance P, duodenal function and, 981t, 983–984
Sucralfate, for esophageal strictures, 237
Sudek's point, 1868
Suicide attempts, caustic ingestions and, 540

Sulcus of Rouviere, 1603
Sulfapyridine, plasma, in constipation, 1932
Sulfasalazine
for Crohn's disease, 1052, 2127
for inflammatory bowel disease, 2089
Sulfonamides, hepatotoxicity of, 1721
Sulindac, for desmoids, in familial adenomatous polyposis, 2162
Sump syndrome, biliary drainage procedures for, 1508
Superior mesenteric artery, 968, 971f, 1292, 1293f
anatomy of, 1237–1238, 1238f, 1849, 1851f, 1852f, 1857, 1867
variations in, 1867
aneurysms of, 1278–1279
clinical findings in, 1278
diagnosis of, 1278–1279
incidence of, 1278
pathogenesis of, 1278
treatment of, 1279
balloon dilation of, 1261, 1264t
communications with celiac axis, 1238–1239, 1239f
communications with inferior mesenteric artery, 1239
embolic occlusion of, 1249b, 1249–1250
embryology of, 1234, 1235f
in mesenteric ischemia, 1247, 1248f. *See also* Mesenteric ischemia.
thrombotic occlusion of, 1250
Superior mesenteric artery syndrome, 974–975, 975f, 976f
Superior mesenteric vein, 968, 972f, 1772
anatomy of, 1869
Superoxide dismutase, for radiation enteritis prevention, 1155
Support, form clinical nurse specialist, in palliative treatment, for esophageal cancer, 497
Suprapubic hernias, repair of, 683–684, 684f
Suprarenal veins, 1603–1604
Supravesical fossa, 639
Surgeons
esophageal, 7–8
on portal hypertension multidisciplinary team, 1767
Surgical stents, for bleeding varices, 1762
Surgical stress, altered hormonal response to, 2378
Surgisis Gold, for ventral herniorrhaphy, 676
Suspicious bleeding, 1883
Suture(s)
Connell, 1085
for esophagogastrostomy, 586, 587f, 588
Halsted, 1085
Lembert, 1084, 1085f
mattress, horizontal, 1085
purse-string, 1085
Suture materials, for bowel anastomosis, 1083–1084
Sutured intestinal anastomoses, 2331, 2331f–2333f, 2333
Sutureless intestinal anastomoses, 2333–2334
Swallowing, 48–55
of air, partial fundoplication for, 279
deglutitive inhibition and, 52–53, 54f
disorders of. *See* Dysphagia.
duration response and, 51
esophageal phase of, 50–55, 51f, 129–132, 132f
esophageal peristalsis and, 51–53, 52f–54f
lower esophageal sphincter and, 53–55, 54t
esophageal propulsive force and, 53
inhibitory relaxation wave and, 53
lower esophageal high-pressure zone and, 132–134, 133f
normal, 374–377, 376f, 377f
oral phase of, 48, 129, 129f–131f
oropharyngeal phase of, imaging of, 66, 66f
pharyngeal peristaltic contraction and, 49
pharyngeal phase of, 48–50, 49f, 50f, 375
pharyngoesophageal phase of, disorders of, 134–135, 135f, 136f
preservation of, with oropharyngeal strictures, 546–547
studies of, 375, 376f
upper esophageal sphincter and, 49–50, 50f, 375–377, 376f, 377f
Swedish adjustable gastric band, 934
Sweet anastomosis, 586, 587f, 588
Sweet's double-rib resection, 579
Sympathetic nerves, low anterior resection and, 2223, 2225
Sympathetic nervous system, prenatal development of, 45–46
Syphilis, anal, in immunocompromised patients, 2383t
Syphilitic lesions, pruritus ani associated with, 2070
Systemic lupus erythematosus, splenectomy for, 1824–1825

T

Tacrolimus
for inflammatory bowel disease, 2092
for islet transplantation, 1424
mechanism of action of, 2377t
Tamoxifen
for desmoids, in familial adenomatous polyposis, 2162
hepatotoxicity of, 1721, 1723
TA-stapler, for splenectomy, partial, 1815
Tazobactam, for cholangitis prophylaxis, 1550t
Teacher, as clinical nurse specialist role, in palliative treatment, for esophageal cancer, 497
Tegaserod
for gastroesophageal reflux disease, 253
for intestinal dysmotility, 926
Telangiectasia
colonic, 1997, 1999
gastric
acquired, 887
congenital, 887
Telangiectasia *(Continued)*
hereditary, 1713
small intestinal, 898–899
Tenderness, in appendicitis, 2142
Tensilon test. *See* Edrophonium test.
Tensor fasciae latae, 687
Teratocarcinoma, retrorectal, 2304–2305
Teratomas
gastric, in pediatric patients, 959
retrorectal, 2302t, 2304–2305
Terbinafine, hepatotoxicity of, 1722
Terminal patients, with esophageal cancer, management of, 497
Testes
blood supply to, injury of, with contralateral inguinal exploration, 709
injury of, with inguinal herniorrhaphy, laparoscopic, 667
undescended, operative management of, 709–711
Testicular descent, with inguinal herniorrhaphy, laparoscopic, 668
Testicular torsion, in children, 711–712
operative management of, 711–712
Tetracyclines
hepatotoxicity of, 1720
for lymphoma, 1209t
pruritus ani associated with, 2069
Thalassemia major, splenectomy for, 1826
Thermotherapy
laser, for hepatocellular carcinoma, 1738
microwave, for hepatocellular carcinoma, 1738
Thiamine, small intestinal absorption of, 1006, 1007t
Thiersch encirclement, for rectal prolapse, 1964f, 1964t, 1964–1965
Third spacing, 1025
Thoracoscopy, for staging of esophageal cancer, 460
Thorium, hepatotoxicity of, 1724
Three-dimensional radiation treatment planning, 1155
Thrombocytopenia
splenectomy for hematologic disorders causing, 1822–1825
human immunodeficiency virus as, 1825
idiopathic thrombocytopenic purpura as, 1822–1824, 1824f
systemic lupus erythematosus as, 1824–1825
thrombotic thrombocytopenic purpura as, 1824
Wiskott-Aldrich syndrome as, 1825
Thromboembolectomy, operative, for mesenteric ischemia, 1255
Thrombosis
deep vein, with inguinal herniorrhaphy, laparoscopic, 667
hepatic artery, 1712–1713, 1713f
liver transplantation and, 1698
mesenteric vein
acute, ischemia due to, 1255–1257, 1256f
following splenectomy, 1838

Thrombosis *(Continued)*
portal vein
with cavernous transformation, in chronic pancreatitis, 1313f, 1313–1314
following splenectomy, 1838
liver transplantation and, 1697, 1698
splenic vein
asymptomatic, 1353
following splenectomy, 1838
in pancreatitis, chronic, 1352–1353
splenectomy for, 1834
Thrombotic thrombocytopenic purpura, splenectomy for, 1824
Thyroid arteries, 20
Tileston, Walter, 338
TIPS. *See* Transjugular intrahepatic portocaval shunt.
Tissue adhesives, for bowel anastomoses, 1089
TNM staging system
for esophageal cancer, 448, 449–450, 450t, 451f, 472t, 472–473, 473t
for residual tumors, 455
for gastric adenocarcinoma, 908, 908b
for hepatocellular carcinoma, 1735
Tobacco use
esophageal cancer and, 444, 466
pancreatic adenocarcinoma and, 1359
smoking cessation for gastroesophageal reflux disease and, 253
Toldt, white line of, 1857, 1860f
Torek, Feranz, 4
Total parenteral nutrition
for biliary surgery, 1622
for liver surgery, 1622
for radiation enteritis, 1157
Total-body irradiation, hepatotoxicity of, 1723
Totally extraperitoneal hernia repair
for femoral hernias, 626, 628–629, 629f
for inguinal hernias, 656, 659, 663–664, 664f, 665t
Toupet fundoplication, 276, 277f
for achalasia, 416
endoscopic examination following, 106
laparoscopic, surgical technique for, 282, 282f
for paraesophageal hernia, 557, 557f
results with, 283, 284t
Toxic megacolon
as emergency surgical indication, 2101
in ulcerative colitis, 2084
Toxins, fulminant liver failure due to, 1703
Trabecular arteries, 1772
Trachea, prenatal development of, 34f, 35, 39f
Tracheal cartilage, 14–15, 15f
Tracheobronchial arteries, 20
Tracheobronchial remnant, 572
Tracheoesophageal atresia, 563–571
abnormalities associated with, 564, 565f
classification of, 564, 565f
clinical findings and diagnostic evaluation of, 565, 566f
development and, 563–564
historical background of, 563
management of, 565–566
Tracheoesophageal atresia *(Continued)*
complications of, 569–571, 571f
operative, 566–569, 567f–570f
recurrent, 570
Tracheoesophageal fistulas, 15
following esophageal resection with visceral esophageal substitution, 613
radiographic appearance of, 76, 78f
Tracheomalacia, with esophageal and tracheoesophageal atresia, 564, 570, 571f
Transabdominal preperitoneal hernia repair
for femoral hernias, 625–626, 628–629
for inguinal hernias, 656, 659, 661–663, 661f–663f, 665t
Transanal endoscopic microsurgery, 2338
for rectal cancer, 2211–2212, 2212f
outcomes with, 2215, 2216t
Transanal excision of rectal tumors, 2338
Transarterial splenic embolization, 1788–1790
anatomy and, 1788, 1789f, 1790f
splenic bleeding and, 1790–1791, 1792f
technique for, 1788–1790, 1790f
Transcatheter arterial embolization/chemoembolization, for hepatocellular carcinoma, 1738
Transducers, for ultrasonography, 111
Transfusion therapy
with biliary surgery, 1619–1620
with liver surgery, 1619–1620
Transhepatic wires, percutaneous, duodenal perforation due to, 1095
Transient lower esophageal sphincter relaxation, 54–55
Transjugular intrahepatic portocaval shunt
for ascites, 1765
for bleeding varices, 1693, 1761–1762
procedure for, 1761f, 1761–1762
for Budd-Chiari syndrome, 1714, 1715
Transmesenteric hernias, 1122f, 1122–1123
clinical features of, 1123
diagnosis of, 1123
treatment of, 1123
Transomental hernias, 1123, 1124f
Transplantation. *See also specific types of transplantation.*
immunosuppression for, 2379
Transversalis fascia, 640–641, 641f, 656–657
Transverse incision
for appendectomy, 2145, 2146f
for colorectal surgery, 2329
Transversus abdominis muscle, 636, 637f, 638, 673, 673f
Trapezoidal flap, for rectovaginal fistulas, 1948–1950, 1949t
Trauma. *See also specific locations, e.g.* Gastric injuries.
esophageal perforation due to, 529
Traumatic hernias, 560
Treatise on Ruptures (Pott), 632
Treitz, ligament of, 968, 970f, 1864
Treves
arch of, 1239
bloodless fold of, 1862
Triangle of doom, 639
Triangle of pain, 639–640
Trichobezoars, 943, 944, 944t, 945
in pediatric patients, 959–960, 960f
Trichophyton infection, pruritus ani associated with, 2070
Trimethoprim/sulfamethoxazole, for cholangitis prophylaxis, 1550t
Triple-tube ostomy, for duodenal injuries, 768
Troglitazone, hepatotoxicity of, 1722
Trusses, for groin hernias, 645, 646f
Tube decompression, for duodenal injuries, 768
Tube feeding, for gastroparesis, 924
Tubular adenomas, small intestinal, 891–892
Tuffeir, Theodore, 4
Tumor(s). *See* Malignancies; Metastases; Neoplastic disorders; *specific neoplasms.*
Tumor cell adherence, suture material and, 1084
Tumor markers, for colorectal cancer, 2200–2201
Tumor necrosis factor, for esophageal cancer, 510
Tumor-releasing parathyroid hormone-related protein, pancreatic neuroendocrine tumors and, 1383
Tunica adventitia, esophageal, 16, 16f
Tunica muscularis, esophageal, anatomy of, 16f, 16–17
Turcot's syndrome, 2159t, 2160
small intestinal, 894t, 895–896
Turner, Grey, 4
Turner's syndrome, 887
24-hour esophageal motor activity monitoring, ambulatory, 136
Tylosis, esophageal carcinoma and, 466
Typhlitis, in immunocompromised patients, 2382–2383

U

Ulcer(s)
aphthous, in Crohn's disease, 1043
peptic. *See* Peptic ulcer disease.
Ulcerative colitis, 2080–2085. *See also* Inflammatory bowel disease.
acute, severe, 2084–2085, 2085f
clinical course of, 2081–2082
colorectal cancer and dysplasia and, 2082–2084
Crohn's disease differentiated from, 1050, 1050f
diagnosis of, 2082, 2082f
diarrhea in, 1880
with dysplasia or cancer, surgical management of, restorative proctocolectomy for, 2335
epidemiology and etiopathogenesis of, 2080
fulminant, as emergency surgical indication, 2101
laparoscopic surgery for
outcomes of, 2356–2357
technical points for, 2357
massive hemorrhage in, 2085

Ulcerative colitis *(Continued)*
medical treatment of, 2089–2093
5-aminosalicylic acid compounds in, 2089–2090
antibiotics in, 2090–2091
biological therapies in, 2092–2093
corticosteroids in, 2090
immunosuppressive agents in, 2091–2092
sulfasalazine in, 2089
pathologic features of, 2081, 2081t, 2082f
surgical treatment of, 2101–2122
colectomy with ileorectal anastomosis for, 2122
ileal pouch–anal anastomosis for. *See* Ileal pouch–anal anastomosis, for ulcerative colitis.
indications for, 2101–2102
for elective surgery, 2101
for emergency surgery, 2101–2102
Kick continent ileostomy for, 2122
panproctocolectomy with ileostomy for, 2122
Ultrasonography
anorectal
with anorectal abscesses, 2049–2051, 2050f–2052f
with anorectal fistulas, 2049–2051, 2050f–2052f
in aortoenteric fistulas, 1272
in appendicitis, 2142–2143
B-mode, 112
with choledochal cysts, 1553
in colorectal trauma, 1974
in Crohn's disease, 1048–1049
of echinococcal cysts, 1637
endorectal. *See* Endorectal ultrasound.
endoscopic. *See* Endoscopic ultrasonography.
fundamentals of, 111–112
gray-scale, 112
with groin hernias, 643
with hepatic abscesses, pyogenic, 1646
of hepatic cysts, solitary, 1630, 1631f
in hepatocellular carcinoma, 1734
in ileocolic aneurysms, 1282f, 1283
intraoperative
in biliary disease, 1627
in liver disease, 1627
in jaundice, obstructive, 1460–1461, 1461f
with liver abscesses, amebic, 1654
in mesenteric ischemia, 1252
in mesenteric venous thrombosis, 1256
in pancreatitis, acute, 1299
percutaneous, for staging of esophageal cancer, 457
real-time, 112
right upper quadrant, in periampullary carcinoma, 1361
with splenic abscesses, 1818
with splenic cysts, 1815
in splenic trauma, 1799
Umbilical anomalies, with Meckel's diverticulum, 787
Umbilical arteries, fetal, 656
Umbilical fissure, 1603
Umbilical folds, 656, 657f
Umbilical hernias
physiologic, 1857
repair of, 681–682
Umbilical plate, 1599, 1603
Umbilical vein, extrahepatic, 1598
Umbilicus, 672
United Network of Organ Sharing, 1691
University of California San Francisco criteria, 1740
"Uphill" varices, 95, 97f
Upper esophageal sphincter
anatomy of, 17
high-pressure zone of, 376–377, 377f
idiopathic dysfunction of, cricopharyngeal myotomy for, 388, 389f
swallowing and, 49–50, 50f, 129, 129f–131f, 375–377, 376f, 377f
Zenker's diverticulum and, 391–392, 392f, 395
Upper gastrointestinal clinical nurse specialist, role of, in palliative treatment, for esophageal cancer, 497–498
Urachus, 656
Ureter(s), identification of, 2412
Ureteral obstruction, in Crohn's disease, 1065–1066
Urge incontinence, 1885
Urinalysis, in appendicitis, 2143
Urinary retention
after anorectal surgery, 2057
with inguinal herniorrhaphy, laparoscopic, 667
Uroguanylin, small intestinal neuroendocrine function and, 1019
Ursodeoxycholic acid
for cholangitis prophylaxis, 1550t
for hepatobiliary disease, with primary sclerosing cholangitis, 1568
hepatotoxicity of, 1722
for pruritus, in primary sclerosing cholangitis, 1567
U-shaped island flaps, for anal stenosis, 2064

V

VACTERL association, 2391
with esophageal and tracheoesophageal atresia, 564
Vacuoles, epithelial
lumen occlusion secondary to, 40, 42f
in prenatal development, 39–40, 40f
Vagal nerve, injury of, during esophageal surgery, 598
Vagina, identification of, 2414
Vaginal delivery, following ileal pouch–anal anastomosis, 2117–2118
Vaginography, with colon, rectal, and anal disorders, 1893
Vagotomy
with antrectomy, for duodenal ulcers, 796, 797, 798t
completion, for gastric outlet obstruction, at gastrojejunostomy site, 1138
Vagotomy *(Continued)*
definition of, 814
with drainage, 811–827
drainage procedures and, 815–818, 817f
for duodenal ulcers, 796, 798t
indications for, 822–826
bleeding ulcers as, 824–825, 825f
obstruction as, 825–826
ulcer intractability as, 822–823
ulcer perforation as, 823–824
for peptic ulcer disease, 818, 820–822
gastric, 820f, 820–822
ulcer recurrence after, 826–827
vagal anatomy and, 812–813, 813f
vagal physiology and, 813–814
vagotomy and, 814f, 814–815
for duodenal ulcers, 792–794
gastric, proximal, 814f, 815, 821–822
technique for, 831, 835f–838f
gastric dysmotility following, 730, 923
highly selective
for duodenal ulcers, 793–794, 794f, 796, 797, 798t
technique for, 831, 838f–840f
with long-limb Roux-en-Y gastric bypass, for Barrett's esophagus, 303–304
minimally invasive versions of, 815
selective, 814f, 814–815
for duodenal ulcers, 792–793, 793f
supradiaphragmatic, for duodenal ulcers, 794
truncal
for duodenal ulcers, 792, 793f
technique for, 831, 832f–835f
thoracoscopic, for gastroparesis, 924
transabdominal, 814, 814f
Vagus nerve, 1294
anatomy of, 25, 719–720, 720f, 812–813, 813f
intraoperative injury of, during hiatal herniorrhaphy, 609
physiology of, 813–814
prenatal development of, 44–45, 45f
Valproic acid, hepatotoxicity of, 1720
Valves of Heister, 1444
Valvular disease, in carcinoid syndrome, 1182
Vancomycin, for *Clostridium difficile* colitis, in immunocompromised patients, 2382
Varices
bleeding, esophageal. *See* Esophageal varices, bleeding.
colonic, 1997
esophageal. *See* Esophageal varices.
gastric
endoscopic appearance of, 739, 739f
in pancreatitis, chronic, 1352–1353
peri-ileostomy, 1081
peristomal, 2373, 2373f
Vas deferens, injury of
with contralateral inguinal exploration, 709
with inguinal herniorrhaphy, laparoscopic, 667
Vascular compression, esophageal, 573–574, 574f

Vascular disorders. *See also specific disorders.*
aneurysms as. *See* Aneurysms.
pseudoaneurysms as. *See* Pseudoaneurysms.
splenectomy for, 1833–1834
for portal hypertension, 1834
for splenic artery aneurysm, 1833–1834
for splenic vein thrombosis, 1834
for "wandering spleen" and splenic torsion, 1834
thrombosis as. *See* Thrombosis.
Vascular ectasia
colonic. *See* Colon, vascular ectasias of.
gastric antral, 886
endoscopic appearance of, 739–740
symptoms and diagnosis of, 886
treatment of, 740, 886
Vascular injury, with inguinal herniorrhaphy, laparoscopic, 665
Vascular lesions, gastric, 886–888
angiodysplasia as, 739, 887
Dieulafoy's lesions as, 740, 740f, 886–887
symptoms and diagnosis of, 887
treatment of, 887
duplication cysts as, 889
glomus tumors as, 887–888
hemangiomas as, 887
lymphangiomas as, 887
telangiectasia as, 887
acquired, 887
congenital, 887
watermelon stomach as, 886
endoscopic appearance of, 739–740
symptoms and diagnosis of, 886
treatment of, 740, 886
Vascular system, foregut, prenatal development of, 42–43, 43f, 44f
Vasculobiliary sheaths, 1599–1600
Vasoactive intestinal peptide
duodenal function and, 981t, 983
small intestinal neuroendocrine function and, 1018
Vasoconstriction
mesenteric, control of, 1242b
splanchnic, mesenteric ischemia due to, 1251
Vasodilation, mesenteric, control of, 1242b
Vatalanib, for colorectal cancer metastases, 2271
Vater, papilla of, 964, 965f
Veins. *See specific veins.*
Vena cava
clamping of, with liver trauma, 1665–1666, 1666f
inferior, 1673, 1673f
Veno-occlusive disease, hepatic, drug-induced, 1723
Venous plexuses, esophageal, 21, 22f
Venous thromboembolism, postoperative, prophylaxis of, 2327, 2328t
Venous thrombosis. *See* Thrombosis.
Venovenous bypass, for liver transplantation, 1695–1696
Ventral hernias, 671–684
anatomy and, 672f, 672–673, 673f
definition of, 671–672
Ventral hernias *(Continued)*
etiology of, 673–674
repair of, obesity and, 684
surgical treatment of
indications for, 674
preparation for, 674–675
principles of, 676–684, 677f–679f
components separation and, 682–683, 683f
laparoscopic operative method and, 678–680, 679f, 680f
minimally invasive vs. open mesh repair and, 680, 680t
obesity and, 684
perioperative considerations and, 680–681
for spigelian hernias, 682
for suprapubic hernias, 683–684, 684f
for umbilical hernia, 681–682
prosthetics for, 675f, 675–676, 676f
symptoms of, 674
types of, 671
Venules, mesenteric, 1241
Veress needle, 1135
perforation due to, 1094
Vermiform appendix, anatomy of, 1846, 1863, 1864f
Verner-Morrison syndrome, 1381
Vertical midline incision, for colorectal surgery, 2329
Videocineroentgenography
for esophageal bolus clearance evaluation, 154, 155f, 156f
for swallowing disorder assessment, 134, 135f
Videoesophagography, in gastroesophageal reflux disease, 59
Videofluoroscopy, for swallowing evaluation, 377–378
Villi, small intestinal, 998
Villous adenomas, small intestinal, 892–893
Vinyl chloride, hepatotoxicity of, 1723, 1724
VIPomas, 1381
Virchow's node, 906, 1361
Visilizumab, mechanism of action of, 2377t
Vitamin(s)
fat-soluble
deficiency of, with primary sclerosing cholangitis, treatment of, 1568, 1568t
for steatorrhea, with primary sclerosing cholangitis, 1588
small intestinal absorption of, 1006–1008, 1007t
Vitamin A
deficiency of, in Crohn's disease, 1054
hepatotoxicity of, 1723
small intestinal absorption of, 1006–1007, 1007t
Vitamin B_{12}
deficiency of
in Crohn's disease, 1054
following gastrectomy, 873
small intestinal absorption of, 1006, 1007t
Vitamin C, small intestinal absorption of, 1006, 1007t
Vitamin D
deficiency of, in Crohn's disease, 1054
small intestinal absorption of, 1006, 1007, 1007t
Vitamin E
deficiency of, in Crohn's disease, 1054
small intestinal absorption of, 1006, 1007, 1007t
Vitamin K
deficiency of, in Crohn's disease, 1054
small intestinal absorption of, 1006, 1007t, 1007–1008
Vitelline blood vessel remnants, 1227
Volvulus
colonic. *See* Colonic volvulus.
gastric, 1037–1039
diagnosis of, 1037–1038, 1038f, 1039f
etiology of, 1037, 1037f
in pediatric patients, 950
treatment of, 1038–1039
small bowel, 1035–1037
diagnosis of, 1036, 1036f
etiology of, 1035–1036, 1036t
treatment of, 1036–1037
types of, 550, 551f
Vomiting
in afferent loop syndrome, 877–878
in appendicitis, 2142
in malrotation, 1216
in small bowel obstruction, 1028
in small intestinal atresia, 1219
V-Y island flaps, for anal stenosis, 2063f, 2063–2064

W

W pouch, 2105
Walaean pedicles, 1599
Walaean sheaths, 1599
"Wandering spleen," splenectomy for, 1834
Wantz, George, 678
Water, small intestinal absorption of, 1001, 1001t
Watermelon stomach, 886
endoscopic appearance of, 739–740
symptoms and diagnosis of, 886
treatment of, 740, 886
Water-soluble contrast enema, with colon, rectal, and anal disorders, 1893
Watson fundoplication, 276, 277f, 278
Wedge resection, hepatic, 1683, 1683f
Weight loss
in achalasia, 407
in Crohn's disease, 1045
in esophageal cancer, 61
esophageal carcinoma and, 468
following gastrectomy, 873
surgery for. *See* Bariatric surgery.
Whipple procedure
for duodenal adenocarcinoma, 915
for pancreatitis, chronic, 1314, 1315
for Zollinger-Ellison syndrome, 868

Whipple's triad, with insulinoma, 1376
Whirl sign
in colonic volvulus, 1981
with transmesenteric hernias, 1123
White blood cell count, in appendicitis, 2142–2143
White line of Toldt, 1857, 1860f
Whitehead deformity, 2062
Whitehead hemorrhoidectomy, 2033
Wilke's syndrome, 974–975, 975f, 976f
Willis, Thomas, 405
Wilson's disease
fulminant liver failure due to, 1703
hepatic laboratory tests in, 1613
Winslow, foramen of, 964, 966f
Wirsung, pancreatic duct of, 964
Wiskott-Aldrich syndrome, splenectomy for, 1825
Witch hazel, pruritus ani associated with, 2069
Witzel gastrostomy, in pediatric patients, 960
Witzel jejunostomy, 757, 758f
Wound complications
after anorectal surgery, 2057
with gastrointestinal fistulas, 1098
infection as
with hernia repair, 654
with inguinal herniorrhaphy, laparoscopic, 668
Wound healing, steroid-induced impairment of, 2378
Wound implants, prevention of, with laparoscopic colorectal surgery, 2348, 2348f–2353f, 2349b, 2351b, 2353
Wound vacuum drainage systems, 1102, 1104f

Y

Yellow phosphorus, hepatotoxicity of, 1720
York-Mason approach, for rectourethral fistulas, 1955
Yo-yo syndrome, 929
Y-V advancement flaps, for anal stenosis, 2063, 2063f

Z

Zacarelli, Adrian, 1813
Zafirlukast, hepatotoxicity of, 1721
ZAP classification, for Barrett's esophagus, 103–104
Zenker, Albert, 6
Zenker's diverticulum, 94–95, 96f, 391–400, 427–433
pathophysiology of, 427–428
physiology and pathophysiology of, 391–395, 392f
contractility studies and, 392, 393f–395f, 393t, 394–395, 395t
recurrent, reoperation for, 431
swallowing disorder in, 134–135, 135f, 136f
symptoms and diagnosis of, 396, 396t, 428, 428f
treatment of, 396–398, 429–433
choice of, 400
cricopharyngeal myotomy for, 378–379, 381
for established diverticula, 381, 383f
Zenker's diverticulum *(Continued)*
for large diverticula, 381, 383f
for minute diverticula, 381
diverticulectomy as, 396
diverticulopexy as, 396
early development of surgery for, 5–6
endoscopic, 397–398, 398f
methods and results of, 431–433, 432f
evolution of, 429
myotomy in, 396–397, 397f, 398f
results of, 398–400, 399t, 400f, 401t–403t
surgical, methods and results of, 429–431, 430f, 431f
Zidovudine, hepatotoxicity of, 1720
Zinc, deficiency of, in Crohn's disease, 1054
Zinman, Leonard, 1955
Z-line, 19
Barrett's esophagus classification and, 103–104
endoscopic appearance of, 101, 101f
in Barrett's esophagus, 103, 103f, 104f
Zollinger-Ellison syndrome, 862–868
carcinoids in, 1181
diagnosis of, 862–863, 863b, 864f
GRFomas in, 1382
localization procedures for, 864–865, 865f
management of
medical, 866, 866f
surgical, 866–868, 867f
metastatic, 868
in pediatric patients, 961
signs and symptoms of, 862
tumor characteristics in, 863–864